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Friedel–Crafts-Type Cyclization of 2,2-Difluorovinyl Ketones via α-Fluorocarbocations and Its Application in Domino Cyclizations

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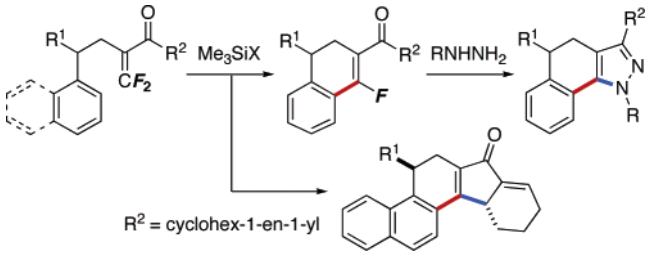
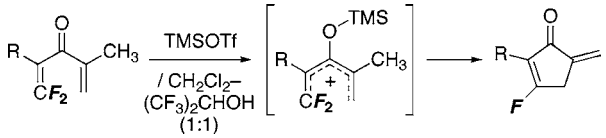
ABSTRACT



2,2-Difluorovinyl ketones bearing an aryl group undergo Friedel–Crafts-type cyclization via carbocations stabilized by α-fluorines on treatment with a trimethylsilylating agent [Me_3SiOTf or $Me_3SiB(OTf)_4$]. The reaction affords 4-fluorinated 3-acyl-1,2-dihydronaphthalenes, which are successfully subjected to a substitution–cyclodehydration process or a Nazarov-type cyclization to construct fused polycyclic systems.

Fluorine has a stabilizing effect on α-carbocations through donation of its unshared electron pair to the vacant p-orbital of the α-carbon, despite its electron-withdrawing inductive effect.[1] Since the former mesomeric effect is operative for α-sp^2 carbon, carbocations are stabilized by α-fluorine. The α-carbocation-stabilizing effect is well exemplified in biomimetic polyene cyclization,[2] where fluoroalkene moieties served as terminators. In contrast, cyclizations initiated by α-fluorocarbocations are quite rare.[3] We have reported one of these examples, the fluorine-directed Nazarov-type cyclization of 2,2-difluorovinyl vinyl ketones, where the initial carbocation is stabilized by the fluorines (Scheme 1).[4]

Scheme 1



The results of the Nazarov-type cyclization implied that treatment of a 2,2-difluorovinylcarbonyl functionality with

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(1) Smart, B. E. In *Organofluorine Chemistry, Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994.

(2) (a) Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800. (b) Johnson, W. S.; Lyle, T. A.; Daub, G. W. *J. Org. Chem.* **1982**, *47*, 161. (c) Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150 and references therein.

(3) (a) Morikawa, T.; Kumadaki, I.; Shiro, M. *Chem. Pharm. Bull.* **1985**, *33*, 5144. (b) Kendrick, D. A.; Kolb, M. *J. Fluorine Chem.* **1989**, *45*, 273. For a related paper, see: (c) Saito, A.; Okada, M.; Nakamura, Y.; Kitagawa, O.; Horikawa, H.; Taguchi, T. *J. Fluorine Chem.* **2003**, *123*, 75.

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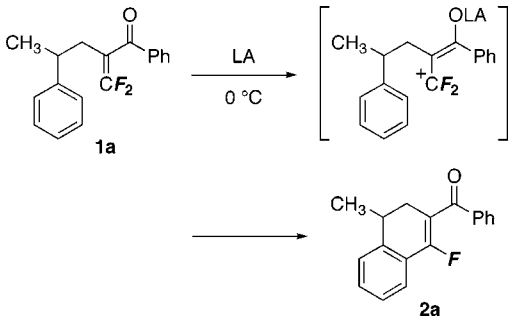
a Lewis acid, such as trimethylsilyl trifluoromethanesulfonate (TMSOTf), effectively generated difluoroallylic cations, which were reactive enough to induce electrocyclization. These results prompted us to investigate the reaction of these cations with an intramolecular aryl group instead of a vinyl group. Herein, we report the Friedel−Crafts-type cyclization of 2,2-difluorovinyl ketones bearing an aryl group.[5]

