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Synthesis of *tert*-Alkyl Amino Hydroxy Carboxylic Esters via an Intermolecular Ene-Type Reaction of Oxazolones and Enol Ethers

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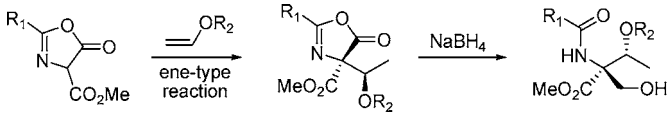
ABSTRACT



***tert*-Alkyl amino hydroxy carboxylic acids are abundantly present within the structure of many biologically active natural products. We describe herein the synthesis of these substrates using an oxazolone-mediated ene-type reaction with enol ethers followed by $NaBH_4$ reduction of the intermediate oxazolone.**

Highly substituted amino hydroxy carboxylic acids are structural features present in numerous microorganism metabolites including the sphingofungins, lactacystins, altemicidin, oxazolomycins, and many others (Figure 1).[1] The diverse and potent biological activity of these metabolites has stimulated many researchers to pursue their total syntheses[2−5] and in-depth biological evaluations.[2a,3a,b,5a,6,7] Construction of the densely functionalized quaternary carbon center found within these molecules has proven to be a significant

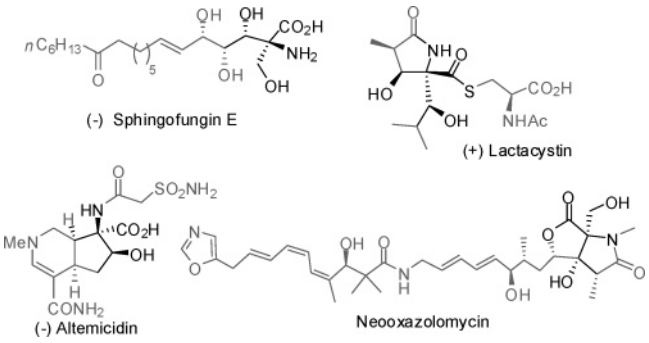


Figure 1. Natural *tert*-alkyl amino hydroxy carboxylic acids.

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(5) For a review of syntheses and biological activities of oxazolomycins, see: (a) Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. *Curr. Drug Discovery Technol.* **2004**, *1*, 181. For a recent synthesis of neooxazolomycin, also see: (b) Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6703.

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synthetic challenge and has been the focus of many research groups.[8−10]

Recently, we reported an intermolecular ene-type reaction utilizing oxazolones (also referred to as azlactones) and enol ethers via its oxazole tautomer (Figure 2).[11] The reaction

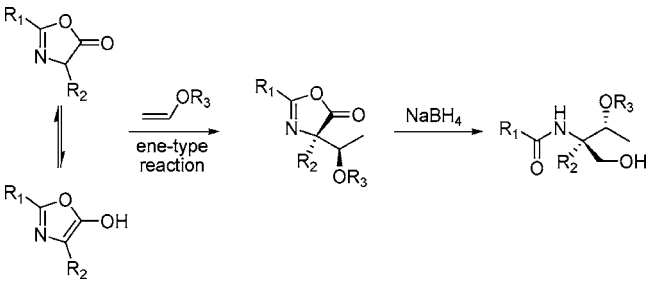
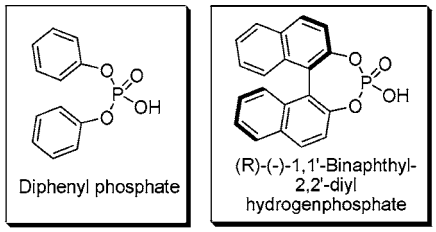


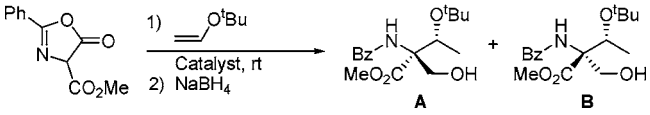
Figure 2. Intermolecular ene reaction utilizing oxazolones and enol ethers followed by reduction.

