

C–C Coupling Reactions of Superstrong CF₃ Groups with C(sp²)–H Bonds: Reactivity and Synthetic Utility of Zero-Valent Niobium Catalyst

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

Abstract: It was found that zero-valent niobium is an efficient catalyst for the intramolecular C–C coupling reactions of *o*-aryl and *o*-alkenyl α,α,α -trifluorotoluene derivatives. The superstrong C–F bonds of CF₃ groups and neighboring C(sp²)–H bonds were doubly activated, and fluorenes and indenes were obtained in good yields. The niobium fluorocarbenoid species is proposed to be the key intermediate.

Keywords: carbenoids • C–C coupling • C–F activation • C–H activation • niobium

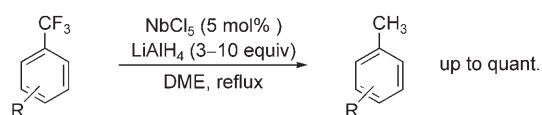
Introduction

The activation of C–F bonds is one of the major interests of synthetic organic chemists.^[1] Although oxidative additions of C–F bonds to metal complexes^[2] and cross-coupling reactions of organofluorine compounds in the presence of metal catalysts have been reported,^[3] methods for activating and utilizing C–F bonds in organic synthesis are still underdeveloped.

Among a wide range of organofluorine compounds, the trifluoromethyl group on aromatic rings is especially difficult to activate, and the synthetic utility of α,α,α -trifluorotoluenes is quite limited. For example, stepwise Mg⁰-promoted synthesis of cyclophanes^[4] and electroreductive bond-forming reactions^[5] have been reported. Trityl cation catalyzed hydrodefluorination of trifluorotoluene derivatives has also been accomplished in recent years.^[6] The CF₃ group, howev-

er, has remained impregnable substituents for synthetic organic chemists from a practical point of view.^[7]

We recently found that the chemical inertness of superstrong CF₃ groups can be overcome by the NbCl₅/LiAlH₄ system (Scheme 1).^[8] Parent and substituted α,α,α -trifluorotoluenes were smoothly reduced with lithium aluminum hydride in the presence of 5 mol % of niobium(V) chloride to give the corresponding toluenes in quite high yields.



Scheme 1. Niobium-catalyzed reductions. DME = 1,2-dimethoxyethane.

The reduction is likely to be catalyzed by Nb⁰ species. It was reported that niobium(V) chloride can be reduced by lithium aluminum hydride to give metallic niobium at low temperature.^[9]

To date, niobium reagents (and catalysts) have been utilized mainly in the +III and +V oxidation states.^[10] It is well-recognized that [NbCl₃(dme)] and its related complexes form niobacycle intermediates when they react with unsaturated functionalities such as alkynes^[11] and imines. The niobacycle intermediates have been utilized as 1,2-dianionic equivalents^[12] or coupling partners.^[13] In recent years, the utility of Nb^V species (particularly NbCl₅) has emerged.^[10a] The strongly Lewis acidic pentavalent niobium has been reported to promote allylations,^[14] Friedel–Crafts reactions,^[15]

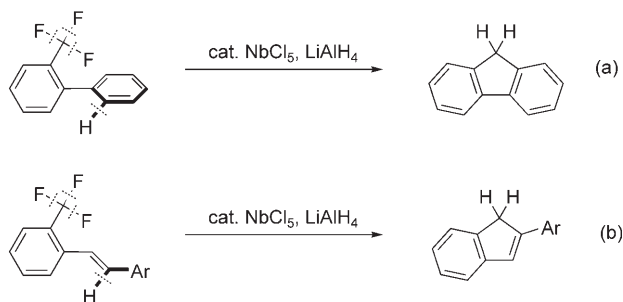
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and other reactions.^[16] Asymmetric inductions by chiral niobium(V) catalysts have also been reported.^[17]

Herein, we disclose Nb⁰-catalyzed C–C bond-forming reactions with α,α,α -trifluorotoluene derivatives. *o*-Aryl- and *o*-alkenyltrifluorotoluenes afforded fluorene and indene derivatives in good yields (Scheme 2). In contrast to the chemistry of Nb^{III} and Nb^V species, the chemistry of Nb⁰ species is still underdeveloped.^[18] We also describe new reactions of the Nb⁰ species.



Scheme 2. Nb⁰-catalyzed C–C coupling reactions.

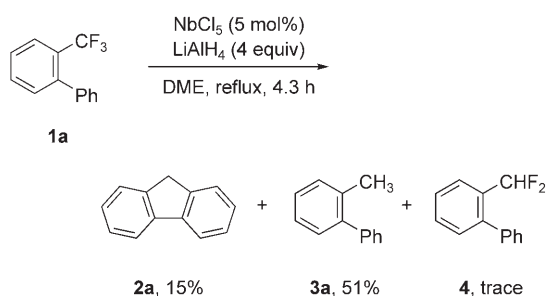
It must be mentioned that these reactions proceed through activation of aromatic and alkenyl C–H bonds. There have been many reports on the activation of C–H bonds in recent years,^[19] but the direct C–C coupling reactions of C–F and C–H bonds have never been reported to date.

Described below are the details of our examination. Mechanistic considerations are also provided.

Results and Discussion

C–C Coupling Reactions of *o*-Phenyltrifluorotoluene: Outset and Optimization

During the course of our study on the Nb⁰-catalyzed reduction of α,α,α -trifluorotoluenes, we found that fluorene (**2a**) was generated from *o*-phenyl- α,α,α -trifluorotoluene (**1a**; Scheme 3).^[20] Compound **1a** was heated at reflux in DME with 4 equivalents of lithium aluminum hydride in the pres-



Scheme 3. Formation of fluorene.

ence of 5 mol % of niobium(V) chloride for 4 h, after which **2a** was isolated in 15% yield, together with conventional reduction product **3a** in 51% yield.

Although research on C–H bond activations is increasing,^[19] simultaneous activation and direct C–C coupling reactions of C–F and C–H bonds have not been accomplished so far. Nb⁰ species was found to be a promising catalyst for the C–F/C–H coupling reaction.

