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Communication

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Biomimetic 2-Imino-Nazarov Cyclizations via Eneallene Aziridination

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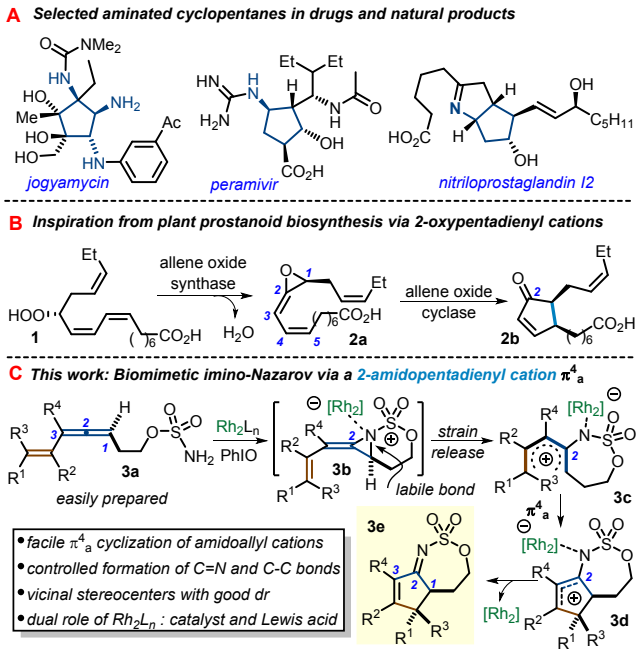
Supporting Information Placeholder

ABSTRACT: Amidoallyl cations are appealing 3-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 oxallyl cations. In this report, we disclose a bio-inspired, 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 anti-protozoal compound jogyamycin, the anti-influenza drug peramivir, and nitriloprostaglandin I2 (PGI_2), which is used in the treatment of arteriosclerosis, cardiac failure and thrombosis (Scheme 1A).

The aza version of the classic Nazarov cyclization[1] 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' as compared to the 3-oxyallyl cation intermediates implicated in a typical Nazarov reaction.[2] Tius, Hsung, West, Huang, and others have reported creative solutions to overcome this issue;[3] nonetheless, reaction development has been hampered by the dearth of methods for convenient generation of 3-amidoallyl cation intermediates.[4] The aza-Piancatelli reaction, which moves the N to C1, has also been used to address this challenge;[5] however, it benefits from a 'push-pull' enol-iminium intermediate that ultimately furnishes the amine-substituted cyclopentenone product.



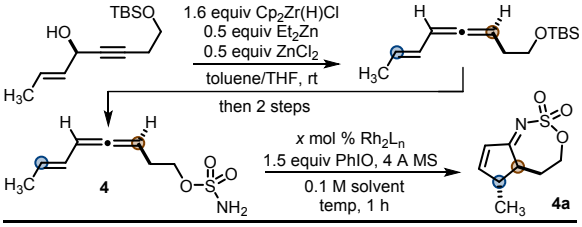
Scheme 1. Background and proposed 2-imino-Nazarov reaction.

Our work was inspired by the biosynthesis of *epi*-jasmonic acid (Scheme 1B), which proceeds *via* a Nazarov-type electrocyclization of allene oxide **2a** to furnish α,β-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.[6] We envisaged 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 **2b**. 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[7] or competing formation of iminocyclopropanes.[6d,f] Additionally, the modified 2-*N*-positioning in **3c** reduces stabilization of the pentadienyl cation relative to traditional intermediate **1b** to facilitate productive cyclization. A 4π-conrotatory electrocyclization of

3c to **3d** and subsequent loss of the Rh complex furnishes **3e**, ideally in high *dr*. The intermediacy of **3d** enables formation of **3e** with predictable positioning of the alkene, as substrate-controlled elimination present in the typical Nazarov 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 vicinal stereocenters installed in conrotatory cyclization of **3c**.[8] This communication describes our '2-imino-Nazarov' reaction, including factors influencing the mechanism and stereoselectivity of the cyclization, the elaboration of products to increase molecular complexity from simple precursors and details 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).[9] Preliminary studies found sulfamates were the best nitrene precursors and 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 2-imino-Nazarov reaction of **4**.[7a] Catalytic $Rh_2(TPA)_4$ (TPA = triphenylacetate) transformed **4** to **4a** in 24% yield and >19:1 *dr* (entry 1). Varying the concentration (entries 2-3) 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).

