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ELECTROPHILIC ASYMMETRIC SYNTHESES OF α-HYDROXY CARBOXYLIC ACIDS

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Asymmetric electrophilic syntheses of α-hydroxy carboxylic acids from chiral amide derivatives of *tert*-butyl- and trialkylsilyl- protected glycolic and lactic acids are described which lead to chiral α-hydroxy carboxylic acids in 60-95% diastereomeric excess.

Asymmetric synthesis has become an established procedure in organic synthesis.[3] Here we describe approaches for asymmetric syntheses of α-hydroxy carboxylic acid derivatives via enolate alkylation employing a variety of chiral auxiliaries which proceed with high stereoselectivity to form tertiary and quaternary centers. Prior asymmetric syntheses of α-hydroxy carboxylic acids have included enolate alkylations and hydroxy alkylations, Prelog-like reactions, chiral ene reactions, asymmetric reduction, enolate oxidation and enzymatic synthesis.[4]

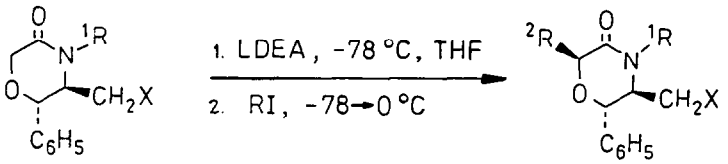
Previously we described electrophilic asymmetric syntheses of mandelic acid derivatives from menthol esters of mandelic acid which proceeded with good stereoselectivity.[5] However, the formation of enediolates from less acidic α-hydroxy carboxylic acid esters such as ethyl glycolate or ethyl lactate was more difficult and the overall synthetic yield in alkylation reactions was lower than was the case for mandelate derivatives. In addition, the ester-enolate Claisen rearrangement[6] of the enediolate intermediates derived from E- and Z-2-butenyl mandelate yielded a mixture of diastereomeric pentenoic acid products in diastereomer ratios of 9:1 and 3:7. The mediocre stereoselectivity of this rearrangement is likely due to the presence of a mixture of stereoisomeric enediolate intermediates. Since the geometrical purity of the intermediate determines the success of an electrophilic asymmetric synthesis and since the generality of formation of vicinal enediolates was problematic, we surveyed several other approaches as described below.

Formation of enolates from protected α-hydroxy carboxylic acid esters has been used previously in synthesis.[4a-c] We found that both trialkylsilyl and *tert*-butyl groups worked well as protecting groups in enolate formation from esters of α-hydroxy carboxylic acids like glycolic and lactic acid. These protecting groups are readily removable by fluoride ion or acid treatment respectively.[7,8] However, we found that decomposition of the intermediate ester enolates derived from O-protected α-hydroxy lactic esters remained a problem. We were able to circumvent this problem by using more stable enolates formed from α-hydroxy carboxylic

acid amides.[9] The preliminary studies reported here deal exclusively with asymmetric syntheses using these more stable species.

Our studies of carboxamide derived enolate precursors of α-hydroxy carboxylic acids first compared the relative efficiency of several chiral directing groups in a system in which there would be little ambiguity about the stereochemistry of the intermediate enolate. The desired cyclic carboxamides 2-4 were prepared by reaction of a hydroxy amine with bromoacetyl bromide to form the amide which was then cyclized using KOH/ethanol to yield the desired morpholin-5-one derivative. Schollkopf has successfully used similar lactim ethers in asymmetric syntheses of α-amino acids.[10]

Cyclic carboxamides 2-4 were deprotonated and alkylated with a variety of alkyl halides in good yield (Table). The stereoselectivity of these reactions was determined by chromatography or NMR spectroscopy. Interestingly, there was less difference between the efficacy of various chiral groups than there was between mono and dilithio anions. Poor stereoselectivities were obtained starting with 2 or 4 while excellent stereoselectivities (up to 96%)



2; R = $-CH_3$, X = -H

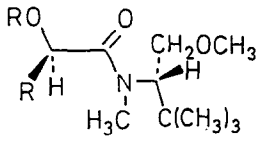
3; R = -H, X = $-OCH_3$

4; R = $-CH_3$, X = $-OCH_3$

were obtained starting with 3. Good yields were obtained in alkylations of 3 with primary alkyl iodides. However, methylation was unsuccessful as noted in the Table. The differences in the diastereoselectivities of electrophilic substitutions of enolates derived from 2-4 appear to be the result of the presence of a substituent on nitrogen in the intermediate mono- or dilithio anion. Apparently, coordination of a directing group to lithium is less effective when such a substituent is present. Support for this hypothesis came from experiments in which 3 was alkylated with Meerwein's reagent to form an imidate ester. Deprotonation of this imidate ester to form a monolithio anion followed by methylation or ethylation proceeded in >90% yield with 70% diastereoselectivity.

