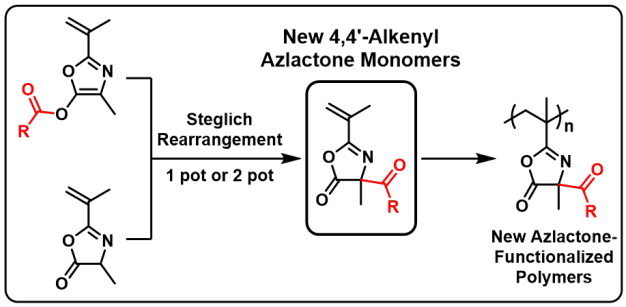
Synthesis, Characterization, and Polymerization of 4'-Acyl(oxy) Alkenyl Azlactone Monomers Designed Using a Steglich Rearrangement Approach

William M. Breining[1] and David M. Lynn[1,2,*]

[1]Department of Chemistry, University of Wisconsin–Madison, 1101 University Ave., Madison, WI 53706, USA; [2]Department of Chemical and Biological Engineering, University of Wisconsin–Madison, 1415 Engineering Dr., Madison, WI 53706, USA; Email: (D.M.L.) dlynn@engr.wisc.edu

For Table of Contents Use Only:



ABSTRACT: Monomers and polymers containing amine-reactive azlactone functionality are useful for the design of a broad range of soft materials. The vinyl monomer 2-vinyl-4,4-dimethylazlactone (VDMA), which can be readily polymerized to poly(2-vinyl-4,4-dimethylazlactone) (PVDMA) using free radical methods, has been widely used for these purposes, but the synthesis of other alkenyl azlactone derivatives having other substituents in the 4-position presents several challenges. Here, we report the synthesis and characterization of novel 4'-acyl(oxy) alkenyl azlactones using approaches based on the Steglich rearrangement. We report both stepwise and one-pot Steglich rearrangement approaches to the synthesis of 2-isopropenyl-4-methyl-4'-acylazlactones from 2-isopropenyl-4-methylazlactone and acyl halides using DMAP and DMAP derivatives as nucleophilic acyl transfer catalysts. This approach enables the synthesis of disubstituted alkenyl azlactone derivatives having a variety of substituted alkyl and aryl ester and ketone groups in the 4-position. The resulting alkenyl azlactones react readily through ring-opening reactions with amine-based nucleophiles and can also be polymerized by AIBN-initiated

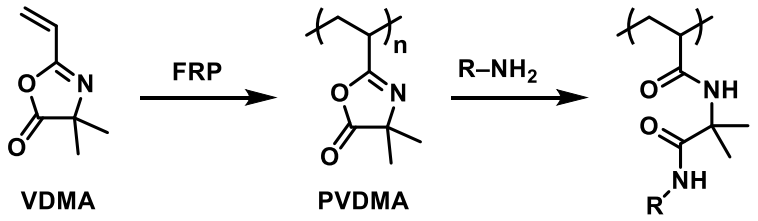
free radical polymerization to yield new amine-reactive polymers. In addition, we demonstrate an approach to the synthesis of enantioenriched alkenyl azlactone monomers using an asymmetric DMAP derivative and a novel procedure for the *in situ* activation of carboxylic acids that eliminates the need for acyl halide-based starting materials during the Steglich rearrangement. Our results provide new and useful approaches to the design of alkenyl azlactone-based monomers and polymers with novel structures that would be difficult to synthesize using conventional methods.

Introduction

Polymers bearing side-chain functionality that can react in a predictable and controlled manner with other agents are useful as building blocks for the design of new materials. Many reactive polymers are synthesized using monomers that contain functional groups that are chemically orthogonal to those used for polymerization but that can react further under specific conditions or with other functional groups after polymerization. For vinyl monomers synthesized by free radical polymerization, the range of secondary functionality that can be selected is quite broad, with so-called 'activated ester' groups, such as N-hydroxysuccinimidyl (NHS) and pentafluorophenyl (PFP) esters, being two salient and widely used examples.[1-5] These activated ester groups can react under relatively mild conditions with a range of nucleophiles, including amine- and hydroxyl-functionalized species, to introduce new side-chain functionality, promote crosslinking, or anchor polymer chains covalently onto other appropriately functionalized surfaces. The fundamental physicochemical behaviors and potential applications of these activated ester monomers and a host of other reactive monomers and polymers are the subject of many comprehensive reviews.[1-8]

The work reported here was motivated broadly by the unique chemistry, versatility, and potential practical utility of polymers functionalized with azlactone groups. Azlactone, or 5(4H)-oxazolone, groups are cyclic structures that can react through ring-opening reactions with a range of nucleophiles, including primary amine, hydroxyl, and thiol groups.[9-15] These ring-opening reactions often occur rapidly, under mild conditions, and, in the case of primary amine-based nucleophiles, in the absence of a catalyst. In contrast to polymers functionalized with NHS or PFP groups, these post-polymerization ring-opening reactions do not generate additional reaction byproducts (e.g., leaving groups, etc.). Several of these useful features are illustrated in Scheme 1,

which shows the free-radical polymerization (FRP) of the vinyl monomer 2-vinyl-4,4-dimethylazlactone (VDMA) to form poly(2-vinyl-4,4-dimethylazlactone) (PVDMA), and (ii) the subsequent side chain functionalization of PVDMA by treatment with an amine-based nucleophile.



Scheme 1. Free radical polymerization of the monomer VDMA to the polymer PVDMA, followed by subsequent ring-opening of the pendant azlactone group using a primary amine nucleophile.

Many past reports on the design of azlactone-functionalized polymers have made use of VDMA as a monomer building block, owing, in part, to the synthetic accessibility of this monomer and, in part, to the stability of the reactive azlactone structure under many free-radical polymerization conditions.[9, 11, 13-23] VDMA and VDMA-based monomers are typically synthesized from the commercially available amino acid 2-methylalanine and acryloyl chloride, and can be readily polymerized (or copolymerized) using a range of conventional or controlled processes to synthesize high molecular weight reactive PVDMA-based materials (that can, in turn, be functionalized, post-polymerization, in many useful ways).[9, 13-15, 17-22, 24-30] While VDMA and PVDMA have proven to be versatile building blocks for the design and functionalization of new reactive materials, there has also been considerable interest in the design of monomers and polymers containing alternative or derivative azlactone structures that could attenuate reactivity and/or be used to tune the physicochemical properties of these materials and open the door to new applications of azlactone-functionalized materials.

Many of the most recent investigations into new azlactone-functionalized monomers and polymers have been reported by Heilmann, Rasmussen, and coworkers at the 3M Corporation, with most literature reports on synthetically useful materials being limited to monomers having alkyl, alkyl spirocycle, or phenyl (Ph) substituents at the 4-position (Figure 1A).[11, 17, 31] In general, disubstitution at the 4-position has been found to be important (e.g., as exemplified by the structure of VDMA; see Figure 1). Although it is possible to synthesize vinyl azlactones containing only one substituent in the 4-position, monomers bearing one alkyl group and a hydrogen in the 4-position are generally less stable and/or have proven difficult to polymerize into useful materials.[9, 11, 13, 32-34] Past studies have reported monosubstituted monomers to undergo rearrangement to a corresponding 'pseudoazlactone' structure (e.g., **p-Az**, Figure 1B) that is no longer useful as a monomer for free-radical polymerizations.[9, 32, 35, 36] Past studies have also reported that the presence of a hydrogen in the 4-position can lead to chain transfer reactions that can prevent the synthesis of high molecular weight materials.[11, 13] While a limited number of disubstituted amino acids outside of 2-methylalanine are commercially available as potential starting materials for the design of new vinyl azlactones, they are generally expensive and the synthesis of new quaternary amino acids increases the number of synthetic steps needed, as well as the number of isolations and purifications necessary, to synthesize and explore the properties of new monomers.

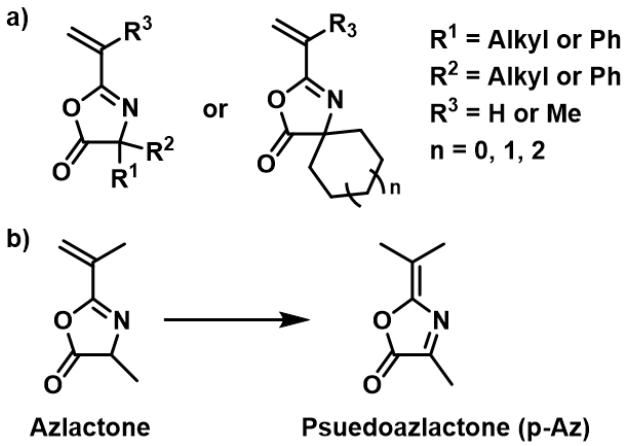


Figure 1. a) Generalized structures of some previously reported alkenyl azlactones. b) Rearrangement of 2-isopropenyl-4-methylazlactone to the corresponding pseudoazlactone (**p-Az**).

The work reported here sought to explore new routes to the synthesis of vinyl azlactones that do not rely on the availability of disubstituted amino acid starting materials required by conventional monomer synthesis schemes. Here we note that, while vinyl-substituted azlactones such as VDMA are particularly useful for polymerization, there is a rich and broad literature describing the synthesis and transformation of many other types of azlactone derivatives (e.g., in the context of natural products synthesis and other organic chemical reactions).[34, 37-39] While many of those structures are substantially more complex and are, in general, not well suited for subsequent polymerization, we reasoned that those past studies could provide guidance useful for the design of new synthetic routes to vinyl azlactones. As one example, we first identified a modified Dakin-West synthesis first reported by Iwakura et. al., from which an intermediate 4'-acyl azlactone could be isolated.[40] This approach initially showed promise, as several alkenyl azlactones had previously been isolated as intermediates as a result of that work, however a series of exploratory studies revealed synthetic conditions to be relatively harsh and, in our hands, isolation typically led to ring-opening of the azlactone.

