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Diastereoselective Addition of γ-Substituted Allylic Nucleophiles to Ketones: Highly Stereoselective Synthesis of Tertiary Homoallylic Alcohols Using an Allylic Tributylstannane/Stannous Chloride System

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Abstract: The diastereoselective addition of γ-substituted allylic nucleophiles to ketones has been accomplished to give tertiary homoallylic alcohols. The reaction of tributylcinnamyltin **1a** with simple ketones **2** in the presence of stannous chloride ($SnCl_2$) gave the tertiary homoallylic alcohols **3**, which include the anti form (based on Ph and OH), with high diastereoselectivity. In the reaction course, transmetalation of tributylcinnamyltin **1a** with $SnCl_2$ proceeds to form an active nucleophile which is tentatively considered to be a cinnamyltin(II) species. A cyclic transition state **A** is favorable because the chlorinated tin(II) center is highly capable of accepting ligands. The other diastereomers (syn form) **4** were obtained in the reaction of tributylcinnamyltin **1a** with ketones **2** by the use of $BF_3{\cdot}OEt_2$ instead of $SnCl_2$. This reaction proceeds through an acyclic transition state in which BF_3 acts as a Lewis acid for activation of ketones. When 3-tributylstannylcyclohexene **1b** or 3-tributylstannylcyclopentene **1c** was used with $SnCl_2$, high diastereoselective formation of the corresponding homoallylic alcohols **6** which have the syn form (based on ring chain and OH) was observed. The selectivity was also explained by the cyclic transition state **B**. When tributylcrotyltin **1d** or **1e** was used, the stereochemistry of the products depends on the additives ($SnCl_2$ or $BF_3{\cdot}OEt_2$), substituents of ketones, and reaction temperature. It is interesting that those additives compensate for each other in terms of diastereoselective alkylation. The alkylation of α-alkoxy, aryloxy, or hydroxyketones **16** was achieved in extremely high selectivity using an allylic tributyltin **1a**−**c**/$SnCl_2$ system. The chelation by carbonyl and β-oxygens provides a rigid transition state (**E** or **F**) for selective reactions. It is noted that the hydroxyketone can be used without protection in this reaction system. The relative stereochemistry of the produced tertiary homoallylic alcohols was determined on the basis of X-ray analyses.

Introduction

A stereoselective carbon−carbon bond formation is one of the most important reactions to construct a carbon skeleton in organic synthesis. A diastereoselective addition of γ-substituted allylic metals to aldehydes is a powerful method for that purpose and has been extensively studied,[1] giving secondary homoallylic alcohols bearing adjacent chiral centers with high selectivity. However, the stereoselective reaction of the γ-substituted allylic metals with simple ketones instead of aldehydes has been rarely reported. This is probably because the conditions achieving the allylation of ketones would be too severe to control the selective addition owing to the much lower reactivity of ketones than that of aldehydes.[2] Additionally, the difference in steric demand between two substituents on the carbonyl carbon, which leads to the stereoselection, is smaller in ketones than in aldehydes.[3] In fact, as far as we know, the stereoselective addition of a cinnamyl nucleophile to ketones has not so far been reported with determination of the stereochemistry of the products which are tertiary homoallylic alcohols.[3a,4−6] A cinnamyl Grignard reagent, which is a common alkylating reagent, gave poor

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(1) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243−249. (c) *Comprehensive Organic Syntheses*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 1. (d) *Comprehensive Organic Syntheses*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 2.

(2) The striking difference in reactivity between aldehydes and ketones sometimes presents a problem in the selective reaction using ketones. For recent papers dealing with the reaction of ketones to overcome their different reactivity from that of aldehydes, see: (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446. (b) Yasuda, M.; Kitahara, N.; Fujibayashi, T.; Baba, A. *Chem. Lett.* **1998**, 743−744. (c) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061−1063.

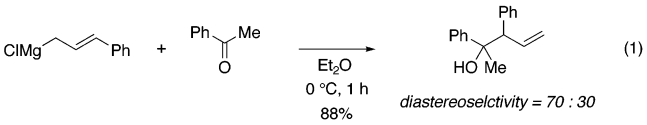
(3) Although a few papers dealing with crotylation of ketones have appeared, they usually afford moderate selectivities. (a) Maeda, H.; Shono, K.; Ohmori, H. *Chem. Pharm. Bull.* **1994**, *42*, 1808−1812. (b) Sjöholm, R. E. *Acta Chem. Scand.* **1990**, *44*, 82−89. (c) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441−1454. (d) Katritzky, A. R.; Fali, C. N.; Qi, M. *Tetrahedron Lett.* **1998**, *39*, 363−366. (e) Rollin, Y.; Derien, S.; Duñach, E.; Gebehenne, C.; Perichon, J. *Tetrahedron* **1993**, *49*, 7723−7732. (f) Hebri, H.; Duñach, E.; Périchon, J. *Tetrahedron Lett.* **1993**, *34*, 1475−1478. (g) Seebach, D.; Wildler, L. *Helv. Chim. Acta* **1982**, *65*, 1972−1981.

