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Indium Triiodide Catalyzed Direct Hydroallylation of Esters

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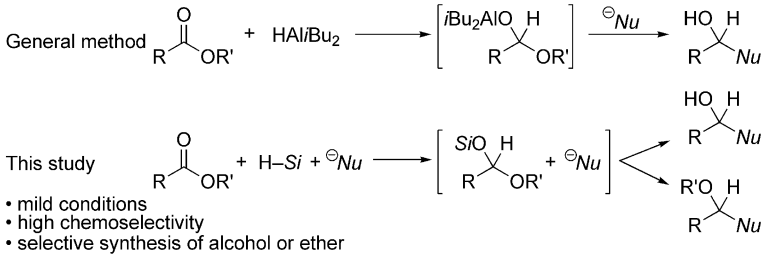
The InI_3-catalyzed hydroallylation of esters by using hydro- and allysilanes under mild conditions has been accomplished. Many significant groups such as alkenyl, alkynyl, cyano, and nitro ones survive under these conditions. This reaction system provided routes to both homoallylic alcohols and ethers, in which either elimination of the alkoxy moiety or of the carbonyl oxygen atom could be freely selected by changing the substituents on the alkoxy moiety and on the hydrosilane. In addition, the hydroallylation of lactones took place without ring cleavage to produce the desired cyclic ethers in high yields.

Introduction

For many years the addition of an organometallic compound to a carbonyl group has been one of the most important reactions in alcohol synthesis.[1] Many elegant reactions have been applied to aldehydes and ketones, whereas esters have seldom been employed in selective carbon–carbon bond formation due to a low electrophlicity. Strong nucleophiles such as Grignard reagents or organolithium compounds are generally required for addition to esters, often causing undesired side reactions. However, because esters have several advantages over other carbonyl reagents – availability, preservation, and variety –, a sophisticated application of them would have a significant value in organic synthesis.

Esters have the valuable quality of simultaneous acceptance of two different kinds of nucleophiles. In order to utilize this property, an aluminum acetal generated by the hydroalumination of esters with DIBAL has attracted much attention, because it can react with various organometallics to furnish the desired secondary alcohols (Scheme 1).[2] Therefore, the combination of DIBAL and nucleophiles is an attractive protocol for the direct transformation of esters, but the high reducing properties of DIBAL considerably limit the chemoselectivity, and most cases require strong nucleophiles like Grignard reagents or equivalent amounts of a Lewis acid.[3] In addition, it is difficult to produce ethers by selectively removing the carbonyl oxygen atom of esters.[4] Instead of hydroalumination, hydrosilylation of esters produces the corresponding silyl acetals that should react with nucleophiles. The transition metal catalyzed hydrosilylation of esters has been achieved, but no example yet exists for a carbon–carbon bond formation by direct use of the resulting silyl acetals.[5] We herein report the direct hydroallylation of esters by using hydro- and allylsilanes. A catalytic amount of InI_3 accelerated this hy-



Scheme 1. Addition of hydride and nucleophile to ester.

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droallylation under mild conditions, and significant functional groups such as alkenyl, alkynyl, cyano, and nitro ones survive under these conditions. Stepwise treatments of hydro- and allylsilane are not required. Notably, either elimination of the alkoxy moiety or the carbonyl oxygen atom could be freely selected by changing the substituents on the alkoxy moiety and on the hydrosilane. To the best of our knowledge, this is the first practical method for the selective synthesis of alcohols or ethers by the addition of hydride and nucleophiles to esters.