During the course of that work, we also identified the Steglich rearrangement as a potential alternative synthetic route to substituted vinyl azlactones. In contrast to the Dakin-West approach and early approaches by Steglich,[40-43] both of which require the use of stoichiometric or excess pyridine, the Steglich rearrangement uses a more reactive nucleophilic acyl transfer reagent at catalytic loadings to promote acyl group transfer from an oxazole carbonate or oxyacyl oxazole starting material to either the C-2 or C-4 position of the heterocycle to form the corresponding azlactone product (Figure 2).[44] It has been reported that the regioselectivity of the acyl transfer is controlled by the functional group located at the C-2 position, with electron withdrawing groups (EWGs) at the C-2 position directing the acyl group to C-2 and electron donating groups (EDGs) directing acyl transfer to the C-4 position.[44, 45] This transformation was first reported by Steglich et. al. in 1970 and typically uses a 4-dimethylaminopyridine (DMAP)- or 4-pyrrolidinopyridine (PPY)-based catalyst.[44] The rearrangement has recently seen renewed interest following the first reported asymmetric Steglich rearrangement by the Fu group in 1998,[46] which has led to many efforts to synthesize asymmetric DMAP- and PPY-based catalysts[39, 46-52] and other novel catalyst designs useful for the synthesis of azlactones and other small molecules in which an O to C acyl transfer takes place.[37, 38, 52-60]

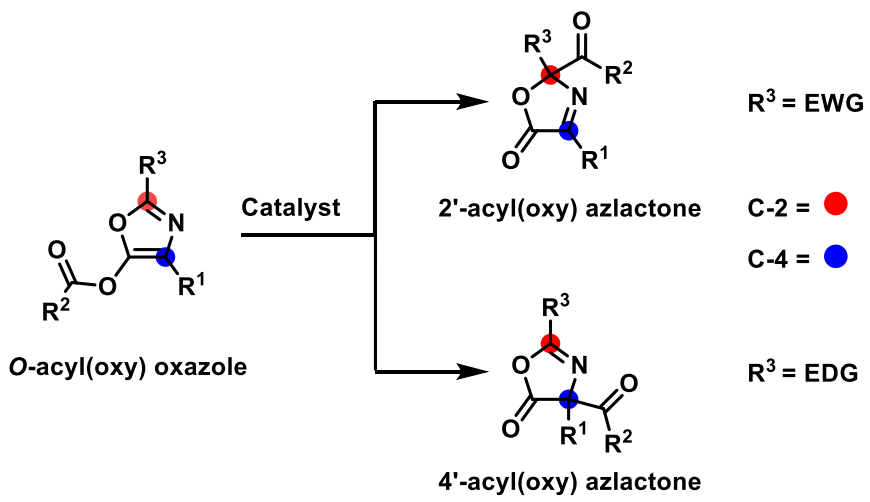


Figure 2. A representative and generalized Steglich-type rearrangement reaction with C-2 and C-4 positions highlighted in red and blue, respectively. The regiochemistry resulting from the Steglich-type rearrangement depends on the identity of the substituent at the C-2 position, R^3. If R^3 is an EWG the acyl group will be transferred to C-2, and if R^3 is and EDG the acyl group will be transferred to C-4.

We reasoned that the Steglich rearrangement could offer a novel route to the synthesis of a wide range of alkenyl azlactone monomers that are disubstituted at the C-4 position and offer several other benefits, including: (i) access to a wider range of 4' functionalities than previously reported, through the wide range of commercially available and readily synthesized acid chlorides and chloroformates, and (ii) the reaction could be conducted without using pyridine as a solvent, improving isolation in comparison to the modified Dakin-West procedure.[44, 46, 48, 49, 51, 53-56] Additionally, in view of past studies on the design of asymmetric acyl transfer catalysts, it occurred to us that this synthetic route could potentially provide access to asymmetric alkenyl azlactones and, thereby, novel asymmetric azlactone-functionalized polymers. It was not clear at the outset of this work, however, whether this transformation would be general toward EDGs located at the C-2 position of the oxazole, as previous reports have focused on Ph or electron donating aryl substituents (most commonly para-methoxyphenyl) at the C-2 position; to the best of our

knowledge, there are no literature reports of Steglich rearrangements with vinyl or isopropenyl functionalities at the C-2 position.[44, 46, 48, 49, 51, 53-56]

In the sections below, we report on the synthesis and characterization of a variety of novel 4'-acyl(oxy)alkenyl azlactones using a Steglich rearrangement approach. We demonstrate that this approach can be used to design disubstituted vinyl azlactone VDMA derivatives having a variety of different alkyl and aryl ester and ketone groups in the 4-position. Several of these new monomers react readily through ring-opening reactions with amine-based nucleophiles and can be polymerized to provide access to novel amine-reactive polymers. In addition, we report (i) a modified and more economic 'one pot' procedure for the synthesis of these monomers that reduces the number of required isolation and purification steps required, (ii) a novel approach to the *in situ* activation of carboxylic acids for Steglich rearrangement, and (iii) the basis of an approach to the synthesis of enantioenriched vinyl azlactone monomers using an asymmetric DMAP-based catalyst. Overall, our results show that the Steglich rearrangement can provide new and useful approaches to the design of new vinyl azlactone-based monomers and, thereby, access to novel reactive polymer structures that would be difficult to synthesize using conventional methods.

Materials and Methods

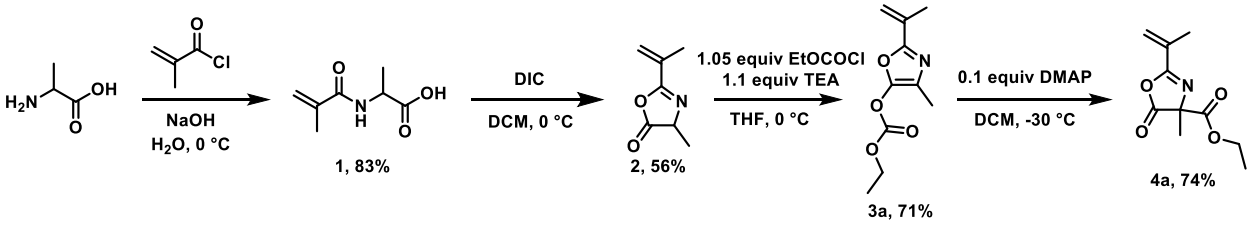
A full account of the materials and methods used in this study can be found in the Supporting Information. This information includes (i) detailed information about all chemicals and materials used and descriptions of all analytical methods used, including instrument types and parameters, (ii) detailed descriptions of general and specific experimental procedures for all starting materials, catalysts, O-acyl oxazoles, 4'-acyl(oxy) azlactones, and azlactone polymers, including all relevant characterization data, (iii) supplemental data for several synthesized O-acyl

oxazoles, the reaction scheme for an asymmetric catalyst, and tables summarizing all monomers and polymers synthesized, characterized, and discussed in the main text, and (iv) NMR spectra for all synthesized starting materials, catalysts, O-acyl oxazoles, 4'-acyl(oxy) azlactones, and azlactone polymers.

Results and Discussion

Steglich Rearrangement to Yield a Model 4'-Acyl Alkenyl Azlactone Monomer

To begin our investigation of the Steglich rearrangement as an approach to the synthesis of alkenyl azlactones, we selected alkenyl azlactone 2-isopropenyl-4-methylazlactone **2** (Scheme 2) as a model substrate. This substrate is monosubstituted in the 4-position with a methyl substituent that we reasoned would minimize potential steric effects that could impact the rearrangement. We selected a substrate having an isopropenyl group, rather than a vinyl group, at the 2-position for these initial studies, based on initial experiments suggesting that this isopropenyl-based monomer exhibited greater stability toward undesired autopolymerization and other forms of degradation than the corresponding vinyl derivatives. Compound **2** can be readily synthesized in two steps from alanine, a readily available amino acid, and methacryolyl chloride by first synthesizing methacryloylalanine **1** through the Schotten-Baumann reaction, followed by dehydrative ring closing using N,N'-diisopropylcarbodiimide (Scheme 2). In general, compound **2** could be isolated in sufficient purity for all subsequent transformations without the need for additional purification steps, preventing loss of yield due to decomposition during purification.



Scheme 2. Synthesis of model monosubstituted alkenyl azlactone **2** and subsequent O-acyloxy oxazole **3a** and Steglich rearrangement to 4,4'-alkenyl azlactone **4a** using ethyl chloroformate as a model acyl group, yielding novel ester functionality at the C-4 position.

Following a procedure similar to that previously reported by Ruble *et. al.*,[46] the addition of ethyl chloroformate and triethylamine (TEA) to compound **2** led to a rapid reaction resulting in oxazole carbonate **3a** in good yield after column purification. A Steglich rearrangement of **3a** was then attempted using conditions again similar to Ruble *et. al.,*[46] using dichloromethane (DCM) as the solvent, as this had previously been reported to be suitable in initial work by Steglich,[44] and DMAP as the nucleophilic acyl transfer reagent. This resulted in a rapid reaction that yielded 4,4'-derivatized azlactone **4a**, exhibiting a novel ethyl ester substituent, in good yield (Scheme 2). As discussed above and illustrated in Figure 2, past studies have suggested that the regiochemistry of the Steglich-type rearrangement can be influenced by the electronic nature of the R^3 substituent at the C-2 position, with electron-donating groups favoring acyl migration to the C-4 position. The observation of successful rearrangement of **3a** to **4a**, along with the results of rearrangements to yield other isopropenyl monomer derivatives discussed below, suggests that the isopropenyl substituent at the R^3 position may behave as an electron-donating group in this context. Additional details of all synthetic protocols, work up procedures, and methods used for purification and characterization of compounds can be found in the Supporting Information. Table S1 of the

Supporting Information provides a tabular summary of the structures and provides other useful information for all new 4,4'-derivatized azlactone monomers synthesized and characterized in this study.

