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Understanding the Fate of the Oxyallyl Cation following Nazarov Electrocyclization: Sequential Wagner−Meerwein Migrations and the Synthesis of Spirocyclic Cyclopentenones

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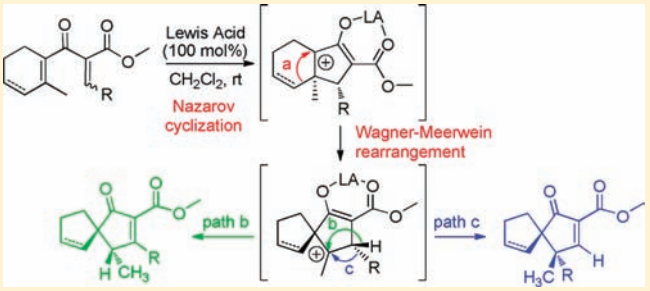
Supporting Information

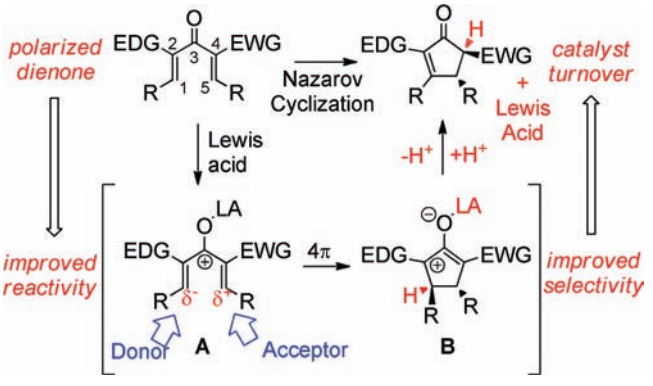
ABSTRACT: A general reaction sequence is described that involves Nazarov cyclization followed by two sequential Wagner−Meerwein migrations, to afford spirocyclic compounds from divinyl ketones in the presence of 1 equiv of copper(II) complexes. A detailed investigation of this sequence is described including a study of substrate scope and limitations. It was found that after 4π electrocyclization, two different pathways are available to the oxyallyl cation intermediate: elimination of a proton can give the usual Nazarov cycloadduct, or ring contraction can give an alternative tertiary carbocation. After ring contraction, either [1,2]-hydride or carbon migration can occur, depending upon the substitution pattern of the substrate, to furnish spirocyclic products. The rearrangement pathway is favored over the elimination pathway when catalyst loading is high and the copper(II) counterion is noncoordinating. Several ligands were found to be effective for the reaction. Thus, the reaction sequence can be controlled by judicious choice of reaction conditions to allow selective generation of richly functionalized spirocycles. The three steps of the sequence are stereospecific: electrocyclization followed by two [1,2]-suprafacial Wagner−Meerwein shifts, the ring contraction and then a hydride, alkenyl, or aryl shift. The method allows stereospecific installation of adjacent stereocenters or adjacent quaternary centers arrayed around a cyclopentenone ring.



INTRODUCTION

Among the Lewis acid-catalyzed reactions with a cationic intermediate, one of the most relevant examples is the Nazarov cyclization.[1] In the Nazarov cyclization, divinyl or aryl vinyl ketones are stereospecifically converted into complex cyclopentenone derivatives.[2] The reaction commences through Lewis acid binding to the carbonyl generating a pentadienyl cation, followed by 4π conrotatory electrocyclization, proton loss, and finally reprotonation to give the product. Prior to 2003, one or more equivalents of either protic or Lewis acids (e.g., $BF_3 \cdot OEt_2$, $TiCl_4$, $SnCl_4$, or $AlCl_3$) were usually required to promote the Nazarov cyclization.[1] In electronic polarization of the Nazarov substrate, one of the vinyl groups is made electrophilic and the other nucleophilic (**A** in Scheme 1) so that the reaction proceeds more readily and under catalytic conditions with mild Lewis acids such as $Cu(OTf)_2$.[3] Furthermore, the charge asymmetry that is produced in oxyallyl cation **B** by the electron-donating and -withdrawing groups results in regioselective elimination. Recent studies describe the use of Cu(II),[3,4] Pd(II),[5] Sc(III),[6] Ir(III),[7] V(IV),[8] Ni(II),[9] Au(I),[10] Fe(II),[11] or Co(I)[11] complexes in substoichiometric amounts for catalysis of the Nazarov cyclization, including several chiral complexes furnishing cyclopentenones with modest to high enantiometric excesses. Several methodologies based on organocatalysis have also emerged to deliver Nazarov products with good enantioselectivity.[12]

Scheme 1. Polarized Nazarov Cyclization



A number of interesting cationic transformations can be coupled to the reaction sequence through the oxyallyl cation

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intermediate. For example, instead of termination via elimination of a proton to give an enone derivative, different types of Wagner−Meerwein rearrangement processes have been observed as products of attempted Nazarov cyclizations.[13,14] These studies have provided valuable insight into the avenues available to the oxyallyl cation intermediate, but the reactions are typically characterized by complex mixtures reflecting the different rearrangement pathways. Higher selectivity has been achieved in some cases of an "interrupted" Nazarov cyclization, which involves interception of the oxyallyl cation intermediate with a suitable trapping agent.[1g] West has shown that trapping of oxyallyl cationic intermediates with a hydride[15] or carbon π-system[16] can compete effectively with the elimination of a proton during the cyclization process. Trapping with heteroatomic solvents such as methanol, acetic acid, trifluoroacetic acid, or formic acid has been observed in photo-Nazarov cyclizations[17] and in cyclizations promoted by protic acids.[18] Intramolecular oxygen interruption is also possible during Lewis acid-promoted cyclization,[19] as well as intermolecular trapping with azides,[20] halides,[21] or amines.[12b,22] In addition to hydride shift and methyl shift, a vinyl migration following electrocyclization of a linear dienyl ketone was also reported by Denmark and co-workers.[14c] Another interesting application is a Nazarov cyclization/Michael addition sequence, which has been used to obtain new polyfunctionalized cyclopentenones.[23]

