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Asymmetric Radical Addition of TEMPO to Titanium Enolates

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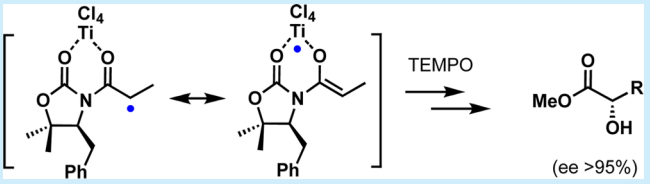
Supporting Information

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.



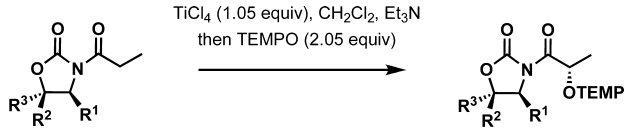
Many methods are available for the α-hydroxylation of carbonyl compounds.[1] Among the most commonly applied is enolate oxidation[1,2] by reagents such as MoO_5·Py·HMPA,[3] MoO_5·Py·DMPU,[4] *N*-sulfonyloxaziridines,[5] peroxides,[6] or hypervalent iodine reagents.[7] Stereoselectivity of enolate oxidations 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 oxidants[8] 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 $NaN(SiMe_3)_2$, which may be incompatible with more functionalized substrates.

Transition-metal-catalyzed direct asymmetric α-hydroxylation reactions using chiral titanium,[10] ruthenium,[9,10] and palladium[11] 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** (R^1 = Bn, R^2 = R^3 = CH_3) immediately revealed that titanium enolates[16] derived from **1** undergo efficient and facile addition of TEMPO with high diastereocontrol (Table 1).

Table 1. Optimization of Reaction Time and Temperature Paramaters[a]



1 2

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*-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

[a]Standard conditions: **1** (0.4 mmol), CH_2Cl_2 (~0.4 M), $TiCl_4$ (1.05 equiv), 0 or 23 °C, 10 min; Et_3N (3.0 equiv), 40 min; TEMPO (2.05 equiv), as 1.0 M solution in CH_2Cl_2 dropwise over 1 min. [b]Conversion 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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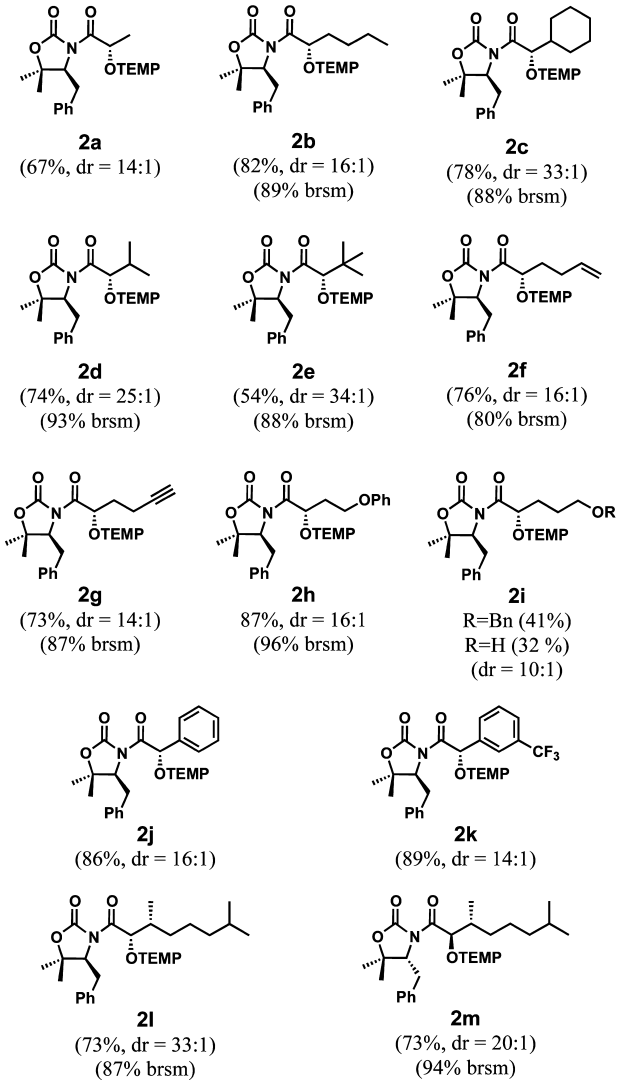
dimethyl substitution also displayed lower diastereocontrol (Table 1, entries 9, 10).

The scope of the aminoxylation reaction was explored next (Table 2). While the diastereoselectivity was somewhat lower at 23 °C, we chose to continue experimentation at this temperature for operational simplicity. Many *N*-acyl oxazolidinones can be successfully α-aminoxylated using the general protocol developed during the course of this investigation. Unfunctionalized *N*-acyl oxazolidinones derived from simple alkanoic acids undergo effective and diastereoselective α-aminoxylation, 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-aminoxylation product.