During our initial work, we found that, while this model reaction is relatively robust, there is a possible side reaction that can occur during the formation of the O-acylated oxazole **3** that leads compound **2** to rearrange to form pseudoazlactone **p-Az**. This well-known rearrangement was discussed briefly in the Introduction, above.[9, 32, 35, 36] We believe that this rearrangement is most likely to occur after the deprotonation of compound **2** by TEA, but before the resulting enolate can react with the acyl chloride (in this case, ethyl chloroformate). Formation of this side product can be addressed, at least in part, by the order of addition of the reagents, for example by adding the base and acyl chloride via co-addition, as this should allow for more rapid reactivity of the enolate of **2**, providing less time in solution to rearrange or react to form other possible side products. We also found, similar to a previous report,[56] that it is important to perform these reactions under anhydrous conditions; in the O-acylation step, it is likely that adventitious water may also assist with proton transfer and rearrangement and thus also promote side reactions. In the Steglich rearrangement step, water can prevent formation of the desired product **4** and result, instead, in the reformation of starting material **2**. The Steglich rearrangement catalytic cycle (Scheme 3) has been previously proposed to proceed through an intermolecular reaction where the azlactone enolate of **2** forms an ion pair with the acyl pyridinium formed by DMAP and the acyl group to be transferred.[46] At this step, the enolate is sufficiently basic to be protonated by water or other proton sources, resulting in the reformation of **2**.

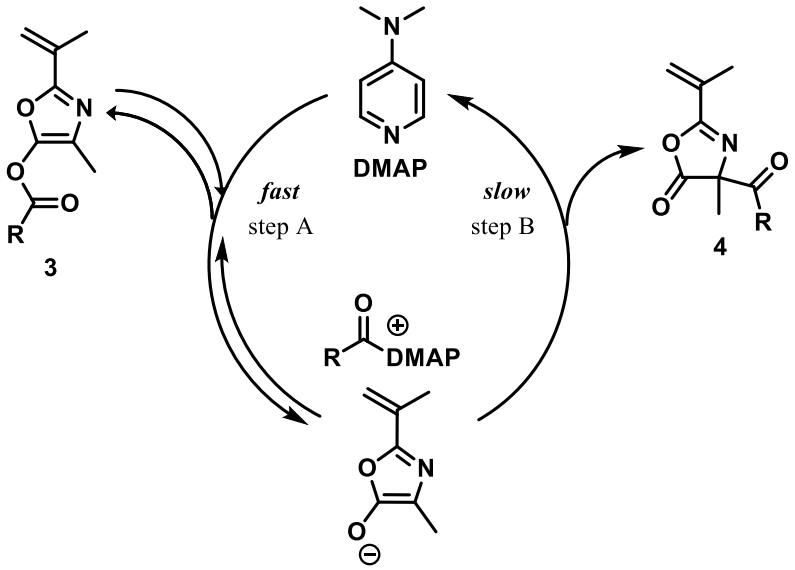
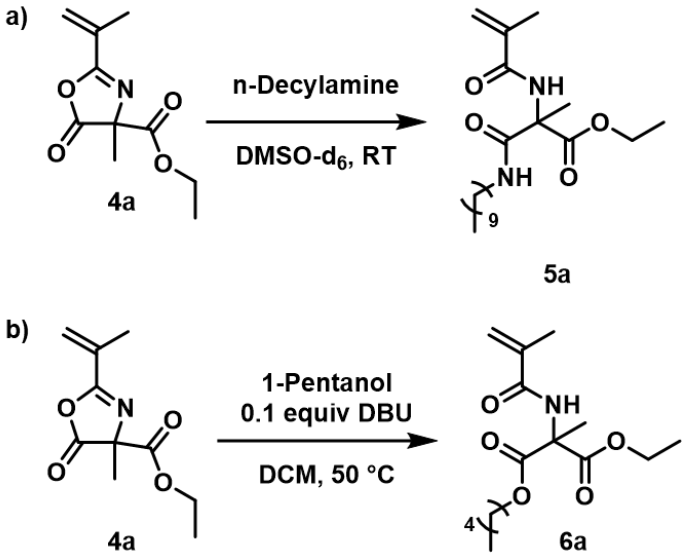


Figure 3. Schematic depicting the general Steglich rearrangement catalytic cycle proposed by Ruble *et. al.,*[46] modified here to show the appropriate substrates and catalyst used in this present study.

*Characterization of Ring-Opening Reactions and Polymerization of Azlactone Monomer **4a***

We next investigated whether novel 4,4'-derivatized azlactone **4a**, having both a methyl and an ester substituent in the C-4 position, would maintain the facile ring-opening reactivity toward primary amines and hydroxyl groups generally associated with azlactones such as VDMA. VDMA and the resulting polymer PVDMA react rapidly with primary amines at room temperature without the need for a catalyst, but only react with primary alcohols in the presence of a base catalyst such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[9, 12, 13, 18, 28] Azlactone **4a** reacted with *n*-decylamine rapidly and quantitatively *in situ* (within 10 minutes) in DMSO-d_6 to yield ring-opened product **5a**, as determined by ^{1}H NMR spectroscopy (Scheme 3; see additional details provided in the Supporting Information for these and all other related experiments described here). As anticipated, we observed no reaction by either ^{1}H or ^{13}C NMR when azlactone **4a** was treated with 1-decanol under otherwise identical conditions. However, we did observe ring-opening when

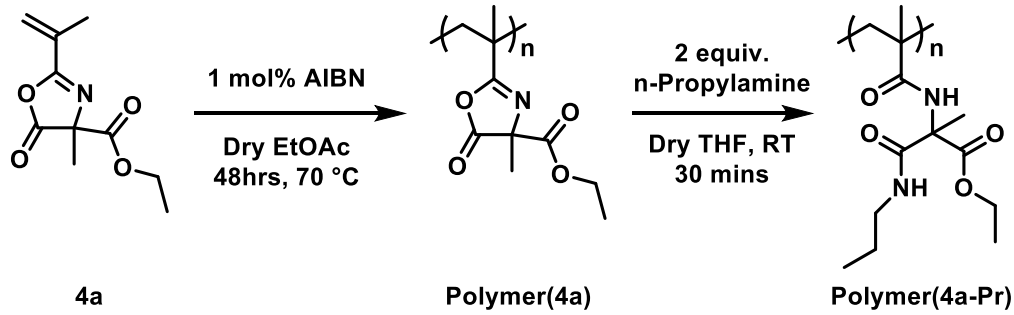
azlactone **4** was treated with primary alcohols in the presence of DBU as a catalyst. As depicted in Scheme 3, treatment of **4a** with pentanol and DBU at 50 °C using conditions similar to a previous report[28] resulted in the complete overnight conversion of **4a** to compound **6a**, as evidenced by ^{1}H and ^{13}C NMR spectroscopy (see additional details in the NMR Spectra section of the Supporting Information). The results of these studies demonstrate that the installation of an acyl group in the C-4 position of the azlactone ring does not negatively influence reactivity with primary amines and alcohols relative to that typically associated with coventional vinyl azlactone-based monomers such as VDMA.



Scheme 3. Reactions of **4a** with the model primary amine *n*-decylamine (a) and the model primary alcohol 1-pentanol (b).

The results of additional experiments demonstrated that novel isopropenyl-functionalized azlactone **4a** could be successfully polymerized using conventional free radical polymerization methods. Initial attempts to polymerize monomer **4a** using AIBN as an initiator and reaction

conditions commonly used to polymerize VDMA (e.g., 60° C for 24 hours)[61] revealed this monomer to polymerize to polymer(**4a**), albeit more slowly and in lower yields (<5 %) relative to VDMA. This result is generally consistent with the results of past studies reporting that isopropenyl derivatives of VDMA polymerize more slowly than vinyl-substituted VDMA.[13] However, we were able to polymerize monomer **4a** to polymer(**4a**) in higher yields (20 %) after polymerization for 48 hours at 70° C (Scheme 4). Characterization of polymer(**4a**) by GPC revealed it to have a monomodal molecular weight distribution (Figure 4) with a number-average molecular weight (M_n) of 11.2 kDa relative to polystyrene standards and a dispersity ($Đ$) of ~1.8 (see Supporting Information; Table S2 of the Supporting Information provides a tabular summary of the structures and provides other useful information for all new azlactone-functionalized and side-chain substituted polymers synthesized and characterized in this study.).



Scheme 4. AIBN-initiated free radical polymerization of monomer **4a** to polymer(**4a**) and subsequent post-polymerization reaction of polymer(**4a**) with *n*-proplyamine to yield side chain substituted polymer(**4a-Pr**).

