

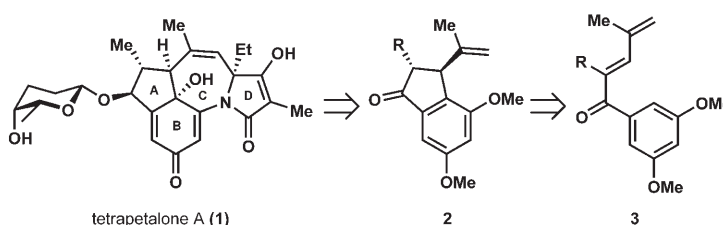
Cyclizations

Pronounced Steric Effects of Substituents in the Nazarov Cyclization of Aryl Dienyl Ketones**

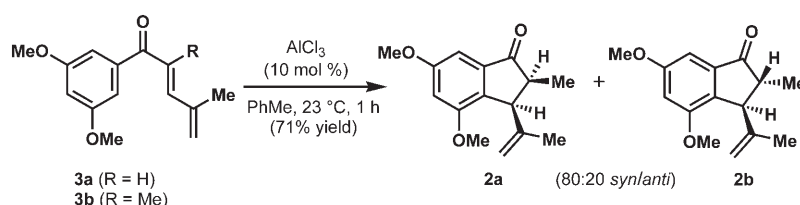
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The acid-catalyzed 4 π -electrocyclic ring closure of a divinyl carbonyl substrate (i.e., the Nazarov cyclization) is a reaction of substantial synthetic utility for pentannulation.^[1] Because of its growing popularity in the arena of complex molecule synthesis, the reaction has evolved to include several variants.^[2,3] We became interested in the Nazarov reaction as a means to access the A and B rings of the natural product tetrapetalone A (**1**, Scheme 1),^[4] which is an attractive synthetic target because of its biological relevance and architectural complexity. To date, there have been no reported syntheses of this natural product.^[5] It was envisioned that indanone **2** would serve as a versatile fragment to which rings C and D could be appended. In turn, **2** could arise from a Nazarov cyclization of aryl dienyl ketone **3**.

Congruent with our plans to utilize indanone **2** as a synthetic starting point for the synthesis of **1**, initial investigations focused on the conversion of readily prepared^[6] aryl dienyl ketones (e.g., **3**) into indanone products such as **2**. Surprisingly, whereas a screen of various Lewis acids and solvents at numerous temperatures produced either no reaction or the eventual decomposition of γ -methyl-



Scheme 1. Retrosynthetic approach to tetrapetalone A.

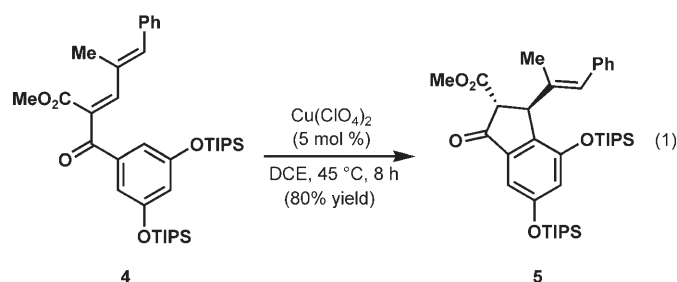


Scheme 2. Unusual facilitation of α -alkyl dienone substrates.

substituted aryl dienone **3a** (Scheme 2), the α,γ -dimethyl substituted aryl dienone **3b** reacted smoothly (23 °C, 1 h) in the presence of catalytic quantities of AlCl_3 to yield the indanones **2a** and **b** as a 4:1 mixture of diastereomers in 71 % yield.^[7]

Prompted by the unexpected reactivity differences observed in the Nazarov cyclization studies of **3a** and **3b**, we perused the literature for related transformations, and found only two examples of using conjugated dienyl ketones in the Nazarov reaction prior to our work.^[8] The previous reports both appear to be special cases, either involving the use of extremely forcing conditions (formic acid/phosphoric acid mixtures, 90 °C, 6 h)^[9] to obtain low yields of pentannulated products or an activated system that contained a polarizing dihydropyran moiety.^[10]

More recently, during the preparation of this Communication, Frontier and co-workers reported that aryl dienyl ketones bearing an electron-withdrawing group at the α position of the diene fragment and a phenyl group at the terminus (e.g., **4**; [Eq. (1)]) undergo the Nazarov cyclization



