OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

Enantioselective Synthesis of γ-Lactams by Lewis Base Catalyzed Sulfenoamidation of Alkenes

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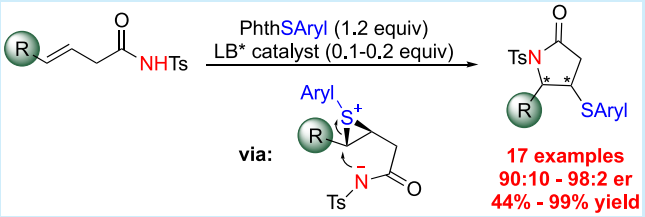
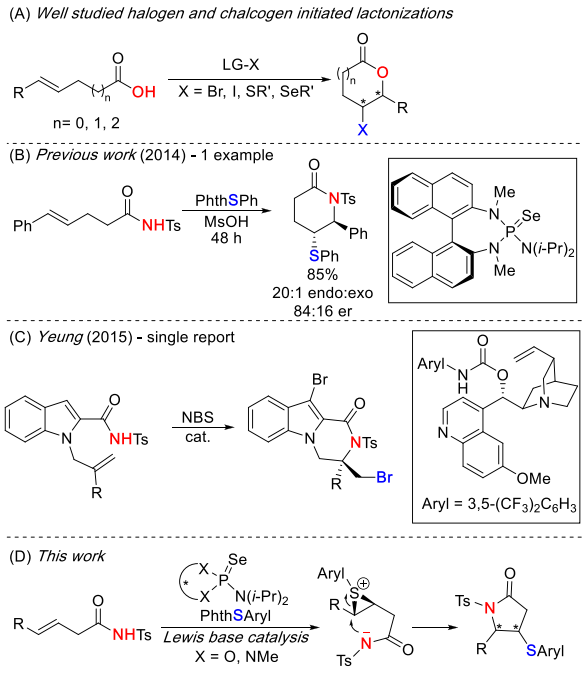
Supporting Information

ABSTRACT: A method for the catalytic, enantioselective, intramolecular 1,2-sulfenoamidation of alkenes is described. Lewis base activation of a suitable sulfur electrophile generates an enantioenriched, thiiranium ion intermediate from a β,γ-unsaturated sulfonyl carboxamide. This intermediate is subsequently intercepted by the sulfonamide nitrogen resulting in cyclization to form γ-lactams. Electron-poor alkenes required the use of a new selenophosphoramidate Lewis base catalyst. Subsequent manipulations of the products harness the latent reactivity of both the amide and thioether functionality.



Alkenes serve as important building blocks for a variety of transformations central to synthetic chemistry.[1] Over the past few decades, enantioselective alkene difunctionalization has received considerable attention as a way to form new, stereochemically defined motifs from simple and abundant starting materials.[2a−e] Whereas the use of Group 16 and 17 electrophiles to activate alkenes has been extensively studied in lactonization processes (Scheme 1A),[2c,3] analogous reports for lactamizations are rare owing to the intrinsic preference for amide nucleophiles to react through the oxygen atom.[4] Furthermore, a long-lived, configurationally stable iranium ion must be generated that allows for *N*-cyclization. In 2014, a preliminary report from these laboratories demonstrated the use of sulfonamides and carbamates as nucleophiles in the catalytic, enantioselective, intramolecular sulfenoamination of unactivated alkenes (Scheme 1B).[5,6] A single example employed an amide nucleophile to give a δ-lactam, albeit with moderate enantioselectivity and under strongly acidic conditions. In 2015, Yeung and co-workers described an enantioselective halolactamization catalyzed by a cinchona-derived carbamate (Scheme 1C).[7]

Scheme 1. Enantioselective Group 16 and 17 Initiated Cyclizations



As part of a longstanding program on the enantioselective difunctionalization of alkenes, our laboratories have developed the Lewis base activation of Group 16 Lewis acid electrophiles to generate stereodefined thiiranium ions from various classes of alkenes followed by diastereospecific capture by a wide range of oxygen, nitrogen, and carbon nucleophiles.[8,9] In 2019, this strategy was exploited for the intermolecular capture of anilines and benzyl amines using hexafluoroisopropyl alcohol (HFIP) as a mildly acidic, activating solvent.[10] With HFIP as both solvent and a weak acid source (pK_a 9.3),[11] we sought to re-examine amides as nucleophiles. The pK_a drop from sulfonamides (∼12.3)[12] to sulfonyl carboxamides (<2)[13] should enable efficient *N*-cyclization to the desired γ-lactams.

