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Fluorine-Directed Nazarov Cyclizations: A Controlled Synthesis of Cross-Conjugated 2-Cyclopenten-1-ones

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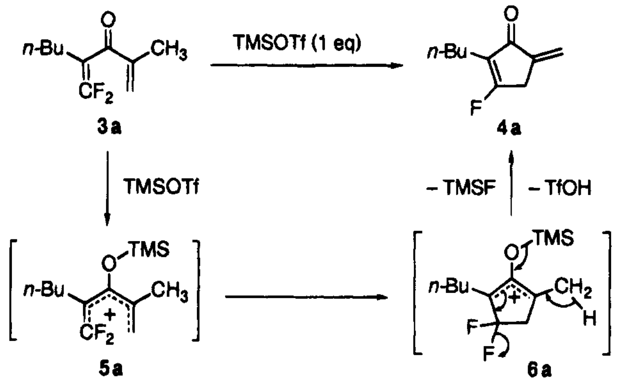
The Nazarov cyclization has been widely used as a method for cyclopentenone annelation.[1] The classical reactions, however, have a major limitation: the lack of control over the position of the double bond in the five-membered ring. The double bond normally occupies the most substituted position because of its thermodynamic stability, which has restricted their use as a general tool for organic synthesis. Among a number of modifications of this reaction, it was the silicon-directed Nazarov cyclization[1ab,2] that overcame this drawback of regiochemistry by making use of two properties of silicon: (i) its *β-cation-stabilizing* effect and (ii) its function as an *electrofuge*, that is, leaving-group ability as a silyl cation (Si^+).[3] In terms of these properties, fluorine is a kind of negative image of silicon. Fluorine possesses a *β-cation-destabilizing* effect and also functions as a *nucleofuge*, the leaving group of a fluoride ion (F^-).[4] These facts suggest that not only silicon but also fluorine might be a controller of the electrocyclic reaction. On the basis of these considerations, we investigated *fluorine-directed* Nazarov cyclizations, using 2,2-difluorovinyl vinyl ketones as the fluorinated substrates. We now report a new Nazarov-type cyclization with defined placement of two double bonds, which leads to the controlled synthesis of cross-conjugated 2-cyclopenten-1-ones bearing one more double bonds compared to normal Nazarov products.[5]

Table 1. Preparation of 2,2-Difluorovinyl Vinyl Ketones 3 from 1

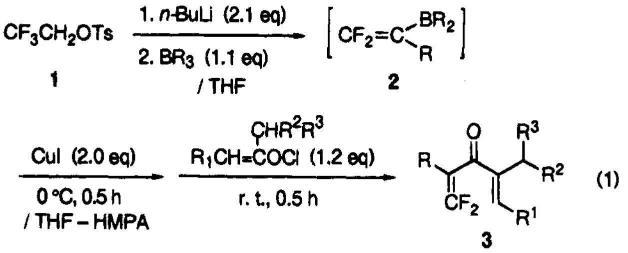
R^1	R^2	R^3	product (**3**)	yield,[a] %
H	H	H	**3a**	54
H	Ph	H	**3b**	62
H	^{n}Pr	H	**3c**	60
H	Me	Me	**3d**	59
Me	H	H	**3e**	58
−$(CH_2)_3$−		H	**3f**	63
−$(CH_2)_4$−		H	**3g**	65

[a] Isolated yields.

Scheme 1



Recently, we have succeeded in the one-pot synthesis of 2,2-difluorovinyl ketones from commercially available 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**), wherein the two processes are included: (i) a boron-mediated alkylation leading to 2,2-difluorovinylboranes **2** and (ii) a copper-mediated acylation of **2** with acyl chlorides.[6] The vinylcarbonylation of *in situ* generated **2** was attempted with α,*β*-unsaturated acyl chlorides under similar conditions to afford the fluorine-containing Nazarov substrates **3a**−**g** in good yields from **1** (eq 1, Table 1).



After treatment of **3a** (R = *n*-Bu, $R^1 = R^2 = R^3 = H$) with several Lewis and Brønsted acids, we found that 1 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane (CH_2Cl_2) readily induced the cyclization at room temperature,[7] leading to 3-fluoro-5-methylene-2-cyclopentenone **4a**[8] in 44% yield without any other cyclized products. This result indicated that the reaction proceeded as expected according to Scheme 1. The Nazarov-type ring closure occurred *via* silylation of the carbonyl oxygen in **3a** to generate the cyclopentenylic cation **6a**, followed by its collapse in a *fluorine-directed* manner with the loss of a fluoride ion and a proton.[9,10] These losses resulted in the regioselective formation of the endocyclic and exocyclic double bonds in **4a**.

