

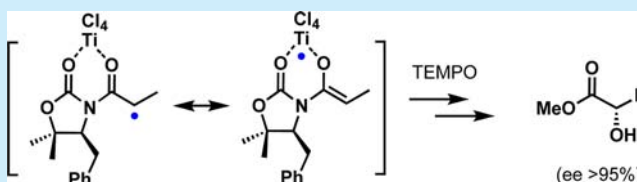
Asymmetric Radical Addition of TEMPO to Titanium Enolates

Phillip J. Mabe and Armen Zakarian*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106-9510, United States

S Supporting Information

ABSTRACT: A mild method for α -hydroxylation of *N*-acyl oxazolidinones by asymmetric radical addition of the 2,2,6,6-tetramethylpiperidine *N*-oxy (TEMPO) radical to titanium enolates was developed. The high diastereoselectivity and broad scope of the reaction show synthetic utility for the α -hydroxylation of substrates that are not tolerant to strongly basic conditions.



Many methods are available for the α -hydroxylation of carbonyl compounds.¹ Among the most commonly applied is enolate oxidation^{1,2} by reagents such as MoO₅·Py·HMPA,³ MoO₅·Py·DMPU,⁴ *N*-sulfonyloxaziridines,⁵ peroxides,⁶ or hypervalent iodine reagents.⁷ Stereoselectivity of enolate oxidations is generally controlled by the approach of the oxidant to the less sterically hindered face of the enolate whether the process is catalytic or auxiliary-controlled.¹ Highly stereoselective α -hydroxylations have been reported through the use of *N*-acyl oxazolidinones with achiral oxidants⁸ or, alternatively, through the use of achiral carbonyl substrates with chiral oxidants such as (camphorylsulfonyl)oxaziridines.⁹ However, these methods require the use of strongly basic reagents such as LDA, or NaN(SiMe₃)₂, which may be incompatible with more functionalized substrates.

Transition-metal-catalyzed direct asymmetric α -hydroxylation reactions using chiral titanium,¹⁰ ruthenium,^{9,10} and palladium¹¹ complexes constitute an important advance in the field. These reactions are currently limited to β -ketoesters. Enantioselective organocatalytic oxygenation reactions using TEMPO have recently been reported.¹² However, the scope of these methods is limited to aldehydes as substrates.

Jahn and co-workers have recently reported an elegant approach to α -oxygenation of enolates derived from esters, amides, ketones, nitriles, and carboxylic acids by treatment with a combination of TEMPO and superstoichiometric amounts of ferrocenium hexafluorophosphate.^{2,13} Renaud, Studer and co-workers recently described the α -oxygenation of enol borinates using TEMPO.¹⁴ Both of these powerful methods provide access to α -(tetramethylpiperidin-1-yl)oxy carbonyl compounds in excellent yields, although examples of asymmetric α -aminoxylation reactions in these reports are isolated.

In line with our interest in exploring the radical reactivity of readily available transition metal enolates,¹⁵ we directed our efforts toward developing a direct asymmetric radical α -hydroxylation of *N*-acyl oxazolidinones using TEMPO. Initial experimentation with 4-benzyl-5,5-dimethyl-*N*-propionyloxazolidin-2-one **1** (R¹ = Bn, R² = R³ = CH₃) immediately revealed that titanium enolates¹⁶ derived from **1** undergo efficient and facile addition of TEMPO with high diastereocontrol (Table 1).

Table 1. Optimization of Reaction Time and Temperature Parameters^a

entry	R ¹ , R ² , R ³	time	temp	dr ^b	conversion, %
1	Bn, Me, Me	30 min	−78 °C	9:1	5
2		1 min	0 °C	20:1	95
3		5 min	0 °C	20:1	100
4		15 min	0 °C	21:1	100
5		3 h	0 °C	17:1	100
6		2 min	23 °C	17:1	98
7		30 min	23 °C	14:1	100
8	<i>i</i> -Pr, Me, Me	50 min	23 °C	7:1	100
9	Ph, Me, H	40 min	23 °C	5:1	100
10	Bn, H, H	40 min	23 °C	4:1	100

^aStandard conditions: **1** (0.4 mmol), CH₂Cl₂ (~0.4 M), TiCl₄ (1.05 equiv), 0 or 23 °C, 10 min; Et₃N (3.0 equiv), 40 min; TEMPO (2.05 equiv), as 1.0 M solution in CH₂Cl₂ dropwise over 1 min. ^bConversion and diastereomeric ratios were determined by 500 or 600 MHz ¹H NMR analysis of the crude mixture of products.