Various early- and late-transition-metal halides afforded **2a** (Table 1, entries 1–11). Among the metal halides exam-

Table 1. Survey of metal complexes.^[a]

Entry	Metal complex	2a [%]	3a [%]	2a/3a	4 [%]	Recovery of 1a [%]
1	ZrCl ₄	40	29	1.4	–	–
2	TiCl ₄	–	–	–	–	70
3	VCl ₃	36	29	1.2	–	–
4	NbCl ₅	61	18	3.4	–	–
5	NbBr ₅	43	33	1.3	–	–
6	NbF ₅	21	34	0.62	–	–
7	TaCl ₅	57	27	2.1	–	–
8	TaBr ₅	16	23	0.70	–	–
9	WCl ₆	4	26	0.15	37	17
10	FeCl ₃	28	70	0.40	–	–
11	PdCl ₂	41	44	0.93	4	–
12	[NbBr ₃ (dme)]	55	26	2.1	–	–
13	[NbCl ₄ (thf) ₂]	55	23	2.4	–	–
14	Nb ₂ O ₅	–	36	–	46	6
15	none	–	11	–	52	33

[a] Conditions: **1a**, metal complex (1.0 equiv), LiAlH₄ (10 equiv), DME, reflux, 6 h.

ined, niobium(V) chloride (1 equiv) gave the highest yield of **2a** (61% yield, **2a/3a**=3.4; Table 1, entry 4). Nb^{III} and Nb^{IV} complexes were found to be less efficient because the yields of **2a** were low with these complexes (Table 1, entries 12 and 13). Niobium(V) oxide did not afford **2a** at all (Table 1, entry 14). Reaction in the absence of metal halides gave partial reduction product **4**, and **2a** was not obtained at all (Table 1, entry 15).

Examination of the reducing agents revealed that lithium aluminum hydride gave the highest yield of **2a** (Table 2, entry 1). Mono- and dialkoxyaluminum hydride reagents also gave **2a** but in low yields (Table 2, entries 2 and 3). On the other hand, lithium tri-*tert*-butoxyaluminum hydride, DIBAL, sodium borohydride, and zero-valent metals did not afford **2a** (Table 2, entries 4–11). Niobium turnings

Abstract in Japanese:

α, α, α -トリフルオロトルエンの炭素–フッ素結合は、きわめて活性化が難しいことが知られている。我々は、塩化ニオブ(V)と水素化アルミニウムリチウムから系中で生成するゼロ価ニオブ種を触媒として利用すると、 α, α, α -トリフルオロトルエン誘導体を炭素–炭素結合形成反応に利用できることを見いだした。すなわち、オルト位にアール基やアルケニル基を有するトリフルオロトルエン誘導体から、収率よくフルオレンおよびインデン誘導体が得られた。本反応では、炭素–フッ素結合は分子内 *sp*²炭素–水素結合とカップリングを起こし、新たな炭素–炭素結合を形成している。本反応は、炭素–フッ素結合と炭素–水素結合の初めてのカップリング反応である。重水素化実験の結果から、我々はニオブカルベノイド種が中間体として生成しているものと考えている。

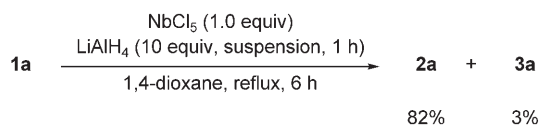
Table 2. Survey of reducing agents.^[a]

Entry	Reducing agent	2a	3a	2a/3a	1a
		[%]	[%]		[%]
1	LiAlH ₄	61	18	3.4	–
2	LiAl(O <i>i</i> Pr) ₃ H ₃	40	33	1.2	–
3	NaAlH ₂ (OCH ₂ CH ₂ OMe) ₂	16	64	0.25	–
4	LiAl(O <i>i</i> Bu) ₃ H	–	–	–	79
5	DIBAL	–	–	–	91
6	NaBH ₄	–	–	–	90
7	Mg turnings	–	–	–	94
8	Zn powder	–	–	–	91
9	Al powder	–	–	–	quant.
10	Sm turnings	–	–	–	84
11	Na ingot ^[b]	3	5	0.6	22
12	Nb turnings ^[c]	–	–	–	80

[a] Conditions: **1a**, NbCl₅ (1.0 equiv), reducing agent (10 equiv), DME, reflux, 6 h. [b] 5 equivalents of sodium was used. [c] NbCl₅ and LiAlH₄ were not used. DIBAL = diisobutylaluminum hydride.

(24 mesh), in the absence of niobium(V) chloride and lithium aluminum hydride, did not give **2a** either (Table 2, entry 12).

The selectivity (**2a/3a**) was improved dramatically when lithium aluminum hydride was slowly added to the reaction medium (Scheme 4); instead of adding solid lithium alumi-



Scheme 4. Selective formation of fluorene.

num hydride to the solution of niobium(V) chloride and **1a** in DME in one portion (**2a/3a** = 3.4; Table 1, entry 4), we prepared a suspension of lithium aluminum hydride in 1,4-dioxane in a dropping funnel, which was fitted to the reaction flask. The suspension was slowly dispensed through the dropping funnel over 1 h. Formation of **3a** was suppressed to only 3%, and **2a** was obtained in 82% yield (**2a/3a** = 27).^[21]

Finally, the solvents were examined (Table 3), and dioxane was found to be the most favorable solvent (Table 3, entry 1).

Table 3. Effect of solvent.^[a]

Entry	Solvent ^[a]	2a [%]	3a [%]	1a [%]
1	1,4-dioxane	82	2	–
2	<i>n</i> Bu ₂ O	10	10	48
3	tetrahydropyran	20	4	49
4	THF	–	–	85
5	Et ₂ O	–	–	87
6	hexane	–	–	26

[a] Conditions: **1a**, NbCl₅ (1.0 equiv), LiAlH₄ (10 equiv), reflux, 3 h (1 h for addition).

Catalytic Synthesis of Fluorenes

The C–C coupling reaction of the CF₃ group and the aromatic C–H bond was accomplished with a catalytic amount of niobium(V) chloride (Table 4).^[20] Model substrate **1a** gave **2a** in 83% yield with 30 mol% of the catalyst (Table 4, entry 1). The loading of niobium(V) chloride could be decreased to 10 mol% with a slight decrease in yield (Table 4, entry 2).

Various *para*-substituted aryl trifluorotoluenes **1b–h** gave the corresponding fluorenes **2b–h** in good yields (Table 4, entries 3–9). Heteroatom substituents, such as alkylthio and amine groups, were tolerant to the conditions (Table 4, entries 5–9). Notably, the C–F bonds of the CF₃ groups were found to be activated prior to the aromatic C–F bond (Table 4, entry 8).

Meta- and *ortho*-substituted aryl trifluorotoluenes **1i–k** gave the corresponding products **2i–k** in good yields (Table 4, entries 10–12), whereas no regioselectivity was observed for **1i** and **1j**. Compound **1l**, which contains an amine group on the core aromatic ring, gave the corresponding product **2f** in high yield (Table 4, entry 13). Synthesis of di- and trisubstituted fluorenes was accomplished by applying this method to di- and trisubstituted trifluorotoluenes **1m** and **1n** (Table 4, entries 14 and 15).

