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

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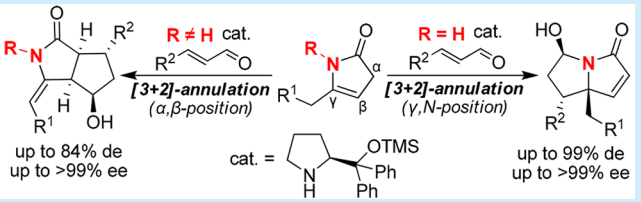
Supporting Information

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 oversees a rapid, controlled, and dramatic enhancement in 3D complexity.

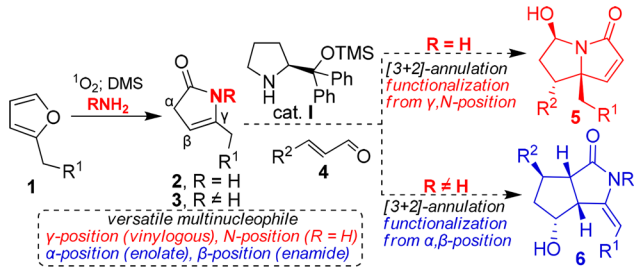


Organocatalysis is a rapidly advancing area yielding many asymmetric transformations useful in synthetic chemistry.[1] It is particularly powerful when combined with tandem reactions because complex enantioenriched polycyclic frameworks can be accessed very rapidly from simple precursors.[2] The most important challenge for such annulations[3] is achieving high degrees of stereoselectivity during the formation of multiple stereogenic centers, especially quaternary carbons.[4] 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 herein.[5]

Chiral γ-lactams[6] represent a ubiquitous heterocyclic motif which appears in a wide range of important compounds.[7] From asymmetric approaches to their synthesis,[8] 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[9]) and offers opportunities for the regiocontrolled functionalization of each carbon of the γ-lactam backbone.[10] However, there is limited substrate flexibility for the lactam precursors. For instance, the γ-alkyl-substituted and the *N*-unprotected 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 diphenylprolinol silyl ether (cat. **I**, Scheme 1),[11] as a highly effective means for accessing these privileged compounds.

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**.[12] We envisioned that the resultant lactams[13] 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.[14] To the best of our knowledge, there is no precedent for these formal [3 + 2] annulations introduced in Scheme 1.

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



To initiate the investigation, we synthesized 2-pyrrolidinone **2a** using the singlet oxygen mediated transformation of furan **1a** (Scheme 2, **1** → **2**).[12,13] 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[15] 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, CH_3CN, or CH_3CN/H_2O (conditions E–G) had reactivity or stereoselectivity issues. Furthermore, the presence of benzoic acid

