Asymmetric and Site-Selective [3 + 2]-Annulations for the Synthesis of High-Value Bicyclic Lactams

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Supporting Information

ABSTRACT: Asymmetric and site-selective formal [3 + 2]-annulations of γ-alkyl-β,γ-unsaturated γ-lactams with α,β-unsaturated aldehydes have been developed. These organocatalysed transformations yield high value enantioenriched bicyclic γ-lactams with up to four new stereocenters (sometimes including a quarternary carbon). The overall transformation starts from simple and readily accessible furans and overviews a rapid, controlled, and dramatic enhancement in 3D complexity.

Organocatalysis is a rapidly advancing area yielding many asymmetric transformations useful in synthetic chemistry. It is particularly powerful when combined with tandem reactions because complex enantioenriched polycyclic frameworks can be accessed very rapidly from simple precursors. The most important challenge for such annulations is achieving high degrees of stereoselectivity during the formation of multiple stereogenic centers, especially quaternary carbons. Successful implementation of these dual focus strategies—addressing both chirality and complexity—can provide very easy and effective access to key targets as we exemplify here.

Chiral γ-lactams represent a ubiquitous heterocyclic motif which appears in a wide range of important compounds. From asymmetric approaches to their synthesis, the stereoselective transformation of N-protected α,β-unsaturated-γ-lactams is considered to be the most attractive since it is atom economic (especially, compared to the corresponding 2-silyloxypyrroles) and offers opportunities for the regiocontrolled functionalization of each carbon of the γ-lactam backbone. However, there is limited substrate flexibility for the lactam precursors. For instance, the γ-alkyl-substituted and the N-protected counterparts have never been utilized. Herein, we introduce a regio-, diastereo-, and enantioselective functionalization of γ-alkyl-β,γ-unsaturated γ-lactams utilizing α,β-unsaturated aldehydes as electrophiles and catalytic diphenyliodonium silyl ether (cat. I, Scheme 1), as a highly effective means for accessing these privileged intermediates.

β,γ-Unsaturated γ-lactams of type 2 or 3 (Scheme 1) were easily prepared by a protocol beginning with the photooxygenation (singlet oxygen) of simple furans of type 1. We envisioned that the resultant lactams might serve as versatile reaction partners via controlled reaction at any one of their multiple nucleophilic positions. It was hoped that they might be partnered with dielectrophilic α,β-unsaturated aldehydes activated through iminium ion catalysis. To the best of our knowledge, there is no precedent for these formal [3 + 2] annulations introduced in Scheme 1.

To initiate the investigation, we synthesized 2-pyrrolidinone 2a using the singlet oxygen mediated transformation of furan 1a (Scheme 2, 1 → 2). Purified 2a was then subjected to various conditions using LUMO-lowering catalysts I−III (cat. I−III) and cinnamaldehyde (4a). Strikingly, cat. I promoted the formation of bicyclic lactam 5aa, bearing three newly formed stereocenters, via vinylogous Michael addition followed by hemiaminalization (Scheme 2). We found that the optimal conditions were conditions A (15 mol % of cat. I at 0 °C to rt, 18 h) in DCE using 1.5 equiv of 4a (90% de, 98% ee, 68% yield for the major diastereoisomer). At room temperature, the same reaction (10% of cat. I in DCM, DCE or toluene) was completed within 12 h albeit with lower de values (see, conditions B and C). Among the other conditions that were tested, cat. II and III (conditions D) proved ineffective, and other solvents such as MeOH, CH₃CN, or CH₃CN/H₂O (conditions E−G) had reactivity or stereoselectivity issues. Furthermore, the presence of benzoic acid

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Scheme 1. Selective Formal [3 + 2]-Annulations of β,γ-Unsaturated γ-Lactams

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Scheme 2. Asymmetric [3 + 2]-Annulations of β,γ-Unsaturated γ-Lactams 2 with α,β-Unsaturated Aldehydes 4

(conditions H) significantly diminished the diastereoselectivity. This result, as well as the outcome of the reactions undertaken in MeOH and CH3CN/H2O, played a substantive role in the mechanistic rationale that is presented. We propose that the stereoselectivity results from an ion-pair transition state (TS1-endo, TS2-exo) that forces the Si face of the γ-lactam to react from the Si face of the iminium ion in the first stage of the transformation (2 + 4 → 5i, Scheme 2). This transition state could easily be disrupted by the presence of an acid or a protic solvent. The aldehyde group in 5ii is subsequently trapped from the Si face to form hemiaminal 5(H-bond directed cyclization). Intermediate 5ii can also be reduced to the corresponding alcohol of type 7. The formation of an enantioenriched quaternary center at the γ-position of the lactams is highly desirable for the synthesis of alkaloids bearing α-tertiary amines.17 Furthermore, compounds of type 5 constitute key building blocks for the common pyrrolizidine alkaloids.18