(4) Sjöholm, R.; Rairama, R.; Ahonen, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1217−1218.

(5) Araki, S.; Hatano, M.; Ito, H.; Butsugan, Y. *J. Organomet. Chem.* **1987**, *333*, 329−335.

10.1021/ja0274047 CCC: $22.00

selectivity in the reaction with acetophenone (eq 1). This result clearly shows that a highly nucleophilic species would give low selectivity for the allylation and a nucleophile which has appropriate reactivity is required.



(1)

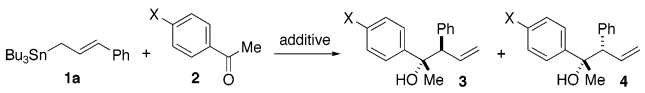
The lack of information to determine the stereochemistry of the products as well as the difficulty of finding a suitable reaction system might have retarded the development of this area of chemistry. In this paper, we report the following: (i) Highly diastereoselective addition of γ-substituted allylic nucleophiles toward simple ketones was achieved to form each diastereomer of tertiary homoallylic alcohols by an allylic tin(IV)$-SnCl_2$ or $-BF_3$ system. Those two systems mostly show different diastereoselectivities (syn or anti). (ii) The stereochemistry of the products was unambiguously determined on the basis of X-ray analysis. (iii) The highly selective allylation of α-alkoxy, aryloxy, or hydroxy ketones was controlled by strong oxophilicity of the Sn(II) species that contributes to form a rigid chelated cyclic transition state.

Results and Discussion

Diastereoselective Alkylation of Aryl Methyl Ketones with Allylic Stannanes. We have previously reported a system using allyltributylstannane with $SnCl_2$,[7] which accomplished the allylation of ketones as well as aldehydes. This system also provided highly diastereoselective addition of γ-substituted allylic stannanes to aldehydes. We then examined this system for cinnamylation of acetophenone, which gave, gratifyingly, a promising result: To a reaction mixture of $SnCl_2$ (1 equiv) and acetophenone **2a** (1 equiv) in acetonitrile was added tributylcinnamyltin **1a** (1 equiv) to give homoallylic alcohol in 82% yield with high diastereoselectivity (**3a**/**4a** (anti/syn) = 92/8) (Table 1, entry 1).[8] Only a small amount of an α-adduct (<5%) was detected in the NMR spectra.[9] In the course of our investigation of other solvents, it was found that the use of dichloromethane, THF, benzene, or hexane resulted in almost no reaction. Varying the substituents, which have an either electron-withdrawing or -donating property on the phenyl ring in acetophenone, did not affect the selectivities (entries 2−5). We turned our attention to Lewis acid-promoted allylation. A $BF_3{\cdot}OEt_2$-accelerated allylation, which is an established method for allylation of aldehydes using allylic stannanes, showed a particular contrast to the reactions using $SnCl_2$. As shown in entries 6−9, the *syn*-homoallylic alcohols **4a**−**d** were preferably formed, although the ketone **2e** bearing an electron-donating group was inert to this reaction system (entry 10). These results show that a switch of diastereoselectivity can be accomplished by the addition of accelerators, $SnCl_2$ or $BF_3{\cdot}OEt_2$.

We next examined the reaction using cyclic allylic stannanes **1b** and **1c**, which have cis geometry at their olefinic moiety.

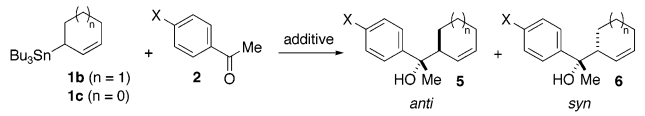
Table 1. Diastereoselective Addition of **1a** to **2**



entry	X	ketone	additive	yield/%	**3**:**4**
1[a]	H	**2a**	$SnCl_2$	82 (**3a**, **4a**)	92:8
2[a]	Cl	**2b**	$SnCl_2$	73 (**3b**, **4b**)	92:8
3[a]	Br	**2c**	$SnCl_2$	84 (**3c**, **4c**)	93:7
4[a]	Me	**2d**	$SnCl_2$	52 (**3d**, **4d**)	94:6
5[a]	OMe	**2e**	$SnCl_2$	56 (**3e**, **4e**)	88:12
6[b]	H	**2a**	$BF_3{\cdot}OEt_2$	49 (**3a**, **4a**)	16:84
7[b]	Cl	**2b**	$BF_3{\cdot}OEt_2$	67 (**3b**, **4b**)	13:87
8[b]	Br	**2c**	$BF_3{\cdot}OEt_2$	83 (**3c**, **4c**)	13:87
9[b]	Me	**2d**	$BF_3{\cdot}OEt_2$	29 (**3d**, **4d**)	11:89
10[b]	OMe	**2e**	$BF_3{\cdot}OEt_2$	0	

[a] Reactions were carried out in acetonitrile with cinnamylstannane **1a** (1.0 mmol), ketone **2** (1.0 mmol), and $SnCl_2$ (1.0 mmol) at room temperature for 3 h. [b] Reactions were carried out in dichloromethane with **1a** (1.0 mmol), **2** (1.0mmol), and $BF_3{\cdot}OEt_2$ (2.0 mmol) at 0 °C for 20 h.