results in the formation of a highly functionalized quaternary center as a pivotal intermediate for the synthesis of α,α-disubstituted amino acids.[12] Reduction of the intermediate oxazolone ester products with sodium borohydride[13−15] results in the formation of quaternary nonproteinogenic amino esters, ideally functionalized for the synthesis of many of these biologically interesting metabolites. Herein, we report the application of our ene-type methodology of oxazolones toward the synthesis of *tert*-alkyl amino hydroxy carboxylic esters along with additional insight into the reaction's mechanism.

During our previous studies, we observed the formation of quaternary oxazolones using these ene-type reactions and found the reactions to proceed with little or no diastereoselectivity.[11] In an effort to make this synthetic approach more broadly applicable, we investigated several reaction conditions to improve the diastereoselectivity. The reaction of 2-phenyl-4-carbomethoxy-5-oxazolone and *tert*-butyl vinyl ether was performed in various solvents, and it was found that the use of less polar solvents such as benzene not only provided stereoselectivity but also decreased the rate of reaction in most cases (Table 1, conditions 1−3).[16] Upon

Table 1. Catalysis of Ene-Type Reaction Using Brønsted Acids





conditions	catalyst	solvent	time[b] (h)	A/B[c]	% yield[d]
1	none	CH_3CN	3	50:50	90
2	none	CH_2Cl_2	1	55:45	91
3	none	benzene	36	67:33	90
4	3,5-dinitrobenzoic acid	benzene	16	70:30	90
5	diphenyl phosphate	benzene	3	75:25	90
6[e]	(*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate	benzene	13	79:21	90
7	CSA	benzene	1	74:26	83
8	TFA	benzene	48	67:33	81
9	$Ti(O^iPr)_4$	benzene	48	67:33	61
10	$Yb(OTf)_3$	benzene	48		0
11	TMSOTf	benzene	48		0
12	$Zn(OTf)_2$	benzene	48	52:48	24
13	$Cu(OTf)_2$	benzene	48		0

[a] Reaction conditions: 2-phenyl-4-carbomethoxy-5-oxazolone (0.5 mmol), *tert*-butyl vinyl ether (0.7 mmol), catalyst (10 mol %), solvent (20 mL), rt. [b] Time is based on the completion of the ene-type reaction. [c] Ratios based on ^1H NMR integration of both the oxazolone intermediate and product. [d] Yield of isolated product. [e] Low solubility of catalyst attributed to increase in reaction time and selectivity.

screening a variety of potential protic catalysts, we found that a substoichiometric amount of diphenyl phosphate improved both the reaction rate and diastereoselectivity (Table 1, condition 5). Brønsted acids less acidic than diphenyl phosphate also improved the diastereoselectivity of the reaction but did little toward increasing the reaction rate (Table 1, condition 4). The use of more acidic Brønsted acids resulted in lower yields of desired product, presumably due to enol ether decomposition (Table 1, conditions 7 and 8). Chiral Brønsted acid (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate provided the highest diastereoselectivity (79:21) of the catalysts investigated but provided no observable enantioselectivity as determined by chiral HPLC (Table

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(16) See the Supporting Information for additional details.

1, condition 6). Several additional Lewis acids were screened, resulting in little or no product formation and low diastereoselectivity (Table 1, conditions 9−13). The significant rate enhancement found when using Brønsted acids and not other Lewis acids is suggestive that the catalyst protonates the enol ether forming an oxonium ion, although coordination to the oxazolone substrate cannot be dismissed. The conditions used in Table 1 produced the same major diastereomer whose crystal structure is depicted in Figure 3.