Similar reactivity was observed for enolates generated with zirconium tetrachloride, although the diastereoselectivity was notably lower (dr = 4:1). While the rate of the addition was low at −78 °C (Table 1, entry 1), a rapid addition was observed at the more experimentally convenient temperatures of 0 °C (Table 1, entries 2–5) and 23 °C (Table 1, entries 6, 7). Prolonged reaction times (0 °C, 3 h) result in the erosion of stereoselectivity (cf. entries 4 and 5).

Replacing the benzyl substituent at the oxazolidinone with an isopropyl group resulted in a lower diastereoselectivity of 7:1 (Table 1, entry 8). Other oxazolidinones lacking the 5,5-

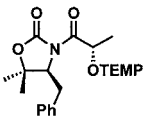
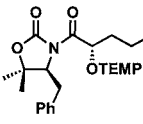
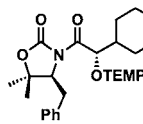
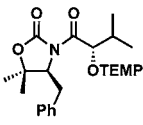
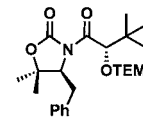
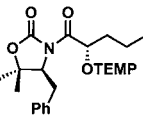
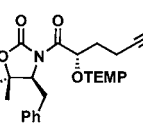
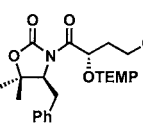
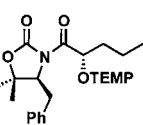
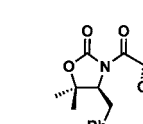

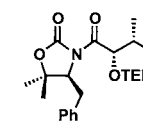
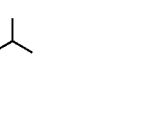
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dimethyl substitution also displayed lower diastereocontrol (Table 1, entries 9, 10).

The scope of the aminooxylation reaction was explored next (Table 2). While the diastereoselectivity was somewhat lower at

Table 2. Scope of *N*-Acyl Oxazolidinones in the α -Aminooxylation Reaction^a

products of α -aminooxylation reaction with TEMPO		
		
2a (67%, dr = 14:1)	2b (82%, dr = 16:1) (89% brsm)	2c (78%, dr = 33:1) (88% brsm)
		
2d (74%, dr = 25:1) (93% brsm)	2e (54%, dr = 34:1) (88% brsm)	2f (76%, dr = 16:1) (80% brsm)
		
2g (73%, dr = 14:1) (87% brsm)	2h 87%, dr = 16:1 (96% brsm)	2i R=Bn (41%) R=H (32%) (dr = 10:1)
		
2j (86%, dr = 16:1)	2k (89%, dr = 14:1)	
		
2l (73%, dr = 33:1) (87% brsm)	2m (73%, dr = 20:1) (94% brsm)	

^aYields of isolated products as a mixture of diastereomers are reported. At least two experiments were carried out to confirm reproducibility. The numbers in parentheses are yields based on recovered starting material (brsm). Diastereomer ratios were determined by 500 or 600 MHz ¹H NMR analysis of the crude mixture of products. ^bFormation of the byproduct (R = H) is attributed to TiCl₄-assisted debenzoylation.

23 °C, we chose to continue experimentation at this temperature for operational simplicity. Many *N*-acyl oxazolidinones can be successfully α -aminooxylated using the general protocol developed during the course of this investigation. Unfunctionalized *N*-acyl oxazolidinones derived from simple alkanolic acids undergo effective and diastereoselective α -aminooxylation, with yields decreasing and stereoselectivity increasing as β -branching of the substrates increases (Table 2, 2a–2e). Diminished yields and improved stereoselectivity with β -branching are consistent with the increasing steric hindrance

in the titanium enolates. However, these reactions are clean transformations with unreacted starting material as the major byproduct, pointing to the lower reactivity of the more hindered substrates. For 4-benzyl-5,5-dimethyl-*N*-propionyloxazolidin-2-one (Table 2, 2a), oxazolidinone cleavage (18%) and oxidative dimerization at the α -position (8%) were observed at room temperature, in addition to the formation of the expected α -aminooxylation product.

