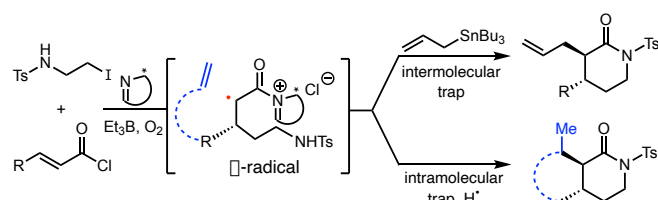


Radical Reactions with Chiral Acylammonium Salts: Synthesis of Functionalized δ -Lactams Through Giese-Initiated Organocascades

Patrick J. Sutter^[a], Ben Walker^[a], Kristiana Kasper^[a], Volga Kojasoy^[b], Dean Tantillo^{*[b]}, and Daniel Romo^{*[a]}

[a] Dr. Daniel Romo, Dr. Patrick J. Sutter, Kristiana Kasper, Ben Walker
Department of Chemistry & Biochemistry
Baylor University
101 Bagby Ave., Waco, Texas, USA
E-mail: Daniel_Romo@baylor.edu

[b] Dr. Dean Tantillo, Dr. Volga Kojasoy
Department of Chemistry
University of California, Davis
Davis, California, USA
E-mail: djtantillo@ucdavis.edu



ABSTRACT: Enantioselective Giese reactions employing chiral α,β -unsaturated acylammonium salts and subsequent diastereoselective trapping followed by lactamization delivers optically active δ -lactams. Alkyl iodides bearing tosylamides undergo radical initiation using triethylborane at low temperatures to provide carbon-centered radicals to initiate the described organocascade. Subsequent diastereoselective inter- or intramolecular trapping of the incipient α -radical lead to highly functionalized, enantioenriched mono- and bicyclic δ -lactams (up to 99:1 er, >19:1 dr) bearing up to three stereogenic centers. Interestingly, benztetramisole imparts diastereoselectivity that contradicts steric considerations alone. DFT calculations rationalized the observed enantio- and diastereoselectivities, revealed an electrostatic interaction between the sulfone oxygens and the ammonium cation in the initial α -radical intermediate, and aided application of this methodology to bicyclic δ -lactams through intramolecular trapping of the α -radical intermediate.

Introduction. The utility of chiral, tertiary amine Lewis bases to activate both saturated and unsaturated carbonyl moieties via acylammonium salt catalysis continues to expand, most recently including their use in dual catalysis systems.¹ In particular, the first use of chiral α,β -unsaturated acylammonium salts was described by Fu in 2006² and since this initial report, several organocatalytic cascades have been developed for the synthesis of enol lactones,³ benzothiazepines,⁴ thiocromenes,⁵ and bicyclic β -lactones⁶ by the groups of Smith, Matsubara, Birman, and our group. The inherent and sequential alternating reactivity of chiral α,β -unsaturated acylammonium salts has thus enabled the development of varied organocascade reactions premised on this reactivity.

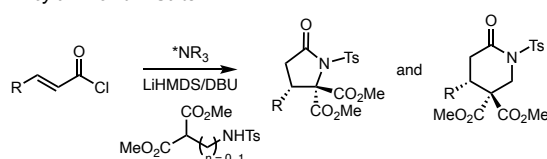
In all aforementioned methods, the organocascade process is initiated by anionic nucleophiles derived from malonate and other relatively acidic pronucleophiles including the nucleophile catalyzed Michael/proton-transfer/lactamization⁷ (NCMPL), which allows access to γ - and δ -lactams (Scheme 1a). We considered Giese additions to unsaturated acylammonium salts since, unlike anionic additions, the use of radical intermediates

would enable ‘traceless’ nucleophilic donors devoid of anionic stabilizing groups (*e.g.* diesters). While our work was in progress, the groups of Melchiorre⁸ and Smith⁹ independently reported a cooperative Lewis base/photoredox catalysis strategy employing radical additions to acylammonium salts to access optically active β -substituted, γ -lactams (Scheme 1b). The polar cross-over mechanism allows for generation of carbon radicals by photoredox catalysis, however, reduction of the subsequent α -radical to the corresponding enolate is rapid due to the high reduction potential of the reduced photocatalyst. Toward fully exploiting the potential of unsaturated acylammonium salts for radical organocascade processes through capture of the incipient α -radical in this reaction, we took inspiration from previous studies of Sibi¹⁰ who reported enantioselective tandem radical reactions using chemical radical initiators such as AIBN and triethylborane, enabling subsequent trapping of the α -radical intermediates.¹¹ Sibi also reported the use of iodoethanol as a radical precursor enabling a Giese addition-lactonization cascade.¹² However, to our knowledge a radical organocascade strategy has not been used to construct optically active lactams

