

Isolation and *syn* Elimination of a Peterson Adduct to Obtain Optically Pure Product in the Diastereoselective Synthesis of Oxazolidinone-Functionalized Enecarbamates

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Received January 17, 2009; Revised April 30, 2009; Accepted April 30, 2009

Abstract: The Peterson reaction of (4*R*)-*N*-(trimethylsilyl)methyl-4-alkyloxazolidin-2-one gives (*E/Z*)-(4*R*)-*N*-(2',3'-diphenylbut-1'-enyl)-4-alkyloxazolidin-2-ones (enecarbamates) with increasing (*Z*)-selectivity and moderate-to-high diastereoselectivity in the individual *E* isomer as a function of increasing temperature. X-ray structure of the Peterson adduct, (4*R*,3'*S*)-*N*-(2',3'-diphenyl-2'-hydroxy-but-1'-enyl)-4-alkyloxazolidin-2-one (enecarbamates), reveals the rationale for the formation of a single isomer through *syn* elimination. The optically pure enecarbamates obtained with the Peterson adduct were further employed for photochemical and photophysical studies.

Keywords: Peterson reaction, diastereoselectivity, asymmetric synthesis, singlet oxygen.

Stereocontrol during the formation of carbon-carbon bonds is an intriguing but challenging subject of research in organic synthesis. During the last few decades, exploitation of the Horner-Wadsworth-Emmons (HWE) and Wittig-type reactions has afforded immense progress in this area [1, 2]. However, a widely known and potentially useful alternative approach to asymmetric induction in C-C bond formation is the Peterson reaction [3-7]. With precursors bearing a trimethylsilyl (TMS) substituent, the generation and subsequent olefination of the silyl carbanion with a carbonyl partner was recently reported to give high enantioselectivities for the α -trimethylsilyl acetate [8], as well as high *Z*-selectivities for a variety of α,β -unsaturated products [9-11]

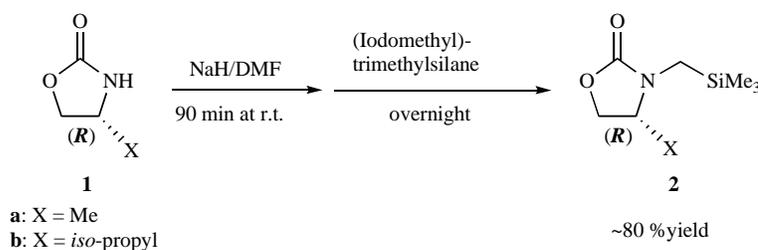
Despite its potential as a versatile synthetic tool in manipulating stereocontrol during C-C double bond formation, considerable effort has not been devoted to studying asymmetric induction in the Peterson olefination to date. In this context, we have investigated the diastereoselective Peterson olefination of (4*R*)-*N*-(trimethylsilyl)methyl-4-alkyloxazolidin-2-one (**2**) with methyldeoxybenzoin (MDB), (**3**), affording (*E/Z*)-(4*R*)-*N*-(2',3'-diphenylbut-1'-enyl)-4-alkyloxazolidin-2-ones (enecarbamates (**4**)) by way of *syn* elimination and have subsequently employed these enecarbamates for photooxygenation reactions.

Enecarbamates, equipped with an oxazolidinone chiral auxiliary, are mechanistically versatile systems to study conformational, stereoelectronic, and steric effects on the stereoselectivity of oxidation reactions [12-14], as well as the diastereoselective photoisomerization at the alkene functionality [15]. Herein we report (a) the role of temperature on the diastereoselectivity in the Peterson olefination of the oxazolidinone **2** with MDB (**3**) and (b) the isolation and characterization of the intermediary (4*R*,3'*S*)-*N*-(2',3'-diphenyl-2'-hydroxy-but-1'-enyl)-4-alkyloxazolidin-2-one (**5**) (Schemes 1, 2 and Fig. 1). The precursors **2** for the Peterson olefination were prepared from the corresponding (4*R*)-alkyloxazolidinones (**1**) in good yields (Scheme 1) [16]. To assess any steric effect during the elimination process, the (4*R*)-methyl- and (4*R*)-isopropyl-substituted oxazolidinone derivatives were synthesized.

