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Using Nazarov Electrocyclization to Stage Chemoselective [1,2]-Migrations: Stereoselective Synthesis of Functionalized Cyclopentenones

Dr. David Lebœuf,

Department of Chemistry, University of Rochester, Rochester, NY 14627

Dr. Jie Huang,

Department of Chemistry, University of Rochester, Rochester, NY 14627

Prof. Vincent Gandon, and

Univ Paris-Sud, ICMO (UMR CNRS 8182), 91405 Orsay, France

Prof. Alison J. Frontier

Department of Chemistry, University of Rochester, Rochester, NY 14627

Alison J. Frontier: frontier@chem.rochester.edu

Abstract

Highly functionalized cyclopentenones are prepared stereospecifically based on a chemoselective copper(II)-mediated Nazarov/Wagner-Meerwein rearrangement sequence. After the initial 4π electrocyclization, this reaction involves two sequential [1,2]-migrations depending upon both migratory ability and steric bulk of the substituents at C1 and C5. This sequence can be achieved by using a catalytic quantity of copper(II) in combination with a weak Lewis acid. The mechanism of the reaction is also supported by DFT computations.

Keywords

copper; homogeneous; catalysis; Nazarov cyclization; Wagner-Meerwein rearrangement; density functional calculations

Since its discovery in 1941, the Nazarov 4π conrotatory electrocyclization has become an elegant and efficient way to prepare substituted cyclopentenones with adjacent stereocenters.^{[1][2]} While some inroads have been made with respect to asymmetric catalysis^[3] or development of new catalytic systems,^[4] substrate scope is often quite limited, especially to construct vicinal quaternary centers. To extend the reactivity related to the Nazarov cyclization, several groups have developed new methodologies involving either the trapping of the oxyallyl cation intermediate by suitable reagents^[5] or rearrangements^{[6][7]} that lead to highly functionalized, synthetically useful cyclopentanone products.

In our early studies of Wagner-Meerwein rearrangements of oxyallylcation intermediates in the Nazarov cyclization,^[7] we found that it was possible to increase the lifetime of the oxyallyl cation intermediate **II**, favoring a new reaction pathway leading to spirocyclic products **V** and **VI** rather than the elimination product **III** (Scheme 1). Only ring contraction

Correspondence to: Alison J. Frontier, frontier@chem.rochester.edu.

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was ever observed: no methyl migration products were identified. In many cases, stoichiometric copper(II) complexes with a large bisoxazoline ligand were necessary to stabilize oxyallyl cation **II** for the rearrangement.

If this rearrangement chemistry could be controlled in a simpler system like **1**, the sequence of stereospecific reactions would lead to cyclopentenones **2** with adjacent stereocenters (Scheme 2). Furthermore, development of a catalytic protocol was an essential step toward asymmetric applications. To achieve chemo- and stereoselectivity in the cyclization/rearrangement sequence, the challenge was to understand and manage *E/Z* isomerization propensities, migratory aptitudes, and geometrical aspects of migration.

In this communication, we describe an efficient, chemoselective method for cyclization and rearrangement of simple divinyl ketone substrates **1**, using copper(II) complexes (Scheme 2). The reaction generates adjacent stereocenters at the α' and β' positions of the cyclopentenone via a stereospecific sequence of cyclization/suprafacial shifts. This reaction does not require the use of a sophisticated ligand, and it can be carried out with a catalytic amount of a copper(II) complex.

We began our investigation with 1,4-dien-3-ones with different substitution patterns at C1 and C2, and a 2,4,6-trimethoxyphenyl (TMP) group at C5 (Table 1). Substrates **1a–h**, were cyclized in dichloromethane in the presence of 100 mol% of (MeCN)₅Cu(SbF₆)₂.^[8] The substitution pattern and the stereochemistry of **2a–h** were consistent with mechanism **A** (Scheme 1). It is important to mention that the cyclization of *E/Z* mixtures of alkylidene β -ketoesters was found to be stereoconvergent: *E/Z* isomerization is facile under the reaction conditions, and only the *Z* isomer cyclizes.^[4b] The relative stereochemistry of the two centers created in the reaction was established by One analysis of cyclopentenone **2a** (see Supporting Information for details). It was possible to achieve chemoselective [1,2]-migration of an aryl group (entries 1–3), a methyl group (entries 4 and 8), a siloxymethyl group (entry 5), and a branched alkyl group (entries 6 and 7) from C1 to C2. A hydride shift was the second [1,2]-migration event observed in all cases, and cyclopentenones **2a–h** were obtained in high yields. In the rearrangement of substrate **1e** (Table 1, entry 5), the formation of two products **2e** and **2'e** was observed, with **2'e** corresponding to the hydroxymethyl compound after loss of the tert-butyldimethylsilyl group. The compounds were obtained in a 1:1 ratio and a combined yield of 90%. This deprotection can be attributed to the presence of the hexafluoroantimonate counterion in solution.^[10]