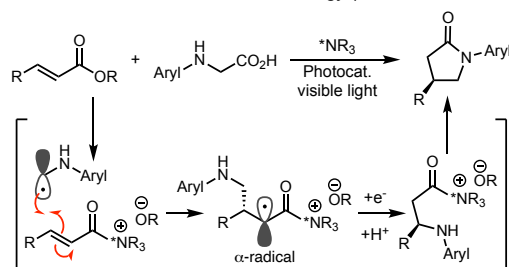
bearing multiple stereogenic centers. Herein, we describe the synthesis of optically active α,β -disubstituted δ -lactams via an organocascade process initiated by a Giese-type addition to chiral acylammonium salts. Subsequent inter- or intramolecular α -radical trapping and lactamization generates up to three stereogenic centers in a single step delivering both mono- and bicyclic δ -lactams. Furthermore, DFT calculations of this radical process provide a rationale for the enantio- and diastereoselectivity observed in this process and aided our use of substrates bearing intramolecular radical traps for the preparation of bicyclic δ -lactams.

Scheme 1. Enantioselective Radical Additions to Unsaturated Acylammonium Salts

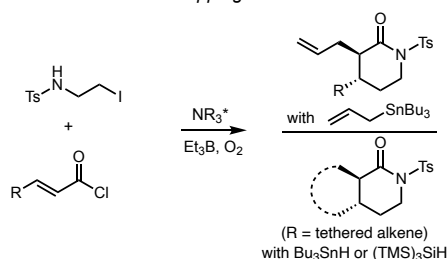
a) Our Previous Anionic Strategy to Lactams Employing Chiral Acylammonium Salts



b) Recent Radical-Polar Crossover Strategy (Smith and Melchiorre)



c) This Work: Chemically-Initiated Giese Addition/Inter- and Intramolecular α -Radical Trapping/Lactamization

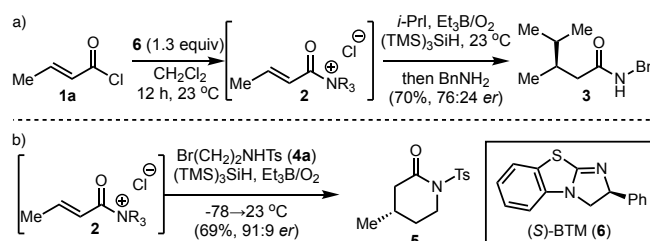


Results and Discussion. Toward the goal of developing a radical chain process that would enable trapping of the incipient α -radical, we initiated our studies using a chemical radical initiator. At the outset, we reasoned that the mild conditions and wide temperature range afforded by use of $\text{Et}_3\text{B}/\text{O}_2$ ¹⁰⁻¹¹ would be the most compatible with unsaturated acylammonium salts. In preliminary studies, we probed the compatibility of unsaturated acylammonium salts under these radical initiation conditions, and briefly surveyed a few chiral amine catalysts (see SI for full details of optimization, Table S1, p. S3). Initially, to avoid a possible achiral background Giese-addition, we employed 1.3 equiv of the chiral Lewis base and pre-formed the unsaturated acylammonium salt **2**. Use of isopropyl iodide as a radical precursor, crotonoyl chloride **1a**, $(\text{TMS})_3\text{SiH}$ to capture the incipient α -radical, and benzylamine to capture the acylammonium salt intermediate, indeed delivered the expected Giese-type adduct **3** in 70% yield (76:24 er, Scheme 2). This demonstrated that unsaturated acylammonium salts were functional Giese-type acceptors, and that benztetramisole

(BTM) **6** imparted the greatest level of enantioselectivity at ambient temperature (23 °C).

We next prepared a radical precursor with a tethered amine nucleophile, namely 2-bromoethyl tosylamide **4a** (Scheme 2b). This type of substrate would enable intramolecular capture of the intermediate acylammonium salt, followed by Giese reaction and hydrogen atom transfer, to provide the targeted δ -lactam. Initial studies again utilized the pre-formed unsaturated acylammonium salt **2** generated from crotonoyl chloride and 1.3 equiv (*S*)-BTM **6** at 23 °C. Following addition of $(\text{TMS})_3\text{SiH}$, a solution of bromide **4a** was introduced, followed by Et_3B and oxygen, affording the desired lactam **5** in 65% yield. However, the lactam was formed as a racemate. Following some experimentation, we discovered that acylation of the sulfonamide by the acylammonium salt was rapid at ambient temperatures. Thus, radical addition was likely proceeding through a 6-endo trig cyclization of an intermediate achiral iodoamide (see SI, Scheme S1 for further details, p. S6).¹³ We thus studied lower temperatures that might slow *N*-acylation while still enabling the desired radical process. Indeed, performing the reaction in an identical manner but cooling the unsaturated acylammonium salt **2**/ $(\text{TMS})_3\text{SiH}$ mixture to -78 °C prior to radical generation delivered the optically active lactam **5** (69%, 91:9 er).