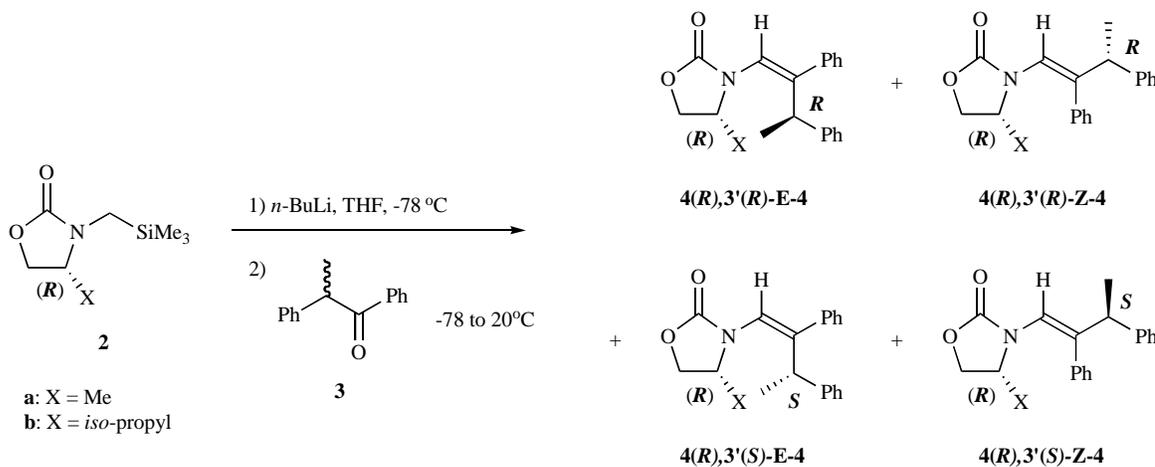
All Peterson reactions were carried out in an anhydrous THF solution in the temperature range from -78 °C to 20 °C (Scheme 2 and Table 1). A THF solution of the silyl derivative (**2**) was stirred under a N₂ atmosphere at -78 °C and *n*-BuLi was added. After the reaction mixture was stirred for 1 h at -78 °C, 0 °C, or 20 °C, a THF solution of (**3**) was added drop wise and the stirring was continued for another 1 h. The work-up with an aqueous NH₄Cl solution and subsequent purification by column chromatography gave the pair of (*Z*-**4**) or (*E*-**4**) diastereomers, each one as a pair of *R/S* epimers at the C-3' position, as displayed in Scheme 2.

The quantitative results of the chemical yields and diastereoselectivities as a function of temperature are

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Scheme 1. Synthesis of the (4R)-N-(trimethylsilyl)methyl-4-alkyl-oxazolidin-2-one (**2**) precursors for the Peterson olefination.



Scheme 2. Synthesis of enecarbamates (**4**) by Peterson olefination of (4R)-N-(trimethylsilyl)methyl-4-alkyl-oxazolidin-2-ones (**2**).

Table 1. Chemical Yields and Diastereoselectivity as a Function of Temperature in the Synthesis of Enecarbamates (**4**) via the Peterson Olefination of (**2**)

X	Temp °C	%yield ^a of <i>E</i> [%de] ^b	%yield ^a of <i>Z</i> [%de] ^b	<i>E</i> : <i>Z</i> ^b
Me (4a)	20	6 [45(<i>S</i>)]	20 [10(<i>R</i>)]	20:80
	0	7 [71(<i>S</i>)]	44 [13(<i>R</i>)]	13:87
	-78	2 ^d	26 [64(<i>S</i>)]	2:98
<i>i</i> Pr (4b)	20	7 [30(<i>S</i>)]	15 [6(<i>S</i>)]	44:56
	20 ^c	14 [38(<i>S</i>)]	20 [5(<i>S</i>)]	41:59
	0	12 [62(<i>S</i>)]	24 [8(<i>S</i>)]	36:64
	-78	4 [98 (<i>S</i>)]	30 [10(<i>R</i>)]	16:84

^aYields obtained by GC analysis ($\pm 7\%$) with 4,4'-di-*tert*-butylbiphenyl (DTBP) as internal standard. ^bDiastereoselectivities (de) of the products ($\pm 6\%$) and *E*:*Z* ratios ($\pm 5\%$) obtained by ¹H NMR spectroscopy; the configuration of the epimer at the C-3' position is shown in the parentheses. ^cChemical yields and diastereoselectivities of isolated products. ^dDiastereoselectivity not determined.

