Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 6340−6344

pubs.acs.org/OrgLett

Synthetic and Computational Study of Tin-Free Reductive Tandem Cyclizations of Neutral Aminyl Radicals

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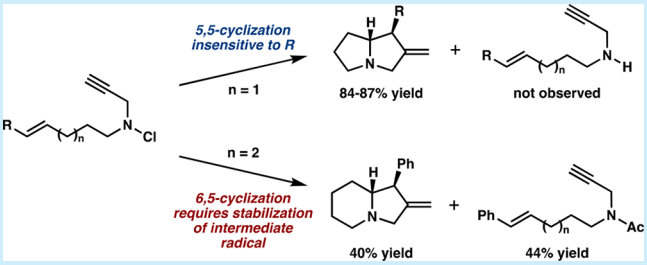
Supporting Information

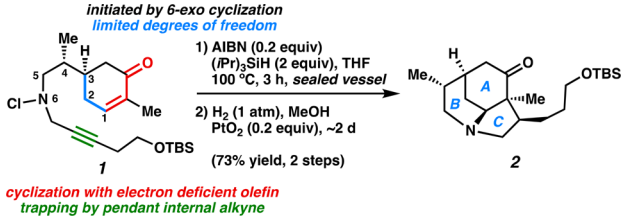
ABSTRACT: 5-*exo*, 5-*exo* Cyclizations of conformationally unbiased propargylic aminyl radicals proceed with excellent yield, chemoselectivity, and diastereoselectivity under tin-free reductive cyclization conditions, regardless of the electronic environments and intermediate radical stabilization resulting from various olefin substituents. These conditions avoid the need for slow addition of initiator and reductant. By contrast, analogous 6-*exo*, 5-*exo* cyclizations require substituents capable of intermediate radical stabilization to avoid premature reduction products. These experimental results are corroborated by computations that further establish the reactivity of these aminyl radicals upon exposure to tin-free cyclization conditions.



Tertiary amines are privileged structures in pharmaceutical lead targets because they improve solubility and decrease lipophilicity, while maintaining potency.[1] Polycyclic molecules bearing tertiary amines are of special interest because they possess the rigid structural framework, high density of sp^3 centers, and low molecular weight profile associated with "drug-like" molecules.[2] We were attracted to the potential utility of neutral aminyl radicals to construct these frameworks because radical cascades have well-established reactivity with predictable bond construction outcomes. While amidyl,[3] iminyl,[4] and aminium[5] radicals are more reactive and tend to cyclize more efficiently[6,7] than the more stable neutral aminyl radicals,[8,9] the latter are strategically appealing because their cyclization reactions lead directly to aliphatic amine-containing products.[10] In this work, we demonstrate the utility of our recently reported[11] tin-free conditions for the cyclization of neutral aminyl radicals. We obtained good yields of 5-*exo*-initiated[12] tandem cyclization products employing electronically differentiated olefins and demonstrated the electronic dependence of 6-*exo* cyclizations of conformationally unbiased[13] substrates. Lastly, we computed the barrier heights and thermodynamics of these cyclizations in the gas phase, toluene, and tetrahydrofuran (THF).

We recently reported the development of tin-free conditions to access the ABC core of the calyciphylline A alkaloids via tandem cyclization of a neutral aminyl radical.[11] In these cyclizations, an existing six-membered ring (**ring A**) reduced the conformational degrees of freedom in the substrate (Scheme 1). The cyclization of *N*-chloroamine **1** is initiated via 6-*exo* cyclization, which is a rare mode of reactivity for aminyl radicals. An electron-deficient olefin was required in these cyclizations as allylic alcohol derivatives led only to N−Cl reduction products.[14] Finally, our experiences indicated that internal and terminal alkynes performed differently in otherwise analogous tandem cyclizations. Because of the unique features of this substrate relative to known cyclizations of aminyl radicals, we sought to establish the utility of these tin-free cyclization conditions, which also avoid slow addition[15] of initiator and H atom donor, in conformationally unbiased systems.

