Allylation of Unactivated Ketones by Tetraallyltin Accelerated by Phenol. Application to Asymmetric Allylation Using a Tetraallyltin-BINOL System

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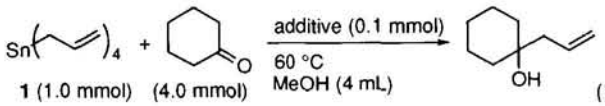
The tetraallyltin-phenol system was mild and effective for allylation of unactivated ketones, giving tertiary alcohols in high yields. The asymmetric allylation was achieved by a tetraallyltin-homochiral BINOL (1,1'-bi-2-naphthol) system. The addition of methanol raised the enantioselectivity to afford the tertiary homoallylic alcohol up to 60% ee.

An asymmetric synthesis of functionalized tertiary alcohols would be valuable for stereoselective organic syntheses. Although the enantioselective allylation of aldehydes is a powerful strategy to afford secondary homoallyl alcohols,[1] few asymmetric allylations of ketones to give tertiary alcohols have been reported;[2] the asymmetric system is limited to use of reactive ketones such as α-oxoketones.[3] This is probably because the conditions for the allylation of unactivated ketones are too severe to control the stereoselectivity, and, therefore, more mild and effective methods are required. Recently, Tietze has addressed this problem by an indirect, two-step procedure involving the diastereoselective synthesis of homoallylic ethers and the reductive cleavage into alcohols.[4] Our work aimed to attain the direct synthesis of these compounds.

The choice of the allylation reagent would be most crucial for asymmetric allylation of ketones. In asymmetric allylation of aldehydes, allyltrialkylstannanes have been widely used.[1b-f] Even in racemic synthesis, however, few examples of allylation of ketones by simple allylic tin reagents such as allyltrialkyltins have been reported owing to their low reactivity. The employment of reactive ketones bearing an electron-withdrawing group[5a,b] or allylic tin reagents with electronegative substituents on tin[5c-g] has led to ketone allylation. We chose modified allylic tin reagents for allylation of ketones because the reactivity of organotin compounds can be controlled easily by modification of the substituents on tin or addition of ligands.[6] In this study, we first had to investigate an effective allylation system for unactivated ketones like acetophenone before examination of asymmetric allylation. We now report a tetraallyltin-phenol system for allylation of ketones, and a tetraallyltin-BINOL (1,1'-bi-2-naphthol) system for asymmetric synthesis.

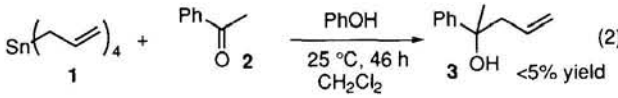
Young has recently reported an effective allylation by tetraallyltin in methanol.[7] In this system, allylation of ketones, however, often proceeded in moderate yields after a long induction period as compared with allylation of aldehydes. We also have independently investigated this type of acceleration using alcohols.[8] Methanol was found to act as an effective trapping reagent of tin alkoxide intermediates formed through the addition of allyltin to carbonyls, furnishing homoallyl alcohols and a methoxyallyltin species. Furthermore, the resulting methoxyallyltin species would have higher allylation-reactivity than the original tetraallyltin owing to their high Lewis acidity.[7,8] This idea was supported by the fact shown in eq.1. The addition of a small amount of $Bu_2Sn(OMe)_2$ completed the allylation of cyclohexanone with tetraallyltin (**1**) in methanol within 0.5 h to give 96% yield, while a long induction period was required without the additive. At an early stage of the reaction with $Bu_2Sn(OMe)_2$, a small amount of a methoxyallyltin species was generated in redistribution between tetraallyltin (**1**) and $Bu_2Sn(OMe)_2$, and promoted the initial allylation step. These results prompted us to investigate other effective additives which could form *O*-substituted allyltin species more easily. We examined the effect of phenol, which would have higher reactivity toward tetraallyltin than methanol and give a reactive allylic phenoxytin species.



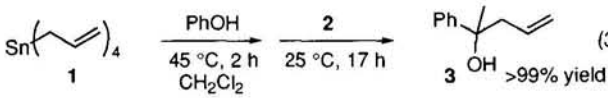
1 (1.0 mmol) (4.0 mmol) (1)

additive; none 4% yield (1.0 h), 96% yield (2.5 h)
$Bu_2Sn(OMe)_2$ 96% yield (0.5 h)

We attempted the reaction of tetraallyltin (**1**) with acetophenone (**2**). Only a trace amount of homoallyl alcohol **3**, however, was obtained in the presence of phenol as an additive at 25 °C for 46 h (eq. 2). A dramatic change in reactivity was observed to afford **3** quantitatively at 25 °C for 17 h, when premixing of **1** and phenol at 45 °C for 2 h was attempted before