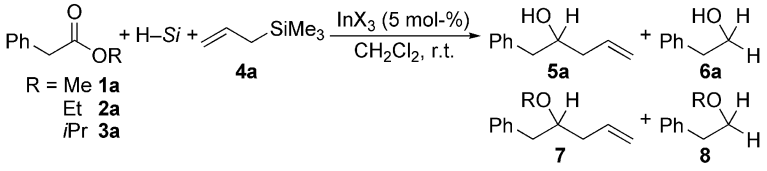
Results and Discussion

In order to find the optimal conditions, ester **1a** as a model substrate was treated with allytrimethylsilane (**4a**) and various hydrosilanes in the presence of indium catalysts (Table 1).[6] $InCl_3$ promoted no reaction, but $InBr_3$ and InI_3 gave the desired hydroallylation product **5a** in 49% and 73% yields, respectively, along with reduction product **6a** (Table 1, Entries 1–3). It is interesting that the use of a stronger Lewis acid, $In(OTf)_3$, resulted in recovery of the starting ester **1a** (Table 1, Entry 4). Also, typical and strong Lewis acids such as $BF_3{\cdot}OEt_2$, $AlCl_3$, and $TiCl_4$ were not effective.[7] $HSiEt_3$ and phenylsilanes, with the exception of $HSiPh_3$, had a good effect (Table 1, Entries 3 and 5–7). The amount of by-product **6a** was reduced by the slow addition of hydrosilanes. Finally, the slow addition of $HSiMe_2Ph$ to a mixture of **1a**, **4a**, and InI_3 was selected as the optimal conditions and resulted in a 96% yield of **5a** (Table 1, Entry 9). Interestingly, in the reaction with $HSiEt_3$, the use of ethyl ester **2a** instead of methyl ester **1a** caused a change in the allylation product from alcohol **5a** to ether **7**, which was generated by the removal of the carbonyl oxygen atom of ester **2a** (Table 1, Entry 11). $HSiMe_2Ph$, however, did not undergo such a change and furnished a high yield of alcohol **5a** (Table 1, Entry 12). Eventually, isopropyl ester **3a** produced a higher yield of the ether product **7** (Table 1, Entries 13 and 14). These results apparently indicate that the determination of the product depends on the differences in the bulkiness of the alkoxy moiety of the ester and of the substitutions on the hydrosilane.

We investigated the scope of applicable esters by using a combination of methyl esters **1** and $HSiMe_2Ph$, which preferentially forms an alcohol **5** (Table 2). High yields of homoallyl alcohols **5** were obtained from simple aliphatic esters such as **1b** and **1c** with the exception of the bulky **1d** (Table 2, Entries 1–3). The reaction with methyl benzoate (**1e**) resulted in a moderate yield even in the presence of 20 mol-% InI_3, because aromatic esters generally have a lower electrophilicity than aliphatic ones (Table 2, Entry 4). Many kinds of functional groups – methoxy, chloro, nitro, cyano, alkenyl, alkynyl, and hydroxy – that could not survive in the previous DIBAL method, were able to tolerate the conditions used in the present study (Table 2, Entries 5–11).[3] It is noteworthy that α-halo esters were also applicable, as they are good alternatives to the corresponding unstable aldehydes (Table 2, Entries 12–15). Substituted allylsilanes **4b** and **4c** also furnished the corresponding alcohols **5q** and **5r**, respectively, in satisfying yields in which the allylations selectively took place in a γ-addition manner (Table 2, Entries 16 and 17).

Next, in order to produce homoallylic ethers **7**, the combination of a bulky ester and a small hydrosilane, isopropyl ester **3** and $HSiEt_3$, was employed. A variety of esters gave

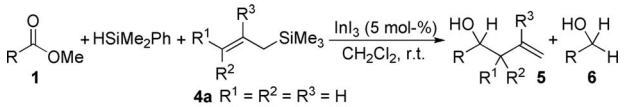
Table 1. Optimization of the conditions for the hydroallylation of esters.[a]

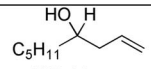
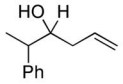
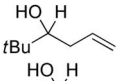
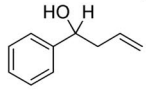
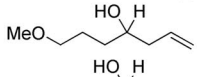
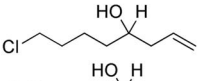
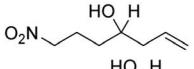
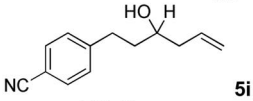
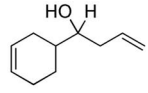
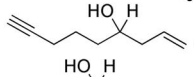
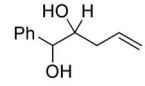
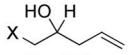
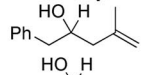
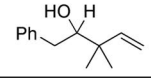


Entry	Ester	HSi	InX_3	Yields [%][d]			
				5a	**6a**	**7**	**8**
1[b]	**1a**	$HSiEt_3$	$InCl_3$	0	0	0	0
2	**1a**	$HSiEt_3$	$InBr_3$	49	17	5	2
3	**1a**	$HSiEt_3$	InI_3	73	25	1	1
4[b]	**1a**	$HSiEt_3$	$In(OTf)_3$	0	0	0	0
5	**1a**	$HSiMe_2Ph$	InI_3	71	29	0	0
6	**1a**	$HSiMePh_2$	InI_3	85	15	0	0
7[b]	**1a**	$HSiPh_3$	InI_3	5	3	0	0
8[c]	**1a**	$HSiEt_3$	InI_3	93	5	0	0
9[c]	**1a**	$HSiMe_2Ph$	InI_3	96	4	0	0
10[c]	**1a**	$HSiMePh_2$	InI_3	90	9	0	0
11	**2a**	$HSiEt_3$	InI_3	7	3	52	29
12	**2a**	$HSiMe_2Ph$	InI_3	59	32	6	3
13	**3a**	$HSiEt_3$	InI_3	3	trace	58	16
14[c]	**3a**	$HSiEt_3$	InI_3	7	trace	74	4