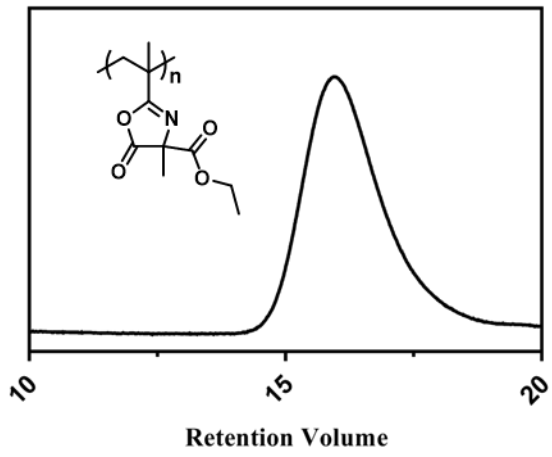


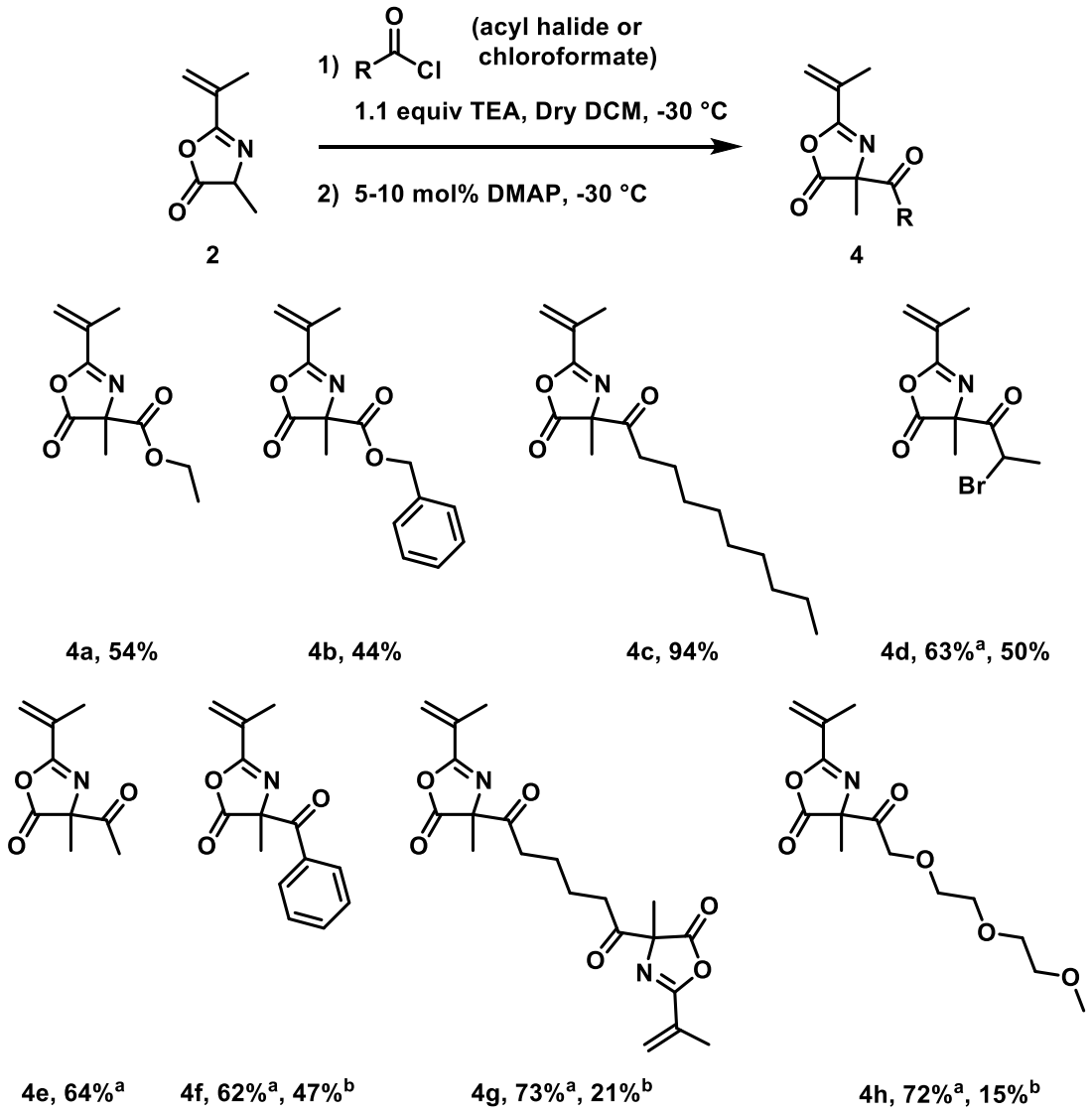
Figure 4. Plot showing the GPC refractive index trace of polymer(**4a**).

Additional quantitative characterization of polymer(**4a**) by ^{13}C NMR showed that the azlactone ring of polymer(**4a**) remained closed and unhydrolyzed during extended polymerization and subsequent isolation. Subsequent treatment of polymer(**4a**) with *n*-propylamine revealed the azlactone side groups to react rapidly and quantitatively to yield ring-opened and propyl-substituted polymer(**4a-Pr**) (Scheme 4; as determined by ^{1}H NMR spectroscopy; see NMR Spectra section of the Supporting Information for additional details). Additionally, there was no evidence of reaction of the primary amine at the 4'-ester group, indicating that the reaction between primary amines and novel azlactones with ester groups at the 4-position can be directed selectively to the azlactone carbonyl carbon. The results of these experiments demonstrate that the novel structure of acyl- and isopropenyl-substituted azlactone **4a** made accessible via the Steglich rearrangement retains both the reactivity and relative stability to undergo free radical polymerization without premature ring-opening of the azlactone ring, as well as the ability to react further, after polymerization, with primary amines to provide access to new substituted polymers with novel structures. In the sections below, we report additional useful modifications of this general approach

and explore the generality and scope of the Steglich rearrangement for the synthesis of additional alkenyl azlactone monomers with novel structures.

Development of a One-Pot Steglich Rearrangement

During our initial work on the synthesis of 4'-acyl azlactone **4a**, we reasoned that it should be possible to adapt the general, two-step Steglich rearrangement procedure described above to a more efficient 'one-pot' approach, in which O-acyl oxazole **3** would be formed *in situ,* followed, without isolation, by the direct addition of DMAP and subsequent rearrangement to azlactone **4**. Such an approach would be a desirable modification to the synthetic procedure we reported above, at least in part because it would obviate the need for the time- and resource-intensive isolation and purification of oxazole **3**. To our knowledge, one-pot procedures for the Steglich rearrangement have only been reported twice previously, with neither approach using a DMAP-based catalyst.[53, 55] During our work on the stepwise Steglich rearrangement, we observed the initial acylation of compound **2** to be rapid and to proceed without the generation of side products that would interfere with the proposed rearrangement catalytic cycle.



Scheme 5. 4'-acyl(oxy) alkenyl azlactone monomers synthesized through a one-pot Steglich rearrangement method. [a]NMR yield of isolated crude product. [b]NMR yield after silica column chromatography. Table S1 of the Supporting Information also provides a tabular summary of the structures and provides other useful information for these and all other new 4,4'-derivatized azlactone monomers synthesized and characterized in this study.

To explore the feasibility of a one-pot approach, we reacted compound **2** with ethyl chloroformate and TEA as previously described, but instead of isolating **3a** once the initial acylation was completed (as monitored by TLC), we added catalytic DMAP, dissolved in anhydrous DCM, directly to the reaction mixture. This one-pot method (Scheme 5) yielded the

desired 4,4'-derivatized azlactone **4a** in 54% yield after isolation and purification (additional details of these procedures are included in the Supporting Information). This yield is identical to the yield of **4a** across the O-acylation and Steglich rearrangement steps in the initial stepwise procedure above (54%, Scheme 2). The results of additional experiments revealed that, for this one-pot method to yield the azlactone product, the acyl halide must be either the limiting reagent or equal in equivalents to compound **2**. If an excess of the acid halide is used in this one-pot approach, the corresponding acyl pyridinium salt will be formed upon the addition of DMAP, with no nucleophile to reform the DMAP catalyst, leading to deactivation of the catalyst and the formation of only the O-acyl oxazole intermediate instead of the desired 4,4'-derivatized azlactone. It is likely that the conditions used for this one-pot transformation could be further optimized to increase overall economy and product yield. Further optimization of this specific reaction was not a direct goal of this current study; the general conditions used above were sufficient to provide a synthetic platform useful for additional exploration of substrate scope and azlactone structure in all other studies described below.

Exploration of Acyl Halide Generality in One-Pot Steglich Rearrangement

We used the one-pot reaction approach described above to investigate the range of different acyl groups that could be used in the Steglich rearrangment to synthesize new alkenyl azlactones with novel ester and ketone substituents. We found that, in addition to reaction with other chloroformates (such as benzyl chloroformate, leading to azlactone **4b**), a range of acyl halides could also be used (Scheme 5). We used decanoyl chloride and 2-bromopropionyl bromide to synthesize azlactones **4c** and **4d** in excellent and moderate isolated yields, respectively, and acetyl

chloride, benzoyl chloride, adipoyl chloride, and 2-(2-(2-methoxyethoxy)ethoxy)acetyl chloride (**S4**) to synthesize azlactones **4e** through **4h,** respectively, in good crude yields.

We found 4'-acyloxy alkenyl azlactones **4a** and **4b** to be readily purified by silica gel column chromatography. However, we found silica gel column chromatography to promote degradation during the purification of 4'-acyl alkenyl azlacatones **4d**-**4h,** with reformation of compound **2** or formation of pseudoazlactone **p-Az** as the terminal product. The fate of the acyl group is unknown; in some cases the corresponding carboxylic acid could be identified by NMR and, in other cases, we could not determine the structure of the terminal degradation product for the acyl group. This degradation reduced the isolated yield of azlactone **4d** and prevented the isolation of azlactones **4e**-**4h** in pure form when silica gel column chromatography was used. We note, in this context, that a past computational study has reported that, while rearrangement from O-acyl(oxy)oxazole to 4'-acyl(oxy)azlactone for both acyloxy (ester) and acyl (ketone) substituents on similar azlactone substrates are energetically favorable, the rearrangement of the 4'-acyl product was approximately 6 kcal/mol less favorable.[62] If such a difference were present in the compounds investigated here, it could play a role in explaining the relative instabilities of the 4'-acyl alkenyl azlactones observed under the silica gel column purification conditons used here. We speculate that silica gel-promoted degradation may occur via elimination of the acyl group, which has previously been reported for compound **4e**, resulting in the reformation of **2**.[40] This previously reported degradation of **4e** was proposed to be promoted by the nucleophilic attack of a carboxylate on the carbonyl of the acyl functional group leading to elimination. Support for this view is provided by the observation of peaks characteristic of **2** in the ^{1}H NMR spectra of the corresponding partially degraded azlactone products after column purification (all other impurities

from the crude were otherwise successfully removed during chromatography, further facilitating this observation).

We also considered the possibility that elimination was being promoted by the acidity inherent to silica gel. However, attenuation of acidity by addition of TEA to either the eluent or as a silica gel pre-wash step was not successful; we were only able to isolate the corresponding hydrolyzed (ring-opened) alkenyl azlactones under these conditions. We were also unable to successfully isolate these products using basic alumina as the solid support for chromatography. We were, ultimately, unable to identify chromatography conditions that would permit the isolation of pure **4e**-**4h** without significant degradation of the product. Additional studies will be required to understand the mechanism of degradation observed here. In addition, we note that samples of crude azlactones **4e**-**4h** arising from the work-up of our one-pot Steglich rearrangements did not degrade further upon standing under ambient conditions in the absence of silica gel. We therefore consider it likely that other purification methods, for example fractional distillation, which was found to be impractical on the scales on which we were operating in this current study, could be used to isolate azlactones **4e**-**4h** in pure forms. Additionally, depending on acyl halide functionality, the corresponding 4'-acyl alkenyl azlactones can be isolated as solids, as is the case for azlactones **4c** and **4d**, allowing for alternative purification methods such as trituration to yield the pure product without degradation side products, as in the case of **4d**.

