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Synthesis of α-Benzyloxyamino-γ-butyrolactones via a Polar Radical Crossover Cycloaddition Reaction

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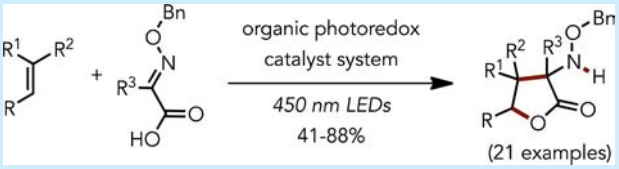
Supporting Information

ABSTRACT: A direct catalytic synthesis of substituted α-benzyloxyamino-γ-butyrolactones is reported, starting from simple oxime acids and alkenes. The substituted *O*-benzyloxime acid starting materials are cyclized with oxidizable alkenes, via Polar Radical Crossover Cycloaddition (PRCC) reactions. The catalytic reaction is carried out using the Fukuzumi acridinium photooxidant and substoichiometric amounts of a redox-active cocatalyst. The utility of this method has been demonstrated through the use of 3 oxime acids and 19 oxidizable olefins.



α-Amino-γ-butyrolactones are a class of bioactive heterocycles that are highly prevalent in nature and medicine. They have shown great utility given the presence of their scaffold in antiallergy and asthma agents,[1] the ease of converting them into γ-hydroxyamino acids,[2] and their prevalence in the microbial world.[3] These lactones have been used in the preparation of γ-hydroxyamino acids as well as amino acids such as methionine and canaline.[2] In their *N*-acylated and *N*-sulfonylated forms, the lactones are regulatory molecules for a bacterial communication mechanism known as quorum sensing (Figure 1).[4,5] Such

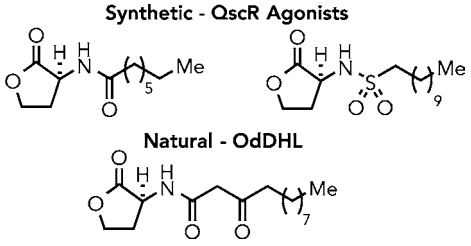


Figure 1. Natural and synthetic *N*-acylated and *N*-sulfonylated α-amino-γ-butyrolactones involved in regulating quorum sensing in bacterial colonies.

communication between microorganisms controls the growth of biofilms and virulence factor production. They have also been used in the synthesis of antibiotics, antifungal peptides, and serine protease inhibitors.[6] This class of lactones has also demonstrated antitumor and anticancer activity toward human colorectal and breast cancer cell lines.[7]

Given their importance, several strategies have been developed to construct α-amino-γ-butyrolactones. The most common method used to generate this class of lactones is through the cyclization of amino acid derivatives, particularly methionine and aspartic acid.[1,4,6−9] However, this strategy limits the substitution pattern and functionality around the lactone ring. Other intramolecular cyclizations have been utilized, including the acid-mediated ring closure of α-amino-γ,δ-unsaturated carboxylic acid esters[10] and the enzymatic cyclization of α-amino ketoesters.[11] Additionally, there are several multicomponent methods that have been reported for generating these butyrolactones, including an aza-Prins cyclization between α-hydroxyhippuric acid and isobutylene.[12] The acid hydrolysis of morpholinones has been demonstrated in the synthesis of α-amino-γ-butyrolactones[13] as well as the ring opening of aziridines following the aziridination of α-ylidene γ-butyrolactones.[14] It has also been demonstrated that α-amination of α-bromo-γ-butyrolactones can be used to prepare this class of lactones.[15] Our proposed transformation efficiently generates α-benzyloxyamino-γ-butyrolactones via the formation of three σ-bonds in a single synthetic manipulation from readily abundant starting materials. Using readily prepared *O*-benzyloxime acids[16] and alkenes as the reaction partners, we demonstrate, herein, a general method to access a diverse library of this important class of lactones.

We have previously demonstrated the use of polar radical crossover cycloadditions (PRCC) as a convergent approach to saturated heterocyclic motifs. Using the Fukuzumi acridinium single electron photooxidant[17] (**Mes-Acr-Me**), paired with a redox-active H atom donor cocatalyst, tetrahydrofurans,[18] α-methylene-γ-butyrolactones,[19] γ-lactams, and pyrrolidines[20] can be forged from a variety of oxidizable olefins and allylic alcohols, unsaturated acids, unsaturated amides, or allylic amines, respectively, as coupling partners (Scheme 1, eq 1). We recently questioned whether this general catalytic protocol could be used to construct α-amino-γ-butyrolactones. Clive has shown that intramolecular radical cyclization onto *O*-benzyloxime acids is possible to furnish the desired lactone derivatives (Scheme 1, eq 2).[21,22] We envisioned that a PRCC catalytic protocol between an *O*-benzyloxime acid and an alkene would give rapid access to a variety of substituted α-benzyloxyamino-γ-butyrolactones (Scheme 1, eq 3).

