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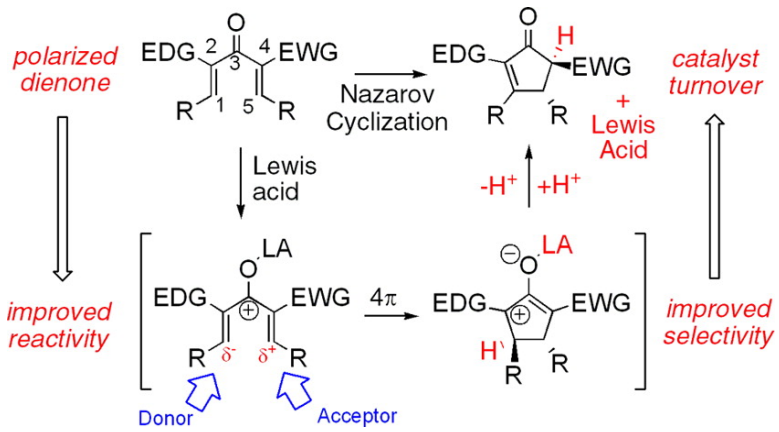

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Polarizing the Nazarov Cyclization: The Impact of Dienone Substitution Pattern on Reactivity and Selectivity

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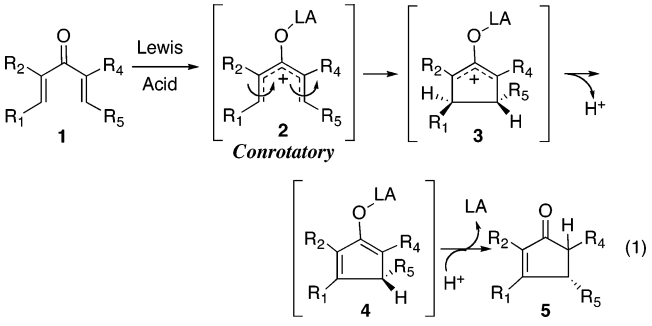
Abstract: The impact of dienone substitution on the Nazarov cyclization has been examined in detail. Substrates bearing different substituents at each of four positions on the dienone backbone were systematically probed in order to identify trends leading to higher reactivity and better selectivity. Desymmetrization of the pentadienyl cation and oxyallyl cation intermediates through placement of polarizing groups at both the C-2 and C-4 positions was found to be particularly effective. These modifications allowed cyclizations to occur in the presence of catalytic amounts of mild Lewis acids. It was also found that stereoconvergent cyclization of mixtures of *E* and *Z* isomers of alkylidene β-ketoesters occurred via an efficient isomerization process that occurred under the reaction conditions.

Introduction

Electrocyclic reactions are powerful synthetic transformations with the ability to create new carbon−carbon bonds stereospecifically by simple orbital reorganization. One type of electrocyclic reaction is a 4π-electron process known as the Nazarov cyclization, involving the conversion of divinyl ketones **1** to cyclopentenones **5** by activation with a Lewis acid (eq 1).[1]



(1)

Cyclization of pentadienyl cation **2** must proceed with conservation of orbital symmetry, dictating conrotatory ring closure to give a product with an *anti* relationship between R_1 and R_2 (see **3**, eq 1). Since disrotatory closure is electronically forbidden in the thermal reaction, stereospecificity is ensured for the bond formation.[2] Experimental data is consistent with this prediction: thermal cyclization under acidic conditions gives the product expected from a conrotatory ring closure,[3] and the photochemical reaction gives the opposite diastereomer, as expected from disrotatory ring closure.[2,4] In some cases, however, isomerization of the dienone complicates analysis.[5]

The Nazarov reaction should be recognized as a valuable synthetic transformation, since the stereospecific electrocyclization can convert achiral molecules into single stereoisomeric products. However, the cyclization of simple dienones like those depicted in eq 1 is often plagued with reactivity and selectivity problems that seriously compromise synthetic utility. Specifically, (1) strong Lewis acids are often necessary to promote cyclization; (2) one or more equivalents of promoter are required in most cases; (3) regioselectivity of the elimination step can be unselective (see **3** → **4**); (4) elimination of the proton often leads to loss of a stereocenter (see **4**); and (5) the final enolate protonation is often unselective (see **4** → **5**). Two strategies addressing some of the problems associated with synthetic utility in Nazarov cyclization have been disclosed, and both involved modification of the substitution pattern of the substrates **1**. Regioselective elimination became possible with the development of Denmark's silicon-directed Nazarov cyclization protocol, in which β-silyl divinyl ketones are employed in the cyclization.[6] West found that the intermediate cation (see **3**, eq

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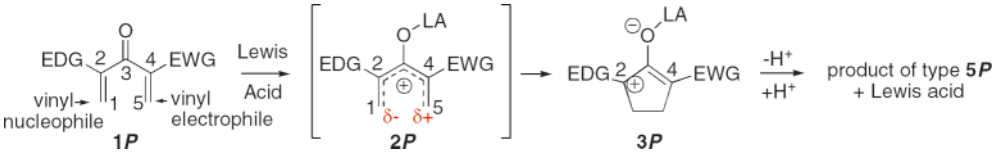
Scheme 1. Polarized Substrates for Nazarov Cyclization



1) could be intercepted by various nucleophilic species.[7,8] This strategy is significant because trapping the intermediate cation postpones elimination, such that both of the stereocenters created in the electrocyclic reaction are retained in the product.

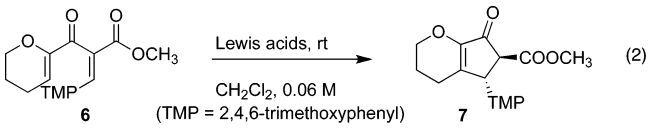
Inspired by the high reactivity engendered by the donor/acceptor relationship of diene and dienophile in the Diels−Alder reactions of Danishefsky[9] and Rawal,[10] we wondered whether polarization or desymmetrization of the intermediate pentadienyl cation **2** might improve the reactivity and selectivity of the Nazarov cyclization. Synthesis and cyclization studies on a divinyl ketone of type **1*P***, bearing an electron-donating group at one α position (e.g., C-2, Scheme 1) and an electron-withdrawing group at the other (e.g., C-4), were planned. It was hoped that treatment of **1*P*** with a Lewis acid would allow the development of complementary orbital coefficients at the termini of intermediate **2*P***, improving reactivity (Scheme 1). The substituents at C-2 and C-4 would also desymmetrize the oxyallyl cation (**3*P*)**, which was expected to improve the selectivity of the elimination step.

