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Development of a Nazarov Cyclization/Wagner−Meerwein Rearrangement Sequence for the Stereoselective Synthesis of Spirocycles

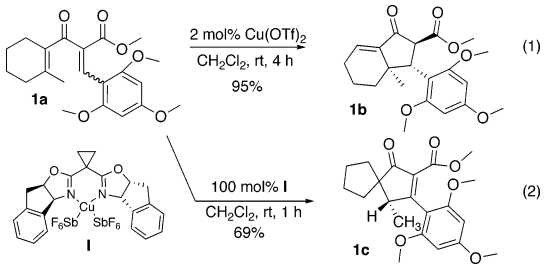
Jie Huang and Alison J. Frontier*

Department of Chemistry, University of Rochester, Rochester, New York 14627

Received March 7, 2007; E-mail: frontier@chem.rochester.edu

The stereodetermining step of the Nazarov cyclization is the conrotatory 4π-electrocyclization of a 3-oxopentadienyl cation to an oxyallyl cation.[1] While the reaction is typically terminated by elimination of a proton to give an enone derivative, it is possible to intercept the oxyallyl cation intermediate if a suitable trapping agent is present. A number of synthetically useful "interrupted" Nazarov cyclizations of this type have been reported.[2] Wagner−Meerwein rearrangement processes[3] have also been observed during Nazarov cyclization.[4] These studies have provided valuable insight into the avenues available to the oxyallyl cation intermediate but are typically characterized by multicomponent product mixtures reflecting competing rearrangement pathways. In this communication, we describe a Nazarov cyclization/Wagner−Meerwein rearrangement pathway that produces unusual spirocyclic products. The transformations are highly stereoselective, efficient for a range of substrate types, and capable of creating adjacent quaternary centers.

In an earlier study, we found that compound **1a** (as a mixture of olefin isomers) underwent Nazarov cyclization when treated with a catalytic amount of copper(II) triflate (eq 1).[5] Bicyclic ketone **1b** was isolated as a single diastereomer.[6] Given this result, it was quite interesting to find that, when **1a** was treated with a stoichiometric amount of copper bisoxazoline complex **I**,[7] the only product obtained was spirocycle **1c**.[8] This unexpected product was formed in 40% ee (eq 2).



Further investigation of this process revealed that product distribution is dependent on both the structure of the catalyst complex and the amount of catalyst present in solution (Table 1). Copper triflate gave predominantly the Nazarov cyclization product **1b** at both low and high catalyst loadings (entry 1). Catalytic amounts (10 mol %) of **I** gave mostly **1b**, but as the loading of **I** was increased, the proportion of spirocyclic product **1c** in the product mixture also increased (entry 2). In the presence of 100 mol % of **I**, **1c** was obtained exclusively. High selectivity for **1c** over **1b** could also be achieved by adding **1a** slowly to 50 mol % of the promoter **I**.

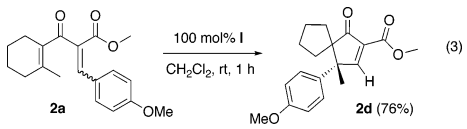
The spirocyclization could also be carried out using 1 equiv of $AgSbF_6$, but selectivity was moderate (entry 3). This result seemed to indicate that the counterion was an important factor and suggested that the ligand might not be necessary. Indeed, the next set of experiments showed that $Cu(SbF_6)_2$[9] was just as effective as chiral complex **I** (entry 4).

Table 1. Optimized Conditions for Spirocycle Formation

		Ratio **1c**/**1b**[a]		
entry	promoter	10 mol %	50 mol %	100 mol %
1	$Cu(OTf)_2$	<5/95	8/92	13/87
2	**I**	20/80	67/33[b]	>95/5
3	$AgSbF_6$	9/91	50/50	70/30[c]
4	$Cu(SbF_6)_2$	20/80[d]	69/31	>95/5

[a] Ratio was determined by ^{1}H NMR of crude mixture. [b] The ratio was 91/9 when substrate was slowly added to promoter. [c] Ratio increased to 84/16 with 200 mol % of promoter. [d] With 5 mol % of promoter.

The study became even more intriguing when the cyclization and rearrangement of *p*-methoxyphenyl derivative **2a** did not give spirocycle **2c** as expected, but instead led to the formation of spirocycle **2d**, which contained adjacent quaternary centers (eq 3).[8]



Cyclizations on different substrates were carried out to explore the scope of the process (Table 2). Depending upon the substituent on the alkylidene β-ketoester of dienone **a**, the sequence selectively produced spirocycles of either type **c** or type **d**. Substrates with cinnamyl substitution rearranged to products of type **d** (entries 3 and 5), while alkyl-substituted substrate **4a** gave spirocycle **4c** (entry 4). The protocol also allowed smooth contraction of a seven-membered ring to give spirocycle **5d** in good yield (entry 5).

Since none of the cases initially studied addressed the question of the stereochemistry of the spirocyclic quaternary center relative to the adjacent chiral center, cyclohexadiene substrates **6a** or **7a** were synthesized and subjected to the reaction conditions. In both cases, smooth cyclization/ring contraction occurred as expected, to give spirocycles **6c** and **7d**, respectively (entries 6 and 7).[8] The stereochemistry of **6c** was assigned by X-ray crystallographic analysis.

In a few cases, the Nazarov cyclization/1,2-sigmatropic rearrangement sequence was examined using $Cu(SbF_6)_2$ as promoter (entries 1, 2, and 6). Under these conditions, both the yield and reaction rates increased relative to the reaction with chiral complex **I**, confirming this protocol as an inexpensive and superior alternative for carrying out the reaction sequence.