Table 1. Selected optimization studies.



entry	solvent	catalyst (mol %)	temp (°C)	% yield[a]	notes
1	CH_2Cl_2	$Rh_2(TPA)_4$ (1)	rt	24	15% rsm
2	CH_2Cl_2 (0.2 M)	$Rh_2(TPA)_4$ (1)	rt	28	-
3	CH_2Cl_2 (0.05 M)	$Rh_2(TPA)_4$ (1)	rt	33	-
4	CH_2Cl_2	$Rh_2(TPA)_4$ (1)	50	41	-
5	CH_2Cl_2	$Rh_2(TPA)_4$ (1)	50	33	catalyst added last
6	CH_2Cl_2	$Rh_2(TPA)_4$ (1)	50	21	$PhI(OAc)_2$
7	$MeNO_2$	$Rh_2(TPA)_4$ (1)	45	23	-
8	**CH_2Cl_2**	**$Rh_2(TPA)_4$ (5)**	**50**	**55**	**LUMO = -2.90 eV**
9	**CH_2Cl_2**	**$Rh_2(TPA)_4$ (5)**	**50**	**58**	0.05 equiv PhIOx3 added every 20 min
10	$ClCH_2CH_2Cl$	$Rh_2(TPA)_4$ (5)	80	49	-
11	CH_2Cl_2	$Rh_2(OAc)_4$ (5)	50	42	LUMO = -2.68 eV
12	CH_2Cl_2	$Rh_2(esp)_2$ (5)	50	41	LUMO = -2.71 eV

[a]NMR yields using mesitylene as internal standard

Switching the oxidant to $PhI(OAc)_2$ (entry 6) or the solvent to $MeNO_2$ (entry 7) gave low yields of 21% and 23%, respectively. However, increasing the loading of $Rh_2(TPA)_4$ to 5 mol % (entries 8-9) in CH_2Cl_2 improved the yield of **4a** to 58%; further increases in temperature in DCE (entry 10) were not beneficial. Interestingly, $Rh_2(OAc)_4$ (entry 11) and $Rh_2(esp)_2$ (entry 12) were inferior to $Rh_2(TPA)_4$. Computations of the LUMO energies for $Rh_2(TPA)_4$ (-2.90 eV), $Rh_2(OAc)_4$ (-2.68 eV), and $Rh_2(esp)_2$ (-2.71 eV) suggested that Lewis acidity of the catalyst was important to reaction success (see the SI for details).

With optimized conditions in hand, the scope of the tandem allene aziridination/2-imino-Nazarov was explored (Table 2). All substrates were either racemic or a 1:1 racemic mixture of diastereomers. Freshly prepared **4** provided **4a** in 63% yield and a *dr* >19:1, bearing an *anti* relationship between the hydrogens at the two newly formed stereocenters through a thermally-allowed, conrotatory 4π-electrocyclization (Table 2, entry 1). Engaging *cis*-eneallene **5** gives **5a** in moderate yield (entry 2), favoring the *syn* isomer (NOESY-NMR studies detailed in the SI); we considered 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 confirm the alkene of **5** does not isomerize in the presence of Rh_2TPA_4 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.

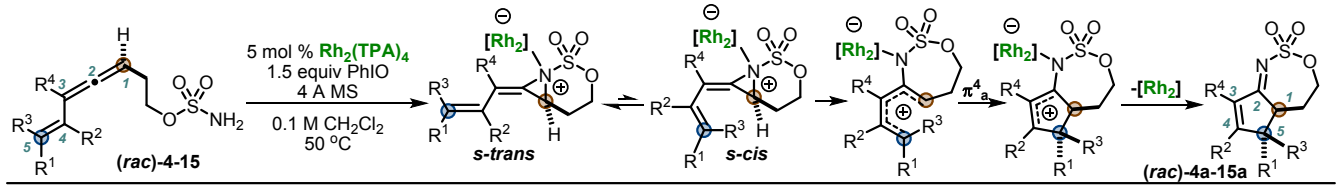
Isopropyl substitution was tolerated in **6** to give **6a** in 74% yield in excellent *dr* (entry 3). To our delight, the preparation of **6a** could be run on a 1 g scale to give a 79% yield and *dr* >19:1. Protected alcohols were suitable precursors, with **7** giving a 65% yield of **7a** in >19:1 *dr* (entry 4). The ability of an external stereocenter in **8** to control *dr* in the all-carbon stereotriad **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 C_3 (R^4) and C_4 (R^2) in **9** and **10** (entries 6-7) gave **9a** and **10a** in good yield; NOE correlations for **10a** show *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** in >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** (*dr* >19:1) 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 adjacent stereocenters ***a***/***b***.