displayed in Table 1. The low total yields (only 20-50%) of the *E/Z* diastereomers are presumably due to the labile nature of the intermediary carbanion and its slow addition to the sterically encumbered carbonyl group of MDB (**3**) [17, 18]. The ratio of *E* : *Z* diastereomers (the last column in Table 1) varied appreciably over the employed temperature range, i.e., it increased in favor of the *Z* isomer with decreasing temperature. For example, with the methyl derivative (**4a**), the *E* : *Z* ratio went from 20 : 80 at 20 °C to 2 : 98 at -78 °C. A similar temperature-dependent trend for the stereoselectivity of the C-3'-*R/S* epimers was observed. In particular, with the (*E*-**4b**), the diastereomeric excess (de) increases substantially in favor of the *S* epimer with decreasing temperature and, in fact, at -78 °C the de value is as high as

98%. Contrastingly, the epimeric differentiation is low for the (*Z*-**4b**) isomer with the de values varying only 5-10% and the selectivity inverting from *S* to *R* as the temperature decreased [19].

When one equivalent of the *n*-BuLi base was used, one of the Peterson adducts (**5**) was isolated as a colorless crystalline solid and subjected to X-ray crystallographic analysis (Fig. 1). The configuration at the C-3' position of the phenethyl side chain in the adduct was inferred from the known configuration at the C-4 position of the chiral oxazolidin-2-one. As additional confirmation of the assignment, the enecarbamate obtained from the *syn* elimination of the Peterson adduct (Fig. 2) afforded a single MDB product on photooxygenation [12-14] (Scheme 3).

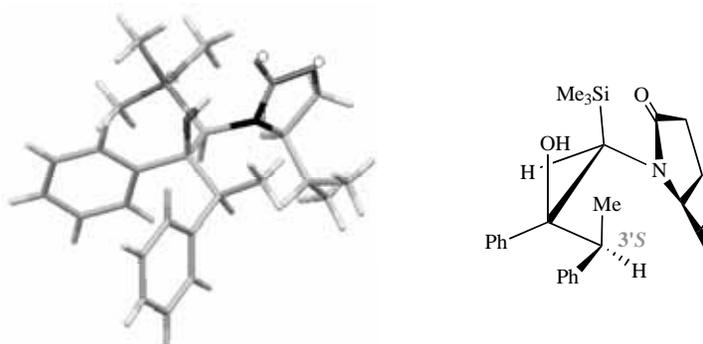


Fig. (1). The X-ray crystallographic structure (deposition number CCDC 652101) of the Peterson adduct (*4R,3'S*)-*N*-(2',3'-diphenyl-2'-hydroxy-but-1'-enyl)-4-isopropylloxazolidin-2-one, the isopropyl derivative of (**5**).