The γ-lactam ring is a privileged scaffold in medicinal chemistry.[14] In addition to expressing a range of biological activities, γ-lactams are useful synthetic intermediates possessing latent reactivity allowing for further diversification.[15] Various catalytic, enantioselective methods have been

Received: December 3, 2019

DOI: 10.1021/acs.orglett.9b04347
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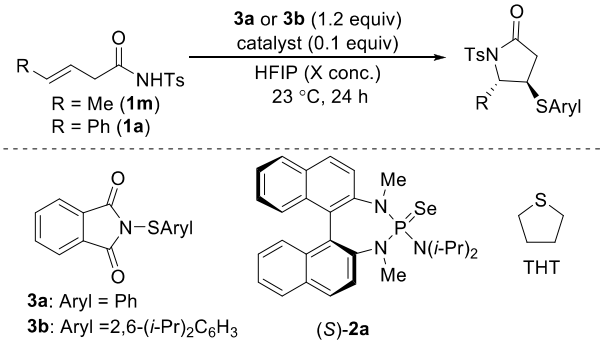
developed for the preparation of γ-lactams with NHCs[16a−d] and transition-metal catalysis.[17] Herein, we disclose a general, enantioselective construction of γ-lactams using sulfenium ion-initiated amidation, in which the reactivity of both electron-rich and electron-poor alkenes have been successfully engaged (Scheme 1D).

Initial optimization studies (Table 1) were performed with (*E*)-*N*-tosylpent-3-enamide (**1m**), sulfenylating agent **3b**, catalyst (*S*)-**2a**, or tetrahydrothiophene (THT) in HFIP as solvent. Without any Lewis base present, no reaction was observed (entry 1). The use of achiral Lewis base THT (entry 2) led to near-quantitative conversion to the desired pyrrolidinone. However, using catalyst (*S*)-**2a** afforded much lower conversion after 24 h (entry 3). To increase the reaction rate a second set of experiments were conducted with a less bulky sulfenylating agent and a more nucleophilic styryl alkene (entries 4 and 5). In both cases, the yields of the racemic and enantioenriched products were high, and an er of 84:16 was obtained. A further increase to the steric bulk of the sulfenylating agent (entry 6) did not appreciably erode the yield, and there was a marked increase in er.

Table 1. Reaction Optimization[a]