Table 2. Diastereoselective Addition of **1b** or **1c** with **2**



entry	allylic tin	X	ketone	additive	yield/%	**5**:**6**
1[a]	**1b**	H	**2a**	$SnCl_2$	79 (**5a**, **6a**)	<1:99
2[a]	**1b**	Cl	**2b**	$SnCl_2$	87 (**5b**, **6b**)	<1:99
3[a]	**1b**	Br	**2c**	$SnCl_2$	96 (**5c**, **6c**)	<1:99
4[a]	**1b**	Me	**2d**	$SnCl_2$	87 (**5d**, **6d**)	<1:99
5[a]	**1b**	OMe	**2e**	$SnCl_2$	92 (**5e**, **6e**)	12:88
6[a]	**1c**	H	**2a**	$SnCl_2$	84 (**5f**, **6f**)	<1:99
7[b]	**1b**	H	**2a**	$BF_3{\cdot}OEt_2$	52 (**5a**, **6a**)	19:81

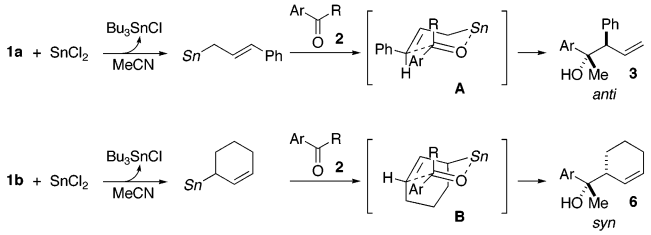
[a] Reactions were carried out in acetonitrile with allylic stannane **1b** or **1c** (1.0 mmol), ketone **2** (1.0 mmol), and $SnCl_2$ (1.0 mmol) at room temperature for 3 h. [b] Reactions were carried out in dichloromethane with **1b** or **1c** (1.0 mmol), **2** (1.0 mmol), and $BF_3{\cdot}OEt_2$ (2.0 mmol) at 0 °C for 2 h.

The results are summarized in Table 2. The reaction of 3-stannylcyclohexene **1b** with acetophenone **2a** in the presence of $SnCl_2$ gave the syn product **6a** in high yield with perfect selectivity (Table 2, entry 1). The product has different stereoconfiguration from that obtained in the reaction of **1a** that has trans geometry. The substituents on the aryl ring did not affect the yield and selectivity. A five-membered cyclic allylic stannane **1c** also gave the syn product **6f** exclusively (entry 6). The $BF_3{\cdot}OEt_2$-mediated reaction of **1b** with **2a** gave preferably the same isomer **6a** in lower yield and selectivity than the reaction using $SnCl_2$ (entries 1 and 7).

These reactions using $SnCl_2$ in Tables 1 and 2 are stereospecific because the geometry on the allylic moiety relates to the stereochemistry of the product; *trans*-allylic stannane gives an anti product, and cis type gives a syn product. A mixture of cinnamylstannane **1a** with $SnCl_2$ in acetonitrile without ketone afforded 92% of Bu_3SnCl, which was monitored by ^{119}Sn NMR. This result strongly suggests the transmetalation between **1a** and $SnCl_2$ and the generation of a new species which could be allylic tin(II).[10] A color change of the suspended solution to dark brown was found in this case without ketone. The addition

(6) The reaction of allylic silicon compounds with ketimine was reported: Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Org. Chem.* **2002**, *67*, 5359−5364.
(7) Yasuda, M.; Sugawa, Y.; Yamamoto, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1996**, *37*, 5951−5954.
(8) The terms anti and syn are used on the basis of the relationship between OH and Ph as shown in the schemes.
(9) 2,5-Diphenyl-4-penten-2-ol was observed as a minor product.[3f]
(10) Unfortunately, an allylic tin species was not confirmed probably because of broadening of its signal in ^{119}Sn NMR.

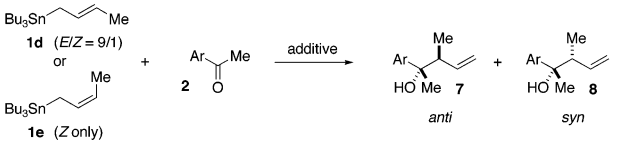
Scheme 1. Plausible Path in the Reaction of **1a** or **1b**

