Direct Alkylation of Alcohols

Direct Substitution of the Hydroxy Group in Alcohols with Silyl Nucleophiles Catalyzed by Indium Trichloride**

*Makoto Yasuda, Takahiro Saito, Masako Ueba, and Akio Baba**

Substitution of the hydroxy group in alcohols by nucleophiles intrinsically requires an equimolar (or greater) amount of acid because of the poor leaving ability of the OH group. To avoid the use of excessive amounts of acid, alcohols are usually transformed into the corresponding halides or related compounds that have good leaving groups before the treatment with the nucleophiles. In this context, direct substitution of alcohols in a catalytic manner under nearly neutral conditions would be a fascinating and ideal procedure for synthetic organic chemistry. We have previously reported the direct dehydroxylation of alcohols under catalytic conditions by using a chlorosilane/catalytic $InCl_3$ system.[1] We have now turned our attention to C–C bond formation by a direct substitution system with allylic nucleophiles.[2] In 1982, Cella reported allylation/dehydroxylation of alcohols by allylsilane in the presence of an excess amount of a Lewis acid.[3] This system, however, is only applicable to a narrow range of alcohols and gives a significant amount of side products. As a special case, hemiacetal is effectively alkylated by allylsilane to give the corresponding alkenes in high yields but this reaction requires more than an equimolar amount of BF_3.[4] Rubin and Gevorgyan recently reported allylation of certain alcohols in the presence of a boron catalyst although dehydration prevents the desired alkylating reaction in some cases.[5] Herein we report the direct substitution of the hydroxy group in alcohols by allyl-, propargyl-, and alkynylsilanes catalyzed by indium chloride. The system allows the desired alkylation of a wide range of applicable substrates under neutral conditions.

We have recently reported the direct reduction of alcohols[1,6] in a reaction with a silyl ether intermediate formed by removal of HCl, as shown in Equation (1). Therefore, we initially chose allylchlorodimethylsilane (**1**) as an allylic nucleophile in the reaction with benzhydrol (**2a**, Table 1). Although the uncatalyzed system resulted in no

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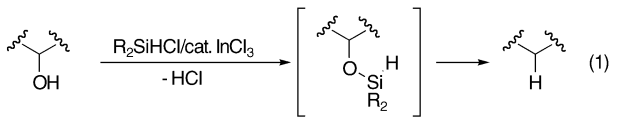
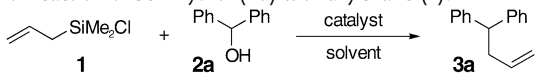


(1)

Table 1: Reaction of benzhydrol (**2a**) with allylsilane (**1**).[a]



Entry	Catalyst	Solvent	Yield [%]
1	none	CH_2Cl_2	0
2	$InCl_3$	CH_2Cl_2	80
3	$AlCl_3$	CH_2Cl_2	0
4	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0
5	$Sc(OTf)_3$[b]	CH_2Cl_2	13
6	$InCl_3$	THF[b]	0
7	$InCl_3$	DMF[b]	0
8	$InCl_3$	hexane	45

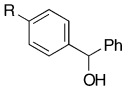
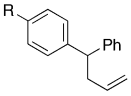
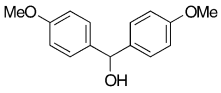
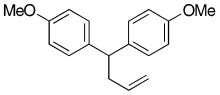
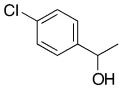
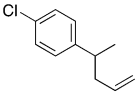
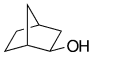
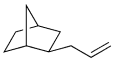
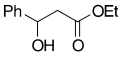
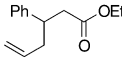
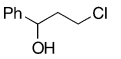
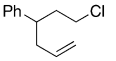
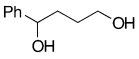
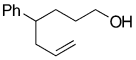
[a] All reactions were carried out in a solvent (1 mL) with allylsilane **1** (2.0 mmol), alcohol **2a** (1.0 mmol), and catalyst (0.05 mmol) at RT for 10 min. [b] Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

reaction (entry 1), the loading of a catalytic amount of $InCl_3$ dramatically accelerated the reaction and led to the production of alkylated product **3a** in 80% yield (entry 2).[7] Strong Lewis acids such as $AlCl_3$ or $BF_3{\cdot}OEt_2$ were not effective for the alkylation (entries 3 and 4), probably because these catalysts are not stable under protic conditions. $Sc(OTf)_3$ only gave a low yield of **3a** (entry 5), even though it can generally be used in a protic solvent. Dichloromethane was the solvent of choice; THF, DMF, and hexane afforded unsatisfactory results (entries 6–8). The reaction was also attempted with the corresponding Grignard reagent (two equivalents of allylmagnesium chloride), which is a typical highly nucleophilic reagent, instead of **1**, but the starting alcohol was recovered after work-up under conditions with or without the $InCl_3$ catalyst. These results strongly suggest that the appropriate nucleophilicity of the allylic reagent and Lewis acidity of the catalyst, as well as tolerance of protic conditions, are important for the direct substitution pathway.

