Organic LETTERS

Letter

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Highly Torquoselective Electrocyclizations and Competing 1,7-Hydrogen Shifts of 1-Azatrienes with Silyl Substitution at the Allylic Carbon

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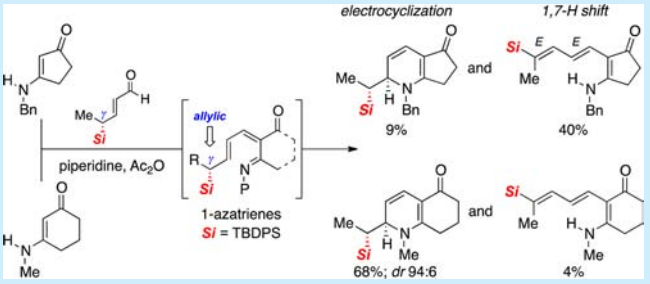
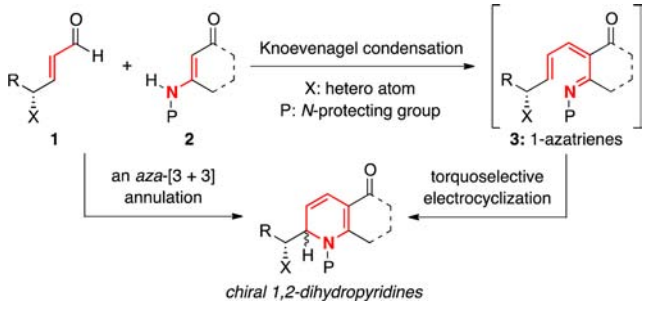
Supporting Information

ABSTRACT: Highly torquoselective electrocyclizations of chiral 1-azatrienes are described. These 1-azatrienes contain an allylic stereocenter that is substituted with a silyl group and are derived *in situ* from condensation of γ-silyl-substituted enals with vinylogous amides. The ensuing stereoselective ring closures are part of a tandem sequence that constitutes an *aza*-[3 + 3] annulation method for constructing 1,2-dihydropyridines. Several mechanisms for the formal 1,7-hydrogen shift of these 1-azatrienes were evaluated computationally.

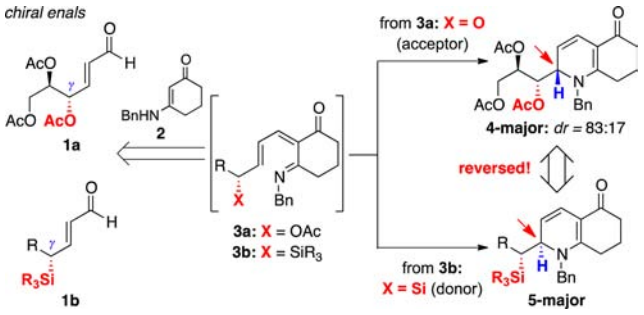


Electrocyclizations represent an important pericyclic process in organic synthesis. Our *aza*-[3 + 3] annulation[1−3] method involving chiral enals **1** and vinylogous amides **2** is a powerful strategy for total syntheses of alkaloids[4] and a unique platform for studying the torquoselectivity of electrocyclizations of 1-azatreienes **3**[5] (Scheme 1). Despite its significance in constructing chiral 1,2-dihydropyridines, efforts to develop and understand torquoselective ring closures of 1-azatrienes **3** have lagged behind with the sole exception of Tanaka and Katsumura's elegant work.[6] Although we have developed highly torquoselective electrocyclizations of a chiral auxiliary substituted 1-azatrienes,[7] a more general and practical approach employing chiral enals has yielded a diastereoselectivity of 83:17 at best (see aza-electrocyclization of **3a** in Scheme 2).[8,9] Recently, our collaborative efforts to understand the origins of the stereoselectivities of a number of pericyclic reactions[10] have led us to model these stereoselective ring closures computationally. A complete stereochemical model for these electrocyclic reactions is still being developed. In the course of our studies, we predicted that the stereochemical outcomes of these electrocyclizations depend on the electronic nature of the allylic substituent X (shown in Scheme 2). If X is a σ donor such as SiR_3 instead of a σ acceptor such as OAc, a reversal of stereoselectivity is predicted (**4** versus **5**). We have now shown that such a reversal occurs and that the electrocyclizations of these silyl-substituted 1-azatrienes are highly torquoselective.

