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Niobium-catalyzed Activation of CF_3 Group on Alkene: Synthesis of Substituted Indenes

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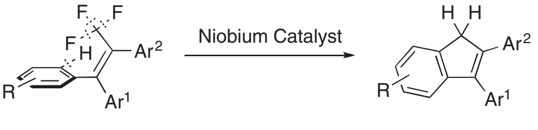
A CF_3 group attached to an alkene functionality was activated by a zero-valent niobium catalyst to generate niobium alkenylcarbenoid species. The niobium carbenoid species then underwent insertion to an internal aromatic C–H σ bond to give indene derivatives in good yields. Isomerization in terms of the alkene geometry was also observed.

CF_3 groups have played important roles in a range of organic molecules for a long time.[1] Molecules bearing CF_3 group(s) in their structures, in general, exhibit enhanced (altered) activities and stabilities, and various useful materials, such as pharmaceuticals[2] and ligands for metal catalysis,[3] have been created and utilized.[4,5]

The CF_3 group is now rapidly gaining importance in synthesis and practical applications despite the fact that its C–F bonds are highly inactive.[6,7] For instance, magnesium-promoted formation of β,β-difluorosilyl enol ethers and *N*-silylenamines from trifluoromethyl ketones and trifluoromethyl imines has provided new synthetic routes for various difluoromethylene compounds.[8] Substitution reactions of fluorines of the CF_3 group were found to proceed smoothly by the use of catalytic[9a] and stoichiometric[9b,9c] amounts of aluminum compounds. Reductions of halogenated hydrocarbons are of environmental importance,[10] and a highly efficient hydrodefluorination process for trifluorotoluenes has been achieved by a silylium catalyst.[11,12]

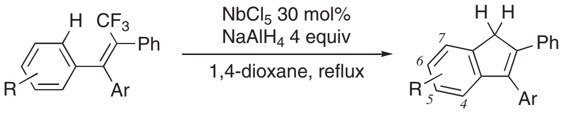
We have also reported that a zero-valent niobium species generated in situ smoothly activates C–F bonds of the CF_3 groups on aromatic nuclei.[13–16] Deuterium labeling experiments suggested that a niobium fluorocarbenoid species is involved in the catalytic cycle and that insertion of the carbenoid center to the neighboring C–H σ bond affords products.[13c] Biologically important *N*-fused indoles, in particular, could be synthesized efficiently with our transition metal-catalyzed method.[13d]

In contrast to recent progress in the reactions of CF_3 groups attached to carbonyl and aromatic functionalities, reactions of CF_3 groups attached to an alkene functionality have not been fully developed yet. Although nonmetal-catalyzed, S_N2'-type reactions of 3,3,3-trifluoropropenes are known,[17] transition metal-catalyzed activation of alkenylated CF_3 groups has been quite limited.[18] We wish to report herein the first, direct activation of the CF_3 groups attached to an alkene functionality by a niobium catalyst. Substituted indenes, which are of importance from viewpoints of medical and material sciences, were synthesized from trifluoropropenes (Scheme 1).[19,20]



Scheme 1.

Table 1. Cyclization of trifluoropropenes (1)



1, Ar = C_6H_4R **2**

Entry	Ar	Time/h	Yield (R)/%[a]
1	Ph, **1a**	4	80 (6-H), **2a**
2[b]	Ph, **1a**	4	72 (6-H), **2a**
3[c]	Ph, **1a**	4	54 (6-H), **2a**
4	*p*-Tol, **1b**	2	63 (6-Me), **2b**
5	C_6H_4(*p*-OMe), **1c**	5	52 (6-OMe), **2c**
6	C_6H_4(*p*-F), **1d**	1	56 (6-F), **2d**[d]
7	3,5-Dimethylphenyl, **1e**	3	54 (5,7-Me_2), **2e**

[a]Trifluoropropenes **1** were consumed completely. [b]10 mol % $NbCl_5$. [c]$LiAlH_4$ was used. [d]Defluorinated indenes were not detected by ^{19}F NMR analysis.