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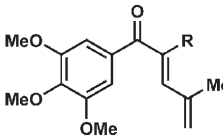
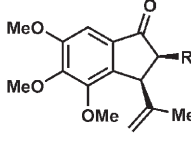
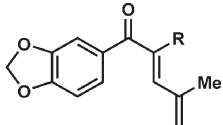
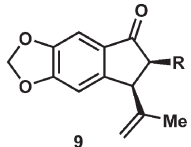
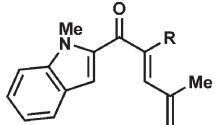
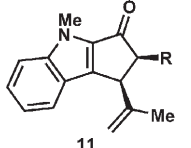
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to yield indanones (e.g., **5**).^[11] This recent study highlights an important difference from our observations in that the 4 π electrocyclizations reported by Frontier and co-workers are electronically driven, whereas we present evidence for a significant steric effect that facilitates the Nazarov cyclization of conjugated dienes bearing α,γ -substitution.

Our preliminary study of the scope of the observed steric effect resulting from the diene substituents reveals it to be quite general for a range of electron-rich aryl dienyl ketones (Table 1).^[12,13] For these aryl and heteroaryl substrates, the Nazarov cyclization is only observed in those cases where both α -Me and γ -Me groups are present.

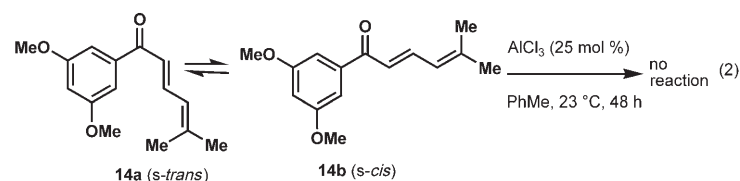
Table 1: Scope of the aryl dienyl ketone Nazarov reaction.^[a]

Entry	Substrate	t [h]	Product
1	 6a (R = H) 6b (R = Me)	24 6	 no reaction 60% yield (82:18 d.r.)
2	 8a (R = H) 8b (R = Me)	16 6	 no reaction 55% yield (75:25 d.r.) ^[b]
3	 10a (R = H) 10b (R = Me)	18 1	 no reaction 84% yield (80:20 d.r.)

[a] All reactions were run at 70°C with 25 mol % of AlCl_3 as the catalyst in PhMe (0.1 M). [b] 31% of the starting material recovered.

It is well documented that Nazarov substrates bearing alkyl groups at the α position undergo pentannulation with high efficiency.^[1a-c] This reactivity is attributable to a higher population of the productive *s-trans* conformer (e.g., **14a**; [Eq. (2)]), which is preferred over the nonproductive *s-cis* conformation (e.g., **14b**).^[14] This effect is certainly a significant component of the observed reactivity for the α,γ -disubstituted substrates presented in Table 1,^[14b-c] but our results demonstrate that this is not the whole story (see below).

To better understand the inherent differences that lead to the observed facilitation of the 4 π electrocyclization with the introduction of alkyl substituents at the α - and γ -positions (e.g., **3a** versus **3b**), a detailed analysis of the cyclizations of Lewis acid bound dienyl ketones was undertaken by using



quantum chemical methods.^[15,16] Geometry optimizations and frequency analyses (to verify that structures are minima or transition-state structures) were carried out at the B3LYP/6-31 + G(d,p) level.^[17] Energy barriers for cyclization of all Lewis acid bound intermediates were computed from the *s-trans* conformation. Figure 1 shows AlCl_3 -bound **3a** and **3b** (**12** and **13**, respectively), and the transition-state structures for their cyclization (**TS-12** and **TS-13**, respectively).

Consistent with our experimental results, the cyclization barrier for **12** ($\Delta G^\ddagger = 30.6 \text{ kcal mol}^{-1}$) is predicted to be considerably larger than that for **13** ($\Delta G^\ddagger = 24.0 \text{ kcal mol}^{-1}$), even though the *s-trans* conformation of the reactant complex

was used for both. This barrier appears to be the result of an unfavorable 1,3-allylic interaction between the two methyl groups in **13** that is not present in **12**. The strain imparted to the AlCl_3 -bound reactant by this interaction (see the distorted