Scheme 1. Torquoselective Electrocyclizations of 1-Azatrienes in *Aza*-[3 + 3] Annulations



Scheme 2. A Prediction of Reversal of the Torquoselectivity

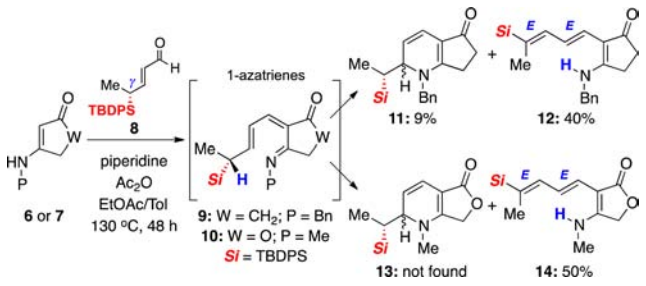


We commenced our investigation by examining *aza*-[3 + 3] annulations of vinylogous amides **6** and **7** with γ-silyl-substituted enal **8**,[11,12] and quickly found that the respective desired *aza*-annulation products **11**/**11′** and **13**/**13′** were minor products (Scheme 3). Major products in these reactions were vinyl silanes **12** and **14** from **6** and **7**, respectively. These isomeric vinyl silanes could be formed by a (formal) 1,7-H shift

Received: March 12, 2015
Published: April 10, 2015

DOI: 10.1021/acs.orglett.5b00727
Org. Lett. 2015, 17, 2138−2141

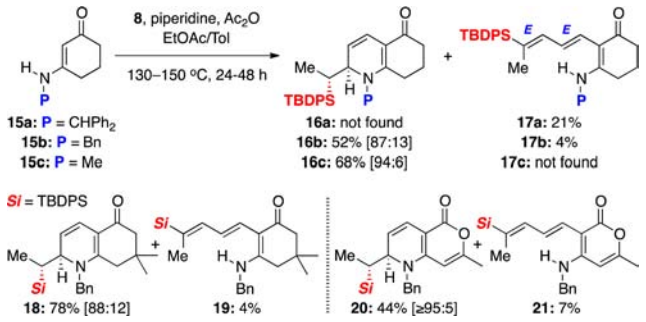
Scheme 3. An Unexpected Competing 1,7-Hydrogen Shift



of 1-azatrienes **9** or **10**. Although the competition of a 1,7-H shift with the desired annulation pathway has been documented,[13] the isomerizations responsible for the formation of **12** and **14** have never been observed before. The *E*-configurations of vinyl silanes **12** and **14** were assigned using NOE experiments.

Annulations using 6-membered ring vinylogous amides were more successful. As shown in Scheme 4, although the reaction

Scheme 4. *Aza*-[3 + 3] Annulations Using 6-Membered Vinylogous Amides as Annulation Partners



of vinylogous amide **15a** still yielded the 1,7-H shift product (**16a**) as the major product, the 1-aztrienes derived from 6-membered ring vinylogous amides **15b** and **15c** predominantly underwent ring closure in high yields and diastereoselectivity. This is also true for the electrocyclizations leading to **18** and **20** with the respective vinyl silanes byproducts **19** and **21** being isolated only in small amounts.