Fluorene is a core structure of various useful and interesting compounds, such as MTP inhibitors,^[22] interferon inducers,^[23] and others.^[24] Fluorenes in polymer form have also attracted much attention as molecular devices for blue-light-emitting materials.^[25] One of the most general methods of forming fluorenes and related compounds are Friedel–Crafts-type, acid-catalyzed cyclizations of *o*-biphenyl carbonyl compounds.^[26] The Nb⁰ catalyst provides a new synthetic route to substituted fluorenes.

Mechanistic Consideration I

To understand the reaction mechanism in greater depth, deuterium-labeling experiments were performed.

At first, pentadeuteriophenyl trifluorotoluene **5** was subjected to the optimized conditions (Scheme 5). Compound **6**, in which the *ortho*-deuterium atom migrated to the methylene moiety, was obtained in good yield (63%, 98% D). This result strongly suggests that insertion of the CF₃ carbon atom into the aromatic C–H bond did take place. All of the deuterium incorporations herein were determined on the basis of signal integration in the ¹H NMR spectra.

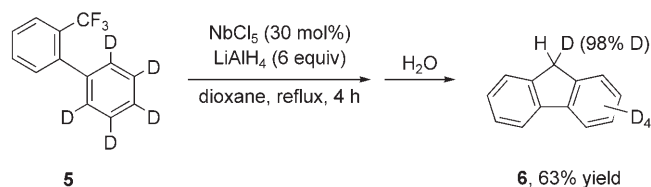
The kinetic isotope effect was not observed for the insertion process (Scheme 6). *o*-(*o'*-Deuteriophenyl)trifluorotoluene (**7**) gave a 1:1 mixture of 9-deuteriofluorene (**8**) and 4-deuteriofluorene (**9**). The products were analyzed by ¹H NMR spectroscopy and mass spectrometry.

Next, **1a** was treated with lithium aluminum deuteride (Scheme 7). In this case, no deuterium was incorporated into the product. It was found that lithium aluminum hydride is not involved in the reaction course leading to **2a**.

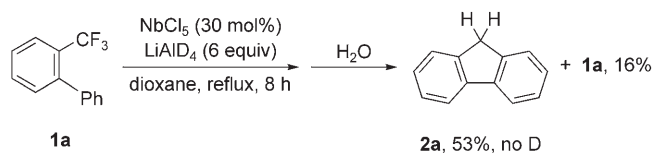
Table 4. Synthesis of fluorenes.

Entry	1	R	<i>t</i> [h]	2 [%]	3 [%]		
1		H	1a	4	83, 2a	3, 3a	
2 ^[a]		H	1a	4	72, 2a	7, 3a	
3		Me	1b	4	80, 2b	5, 3b	
4		<i>t</i> Bu	1c	4	82, 2c	6, 3c	
5		OEt	1d	4	92, 2d	5, 3d	
6		SMe	1e	4	89, 2e	4, 3e	
7		NMe ₂	1f	6	74, 2f	4, 3f	
8		F	1g	2	85, 2g	6, 3g	
9		SiMe ₃	1h	5	40, 2h	15, 3h ^[b]	
10		OEt	1i	4	 2i + 2j	80 (2i/2j' = 46:54)	4, 3i
11		Me	1j	4		81 (2j/2j' = 43:57)	5, 3j
12 ^[c]			1k	4	 2k	52, 2k	2, 3k
13			1l	6	 2l	86, 2l	5, 3l
14			1m	4	 2m	54, 2m	11, 3m
15 ^[c]			1n	4	 2n	62, 2n	19, 3n

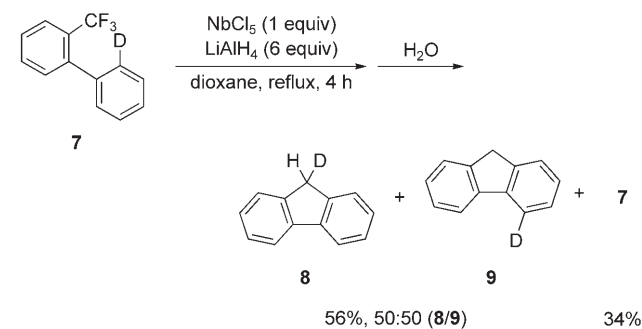
[a] NbCl₅ (10 mol %), LiAlH₄ (5 equiv). [b] Compound **1h** was recovered in 19% yield. [c] NbCl₅ (1.0 equiv), LiAlH₄ (10 equiv).



Scheme 5. Deuterium-labeling experiment 1.



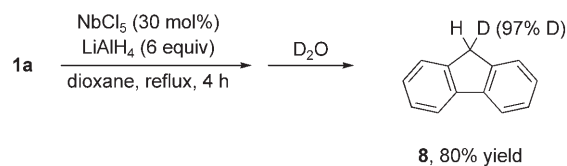
Scheme 7. Deuterium-labeling experiment 2.



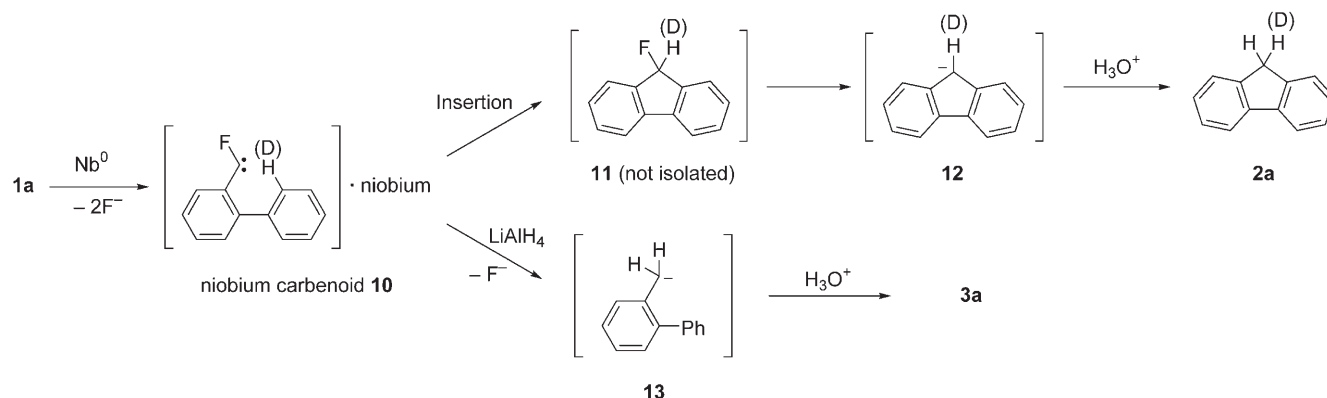
Scheme 6. Kinetic isotope effect.