DFT calculations (see 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 the methyleneaziridine **16**, 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 amidoallyl cation **INT2** through **TS1**, a saddle point associated with aziridine ring-opening ($\Delta E^{\neq}$ = 13.6 kcal/mol). The intermediacy of this achiral intermediate was supported by subjecting enantioenriched **4** (92% *ee*, see 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

Table 2. Scope of the tandem allene aziridination/2-imino-Nazarov reaction.



entry	R^1-R^4	product	% yield[a], *dr*
1	R^1 = Me, R^2 = H, R^3, R^4 = H	**4a**	63%[c], *dr* > 19:1
2	R^1 = H, R^2, R^4 = H, R^3 = Me	**5a**	36%, *dr* = 2.4:1
3	R^1 = ^{i}Pr, R^2 = H, R^3, R^4 = H	**6a**	74%, *dr* > 19:1; **79%, 1 g scale**
4	R^1 = $(CH_2)_3$OBPS, R^2 = H, R^3 = H, R^4 = H	**7a**	65%, *dr* > 19:1
5	R^1 = Ph(CH)CH_3, R^2, R^3 = H, R^4 = H	**8a**	71%, $dr_{a,b}$ >19:1, $dr_{ab,c}$ 1.2:1
6	R^1 = Me, R^2 = H, R^3 = H, R^4 = Me	**9a**	65%, *dr* 4.1:1
7	R^1 = Me, R^2 = Me, R^3, R^4 = H	**10a**	46%[b], *dr* = 3.9:1
8	R^1 = Ph, R^2 = H, R^3 = H, R^4 = H	**11a**	36%, *dr* > 19:1
9	R^1 = (*E*)-$C_{11}H_{19}$, R^2 = H, R^3 = Me, R^4 = H	**12a**	31%, *dr* >19:1
10	R^1, R^2 = $(CH_2)_3$, R^3 = H, R^4 = H	**13a**	62%, *dr* = 14:1
11	R^1, R^2 = $(CH_2)_4$, R^3 = H, R^4 = H	**14a**	74%, *dr* = 3.0:1
12	R^1, R^2 = ring, R^3 = H, R^4 = H	**15a**	77%, $dr_{a,b}$ >19:1, $dr_{ab,c}$ 1.2:1

[a]Isolated yield. [b]Used 1 mol % $Rh_2(TPA)_4$. [c]Yield decreases as allene ages.

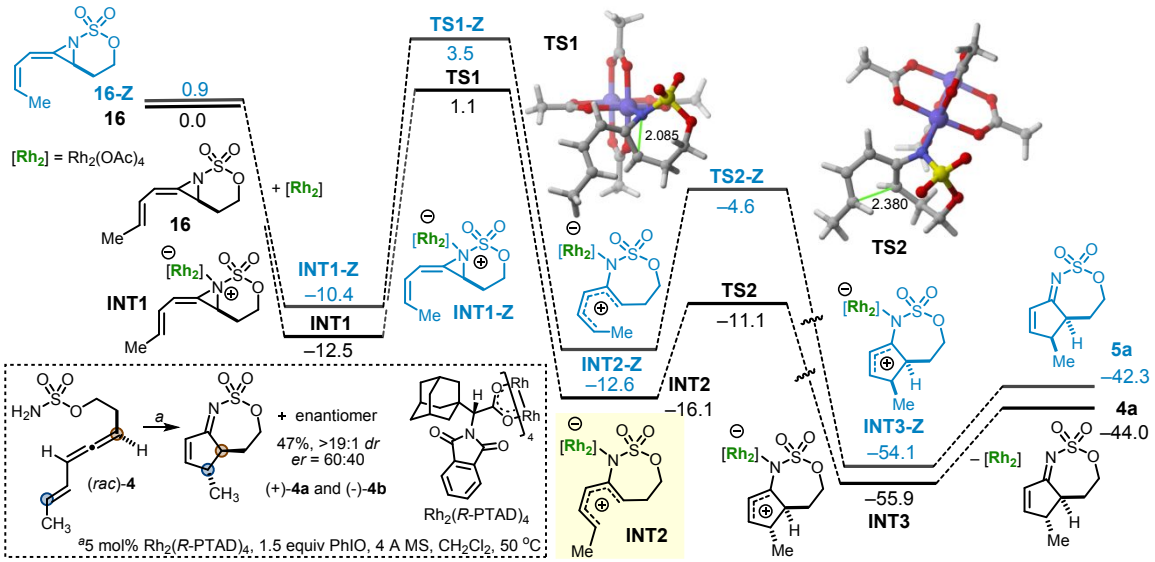


Figure 1. Computed reaction profile for the 2-imino-Nazarov of aziridine **16**. Relative energies and bond distances given in kcal/mol and angstroms, respectively. All data computed SMD(CH_2Cl_2)-B3LYP-D3/def2-TZVPP//SMD(CH_2Cl_2)-B3LYP-D3/def2-SVP level.