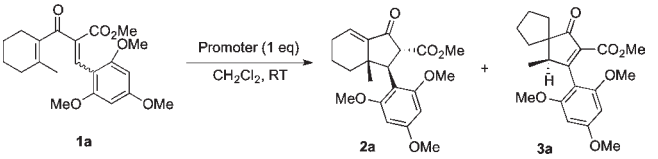
Characterization of these competing rearrangements was valuable in gathering mechanistic details about the Nazarov reaction, but these pathways were viewed as a liability, limiting the synthetic utility for the Nazarov cyclization. Therefore, the present article is devoted to the investigations in our laboratory on the Nazarov cyclization/Wagner−Meerwein rearrangement. In contrast to other carbocation rearrangements linked to the Nazarov cyclization, this sequence is efficient and highly selective.[24] Moreover, the reaction pathway can be controlled by using an appropriate catalyst and, remarkably, specific catalyst loading. Studies probing the scope and limitations of the rearrangement have been performed, as well as reactions using chiral catalysts, with the aim for an enantioselective electrocyclization. The ultimate goal is to develop an efficient and stereospecific methodology for constructing novel spirocyclic structures containing quaternary centers, for application in the synthesis of bioactive molecules.

RESULTS AND DISCUSSION

1. Identification of Spirocycle 3a. Our initial investigation of acid-catalyzed Nazarov cyclization of **1a** with one or more equivalents of H_3PO_4 or H_2SO_4 found a mixture of the expected cyclopentenone **2a** and a second isomeric compound, which was not identified at the time (Table 1, entries 1−3). Later studies revealed that the isomer was formed exclusively when 1 equiv of chiral copper(II) bisoxazoline (box) complexes was used to promote the cyclization (Table 1, entry 8). At this point, the isomer was isolated and identified as spirocycle **3a** through spectroscopic studies including X-ray crystallography (Figure 1). Other acids (HBF_4, $HNTf_2$, $HSbF_6$, or TfOH) were screened but did not give rise to the spirocyclic compound (Table 1, entries 4−7).

2. Optimization. *2.1. Catalyst Loading.* It was especially surprising to see exclusive formation of the spirocycle using the copper(II) bisoxazoline complex **4**, since previous experiments with complex **4** had given Nazarov product **2a**. The only difference was the amount of catalyst used: in the earlier experiments, no more than 5 mol % of **4** had been present. Experiments with different catalyst loadings confirmed these findings: the

Table 1. Discovery of Nazarov Cyclization/Rearrangement Pathway



entry	promoter	time (h)	ratio **2a**/ **3a**	yield (%)
1	H_3PO_4 (85%)	12	8.4:1	67
2	H_3PO_4 (85%)[a]	12	2:1	50
3	H_2SO_4 (96.5%)[b]	2	5.5:1	56
4	HBF_4	0.5	**2a** only	62
5	$HNTf_2$	0.5	**2a** only	55
6	$HSbF_6$	0.5	**2a** only	85
7	HOTf	0.2	complex mixture	–
8	[Cu(II)(box)]$(SbF_6)_2$ (**4**)	0.5	**3a** only	69

[a] Reaction was conducted in toluene. [b] Two equivalents of promoter used.

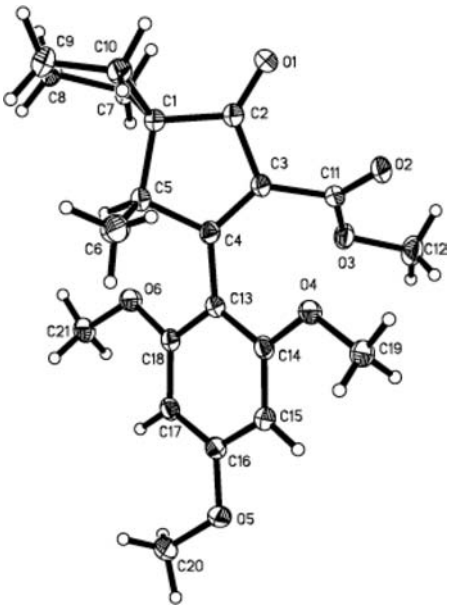


Figure 1. ORTEP drawing of **3a**.

Table 2. Product Distribution as a Function of Catalyst Loading

entry	**4** (mol %)	yield (%); product ratio **3a**:**2a**
1	5	83; <20:1
2	10	62; 1:4
3	30	59; 1:3
4	50	54; 1:1.7
5	80	57; 6.2:1
6	100	69; >20:1

ratio of **3a**:**2a** increased as more [Cu(II)(box)](SbF$_6$)$_2$ was added (Table 2).

2.2. Copper(II) and Silver(I) Complexes as Promoters. Alternative promoters were examined in cyclizations of substrate **1a**, to further explore the impact of transition metal salts on the product distribution. It was cyclized in the presence of a stoichiometric amount of copper(II) salts and silver(I) salts. The results are documented in Table 3. As expected, copper(II) triflate (the catalyst we typically use for polarized Nazarov cyclization)[3] gave mostly Nazarov product **2a**, even when 1 equiv was present (Table 3, entry 1). This is in contrast to the results with the copper(II) bisoxazoline complex (spirocycle, entry 2) and copper(II) chloride (no reaction, entry 3). Experiments with silver(I) salts gave an interesting range of results. AgOTf was the most effective catalyst for the cyclization, which was complete within 1 h (Table 2, entry 5), whereas AgBF$_4$ was not as reactive, requiring heating to 55 °C (entry 6). The distribution of the product changed depending on which silver salt was used. The highest ratio of rearranged product **3a** to Nazarov product **2a** was obtained using AgPF$_6$ (entry 9). AgOTf and AgClO$_4$ provided Nazarov cycloadduct **2a** as the major product (entries 4 and 5). AgBF$_4$, however, gave an equal amount of **2a** and **3a** in the reaction mixture. According to these results, when complexes with the non-coordinating counterions hexafluoroantimonate and hexafluorophosphate are used, a higher rate of spirocycle formation is observed.