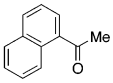


of acetophenone **2a** to the stirred mixture of **1a** and $SnCl_2$ for 20 min in acetonitrile gave a lower yield (41%) than that in Table 1. The active species generated by transmetalation might be gradually decomposed or deactivated by oligomerization. Interestingly, no color change was found during the general reaction procedure in which **1a** was added to the premixed suspension of **2a** and $SnCl_2$. In this case, the active species is immediately consumed and smoothly gives the product.[11] On the basis of the stereochemical outcome, plausible reaction paths are proposed in Scheme 1. At first, transmetalation of **1a** with $SnCl_2$ proceeds to form an active nucleophile which is tentatively considered to be a cinnamyltin(II) species.[7,12,13] A cyclic transition state is favorable because the chlorinated tin(II) center is highly capable of accepting ligands.[13a,b,14] In this transition state **A**, a methyl group in ketone **2** (R = Me) occupies an axial position owing to its less steric hindrance than that of the aryl group (Ar), giving highly diastereoselective formation of homoallylic alcohols **3** (anti product). The alkylation with allylic stannanes **1b** or **1c** which have a cis olefinic site also proceeds through cyclic transition state **B** to give **6** (syn product). When cinnamyl Grignard was used instead of **1a** as an alkyl source for transmetalation with $SnCl_2$, no reaction with acetophenone was observed.[15,16] This result shows tin reagents are indispensable to generate an active species for the alkylation in which Bu_3SnCl probably plays a key role to form a monomeric active tin(II) species.[13a]

Because there are many precedents of the reaction courses of Lewis acid-accelerated allylation of aldehydes using allylic stannanes,[17] we assume that the reactions with ketones using $BF_3{\cdot}OEt_2$ proceed through an acyclic transition state as proposed by Yamamoto[1b] or Keck.[18] In the reaction system, the stereochemistry of the major products is independent of the geometry of the olefinic moiety in the starting allylstannanes. For the $BF_3{\cdot}OEt_2$ reactions with ketones in Tables 1 and 2, in fact, syn-type products were predominantly obtained.

Table 3. Diastereoselective Addition of **1d** or **1e** with **2**[a]



entry	allylic tin	ketone	additive	conditions	yield/%	7 : 8
1[a]	**1d**	**2a**	$SnCl_2$	rt, 3 h	100 (**7a**, **8a**)	33:67
2[a,b]	**1d**	**2a**	$SnCl_2$	rt, 3 h	78 (**7a**, **8a**)	24:76
3[a]	**1e**	**2a**	$SnCl_2$	rt, 3 h	100 (**7a**, **8a**)	30:70
4[a]	**1d**	**2a**	$SnCl_2$	rt, 2 h then 82 °C, 2 h	65 (**7a**, **8a**)	77:23
5[a]	**1e**	**2a**	$SnCl_2$	rt, 2 h then 82 °C, 2 h	61 (**7a**, **8a**)	83:17
6[a]	**1d**	**2b**	$SnCl_2$	rt, 3 h	100 (**7b**, **8b**)	32:68
7[a,b]	**1d**	**2b**	$SnCl_2$	rt, 3 h	42 (**7b**, **8b**)	29:71
8[c]	**1d**	**2a**	$BF_3{\cdot}OEt_2$	-60 °C, 60 h	58 (**7a**, **8a**)	79:21
9[c]	**1e**	**2a**	$BF_3{\cdot}OEt_2$	-60 °C, 60 h	30 (**7a**, **8a**)	80:20
10[c]	**1d**	**2a**	$BF_3{\cdot}OEt_2$	0 °C, 3 h	83 (**7a**, **8a**)	39:61
11[c]	**1d**	**2b**	$BF_3{\cdot}OEt_2$	-60 °C, 60 h	17 (**7b**, **8b**)	67:33
12[a]	**1d**	 **2f**	$SnCl_2$	0 °C, 3 h	100 (**7f**, **8f**)	93: 7
13[a]	**1e**		$SnCl_2$	0 °C, 3 h	100 (**7f**, **8f**)	92: 8
14[a]	**1d**		$SnCl_2$	82 °C, 2 h	75 (**7f**, **8f**)	94: 6
15[a]	**1e**		$SnCl_2$	82 °C, 2 h	72 (**7f**, **8f**)	98: 2

[a] Allylic stannane **1** was added to the mixture of **2** and $SnCl_2$ in acetonitrile. [b] The ketone **2** was added to the mixture of **1** and $SnCl_2$ in acetonitrile. [c] All reactions were carried out in dichloromethane with **1** (1.0 mmol), **2** (1.0 mmol), and $BF_3{\cdot}OEt_2$ (2.0 mmol).

On the contrary, the reaction of crotylstannane showed unexpected results as depicted in Table 3. Crotylstannane can be prepared as the *E*-rich form **1d** or *Z*-form **1e**. The use of *E*-rich crotylstannane **1d** provided the corresponding homoallylic alcohols **7a** and **8a** in syn selectivity (entry 1). The selectivity was improved to 24/76 when the ketone was added to the mixture of **1d** and $SnCl_2$ in acetonitrile (entry 2). Surprisingly, the use of *Z*-crotylstannane **1e** gave the same isomer **8a** as a major product in 70% selectivity (entry 3). Ketone **2b** also gave preferably syn product **8b** using either **1d** or **1e** (entries 6 and 7). On the other hand, the reactions with **2a** using either **1d** or **1e** at higher temperature after stirring at room temperature gave anti product **7a** as a major product (entries 4 and 5). These results suggest that the intermediate nucleophiles are identical in both cases using **1d** and **1e** and that the homoallylic alcohol **8a** is a kinetic product and **7a** is a thermodynamic product. Interestingly, the $BF_3{\cdot}OEt_2$-accelerated alkylation showed opposite selectivity as compared with the reactions using $SnCl_2$. The reaction of **1d** and/or **1e** in the presence of $BF_3{\cdot}OEt_2$ gave anti product **7a** as the major product at −60 °C (entries 8 and 9) and syn alcohol **8a** at higher temperature (entry 10).