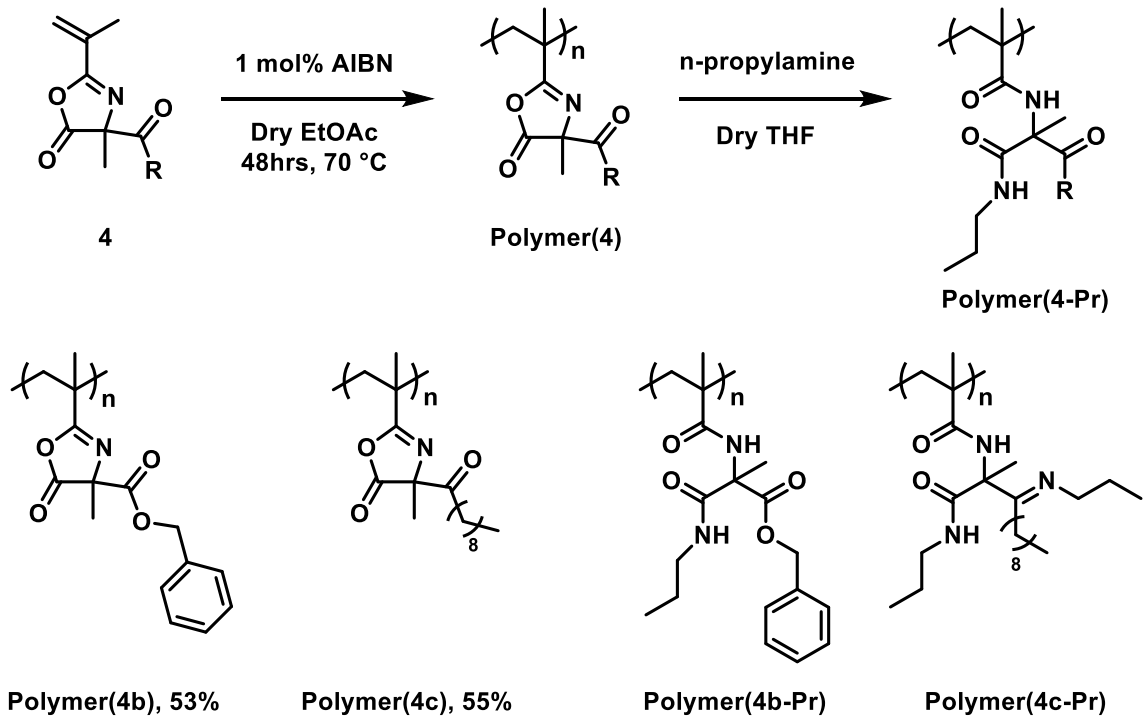
Despite challenges associated with the silica gel column purification of certain 4'-acyl-based compounds, the results above, when combined, demonstrate that the one-pot Steglich rearrangement can provide a useful, generalized, and modular approach to the incorporation of a wide range of acyloxy (ester) and acyl (ketone) functionality to alkenyl azlactones of potential utility in the context of polymer chemistry. In general, we found alkyl (**4a**, **4b**, **4c**, and **4e**), benzyl

(**4b**), aryl (**4f**), oligoethylene glycol (**4h**), halogen containing functional groups (**4d**), and even bis-ketoalkyl (**4g**) functionalities to be tolerated (Scheme 5). Only in the case where there was significant steric bulk alpha to the acyl group, such as when α-bromoisobutyryl bromide was used as the acylating reagent (**3j**), did rearrangement not occur; in such cases, the intermediate O-acyl oxazole could be isolated in good yield (e.g., see details for compound **3j** in the Supporting Information).

In the general context of polymer chemistry, the one-pot Steglich rearrangement provides access to a broad range of new functionalities and offers approaches to rapidly synthesize and screen for monomers and polymers with new physicochemical properties. We note here, however, that while the one-pot Steglich approach is straightforward and economical, the two-step Steglich approach also provides opportunities to isolate and purify new O-acyl oxazoles (e.g., by executing only the first step of the stepwise process illustrated in Scheme 2). In addition to the one-pot synthesis of the acyl azlactone products described above, we also synthesized and isolated novel O-acyl oxazoles **3c**, **3i**, and **3j** using this approach (Scheme S1); the full synthesis and characterization of these additional compounds are included in the Supporting Information. Interestingly, O-acyl oxazoles are stable to purification by silica gel column chromatography, unlike their corresponding azlactone derivatives (*vide supra*). Although these O-acyl oxazoles were not a direct focus of this current study, these novel compounds could also be useful as monomers for the synthesis of new oxazole polymers, which could possibly be transformed, post-polymerization, into the corresponding 4'-acyl azlactone polymer derivatives by polymer analogous Steglich rearrangement. Additional studies of the free radical polymerization and characterization of the post-polymerization reactivities of these novel ester- and ketone-functionalized azlactone monomers are described below.

*Polymerization and Post-Polymerization Modification of Ester- and Ketone-Containing Azlactone Monomers **4b** and **4c***

We next performed a series of studies to explore the impacts of novel 4-acyl substituents described above on the behaviors of these compounds during conventional AIBN-initiated free radical polymerization (Scheme 6). Both monomers **4b** and **4c** polymerized readily and the resulting polymers [polymer(**4b**) and polymer(**4c**)] were subsequently characterized by FTIR, NMR, and GPC. As anticipated based on our experience with the polymerizaiton of monomer **4a**, discussed above, FTIR and NMR revealed the the cyclic azlactone functionality in both polymers to remain intact and unhydrolyzed after polymerization and isolation. Analysis of polymer(**4c**) revealed it to have a monomodal molecular weight distribution (Figure 5) with a $Đ$ of ~1.6 and a M_n of 18.9 kDa relative to polystyrene standards. In contrast, polymer(**4b**) exhibited a bimodal molecular weight distribution (Figure 5), with one large peak with an estimated M_n of 10.3 kDa ($Đ$ ~1.8) and a smaller peak with a substantially higher molecular weight (this peak was not baseline separated from the larger peak, but had a very high estimated/apparent M_n of ~300 kDa relative to polystyrene standards). The reasons for this bimodal distribution are not clear; we observed this higher molecular weight peak in polymer isolated from the polymerization of monomer **4b** in multiple polymerization reactions under several different stringent and air-free reaction conditions. Characterization of the isolated polymer by NMR and FTIR revealed peaks consistent with the free-radical polymerization of **4b** and did not reveal evidence of ring-opening reactions or other side reactions of the monomer or polymer.



Scheme 6. Polymerization of alkenyl azlactones synthesized through the one-pot procedure and subsequent post-polymerization reaction with excess propylamine.

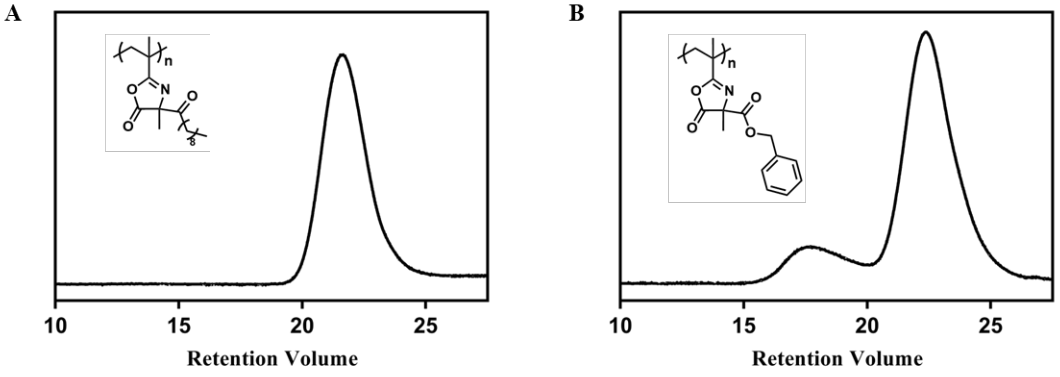


Figure 5. GPC refractive index traces for polymer(**4c**) (A) and polymer(**4b**) (B).

Polymer(**4b**) reacted rapidly and exhaustively via the anticipated azlactone ring-opening reaction when treated with an excess of *n*-propylamine in solution to form polymer(**4b-Pr**)

(Scheme 6), similar to results discussed above for polymer(**4a**) and past reports on the reactivity of other azlactone-containing polymers, including PVDMA. Polymer(**4c**), which contains a ketone-functionalized subsituent in the 4-position rather than the ester functionality found in polymer(**4a**) and polymer(**4b**), also reacted rapidly and quantitatively when treated with an excess of *n*-propylamine. However, careful characterization of the product polymer by NMR revealed evidence of both exhaustive azlactone ring-opening and exhaustive reaction of propylamine with the side chain ketone functionality to yield the corresponding and novel imine-functionalized product polymer(**4c-Pr**) (see Scheme 6). This observation of imine formation is interesting, albeit not completely unexpected, and represents, to our knowledge, a new mode of dual reactivity for alkenyl azlactone monomers that can provide access to polymers with novel structures and that may exhibit new properties. Additional investigation will be required to understand the potential scope of this approach and the extent to which it can be further tuned and controlled; it is not yet clear, for example, whether ring-opening and imine formation could be performed selectively or independently under certain conditions, which could lead to new routes for dual functionalization of these reactive polymers. It is also worth noting, in this context, that the possibility of leveraging the reactivity of the ketone under conditions that do not promote ring-opening could also provide new routes to novel monomer structures.

We initially synthesized α-bromo-functionalized alkenyl azlactone **4d** (Scheme 5) to explore the range of functionality that could be installed in this class of monomer using our one-pot Steglich rearrangement conditions, as discussed above and, in part, because of the structural similarity of that monomer to other 2-bromoisobutyryloxy-functionalized 'inimer' monomers used for the controlled radical polymerization of polymer brushes and other highly branched materials.[63] This monomer did not polymerize cleanly using the conventional radical polymerization methods

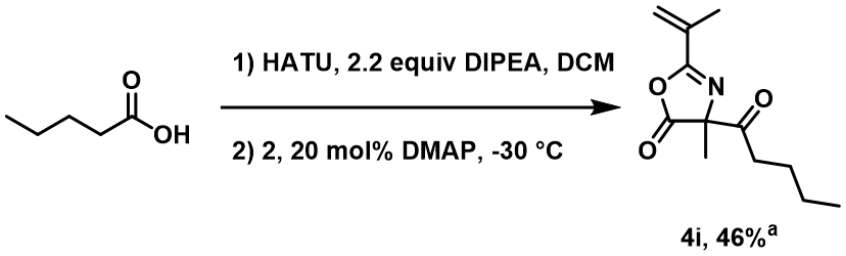
explored in this study. Characterization by GPC revealed a multimodal trace indicating low molecular weight polymer and oligomers, and NMR spectroscopy revealed a mixture of peaks that could not be identified as an expected polymer product.