In addition to the Nazarov product and the rearranged product, an OH-trapped Nazarov product **5** was also observed (entries 4 and 6). The structure was determined by X-ray crystallography (Figure 2). This product was the result of oxyallyl cation capture with an oxygen nucleophile. In these experiments, the nucleophile could be water caught in the hygroscopic silver salts or the oxygen of the silver(I) perchlorate counterion.

2.3. Counterion for Copper(II)(Box) Complexes. Cyclization experiments were also run with different counterions in the Cu(II)(box) complex cyclization of **1a**. In our laboratory, previous studies have shown that the complex [Cu(II)(box)](OTf)$_2$ (**6**) was particularly efficient for the enantioselective Nazarov cyclization.[27] Higher enantiomeric excess was obtained when a higher catalyst loading (1 equiv) was used, but **3a** was not formed (Table 4, entry 1). Complex **7** (with a perchlorate counterion) did provide rearranged product **3a**, in a ratio 1.2:1 with the Nazarov product **2a** (entry 2). The more weakly coordinating counterions hexafluoroantimonate and -phosphate are known to accelerate reactions catalyzed by cationic metal complexes with better asymmetric induction,[25] yet it is interesting to note that the enantiomeric excesses of **2a** and **3a** were higher using complex **7** (perchlorate counterion) than complex **4** (hexafluoroantimonate counterion: compare entries 2 and 3, Table 4). It was not possible to improve these enantiomeric excesses by employing hexafluorophosphate as counterion (entry 4).

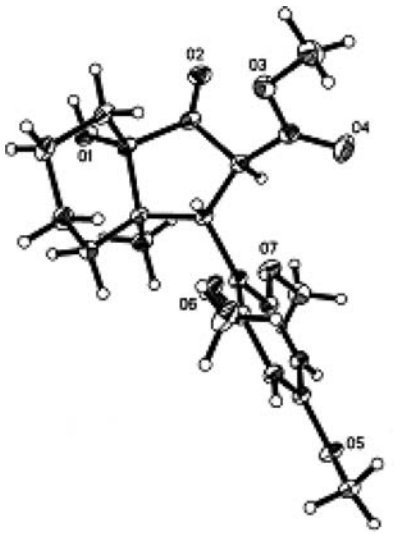
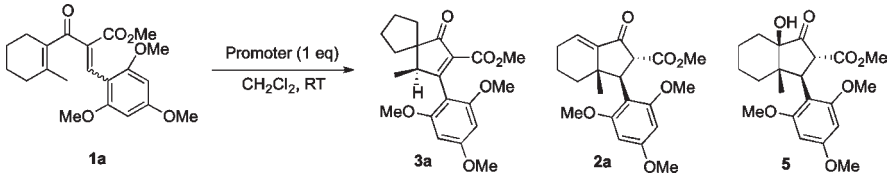


Figure 2. ORTEP drawing of **5**.

Table 3. Effect of Lewis Acid on Product Distribution



entry	promoter	time (h)	ratio **3a**:**2a**:**5**	yield of **3a** (%)
1	Cu(OTf)$_2$	1	1:7.1:0	11
2	[Cu(II)(box)](SbF$_6$)$_2$ (**4**)	0.5	**3a** only	69
3	CuCl$_2$	24	no reaction	–
4	AgClO$_4$	8	0:3.3:1	nd[a]
5	AgOTf	1	1:23:0	nd
6	AgBF$_4$	5[b]	1:1:2	nd
7	AgSbF$_6$	20	2.3:1:0	nd
8	AgSbF$_6$[c]	8	5.5:1:0	72
9	AgPF$_6$	3	**3a** only	86

[a] nd = not determined. [b] Reaction was conducted at reflux. [c] Two equivalents of promoter used.

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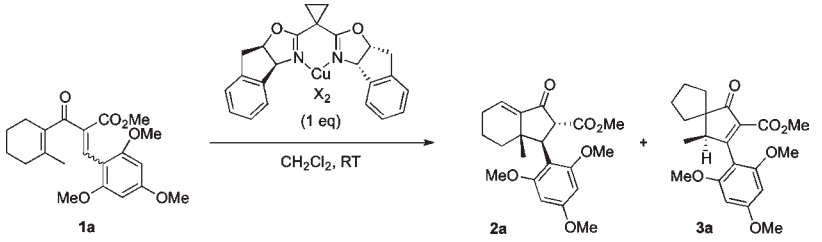
Table 4



entry	counterion (X)	time (h)	combined yield (%)	product (ratio)	% ee
1	OTf (**6**)	12	66	**2a**	89
2	ClO_4 (**7**)	5	90	**2a**/**3a** (1.2:1)	55/47
3	SbF_6 (**4**)	1	69	**3a**	39
4	PF_6 (**8**)	1	55[a]	**3a**	16
5	BARF (**9**)	12	complex mixture	–	–

[a] Yield of pure **3a**; an unidentified byproduct is formed in this reaction.

On the basis of these experiments, we identified the hexafluoroantimonate complex **4** as the optimal one for the formation of **3a** (entry 3). Use of complexes **6** and **7** resulted in preferential formation of **2a** (entries 1 and 2), and while no **2a** was formed in the reaction with complex **8**, an unidentified byproduct was formed and the yield of **3a** was lower (entry 4). Attempts to use the highly non-coordinating 3,5-bis(trifluoromethyl)-phenylborate (BARF) as a counterion were not successful (entry 5).

