Communications

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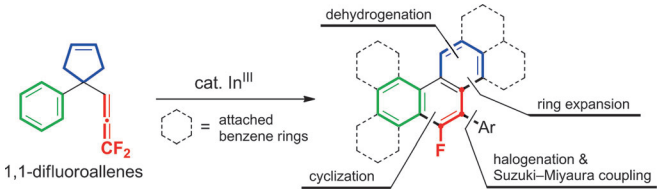
K. Fuchibe, Y. Mayumi, N. Zhao, S. Watanabe, M. Yokota, J. Ichikawa* ——— ■■■■–■■■■

Domino Synthesis of Fluorine-Substituted Polycyclic Aromatic Hydrocarbons: 1,1-Difluoroallenes as Synthetic Platforms



Rather crafty: 1,1-Difluoroallenes bearing an aryl group and a cyclopentene moiety undergo indium(III)-catalyzed Friedel–Crafts-type cyclization with subsequent ring expansion and dehydrogenation to afford fluorinated polycyclic aromatic hydrocarbons in high yields. The introduction of an Ar group was effected by in situ halogenation of the intermediary indium species and a subsequent Suzuki–Miyaura reaction.

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Domino Synthesis of Fluorine-Substituted Polycyclic Aromatic Hydrocarbons: 1,1-Difluoroallenes as Synthetic Platforms**

*Kohei Fuchibe, Yuka Mayumi, Nan Zhao, Shumpei Watanabe, Misaki Yokota, and Junji Ichikawa**

Fluorinated unsaturated compounds such as 1,1-difluoro-1-alkenes are useful synthetic intermediates because of the unique properties of the fluorine substituents, which stabilize α carbocations by donating their lone pairs into the vacant p orbitals of the cationic centers (+M effect, Figure 1).[1] A fluorine substituent, in addition, can also act as a leaving group (F^-). By using these unique properties, we have been studying the chemistry of fluorine-stabilized carbocations (CF_2 cations) generated from 1,1-difluoro-1-alkenes (Scheme 1).[2]

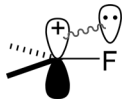
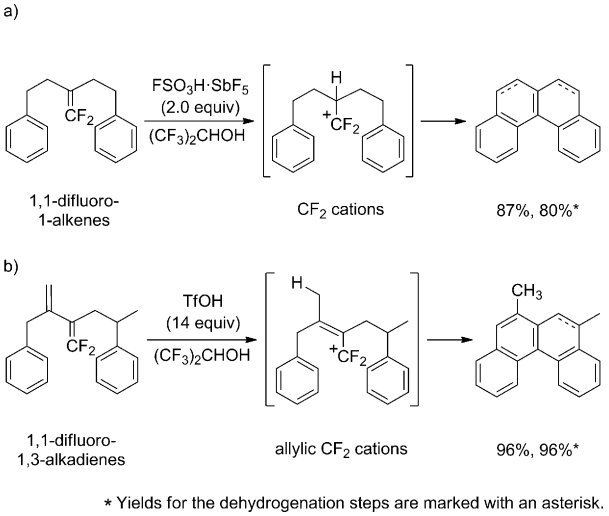


Figure 1. α-Cation-stabilizing effect of fluorine substituent (+M Effect).

Difluoroalkenes bearing two aryl groups were treated with a stoichiometric amount of Magic Acid ($FSO_3H{\cdot}SbF_5$) which has a Hammett acidity function Ho = −22.9 (Scheme 1a).[3] Selective protonation took place at the position β to the fluorine substituents to form CF_2 cations, which readily underwent Friedel–Crafts-type cyclization in a domino fashion to give helicenes and related polycyclic aromatic hydrocarbons (PAHs) in good to high yields.[4]

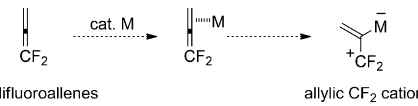
Although the above-mentioned reactions are useful, they have one drawback: they use a highly acidic reagent, Magic Acid, to protonate the electron-deficient difluoroalkene moiety. This drawback was overcome by introducing a fluorine-free alkene moiety to the 1,1-difluoroalkene, that is, using 1,1-difluoro-1,3-alkadienes as substrates (Scheme 1b).[5] Protonation at the electron-rich termini enabled the generation of allylic CF_2 cations by using a relatively mild acid, trifluoromethanesulfonic acid (TfOH, $pK_a = -14$), to promote the Friedel–Crafts-type cyclization.