The reaction course of crotylstannane with $SnCl_2$ can be explained as shown in Scheme 2. The transmetalation of either **1d** or **1e** gives a common intermediate 3-metallobut-1-enyl species by rearrangement, which kinetically transforms to a *Z*-crotyl species.[19] The *Z*-crotyl species might then lead to **8Sn** preferably through cyclic transition state **D**. Under the reversible reaction conditions, the product ratio was thermodynamically controlled between **7Sn** and **8Sn**. Although the reaction mechanism using $BF_3{\cdot}OEt_2$ is not clear yet, it is quite interesting that the Lewis acid-accelerated system has complementary selectivity to the $SnCl_2$-mediated system. The reported examples

(11) The mixture of **1a** and $SnCl_2$ in dichloromethane gave Bu_3SnCl in 13% even after 7 h. The $SnCl_2$-mediated reaction of **1a** with **2a** in dichloromethane gave no product as described above. Thus, the correlation between transmetalation and yield was observed.

(12) Yasuda, M.; Matsukawa, Y.; Okamoto, K.; Sako, T.; Kitahara, N.; Baba, A. *Chem. Commun.* **2000**, 2149−2150.

(13) A referee suggested that the tin(II) species is unlikely to exist as a monomeric structure. The result of stereoselectivity apparently shows the cyclic transition state as illustrated in Scheme 1. The monomeric tin(II) compounds coordinated by two appropriate ligands are reported, and the tin center coordinates to Lewis acid. Therefore, in the transition state, the actual species could be chlorinated allylic tin(II) coordinated by carbonyl oxygen and acetonitrile and interacting with Bu_3SnCl. (a) Drost, C.; Hitchcock, P. B.; Lappert, M. F. *Organometallics* **1998**, *17*, 3838−3840. (b) Barret, M. C.; Mahon, M. F.; Molloy, K. C.; Steed, J. W.; Wright, P. *Inorg. Chem.* **2001**, *40*, 4384−4388.

(14) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923.

(15) To a solution of cinnamyl Grignard reagent (2 equiv) and $SnCl_2$ (2 equiv) in Et_2O was added acetophenone (1 equiv) at 0 °C, and the mixture was stirred for 3 h.

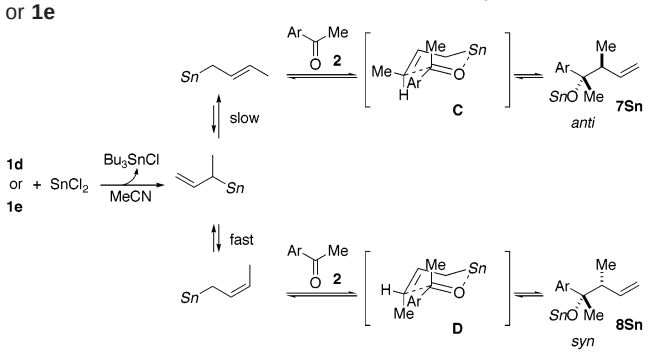
(16) The color change from gray to red-brown was observed when mixing the cinnamyl Grignard reagent and $SnCl_2$. This system probably gives an inactive species, for example, bis(cinnamyl)tin(II), by transmetalation.

(17) Nishigaichi, Y.; Takuwa, A.; Naruta, Y.; Maruyama, K. *Tetrahedron* **1993**, *49*, 7395−7426.

(18) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889−7896.

(19) Miyake, H.; Yamamura, K. *Chem. Lett.* **1992**, 1369−1372. In a cinnamyl case, the *Z*-form is too unstable to form, and then the *E*-form, which is a thermodynamic product, acts as the active species.

Scheme 2. Plausible Path in the Reaction of Crotylstannane **1d** or **1e**

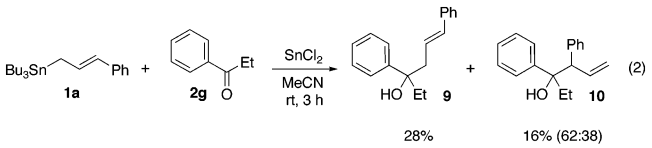


for crotylation of acetophenone mostly give **7a** as a major product or nonselectivity.[3] Only the crotyl Grignard is reported to provide **8a** as a major product, although the selectivity is lower than that of our results.[3b]

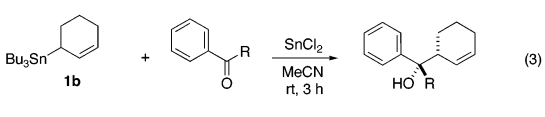
When 2-acetonaphthone **2f** was used as a substrate, both yield and selectivity were high in the $SnCl_2$-mediated reaction employing either **1d** or **1e** to give anti **7f** (entries 12 and 13 in Table 3). Elevating the temperature up to 82 °C gave no change in the stereochemistry (entries 14 and 15). The different diastereoselectivity giving the anti form observed in this case is not explainable at this stage. As can be seen, the crotylation of ketones is a characteristic feature in synthetic organic chemistry. There are more factors to control the diastereoselectivity as compared with the reaction with aldehydes.