C-C-C angle, 132°, in **13**, Figure 1; note also that the Me...Me distance is significantly greater for **TS-13** than for **13**) is reduced as the transition-state structure is reached.^[18,19] Replacement of the γ -methyl groups of **12** and **13** with hydrogen atoms reduces the energy difference (3.2 kcal mol^{-1}) between the corresponding barriers for cyclization (compare to the 6.6 kcal mol^{-1} difference between **12** and **13**), additionally demonstrating the importance of the 1,3-allylic steric interaction.^[14c]

In accord with our previous findings, δ,δ -dimethyl dienyl ketone **14**, which does not possess an α -Me or γ -Me substituent, is unreactive under the standard reaction conditions (25 mol % AlCl_3 , 0.1 M in PhMe, 23°C) over 48 h. The computed ΔG^\ddagger for this reaction is 31.9 kcal mol^{-1} (based on AlCl_3 -complexed **14**), which is slightly higher than that for **12**.

However, smooth conversion of aryl dienones **15** and **16** (both of which possess α Me but not γ Me substituents) into indanone products **17a** and **b** and **18a** and **b**, respectively, is observed under identical reaction conditions after 2 hours. The computed free energy barriers for these systems are 27.4 kcal mol^{-1} and 27.3 kcal mol^{-1} , respectively—higher than that for **13**, which points to the importance of a γ -Me substituent in lowering the activation barrier, but significantly lower than those associated with **12** and AlCl_3 -complexed **14**.

The mixture of diastereomers **17a** and **b** was readily equilibrated to a 4:1 mixture favoring **17b**^[20] upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) over 10 hours at 23°C.^[21]

The facile electrocyclization of **15** and **16** may be rationalized by a preference for the productive *s-trans* conformation for these substrates, which is dictated by the α -Me substituent. Additionally,

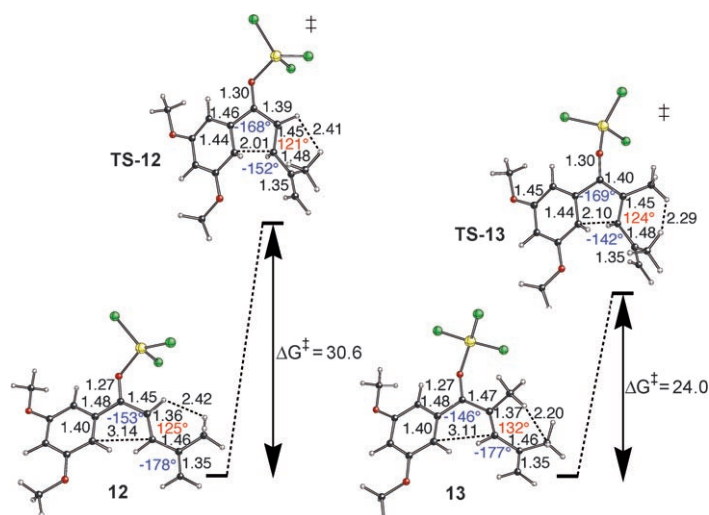
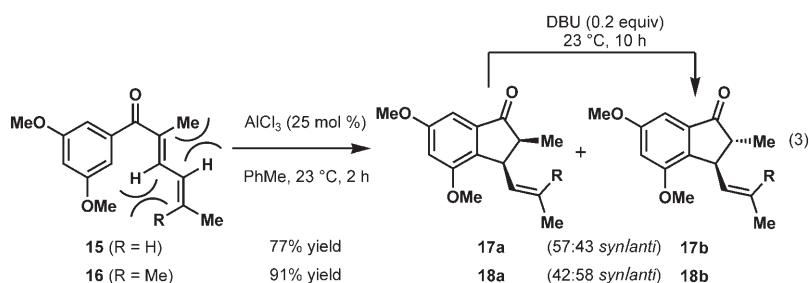


Figure 1. Computed structures and relative energies (B3LYP/6-31 + G(d,p) [17]) for cyclization of **12** and **13** (energies in kcal mol⁻¹; black numbers correspond to distances in Å; blue numbers correspond to X-C-C=C dihedral angles; red numbers correspond to C-C-C bond angles).