Scheme 1. Domino cyclizations of 1,1-difluoro-1-alkenes and 1,1-difluoro-1,3-alkadienes via CF_2 cations (a) and allylic CF_2 cations (b). Tf = trifluoromethanesulfonyl.

The results suggested that introducing an electron-rich alkene moiety to 1,1-difluoroalkenes provides easy access to CF_2 cations under mild reaction conditions. We next tried to generate allylic CF_2 cations starting from other substrates, 1,1-difluoroallenes, which have an electron-rich alkene moiety next to the electron-deficient difluoroalkene moiety (Scheme 2).[6] A metal catalyst would readily interact with difluoroallenes through π coordination with the non-fluorinated electron-rich alkene moiety,[7,6f] thus leading to the formation of allyllic CF_2 cations followed by the cyclizations described above. Herein we describe the efficient synthesis of fluorine-substituted PAHs (F-PAHs) on the basis of a catalytic domino ring-forming process of 1,1-difluoroallenes. F-PAHs are promising basic molecules for the synthesis of advanced materials such as semiconductors and pharmaceuticals.[8]

The required 1,1-difluoroallenes **1a–h** (Figure 2) were readily prepared from aldehydes using our difluorovinylidenation method (Scheme 3).[9] Benzylic nitriles **2** were subjected to double allylation under basic conditions to introduce a cyclopentene moiety, which was reserved for the formation of an extra benzene ring (see below). Nitriles **3**, thus obtained,



Scheme 2. Concept for the catalytic generation of allylic CF_2 cations from 1,1-difluoroallenes.

[*] Dr. K. Fuchibe, Y. Mayumi, N. Zhao, S. Watanabe, Dr. M. Yokota, Prof. Dr. J. Ichikawa
Division of Chemistry, Faculty of Pure and Applied Sciences
University of Tsukuba
Tsukuba, Ibaraki 305-8571 (Japan)
E-mail: junji@chem.tsukuba.ac.jp
Homepage: http://www.chem.tsukuba.ac.jp/junji/index.html

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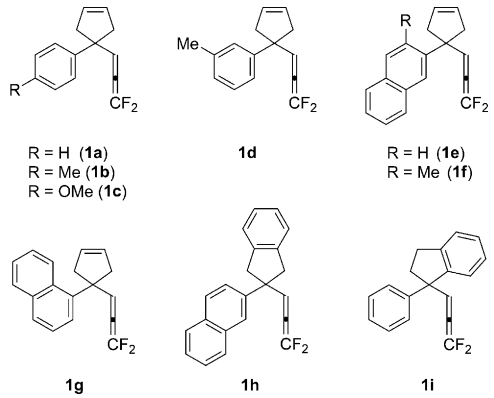
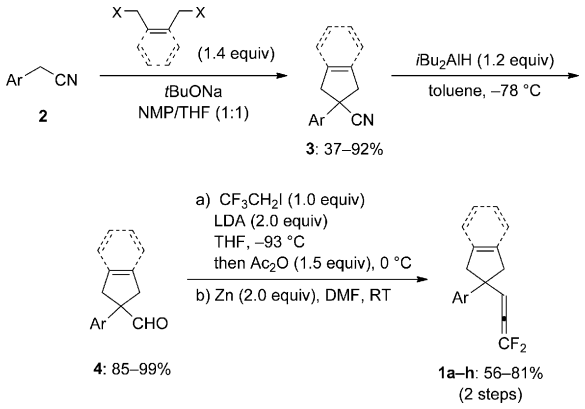
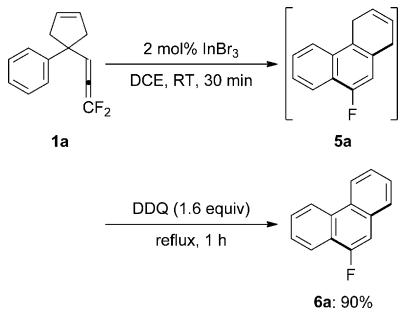