Finally, the reaction of **1a** was quenched with deuterium oxide, and 9-deuteriofluorene **8** was obtained in good yield (Scheme 8).

We propose that the reaction proceeds via a niobium carbenoid intermediate (Scheme 9); niobium(V) chloride is reduced with lithium aluminum hydride to give Nb⁰ species



Scheme 8. Deuterium-labeling experiment 3.

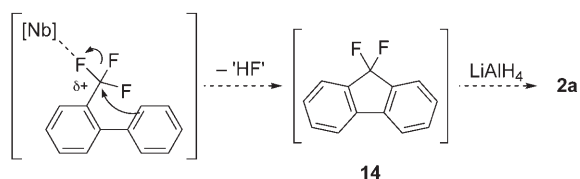


Scheme 9. Proposed mechanism.

(not shown).^[9] Compound **1a** and the Nb⁰ species generate niobium fluorocarbenoid intermediate **10** by elimination of two fluoride ions. Fluorocarbenoid **10** undergoes carbenoid insertion into the neighboring aromatic C–H bond. The resulting fluorofluorene intermediate **11** is further reduced under the reaction conditions to give fluorenyl anion (**12**).^[27] Protonation of **12** gives **2a**. The results of the deuterium-labeling experiments are well-rationalized by this mechanism.^[28]

On the other hand, we previously reported that fluorocarbenoid intermediate **10** is decomposed by lithium aluminum hydride to form the conventional reduction product,^[8b] **10** reacts with excess lithium aluminum hydride to give benzyl anion equivalent **13**. Intermediate **13** is protonated when the reaction is quenched with water to give **3a**. It is likely that the slow addition of lithium aluminum hydride suppresses the LiAlH₄-induced decomposition of **10** to achieve a high **2a/3a** ratio.

It must be emphasized that this reaction cannot be rationalized by the Friedel–Crafts-like mechanism (Scheme 10).



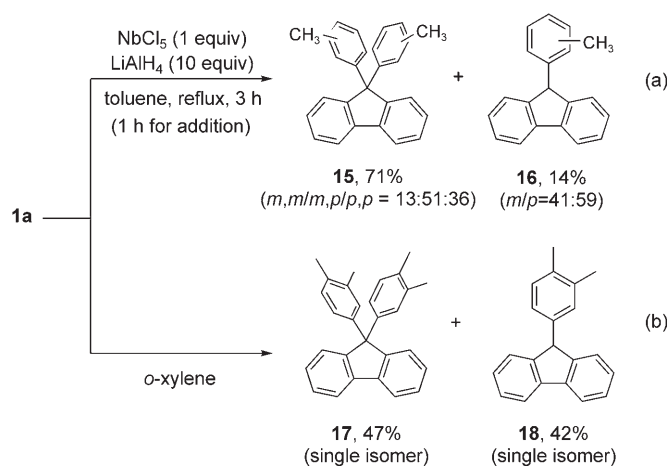
Scheme 10. Friedel–Crafts-like mechanism (rejected).

We previously speculated that the niobium-assisted intramolecular aromatic substitution affords 9,9-difluorofluorene (**14**).^[29] However, the *ortho*-hydrogen atom will not shift to the methylene moiety by following the mechanism.

The insertion of carbenoid centers into C–H bonds has been extensively studied in recent years with rhodium, copper, and other metal catalysts.^[30] However, these carbenoid species insert mainly into C(sp³)–H bonds, and insertions into aromatic C–H bonds are quite limited.^[31] We found that niobium carbenoids have remarkably high reactivity for insertion into aromatic C–H bonds.

Mechanistic Consideration II

In our previous communication,^[20] we reported that 9,9-diarylfuorenes were formed when the reaction was performed in aromatic solvents; **1a** was treated with a stoichiometric amount of niobium(V) chloride and 10 equivalents of lithium aluminum hydride in toluene (Scheme 11 a). We could

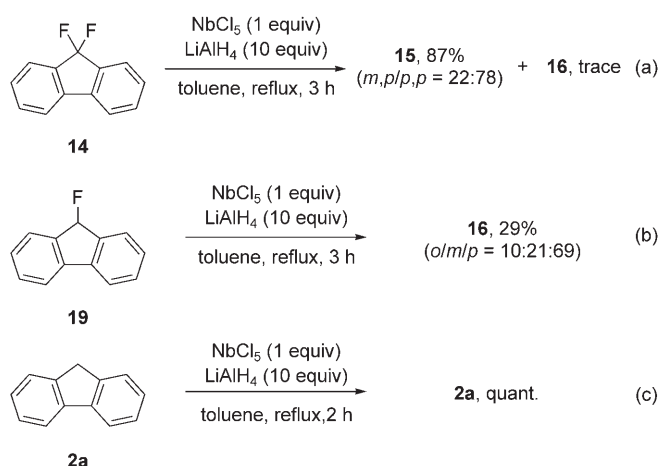


Scheme 11. Formation of 9,9-diarylfuorenes.

not detect parent fluorene **2a** by ¹H NMR spectroscopy. Instead, 9,9-ditolylfuorenes **15** and 9-tolylfuorenes **16** were obtained in good yields. Similar results were obtained when the reactions were carried out in *o*-xylene (Scheme 11 b).

On the other hand, **14**, which was separately prepared from commercially available 9-fluorenone and diethylamino-sulfur trifluoride (DAST),^[32] gave **15** and **16** under identical conditions (Scheme 12 a). 9-Fluorofluorene (**19**) and **2a** did not afford **15** (Scheme 12 b and c). These results suggest that difluorofluorene **14** is generated when the reaction is carried out in aromatic solvents.

This is apparently incompatible with our proposed mechanism, in which monofluorofluorene **11** is generated (Scheme 9). We now suppose that **11** is generated in dioxane through carbenoid insertion and that difluorofluorene **14** is generated in aromatic solvents by a Friedel–Crafts-like



Scheme 12. Survey of the intermediate.