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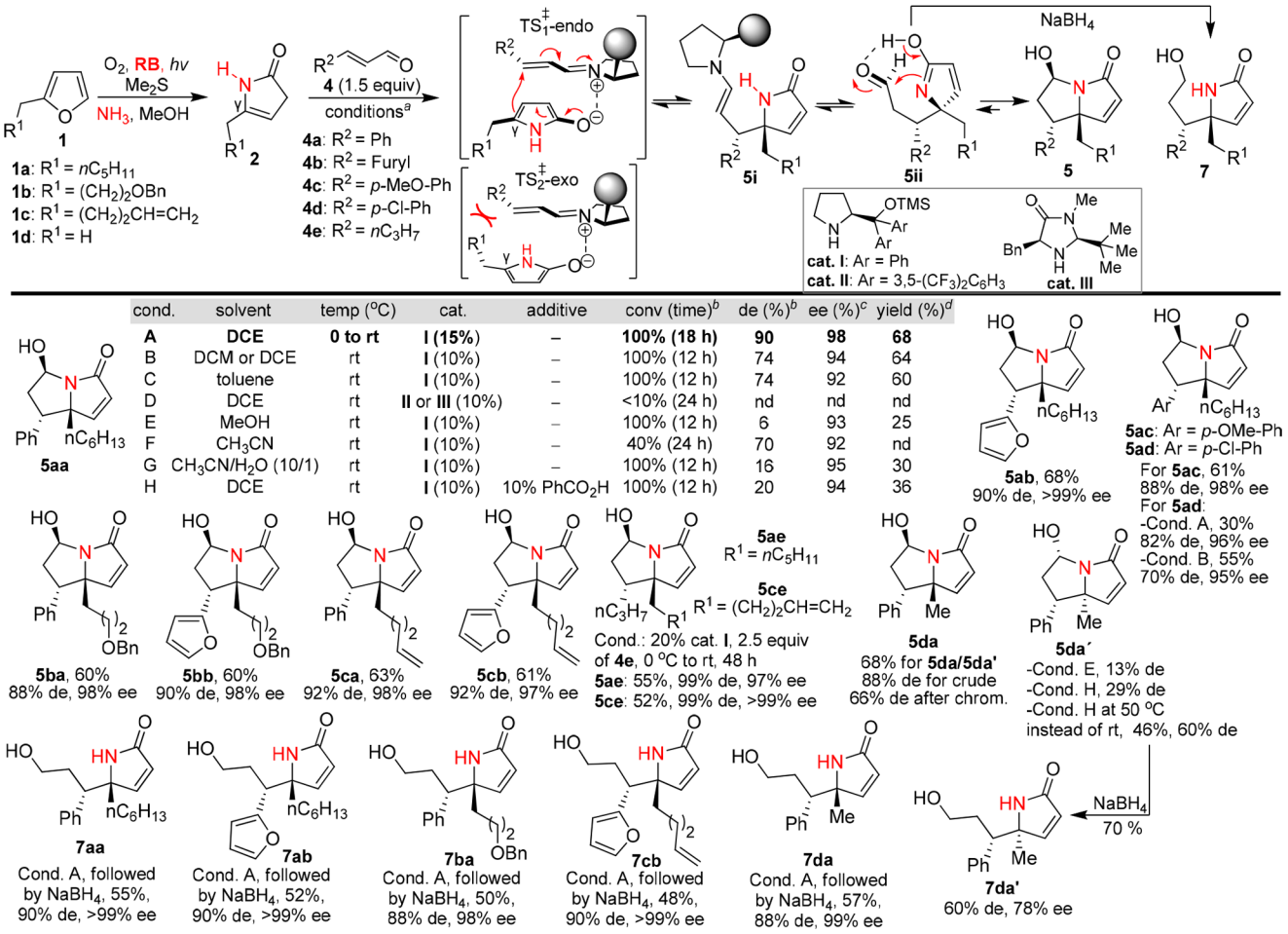
Scheme 2. Asymmetric [3 + 2]-Annulations of β,γ-Unsaturated γ-Lactams 2 with α,β-Unsaturated Aldehydes 4



	cond.	solvent	temp (°C)	cat.	additive	conv (time)[b]	de (%)[b]	ee (%)[c]	yield (%)[d]
	A	**DCE**	**0 to rt**	**I (15%)**	–	**100% (18 h)**	**90**	**98**	**68**
	B	DCM or DCE	rt	**I** (10%)	–	100% (12 h)	74	94	64
	C	toluene	rt	**I** (10%)	–	100% (12 h)	74	92	60
	D	DCE	rt	**II** or **III** (10%)	–	<10% (24 h)	nd	nd	nd
	E	MeOH	rt	**I** (10%)	–	100% (12 h)	6	93	25
	F	CH_3CN	rt	**I** (10%)	–	40% (24 h)	70	92	nd
	G	CH_3CN/H_2O (10/1)	rt	**I** (10%)	–	100% (12 h)	16	95	30
	H	DCE	rt	**I** (10%)	10% $PhCO_2H$	100% (12 h)	20	94	36

[a]All the reactions were performed using 0.2 mmol of **2**. [b]Determined by crude ^1H NMR spectrum. [c]Determined by chiral HPLC analysis of the major diastereoisomer. [d]Isolated yield for major diastereoisomer.

(conditions H) significantly diminished the diastereoselectivity. This result, as well as the outcome of the reactions undertaken in MeOH and CH_3CN/H_2O, played a substantive role in the mechanistic rationale that is presented. We propose that the stereoselectivity results from an ion-pair transition state (TS_1-*endo*, TS_2-*exo* is disfavored due to the steric hindrance between the $-CH_2R^1$ and $-R^2$ groups) 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).[16] 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-unsaturated aldehydes **4** and 2-pyrrolidinones **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 $NaBH_4$ 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-pyrrolidinone **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 $NaBH_4$ (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 exami-