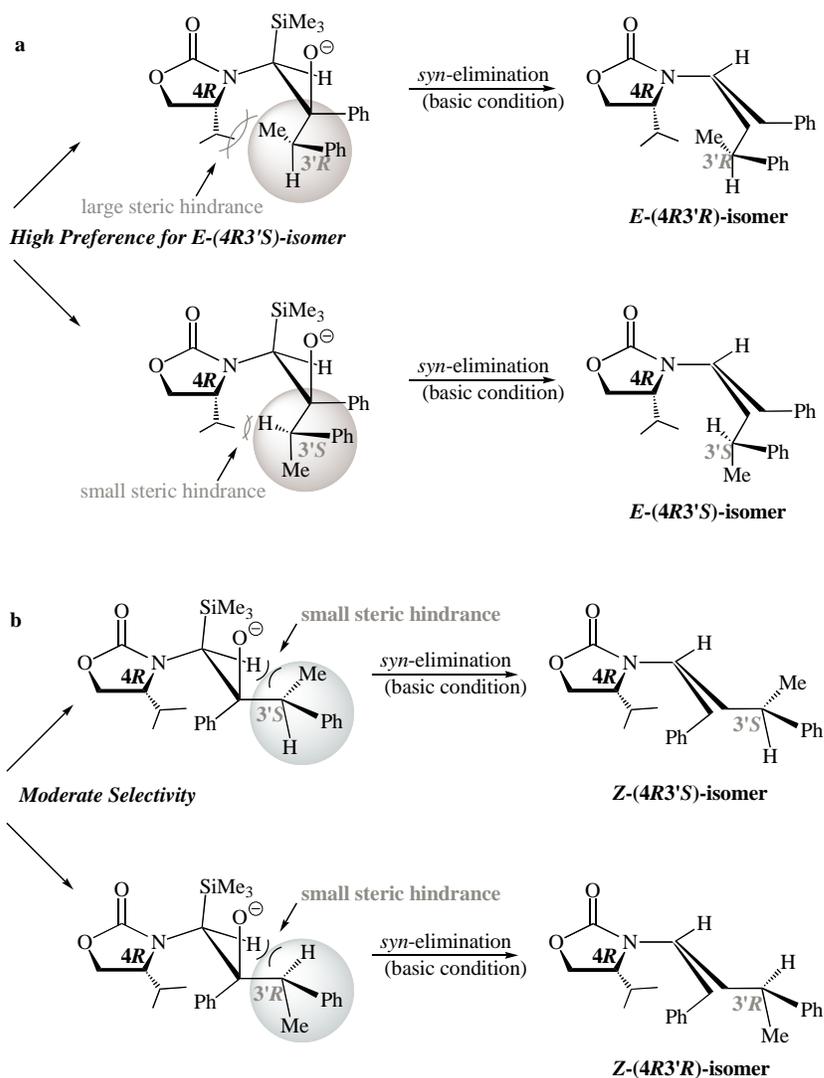
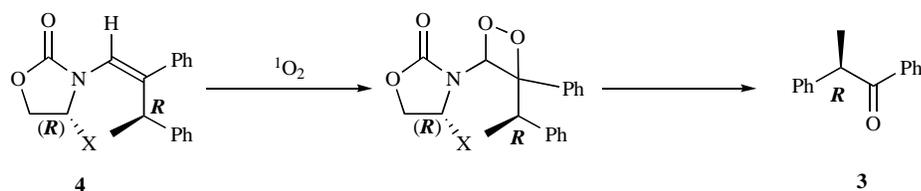


Fig. (2). The proposed mechanism of stereo-control for the formation of the (*E-4b*) (a) and (*Z-4b*) (b) diastereomers in the Peterson olefination of oxazolidinone (**2b**).

The X-ray structural analysis (Fig. 1) of (**5**) clearly shows that the oxazolidinone ring points perpendicularly to the newly formed C-C bond, to minimize steric interactions with the phenethyl substituent at the C-3' position. Presumably, this steric interaction is responsible for the high

diastereoselectivity of 98% at $-78\text{ }^{\circ}\text{C}$ for the (*E-4b*) diastereomer. The *syn* elimination of adduct (**5**) under a basic condition gave exclusively and quantitatively the C-3'S epimer of the (*E-4b*) isomer (see Supplementary data). This result unambiguously demonstrates that the elimination



Scheme 3. Photooxygenation of enecarbamate (**4**) with $^1\text{O}_2$ to yield the dioxetane which then decomposes to MDB (**3**) isomer and the oxazolidinone aldehyde.

process is not reversible; only one C-3' epimer is formed from the Peterson adduct.

These remarkable stereochemical findings for the present Peterson olefination require a mechanistic rationalization in terms of appropriate transition structures. A mechanism consistent with the stereoselectivity observed in the case of substrate (**2b**) is proposed in Fig. (2), which is based on the established *syn* elimination under basic conditions [5]. Fig. (**2a**) reveals that in the adduct leading to the (*E*-**4b**) isomer, there is a severe steric hindrance between the isopropyl group of the oxazolidinone and the phenethyl substituent at the C-3' position for the 3'(*R*) than for the 3'(*S*) epimer. Thus, the transition state for the formation of the 3'(*S*) epimer of the (*E*-**4b**) diastereomer is energetically favored, which accounts for the high diastereoselectivity obtained especially at low temperatures (Table 1). In the case of (*Z*-**4b**), however, the difference in the steric hindrances between the 3'*R* and 3'*S* epimers is much less pronounced, since the phenethyl substituent points away from the isopropyl group in the adduct. Consequently, only a moderate diastereoselectivity is observed for the (*Z*-**4b**) isomer even at low temperature. The reversal in the chiral sense of the preferred epimer (3'*R* versus 3'*S*) for the (*Z*-**4a**) isomer is difficult to rationalize reliably for such low stereo-control, but subtle structural and environmental factors likely play an important role [20, 21].

