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$InCl_3/I_2$-Catalyzed Cross-Coupling of Alkyl Trimethylsilyl Ethers and Allylsilanes via an in Situ Derived Combined Lewis Acid of $InCl_3$ and Me_3SiI

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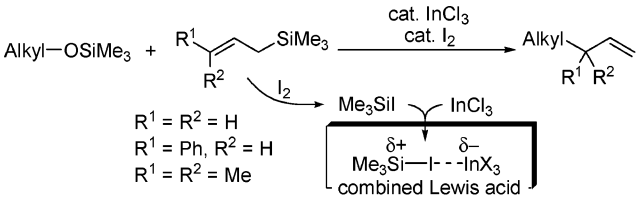
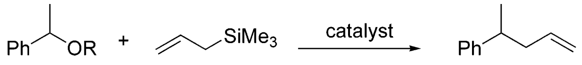
Received July 12, 2007



Direct $C_{sp3}-C_{sp3}$ coupling of various aliphatic trimethylsilyl ethers and allylsilanes is effectively catalyzed by $InCl_3$ and I_2. The transformation is thought to involve an in situ-derived combined Lewis acid of $InCl_3$ and Me_3SiI. The reaction can be used for the construction of quaternary−quaternary and quaternary−tertiary carbon−carbon bonds. This system enabled a highly chemoselective coupling to be conducted with a trimethylsilyl ether including an aryl halide moiety. Furthermore, couplings were possible using an alkynyltrimethylsilane and a trimethylsilyl ketene acetal.

Metal-catalyzed cross-coupling is one of the most important carbon−carbon bond-forming reactions in organic synthesis, and its application to the use of inexpensive and readily available substrates, such as alcohols[1] and their derivatives, is of current interest. However, this is a considerable challenge due to the strength of RC−OR′ bond and the poor leaving ability of the OR′ component. Recently, Gevorgyan et al.[2] demonstrated that a strong Lewis acid like $B(C_6F_5)_3$ promoted the substitution of the acetoxy group with carbon nucleophiles in high yield and the substitution of the hydroxyl group in low yield, but the siloxy group was not examined (Figure 1). Furthermore, Cho et al.[3] reported that $InBr_3$ itself also promoted the substitution of the acetoxy group, but not the hydroxyl group. The leaving ability is generally arranged in the following order: OAc > OH ≫ $OSiMe_3$. However, direct substitution of siloxy groups, which are widely utilized as protecting groups, would be a very important transformation protocol.[4] Such a method would circumvent the need for deprotection of silyl-derivatized hydroxyls and their subsequent transformation into good leaving groups, such as halides and esters, in preparation for coupling. As noted in Figure 1, our combined system involving indium and silicon reversed the reactivity order of acetoxy and hydroxyl moieties.[5] In view of this situation, our group focused on the direct substitution of siloxy moiety.



catalyst	OR		
	$OSiMe_3$	OH	OAc
$B(C_6F_5)_3$ (ref. 2)	0%	15-20%	96%
$InBr_3$ (ref. 3)	-	0%	38% (95% at 40 °C)
In/Si Combined Lewis Acid	***This Study***	77%	trace

FIGURE 1. Reverse of reactivity order.

A few direct couplings between silyl ethers and allylic silanes which have been catalyzed by such the Lewis acids as Ph_3CCl/NaTFPB[6] and Ti−fluoride complex have been reported.[7] However, these elaborately prepared Lewis acid catalysts are limited to the coupling with benzylic silyl ethers or silyl acetals that form very stable carbocations. The coupling reaction promoted readily by $ZnCl_2$ has been reported, but is also limited to the allylic silyl ethers.[8] Simple tertiary aliphatic silyl ethers have not been used in such couplings[9] but would be of considerable value in the construction of quaternary carbon centers. Moreover, only a few reports of $C_{sp3}-C_{sp3}$ coupling via simple tertiary aliphatic organic halides are known,[10] given their tendency to undergo the β-elimination.[11] In this paper, we wish to report the cross-coupling reaction of simple tertiary aliphatic silyl ethers and allylsilanes catalyzed by $InCl_3$ and I_2 via a putative, in situ-derived combined Lewis acid of $InCl_3$ and Me_3SiI. Our system is very convenient and characteristically works just when the both components are combined, while each of them separately has no activity.