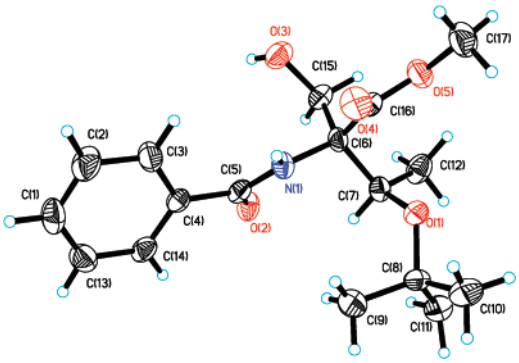


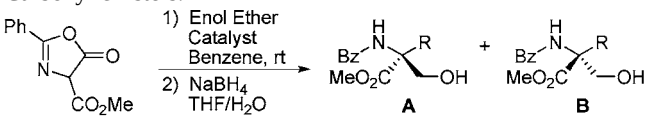
Figure 3. X-ray crystal structure of the major diastereomer of entry 1, Table 2.

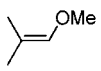
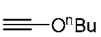
Utilizing conditions optimized for diastereoselectivity, the scope of the reaction was further explored. Exposing 2-phenyl-4-carbomethoxy-5-oxazolone to various vinyl enol ethers in the presence of 10% of diphenyl phosphate resulted in high yields of the desired products after sodium borohydride reduction (Table 2). The *tert*-butyl and benzyl protecting groups yielded better diastereoselectivity than the ethyl protecting group (Table 2, entries 1−3), which indicates that enol ethers containing more sterically demanding oxygen protecting groups generally produce better diastereoselectivities. The less reactive higher substituted enol ethers gave lower yields and required the use of heat (Table 2, entries 4−6) to produce the desired products in good yields. Both butoxyethyne and 2-methoxypropene (Table 2, entries 7 and 8, respectively) also provided reasonable yields of products.

The role of the 2-position of the oxazolone scaffold was investigated for its effect on reactivity and selectivity (Table 3). Several oxazolones with substitutions in the 2-position were prepared and reacted with *tert*-butyl vinyl ether in the presence of diphenyl phosphate. Oxazolones with aryl substituents gave high yields, and erosion of diastereoselectivity was observed as electron deficiency increased (Table 3, entries 9−11). Selectivity was all but lost when oxazolones containing alkyl substituents were used (Table 3, entries 12 and 13).

The decrease in both stereoselectivity and yield in the reactions involving 2-alkyloxazolones as compared to those involving 2-aryloxazolones may potentially be explained by a difference in mechanism. To investigate this phenomenon, we treated both 2-ethyl-4-carbomethoxy-5-oxazolone and 2-phenyl-4-carbomethoxy-5-oxazolone with *tert*-butyl vinyl

Table 2. Two Step Synthesis of Quaternary Amino Hydroxy Carboxylic Esters.

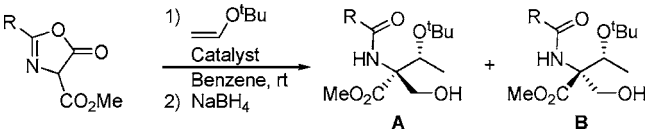


entry	substrate	R	temp (°C)	A:B[b]	% yield[c]
1			25	75 : 25	90
2			25	75 : 25	77
3			25	67 : 33	85
4			50	38 : 62	57
5	 (5:1 trans to cis)		50	69 : 31	48
6			50	60 : 40	33
7[d,e]			25	---	67
8[e]			25	---	62

[a] Reaction conditions: 2-phenyl-4-carbomethoxy-5-oxazolone (0.5 mmol), enol ether (0.7 mmol), diphenyl phosphate (10 mol %), benzene (20 mL), rt. [b] Ratios based on ^{1}H NMR integration of both the oxazolone intermediate and product. [c] Yield of isolated product. [d] CH_2Cl_2 used as solvent. [e] No catalyst used.

ether in the absence of catalyst (Scheme 1). Analysis of the crude reaction mixtures revealed an O-alkylated oxazole intermediate in the reaction involving 2-ethyl-4-carbomethoxy-5-oxazolone, while the 2-phenyl-4-carbomethoxy-5-oxazolo-