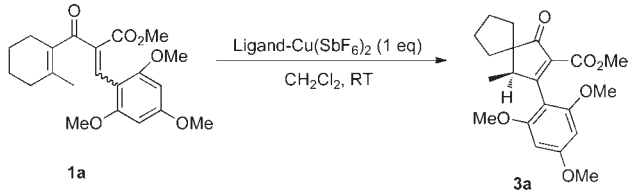
2.4. Ligands for Copper(II) Hexafluoroantimonate Complexes. To make this methodology practical, an inexpensive and readily available promoter needed to be identified to replace the chiral complex **4**. The impressive profile of the hexafluoroantimonate counterion (Tables 3 and 4) suggested we screen copper(II) hexafluoroantimonate complexes with achiral ligands, as well as exploring the behavior of alternative chiral ligands. Since Aggarwal et al. found hexafluoroantimonate to be the counterion of choice in asymmetric Nazarov cyclizations,[4a] the initial screen focused on hexafluoroantimonate complexes (Table 5). In general, these new promoters were prepared by forming the ligand−$CuCl_2$ complex followed by anion exchange with $AgSbF_6$. Due to poor solubility of the final promoters in dichloromethane, dienyl substrate **1a** was directly added to the suspensions. Thus, commercially available achiral phenanthroline and bipyridine complexes were used to prepare copper(II)·$2SbF_6$ complexes **10** and **11**. The colored suspension dissolved immediately upon addition of the substrate, leaving white sediment (AgCl) and a brown reaction solution. As illustrated in Table 5, complexes **10** and **11** promoted the formation of spirocycle **3a** when a stoichiometric amount of the complexes was used (entries 1 and 2). On the other hand, the ligands BPY and BBOT (Table 5, entries 3 and 4) proved to be significantly less effective for the cyclization. In these cases, the suspension did not dissolve in the presence of the substrate, indicating unsuccessful coordination of carbonyls to the copper. The ligands used in preparation of complexes **14**, **15**, and **16** were chosen because they have been reported as effective as promoters of Nazarov cyclizations.[26] The reaction can be achieved successfully with various ligands (Table 5, entries 6−8), but the enantiomeric excesses were moderate.

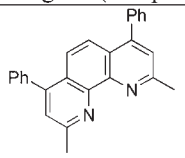
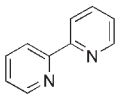
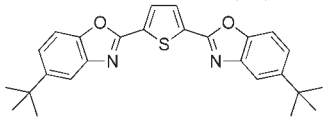
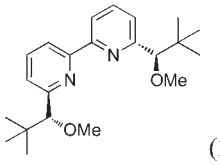
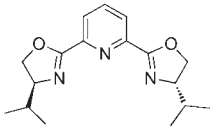
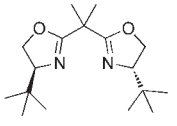
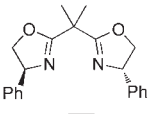
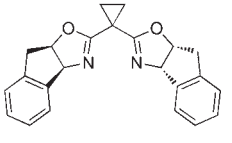
Finally, attempts were made to prepare a copper(II) hexafluoroantimonate complex without a bidentate ligand. The procedure described by Winfield[27] was employed: copper(II) chloride reacted with silver(I) hexafluoroantimonate in acetonitrile to give solvated copper(II) bishexafluoroantimonate, pentakis(acetonitrile) **17**. Reaction of **1a** with this complex gave **3a**, with results comparable to those obtained for the reactions with complexes **5** and **6** (entry 9). The analogous complex with hexafluorophosphate was prepared, but this complex was less stable than **17**. The copper(II)/BARF complex was also prepared but had poor solubility in dichloromethane, and the reaction gave a complex mixture containing only trace quantities of the spirocyclic compound.

2.5. Solvent Optimization. Cyclizations in the presence of various Cu(II) complexes were also performed in different solvent systems (Table 6). Dichloromethane, dichloroethane, and nitroethane were all effective solvents for the rearrangement (Table 6, entries 1−7). Although the *in situ* prepared promoters dissolved well in THF and acetonitrile, they did not provide access to the desired spirocyclic compound. Using THF as solvent promoted the formation of Nazarov product as the sole compound in 92% yield instead of the spirocycle, whereas, in acetonitrile, a complex mixture was observed. Reactions carried out in toluene were not efficient due to the limited solubility of the Cu(II) complexes in this nonpolar solvent.

3. Scope: Formation of Spirocycles 3 Mediated by Cu(II) Complexes. To explore the scope and limitations of the Nazarov cyclization/Wagner−Meerwein rearrangement sequence, cyclizations were carried out with substrates bearing different aromatic substituents at C5 (Table 7). Almost all the reactions required heating at reflux in dichloromethane in the presence of 100 mol % of complex **4**. At room temperature, the cyclization was slow, and competing substrate decomposition was observed prior to the complete consumption of the starting material. In most cases, a spirocyclic product was obtained as the major product. In an interesting twist, the spirocyclic compounds generated from substrates **1b**, **1e**, and **1i**−**k** were different from the one observed during cyclization of **1a**: the signal of the methyl group at C1 remained a singlet in ^1H NMR of these

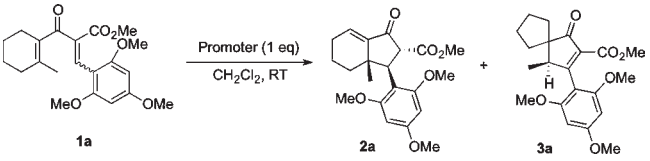
Table 5



entry	ligand (complex)	yield (%)	ee (%)
1	 (**10**)	91	-
2	 (**11**)	76	-
3	 (**12**)	25	-
4	 (**13**)	traces	-
5	 (**14**)	33	8
6	 (**15**)	85	18
7	 (**16**)	78	24
8	 (**4**)	69	39
9	5(H_3CCN) (**17**)	76	-

products. However, new vinyl protons were detected at chemical shifts greater than δ 8.0 ppm. On the basis of the above data, the structures of the new spirocyclic compounds were assigned as having a different skeleton, which we will call **3′** (see Table 7). The only substrate that did not cyclize was **1l** (with pyridine substitution, entry 12), which was most likely due to the coordinating ability of the pyridine nitrogen.[28]

Table 6



entry	solvent	copper(II) complex	time (min)	yield (%)	ratio (**2a**:**3a**)
1	CH_2Cl_2	**4**	60	69	<1:20
2	CH_2Cl_2	**17**	15	76	<1:20
3	CH_2Cl_2	**11**	60	76	<1:20
4	CH_3NO_2	**4**	40	68	<1:20
5	CH_3NO_2	**17**	10	71	<1:20
6	CH_3NO_2	**11**	40	65	<1:20
7	$(CH_2Cl)_2$	**17**	15	75	<1:20
8	THF	**17**	20	94	7:1
9	THF	**11**	60	92	>10:1
10	CH_3CN	**17**	20	—[a]	—
11	toluene[b]	**4**, **17**	—	—	—

[a] Complex mixture. [b] Copper(II) complexes are not soluble in toluene.