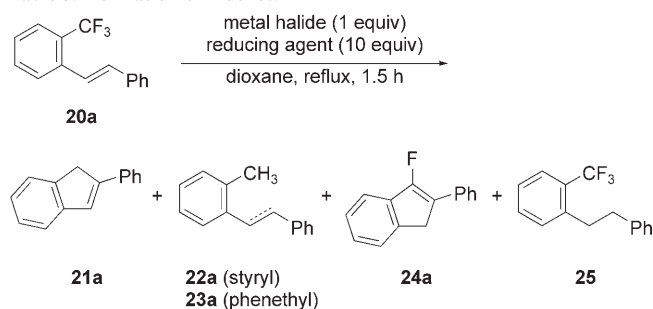
mechanism. It seems likely that Friedel–Crafts-type formation of **14** in aromatic solvents takes place more readily than in DME or dioxane because the former are less Lewis basic than the latter (Scheme 10).

Catalytic Synthesis of Indenes

It was found that carbenoid centers insert into not only aromatic C–H bonds but also alkenyl C–H bonds (Table 5).^[33] Insertions into alkenyl C–H bonds^[34] are more limited than those into aromatic C–H bonds.^[31]

o-Styryl- α,α,α -trifluorotoluene (**20a**), which was prepared by the Heck reaction of commercially available *o*-iodo- α,α,α -trifluorotoluene and styrene, gave desired indene **21a** in 64% yield under similar conditions (Table 5, entry 1). Compound **21a** was accompanied by conventional reduction

Table 5. Formation of indenenes.



Entry	Reagents	Yield [%]				
		21a	22a+23a (ratio)	24a	25	20a
1	NbCl ₅ , LiAlH ₄ ^[a]	64	22 (55:45)	–	–	–
2	TaCl ₅ , LiAlH ₄ ^[a]	42	23 (56:44)	11	–	–
3	WCl ₆ , LiAlH ₄ ^[a]	16	12 (83:17)	18	–	39
4	PdCl ₂ , LiAlH ₄ ^[a]	4	16 (76:24)	7	44	7
5	NbCl ₅ , Red-Al	11	71 (18:82)	6	–	–
6	NbCl ₅ , DIBAL	–	–	–	–	86
7	NbCl ₅ , NaBH ₄	–	–	–	–	97

[a] The suspension of LiAlH₄ in dioxane was added over 1.5 h. Red-Al = sodium bis(methoxyethoxy)aluminum hydride.

product **22a** and complete reduction product **23a** (22%, 55:45).

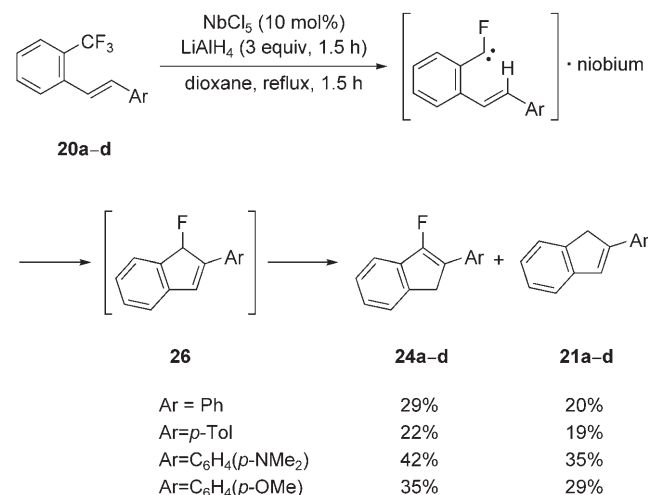
The product distribution was influenced by the choice of the reagents. It was found that the trend was similar to that observed for *o*-aryl trifluorotoluenes. The yield of **21a** decreased slightly and dramatically when TaCl₅ and WCl₆ were used, respectively (Table 5, entries 2 and 3). Notably, a small amount of 3-fluoroindene **24a**, in which one fluorine atom remained intact, was obtained in these cases. Red-Al gave complete reduction product **23a** preferentially (Table 5, entry 5). When mild reduction agents, such as DIBAL and sodium borohydride, were used, no reaction took place (Table 5, entries 6 and 7).

Interestingly, palladium(II) chloride gave a considerable amount of phenethyl trifluorotoluene **25**, in which the CF₃ group was not affected but the alkene moiety was saturated. This result clearly demonstrates the high fluorophilicity of the Nb⁰ species.

A variety of substituted indenenes could be synthesized by the Nb⁰ catalyst (Table 6). *o*-(β -Arylviny)trifluorotoluenes **20a–i** gave the corresponding 2-aryl indenenes **21a–i** in good yields (Table 6, entries 1–9). Both alkoxy and amine groups were completely tolerant to the reaction conditions. Trifluorotoluene **20j**, which bears a methyl group on the α position, smoothly gave the corresponding products **21j** and **21j'** (Table 6, entry 10). The reaction of **20k**, which bears a cyclic 2-indenyl moiety, furnished tetracyclic indenoindene **21k** (Table 6, entry 11).

Two of the most familiar methods of synthesizing indene derivatives are (Lewis) acid-mediated Nazarov-type cyclizations^[35] and intramolecular electrophilic aromatic substitutions.^[36] However, indenenes with complex structures, such as **21k**, are difficult to synthesize by the conventional methods. Our method, in which the carbenoid centers have direct access to C(sp²)–H bonds, realizes the facile synthesis of complex indenenes.

In general, the ratios of insertion product **21** to reduction products **22** and **23** were lower than those of *o*-aryl trifluoro-



Scheme 13. Formation of fluorindenenes. Tol = tolyl.

Table 6. Catalytic synthesis of arylindenes.

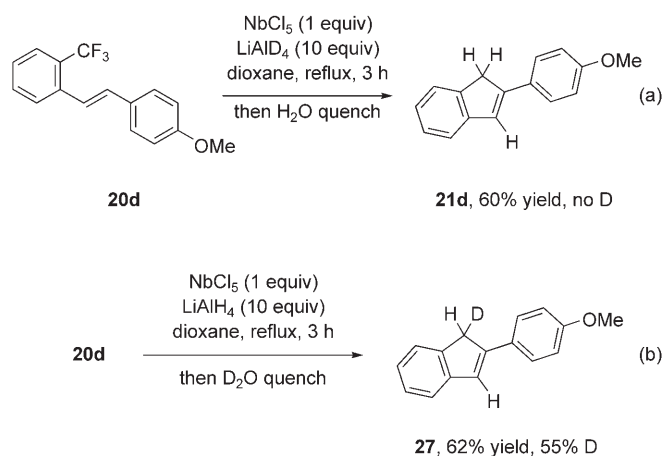
Entry	20	R	21	Yield [%]	22 + 23 [%] (ratio)
1			21a	64	22 (55:45)
2		R = Me, 20b		61, 21b	21 (52:48)
3		R = NMe ₂ , 20c		64, 21c	24 (83:17)
4		R = OMe, 20d		66, 21d	24 (54:46)
5		20e		62, 21e	23 (57:43)
6		20f		57, 21f	22 (100:0)
7		20g		62, 21g	20 (71:29)
8		20h		64, 21h	20 (100:0)
9 ^[a]		20i		61 (21i / 21i' = 32:68)	19 (88:12)
10		20j		61 (21j / 21j' = 80:20)	3 (75:25)
11		20k		68, 21k	5 (100:0)

[a] NbCl₅ (100 mol %), LiAlH₄ (10 equiv), 10 h.

toluenes. The rotation around the C(Ar)–C(alkenyl) axis should be responsible for the difference.