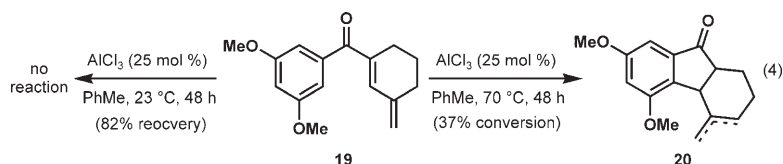
however, we believe that compounded steric effects (i.e. pseudo 1,3-allylic interactions; [Eq. (3)]) of the methyl substituents in **16**, which are manifested in a variety of small geometric distortions,^[6] also contribute to efficient cyclization for this substrate. These effects are borne out in the computed barriers for these reactions, which are calculated by using the *s-trans* reactants.



To distinguish the effect of γ -alkyl substituents from the previously established facilitation by α -alkyl substituents for this subset of Nazarov substrates, cyclic aryl dienyl ketone **19** [Eq. (4)] was designed. We hypothesized that this substrate would be unlikely to undergo a Nazarov cyclization under our standard conditions at room temperature, despite the fact that the *s-trans* conformation should be favored by virtue of the α -alkyl substitution (our calculations suggest that the *s-trans* conformation is favored by ≈ 2 kcal mol⁻¹ over the *s-cis* conformation^[14]). The lack of reactivity of **19** was anticipated because 1,3-steric clashes for the α and γ substituents on the diene fragment are replaced by a covalent tether. This design should pre-

serve any electronic effects while removing the steric effect that we suggest is dominating the reactivity. Exposure of **19** to the reaction conditions at 23 °C over 48 hours returns the starting substrate (**19**, 82% recovery), in line with our prediction. The computed free energy barrier for Lewis acid complexed **19** is 29.2 kcal mol⁻¹, again higher than those for the Lewis acid complexes of **3b**, **15**, and **16**, and not much higher than those for the complexes of **15** and **16**. Consequently, we hypothesized that **19** might be prone to cyclization if heated. In fact, increasing the temperature to 70 °C led to a 37% conversion of **19** into a 1.8:1 mixture of double bond isomers of tricycle **20**.^[22]

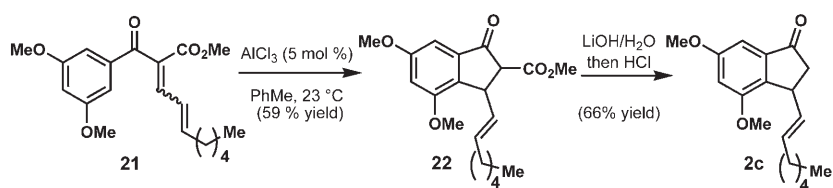
On the basis of the experimentally observed reactivity and the quantum calculations described above, it would appear that systems for which free energy barriers for cyclization of *s-trans* Lewis acid bound reactants are computed to be less than 28 kcal mol⁻¹ are likely to undergo Nazarov cyclization under our standard conditions.^[23] Conversely, those with computed barriers greater than 29 kcal mol⁻¹ are unlikely to



cyclize under these conditions, even if they possess an α -alkyl substituent. This result should be taken as a rough guideline for predicting reactivity, especially for systems with computed barriers near to the 28–29 kcal mol⁻¹ range. For systems with computed barriers below, but near to this range, cyclization may be effected by increasing the temperature.^[24]

Finally, to access indanone products that do not possess an α -alkyl substituent, a removable activating group, similar to the method of Frontier and co-workers,^[11] may be applied. For example, the cyclization of **21** (Scheme 3) proceeds in 59% yield at 23 °C to afford β -ketoester **22**. Saponification of **22** and subsequent decarboxylation upon workup affords indanone **2c**.

In conclusion, we have found the Nazarov cyclization of aryl dienyl ketones to be dependent on steric interactions between diene substituents at the α - and γ -positions.^[25] The proposed models are highly predictive for a range of aryl



Scheme 3. Synthesis of indanones without α substituents.

dienone compounds possessing alkyl substituents, and provide a more complete picture of the reactivity of this subset of Nazarov substrates.^[26] Our current efforts are focused on applying these reactions to a total synthesis of tetrapetal-one A.

