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Highly diastereoselective $TiCl_4$ mediated addition of (*E*)-cinnamyl(tributyl)tin to α-keto esters

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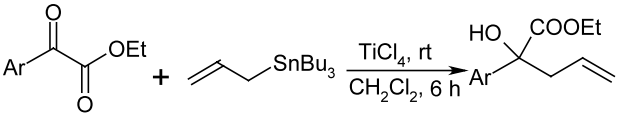
Abstract—Highly *syn*-(87–98%) diastereoselective addition of (*E*)-cinnamyl(tributyl)tin to α-keto esters under the influence of titanium tetrachloride, leading to the isolation of pure alkyl *syn*-2-aryl-2-hydroxy-3-phenylpent-4-enoates in 50–80% yields, is described.

Allylation of carbonyl compounds using various allyltin reagents has become a well established methodology for the stereoselective construction of carbon–carbon bonds providing an elegant synthesis of homoallylic alcohols.[1–9] It is also well established in the literature that the reaction of various crotyl and cinnamyltin reagents with a variety of aldehydes provides the corresponding homoallylic alcohols with high diastereoselectivities under the influence of selected Lewis acids.[1,10–13] However, the application of α-keto esters, yet another class of electrophiles, has not been studied systematically in such reactions and there are only a few reports in the literature describing the reaction of α-keto esters (pyruvate esters) with crotyltin reagents with low diastereoselectivities.[14,15] To the best of our knowledge, the reaction of (*E*)-cinnamyl(tributyl)tin with α-keto esters has not been reported so far. In continuation of our interest[16–21] in the applications of α-keto esters and $TiCl_4$ in organic synthesis, we herein describe the highly diastereoselective synthesis of alkyl *syn*-2-aryl-2-hydroxy-3-phenylpent-4-enoates via the reaction between α-keto esters and (*E*)-cinnamyl(tributyl)tin under the influence of titanium tetrachloride.

Tertiary-α-hydroxy acids and their derivatives constitute an integral part of many biologically active molecules[22–25] and hence the development of convenient methodologies for the diastereoselective synthesis of such compounds continues to attract the attention of organic chemists. It occurred to us that the reaction of cinnamyl(tributyl)tin with α-keto esters under the appropriate conditions might result in the development of a suitable methodology for diastereoselective syntheses of *tertiary*-α-hydroxy acids/esters. Accordingly, we have undertaken a research program to examine the reaction of (*E*)-cinnamyl(tributyl)tin with α-keto esters, with a view to understanding the stereochemical outcome of this reaction. As a preliminary study, we first examined the reaction of allyl(tributyl)tin with representative α-keto esters under the influence of titanium tetrachloride, which provided the desired *tertiary*-homoallylic alcohols in good yields (Eq. (1)).



Ar = phenyl	89%
p-bromophenyl	52%
naphth-1-yl	64%

(1)

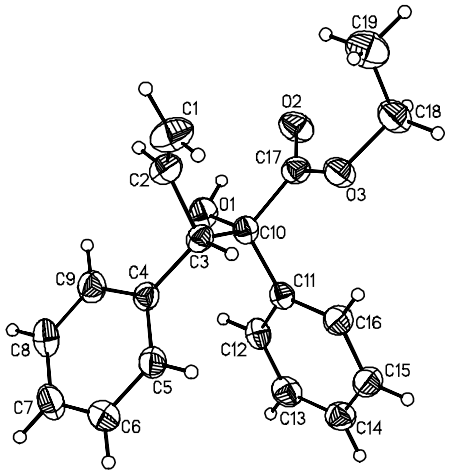


Figure 1. ORTEP diagram of compound **2a**.

Keywords: allylation; titanium tetrachloride; α-keto esters; cinnamyl-(tributyl)tin; diastereoselectivity.

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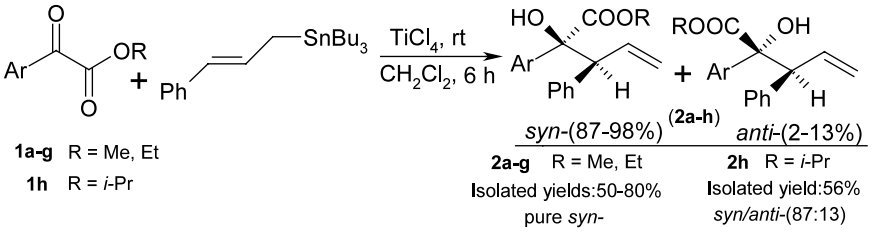

(2)