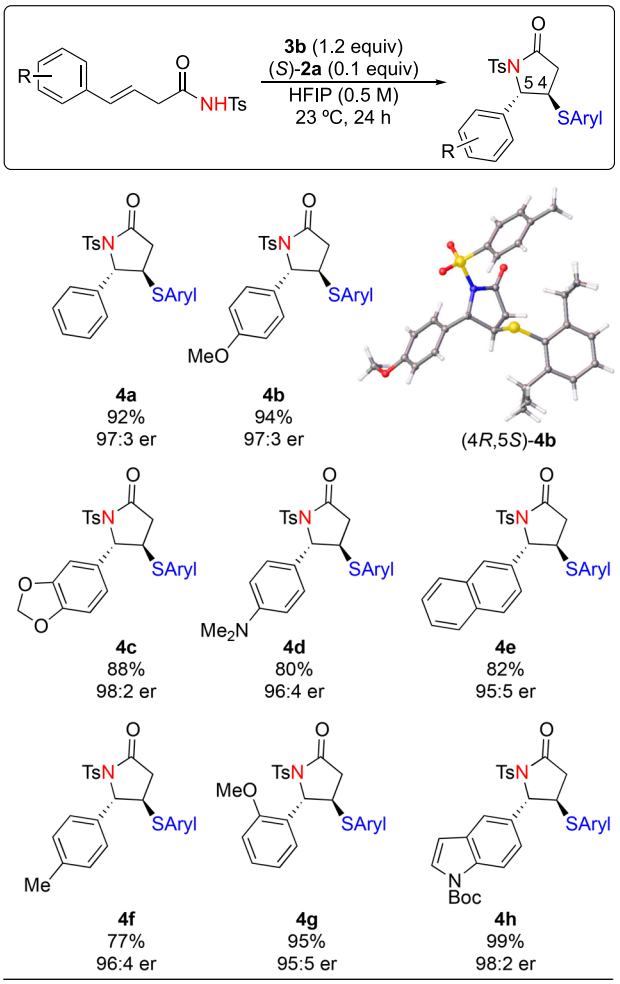


entry	1	sulfenylating agent	catalyst	concn (M)	yield[b] (%)	er[c]
1	**1m**	**3b**		0.2	0	
2	**1m**	**3b**	THT	0.2	85 (93)	
3	**1m**	**3b**	(*S*)-**2a**	0.2	(12)	ND
4	**1a**	**3a**	THT	0.5	85 (88)	
5	**1a**	**3a**	(*S*)-**2a**	0.5	83 (83)	84:16
6	**1a**	**3b**	(*S*)-**2a**	0.5	76 (85)	98:2

[a]Reactions performed on 0.1 mmol scale. [b]Yield in parentheses determined by ^{1}H NMR spectroscopic analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by CSP-HPLC analysis.

Although yet fully optimized, the scope of the sulfeno-lactamization with styryl-derived alkenes was explored using catalyst (*S*)-**2a** along with sulfenylating agent **3b** (Table 2). Electron-rich styryl alkenes proved to be competent reaction partners to generate highly enantioenriched γ-lactams. The parent β,γ-unsaturated sulfonamide **1a** gave product **4a** in 92% yield and 97:3 er. Furthermore, electron-rich aryl groups (**4b**−**4d**) led to similarly good yields and high enantioselectivities. The (4*R*,5*S*)-configuration for the major enantiomer of **4b** was established by single-crystal X-ray analysis, which is in agreement with the stereochemical model from previous studies.[8g] 2-Naphthyl and 4-tolylsulfonamide **1e** and **1f** afforded cyclized pyrrolidinones **4e** and **4f** in slightly reduced yields but maintained high enantioselectivity.

Table 2. Sulfenoamidation of Electron-Rich Styrenes[a−c]



[a]All reactions performed on a 1.00 mmol scale. [b]Yield of isolated analytically pure product. [c]Enantiomeric ratio determined by CSP-HPLC analysis.

Substitution at the *ortho*-position on the styryl arene with an electron-rich group (**4g**) was efficiently accommodated, and indole sulfonamide **1h** was compatible under the reaction conditions to afford lactam **4h** in nearly quantitative yield and 98:2 er.

As was observed with aliphatic substrate **1m**, electron-deficient alkenes were much less reactive leading to low yields even after extended reaction times. To address this problem, two potential solutions were considered: (1) decrease the electron density on the sulfenylating agent to facilitate sulfenyl group transfer to the alkene, and (2) modify the catalyst itself to enhance reactivity of the sulfenium group. On the basis of previous studies, it was found that electronic perturbations of sulfenylating agents had little impact on the rate of sulfenium ion transfer.[8g] Instead, a catalyst modification was envisioned such that a *decrease* in Lewis basicity was postulated to increase the rate of the sulfenium ion transfer. The justification for this counterintuitive hypothesis was that the attenuated Lewis basicity would increase the electrophilicity of the sulfenium ion so long as it retained sufficient Lewis basicity to form the catalytically active intermediate. To test this hypothesis, the simplest modification was to change from a BINAM-derived catalyst

DOI: 10.1021/acs.orglett.9b04347
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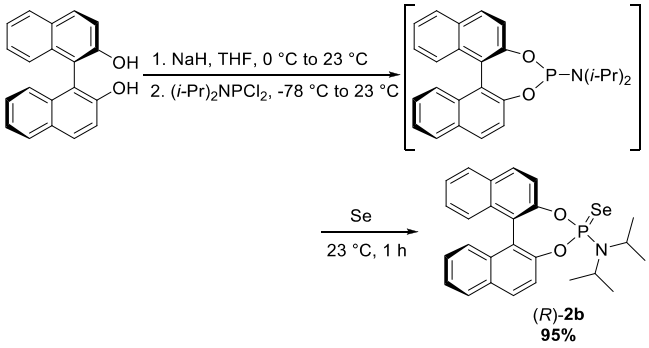
to one derived from BINOL.[18] The synthesis began with enantioenriched (*R*)-BINOL which was deprotonated with NaH and then treated with diisopropylaminochlorophosphine to generate the P(III) intermediate and then was immediately oxidized with elemental selenium to form (*R*)-**2b** (Scheme 2). The preparation of this new Lewis base catalyst proved advantageous in several ways: the starting material is readily available, milder conditions are required for deprotonation, and the catalyst itself could be obtained in nearly quantitative yield after a simple filtration.

