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Direct Coupling Reaction between Alcohols and Silyl Compounds: Enhancement of Lewis Acidity of Me_3SiBr Using $InCl_3$

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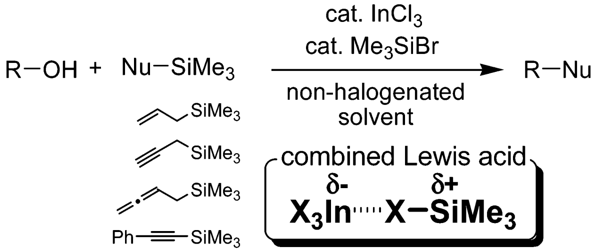

The combination of $InCl_3$ and Me_3SiBr provided an enhanced Lewis acid system that can be used to promote a wide range of direct coupling reactions between alcohols and silyl nucleophiles in non-halogenated solvents, such as hexane or MeCN. The enhanced Lewis acidity of this system was measured by the ^{13}C NMR in terms of the coordination to an alcohol. Moreover, the interaction between Me_3SiBr and the In(III) species was revealed by ^{29}Si NMR spectral analysis. Highly chemoselective allylations toward a hydroxyl moiety over ketone and acetoxy ones have been demonstrated.

Introduction

Lewis acid-promoted carbon−carbon bond formation is one of the most important processes in organic syntheses. Classically, Friedel−Crafts, ene, Diels−Alder, Mukaiyama, and Hosomi−Sakurai reactions have been mediated by typical Lewis acids, such as $AlCl_3$, $TiCl_4$, $BF_3\cdot OEt_2$, or $SnCl_4$, in which the elements used as Lewis acids have all its own characteristic features.[1] Among them, group 13 elements, aluminum, and boron are the most traditional and representative Lewis acids, but any practical utilizations of indium species had been scarcely exploited because of its lower Lewis acidity.[2] Over the past decade, indium species, however, have been paid much attention owing to their moderate Lewis acidity and water tolerance, applying to catalytic reactions under protic conditions.[3] In a series of these reactions, the protection of alcohols has been reported, but there are few reports for the application for C−C bond formation using alcohols.[4] Since alcohols are common and important compounds for natural products and key precursors for other functionalized compounds, such as carbonyls, ethers, and alkenes, the C−C bond formation by direct substitution of their hydroxyl groups would be a quite important process to provide useful building blocks in organic synthesis. However, the low leaving ability of the hydroxyl group often retards the direct substitution.[5]

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(1) For an excellent and comprehensive use of Lewis acids in organic synthesis, see: *Lewis Acids in Organic* Synthesis; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vols. 1 and 2.

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(3) (a) Frost, C. G.; Hartley, J. P. *Mini-Rev. Org. Chem*. **2004**, *1*, 1−7. (b) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015−3019. (c) Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16−22. (d) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347−2356. (e) Araki, S.; Hirashita, T. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 8, pp 323−386.

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10.1021/jo061512k CCC: $33.50

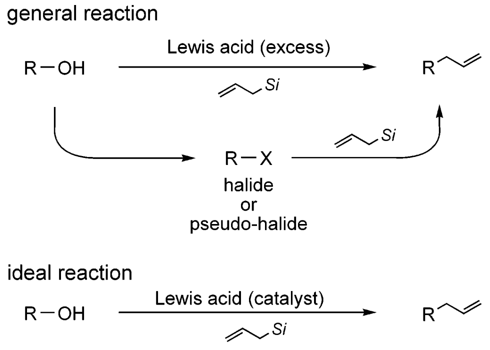
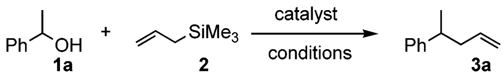


FIGURE 1. Lewis acid-mediated allylation of alcohol.

Direct substitution of alcohols with allylsilane was first demonstrated by Cella,[6] which some groups have also developed.[7] All examples, however, have required excessive amounts of Lewis acids. To avoid the excessive use of acid, the hydroxy moieties have to be transformed into their corresponding good leaving groups, such as halogens or related moieties, before treatment with nucleophiles (Figure 1).[8−11] The development of an efficient and practical method for the catalytic substitution of alcohols is in demand and still a challenging goal.

Although a few examples of catalytic allylations of alcohols with allyltrimethylsilane were reported using such acids as HN(SO$_2$F)$_2$[12] and B(C$_6$F$_5$)$_3$,[10] these procedures are limited to the employment of alcohols possessing strong cation-stabilizing aromatic substituents.[13,14] We have recently overcome this problem by developing the InCl$_3$-catalyzed direct substitution of various alcohols.[15] In any case of direct allylations, including ours, the use of environmentally hazardous halogen-containing solvents, such as dichloromethane or 1,2-dichloroethane, is essential. In this context, the development of a new direct substitution method of alcohols and the replacement of the halogenated solvent are both very important objectives. Recently, we have preliminarily developed a non-halogenated version promoted by the combination catalyst of InCl$_3$ and Me$_3$SiBr.[16] Herein, we wish to report the systematic studies, including NMR observation, of combined active species and some characteristic applications to chemoselective reactions.

