

# Biomimetic 2-Imino-Nazarov Cyclizations via Eneallene Aziridination

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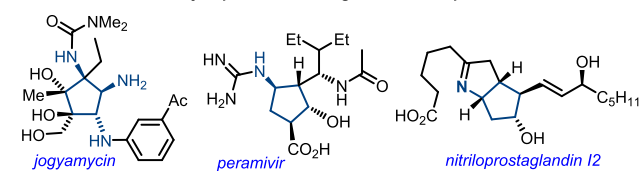
Supporting Information

**ABSTRACT:** Amidoallyl cations are appealing three-carbon synthons for the preparation of complex amine-containing carbocycles; however, methods to generate and utilize these reactive species are limited and underexplored compared to those for oxallyl cations. Here we disclose a bioinspired strain-driven ring opening of bicyclic methyleneaziridines to 2-amidopentadienyl cation intermediates that readily engage in Nazarov cyclizations. Advantages of this strategy include ease of generation and improved reactivity compared to 3-pentadienyl cations, control over the ultimate position of the alkene, the potential for high *dr* between vicinal stereocenters, and the ability to further elaborate the products to fully substituted aminocyclopentanes. Experimental and computational studies support a dual role for the  $Rh_2L_n$  complex as both a nitrene transfer catalyst and a Lewis acid promoter, insight that provides a framework for the future development of asymmetric 2-imino-Nazarov cyclizations.

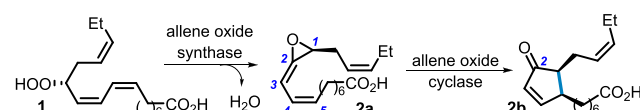
Flexible methods to construct functionalized, densely substituted carbocycles have long been of intense interest to the synthetic community, as these motifs occur frequently in useful bioactive molecules and natural products. For example, amine-bearing cyclopentanes are found in diverse natural products and pharmaceuticals, including the antiprotozoal compound jogyamycin, the anti-influenza drug peramivir, and nitric oxide synthase inhibitor nitroglycerin (Scheme 1A).

## Scheme 1. Background and Proposed 2-Imino-Nazarov Reaction

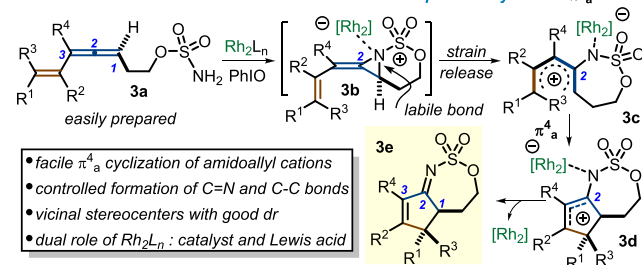
### A Selected aminated cyclopentanes in drugs and natural products



### B Inspiration from plant prostanoid biosynthesis via 2-oxypentadienyl cations



### C This work: Biomimetic imino-Nazarov via a 2-amidopentadienyl cation $\pi^4_a$



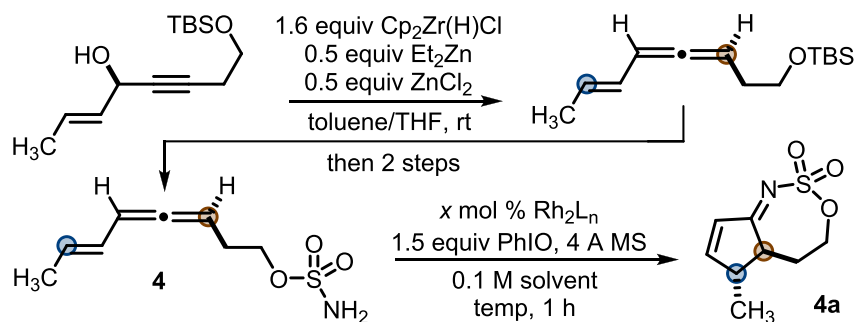
The aza version of the classic Nazarov cyclization<sup>1</sup> of divinyl ketones to prepare 2-cyclopenten-1-imines is challenging. This is due to better stabilization of the key pentadienyl cation in a “3-imino-Nazarov” reaction compared with the 3-oxallyl cation intermediates implicated in a typical Nazarov reaction.<sup>2</sup> Tius, Hsung, West, Huang, and others have reported creative solutions to overcome this issue;<sup>3</sup> nonetheless, reaction development has been hampered by the dearth of methods for convenient generation of 3-amidoallyl cation intermediates.<sup>4</sup> The aza-Piancatelli reaction, which moves the N to C1, has also been used to address this challenge;<sup>5</sup> however, it benefits from a “push-pull” enol-iminium intermediate that ultimately furnishes the amine-substituted cyclopentenone product.