Using the single crystal X-ray structure of **16b** (Figure 1), we were able to unambiguously assign the stereochemistry of **16b**

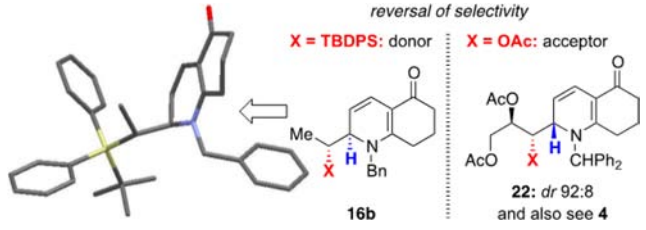


Figure 1. X-ray structure of 1,2-dihydropyridine **16b**.

and confirm the prediction of a complete reversal of selectivity for electrocyclizations of these silyl-substituted 1-azatrienes. The attempted *aza*-annulations of 1-azatrienes bearing a large *N*-substituent (such as the *N*-$CHPh_2$ group of **15a**) would still yield products of the 1,7-H shift. This is presumably due to enhanced steric repulsion between the larger *N*-substituent and the TBDPS group at the electrocyclization transition state. It is noteworthy that, in direct contrast, *aza*-annulations of **15a** with nonsilylated chiral enals were feasible and the most diastereoselective as demonstrated by **22**.[8a]

Table 1 illustrates the generality of this stereoselective *aza* annulation; an array of different γ-silyl-substituted enals **25a–h**,

Table 1. A Highly Torquoselective Electrocyclization[a,b]

entry	chiral enals	electrocyclization products	1,7-H shift products
1	**25a**: R = Et	**26a**: 55% [*dr* 92:8][a,b]	**27a**: 7%
2	**25b**: R = *i*-Bu	**26b**: 53% [*dr* >95:5]	**27b**: 3%
3	**25c**: R = *n*-hex	**26c**: 53% [*dr* >95:5]	**27c**: 6%
4	**25d**: R = $Ph(CH_2)_3$	**26d**: 60% [*dr* >95:5]	**27d**: 5%
5	**25e**: R = allyl	**26e**: 54% [*dr* >95:5]	**27e**: 5%
6	**25f**: R = Bn	**26f**: 59% [*dr* >95:5]	**27f**: 4%
7	**25g**: R =	**26g**: 73% [*dr* >95:5]	**27g**: 4%
8	**25h**: R = Me	**26h**: 35% [*dr* ≥95:5]	**27h**: 3%

[a]All reactions were carried out with vinylogous amide **15c** using piperidine and Ac_2O, and reactions were heated at 130 °C for 24 h. [b]All are isolated yields, and *dr* ratios are determined using ^1H NMR analysis of the crude reaction mixture.

including one substituted with a TBS group, were successfully used as annulation partners. In all cases, the selectivity is very high while the competing 1,7-H shift is by and large mitigated. It is noteworthy that this is the first time a very high level of diastereoselectivity could be achieved in *aza*-[3 + 3] annulations using acyclic chiral enals.

To better understand why 1-azatrienes annulated with 5-membered rings (**9** and **10**) undergo competitive formal 1,7-hydrogen shifts rather than the desired aza-electrocyclizations, we modeled the reaction of truncated 1-azatrienes **28** and **30** (see Figure 2) computationally.[15] In Scheme 5, a summary of four possible mechanisms by which isomerization may occur is shown. All pathways assume the intermediacy of 1-azatriene **I**, and pathways 1, 2, and 4 feature key steps that are concerted in

DOI: 10.1021/acs.orglett.5b00727
Org. Lett. 2015, 17, 2138–2141

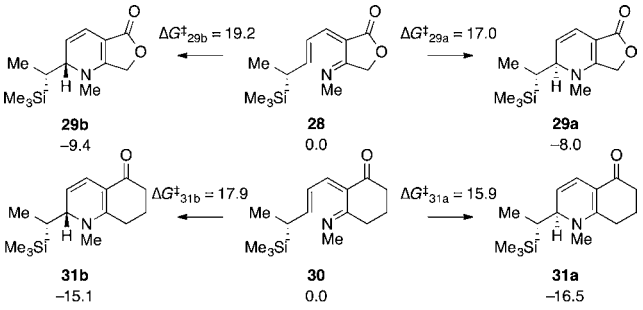
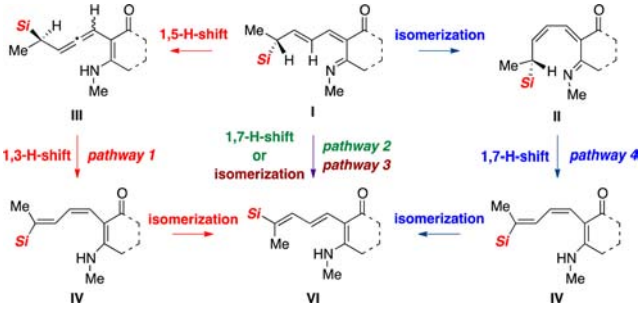