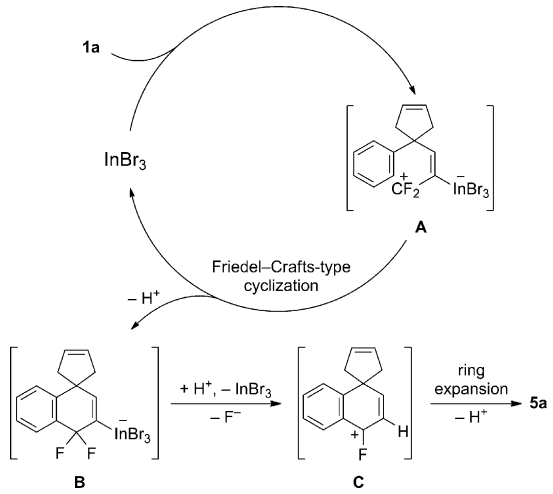
Figure 2. List of substrates.



Scheme 3. Preparation of 1,1-difluoroallenes. DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, NMP = *N*-methylpyrrolidone, THF = tetrahydrofuran.



Scheme 4. Synthesis of fluorophenanthrene. DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.



Scheme 5. Plausible catalytic cycle and reaction mechanism.

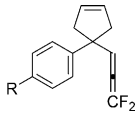
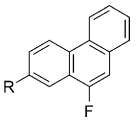
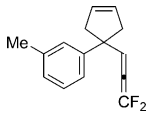
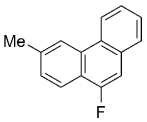
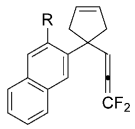
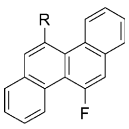
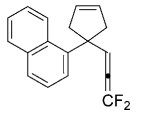
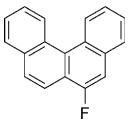
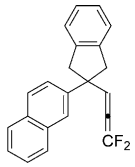
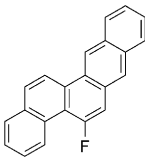
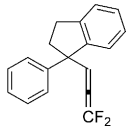
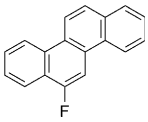
were subjected to half reduction with diisobutylaluminum hydride (DIBAL) to afford aldehydes **4** in high yield. Aldehydes **4** were converted into 3,3-difluoroallylic acetates (not shown), which in turn underwent β elimination upon treatment with zinc metal to give **1a–h** in good yields. Difluoroallene **1i** was prepared from the corresponding 1-phenylindan-1-carbonitrile, which was obtained from 1-indanol in three steps.[10]

After several attempts, we found that a catalytic amount of indium(III) bromide specifically promoted the generation of the desired allylic CF_2 cations, and the domino cyclization/ring expansion took place readily (Scheme 4).[11] The difluoroallene **1a** was treated with 2 mol% of indium(III) bromide in 1,2-dichloroethane (DCE) at room temperature. After stirring for 30 minutes, ^{19}F NMR and mass analysis revealed that the fluorodihydrophenanthrene **5a** was formed. Subsequent addition of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) smoothly promoted the dehydrogenation of **5a** to afford a 90% yield of 9-fluorophenanthrene (**6a**) in a one-pot operation.

