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Stereoselective Nazarov Cyclizations of Bridged Bicyclic Dienones

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Abstract

Bridged bicyclic dienones underwent silyl-directed Nazarov cyclization with generally very high diastereoselectivity. In most cases, a strong preference for cyclization to the product with an *exo*-disposed cyclopentenone was seen. However, the presence of additional unsaturation in the three-carbon bridge of a bicyclo[3.2.1]octadiene system caused complete reversal in selectivity with exclusive formation of the *endo*-cyclopentenone. The observed selectivities are believed to result from a combination of steric and electronic effects.

The Nazarov cyclization[1]and related annulations[2] offer an efficient method for construction of cyclopentenone rings from simple acyclic precursors. Recent variations include methods for diverting the initially formed oxyallyl cation intermediate into domino bond-forming processes,[3] conditions employing catalytic amounts of Lewis acid,[4] retrograde Nazarov reaction,[5] and asymmetric catalysis. An important question for this and other electrocyclic processes is whether the absolute configuration at the newly formed sp^3 centers can be controlled. There are a number of examples of diastereoselective Nazarov processes in which preexisting stereogenic centers exerted significant control.[6] Asymmetric induction by pendant chiral auxiliaries has been observed,[7] and allenes have been shown to participate in the Nazarov cyclization with a high degree of chirality transfer.[8] Most recently, preliminary examples of asymmetric catalysis by chiral Lewis acids have been reported.[5c,9]

One potential drawback to asymmetric Nazarov reactions is the annihilation of one of the two sp^3 stereocenters generated during the electrocyclization by the usual eliminative termination event (Scheme 1), although the remaining stereocenter may influence the configuration at the α' position during protonation. Coupling the cyclization with a subsequent bond-forming reaction in an overall domino process[4] is one possible solution. In an alternative strategy, *cis* ring-fusion preferences of strained bicyclic systems could permit the remaining chiral center to dictate the configuration at the neighboring cyclopentenone α' carbon upon enol protonation. We have applied the latter strategy in a series of bridged bicyclic dienones, and here report their Nazarov cyclization to provide complex tricyclic products with moderate to complete diastereoselectivity.

The silyl-directed Nazarov cyclization was used in this study to assure complete regioselectivity in the elimination step.[10] Dienone substrate **6a** was prepared by addition of bornenyllithium **1a** into enal **2a** and oxidation of the resulting dienol (Scheme 2). Unsatisfactory yields in this route prompted an examination of an alternative strategy. A more direct approach was found in the form of Stille cross-coupling of enol triflates (**4 a – f**) with

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alkenylstannanes (**5a,b**) under carbonylative conditions[11] using co-catalytic copper(I) iodide[12] to furnish dienones **6b–i** in good yields.

Initial studies were carried out with camphor-derived substrates **6a,b** and norcamphor-derived substrates **6c,d** (Table 1, entries 1–4). Low temperature treatment of **6a** with BF_3•OEt_2 and warming to 0 °C furnished tricyclic cyclopentenones **7a** and **8a** in 75% yield and as a 10:1 ratio in favor of *exo* isomer **7a**.[13] Complete *exo* selectivity was seen with methyl-substituted dienone **6b**. Substrates **6c,d** also underwent Nazarov cyclization with high or complete selectivity for the *exo* product. Alternative Lewis acids such as $FeCl_3$ also effected the desired cyclization (entry 5), although with somewhat lower selectivity.

Other ring systems were then examined (entries 6–10). To our surprise, bicyclo[3.2.1]-octadiene **6e** rearranged with complete selectivity for the *endo* isomer, furnishing **8e** and a small amount of silyl-containing product **9**. Compound **9** is believed to form via an ene-like pericyclic process involving the intermediate 2-oxidoallyl cation and the adjacent trisubstituted alkene, followed by fragmentative opening of the resulting cyclopropyl ketone.[14] In contrast to **6e**, isomeric bicyclo[3.2.1]octadienes **6 f,g** furnished only the *exo* cyclization products **7f,g**. The behavior of substrates **6h,i**, which contain the same carbon skeleton as **6e** but lack the remote olefin, is also notable. Both diastereomers underwent *exo*-selective cyclization, though isomer **6i**, with and *endo*-disposed methyl on the 3-carbon bridge, showed higher selectivity.

The high *exo* selectivity seen with bicyclo[2.2.1]heptene substrates **6a–d** follows the well known preference for electrophilic addition to norbornene derivatives from the *exo* face. This phenomenon has previously been ascribed to torsional strain,[15] steric crowding,[16] nonequivalent orbital extension,[17] and a combination of alkene pyramidalization[18] and transition state allylic bond staggering.[19] Interaction of the pentadienyl termini in the pericyclic transition state of the Nazarov reaction is not analogous to electrophilic addition, but should be similarly subject to any of these effects with the possible exception of crowding by the remote ethylene bridge. Any steric impediment by the dimethyl substitution on the one-carbon bridge is clearly outweighed by the factor(s) responsible for the expected *exo* preference.