Before these studies were begun, little data concerning the reactivity of dienones bearing electron-donating and electron-withdrawing groups was available. It had been reported that dienones bearing a C-2 heteroatom cyclized efficiently, although like most other documented Nazarov cyclizations, a protic acid medium or treatment with stoichiometic amounts of strong Lewis acids was usually required to promote the reaction.[11−13] The cyclization of C-4 carboalkoxy and carbamate-substituted divinyl ketone substrates had been studied by Marino,[14] Regan,[15] and Takeda,[16] who found that superstoichoimetric amounts of the strong promoters $SnCl_4$ and TMSI were required. The reactions were typically slow (24 h) and low-yielding (<50%), indicating multiple competitive reaction pathways. Better success in the cyclization of these electron-poor substrates was reported in two more recent studies: both Kerr[17] and Aggarwal[18] were able to achieve efficient cyclization of dienones bearing electron-withdrawing groups using alternative Lewis acidic promoters. However, Nazarov cyclizations of substrates bearing both an electron-donating group at C-2 and an electron-withdrawing group at C-4 had not been explored.

Our initial study[19] and the closely related studies of Trauner,[20] Tius,[21] and Occhiato[22] have established that divinyl ketones bearing a heteroatom donor at one of the α-positions are indeed more reactive and cyclize efficiently in the presence of catalytic amounts of various Lewis acids. A full account of our study on Nazarov cyclizations of polarized divinyl ketones of type **1*P*** is given in this article.

Results and Discussion

Development of the Catalytic Nazarov Cyclization of Polarized Substrates. Initial screening was carried out on 2,4,6-trimethoxyphenyl-substituted dihydropyran substrate **6**. The cyclization was very rapid (<1 min) even at room temperature with stoichiometric $AlCl_3$, $Al(OTf)_3$, $Sc(OTf)_3$, and $Cu(OTf)_2$, as well as acetic acid, and the *β*-ketoester product **7** was isolated in nearly quantitative yield (eq 2). Furthermore, highly efficient cyclization of **6** was also observed upon treatment with 2 mol % of either $Cu(OTf)_2$, $Sc(OTf)_3$, or $Al(OTf)_3$ in CH_2Cl_2. The reaction was fast (<5 min) and high yielding (>99%) in all three cases. Since it was likely that triflic acid could also serve as a catalyst for the cyclization, we carried out control experiments to rule out the possibility of expeditious catalysis by triflic acid, often present in the commercial $Cu(OTf)_2$ reagent. Thus, when a solution of $Cu(OTf)_2$ was treated with excess potassium carbonate prior to addition of substrate, the cyclization behavior of **6** was unchanged.



(2)

Encouraged by the successful catalytic Nazarov cyclization of substrate **6**, a series of dihydropyran substrates were prepared to explore the scope of the method (Table 1). While it was possible to effect the cyclization using a catalytic amount of a number of different Lewis acids, we chose to study the reaction using $Cu(OTf)_2$ because of the documented performance of copper (II)−chiral ligand complexes in asymmetric reaction

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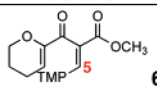
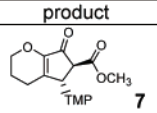
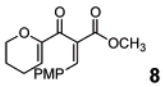
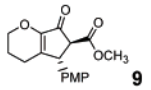
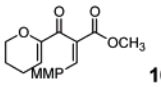
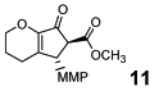
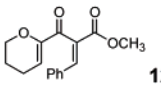
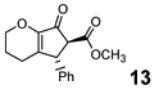
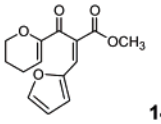
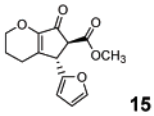
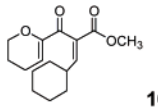
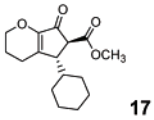
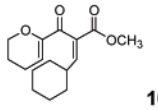
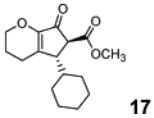
Table 1. Nazarov Cyclization of Dihydropyrans:[a] C-5 Variants

entry	dienone[b]	time (h)	product	yield (%)
1	 **6**	<<1	 **7**	>99
2	 **8**	3.5	 **9**	99
3	 **10**	48	 **11**	96
4	 **12**	108	 **13**	99
5	 **14**	12	 **15**	99
6	 **16**	240	 **17**	<50
7[c]	 **16**	2	 **17**	99

[a] Reaction Conditions: 2 mol % $Cu(OTf)_2$, CH_2Cl_2 (0.06 M), rt. [b] TMP = 2,4,6-trimethoxyphenyl, PMP = *p*-methoxyphenyl, MMP = *m*-methoxyphenyl. [c] Optimized conditions: $Cu(OTf)_2$, 2 mol %, dichloroethane (0.5 M), 55 °C.

chemistry.[23] Standard reaction conditions involving 2 mol % of $Cu(OTf)_2$ in chlorinated solvent led to efficient cyclization of all substrates studied (Table 1), results that represented one of the first examples of a general, efficient method for catalytic Nazarov cyclization.

A strong correlation between electron-donating ability of the C-5 substituent and reaction rate was found. Among the C-5 aryl-substituted cases (entries 1−5), the relative reaction rates were as follows: 2,4,6-trimethoxyphenyl (TMP) > *p*-methoxyphenyl (PMP) > 2-furyl > 3-methoxyphenyl (MMP) > phenyl (Ph). An alkyl substitution at C-5 was much less reactive: cyclization of **16** was very slow when carried out at room temperature, and decomposition of the substrate started to compete with the cyclization (entry 6). However, if the cyclization was carried out at elevated temperature and higher concentration, efficiency improved (entry 7).

