Stereoselective Oxidation of Titanium(IV) Enolates with Oxygen

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Abstract A novel approach to synthesize enantiomerically pure α-hydroxy carboxylic derivatives is reported. A highly stereoselective oxidation of titanium(IV) enolates from chiral N-acyloxazolidinones is performed with oxygen under simple experimental conditions that do not require any reducing steps. The success of this approach depends on the biradical character of titanium(IV) enolates.

Key words stereoselective synthesis, hydroxylation, titanium enolates, chiral auxiliaries, oxygen, radicals

The chemo-, site-, and stereoselective oxidation of the carbon backbone of organic molecules is a formidable challenge that has attracted increasing interest in recent years. It goes without saying that the wide range of functional groups and positions that can be oxidized makes such a synthetic approach very complicated. Hence, the oxidation of metal enolates is an appealing way to tackle such a challenge and gain access to enantiomerically pure α-hydroxy derivatives. This approach very complicated. Hence, the oxidation of metal enolates is an appealing way to tackle such a challenge and gain access to enantiomerically pure α-hydroxy derivatives.

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Titanium(IV) enolates prepared by enolization with TiCl₃(i-PrO)/i-Pr₂NEt did not add any benefit and milder TiCl₂(i-PrO)₂ or TiCl(i-PrO)₃ Lewis acids are known to be unable to promote an appropriate enolization of such oxazolidinones. In turn, the oxidation of the corresponding sodium or boron enolates using the same conditions was unsuccessful; whereas the oxidation of zirconium(IV) enolates produced the α-hydroxylated adduct 3a in a yield of 18%. Remarkably, careful analysis of the crude reaction mixtures indicated the generation of low, but significant amounts of the by-products 4 shown in Figure 1.

A comprehensive optimization of the reaction conditions indicated that the oxidation was much more reliable by a simple stirring of the solution containing the titanium(IV) enolate in an oxygen atmosphere at room temperature. Indeed, enolization of 1a with TiCl₄/i-Pr₂NEt at 0 °C for 40 minutes in a nitrogen atmosphere and further stirring of the resulting deep red solution under an oxygen atmosphere (1 atm) at room temperature for 3 hours produced the α-hydroxy adduct 3a in a yield of 45% without consuming all the starting material (see Figure 2). Interestingly, the color of the reacting mixture changed to orange or dark yellow, which facilitated the monitoring of the oxidation.

Although the underlying mechanism of such α-hydroxylation is still unclear, the abovementioned results suggest that the oxidation of titanium(IV) enolates might be rationalized by considering the biradical character of such species. Indeed, we hypothesized that a radical-like reaction of triplet oxygen with the biradical titanium enolate II might trigger the formation of the peroxide III shown in Scheme 2. The observed high π-face selectivity may be due to the chelated character of II. Taking into account a previous report by Adam, the internal autoxidation of the titanium(III) center of the resulting species might then generate a peroxytitanate intermediate like IV, which could be responsible for the further oxidation of a titanium(IV) enolate that is not yet oxidized.

Aiming to assess the scope of the reaction, we next applied the optimized reaction conditions to TiCl₄-enolates from N-acyloxazolidinones 1 containing a wide array of R groups (Scheme 3). All these reactions provided in moderate yields a single diastereomer of the corresponding oxygenated adducts, which were easily isolated by column chromatography (Scheme 3). The yields from 1a-d indicated that the reaction is sensitive to the steric hindrance of the R groups. Otherwise, the benzylc position in 1e (R: Bn),
the double and triple carbon bonds in 1f and 1g, respectively, or the ester group in 1h did not affect the result, which proves the high site-selectivity and chemoselectivity achieved in this oxidation of the Cα position.

Finally, the smooth removal of the chiral auxiliary from model adduct 3e, following reported procedures,21 generated excellent yields of up to 95% of the α-hydroxy ester 5 and 1,2-diol 6 (Scheme 4). This also enabled the S-configuration of the α-stereocenter to be established.