Finally, we note that, as discussed above, we were unable to adequately purify some of the 4-acyl-substituted monomers described above due to their sensitivity to degradation during silica gel chromotography. Nevertheless, we also conducted preliminary polymerization studies using impure samples of these monomers to explore feasibility and gain potential insights into the impacts of new 4'-functionality on polymerization behavior. As one example, we explored the AIBN-initiated polymerization of benzoyl-substituted monomer **4f**. Characterization by GPC revealed a multimodal trace consistent with the formation of polymer, and characterization by NMR revealed peaks consistent with the desired vinyl polymer, suggesting that the phenyl substituent does not prevent polymerization. However, we are unable to draw additional conclusions on the structures or properties of the polymer product on the basis of our initial studies using this crude monomer.

Streamlined Monomer Synthesis via in situ Activation of Carboxylic Acids During Steglich Rearrangment

During the course of the studies above, we conducted additional investigations to determine whether it was possible to modify our one-pot approach to the Steglich Rearrangement to synthesize 4'-acyl alkenyl azlactones directly using carboxylic acids rather than the highly reactive and more expensive acyl halides used above. This approach would be attractive for several reasons and seemed reasonable because the mechanism of this reaction, as exemplified for the synthesis of monomer **4a** from isopropenyl azlactone **2** in Scheme 2, relies on the formation of the ion pair

of the enolate of azlactone **2** and the acyl pyridinium formed by the acylation of DMAP (see also Figure 3). While this ion pair is generally achieved by the reaction of O-acyl oxazole **3** with DMAP (Scheme 2), it is also reasonable to deprotonate **2** to the enolate with bases such as TEA, as the pKa of **2** has been noted to be ~9,[34, 64] and several carboxylic acid activating reagents described in the peptide coupling literature allow for the formation of the acyl pyridinium if DMAP is in solution.[65] We reasoned that, under appropriate reaction conditions, it should be possible to enter the catalytic cycle not at oxazole **3** (e.g., Figure 3) but at the ion-pair, which should then behave as expected in the Steglich rearrangment (Figure 3).



Scheme 7. One-pot *in situ* activation of carboxylic acids and Steglich rearrangement. [a]NMR yield after silica column chromatography.

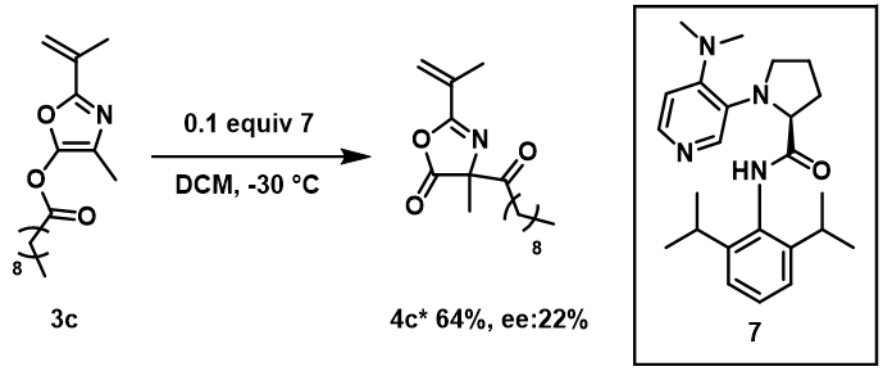
We conducted screening studies using several different carboxylic acid activating agents and identified, at least in the context of this current study, the combination of hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU) and N,N-diisopropylethylamine (DIPEA) to be a useful carboxylic acid activating agent for this transformation. After activation of the carboxylic acid using this approach, the DMAP catalyst could be added, along with azlactone starting material **2** (Scheme 7). We found that slow addition of compound **2** allowed for better yield of **4** and less byproduct resulting from the rearrangement of compound **2** to the pseudoazlactone **p-Az** (see additional discussion of this rearrangement above). As a model to demonstrate feasibility, we used this approach of *in situ* activation to synthesize azlactone **4i** in 46% yield from the one-pot *in situ*

activation of valeric acid, followed by subsequent reaction and Steglich rearrangement using compound **2**. Similar to the 4' ketone products reported from our one-pot Steglich rearrangement above **4e-h** (Scheme 5), **4i** also exhibited instability during silica column chromatography. The synthesis of **4i** establishes proof of concept for this *in situ* activation-based approach. Overall, we anticipate this approach to be general; with additional development, it could open the door to the synthesis of alkenyl azlactone derivatives having a broader range of ketone functional groups without the need to synthesize or purchase acyl chlorides, or store, handle, and manipulate these highly reactive reagents.

Toward Stereoselective Synthesis of Novel Azlactone Monomers: Stereoselective Steglich Rearrangement Using an Asymmetric DMAP Derivative

We note that the novel alkenyl azlactones described above are disubstituted at the C-4 position and, because these two substituents are different, contain a stereogenic center at that position. While the rearrangments that lead to those monomers are expected to occur without stereoselectivity because DMAP is achiral, it is possible that the stereochemistry could be biased if appropriate asymmetric catalysts were untilized.[39, 46-51] In a final series of experiments, we explored the use of an asymmetric DMAP-based catalyst in the Steglich rearrangement to affect the asymmetric rearrangement of O-acyl oxazole **3** to yield enantioenriched azlactone monomer **4**. From a range of previously reported asymmetric DMAP-based catalysts, we selected catalyst **7**, previously reported by Cao *et. al.,*[47] because it is relatively straightforward to synthesize (four steps) and is scalable. To explore the general feasibility of this approach, we attempted the asymmetric rearrangement of **3c** to **4c*** (Scheme 8; ***** indicating the use of the asymmetric catalyst **7**, and resulting enantioenrichment of the product monomer) using catalyst **7**, as we had previously

achieved excellent yields for this rearrangement (94%) and were able to obtain the monomer **4c** as a pure product.



Scheme 8. Asymmetric Steglich rearrangement of **3c** to the enantioenriched product **4c*** using asymmetric DMAP-based catalyst **7**.

The product of this reaction was then analyzed by supercritical fluid chromatography-mass spectrometry (SFC-MS) using a chiral column. This analysis revealed the enantiomeric excess (ee) of resulting disubstituted monomer **4c*** to be 22% (additional results of chiral chromatography and other structural characterization of monomer **4c*** can be found in the Supporting Information). Although this level of enantioerichment is low, this result demonstrates that it is possible to use this chiral catalyst approach to influence the stereochemistry of 4,4'-disubstituted alkenyl azlactone monomers. We did not seek to further optimize the conditions of this reaction to achieve higher enantioselectivity as part of this current study. With further development, however, this approach could prove useful for the synthesis of monomers and reactive, azlactone-functionalized polymers with optical activities or other novel behaviors that could arise from control over the stereochemistry at this position of a subsequently functionalized polymer (e.g., after ring-opening by treatment with an amine-based nucleophile, etc.).

Summary and Conclusions

We have reported new stepwise and one-pot approaches to the synthesis of alkenyl azlactone monomers based on the Steglich rearrangement. These approaches enable the synthesis of a family of novel 2-isopropenyl-4-methyl-4'-acylazlactones that would be difficult or impractical to synthesize using other methods reported for the synthesis of alkenyl azlactone-based monomers. These novel monomers, which have a variety of different substituted alkyl and aryl ester and ketone groups in the 4-positions of their rings, retained the anticipated reactivity of the azlactone functionality with nucleophiles and can be polymerized using conventional, AIBN-initiated free radical polymerization methods to synthesize novel amine-reactive polymers.

Building from a base provided by the classical stepwise Steglich rearrangement, we also developed a one-pot procedure allowing for the *in situ* formation and subsequent reaction of O-acyl oxazoles to the corresponding azlactone monomers without isolation and purification of the oxazole intermediate. This method allowed us to more efficiently explore the generality of the Steglich rearrangement, showing that a broad range of acyl halides (e.g., containing alkyl, aryl, benzyl, oligoethylene glycol, bis-acyl halide, and halogen-containing functional groups) are compatible with the rearrangement. Polymers synthesized from several of these monomers were demonstrated to retain azlactone functional group ring-opening reactivity when treated with nucleophilic primary amines, with polymers possessing ketone functionality also able to form the corresponding imine product when treated with excess amine. Finally, we also reported conditions useful for (i) the synthesis of enantioenriched alkenyl azlactone monomers and (ii) the *in situ* activation and subsequent reaction of carboxylic acids that removes the need to use acyl halides to promote the Steglich rearrangement.

Overall, the results of this study provide new and useful approaches to the design of alkenyl azlactone-based monomers and polymers with novel structures. Our results also demonstrate that the stepwise Steglich rearrangement approach can be used to isolate new O-acyl oxazole intermediates that could also provide access to new monomer and polymer structures. Additional studies to characterize and further explore the structures, properties, and behaviors of polymers and other materials synthesized from the new alkenyl azlactone monomers reported here are currently underway. The results of these additional studies will be reported in due course.

Acknowledgments. Financial support for this work was provided in part by the Wisconsin Alumni Research Foundation (WARF) through the WARF Accelerator Program and, in part, by the National Institutes of Health (NIH; R21 EB034811). We acknowledge the support of the following instrumentation in the Paul Bender Chemistry Instrumentation Center at UW-Madison: a Thermo Q Exactive™ Plus (supported by the NIH; 1S10 OD020022-1); a Bruker Avance-400 (supported by the NSF; CHE-1048642); a Bruker Avance-500 (supported by a generous gift from Paul J. and Margaret M. Bender); and a Bruker Avance-600 (supported by the NIH; S10 OD012245). The authors acknowledge the use of instrumentation supported by the NSF through the UW MRSEC (DMR-2309000). We thank Prof. Dan Weix and his research group at UW-Madison for generously allowing the use of their SFC-MS.

Supporting Information. A full account of materials used, general considerations, supplemental data, detailed experimental procedures, characterization data for isolated compounds, and copies of NMR data are included (PDF). This material is available free of charge via the Internet.