The survey of C-1/C-2 substituent effects began with alkylidene β-ketoester substrates shown in Table 2. Five substrates were studied, all bearing a carbomethoxy substituent on C-4 and the 2,4,6-trimethoxyphenyl group at C-5 but differing at C-1 and C-2. All substrates cyclized efficiently with 2 mol % or 5 mol % $Cu(OTf)_2$ in chlorinated solvents. Cyclization of substrate **18** gave a mixture of cyclohexene isomers (entry 1), a result of unselective elimination in the final step (see eq 1). The cyclization of aromatic substrate **22** required higher temperatures, but cyclization was still efficient with 5 mol % $Cu(OTf)_2$ (entry 3). Cyclization of acyclic substrates **24** and **26** was slower and product yields were lower (entries 4 and 5).[24]

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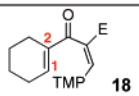
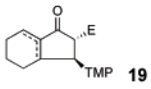
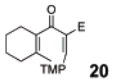
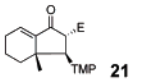
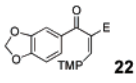
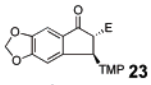
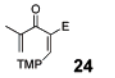
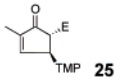
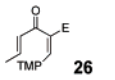
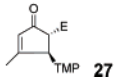
Table 2. Cyclization of Alkylidene β-Ketoesters:[a] C-1/C-2 Variants

entry	dienone[b,c]	time (h)	temp (°C)	product	yield (%) (exo:endo)[d]
1	 **18**	0.2	40	 **19**	86 (1:1)
2	 **20**	4	25	 **21**	95
3	 **22**	20	55	 **23**	93
4	 **24**	8	55	 **25**	75
5	 **26**	44	55	 **27**	58

[a] Reaction Conditions: 2 mol % $Cu(OTf)_2$ in dichloromethane (rt) or dichloroethane (higher temperatures). [b] E = COOMe; TMP = 2,4,6-trimethoxyphenyl. [c] Even though shown in an *E*-configuration, substrates sometimes contain *Z*-isomers. [d] Denotes position of double bond after elimination.

Cyclization of **26** was particularly complex, resulting in a mixture of regioisomers with **27** as the major component.

For most of the cyclizations examined in Tables 1 and 2, elimination was regioselective and products were isolated as single diastereoisomers. In contrast to the typically unselective elimination pathways observed for unpolarized substrates (**3** → **4**, eq 1), in these polarized substrates elimination of protons adjacent to the C-2 terminus of the oxyallyl cation was favored. This selectivity can be attributed to the electron-donating, cation-stabilizing group at the C-2 position and is further illustrated by the outcome of the cyclization of **26**. The electron-withdrawing group at C-4 was also found to be essential to diastereoselectivity in the final protonation step (**4** → **5**, eq 1). In contrast to the typically poor facial selectivity observed in the protonation of the enolate intermediate in substrates lacking an electron-withdrawing group,[6e,7f,20] the relative stereochemistry at C-4 and C-5 of β-ketoester products in Table 2 was predominantly *trans*, with minor (<10%) *cis* product detected in a few cases. The *trans* relationship was indicated by the coupling constant between the α-proton and the β-proton (1.4−2.2 Hz), an assignment that was later confirmed by X-ray single crystallography of **7** (Figure 1).

In these α, β-substituted cyclopentenones, it is expected that fewer unfavorable steric interactions would exist in the *trans* isomer relative to the *cis*. It has been assumed that a thermodynamic equilibration at the C-4 carbon of the product β-ketoester occurs under the acidic reaction conditions of the Nazarov cyclization, accounting for the diastereoselectivity of the protonation in these cases.[6a,15,17] Evidence for this has been provided by NMR experiments: the kinetically favored *cis* product is observed at low temperature and undergoes slow conversion to the thermodynamically favored *trans* product under the reaction conditions.[25] No further epimerization at the α-position of **7** was observed when the compound was treated

(24) Concurrent to our studies, Flynn and co-workers cyclized similar substrates with a stoichiometric amount of methylsulfonic acid ($MeSO_3H$): see ref 17.

(25) Carbon numbers in Figure 1 were assigned for the purposes of X-ray structure analysis and are not consistent with the numbering scheme used in the rest of the article.

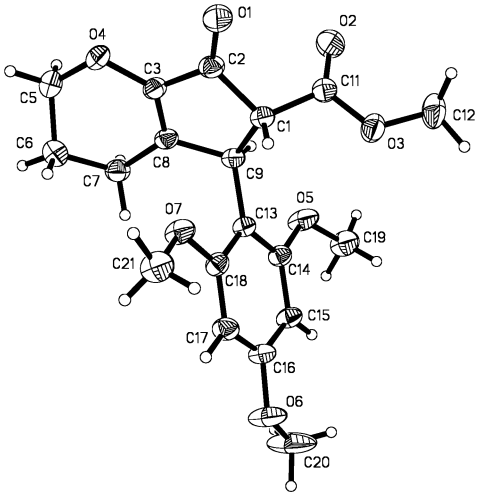
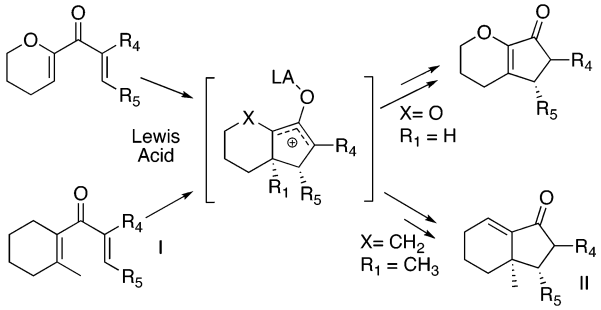


Figure 1. X-ray crystal structure of **7**.[25]

Scheme 2. Formation of Vicinal Stereocenters via Nazarov Cyclization



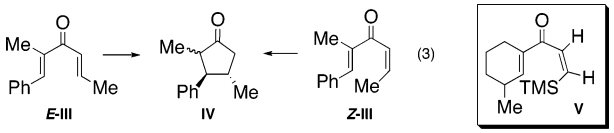
with NaOH/MeOH in THF at 55 °C, indicating that the product mixture already reflected the thermodynamic distribution of diastereoisomers.

Stereoconvergent Cyclization of Alkylidene *β*-Ketoesters. In many Nazarov cyclization applications, the elimination step leads to the loss of a stereocenter during cyclization (Scheme 2; top). If the dienone substrate has a strategically placed tetrasubstituted olefin, stereocenter loss does not occur and two new stereocenters are created (**I** to **II**, Scheme 2).