We have previously reported the direct allylation of alcohols effectively catalyzed by the combined Lewis acid system of $InCl_3/Me_3SiBr$.[5] We therefore tried to apply the system to the direct allylation of the simple tertiary aliphatic silyl ether **1a**

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(1) For recent reviews, see: (a) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647−2656. (b) Muzart, J. *Tetrahedron* **2005**, *61*, 4179−4212.

(2) (a) Rubin, M.; Gevorgyan, V. *Org. Lett.* **2001**, *3*, 2705−2707. (b) Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1999−2001.

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(5) (a) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516−8522. (b) Saito, T.; Yasuda, M.; Baba, A. *Synlett* **2005**, 1737−1739. (c) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1414−1416.

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(7) For the asymmetric transformation of silyl ethers mediated by titanium(IV) complexes, see: Braun, M.; Kotter, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 514−517.

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(9) Dau-Schmidt, J.-P.; Mayr, H. *Chem. Ber.* **1994**, *127*, 205−212.

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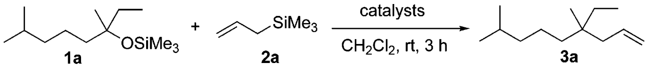
(11) For recent reviews of $C_{sp3}-C_{sp3}$ coupling, see: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. (b) Netherton, M. R.; Fu. G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532.

10.1021/jo7015289 CCC: $37.00

TABLE 1. Direct Coupling by Combined Lewis Acid[a]



entry	catalyst (mol %)	yield (%)
1	$InCl_3$ (5) + Me_3SiCl (20)	32
2	$InCl_3$ (5) + Me_3SiBr (20)	34
3	$InCl_3$ (5) + Me_3SiI (20)	61
4	$InCl_3$ (5) + I_2 (20)	76
5	I_2 (20) or Me_3SiI (20)	0
6	$InCl_3$ (5)	0
7	$AlCl_3$ (5) + I_2 (20)	0
8	$B(C_6F_5)_3$ (5) + I_2 (20)	0
9	$ZnCl_2$ (5) + I_2 (20)	27
10	$Yb(OTf)_3$ (5) + I_2 (20)	26

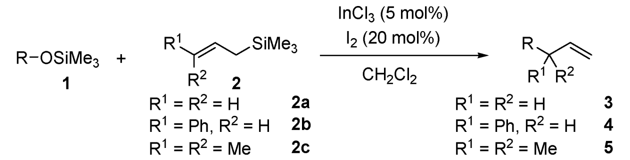
[a] All reactions were carried out in dichloromethane (1 mL) with allylsilane **2a** (3.0 mmol) and silyl ether **1a** (1.0 mmol) at rt.

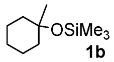
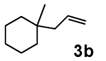
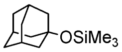
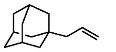
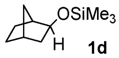
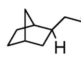
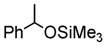
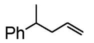
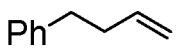
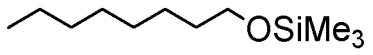
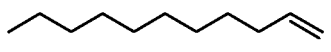
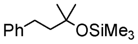
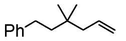
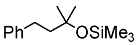
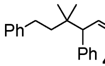
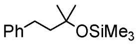
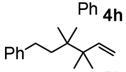
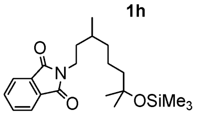
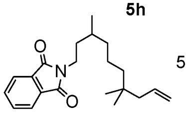
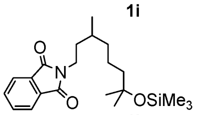
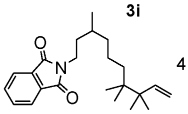
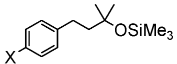
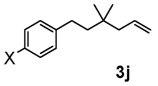
with allylsilane **2a**, and the desired product **3a** was obtained in only 34% yield (Table 1, entry 2). Using a combination of $InCl_3$/Me_3SiI, which represents stronger Lewis acidity,[5a] increased the yield up to 61% at room temperature in dichloromethane (entry 3). The highest yield (76%) was obtained by means of the combination of $InCl_3$ and I_2, where Me_3SiI is presumably generated in situ from I_2 and allylsilane **2a** (entry 4).[12] The sole use of $InCl_3$ or Me_3SiI showed no activity (entries 5 and 6). Representative Lewis acids such as $AlCl_3$ and $B(C_6F_5)_3$ were ineffective, even in the presence of I_2 (entries 7 and 8). Interestingly, the milder acids, $ZnCl_2$ and $Yb(OTf)_3$,[13] gave the desired product in low yields (entries 9 and 10).