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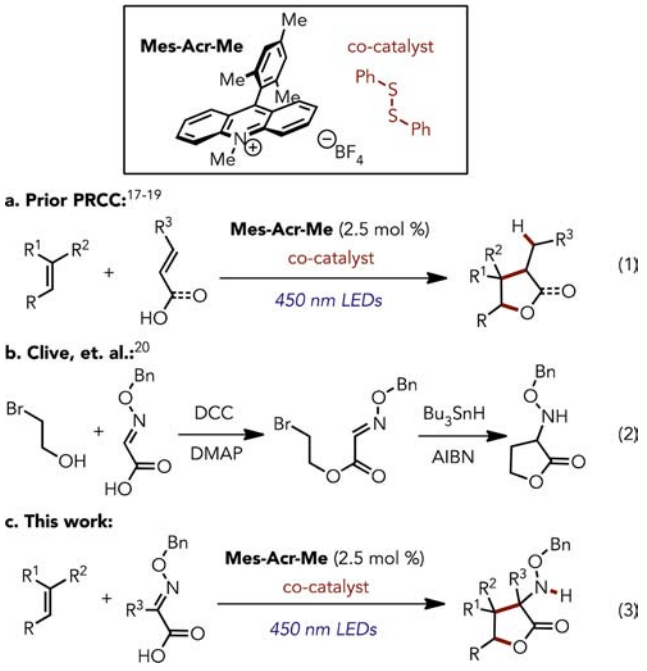
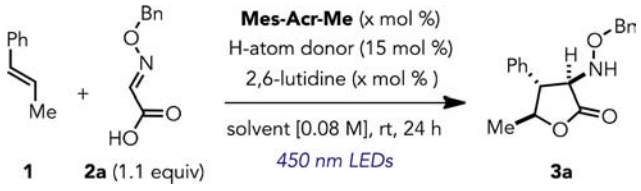
Scheme 1. (a) Previous Photoredox Polar Radical Cyclization Work;[17−19] (b) Precedent for Radical Cyclization Using *O*-Benzyloxime Acids;[20] (c) Proposed Redox-Neutral Formation of α-Benzyloxyamino-γ-butyrolactones



The original investigation of this reaction began with conditions similar to those previously developed for the synthesis of a separate class of butyrolactones carried out in our laboratory,[19] using β-methylstyrene **1** and *O*-benzyloxime acid **2a** as the two potential reaction partners. These conditions resulted in a moderate yield (57%) of the desired γ-butyrolactone product (Table 1, entry 1). A survey of solvents with varying polarities, including DCE, chloroform, and acetone, afforded the desired adduct in lower yields (Table 1, entries 2−4). Various cocatalysts were investigated (Table 1, entries 5−6) to determine the effect of its identity on the reaction efficiency. We found that diphenyl disulfide acted as the most efficient cocatalyst, presumably forming thiophenol *in situ* as an H atom donor.[23] Catalytic quantities of 2,6-lutidine were also beneficial, likely due to the need to form the more nucleophilic carboxylate (Table 1, entries 7−10), with the optimal loading determined to be 15 mol %, resulting in a 69% yield (Table 1, entry 9). We were pleased to find that an increase in the loading of **Mes-Acr-Me** was not required to optimize the reaction conditions, while a control experiment, omitting **Mes-Acr-Me**, demonstrated its necessity in the system (Table 1, entries 11−13). Omitting the cocatalyst resulted in a significant decrease in yield to 40% (Table 1, entry 14). Further optimization revealed that a change in the ratio of alkene to oxime from 1:1.1 to 1.5:1, along with lowering the disulfide loading to 10%, improved the yield of the final lactone product to 88% (Table 1, entry 15). The diastereomeric ratio of the products was consistently 2:1 and was determined in reference to the relationship between the α- and β-stereocenters with the relationship between the β- and γ-centers set as *trans*.[19]