Substrates with alkyl groups at the C5 reacted more slowly and required elevated temperatures in dichloroethane to furnish the spirocyclic products **3m** and **3n** (Table 8, entries 1 and 2). A substrate (**1o**) with cinnamyl substitution gave product **3′o** exclusively (Table 8, entry 3). Moreover, the reaction was not limited to substrates with cyclohexene substitution pattern; for example, the dienone **18** gave spirocycle **19** in high yield (91%).

Substrates bearing different substituents at C1 (hydrogen, vinyl, and phenyl in lieu of methyl) were also prepared and cyclized under the same reaction conditions. Only standard Nazarov cyclization products **21**/**22** and **24** were observed with the substrates **20** and **23**, indicating that the methyl group at C1 is important for the formation of spirocyclic products (eqs 1 and 2). This is understandable because the generation of a secondary carbocation from a tertiary one is an energetically disfavored process. It was interesting to find that the ratio of products **21**−**22** changed depending upon the catalyst used. In the experiment using 5 mol % of $Cu(OTf)_2$, a 1:1 mixture of **21**/**22** was obtained, while 100 mol % of catalyst **4** gave a 4:1 ratio of 21/22. The bulky ligand may hinder elimination at the exocyclic position.

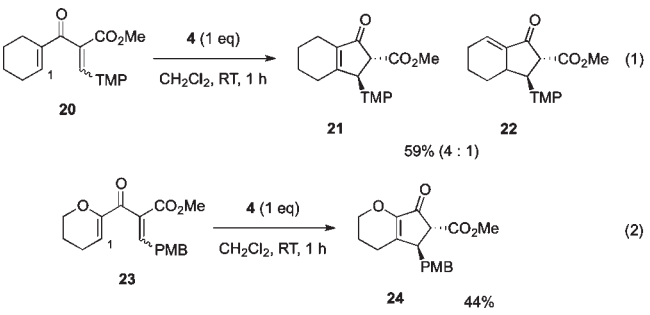


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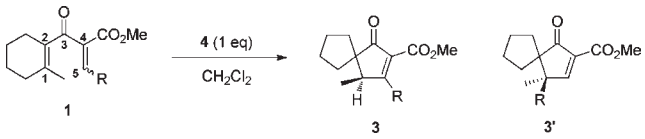
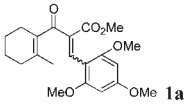
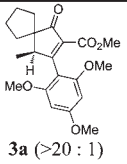
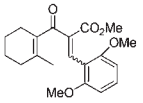
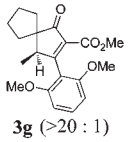
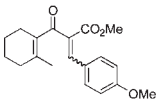
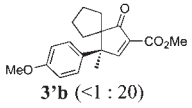
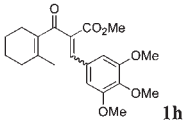
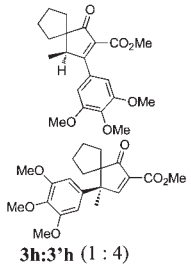
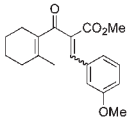
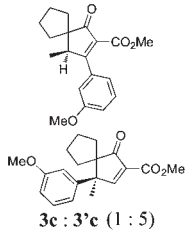
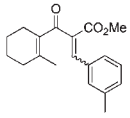
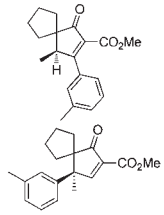
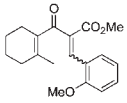
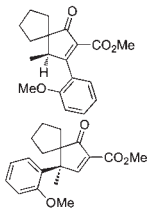
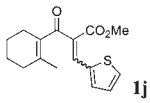
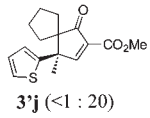
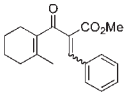
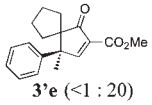
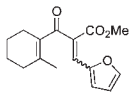
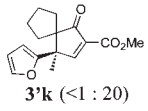
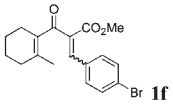
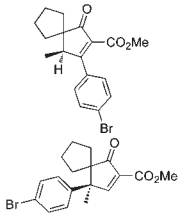
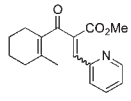
Table 7.[a]



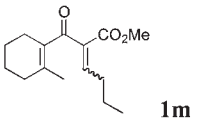
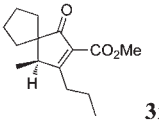
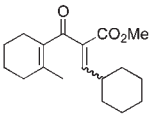
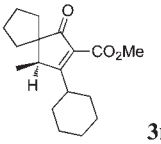
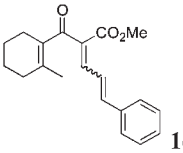
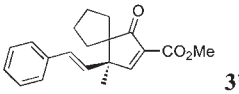
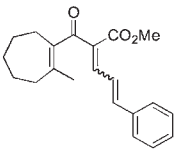
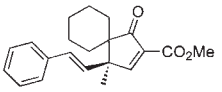
entry	R	temp (°C)	time (h)	products (ratio **3** :**3'**)	yield (%)	entry	R	temp (°C)	time (h)	products (ratio **3** :**3'**)	yield (%)
1	 **1a**	25	0.5	 **3a** (>20 : 1)	69	7	 **1g**	45	2	 **3g** (>20 : 1)	86
2	 **1b**	25	1	 **3'b** (<1 : 20)	76[b]	8	 **1h**	45	1	 **3h:3'h** (1 : 4)	82
3	 **1c**	45	2	 **3c** : **3'c** (1 : 5)	79	9	 **1i**	45	4	 **3i** :**3'i** (1 : 10)	78
4	 **1d**	25	2	 **3d** : **3'd** (2 : 1)	93	10	 **1j**	45	4	 **3'j** (<1 : 20)	88
5	 **1e**	45	3	 **3'e** (<1 : 20)	75	11	 **1k**	45	4	 **3'k** (<1 : 20)	80[c]
6	 **1f**	45	3	 **3f** : **3'f** (1 : 1.1)	88	12	 **1l**	45	16	-	