The complete *endo* selectivity of **6e** is unique in this study. The presence of the remote olefin is critical, as can be seen from the *exo* selectivity of dihydro examples **6h,i**. However, **6f,g**, also containing a remote olefin in similar orientation to the dienone, gave only the *exo* isomers **7f,g**. In this case, transposition of the geminal dimethyl substitution from the 1-bridge to the 3-bridge may permit steric effects to overcome the inherent *endo*-preference shown by **6f**. A higher *exo* preference in the cyclization of **6i** over that of **6h** may result from enforcement of a chair conformation with an equatorially disposed methyl group in the six-membered ring, creating additional steric demand on the *endo* face of the bicyclic system (Figure 1). Diastereomeric **6h** may adopt a boat-like conformation, resulting in a relatively open *endo* face, and leading to greater amounts of isomer **8 i**. Finally, the greater selectivity generally seen for methyl-substituted dienones (entries 2, 4, 6 and 8) can be attributed to the lower cyclization temperature that is permitted in these more highly substituted cases.

We have described a novel approach to stereocontrol in the Nazarov electrocyclization using the innate facial preferences of rigid bicyclic ring systems. Most notably, substrate **6e** displayed a complete reversal of the usual *exo* preference. Efforts to understand the origins of this selectivity along with its applications in synthesis will be reported elsewhere in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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13. Relative stereochemistry of *exo* and *endo* cyclopentenones **7** and **8** was determined using 2D-NOESY NMR experiments, x-ray diffraction analysis (**7i**). and spectral analogy. See Supporting Information for a discussion of characteristic chemical shift trends for *exo* and *endo* isomers.
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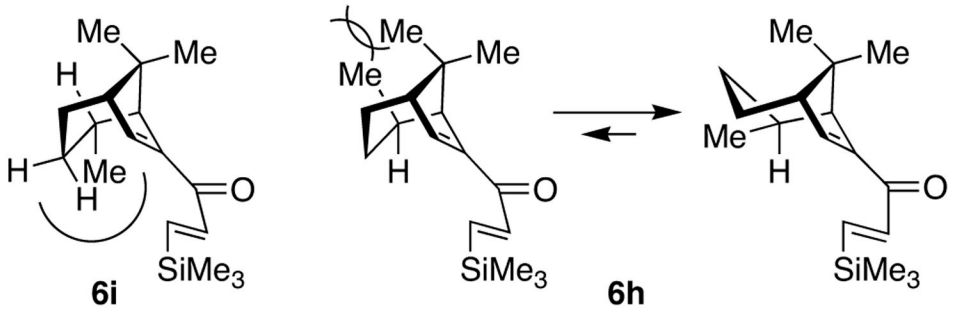
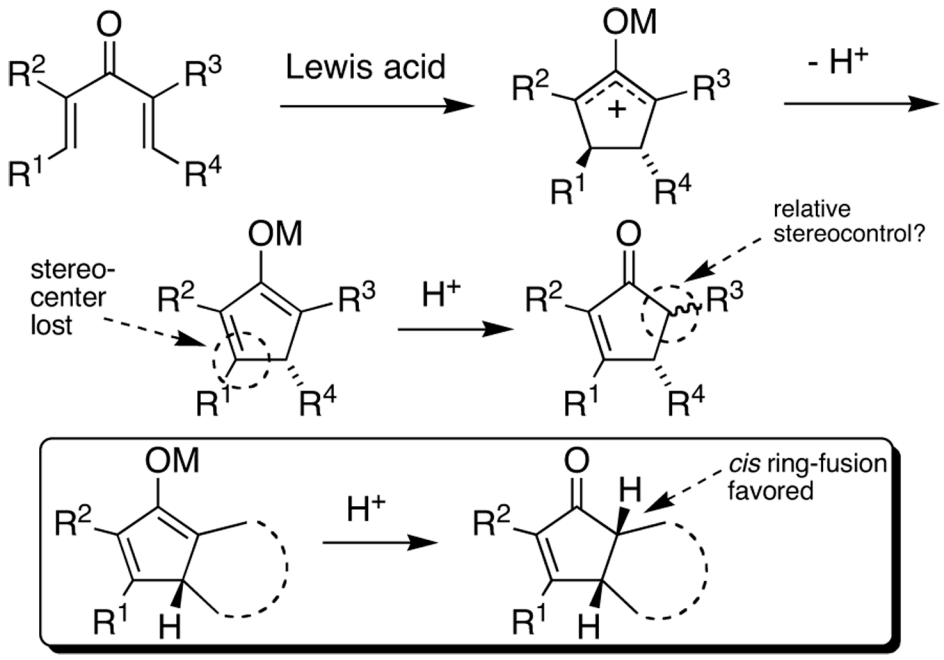
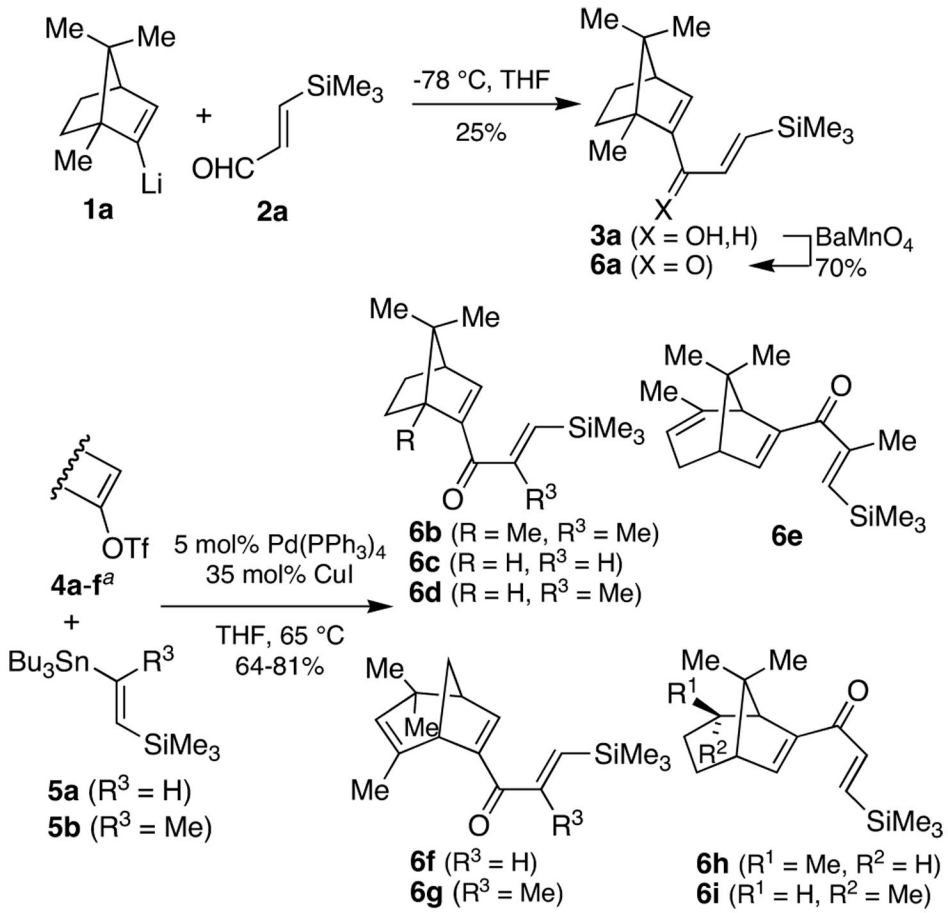