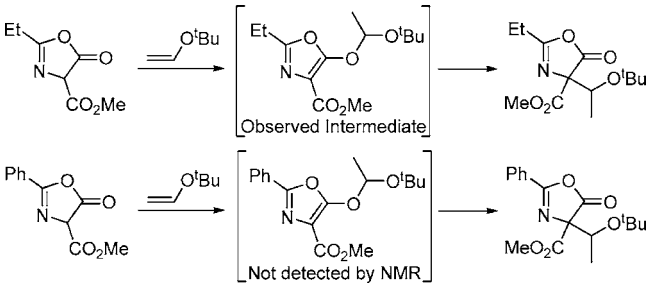
Table 3. Alkylation of Various Oxazolones Using *tert*-Butyl Vinyl Ether



entry	R	A/B[b]	% yield[c]
9	Ph	75:25	90
10	4-MeO−Ph	74:26	88
11	4-CF_3-Ph	67:33	81
12	Et	43:57	50
13	Bn	52:48	58

[a] Reaction conditions: oxazolone (0.5 mmol), *tert*-butyl vinyl ether (0.7 mmol), diphenyl phosphate (10 mol %), benzene (20 mL), rt. [b] Ratios based on ^{1}H NMR integration of both the oxazolone intermediate and product. [c] Yield of isolated product.

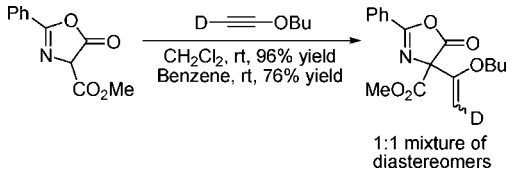
Scheme 1. Mechanistic Investigation Using Various Oxazolones



ne reaction produced only C-alkylated product. Upon standing, we observed the conversion of the O-alkylated intermediate to the C-alkylated product along with some degradation of the enol ether component. This observation infers that these ene-type reactions might proceed through an O to C migration,[13,17,18] although this was never observed for any of the 2-aryl-substituted oxazolones.

The possibility of these reactions proceeding via an O to C migration contrasts our original hypothesis that they occur via a stereospecific-concerted mechanism.[11] To provide additional insight into the nature of the mechanism, we conducted a deuterium study using a deuterium-labeled alkoxyalkyne and 2-phenyl-4-carbomethoxy-5-oxazolone (Scheme 2). The reaction resulted in a 1:1 mixture of

Scheme 2. Labeling Studies Using Deuterium-Labeled Alkoxyalkyne



diastereomers, indicating that these ene-type reactions may also proceed via a stepwise mechanism. Supported by the significant rate enhancement found using only Brønsted acids, we hypothesize that the acidic proton of the oxazolone[19] in the absence of catalyst, or in this case the catalyst itself, protonates the enol ether, forming an oxonium ion. However, coordination of the catalyst to the oxazolone substrate, as typically seen with oxazolones, cannot be dismissed.[20] Therefore, it is likely that the mechanistic nature of these ene-type reactions is highly dependent on both the oxazolone and enol ether being used in the reaction. Further studies to characterize the mechanistic details of these new ene-type reactions are currently under examination in our laboratories.

In summary, we report here the efficient synthesis of *tert*-alkyl amino hydroxy carboxylic esters via a two-step sequence using oxazolones with enol ethers or alkoxy ethynes followed by hydride reduction. Additionally, the mechanistic nature of these ene-type reactions using oxazolones and enol ethers appears to be substrate dependent. The role of the catalyst, asymmetric version of these reactions, and mechanistic effect of substrate variation are under further investigation in our laboratory.

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Supporting Information Available: Experimental procedures, IR and ^{1}H and ^{13}C NMR data for all new compounds, and X-ray structures for entry 1, Table 2 (major diastereomer), and entry 12, Table 3 (major diastereomer). This material is available free of charge via the Internet at http://pubs.acs.org.

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