Intramolecular hydrogen bond-promoted C–C bond formation: reaction rate enhancement and regioselective allylation of carbonyl compounds

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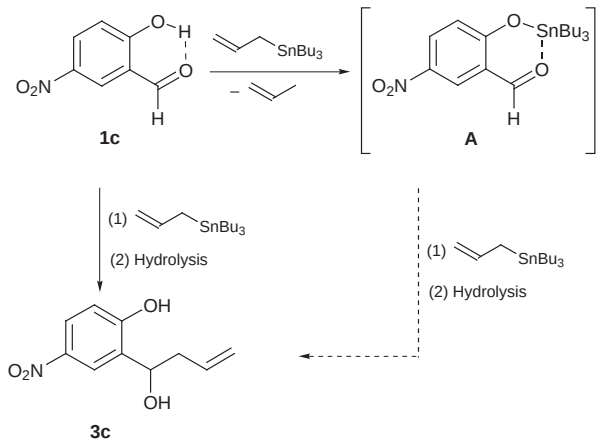
An intramolecular hydrogen bond promotes rate enhancement in both the allylation and the reduction of carbonyl compounds and also regioselective allylation.

For the design of synthetic reactions, external catalysts or mediators are usually utilized for improving selectivity and mildness of reaction conditions.[1] In the allylation reaction of carbonyl compounds with an allylmetal reagent such as an allylsilane or allyltin, Lewis and Brønsted acid catalysts are often employed for this purpose.[2–4] Usually, the strong acidity of the Lewis or Brønsted acid is needed to complete the reaction. However, the strong acid sometimes causes decomposition of both the allylmetal reagent and the substrate. In order to overcome this drawback, we have introduced an intramolecular hydrogen bond into the substrate to activate the substrate and to stabilize the transition state of the reaction. Although active arguments for the contribution of hydrogen bonds in the transition state of an enzymatic system have been presented, there are fewer reports on the utilization of the stabilization effect of the hydrogen bond in the transition state in C–C bond formation between carbonyl compounds and organometallic reagents.[5,6] To explore the synthetic utility of the hydrogen bond, we focused our attention on the features of the intramolecular hydrogen bond. Its moderate acidity and localization in a specific position in the substrate serve synthetic utility. Here we describe rate enhancement in the allylation and the reduction of a carbonyl group and the regioselective allylation promoted by an intramolecular hydrogen bond.

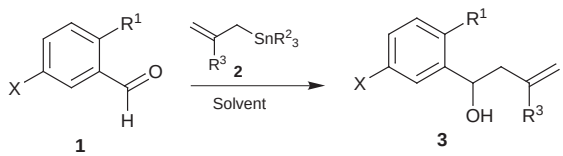
There are numerous reports on the condensation reaction of an aldehyde with trialkylallyltin promoted by a Lewis or Brønsted acid catalyst.[3–5] The thermal reactions of trialkylallyltin with carbonyl compounds at high temperature or high pressure have also been reported. In our first series of experiments, the activation effect of an intramolecular hydrogen bond in the nucleophilic reaction of organotin compounds was measured at low temperature without the addition of an acid catalyst (Table 1).

Under THF reflux conditions without the addition of a Lewis acid, no adducts were observed for a mixture of tributylallyltin and benzaldehyde, which has no intramolecular hydrogen bond. Although salicylaldehyde **1a** reveals a relatively strong intramolecular hydrogen bond between the hydroxy group and the oxygen atom in the carbonyl group, attempts to afford an allylation product were unsuccessful under the same conditions (entry 1). Introduction of an electron-withdrawing substituent *para* to the hydroxy group provided allylation product **3b** in moderate yield (entry 2). A nitro group *para* to the hydroxy group was most efficient and gave products **3c**,**d** in good yields even at room temperature (entries 3–5). In entry 4, unreacted allyltin was recovered almost quantitatively. Next, in order to clarify the role of the hydroxy group in this reaction, we carried out experiments using carbonyl compounds **1d**,**e** which have no hydrogen bond, and found that such substrates gave no adduct under the same conditions described above (entries 6 and 7). Addition of *p*-nitrophenol was not effective for the allylation



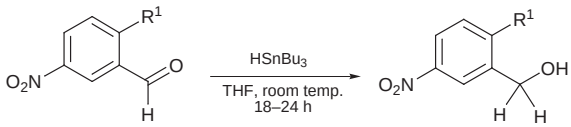
Scheme 1

Table 1 *ortho* Substituent effect in allylation reaction of carbonyl compounds[a]