Our work was inspired by the biosynthesis of *epi*-jasmonic acid (Scheme 1B), which proceeds via a Nazarov-type electrocyclic cyclization of allene oxide **2a** to furnish  $\alpha,\beta$ -unsaturated cyclopentenone **2b**. This enzyme-catalyzed process readily controls the site of unsaturation in the product and yields excellent *dr* and *ee* of the new vicinal stereocenters.<sup>6</sup> We envisaged that a nitrogen version of this process could be readily mimicked by a tandem allene aziridination/electrocyclization (Scheme 1C) from easily obtained eneallenes of the form **3a**.  $Rh_2$ -catalyzed nitrene transfer yields conjugated bicyclic methyleneaziridine **3b**, analogous to **2a**. The ring strain inherent in **3b** (~35 kcal/mol) provides kinetically competent access to versatile 2-amidoallyl cation intermediate **3c** without the need for stoichiometric Lewis or Brønsted acids<sup>7</sup> or competing formation of iminocyclopropanes.<sup>7d,f</sup> Additionally, the modified 2-N positioning in **3c** reduces

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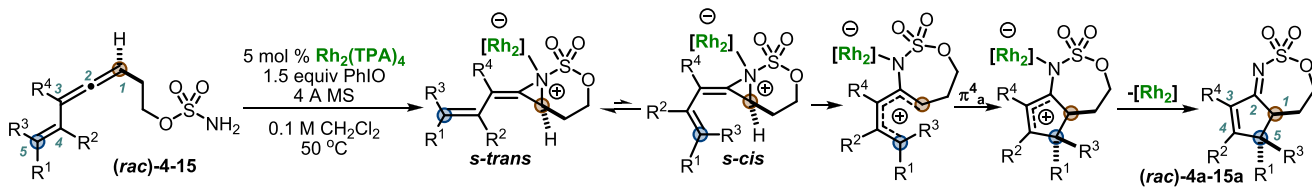
Table 1. Selected Optimization Studies



entry	solvent	catalyst (mol %)	temp (°C)	yield (%) <sup>a</sup>	notes
1	CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (TPA) <sub>4</sub> (1)	rt	24	15% rsm
2	CH <sub>2</sub> Cl <sub>2</sub> (0.2 M)	Rh <sub>2</sub> (TPA) <sub>4</sub> (1)	rt	28	—
3	CH <sub>2</sub> Cl <sub>2</sub> (0.05 M)	Rh <sub>2</sub> (TPA) <sub>4</sub> (1)	rt	33	—
4	CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (TPA) <sub>4</sub> (1)	50	41	—
5	CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (TPA) <sub>4</sub> (1)	50	33	catalyst added last
6	CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (TPA) <sub>4</sub> (1)	50	21	PhI(OAc) <sub>2</sub>
7	MeNO <sub>2</sub>	Rh <sub>2</sub> (TPA) <sub>4</sub> (1)	45	23	—
8	CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (TPA) <sub>4</sub> (5)	50	55	LUMO = -2.90 eV
9	CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (TPA) <sub>4</sub> (5)	50	58	0.05 equiv of PhIO × 3, added every 20 min
10	CICH <sub>2</sub> CH <sub>2</sub> Cl	Rh <sub>2</sub> (TPA) <sub>4</sub> (5)	80	49	—
11	CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (OAc) <sub>4</sub> (5)	50	42	LUMO = -2.68 eV
12	CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (esp) <sub>2</sub> (5)	50	41	LUMO = -2.71 eV