Scheme 1. Structural Features of Substrate for Calyciphylline A Alkaloid Synthesis



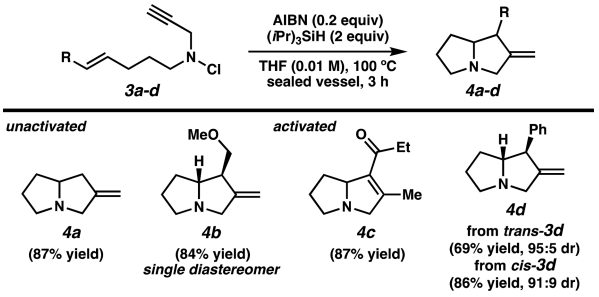
We hypothesized that cascades beginning with cyclization of the relatively nucleophilic[16] aminyl radicals would have lower barriers when cyclizing with electron-deficient olefins than with nonactivated olefins.[17] Findings that enones analogous to substrate **1** cyclized efficiently while the corresponding allylic alcohol[14] led only to N−Cl reduction ($R_2N-Cl \rightarrow R_2N-H$) were consistent with our hypothesis but were insufficient to provide insight into 5-*exo* and 6-*exo* cyclizations of conformationally unbiased substrates. Thus, we selected representative unactivated and activated olefin substituents to investigate

Received: August 1, 2018
Published: September 28, 2018

DOI: 10.1021/acs.orglett.8b02456
Org. Lett. 2018, 20, 6340−6344

under these conditions. For convenience, we retained the terminal alkyne in the second cyclization, thus minimizing potential complications arising from the formation of multiple diastereomers. We found that unactivated substrates **3a**–**3b**[18] afforded good to excellent yields of cyclized products **4a**–**4b** when treated with azobisisobutyronitrile (AIBN) and the weak H-atom donor $(i\text{Pr})_3\text{SiH}$ at 100 °C in THF.[14,19] Bicyclic amine **4b** was formed as a single diastereomer. The relative stereochemistry is consistent with previous stereochemical studies of 5-*exo*, 5-*exo* tandem cyclizations.[20] Enone substrate **3c** also cyclized efficiently, and following thermal isomerization of the exocyclic olefin, bicyclic amine **4c** was isolated in 87% yield. Cyclization of *trans*-**3d** led to a 69% yield of **4d** with 95:5 dr (Scheme 2). The *cis*-isomer of the styrenyl substrate (*cis*-**3d**)

Scheme 2. Tin-Free Cyclization of Unactivated and Activated *N*-Chloro Propargylamines

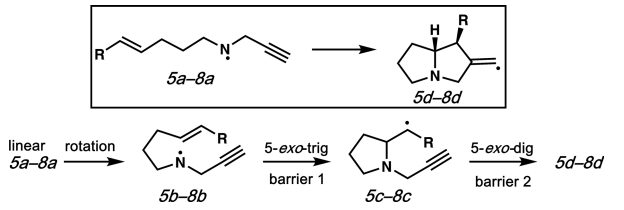


performed similarly to enone **3c** with an isolated yield of 86% and 91:9 dr. Isomerization of the exocyclic olefin was not observed in either case, and the major product diastereomer was *trans* for both cyclizations.[21]

Previously, we observed that cyclization of *N*-chloroenone **1** in THF with $(i\text{Pr})_3\text{SiH}$ as an H atom donor led to fewer reduction products than did the same cyclization in toluene with Bu_3SnH.[11] We presumed that the change in H atom donor was the primary contributor to this reactivity; however, both solvents can also donate hydrogen atoms. The calculated energy barrier for intermolecular H atom transfer from the solvent to radical **8a** was 13.4 kcal/mol in implicit THF and 15.4 kcal/mol in implicit toluene (calculations were performed using the Gaussian 09 software[22] and the ωB97xD level of theory and 6-31+G(d,p) basis set at 100 °C).[23] The barrier to hydrogen atom transfer from each reducing agent to radical **8a** was also calculated at 100 °C. For Et_3SnH,[24] the barrier is 4.8 kcal/mol in implicit THF and 5.0 kcal/mol in implicit toluene. For $(i\text{Pr})_3\text{SiH}$, the barrier is 13.7 kcal/mol in implicit THF and 14.4 kcal/mol in implicit toluene. Thus, the reduction products observed in toluene/tin hydride conditions likely arise due to H atom transfer from the stannane, not toluene. These labeling experiments and computational data support our hypothesis that a weaker H atom donor should favor tandem cyclization products in preference to N–H bond formation.[11]

