

Ring constructions by the use of fluorine substituent as activator and controller*

Junji Ichikawa[†]

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

Abstract: By using the properties of fluorine such as electronic effects and leaving-group ability, two types of ring-forming reactions have been achieved starting from fluoroolefins: (i) fluorinated vinyl ketones with a vinyl and/or an aryl group, which undergo fluorine-directed and/or -activated Nazarov, Friedel–Crafts, and tandem cyclizations in their combination to construct highly functionalized and fused ring systems and (ii) *gem*-difluoroolefins bearing a nucleophilic center on the carbon δ to the fluorines undergo intramolecular substitution for the fluorine via “anti-Baldwin” 5-*endo*-trig closures leading to ring-fluorinated heterocycles. Throughout these reactions, fluorines function as an activator of the substrates and a controller over the reaction pathways.

INTRODUCTION

Fluorine-containing compounds have been attracting much interest in various fields ranging from medicinal and agricultural chemistry to material science, due to their distinctive biological activities and physical properties. However, compared to other heteroatoms, the potential of fluorine as a tool in organic synthesis has not been fully realized, and synthetic methodologies that make extensive use of the unique properties of fluorine are yet to be developed. It is well known that fluorine has high electronegativity, which leads to the (i) β -cation-destabilizing effect, (ii) β -anion-stabilizing effect, and (iii) good leaving-group ability as a fluoride ion (F^-). In addition, (iv) fluorine stabilizes α -cations and (v) destabilizes α -anions due to its lone pairs [1]. We were prompted to investigate the application of these unique properties in organic synthesis. In order to generate fluorinated cations and anions and utilize the effects of fluorine on them both, fluoroolefins seemed to be an ideal choice as a substrate. Based on these considerations, we achieved two types of ring-forming reactions starting from fluoroolefins, one which proceeds via fluorine-containing carbocations and another via fluorine-containing carbanions.

CATIONIC CYCLIZATIONS

Fluorine-directed and -activated Nazarov cyclizations: Regioselective synthesis of fluorinated cyclopentenones

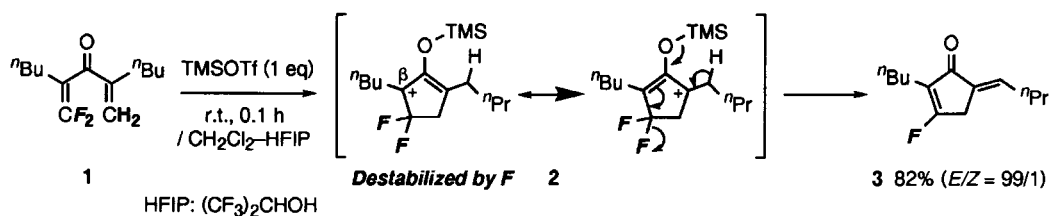
The Nazarov cyclization is a versatile protocol for the construction of the cyclopentenone framework, a structural motif found in a number of natural products. While the classical reactions had limited utility due to the lack of control over the position of the endocyclic double bond, their improved versions, silicon- and tin-directed Nazarov cyclizations have successfully overcome the problem of double-bond positional selectivity [2].

In the course of our studies on utilizing the properties of fluorine in synthetic reactions [3], we have developed two kinds of fluorine-directed Nazarov cyclizations by making use of the β -cation-destabilizing effect of fluorine. These fluorine-directed cyclizations proceed on treatment of 2,2-diflu-

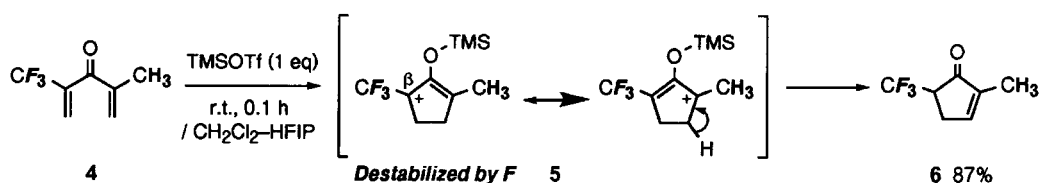
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[†]E-mail: junji@chem.s.u-tokyo.ac.jp

orovinyl vinyl ketone **1** and 1-trifluoromethylvinyl vinyl ketone **4** with TMSOTf to provide the selective synthesis of 5-alkylidene-3-fluoro-2-cyclopentenone **3** (Scheme 1) [4] and 5-trifluoromethyl-2-cyclopentenone **6** (Scheme 2) [5], respectively. Regioselectivity is achieved by the electronic effect of fluorine on the intermediary cyclopentenyl cations **2** and **5**, which direct the position of the double bonds regardless of the substitution patterns of the substrates.

