

ASYMMETRIC SYNTHESIS OF α -HYDROXY-ESTERS VIA ESTER ENOLATES

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ABSTRACT: 3-Phenylpropionates of chiral alcohols derived from (+)-camphor are oxidized by $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPT}$ (MoOPH) with high diastereoselectivity.

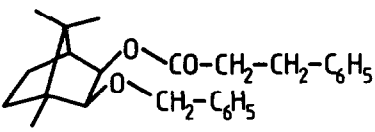
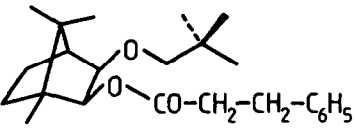
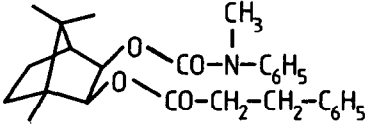
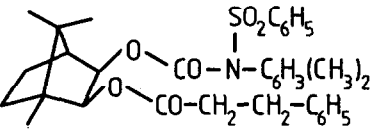
Unbranched chiral α -hydroxy-esters are often used as intermediates in natural product syntheses. Several methods are available for their preparation in a high optical purity ranging from 90 to 100% ee, for instance asymmetric reduction of α -keto-esters ¹, LiAlH_4 reduction of chiral β -keto-sulfoxides ², addition of Grignard reagents to chiral α -formyl-aminals ³, addition of various organometallics to chiral glyoxylate esters ⁴, ene reactions of chiral glyoxylate esters ⁵, asymmetric alkylation of chiral glycolates ⁶ and the permanganate oxidation of chiral propargyl alcohols ⁷.

In this communication we report preliminary results on the direct hydroxylation of chiral ester enolates.

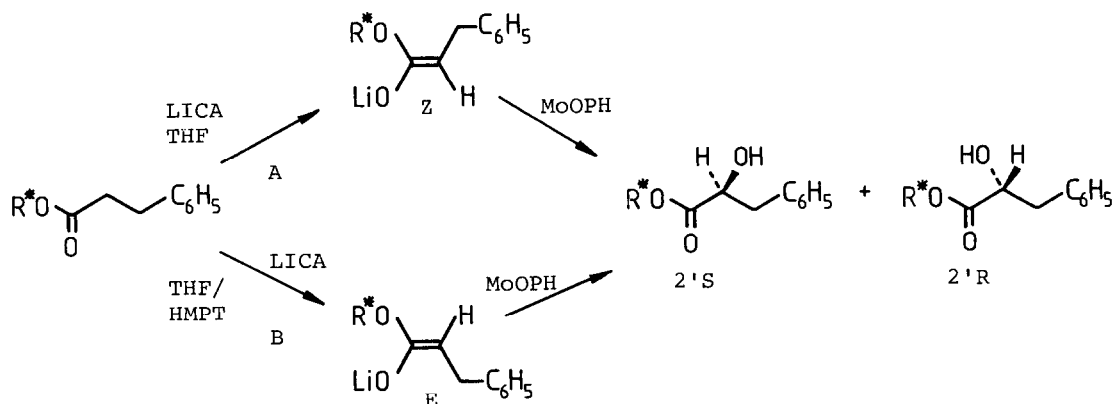
The hydroxylation of enolates has been investigated extensively by Vedejs ⁸. However, in contrast to the alkylation ⁹, almost no attention has been paid to the diastereoselection of this reaction. The few known examples are only concerned with intraanular chirality transfer ¹⁰. Our studies on the synthesis of verrucarinic acid ¹¹ has prompted us to explore the possibility of diastereoselective hydroxylation of chiral ester enolates with $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPT}$ (MoOPH) ⁸. The esters of chiral alcohols, as developed by Helmen ¹² and Oppolzer ¹³, have exhibited excellent diastereoselection in various types of reactions e.g. the Diels-Alder reaction and the alkylation of ester enolates. We therefore have tested ester enolates of some of these alcohols for the diastereoselectivity of MoOPH reagent hydroxylation. Esters of 3-phenylpropionic acid served as substrates. 3-Phenylpropionates 1a ¹², 1b ¹³, 1c ¹² and 1d ¹² were prepared from chiral alcohols ($\text{R}^* \text{-OH}$) derived from (+)-camphor. The deprotonation was performed using LICA and LICA/HMPT complex as base in THF ¹², respectively, because under these conditions both the Z and E isomers of the enolates are accessible ¹⁴. The results are summarized in the Table.

Table

Diastereoselective Hydroxylation of the (E)- and (Z)-Enolates Derived from Esters 1a - 1d with MoOPH Complex

Ester	No.	Deprotonation ^a	Yield ^b	Ratio ^c (2'R): (2'S) ^d
 <u>1a</u>	1	A	[50]	36 : 64
 <u>1b</u>	2	A	39	67 : 33
 <u>1c</u>	3	A	80	20 : 80
	4	B	50	14 : 86
	5	C	57	43 : 57
 <u>1d</u>	6	A	47	33 : 67
	7	B	50 [40]	7 : 93
	8	B	25	3 : 97
	9	C	60 [55]	82 : 18

^a Deprotonation conditions: -78° , 2 eq. LICA, A: in THF, B: in 20% vol HMPT in THF, C: in THF followed by 20% vol HMPT at -52° ; hydroxylations were carried out at -52° (No. 5, 7, 9), at -78° (No. 4, 8) or in between (No. 1, 2, 3, 6). ^b Combined yields of both diastereomers according to HPLC (LiChrospher Si 100 5 μ m, Merck); values in brackets: isolated yields; yields corrected with respect to recovered starting material were in all cases $\geq 90\%$. ^c Absolute configuration was determined by degradation to the known hydroxyacid. ^d Determined by HPLC (LiChrospher Si 100 5 μ m, Merck, ether-petroleumether).



Whereas the hydroxylation of esters la and lb via (Z) -enolates (LICA, THF, conditions A) led preferentially to the expected diastereomers, albeit with low selectivity, esters lc and ld yielded mainly the unpredicted ones. On the other hand, the (E) -enolates (LICA, 20% vol HMPT in THF, conditions B) of the esters lc and ld were hydroxylated mostly with excellent diastereoselection yielding the products which are formed by an attack from the less hindered side of the (E) -enolate.

The somewhat puzzling results obtained with esters lc and ld in weakly complexing solvents (conditions A) may be explained by the assumption that at first fast coordination of MoOPH to the shielding group takes place. The subsequent hydroxylation occurs in a quasi intramolecular fashion from the more hindered side. In order to test this hypothesis we added the strong complexing agent HMPT, to inhibit this first step, to the reaction mixture after the deprotonation of the esters lc and ld in THF had taken place (conditions C). A dramatic change of diastereoselectivity with ester ld was observed now favouring the $(2'R)$ -diastereomer. In the case of ester lc the trend was the same; however, the resultant selectivity is synthetically not useful.

According to these results it is possible to obtain either the $(2'S)$ or the $(2'R)$ -diastereomer in high optical purity. Further applications of this approach are in progress.

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