We next calculated the energetics of the cyclization pathway from the aminyl radicals **5a**–**8a** to vinylic radicals **5d**–**8d** via the Beckwith–Houk transition states of each substrate (Table 1).[25,26] For 5-*exo*-initiated cyclizations, the initial cyclization barriers (i.e., barrier 1 = $\Delta G^{\ddagger}$ for **5b**–**8b** → **5c**–**8c**) range from 9.3 to 14.2 kcal/mol in implicit solvent, with the barrier for **7b** in THF as an apparent outlier. These data are consistent with published computational results for aminyl radical monocyclization.[7a] The reverse reaction barriers range from

Table 1. Activation Barriers and Relative Energies of Radical Intermediates in the 5-*exo*, 5-*exo* Pathway[a]



R	solvent	5–8b	barrier 1[b]	int 5–8c[c]	barrier 2	int 5–8d
H (5)	(gas)	0.0	13.2	−6.2	12.4	−26.6
H	PhMe	0.5	13.9	−4.2	11.6	−24.5
H	THF	0.9	14.2	−3.1	10.8	−23.0
CH_2OMe (6)	(gas)	2.3	11.8	−6.3	6.5	−26.4
CH_2OMe	PhMe	2.4	12.0	−5.8	6.9	−24.8
CH_2OMe	THF	3.1	12.7	−6.8	7.2	−20.9
COEt (7)	(gas)	−1.0	11.4	−12.6	12.4	−25.6
COEt	PhMe	−0.3	11.4	−11.6	13.9	−23.3
COEt	THF	0.8	7.3	−10.4	13.3	−21.5
Ph (8)	(gas)	−1.2	10.1	−15.0	15.6	−24.4
Ph	PhMe	0.7	10.1	−17.5	16.2	−21.7
Ph	THF	0.6	9.3	−12.7	16.3	−20.4

[a] ωB97xD functional and Gibbs free energies were calculated at 100 °C. All values in kcal/mol. [b] Barrier 1 is calculated from the prearranged conformation (**5**–**8b**). [c] All intermediate values are relative to the energy of the fully elongated, staggered aminyl radical (**5**–**8a**).

15.4 to 26.9 kcal/mol depending on the substrate and solvent. These data suggest that the first 5-*exo* cyclization event is likely irreversible for most of these substrates. These results are consistent with some[7,27,28] previous experimental rate studies.[29] For all evaluated substrates, the transformation of the N-centered radical (**5a**–**8a**) to the vinylic radical (**5d**–**8d**) is exothermic owing to the formation of two C–C bonds and a fused bicyclic system.

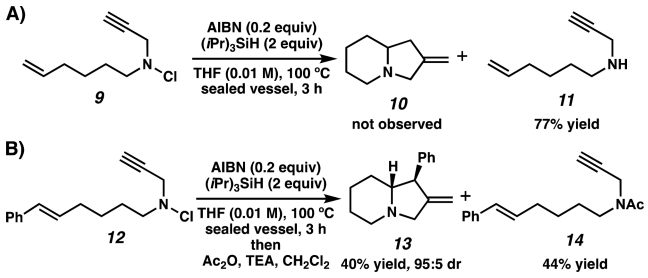
As expected, barrier 1 tracks the stability of the intermediate radicals **5c**–**8c**. The barrier for the terminal olefin (**5b**) was 1.4–1.9 kcal/mol higher in energy than for methoxymethyl-substituted **6b**. The barrier for enone **7b** was 1.8–2.5 kcal/mol lower than for **5b** in the gas phase or implicit toluene, while in THF, the gap is larger than expected at 6.9 kcal/mol. The barrier for styrenyl substrate **8b** was 2.5–3.5 kcal/mol lower than for **5b**. While these energy differences follow the expected trend, they are relatively small, and the high temperature for cyclization is sufficient to enable cyclization even in the highest barrier case (R = H). Interestingly, barrier 1 is higher in THF than in toluene for **5b** and **6b** and lower for **7b** and **8b**. For substrates capable of generating a stabilized C-centered radical intermediate (i.e., **7c** and **8c**), the barrier height for the second cyclization (barrier 2) is significantly larger than for radicals **5c** and **6c**. α-Keto radical **7c** is 7.3–7.4 kcal/mol more stabilized than primary radical **5c** in implicit THF and toluene solvent, respectively. For styrenyl substrate **8c**, these values increase to 9.6–13.3 kcal/mol, respectively.