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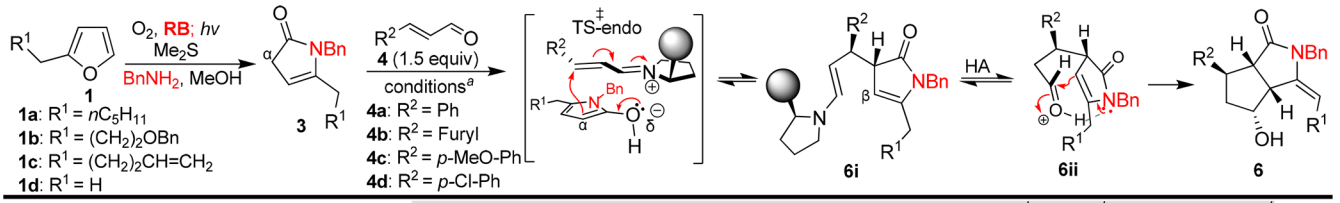
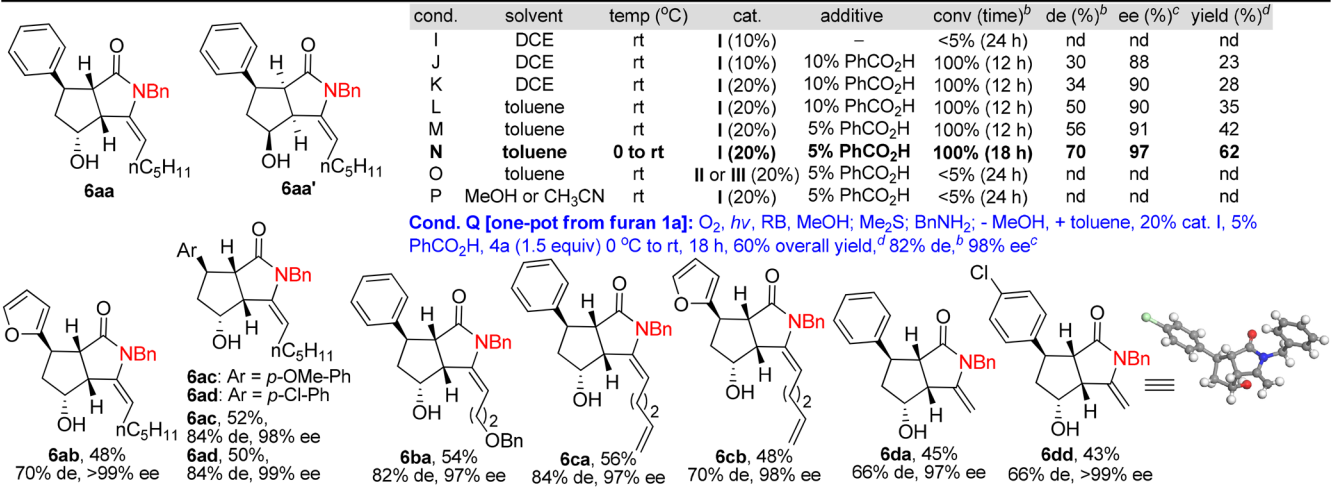
Scheme 3. Asymmetric [3 + 2]-Annulations of β,γ-Unsuturated γ-Lactams 3 with α,β-Unsaturated Aldehydes 4



cond.	solvent	temp (°C)	cat.	additive	conv (time)[b]	de (%)[b]	ee (%)[c]	yield (%)[d]
I	DCE	rt	**I** (10%)	–	<5% (24 h)	nd	nd	nd
J	DCE	rt	**I** (10%)	10% $PhCO_2H$	100% (12 h)	30	88	23
K	DCE	rt	**I** (20%)	10% $PhCO_2H$	100% (12 h)	34	90	28
L	toluene	rt	**I** (20%)	10% $PhCO_2H$	100% (12 h)	50	90	35
M	toluene	rt	**I** (20%)	5% $PhCO_2H$	100% (12 h)	56	91	42
N	**toluene**	**0 to rt**	**I (20%)**	**5% $PhCO_2H$**	**100% (18 h)**	**70**	**97**	**62**
O	toluene	rt	**II** or **III** (20%)	5% $PhCO_2H$	<5% (24 h)	nd	nd	nd
P	MeOH or CH_3CN	rt	**I** (20%)	5% $PhCO_2H$	<5% (24 h)	nd	nd	nd