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[1] Reviews of the Nazarov cyclization: (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 45, pp 1−158. (b) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 751−784. (c) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429−442. (d) Ramaiah, M. *Synthesis* **1984**, 529−570.

[2] (a) Silicon-directed Nazarov cyclizations: Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642−2645. Denmark, S. E.; Wallace, M. A.; Walker, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 5543−5545. Kang, K.-T.; Kim, S. S.; Lee, J. C.; U, J. S. *Tetrahedron Lett.* **1992**, *33*, 3495−3498. (b) Tin-directed Nazarov cyclizations: Peel, M. R.; Johnson, C. R. *Tetrahedron Lett.* **1986**, *27*, 5947−5950.

[3] Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: London, 1988; pp 1−4.

[4] Chambers, R. D. *Fluorine in Organic Chemistry*; Antony Rowe: Chippenham, 1973; pp 1−13. Allen, A. D.; Tidwell, T. T. In *Advances in Carbocation Chemistry*; Creary, X., Ed.; JAI Press: Greenwich, 1989; Vol. 1, pp 1−44.

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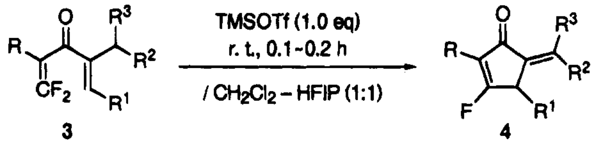
[6] Ichikawa, J.; Hamada, S.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1992**, *33*, 337−340.

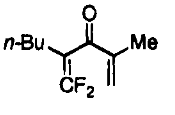
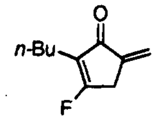
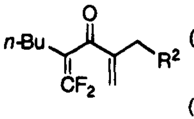
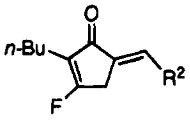
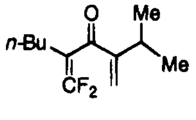
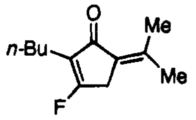
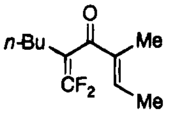
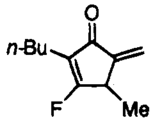
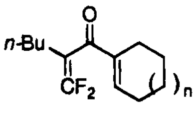
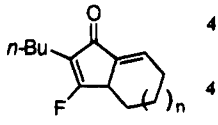
[7] TMSOTf was a superior choice for this cyclization among the examined acids such as $BF_3 \cdot OEt_2$, $FeCl_3$, polyphosphoric acid, and TfOH. Neither TMSI nor TMSOMe promoted this cyclization at all in CH_2Cl_2. For a report on the Nazarov cyclization using TMSOTf, see: Andrews, J. F. P.; Regan, A. C. *Tetrahedron Lett.* **1991**, *32*, 7731−7734.

[8] All new compounds were fully characterized by ^1H, ^{19}F, ^{13}C NMR, IR, MS, and combustion analysis (±0.3%) and/or HRMS.

0022-3263/95/1960-2320$09.00/0

Table 2. Fluorine-Directed Nazarov Cyclization of 2,2-Difluorovinyl Vinyl Ketones 3

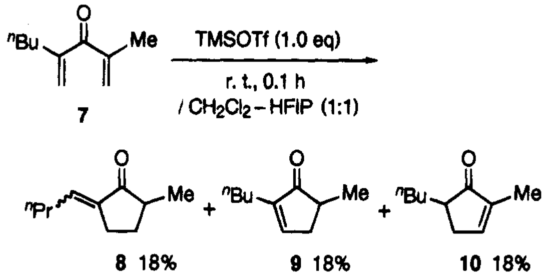


entry	substrate (3)		product (4)	yield,[a] % (E/Z)[b]
1		3a		4a 73
2		3b (R²=Ph)		4b 71[c] (99/1)[d]
3		3c (R²=n-Pr)		4c 82 (99/1)[e]
4		3d		4d 78
5		3e		4e 86
6		3f (n = 1)		4f 92
7		3g (n = 2)		4g 97

[a] Isolated yields. [b] E/Z ratio on the exocyclic double bond. [c] The reaction was conducted at 0 °C in HFIP for 0.7 h. [d] Determined by ^{19}F NMR. [e] Determined by GLC.