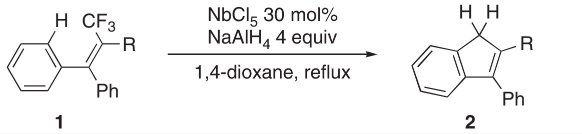
Requisite 3,3,3-trifluoropropenes **1** were prepared according to a method developed by Hiyama and co-workers,[21] and were treated with a niobium catalyst. To a dioxane solution of β,β-diphenyltrifluoropropene **1a** and niobium(V) chloride (30 mol %) was added 4 molar equivalents of solid sodium aluminum hydride (Table 1, Entry 1).[13d,16] After refluxing for 4 h, the reaction was quenched with pH 7 phosphate buffer. Chromatographic purification of the products afforded phenylindene **2a** in 80% yield, which suggests that the CF_3 group was successfully activated. ^1H NMR analysis showed that only a trace amount of the conventional reduction product (non fluorine-substituted propene) was formed. The reaction also proceeded readily when the catalyst loading was decreased to 10 mol % (Entry 2).

Use of lithium aluminum hydride in place of sodium aluminum hydride gave a diminished yield of **2a** (54% yield, Entry 3). Treatment of isolated **2a** with lithium aluminum hydride alone resulted in 44% recovery of **2a** (not shown), whereas **2a** was recovered in 58% yield when treated with sodium aluminum hydride. It is likely that the decomposition of the product in the reaction medium was promoted when a more reactive lithium congener was used.[22]

Other 1,1-homodiarylated trifluoropropenes also afforded the corresponding indenes in good yields.[23] Not only parent **1a** but also electron-donating and electron-withdrawing *p*-tolyl-, *p*-methoxyphenyl-, and *p*-fluorophenyl-substituted trifluoropropenes **1b**–**1d** afforded the corresponding indenes **2b**–**2d** in good yields (Entries 4–6). Sterically demanding **1e** also worked well (Entry 7). It is noted that the CF_3 group was selectively activated in preference to the aromatic C–F moiety under the reaction conditions (Entry 6).[24]

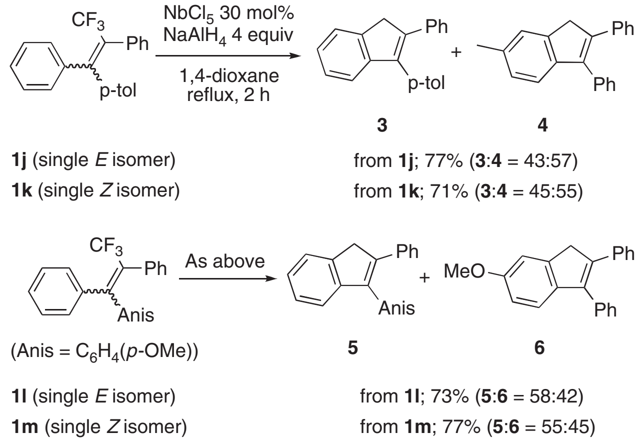
Substituents α to the CF_3 group also exhibited wide generality (Table 2). Substituted phenyl- and heteroaryltrifluo-

Table 2. Cyclization of trifluoromethylalkenes (2)



Entry	R	Time/h	Yield/%
1	*p*-$MeOC_6H_4$, **1f**	2	80, **2f**
2	*p*-FC_6H_4, **1g**	2	71,[a] **2g**
3	2-Thienyl, **1h**	2	83, **2h**
4	Me, **1i**	2	53, **2i**

[a] 7% yield of 2,3-diphenylindene was obtained.



Scheme 2.

ropropenes **1f**–**1h** gave the corresponding **2f**–**2h** in good yields (Entries 1–3). Not only 2-arylated trifluoropropenes but also 2-alkylated trifluoropropene **1i** afforded the corresponding indene **2i** (Entry 4).