In summary, we have reported a novel stereoselective approach of synthesizing α-hydroxy carboxylic derivatives based on the oxidation of titanium(IV) enolates from chiral acyl oxazolidinones with environmentally friendly oxygen using simple experimental conditions. This transformation produces moderate yields, but in a highly selective manner, of the corresponding α-hydroxy adducts, which can then be easily converted into enantiomerically pure and synthetically useful intermediates. Importantly, the isolation of the α-hydroxy adducts does not require any additional reducing agent, suggesting that the overall reaction involves an internal redox step that is probably linked to the biradical character of titanium(IV) enolates.

Unless otherwise stated, reactions were conducted in oven-dried glassware under an inert atmosphere of N2 with anhydrous solvents. The solvents and reagents were dried and purified, when necessary, according to standard procedures. All commercial reagents were used as received. Column chromatography were carried out under low pressure (flash) conditions and performed on SDS silica gel 60 (35–70 μm). Analytical TLC were carried out on Merck silica gel 60 F254 plates and analyzed by UV (254 nm) and stained with phosphomolybdic acid or p-anisaldehyde. Rf values are approximate. Melting points were determined with a Stuart Scientific SMP10 or a Gallenkamp apparatus and are uncorrected. Specific rotations ([α]D) were determined at 589 nm and at 20 °C on a PerkinElmer 241 MC polarimeter. IR spectra (Attenuated Total Reflectance, ATR) were recorded on a Nicolet 4700 FT-IR spectrophotometer.
Acetylation of the Chiral Auxiliary (S)-4-Benzyl-5,5-dimethyl-1,3-oxazolidin-2-one: General Procedure

A 2.5 M solution of n-BuLi in hexanes (2.2 mL, 5.5 mmol) was added dropwise to a solution of (S)-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (1.03 g, 5.0 mmol) in THF (25 mL) at –78 °C under N₂. The solution was stirred for 15 min and the corresponding acyl chloride (6.5 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min, allowed to warm to r.t., stirred for 2 h, and quenched with sat. aq NH₄Cl (2 mL) at r.t. with vigorous stirring. The mixture was partitioned between H₂O and EtOAc (20 mL each). The combined organic extracts were washed with sat. aq NaHCO₃ (15 mL) and brine (15 mL), dried (MgSO₄), filtered, and concentrated. The residue was purified by column chromatography to give the respective acylated chiral auxiliary 1a-h in yields higher than 90%.

Direct Oxidation of 1; General Procedure

Neat TiCl₄ (61 µL, 0.55 mmol) was added dropwise to a solution of 1a-h (0.50 mmol) in CH₂Cl₂ (2 mL) at 0 °C under N₂ and the resultant yellow suspension was stirred for 5 min. Then, i-Pr₂NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. The reaction flask was purged with H₂SO₄-dried O₂ for 5 min at 0 °C and stirring was continued at r.t. for 2–5 h under an O₂ atmosphere. The reaction was quenched by the addition of a sat. aq NH₄Cl (20 mL) at r.t. with vigorous stirring. The mixture was partitioned between CH₂Cl₂ (10 mL) and H₂O (10 mL), and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with sat. aq NaHCO₃ (15 mL) and brine (15 mL), dried (MgSO₄), filtered and concentrated. The residue was analyzed by ¹H NMR and purified by column chromatography to afford a single diastereomer of the corresponding hydroxylated compound 3a-h.

(5)-4-Benzyl-N-[(S)-2-hydroxypropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3a)

Prepared according to the General Procedure from (S)-4-benzyl-N-propanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (1a, 131 mg, 0.55 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 62 mg (0.22 mmol, 45%) of 3a as a white solid; mp 45–47 °C; [α]₂⁰ = 36.5 (c 1.1, CHCl₃); Rf = 0.20 (hexanes–EtOAc, 80:20).


(5)-4-Benzyl-N-[(S)-2-hydroxybutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3b)

Prepared according to the General Procedure from (S)-4-benzyl-N-butanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (1b; 137 mg, 0.55 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 63 mg (0.22 mmol, 43%) of 3b as a white solid; mp 67–68 °C; [α]₂⁰ = 30.7 (c 1.0, CHCl₃); Rf = 0.30 (hexanes–EtOAc, 80:20).

