Low-valent Niobium-mediated Synthesis of Indenes: Intramolecular Coupling Reaction of CF_3 Group with Alkene C–H Bond

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CF_3 group of *o*-alkenyl-α,α,α-trifluorotoluenes underwent intramolecular coupling reaction with the alkene C–H bond under $NbCl_5/LiAlH_4$ system. Substituted indenes were obtained in good yields.

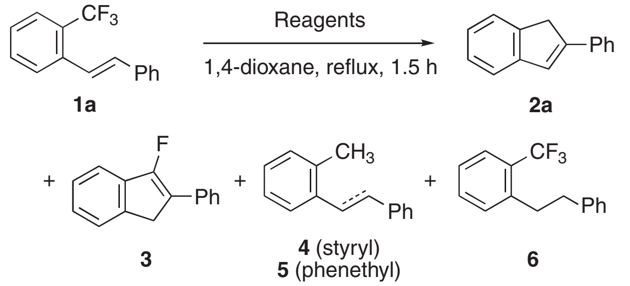
Indene is a ubiquitous component of organic molecules and plays important roles in various fields of chemistry. For instance, substituted indene derivatives frequently occur in natural products and exhibit biological activity.[1] Anions prepared from indene derivatives and appropriate bases are representative variations of Cp ligands, and the π-coordinated indenyl complexes sometimes exhibit remarkable catalytic activities.[2] In recent years, indene skeletons have attracted much attention as core parts of functional materials such as conducting polymers[3] and discotic liquid crystals.[4] Development of novel synthetic method of the indene derivatives is, thus, extremely important to these areas of research.

A number of methods have been reported for the construction of the five-membered carbocycles. Cation-mediated reactions such as the Nazarov-type π-cyclization and intramolecular electrophilic aromatic substitution are one of the most familiar methods.[5] Intramolecular nucleophilic attack of carbanion equivalents to carbonyl groups affords the indene or its related compounds.[6] Insertions of alkynes to aryl metals also give indene derivatives.[7,8]

On the other hand, we have previously reported a low-valent niobium-mediated synthesis of substituted fluorenes from *o*-aryl-α,α,α-trifluorotoluenes.[9] In this protocol, the CF_3 group is activated by the low-valent niobium,[10] and coupled with the neighboring aromatic C–H bond.[11] Keeping this success in mind, we planned to synthesize indene derivatives from *o*-alkenyl-α,α,α-trifluorotoluenes (Scheme 1).

At the outset, we attempted a reaction of *o*-styryl-α,α,α-trifluorotoluene (**1a**) (Table 1). To a dioxane solution of **1a** and an equimolar amount of $NbCl_5$, dioxane suspension of $LiAlH_4$ was added over a period of 1.5 h. During the addition, the reaction mixture was allowed to reflux. When the addition was completed, the reaction was quenched with water. The desired indene **2a** was obtained in 64% yield and conventional reduction products (hydrodefluorination products) **4** and **5** were obtained in 22% yield (Entry 1).

Table 1. Optimization of reagents



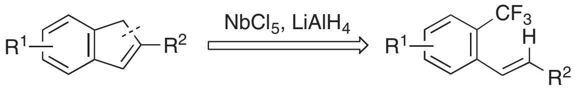
Entry	Reagents[a]	Yield/%				
		2a	**3**	**4** + **5** (ratio)	**6**	**1a**
1	$NbCl_5$, $LiAlH_4$[b]	64	—	22 (55:45)	—	—
2	$TaCl_5$, $LiAlH_4$[b]	42	11	23 (56:44)	—	—
3	WCl_6, $LiAlH_4$[b]	16	18	12 (83:17)	—	39
4	$PdCl_2$, $LiAlH_4$[b]	4	7	16 (76:24)	44	7
5	$NbCl_5$, Red-Al	11	6	71 (18:82)	—	—
6	$NbCl_5$, DIBAL	—	—	—	—	86
7	$NbCl_5$, $NaBH_4$	—	—	—	—	97

[a] 100 mol % of metal salt and 10 molar amounts of reducing agent were used for each entries. [b] Dioxane suspension of $LiAlH_4$ was added over 1.5 h.