Scheme 2. Preliminary Studies of Giese-type Additions: Pre-formed Chiral Unsaturated Acylammonium Salts and Chemical Radical Initiation

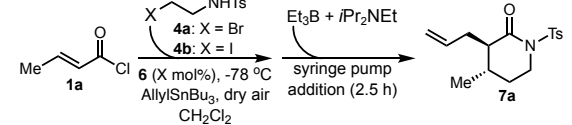


We next turned toward our ultimate goal of exploiting the incipient α -radical to generate an additional stereocenter. For this purpose, we first studied allyltributylstannane while still employing 1.3 equiv of (*S*)-BTM **6**. This indeed delivered the desired α -allylated lactam **7a** (41% yield, 23:1 dr, 99:1 er; Table 1, entry 1). We then studied the use of a stoichiometric achiral Brønsted base toward enabling catalyst turnover, and use of Hünig's base (1.3 equiv) with 50 mol% (*S*)-BTM **6** led to comparable yields and both diastereo- and enantioselectivity as with stoichiometric chiral Lewis base (entry 2). We noted considerable amounts of recovered *N*-Ts amino bromide **4a**, indicating incomplete radical generation, which led us to study the use of *N*-Ts amido iodide **4b** as the radical precursor. This delivered lactam **7a** in significantly improved yield (entry 3; 90%, 97:3 er, 15:1 dr). Further attempts to lower the catalyst loading to 40 and 30 mol% (entries 4, 5) delivered comparable yields and enantioselectivity, however the diastereoselectivity was impacted (15:1 $\rightarrow$ 8-9:1, dr). Decreasing the amount of Brønsted base to 0.9 equiv (entry 6) only led to decreases in yield with no change in diastereoselectivity dispelling concerns that the amine/ Et_3B combination was causing α -epimerization, however we have not excluded the possibility of ketene intermediates. Alternative tertiary amine bases and various

nitrogen protecting groups of the bis-nucleophile were screened, however none of these alterations led to improvements in diastereoselectivity (see SI, Figure S1 for details, p. S8). Attempts to avoid the use of tin were not met with success as use of allyl silane¹⁷ or allyl ethyl sulfone,¹⁸ typically used under thermal radical initiation conditions, did not deliver lactam **7a** but instead led to complex reaction mixtures.

Extensive studies were conducted to extend this radical organocascade to the use of catalytic quantities of chiral Lewis base **6**, however only lactams **7a**, **7d**, and **7i** (Table 2) provided consistent yields of the desired product with sub-stoichiometric Lewis base (0.5 equiv). Lower loadings typically led to yields that matched the amount of Lewis base employed indicating no catalyst turnover. We suspect that competitive coordination of the boron by-products derived from Et₃B with BTM preclude turnover. The use of excess amine base, *e.g.* *i*Pr₂NEt or 2,6-lutidine, to liberate the catalyst from the boron Lewis acid species led to low reaction yields. Comparison of Lewis basicities and nucleophilicities of BTM (**6**) (*N* parameter 13.45 (20 °C) in CH₂Cl₂)^{1a} and the achiral amine bases studied (2,6-lutidine, *N* 9.87) or the steric bulk of *i*Pr₂NEt¹⁴ support this conclusion.¹⁵ Thus, we elected to maintain a higher catalyst loading (50 mol%) so as not to sacrifice diastereoselectivity while maintaining optimal yields.

Table 1. Optimization of the Enantioselective Giese Addition/ α -Radical Trapping/Lactamization Organocascade^[a]



