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ASYMMETRIC SYNTHESIS OF α-HYDROXY CARBOXYLIC ACIDS: DIRECT OXIDATION OF CHIRAL AMIDE ENOLATES USING 2-SULFONYLOXAZIRIDINES

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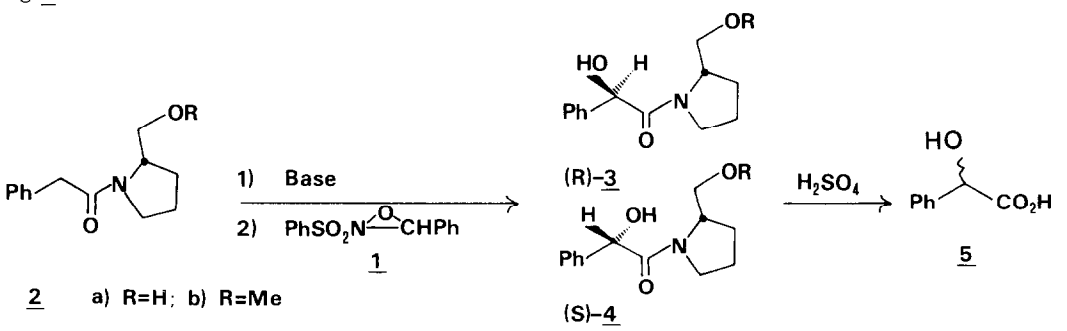
ABSTRACT: The direct oxidation of chiral amide enolates to optically active mandelic acid using 2-sulfonyloxaziridine 1 is described. The diastereoselectivity is counterion dependent.

Optically active α-hydroxy carboxylic acids ($R_2C(OH)CO_2H$) are structural subunits of natural products and important intermediates for asymmetric synthesis.[1] Although a number of strategies have been devised for their preparation in high optical purity (90-100% ee), a disadvantage is that many of these methods are multistep. An attractive route to these valuable compounds, based on Evans' pioneering studies on the asymmetric alkylation of enolates,[4,5] is the direct oxidation of chiral enolates. Indeed, moderate to good levels of diastereoselection (14-93% de) were reported by Tamm and co-workers for the MoOPH oxidation of ester enolates using a camphor-based chiral auxiliary.[2] The α-acetoxylation of O-silylated camphorsulfonamide esters with lead tetraacetate (88-96% de) has also been described by Oppolzer and Dudfield.[3]

Recently we reported the direct oxidation of ketone and ester enolates to α-hydroxy carbonyl compounds using 2-(phenylsulfonyl)-3-phenyloxaziridine (1).[6] This reagent afforded -hydroxy carbonyl compounds in higher yield and with better stereoselectivity than other oxidants such as O_2 or MoOPH. A logical extension of these studies is the direct oxidation of chiral enolates using 1. We report that oxidation of amide enolate, 2a, derived from phenylacetic acid and the commercially available (ℓ)-2-pyrrolidinemethanol[7] chiral auxiliary by oxaziridine 1 affords mandelic acid (5) in high optical purity (90->95% ee). Evans et al. have observed similar high diastereoselectivities using 1 and oxazolidinone carboximide chiral auxiliaries.[8]



Hydroxy amide 2a (R=H) was prepared in good yield by reaction of phenylacetic acid anhydride (85%) or phenylacetyl chloride (75%) with (ℓ)-2-pyrrolidinemethanol.[9] The methyl ether amide, 2b (R=Me) was prepared from (+)-(S)-2-(methoxymethyl)pyrrolidine and phenylacetyl chloride in 87% yield.[9] Typically oxidation involves generation of the enolate by addition of 2 (0.5 mmoles) to the appropriate base, lithium diisopropylamide (LDA) or sodium bis(trimethylsilyl)amide (NHMDS) in 15-20 mL of solvent at 25 °C (30 min). The enolate is cooled to -78 °C (30 min) followed by addition of the solid oxaziridine in one portion (15-20 min). The solution is warmed to room temperature (30 min), cooled to -78 °C and quenched with 0.5 mL of triethylamine followed by sat. NH_4Cl solution. After removal of the solvent the residue is extracted into methylene chloride, washed with water followed by brine and dried over anhydrous sodium sulfate. Products were analyzed by GLC and isolated by prep. TLC or flash chromatography (silica gel). The composition of the diastereomers 3/4, were determined by 90 and 250 MHz ^1H-nmr.[10] These results are summarized in the Table.

Significantly, the lithioenolate of 2a affords a single hydroxy amide (S)-4a (>95% de) while the sodioamide gives (R)-3a, (93% de), both in high chemical yield (93%) (entries 1 and 3).[11] Hydrolysis of (R)-3a and (S)-4a (2M H_2SO_4 reflux, 3 h; >90% isolate yield) gives (-)-(R)- and (+)-(S)-mandelic acid (5) in 90% and 95% optical purities. Not only do these results confirm the diastereomer ratios obtained by nmr, but they demonstrate that the chiral auxiliary is easily removed, in high yield, without racemization.