We believe that **5a** was formed by the mechanism shown in Scheme 5. The difluoroallene **1a** is transformed into the allylic CF_2 cation **A**, which undergoes Friedel–Crafts-type cyclization to generate the organoindium intermediate **B**.[12] The protonolysis of the C–In bond and elimination of F^- generates the second cationic intermediate **C**,[13–15] which undergoes 1,2-migration, ring expansion to give **5a**.[16,17]

The indium(III)-catalyzed domino reaction of 1,1-difluoroallenes was applied to the synthesis of F-PAHs (Table 1). The difluoroallenes **1b** and **1c** with a *para* substituent gave the corresponding fluorophenanthrenes **6b** and **6c** in 93% and 66% yields, respectively (entries 2 and 3). Cyclization of the *meta*-substituted 1,1-difluoroallene **1d** proceeded and fluorophenanthrenes **6d**/**6d′** were obtained in 96% yield (entry 4). The domino reaction of the 2-naphthyl-substituted difluoroallenes **1e** and **1f** proceeded exclusively at the α position to give 5-fluorochrysenes **6e** and **6f**, respectively (entries 5 and 6), and shows that the regioselectivity follows the same trend as the conventional Friedel–Crafts reaction of naphthalene. The reaction of the 1-naphthyl-substituted difluoroallene **1g** afforded the corresponding 6-fluoro[4]-helicene (**6g**) along with 5-fluorochrysene (**6e**), which was formed by sequential cyclization at the *ipso* position and a double ring expansion (entry 7). The substrate **1h**, which has a benzocyclopentene moiety, reacted well, thus giving benzochrysene **6h** in 84% yield (entry 8). Ring expansion in the domino reaction of substrate **1i**, which has an indane moiety, proceeded exclusively with the migration of the sp^2-carbon atom to give 6-fluorochrysene (**6i**) in 88% yield (entry 9). The selective formation of each of the regioisomers **6e** and **6i**

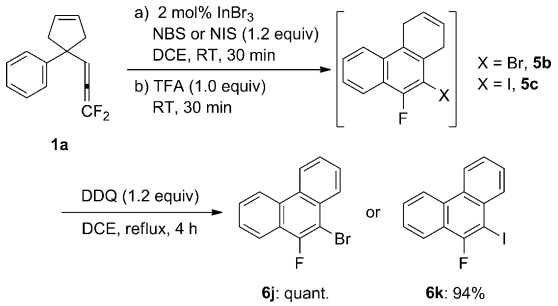
Table 1: Synthesis of F-PAHs by the domino cyclization/ring expansion of 1,1-difluoroallenes.[a]

Entry	Difluoroallene	1 (R)	F-PAH	6	Yield [%][b]
1		**1a** (H)		**6a**	90
2		**1b** (Me)		**6b**	93
3		**1c** (OMe)		**6c**	66[c]
4		**1d** (Me)		**6d** + **6d′**	96 (52:48)[d]
5		**1e** (H)		**6e**	85[e]
6		**1f** (Me)		**6f**	98
7		**1g**		**6g** + **6e**	80 (75:25)[d]
8		**1h**		**6h**	84
9		**1i**		**6i**	88

[a] Reaction conditions: a) 2 mol% $InBr_3$, **1**, DCE, RT, 30 min. b) DDQ (1.6 equiv), DCE, reflux, 1 h. [b] Yield of isolated product. [c] 10 mol% $InBr_3$. [d] The regioisomeric ratio was determined by ^{19}F NMR spectroscopy. [e] Single regioisomer.

(entries 5 and 9) was accomplished, thus clearly showing the potential of this method for the synthesis of F-PAHs.[18]

The functionalization of F-PAH skeletons was successfully accomplished using the C–In bond involved in the intermediate **B** (Scheme 6). The difluoroallene **1a** was treated with 2 mol% of indium(III) bromide in the presence of *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS). After sequential addition of trifluoroacetic acid (TFA)[19] and DDQ, bromine- and iodine-substituted fluorophenanthrenes (**6j**,**k**) were obtained in quantitative and 94% yields, respectively. The bromophenanthrene **6j** readily underwent the Suzuki–Miyaura cross-coupling reaction with aryl boronic acids to give the corresponding arylated fluorophenanthrenes in high yield (not shown).[10]