1,1-Heterodiarylated trifluoropropenes also gave the corresponding indenes and in this case, unexpected isomerization in terms of the alkene geometry took place (Scheme 2); (*E*)-1,2-diphenyl-1-*p*-tolyl-3,3,3-trifluoropropene (**1j**) (single *E*-isomer) gave a 43:57 mixture of phenyltolylindene **3** and methyldiphenylindene **4** in 77% yield. Isomer **1k** (single *Z*-isomer) also gave essentially the same isomeric mixture. These phenomena were also observed when *E*- and *Z*-trifluoropropenes **1l** and **1m** were used. The structure of **4** was determined by X-ray crystal structure analysis (Figure 1).[25]

The formation of indenes and the geometric isomerization described in Scheme 2 can be explained by our presumed catalytic cycle (Scheme 3). Reduction of niobium(V) chloride with sodium aluminum hydride gives Nb(0) species.[26] Fluorine-substituted alkenylcarbenoid intermediates **A** are reductively formed from the Nb(0) species and substrates **1**.[13c] The carbenoid intermediates **A** undergo intramolecular insertion to an aromatic C–H σ bond[27] to give fluoroindene intermediates **B**,[28] liberating niobium species in higher oxidation state [Nb(*n*)]. Re-reduction of the liberated Nb(*n*) to Nb(0) initiates again the catalytic cycle, and fluoroindenes **B** are hydrodefluorinated in situ to give products **2** after aqueous work-up.[13c] Isomerization of the alkene geometry of **A**[27b] and the C–H insertion of the thus-formed isomeric fluorine-substituted alkenylcarbenoid intermediates (not shown) afford the isomeric indenes. The *E*- and *Z*-alkenylcarbenoid intermediates are in equilibrium, based on the fact that the same isomeric mixtures **3**/**4** and **5**/**6** were obtained regardless of the alkene geometry of **1j**–**1m**.

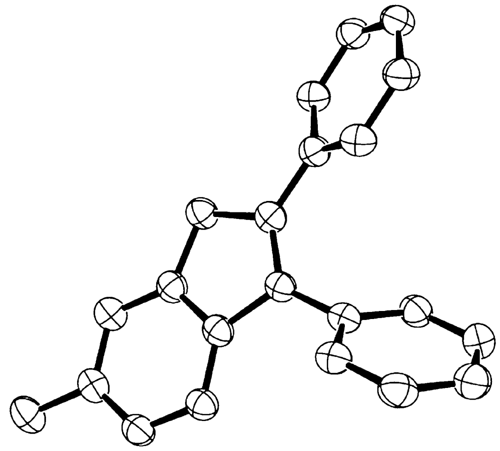
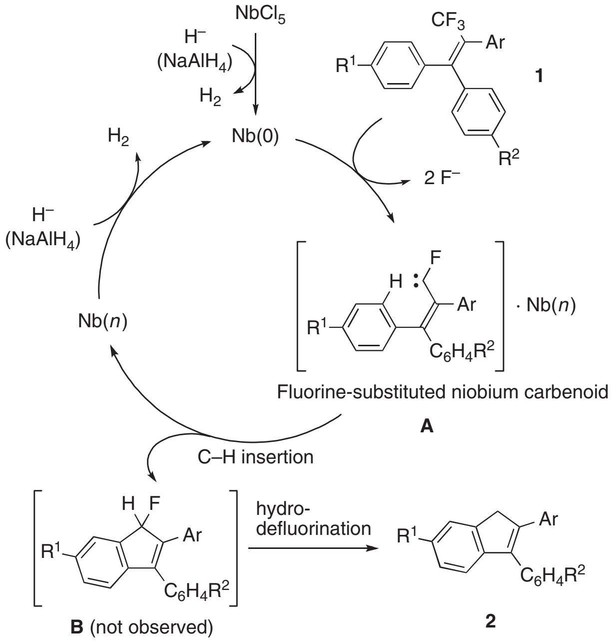


Figure 1. ORTEP diagram of **4**.