On the basis of the computational results outlined above, we hypothesized that 6-*exo*-initiated cyclizations would be more sensitive to substitution changes because of the significantly reduced reactivity of these substrates. We selected H and Ph groups as representative electron-normal and electron-withdrawing substituents. Attempted cyclization of *N*-hexenyl-*N*-

DOI: 10.1021/acs.orglett.8b02456
Org. Lett. 2018, 20, 6340–6344

propargyl chloroamine **9** with THF/$(i\text{Pr})_3$SiH conditions led to recovery of 77% reduced amine **11** (Scheme 3A). Bicycle **10**

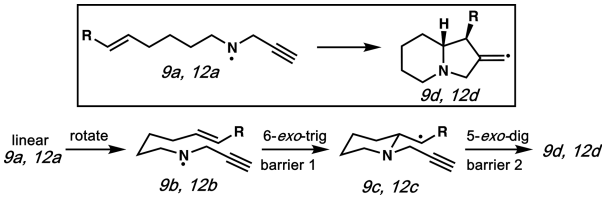
Scheme 3. Sensitivity of 6-*exo*, 5-*exo* Initiated Cyclizations to Olefin Electronics



was not observed in the crude NMR. For the styrenyl analogue of this substrate (**12**), cyclization product **13** was isolated in 40% yield after an acetic anhydride workup, which was required to facilitate isolation of **14** (44% yield, Scheme 3B). Presumably, formation of the reduced products (*pre*-**11**, *pre*-**14**) in these cases occurs via both intramolecular and intermolecular H-atom transfer. This is particularly true in the styrenyl system where the allylic radical is highly stabilized.[20a]

The computational analysis for these two cyclizations is consistent with the drop in both overall reactivity for 6-*exo* cyclizations and in the relative success of the two substrates (Table 2). Interestingly, once the substrate (**9a** and **12a**)

Table 2. Activation Barriers and Relative Energies of Radical Intermediates in the 6-*exo*, 5-*exo* Pathway[a]



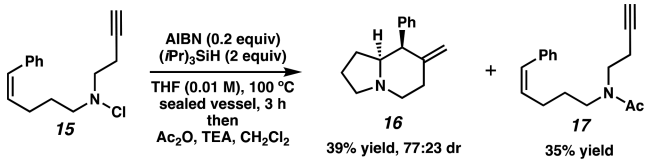
R	solvent	**9b**, **12b**	barrier 1[b]	int **9c**, **12c**[c]	barrier 2	int **9d**, **12d**[c]
H (**9**)	(gas)	3.1	10.5	−8.3	8.9	−29.2
H	PhMe	2.1	12.3	−7.1	8.7	−28.3
H	THF	2.6	12.7	−5.8	8.6	−26.8
Ph (**12**)	(gas)	1.0	8.4	−17.4	12.9	−28.3
Ph	PhMe	2.9	8.1	−16.2	13.8	−25.2
Ph	THF	4.0	8.3	−14.0	13.3	−23.2

[a]ωB97xD functional and Gibbs free energies were calculated at 100 °C. All values in kcal/mol. [b]Barrier 1 is calculated from the prearranged conformation (**9b**, **12b**). [c]All intermediate values are relative to the energy of the fully elongated, staggered aminyl radical (**9a**, **12a**).

adopts the appropriate conformation for cyclization (**9b** and **12b**), the barrier 1 values for 6-*exo* cyclization are not significantly different from the 5-*exo* substrates. However, the energy required to adopt these precyclization conformations is significant. In THF, combining the uphill conformational change with the activation barrier gives an overall transition state energy ($\Delta G^{\ddagger}$) of 15.3 kcal/mol. Thus, it is unsurprising that the reduction pathway, which had a barrier of 13.4 kcal/mol for H atom transfer from THF to **8a**, outcompetes the cyclization. However, for the styrenyl substrate, the $\Delta G^{\ddagger}$ is 12.3 kcal/mol. It is thus expected to be competitive with reduction, and a mixture of products (**13** and **14**) is observed. As expected, the barrier 2 heights and overall thermodynamics are similar to the 5,5-cyclization pathway. Overall, these computational data suggest that the rate differences between these 5-*exo* and 6-*exo* radical cyclizations are primarily derived from entropic factors associated with substrate prearrangement rather than an inherent decrease in reactivity for 6-*exo* cyclization resulting from an issue with alignment of the participating molecular orbitals.