TABLE 1. Allylation by Using Combined Lewis Acid[a]



entry	catalyst (mol %)	solvent	conditions	yield (%)
1[b]	InCl$_3$ (5)	ClCH$_2$CH$_2$Cl	80 °C, 3 h	51
2	InCl$_3$ (5)	hexane	reflux, 8 h	0
3	InCl$_3$ (5) + Me$_3$SiBr (10)	hexane	rt, 2 h	77
4	Me$_3$SiBr (10)	hexane	rt, 8 h	0
5	InCl$_3$ (5) + Me$_3$SiBr (10)	CH$_2$Cl$_2$	rt, 2 h	66
6	InCl$_3$ (5) + Me$_3$SiBr (10)	toluene	rt, 2 h	66
7	InCl$_3$ (5) + Me$_3$SiBr (10)	MeCN	rt, 2 h	22
8	InCl$_3$ (5) + Me$_3$SiBr (10)	Et$_2$O	rt, 2 h	2
9	InCl$_3$ (5) + Me$_3$SiBr (10)	THF	rt, 2 h	0

[a] Reactions were carried out in a solvent (1 mL) with allylsilane **2** (2.0 mmol) and alcohol **1a** (1.0 mmol). [b] See ref 15a.

Results and Discussion

1. Catalytic Allylation of Alcohols with Allyltrimethylsilane. We have previously reported the direct allylation of 1-phenylethanol (**1a**) with allyltrimethylsilane (**2**) in 1,2-dichloroethane at 80 °C in the presence of a catalytic amount of InCl$_3$ (Table 1, entry 1).[15a] When the solvent was changed to hexane, no reaction was observed even under reflux conditions (entry 2). To our delight, however, the combined use of InCl$_3$ and Me$_3$SiBr as a catalyst was found to give the desired product **3a** in 77% yield at room temperature (entry 3). Since Me$_3$SiBr did not exhibit any catalytic ability on its own, the combination was essential for the allylation (entry 4).[17] It is noteworthy that halogenated solvent was no longer requisite because only moderate yield was obtained in CH$_2$Cl$_2$ (entry 5). While the reaction in toluene gave **3a** in 66% yield (entry 6), the use of coordinative solvents resulted in low yields (entries 7−9). In particular, strong coordination of Et$_2$O and THF completely shut down the reaction. Other Lewis acids, such as BF$_3$·OEt$_2$, AlCl$_3$, GaCl$_3$, Yb(OTf)$_3$,[18] Sc(OTf)$_3$, ZnCl$_2$, BiCl$_3$,[19]

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(12) Kaur, G.; Kaushik, M.; Trehan, S. *Tetrahedron Lett.* **1997**, *38*, 2521−2524.

(13) For example, HN(SO$_2$F)$_2$, B(C$_6$F$_5$)$_3$, and InBr$_3$ did not catalyze the reaction of the acid-sensitive alcohol such as 1-phenylethanol.

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(16) Saito, T.; Yasuda, M.; Baba, A. *Synlett* **2005** 1737−1739.

(17) Mukaiyama and we have reported the InCl$_3$−Me$_3$SiCl combined Lewis acid catalyst for Hosomi−Sakurai, Friedel−Crafts, and Mukaiyama aldol reaction in which the Lewis acidity of the silicon center would be enhanced by the coordination of chlorine on silicon to the indium. See: (a) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227−8235. (b) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578−1581. (c) Miyai, T.; Onishi, Y.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 6291−6294. (d) Miyai, T.; Onishi, Y.; Baba, A. *Tetrahedron* **1999**, *55*, 1017−1026. (e) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2524−2527. (f) Mukaiyama, T.; Ohno, T.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1991**, *20*, 949−952. For other reports of combination of indium and silicon, see: (g) Lee, P. H.; Seomoon, D.; Kim, S.; Nagaiah, K.; Damle, S. V.; Lee, K. *Synthesis* **2003**, 2189−2193. (h) Lee, P. H.; Lee, K.; Sung, S.-y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646−8649. (i) Sakai, N.; Annaka, K.; Konakahara, T. *Tetrahedron Lett.* **2006**, *47*, 631−634. (j) Bandini, M.; Fagioli, M.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2003**, 397−402.

(18) For a report of the combination of Yb(OTf)$_3$−Me$_3$SiCl or Yb(OTf)$_3$−Me$_3$SiOTf, see: Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159−161.

(19) Recently, direct allylation of 1-phenylethanol (**1a**) was achieved using BiCl$_3$ in CH$_2$Cl$_2$. See: De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 8345−8350.

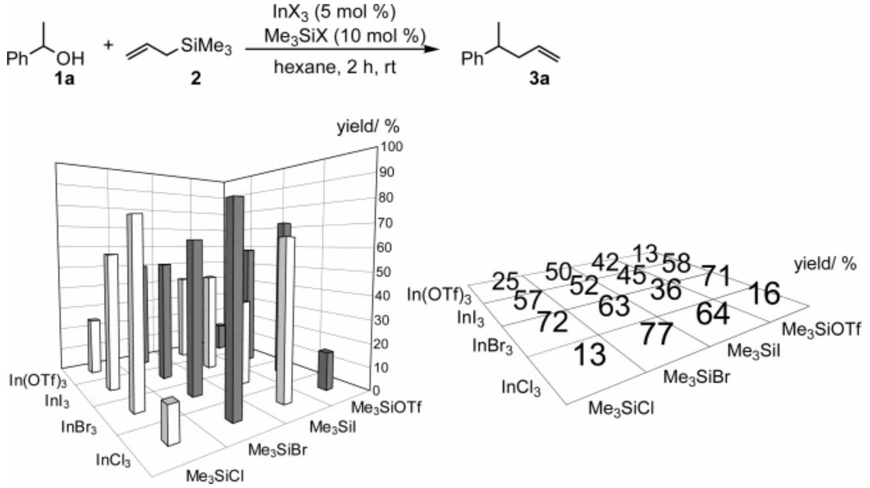


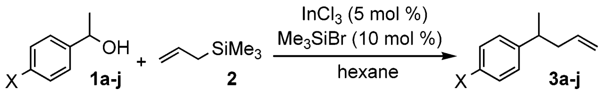
FIGURE 2. Screening of In(III) species and Me_3SiX for the allylation of 1-phenylethanol (**1a**).