Next, we selected ethyl phenylglyoxylate (**1a**) as a substrate for reaction with (*E*)-cinnamyl(tributyl)tin. The best results were obtained when a solution of ethyl phenylglyoxylate (**1a**) (1 mM) and titanium tetrachloride (1 mM) in dichloromethane was treated with (*E*)-cinnamyl(tributyl)tin (1.1 mM) (*normal addition*)[1] at room temperature for 6 h thus providing the required *tertiary*-homoallylic alcohol i.e. ethyl *syn*-2,3-diphenyl-2-hydroxypent-4-enoate (**2a**) in 80% yield after column chromatography.[26,27] The *syn*-stereochemistry[28] of compound **2a** was confirmed by single crystal X-ray data[29] (Fig. 1). With a view to understanding the generality of the reaction, we carried out the reaction of representative α-keto esters (**1b**–**h**) with (*E*)-cinnamyl-(tributyl)tin in the presence of titanium tetrachloride under similar conditions. These reactions were found to be highly *syn*-diastereoselective (87–98%).[27] The required pure *syn-tertiary*-homoallylic alcohols i.e. alkyl *syn*-2-aryl-2-hydroxy-3-phenylpent-4-enoates (**2b**–**g**) [while **2h** was obtained as a colorless liquid as a mixture of diastereomers (*syn*:*anti*/87:13) after purification] were isolated in 50–66% yields as colorless solids after purification by column chromatography (Eq. (2) and Table 1).[27] From Table 1 it is clear that both methyl and ethyl esters of α-keto acids provide almost similar diastereoselectivities, however *iso*-propyl *p*-tolylglyoxylate (**1h**) provides slightly inferior diastereoselectivity. The *syn*-diastereoselectivity in these reactions may be explained by considering the transition state models as described in Scheme 1.[30]

In conclusion, for the first time this methodology describes highly diastereoselective addition of (*E*)-cinnamyl(tributyl)tin to α-keto esters in the presence of titanium tetrachloride, leading to the isolation of pure alkyl *syn*-2-aryl-2-hydroxy-3-phenylpent-4-enoates in 50–80% yields.

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Table 1. Reaction of (*E*)-cinnamyl(tributyl)tin with α-keto esters: synthesis of alkyl *syn*-2-aryl-2-hydroxy-3-phenylpent-4-enoates[a,b,c]

Keto ester	Ar	R	Product[d]	Mp (°C)[e]	Yield[f] (%)	*syn*:*anti*[g]
1a	Phenyl	Et	**2a**[h]	98–100	80	>98:<2
1b	*p*-Tolyl	Et	**2b**	87–89	55	97:3
1c	*p*-Bromophenyl	Et	**2c**	84–86	63	97:3
1d	*p*-Methoxyphenyl	Et	**2d**	93–95	54	>98:<2
1e	Phenyl	Me	**2e**	96–98	66	93:7
1f	*p*-Tolyl	Me	**2f**	102	50	90:10
1g	*p*-Bromophenyl	Me	**2g**	110–112	51	>98:<2
1h	*p*-Tolyl	*i*-Pr	**2h**[i]	–	56[i]	87:13[i]

[a] All reactions were carried out on a 1 mM scale (α-keto ester). To a stirred solution of α-keto ester (1 mM) and titanium tetrachloride (1 mM) in dichloromethane was added (*E*)-cinnamyl(tributyl)tin (1.1 mM) (*normal addition*)[1] at 0°C and stirred at room temperature for 6 h.

[b] All products (**2a**–**h**) were characterized by IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) and elemental analyses; compounds **2a** and **2g** were also characterized by mass spectral analysis.

[c] ^{1}H NMR spectra of the crude products (**2a**–**h**) clearly indicated the presence of the starting materials i.e. keto esters (**1a**–**h**) in ≈11, 28, 17, 36, 10, 33, 39, 30%, respectively. In fact, we isolated the starting materials (the α-keto esters) in 29 and 31% yields in the case of **1d** and **1g**, respectively.

[d] The isolated products were obtained as colorless solids with pure *syn* stereochemistry[27] after column chromatography (silica gel, 1.5% EtOAc in hexanes).

