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# Self-assembled Organic Nanotube Promoted Allylation of Ketones in Aqueous Phase

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**A self-assembled organic nanotube was found to promote the allylation of ketone reaction in aqueous phase.**

Multiple non-covalent interactions are involved in enzyme for activating substrates and stabilizing reaction transition state, thus lowering the activation energy and promoting the reaction under mild condition.[1] With the aim of mimicking enzyme, artificial supramolecular catalysts have been developed via non-covalent self-assembly of functional units. The catalytic performances, such as the reactivity and enantioselectivity, have been significantly improved in some supramolecular catalysis systems.[2] Especially, the reactivity could be enhanced hundreds of times in self-assembled cage catalytic system.[3] Therefore, it is highly desirable to develop self-assembled supramolecular catalytic system for promoting the inert or unfavorable reactions under mild conditions.

Allylation of carbonyl compounds offers an efficient method to prepare allylic alcohols, which are important bioactive intermediates.[4, 5] However, it is still more challenging to synthesize the tertiary homoallylic alcohols via allylation of ketone due to the fact that the ketone is more inert than aldehyde toward the catalyst.[6] A series of Lewis acids, such as Ti (IV), In (III), Cu (II), Cr (III), Fe (II) and Zn (II) species have been employed for activating ketone and promoting the reaction.[7] For these species, higher amounts of catalysts were needed in some cases and the reactions were usually performed in organic solvent system.[7, 8] In the enzyme catalysis system, ketone is generally activated via synergistic interaction of multi-hydrogen bonds.[9] Thus, it is appealing if the selective allylation of ketone could be performed in aqueous phase and under mild conditions using a supramolecular catalytic system.

Previously, we have developed self-assembled metal-nanotube to catalyze asymmetric Diels-Alder, Mukaiyama aldol reactions and both significantly increased reactivity and enantioselectivity were obtained in comparison with monomolecular component.[10] Herein, the self-assembled nanotube was employed for promoting the allylation of ketone reaction. It was found that the tetraallyltin which acted as an allylating reagent was able to integrate on the nanotube. Interestingly, through such c0-assembly, ketone could be efficiently activated by the synergistic effect from Sn species and the hydrogen bond effect from nanotube. The reaction progressed smoothly in the aqueous media together with moderate enantioselectivity.

**HDGA**, as shown in Figure 1, was used to as a starting building block for obtaining self-assembled nanotube. In experiments, HDGA was firstly added into water and heated to dissolve into a transparent solution. Then a hydrogel with was formed upon cooling.[10] During such process, self-assembled helical nanotube was formed.[10] Acetophenone was selected as ketone substrate, and several allylating reagents were selected as allylic precursors. Both the ketone substrate and allylating reagents were added into aqueous dispersion of **HDGA** nanotube and the reaction was carried out at room temperature. The results were shown in Figure 1. Almost no reaction happened when allyltriphenyltin (**1**), allyltributylstannane (**2**), allylboronic acid pinacol ester (**3**) were used as allylating reagents. However, the reaction progressed smoothly when tetraallyltin (**4**) was employed as the allylic precursor, and 91% yield was obtained after 24 h (Figure 1). While an extra Lewis acid was always needed for catalyzing the reaction in previous researches,[7] here, only the self-assembled nanotube was found to promote the reaction.

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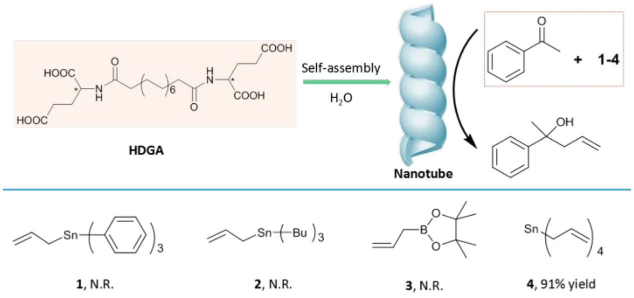
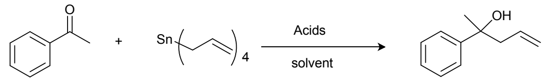


**Figure 1** Allylation of ketone in aqueous dispersion of **HDGA** nanotube under various Sn reagents. The reaction condition: **HDGA** (1 equiv), acetophenone (1 equiv), Sn reagents (1 equiv), the reaction was performed in aqueous solution at room temperature for 24 h.

For searching the actual reason why nanotube could promote the reaction, a series of experiments were performed. Firstly, considering that proton may activate the carbonyl group of acetophenone via hydrogenation bond interaction, a series of organic and inorganic acids were employed instead of self-assembled nanotube. In case of $CH_3COOH$ as activator, no product could be detected (Table 1, entry 1). The reaction was retarded when $CF_3COOH$ or HCl was involved, which gave 35% and 3% yield, respectively (entry 2 and entry 3). Furthermore, when Boc-Glu was used as organic acid for promoting the reaction, no conversion was observed either (entry 4). Secondly, in several polar solvents such as DMF, DMSO and $CH_3OH$, where **HDGA** completely dissolved in a molecular state, no allylating reaction was proceeded (entry 5-7).