One would expect that successful implementation of this strategy would require synthesis of dienone I with geometric fidelity, since a number of studies of the Nazarov cyclization have indicated that the reaction proceeds with stereochemical predictability according to the Woodward−Hoffmann rules.[4,5] In most of these studies, substituents on the terminal carbons of the pentadienyl cation system are fixed in one position (as a member of a ring, for example), or the *β*-substituent is oriented *trans* to the central carbonyl of the dienone (as the dienone R_5 substituents are in Scheme 2). In these cases, olefin geometry translates directly to the new sp^3 stereocenters. However, experiments have revealed that in cyclizations of acyclic *Z* dienones,[7f] cyclic *Z* dienones with significant angle strain,[5] and acyclic alkylidene *β*-ketoesters (vide infra), olefin geometry did not translate to the two new stereocenters of the product as one would predict based on the conservation of orbital symmetry. Because these substrate dienones were not fixed in an *E* or *Z* configuration, they underwent isomerization under the reaction conditions, which explains the apparent violation of the Woodward−Hoffmann rules.

We have found that cyclization of a mixture of *E* and *Z* alkylidene *β*-ketoesters of type **I** is stereoconvergent, giving a single diastereomeric product **II**. This result contradicts the commonly held belief that the olefin geometry of the substrate is directly translated to the stereocenters of the product. The Knoevenagel condensation of *β*-ketoesters with aldehydes, a method often used to synthesize alkylidene *β*-ketoesters, is a thermodynamically controlled process[26] that gives a mixture of *E* and *Z* isomers (see Table 3).[27] The major component of the mixture usually has *E* geometry, but in many cases the energy difference between the isomers is not great. The isomers can sometimes be isolated by chromatography, but reversion to the thermodynamic equilibrium mixture is reported to occur upon standing at or even below room temperature.[17,28,29] This behavior has complicated the study of the individual isomers.

Therefore, we were pleased to discover that when the mixture of *E* and *Z* diastereomers was treated with catalytic copper triflate, a high yield of a single Nazarov cyclization product diastereomer was isolated. Interestingly, the stereochemistry of the product corresponded to the expected conrotatory cyclization of the *minor Z* isomer.[30] Stereoconvergent behavior of this kind was also observed in studies of reductive Nazarov cyclization: both ***E*-III** and ***Z*-III** were converted to the same product mixture **IV** (eq 3).[7b,7f] Similarly, in one of Denmark's early studies, it was found that the analogous *cis*-disubstituted *β*-silyl enone **V** isomerized before it cyclized.[6d] However, it was not clear whether this kind of isomerization could always be expected to occur prior to cyclization, and in particular, no studies addressing isomerization behavior in trisubstituted olefins had been conducted. The efficiency and selectivity of the coupled isomerization/cyclization prompted us to carry out a more thorough study of stereoconvergence in the Nazarov cyclization of alkylidene *β*-ketoesters.



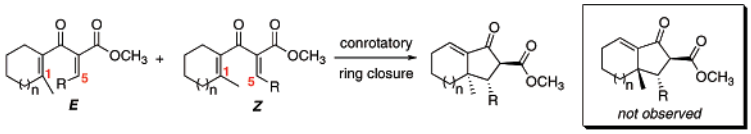
Reaction conditions: BF_3-OEt_2 (1.1 equiv.), Et_3SiH (10 equiv.)

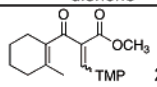
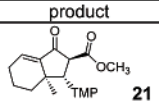
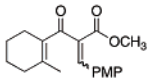
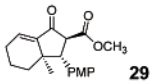
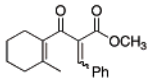
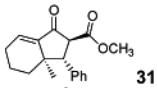
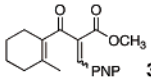
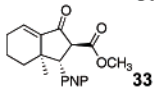
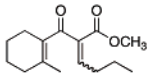
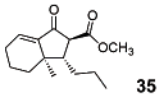
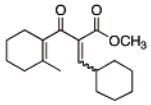
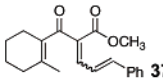
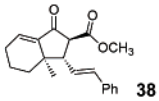
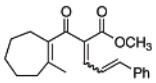
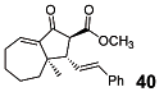
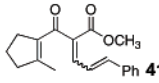
Stereoconvergent cyclization behavior was observed in dienones with both aryl and alkyl substituents, as shown in Tables 3 and 4. Both [5,6]- and [5,7]-fused ring systems were formed in good yield. However, cyclization of substrates with an internal methyl substituent at C-1 and R = alkyl substitution was sluggish (**34E/Z**) or completely inhibited (**36E/Z**). Cyclopentenyl enone **41E/Z** did not cyclize.[31]

Creation of vicinal tertiary centers was also possible but compromised by competing internal elimination of a proton (and loss of a stereocenter) to give a mixture of products of types **A**

(26) Janka, M.; He, W.; Frontier, A.; Flaschenriem, C.; Eisenberg, R. *Tetrahedron* **2005**, *61*, 6193.
(27) (a) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 341. (b) Tanikaga, R.; Konya, N.; Hamamura, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3211.
(28) Assignment of *E* and *Z* isomers was accomplished by analysis of $^3J_{C,H}$ coupling constants: see Kingsbury, C. A.; Draney, D.; Sopchik, A.; Rissler, W.; Durham, D. *J. Org. Chem.* **1976**, *41*, 3863.
(29) We observed slow reversion of a neat sample of a single isomer (isolated by chromatography) to the thermodynamic mixture in days at 25°C.
(30) The same result was obtained with catalytic $Sc(OTf)_3$, $AlCl_3$, or [IrMe(CO)(dppe)(DIB)]$(BARF)_2$.
(31) NOE data were used to assign stereochemistry: see Supporting Information.

Table 3. Nazarov Cyclization of Alkylidene β-Ketoesters I:[a] C-5 Variants; Internal C-1 Substituent = CH_3



entry	dienone[c]	ratio *E*/*Z*	time (h)	temp (°C)	product	yield (%)
1	 **20E/Z**	40/60	4	25	 **21**	95
2	 **28E/Z**	62/38	1	55	 **29**	>99
3	 **30E/Z**	71/29	10	55	 **31**	65
4	 **32E/Z**	89/11	14	55	 **33**	72
5	 **34E/Z**	51/49	10	75	 **35**	25
6	 **36E/Z**	57/43	>24	75	-[d]	-
7	 **37E/Z**[e]	57/43	10	75	 **38**	60
8	 **39E/Z**[e]	51/49	9	55	 **40**	85
9	 **41E/Z**[e]	78/22	12	45	-[f]	-

[a] $Cu(OTf)_2$ (5 mol %), $Cl(CH_2)_2Cl$ (0.2 M). [b] TMP=2,4,6-trimethoxyphenyl; PMP = *p*-methoxyphenyl; PNP = *p*-nitrophenyl. [c] Dienones **36E/Z** were recovered unchanged. [d] Run at 0.5 M in $Cl(CH_2)_2Cl$. [e] Significant decomposition occurred; no desired product was isolated.

