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Asymmetric Synthesis of the Both Enantiomers of Tertiary Aryl Homoallyl Alcohols and Diols by Diastereoselective Addition of Allyltrimethylsilane to Chiral α-Keto Imides[†]

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Both enantiomers of homoallyl-alcohols and -diols are obtained in high enantiomeric excesses (91 - >98% e.e.) by titanium tetrachloride promoted diastereoselective addition of allyltrimethylsilane to chiral α-keto imides.

In spite of the recent development of asymmetric synthesis, only limited number of methods has been reported on asymmetric synthesis of optically active tertiary alcohols of high enantiomeric excesses(e.e.).[1)] On the other hand, increasing interest has been focused on diastereoselective allylation of chiral carbonyl compounds with allylsilanes.[2)] The resulting homoallyl alcohols are important synthetic intermediates.[3)] However, very few investigations have been reported on the diastereoselective allylation of chiral ketones which affords optically active tertiary homoallyl alcohols.[4)] Diastereoselective allylation of chiral α-keto ester derived from chiral menthol shows moderate diastereoselectivities.[4a)] We previously reported diastereoselective allylation of chiral α-keto amides derived from (S)-proline esters.[4b)]

We wish to describe diastereoselective allylation of chiral α-keto imides (**3a-d**) with allyltrimethylsilane in the presence of titanium tetrachloride($TiCl_4$).

Chiral α-keto imides(**3a-d**) were prepared by the condensation of α-keto acid chloride(**1a,b**) and chiral oxazolidin-2-ones(**2a,b**) derived from (1S,2R)-

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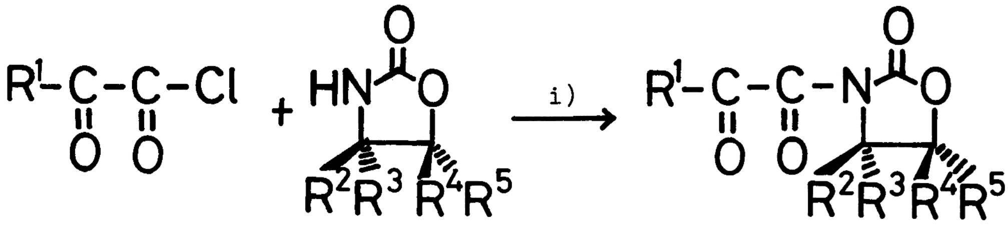
[†] Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.



1 2 3

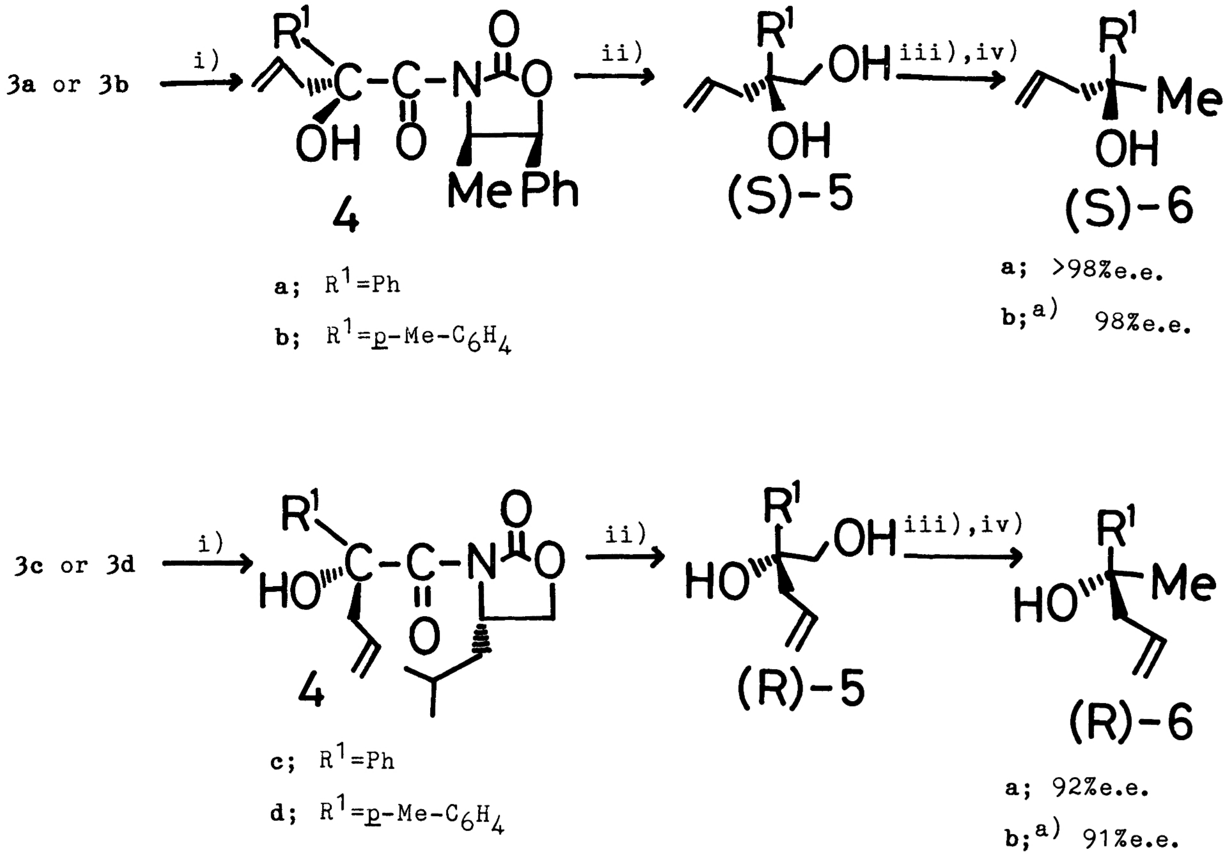
1	2	3
a; R^1=Ph	**a**; R^2=Me,R^3=H,R^4=Ph,R^5=H	**a**; R^1=Ph,R^2=Me,R^3=H,R^4=Ph,R^5=H
b; R^1=*p*-Me-C_6H_4	**b**; R^2=H,R^3=i-Bu,R^4=R^5=H	**b**; R^1=*p*-Me-C_6H_4,R^2=Me,R^3=H,R^4=Ph,R^5=H
		c; R^1=Ph,R^2=H,R^3=i-Bu,R^4=R^5=H
		d; R^1=*p*-Me-C_6H_4,R^2=H,R^3=i-Bu,R^4=R^5=H