and $B(C_6F_5)_3$, hardly exhibited catalytic activity in hexane even when combined with Me_3SiBr.[20]

To determine the optimal combination, screening of indium and silyl species was undertaken using the reaction of 1-phenylethanol (**1a**) with allylsilane **2** in hexane, and the results are illustrated in Figure 2. A combination of $InCl_3$ and Me_3SiBr gave the highest yield (77%), while the allylation with $InBr_3$−Me_3SiCl[17h,i] and $InBr_3$−Me_3SiOTf systems was also effective.[21] The use of Me_3SiI resulted in lower yields of **3a** along with some side products because of its very high reactivity. In contrast, the combination of $InCl_3$ and Me_3SiOTf could not complete the allylation, and the starting alcohol was considerably recovered. In general, Lewis acidity of Me_3SiX is arranged in the following order: $Me_3SiCl < Me_3SiBr \ll Me_3SiOTf < Me_3SiI$.[22] Therefore, the higher activity of the Me_3SiOTf system than that of Me_3SiCl or Me_3SiBr had been expected, but this system exhibited only low activity. It is noteworthy that the activity of the combined Lewis acid does not necessarily depend on the Lewis acidity of the silicon. We believe that the appropriate combination between indium and silicone species is essential for the allylation, and that low oxophilicity and high halophilicity of indium are the reasons of the reactivity observed. On the whole, the combination of $InCl_3$ and Me_3SiBr can act as the most active catalyst in this allylation system.

Allylation of 1-arylethanols **1** bearing various substituents was investigated under the optimized conditions, and the results are summarized in Table 2. The yield of allylated product **3a** increased up to 87% by slow addition of **1a** to the solution of 3 equiv of allylsilane **2** at 50 °C (entries 1 and 2). The alcohols **1b** and **1c** bearing the electron-donating groups were allylated in excellent yield (entries 3 and 4). The phenolic OH could tolerate the allylation conditions, in which MeCN solvent was required because of the poor solubility of **1d** in hexane (entry 5). In this case, the high reactivity of **1d** showed that the reaction was unaffected by coordination of MeCN. Alcohols **1e**−**h** possessing halogen substituents also gave the allylated products **3e**−**h** in high yields (entries 6−9). OTf-substituted alcohol **1i** could provide the desired product **3i**, although severe conditions were required (entry 10). A strong electron-withdrawing NO_2 moiety strongly disturbed the reaction to give only 19% yield (entry 11). Because the reactivity pattern observed is similar to that of the allylation using benzylic chlorides[8a] or ethers[8b] reported by Mayr, our system would also proceed via the S_N1 mechanism.

TABLE 2. Allylation of Various 1-Arylethanols by Using Combined Lewis Acid[a]



entry	X	conditions	yield (%)
1	H (**1a**)	rt, 2 h	77
2[b,c]		50 °C, 2 h	87
3	Me (**1b**)	50 °C, 3 h	91
4[c]	OMe (**1c**)	50 °C, 3 h	>99
5[c,d]	OH (**1d**)	rt, 1 h	>99
6	F (**1e**)	rt, 3 h	92
7[c]	Cl (**1f**)	reflux, 3 h	>99
8	Br (**1 g**)	50 °C, 3 h	90
9	I (**1h**)	reflux, 3 h	87
10[c,e]	OTf (**1i**)	50 °C, 6 h	71
11[f]	NO_2 (**1j**)	reflux, 3 h	19

[a] Reactions were carried out in hexane (1−2 mL) with allylsilane **2** (2.0 mmol), alcohol **1** (1.0 mmol), Me_3SiBr (0.1 mmol), and $InCl_3$ (0.05 mmol). [b] A hexane solution of alcohol was added dropwise. [c] Allylsilane (3 mmol). [d] MeCN was used as a solvent. [e] Me_3SiBr (1.0 mmol). [f] Me_3SiBr (0.2 mmol).