After identifying the optimal reaction parameters, we turned our attention to studying the scope of the transformation with respect to the benzyloxime acid (Scheme 2). Using β-methylstyrene **1** and unsubstituted oxime **2a**, lactone **3a** was

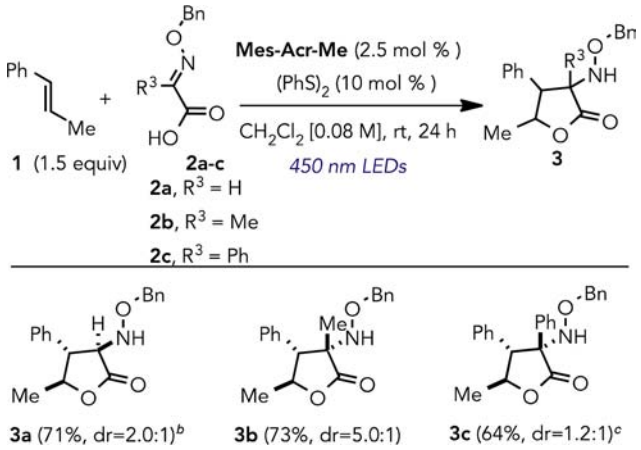
Table 1. Optimization of Reaction Conditions[a]



entry	H atom donor	Mes-Acr-Me (mol %)	base (mol %)	solvent	yield[b] (%)
1[c]	$(PhS)_2$	2.5	0	CH_2Cl_2	57
2	$(PhS)_2$	2.5	0	$CHCl_3$	35
3	$(PhS)_2$	2.5	0	acetone	0
4	$(PhS)_2$	2.5	0	DCE	39
5[c]	4-(MeO)PhSH	2.5	0	CH_2Cl_2	40
6[c]	4-(NH_2)PhSH	2.5	0	CH_2Cl_2	40
7	$(PhS)_2$	2.5	0	CH_2Cl_2	38
8	$(PhS)_2$	2.5	5	CH_2Cl_2	53
9	$(PhS)_2$	2.5	15	CH_2Cl_2	69
10	$(PhS)_2$	2.5	20	CH_2Cl_2	51
11[d,e]	$(PhS)_2$	0	15	CH_2Cl_2	0
12	$(PhS)_2$	5.0	0	CH_2Cl_2	42
13	$(PhS)_2$	7.5	0	CH_2Cl_2	39
14[e]	None	2.5	15	CH_2Cl_2	40
15[d,e]	$(PhS)_2$	2.5	15	CH_2Cl_2	88

[a]Reactions were carried out on a 0.33 mmol scale in N_2-sparged solvent [0.08 M] under two LED lamps (λ_{max} = 450 nm) for 24 h. [b]Yields were obtained relative to $(Me_3Si)_2O$ ^1H NMR internal standard of crude reaction mixtures. [c]Reaction was run at [0.15 M] [d]10 mol % disulfide. [e]**1**/**2a** = 1.5:1.

Scheme 2. Lactone Products: *O*-Benzyloxime Acid Scope[a]



[a]Reactions were carried out in N_2-sparged CH_2Cl_2 [0.08 M] on a 0.33 mmol scale under two LED lamps (450 *nm* λ_{max}) for 24 h. Yields represent an average of two isolated yields on a 0.33 mmol scale. [b]Reaction ran with 15 mol % 2,6-lutidine. [c]Reaction ran on a 0.17 mmol scale, [0.02 M].

obtained in 71% isolated yield. We also demonstrated that it was possible to obtain α-quaternary substituted lactones using pyruvic acid, **2b**, and phenylglyoxylic acid, **2c**, derived oximes without diminishing the yield of compounds **3b** and **3c**.

The scope of the transformation with respect to the alkene component was then evaluated using benzyloxime acid **2a** (Scheme 3). The alkenes were utilized as a mixture of *E*/*Z* isomers without a deleterious effect on reactivity.[19,20] To begin, β-methylstyrene derivatives were tested in this reaction setting