Table 2. Scope of *N*-Acyl Oxazolidinones in the α-Aminoxylation Reaction[a]

products of α-aminoxylation 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)

[a]Yields 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 ^{1}H NMR analysis of the crude mixture of products. [b]Formation of the byproduct (R = H) is attributed to $TiCl_4$-assisted debenzylation.

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 $TiCl_4$-mediated debenzylation, resulting in the formation of the debenzylated 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 $CDCl_3$, 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*)-hydrocitronellic 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 $TiCl_4$.[18] Using 0.20 equiv of $TiCl_4$ 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 $TiCl_4$, 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.

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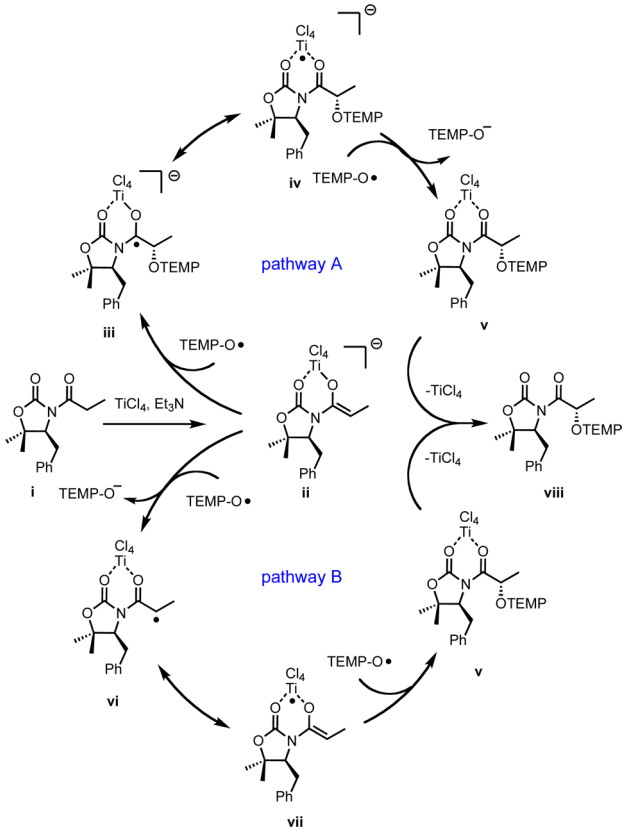
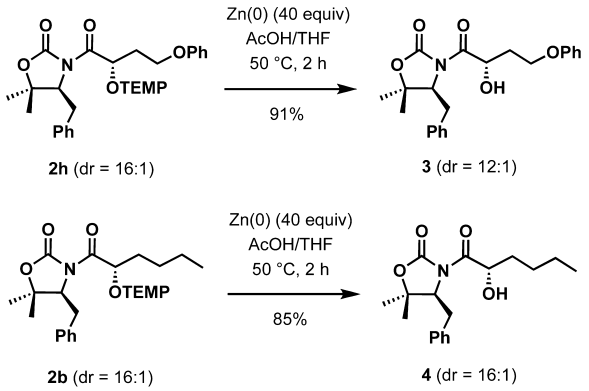
Scheme 2. Mechanistic Overview of Radical α-Aminoxylation of Titanium Enolates with TEMPO



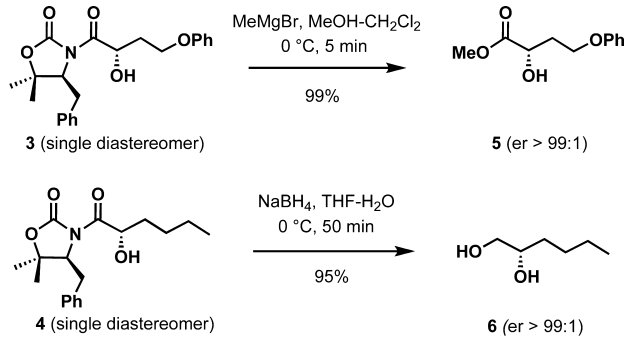
Scheme 3. N−O Bond Cleavage of α-Aminoxylated Intermediate



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 $NaBH_4$ in aqueous THF[21] 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 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.

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



[a]The chiral auxiliary is recovered in nearly quantitative yield for all reactions

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(17) Similar observations are described in ref 8b.
(18) Effective catalytic turnover of $TiCl_4$ has been achieved previously in radical haloalkylation reactions; see ref 15b.
(19) Catecholeboron enolates have been shown to be readily oxidized by TEMPO resulting in the formation of an α-enoyl radical; see ref 14.
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