Further, a variety of alcohols were subjected to allylation using the $InCl_3$−Me_3SiBr system (Table 3). The tertiary and primary benzylic alcohols **4a** and **4b** gave the corresponding products **5a** and **5b** in 75 and 68% yields, respectively (entries 1 and 2). Benzhydrol (**4c**) was quantitatively transformed to the allylated product **5c** (entry 3). The yield of allylation of the alcohol bearing ferrocenyl moiety **4d** was increased to 94% in MeCN (entry 4) as compared to the reaction in other solvents (e.g., 12 and 58% yields in hexane and toluene, respectively[16]). 2-Cyclohexen-1-ol (**4e**) provided the desired product **5e** in 81% (entry 5). The allylation of 1-methyl-2-cyclohexen-1-ol (**4f**) took place at the 3-position to give **5f** in 98%. This result apparently suggests the involvement of an allylic carbocation. The two aliphatic alcohols, exo-norborneol (**4g**) and 1-adamantanol (**4h**), gave the allylated products **5g** and **5h**, respectively (entries 7 and 8). Unfortunately, a simple aliphatic alcohol, such as

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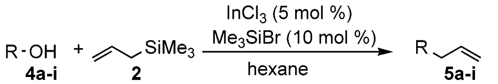
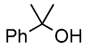
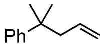
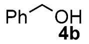
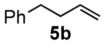
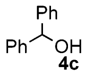
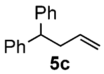
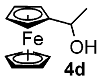
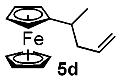
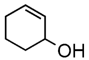
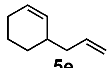
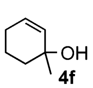
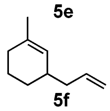
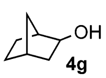
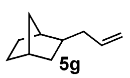
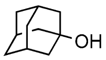
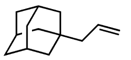
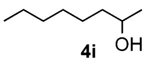
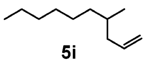
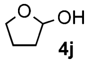
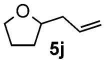
[20] See Supporting Information.

[21] Recently, direct allylation of alcohol using $InBr_3$ was reported, but only a dimeric ether was obtained by sole use of $InBr_3$ (see ref 11).

[22] Dilman, A. D.; Ioffe, S. L. *Chem. Rev.* **2003**, *103*, 733−772.

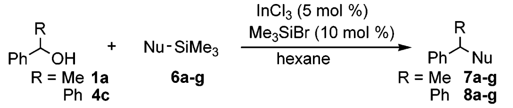
TABLE 3. Scope of Allylation of Alcohol by Using Combined Lewis Acid[a]

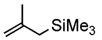
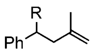
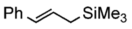
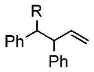
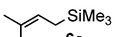
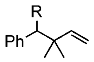
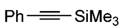
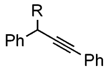
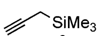
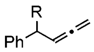
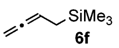
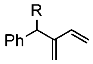


entry	alcohol	conditions	product	yield (%)
1[b,c]	 4a	50 °C, 0.5 h	 5a	75
2[b,d]	 4b	reflux, 4 h	 5b	68
3	 4c	50 °C, 1 h	 5c	>99
4[c,f]	 4d	rt, 2 h	 5d	94
5[c]	 4e	reflux, 1 h	 5e	81
6[f]	 4f	0 °C, 3 h	 5f	98
7[e]	 4g	reflux, 3 h	 5g	22
8[d,e]	 4h	reflux, 3 h	 5h	66
9[d,e]	 4i	reflux, 3 h	 5i	0
10[f]	 4j	reflux, 2 h	 5j	85

[a] Reactions were carried out in hexane (1−2 mL) with allylsilane **2** (2.0 mmol), alcohol **4** (1.0 mmol), Me_3SiBr (0.1 mmol), and $InCl_3$ (0.05 mmol). [b] A hexane solution of alcohol was added dropwise. [c] Allylsilane (3 mmol). [d] Allylsilane (4 mmol). [e] Me_3SiBr (0.5 mmol). [f] MeCN was used as a solvent.

TABLE 4. Coupling of Alcohol with Various Nucleophiles[a]



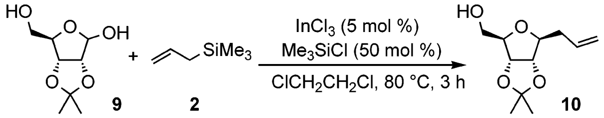
entry	alcohol	Nu-SiMe3	conditions	product	yield/ (%)
1[b,c]	R = Me (**1a**)	 **6a**	50 °C, 12 h	 (**7a**)	74
2[b]	Ph (**4c**)		50 °C, 12 h	(**8a**)	94
3	Me (**1a**)	 **6b**	50 °C, 3 h	 (**7b**)	86 (61:39)
4	Ph (**4c**)		reflux, 2h	(**8b**)	74
5[b]	Me (**1a**)	 **6c**	reflux, 2 h	 (**7c**)	85
6[b]	Ph (**4c**)		reflux, 2 h	(**8c**)	69
7[b]	Me (**1a**)	 **6d**	reflux, 4 h	 (**7d**)	46
8	Ph (**4c**)		reflux, 4 h	(**8d**)	71
9	Me (**1a**)	 **6e**	reflux, 1 h	 (**7e**)	36
10	Ph (**4c**)		50 °C, 4 h	(**8e**)	41
11[b]	Me (**1a**)	 **6f**	reflux, 7 h	 (**7f**)	39
12[b]	Ph (**4c**)		reflux, 7 h	(**8f**)	72

[a] Reactions were carried out in hexane (1−2 mL) with nucleophile **6** (2.0 mmol), alcohol **1a** or **4c** (1.0 mmol), Me_3SiBr (0.1 mmol), and $InCl_3$ (0.05 mmol). [b] Nucleophile (3 mmol). [c] Me_3SiBr (0.2 mmol).