**Table 1** Allylation of ketone under various acid media[a]



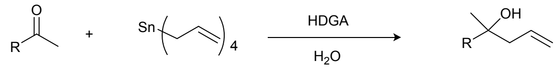
| Entry | Acid | Solvent | Yield(%) |
|---|---|---|---|
| 1 | CH3COOH | $H_2O$ | - |
| 2 | CF3COOH | $H_2O$ | 35 |
| 3 | HCl | $H_2O$ | 3 |
| 4 | Boc-Glu | $H_2O$ | - |
| 5 | **HDGA** | DMF | - |
| 6 | **HDGA** | DMSO | - |
| 7 | **HDGA** | $CH_3OH$ | - |
| 8[b] | **HDGA** | $H_2O$ | 89 |
| 9 | Poly(acrylic acid) | $H_2O$ | 6 |
| 10 | Hexadecanedioic acid | $H_2O$ | - |

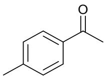
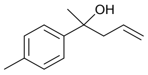
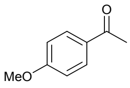
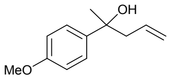
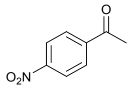
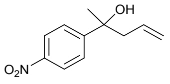
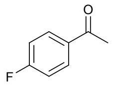
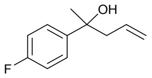
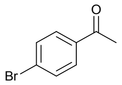
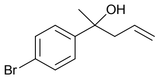
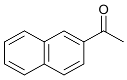
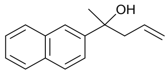
a) In all the experiments, the reaction was carried out using tetraallyltin (1 equiv), acetophenone (1 equiv), and acid (1 equiv) at room temperature for 24 h; b) the reaction was carried out using tetraallyltin (1 equiv), acetophenone (1 equiv), and HDGA (0.3 equiv) at room temperature for 48 h.

Thirdly, the reaction proceeded smoothly with 0.3 equiv of **HDGA** nanotube in water after prolonging the reaction time (entry 8). When Poly(acrylic acid), which possess many carboxylic acid groups and does not form nanostructure, was used as the activator, only trace product could be detected (entry 9). Finally, in consideration of heterogeneous system of **HDGA** nanotube dispersion, Hexadecanedioic acid, which forms amorphous precipitation in water, was also used as activator, and almost no reaction happened (entry 10). These results indicated that self-assembled **HDGA** nanotube played a vital role in promoting the reaction.

The substrate scope of the reaction was further investigated and the results were shown in Table 2. When para-methyl acetophenone was used as a substrate, 72% yield of product was obtained (Table 2, entry 1). The yield was decreased to 44% in case of electron donor para-methoxy substituted acetophenone as the substrate (Table 2, entry 2). Nearly full conversion were reached when para-(fluoro, nitro and bromo) acetophenone were used as substrates, indicated that electron-withdraw groups on the benzene were more favorable for the reaction (Table 2, entry 3-5). Also, when acetonaphthone was employed as a substrate, 88% yield was reached, indicating that this catalytic system was efficient on a range of substrates in aqueous media.

**Table 2** substrate scope of allylation reaction[a]



| Entry | Ketone | products | Yield(%) |
|---|---|---|---|
| 1 |  |  | 72 |
| 2 |  |  | 44 |
| 3 |  |  | 97 |
| 4 |  |  | 96 |
| 5 |  |  | 96 |
| 6 |  |  | 88 |

a) In all the experiments, the reaction was carried out using tetraallyltin (1 equiv), ketone (1 equiv), and **HDGA** (1 equiv) at room temperature for 24 h.

Tetraallyltin is prone to leave one or more allylic groups and forms carboxylic substituted allyltin after reacting with the organic acid.[11] In **HDGA** nanotube system, it was difficult to detect the actual Sn product after tetraallyltin being added into nanotube aqueous dispersion. CD spectra were used to investigate their interactions due to the chiral feature of helical nanotube. The results were shown in Figure 2. No CD signal could be detected for **HDGA** self-assembled nanotube in the absorption region of tetraallyltin (Figure 2, black line). However, a negative and positive Cotton effect at 256 nm and

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217 nm with a crossover at 238 nm was observed after addition of tetraallyltin in HDGA nanotube dispersion (4 hours later), which was coincident with the UV-absorption of tetraallyltin (Figure 2, red line). This proved that tetraallyltin was co-assembled with the nanotube during the reaction process and aligned in a chiral manner. Furthermore, the morphology of assembled nanotube was investigated after tetraallyltin being added into **HDGA** nanotube water dispersion, and nanotube structure was found to be well preserved (AFM and TEM images were shown in Figure S1).

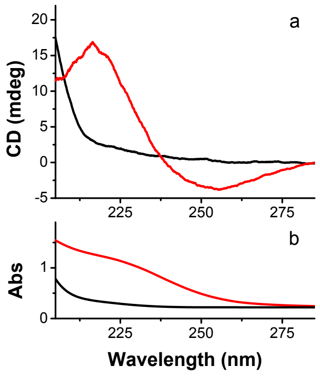


**Figure 2** a) CD spectra of **HDGA** before (black line) and after addition of tetraallyltin (red line), upper column; b) UV/Vis spectra of HDGA before (black line) and after addition of tetraallyltin (red line).