Scheme 2. Synthesis of BINOL-Derived Lewis Base Catalyst (*R*)-2b

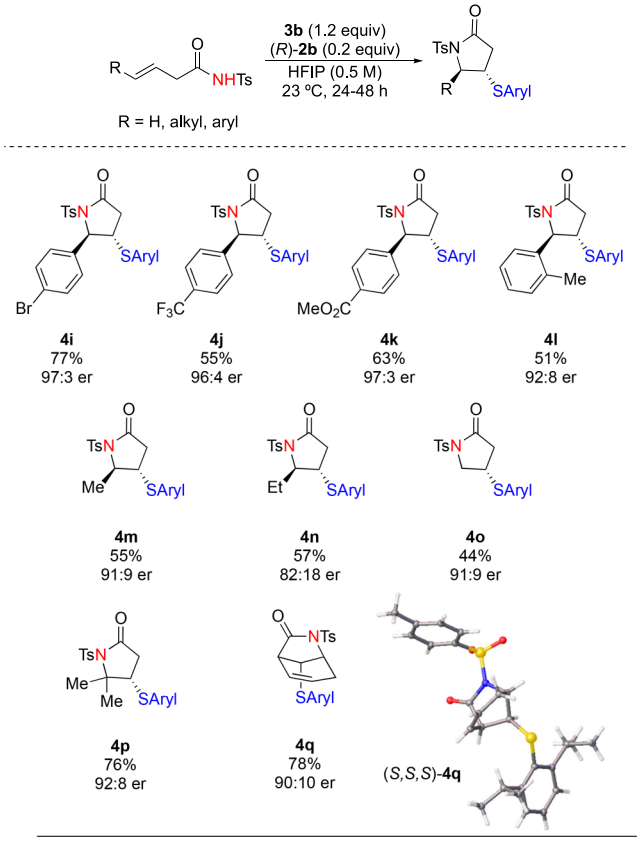


To test the viability of Lewis base (*R*)-**2b**, a comparison experiment was performed in which sulfonamide **1b** and (*R*)-**2b** were combined to determine if (*R*)-**2b** would function with a competent substrate. The BINOL-derived catalyst delivered (4*S*,5*R*)-**4b**[19] in 93% yield and 97:3 er, demonstrating that the two catalysts behave similarly with this substrate. Next, electron-deficient alkenes **1i**, **1j**, and **1k** were subjected to the standard reaction conditions with (*R*)-**2b** and afforded the corresponding cyclized products (**4i**, **4j**, **4k**) in synthetically acceptable yields and excellent enantioselectivities (Table 3). The presence of an *ortho* substituent on the styryl group resulted in the reduced yield and enantioselectivity (**4l**). If a second *o*-methyl group was incorporated, the reaction failed.

Next, catalyst (*R*)-**2b** was evaluated with the previously refractory substrates (*E*)-alkenes bearing alkyl substituents. Sulfenoamidation of alkenes **1m** and **1n** still proved sluggish but nevertheless afforded products **4m** and **4n** in 55% and 57% yields, respectively, with a moderate drop in er for **4n**. 3-Butenamide substrate **1o** also exhibited a further drop in yield but maintained a 91:9 er. Prenyl sulfonamide **1p** performed better than its other alkyl counterparts in both yield and enantioselectivity, matching that of aryl substrates. Finally, the cyclic skipped diene **1q** was afforded the desymmetrized product **4q** in 78% yield and 90:10 er. The respectable enantioselectivity observed for this substrate was unexpected in view of the generally poor selectivity seen previously with (*Z*)-alkenes.[8g] Furthermore, given that the opening of thiiranium ions is diastereospecifically *anti*, this result demonstrates that (*R*)-**2b** is capable of enantiotopic group differentiation.[20]

To illustrate the utility of these products, synthetic manipulations of enantioenriched γ-lactam **4a** were explored (Scheme 3) following recrystallization to ≥99:1 enantiopurity. Detosylation was carried out with magnesium in methanol in 85% yield to unveil deprotected lactam **5**. A