To explore the scope of the reaction, different α,β-un saturated aldehydes 4 and 2-pyrrrolidinones 2 were tested under conditions A (Scheme 2). In most cases, the reactions proceeded with excellent diastereo- and enantioselectivity and with good isolated yields for the major diastereoisomer. Among the aldehydes that were used, 4d proved to be less reactive under conditions A, since its reaction with 2a did not reach completion after 18 h (conv 60%, 30% yield). However, when the same substrates were subjected to conditions B (in DCE) consumption of 2a within 12 h affording 5ad was observed (Scheme 2). An adjustment in the conditions was also needed for the alkyl chain-bearing aldehyde 4e (2.5 equiv of 4e, 20% cat. I, 0 °C to rt) to achieve complete consumption of the starting 2-pyrrolidinones 2a and 2c within 48 h [see the Supporting Information (SI)]. The resulting compounds, 5ae and 5ce, were delivered with excellent diastereo- and enantioselectivity albeit in slightly lower yields. For many of the aforementioned cases, the reaction was terminated at the final stage of the process by adding NaBH4 leading to enantiopure compounds 7 (Scheme 2). The de of 7 remains unchanged when compared with the precursor compounds 5, meaning that the hemiaminal stereocenter is not responsible for the observed diastereoselectivity.

An interesting observation emerged via the reaction of 2-pyrrrolidinone 2d with aldehyde 4a. Even though the [3 + 2]-annulation proceeded as expected and the crude NMR spectrum revealed the formation of product 5da with 88% de, this de value was significantly reduced to 66% during the chromatographic purification of the product.19 Similar de values were measured after reduction of 5da with NaBH4 (for product 7da: 88% de when 5da was not isolated and 66% de when starting from purified 5da). This result is a consequence of the reversibility of the reaction under chromatography conditions. For further exa-
nation of the reaction, the minor stereoisomer 5d′a was synthesized and characterized. Specifically, the reaction of 2d with 4a under conditions E or H favored this diastereomer, while conditions H at 50 °C significantly shifted the de toward to 5d′a (60% de, Scheme 2). In addition, isomerization (5d′a → 5d′a′) was observed when purified 5d′a was subjected to the same conditions. These observations not only support the contention that the reaction is reversible but also lend credence to the mechanistic proposal, meaning that any factor that intervenes at the TS1 (e.g., protic solvent or PhCO2H) leads to diminished de values.

The relative configuration of compounds of type 5, and consequently, for compounds 7, was determined via NOE studies for representative compounds of type 5. The absolute configuration of the major diastereoisomer was determined via the derivatization of compound 5cb into the corresponding (R)- and (S)-MTPA esters (Mosher ester analysis).20 Our efforts turned next to examining the influence of the N-substituent of the starting lactam. N-Benzyl-2-pyrrolidinone 3a was synthesized using the singlet oxygen based protocol21,22 and, subsequently, treated with 1.5 equiv of cinnamaldehyde (4a) and 10% of cat. I in DCE (conditions I, Scheme 3). No reaction was observed after 24 h at rt. To our delight, however, addition of benzoic acid (10 mol %) dramatically shifted the reaction toward 6aa (60% de, Scheme 2). In addition, isomerization (5da → 5da′) was observed when purified 5da was subjected to the same conditions. These observations not only support the contention that the reaction is reversible but also lend credence to the mechanistic proposal, meaning that any factor that intervenes at the TS1 (e.g., protic solvent or PhCO2H) leads to diminished de values.

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group into an anti conformation, which explains the E-configured double bond in the final product. Since the vinylogous Michael addition ($2 \rightarrow Si$, Scheme 2) is reversible and the presence of the N-benzyl group is blocking the formation of lactam of type 5 ($5ii \rightarrow S$ is blocked), the reaction proceeds reversibly to intermediate 6i. Benzoic acid may be responsible for accelerating a hydrogen-bond directed cyclization ($6ii \rightarrow 6$) in which the aldehyde is attacked on its $Si$ face, thus establishing the stereochemistry of the final two stereocenters.

In summary, we have disclosed novel asymmetric formal [3 + 2]-annulations of $\gamma$-alkyl-$\beta,\gamma$-unsaturated $\gamma$-lactams (readily prepared by photooxygenation of simple furans) with $\alpha,\beta$-unsaturated aldehydes catalyzed by an organocatalyst. These site-selective cyclizations afford high value chiral bicyclic $\gamma$-lactams bearing up to four stereocenters with significant levels of diastereo- and enantioselectivity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00076.

Accession Codes

CCDC 1586973 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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