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# The nucleophilic 5-*endo-trig* cyclization of *gem*-difluoroolefins with homoallylic functional groups: syntheses of ring-fluorinated dihydroheteroaromatics

**Junji Ichikawa,*[a] Masaki Fujiwara,[a] Yukinori Wada,[a] Tatsuo Okauchi[b] and Toru Minami*[b]**

[a] *Department of Chemistry, Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: junji@chem.s.u-tokyo.ac.jp; Fax: +81-3-5841-4345; Phone: +81-3-5841-4345*

[b] *Department of Applied Chemistry, Kyushu Institute of Technology, Sensui-cho, Tobata, Kitakyushu 804-8550, Japan*

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**_gem_-Difluoroolefins bearing homoallylic tosylamido, hydroxy, or mercapto groups undergo intramolecular nucleophilic substitution of the nitrogen, oxygen, or sulfur with loss of fluorine *via* a 5-*endo-trig* process, leading to 2-fluoro-2-pyrrolines, 5-fluoro-2,3-dihydrofurans, or -thiophenes in high yields.**

5-*endo-trig* cyclization has long been considered to be a geometrically disfavored process in accord with Baldwin's rules.[1] Efficient examples of the cyclization, however, have been recently devised in radical-initiated[2] and electrophile-driven[3] ring closures. In contrast with these two types of 5-*endo-trig* cyclizations, the corresponding nucleophile-driven ring closure has still rarely been observed in synthetic chemistry.[4,5]

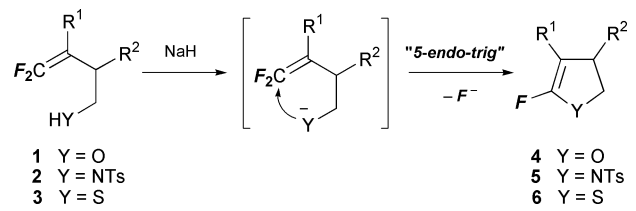
*gem*-Difluoroolefins possess remarkable reactivity toward nucleophilic substitution for their fluorine atoms *via* addition–elimination processes.[6] As one of its applications, we have recently disclosed that β,β-difluorostyrenes bearing *ortho*-nitrogen, oxygen, or sulfur heteroatoms readily undergo nucleophilic 5-*endo-trig* cyclization to provide ring-fluorinated heteroaromatics: 2-fluorinated indoles, benzo[*b*]furans, and benzo[*b*]thiophenes.[5] Such unique reactivity of *gem*-difluoroolefins is exerted presumably due to (i) the highly polarized C–C double bond (significant single bond character implied by $^{13}C$ NMR: *ca.* 150 and 90 ppm for $CF_2$=C), which would allow initial 5-membered ring formation, and (ii) the successive elimination of fluoride ion suppressing the reverse ring opening. In this ring-forming reaction the substrates had a benzene ring as an $sp^2$-carbon linker between the nucleophilic functional group and the difluoroolefin part.

In order to broaden the scope of this nucleophilic 5-*endo-trig* cyclization and rule out the possibility of an 6π-electrocyclization mechanism, we investigated the reaction of *gem*-difluoroolefins **1**–**3** bearing an *N*-, *O*-, or *S*-functional group which was linked by two $sp^3$ carbons to the olefinic carbon. Herein we report a facile synthesis of selectively ring-fluorinated pyrroline **5**, dihydrofuran **4**, and dihydrothiophene **6** (Scheme 1), which are difficult to access despite the potential uses of ring-fluorinated heterocycles as components of agrochemicals, pharmaceuticals, and dyestuffs.[7]