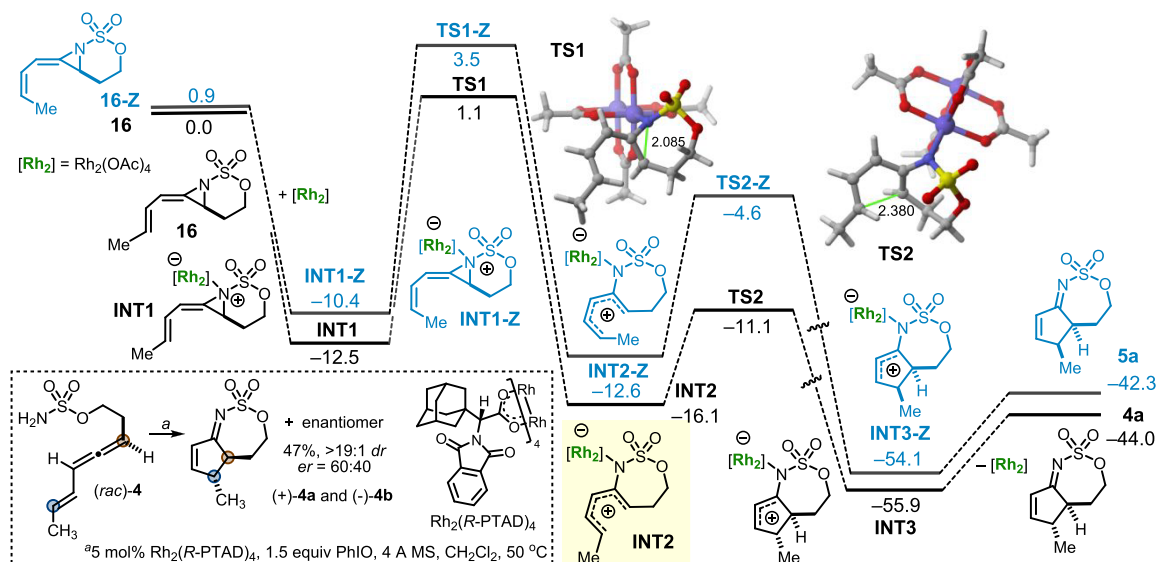
<sup>a</sup>NMR yields using mesitylene as an internal standard.

Table 2. Scope of the Tandem Allene Aziridination/2-Imino-Nazarov Reaction



entry	R <sup>1</sup> -R <sup>4</sup>	product	% yield <sup>a</sup> , dr	entry	R <sup>1</sup> -R <sup>4</sup>	product	% yield <sup>a</sup> , dr	entry	R <sup>1</sup> -R <sup>4</sup>	product	% yield <sup>a</sup> , dr
1	R <sup>1</sup> = Me R <sup>2</sup> = H R <sup>3</sup> , R <sup>4</sup> = H		63% <sup>c</sup> dr > 19:1	5	R <sup>1</sup> = Ph(CH) <sub>2</sub> CH <sub>3</sub> R <sup>2</sup> , R <sup>3</sup> = H R <sup>4</sup> = H		71% dr <sub>a,b</sub> > 19:1 dr <sub>ab,c</sub> 1.2:1	9	R <sup>1</sup> = (E)-C <sub>11</sub> H <sub>19</sub> R <sup>2</sup> = H R <sup>3</sup> = Me R <sup>4</sup> = H		31% dr > 19:1
2	R <sup>1</sup> = H R <sup>2</sup> , R <sup>4</sup> = H R <sup>3</sup> = Me		36% dr = 2.4:1	6	R <sup>1</sup> = Me R <sup>2</sup> = H R <sup>3</sup> = H R <sup>4</sup> = Me		65% dr 4.1:1	10	R <sup>1</sup> , R <sup>2</sup> = (CH <sub>2</sub> ) <sub>3</sub> R <sup>3</sup> = H R <sup>4</sup> = H		62% dr = 14:1
3	R <sup>1</sup> = <sup>i</sup> Pr R <sup>2</sup> = H R <sup>3</sup> , R <sup>4</sup> = H		74% dr > 19:1 79%, 1 g scale	7	R <sup>1</sup> = Me R <sup>2</sup> = Me R <sup>3</sup> , R <sup>4</sup> = H		46% <sup>b</sup> dr = 3.9:1	11	R <sup>1</sup> , R <sup>2</sup> = (CH <sub>2</sub> ) <sub>4</sub> R <sup>3</sup> = H R <sup>4</sup> = H		74% dr = 3.0:1
4	R <sup>1</sup> = (CH <sub>2</sub> ) <sub>3</sub> OBPS R <sup>2</sup> = H R <sup>3</sup> = H R <sup>4</sup> = H		65% dr > 19:1	8	R <sup>1</sup> = Ph R <sup>2</sup> = H R <sup>3</sup> = H R <sup>4</sup> = H		36% dr > 19:1	12	R <sup>1</sup> , R <sup>2</sup> = ring R <sup>3</sup> = H R <sup>4</sup> = H		77% dr <sub>a,b</sub> > 19:1 dr <sub>ab,c</sub> 1.2:1

<sup>a</sup>Isolated yields. <sup>b</sup>Using 1 mol % Rh<sub>2</sub>(TPA)<sub>4</sub>. <sup>c</sup>The yield decreased as allene aged.