[a] Reaction conditions: substrate in CH_2Cl_2 (0.03 M) in the presence of 1 equiv of **4** at the indicated temperature [b] Enantiomeric excess was 45%. [c] The product is obtained in mixture with an unidentified compound (see Supporting Information).

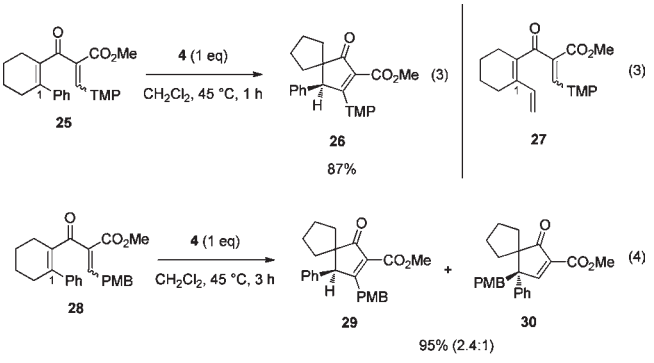
In the case of substrate **25**, the reaction required elevated temperatures to obtain complete conversion, but spirocyclic product **26** was obtained in 87% yield (eq 3). In comparison, both spirocyclic compounds **29** and **30** were formed from the precursor **28** (eq 4). This is the only case among the reactions of PMB-substituted derivatives in which the migration of the *p*-methoxyphenyl group was not dominant. Compound **27** was also synthesized, but attempted cyclization led only to decomposition of the substrate.

dx.doi.org/10.1021/ja111504w |*J. Am. Chem. Soc.* 2011, 133, 6307–6317

Table 8.[a]

entry	dienone	temp (°C)	time (h)	product	yield (%)
1	 **1m**	80	24	 **3m**	84[b]
2	 **1n**	80	16	 **3n**	62
3	 **1o**	25	20	 **3'o**	96[c]
4	 **18**	25	6	 **19**	91

[a] Reaction conditions: substrate in CH_2Cl_2 (0.03 M) in the presence of 1 equiv of **4** at the indicated temperature. [b] Enantiomeric excess was 20%. [c] Enantiomeric excess was 42%.



4. Proposed Mechanism. After the 4π conrotatory electrocyclization (Scheme 2), the oxyallyl cationic intermediate **31** is generated and either can undergo a [1,2]-shift resulting in ring contraction to furnish cationic intermediate **33** or is subjected to a β-H elimination to give normal Nazarov product **32** (pathway a). A [1,2]-hydride shift (pathway b) generates intermediate **34**, which is converted to the final product **31** with loss of the Lewis acid. Alternatively, if intermediate **33** undergoes a [1,2]-carbon shift instead (pathway c), intermediate **36** is obtained, leading to final product **37** after the decomplexation of the Lewis acid.

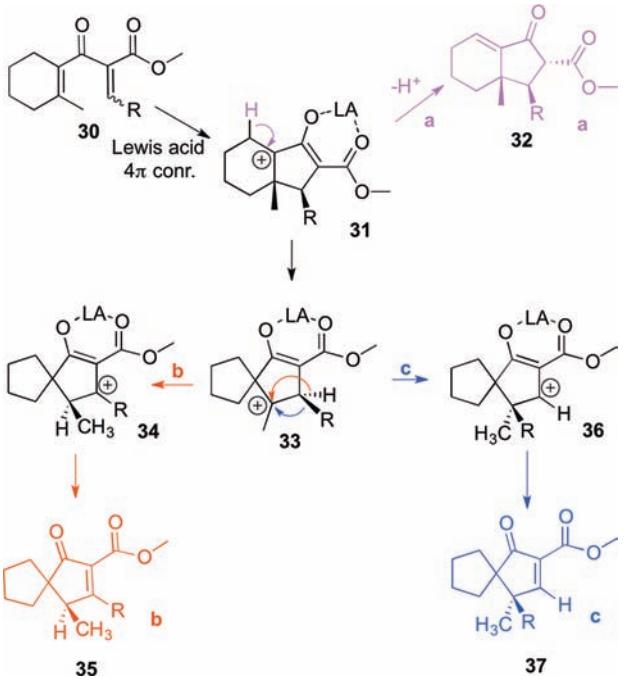
The results of a deuterium labeling experiment were also consistent for our proposed mechanism (Scheme 3): cyclization of **38** provided access to the spirocyclic compound **39** with the complete transfer of deuterium from C1 to C5.

