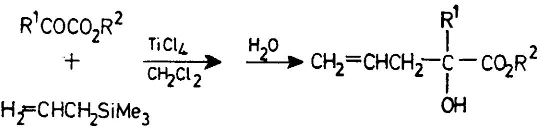
Asymmetric Addition of Allyltrimethylsilane to (—)-Menthyl Pyruvate and Phenylglyoxylate

By Iwao Ojima,* Yuji Miyazawa, and Miyoko Kumagai
(*Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan*)

Summary The reaction of allyltrimethylsilane with α-keto esters in the presence of titanium tetrachloride afforded a γδ-unsaturated α-hydroxyvalerate in high yield, which with chiral α-keto esters in asymmetric synthesis gave 16–55% enantiomeric excess product.

Recently, allyltrimethylsilane was shown to be potentially useful in the allylation of acyl halides[1] or carbonyl compounds.[2] We found that the reaction of allyltrimethylsilane with α-keto esters in the presence of titanium tetrachloride proceeded readily even at −78 °C to give γδ-unsaturated α-hydroxyvalerates in high yields [equation (1); Table 1]. Although alkylation or arylation of α-keto esters using Grignard reagents is well known,[3] the allylation of α-keto esters gave only poor yields.



$$\begin{array}{c} R^1COCO_2R^2 \\ + \\ CH_2{=}CHCH_2SiMe_3 \end{array} \xrightarrow[CH_2Cl_2]{TiCl_4} \xrightarrow{H_2O} CH_2{=}CHCH_2-\overset{R^1}{\underset{OH}{C}}-CO_2R^2 \qquad (1)$$

Thus, the present reaction may provide a useful route to γδ-unsaturated α-hydroxyvalerates.

Table 1. Preparation of γδ-unsaturated α-hydroxyvalerates [equation (1)].

R^1	R^2	Time/min[a]	b.p/°C (mmHg)	% Yield
Me	Me	30	70 (22)	86
Me	Et	30	68 (22)	85
Me	Bu^n	20	87 (22)	92
Me	PhCH$_2$	20	74 (0·5)	82
Ph	Et	20	90 (0·2)	82

[a] In a typical run, allyltrimethylsilane (30 mmol), the α-keto ester (20 mmol), and $TiCl_4$ (20 mmol) were allowed to react in CH_2Cl_2 (60 ml) at −78 °C.

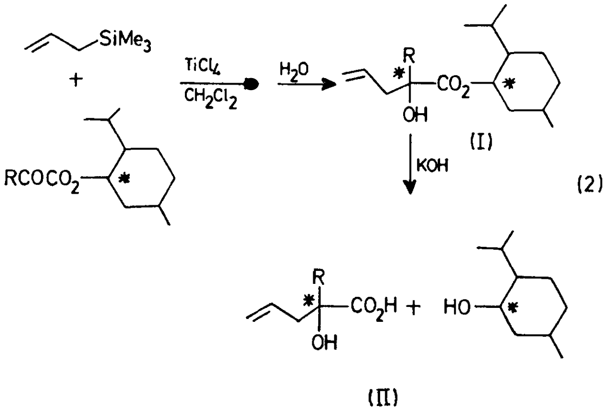
Accordingly, we applied the reaction to the asymmetric synthesis of optically active γδ-unsaturated α-hydroxyvaleric acid, employing (—)-menthyl pyruvate and phenylglyoxylate as substrates [equation (2)]. There is a similarity between this reaction and that of the asymmetric Grignard addition to α-keto esters, *e.g.*, Prelog's atrolactic acid asymmetric synthesis,[3] and thus it may be possible to obtain some information concerning the stereochemical course of the present reaction.

Table 2. Asymmetric addition of allyltrimethylsilane to chiral α-keto esters [equation (2)].

R	Temp/°C[a]	% Chemical yield	Optical yield (% e.e.)[b]	$[\alpha]^{20}_D$ of (II)[c]
Me	20	79	34	+3·83(*S*)
Me	2	82	37	+4·17(*S*)
Me	−16	92	40·5	+4·56(*S*)
Me	−75	93	55	+6·20(*S*)
Ph	20	82	16	−3·10(*R*)
Ph	−75	86	23	−4·46(*R*)

[a] In a typical run, allyltrimethylsilane (30 mmol), the α-keto ester (20 mmol), and $TiCl_4$ (20 mmol) were allowed to react in CH_2Cl_2 (60 ml) for 0·5 h. [b] Estimated from the n.m.r. spectra using Eu(fod)$_3$ of the ester (I). [c] In EtOH. The configuration of the α-hydroxy acid (II) was tentatively assigned by postulating that the reaction follows Prelog's generalization (ref. 4).

The reaction was carried out at −75 °C in the presence of an equimolar amount of titanium tetrachloride to afford the corresponding hydroxyvalerate (I) in high yield. The extent of asymmetric induction was determined by means of n.m.r. spectroscopy using the shift reagent, Eu(fod)$_3$; thus, fractionation during the isolation process could be excluded. The α-hydroxyvaleric acid (II) was obtained by alkaline hydrolysis of the ester (I).



As Table 2 shows, the reaction with (—)-menthyl pyruvate gives good results and the optical yield obtained is far better than that with (—)-menthyl phenylglyoxylate. This trend is unexpected since the asymmetric Grignard addition to (—)-menthyl phenylglyoxylate gave better results [20–30% enantiomeric excess (e.e.) for MeMgX] than did the addition to (—)-menthyl pyruvate (14—18% e.e for PhMgX).[3] The activation parameters for the reaction of allyltrimethylsilane with (—)-menthyl pyruvate were estimated as follows: $\Delta\Delta H^{\ddagger} = -640$ cal mol^{-1}, $\Delta\Delta S^{\ddagger} = -0{\cdot}79$ cal K^{-1} mol^{-1}.

Since the asymmetric addition of allyl Grignard reagents to chiral α-keto esters has not been reported, we examined the products of the addition of allyl magnesium chloride to (—)-menthyl pyruvate (0 °C in ether) by the established procedure.[5] However, the chemical yield was low (23%)† and any asymmetric induction which did occur could not be observed by n.m.r. spectroscopy.

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† The main products were (—)-menthol and a glycol obtained from the reaction with a menthoxy carbonyl group as well as an α-keto group.

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