Direct coupling of a variety of silyl ethers **1** with allylsilanes **2** was investigated under the optimized conditions (Table 2).

The cyclic tertiary silyl ether **1b** was allylated in good yield (entry 1). The transformation of adamantyl silyl ether **1c** into the desired product **3c** proceeded in 77% yield at 70 °C (entry 2). In the case of secondary ethers, norbornyl and benzylic systems were easily allylated, and the former gave the product **3d** as a single isomer (entries 3 and 4). Benzyl silyl ether **1f** was also allylated using the combined Lewis acid system, although simple normal silyl ether **1g** was unreactive (entries 5 and 6). These results strongly suggest that our system proceeds through the S_N1 mechanism including a carbocation. The tertiary aliphatic silyl ether **1h** was transformed to the corresponding coupling products **3h**, **4h**, and **5h** from allyl-, cynnamyl-, and prenylsilane in 73, 66, and 81% yields, respectively (entries 7, 8, and 9). The reaction conditions are compatible with phthalimide moiety to give the allylated and prenylated products **3i** and **5i** in moderate yields (entries 10 and 11). The formation of carbon skeletons connecting two quaternary carbons was accomplished by means of the $InCl_3$/Me_3SiI system (entries 9 and 11). Our system also tolerates the phenolic OH to give the desired product **3j** in 83% yield (entry 12). The silyl ethers bearing chlorine and bromine moieties were transformed to the desired products **3k** and **3l** without affecting the halide moieties (entries 13 and 14).

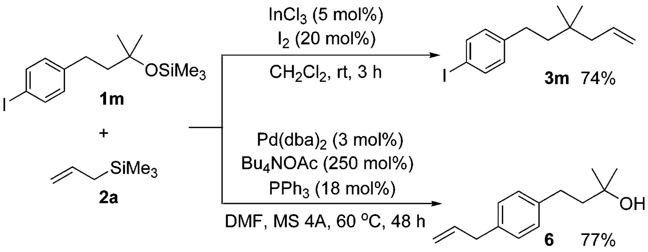
TABLE 2. Direct Allylation of Silyl Ethers by $InCl_3$/Me_3SiI[a]



entry	silyl ether	allylsilane	conditions	product	yield (%)
1[b]	 **1b**	**2a**	rt, 3 h	 **3b**	70
2[c]	 **1c**	**2a**	70 °C, 1 h	 **3c**	77
3	 **1d**	**2a**	rt, 3 h	 **3d**	90
4	 **1e**	**2a**	rt, 30 min	 **3e**	88
5[d]	 **1f**	**2a**	rt, 1 h	 **3f**	70
6[c]	 **1g**	**2a**	70 °C, 1 h	 **3g**	0
7	 **1h**	**2a**	rt, 3 h	 **3h**	73
8[e]	 **1h**	**2b**	rt, 3 h	 **4h**	66
9	 **1h**	**2c**	rt, 3 h	 **5h**	81
10[b]	 **1i**	**2a**	rt, 3 h	 **3i**	58
11[b]	 **1i**	**2c**	rt, 3 h	 **5i**	41
					
12[e]	X = OH **1j**	**2a**	rt, 3 h	**3j**	83
13	Cl **1k**	**2a**	0 °C to rt, 3 h	**3k**	82
14[c]	Br **1l**	**2a**	50 °C, 3 h	**3l**	78

[a] Reactions were carried out in dichloromethane (1 mL) with silyl ether **1** (1.0 mmol), silyl nucleophile **2** (3.0 mmol), I_2 (0.2 mmol), and $InCl_3$ (0.05 mmol) at rt unless otherwise stated. [b] Allylsilane (6 mmol). [c] 1,2-Dichloroethane (2 mL) was used as a solvent. [d] Allylsilane (4 mmol). [e] Allylsilane (5 mmol).