The $SnCl_2$-mediated allylation using cinnamyltin, cycloalkenyltin, or crotyltin gave high selectivity for allylation of ketones. Especially for the reaction of cinnamyl and crotyltins, $SnCl_2$ and BF_3 systems show the opposite selectivity. This point greatly contributes to stereoselective synthetic organic synthesis.

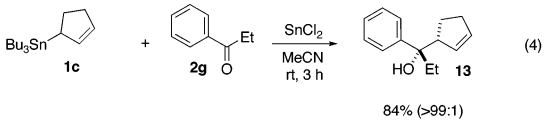
$SnCl_2$-Mediated Alkylation of Other Simple Ketones by Allylic Stannanes. When propiophenone **2g** was used for the $SnCl_2$-mediated reaction with **1a**, homoallylic alcohol **10** (γ-adduct) was obtained in poor diastereoselectivity accompanied with a significant amount of α-adduct **9** (eq 2).[20] The reaction of cyclic allylic species **1b** and **1c** gave single isomers in high yields and selectivities as shown in eqs 3 and 4. High selectivity was observed even using butyl ketone **2h**. In transition state **A** (R = Et), the steric hindrance between Ph and Et in gauche



(2)



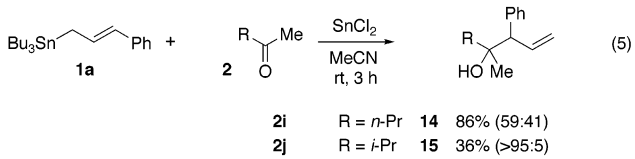
(3)



(4)

conformation accounts for the low selectivity in eq 2. On the contrary, the stability of transition state **B** (R = Et or Bu) is not sterically affected by the R group because ring methylenes are positioned in trans conformation to R, leading to high selectivity in the reaction of **1b** or **1c** in eqs 3 and 4.

In the reaction with dialkyl ketones, steric demand on the carbonyl group was an important factor for diastereoselectivity. In fact, while methyl *n*-propyl ketone **2i** gave low selectivity (59:41), high selectivity was obtained in the reaction with isopropyl methyl ketone **2j** to give **15** (eq 5).



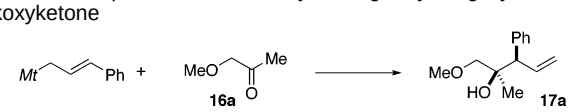
(5)

Diastereoselective Addition to α-*O*-Substituted Ketones. As shown in eq 5, methyl *n*-propyl ketone **2i** gave poor selectivity in the $SnCl_2$-mediated reaction. However, a single diastereomer **17a** was obtained in the reaction with 1-methoxy-2-propanone **16a**, which has similar steric demand with **2i** (Table 4, entry 1). The reaction using $BF_3{\cdot}OEt_2$ gave lower selectivity and yield (entry 2). Other alkylating systems for the reaction of cinnamyl nucleophiles were tried but showed poor selectivities; a zinc/halide system and a Grignard reagent gave 78:22 and 54:46 selectivities, respectively (entries 3 and 4).

We then investigated the generality of the $SnCl_2$-stannane system for α-*O*-substituted ketones **16**, and the results are summarized in Table 5. Phenoxyacetone **16b** and methoxyacetophenone **16c** afforded the products in high yields with perfect selectivities (entries 2 and 3). It is surprising that hydroxyketones **16d** and **16e** can be directly used without protection of the OH group and afford the product **17d** and **17e**, respectively, as single isomers (entries 4 and 5).

Because a tin(II) species is reported to accept two ligands and has oxophilicity, we expected a rigid transition state especially for oxo-functionalized substrates.[13a,b,21] The stereo-

Table 4. Comparison of Selectivity among Alkylating Systems for Alkoxyketone



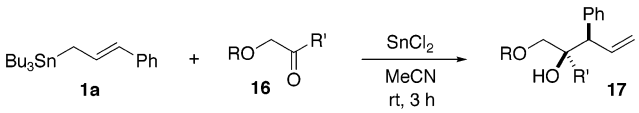
entry	reaction system	conditions	yield/% (ds)[a]
1	Bu_3Sn–Ph / $SnCl_2$	rt, 3 h	>99 (>99:1)
2	Bu_3Sn–Ph / $BF_3{\cdot}OEt_2$	0 °C, 12 h	71 (75:25)
3	Cl–Ph / Zn	rt, 3 h	58 (78:22)
4	ClMg–Ph	-78 °C, 1 h	75 (54:46)

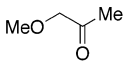
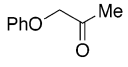
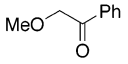
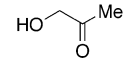
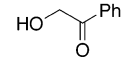
[a] The alcohol **17a** was obtained as a major product with its diastereomer. Yields were given as the total amount of diastereomers.