Table 3. Sulfenoamidation of Electron-Deficient Styrenes and Alkenes[a–c]



[a]All reactions performed on a 1.00 mmol scale. [b]Yield of isolated analytically pure product. [c]Enantiomeric ratio determined by CSP-HPLC analysis.

one-pot procedure to generate a mixture of sulfoxides followed by spontaneous elimination upon addition of aqueous $Na_2S_2O_3$ proceeded to form the unsaturated lactam **6**. Deoxygenation of **4a** proceeded smoothly with $BH_3{\cdot}SMe_2$ to give enantiomerically enriched 2,3-disubstituted pyrrolidine **7** in 95% yield. Treatment with $LiAlH_4$ resulted in formation of ring-opened amino alcohol **8** in excellent yield. Conversely, using DIBAL as a weaker reductant yielded a mixture of diastereomeric hemiaminal products which epimerized on silica gel to diastereomerically enriched intermediate **9** in 94% yield. The hemiaminal could undergo further transformations such as stereoselective cyanation with TMSCN in 96% yield (**10**) and allylation with allyltrimethylsilane in 65% yield (**11**) albeit in reduced yield owing to competitive formation of a pyrrole side product. Lastly, treatment with TFAA and lutidine allowed for the facile conversion of lactam **4a** to highly enantioenriched 4,5-disubstituted-2-pyrroline **12** in 98% yield.

In summary, an enantioselective Lewis base catalyzed sulfenolactamization of β,γ-unsaturated sulfonyl carboxamides has been described. The reaction proceeds under mild conditions through formation of an enantiomerically enriched thiiranium ion followed by a diastereospecific capture with nitrogen to afford highly functionalized γ-lactams. The development of a new Lewis base catalyst has allowed for an expanded substrate scope of less nucleophilic alkenes. Moreover, the lactam products have been shown to undergo

DOI: 10.1021/acs.orglett.9b04347
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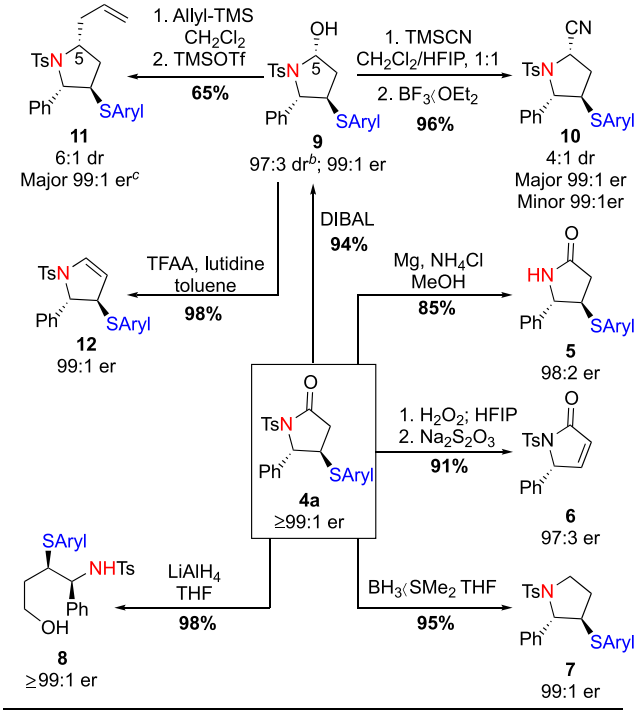
a variety of manipulations harnessing both the amide and thioether functionality to reach valuable synthetic targets.

Scheme 3. Product Manipulations[a]



[a]All reactions performed on 1.00 mmol scale. Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Enantiomeric ratio determined by CSP-HPLC analysis. [b]Product epimerized at C(5) upon silica gel chromatography. [c]Product epimerized at C(5) upon CSP-HPLC analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04347.

Experimental Procedures, characterization data for all new compounds along with copies of spectra and chromatograms (PDF)

Accession Codes

CCDC 1952721−1952722 contain 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.

■ ACKNOWLEDGMENTS

We are grateful to the National Institutes of Health (GM R35 127010) for generous financial support. We also thank the UIUC SCS support facilities (microanalysis, mass spectrometry, X-ray, and NMR spectroscopy) for their assistance.

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