Synthetic Methods

DOI: 10.1002/anie.201104870

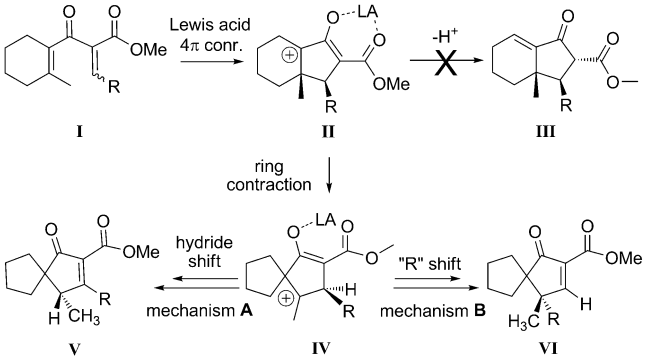
Using Nazarov Electrocyclization to Stage Chemoselective [1,2]-Migrations: Stereoselective Synthesis of Functionalized Cyclopentenones**

*David Lebœuf, Jie Huang, Vincent Gandon, and Alison J. Frontier**

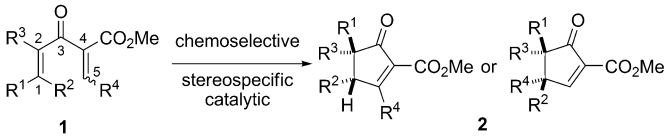
Since its discovery in 1941, the Nazarov 4π-conrotatory electrocyclization has become an elegant and efficient way to prepare substituted cyclopentenones with adjacent stereogenic centers.[1,2] Although some inroads have been made with respect to asymmetric catalysis[3] or development of new catalytic 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 methods 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**, thus favoring a new reaction pathway leading to spirocyclic products **V** and **VI** rather than the elimination product **III** (Scheme 1). Only ring contraction was ever observed: no products resulting from methyl migration were identified. In many cases, stoichiometric amounts of copper(II) complexes bearing 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 stereogenic centers (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 the propensity for *E*/*Z* isomerization, migratory aptitudes, and geometric aspects of migration.



Scheme 1. Spirocycle synthesis through a Nazarov/Wagner–Meerwein rearrangement sequence. conr. = conrotatory, LA = Lewis acid.



Scheme 2. The challenge: selectivity in cyclopentenone synthesis.

Herein, 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 stereogenic centers at the α′ and β′ positions of the cyclopentenone through 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.

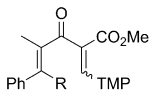
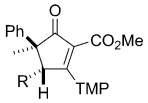
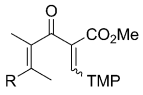
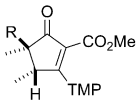
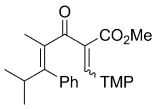
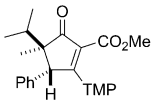
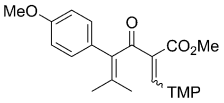
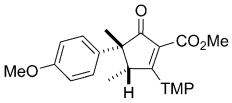
We began our investigation with 1,4-dien-3-ones bearing different substitution patterns at C1 and C2, and a 2,4,6-trimethoxylphenyl (TMP) group at C5 (Table 1). Substrates **1a**–**h** were cyclized in dichloromethane in the presence of 1 equivalent of $[(MeCN)_5Cu(SbF_6)_2]$.[8] The substitution pattern and the configuration of **2a**–**h** were consistent with mechanism **A** (see Scheme 1). Importantly, the cyclization of *E*/*Z* mixtures of alkylidene β-keto esters was found to be stereoconvergent: *E*/*Z* isomerization is facile under the reaction conditions, and only the *Z* isomer cyclizes.[4b] The relative configuration of the two stereogenic centers created in the reaction was established by nOe analysis of cyclopentenone **2a** (see the Supporting Information for details). It was possible to achieve chemoselective [1,2]-migration of an

[*] Dr. D. Lebœuf, Dr. J. Huang, Prof. A. J. Frontier
Department of Chemistry
University of Rochester
Rochester, NY 14627 (USA)
E-mail: frontier@chem.rochester.edu
Prof. V. Gandon
Univ Paris-Sud, ICMMO (UMR CNRS 8182)
91405 Orsay (France)

[**] We thank the National Institutes of Health (NIGMS R01 GM079364, supporting J.H.) and the National Science Foundation (grant no. CHE-0847851, supporting D.L.) for funding this research. We thank R. Eisenberg for useful discussions. We used the computing facility of the CRIHAN (project no. 2006-013).

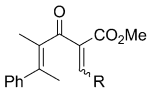
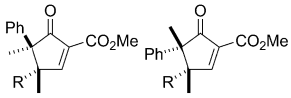
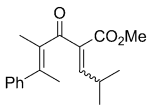
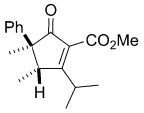
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104870.