Figure 2. Energetics of the electrocyclic ring closures of model 1-azatrienes **28** and **30**. Energies are Gibbs free energies in kcal mol^{-1} determined at the M062-X/def2-QZVPP//M06-2X/6-31+G(d,p) level.

Scheme 5. Potential Mechanism for the Competitive Isomerization



nature. Consequently, in addition to modeling the electrocyclizations of **28** and **30**, we have also modeled steps of these three pathways. The intermediacy of 1-azatriene **I** in pathway 3, which involves base-mediated proton transfer, has not been modeled; however, such a mechanism is a plausible alternative.

The energetics of the electrocyclizations of 1-azatrienes **28** and **30** are shown in Figure 2. At 130 °C, the aza-electrocyclizations of **28** and **30** are facile reactions ($\Delta G^{\ddagger}$ < 20 kcal mol^{-1}) that under kinetic control stereoselectively yield dihydropiperidines **29a** and **31a**, respectively. Electrocyclization of **30** is, according to theory, only slightly more facile than that of **28**; however, it is significantly more exergonic than the ring closure of **28** (ca. 8 kcal mol^{-1}).[16]

Based on computations, pathways 1 and 2, involving a direct 1,7-hydrogen shift or 1,5-hydrogen shift of 1-azatriene **28**,[6d] respectively, are unlikely. These sigmatropic rearrangements have free energy barriers of at least 30 kcal mol^{-1}. However, the free energy of activation for the 1,7-hydrogen shift involved in pathway 4 is 17 kcal mol^{-1}. Thus, pathway 4 is a plausible mechanism, as long as the required isomerizations (presumably promoted by base) are facile processes.

Interestingly, the rate of 1,7-hydrogen shift is 100-fold slower ($\Delta\Delta G^{\ddagger}$ = 2.7 kcal mol^{-1}) than the ring closure of 1-azatriene **30**. However, for 1-azatriene **28**, these two processes are very similar in activation free energies (Figure 3). These differences in reactivity may be (partially) responsible for the distinct product outcomes observed for the ring closures of these 1-azatrienes.

The lowest energy transition structures of the 1,7-hydrogen shift of **II** derived from substrates **28** and **30** (**TS29c** and **TS31c**) are shown in Figure 2. **TS31c** is destabilized by the A^{1,3} strain between the *N*-methyl substituent and annulated cyclohexanone (see green lines in Figure 3). This destabilizing

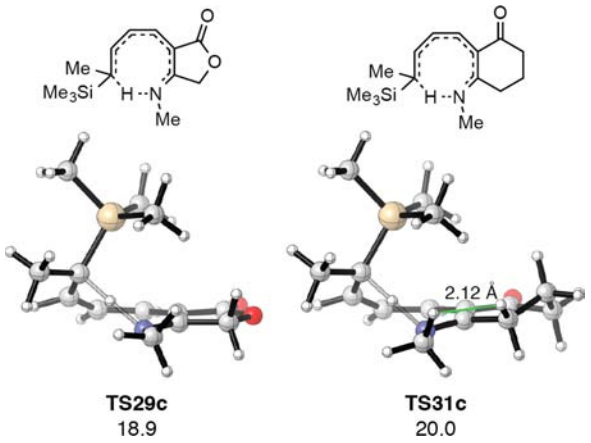


Figure 3. M06-2X/6-31+G(d,p)-optimized transition structures of lowest 1,7-hydrogen shift featured in pathway 4. Energies are Gibbs free energies in kcal mol^{-1} determined at the M06-2X/def2-QZVPP//M06-2X/6-31+G(d,p) level.

interaction is less severe in **TS29c** featuring the γ-lactone because this moiety, unlike the corresponding cyclohexanone in **TS31c**, is planar.