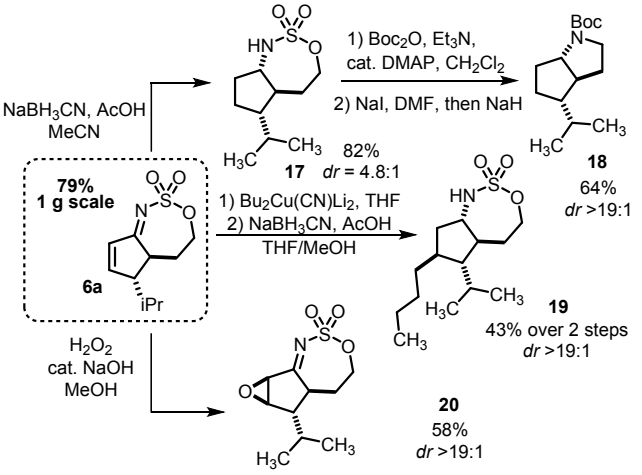
bond. The lower barrier ($\Delta E^{\neq}$ = 5.0 kcal/mol) of this step is consistent with its computed high exothermicity (ΔE_R = –39.8 kcal/mol); however, the barrier is similar to an aza-Piancatelli reaction, with the N at C1, highlighting the favorable

electronic benefits of positioning the N at C2 *vs.* C3.[5] 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 the energies computed for **16** along the entire reaction coordinate. In addition, the *E*/*Z* isomerization barriers computed for either **INT1** or **INT2** are much higher (>20 kcal/mol, see Figure S-2 in the computational portion of the SI) than the barriers associated with the ring opening and subsequent cyclization. This finding could help to explain the higher yields noted with **4** *vs.* **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 precedented individually, there are few examples where both features of a Lewis acidic dinuclear Rh catalyst are utilized in a synergistic fashion.[10] During optimization studies, higher catalyst loadings of the most Lewis acidic Rh_2L_n complex gave more efficient cyclization. Dissociation of Rh_2OAc_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 when 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 aminocyclopentenes 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 flexible intermediates for preparation of complex aminated cyclopentanes. As shown in Scheme 3, a variety of transformations were successfully carried out on **6a** (see the SI for conditions). Global reduction of **6a** with $NaBH_3CN$ produces **17** in 82% yield and 4.8:1 *dr*. Boc-protection of the amine, separation of the diastereomers, and double displacement with NaI/NaH, generates the fused pyrrolidine **18** in 64% yield over two steps (>19:1 *dr*), showcasing one of many potential uses of the tether.[6a] 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 affords **19** in >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 provides **20** in 58% yield and >19:1 *dr*.

Scheme 3. Flexible transformations of **6a**.



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 α,β-iminocyclopentene scaffolds in good yield and *dr*. Investigation of the reaction mechanism suggests formation of discrete achiral intermediates, implying strain-promoted methyleneaziridine ring opening to a 2-amidopentadienyl cation is operative. Computations indicate 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 contains experimental procedures and spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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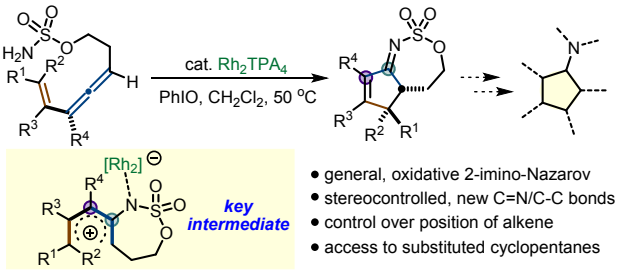
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PhIO, CH2Cl2, 50 °C
[Rh2]
key intermediate
• general, oxidative 2-imino-Nazarov
• stereocontrolled, new C=N/C-C bonds
• control over position of alkene
• access to substituted cyclopentanes