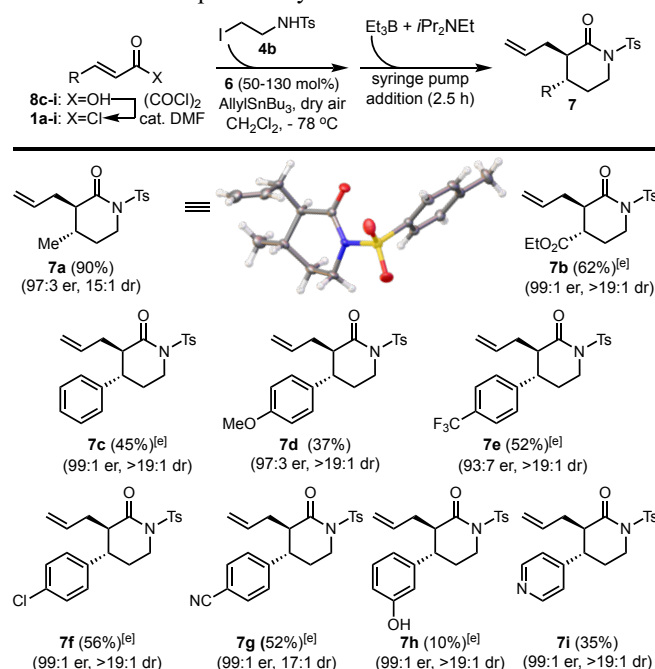
entry	cat. mol%	halide	% yield ^[b]	<i>er</i> ^[c]	<i>dr</i> ^[d]
1 ^[e]	130	4a	41	99:1	23:1
2	50	4a	42	91:9	17:1
3	50	4b	90	97:3	15:1
4	40	4b	90	94:6	9:1
5	30	4b	92	94:6	8:1
6 ^[f]	30	4b	68	95:5	9:1

[a] Reactions were generally performed with acid chloride **1a** (1.0 equiv), *N*-Ts amino halide **4a** or **4b** (1.3 equiv), allyltributylstannane (1.5 equiv), *i*Pr₂NEt (1.3 equiv), Et₃B (1.5 equiv). [b] Yields refer to isolated, purified product. [c] Determined by chiral HPLC. [d] Determined by ¹H-NMR analysis (integration of internal vinyl CH) following purification. [e] *i*Pr₂NEt was not added [f] 0.9 equiv of *i*Pr₂NEt was used.

Applying these optimized conditions developed with crotonoyl chloride **1a** to various acid chlorides led to several allylated β -substituted δ -lactams **7b-i** (Table 2). In cases where the acid chloride was either not commercially available or reasonably priced (**1c-i**), acid chloride substrates were generated immediately prior to use using oxalyl chloride and yields are thus reported for the two steps of acid chloride formation/radical organocascade based on the starting carboxylic acid. Use of commercially available ethyl fumaroyl chloride **1b** delivered the ethyl ester-substituted δ -lactam **7b** (62%, 99:1 *er*, >19:1 *dr*). Several β -aryl substituted acid chlorides including electron poor (*p*-CF₃) and electron rich (*p*-OMe) substrates participated in this organocascade leading to δ -lactams **7c-7e** albeit in moderate

yields (37-52%) however consistently with high diastereo- and enantioselectivity (93:7-99:1 *er*, >19:1 *dr*). Both *p*-Cl and *p*-CN substituted aryl substrates were tolerated delivering the desired δ -lactams **7f** (56%, 99:1 *er*, >19:1 *dr*) and **7g** (52%, 99:1 *er*, 17:1 *dr*), respectively. We also tested the tolerance of a free phenol **7h** (10%, 99:1 *er*, >19:1 *dr*) and a basic nitrogen **7i** (35%, 99:1 *er*, >19:1 *dr*) which led to greatly reduced yields but without sacrifice to diastereo- and enantioselectivity. The β -methyl substituted lactam **7a** could be recrystallized, and X-ray analysis confirmed both the relative and absolute stereochemistry (inset, Table 2). Thus, the absolute stereochemistry of all other δ -lactams **7** was assigned in analogy to lactam **7a**. Several other acid chlorides and radical precursors (see SI, Figure S3, p. S16) were explored that did not lead to the desired lactams.

Table 2. Scope of the Enantioselective Giese Addition/ α -Radical Trapping/Lactamization Organocascade^[a-d]; ellipsoid shown at the 50% probability level.



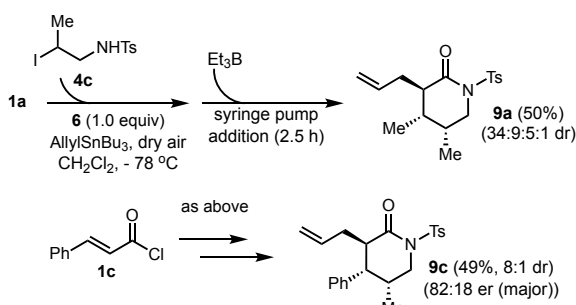
[a] Reactions were generally performed with acid chloride **1** (1.0 equiv), (*S*)-BTM (0.5-1.3 equiv), amino iodide **4b** (1.3 equiv), allyltributylstannane (1.5 equiv), *i*Pr₂NEt (1.3 equiv), and Et₃B (1.5 equiv). [b] Yields refer to isolated, purified product. [c] Determined by chiral HPLC. [d] Determined by ¹H-NMR analysis following purification. [e] These substrates required 1.0-1.3 equiv of BTM **6** for consistent yields and *i*Pr₂NEt was unnecessary in these cases.

