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Enantioselective Nazarov Reactions through Catalytic Asymmetric Proton Transfer

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Nazarov cyclizations are among the few electrocyclic reactions that are subject to catalysis. Known since the 1940s, they have been mechanistically studied in detail and developed into a very useful synthetic tool.[1] Somewhat surprisingly, however, it was not until the end of 2003 that catalytic asymmetric variants began to surface in the literature.

The reasons for this may lie in the complex mechanism of the reaction (Scheme 1). Coordination of a proton or Lewis acid (LA) to the dienone substrate **1** triggers a conrotatory 4π electrocyclization of the resulting pentadienyl cation **2**, followed by loss of a proton (**3**→**4**) and reprotonation (**4**→**5**). These individual steps are fraught with regio- and stereoselectivity problems. The product, cyclopentenone **5**, is potentially subject to racemization if the cyclization proceeds slowly, which is the case if the dienone substrate **1** is biased toward the s-cis/s-cis conformation. Furthermore, catalyst turnover may be a concern, as evidenced by the fact that most Nazarov cyclizations reported require acidic solvents or stoichiometric amounts of a Lewis acid.[2]

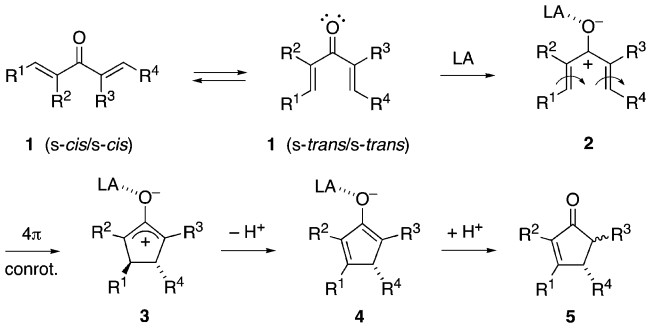
To address these issues, our group has developed 2-alkoxy-1,4-pentadien-3-ones as substrates for Nazarov cyclizations.[3] We reasoned that these substrates not only would be highly reactive but also would allow for bidendate coordination of a chiral Lewis acid. As a first example of an asymmetric cyclization, we recently reported the cyclization of dienone **6** in the presence of 20 mol % of the chiral scandium triflate pybox complex **8** (Scheme 2, eq 1). The product **7** was formed in 53% yield and 61% enantiomeric excess (ee).

Concomitant with our report, Aggarwal et al. disclosed the asymmetric cyclization of substrates of type **9** with 50−100 mol % of copper-box and -pybox complexes, for instance **11**, as Lewis acid (Scheme 2, eq 2).[4] The products of type **10** were obtained with modest to good ee's. Finally, Frontier and co-workers described efficient Nazarov cyclizations of substrates of type **12**, which essentially combine Aggarwal's substrates with ours (Scheme 2, eq 3).[5] However, no asymmetric studies involving these systems have been reported to date.

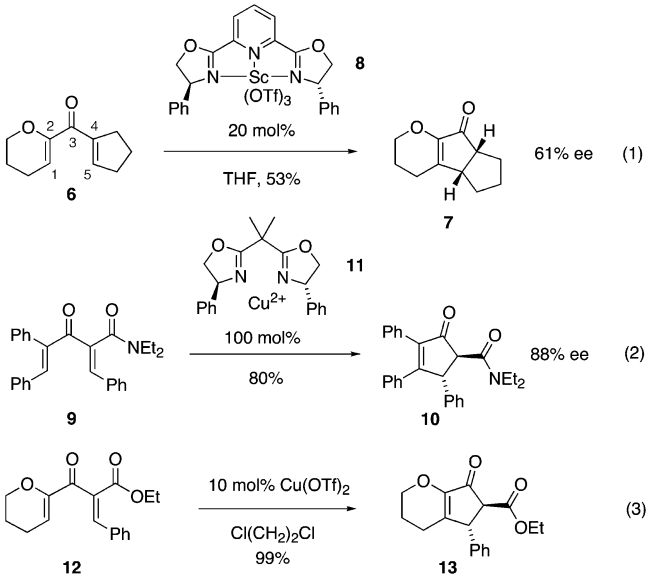
We now report the further development of catalytic asymmetric Nazarov cyclizations involving 2-alkoxy-1,4-pentadien-3-ones. While our attempts to improve the enantioselectivity of the conrotatory electrocyclization have remained moderately successful, we have achieved a truly catalytic and highly enantioselective version of the overall reaction that involves an asymmetric protonation as the key step.

Following an extensive survey of Lewis acids, chiral ligands, and solvents, it was found that scandium-pybox systems (e.g. **8**, **16**) in acetonitrile in the presence of 3 Å molecular sieves provided the best results.[6] Initially, however, efforts to optimize asymmetric Nazarov cyclizations under these conditions proved to be frustrating. The reactions were often found to be low yielding, difficult to reproduce, and highly sensitive to slight variations in the substrate.

Scheme 1. Mechanism of the Nazarov Cyclization



Scheme 2. Catalytic (Asymmetric) Nazarov Cyclizations



Alkoxy dienone substrates analogous to **6** bearing only a trans substituent in position 5 were generally found to cyclize with low yields and enantioselectivities (25−58% ee). In the case of substrates that could yield diastereomers, the situation was even more complicated (Scheme 3).