The proposed mechanism of the Nazarov cyclization/rearrangement sequence is shown in Scheme 1. After the 4π conrotatory electrocyclic process, oxyallyl cation intermediate **A** is generated. Elimination of a proton gives the normal Nazarov product of type **b** (path 1), whereas ring contraction leads to spirocyclic cation **B** (path 2). Then, depending on the migratory ability of the substituent

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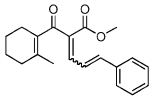
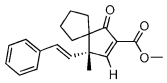
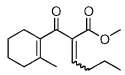
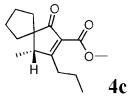
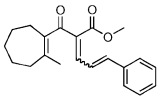
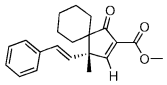
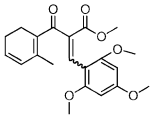
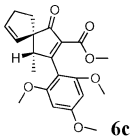
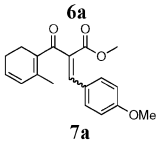
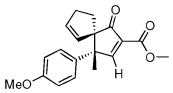
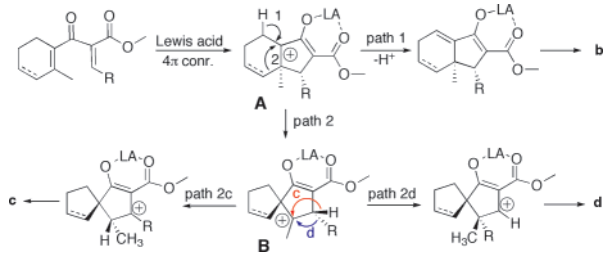
Table 2. Spirocycle Formation from Dienones **1a**−**7a**[a]

entry	dienone substrate	time[b]	product[c]	% yield[b]
1	**1a**	1 h (0.5 h)	**1c**	69 (76)
2	**2a**	1 h (0.5 h)	**2d**	76 (91)
3	 **3a**	20 h	 **3d**	96
4	 **4a**	12 h[d]	 **4c**	84
5	 **5a**	6 h	 **5d**	91
6	 **6a**	5 h (1 h)	 **6c**	79 (88)
7	 **7a**	3 h	 **7d**	71

[a] Reaction conditions: substrate **a** in CH_2Cl_2 (0.03 M); 100 mol % of **I**; 25 °C. [b] Values in parentheses were obtained using 100 mol % $Cu(SbF_6)_2$. [c] The enantiomeric excess of products cyclized using **I** ranged from 29 to 64% (unoptimized). [d] Heated to 100 °C in dichloroethane.

Scheme 1. Proposed Mechanism of Spirocycle Formation



R,[10] either a hydride shift (path 2c) or an sp^2 carbon shift (path 2d) occurs. Finally, loss of Lewis acid gives products **c** and **d**, respectively. Our results indicate that the alkyl shift (path 2d) is favored when the R group is electron-rich and can stabilize the adjacent tertiary cation (Table 2, entries 2, 3, 5, and 7).[11] The governing principle behind the selective formation of products **c** is not as clear. R groups that cannot provide strong stabilization for the cation intermediate **B**, for either steric (entry 1) or electronic reasons (entries 4 and 6), may favor the hydride shift (path 2c).

The stereochemical results from the rearrangements of substrates **6a** and **7a** were consistent with the proposed mechanism. Suprafacial shift of the hydride in intermediate **B** would be expected to place the hydrogen *syn* to the vinyl group, and the only diastereomer observed in the rearrangement of **6a** was **6c**. Similarly, suprafacial shift of carbon would be expected to place the preexisting methyl group *syn* to the vinyl group, as seen in the rearrangement of **7a** to **7d**.

The highest selectivity is observed when 1 equiv of a Cu(II) complex is present. This would seem to indicate that both carbonyl oxygens must be bound to the promoter before efficient rearrangement to products **c** and **d** can occur (see **A**, Scheme 1). One explanation is that free carbonyl groups can act as Lewis bases, accelerating the elimination step (path 1) that leads to products **b**. Several lines of evidence support this idea. First, ratios of **1c**/**1b** were highest when enough promoter was used to provide one coordination site for each carbonyl oxygen in the reaction mixture (i.e., 1 equiv of a Cu(II) salt or 2 equiv of a Ag(I) salt; see Table 1). Second, reactions carried out in noncoordinating solvents (dichloromethane or nitroethane) favored products **c** and **d**, while product **b** dominated when the Lewis basic solvent THF was used (with 100 mol % of $Cu(SbF_6)_2$, **1a** gave a 7:1 ratio of **1b** to **1c** in 94% combined yield).[12] Third, promoters containing the noncoordinating counterion SbF_6^- were optimal, suggesting that a reaction medium devoid of Lewis basic species allows rearrangement (path 2) to compete with elimination (path 1).

In summary, a 4π-electrocyclization/1,2-sigmatropic rearrangement sequence has been developed. The efficient synthesis of richly functionalized spirocycles using an inexpensive promoter was demonstrated. Most promising for potential synthetic application was the finding that adjacent stereocenters, including adjacent quaternary centers, could be installed with high selectivity using this protocol. Future efforts in our laboratory will focus on applications of the method to natural product synthesis, as well as development of a catalytic, enantioselective version of the reaction.

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Supporting Information Available: Experimental procedures, spectroscopic data for all new compounds, and X-ray structure data of **1c** and **6c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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