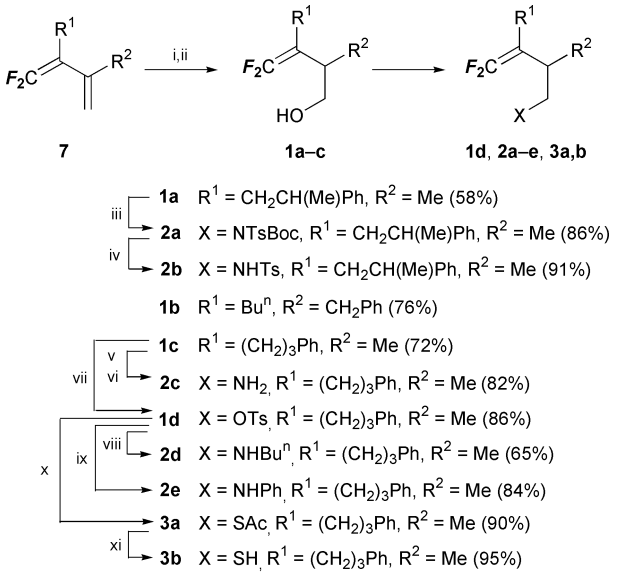
*gem*-Difluoroolefin substrates were designed to bear a nucleophilic nitrogen, oxygen, or sulfur atom at the homoallylic position suitable for substitution in a 5-*endo-trig* fashion. To introduce a functional group (HY) at the *gem*-difluoro-homoallylic position, we tried the regioselective hydroboration of 1,1-difluoro-1,3-dienes **7**, which were readily prepared from 2,2,2-trifluoroethyl toluene-*p*-sulfonate and vinyl halides in a one-pot operation according to our method.[8] The electron-rich, non-fluorinated double bond in **7** might be more reactive toward borane reagents. Treatment of difluorodienes **7** with 9-borabicyclo[3.3.1]nonane (9-BBN) under reflux in THF selectively promoted hydroboration as expected to generate difluorohomoallylboranes, and successive treatment with alkaline aqueous hydrogen peroxide gave *gem*-difluorohomoallyl alcohols **1a**–**c** in good yields (Scheme 2). The corresponding nitrogen- and sulfur-containing substrates **2a**–**e**, **3a**,**b** were easily obtained from **1** as shown in Scheme 2.

The cyclization of homoallyl alcohols **1a**,**b** was attempted by treatment with 1.2 eq. of NaH in several solvents. While the use DMPU or NMP gave no cyclized products, DMF, DMA, or DMSO successfully promoted the 5-*endo-trig* cyclization to afford 5-fluoro-2,3-dihydrofurans **4a**,**b** in good yields (Table 1, Entries 1,2).[9]† KH was less effective than NaH, and high-dilution conditions ([**1a**] = 0.03 mol $L^{-1}$) raised the yield by 10% compared to the case of [**1a**] = 0.2 mol $L^{-1}$.

Moreover, we examined the 5-*endo-trig* cyclization of the substrates with *N*-nucleophiles under similar conditions. Whereas *N*-unsubstituted and *N*-butylhomoallylamines **2c**,**d** did not cyclize, the *N*-phenyl substrate **2e** afforded 4-methyl-1-phenyl-3-(3-phenylpropyl)-2-pyrrolidone **8** *via* hydrolysis of




**Scheme 1** Nucleophilic 5-*endo-trig* cyclization of *gem*-difluoroolefins **1**–**3**.




**Scheme 2** Preparation of *gem*-difluoroolefins **1**–**3**. *Reagents and conditions*: i, 9-BBN (1.1–1.4 eq.), THF, reflux, 6–7 h; ii, aq.$H_2O_2$, aq. NaOH, 0 °C, 2 h; iii, BocNHTs (1 eq.), $PPh_3$ (1 eq.), $EtO_2CN{=}NCO_2Et$ (1 eq.), THF, rt, 2 h; iv, $CF_3CO_2H$ (15 eq.), $CH_2Cl_2$, rt, 2 h; v, phthalimide (1 eq.), $PPh_3$ (1 eq.), $EtO_2CN{=}NCO_2Et$ (1 eq.), THF, rt, 2 h; vi, $NH_2NH_2{\bullet}H_2O$ (2 eq.), EtOH, reflux, 2 h; vii, TsCl (1 eq.), Py, rt, 8 h; viii, $Bu^nNH_2$ (26 eq.), reflux, 6 h; ix, $PhNH_2$ (26 eq.), reflux, 6 h; x, AcSNa (1 eq.), DMF, 70 °C, 3 h; xi, $K_2CO_3$ (1 eq.), MeOH, 0 °C, 1 h.

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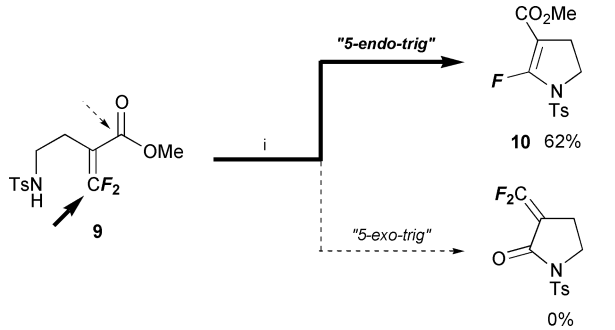
**Table 1** Synthesis of ring-fluorinated dihydroheteroaromatics **4**–**6**[a]