2-octanol (**4i**), was not applicable for the reaction system (entry 9). Even the direct allylation of a hemiacetal, which has a high reactivity due to the formation of an oxocarbenium ion, has been reported to require an excess amount of acids.[23] In contrast, our system catalytically promoted the allylation of hemiacetal **4j** in high yield (entry 10).

2. Substitution of Alcohols with Various Silyl Nucleophiles. A series of silyl nucleophiles **6**, including allylic, allenyl, alkynyl, and propargyl moieties, were allowed to react with 1-phenylethanol (**1a**) or benzhydrol (**4c**) in non-halogenated solvent using the combination of $InCl_3$ and Me_3SiBr (Table 4). Methallylation of **1a** and **4c** with **6a** furnished the desired products **7a** and **8a** in high yields, although 20 mol % of Me_3SiBr was required in the case of **1a** (entries 1 and 2). It is interesting that γ-substituted allylsilanes **6b** and **6c** gave the highly substituted products **7b**, **8b**, **7c**, and **8c** in exclusive γ-addition manner (entries 3−6). Alkynylsilane **6d** provided the corresponding adducts **7d** and **8d** (entries 7 and 8). Selective formation of allenes from propargylsilane **6e** took place through exclusive γ-addition (entries 9 and 10). The transformation of allenylmethylsilane **6f** into the dienes **7f** and **8f** was the first demonstration under neutral conditions (entries 11 and 12).

3. Application to Chemoselective Reactions. Next, for an application of the direct substitution of hydroxyl moieties, we demonstrated saving steps in the allylation of hemiacetal. In the total synthesis of pinolidoxin by Fürstner and co-workers, ribose derivative **9** was transformed into the allylated adduct after the acetylation of both hydroxyl moieties, in which the deprotection of another acetoxy moiety was required after the allylation of the target acetal moiety.[24] In contrast, in our catalyst system, the direct transformation from the hemiacetal **9** into **10** could be achieved in a single step with high stereoselectivity, in which the protection of the primary alcohol moiety was never required (eq 1). We could have saved the protection and deprotection steps by the use of the indium and silicon system, although the yield is in a range similar to that of the multistep one.



44% (83 : 17)

(1)

On the basis of this result, we tried to compare the reactivity between hydroxyl moieties and acetoxy ones. Gevorgyan et al. reported that a $B(C_6F_5)_3$ catalyst readily promoted the allylation of an acetoxy moiety, while the reaction toward hydroxyl moieties hardly took place.[10] Apparently, acetylation is again an important step in increasing the leaving ability of a hydroxyl

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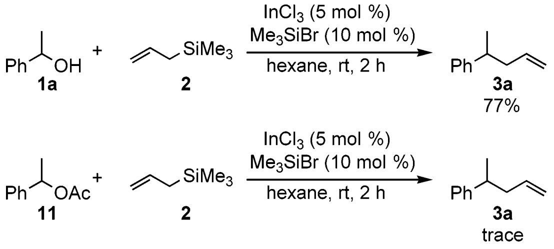
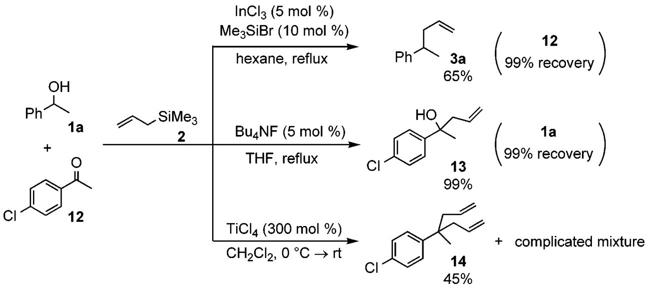
(23) For a review on the substitution of OH in hemiacetal, see: (a) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711−1754. For a recent report of the stereoselective reaction, see: (b) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2001**, 1169−1174. (c) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893−3901. (d) Schmitt, A.; Reissig, H.-U. *Chem. Ber.* **1995**, *128*, 871−876. (e) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063−2066.

(24) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061−7069.

SCHEME 1. Higher Reactivity toward Alcohol over Acetate



SCHEME 2. Competitive Reaction between Alcohol and Ketone

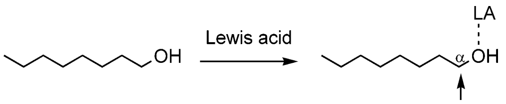


moiety. As aforementioned, 1-phenylethanol (**1a**) was successfully allylated with the $InCl_3-Me_3SiBr$ system. We interestingly found the fact that no reaction took place in the allylation of 1-phenylethyl acetate (**11**) by our catalytic system, as shown in Scheme 1.[25] Under the conditions optimized for the direct allylation of 1-phenylethanol (77% yield), no substitution of the acetoxy moiety was observed. Consequently, the $InCl_3-Me_3SiBr$ system has reversed chemoselectivity to general procedures.