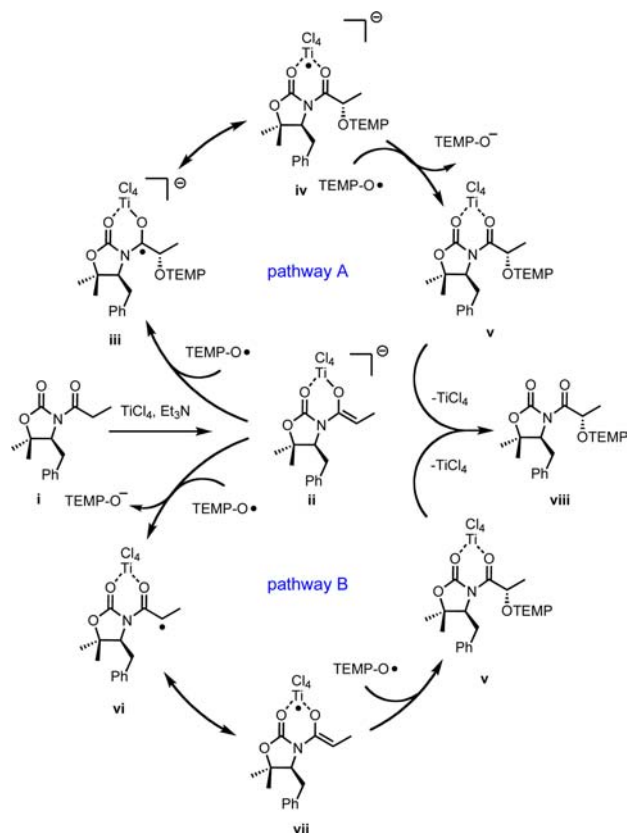
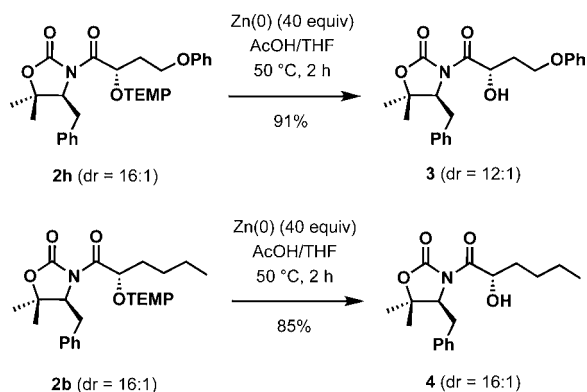
Substrates with terminal alkene, alkyne, benzyl, and aryl ether functional groups are well tolerated (Table 2, 2f–2i). The reduced yield for the reaction of the benzyl ether (Table 2, 2i) is attributed to TiCl₄-mediated debenzoylation, resulting in the formation of the debenzoylated byproduct (32%), and a minor degree of oxazolidinone cleavage (7%). Substrates derived from arylacetic acids are also suitable starting materials (Table 2, 2j, 2k). Notably, pure products 2j and 2k are somewhat unstable and have been observed to undergo a spontaneous epimerization at the α -position in solution in CDCl₃, with a 1:1.7 mixture of diastereomers formed from a 14:1 mixture after 12 days at ambient temperature.¹⁷

High diastereoselectivity was achieved with both diastereomers of the imide derived from (*R*)-hydrocitronellonic acid irrespective of the relative configuration at the β -position (Table 2, 2l and 2m).