The facial selectivity of the initial Giese addition, as evidenced by the X-ray crystal structure of lactam **7a**, is consistent with Michael-type additions to isothiourea-derived unsaturated, acylammonium salts reported to date.^{3, 16} However, to a gain a better understanding of the observed facial selectivity for the allylation step and rationalize some observed trends in acid chlorides that did not successfully deliver δ -lactams, both experimental and computational studies were undertaken. In particular, we observed that several α -substituted, β,β -disubstituted, and cyclic unsaturated acid chlorides did not deliver δ -lactams (see SI, Figure S2, p. S16). We reasoned that this may be due to a slow α -allylation following the initial Giese reaction since similar radical additions to both α,β -

disubstituted¹⁷ and α,β,β' -trisubstituted¹⁸ carbonyl compounds are well-established, albeit in an intramolecular fashion.

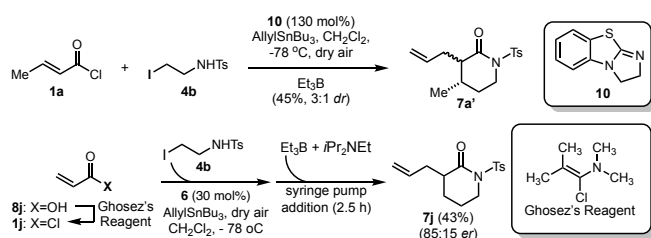
We also studied a secondary iodide **4c** which would lead to an additional stereocenter proceeding through an achiral secondary radical (Scheme 3). With crotonyl chloride **1a**, the β,γ -selectivity of **9a** was modest leading to a mixture of all four possible diastereomers (34:9:5:1). Greater β,γ -diastereoselectivity was obtained with cinnamic acid chloride **1c**, and in this case only two diastereomers were generated (8:1 dr), however the enantioselectivity was modest for the major diastereomer of lactam **9c** (82:18 er).

Scheme 3. Giese Addition/ α -Radical Trapping/Lactamization with a secondary iodide **4c**.



To differentiate factors likely impacting the diastereoselectivity of the α -allylation step, control experiments were designed to reveal the respective contributions of the substrate and the Lewis base (Scheme 4). β -Methyl lactam **7a'** was prepared using the achiral BTM analog **10** (1.3 equiv), devoid of the phenyl ring that is responsible for the facial selectivity of the initial Giese reaction in the optically active series. In this case, the diastereoselectivity is dramatically decreased providing lactam **7a'** as a 3:1 diastereomeric mixture (vs 15:1 dr for lactam **7a**) suggesting that the Lewis base, BTM (**6**), is indeed impacting the diastereoselectivity of allylation. We next studied acryloyl chloride (**1j**) which lacks a β -substituent but in this case employing (*S*)-BTM. This gave allyl δ -lactam **7j** in 43% yield and slightly lower enantioselectivity (85:15 er) relative to β -methyl acrylate (97:3 er). These results suggest that the phenyl ring of BTM (**6**) plays a major role in guiding the diastereoselectivity of the allylation step working in concert with the β -substituent of the intermediate α -radical **II** (see Fig. 1). However, the β -substituent has a lesser impact on facial selectivity.

Scheme 4. Control Experiments to Study Diastereoselectivity of the Allylation Step



A rationale for facial selectivity during the initial Giese addition based on computational studies was reported by Melchiorre.¹⁵ They proposed shield of the α -face of the unsaturated acylammonium salt by the C-H bonds of the BTM arene moiety in line with rationales invoked for additions of ionic species to these substrates. Toward providing a rationale for the observed diastereoselectivity during capture of the incipient α -radical, we employed density functional theory (DFT) at the UPBE0-D3/def2-SVP¹⁹ level of theory to rationalize this diastereoselectivity. To test the robustness of our method, we conducted benchmark studies with other functionals and basis sets (see SI, Table S2-S4, p. S24). In our computations, allyltrimethylstannane was selected as the model allylating reagent for capture of the incipient α -radical **II** (Figure 1).