Since the predominant reactivity toward hydroxy moieties over acetoxy ones was demonstrated, we next focused on the difference in the reactivity between the hydroxyl and ketone moieties (Scheme 2). When we treated allyltrimethylsilane (**2**) with an equimolar amount of 1-phenylethanol (**1a**) and *p*-chloroacetophenone (**12**) in the presence of a catalytic amount of $InCl_3$ and Me_3SiBr, the alcohol **1a** was exclusively allylated in contrast to complete recovery of the starting ketone **12**. This result is very interesting because we have already reported how the $InCl_3/Me_3SiCl$ system effected the allylation of ketones.[17a,b] The combined catalyst apparently activated a hydroxyl moiety far more strongly than a ketone. In contrast, Bu_4NF, which is a representative and effective catalyst for the allylation of carbonyl compounds,[26] promoted the exclusive allylation of ketone **12**. The catalyst systems of $InCl_3-Me_3SiBr$ and Bu_4NF were found to be complementary to each other. On the other hand, a representative Lewis acid, $TiCl_4$, gave a complicated mixture, including 45% of the double allylated product **14** of ketone, in which alcohol **1a** was completely consumed.[27,28]

From these results, it is apparent that the combined system of $InCl_3$ and Me_3SiBr makes possible the selective activation of alcohols over ketones.

TABLE 5. Effect of Lewis Acids on the Chemical Shifts, $\delta(^{13}C)$, of the α-Carbon in 1-Octanol[a]



entry	Lewis acid	$\delta(^{13}C)$/ppm	$\Delta\delta(^{13}C)$/ppm
1	none	62.7	0
2	Me_3SiCl	62.8	+0.1
3	Me_3SiBr	64.0	+1.3
4	$InCl_3$	65.2	+2.5
5	$InBr_3$	65.2	+2.5
6	$InCl_3 + Me_3SiCl$	66.0	+3.3
7	$InCl_3 + Me_3SiBr$	66.3	+3.6
8	$InBr_3 + Me_3SiCl$	67.4	+4.7
9	$InBr_3 + Me_3SiBr$	70.2	+7.5

[a] 1-Octanol and Lewis acids (1.0 M each) in MeCN at room temperature.

4. NMR Study. The enhanced Lewis acidity was confirmed by monitoring the NMR chemical shifts, $\delta(^{13}C)$, of the α-carbon of 1-octanol in the mixture with InX_3 and Me_3SiX, as noted in Table 5.[29] Reasonable downfield shifts of the α-carbon which represent the strength of their acidity were observed in the presence of Lewis acids, such as Me_3SiCl, Me_3SiBr, $InCl_3$, or $InBr_3$ (entries 2−5), which indicates that these species act as moderate Lewis acids. In comparison to these values, combined Lewis acid systems caused larger downfield shifts (entries 6−9), and particularly, the combination of $InBr_3$ and Me_3SiBr showed the largest value examined (+7.5 ppm, entry 9). This result indicates that this combination would act as the most effective catalyst. However, this $InBr_3-Me_3SiBr$ system gave a slightly lower yield relative to that of the $InCl_3-Me_3SiBr$ system perhaps because of the instability of stronger Lewis acid (Figure 2). Therefore, the suitable combination, $InCl_3/Me_3SiBr$, should be chosen to accomplish the reaction.

Next, ^{29}Si NMR studies were performed. Upon mixing with equimolar amounts of Me_3SiBr and $InCl_3$ (1.0 M each), a facile halogen exchange gave a broadened signal of Me_3SiCl at around 33.0 ppm ((iii) in Figure 3).[30] In the combination of Me_3SiCl and $InBr_3$, only the signal corresponding to Me_3SiCl was broadened ((iv) in Figure 3). Therefore, this broadening plausibly indicates the range of interaction between Me_3SiCl and In(III) halide **15**, as shown in Scheme 3.[17a,e,31] A mixing of Me_3SiBr and $InBr_3$, which caused the most downfield shift of the α-carbon of the alcohol, noted in Table 5, gave the most broadened signal of Me_3SiBr ((v) in Figure 3). This interaction is weakened at low temperature because the signal became sharp.[20] In the case of $AlCl_3$ and $BF_3{\cdot}OEt_2$, halogen exchange with Me_3SiBr also took place at room temperature. The generated Me_3SiCl and Me_3SiF, however, do not seem to

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(25) 1-Phenylethyl acetate (**11**) and 1-phenylethanol (**1a**) were obtained in 75 and 12% yields, respectively.

(26) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, *33*, 3043−3046.

(27) When an equimolar amount of titanium(IV) chloride was used, only chlorination of alcohol was promoted.

(28) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295−1298.

(29) We did not use hexane as a solvent owing to the poor solubility of $InCl_3$. When $AlCl_3$ or $BF_3{\cdot}OEt_2$ instead of InX_3 was used in MeCN, these NMR charts were complicated by the concomitant formation.

(30) In the presence of 1-octanol, the similar broadening of the combination of Me_3SiCl and $InCl_3$ on ^{29}Si NMR in MeCN was observed.

(31) For reports of silylium ion, see: (a) Kim, K.-C.; Reed, C. A.; Elliott, D. W.; Mueller, L. J.; Tham, F.; Lin, L.; Lambert, J. B. *Science* **2002**, *297*, 825−827. (b) Lambert, J. B.; Zhao, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 400−401. (c) Lambert, J. B.; Lin, L. *J. Org. Chem.* **2001**, *66*, 8537−8539. (d) Lambert, J. B.; Zhao, Y.; Zhang, S. M. *J. Phys. Org. Chem.* **2001**, *14*, 370−379. Gabbaï et al. reported a working model in which the mercury atom on Me_3SiCl is activated by coordination of bidentate mercury Lewis acid and the interaction between Ga(III) and Cl on Sn(IV) was confirmed by X-ray single-crystal analysis: (e) King, J. B.; Gabbaï, F. P. *Organometallics* **2003**, *22*, 1275−1280. (f) Tschinkl, M.; Hoefelmeyer, J. D.; Cocker, T. M.; Bachman, R. E.; Gabbaï, F. P. *Organometallics* **2000**, *19*, 1826−1828.