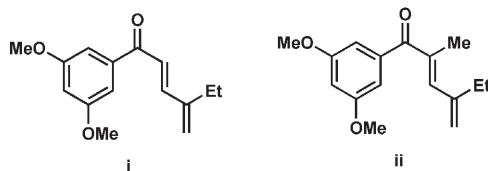
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- [6] For details, see the Supporting Information.
- [7] Similarly, **i** was unreactive under the standard conditions, whereas **ii** provided the corresponding indanone in 58% yield as a 92:8 mixture of diastereomers.
- [8] The work detailed in this manuscript was presented by RS and APM in poster sessions at a Gordon Research Conference (July 16–21, 2006, Organic Reactions and Processes, Bryant University) and 232nd ACS National Meeting (San Francisco, CA, United States, Sept. 10–14, 2006, ORGN-523), respectively.
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- [14] a) For a detailed discussion, see the recent reviews on this subject (references [1a–c]); b) Our quantum chemical calculations also bear this out. For example, the *s-trans* form of **12** is ca. 2 kcal mol^{−1} higher in energy than the *s-cis* form, whereas the *s-trans* form of **13** is ca. 1 kcal mol^{−1} lower in energy than the *s-cis* form; c) See the Supporting Information for details and additional related examples.
- [15] Cyclization is expected to be the rate-determining step of the entire transformation. For a discussion, see reference [1].
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- [17] a) A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648–5652; b) A. D. Becke, *J. Chem. Phys.* **1993**, 98, 1372–1377; c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, 37, 785–789; d) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, 98, 11623–11627; e) These calculations were run by using Gaussian03 (full citation can be found in the Supporting Information, along with additional details on these calculations, including test calculations in toluene). Free energy barriers include entropy corrections computed for 25°C.
- [18] Initially we expected this strain to manifest itself by twisting the diene out of conjugation, which would thereby prepare it for the cyclization reaction, during which the conjugation is necessarily reduced as the transition-structure is reached and the cyclic delocalization typical for a pericyclic reaction develops in its place. However, only small deviations from planarity are observed in our computed structures for AlCl₃-complexed reactants (see Figure 1 and the Supporting Information). Twisting of 2,4-dialkyl 2-*trans*-4-*trans* pentadienals has been studied: H. Ogawa, Y. Taketugu, T. Imoto, Y. Taniguchi, H. Kato, *Tetrahedron Lett.* **1979**, 20, 3457–3460.
- [19] The relative stabilities of the uncomplexed aryl dienyl ketones (e.g., **3a** and **3b**) may also be an important component. However, in our studies, consideration of the reactive Lewis acid bound structures were found to be a more significant predictor of reaction facility since no sizable differences in the λ_{\max} values were found for the aryl dienone substrates.^[6]
- [20] The *syn* and *anti* determinations were made on the basis of coupling constants by using the Karplus correlation and NOESY analysis.^[6]
- [21] This equilibration protocol to enrich the product in one diastereomer was found to be general for all the indanones (see Table 1) obtained and in all other cases gave diastereomeric ratios $\geq 9:1$.^[6]
- [22] Presumably, the exocyclic double bond isomerizes to an endocyclic position under the reaction conditions.
- [23] At this level of theory, and for systems bearing 3,5-dimethoxyphenyl groups (additional calculations are required to assess the limitations of this energetic criterion). Note also that these barriers should not be compared directly—in terms of their absolute magnitudes—with experimental barriers, since they are based on complexed reactants and do not include the effects of solvation.^[19]
- [24] Barriers for several other systems have been calculated ahead of experimental testing. See the Supporting Information for details.
- [25] Although we have shown that the propensity of aryl dienyl ketone substrates is to undergo Nazarov cyclization, those substrates not expected to undergo the cyclization may participate in alternate transformations. For example, upon exposure of **23a** [Eq. (5)] to catalytic AlCl₃ at 23°C, a 50% yield of Diels–Alder dimer **24** is formed. On the other hand, related substrate **23b** [Eq. (6)] bearing an α -methyl substituent undergoes the

Nazarov cyclization as expected. Calculations on Nazarov cyclizations for these substrates can be found in the Supporting Information. Aryl dienyl ketone substrates possessing non-electron-rich aryl groups do not undergo the Nazarov reaction even at elevated temperatures. For example, **26**, bearing a tolyl group undergoes an “anomalous” Nazarov cyclization^[27] at 70 °C to provide cyclopentenone **28** (via **27**) in 61 % yield [Eq. (7)]. Efforts to understand the underlying selectivity principles for these latter transformations are underway.

[26] Interestingly, problems with Cu-promoted Nazarov cyclization of an α -substituted (NO_2), γ -unsubstituted aryl dienyl ketone were also described in reference [11] (see Table 7 therein).

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