IR (ATR): 3412, 2967, 2927, 2874, 1770, 1672, 1352 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.34–7.22 (5 H, m), 4.95 (1 H, td, J = 7.6, 3.8 Hz), 4.47 (1 H, dd, J = 9.6, 3.6 Hz), 3.44 (1 H, d, J = 7.6 Hz), 3.21 (1 H, dd, J = 14.5, 3.6 Hz), 2.93 (1 H, dd, J = 14.5, 9.6 Hz), 1.91–1.81 (1 H, m), 1.68–1.57 (1 H, m), 1.39 (3 H, s), 1.39 (3 H, s), 1.03 (1 H, t, J = 7.6 Hz).

13C NMR (100.6 MHz, CDCl₃): δ = 175.0, 152.4, 136.6, 129.0, 128.7, 126.9, 83.5, 71.8, 64.0, 35.0, 28.5, 27.3, 22.1, 9.4.


(5)-4-Benzyl-N-[(S)-2-hydroxy-3-methylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3c)

Prepared according to the General Procedure from (S)-4-benzyl-N-(3-methylbutanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1c; 145 mg, 0.55 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 43 mg (0.14 mmol, 28%) of 3c as a white solid; mp 65–66 °C; [α]₂⁰ = 18.0 (c 1.0, CHCl₃); Rf = 0.30 (hexanes–EtOAc, 80:20).

IR (ATR): 3430, 2972, 2923, 2869, 1766, 1694, 1672, 1347 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.34–7.22 (5 H, m), 4.98 (1 H, dd, J = 8.3, 3.3 Hz), 4.46 (1 H, dd, J = 9.7, 3.5 Hz), 3.21 (1 H, dd, J = 14.5, 3.5 Hz), 3.19 (1 H, d, J = 8.3 Hz), 2.94 (1 H, dd, J = 14.5, 9.7 Hz), 2.12–2.04 (1 H, m), 1.38 (6 H, s), 1.09 (3 H, d, J = 6.8 Hz), 0.84 (3 H, d, J = 6.8 Hz).

13C NMR (100.6 MHz, CDCl₃): δ = 175.1, 152.2, 136.6, 129.0, 128.7, 126.9, 83.4, 74.7, 64.2, 35.0, 31.4, 28.4, 22.1, 19.7, 15.1.


(5)-4-Benzyl-N-[(S)-2-cyclopropyl-2-hydroxyacetyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3d)

Prepared according to the General Procedure from (S)-4-benzyl-N-(2-cyclopropylacetoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1d; 99 mg, 0.35 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 28 mg (0.11 mmol, 32%) of 3d as a white solid; mp 106–108 °C; [α]₂⁰ = 30.9 (c 1.0, CHCl₃); Rf = 0.20 (hexanes–EtOAc, 80:20).

IR (ATR): 3404, 2963, 2918, 2851, 1780, 1668, 1352, 1160, 1094 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.34–7.22 (5 H, m), 4.82 (1 H, dd, J = 8.0, 6.1 Hz), 4.49 (1 H, dd, J = 9.6, 3.6 Hz), 3.39 (1 H, d, J = 8.0 Hz), 3.21 (1 H, dd, J = 14.5, 3.6 Hz), 2.95 (1 H, dd, J = 14.5, 9.6 Hz), 1.41 (3 H, s), 1.40 (3 H, s), 1.29–1.22 (1 H, m), 0.61–0.39 (4 H, m).

13C NMR (100.6 MHz, CDCl₃): δ = 174.7, 152.6, 136.6, 129.0, 128.7, 126.9, 83.6, 71.4, 64.2, 35.1, 28.5, 22.1, 13.7, 1.5, 0.9.