(20) The steric effect causes a formation of α-product because γ-alkylation product, which would be kinetically formed, is unstable under these conditions and transforms to α-adduct by thermodynamic control. An example for the transformation from γ-adduct to α-adduct: Sumida, S.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310−1313.

(21) (a) Yasuda, M.; Okamoto, K.; Sako, T.; Baba, A. *Chem. Commun.* **2001**, 157−158. (b) Yasuda, M.; Tsuchida, M.; Baba, A. *Chem. Commun.* **1998**, 563−564.

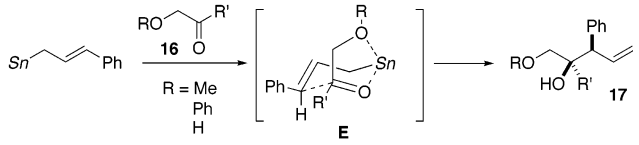
Table 5. Diastereoselective Addition of **1a** to **16**[a]



entry	ketone		yield/%	ds
1		**16a**	>99 (**17a**)	>99:1
2		**16b**	>99 (**17b**)	>99:1
3		**16c**	>99 (**17c**)	>99:1
4		**16d**	>99 (**17d**)	>99:1
5		**16e**	92 (**17e**)	>99:1

[a] All reactions were carried out in acetonitrile with cinnamylstannane **1a** (1.0 mmol), ketone **16** (1.0 mmol), and $SnCl_2$ (1.0 mmol) at room temperature for 3 h.

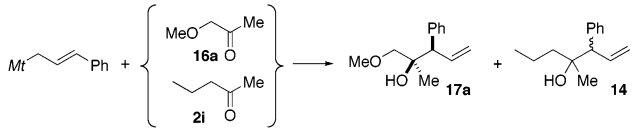
Scheme 3. Plausible Mechanism through Chelated Cyclic Transition State

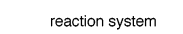
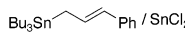
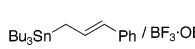


chemical outcome using $SnCl_2$ in Table 5 suggests the cyclic transition state with oxygen-coordinated mechanism as shown in Scheme 3. The generated cinnamyl tin(II) species and alkoxy, aryloxy, or hydroxy ketone gave the chelated cyclic transition state **E**.[22] The oxyalkyl group (CH_2OR) occupies an axial position even when R′ has less bulkiness than CH_2OR. The high affinity of the tin center with oxygen strongly causes axial preference of the oxyalkyl group. Sakurai and Kira reported the same type of bicyclic transition state model for highly selective allylation of hydroxyketones using allylic silanes.[23] Their reaction requires an equimolar amount of a base to form a covalent O−metal bond for a rigid transition state. On the contrary, the present allylation system can be applied to alkoxy ketones and gives a transition state with coordinative interaction between O and the metal center. It is noted that hydroxyketones can be directly utilized without any base and form a rigid bicyclic transition state with coordination of the hydroxy group to the tin center.

The effect of chelation on the acceleration of reaction rate was clearly shown by the competitive reaction between alkoxyketone **16a** and dialkyl ketone **2i** (Table 6). A cinnamylstannane/$SnCl_2$ system gave only **17a** with high diastereoselectivity (entry 1). Although the BF_3-mediated allylic stannane system resulted in selective alkylation of alkoxyketone, the yield and diastereoselectivity were low (entry 2). Neither a zinc/halide system nor a Grignard reagent showed selective reactions (entries 3 and 4). These results in Tables 5 and 6 describe that the $SnCl_2$-mediated system is the best choice for the selective alkylation of α-*O*-substituted ketones.

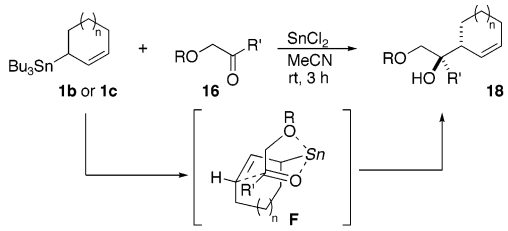
Table 6. Competitive Reaction between α-Alkoxy and Alkyl ketones

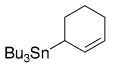
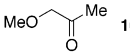
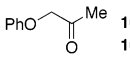
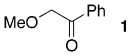
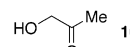
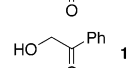
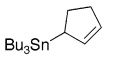
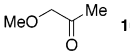
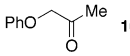


entry	reaction system	conditions	yield/% (ds)[a] **17a**	yield/% (ds)[b] **14**
1		rt, 1 h	96 (>99:1)	0
2		0 °C, 20 h	69 (78:22)	0
3		rt, 5 h	47 (70:30)	25 (56:44)
4		-78 °C, 1 h	15 (55:45)	41 (62:38)

[a] The alcohol **17a** was obtained as a major product with its diastereomer. Yields were given as the total amount of diastereomers. [b] The exact stereochemistry of the diastereomers was not determined. Yields were given as the total amount of diastereomers.

