

Niobium-catalyzed Activation of CF₃ Group on Alkene: Synthesis of Substituted IndenesKohei Fuchibe,[†] Kohei Atobe, Yukari Fujita, Keiji Mori, and Takahiko Akiyama*

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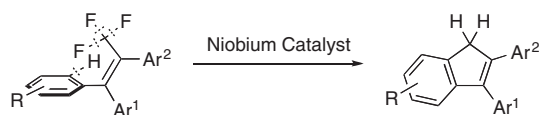
A CF₃ group attached to an alkene functionality was activated by a zero-valent niobium catalyst to generate niobium alkenylcarbenoid species. The niobium carbenoid species then underwent insertion to an internal aromatic C–H σ bond to give indene derivatives in good yields. Isomerization in terms of the alkene geometry was also observed.

CF₃ groups have played important roles in a range of organic molecules for a long time.¹ Molecules bearing CF₃ group(s) in their structures, in general, exhibit enhanced (altered) activities and stabilities, and various useful materials, such as pharmaceuticals² and ligands for metal catalysis,³ have been created and utilized.^{4,5}

The CF₃ 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 CF₃ 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 CF₃ 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 CF₃ groups attached to carbonyl and aromatic functionalities, reactions of CF₃ 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 CF₃ groups has been quite limited.¹⁸ We wish to report herein the first, direct activation of the CF₃ groups attached to an alkene functionality by a niobium catalyst. Substituted indenenes, 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**)

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	<i>p</i> -Tol, 1b	2	63 (6-Me), 2b
5	C ₆ H ₄ (<i>p</i> -OMe), 1c	5	52 (6-OMe), 2c
6	C ₆ H ₄ (<i>p</i> -F), 1d	1	56 (6-F), 2d ^d
7	3,5-Dimethylphenyl, 1e	3	54 (5,7-Me ₂), 2e

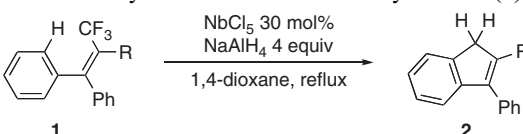
^aTrifluoropropenes **1** were consumed completely. ^b10 mol % NbCl₅. ^cLiAlH₄ was used. ^dDefluorinated indenenes were not detected by ¹⁹F NMR analysis.

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 CF₃ 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).

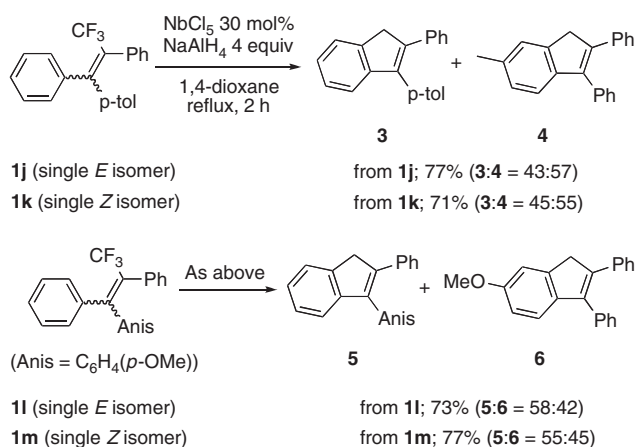
Use of lithium aluminum hydride in place of sodium aluminum hydride gave a diminished yield of **2a** (54% yield, Entry 3). Treatment of isolated **2a** with lithium aluminum hydride alone resulted in 44% recovery of **2a** (not shown), whereas **2a** was recovered in 58% yield when treated with sodium 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-homodiarlylated trifluoropropenes also afforded the corresponding indenenes 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 indenenes **2b–2d** in good yields (Entries 4–6). Sterically demanding **1e** also worked well (Entry 7). It is noted that the CF₃ group was selectively activated in preference to the aromatic C–F moiety under the reaction conditions (Entry 6).²⁴

Substituents α to the CF₃ group also exhibited wide generality (Table 2). Substituted phenyl- and heteroaryltrifluo-

Table 2. Cyclization of trifluoromethylalkenes (**2**)


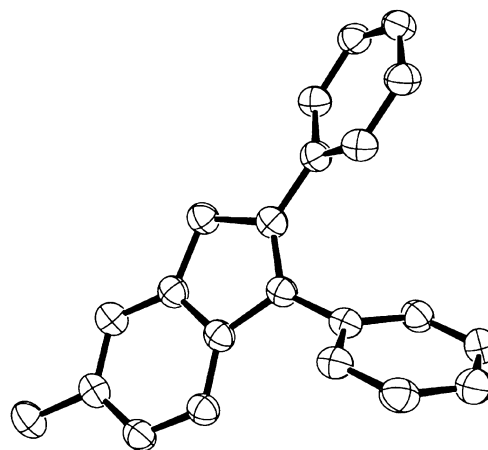
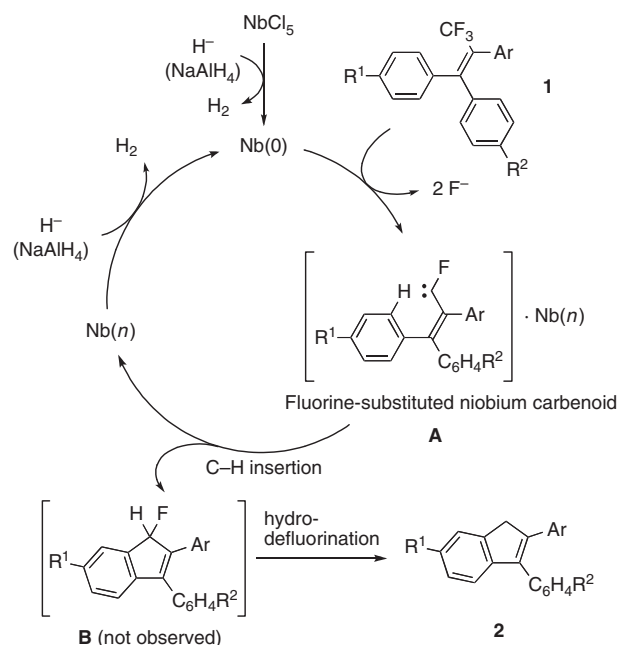
Entry	R	Time/h	Yield/%
1	<i>p</i> -MeOC ₆ H ₄ , 1f	2	80, 2f
2	<i>p</i> -FC ₆ H ₄ , 1g	2	71, ^a 2g
3	2-Thienyl, 1h	2	83, 2h
4	Me, 1i	2	53, 2i

^a7% 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 methylindene **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 bond²⁷ 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 in-

**Figure 1.** ORTEP diagram of **4**.**Scheme 3.**

termediates (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**.

In summary, we have developed a niobium-catalyzed method for the activation of the CF₃ 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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- 29 Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.