To examine the reactivity of compounds with different C5 substituents, dienones **1i–n** were prepared and subjected to the usual reaction conditions (Table 2). Compounds with aromatic, heteroaromatic, alkenyl and alkyl functionalities were tested. From these experiments, it was possible to obtain cyclopentenones containing adjacent stereocenters in high yields (entries 1–5), or the tetrasubstituted cyclopentenone **2n** as a single diastereomer (entry 6).

In many of the Table 2 examples, a diastereoisomer was observed in varying amounts. Since each one of the three steps of the reaction sequence is stereospecific (Scheme 1), the isomer must arise from isomerization of the C1–C2 bond of the substrate in the presence of the copper(II) complex.

Our original experiments indicated that both migratory aptitudes and steric effects influenced which group underwent a [1,2]-Wagner-Meerwein shift.^[7] Thus, the chemoselectivity of the reactions in Tables 1 and 2 is remarkable. In general, the [1,2]-migration of an aromatic group occurred in preference to a methyl or hydride migration, consistent with expectations based on migratory aptitude.^[9] Exceptions to this are reactions

of substrates with the 2,4,6-trimethoxyphenyl (TMP) group (Table 1) or a hindered phenyl (**1g**, Table 1). In both cases, steric factors prevent migration of the aromatic ring. Also consistent with migratory aptitudes, substituted alkyl groups underwent [1,2]-migration in preference to methyl groups (Table 1, entries 5 and 6), and hydride migration was more favourable than isopropyl migration (Table 2, entry 6).

An asymmetric version of this reaction was examined briefly. We chose the bis(oxazoline) ligand (**box**), which had already been shown to be an efficient promoter of the Nazarov/Wagner-Meerwein sequence and able to induce enantioselectivity for this transformation.^[7b] The rearrangement of compound **1h** was especially promising, affording cyclopentenone **2h** in 80% yield and 95% *ee* (Scheme 3).

We next turned our attention to developing a catalytic version of this reaction. Our hypothesis accounting for the requirement for stoichiometric copper(II) is this: the carbonyl lone pair must be bound to the promoter throughout the reaction, otherwise the basic carbonyl facilitates loss of a proton from oxyallyl cation **II** to give **III** (Scheme 1).^[7] Our goal was to identify an additive that could coordinate the carbonyl lone pair without promoting the cyclization. If the additive could readily exchange with a catalyst for the reaction, the rearrangement could be achieved selectively using the combination of additive and catalyst. Our initial attempts to achieve a catalytic rearrangement of **1o** by using a combination of 10 mol% of (MeCN)₅Cu(SbF₆)₂ and 90 mol% of several additives, including Zn(OAc)₂, Mn(acac)₂, Fe(acac)₂, LiClO₄, Mg(OTf)₂, NaSbF₆, NaPF₆ and NaBPh₄, failed.^[11] The reactions slowed down considerably, leading to mixtures of products in low yields. Furthermore, all these Lewis acids displayed a poor solubility in dichloromethane. Experiments with NaBAr₄^f had been promising in another context,^[4d] and proved to be effective as an additive for catalytic rearrangements with Cu(II) complexes. No reaction of dienone **1o** occurred in the presence of a stoichiometric amount of NaBAr₄^f, but in the presence of (MeCN)₅Cu(SbF₆)₂ (10 mol%) and NaBAr₄^f (90 mol%), cyclopentenone **2o** was formed in 90% yield as expected (Scheme 4).^[12]

These catalytic reaction conditions could be employed for the cyclization/rearrangement of other substrates as well. (Chart 1). Yields and efficiency were comparable to experiments conducted with stoichiometric copper(II) complexes.^[7]

The combination of the BAr₄^f counterion's non-coordinating behavior and the solubility of the NaBAr₄^f salt are thought to account for the singular success of this additive. The finding that the Na⁺ cation is enough to suppress the elimination pathway is interesting, because it suggests that the basicity of only one carbonyl must be suppressed.