Fluoroindenes **24** were also obtained with niobium catalyst under mild conditions (Scheme 13). With lower catalyst loadings, smaller amounts of lithium aluminum hydride, and shorter reaction times, the formation of indenes **21a–d** was accompanied by that of **24a–d** in 29–42% yield. Compounds **24a–d** were generated by the isomerization of insertion products **26**.^[37]

Deuterium-labeling experiments gave essentially similar results to those of *o*-aryl trifluorotoluenes (Scheme 14). When the reaction was performed with lithium aluminum deuteride and quenched with water, no deuterium was incorporated into the product **21d** (Scheme 14a). On the other hand, when the reaction was performed with lithium aluminum hydride and quenched with deuterium oxide, 1-deuterioindene **27** was obtained (55% D; Scheme 14b).



Scheme 14. Deuterium-labeling experiments on *o*-alkenyltrifluorotoluene **20d**.

It was found that the reactivities of Nb⁰ catalyst toward *o*-alkenyl trifluorotoluenes are analogous to those toward *o*-aryl trifluorotoluenes.

Scope and Limitations

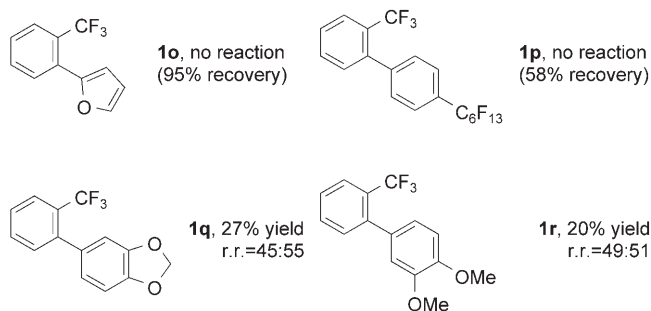
The reactions of fluoroalkyl substituents other than the CF₃ group were examined (Table 7). First, difluorotoluene deriv-

Table 7. Scope and limitations 1.

Entry	R	Ar	2a [%]	3a [%]	Recovery [%]
1	CHF ₂ (4)	Ph	12	62	–
2	CH ₂ F (28)	Ph	–	82	–
3	<i>n</i> -C ₆ F ₁₃ (29)	Ph	–	–	83 (29)

ative **4** was subjected to standard conditions to obtain fluorene (**2a**), albeit in low yield.^[38] On the other hand, when monofluorotoluene derivative **28** was used, **2a** was not obtained at all. It is likely that at least two fluorine atoms are necessary to generate the carbenoid center. The reaction of perfluorohexyl derivative **29** resulted in recovery of the starting material. The stability of the higher-order perfluoroalkyl group could not be overcome by the Nb⁰ catalyst.

Electron-rich **1o** was recovered in nearly quantitative yield (Scheme 15). The reductive C–F bond-activation pro-



Scheme 15. Scope and limitations 2 (30 mol% NbCl₅, 6 equiv LiAlH₄). r.r. = regioisomer ratio.

cess by Nb⁰ species (**1a**→**10** in Scheme 9) seems not to be suitable for the highly electron rich substrate. It is of great interest that electron-deficient **1p** was also recovered. The perfluoroalkyl substituent on the *ortho*-phenyl group seems to increase the global stability of **1p**. Compounds **1q** and **1r**, which bear two oxygen functionalities on the *ortho*-phenyl groups, gave low yields of the corresponding fluorenes. The reaction became complex in these cases.

(α -Styryl)trifluorotoluene **20l** and (β -alkylvinyl)trifluorotoluene **20m** gave complex mixtures (Table 8, entries 1 and

Table 8. Scope and limitations 3.^[a]

Entry	20	Yield [%]				
		21	22	23	20	
1		20l	–	–	–	17
2		20m	3	5	6	–
3		20n	–	–	–	64

[a] Conditions: NbCl₅ (1 equiv), LiAlH₄ (10 equiv), DME, reflux, 1.5 h.

2). β -Aryl groups on the alkenyl moieties were found to be essential for the formation of carbenoid centers because even conventional reduction products **22** and **23** were obtained only in miserable yields. (β -Perfluoroalkylvinyl)trifluorotoluene **20n** was stable under the same conditions and was recovered in 64% yield (Table 8, entry 3).

Conclusions

The chemical inertness of α,α,α -trifluorotoluene derivatives was overcome by the Nb⁰ catalyst. It is supposed that niobium fluorocarbenoid intermediates are generated from the CF₃ groups and that the resulting carbenoid centers undergo carbenoid insertion into neighboring aromatic and alkenyl C–H bonds. This is the first report that describes the direct C–C coupling reactions of C–F bonds with C–H bonds.

Experimental Section

General

1,4-Dioxane was distilled from LiAlH₄ after heating at reflux for 3 h. The distilled dioxane was stored over 4-Å molecular sieves under nitrogen atmosphere. Toluene was distilled after azeotropic removal of water and stored over 4-Å molecular sieves under nitrogen atmosphere. NbCl₅ was used as purchased from Sigma–Aldrich Co and handled under argon atmosphere. LiAlD₄ was purchased from Kanto Chemical Co., Inc. and used as obtained. All reactions were carried out under argon atmosphere.

Column chromatography was conducted on silica gel (PSQ 60B, Fuji Silysia Chemical, Ltd.). Preparative thin-layer chromatography (TLC) was conducted on silica gel (Wakogel B5-F, Wako Pure Chemical Industries). Purification by preparative HPLC was performed on an LC-918 instrument (Japan Analytical Industry Co., CHCl₃).