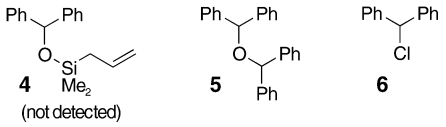
To investigate the scope and limitations of this reaction system with catalytic $InCl_3$, various alcohols **2** were examined and some of the results are shown in Table 2. Benzhydrol (**2a**) or its derivatives **2b**–**f** which have electron-donating or -withdrawing groups on the aryl rings were effectively allylated at room temperature in 10 min (entries 1–6). The reaction with 1-phenylethanol (**2g**) gave the corresponding alkene **3g** (entry 7) with side products that probably came from polymerization and/or a Friedel–Crafts reaction through the benzylic cationic species.[8] Use of three equivalents of silane **1** gave a higher yield of **3g** (entry 8). The simple benzyl alcohol gave intractable polymers rather than the desired product. The tertiary benzylic alcohol **2h** afforded the product **3h** (entries 9 and 10). Unfortunately, simple aliphatic alcohols, for example, 2-decanol, were not suitable substrates for the reaction system and gave none of the desired product. However, the norborneol **2j** gave allylated product **3j** in 52% yield as a single isomer (entry 13). The reaction with β-hydroxy ester **2k** gave the δ,ε-unsaturated ester **3k** without any side products modified at the ester moiety (entry 14).[9] Since there are few general methods to synthesize δ,ε-unsaturated esters by conjugate allylation of α,β-unsaturated esters, this type of reaction will provide an important way to access these compounds.[10] The chlorinated alcohols **2i** and **2l** were selectively transformed into **3i** and **3l**, respectively, with reaction at the hydroxy sites without affecting the chloride moieties (entries 11, 12, and 15). The diol **2m** was allylated selectively at the benzylic site to afford the primary alcohol **3m** after the workup with Bu_4NF (entry 16).

We performed an NMR spectroscopy study on a mixed solution of benzhydrol (**2a**), allylchlorodimethylsilane (**1**), and a catalytic amount of $InCl_3$ in CD_2Cl_2 at room temperature to investigate the reaction mechanism.[11] We had expected the silyl ether **4** to be formed by removal of HCl, as observed in the reduction system with $Ph_2SiClH/InCl_3$ reported by us [Eq. (1)].[1] However, species **4** was not

Table 2: Allylation of alcohols **2** with allylsilane **1** catalyzed by $InCl_3$.[a]

Entry	Alcohol		t [min]	Product		Yield [%]
1		**2a**: R = H	10		**3a**	80
2		**2b**: R = Me	10		**3b**	86
3		**2c**: R = Cl	10		**3c**	92
4		**2d**: R = NO_2	10		**3d**	80
5		**2e**: R = MeO	10		**3e**	82
6		**2f**	10		**3f**	67
7		**2g**	30		**3g**	46
8[b]			30			87
9		**2h**	30		**3h**	47
10[b]			30			59
11		**2i**	180		**3i**	62
12[b]			180			96
13[b]		**2j**	180		**3j**	52
14[c]		**2k**	60		**3k**	66
15		**2l**	180		**3l**	59
16[d,e]		**2m**	60		**3m**	56

[a] The reactions were carried out in dichloromethane (1 mL) with allylsilane **1** (2.0 mmol), alcohol **2** (1.0 mmol), and $InCl_3$ (0.05 mmol) at RT unless otherwise stated. [b] Allylsilane **1** (3.0 mmol), dichloromethane (2 mL). [c] Allylsilane **1** (3.0 mmol), dichloroethane (2 mL), 80°C. [d] Allylsilane **1** (4.0 mmol). [e] Bu_4NF was added during the workup.

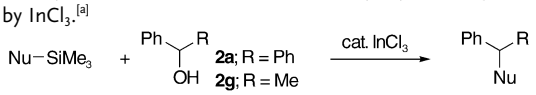


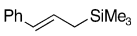
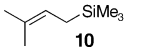
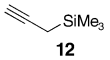
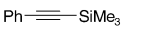
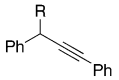
detected; signals for the dimeric ether **5** and a small amount of chloride **6** were observed instead (RT, 20 min), together with the allylated product **3a**.[12] In fact, no HCl was detected during the course of this reaction, whereas the reduction system with Ph_2SiHCl definitely generates HCl.[1] These results surprised us and showed that the mechanism of allylation is different from that of the reduction system,[1] although the exact reaction course is not yet clear.[13] The most important factor in this reaction is the unique character of the indium catalyst, which has 1) enough Lewis acidity to activate the C–O bond, 2) low oxophilicity to regenerate a catalysis from the substrate, and 3) stability under protic conditions. Those factors were realized in the direct substitution system with alcohols.