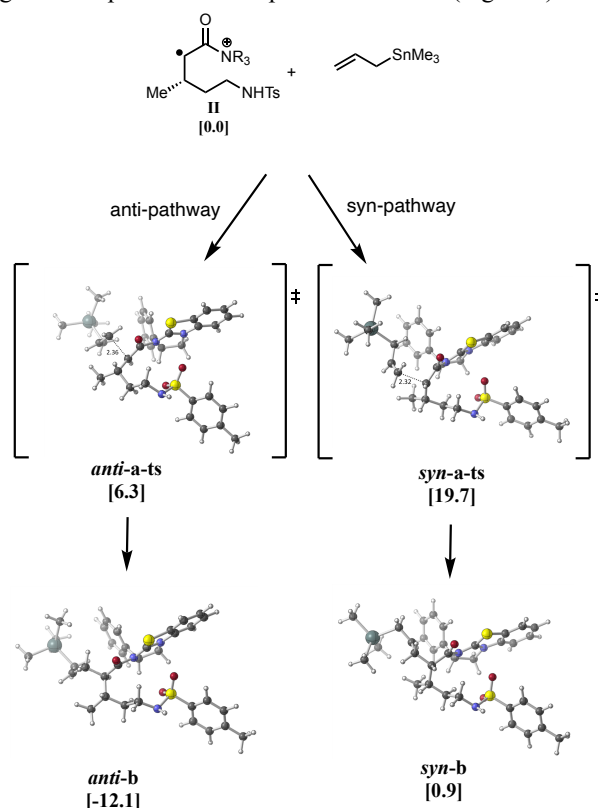


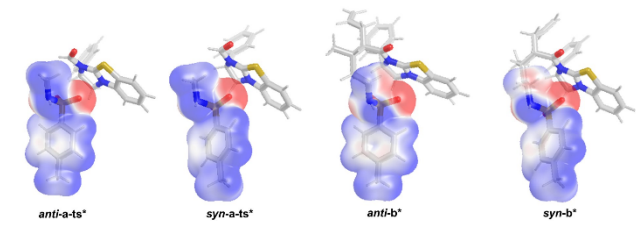
Figure 1. Computed (UPBE0-D3/def2-SVP) relative free energies ([kcal/mol]) for minima and transition structures involved in the reaction of **II** and allyltrimethylstannane. The relative free energies are with respect to reactants **II** and allyltrimethylstannane at infinite separation. Distances shown in Å. (NR₃ = (*S*)-BTM).

The energy barrier for the allylation of the α -radical leading to the *anti*-allylated adduct *anti-b* is calculated to be 6.3 kcal/mol, whereas the barrier leading to the *syn*-allylated adduct *syn-b* is predicted to be 19.7 kcal/mol (Figure 1). The preferential formation of *anti-b* is consistent with the experimentally observed diastereoselectivity. To investigate the source of the relative stability of *anti* and *syn* transition structures (*anti-a-ts* and *syn-a-ts*) and allylated adducts (*anti-b* and *syn-b*), we performed symmetry adapted perturbation theory (SAPT) analysis,²⁰ which decomposes interaction energies into physically meaningful components (i.e., electrostatic, exchange, induction, dispersion). For SAPT analysis, we were particularly interested in the interaction between the acylammonium ion and the NHTs group. Therefore, we truncated *anti-a-ts* and *syn-a-ts*

to complexes of fragments terminated by CHO and CH₃ groups for acylammonium and NHTs substructures, respectively, keeping the relative positions of these fragments unchanged (Table 3, *anti*-a-ts* and *syn*-a-ts*). Intramolecular SAPT analysis was also performed on the allylated adducts formed after the dissociation of the trimethyltin radical (Table 3, *anti*-b* and *syn*-b*). This analysis suggests that electrostatic attraction, presumably and primarily between the sulfonamide oxygen and the cationic π -system of the isothioureia-derived acylammonium salt, is the major type of electrostatic interaction for both transition structures and adducts.²¹ In addition, these electrostatic contributions for the *anti*-transition structure and *anti*-adduct are much greater than their *syn* analogs, while differences in other interaction terms are smaller. This leads to a model in which diastereoselectivity, during the allylation step of radical **II**, results from the orientation of the π -system of the cationic acylammonium ion and the sulfonamide oxygen atoms so as to maximize their electrostatic interaction.