2,2-Difluorovinyl ketones **1** bearing an aryl group were designed as the Friedel−Crafts substrates to trap the generated cations with an intramolecular aryl moiety, leading to 4-fluorinated 3-acyl-1,2-dihydronaphthalenes **2**. 2,2-Difluorovinyl ketones **1** were readily synthesized by our method in a one-pot operation, starting from commercially available 2,2,2-trifluoroethyl *p*-toluenesulfonate, acid chlorides, and trialkylboranes, prepared by hydroboration of styrene derivatives.[6]

We attempted the generation of the α-fluorocarbocation from 2,2-difluorovinyl ketone **1a** (R^1 = Me, R^2 = R^3 = R^4 = H, R^5 = Ph), which was expected to yield acyldihydronaphthalene **2a** via Friedel−Crafts-type alkylation accompanied by the loss of a fluoride ion. When **1a** was treated with 1.0 equiv of TMSOTf in dichloromethane, the cyclized product **2a** was obtained, albeit in low yield (Table 1, entry 1). The addition of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as a cosolvent dramatically accelerated the cyclizaion to give **2a** in 84% yield, along with a trace amount of an HFIP substitution product of **1a** (Table 1, entry 3).[4] This result indicates that HFIP is a superior solvent for cationic reactions due to its high ionizing power and low nucleophilicity.[7] Among the Lewis acids tested, including TMSOTf, TMSB-$(OTf)_4$,[8] BF_3·OEt_2, $AlEt_3$, and $TiCl_4$, the silylating reagents were especially effective for this cyclization, affording **2a** in high yield (Table 1, entries 3 and 4). The stronger silylating agent, $TMSB(OTf)_4$, drove the cyclization to completion without HFIP. Moreover, the cyclization was also promoted by a protic acid, CF_3SO_3H, to afford **2a** in 77% yield (Table 1, entry 8).[9]

The reaction of several other substrates **1** was examined under conditions similar to those used in entry 3 (TMSOTf in CH_2Cl_2−HFIP) and entry 4 [$TMSB(OTf)_4$ in CH_2Cl_2] in Table 1. The corresponding dihydronaphthalenes **2** bearing several substituents were obtained in high to excellent yield, as summarized in Table 2.

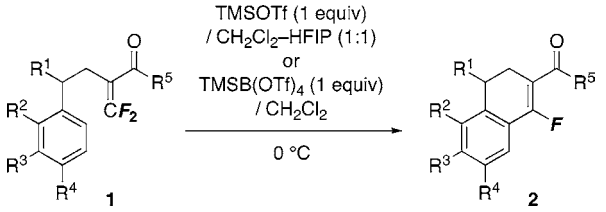
Table 1. Effect of Lewis Acids (LA) and Solvents on the Friedel−Crafts-Type Cyclization of **1a**



entry	LA (equiv)	solvent	time/min	yield/%
1	TMSOTf (1)	CH_2Cl_2	110	30
2	TMSOTf (1)	HFIP	60	70
3	TMSOTf (1)	CH_2Cl_2−HFIP (1:1)	25	84
4	$TMSB(OTf)_4$ (1)	CH_2Cl_2	10	91
5	BF_3·OEt_2 (2)	HFIP	40	54
6[a]	$AlEt_3$ (3)	HFIP	180	31
7	$TiCl_4$ (1)	HFIP	110	58
8	CF_3SO_3H (1)	CH_2Cl_2−HFIP (1:1)	20	77

[a] The reaction was conducted at rt.

Table 2. Synthesis of 4-Fluoro-1,2-dihydronaphthalenes **2** via Friedel−Crafts-Type Cyclization of **1**

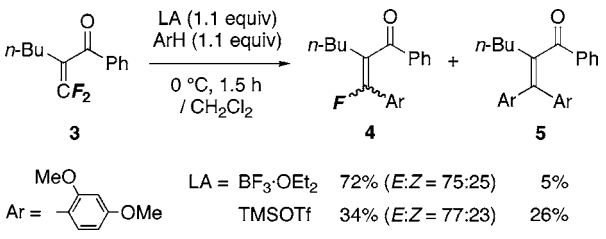


entry	R^1	R^2	R^3	R^4	R^5	time/min	**2**	yield[a]/%
1	H	H	H	H	Ph	20	**2b**	89
2	H	H	H	CH_3	Ph	15	**2c**	71 (80)
3	CH_3	H	H	H	Ph	25	**2a**	84 (91)
4	CH_3	−$(CH)_4$−		H	Ph	5	**2d**	86
5	CH_3	H	H	H	*c*-Hex	15	**2e**	70 (93)
6	−$(CH_2)_3$−		H	H	Ph	10	**2f**	84 (92)

[a] Numbers in parentheses indicate yields of **2** in the reaction conducted with $TMSB(OTf)_4$ in CH_2Cl_2.