Table 1: Cyclization/rearrangement of C1/C2 variants of **1a–h**.[a]

Entry	Substrate	Product (yield [%][b])
1		
	1a, R = Me	**2a** (92)
2	**1b**, R = Et	**2b** (95)
3[c]	**1c**, R = Ph	**2c** (95)
4		
	1d, R = Me	**2e** (51)
5	**1e**, R = CH_2OTBS	**2e** (45)[d]
6	**1f**, R = *i*Pr	**2f** (79)
7[c]		
	1g	**2g** (98)
8		
	1h	**2h** (82)

[a] Reaction conditions: substrate in CH_2Cl_2 (0.03 M) in the presence of $[(MeCN)_5Cu(SbF_6)_2]$ (1 equiv) at RT for 10 min. [b] Yield of isolated product. [c] Reaction carried out at 45 °C. [d] The desilylated product was also isolated in 45% yield. TBS = *tert*-butyldimethylsilyl.

Table 2: Cyclization/rearrangement of C5 variants of **1k–p**.[a]

Entry	Substrate	Product (yield [%][b], d.r.)
1[c]		
	1i, R = PMP[d]	**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 CH_2Cl_2 (0.03 M) in the presence of $[(MeCN)_5Cu(SbF_6)_2]$ (1 equiv) at 45 °C for 0.5–3 h. [b] Yield of isolated product. [c] Reaction carried out at RT. [d] PMP = *para*-methoxyphenyl.

aryl group (Table 1, entries 1–3), a methyl group (Table 1, entries 4 and 8), a siloxymethyl group (Table 1, entry 5), and a branched alkyl group (Table 1, 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%. The removal of the protecting group can be attributed to the presence of the hexafluoroantimonate counterion in solution.[9]

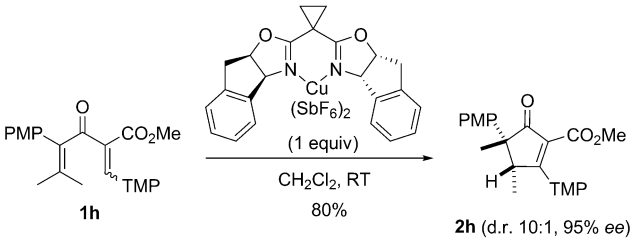
To examine the reactivity of compounds with different substituents at C5, dienones **1i–n** were prepared and subjected to the usual reaction conditions (Table 2). Compounds with aromatic, heteroaromatic, alkenyl, and alkyl functionalities were tested. From these experiments, it was possible to obtain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

In many of the examples in Table 2, a diastereoisomer was observed in varying amounts. Because 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 Table 1 and Table 2 is remarkable. In general, the [1,2]-migration of an aromatic group occurred in preference to a methyl or hydride migration, and is consistent with expectations based on migratory aptitude.[10] Exceptions to this are reactions of substrates with the 2,4,6-trimethoxyphenyl (TMP) group (Table 1) or a hindered phenyl group (**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 favorable than isopropyl migration (Table 2, entry 6).

An asymmetric version of this reaction was briefly examined. 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, and afforded cyclopentenone **2h** in 80% yield and 95% *ee* (Scheme 3).

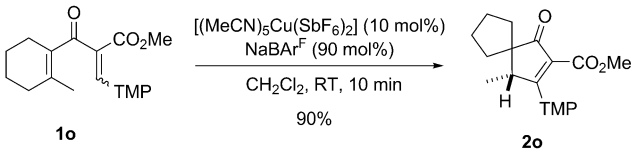
We next turned our attention to developing a catalytic version of this reaction. Our hypothesis accounting for the requirement of a stoichiometric amount of copper(II) is this: the lone pair of electron on the carbonyl group must be bound to the promoter throughout the reaction, otherwise the basic



Scheme 3. Copper-mediated enantioselective cyclization of dienone **1h**.

carbonyl unit facilitates loss of a proton from oxyallyl cation **II** to give **III** (see Scheme 1).[7] Our goal was to identify an additive that could coordinate the carbonyl lone pair electrons 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** using a combination of 10 mol% of $[(MeCN)_5Cu(SbF_6)_2]$ and 90 mol% of several additives, including $Zn(OAc)_2$, $[Mn(acac)_2]$, $[Fe(acac)_2]$, $LiClO_4$, $Mg(OTf)_2$, $NaSbF_6$, $NaPF_6$, and $NaBPh_4$ all failed.[11] The reactions slowed down considerably, thus leading to mixtures of products in low yields. Furthermore, all these Lewis acids displayed a poor solubility in dichloromethane. Experiments with $NaBAr^F$ 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 $NaBAr^F$, but in the presence of $[(MeCN)_5Cu(SbF_6)_2]$ (10 mol%) and $NaBAr^F$ (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