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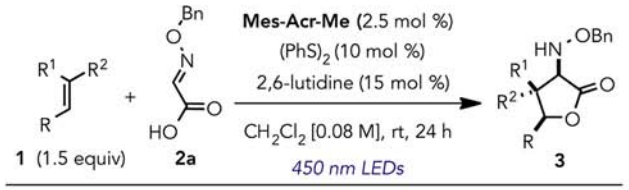
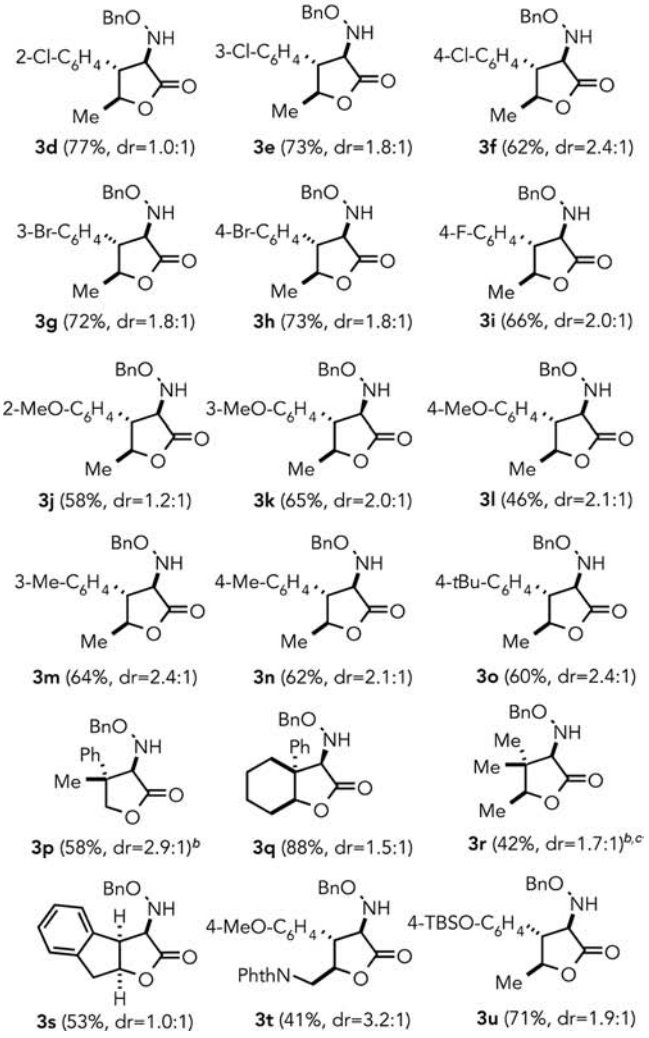
Scheme 3. Lactone Products: Alkene Scope[a]



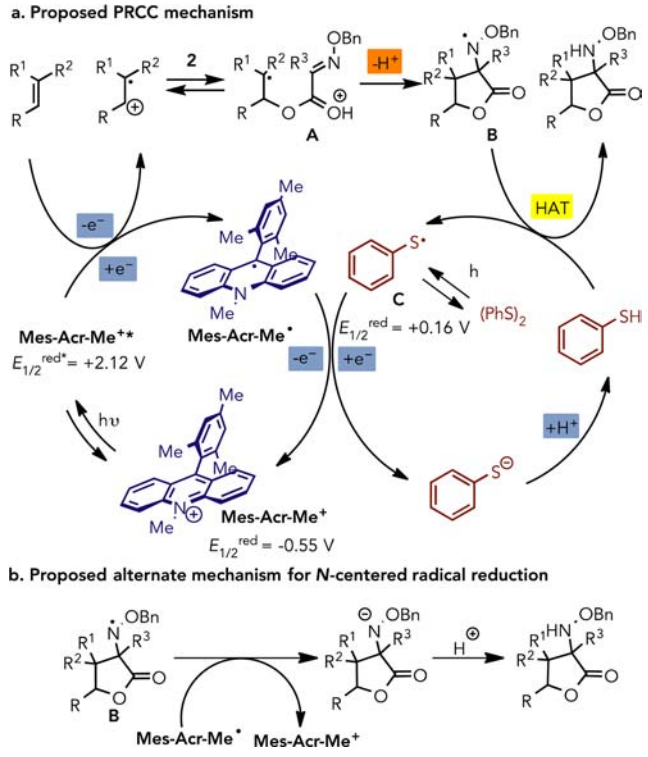


[a]Reactions were carried out in N_2-sparged CH_2Cl_2 [0.08 M] on a 0.33 mmol scale under two LED lamps (450 *nm* λ_{max}) for 24 h. Yields represent an average of two isolated yields on a 0.33 mmol scale. [b]Reaction ran with **Mes-Acr-Ph**. [c]Reaction ran with 3 equiv of 2-methyl-2-butene.