Scheme 3.

In summary, we have developed a niobium-catalyzed method for the activation of the CF_3 group on alkene functionality. Treatment of 3,3,3-trifluoropropenes with zero-valent niobium species successfully gave substituted indenes in good yields. Niobium alkenylcarbenoid species are presumed to be generated as key intermediates.[29]

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References and notes

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1 Fundamental reviews on organofluorine chemistry: a) K. Uneyama, *Organofluorine Chemistry*, Blackwell Publishing, Oxford, **2006**, Chap. 1, pp. 1–100. b) T. Hiyama, *Organofluorine Compounds: Chemistry and Applications*, Springer-Verlag, Berlin, **2000**, Chap. 1, pp. 1–23.

2 a) M. Zanda, *New J. Chem.* **2004**, *28*, 1401. b) K. Uneyama, *Organofluorine Chemistry*, Blackwell Publishing, Oxford, **2006**, Chap. 6, pp. 206–222. c) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305.

3 K. Uneyama, *Organofluorine Chemistry*, Blackwell Publishing, Oxford, **2006**, Chap. 5, pp. 186–205.

4 See also: K. Mikami, Y. Itoh, M. Yamanaka, *Chem. Rev.* **2004**, *104*, 1.

5 A recent review and reports on the synthesis of CF_3 compounds: a) J.-A. Ma, D. Cahard, *J. Fluorine Chem.* **2007**, *128*, 975. b) G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600. c) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909. d) H. Kawai, A. Kusuda, S. Nakamura, M. Shiro, N. Shibata, *Angew. Chem., Int. Ed.* **2009**, *48*, 6324. e) V. V. Grushin, *Acc. Chem. Res.* **2010**, *43*, 160.

6 The C–F bond dissociation energy of CHF_3 is 128.0 kcal mol^{-1}: J. Burdeniuc, B. Jedlicka, R. H. Crabtree, *Chem. Ber.* **1997**, *130*, 145. This value is much larger than those of CH_3–F (109.0 kcal mol^{-1}) and CH_3–H (98.0 kcal mol^{-1}).

7 General reviews on C–F bond activation: a) T. G. Richmond, in *Activation of Unreactive Bonds and Organic Synthesis*, ed. by S. Murai, Springer, New York, **1999**, pp. 243–269. b) J. L. Kiplinger, T. G. Richmond, C. E. Osterberg, *Chem. Rev.* **1994**, *94*, 373. c) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119.

8 a) H. Amii, K. Uneyama, in *Fluorine-Containing Synthons*, ed. by V. A. Soloshonok, American Chemical Society, Washington DC, **2005**, Chap. 27, pp. 455–475. b) K. Uneyama, H. Amii, *J. Fluorine Chem.* **2002**, *114*, 127. See also: c) H. Amii, Y. Hatamoto, M. Seo, K. Uneyama, *J. Org. Chem.* **2001**, *66*, 7216.

9 a) W. Gu, M. R. Haneline, C. Douvris, O. V. Ozerov, *J. Am. Chem. Soc.* **2009**, *131*, 11203. b) J. Terao, M. Nakamura, N. Kambe, *Chem. Commun.* **2009**, 6011. See also: c) M. Ali, L.-P. Liu, G. B. Hammond, B. Xu, *Tetrahedron Lett.* **2009**, *50*, 4078.

10 a) M. J. Molina, F. S. Rowland, *Nature* **1974**, *249*, 810. b) D. G. Victor, G. J. MacDonald, *Clim. Change* **1999**, *42*, 633. c) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2002**, *102*, 4009.

11 a) C. Douvris, O. V. Ozerov, *Science* **2008**, *321*, 1188. b) V. J. Scott, R. Çelenligil-Çetin, O. V. Ozerov, *J. Am. Chem. Soc.* **2005**, *127*, 2852. c) C. Douvris, C. M. Nagaraja, C.-H. Chen, B. M. Foxman, O. V. Ozerov, *J. Am. Chem. Soc.* **2010**, *132*, 4946. d) R. Panisch, M. Bolte, T. Müller, *J. Am. Chem. Soc.* **2006**, *128*, 9676.