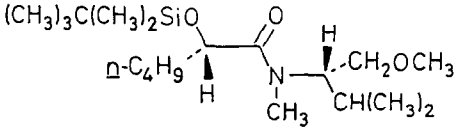
The cyclic systems 2-4 provide some insights into the factors which are important in achieving high stereoselectivity in electrophilic asymmetric syntheses starting with amides of α-hydroxy carboxylic acids. However, conversion of the products derived from 2-4 into α-hydroxy carboxylic acids was not attempted since the required hydrogenolysis in these systems can be problematic and since the chiral auxiliary is destroyed in this reaction. We instead turned our attentions to acyclic O-protected glycolic and lactic acid carboxamides which can be more readily converted into an α-hydroxy carboxylic acid. These studies employed as chiral auxiliaries amino alcohols readily derived from α-amino acids. The

results of electrophilic substitution reactions employing such species (5-8) roughly paralleled those with 2-4. Good diastereoselectivities were seen (44-82% d.e.) when monolithiated intermediates which had a methyl group on nitrogen were alkylated. Slightly higher stereoselectivity was seen in alkylations of the related dilithio anions, but electrophilic substitution reactions of these dilithio anions were complicated by variable conversions of starting materials to products.



5; $^1R = -C(CH_3)_3, ^2R = -CH_3$

6; $^1R = -Si(CH_3)_2C(CH_3)_3, ^2R = -H$



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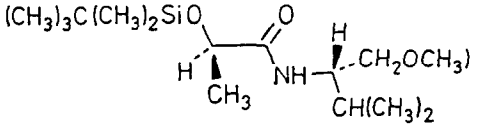

8

Table. Asymmetric Synthesis of α-Hydroxy Carboxylic Acid Derivatives.

Starting Material	Electrophile	Yield (%)[a]	Stereoselectivity
2	n-C_4H_9I	85	54:46
2	CH_3I, then n-C_4H_9I	72	76:24
3	CH_3I	0	-
3	n-C_4H_9I	99[c]	>98: 2
3	CH_3CH_2I	84[c]	95: 5
4	CH_3I	>95[c]	55:45
5	CH_3CH_2I	65	92: 8[d]
5	n-C_4H_9I	35	92: 8[d]
5	$C_6H_5CH_2Br$	58[b]	97: 3[d]
6	CH_3I	97[c]	80:20
6	n-C_4H_9I	92[c]	72:28
7	CH_3I	92	91: 9
8	n-C_4H_9I	85[e]	85:15
8	CH_3CH_2I	95[e]	84:16

[a] Alkylations were typically carried out at -78 °C using 0.1-0.2 N solutions of enolates. Yields were determined by gas chromatography unless otherwise stated. [b] The new chiral center had the *R* configuration. The diastereomeric ratio of this product was reversed by a second deprotonation and protonation. [c] Isolated yield of product characterized by gc, ^1H and ^{13}C NMR spectroscopy. [d] The alkylation was carried out in a 2:1 (v/v) mixture of toluene and THF. The stereoselectivity of the alkylation dropped to only 50 % if the reactions were run in pure THF as solvent. [e] Deprotonation to form a dianion required use of *tert*-butyl lithium as a base.

The stereoselectivities of the alkylations of 5 increased from ca. 40-50% to 85-94% when the 2:1 (v:v) mixture of toluene and THF was used in place of THF as solvent. This effect was not the result of a change in the stereoselectivity of the deprotonation step since addition of toluene either before or after the deprotonation resulted in the same change in stereoselectivity. Hydrolysis (HCl, reflux, 8 h) of the alkylation products gave the corresponding substituted α-hydroxy carboxylic acids without racemization. Milder hydrolyses were possible when the carboxamide product was converted to an imidonium salt using triethyloxonium tetrafluoroborate. However, such hydrolyses were accompanied by the formation of some by-product amide.

The studies in this paper demonstrate that a variety of protected α-hydroxy carboxylic acid derivatives can be readily deprotonated and alkylated in high yield and that stereoselectivities as high as 96% can be obtained with readily available chiral auxiliaries. The solvent effects observed in alkylations of the monolithium enolates of the chiral tertiary α-hydroxy carboxamides derived from lactic acid resulted from changes in the stereoselectivity of the alkylation step and might be found in other enolate alkylations.

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