Figure 1.
Conformational preferences of dienones **6 i** and **6h**.



Scheme 1.

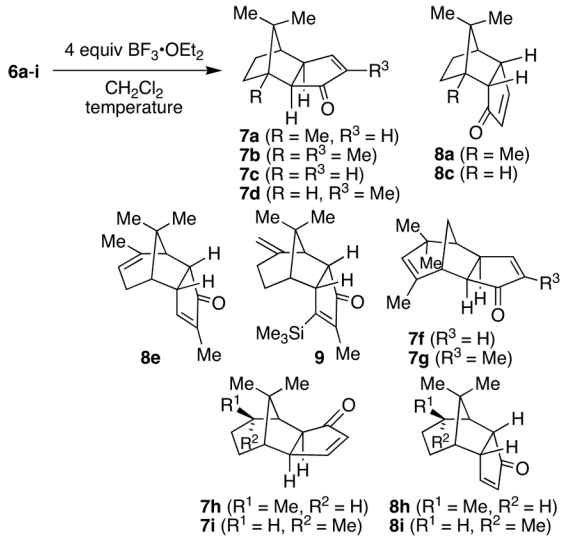


Scheme 2.

[a]See Supporting Information for details regarding enol triflates **4a–f**.

Table 1

Nazarov cyclization of bridged bicyclic dienones **6**.[a]



entry	substrate	temperature[a]	yield 7+8 (%)[b]	ratio 7:8
1	**6a**	−78→0 °C	75	10:1
2	**6b**	−78→−40 °C	71	>33:1[c]
3	**6c**	−78→0 °C	66	12:1
4	**6d**	−78→−40 °C	70	>33:1[c]
5[d]	**6c**	−78 °C→r.t.	70	6:1
5	**6e**	−78→−40 °C	81[e]	<1:33[c]
6	**6f**	−78→0 °C	63	>33:1[c]
7	**6g**	−78→−40 °C	93	>33:1[c]
8	**6h**	−78→0 °C	70	6:1
9	**6i**	−78→0 °C	70	19:1

[a] Reactants were combined at −78 °C and allowed to warm to the indicated temperature, then stirred until complete consumption of s.m. (typically 1.25–2 h).

[b] Yields based on isolated material after chromatography.

[c] None of the minor isomer was detected to the limits of detection by ^{1}H NMR spectroscopy or TLC.

[d] $FeCl_3$ (1.5 equiv.) was used in place of BF_3•OEt_2.

[e] An additional 10% of product **9** was isolated.