Table 3. Calculated (SAPT0/jun-cc-pVDZ//UPBE0-D3/def2-SVP) total and decomposed interaction energies (in kcal/mol) between the circled groups in the truncated transition structures (i.e., *anti*-a-ts* and *syn*-a-ts*) and allylated adducts formed after the dissociation of the trimethyltin radical (i.e., *anti*-b* and *syn*-b*). Electrostatic potential maps are shown for the CH₃-NHTs groups

$anti-b \rightarrow anti-b^* + \cdot SnMe_3$
 $syn-b \rightarrow syn-b^* + \cdot SnMe_3$



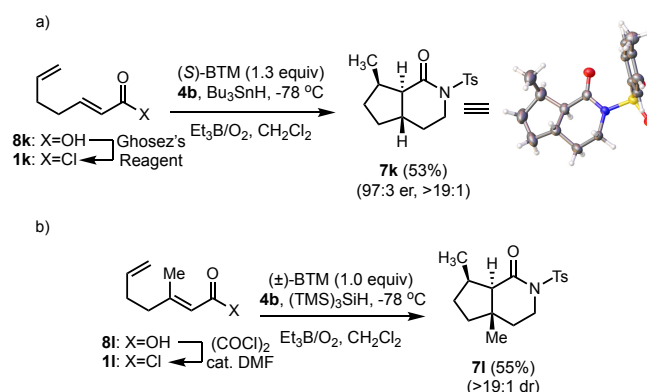
	Electrostatic	Exchange	Induction	Dispersion	Total
<i>anti</i> -a-ts*	-24.0	18.9	-6.9	-11.5	-23.5
<i>syn</i> -a-ts*	-19.3	14.5	-6.1	-10.4	-21.3
<i>anti</i> -b*	-16.6	17.9	-6.4	-11.7	-16.8
<i>syn</i> -b*	-10.9	13.7	-6.3	-9.8	-13.3

We also explored the diastereoselectivity for a scenario in which α -allylation of the intermediate α -radical **II** occurs after the lactamization step. The relative free energies calculated for the *anti* and *syn* transition structures again predict a preference for the *anti*-transition state *anti*-c-ts ($\Delta\Delta G$ 7.8 kcal/mol) although allylation of the acylammonium intermediate **II** results in a more significant difference (Figure 1) leading to the observed major diastereomeric adduct, *anti*-d (see SI, Figure S4, p. S25).

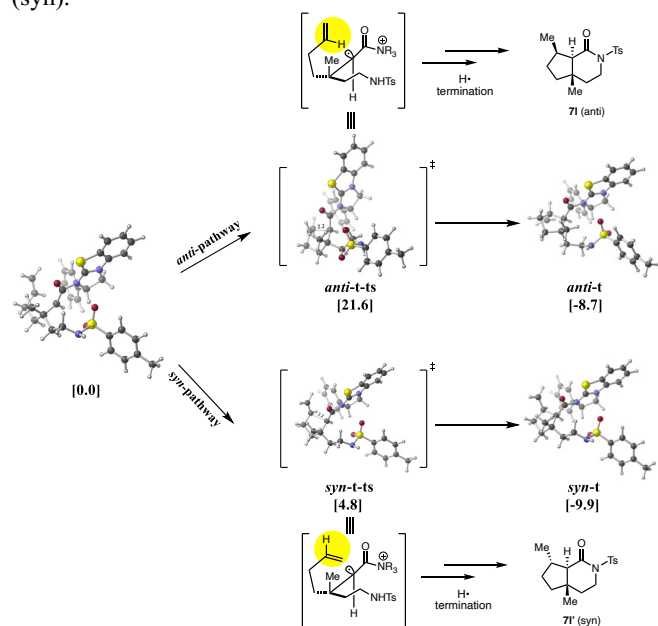
Taken together, the described experimental and computational studies reveal highly sterically congested transition state arrangements during these radical processes. In addition to the lack of reaction with certain acid chlorides (e.g. cyclic and β,β -disubstituted acid chlorides), the data suggests that there are steric issues associated with capture of the incipient α -radical following the initial Giese reaction. This led us to consider intramolecular trapping of the α -radical by use of unsaturated acid chlorides bearing pendant alkenes that would deliver bicyclic δ -lactams. The dienyl acid chloride **1k** was prepared by known procedures,²² and when subjected to typical radical

conditions described above, a 5-exo-trig cyclization of the α -radical with the pendant alkene occurred to deliver the anticipated bicyclic lactam **7k** following H-atom capture with Bu₃SnH (53%, 97:3 er, >19:1 dr). The structure of this bicyclic lactam including relative and absolute stereochemistry was confirmed by X-ray analysis (inset, Scheme 5) with the absolute stereochemistry being consistent with what is typically observed with (*S*)-BTM-derived acyl ammonium salts. Importantly, this bis-cyclization could be extended to a β,β -disubstituted acid chloride **1l**, in this case terminating with (TMS)₃SiH as hydrogen atom donor delivering bicyclic lactam **7l** (dr >19:1), which suggests that the problematic step with both β,β -disubstituted and cyclic acid chlorides is the intermolecular allylation step potentially caused by steric issues in these congested transition state arrangements. The diastereoselectivity at the methyl bearing stereogenic center, derived from facial selectivity of the pendant alkene, can be rationalized by the preferred approach of the alkene to the intermediate α -radical which was supported by computational studies (Scheme 6)). Attempts to render this reaction enantioselective using (*S*)-BTM (1.0 equiv) led to drastically reduced yields (8%) but with some degree of enantioselectivity (87:13 er).