ORCID

William M. Breining: 0000-0001-6022-766X
David M. Lynn: 0000-0002-3140-8637

References

(1) Arshady, R. Polymer synthesis via activated esters: A new dimension of creativity in macromolecular chemistry. In *Polymer Synthesis*, Springer Berlin Heidelberg, 1994; pp 1-41.

(2) Theato, P. Synthesis of well-defined polymeric activated esters. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46* (20), 6677-6687. DOI: 10.1002/pola.22994.

(3) Das, A.; Theato, P. Activated Ester Containing Polymers: Opportunities and Challenges for the Design of Functional Macromolecules. *Chem. Rev.* **2016**, *116* (3), 1434-1495. DOI: 10.1021/acs.chemrev.5b00291.

(4) Du, Y.; Zeng, Q.; Yuan, L.; He, L. Post-polymerization modification based on reactive fluorinated polymers reaction. *J. Macromol. Sci., Part A: Pure Appl.Chem.* **2021**, *58* (8), 521-538. DOI: 10.1080/10601325.2021.1903328.

(5) Tanaka, T. Recent Advances in Polymers Bearing Activated Esters for the Synthesis of Glycopolymers by Postpolymerization Modification. *Polymers* **2024**, *16* (8). DOI: 10.3390/polym16081100.

(6) Gauthier, M. A.; Gibson, M. I.; Klok, H. A. Synthesis of functional polymers by post-polymerization modification. *Angew. Chem. Int. Ed.* **2009**, *48* (1), 48-58. DOI: 10.1002/anie.200801951.

(7) Boaen, N. K.; Hillmyer, M. A. Post-polymerization functionalization of polyolefins. *Chem. Soc. Rev.* **2005**, *34* (3), 267-275. DOI: 10.1039/b311405h.

(8) Golas, P. L.; Matyjaszewski, K. Marrying click chemistry with polymerization: expanding the scope of polymeric materials. *Chem. Soc. Rev.* **2010**, *39* (4), 1338-1354. DOI: 10.1039/b901978m.

(9) Taylor, L. D.; Kolesinski, H. S.; Mehta, A. C.; Locatell, L.; Larson, P. S. Synthesis of Poly(4,4-Dimethyl-2-Vinyl-5-Oxazolone) an Interesting Material for Preparing Polymeric Agents. *Makromol Chem-Rapid* **1982**, *3* (11), 779-782. DOI: 10.1002/marc.1982.030031105.

(10) Rasmussen, J. K.; Heilmann, S. M.; Palensky, F. J.; Smith, H. K.; Melancon, K. C. Chemistry of Alkenylazlactones .2. Reaction with Thiols. *Makromol Chem-Rapid* **1984**, *5* (2), 67-70. DOI: 10.1002/marc.1984.030050202.

(11) Rasmussen, J. K.; Heilmann, S. M.; Krepski, L. R. Polyazlactones. In *Encyclopedia of Polymer Science & Engineering*, 2 ed.; 1988; Vol. 11, pp 558-571.

(12) Heilmann, S. M.; Moren, D. M.; Krepski, L. R.; Pathre, S. V.; Rasmussen, J. K.; Stevens, J. The chemistry of 2-alkenyl-5(4H)-oxazolones. VIII - Acid-catalyzed reaction with alcohols. *Tetrahedron* **1998**, *54* (40), 12151-12160. DOI: 10.1016/S0040-4020(98)00751-0.

(13) Heilmann, S. M.; Rasmussen, J. K.; Krepski, L. R. Chemistry and technology of 2-alkenyl azlactones. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39* (21), 3655-3677. DOI: 10.1002/pola.10007.

(14) Ho, H. T.; Levere, M. E.; Fournier, D.; Montembault, V.; Pascual, S.; Fontaine, L. Introducing the Azlactone Functionality into Polymers through Controlled Radical Polymerization:

Strategies and Recent Developments. *Aust. J. Chem.* **2012**, *65* (8), 970-977. DOI: 10.1071/Ch12192.

(15) Messman, J. M.; Lokitz, B. S.; Pickel, J. M.; Kilbey, S. M., II. Highly Tailorable Materials based on 2-Vinyl-4,4-dimethyl Azlactone: (Co)Polymerization, Synthetic Manipulation and Characterization. *Macromolecules* **2009**, *42* (12), 3933-3941. DOI: 10.1021/ma900316t.

(16) Hübner, V. K.; Kollinsky, F.; Markert, G.; Pennewiss, H. Synthese und Reaktionen von 2-Alkenyloxazolonen. *Die Angewandte Makromolekulare Chemie* **1970**, *11* (1), 109-124. DOI: 10.1002/apmc.1970.050110110.

(17) Heilmann, S. M.; Jensen, K. M.; Krepski, L. R.; Moren, D. M.; Rasmussen, J. K.; Smith, H. K. A One-Pot Transformation of Ketones into N-(Meth)Acryloyl-2 Amino-Acids. *Synth. Commun.* **1987**, *17* (7), 843-862. DOI: Doi 10.1080/00397918708063942.

(18) Buck, M. E.; Lynn, D. M. Azlactone-Functionalized Polymers as Reactive Platforms for the Design of Advanced Materials: Progress in the Last Ten Years. *Polym. Chem.* **2012**, *3* (1), 66-80. DOI: 10.1039/C1PY00314C.

(19) François, F.; Gody, G.; Wilson, J.; Fontaine, L.; Pascual, S. Azlactone-based copolymers by redox-initiated MADIX polymerization at room temperature in ethanol. *Polym. Chem.* **2024**, *15* (14), 1453-1459. DOI: 10.1039/d4py00070f.

(20) Tully, D. C.; Roberts, M. J.; Geierstanger, B. H.; Grubbs, R. B. Synthesis of reactive poly(vinyl oxazolones) via nitroxide-mediated "living" free radical polymerization. *Macromolecules* **2003**, *36* (12), 4302-4308. DOI: 10.1021/ma025817m.

(21) Lokitz, B. S.; Messman, J. M.; Hinestrosa, J. P.; Alonzo, J.; Verduzco, R.; Brown, R. H.; Osa, M.; Ankner, J. F.; Kilbey, S. M. Dilute Solution Properties and Surface Attachment of RAFT Polymerized 2-Vinyl-4,4-dimethyl Azlactone (VDMA). *Macromolecules* **2009**, *42* (22), 9018-9026. DOI: 10.1021/ma9015399.

(22) Lokitz, B. S.; Wei, J.; Hinestrosa, J. P.; Ivanov, I.; Browning, J. F.; Ankner, J. F.; Kilbey, S. M., II; Messman, J. M. Manipulating Interfaces through Surface Confinement of Poly(glycidyl methacrylate)-block-poly(vinyldimethylazlactone), a Dually Reactive Block Copolymer. *Macromolecules* **2012**, *45* (16), 6438-6449. DOI: 10.1021/ma300991p.

(23) Carter, M. C. D.; Jennings, J.; Appadoo, V.; Lynn, D. M. Synthesis and Characterization of Backbone Degradable Azlactone-Functionalized Polymers. *Macromolecules* **2016**, *49* (15), 5514-5526. DOI: 10.1021/acs.macromol.6b01212.

(24) Fournier, D.; Pascual, S.; Fontaine, L. Copper-mediated living radical polymerization of 2-vinyl-4,4-dimethyl-5-oxazolone. *Macromolecules* **2004**, *37* (2), 330-335. DOI: 10.1021/ma035012u.

(25) Buck, M. E.; Zhang, J.; Lynn, D. M. Layer-by-layer assembly of reactive ultrathin films mediated by click-type reactions of poly(2-alkenyl azlactone)s. *Adv. Mater.* **2007**, *19* (22), 3951. DOI: 10.1002/adma.200700822.

(26) Pascual, S.; Blin, T.; Saikia, P. J.; Thomas, M.; Gosselin, P.; Fontaine, L. Block Copolymers Based on 2-Vinyl-4,4-dimethyl-5-oxazolone by RAFT Polymerization: Experimental and Computational Studies. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48* (22), 5053-5062. DOI: 10.1002/pola.24303.

(27) Sun, B.; Liu, X.; Buck, M. E.; Lynn, D. M. Azlactone-functionalized polymers as reactive templates for parallel polymer synthesis: synthesis and screening of a small library of cationic polymers in the context of DNA delivery. *Chem. Commun.* **2010**, *46* (12), 2016-2018. DOI: 10.1039/b921664b.

(28) Carter, M. C. D.; Lynn, D. M. Covalently Crosslinked and Physically Stable Polymer Coatings with Chemically Labile and Dynamic Surface Features Fabricated by Treatment of Azlactone-Containing Multilayers with Alcohol-, Thiol-, and Hydrazine-Based Nucleophiles. *Chem. Mater.* **2016**, *28* (14), 5063-5072. DOI: 10.1021/acs.chemmater.6b01897.

(29) Carter, M. C. D.; Jennings, J.; Speetjens, F. W., II; Lynn, D. M.; Mahanthappa, M. K. A Reactive Platform Approach for the Rapid Synthesis and Discovery of High χ/Low N Block Polymers. *Macromolecules* **2016**, *49* (17), 6268-6276. DOI: 10.1021/acs.macromol.6b01268.

(30) François, F.; Nicolas, C.; Forcher, G.; Fontaine, L.; Montembault, V. Poly(norbornenyl azlactone) as a versatile platform for sequential double click postpolymerization modification. *Eur. Polym. J.* **2020**, *141*, 110081. DOI: 10.1016/j.eurpolymj.2020.110081.

(31) Rasmussen, J. K.; Heilmann, S. M.; Palensky, F. J. Acrylamidoacylated oligomers. EP0091956B1, 1982.

(32) Iwakura, Y.; Toda, F.; Torii, Y.; Sekii, R. Copolymerization of 2-Isopropenyl-4,4-Dialkyl-5-Oxozolones with Styrene. *J. Polym. Sci., Part A: Polym. Chem.* **1968**, *6* (9pa1), 2681-&. DOI: 10.1002/pol.1968.150060924.

(33) Lynn, J. Notes- A Vinyl Azlactone. *J. Org. Chem.* **1959**, *24* (7), 1030-1031. DOI: 10.1021/jo01089a629.