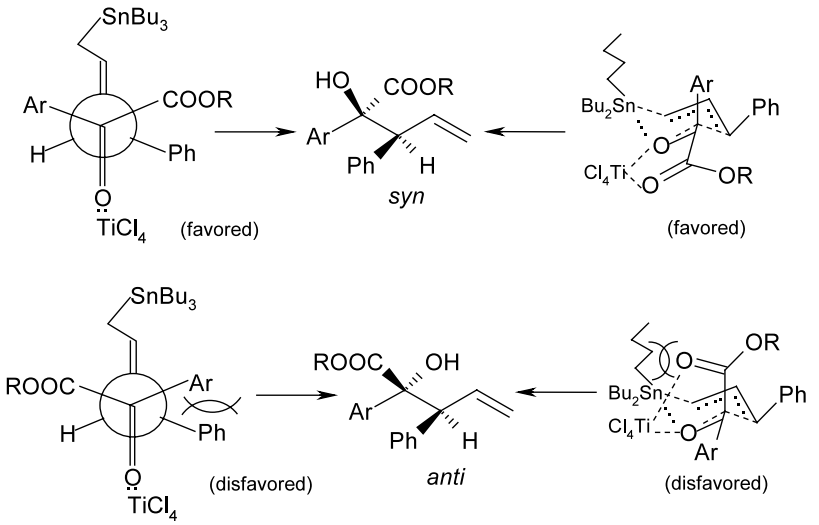
[e] Melting points are of the pure *syn* diastereomers.

[f] Yields of the pure *syn* isomeric products (based on α-keto esters) after column chromatography.

[g] This ratio was determined by ^{1}H NMR studies of the crude products.[27]

[h] The structure and stereochemistry of compound **2a** were established by single crystal X-ray data (crystallization from hexanes).

[i] The compound **2h** was isolated (as a mixture of diastereomers) as a colorless liquid after column chromatography.



Scheme 1.

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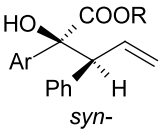
26. Spectral data for compound **2a**: IR (KBr): 3487, 1712 cm^{-1}; ^1H NMR (200 MHz) ($CDCl_3$): δ 1.34 (t, 3H, $J=7.2$ Hz), 3.98 (s, 1H), 4.18–4.37 (m, 3H), 5.12–5.26 (m, 2H), 6.19–6.41 (m, 1H), 7.01–7.24 (m, 8H), 7.48–7.58 (m, 2H); ^{13}C NMR (50 MHz): δ 14.06, 58.03, 62.79, 81.19, 117.40, 126.10, 126.38, 127.35, 127.64, 127.72, 129.65, 137.40, 138.76, 140.08, 174.64; FABMS (M^++1): 297. Anal. calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found C, 77.12; H, 6.79.
27. The *syn* stereochemistry of the major diastereomers (**2b**–**h**) was assigned in analogy with **2a**. The ^1H NMR spectrum of the purified (as well as crude) product **2h** shows two singlets at δ 2.22 & 2.35 ($\approx$87:13) for CH_3 protons (tolyl methyl) and two singlets at δ 3.90 & 3.98 ($\approx$13:87) for the OH proton. Also, the ^{13}C NMR spectrum of the purified compound **2h** shows peaks at δ 70.73 (with low intensity) and δ 70.91 for [O-CH$(CH_3)_2$]. (The underlined chemical shift values were attributed to the minor *anti*-diastereomer). The ^1H NMR spectra of the pure (as well as crude) products (**2a**, **2d**, **2g**) do not show the presence of any other diastereomers (*anti*-). The ^1H NMR spectra of the crude products (**2e**, **2f**) show two singlets at δ 3.77 & 3.84 ($\approx$7:93) and δ 3.75 & 3.82 ($\approx$10:90) for COOCH_3 protons, respectively. (The underlined chemical shift values were attributed to the minor *anti*-diastereomers). The ^1H NMR spectra of the crude products (**2b**, **2c**) show two singlets at δ 3.88 & 3.95 ($\approx$3:97) and δ 3.87 & 4.02 ($\approx$3:97) for the OH proton, respectively. Though OH proton signals are not normally used for the determination of diastereomeric composition, by analogy with that of **2h** the underlined chemical shift values might be attributed to the minor *anti*-diastereomers. (Isolated yields of the products and the amounts of starting materials present in the crude mixture also support our assumption).

28. We have assigned *syn* stereochemistry to the molecules shown below (the 2-hydroxy group and 3-phenyl groups are on the same side in the extended conformation).



syn-

29. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK. (For compound **2a** CCDC # 173594). Crystal data for **2a**: empirical formula, $C_{19}H_{20}O_3$; formula weight, 296.35; crystal color, habit: colorless, prism; crystal dimensions, 0.48×0.48×0.36 mm; crystal system, monoclinic; lattice type, primitive; lattice parameters, $a=18.237(4)$ Å, $b=5.7783$ (12) Å, $c=16.679$ (3) Å; $\beta=115.67$ (3); $V=1584.1$ (6) Å^3; space group, $P\,2_1/C$ (No. 14); $Z=4$; $D_{calcd}=1.243$ g/cm^3; $F_{ooo}=632.00$; (Mo K_α) = 0.71073 Å; residuals, $R=0.0494$, $wR^2=0.1040$.

30. A similar mechanism for allylation reactions is known in the literature. See Ref. 1.