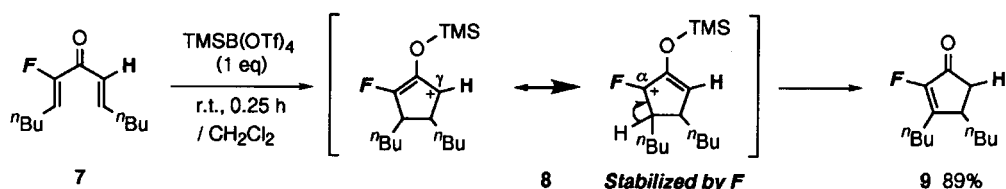


Scheme 1



Scheme 2

In the above reactions the enhancement of the reactivity by fluorine could not be expected because the intermediates **2** and **5** generated in the rate-determining electrocyclization event are destabilized. In addition to the cation-destabilizing effect, fluorine possesses an α -cation-stabilizing effect due to donation of its lone pairs. We then attempted to utilize this cation-stabilizing effect to accomplish another type of fluorine-directed Nazarov cyclizations, where the cyclized cationic intermediate **8** would be stabilized by the α -fluorine. The cyclization of 1-fluorovinyl vinyl ketone **7** is readily induced by $\text{TMSB}(\text{OTf})_4$ [6] to afford the corresponding cyclopentenone **9** in high yield with defined placement of the double bond (Scheme 3). Thus, in this reaction not only the control of regiochemistry, but also the activation of the cyclizations has been accomplished by the fluorine substituent.

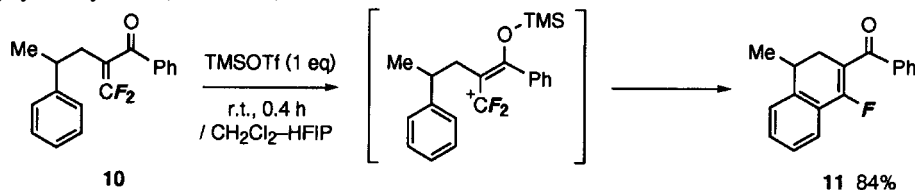


Scheme 3

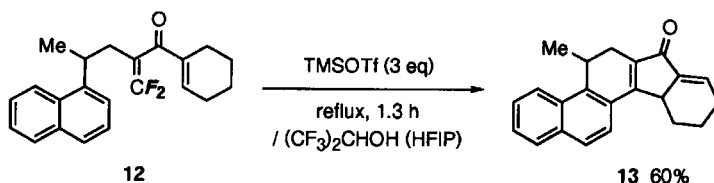
Fluorine-activated Friedel–Crafts cyclizations and tandem cyclizations

The results on the Nazarov-type cyclization implied that treatment of *gem*-difluorovinyl ketones like **1** with TMSOTf effectively generated the corresponding difluoroallyl cations, which are reactive enough to induce electrocyclization. We next attempted to trap these cations with an aryl group instead of a vinyl group, that is, the Friedel–Crafts reaction. When difluorovinyl ketone **10** with an aryl group was treated with TMSOTf under similar conditions, the expected cyclization proceeded smoothly to give the fluorinated dihydronaphthalene **11** in high yield (Scheme 4). This cyclization was accompanied by the loss of a fluoride ion, which resulted in the replacement of the fluorine by the aryl group under acidic conditions, in contrast to the substitution under basic conditions via addition–elimination process as described in the following section.

After having accomplished Nazarov and Friedel–Crafts cyclizations, we tried a tandem cyclization which combined these reactions by using two vinylic fluorines. When difluorovinyl ketone **10** bearing a vinyl and an aryl group was exposed to TMSOTf, successive trapping of intermediary α -fluorocarocations was effected with the two unsaturated bonds, thus providing an efficient approach to a fused polycyclic system (Scheme 5).



Scheme 4



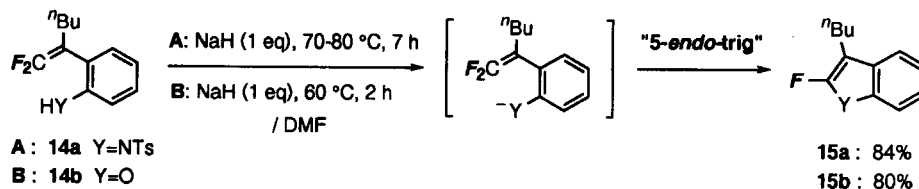
Scheme 5

INTRAMOLECULAR NUCLEOPHILIC SUBSTITUTIONS

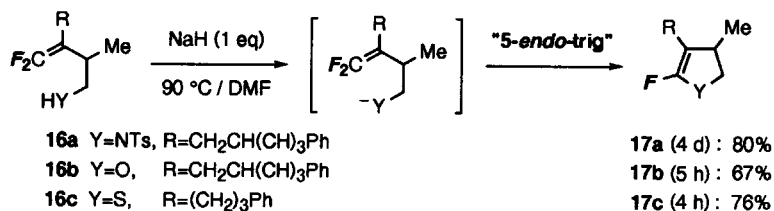
Nucleophilic 5-*endo*-trig cyclizations of *gem*-difluoroolefins: Regioselective synthesis of ring-fluorinated heterocycles