12 Other reactions of trifluorotoluenes: a) C. Saboureau, M. Troupel, S. Sibille, J. Périchon, *J. Chem. Soc., Chem. Commun.* **1989**, 1138. b) D. Ferraris, C. Cox, R. Anand, T. Lectka, *J. Am. Chem. Soc.* **1997**, *119*, 4319. c) P. Clavel, M.-P. Léger-Lambert, C. Biran, F. Serein-Spirau, M. Bordeau, N. Roques, H. Marzouk, *Synthesis* **1999**, 829.

13 Niobium-catalyzed double C–F/C–H activations: a) K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2006**, *128*, 1434. b) K. Fuchibe, K. Mitomi, T. Akiyama, *Chem. Lett.* **2007**, *36*, 24. c) K. Fuchibe, K. Mitomi, R. Suzuki, T. Akiyama, *Chem. Asian J.* **2008**, *3*, 261. d) K. Fuchibe, T. Kaneko, K. Mori, T. Akiyama, *Angew. Chem., Int. Ed.* **2009**, *48*, 8070. e) K. Fuchibe, T. Akiyama, *J. Synth. Org. Chem., Jpn.* **2009**, *67*, 208. See also: f) T. G. Driver, *Angew. Chem., Int. Ed.* **2009**, *48*, 7974.

14 Niobium-catalyzed hydrodefluorination of trifluorotoluenes: a) K. Fuchibe, T. Akiyama, *Synlett* **2004**, 1282. b) K. Fuchibe, Y. Ohshima, K. Mitomi, T. Akiyama, *Org. Lett.* **2007**, *9*, 1497. c) K. Fuchibe, Y. Ohshima, K. Mitomi, T. Akiyama, *J. Fluorine Chem.* **2007**, *128*, 1158.

15 Reviews on reactivity of niobium: a) A. Otero, A. Antiñolo, A. Lara, in *Comprehensive Organometallic Chemistry III*, ed. by R. H. Crabtree, D. M. P. Mingos, **2007**, Elsevier, New York, Vol. 5, Chap. 2, pp. 61–100. b) C. K. Z. Andrade, *Curr. Org. Synth.* **2004**, *1*, 333. Selected reports on reaction of Nb(III): c) E. J. Roskamp, S. F. Pedersen, *J. Am. Chem. Soc.* **1987**, *109*, 6551. d) J. B. Hartung, S. F. Pedersen, *Organometallics* **1990**, *9*, 1414. e) S. Arai, S. Takita, A. Nishida, *Eur. J. Org. Chem.* **2005**, 5262. f) Y. Obora, M. Kimura, T. Ohtake, M. Tokunaga, Y. Tsuji, *Organometallics* **2006**, *25*, 2097. g) Y. Obora, K. Takeshita, Y. Ishii, *Org. Biomol. Chem.* **2009**, *7*, 428. Selected reports on reaction of Nb(V): h) S. Arai, Y. Sudo, A. Nishida, *Tetrahedron* **2005**, *61*, 4639. i) J. S. Yadav, B. V. S. Reddy, B. Eeshwaraiah, P. N. Reddy, *Tetrahedron* **2005**, *61*, 875. j) S. S. Kim, G. Rajagopal, *Synthesis* **2007**, 215. k) K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 8103. See also: l) M. Kirihara, J. Yamamoto, T. Noguchi, A. Itou, S. Naito, Y. Hirai, *Tetrahedron* **2009**, *65*, 10477.