NMR spectra were recorded on Unity Inova-400 (Varian, Ltd., 400 MHz for ¹H, 100 MHz for ¹³C) and JNM-AI300 instruments (JEOL, 300 MHz for ¹H, 75 MHz for ¹³C) with CDCl₃ as solvent. Chemical shifts (δ) for ¹H are referenced to tetramethylsilane (TMS; δ = 0.00 ppm) as an internal standard. Chemical shifts (δ) for ¹³C are referenced to the solvent signal (CDCl₃, δ = 77.0 ppm). IR spectra were recorded on an FTIR-8600PC instrument (Shimadzu Co.) with CHCl₃ as solvent. Elemental analysis was carried out on an EA1110 instrument (Amco, Inc.). GC analysis was performed on a Hitachi G-5000 instrument (Hitachi Hitech, Ltd.). Low-resolution mass spectrometry (LRMS) was conducted with 70-eV electron impact ionization on a GCMS-QP5000 instrument (Shimadzu Co.).

Synthesis of Fluorenes

Preparation of *o*-aryl trifluorotoluenes: The preparations of **1a–g** and **1i–n** are described in our previous Supporting Information.^[20] Compound **1h** was prepared by the same procedure.

Typical procedure for the synthesis of substituted fluorenes (Table 4, entry 1): Apparatus: A reaction vessel was equipped with a dropping funnel, which contained a stirrer bar. The reaction apparatus was placed on a magnetic stirrer, and a second magnetic stirrer was placed on the side of the dropping funnel. The suspension of LiAlH₄ in dioxane was stirred by the second stirrer during addition of the suspension. Procedure: A solution of **1a** (209 mg, 0.941 mmol) in dioxane (8 mL) was added to NbCl₅ (77 mg, 0.28 mmol). Immediately after the flask was immersed in an oil bath at 110 °C, addition of a suspension of LiAlH₄ in dioxane (prepared from 214 mg, 5.64 mmol of LiAlH₄ and 4 mL of 1,4-dioxane) was started. The suspension of LiAlH₄ was added over 2 h. The reaction mixture was heated at reflux for a further 2 h, and the reaction was quenched with water at 0 °C. After 0.2 g of sodium tartrate was added, the mixture was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. Evaporation and purification by preparative TLC (SiO₂, hexane) gave **2a** (130 mg, 0.782 mmol, 83 % yield, *R*_f = 0.45).

Characterization of substituted fluorenes: The characterization data of **2a–g**, **2i–m**, **3a**, and **4** are described in our previous Supporting Information.^[20] Compounds **3b–n** were characterized by analogy.

2h: IR (CHCl₃): $\tilde{\nu}$ = 2957, 1406, 1250, 1088, 841 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 0.33 (s, 9H; SiMe₃), 3.91 (s, 2H; CH₂), 7.31 (t, ³*J*_(H,H) = 7.2 Hz, 1H; CH), 7.38 (t, ³*J*_(H,H) = 7.2 Hz, 1H; CH), 7.55 (d, ³*J*_(H,H) = 7.2 Hz, 2H; CH), 7.72 (s, 1H; CH), 7.79 (d, ³*J*_(H,H) = 7.6 Hz, 1H; CH), 7.80 ppm (d, ³*J*_(H,H) = 7.6 Hz, 1H; CH); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = -0.9, 36.8, 119.3, 120.0, 125.0, 126.7, 126.8, 129.9, 131.7, 138.7, 141.7, 142.3, 142.6, 143.3 ppm; MS (70 eV, EI): *m/z* (%) = 238 (28) [M]⁺, 223 (100) [M–CH₃]⁺, 165 (14) [M–SiMe₃]⁺.

Deuterium-labeling experiments: Compound **5** was prepared by the same procedure as for **1a**. Compound **7** was also prepared by the same procedure with 2-deuterioiodobenzene. 2-Deuterioiodobenzene was prepared as below.

Preparation of 2-deuterioiodobenzene: A solution of *o*-chlorobromobenzene (19.6 g, 102 mmol) in diethyl ether (40 mL) was added dropwise to a mixture of magnesium turnings (2.51 g, 103 mmol) in diethyl ether (10 mL). After the mixture was heated at reflux to initiate formation of the Grignard reagent, it was maintained at 0 °C. After 5.5 h of stirring, the reaction was quenched with D₂O (6 mL) at 0 °C. Diethyl ether was roughly removed by distillation under atmospheric pressure, then *o*-deuteriochlorobenzene was distilled under reduced pressure (76–100 mmHg, 33–63 °C). A mixture (7.5 g) of *o*-deuteriochlorobenzene and D₂O was obtained. D₂O was removed by adding anhydrous magnesium sulfate, and the drying agent was removed by filtration. The filtrate was again distilled to give the desired *o*-deuteriochlorobenzene in pure form (91 mmHg, 65–75 °C, 4.25 g, 37.4 mmol, 37 %). A solution of *o*-deuteriochlorobenzene (226 mg, 1.99 mmol) and iodomethane (290 mg, 2.04 mmol) in THF (1.5 mL) was added to a mixture of magnesium turnings (113 mg) in THF (0.5 mL). The mixture was heated at reflux for 5 h. The reaction was quenched with a solution of iodine (I₂, 1.34 g, 5.28 mmol) in THF (3 mL) at 0 °C. After excess iodine was removed with saturated aqueous Na₂SO₃, the products were extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate. The solvents were removed under vacuum, and purification by column chromatography gave 2-deuterioiodobenzene (189 mg, 0.92 mmol, 46 %). The deuterium content was estimated to be >99 % by mass spectrometry.

6 (Scheme 5): 1,2,3,4,9-Pentadeuteriofluorene: Deuterium incorporation was determined by signal integration in the ¹H NMR spectra. ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 3.85–3.91 (m, 1.02H; CHD), 7.30 (t, ³*J*_(H,H) = 8.0 Hz, 1H; CH), 7.38 (t, ³*J*_(H,H) = 8.0 Hz, 1H; CH), 7.54 (d, ³*J*_(H,H) = 8.0 Hz, 1H; CH), 7.80 ppm (d, ³*J*_(H,H) = 8.0 Hz, 1H; CH). Scanned ¹H and ¹³C NMR and mass spectra are provided in the Supporting Information.

Mixture of 9-deuteriofluorene (**8**) and 4-deuteriofluorene (**9**) (1:1; Scheme 6): ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 3.85–3.90 (m, 1.54H; CHD + CH₂), 7.29 (t, ³*J*_(H,H) = 8.0 Hz, 2H; CH), 7.37 (t, ³*J*_(H,H) = 8.0 Hz, 2H; CH), 7.54 (d, ³*J*_(H,H) = 8.0 Hz, 2H; CH), 7.78 ppm (d, ³*J*_(H,H) = 8.0 Hz, 1.50H; CH + CD). Scanned ¹H and ¹³C NMR and mass spectra are provided in the Supporting Information.