Cond. Q [one-pot from furan 1a]: O_2, *hv*, RB, MeOH; Me_2S; $BnNH_2$; - MeOH, + toluene, 20% cat. I, 5% $PhCO_2H$, 4a (1.5 equiv) 0 °C to rt, 18 h, 60% overall yield,[d] 82% de,[b] 98% ee[c]



[a]All of the reactions were performed using 0.2 mmol of **3** or **1** (in case of cond Q). [b]Determined by the crude ^{1}H NMR spectrum. [c]Determined by chiral HPLC analysis of the major diastereoisomer. [d]Isolated yield for the major diastereoisomer.

nation of the reaction, the minor stereoisomer **5da′** 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 **5da′** (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 TS_1 (e.g., protic solvent or $PhCO_2H$) 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 protocol[12,13] 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 compound **6aa** bearing four newly formed stereogenic centers and an *E*-configured double bond (conditions J, 30% de, 88% ee, the minor diastereoisomer was **6aa′**). In this case, the product was derived by a Michael addition of lactam **3a** from its α-position to the LUMO-activated aldehyde **4a** (**3** + **4** → **6i**) followed by the trapping of the aldehyde group by the enamide double bond (**6ii** → **6**, Scheme 3). Bicycles of type **6** also constitute building block for naturally occurring alkaloids.[21] Various conditions were tested in order to optimize this second annulation process. Toluene was found to be a better solvent for the reaction (on going from conditions K to L, the de increased). In addition, decreasing the amount of $PhCO_2H$ from 10% (conditions L) to just 5% (conditions M) further increased the de value. Reduction of the temperature led to improvements in the yield, diastereoselectivity, and enantioselectivity (conditions N, 62%, 70% de and 97% ee). Other catalysts or solvents did not effectively promote the reaction (conditions O and P). Most interestingly, when the reaction was performed as a one-pot process from furan **1a** (without purification of **3a**), the final product **6aa** was obtained in good overall isolated yield (60% for the major diastereoisomer) and with very good stereoselectivities (conditions Q, 82% de and 98% ee).[22] After the optimized conditions were established (conditions Q), various furan substrates and aldehydes were tested for the preparation of different enantiopure bicycles of type **6**. The results are reported in Scheme 3. The overall isolated yields are very good considering that five contiguous reactions are included in this one-pot process.

The relative configuration as well as the geometrical configuration of the compounds of type **6** was elucidated via NOE studies of some representative compounds.[20] The absolute configuration was determined via the derivatization of compounds **6aa** and **6aa′** into the corresponding (*R*)- and (*S*)-MTPA esters[20] and was unambiguously confirmed via single-crystal X-ray analysis of product **6dd**.

We propose that this reaction proceeds through an ion−dipole transition state (TS-*endo*, Scheme 3) that defines the diastereo- and enantioselectivities (the *Si* face of the 2-pyrrolidinone reacts with the *Si* face of the iminium ion). This type of interaction is weaker compared to the ion-pair transition state proposed for the synthesis of bicycles **5** (Scheme 2), thus explaining the small reduction in the de values (up to 84% compared with up to 99% for **5**). It is notable that the TS-*endo* here differs from the TS_2-*exo* described in Scheme 2 because the nucleophile **3** is at the right position for α-attack and, thus, avoids the unfavorable R^1/R^2 interaction. Furthermore, the R^1 groups are forced by the benzyl

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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** → **5i**, Scheme 2) is reversible and the presence of the *N*-benzyl group is blocking the formation of lactam of type **5** (**5ii** → **5** is blocked), the reaction proceeds reversibly to intermediate **6i**. Benzoic acid may be responsible for accelerating a hydrogen-bond directed cyclization (**6ii** → **6**) in which the aldehyde is attacked on its *Si* face, thus establishing the stereochemisty of the final two stereocenters.

In summary, we have disclosed novel asymmetric formal [3 + 2]-annulations of γ-alkyl-β,γ-unsaturated γ-lactams (readily prepared by photooxygenation of simple furans) with α,β-unsaturated aldehydes catalyzed by an organocatalyst. These site-selective cyclizations afford high value chiral bicyclic γ-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.

Detailed experimental procedures, spectral data, and analytical data (PDF)

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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(19) This alteration in de was also observed with other products of type **5**, however, at significantly lower levels than that seen for **5da**.

(20) For assignment of the stereochemistry, see the SI.

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(22) The one-pot process was also tested for the reaction leading to compounds of type **5** (**1**→**5**); however, products were formed with poor de values and isolated yields.

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