and **B** (Table 4). Only one diastereomer of product type **A** was observed (again corresponding to *Z* isomer cyclization), even though the starting alkylidene was greater than 95% *E* geometry. Cyclization occurred efficiently for **42E/Z** and **44E/Z**, in contrast to the poor reactivity observed in the analogous tetrasubstituted systems (Table 3, **34E/Z** and **36E/Z**). Apparently, if the substituents at the internal β-positions of the dienone (C-1 and C-5) experience too much steric congestion, cyclization efficiency is compromised.[32]

Observed cyclization times for pure *E* and *Z* isomers are presented in Table 5. For each pair, cyclization of the individual isomers led to the same diastereomeric product. **20E** and **20Z** cyclized at the same rate and so did **28E** and **28Z** (entries 1−4).[33] It was found that **42Z** isomer cyclized faster and slightly more efficiently than the **42E** isomer (entry 7 vs entry 8). Similarly, although **30E** and **30Z** were inseparable, **30Z** was consumed more quickly than **30E** (entry 5). After 1 h, it was possible to isolate **31** and unreacted **30E**, which allowed us to carry out cyclization of pure **30E** (entry 6).

According to the results in Table 5, isomerization can be either faster or slower than ring closure, depending on dienone substitution. When R is an electron-rich aromatic (entries 1−4), observed reaction time is the same for both isomers, so isomerization must be faster than ring closure.[34] In contrast, when R = phenyl or *n*-propyl (entries 5−8), the *Z* isomer cyclizes faster than the *E* isomer, indicating that $E_{cation}-Z_{cation}$ isomerization must be slow relative to ring closure of Z_{cation}.

Quaternary center formation was found to be most efficient for substrates with aromatic substitution, giving products with limited synthetic utility (Table 3). Fortunately, cleavage of the styrenyl double bond of **38** could be accomplished via ozonolysis, to give versatile aldehyde **48** in 61% yield (Scheme 3).

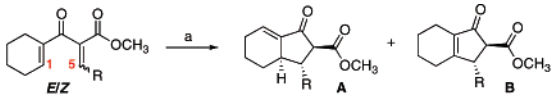
A proposed mechanistic pathway is shown in Scheme 4. Lewis acid activation of the *E* or *Z* dienone provides the corresponding pentadienyl cation intermediates. While multiple rotational conformers can exist, only two are properly aligned for cyclization (E_{cation} and Z_{cation}; Scheme 4). The stereochemistry of the product observed indicates that E_{cation} does not

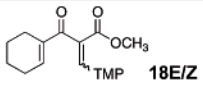
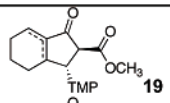
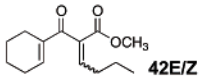
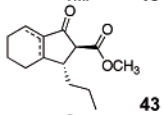
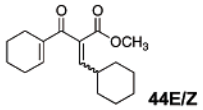
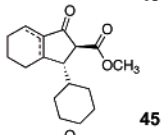
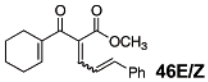
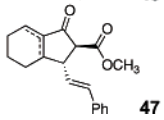
(32) The poor reactivity of cyclopentenyl-substituted β-ketoester alkylidenes has been documented: see ref 16.

(33) Harmata, M.; Schreiner, P. R.; Lee, D. R.; Kirchhoefer, P. L. *J. Am. Chem. Soc.* **2004**, *126*, 10954.

(34) Further evidence: the *E*/*Z* isomer ratio (as observed by ^1H NMR) did not change over the course of cyclization with either copper triflate or [IrMe(CO)(dppe)(DIB)](BARF)$_2$ as catalyst. When pure *E*/*Z* **20** or **28** was subjected to copper triflate, the interconversion was observed within 5 min of mixing by NMR at rt. The isomers had reached equilibrium before any cyclization took place.

Table 4. Nazarov Cyclization of Alkylidene β-Ketoesters II: C-5 Variants; Internal C-1 Substituent = H



entry	dienone[b]	ratio *E*/*Z*	time (h)	temp (°C)	product	yield (% **A**+**B**) (**A**:**B**)
1	 **18E/Z**	95/5	0.17	25	 **19**	89, 1:1
2	 **42E/Z**	92/8	10	65	 **43**	70,1:2
3	 **44E/Z**	94/6	24	65	 **45**	72, 3:1
4	 **46E/Z**	75/25	2.5	65	 **47**	66, 1:1.7

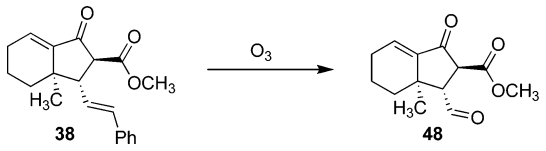
[a] $Cu(OTf)_2$ (5 mol %), $Cl(CH_2)_2Cl$ (0.2 M). [b] TMP = 2,4,6-trimethoxyphenyl.

Table 5. Comparison of *Z* versus *E* Alkylidene β-Ketoester Cyclization[a]

entry	dienone	time (h)	temp (°C)	yield (%)	product
1	**20Z**	4	25	~99	**21**
2	**20E**	4	25	~99	**21**
3	**28Z**	0.75	45	97	**29**
4	**28E**	0.75	45	96	**29**
5	**30Z**	1[b]	65	71[c]	**31**
6	**30E**	10	65	60	**31**
7	**42Z**	2	65	75	**43A/B**[d]
8	**42E**	10	65	68	**43A/B**[d]

[a] Reaction conditions: $Cu(OTf)_2$ (5 mol %), $Cl(CH_2)_2Cl$ (0.2 M). [b] Time observed for consumption of **30Z** during cyclization of the **30E**/**30Z** mixture. [c] Estimated yield based on recovered **30E.** [d] Ratio of **43A/B** was 1:2.

Scheme 3. Ozonolysis of Cinnamyl-Substituted Nazarov Cyclization Products



cyclize, probably because of the significant steric interactions between R_1 and R_2. However, E_{cation} can isomerize via σ bond rotation to Z_{cation}, which is able to cyclize.[35−37]

In summary, our findings indicate that alkylidene β-ketoesters with *E* geometry undergo Nazarov cyclization to give products that *do not* bear the stereocenters expected from conrotatory cyclization. Instead, *E*/*Z* isomerization occurs prior to cyclization, to give a single product with stereochemistry corresponding to *Z* isomer cyclization. It is likely that unfavorable steric interactions in the *E*-configured pentadienyl cation intermediate prevent cyclization. This stereoconvergent cyclization behavior is significant for the future planning of asymmetric cyclization strategies: a nonracemic chiral catalyst could allow enantioselective synthesis of both types of targets shown in Scheme 4, from a mixture of *E* and *Z* stereoisomers.