For instance, reaction of alkoxy dienone **14** with the sterically demanding indane-pybox complex (1*S*,2*R*)-**16** gave a mixture of diastereomers **15a** and **15b** in 40% and 79% ee, respectively, with a diastereomeric ratio of 3.4:1. This result can be interpreted by invoking double diastereoselection in the reprotonation step following the asymmetric electrocyclization. Using an achiral Lewis acid ($AlCl_3$), this diastereomeric ratio was found to be 1.5:1.[3]

Consistently high yields and enantioselectivities were finally obtained by switching to substrates lacking a substituent at the terminal position (R^4 = H). Using only 10 mol % of the chiral scandium indane-pybox complex (1*S*,2*R*)-**16** in acetonitrile at room

10.1021/ja0476664 CCC: $27.50

Scheme 3

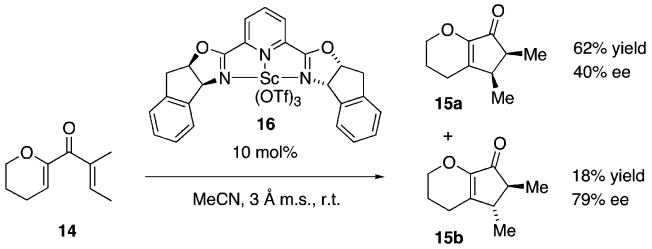
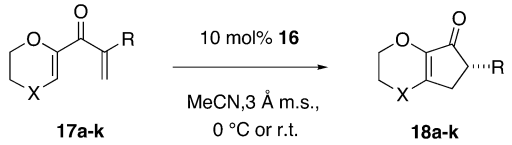


Table 1. Highly Enantioselective Nazarov Cyclizations



entry	X	R	yield[a] (%)	ee (%)
a	CH_2	Me	65	85
b	CH_2	Et	75	92
c	CH_2	*n*-Pr	70	93
d	CH_2	*n*-Bu	70	94
e[b]	CH_2	*i*-Pr	88	95
f	CH_2	*t*-Bu	94	97
g	CH_2	Cy	76	76
h	CH_2	Ph	65	87
j[b]	O	*i*-Pr	65	72
k	O	*t*-Bu	80	91

[a] Isolated yield after silica gel column chromatography. [b] Reaction performed at 0 °C (3 h).

temperature or below, alkoxy dienones **17a**−**k** cleanly afforded products **18a**−**k** within 0.5−3 h (Table 1). Under these conditions, racemization was not found to be a problem.

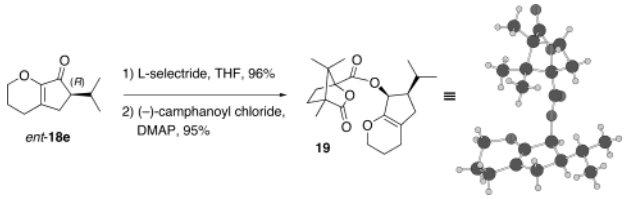
With the exception of cyclohexyl derivative **17g**, substrates carrying bulky substituents in position 4, e.g. **17e**,**f** and **17k**, proved to be most reactive and provided the highest levels of enantioselectivity. For instance, *tert*-butyl-substituted dienone **17f** gave the corresponding cyclopentenone **18f** in 94% yield and 97% ee. Even phenyl-substituted cyclopentenone **18h** was formed with relatively high ee. By contrast, dioxenes **17j** and **17k** were found to cyclize with slightly reduced enantioselectivities.

Notably, in the case of substrates **17**, the only stereocenter formed in the course of the 4π-electrocyclization is destroyed upon deprotonation of the allylic cation (cf. **3** in Scheme 1). The absolute configuration of the products is therefore established in the course of the reprotonation of the dienolate intermediate (cf. **4**) in position 4. The influence of the chiral ligand sphere surrounding the Lewis acid, which is presumably bound to the substrates in a bidendate fashion, should be greater in this position than at the termini of the alkoxy dienone system. This may explain the higher levels of enantioselectivity observed with substrates of type **17**.

Several catalytic asymmetric proton-transfer reactions have been described in the literature,[7] including one that involves 1,4-addition and diastereoselective protonation of a rhodium enolate.[7e] None of these, however, proceeds with concomitant cyclization and all require an *external* proton source.

The absolute configuration of the products **18** was investigated using compound *ent*-**18e** as a representative. Diastereoselective reduction of *ent*-**18e**, followed by esterification, gave camphanoyl ester **19**, whose relative configuration was established by X-ray

Scheme 4. Elucidation of the Absolute Configuration



crystallography (Scheme 4). Accordingly, *ent*-**18e** is (*R*)-configured and **18e** is (*S*)-configured. We assume that the absolute configurations of compounds **18a**−**d**,**f**−**k** corresponds to **18e**.

In summary, we have described the first truly catalytic asymmetric Nazarov reactions that proceed with high levels of enantioselectivity and in good yields. Although we cannot claim to have achieved highly enantioselective electrocyclizations, we have developed catalytic asymmetric proton-transfer reactions, a concept that will be further explored in our laboratories. The application of other chiral Lewis acids[8] as well as substrates with different olefin geometries and heteroatom substituents to asymmetric Nazarov cyclizations is also being actively investigated in our laboratories.

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Supporting Information Available: Synthetic procedures and spectroscopic data for compounds **17a**−**k**, **18a**−**k**, and **19** including X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. The crystal structure of **19** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 238395).

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