Scheme 5. Use of an intramolecular α -radical trap leading to the bicyclic δ -lactams **7k** and **7l**; ellipsoid shown at the 50% probability level.

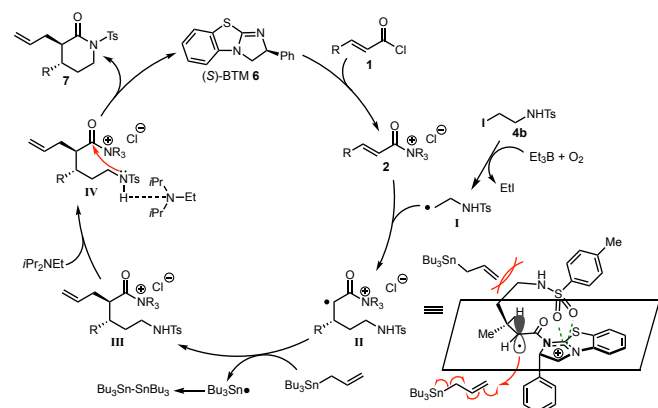


Scheme 6. Computed (UPBE0-D3/def2-SVP) relative free energies (in kcal/mol) for minima and TSSs involved in the reaction forming bicyclic lactam **7i** (anti) and diastereomer **7i'** (syn).



Our studies of this radical organocascade, both experimental and computational, led to the proposed catalytic cycle and transition state arrangements shown in Scheme 7. Following acylation of the Lewis base catalyst, (*S*)-BTM **6**, by the α,β -unsaturated acid chloride **1**, the unsaturated acylammonium salt **2** is generated. Triethylborane initiates the radical cascade through initial generation of Et $\cdot$ and reaction with iodide **4b** to give the alkyl radical **I**. An enantioselective Giese addition of radical **I** ensues with unsaturated acylammonium salt **2**, delivering the α -radical intermediate **II**. Termination of radical **II** proceeds through a diastereoselective Keck allylation with allyltributylstannane, giving rise to the acylammonium amine **III**. Hunig's base presumably assists the lactamization at low temperatures delivering δ -lactams **7** with concomitant release of the Lewis base.

Scheme 7. Proposed cycle for the Giese-initiated radical cascade/lactamization process.



In summary, an enantio- and diastereoselective radical organocascade process was developed involving chiral, unsaturated acylammonium salts to deliver optically active δ -

lactams bearing up to three stereogenic centers. The use of chemically-initiated radical generation enables capture of the intermediate α -radical through both inter- and intramolecular trapping leading to both mono- and bicyclic lactams. Experimental and computational studies shed light on the facial selectivity observed and also the steric issues that needed to be overcome in the allylation step providing a rationale for the lack of reactivity of certain substrates. This led to the study of intramolecular capture of the incipient α -radical which indeed enabled the synthesis of an optically active bicyclic δ -lactam **7k** bearing three stereogenic centers. Future studies will make use of alternate conditions for radical initiation to avoid Lewis acidic boron species enabling lower catalyst loading.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

Experimental Procedures and ^1H and ^{13}C NMR spectra for all new compounds, CIF files for compounds **7a**, **7j**, **S5** (CCDC#: 2366330, 236631, 2366553) structures of unsuccessful substrates, radical precursors and trapping agents, and additional computational data are provided. Supporting information for this article is given via a link at the end of the document.

AUTHOR INFORMATION

Corresponding Author

Daniel Romo – Department of Chemistry and Biochemistry, Baylor University, Waco, Texas, 76706, United States;
<https://orcid.org/0000-0003-3805-092X>;

Email: Daniel_Romo@baylor.edu

Dean Tantillo – Department of Chemistry, University of California, Davis, California, 95616, United States;
<https://orcid.org/0000-0002-2992-8844>

Email: djtantillo@ucdavis.edu

Authors

Patrick J. Sutter¹ – Department of Chemistry and Biochemistry, Baylor University, Waco, Texas, 76706, United States

Ben Walker – Department of Chemistry and Biochemistry, Baylor University, Waco, Texas, 76706, United States

Kristiana Kasper – Department of Chemistry and Biochemistry, Baylor University, Waco, Texas, 76706, United States

Volga Kojasoy² – Department of Chemistry, University of California, Davis, California, 95616, United States

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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