The enantioselectivity for the reaction was also investigated with the acetophenone as substrate. Moderate enantiomeric excess of the product with 25% ee was obtained at room temperature (Table 3, entry 1). The ee value could be increased to 43% when the reaction was performed at 0 °C (Table 3, entry 2).

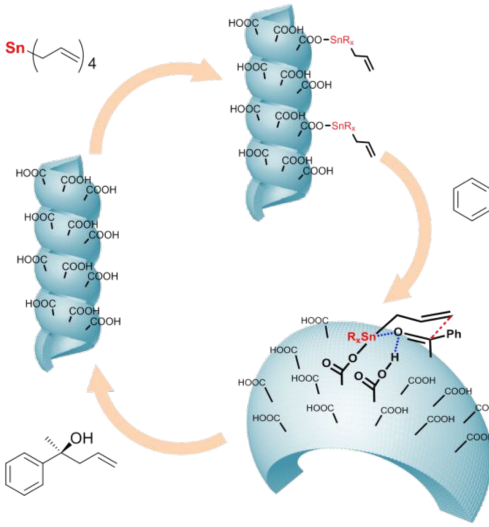
**Table 3** Allylation of ketone under mixture solution of MeOH and $H_2O$[a]

| Entry | Solvent (MeOH: $H_2O$) | Yield (%) | ee (%) |
|---|---|---|---|
| **1** | 0:1 | 91 | 25 |
| **2**[b] | 0:1 | 74 | 43 |
| **3** | 1:2 | 60 | 15 |
| **4** | 1:1 | 22 | 10 |
| **5** | 2:1 | 14 | 4 |
| **6**[c] | 0:1 | 13 | 3 |

a) In all the experiments, the reaction was carried out using tetraallyltin (1 equiv), acetophenone (1 equiv), and **HDGA** (1 equiv) at room temperature for 24 h. b) The reaction was performed at 0 °C. c) 3 equiv of NaOH was added to dissolve the **HDGA** hydrogel.

The enantioselective catalytic performance of **HDGA** assembly was further investigated in the methanol-$H_2O$ mixed solvents. When the volume ratio of MeOH:$H_2O$ was 0.5:1, where a gel was formed and nanotube structure still remained (AFM, Figure S2b), the reactivity and stereoselectivity was slightly decreased (Table 3, entry 3). Further increment of the MeOH (MeOH:$H_2O$, 1:1 and 2:1) caused the gel collapse (Figure S2c and S2d). In these cases, both the reactivity and enantioselectivity decreased significantly (Table 3, entry 4 and entry 5). Furthermore, when NaOH was involved to dissolve the hydrogel (Figure S3), only small amount of product with poor enantioselectivity was obtained (Table 3, entry 6). These results indicated that the self-assembled nanotube was essential for promoting the reaction and offering the enantioselectivity.

Based on the above research results, a hypothesis for the reaction mechanism was proposed in Scheme 1. In the first step, tetraallyltin was incorporated into the nanotube, as verified from the CD spectra. When another substrate acetophenone was added, once acetophenone was closed to Sn site, the carbonyl group may be synergistically activated by the Lewis acid effect of Sn complex and hydrogen bond interaction of adjacent carboxylic acids, thus promoted the reaction. Here, the multi-carboxylic acid groups are very important. It should be noted that the close chiral alignment of carboxylic acids on the self-assembled nanotube enabled the reactivity and enantioselectivity for the allylating reaction. This hypothesis can be supported by the following facts. When the non-assembled organic acids were employed as activator, tetraallyltin was also able to covalently bond to organic acid, and acetophenone could also close to Sn precursor. However, unlike the self-assembled nanotube where Sn sites were surrounded by the carboxylic acid groups, the non-assembled system has only discrete organic acid sites and could not activate both Sn sites and acetophenone simultaneously, thus giving low catalysis activity for the reaction. Moreover, the curved surfaces of the nanotube could offer an asymmetric microenvironment, which provided the prerequisite for the enantioselectivity of reaction.



**Scheme 1** Proposed mechanism for **HDGA** promoting the allylation of ketone. The first step, tetraallyltin was incorporated onto nanotube via leaving one or more allylic groups. Second, acetophenone was added, once it close to Sn sites, it can be activated by the synergistic effect of Sn specious and carboxylic acids, thus promoted the reaction.

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In conclusion, a self-assembled helical nanotube was found to serve as a platform for promoting allylation of ketone in aqueous media. When tetraallyltin was connected to the nanotube, a catalytic transformation site was formed. Another substrate acetophenone can be synergistically activated by the Sn species and hydrogen bond interaction from adjacent carboxylic acids on the nanotube, thus promoted the reaction. While extra Lewis acid should be involved in the previously reported molecular catalytic system for the allylation of ketone, here, only the nanotube can work well. It demonstrated that self-assembled architecture can provide synergistic activation effect on both catalyst and substrate to promote the reaction.

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## Conflicts of interest

There are no conflicts to declare.

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