Effect of C-4 Electron-Withdrawing Groups on Reaction Rate. Divinyl ketone substrates bearing different C-4 substituents were also studied. In order to a make meaningful assessment, identical reaction conditions were used for all the cyclizations: 2 mol % $Cu(OTf)_2$, in dichloromethane or dichloroethane, at 0.5 M concentration. Substrates bearing 2,4,6-trimethoxyphenyl substitution at C-5 were examined so that isomerization would be faster than cyclization, and cyclization rates could be more accurately compared (Table 6).

Most of the substrates cyclized with 2 mol % $Cu(OTf)_2$ in good to excellent yields. Significant decomposition was observed in the reaction of **51**, and product yield was low (entry 3). Since this substrate is not "polarized," it was expected to be less reactive. When the C-4 substituent was not an ester, the stereoselectivity of the enolate protonation (see **4** → **5**, eq 1) was poor (entries 7 and 8). Overall, the reaction rates did correlate with C-4 electron-withdrawing ability (CO_2R > Cl > H > CH_3, entries 5−8), but the rate differences observed were very modest.

The versatile Knoevenagel condensation was the standard protocol used to synthesize alkylidene β-ketoesters for Nazarov cyclization studies. However, the relatively harsh conditions of this procedure, such as high temperatures, lengthy reaction times, and difficulties in making starting material, did not allow

(35) E_{cation} is most efficiently delocalized in these substrates, accounting for the facility of the isomerization.
(36) Since selectivity arises from the differential reactivity of two isomers in equilibrium (E_{cation} and Z_{cation}), the process could be viewed as an example of *dynamic kinetic diastereoselection.*
(37) It is likely that a similar process is responsible for the stereoselectivity observed in the rearrangement of furfuryl carbinols to 3-hydroxycyclopentenones: (a) Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, *17*, 3555. For a theoretical analysis of this reaction with conclusions consistent with our experimental findings, see (b) Faza, O. N.; Lopez, C. S.; Alvarez, R.; de Lera, A. R. *Chem. Eur. J.* **2004**, *10*, 4324.
(38) (a) Padwa, A.; Meske, M.; Ni, Z. *Tetrahedron* **1995**, *51*, 89. (b) Padwa, A.; Chiacchio, U.; Kline, D. N.; Perumattam, J. *J. Org. Chem.* **1988**, *53*, 2238.
(39) (a) Canterbury, D. P.; Frontier, A. J.; Um, J. M.; Cheong, P. H.-Y.; Goldfeld, D. A.; Huhn, R. A.; Houk, K. N. Unpublished results.

Scheme 4. Stereoconvergent Behavior of *E*/*Z* Mixtures in Nazarov Cyclization: Proposed Mechanism

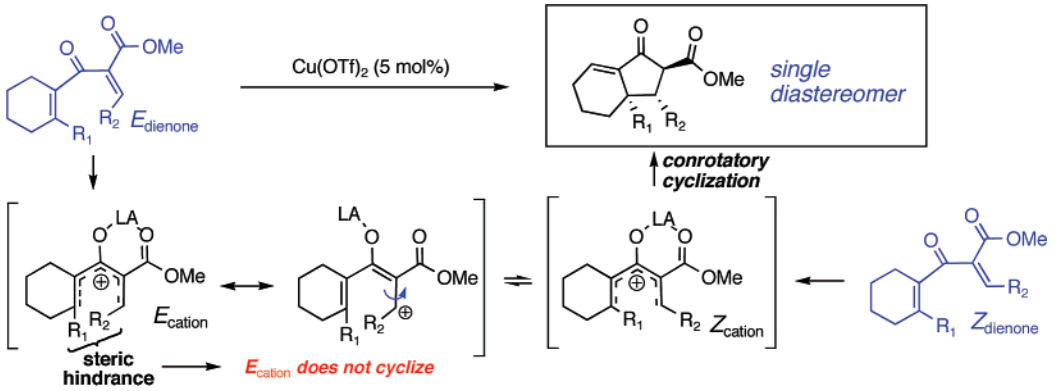
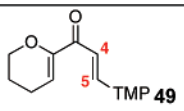
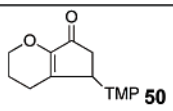
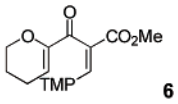
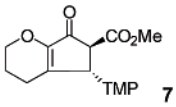
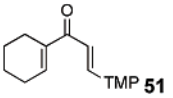
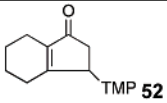
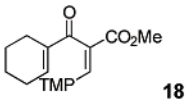
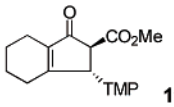
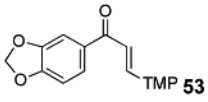
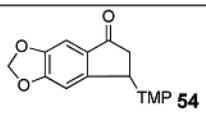
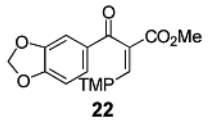
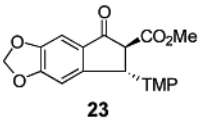
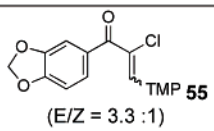
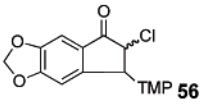
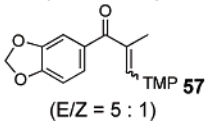
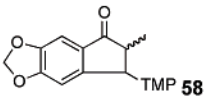


Table 6. Cyclization of C-5 Trimethoxyphenyl-Substituted Dienones: C-4 Variants

entry	dienone[a,b]	time (h)	temp (°C)	product	yield (%) (cis:trans)[c]
1	 **49**	0.3	25	 **50**	86
2	 **6**	<0.1	25	 **7**	99
3	 **51**	5	40	 **52**	35[d]
4	 **18**	0.25	40	 **19**	86
5	 **53**	3	65	 **54**	82
6	 **22**	0.5	65	 **23**	90
7	 **55** (E/Z = 3.3 :1)	1.5	65	 **56**	82 (5:4)
8	 **57** (E/Z = 5 : 1)	4.5	65	 **58**	71 (1:5)

[a] The olefin geometry was determined by coupling constants. [b] General reaction conditions: 2 mol % $Cu(OTf)_2$, dichloroethane, 0.5 M. [c] Ratio of *cis*/*trans* isomers at C-4.. [d] A complicated mixture was obtained. ^{1}H NMR revealed the possible presence of other regioisomeric products. However, only the product shown was isolated and characterized.

synthesis of certain dienone targets. In order to access the desired alkylidene β-ketoesters, a reaction sequence reported by Padwa[38] was adopted as a mild alternative (Scheme 5).[39] The one-pot procedure commences with a (3 + 2) cyclization of an alkyne and a nitrone to form an isoxazoline (**VII**), followed by oxidative extrusion of nitrosomethane by *m*-CPBA to form the appropriate divinyl ketone (**VIII**).