An intermolecular version of the Friedel−Crafts-type vinylation of arenes was examined using 2,2-difluorovinyl ketone **3**. The expected reaction of **3** proceeded with *m*-dimethoxybenzene, which resulted in the replacement of one or two vinylic fluorines by aryl groups under acidic conditions to give **4** and **5** (Scheme 2).[5,10] The intermolecular reaction of **3** did not proceed with anisol, which is more reactive than alkylbenzenes, indicating that substrates **1** were

Scheme 2

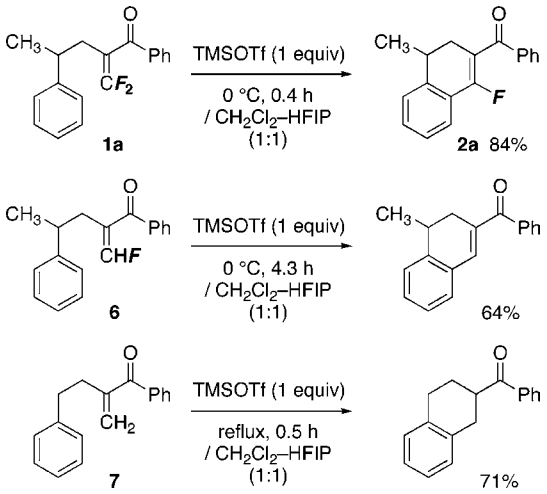


(4) (a) Ichikawa, J.; Miyazaki, S.; Fujiwara, M.; Minami, T. *J. Org. Chem.* **1995**, *60*, 2320. See also: (b) Ichikawa, J.; Jyono, H.; Kudo, T.; Fujiwara, M.; Yokota, M. *Synthesis* **2005**, 39.

highly activated toward the Friedel−Crafts-type reaction by the intramolecular aryl groups.

To confirm the effect of fluorine on the reactivity, we studied the reaction of the corresponding monofluorinated and fluorine-free substrates (Scheme 3). While all of the

Scheme 3

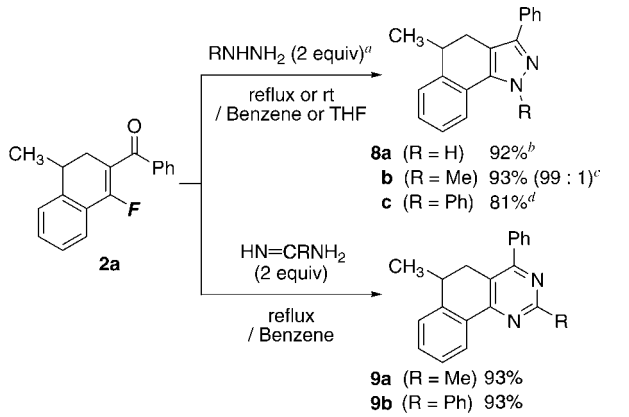


substrates underwent the Friedel−Crafts-type cyclization, the conditions required for completion of the reaction were different: The monofluorinated substrate **6** needed a reaction time 10 times longer than **1a**. The fluorine-free substrate **7** gave no cyclized products until being heated under reflux. These results clearly show that the vinylic fluorine acts as an activating group, presumably due to its stabilizing effect on the α-carbocations.[11]

Acyldihydronaphthalenes **2** thus obtained are a versatile class of compounds because of their 2-fluorovinylcarbonyl functionality, which readily reacts with nucleophiles to provide a variety of polysubstituted naphthalene derivatives.[10]

For example, **2a** was treated with both hydrazines and amidines as bifunctional nucleophiles to construct heterocycles via consecutive addition−elimination and cyclodehydration processes (Scheme 4).[12] The reactions afforded