(34) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. The diverse chemistry of oxazol-5-(4H)-ones. *Chem. Soc. Rev.* **2007**, *36* (9), 1432-1440. DOI: 10.1039/b511113g.

(35) Iwakura, Y.; Toda, F.; Torii, Y. Copolymerization of Isopropenyl and Isopropylidene Oxazolones with Styrene. *J. Polym. Sci., Part A: Polym. Chem.* **1966**, *4* (10pa), 2649-&. DOI: 10.1002/pol.1966.150041026.

(36) Iwakura, Y.; Toda, F.; Torii, Y. The Isolation of Isomeric 5-Oxazolones and the Assignment of Their Structures by Means of NMR Spectroscopy. *Bull. Chem. Soc. Jpn.* **1967**, *40* (1), 149-153. DOI: 10.1246/bcsj.40.149.

(37) Alba, A. N.; Rios, R. Oxazolones in organocatalysis, new tricks for an old reagent. *Chem. Asian J.* **2011**, *6* (3), 720-734. DOI: 10.1002/asia.201000636.

(38) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. Azlactone Reaction Developments. *Chem. Eur. J.* **2016**, *22* (30), 10294-10318. DOI: 10.1002/chem.201600071.

(39) Marra, I. F. S.; de Castro, P. P.; Amarante, G. W. Recent Advances in Azlactone Transformations. *Eur. J. Org. Chem.* **2019**, *2019* (34), 5830-5855. DOI: 10.1002/ejoc.201901076.

(40) Iwakura, Y.; Toda, F.; Suzuki, H. Synthesis of N-[1-(1-substituted 2-oxopropyl)]acrylamides and -methylacrylamides. Isolation and some reactions of intermediates of the Dakin-West reaction. *J. Org. Chem.* **1966**, *32* (2), 440-443. DOI: 10.1021/jo01288a039.

(41) Steglich, W.; Höfle, G. Zum mechanismus der dakin-west reaktion. *Tetrahedron Lett.* **1968**, *9* (13), 1619-1624. DOI: 10.1016/s0040-4039(01)99016-1.

(42) Steglich, W.; Höfle, G. 5-Acyloxyoxazoles and their Rearrangement to 4-Acyloxazol-5-ones. *Angew. Chem., Int. Ed. Engl.* **1968**, *7* (1), 61-61. DOI: 10.1002/anie.196800611.

(43) Steglich, W.; Höfle, G. Reaktionen von Oxazolon-(5)-Anionen, V. Carbanion-Carbonium-Ionenpaare als Zwischenstufen bei Synthese, Umlagerung und Reaktionen der [N-Acyl-dihydropyridyl]-oxazolone-(5) und -pseudooxazolone-(5). *Chem. Ber.* **1969**, *102* (4), 1129-1147. DOI: 10.1002/cber.19691020407.

(44) Steglich, W.; Höfle, G. Über eine einfache darstellung von acyl-oxazolinonen-(5) aus 5-acyloxy-oxazolen II. Mitteilung über hypernucleophile acylierungskatalysatoren. *Tetrahedron Lett.* **1970**, *11* (54), 4727-4730. DOI: 10.1016/s0040-4039(00)89379-x.

(45) Höfle, G.; Steglich, W.; Vorbrüggen, H. 4-Dialkylaminopyridines as Highly Active Acylation Catalysts. [New synthetic method (25)]. *Angew. Chem. Int. Ed.* **1978**, *17* (8), 569-583. DOI: 10.1002/anie.197805691.

(46) Ruble, J. C.; Fu, G. C. Enantioselective construction of quaternary stereocenters: Rearrangements of O-acylated azlactones catalyzed by a planar-chiral derivative of 4-(pyrrolidino)pyridine. *J. Am. Chem. Soc.* **1998**, *120* (44), 11532-11533. DOI: 10.1021/ja982890c.

(47) Cao, L.; Zhang, X. P.; Xie, M. S.; Guo, H. M. Cu-Catalyzed N-Arylation of Prolinamides: Access to Enantioenriched DMAP Analogues and Its Application in Black Rearrangement. *J. Org. Chem.* **2023**, *88* (1), 341-346. DOI: 10.1021/acs.joc.2c02368.

(48) Xie, M. S.; Zhang, Y. F.; Shan, M.; Wu, X. X.; Qu, G. R.; Guo, H. M. Chiral DMAP-N-oxides as Acyl Transfer Catalysts: Design, Synthesis, and Application in Asymmetric Steglich

Rearrangement. *Angew. Chem. Int. Ed.* **2019**, *58* (9), 2839-2843. DOI: 10.1002/anie.201812864.

(49) Li, Q. H.; Zhang, G. S.; Wang, Y. H.; Mei, M. S.; Wang, X.; Liu, Q.; Yang, X. D.; Tian, P.; Lin, G. Q. A novel chiral DMAP-thiourea bifunctional catalyst catalyzed enantioselective Steglich and Black rearrangement reactions. *Org. Chem. Front.* **2019**, *6* (15), 2624-2629. DOI: 10.1039/c9qo00691e.

(50) Mandai, H.; Fujii, K.; Suga, S. Recent topics in enantioselective acyl transfer reactions with dialkylaminopyridine-based nucleophilic catalysts. *Tetrahedron Lett.* **2018**, *59* (19), 1787-1803. DOI: 10.1016/j.tetlet.2018.03.016.

(51) Yamamoto, T.; Murakami, R.; Suginome, M. Single-Handed Helical Poly(quinoxaline-2,3-diyl)s Bearing Achiral 4-Aminopyrid-3-yl Pendants as Highly Enantioselective, Reusable Chiral Nucleophilic Organocatalysts in the Steglich Reaction. *J. Am. Chem. Soc.* **2017**, *139* (7), 2557-2560. DOI: 10.1021/jacs.6b12349.

(52) Candish, L.; Nakano, Y.; Lupton, D. W. Lewis Base Catalysis of Three n–π* Mediated Reactions with N-Heterocyclic Carbenes (NHCs), Isothioureas, Bicyclic Tertiary Amines, and Electron-Rich Pyridyls. *Synthesis* **2014**, *46* (14), 1823-1835. DOI: 10.1055/s-0033-1338653.

(53) Wang, M.; Zhou, M.; Zhang, L.; Zhang, Z.; Zhang, W. A step-economic and one-pot access to chiral C(alpha)-tetrasubstituted alpha-amino acid derivatives via a bicyclic imidazole-catalyzed direct enantioselective C-acylation. *Chem. Sci.* **2020**, *11* (18), 4801-4807. DOI: 10.1039/d0sc00808g.

(54) Viswambharan, B.; Okimura, T.; Suzuki, S.; Okamoto, S. Synthesis and catalytic properties of 4-aryl-2,3-dihydro-4H-pyrimido[2,3-b]benzothiazoles for asymmetric acyl or carboxyl group transfer reactions. *J. Org. Chem.* **2011**, *76* (16), 6678-6685. DOI: 10.1021/jo200984n.

(55) Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A. C.; Smith, A. D. Tandem multi-step synthesis of C-carboxyazlactones promoted by N-heterocyclic carbenes. *Chem. Commun.* **2008**, (30), 3528-3530. DOI: 10.1039/b806816j.

(56) De, C. K.; Mittal, N.; Seidel, D. A dual-catalysis approach to the asymmetric Steglich rearrangement and catalytic enantioselective addition of O-acylated azlactones to isoquinolines. *J. Am. Chem. Soc.* **2011**, *133* (42), 16802-16805. DOI: 10.1021/ja208156z.

(57) Zhang, Y.; Chen, Y. Recent advances in catalytic asymmetric [1,3]-rearrangement reactions. *Org. Chem. Front.* **2022**, *9* (17), 4744-4756. DOI: 10.1039/d2qo01027e.

(58) Kluga, R.; Kinens, A.; Suna, E. Chiral 4-MeO-Pyridine (MOPY) Catalyst for Enantioselective Cyclopropanation: Attenuation of Lewis Basicity Leads to Improved Catalytic Efficiency. *Chem. - Eur. J.* **2024**, *30* (10), e202301136. DOI: 10.1002/chem.202301136.

(59) Wang, M.; Zhang, Z.; Zhang, W. Design, Synthesis, and Application of Chiral Bicyclic Imidazole Catalysts. *Acc. Chem. Res.* **2022**, *55* (18), 2708-2727. DOI: 10.1021/acs.accounts.2c00455.

(60) Zhang, Z.; Xie, F.; Jia, J.; Zhang, W. Chiral Bicycle Imidazole Nucleophilic Catalysts: Rational Design, Facile Synthesis, and Successful Application in Asymmetric Steglich Rearrangement. *J. Am. Chem. Soc.* **2010**, *132* (45), 15939-15941. DOI: 10.1021/ja109069k.

(61) Carter, M. C. D.; Wong, M. S.; Wang, F. R.; Lynn, D. M. Influence of Side Chain Hydrolysis on the Evolution of Nanoscale Roughness and Porosity in Amine-Reactive Polymer Multilayers. *Chem. Mater.* **2020**, *32* (16), 6935-6946. DOI: 10.1021/acs.chemmater.0c02095.

(62) De Castro, P. P.; Dos Santos, J. A.; De Siqueira, M. M.; Batista, G. M. F.; Dos Santos, H. F.; Amarante, G. W. Quantum Chemical-Guided Steglich Rearrangement of Azlactones and Isoxazolones. *J. Org. Chem.* **2019**, *84* (19), 12573-12582. DOI: 10.1021/acs.joc.9b02099.

(63) Wang, X.; Gao, H. Recent Progress on Hyperbranched Polymers Synthesized via Radical-Based Self-Condensing Vinyl Polymerization. *Polymers* **2017**, *9* (6). DOI: 10.3390/polym9060188.

(64) Goodman, M.; Levine, L. Peptide Synthesis via Active Esters. IV. Racemization and Ring-Opening Reactions of Opitcally Active Oxazolones. *J. Am. Chem. Soc* **2002**, *86* (14), 2918-2922. DOI: 10.1021/ja01068a030.

(65) El-Faham, A.; Albericio, F. Peptide coupling reagents, more than a letter soup. *Chem. Rev.* **2011**, *111* (11), 6557-6602. DOI: 10.1021/cr100048w.