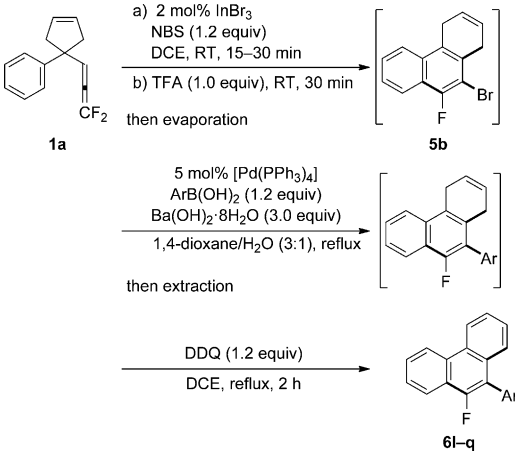


Scheme 6. Halogenation of the domino intermediate **B**.

Finally, an aryl group was introduced without isolating **6j** by applying the Suzuki–Miyaura cross-coupling reaction to the intermediate **5b** (Table 2). The 1,1-difluoroallene **1a** was treated with 2 mol% of indium(III) bromide in the presence of NBS (1.2 equiv), followed by 1.0 equivalents of TFA. After confirming the formation of **5b** by TLC analysis, the crude reaction mixture was subjected to coupling conditions with phenyl boronic acid. Extraction and DDQ dehydrogenation of the intermediate gave the corresponding fluorinated phenylphenanthrene **6l** in 64% yield from **1a** through the formation of three C–C bonds (entry 1). Electron-donating, electron-withdrawing, and sterically demanding aryl boronic acids also afforded the corresponding phenanthrenes **6m–o** in good yields (entries 2–4). 1- and 2-Naphthyl boronic acids successfully afforded the fluorinated naphthylphenanthrenes **6p** and **6q** in 62% and 63% yield, respectively (entries 5 and 6).

In summary, we have developed a novel method for generating allylic CF_2 cations from 1,1-difluoroallenes with an indium(III) catalyst. The generated allylic CF_2 cations readily underwent a sequential process of Friedel–Crafts-type cyclization/ring expansion and subsequent one-pot dehydrogenation with DDQ to afford F-PAHs. The C–In bond involved in the intermediates was successfully used to functionalize the F-PAH frameworks through halogenation and cross-coupling reaction.

Table 2: Facile Synthesis of fluorine-substituted arylphenanthrenes by the sequential cyclization/ring expansion/bromination/coupling of 1,1-difluoroallenes.



Entry	Ar	Yield [%][a]
1	Ph	**6l**: 64
2	*p*-MeC_6H_4	**6m**: 48
3	*p*-ClC_6H_4	**6n**: 49
4	*o*-PhC_6H_4	**6o**: 83
5	1-Naphtyl	**6p**: 62
6	2-Naphtyl	**6q**: 63

[a] Yield of isolated product. TFA = trifluoroacetic acid.

Experimental Section

Synthesis of 9-fluorophenanthrene (**6a**): $InBr_3$ (2 mg, 0.006 mmol) was added to a DCE solution (6 mL) of 1,1-difluoroallene **1a** (53 mg, 0.24 mmol) at room temperature. After being stirred for 30 min at the temperature, DDQ (65 mg, 0.29 mmol) was added in a solid form. After being refluxed for 1.5 h, the reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (*n*-hexane) on silica gel to give **6a** (42 mg, 90%).

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Keywords: allenes · arenes · cyclization · fluorine · indium

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[10] See the Supporting Information.

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[12] For reactions involving indium(III) alkene/π complexes, see: a) Y. Nishimoto, H. Ueda, Y. Inamoto, M. Yasuda, A. Baba, *Org. Lett.* **2010**, *12*, 3390–3393; b) Y. Yuan, Z. Shi, *Synlett* **2007**, 3219–3223; c) M. Weïwer, L. Coulombel, E. Duñach, *Chem. Commun.* **2006**, 332–334; d) T. Tsuchimoto, S. Kamiyama, R. Negoro, E. Shirakawa, Y. Kawakami, *Chem. Commun.* **2003**, 852–853.