Since the removal of HCl was not observed during the course of the reaction, it might not be necessary to use the silane bearing the chlorine atom on its metal center. We examined some allylsilanes such as allyltrimethyl-, diallyldimethyl-, and trimethoxysilanes for the allylation of alcohols. Among these silanes, the desired alkylated product was only formed in satisfactory yield in the reaction with **2a** when allyltrimethylsilane (**7**) was used at 80 °C in dichloroethane (Table 3, entry 1). The reaction performed at room temperature gave no alkylated product. No **3a** was formed in the absence of the $InCl_3$ catalyst (entry 2). Gratifyingly, 1-phenylethanol (**2g**) gave **3g** without any side products (entry 3) while the reaction using allylchlorosilane (**1**) gave polymeric side products (see Table 2, entries 7 and 8). As those side products probably came from the benzylic chloride generated in situ, the Cl-free system with **7** was able to give a clean reaction with **2g**. The yield was increased to 87% by using three equivalents of **7** (entry 4). It is interesting that the reaction of γ-substituted allylsilanes **8** and **10** gave the products regioselectively in an exclusively γ-addition manner (entries 5–8). This system can be applied to other types of nucleophiles. In the case of the propargylsilane **12**, the regioselective formation of the allene **13** occurred exclusively through γ-addition (entries 9 and 10). The alkynylsilane **14** gave the desired products **15** in high yields (entries 11 and 12). As various types of trimethylsilyl compounds are available, the Cl-free system will expand the synthetic applications of this method.

In summary, we have demonstrated the direct substitution of the hydroxy group in alcohols by nucleophiles such as allylic-, propargyl-, and alkynylsilanes. The silyl nuclophile and $InCl_3$ make an indispensable combination to accelerate the unprecedented alkylative substitution with formation of a C–C bond. The details of the mechanism are now under investigation.

Table 3: Alkylation of alcohols **2** with trimethylsilyl nucleophiles catalyzed by $InCl_3$.[a]



Entry	Silane	Alcohol	*t* [h]	Product	Yield [%]
1	 **7**	**2a**	3	 **3a**	99
2[b]		**2a**	3		0
3		**2g**	3	**3g**	51
4[c]		**2g**	3		87
5	 **8**	**2a**	3	 **9a**	100
6	 **10**	**2a**	3	 **11a**	64
7		**2g**	3	**11g**	72
8[c]		**2g**	3		81
9	 **12**	**2a**	3	 **13a**	64
10		**2g**	6	**13g**	55
11	 **14**	**2a**	2	 **15a**	93
12[c]		**2g**	3		62

[a] The reactions were carried out in 1,2-dichloethane (2 mL) with silane (2.0 mmol), alcohol **2** (1.0 mmol), and $InCl_3$ (0.05 mmol) at 80 °C. [b] $InCl_3$ was not added. [c] Silane (3.0 mmol).

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Keywords: alcohols · alkylation · homogeneous catalysis · indium · silanes

[1] M. Yasuda, Y. Onishi, M. Ueba, T. Miyai, A. Baba, *J. Org. Chem.* **2001**, *66*, 7741–7744.
[2] For recent reports of transition-metal-catalyzed C–C bond formation through direct substitution of allylic or propargylic alcohols with nucleophiles other than allylic ones, see: a) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 10968–10969; b) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2002**, *124*, 11846–11847.
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[7] For $InCl_3$-catalyzed allylation of *gem*-diacetates by allylsilane, see: J. S. Yadav, B. V. Subba Reddy, C. Madhuri, G. Sabitha, *Chem. Lett.* **2001**, 18–19.
[8] The polymeric side products were observed in a similar type of reaction.[3,5]
[9] About 10% of a dehydrated product, ethyl 3-phenyl-2-propenoate, contaminated the reaction mixture and could be separated from the product by column chromatography.
[10] N. Kuhnert, J. Peverley, J. Robertson, *Tetrahedron Lett.* **1998**, *39*, 3215–3216.
[11] The NMR spectroscopy experiment was performed in dilute conditions (approximately 0.1 M) to slow down the reaction.
[12] Our previous report[13b] suggests that the allylated silyl ether **4** could be formed by silanes, but **4** was not found in the reaction described in this paper.
[13] For the example including C–O bond cleavage with the silicon–indium system, see: a) Y. Onishi, D. Ogawa, M. Yasuda, A. Baba, *J. Am. Chem. Soc.* **2002**, *124*, 13690–13691; b) Y. Onishi, T. Ito, M. Yasuda, A. Baba, *Tetrahedron* **2002**, *58*, 8227–8235.