SCHEME 1. Chemoselective Allylation toward Iode-Substituted Silyl Ether



Even when the silyl ether **1m** including the iodine moiety was used, our system selectively provided the silioxy-coupling product **3m** in 74% yield (Scheme 1). This transformation was used to compliment allylation to the palladium-catalyzed Hiyama-coupling reaction with the aryl iodide to give **6**.[14]

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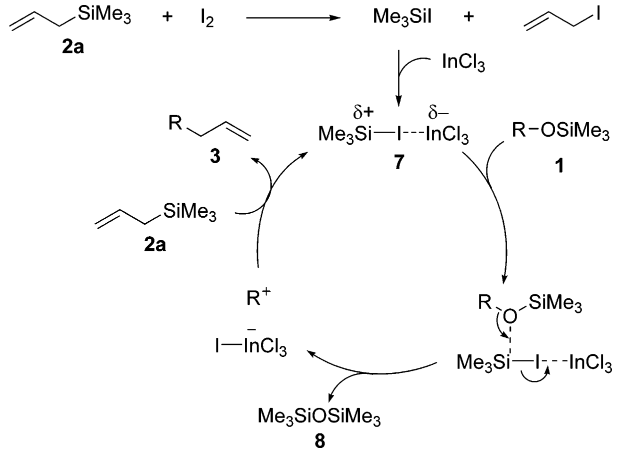
[12] (a) Jung, M. E.; Blumenkopf, T. A. *Tetrahedron Lett.* **1978**, *19*, 3657−3660. (b) For a review of silicon Lewis acids, see: Dilman, A. D.; Loffe, S. L. *Chem. Rev.* **2003**, *103*, 733−772.

[13] Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159−161.

[14] Jeffery, T. *Tetrahedron Lett.* **2000**, *41*, 8445−8449.

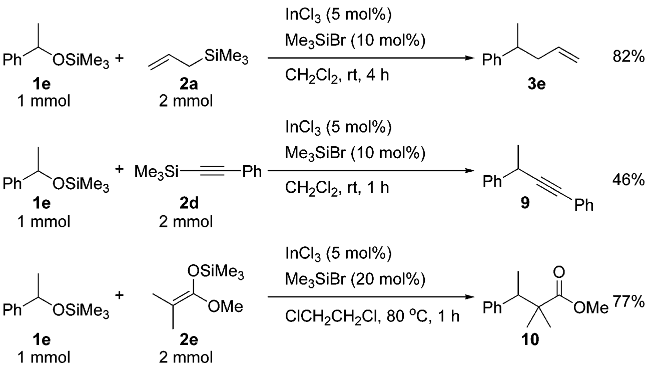
SCHEME 2. Plausible Mechanism



Scheme 2 proposes a plausible reaction route for the direct coupling between silyl ether **1** and allylsilane **2a** catalyzed by $InCl_3/I_2$ combined system (Scheme 2). At first, I_2 reacts with **2a** to give Me_3SiI[12] which generates the combined Lewis acid **7**. The Lewis acidity of the silicon center is enhanced by coordination from iodine to indium trichloride. The C−O bond of **1** is activated by the coordination from the siloxy oxygen to the silicon center of the combined catalyst to form a carbocation and hexamethyldisiloxane (**8**). Then, nucleophilic attack of **2a** on the carbocation gives the coupling product **3** with regeneration of the combined catalyst ($InCl_3/Me_3SiI$). It is noted that the low oxophilicity of the indium species aids in completing the catalytic cycle.[5,15] If stronger, the promoter species would be trapped by siloxane. The fact that **7** is the true catalyst is supported by the result of the reaction of **1a** with **2a** in the presence of $InCl_3$, Me_3SiI and allyl iodide.[16] In contrast to the reaction with alcohols, Me_3SiI is hardly decomposed because of the absence of active proton, and the facile formation of $Me_3SiOSiMe_3$ **8** may prevent the β-elimination, as seen for tertiary alcohols or halides.