[a] Ester (1 mmol), hydrosilane (2 mmol), allyltrimethylsilane (**4a**) (4 mmol), InX_3 (0.05 mmol), CH_2Cl_2 (1 mL), room temperature, 30 min. [b] >90% of **1a** was recovered. [c] 2 mmol of allyltrimethylsilane was used. Hydrosilane (2 mmol, 1 M of CH_2Cl_2 solution) was added in 90 min, and the mixture was stirred for 10 min. [d] Yields were determined by ^1H NMR analysis.

Table 2. Selective synthesis of homoallyl alcohol **5** by using various methyl esters **1**.[a]

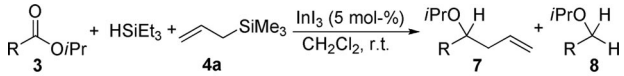


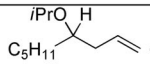
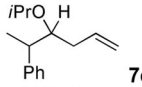
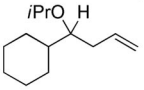
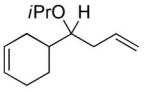
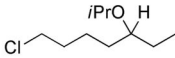
Entry	1	Product 5	Yield [%] 5[b]	6
1	1b	 5b	97 (90)	3
2[c]	1c	 5c	92 (84)	8
3	1d	 5d	40 (30)	29
4[d]	1e	 5e	57 (32)	trace
5[e]	1f	 5f	67 (51)	11
6	1g	 5g	92 (71)	8
7	1h	 5h	68 (37)	5
8[d]	1i	 5i	41 (20)	trace
9[f]	1j	 5j	91 (68)	9
10	1k	 5k	57 (40)	22
11[h]	1l	 5l	85 (86)	15
12[d,g]	1m	 X = F 5m	55	trace
13[d,g]	1n	Cl 5n	56	trace
14	1o	Br 5o	40	trace
15[i]	1p	I 5p	36	trace
16	1a	 5q	83 (83)	4
17	1a	 5r	83 (72)	9

[a] To the mixture of **1** (1 mmol), allylsilane (2 mmol), and InI_3 (0.05 mmol), the hydrosilane (2 mL, 1 M of CH_2Cl_2 solution) was added in 90 min, and the mixture was stirred for 10 min. [b] Yields were determined by ^1H NMR analysis. Values in parentheses indicate isolated yield in different batch reactions and on different scales. [c] Diastereomer ratio: 59:41. [d] InI_3 (0.2 mmol); hydrosilane (2 mmol, 1 M of CH_2Cl_2 solution) was added in 150 min, and the mixture was stirred for 30 min. [e] Hydrosilane (2 mmol, 1 M of CH_2Cl_2 solution) was added in 150 min, and the mixture was stirred for 30 min. [f] Diastereomer ratio: 58:42. [g] Allylsilane (4 mmol). [h] Diastereomer ratio: 53:47. [i] $InBr_3$ (0.05 mmol).

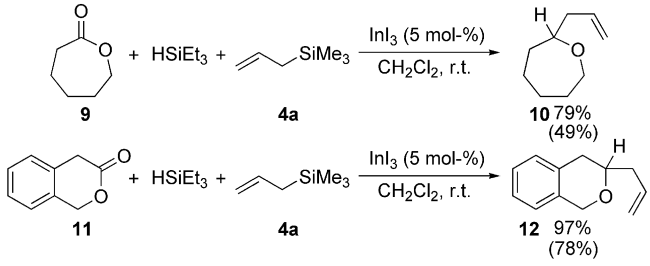
the corresponding homoallyl ethers **7** in high yields and in high selectivities, as shown in Table 3. In addition, we accomplished the hydroallylation of lactones **9** and **11** (Scheme 2). As expected, both lactones were effectively allylated without ring cleavage to produce the desired cyclic ethers **10** and **12** in 79% and 97% yields, respectively.