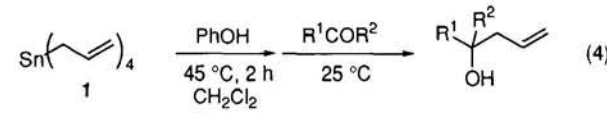
1 **2** **3** (2) <5% yield



1 **3** (3) >99% yield

1 (1.0 mmol), **2** (1.0 mmol), PhOH (2.0 mmol), CH_2Cl_2 (1 mL).

adding **2** (eq. 3). These results of eqs 2 and 3 demonstrate that an active phenoxytin species would be sufficiently effective to realize the allylation. On the contrary, the employment of HCl, which was reported to be an effective activator of aldehyde-allylation,[9] led to decomposition of tetraallyltin because of sluggish allylation of ketones. In fact, only *ca.* 30% of tetraallyltin was recovered from the solution of **1** in HClaq (1 equiv)/THF at 25 °C for 1 h. These results showed the efficiency of phenol as a mild generator of the initial active species,[10] owing to its medium reactivity toward tetraallyltin. This system was applicable to various



1 (4)

R^1 = Pr	R^2 = Me	1 h	>99% yield
R^1 = $PhCH_2CH_2$	R^2 = Me	5 h	87%
R^1 = $-(CH_2)_5-$ = R^2		0.5 h	>99%
R^1 = (*E*)-PhCH=CH	R^2 = Me	20 h	>99%

ketones such as aromatic, aliphatic, and cyclic substrates under mild conditions, giving tertiary alcohols in high yields (eqs 3 and 4). In the reaction with the α,β-unsaturated ketone, exclusive 1,2-addition was observed (eq. 4).

Next, we explored the application to enantioselective allylation of simple ketones. Since phenol showed high efficiency as a promoter, we examined (*R*)-BINOL (**4**) bearing similar hydroxy groups as an additive (Table 1). A mixture of **1** and **4** was heated at 45 °C for 2 h and then was treated with an equimolar amount of acetophenone (**2**) at 25 °C to afford the homoallyl alcohol **3** in 16%ee (entry 1).[11] The treatment at 0 °C for 7 h improved both the yield and the enantioselectivity (entry 2). Variations of the molar ratio of **1/2/4** were investigated and gave higher value of ee at the ratio of 3/1/2 (entry 4). An interesting effect of alcohols on the enantioselectivity was observed (entries 8-10). Two equivalents of methanol raised ee from 52 to 60%. The addition of excessive amount of methanol gave a low ee (entry 12). The reaction at -10 °C was sluggish and lacked enantioselectivity (entry 13). The system in entry 10 is the best result of asymmetric allylation of acetophenone to form directly a homoallylic tertiary alcohol, as far as we know. The reaction with 4-phenyl-3-buten-2-one under similar conditions of entry 10 (0 to 20 °C, for 65 h) afforded the product in 34% ee (95% yield). The allylic aryloxytin at the premixing step is thought to be generated although the detail investigation has not been performed yet.

We are currently developing this methodology for other substrates and reagents.

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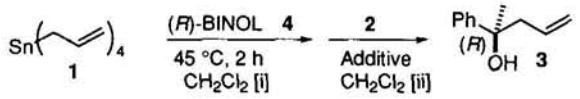
Table 1. Asymmetric allylation of acetophenone



Entry	1 : 2 : 4[a]	Add. (mmol)	Temp./°C	Time/h	Yield/%	Ee/%[b]
1[c]	1 : 1 : 1	none	25	2	65	16
2[c]	1 : 1 : 1	none	0	7	79	41
3[c]	3 : 1 : 1	none	0	19	98	43
4[d]	3 : 1 : 2	none	0	19	>99	52
5[e]	3 : 1 : 3	none	0	22	99	47
6[d]	3 : 2 : 2	none	0	7	82	31
7[d]	3 : 3 : 2	none	0	6	71	15
8[d]	3 : 1 : 2	*t*-BuOH (2)	0	24	>99	48
9[d]	3 : 1 : 2	*i*-PrOH (2)	0	18	>99	57
10[d]	3 : 1 : 2	MeOH (2)	0	18	>99	60
11[d]	3 : 1 : 2	MeOH (2)	25	3.5	>99	50
12[d]	3 : 1 : 2	MeOH (3 mL)	0 to 25	60	32	15
13[d]	3 : 1 : 2	MeOH (2)	-10	48	40	9.4

[a] mmol. [b] Ee values were determined by chiral HPLC analysis (DAICEL CHIRALCEL OJ). [c] CH_2Cl_2, [i]; 4 mL and [ii]; 8 mL. [d] CH_2Cl_2, [i]; 8 mL and [ii]; 4 mL. [e] CH_2Cl_2, [i]; 12 mL and [ii]; 0 mL.

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10 Other investigations using MeOH or ^{i}PrOH instead of phenol failed. A trace amount of **3** was obtained under the same conditions.

11 The absolute configuration was determined by comparison of the optical rotation with that reported in the literature (Ref. 3b).