The optically pure enecarbamates thus synthesized were invaluable for the elucidation of the reaction mechanism of photooxygenation and for ascertaining the role of vibrational deactivation [22] in such processes. For the experiment it was necessary to obtain compounds that were optically pure and the isolation of the Peterson adduct allowed us to do so in great quantities. The optically pure (*E*-**4b**) isomers showed that the rate of physical quenching is substantially different in the diastereomers that differ in the C-3' position (Table 2) [22]. This difference in the quenching efficiency was reflected in the enantiomeric excess (63% [R-MDB]) upon photooxygenation in the MDB product that was rationalized in our previous investigations [12-14, 19].

In conclusion, the Peterson olefination of the oxazolidinones (**2a**) and (**2b**) with racemic MDB (**3**) affords the chiral enecarbamates (**4a**) and (**4b**) in high stereoselectivity, especially at low temperature. The stereo-control of the *E/Z* diastereomers and of the *R/S* epimers in the enecarbamates (**4a**) and (**4b**) is dictated by the steric interactions between the oxazolidinone ring and the phenethyl side chain in the transition states for the C-C bond formation. The X-ray crystal structure of the intermediary Peterson adduct (**5**) substantiates these mechanistic speculations. This Peterson olefination is not reversible, which strongly indicates that the stereoselectivity is determined at the stage of the C-C bond formation. In this unique approach to kinetic resolution utilizing the combination of chiral auxiliary and the Peterson olefination, the chiral enecarbamates were subjected to photooxidation with singlet oxygen to yield the MDB product in high enantioselectivities. Taken altogether, these results demonstrate the usefulness of the Peterson olefination reaction in controlling the *cis-trans* geometry about double bonds and, more significantly, as a potentially valuable tool to include in our still sparse repertoire of asymmetric induction methods. Succinctly, the steric and directing effects of the oxazolidinone chiral auxiliary in concert with the Peterson olefination reaction can serve to effect stereocontrol when forming chiral C-C bonds. We were able to employ the optical pure isomers, obtained through the isolation of the Peterson adduct, to study both the chemical and physical quenching of singlet oxygen and the factors that lead to stereoselectivity and kinetic resolution.¹⁹ Thus synthesizing optically pure enecarbamates *via* Peterson's olefination enabled us to better understand the reactivity of excited state molecular oxygen (singlet oxygen).

ACKNOWLEDGEMENTS

The authors at Columbia thank the NSF (CHE-04-15516, CHE-07-17518) for generous support of this research. W.A. gratefully acknowledges previous financial support from the Deutsche Forschungsgemeinschaft, Alexander von Humboldt-Stiftung, and the Fonds der Chemischen Industrie.

Table 2. Ratio of Physical Quenching (k_{pQ}) and Chemical Quenching (k_{cQ}) Obtained in CDCl_3 Using *trans*-4-Octene as a Standard. Optically Pure Enecarbamates were Obtained *via syn* Elimination of the Peterson Olefination Adduct

X	Stereochemistry		k_{pQ}/k_{cQ}^a
	C-4	C-3'	
¹ Pr (<i>E</i> - 4b)	<i>R</i>	<i>S</i>	0.13
	<i>S</i>	<i>S</i>	0.21 ^b

^aBased on reactive and physical quenching rate constants (Reference [22]).

^bThe C-4*R*,C-3'*R* and C-4*S*,C-3'*S* enecarbamates are optical antipodes.

J.S. thanks NDSU for Faculty Start-up award and the National Science Foundation for the CAREER award (CHE-0748525). H.S. is grateful for a JSPS research fellowship (No. 08384) given to young scientists, to conduct part of this work in Professor Turro's laboratory at the Columbia University. The authors thank Professor Gerald Parkin, Columbia University, for the X-ray structure determination of the Peterson adduct.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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