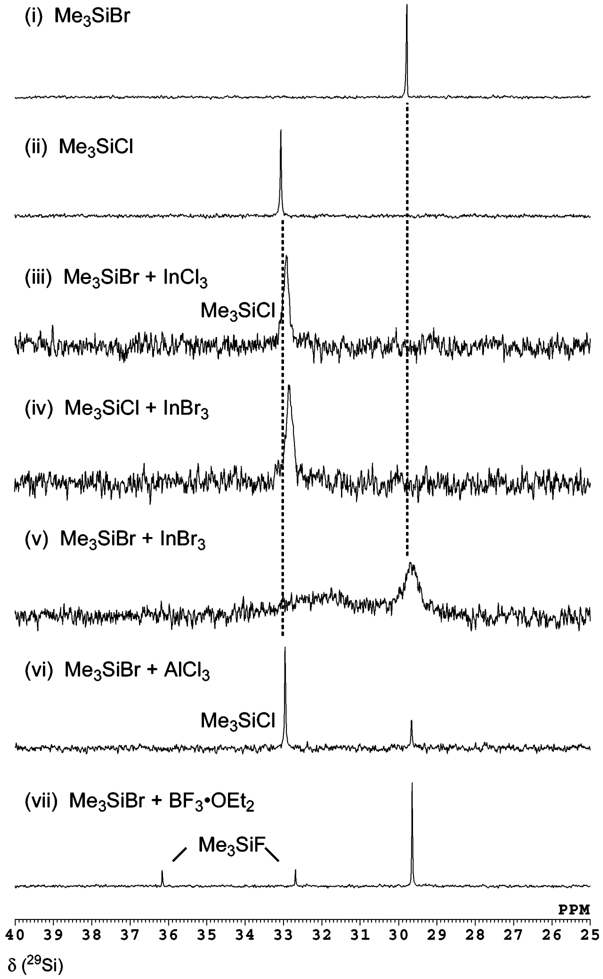
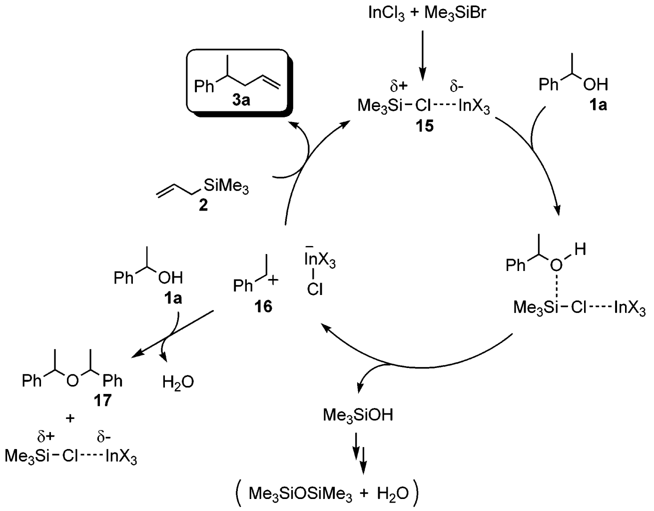


FIGURE 3. ^{29}Si NMR spectra of the mixture of Me_3SiX and Lewis acids in MeCN at room temperature (79 MHz, TMS external standard).

SCHEME 3. Plausible Mechanism



interact with aluminum or boron halides because of the observation of the sharp signal ((vi) and (vii) in Figure 3). This is perhaps the reason why the $InCl_3-Me_3SiBr$ system is more effective than $AlCl_3-Me_3SiBr$, as the catalytic activity depends on the interaction.

5. Possible Mechanism. On the basis of the discussions involving cation species and the strong Lewis acidity of the combined system, we propose a plausible mechanism using the reaction of 1-phenylethanol (**1a**) with allyltrimethylsilane (**2**) catalyzed by $InCl_3/Me_3SiBr$ (Scheme 3). At first, the combined Lewis acid **15**[32] activates the hydroxyl moiety by strong coordination to the silicone center to promote the formation of carbocation **16**. Addition of allylsilane **2** to the cation **16** gives the allylated product **3a** with regeneration of the combined catalyst,[33] consequently completing the catalytic cycle of the direct allylation of alcohols. When alcohol **1a** reacted with the cation **16**, dimeric ether **17** would be produced.[34] The ether may be incorporated in this allylation when the combined Lewis acid activated the ether. The optimized reaction conditions, however, required an excess amount (2-fold) of silyl compounds. In addition, in some cases, slow and dropwise addition of the alcohol was essential for high yields (entry 2 in Table 2, entries 1 and 2 in Table 3). These results plausibly suggest that the direct attack of **2** to the cation **16** is favorable for the effective substitution of alcoholic hydroxyl moieties. An additional important factor for the completion of the catalytic cycle is the low oxophilicity and high halophilicity of indium halides because high oxophilicity disturbs the regeneration of the combined catalyst. Perhaps $AlCl_3$ is the case of high oxophilicity and has no catalytic ability.