Use of other reagent in place of $NbCl_5$ or $LiAlH_4$ gave inferior results: $TaCl_5$ partially gave fluoroindene **3**,[12] in which one fluorine atom survived (Entry 2). WCl_6 gave significant amount of the starting material **1a** (Entry 3). In the case of $PdCl_2$, the alkene moiety was affected prior to the CF_3 group (Entry 4) to give **6**.[13] Use of Red-Al [sodium bis(methoxyethoxy)aluminum hydride], DIBAL, and $NaBH_4$ resulted in formation of the conventional reduction products **4** and **5** (Entry 5), or recovery of **1a** (Entries 6 and 7). The intramolecular coupling reaction was thus accomplished by the $NbCl_5/LiAlH_4$ system.

Solid $LiAlH_4$, in place of the dioxane suspension of the reducing agent, decreased the yield of **2a** and increased the yield of **4** and **5** (Scheme 2). Excess amount of the reducing agent in the reaction medium likely promoted conventional reduction process, leading to the formation of **4** and **5**.[9a]

The use of a catalytic amount (30 mol %) of $NbCl_5$ was found to be effective for the present coupling reactions. As shown in Table 2, arylvinyl-α,α,α-trifluorotoluenes gave arylindenes in good yields (Entries 1–11). It is worth noting that this reaction smoothly gave aminoindene **2i** and fused **2k**, which are potentially inaccessible by existing acid-promoted cyclizations[5a,5b] or the Heck-type arylations of parent indenes.[14]

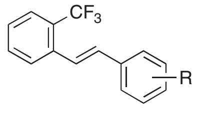
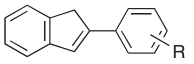
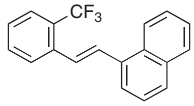
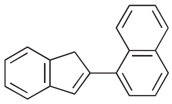
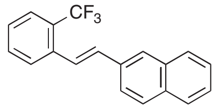
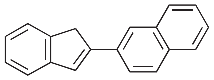
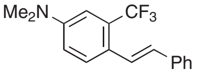
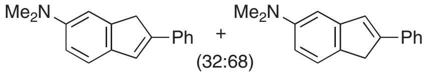
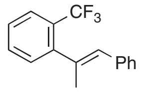
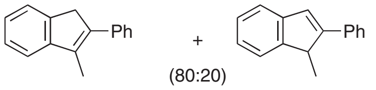
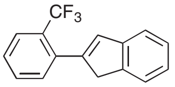
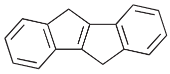


Scheme 1. Our approach to indene skeletons.

$$\mathbf{1a} \xrightarrow[\text{1,4-dioxane, reflux, 3 h}]{\text{NbCl}_5\text{ 100 mol\%, Solid LiAlH}_4\text{ 10 mol. amt.}} \underset{34\%}{\mathbf{2a}} + \underset{19\%}{\mathbf{4}} + \underset{17\%}{\mathbf{5}}$$

Scheme 2.

Table 2. Low-valent niobium-mediated synthesis of substituted indenes[a]

Entry	Alkenyltrifluorotoluene	(R)	Product(s)	Yield/%[b]
1		**1a** (H)		64, **2a**
2		**1b** (*p*-Me)		61, **2b**
3		**1c** (*p*-NMe$_2$)		64, **2c**
4		**1d** (*p*-OMe)		66, **2d**
5		**1e** (*m*-OMe)		62, **2e**
6		**1f** (*o*-OMe)		57, **2f**
7		**1g**		62, **2g**
8		**1h**		64, **2h**
9[c]		**1i**		61, **2i**
10		**1j**		61, **2j**
11		**1k**		68, **2k**

[a]Conditions: NbCl$_5$ 30 mol %, LiAlH$_4$ 5 mol. amt. (dioxane suspension, over 1.5 h), 3 h. [b]NMR yield. Conventional reduction products corresponding to **4** and **5** were obtained in 19–24% yields. [c]NbCl$_5$ 100 mol %, LiAlH$_4$ 10 mol. amt., 10 h.

We now surmise that this reaction proceeds as we have previously described for our fluorene synthesis.[9a] Further studies on mechanistic aspects are in progress.

In summary, we have developed a novel low-valent niobium-mediated synthetic method of indenes. We could obtain various substituted indenes in good yields, starting from *o*-alkenyl-α,α,α-trifluorotoluenes via intramolecular coupling reaction of the CF$_3$ group and the alkene C–H bond.

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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