Table 7. Diastereoselective Addition of **1b** or **1c** to **16**[a]



entry	allylic tin		ketone		yield/%	ds
1		**1b**		**16a**	86 (**18a**)	>99:1
2	**1b**			**16b**	78 (**18b**)	76:24
3[b]	**1b**			**16b**	65 (**18b**)	81:19
4	**1b**			**16c**	92 (**18c**)	>99:1
5	**1b**			**16d**	51 (**18d**)	>99:1
6	**1b**			**16e**	68 (**18e**)	>99:1
7		**1c**		**16a**	76 (**18f**)	>99:1
8	**1c**			**16b**	92 (**18g**)	91:9

[a] All reactions were carried out in acetonitrile with allylic stannane **1b** or **1c** (1.0 mmol), ketone **16** (1.0 mmol), and $SnCl_2$ (1.0 mmol) at room temperature for 3 h. [b] The reaction was performed at 0 °C for 3 h.

The cyclic stannanes **1b** or **1c** were also applied to selective alkylation to α-*O*-substituted ketones **16** (Table 7). The products **18** were obtained through the transition state **F**. Highly selective alkylations were accomplished in most cases, although phenoxyketone gave slightly lower selectivities (entries 2, 3, and 8).

Determination of Relative Stereochemistry of Tertiary Homoallylic Alcohols. Determining the relative stereochemistry

(22) Examples for interaction of two donors with the tin(II) center: refs 13a and 13b. The carbonyl and β-oxygens in **16** now act as donors.
(23) Sato, K.; Kira, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 6429−6431.

of the products bearing a quaternary carbon is an essential step to discuss the reaction mechanism. The relative stereochemistry of the products was determined by X-ray analyses of the products or their derivatives. Details are shown in the Supporting Information.

Conclusions

We have demonstrated a highly diastereoselective alkylation of ketones by γ-substituted allylic reagents to form tertiary homoallylic alcohols. For the reaction of simple ketones with cinnamyl nucleophiles, the **1a**/$SnCl_2$ system gave the anti product **3** with high diastereoselectivity, while the opposite isomer **4** was preferably obtained by the **1a**/BF_3·OEt_2 system. The cyclic allylic reagents **1b** or **1c** gave syn alcohol **6** selectively by either $SnCl_2$ or the BF_3·OEt_2-mediated reaction. In this case, higher selectivity was obtained by the $SnCl_2$-mediated reaction. The allylic stannane/$SnCl_2$ system provides a tin(II) reagent as an active species by transmetalation and proceeds through the cyclic transition state. In the reaction with crotyltins **1d** or **1e**, $SnCl_2$- and BF_3·OEt_2-mediated reactions always give different selectivity and compensate for each other. The selectivity depends on the additives ($SnCl_2$ or BF_3·OEt_2), substituents of ketones, and temperature. A highly selective alkylation was observed in the $SnCl_2$-mediated reaction of allylic stannane with α-alkoxy, aryloxy, or hydroxy ketones. The chelation by carbonyl and β-oxygens provides a rigid transition state for selective reactions. The stereochemistry of the products obtained as tertiary homoallylic alcohols was unambiguously determined on the basis of X-ray analyses.

Experimental Section

General Procedure (I) for Synthesis of Homoallylic Alcohols Using $SnCl_2$. To a mixture of $SnCl_2$ (1.0 mmol) and ketone **2** or **16** (1.0 mmol) in dry acetonitrile (2 mL) was added allylic stannane **1** (1.0 mmol) under nitrogen. The reaction mixture was stirred under the reaction conditions noted in the text. Diethyl ether (30 mL) and an aqueous NH_4F (15%; 15 mL) were added, and the resulting Bu_3SnF was filtered off. The filtrate was washed with water (30 mL × 2), dried ($MgSO_4$), and evaporated. Column chromatography of the resultant residue on silica gel followed by distillation or recrystallization gave pure products.

General Procedure (II) for Synthesis of Homoallylic Alcohols Using BF_3·OEt_2. To a mixture of BF_3·OEt_2 (2.0 mmol) and ketone **2** or **16** (1.0 mmol) in dry dichloromethane (1 mL) was added allylic tributylstannane **1** (1.0 mmol) under nitrogen. The reaction mixture was stirred under the reaction conditions noted in the text. Diethyl ether (30 mL) and aqueous NH_4F (15%; 15 mL) were added, and the resulting Bu_3SnF was filtered off. The filtrate was washed with water (30 mL × 2), dried ($MgSO_4$), and evaporated. Column chromatography of the resultant residue on silica gel followed by distillation or recrystallization gave pure products.

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Supporting Information Available: Experimental procedures and spectral data; determination of relative stereochemistry of the products; details and tables for X-ray crystal structures of **3aE**, **6bE**, **8bE**, **7fE**, **17dE**, **17e**, and **19** (PDF); X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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