gem-Difluoroolefins possess remarkable reactivity toward nucleophilic substitution for their fluorine atoms via addition–elimination processes [1]. This unique reactivity prompted us to explore the 5-*endo*-trigonal ring closure of *gem*-difluoroolefins with a nucleophilic functional group leading to ring-fluorinated heterocycles, even though this cyclization is disfavored according to Baldwin's rules [7]. We expected that (i) the highly polarized C–C double bond (significant single bond character implied by ^{13}C NMR: ca. 150 ppm and 90 ppm for $\text{CF}_2=\text{C}$) would allow initial 5-membered ring formation and (ii) the successive elimination of fluoride ion could suppress the reverse ring opening.

Treatment of β,β -difluorostyrenes **14a,b** bearing a *p*-toluenesulfonamido or a hydroxy group with NaH promotes the “disfavored” 5-*endo*-trig cyclization. The substitutions of nitrogen and oxygen for the fluorine afford 2-fluorinated indole **15a** and benzo[*b*]furan **15b** in high yields, respectively (Scheme 6) [8]. A similar cyclization of sulfur atom is also achieved to give 2-fluorobenzo-*[b]*thio-



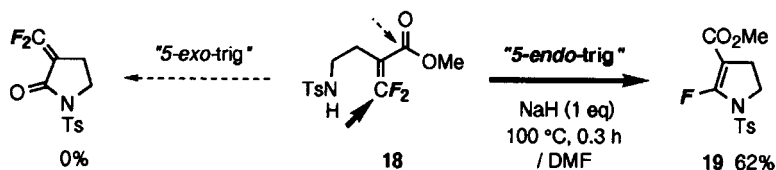
Scheme 6



Scheme 7

phene. In addition, we attempted the 5-*endo*-trig cyclizations of *gem*-difluoroolefins **16a–c**, (Scheme 7) whose nucleophilic N-, O-, or S-functional group was linked by two sp^3 carbons to the olefin. The ring closures readily proceed as above to give fluorinated dihydropyrrole **13a**, -furan **13b**, and -thiophene **13c**, which broadens the scope of the cyclization and rules out the possibility of 6π -electrocyclization mechanism [9].

In order to demonstrate the favored nature of 5-*endo*-trig cyclization in *gem*-difluoroolefins, we tried the competitive reaction between 5-*endo*-trig (the Michael reaction) and 5-*exo*-trig (the transacylation) processes in β,β -difluoro- α,β -unsaturated ester **18** bearing a 2-*p*-toluenesulfonamidoethyl group. On treatment of **18** with NaH in DMF, the 5-*endo*-trig cyclization proceeds to lead exclusively to the 2-fluorinated pyrroline derivative **19** [9]. These “anti-Baldwin” results indicate that some of the unique reactivity of *gem*-difluoroolefins may be derived from a partial single bond character of the olefin.



Scheme 8

CONCLUSION

The remarkable properties of fluorine, which include (i) electronic effects on anions and cations and (ii) leaving-group ability as a fluoride ion, can be utilized to activate substrates and control reaction pathways to provide new methodologies for synthesizing a variety of compounds inaccessible by other conventional methods. Thus, we have disclosed a new function of fluorine as a versatile synthetic tool (an activator and a controller), opening a novel area of fluorine chemistry in organic synthesis.

ACKNOWLEDGMENTS

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3. For example, see: J. Ichikawa, M. Kobayashi, N. Yokota, Y. Noda, T. Minami. *Tetrahedron* **50**, 11637 (1994); J. Ichikawa, N. Yokota, M. Kobayashi, K. Amano, T. Minami. *Synlett*. 243 (1996). J. Ichikawa, M. Kobayashi, Y. Noda, N. Yokota, K. Amano, T. Minami. *J. Org. Chem.* **61**, 2763 (1996).
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6. A. P. Davis, J. E. Muir, S. J. Plunkett. *Tetrahedron Lett.* **37**, 9401 (1996) and references therein. TMSB(OTf)₄ also quite effectively promotes the Nazarov and Friedel–Crafts cyclizations of **1**, **4**, and **10** in CH₂Cl₂.
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