The benzylic silyl ether **1e** coupled with the allylsilane **2a** in good yield under the mild combined Lewis acid of $InCl_3$ and Me_3SiBr (Scheme 3). This system can be applied to other types of nucleophiles. The alkynylsilane **2d** gave the product **9** in an α-addition manner. The coupling with trimethylsilyl ketene acetal **2e** smoothly proceeded to afford the desired ester **10** in high yield.[17]

SCHEME 3. Direct Coupling by Combined Lewis Acid of $InCl_3/Me_3SiBr$



In conclusion, we have demonstrated the direct formation of quaternary carbon centers by the direct coupling reaction between tertiary aliphatic silyl ethers and allylsilanes by the catalytic use of the indium-silicon combined system. The system has high chemoselectivity for the coupling with silyl ether moieties in contrast to Pd-catalyzed coupling.

Experimental Section

Typical Procedure for Allylation of 1a (Table 1, Entry 3). To a suspended solution of $InCl_3$ (0.05 mmol) and allyltrimethylsilane **2a** (3 mmol) in CH_2Cl_2 (1 mL) was added I_2 (0.2 mmol). To the mixture was added 3,7-dimethyl-3-trimethylsiloxyoctane **1a** (1.0 mmol) at room temperature. The mixture was stirred for 3 h at room temperature and then quenched by saturated $NaHCO_3$ aq (30 mL). The mixture was extracted with diethyl ether (10 × 3 mL). The collected organic layer was dried ($MgSO_4$). The evaporation of the ether solution gave the crude product which was analyzed by NMR. The details of further purification performed for the new compounds are described in the Supporting Information.

Hiyama Cross-Coupling Reaction of 2a with 1m (Scheme 1). A suspended solution of Bu_4NOAc (7.5 mmol) and 4A MS in DMF (6 mmol) was stirred for 1 h. To the stirred solution were added $Pd(dba)_2$ (0.12 mmol), PPh_3 (0.54 mmol), 4-(4-iodophenyl)-2-methyl-2-trimethylsiloxybutane **1m** (3 mmol), and allyltrimethylsilane **2a** (15 mmol). The reaction mixture was stirred at 60 °C for 40 h. After the mixture was cooled to room temperature, diethyl ether (10 mL) was added and the resulting mixture filtered over Celite. The filtrate was washed with water (10 mL) and dried over $MgSO_4$. The evaporation of the ether solution gave the crude product which was analyzed by NMR. The details of further purification performed for the new compounds are described in the Supporting Information.

Allylation of 1e Using Combined Lewis Acid of $InCl_3/Me_3SiBr$ (Scheme 3). To a mixture of $InCl_3$ (0.05 mmol) and 1-phenylethanol **1e** (1.0 mmol) in CH_2Cl_2 (1 mL) was added allyltrimethylsilane **2a** (2.0 mmol) and Me_3SiBr (0.1 mmol) under nitrogen. The mixture was stirred for 4 h at room temperature and then quenched with saturated $NaHCO_3$ aq (30 mL). The mixture was extracted with diethyl ether (10 × 3 mL). The collected organic layer was dried ($MgSO_4$). The evaporation of the ether solution gave the crude product which was analyzed by NMR. The details of further purification performed for the new compounds are described in the Supporting Information.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research on Priority Areas (No. 18065015, "Chemistry of Concerto Catalysis" and No. 19027038, "Synergistic Effects for Creation of Functional Molecules") and for Scientific Research (No. 19550038) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. M.Y. acknowledges financial support from Tokuyama Science Foundation, Mitsubishi Chemical Corporation Fund, and Kansai Research Foundation for Technology Promotion (KRF).

Supporting Information Available: Reaction procedures and spectroscopic details of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7015289

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(16) The reaction of **1a** (1 mmol) with **2a** (3 mmol) in the presence of $InCl_3$ (0.05 mmol), Me_3SiI (0.2 mmol), and allyl iodide (0.2 mmol) at room temperature afforded **3a** in 59% yield.

(17) In cases of the alkynylsilane and the silyl enolate, $InCl_3/Me_3SiBr$ system was superior to $InCl_3/Me_3SiI$ system.