To gain some insight into the mechanistic issues raised during this study, we carried out DFT computations using dienone **1a** as model substrate and Cu²⁺ as promoter (see Supporting Information for all details).^{[13][14][15]} From complex **a1** (Scheme 5), the transition state corresponding to the conrotatory 4 π electrocyclization could be located at $\Delta G^\ddagger_{298} = 18.98$ kcal/mol. It connects **a1** with the 5-membered ring intermediate **b1** lying 8.74 kcal/mol above. The suprafacial 1,2-methyl shift from **b1** to give **c1** requires a prohibitively high free energy of activation, **TS_{b1-c1}** lying at 27.50 kcal/mol. On the other hand, the 1,2-phenyl shift leading to **c2** is much more accessible (19.07 kcal/mol). From **c2**, the H-shift transition state lies higher than that of the TMP shift (17.59 vs 14.22 kcal/mol). However, the formation of **d2** is endergonic ($\Delta G_{298} = 9.38$ kcal/mol) and readily reversible, while that of the fully conjugated complex **d1** is appreciably exergonic ($\Delta G_{298} = -11.33$ kcal/mol). Thus, the calculations predict the observed product **2a**, with a *cis* relationship between the two methyl groups. The preference for **d1** does not seem to have a kinetic origin since the TMP-migration transition state is more accessible than that of the H-migration.

However, in spite of the formation of a phenonium framework in **d2**, the stabilization of the carbocation is more efficient in **d1**.^[16]

To support the proposed Cu²⁺-mediated *E/Z*-isomerization observed in some of the tetrasubstituted substrates (Table 2), additional computations were performed. The *E/Z* inversion shown in Scheme 5 could be modelled in four steps from **a1**: Complex **a1**, which is conformationally aligned for a 4 π electrocyclization (*s-trans/s-trans*), readily rearranges through **T_{a1-a2}** into the slightly more stable conformer **a2** ($\Delta G^\ddagger_{298} = 8.98$ kcal/mol, $\Delta G_{298} = -0.63$ kcal/mol). The diastereomutation then takes place to give **a3**, slightly less stable than **a1** ($\Delta G_{298} = 0.99$ kcal/mol). The corresponding transition state, **TS_{a2-a3}**, is the lowest-lying of this sequence at $\Delta G^\ddagger_{298} = 19.10$ kcal/mol. Then, **a3** isomerizes into the more stable complex **a4** in which copper coordinates the phenyl group.^[14] This coordination is appreciably exergonic ($\Delta G_{298} = -6.37$ kcal/mol), indicating that formation of the *Z* isomer **a4** should be favored over formation of the *E* isomer **a2**. However, a close look at the energy values suggests that the formation of products from the *Z* isomer is unlikely. First, the isomerization of **a4** into the appropriately preorganized conformer **a5** passes through the low-lying **TS_{a4-a5}** ($\Delta G^\ddagger_{298} = 1.39$ kcal/mol), but is quite endergonic ($\Delta G_{298} = 2.04$ kcal/mol). Second, the electrocyclization of **a5** to give **b2** requires 25.70 kcal/mol of free energy of activation and is strongly endergonic ($\Delta G_{298} = 19.68$ kcal/mol). From **b2**, both shifts display high activation barriers (25.91 vs 23.65 kcal/mol). Overall, due to the steric interaction between the phenyl and the TMP groups, the cyclization of **a1** to **b1** is more favourable than the cyclization of **a5** to **b2** both kinetically and thermodynamically. Thus, starting from either **a1** or **a5**, the same final result is expected: formation of complex **d1** and then product **2a**.