[13] We suppose that the elimination of a fluoride ion is also promoted by indium(III) and that the dual role of indium(III), as both a π and a σ acid, is a key feature in the domino cyclization of 1,1-difluoroallenes. See: T. Tsuchimoto, H. Matsubayashi, M. Kaneko, Y. Nagase, T. Miyamura, E. Shirakawa, *J. Am. Chem. Soc.* **2008**, *130*, 15823–15835.

[14] For elimination of bromide ion by indium(III) catalyst, see: a) G. R. Cook, R. Hayashi, *Org. Lett.* **2006**, *8*, 1045–1048. See also: b) Y. Onishi, T. Ito, M. Yasuda, A. Baba, *Eur. J. Org. Chem.* **2002**, 1578–1581; c) T. Mukaiyama, T. Ohno, T. Nishimura, J. S. Han, S. Kobayashi, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2524–2527.

[15] Alternatively, a transient six-membered cyclic monofluoroallene could be formed by cyclization followed by elimination of a fluoride ion. Its subsequent protonation might lead to the formation of the carbocation **C**.

[16] For recent publications on reactions catalyzed or mediated by indium(III) species, see: [reactions of alkynes] a) K. Takahashi, M. Midori, K. Kawano, J. Ishihara, S. Hatakeyama, *Angew. Chem.* **2008**, *120*, 6340–6342; *Angew. Chem. Int. Ed.* **2008**, *47*, 6244–6246; b) Y. Itoh, H. Tsuji, K. Yamagata, K. Endo, I. Tanaka, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 17161–17167; [reactions of alcohols] c) G. Chen, Z. Wang, J. Wu, K. Ding, *Org. Lett.* **2008**, *10*, 4573–4576; d) M. Yasuda, T. Saito, M. Ueba, A. Baba, *Angew. Chem.* **2004**, *116*, 1438–1440; *Angew. Chem. Int. Ed.* **2004**, *43*, 1414–1416; [reactions of aldehydes or imines] e) Y. Kuninobu, T. Tatsuzaki, T. Matsuki, K. Takai, *J. Org. Chem.* **2011**, *76*, 7005–7009; f) K. Miura, K. Yamamoto, A. Yamanobe, K. Ito, H. Kinoshita, J. Ichikawa, A. Hosomi, *Chem. Lett.* **2010**, *39*, 766–767; g) S. Harada, R. Takita, T. Ohshima, S. Matsunaga, M. Shibasaki, *Chem. Commun.* **2007**, 948–950; h) R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima, M. Shibasaki, *Org. Lett.* **2005**, *7*, 1363–1366; i) N. Sakai, M. Hirasawa, T. Konakahara, *Tetrahedron Lett.* **2003**, *44*, 4171–4174; [cross-coupling reactions] j) Y. Nishimoto, R. Moritoh, M. Yasuda, A. Baba, *Angew. Chem.* **2009**, *121*, 4647–4650; *Angew. Chem. Int. Ed.* **2009**, *48*, 4577–4580; k) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem.* **2009**, *121*, 2270–2273; *Angew. Chem. Int. Ed.* **2009**, *48*, 2236–2239; l) K. Takami, H. Yorimitsu, K. Oshima, *Org. Lett.* **2004**, *6*, 4555–4558; m) M. A. Pena, I. Perez, J. P. Sestelo, L. A. Sarandeses, *Chem. Commun.* **2002**, 2246–2247.

[17] Reactions of allenes catalyzed or mediated by indium(III) are limited. See: a) N. Hayashi, Y. Hirokawa, I. Shibata, M. Yasuda, A. Baba, *Org. Biomol. Chem.* **2008**, *6*, 1949–1954; b) E. Soriano, J. Marco-Contelles, *Organometallics* **2006**, *25*, 4542–4553.

[18] X ray crystal structure analysis of single crystals of **6e** and **6i** confirmed that they have the fluorine substituent at the predicted 5- and 6-positions. CCDC 911785 (**6e**) and 911786 (**6i**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] Treatment with TFA was necessary to promote the ring expansion, especially when the reaction was performed in the presence of NIS.