| Entry | YH | $R^1$ | $R^2$ | Substrate | Base (eq.) | Time | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | OH | $CH_2CH(Me)Ph$ | Me | **1a**[c] | NaH (1.2) | 7 h | **4a**[c] | 67 |
| 2 | OH | $Bu^n$ | $CH_2Ph$ | **1b** | NaH (1.2) | 11 h | **4b** | 62 |
| 3 | PhNH | $(CH_2)_3Ph$ | Me | **2e** | NaH (1.1) | 24 h | **8** | 62 |
| 4 | TsNH | $CH_2CH(Me)Ph$ | Me | **2b**[c] | NaH (1.1) | 4 d | **5**[c] | 80 |
| 5 | SH | $(CH_2)_3Ph$ | Me | **3b** | NaH (1.1) | 4 h | **6** | 76 |
| 6 | SC(O)Me | $(CH_2)_3Ph$ | Me | **3a** | NaOMe (1.0) | 8 h | **6** | 69 |

[a] The reaction was conducted in DMF at 90 °C. [Substrate] = 0.02–0.03 mol $L^{-1}$. [b] Isolated yield. [c] 1:1 Diastereomer mixture.




**Scheme 3** Competitive cyclization: 5-*endo-trig vs*. 5-*exo-trig Reagents and conditions*: i, NaH (1.1 eq.), DMF, 100 °C, 0.3 h.

the expected 2-fluoropyrroline (Entry 3). The *N*-4,4-difluorobut-3-enyltoluene-*p*-sulfonamide **2b** underwent the desired ring closure to give 2-fluorinated pyrroline **5** in 80% yield (Entry 4).[10]‡

As a further example of the cyclization, the intramolecular substitution of sulfur nucleophiles (which Baldwin's rules allow for the normally disfavored 5-*endo-trig* process) was also examined.[1b] The reaction of **3b** under similar conditions to those for **1** and **2** provided 5-fluorinated dihydrothiophene **6** in 76% yield (Entry 5).[11] In addition, treatment of thioacetic *S*-acid ester **3a** with sodium methoxide allowed the cyclization *via in situ* generated thiolate to give **6** (Entry 6).§

In order to demonstrate the favored nature of 5-*endo-trig* cyclization in *gem*-difluoroolefins, we tried the competitive reaction between 5-*endo-trig* and 5-*exo-trig* processes. The β,β-difluoro-α,β-unsaturated ester **9** bearing a 2-toluene-*p*-sulfonamidoethyl group was designed as a substrate which could undergo the Michael reaction and the transacylation *via* 5-*endo-trig* and 5-*exo-trig* processes, respectively. Compound **9** was prepared by the $S_N2'$ reaction of methyl 2-(trifluoromethyl)propenoate[12] with benzyloxymethylcopper[13] and successive deprotection of the benzyl group, followed by the introduction of an NHTs group according to the same procedure for **2b**. On treatment of **9** with NaH in DMF, the 5-*endo-trig* cyclization proceeded to lead exclusively to the 2-fluorinated pyrroline derivative **10** as shown in Scheme 3.¶‖

In conclusion, normally 'disfavored' 5-*endo-trig* ring closures are successfully achieved in the intramolecular addition–elimination reaction of *gem*-difluoroolefins bearing nucleophilic heteroatoms linked by two $sp^3$ carbons to the vinylic carbon as well as two $sp^2$ carbons.[5] Thus, *gem*-difluorohomoallylamine, alcohol, and thiol derivatives open a new way to the syntheses of selectively ring-fluorinated heterocyclic compounds.

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## Notes and references

† **4b**: $\delta_F$ (471 MHz, $CDCl_3$–$C_6F_6$) 42.4 (1F, s).
‡ **5**: $\delta_F$ (471 MHz, $CDCl_3$–$C_6F_6$) 36.2 (0.5F, s), 36.6 (0.5F, s).
§ **6**: $\delta_F$ (471 MHz, $CDCl_3$–$C_6F_6$) 35.7 (1F, br s).
¶ The fluorine-free analogue, dimethyl 4-methyleneglutamate was reported to cyclize to 5-methoxycarbonyl-3-methylene-2-pyrrolidone *via* 5-*exo-trig* pathway without formation of the 5-*endo-trig* product.[1b,14]
‖ **10**: $\delta_F$ (471 MHz, $CDCl_3$–$C_6F_6$) 61.8 (1F, t, $J_{FH}$ = 4.8 Hz).

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