This methodology was used to synthesize a series of aromatic Nazarov substrates bearing different electron-withdrawing groups (Table 7). This series of dienones was chosen for study because

(40) (a) Boger, D. L.; Lerner, R. A.; Cravatt, B. F. *J. Org. Chem.* **1994**, *59*, 5078. (b) Yamamura, K.; Watarai, S.; Kinugasa, T. *B. Chem. Soc. Jpn.* **1971**, *44*, 2440. (c) Dornow, A.; Menzel, H. *Ann.* **1954**, *588*, 40.
(41) Gilmartin, B.; Eisenberg, R. Unpublished results.

Scheme 5. Sequential (3 + 2)Dipolar Cycloaddition/Oxidative Extrusion Protocol for the Synthesis of Alkylidene β-Ketoesters

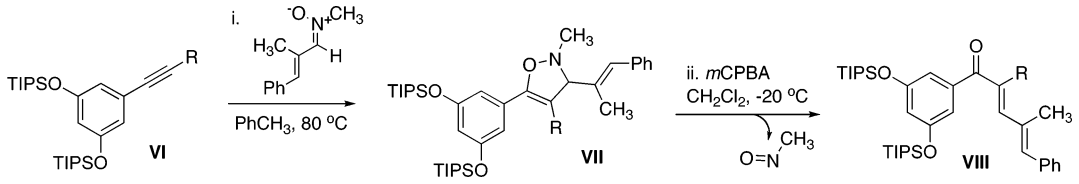
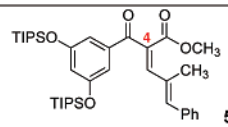
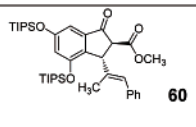
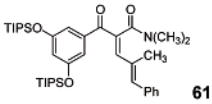
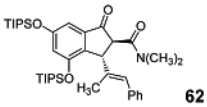
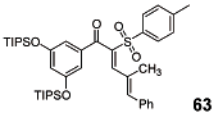
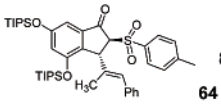
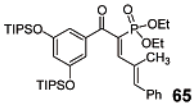
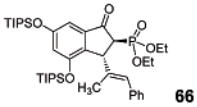
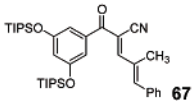
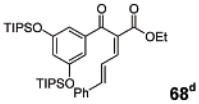
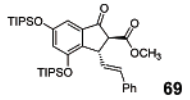
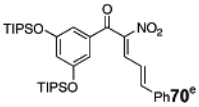


Table 7. Cyclization of Aryl Enones: C-4 = Electron-Withdrawing Group Variants

entry	dienone[a,b]	Z/E	time (h)	temp (°C)	product	yield (%)
1	 **59**	>19:1	8	45	 **60**	80%
2	 **61**	>19:1	14	45	 **62**	92%
3	 **63**	>19:1	7	80	 **64**	85%
4	 **65**	>19:1	24	80	 **66**	90%
5	 **67**	>19:1	12	80		--[c]
6	 **68**[d]	>1:19	26	45	 **69**	83%
7	 **70**[e]	>19:1	72	80		--[c]

[a] Reaction conditions: 5 mol % $Cu(ClO_4)_2$, 0.1 M dichloroethane. [b] All dienones were prepared by nitrone sequence shown in Scheme 5 unless otherwise noted. [c] No cyclization was observed before decomposition of the starting ketone. [d] Prepared by Knoevenagel condensation. [e] Prepared by a modified Knoevenagel condensation.[40]

the nitrone synthetic strategy (Scheme 5) made them available as single isomers with *Z* (out) geometry, rather than as the thermodynamic mixture of *E*/*Z* isomers expected from synthesis via Knoevenagel condensation. Studying the cyclization of substrates with exclusively *Z* geometry avoids complications caused by the isomerization processes noted for the *E* isomers (see Table 1), allowing access to true relative reaction rates. In fact, a pair of closely related *Z* and *E* isomers in this series provides another example of this pattern: cyclization of the *Z* isomer is complete in 8 h (entry 1), while the *E* isomer requires 26 h for conversion to product (entry 6), presumably because isomerization is slow and must occur before cyclization does. The results of selective ^{1}H-decoupled ^{13}C NMR and NOE experiments indicate *Z* stereochemistry for α-nitroenone **70**, although this geometry is opposite to the results typically obtained from Knoevenagel condensation (vide supra) and from the results reported for synthesis of analogous alkylidene α-nitroketones.[40a,b]

Finally, varying the electron-withdrawing group at C-4 in the aryl enones with *Z* olefin geometry provided the following relative rates: ester > amide > sulfone > phosphonate (entries 1−4). The ester (**59**) and amide (**61**) aryl enones cyclized at 45 °C, while the sulfone (**63**) and phosphonate (**65**) enones did not begin to cyclize until the temperature was elevated to 80 °C. In all cases of successful cyclization, the product was isolated in high yield as a single diastereomer with a *trans* relationship between the α- and β-substituents on the product indanone. Two substrates tested (α-cyanoenone **67**; entry 5 and α-nitroenone **70**; entry 7) did not cyclize at 45 °C and then decomposed at elevated temperatures. No cyclization products were detected in the reaction mixtures, and higher catalyst loadings did not improve the results. It is likely that the cyano group (entry 5) does not cyclize because the Lewis acid binds preferentially at the terminal nitrogen.[41] In this linear arrangement, the Lewis acid sits too far away from the ketone carbonyl to allow formation of the pentadienyl cation. In the case of the α-nitroketone, rapid decomposition occurs under the cyclization conditions.