Table 3. Selective synthesis of homoallylic ethers **7** by using isopropyl esters **3**.[a]



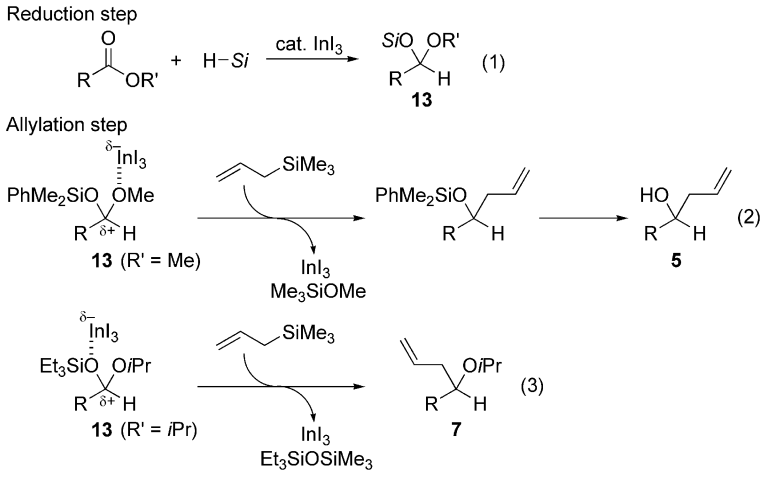
Entry	3	Product 7	Yield [%] 7[b]	8
1	3b	 7b	74 (42)	11
2[c]	3c	 7c	64 (41)	5
3	3d	 7d	80 (57)	10
4[d]	3e	 7e	85 (66)	trace
5	3f	 7f	74 (59)	14

[a] To the mixture of **1** (1 mmol), allylsilane (2 mmol), InI_3 (0.05 mmol), and CH_2Cl_2 (1 mL), the hydrosilane (2 mmol, 1 M of CH_2Cl_2 solution) was slowly added in 90 min, and the mixture was then stirred for 10 min. [b] Yields were determined by ^1H NMR analysis. Values in parentheses indicate isolated yield in different batch conditions on different scales. [c] Diastereomer ratio: 70:30. [d] Diastereomer ratio: 62:38.



Scheme 2. Hydroallylation of lactones. Yields were determined by ^1H NMR analysis. Values in parentheses indicate isolated yields in different batch reactions on different scales.

A putative mechanism is illustrated in Scheme 2. First, InI_3-catalyzed hydrosilylation of an ester takes place to generate silyl acetal **13**.[8] In the successive allylation, there are two possible routes: one produces alcohol product **5** and the other produces ether product **7**.[4,9] The determination of the route mainly depends on the steric hindrance of the alkoxy and siloxy groups. In the case of the methyl ester **1**/$HSiMe_2Ph$ system, InI_3 interacts with the small methoxy group rather than the large siloxy one, and the nucleophilic attack of an allylsilane promotes the elimination of the methoxy group to give homoallyl alcohol **5** [Scheme 3, Equation (2)]. By contrast, in the isopropyl ester **3**/$HSiEt_3$ system, the hindered isopropoxy group accelerates the interaction between InI_3 and the siloxy group to provide the ether product **7** [Scheme 3, Equation (3)].



Scheme 3. Putative mechanism.

Conclusions

The InI_3-catalyzed hydroallylation of an ester by using hydro- and allylsilanes has been accomplished, providing routes to both homoallylic alcohols and ethers. The determination of the route depended on the combination of the alkoxy moiety of the ester and the substituents of the hydrosilane. In addition, this reaction system has a high chemoselectivity, and various functional groups survived (nitro, cyano, alkenyl, alkynyl, hydroxy). Further application and study of the details of this reaction mechanism are ongoing.

Experimental Section

Typical Procedure for the Hydroallylation of 1b (Table 2, Entry 1): Dimethylphenylsilane (2 mmol, 1 M of CH_2Cl_2 solution) was slowly (90 min) added to a suspended solution of InI_3 (0.05 mmol), **1b** (1 mmol), and allyltrimethylsilane (2 mmol) in dichloromethane (1 mL) by using a syringe pump at room temperature. The reaction mixture was stirred for 10 min and then quenched with TBAF (5 mmol of a 1 M THF solution). The resulting mixture was poured into 1 M aq. HCl (10 mL) and extracted with Et_2O. The organic layer was dried with $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude product, which was analyzed by NMR spectroscopy.

Supporting Information (see footnote on the first page of this article): General information and procedures, characterization data of the prepared compounds.

Acknowledgments

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