Entry	1	X	R^1	R^2	R^3	*T*/°C	3	Yield (%)
1	**1a**	H	OH	Bu	H	reflux	**3a**	0
2	**1b**	Cl	OH	Bu	H	reflux	**3b**	49
3	**1c**	NO_2	OH	Me	H	room temp.	**3c**	96
4	**1c**	NO_2	OH	Bu	H	room temp.	**3c**	97
5[b]	**1c**	NO_2	OH	Bu	Me	room temp.	**3d**	quant.
6	**1d**	NO_2	H	Bu	Me	room temp.	**3e**	0
7	**1e**	NO_2	OMe	Bu	Me	room temp.	**3f**	0
8[c]	**1d**	NO_2	H	Bu	Me	room temp.	**3g**	8

[a] A mixture of an aldehyde (0.5 mmol) and a trialkylallyltin (1.0 mmol) was stirred in THF (1.0 ml) for 48 h. [b] 1 equiv. of trialkylallyltin was used. [c] 4-Nitrophenol (1.0 equiv.) was added to the reaction.



1c R^1 = OH
d R^1 = H
e R^1 = OMe

4a 92%
b 18%
c 12%

Scheme 2

(entry 8). These results clearly show that the hydroxy group of the substrate enhanced the reaction rate of the allylation. In view of the reaction mechanism, two paths are proposed for this rate enhancement (Scheme 1). The first one is that the intramolecular hydrogen bond directly promotes the allylation involving the stabilization of the transition state. In the second path, metalation of the hydroxy group first occurrs to give intermediate **A**. Another nucleophile attacks the carbonyl group of **A** activated by coordination to the internal stannyl group to give the product. The second path is not acceptable on the basis of the experimental result, namely, that 1 equiv. of tributylallyltin is sufficient to complete the reaction. The low reactivity of intermediate **A**, generated *in situ* by the reaction of **1c** with tributyltin methoxide, also suggests the second path can be ruled out.[7,8] These results indicate that the intramolecular hydrogen bond directly promoted the allylation reaction.

The intramolecular hydrogen bond also mediates reduction of carbonyl compounds with tributyltin hydride (Scheme 2). Similar reactivity tendency was also observed in this case. The substrate having an intramolecular hydrogen bond gave reduced product **4a** in good yield.

The immobility of the proton in the hydrogen bond made possible regioselective reaction of a multi-functional compound.[9] An aldehyde which has two carbonyl groups was prepared to examine the selectivity of the allylation.[10] The carbonyl group which is activated by the hydrogen bond was selectively allylated with tributylallyltin (Table 2). The selectivity was very high and minor product **7** was scarcely observed in these cases (entries 1 and 2). Substrates that have no hydrogen bond gave allylated products in poor yield (entries 3 and 4). These results show that an intramolecular hydrogen bond activates a particular functional group in the substrate selectively and stabilizes the transition state to enhance the reaction rate.

In conclusion, a low-acidic intramolecular hydrogen bonding promotes nucleophilic reaction to a carbonyl group. Although the precise mechanism of these reactions involving a low-barrier hydrogen bond (LBHB) is still unclear, this method offers a new tool in organic synthesis.[6]

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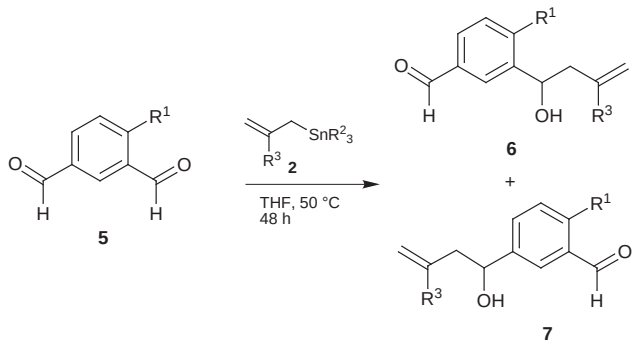
Table 2 Site selective allylation of carbonyl compounds using an intramolucular hydrogen bond[a]



Entry	5	R^1	R^2	R^3	Yield (%)	Ratio 6:7
1	**5a**	OH	Bu	H	95	> 50: < 1
2[b]	**5a**	OH	Bu	Me	99	> 50: < 1
3	**5b**	H	Bu	H	12	—
4	**5c**	OMe	Bu	H	not found	—

[a] A mixture of an aldehyde (0.5 mmol) and a trialkylallyltin (1.0 mmol) was stirred in dry THF (2.0 ml) at 50 °C for 48 h. [b] 5.0 ml of THF was used.

Notes and references

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7 After the addition of tributyltin methoxide and the removal of MeOH, the disappearance of **1c** and the appearance of a new set of signals attributed to the quantitative formation of **A** was observed by NMR analysis: δ_H(270 MHz, $CDCl_3$) 0.86 (t, *J* 7.3, 9H), 1.20–1.65 (m, 18H), 8.18 (d, *J* 9.2, 1H), 8.20 (d, *J* 9.2, 3.0, 1H), 8.54 (d, *J* 3.0, 1H), 10.28 (s, 1H).
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