**Figure 1.** Computed reaction profile for the 2-imino-Nazarov reaction of aziridine **16**. Relative energies and bond distances are given in kcal/mol and angstroms, respectively. All of the data were computed at the SMD(CH<sub>2</sub>Cl<sub>2</sub>)-B3LYP-D3/def2-TZVPP//SMD(CH<sub>2</sub>Cl<sub>2</sub>)-B3LYP-D3/def2-SVP level.

stabilization of the pentadienyl cation relative to traditional 3-amidopentadienyl cations to facilitate productive cyclization. A  $4\pi$  conrotatory electrocyclicization of **3c** to **3d** and subsequent loss of the Rh complex furnishes **3e**, ideally with high *dr*. The intermediacy of **3d** enables the formation of **3e** with predictable positioning of the alkene, as substrate-controlled elimination present in the typical Nazarov reaction is not operative here. In fact, no elimination or tautomerization is required from **3d** in this oxidative manifold, which avoids loss of stereochemical information between the vicinal stereocenters installed in the conrotatory cyclization of **3c**.<sup>8</sup> This Communication describes our “2-imino-Nazarov” reaction, including factors influencing the mechanism and stereo-selectivity of the cyclization, the elaboration of the products to increase molecular complexity from simple precursors, and potential strategies to secure enantioenriched products.

Hydrozirconation/Zr=O elimination of allyl propargyl alcohol with Schwartz’s reagent enables rapid access to eneallene **4** (Table 1).<sup>9</sup> Preliminary studies found that sulfamates were the best nitrene precursors and that a two-carbon tether between the allene and the sulfamate was optimal. Nitrene transfer conditions previously reported by our group served as a starting point for investigating the feasibility of the 2-imino-Nazarov reaction of **4**.<sup>7a</sup> Catalytic Rh<sub>2</sub>(TPA)<sub>4</sub> (TPA = triphenylacetate) transformed **4** to **4a** in 24% yield with >19:1 *dr* (entry 1). Varying the concentration (entries 2 and 3) had little impact; however, increasing the temperature to 50 °C (entry 1 vs 4) improved the yield of **4a** to 41%. Adding the catalyst last, as opposed to the oxidant, was not beneficial (entry 5).

Switching the oxidant to PhI(OAc)<sub>2</sub> (entry 6) or the solvent to MeNO<sub>2</sub> (entry 7) gave low yields of 21% and 23%, respectively. However, increasing the loading of Rh<sub>2</sub>(TPA)<sub>4</sub> to 5 mol % (entries 8 and 9) in CH<sub>2</sub>Cl<sub>2</sub> improved the yield of **4a** to 58%; further increases in temperature in DCE (entry 10) were not beneficial. Interestingly, Rh<sub>2</sub>(OAc)<sub>4</sub> (entry 11) and Rh<sub>2</sub>(esp)<sub>2</sub> (entry 12) were inferior to Rh<sub>2</sub>(TPA)<sub>4</sub>. Computations of the LUMO energies for Rh<sub>2</sub>(TPA)<sub>4</sub> (−2.90 eV), Rh<sub>2</sub>(OAc)<sub>4</sub> (−2.68 eV), and Rh<sub>2</sub>(esp)<sub>2</sub> (−2.71 eV) suggested

that Lewis acidity of the catalyst was important to reaction success (see the Supporting Information (SI) for details).