Scheme 1. i) n-BuLi.

norephedrine and (*S*)-leucinol respectively in 54 - 73%[5,6](Scheme 1).

Diastereoselective allylation of **3a** with allyltrimethylsilane in the presence of $TiCl_4$ afforded the corresponding homoallyl alcohol **4a** in 91% yield(Scheme 2). Reductive removal of the chiral auxiliary from **4a** with lithium aluminium hydride($LiAlH_4$) gave (*S*)-(-)-2-phenyl-4-penten-1,2-diol (**5a**) {$[\alpha]_D^{16}$ -51.6° (c 1.00, $CHCl_3$)} in >98% e.e.[7] Absolute configuration was determined by the comparison of the sign of optical rotation of the sample (*S*)-**5a** {$[\alpha]_D$ -46.6°}, which had been prepared by the reduction of (*S*)-α-allylmandelic acid[8] with $LiAlH_4$. The primary alcohol of (*S*)-**5a** prepared by the present allylation was converted selectively to the corresponding monotosylate, and the subsequent reduction with $LiAlH_4$ afforded (*S*)-(-)-2-phenyl-4-penten-2-ol (**6a**) {$[\alpha]_D^{22}$ -58.4° (c 0.37, $CHCl_3$)}. ^{1}H-NMR analysis using chiral shift reagent [$Pr(hfc)_3$] showed that the obtained (*S*)-**6a** was >98% e.e. On the other hand, when starting from **3c** instead of **3a**, the opposite enantiomers were obtained in high e.e.'s [(*R*)-**5a** {$[\alpha]_D^{20}$ +49.5° (c 1.01, $CHCl_3$)} and (*R*)-**6a** (92% e.e. by NMR)].

In a similar manner, the enantiomers of either configurations desired were also obtained respectively in high e.e.'s from the diastereoselective allylations of **3b** and **3d**. (-)-Isomers [(-)-**5b** {$[\alpha]_D^{24}$ -47.1° (c 1.00, $CHCl_3$)} and (-)-**6b** {$[\alpha]_D^{25}$ -56.7° (c 1.00, $CHCl_3$)}, 98% e.e. by NMR] were obtained from the allylation of **3b**. On the other hand, (+)-isomers were obtained from the allylation of **3d** [(+)-**5b** {$[\alpha]_D^{23}$ +45.3° (c 1.00, $CHCl_3$)} and (+)-**6b** {$[\alpha]_D^{27}$ +54.3° (c 1.00, $CHCl_3$)}, 91% e.e. by NMR].



Scheme 2. i) $CH_2=CHCH_2SiMe_3$, $TiCl_4$; ii) $LiAlH_4$; iii) p-TsCl, $C_5H_5N(4\text{-}Me_2N\text{-}C_5H_4N)$; iv) $LiAlH_4$.
a) Configuration of **6b** is tentatively assigned.

Thus, the both enantiomers of optically active tertiary homoallyl alcohols (**6a** and **b**) and diols (**5a** and **b**) of high e.e.'s were synthesized by the present diastereoselective allylation of chiral α-keto imides with allyltrimethylsilane.[9)]

Typical experimental procedure is as follows: To a dichloromethane(CH_2Cl_2) solution of **3a** (1.0 mmol) in an ice bath under an argon atmosphere, $TiCl_4$ (3 mmol) was added over a period of 2 min and the mixture was stirred for 5 min. Then allyltrimethylsilane (1.5 mmol) was added, and the mixture was further stirred for 24 h. The reaction was quenched with pH 7 phosphate buffer solution. After the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2. Combined extracts were dried over anhydrous sodium sulfate and were evaporated under reduced pressure. Purification by column chromatography (chloroform as elute) afforded **4a** in 91% yield. Reduction of **4a** with $LiAlH_4$(3 molar equiv.) in THF at 0°C for 2 h afforded (S)-(-)-**5a**(41%). The diol(**5a**, 0.038g, 0.21 mmol) was tosylated selectively by the reaction with p-toluenesulfonyl chloride(0.044g, 0.23 mmol) in pyridine (in the tosylations of **5** derived from **3b** and **3d**, a few drops of 4-dimethylaminopyridine was added) at room temperature for 17 h. The resulting monotosylate(0.071g) was reduced with $LiAlH_4$(0.028g, 0.72 mmol) in ether(3.5 ml) at reflux temperature for 0.5 h to afford (S)-(-)-**6a** in 70% overall yield from **5a**.

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