Furthermore, the carbonyl group can act as a Brönsted base and promote the elimination pathway (pathway a), leading to the formation of the Nazarov product. At the beginning of the reaction, when 1 equiv of promoter is present we would expect the carbonyl groups of substrates to be bound to the promoter, which might slow down the elimination pathway and allow the spirocycle formation to dominate. To test this hypothesis, the substrate was slowly added to a solution of the catalyst, in order to keep the concentration of promoter high relative to substrate. Since the rearrangement reaction is fast relative to the rate of addition, we would expect a high proportion of substrate carbonyl groups to be bound to the promoter under these conditions, even when the promoter is present in substoichiometric amounts. Indeed, when the substrate is added to a substoichiometric solution of promoter **4** (50 mol %), the observed product ratio of **2a** to **3a** was 1:10. As comparison, when all reactants were added together to the reaction mixture with 50 mol % of promoter, the ratio of **2a** to **3a** observed is 1.7:1 (Table 2, entry 3). Also supporting the idea that basic media increases the rate of elimination (formation of **2a**) was the observation that the more non-coordinating the counterion, the more spirocyclic product **3a** was formed. Lastly, we found that when the spirocycle-forming experiment was run in THF (a basic solvent), only the elimination product **2a** was formed. Thus, in the optimal reaction conditions for spirocycle formation, 1 equiv of promoter is used (to coordinate all the basic carbonyl groups in solution) and a non-coordinating counterion is present (hexafluoroantimonate) in a nonbasic solvent (dichloromethane).

Finally, experiments were conducted to explore the reversibility of the reaction sequence. When spirocycle **3a** was subjected to 100 mol % of $(MeCN)_5Cu(SbF_6)_2$, Nazarov product **2a** was not detected, and conversely, exposure of Nazarov product **2a** to the same reaction conditions did not produce spirocycle **3a**. Thus, under the optimized reaction conditions, the elimination-terminated Nazarov cyclization product **2a** does not appear to be an intermediate in the cyclization/Wagner–Meerwein rearrangement sequence that produces **3a**.

dx.doi.org/10.1021/ja111504w | J. Am. Chem. Soc. 2011, 133, 6307–6317

Scheme 2. Mechanistic Proposal for the Spirocycle Formation



Scheme 3. Deuterium Labeling Experiment

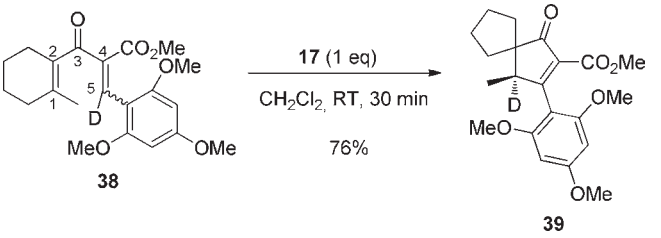
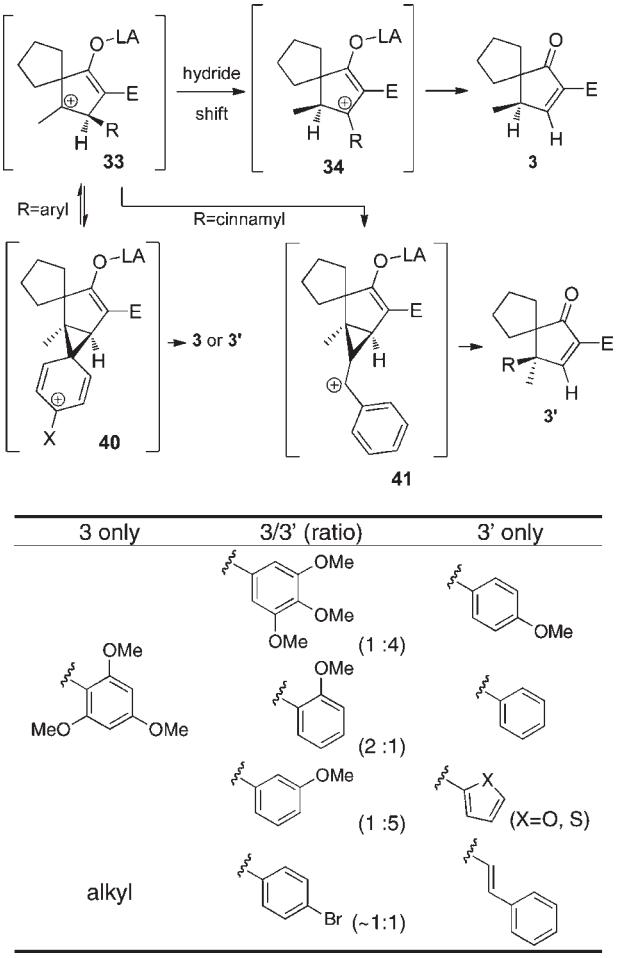


Chart 1



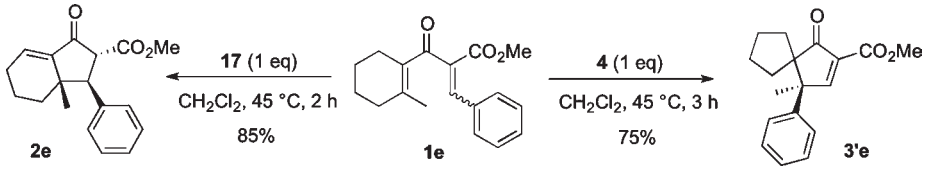
5. Rationale for Formation of 3 versus 3′. The selective formation of products **3** or **3′** in most cases requires some discussion, since the selectivity does not follow the expected migratory aptitude trends (Chart 1).[29] Formation of **3** vs **3′** depends upon the fate of carbocation intermediate **25** (Scheme 2), in which either a hydride shift leads to products **3** or a vinyl/aryl shift leads to products **3′**, presumably via a phenonium ion intermediate **40** or the corresponding vinylogous version **41**.[30] One would expect that electron-donating aryl groups would facilitate the aryl shift, whereas electron-withdrawing ones would destabilize the phenonium and allow hydride migration to occur. The results of the reactions of *p*-methoxyphenyl substrate **1b** (**3′** only) and *p*-bromophenyl substrate **1f** (**3f**/**3′f** ratio ≈ 1:1) are consistent with this expectation. However, the highly electron-rich substrate **1a** (R = 2,4,6-trimethoxyphenyl) gives exclusively the spirocyclic compound **3a** with H-migration. This result suggests that phenyl migration is also affected by steric factors that hinder the formation of the bridged cation intermediate **40**. Experiments with substrate **1d**, bearing an *o*-methoxyphenyl group, support this hypothesis. The electron-donating character is equivalent to that of *p*-methoxyphenyl **1b**, but the steric impact of the methoxy group should be more significant. Indeed, a mixture of two spirocyclic compounds **1d** and **1′d** is obtained in a ratio 2:1, indicating that the hydride shift is slightly favored due to the steric bulk at the ortho position. On the other hand, the substrate **1g** bearing an *o*-dimethoxyphenyl group gives only the product **3g** with hydride shift. The electronic influence of the aryl substituent can also be seen in substrates **1c**, **1h**, and **1i**, which have methoxy and methyl groups at the meta position. The compounds **1c** and **1h** (Hammett constant $\sigma_{meta}(OCH_3)$ = 0.12) favor aryl migration, but not as strongly as substrate **1b** ($\sigma_{para}(OCH_3) = -0.27$). However, the result obtained with the substrate **1i** ($\sigma_{meta}(CH_3) = -0.07$) compared to **1e** (R = phenyl, $\sigma_{meta}(H) = 0$) suggests that there may be a slight steric impact on the aryl shift caused by the meta substituent on the ring.