This prediction is corroborated by the experimental result depicted in Scheme 6: When the *Z* isomer **1r** was subjected to the reaction conditions, product **2a** was isolated in 95% yield. The same result was described in Table 1, except the cyclization substrate was the *E* isomer **1a**.

In summary, we have developed an efficient, chemoselective method for preparation of highly functionalized cyclopentenones based on a stereospecific, copper(II)-mediated Nazarov cyclization/Wagner-Meerwein rearrangement sequence. The chemoselectivity of the [1,2]-migrations depended on both the migratory ability and the steric demand of the substituents at C1 and C5. Experiments with a series of alkylidene β -ketoester substrates led to the creation of adjacent stereocenters, including adjacent quaternary centers. It was found that partial *E/Z* isomerization of the enone moiety occurs in some cases, which affects the selectivity of the reaction by compromising the stereochemical fidelity of the substrates. DFT computations support the possibility of a Cu²⁺-mediated double bond isomerization to rationalize this finding. It was also found that selective cyclization/rearrangement could be achieved with a catalytic amount of the copper promoter in combination with a weakly Lewis acidic sodium salt. Continuing efforts in our laboratory are focused on the development of the asymmetric version of this reaction, and application of this strategy toward the synthesis of natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Spirocycle Synthesis via Nazarov/Wagner-Meerwein Rearrangement Sequence.

Scheme 2.

The Challenge: Selectivity in Cyclopentenone Synthesis.

Scheme 3.

Copper-mediated Enantioselective Cyclization of 1,4-Dien-3-one **1h**; TMP = 2,4,6-trimethoxyphenyl. PMP = *p*-methoxyphenyl.

Scheme 4.

Copper-catalyzed Cyclization of 1,4-Dien-3-one **1o**; TMP = 2,4,6-trimethoxyphenyl.

Scheme 5. Calculated Free Energies (ΔG , kcal/mol) for the Cu^{2+} -mediated Cyclization of Dienone **1a**.

Scheme 6.
Copper-mediated Cyclization of 1,4-Dien-3-one **1r**.

[a] Reaction conditions: substrate in CH_2Cl_2 (0.03 M) in the presence of NaBAR_4^f (90 mol%) and $(\text{MeCN})_5\text{Cu}(\text{SbF}_6)_2$ (10 mol%) at rt for 0.1-0.5 h. [b] Reaction carried out at 45 °C. BAR_4^f = 3,5-bis(trifluoromethyl)phenylborate. TMP = 2,4,6-trimethoxyphenyl. PMP = *para*-methoxyphenyl.

Chart 1.

Results of Cyclization/Rearrangement using Catalytic Protocol.

Table 1

Cyclization/rearrangement of C1/C2 variants of **1a–h**

Entry	Substrate	Product ^[a] (yield)

1	1a R = Me	2a (92%)
2	1b R = Et	2b (95%)
3 ^[b]	1c R = Ph	2c (95%)

4	1d R = Me	2d (51%)
5	1e R = CH ₂ OTBS	2e (45%) ^[c]
6	1f R = <i>n</i> Pr	2f (79%)

7	1g	2g (98%)

8	1h	2h (82%)

^[a] Reaction conditions: substrate in CH₂Cl₂ (0.03 M) in the presence of (MeCN)₅Cu(SbF₆)₂ (1 equiv.) at rt for 10 min.^[b] Reaction carried out at 45 °C.^[c] The desilylated product was also isolated in 45% yield. TMP = 2,4,6-trimethoxyphenyl.

Table 2

Cyclization/rearrangement of C5 variants of **1k–p**.

Entry	Substrate	Product ^[a] (yield, d.r.)

1 ^[b]	1i R = <i>p</i> -methoxyphenyl	2i (86%, 5:1)
2	1j R = phenyl	2j (80%, 20:1)
3	1k R = 2-thienyl	2k (95%, 7:1)
4	1l R = 2-furyl	2l (86%, 4:1)
5	1m R = cinnamyl	2m (85%, 10:1)
6	1n	2n (68%)

^[a] Reaction conditions: substrate in CH₂Cl₂ (0.03 M) in the presence of (MeCN)₅Cu(SbF₆)₂ (1 equiv.) at 45 °C for 0.5–3 h.

^[b] Reaction carried out at rt.