16 M. Sato, K. Oshima, *Chem. Lett.* **1982**, 157.

17 a) D. A. Kendrick, M. Kolb, *J. Fluorine Chem.* **1989**, *45*, 265. b) J.-P. Bégué, D. Bonnet-Delpon, M. H. Rock, *Synlett* **1995**, 659. c) J.-P. Bégué, D. Bonnet-Delpon, M. H. Rock, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1409. d) J. Ichikawa, Y. Iwai, R. Nadano, T. Mori, M. Ikeda, *Chem. Asian J.* **2008**, *3*, 393. e) See also: K. Hirano, K. Fujita, H. Yorimitsu, H. Shinokubo, K. Oshima, *Tetrahedron Lett.* **2004**, *45*, 2555.

18 S_N2'-type reactions are also promoted with Pd- and Rh-catalysts: a) J. Ichikawa, R. Nadano, N. Ito, *Chem. Commun.* **2006**, 4425. b) T. Miura, Y. Ito, M. Murakami, *Chem. Lett.* **2008**, *37*, 1006.

19 Useful compounds with the indene core structure: a) Y. Zhou, Y. Su, B. Li, F. Liu, J. W. Ryder, X. Wu, P. A. Gonzalez-DeWhitt, V. Gelfanova, J. E. Hale, P. C. May, S. M. Paul, B. Ni, *Science* **2003**, *302*, 1215. b) C. Haanen, *Curr. Opin. Invest. Drugs* **2001**, *2*, 677. c) J. Yang, M. V. Lakshmikantham, M. P. Cava, D. Lorcy, J. R. Bethelot, *J. Org. Chem.* **2000**, *65*, 6739. d) R. Leino, P. Lehmus, A. Lehtonen, *Eur. J. Inorg. Chem.* **2004**, 3201.

20 Recent reports on the synthesis of indenes: a) R. L. Halterman, C. Zhu, *Tetrahedron Lett.* **1999**, *40*, 7445. b) Y. Kuninobu, A. Kawata, K. Takai, *J. Am. Chem. Soc.* **2005**, *127*, 13498. c) X. Zhu, C. Mitsui, H. Tsuji, E. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 13596. d) S. Yang, Z. Li, X. Jian, C. He, *Angew. Chem., Int. Ed.* **2009**, *48*, 3999. e) H. Kurouchi, H. Sugimoto, Y. Otani, T. Ohwada, *J. Am. Chem. Soc.* **2010**, *132*, 807.

21 a) X. Liu, M. Shimizu, T. Hiyama, *Angew. Chem., Int. Ed.* **2004**, *43*, 879. Other reports on the synthesis of trifluoropropenes: b) Y. Takeda, M. Shimizu, T. Hiyama, *Angew. Chem., Int. Ed.* **2007**, *46*, 8659. c) J. J. Gajewski, K. R. Gee, J. Jurayj, *J. Org. Chem.* **1990**, *55*, 1813. d) B. Jiang, Q.-F. Wang, C.-G. Yang, M. Xu, *Tetrahedron Lett.* **2001**, *42*, 4083. e) O. Kobayashi, D. Uraguchi, T. Yamakawa, *J. Mol. Catal. A: Chem.* **2009**, *302*, 7.

22 a) H. C. Brown, J. A. Soderquist, *J. Org. Chem.* **1980**, *45*, 846. b) J. S. Cha, H. C. Brown, *J. Org. Chem.* **1993**, *58*, 4727.

23 All of the produced indenes were obtained as single regioisomers with respect to their double bond.

24 Selective reduction of the CF_3 group over the aromatic C–F moiety was reported in our previous reports. See refs. 14b and 14c.

25 CCDC 772229 contains 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.

26 M. E. Kost, A. I. Golovanova, *Zh. Neorg. Khim.* **1977**, *22*, 977.

27 a) P. Müller, N. Pautex, M. P. Doyle, V. Bagheri, *Helv. Chim. Acta* **1990**, *73*, 1233. b) H. M. L. Davies, L. M. Hodges, J. J. Matasi, T. Hansen, D. G. Stafford, *Tetrahedron Lett.* **1998**, *39*, 4417.

28 **B** was not observed in this system. However, in our preliminary report, fluorinated intermediates corresponding to **B** were isolated in reasonable yields. See ref. 13c.

29 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.