With the optimized conditions in hand, the scope of the tandem allene aziridination/2-imino-Nazarov reaction was explored (Table 2). All of the substrates were either racemic or a 1:1 racemic mixture of diastereomers. Freshly prepared **4** provided **4a** in 63% yield with >19:1 *dr*, bearing an *anti* relationship between the hydrogens at the two newly formed stereocenters through a thermally allowed conrotatory  $4\pi$  electrocyclicization (Table 2, entry 1). Engaging *cis*-eneallene **5** gave **5a** in moderate yield (entry 2), favoring the *syn* isomer (NOESY-NMR studies detailed in the SI); we considered that the lower *dr* compared to **4a** could result from isomerization of the alkene geometry in **5**, partial epimerization of **5a** under the reaction conditions, or a competing “non-Nazarov” pathway. Control experiments confirmed that the alkene of **5** does not isomerize in the presence of Rh<sub>2</sub>TPA<sub>4</sub> or PhIO, while epimerization of **5a** is unlikely, as we would expect a similar *dr* for **4a** if this pathway were operative. Isomerization of intermediate species or a competing non-Nazarov pathway cannot be ruled out.

Isopropyl substitution was tolerated in **6** to give **6a** in 74% yield with excellent *dr* (entry 3). To our delight, the preparation of **6a** could be run on a 1 g scale to give a 79% yield with >19:1 *dr*. Protected alcohols were suitable precursors, with **7** giving **7a** in 65% yield with >19:1 *dr* (entry 4). The ability of the external stereocenter in **8** to control the *dr* in the all-carbon stereotriad in **8a** was investigated (entry 5); while the *dr* between *a* and *b* was >19:1, the *dr* between *a/b* and *c* was only moderately improved to 1.2:1.

Substitution at C3 (R<sup>4</sup>) and C4 (R<sup>2</sup>) in **9** and **10** (entries 6 and 7) gave **9a** and **10a** in good yields; NOE correlations for **10a** showed *anti* stereochemistry in the major diastereomer. Here, moderate *dr* may result from isomerization of either the precursor or intermediates, although a competing non-Nazarov pathway is also possible. Extending the conjugation of the alkene in styrenyl allene **11** (entry 8) resulted in an unoptimized 36% yield of **11a** with >19:1 *dr*, though this

substrate was prone to decomposition at high temperatures. Increased steric congestion in eneallenes **12** (entry 9), where both  $R^1$  and  $R^3$  are alkyl substituents, gave lower yields but excellent *dr* in forming a challenging all-carbon quaternary center in **12a**. Eneallenes **13–15**, where both  $R^1$  and  $R^2$  are substituted, gave good yields of the 2-cyclopenten-1-imines **13a–15a**. As the alkene in these cases cannot undergo isomerization, the less-than-perfect *dr* is puzzling. Prolonged exposure of **14a** as a mixture to the reaction conditions revealed no change in *dr* over 24 h, while resubjecting diastereomerically pure *anti*-**14a** (>19:1 *dr*) to the reaction conditions gave no change in the *dr*, providing support for lack of epimerization of the imine itself (see the SI for details). The isopropenyl substituent on cyclohexene **15a** promotes high *anti* selectivity between the adjacent stereocenters *a* and *b*.

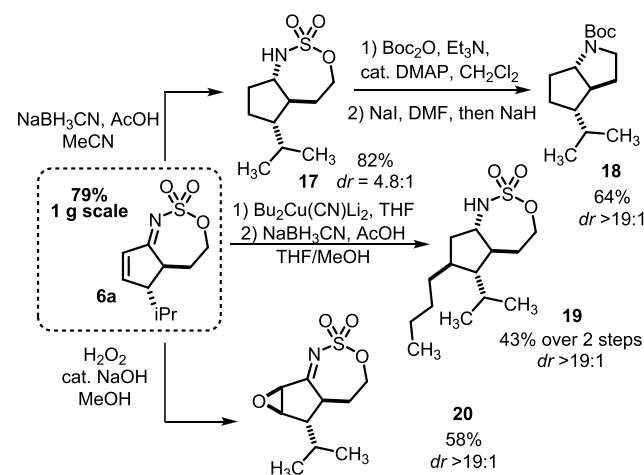
Density functional theory calculations (see the SI for computational details) were carried out to gain more insight into the mechanism of this unusual 2-imino-Nazarov reaction (Figure 1). The fate of methyleneaziridine **16**, which is readily formed upon reaction of eneallene **4a** with  $Rh_2$  catalyst in the presence of PhIO, was explored first. Exothermic coordination of the aziridine nitrogen to the  $Rh_2$  catalyst leads to INT1, which evolves to amidallyl cation INT2 through TS1, a saddle point associated with aziridine ring opening ( $\Delta E^\ddagger = 13.6$  kcal/mol). The intermediacy of this achiral intermediate was supported by subjecting enantioenriched **4** (92% *ee*; see the SI for details) to the standard conditions and noting degradation of the axial chirality to only 12% *ee* in the product **4a**. Ring closure converts INT2 into bicyclic INT3 via TS2, which is associated with the formation of a new C–C bond. The lower barrier for this step ( $\Delta E^\ddagger = 5.0$  kcal/mol) is consistent with its computed high exothermicity ( $\Delta E_R = -39.8$  kcal/mol); however, the barrier is similar to that for an aza-Piancatelli reaction with the N at C1, highlighting the favorable electronic benefits of positioning the N at C2 versus C3.<sup>5</sup> Decoordination of the  $Rh_2$  fragment gives the observed product **4a** and releases the catalyst. The reaction profile for the corresponding (*Z*)-eneallene isomer **16-Z** was computed to be higher in energy than that computed for **16** along the entire reaction coordinate. In addition, the *E/Z* isomerization barriers computed for either INT1 or INT2 (>20 kcal/mol; see Figure S-2 in the computational portion of the SI) are much higher than the barriers associated with the ring opening and subsequent cyclization. This finding could help to explain the higher yields noted with **4** versus **5**.