Screening of solvents in the above reaction of **3a** revealed that the addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a cosolvent dramatically promoted and accelerated the cyclization, probably due to its high ionizing power and low nucleophilicity.[11,12] Conducting the reaction in CH_2Cl_2–HFIP (1:1) at room temperature improved the yield of the desired product **4a** up to 73%. Under the conditions thus obtained, other fluorinated divinyl ketones **3b–g**, including cyclic systems as well as acyclic ones, underwent the reaction very rapidly to afford the corresponding cyclopentenones **4b–g**[8] in good to excellent yields (Table 2). The double bonds are selectively placed under the strict control of fluorine regardless of the substrates. In addition, concerning the configuration of the exocyclic double bond, *E* isomers were almost exclusively obtained (Table 2, entries 2 and 3).[13]

In order to confirm the effect of fluorine on the regiochemistry, we conducted the reaction employing a fluorine-free substrate. While **3a** gave a single product as shown above (Table 2, entry 1), its nonfluorinated counterpart **7** afforded a mixture of three products **8–10** without control (eq 2). Furthermore, in the case of the symmetrical substrate **3c** except for fluorine, the reaction proceeded through a defined pathway to give **4c**, not yielding a product with an exocyclic double bond on the other side of the carbonyl group (Table 2, entry 3). Therefore, fluorine plays a critical role in producing the regioselective cyclization.



(2)

Thus, the remarkable properties of fluorine, which include (i) electronic effect on carbocations and (ii) leaving-group ability as a fluoride ion, control the reaction and permit a new Nazarov-type cyclization to provide a facile approach to highly functionalized cyclopentanone derivatives, which are ready for a variety of further synthetic elaborations.[14]

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Supplementary Material Available: Experimental procedure for the preparation of 3 and 4, and characterization data for new compounds 3 and 4 (8 pages).

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(9) For reports where the effect of fluorine on carbocations was advantageously applied in organic synthesis, see: Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800–7802. Johnson, W. S.; Lyle, T. A.; Daub, G. W. *J. Org. Chem.* **1982**, *47*, 161–163. Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150–6152 and references cited therein.

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(11) Schadt, F. L.; Schleyer, P. v. R.; Bentley, T. W. *Tetrahedron Lett.* **1974**, 2335–2338. Allard, B.; Casadevall, A.; Casadevall, E.; Largeau, C. *Nouv. J. Chim.* **1979**, *3*, 335–342. See also: Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakura, T. *Tetrahedron Lett.* **1991**, *32*, 4321–4324.

(12) HFIP from Central Glass Co., Ltd. (purity 99.9%) was distilled from and stored over 3A molecular sieves. The possibility that the effect of HFIP was the generation of TfOH can be ruled out. See ref 7.

(13) The corresponding *Z* isomers were obtained *via* the isomerization of *E* isomers by irradiation with sunlight to assure the *E*/*Z* ratio and the configurational assignment. See the supplementary material.

(14) Recently we have reported that the fluorines on the β-carbon of α,β-unsaturated ketones are easily replaced by carbon and heteroatom nucleophiles *via* addition–elimination process; see: Ichikawa, J.; Yokota, Y.; Kobayashi, M.; Minami, T. *Synlett* **1993**, 186–188. Ichikawa, J.; Kobayashi, M.; Yokota, Y.; Noda, Y.; Minami, T. *Tetrahedron* **1994**, *50*, 11637–11646. On treatment with carbon nucleophiles, **4a** underwent (i) 1,2-addition accompanied by spontaneous 1,3-carbonyl transposition,[15] (ii) *exo*-1,4-addition in the presence of a Lewis acid, or (iii) *endo*-1,4-addition and successive elimination of a fluoride ion in the presence of a bulky Lewis acid. Details of these transformations will be reported in due course.

(15) Crimmins, M. T.; Dedopoulou, D. *Synth. Commun.* **1992**, *22*, 1953–1958.