In the case of the phenyl substrate **1e**, it was interesting to note that the reaction pathway changed depending upon the catalyst used (Scheme 4). These results suggest that the large bisoxazoline ligand can also extend the lifetime of carbocation **31** (Scheme 2) by reducing the rate of the elimination pathway leading to the Nazarov product.

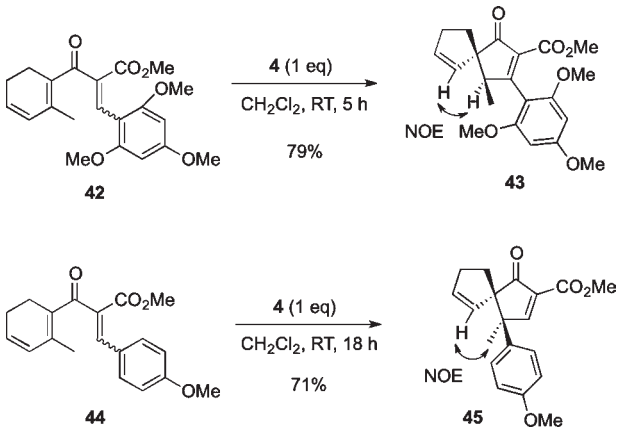
To address the question of relative stereochemistry between the new generated quaternary center and an adjacent stereocenter, substrates **42** and **44** were synthesized and subjected to

dx.doi.org/10.1021/ja111504w | *J. Am. Chem. Soc.* 2011, 133, 6307–6317

Scheme 4. Influence of the Ligand on the Reactivity



Scheme 5



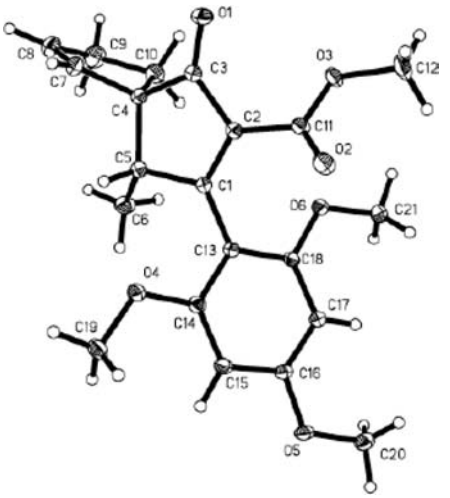


Figure 3. ORTEP drawing of **43**.

the reaction conditions (Scheme 5). To our great pleasure, the rearrangement of substrates **42** and **44** provided the expected spirocyclic compounds **43** and **45** with complete stereocontrol. In each case, only one diastereoisomer was observed. The diastereochemistry was proved by NOE analysis, and the structure of spirocyclic compound **43** was further confirmed by X-ray crystallography (Figure 3). In each case, the stereochemistry observed was consistent with the proposed mechanism: stereospecific Nazarov cyclization (conrotatory) followed by two Wagner–Meerwein shifts (suprafacial).

SUMMARY, CONCLUSIONS, AND PERSPECTIVES

In summary, our study of the Nazarov cyclization has revealed that alternative reaction pathways (sequential Wagner–Meerwein rearrangements with ring contraction) can be accessed when reaction conditions are properly controlled. Rearrangement occurs when a stoichiometric amount of a copper(II) complex with a non-coordinating counterion is employed. The different reaction pathways are rationalized as follows: under reaction conditions employing catalytic copper(II) triflate, the basic carbonyl groups and triflate counterion help promote the elimination pathway. However, when stoichiometric amounts of a copper(II) hexafluoroantimonate promoter are used, the amount of Brönsted base in solution is minimized, the rate of elimination is slowed, and the migration pathways become dominant. In this manner, it is possible to achieve stereospecific synthesis of unusual spirocyclic compounds with adjacent stereocenters, including adjacent quaternary centers. In addition, it was found that the selectivity of the alternative Nazarov/Wagner–Meerwein sequences depends upon the nature of the substituent at C5. It is possible to correlate selectivity with both migratory ability and steric bulk of the substituents at C5. Electron-rich aromatic substitutions, including *p*-methoxyphenyl and cinnamyl, tend to favor the migration of the substituent and afford compounds of type **3′**, while electron-poor substitutions such as alkyl or *p*-bromophenyl groups decrease the ability to migrate, and in these cases, type **3** spirocyclic compounds are generated due to the competitive hydride migration. However, it was found that steric hindrance can interfere with the formation of phenonium intermediates and disfavor aryl migration. This study revealed the following limitations: one full equivalent of Lewis acid promoter is required, and the enantiomeric excesses (ranging from 20% to 45%) are moderate. Studies focused on the development of a catalytic, enantioselective version of this reaction sequence are underway, as well as extension of this methodology to acyclic substrates. We are also exploring the viability of this strategy to the synthesis of natural products.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds, X-ray crystal structure coordinates, and CIF file for **5**. This material is available free of charge via the Internet http://pubs.acs.org.

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