We also investigated the applicability of these conditions to the 5-*exo*, 6-*exo* substrate chloroamine **15** (Scheme 4). The

Scheme 4. Sensitivity of 6-*exo*, 5-*exo* Initiated Cyclizations to Olefin Electronics



desired product was formed in 39% yield and 77:23 dr. The lower dr here presumably arises from competitive rotation of the Ph group to the pseudoequatorial position in the transition state. Interestingly, despite the initial formation of a 5-membered ring, significant amounts of reduction product (isolated as the acetate, **17**) were observed (35% yield). The dependence of the formation of reduced amine on the size of the second ring suggests reversibility in the first cyclization. Meanwhile, our computational results from Table 1 support irreversible cyclization of the N-centered radical with a reverse barrier of ∼23 kcal/mol for **8c** → **8b**. The retention of stereochemistry in reduction product **17** suggests that intermolecular H-atom transfer to the aminyl radical is faster than 5-*exo* cyclization in this substrate. By contrast, no reduction is observed in any of our 5-*exo*, 5-*exo* tandem cyclizations. Combining previous rate studies with these new computational and experimental data, one can conclude that the reversibility of neutral aminyl cyclizations is dependent on the intermediate radical stability, the reaction conditions, and the effects of impurities[27] in the reaction.

In summary, kinetically favorable 5-*exo*, 5-*exo* cyclizations of propargyl-appended aminyl radicals proceed efficiently in tin-free conditions employing a weak H atom donor in THF, regardless of the electronic nature of the substitution on the olefin. Importantly, these conditions avoid kinetic tricks such as slow addition of the radical initiator and reducing agent. By contrast, a radical stabilizing group is essential to facilitate cyclization in 6-*exo*, 5-*exo* cyclizations of propargylic aminyl radicals. These results are supported by computational data. Finally, application to a 5-*exo*, 6-*exo* cyclization reveals a dependence on the size of the second ring in determining the ratio of cyclization to reduction. Overall, the weak H atom donating ability of $(i\text{Pr})_3$SiH and THF results in an unusual, if apparently synergistic, solvent/H atom donor combination that is effective for a range of tandem cyclizations. We anticipate that these experimental and computational data will be useful for future synthetic design using neutral aminyl radicals. Further investigation into the factors influencing reversibility is ongoing in our laboratories.

DOI: 10.1021/acs.orglett.8b02456
Org. Lett. 2018, 20, 6340−6344

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02456.

Experimental procedures and spectroscopic data (PDF)
Computational methodology and Cartesian coordinates (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Institutes of Health (R00-GM097095 for 5,5-cyclizations with R = H, R = Ph), the National Science Foundation (CAREER Award to JLS: CHE-1554752 for all remaining experiments, Grant to BHS: CHE-1464450), and Wayne State University for generous financial support (startup funds to JLS, Rumble-Schaap Fellowship to HSS, and use of the computational grid). We thank Materia, Inc. for the kind donation of all metathesis catalysts used in the substrate syntheses. We are grateful to the staff of the WSU Lumigen Instrument Center, especially Nicholas Peraino, for spectroscopic support, and we thank Dr. Ahmad A. Ibrahim (WSU) for helpful discussions.

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(18) See the Supporting Information for experimental details and substrate synthesis.

(19) The cyclization of **3a** was performed on a 1.1 mmol scale, resulting in 81% yield of **4a**. See the Supporting Information for details.

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DOI: 10.1021/acs.orglett.8b02456
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DOI: 10.1021/acs.orglett.8b02456
Org. Lett. 2018, 20, 6340−6344