To confirm the low oxophilicity of $InCl_3$ for regenerating the combined catalyst, the interaction between Me_3SiOMe and some Lewis acids was monitored with ^{29}Si NMR.[20] No interaction was observed in the mixture of indium halide and Me_3SiOMe, while the reaction with $AlCl_3$ or $BF_3•OEt_2$ rapidly took place to give Me_3SiCl or Me_3SiF, respectively. The strong oxophilicity of Al and B species disturbs the regeneration of the catalytic species in contrast to the indium−silicone system. These results, including Figure 3, also represent the strong halophilicity enough to enhance the Lewis acidity of the silicon center.

Conclusion

A direct allylation of alcohols was established by using $InCl_3$ and Me_3SiBr. This combination catalyst was essential for the reaction in a non-halogenated solvent and applied to the reaction of a wide range of alcohols and silyl nucleophiles, such as methallyl-, cinnamyl-, prenyl-, alkynyl-, propargyl-, allenyl, and allenylmethylsilane. We also demonstrated the predominant allylation to a hydroxyl moiety over ketone and acetoxy ones. It was proved that In(III) exhibited specific characteristics of high halophilicity and low oxophilicity.

Experimental Section

Typical Procedure for Allylation of 1a (Table 1, Entry 3). To a mixture of $InCl_3$ (0.05 mmol) and 1-phenylethanol (**1a**, 1.0 mmol) in hexane (1 mL) were added allyltrimethylsilane (**2**, 2.0 mmol) and Me_3SiBr (0.1 mmol) under nitrogen. The reaction mixture was stirred under the reaction conditions noted in the text. The resulting mixture was poured into Et_2O (50 mL) and aqueous $NaHCO_3$ (30 mL). The solution was extracted with Et_2O, and the organic layer was dried over $MgSO_4$. The evaporation of the ether

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[32] The halogen exchange between Me_3SiBr and $InCl_3$ was also observed in hexane as well as MeCN.

[33] An S_N1 mechanism is also supported by the result that racemization took place in the direct allylation of enantiomerically pure 1-phenylethanol; see Supporting Information.

[34] In fact, a small amount of ether **17** can be observed when the reaction was quenched in the early stage.

solution gave the crude product, which was analyzed by NMR. The details of further purification performed for the new compounds are described in Supporting Information.

Allylation by Slow Addition of 1a (Table 2, Entry 2). To a mixture of $InCl_3$ (0.05 mmol), Me_3SiBr (0.1 mmol), and allyltrimethylsilane (**2**, 3.0 mmol) in hexane (1 mL) was slowly added a solution of 1-phenylethanol (**1a**, 1.0 mmol) in hexane (1 mL) for 10 min under nitrogen. The reaction mixture was stirred under the reaction conditions noted in the text. The workup employed is the same as that described in the typical reaction procedure.

Allylation of 9 (eq 1). To a mixture of $InCl_3$ (0.05 mmol) and alcohol **9** (1.0 mmol) in 1,2-dichloroethane (2 mL) were added allyltrimethylsilane (**2**, 4.0 mmol) and Me_3SiCl (0.5 mmol) under nitrogen. The reaction mixture was stirred at 80 °C for 3 h. The workup employed is the same as that described in the typical reaction procedure.

Competitive Reaction between 1a and 12 Using the $InCl_3$/Me_3SiBr System (Scheme 2). To a solution of 1-phenylethanol **1a** (1 mmol) and *p*-chloroacetophenone **12** (1 mmol) in hexane (2 mL) were added allyltrimethylsilane (**2**, 2.0 mmol) and Me_3SiBr (0.1 mmol) under nitrogen. The reaction mixture was stirred under reflux for 6 h. The resulting mixture was poured into Et_2O (50 mL) and aqueous $NaHCO_3$ (30 mL). The solution was extracted with Et_2O, and the organic layer was dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by TLC (hexane/AcOEt, 95/5, $R_f = 0.72$ and 0.22) affording **3a** (65%) and **12** (99%).

Competitive Reaction between 1a and 12 Using Bu_4NF (Scheme 2).[26] To a mixture of Bu_4NF (0.05 mmol), 4 Å molecular sieves (25 mg), 1-phenylethanol **1a** (1 mmol), and *p*-chloroacetophenone **12** (1 mmol) in THF (4 mL) was added allyltrimethylsilane (**2**, 3.0 mmol) under nitrogen. The reaction mixture was stirred under reflux for 3 h. After treatment of the reaction mixture with MeOH (5 mL) and 1 N HCl (5 mL) at room temperature for 30 min, the solution was extracted with Et_2O, and the organic layer was dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by TLC (hexane/AcOEt, 80/20, $R_f = 0.28$ and 0.44) affording **1a** (99%) and **13** (99%).

Competitive Reaction between 1a and 12 Using $TiCl_4$ (Scheme 2).[28] To a solution of a 1-phenylethanol **1a** (1 mmol) and *p*-chloroacetophenone **12** (1 mmol) in dichloromethane (2 mL) was added $TiCl_4$ (3 mmol) dropwise with a syringe at 0 °C. After stirring for 5 min, allyltrimethylsilane (**2**, 3 mmol) was added to the mixture. The reaction mixture was stirred at 0 °C → room temperature for 30 min. The resulting mixture was poured into Et_2O (50 mL) and water (30 mL). The solution was extracted with Et_2O, and the organic layer was dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by TLC (hexane/AcOEt, 95/5, $R_f = 0.67$) affording **14** (45%).

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

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