Further inquiry probed mechanistic details of the radical addition of TEMPO to the titanium enolates, first testing the potential for catalytic turnover of TiCl₄.¹⁸ Using 0.20 equiv of TiCl₄ and 4-benzyl-5,5-dimethyl-*N*-propionyloxazolidin-2-one (1) under the standard reaction conditions (23 °C, 30 min) or upon heating and prolonged reaction times (40 °C, 17 h) resulted in ~20% conversion, indicating no turnover of titanium tetrachloride. Similar observations were noted when triethylamine, which may have an inhibitory effect, was replaced with 1,2,2,6,6-pentamethylpiperidine.¹⁴ These results suggest that the product may be an effective ligand for titanium tetrachloride, leading to strong product inhibition. Erosion of stereochemistry in the product upon prolonged reaction times also indicates that the product remains bound to the Lewis acid and is subject to a relatively slow but observable enolization.

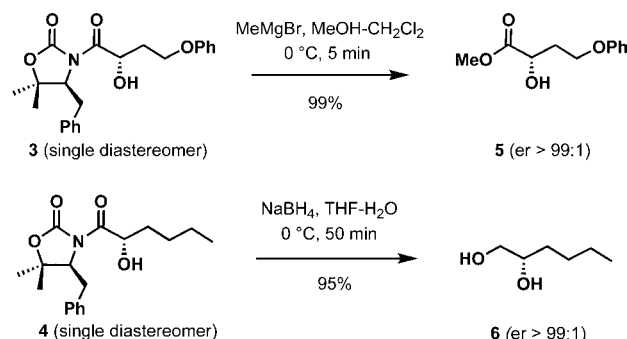
Two alternative pathways for the radical addition of TEMPO are envisioned as outlined in Scheme 2. After the initial generation of Ti enolate ii, pathway A calls for the direct addition of the TEMPO radical, affording the delocalized open shell system represented by resonance structures iii and iv. Subsequent oxidation with the second equivalent of TEMPO affords the product as a complex with TiCl₄, which delivers free product viii after decomplexation upon quench. In pathway B, Ti enolate ii is *first* oxidized by TEMPO to the enol radical represented by resonance structures vi and vii. The resulting radical undergoes a radical–radical coupling with TEMPO giving v and ultimately product viii upon quench. We currently favor pathway B due to mechanistic similarity with catecholboron enolate oxidation by TEMPO,¹⁹ in addition to indirect experimental evidence, primarily isolation of the enolate dimerization byproducts in certain reactions (i.e., Tables 2, entry 1).

The utility of products described in this study was first demonstrated by the N–O bond scission to reveal the products of α -hydroxylation. The N–O bond could be cleaved in high yield by a reaction with Zn(0) dust (40 equiv) in AcOH/THF (3/1) at 50 °C for 2 h (Scheme 3).² We generally observed high integrity for the stereochemistry at the α -position bearing the unmasked free hydroxy group.

Scheme 2. Mechanistic Overview of Radical α -Aminoxylation of Titanium Enolates with TEMPOScheme 3. N–O Bond Cleavage of α -Aminoxylation Intermediate

Diastereomeric mixtures of α -hydroxylated oxazolidinone products were readily separable by column chromatography and afforded **3** and **4** as single diastereomers. Removal of the chiral auxiliary was accomplished by the use of MeOMgBr generated in situ,²⁰ affording α -hydroxylated methyl ester **5** in nearly quantitative yield (er >99:1, Scheme 4). Reductive removal of the chiral auxiliary with NaBH₄ in aqueous THF²¹ afforded diol **6** in 95% yield (er >99:1).

In summary, the stereoselective radical addition of TEMPO to Ti enolates generated in situ provides a mild and experimentally convenient alternative for α -hydroxylation of base-sensitive ester derivatives. The N–O bond in the products can be removed under mild reductive reaction conditions, and the chiral auxiliary can also be cleaved reductively or

Scheme 4. Preparation of Enantioenriched Hydroxylated Building Blocks by Removal of the Chiral Auxiliary^a via Esterification and Reduction

^aThe chiral auxiliary is recovered in nearly quantitative yield for all reactions

solvolitically while maintaining the integrity of the α -hydroxylated stereocenter. Further studies into the mechanism of the reaction and radical reactivity of enolates produced by soft enolization are underway in our laboratory.

■ ASSOCIATED CONTENT

§ Supporting Information

General experimental procedures, characterization data, and copies of ¹H and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zakarian@chem.ucsb.edu.

Notes

The authors declare no competing financial interest.

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