We have described here a highly torquoselective electrocyclization of a series of novel chiral 1-azatrienes. These 1-azatrienes contain an allylic stereocenter substituted with a silyl group and are generated in situ by condensing γ-silyl-substituted enals with vinylogous amides. Theoretical calculations have provided mechanistic insights into a previously unknown competing 1,7-hydrogen shift from the same 1-azatriene intermediate. Efforts to explore synthetic applications of this torquoselective electrocyclization are underway. Full details regarding the stereochemical model that rationalizes the observed torquoselectivities will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as NMR spectra, characterizations, and X-ray structure file for all newly synthesized compounds, Cartesian coordinates for all computed structures, their electronic energies, zero point energies (ZPE), thermal, and free energy corrections for all QM-optimized structure, and the imaginary frequencies of transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NIH (GM-66055 to R.P.H.) and NSF (CHE-1059084 and CHE-1361104 to K.N.H.). A.P. thanks the Chemistry-Biology Interface Training Program (NIH Grant T32 GM 008496) for its support and the University of California, Los Angeles (UCLA) for funding. UCLA's Beowulf cluster, Hoffman2, and the Extreme Science and Engineering

DOI: 10.1021/acs.orglett.5b00727
Org. Lett. 2015, 17, 2138–2141

Discovery Environment's (Grant TG CHE 040013N) Gordon and Trestles supercomputer at the San Diego Supercomputing Center were used to perform computations. We also thank Dr. Victor Young at the University of Minnesota for X-ray structural analysis.

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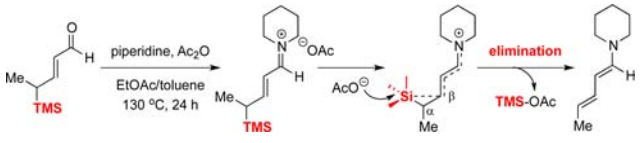
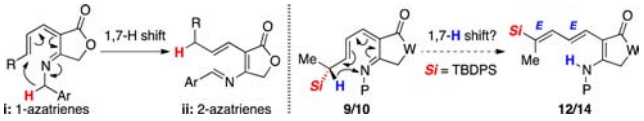
(11) See Supporting Information.

(12) We used TBDPS-substituted enals, because we failed in our initial attempts of using TMS-substituted enals. Peterson-like elimination of the TMS group was observed instead of the desired ring closure. We attempted reactions of enals substituted with silyl groups of intermediate sizes (Ph_3Si and Ph_2MeSi). However, synthesis of these enals proved difficult.



(13) A 1,7-H shift of 1-azatriene **i** was also observed, giving 2-azatriene **ii**. This shift is quite distinct from the rearrangement of **9**/**10** to **12**/**14**. See: Sydorenko, N.; Hsung, R. P.; Darwish, O. S.; Hahn, J. M.; Liu, J. *J. Org. Chem.* **2004**, *69*, 6732.



(14) Azatrienes **28** and **30** (see Figure 2) are truncated model substrates featuring a TMS substituent instead of the bulky TBDPS group.

(15) All computations were performed using *Gaussian09*. The calculations reported herein were performed using the M06-2X/def2-QZVPP//M06-2X/6-31+G(d,p) model chemistry, and all energies reported are Gibbs free energies. Additional details and relevant references can be found in the Supporting Information.

(16) Further discussion of the thermodynamics of the ring closures of **28** and **30** has been related to the Supporting Information.

(17) See Supporting Information for details regarding pathways 1 and 2.

DOI: 10.1021/acs.orglett.5b00727
Org. Lett. 2015, 17, 2138−2141