Enolate oxidation of 2b (R=Me) gives results which are quite different than those observed for 2a (R=H).[12] Not only are the diastereoselectivities lower, but the configuration of 3b/4b is solvent dependent. In the absence of HMPA or at low HMPA concentrations (R)-4b is preferentially formed (entries 4-5, 8), whereas at high levels of HMPA (S)-3b is favored (entries 6,7).

The importance of generating a rigid chiral auxiliary via intramolecular metal chelation as a prerequisite for high diastereoselectivities is well known.[5,13] The results in the Table can be explained in terms of this concept. Making the reasonable assumption that the enolates derived from 2 have the Z-geometry, 6,[4] then attack by 1 is sterically favored from the Si-face in the intramolecular chelated species 6a (R=H). Replacing H by Me in 2 or changing the counterion from Li to a larger and more poorly coordinating Na ion may inhibit formation of 6a to such an extent that intermolecular chelation, 6b (R=Me), becomes important. In 6b attack of the oxaziridine is now favored from the Re-face. The effect of adding HMPA is to disrupt the intermolecular chelation in 6b increasing competition for the oxaziridine by 6a. A definitive explanation for the high diastereoselectivity (93% de) observed for the sodium enolate of 2a awaits further studies.

In summary, our result and those of Evans[8] demonstrate that the reagent of choice for achieving high diastereoselectivities in the direct oxidation of chiral enolates is 2-sulfonyloxaziridine 1.

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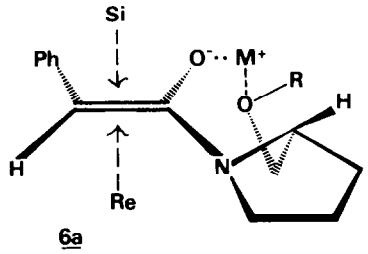
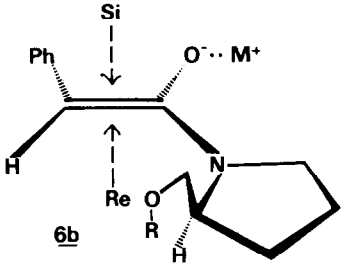
Table: Oxidation of Amide Enolates using 2-(Phenylsulfonyl)-3-phenyloxaziridine (1) at -78 °C.

Entry	Amide (2) (R=)	Conditions Base/Solvent (amide/base/1)[a]	Products %Yield[b]	%De[c]	Configuration[d]
1	H	LDA/THF (1:3:4)	96(85)[e]	>95%	(S)
2	H	LDA/(4:1)THF-HMPA (1:3:4)	94	8%	(S)
3	H	NHMDS/THF (1:3:4)	93(87)[e]	93%	(R)
4	Me	LDA/Et_2O (1:3:4)	70	46%	(R)
5	Me	LDA/(30:1)Et_2O-HMPA (1:3:4)	65(55)[e]	33%	(R)
6	Me	LDA/(3:1)Et_2O-HMPA (1:3:4)	60	18%	(S)
7	Me	LDA/(3:1)THF-HMPA (1:3:4)	68(60)e	32%	(S)
8	Me	NHMDS/THF (1:1.2:2.2)	80	17%	(R)

a) Molar ratio of amide:base:oxaziridine.
b) Yield determined by GLC using a 6 ft. x 1/8 in. 3% OV-17 column on 80/100 Supelcoport.
c) %De's determined by nmr; see reference 10.
d) Configuration of major diastereomer determined by hydrolysis to mandelic acid (5).
e) Isolated yields



6a



6b

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7. (ℓ)-2-pyrrolidinemethanol was purchased from Aldrich Chem. Co.

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9. The hydroxy amides were prepared according to methodology previous described.[5] 2a had the following properties: colorless oil; $[\alpha]_D$-43.3° (c 7.55, MeOH). 2b had the following properties: colorless oil; $[\alpha]_D$-61.68° (c 3.63, MeOH). All new compounds were characterised by ^{1}H-NMR, IR, MS and gave satisfactory elemental analysis.

10. Diastereomeric mixtures of 3/4 were prepared by heating (60°C/4 h) (ℓ)-2-pyrrolidinemethanol or (+)-(S)-2-(methoxymethyl)pyrrolidine with the 1,3-dioxolan-4-one prepared from acetone and (±)-mandelic acid. At 250 MHz the α-proton in (R)-3a appears at δ5.09 ppm and in (S)-4a at 5.12 ppm. At 90 MHz the OMe protons in (R)-3b appear at δ 3.31 and in (S)-4b at δ 3.21 ppm. All attempts to separate 3/4 by capillary GLC have been unsuccessful to date.

11. Hydroxy amide (-)(R)-3a had the following properties: oil, IR (neat) 3405 and 1630 (amide) cm^{-1}; $[\alpha]_D$-31.5° (c 1.8, $CHCl_3$). (+)(S)-4a had the following properties: oil; IR (neat) 3400 (OH) and 1630 (amide) cm^{-1}; $[\alpha]_D$+34.2° (c 1.8, $CHCl_3$).

12. Changes in configuration have been observed in asymmetric alkylation studies of derivatives related to 2 (Ph = alkyl).[5]

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