According to Hammett constants, the expected order of reactivity based on electron-withdrawing character for the groups studied should be nitro > sulfone > cyano > phosphonate > ester > amide.[42] Since phosphonate **65** and sulfone **63** were both less reactive than ester **59** and amide **61** (Table 7), cyclization rates are not dependent on the electron-withdrawing ability of the C-4 substituent alone. However, reactivity will also depend upon how well the substrate (acting as a bidentate ligand) and the Lewis acid catalyst are able to coordinate to produce an intermediate with strong cationic character at the C-5 position. Facility of coordination will depend upon the σ-donating ability of the C-4 substituent as well as the geometry the substrate adopts as a bidentate ligand. Bond lengths increase as heteroatoms are introduced at the C-4 position, and in the case of sulfone **63** and phosphonate **65**, this could lead to significant skewing of the angle at which the oxygen of the C-4 substituent sits, thus distorting the binding site for the catalyst. This could explain the necessary increase in reaction temperature, as well as the slower relative reaction rates. It is also possible that with stronger electron-withdrawing groups, the Lewis acid binds more tightly to the product indanones (compare **60** and **62**), and the slower reaction rates are a reflection of slower rates of catalyst turnover rather than slower cyclization.[43]

Summary

A series of Nazarov substrates bearing electron-donating substituents at C-2 and electron-withdrawing substituents at C-4 were synthesized (**1*P***). Treatment with catalytic amounts of a mild Lewis acid (2 mol % $Cu(OTf)_2$) gave high yields of the Nazarov product for these substrates, which were expected to cyclize via "polarized" pentadienyl cation intermediates. De-

(42) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(43) Experiments conducted with high loadings of catalyst were complicated by poor solubility of the copper(II) salts in chlorinated solvents.

symmetrization of the pentadienyl cation through substrate engineering is thought to improve reactivity, by creating an electron-donating terminus and an electron-accepting terminus (**2*P***). Similarly, the asymmetry of the resulting oxallyl cation is thought to allow greater selectivity in the final elimination step, which occurs adjacent to the terminus with the highest population of positive charge (i.e., C-2, **3*P***). The electron-withdrawing group at C-4 also allows thermodynamic equilibration to occur under the reaction conditions at that stereocenter, delivering the more stable *trans* diastereomer with high diastereoselectivity (**5*P***). Little or no *cis* diastereomer was observed.

Systematic variation of the substituents on the C-1, C-2, C-4, and C-5 revealed the steric and electronic impact of substitution on each position of the polarized Nazarov substrate. The findings can be summarized as follows:

Substitution at C-2. Substituents at this position had the most profound impact on reaction rate. If the results in Tables 1 and 2 are compared, it is clear that dihydropyran substrates in Table 1 (oxygen substituent at C-2) cyclize much faster than the cyclohexenyl counterparts in Table 2 (alkyl substituent at C-2).

Internal substitution at C-1 was found to slow cyclization because of steric interactions with internal substituents at C-5: the larger the internal C-1 substituent, the slower the cyclization. The same steric limitations would be expected for internal substituents at C-5, except that in alkylidene β-ketoesters, isomerization can occur, meaning that the identity of the internal substituent is not fixed.

Substitution at C-5. An unusual reactivity trend was observed: 2,4,6-trimethoxyphenyl > 4-methoxyphenyl > 2-furyl > 3-methoxyphenyl > phenyl > cyclohexyl (entries 1−7, Table 1). This trend was initially difficult to rationalize, since it did not correlate with steric bulk or with the expected electronic impact of substituents at this position on the reactivity of reaction intermediates. It was eventually determined that in the alkylidene β-ketoester substrates studied, the C-5 substituent has a significant impact on *E*/*Z* isomerization rates of alkylidene β-ketoester substrates. When the C-5 substituent was 2,4,6-trimethoxyphenyl or 4-methoxyphenyl, isomerization was faster than cyclization, so the reaction times for entries 1 and 2 in Table 1 reflect cyclization rate. However, entries 3−6 in Table 1 do not represent rates of cyclization but rather rates of isomerization prior to cyclization because isomerization is slow.

Substitution at C-4. Since the rate of *E* to *Z* isomerization complicated the measurement of relative cyclization rates for many of the substrates studied, careful design of substrates was necessary to assess the impact of C-4 substituents. Two studies were conducted: one employed substrates with *E* geometry bearing the 2,4,6-trimethoxyphenyl substituent at C-5, which isomerize faster than they cyclize, and the second focused on substrates with exclusively *Z* geometry. These studies showed that the role of the C-4 substituent in catalytic Nazarov cyclization is complex, and that reaction rate is probably affected by a combination of factors. The electron-withdrawing ability of the C-4 substituent, the efficiency and geometry of substrate/catalyst binding, and the facility of catalyst turnover are all variables that could impact reaction rate, depending on the substrate. It was found that substrates with a C-4 ester substituent cyclized most readily, suggesting that this substituent has the combination of electron-withdrawing ability and catalyst binding profile most able to facilitate the Nazarov cyclization.

In conclusion, the reactivity and selectivity of the Nazarov cyclization can be controlled by careful positioning of substituents on the five-carbon dienone backbone. Desymmetrization of the intermediates **2** and **3** through placement of polarizing groups at both the C-2 and C-4 positions was found to be particularly effective. These modifications allowed cyclizations to occur in the presence of catalytic amounts of mild Lewis acids, which could lead to the eventual development of a general method for catalytic asymmetric Nazarov cyclization.[44] During the course of these studies, an efficient isomerization process leading to the stereoconvergent cyclization of mixtures of *E* and *Z* isomers of alkylidene β-ketoesters was fully characterized, demonstrating that geometric fidelity is not guaranteed in substrates with internal substituents at the C-5 position.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, X-ray crystal structure coordinates, and files for compound **7** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(44) Asymmetric Nazarov cyclization has been accomplished with the use of chiral auxiliaries; see ref 17 and (a) Tius, M. A.; Harrington, P. E. *Org. Lett.* **2000**, *2*, 2447. (b) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091. (c) Pridgen, L. N.; Huang, K.; Shilcrat, S.; Tickner-Eldridge, A.; DeBrosse, C.; Haltiwanger, R. C. *Synlett* **1999**, 1612. (d) delos Santos, D. B.; Banaag, A. R.; Tius, M. A. *Org. Lett.* **2006**, *8*, 2579. (e) Banaag, A. R.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 5328. For the use of chiral Lewis acids, (f) see ref 18 and Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544. Recently, catalytic asymmetric Nazarov cyclization has been achieved using chiral Bronsted acids: (g) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097.