Scheme 4



[a] For **8a** and **8b**: $RNHNH_2$ (2.0 equiv), benzene, reflux or rt. For **8c**: $PhNHNH_2$ (2.0 equiv), *n*-BuLi (2.0 equiv), THF, rt. [b] Pyrazole **8a** existed in a tautomeric mixture. [c] Regioisomer ratio determined by GC analysis. [d] The precise regiochemistry of **8c** was established by X-ray crystallography.

pyrazole- or pyrimidine-fused ring systems, 4,5-dihydrobenzo[*g*]indazoles **8**[13] or 5,6-dihydrobenzo[*h*]quinazolines **9**,[14] in excellent yield with extremely high regioselectivity in the pyrazole formation.

Furthermore, we attempted to use the two vinylic fluorines in domino cyclization by combining the Friedel−Crafts-type cyclization with the Nazarov-type cyclization depicted in Scheme 1. When 2,2-difluorovinyl ketones **1** bearing both a vinyl and an aryl group were exposed to TMSOTf in HFIP, the Friedel−Crafts-type and the Nazarov-type cyclizations proceeded sequentially via intermediary 2-fluorovinyl ketones **2**.[15] The reaction provided fused polycyclic systems **10** and/or **11** bearing the steroid skeleton[16] in good yield with high diastereoselectivity in a one-pot operation (Table 3).

Compound **10c** was obtained as a single diastereomer, which indicates that torquoselectivity in the conrotatory

(5) For recent reports on Friedel−Crafts-type reactions with conjugated enones and enals, see: (a) Imachi, S.; Onaka, M. *Chem. Lett.* **2005**, *34*, 708 and references therein. (b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (c) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942 and references therein. (d) Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. *Adv. Synth. Catal.* **2003**, *345*, 1247. For a Friedel−Crafts-type cyclization of a conjugated enal, see: (e) Rettig, M.; Sigrist, A.; Rétey, J. *Helv. Chim. Acta* **2000**, *83*, 2246.

(6) Ichikawa, J. *J. Fluorine Chem.* **2000**, *105*, 257.

(7) For recent reports on the cationic reactions conducted in HFIP, see ref 4b and references therein.

(8) Davis, A. P.; Muir, J. E.; Plunkett, S. J. *Tetrahedron Lett.* **1996**, *37*, 9401.

(9) Recently, we reported that CF_3SO_3H was less effective and that a stronger acid such as Magic Acid ($FSO_3H{\cdot}SbF_5$) was needed to activate simple 1,1-difluoro-1-alkenes without a carbonyl group toward Friedel−Crafts cyclization.[4b] These results show that a carbonyl substituent assists the formation of α-fluorocarbocation.

(10) Sequential substitution of the two fluorines in 2,2-difluorovinyl ketones has been achieved under basic conditions with combinations of *C*-, *O*-, *S*-, and *N*-nucleophiles; (a) Ichikawa, J.; Fujiwara, M.; Miyazaki, S.; Ikemoto, M.; Okauchi, T.; Minami, T. *Org. Lett.* **2001**, *3*, 2345 and references therein. (b) Ichikawa, J.; Kobayashi, M.; Yokota, N.; Noda, Y.; Minami, T. *Tetrahedron* **1994**, *50*, 11637. (c) Xiao, L.; Kitazume, T. *J. Fluorine Chem.* **1997**, *86*, 99. (d) Huang, X.; He, P.; Shi, G. *J. Org. Chem.* **2000**, *65*, 627.

(11) The rate of these Friedel−Crafts-type reactions seems to be controlled by the generation of carbocations from the alkenes. For reviews on the alkylation mechanisms, see: Roberts, R. M.; Khalaf, A. A. *Friedel−Crafts alkylation chemistry: a century of discovery*; Marcel Dekker: New York, 1984; Chapter 3 and references therein.