to afford both electron-rich and -poor α-benzyloxyamino-γ-butyrolactones **3d**–**3o**. Various halogenated derivatives **3d**–**3i** produced the desired lactones in good to excellent yields regardless of the substitution pattern. Anethole and its regioisomers **3j**–**3l** also demonstrated a tolerance for varying electronic as well as steric effects in the system, furnishing the resulting lactones in moderate to good yields. Alkyl-substituted β-methylstyrene derivatives gave the anticipated lactones **3m**–**3o** in good yields. The use of α-methylstyrene produced β-quaternary substituted lactone **3p** in 58% yield. Trisubstituted oxidizable olefins were viable coupling partners but provided the lactone products in varying yields. An excellent yield of **3q** (88%) was obtained using trisubstituted 1-phenylcyclohexene; however, 2-methyl-2-butene proved to be less efficient, furnishing the lactone product **3r** in moderate yields (42%), while indene produced tricyclic lactone **3s** in a 53% yield. Phthalamide-protected amines **3t** were readily tolerated as was an alcohol protected with a *tert*-butyldimethylsilyl (TBS) group **3u**.

We propose the proceeding mechanism based on prior art from our laboratory (Scheme 4a).[19,20,24] Following excitation of

Scheme 4. Proposed Mechanism



the acridinium catalyst **Mes-Acr-Me**$^+$, single electron oxidation of the alkene by the excited state **Mes-Acr-Me**$^{+*}$ affords an electrophilic alkene cation radical. Addition of the oxime acid **2** to the cation radical likely results in the formation of radical **A**. Following deprotonation, rapid 5-*exo*-trig radical cyclization onto the oxime furnishes *N*-centered radical **B**. The H atom donor functions in a parallel redox cycle in which phenylthiyl radical **C** is presumably generated by photolytic homolysis of diphenyl disulfide and subsequently acts as a single electron oxidant to regenerate the acridinium ground state **Mes-Acr-Me**$^+$. Thiophenol is produced from the resulting thiolate via proton transfer.[24] Hydrogen atom transfer from the generated thiophenol to **B** furnishes the desired α-benzyloxyamino-γ-butyrolactone product.

Based on the observation that a moderate amount of **3a** is generated in the absence of diphenyl disulfide (Table 1, entry 14), an additional pathway likely operates without the use of H atom donor cocatalyst. To account for this observation in the mechanism, we propose that the *N*-centered radical **B** can be reduced by the acridine radical **Mes-Acr-Me**· to generate a hydroxylamine anion and regenerate the acridinium ground state **Mes-Acr-Me**$^+$ (Scheme 4b). This mechanistic variation would allow for the observed product formation following protonation of the anion, likely via lutidinium or an equivalent of the acid starting material.

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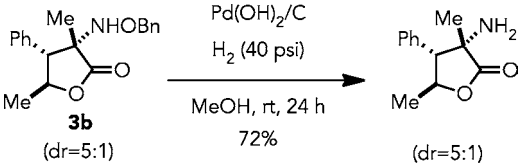
The relative stereochemistry of the products was determined using selective 1D-NOESY NMR experiments (see Supporting Information for details). Product **3j** was used as a model to define the stereochemistry for β-methylstyrene derived products. Using this method, we determined that the major diastereomer was the all-*trans* product with the minor diastereomer epimeric at the α-carbon. This diastereomeric preference matches the stereochemical relationship observed in previous PRCC transformations.[19] The stereochemistry of lactones **3b** and **3p**−**3s** were assigned separately from their respective spectra using selective 1D-NOESY.

Lastly, we sought to demonstrate a facile reduction of the *N*−*O* bond in the lactone product. Using an adaptation of a previously reported method,[25] we were able to carry out a successful, high-pressure (40 psi) hydrogenation of lactone **3b** using Pearlman's catalyst $Pd(OH)_2/C$, to give the α-amino-γ-butyrolactone in good yield (Scheme 5).

Scheme 5. Benzyloxyamine Reduction



In summary, we have developed a convergent method for the synthesis of substituted, α-benzyloxyamino-γ-butyrolactones from easily accessible oxime acid starting materials and simple, often commercially available alkenes. The scope of the transformation exhibited both a steric and electronic tolerance as well as functional group compatibility. We are confident that the use of PRCC for the generation of α-benzyloxyamino-γ-butyrolactones will be useful in small molecule synthesis and can be used to further develop a class of lactones that can be studied for biological activity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03113.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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