8 (Scheme 8): ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 3.87 (s, 1.03H; CHD), 7.29 (t, ³*J*_(H,H) = 8.0 Hz, 2H; CH), 7.37 (t, ³*J*_(H,H) = 8.0 Hz, 2H; CH), 7.54 (d, ³*J*_(H,H) = 8.0 Hz, 2H; CH), 7.78 ppm (d, ³*J*_(H,H) = 8.0 Hz, 2H; CH). The scanned ¹H NMR spectrum is provided in the Supporting Information.

Synthesis of 9-arylated and 9,9-diarylated fluorenes (Scheme 11): The reaction in toluene is described (Scheme 11 a). The reaction was carried out under conditions similar to those for the synthesis of **2a**, with **1a** (79 mg, 0.36 mmol), LiAlH₄ (132 mg, 3.47 mmol), and NbCl₅ (88 mg, 0.33 mmol) in toluene. The crude mixture was purified by column chromatography (SiO₂, hexane) to give **15** (88 mg, 0.25 mmol, 71 % yield, *R*_f = 0.50 (hexane)) and **16** (13 mg, 0.05 mmol, 14 % yield, *R*_f = 0.53 (hexane)). Regioisomer ratios of **15** and **16** were determined by GC analysis to be 13:51:36 (*m,m/m,p/p*) and 41:59 (*m/p*), respectively (Ultra ALLOY-8H, Hitachi Hitech, Ltd.).

Characterization data of 9,9-diarylfuorenes: Characterization data of di-*tolyl*fluorenes **15** (*para,para*, *meta,para*, and *meta,meta* isomers) and mono-*tolyl*fluorenes **16** (*para* and *meta* isomers) are described in our previous Supporting Information.^[20]

17: 9,9-Bis(3,4-dimethylphenyl)fluorene: IR (CHCl₃): $\tilde{\nu}$ = 3007, 1501, 1448, 1250, 756 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 2.11 (s, 6H; CH₃), 2.17 (s, 6H; CH₃), 6.93 (d, ³*J*_(H,H) = 6.0 Hz, 2H; CH), 6.94 (s, 2H; CH), 6.96 (d, ³*J*_(H,H) = 6.0 Hz, 2H; CH), 7.23 (t, ³*J*_(H,H) = 7.6 Hz, 2H; CH), 7.31 (t, ³*J*_(H,H) = 7.6 Hz, 2H; CH), 7.40 (d, ³*J*_(H,H) = 7.6 Hz, 2H; CH), 7.72 ppm (d, ³*J*_(H,H) = 7.6 Hz, 2H; CH); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 19.3, 19.9, 64.8, 120.0, 125.7, 126.1, 127.2, 127.6, 129.2, 129.3, 134.7, 136.2, 140.0, 143.5, 151.7 ppm; MS (70 eV, EI): *m/z* (%) = 374 (100) [M]⁺, 359 (55) [M–CH₃]⁺, 269 (41) [M–C₆H₃Me₂]⁺.

18: 9-(3,4-Dimethylphenyl)fluorene: The ¹H NMR spectrum is in complete agreement with those in the literature.^[39]

14: 9,9-Difluorofluorene: Prepared according to the method in the literature.^[32] The characterization data are described in our previous Supporting Information.^[20]

19: 9-Fluorofluorene: Colorless solid, prepared according to the method in the literature.^[32] This material readily underwent decomposition at room temperature after concentration and was used just after purification. ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 6.32 (d, ²*J*_(H,F) = 54 Hz, 1H; CH), 7.32 (t, ³*J*_(H,H) = 8.0 Hz, 2H; CH), 7.43 (t, ³*J*_(H,H) = 8.0 Hz, 2H; CH), 7.64 ppm (d, ³*J*_(H,H) = 8.0 Hz, 4H; CH); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 91.6 (d, ¹*J*_(C,F) = 177 Hz), 120.1, 125.9, 128.0, 130.2, 140.8 (d, ³*J*_(C,F) = 3.0 Hz), 141.0 ppm (d, ²*J*_(C,F) = 15 Hz).

Synthesis of Indenes

Preparation of *o*-alkenyl trifluorotoluenes: The preparation and characterization data of **20a–k** are described in our previous Supporting Information.^[33]

Typical procedure for the synthesis of substituted indenes (Table 6, entry 1): A solution of *o*-styryl- α,α,α -trifluorotoluene (**20a**; 209 mg, 0.941 mmol) in dioxane (8 mL) was added to NbCl₅ (77 mg, 0.28 mmol) in a reaction vessel. Immediately after the flask was immersed in an oil bath (110 °C), a suspension of LiAlH₄ in dioxane (prepared from 214 mg of LiAlH₄ and 4 mL of 1,4-dioxane, 5.64 mmol) was added over 1.5 h. The reaction mixture was heated at reflux for a further 1.5 h, and the reaction was quenched with water at 0 °C. Sodium tartrate (\approx 0.2 g) was added for ease of operation, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate. Evaporation and purification by column chromatography (SiO₂, hexane) gave a mixture of **21a**, **22a**, and **23a** (130 mg). The mixture was analyzed by ¹H NMR spectroscopy and GC–MS, and the yields of the products were determined by signal integration in the ¹H NMR spectra (**21a**: 64 %; **22a**: 12 %; **23a**: 10 %).

Characterization of substituted indenenes: Indenenes **21** were isolated from **22–24** by preparative HPLC. The characterization data of **21a–k** are described in our previous Supporting Information.^[33]

24a: 3-Fluoro-2-phenylindene: The ¹H NMR spectrum was in complete agreement with those in the literature.^[40] The structures of **24b–d** were determined by analogy with their ¹H NMR spectra.

Deuterium-labeling experiments: **27**: 1-Deuterio-2-(*p*-methoxyphenyl)indene (Scheme 14b): ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ = 3.70–3.76 (m, 1.45H; CDH), 3.83 (s, 3H; OCH₃), 6.91 (d, ³J_(H,H) = 8.0 Hz, 2H; CH), 7.08 (s, 1H; CH), 7.14 (t, ³J_(H,H) = 8.0 Hz, 1H; CH), 7.24 (t, ³J_(H,H) = 8.0 Hz, 1H; CH), 7.36 (d, ³J_(H,H) = 8.0 Hz, 1H; CH), 7.44 (d, ³J_(H,H) = 8.0 Hz, 1H; CH), 7.56 ppm (d, ³J_(H,H) = 8.0 Hz, 2H; CH). The scanned ¹H spectrum is provided in the Supporting Information.

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