The dual role of the  $Rh_2L_n$  nitrene transfer catalyst as a Lewis acid promoter was intriguing; while these modes of reactivity are preceded individually, there are few examples where both features of a Lewis acidic dinuclear Rh catalyst are utilized in a synergistic fashion.<sup>10</sup> During optimization studies, higher catalyst loadings of the most Lewis acidic  $Rh_2L_n$  complex gave more efficient cyclization. Dissociation of  $Rh_2(OAc)_4$  prior to cyclization had a prohibitively large computed energy barrier, leading to the hypothesis that the use of a racemic allene with a chiral  $Rh_2L_n$  catalyst might generate enantioenriched products. Indeed, subjecting (*rac*)-**4** (Figure 1 inset) to the reaction conditions using  $Rh_2(R-PTAD)_4$  produced (+)-**4a** and (–)-**4b** in a 60:40 *er*, a promising result considering the large distance between the catalyst and the site of the stereodetermining C–C bond formation event. Efforts to identify better chiral  $Rh_2L_n$  catalysts and counteranions for accessing enantioenriched, densely functionalized amino-cyclopentenes are currently underway. This result also provides

compelling evidence that  $Rh_2$  is involved in promoting cyclization as a Lewis acid, in addition to facilitating the nitrene transfer.

Finally, the 2-cyclopenten-1-imine products of tandem allene aziridination/2-imino-Nazarov reaction proved to be flexible intermediates for the preparation of complex aminated cyclopentanes. As shown in Scheme 2, a variety of trans-

Scheme 2. Flexible Transformations of **6a**



formations were successfully carried out on **6a** (see the SI for conditions). Global reduction of **6a** with  $NaBH_3CN$  produced **17** in 82% yield with 4.8:1 *dr*. Boc protection of the amine, separation of the diastereomers, and double displacement with NaI/NaH generated fused pyrrolidine **18** in 64% yield over two steps (>19:1 *dr*), showcasing one of many potential uses of the tether.<sup>6a</sup> Higher-order cuprates, such as  $Bu_2Cu(CN)Li_2$ , gave diastereoselective 1,4-addition to **6a**; subsequent protonation of the metalloenamine and imine reduction afforded **19** with >19:1 *dr*. Lastly, to demonstrate the application of **6a** to the synthesis of fully substituted aminated cyclopentanes, nucleophilic epoxidation with  $H_2O_2$  and catalytic NaOH provided **20** in 58% yield with >19:1 *dr*.

In conclusion, we have developed an efficient 2-imino-Nazarov cyclization reaction from simple precursors. Stereocontrolled, site-selective  $Rh_2$ -catalyzed eneallene aziridination initiates an electrocyclization that furnishes structurally diverse  $\alpha,\beta$ -iminocyclopentene scaffolds in good yields and *dr*. Investigation of the reaction mechanism suggested the formation of discrete achiral intermediates, implying that strain-promoted methyleneaziridine ring opening to give a 2-amidopentadienyl cation is operative. Computations indicated that the nitrene transfer catalyst remains associated during cyclization as a mild Lewis acid, providing a new framework for developing asymmetric 2-imino-Nazarov electrocyclizations.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c02441>.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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## Notes

The authors declare no competing financial interest.

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