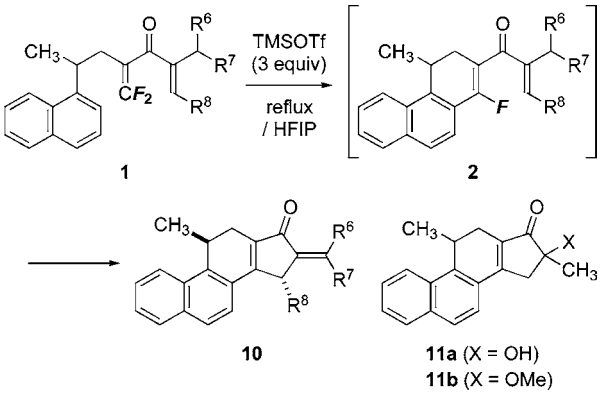
(12) Ichikawa, J.; Kobayashi, M.; Noda, Y.; Yokota, N.; Amano, K.; Minami, T. *J. Org. Chem.* **1996**, *61*, 2763.

(13) For recent reports on 4,5-dihydrobenzo[*g*]indazole derivatives, see: (a) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 10030. (b) Murineddu, G.; Ruiu, S.; Mussinu, J.-M.; Loriga, G.; Grella, G. E.; Carai, M. A. M.; Lazzari, P.; Pani, L.; Pinna, G. A. *Bioorg. Med. Chem.* **2005**, *13*, 3309.

(14) 5,6-Dihydrobenzo[*h*]quinazoline derivatives are potent protein kinase inhibiors. Rapecki, S.; Allen, R. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 1325 and references therein.

(15) On treatment with 1.0 equiv of TMSOTf at rt for 5 min, **1** [R^6 = H, R^7, R^8 = $-(CH_2)_3-$] afforded the corresponding 1-fluoro-3,4-dihydrophenanthrene **2** in 76% yield as a single cyclized product via the Friedel−Crafts-type cyclization.

Table 3. Domino Reaction of the Friedel−Crafts-Type and the Nazarov-Type Cyclizations



entry	R^6	R^7	R^8	time/h	product	yield/%
1	H	*n*-Pr	H	2	**10a**	67
2	CH_3	CH_3	H	2.5	**10b**	61
3	H	$-(CH_2)_3-$		2.5	**10c**	60[a]
4	H	H	H	3	**11a**	25 (15:1)[b]
5[c]	H	H	H	3	**11b**	69 (11:1)[d]

[a] Single diastereomer. The precise stereochemistry of **10c** was established by X-ray crystallography of its hydrogenated product, obtained by selective reduction of the trisubstituted double bond in **10c** (H_2, 5 mol % of PtO_2 in 1% AcOH/AcOEt). [b] Diastereomer ratio determined by ^{13}C NMR measurement (peak heights). [c] $B(OMe)_3$ (1.1 equiv) was added. [d] Diastereomer ratio determined by ^1H NMR measurement.

Nazarov-type cyclization was strictly controlled by the benzylic methyl group (Table 3, entry 3).[17] While the domino cyclization of substrate **1** ($R^6 = R^7 = R^8 = H$) was accompanied by attack of water leading to **11a** as well as deprotonation, $B(OMe)_3$ successfully trapped the intermediary cation to give **11b** selectively (Table 3, entry 5).

In summary, we have accomplished a fluorine-accelerated Friedel−Crafts-type cyclization of 2,2-difluorovinyl ketones bearing an aryl group. The reaction readily proceeded via α-fluorocarbocations, generated by silylation of the carbonyl oxygen in the substrates, leading to vinylation of the aromatic ring. Domino cyclizations combined with the substitution−cyclodehydration process or the Nazarov-type cyclization allowed the construction of fused polycyclic systems. Thus, the fluorine substituent has proven to be useful in electrophilic reactions, due to its α-cation-stabilizing effect and leaving group ability.

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Note Added after ASAP Publication. Yield and substituent data were missing in Scheme 4 in the version published ASAP June 21, 2006; the corrected version was published ASAP June 23, 2006.

Supporting Information Available: Spectroscopic data and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Steroids are an important class of compounds, because of their bioactivities and medicinal actions. For recent reports on the synthesis of steroids, see: Ma, S.; Lu, P.; Lu, L.; Hou, H.; Wei, J.; He, Q.; Gu, Z.; Jiang, X.; Jin, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 5275 and references therein.

(17) For recent reviews of the Nazarov cyclization, see: (a) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (c) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (d) Harmata, M. *Chemtracts: Org. Chem.* **2004**, *17*, 416.