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(5)-4-Benzyl-N-[(5)-2-hydroxy-3-phenylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3e)
Prepared according to the General Procedure from (5)-4-benzyl-5,5-dimethyl-N-[(3-phenylpropanoyl)-1,3-oxazolidin-2-one (1e; 168 mg, 0.5 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 60 mg (0.17 mmol, 34%) of 3e as a white solid; mp 98–99 °C; [α]20 -13.1 (c 1.0, CHCl3); Rf = 0.20 (hexanes–EtOAc, 80:20).

IR (ATR): 3425, 2949, 2851, 1757, 1703, 1352, 1245 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.34–7.22 (5 H, m), 5.84–5.75 (1 H, m), 5.07 (1 H, dq, J = 17.1, 1.6 Hz), 5.01–4.95 (2 H, m), 4.47 (1 H, dd, J = 9.6, 3.7 Hz), 3.52 (1 H, dd, J = 7.6 Hz), 3.19 (1 H, dd, J = 14.5, 7.6 Hz), 2.93 (1 H, dd, J = 14.5, 9.6 Hz), 2.22–2.24 (2 H, m), 1.94–1.85 (1 H, m), 1.71–1.62 (1 H, m), 1.40 (3 H, s), 1.39 (3 H, s).

13C NMR (100.6 MHz, CDCl3): δ = 174.9, 152.4, 137.5, 136.6, 129.0, 128.7, 126.9, 115.3, 83.5, 70.2, 64.0, 35.0, 33.1, 29.4, 28.5, 22.1.


(5)-4-Benzyl-N-[(5)-2-hydroxy-5-hexynoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3f)
Prepared according to the General Procedure from (5)-4-benzyl-N-(5-hexynoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1f; 150 mg, 0.5 mmol). Purification of the residue by column chromatography (hexanes–EtOAc, 80:20) afforded 51 mg (0.16 mmol, 32%) of 3f as a white solid; mp 90–92 °C; [α]20 –21.0 (c 1.1, CHCl3); Rf = 0.30 (hexanes–EtOAc, 80:20).

IR (ATR): 3425, 2949, 2972, 2940, 2980, 2851, 1766, 1703, 1361, 1281 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.34–7.22 (5 H, m), 5.84–5.75 (1 H, m), 5.07 (1 H, dq, J = 17.1, 1.6 Hz), 5.01–4.95 (2 H, m), 4.47 (1 H, dd, J = 9.6, 3.7 Hz), 3.52 (1 H, dd, J = 7.6 Hz), 3.19 (1 H, dd, J = 14.5, 7.6 Hz), 2.93 (1 H, dd, J = 14.5, 9.6 Hz), 2.22–2.24 (2 H, m), 1.94–1.85 (1 H, m), 1.71–1.62 (1 H, m), 1.40 (3 H, s), 1.39 (3 H, s).

13C NMR (100.6 MHz, CDCl3): δ = 174.2, 152.4, 136.5, 129.5, 129.0, 128.7, 126.9, 83.5, 71.7, 64.0, 40.2, 35.0, 28.5, 22.2.


Synthesis
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5,5-dimethyl-1,3-oxazolidin-2-one and 21 mg (0.14 mmol, 95%) of (5)-3-phenyl-1,2-propanediol (6) as a clear colorless oil; [α]D20 = −18.3 (c 1.3, CHCl3) [lit.6a [α]D20 = −18.6 (c 1.3, CHCl3)]; Rf = 0.20 (hexanes–EtOAc, 85:15).

IR (ATR): 3221, 3024, 2917, 2850, 1495, 1451, 1070, 1036 cm−1.

1H NMR (400 MHz, CDCl3): δ = 7.33–7.20 (5 H, m), 3.49 (1 H, dd, J = 11.2, 2.7 Hz), 2.80–2.70 (2 H, m), 2.39 (2 H, br s).

13C NMR (100.6 MHz, CDCl3): δ = 137.7, 129.3 (2 ×), 128.6 (2 ×), 126.6, 73.0, 66.0, 39.8.


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Supporting Information

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(15) Zirconium(IV) enolates from 1a were prepared according the experimental procedure reported in reference 11b.

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