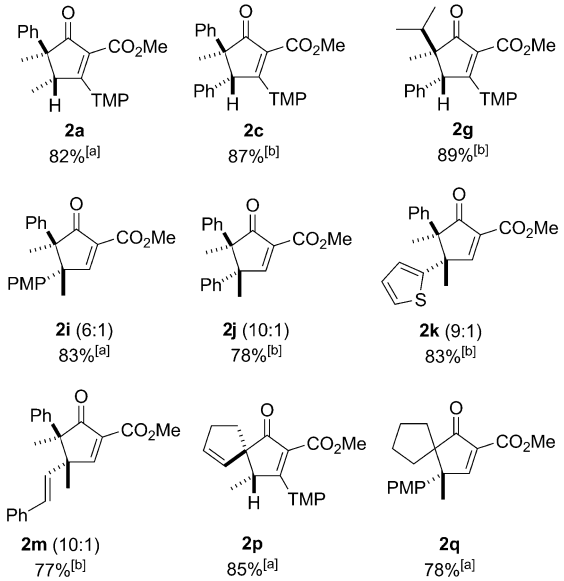


Scheme 4. Copper-mediated cyclization of 1,4-dien-3-one **1o**.

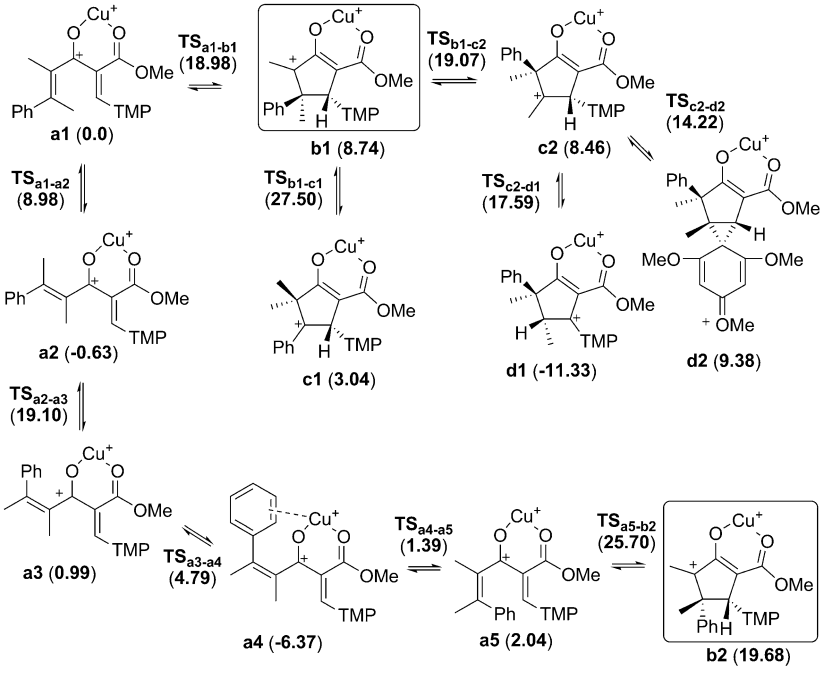
(Scheme 5). Yields and efficiency were comparable to experiments conducted with stoichiometric amounts of copper(II) complexes.[7]

The combination of the BAr^F counterion's noncoordinating behavior and the solubility of the $NaBAr^F$ salt are thought to account for the singular success of this additive. The finding that the Na^+ ion is enough to suppress the elimination pathway is interesting, because it suggests that the basicity of only one carbonyl group must be suppressed.

To gain some insight into the mechanistic issues raised during this study, we carried out DFT studies using dienone **1a** as the model substrate and Cu^{2+} as the promoter (see the Supporting Information for all details).[13–15] From complex **a1** (Scheme 6), the transition state corresponding to the conrotatory 4π electrocyclization could be located at $\triangle G^{\ddagger}_{298} = 18.98$ kcal mol^{-1}. It connects **a1** with the five-membered ring intermediate **b1** that lies 8.74 kcal mol^{-1} above **a1** in free energy. The suprafacial 1,2-methyl shift from **b1** to give **c1** requires a prohibitively high free energy of activation, where $\mathbf{TS_{b1\text{-}c1}}$ lies at 27.50 kcal mol^{-1}. On the other hand, the 1,2-phenyl shift that leads to **c2** is much more accessible (19.07 kcal mol^{-1}). From **c2**, the hydride-shift transition state lies higher than that of the TMP shift (17.59 vs. 14.22 kcal mol^{-1}). However, the formation of **d2** is endergonic ($\Delta G_{298} = 9.38$ kcal mol^{-1}) and readily reversible, while that of the fully conjugated complex



Scheme 5. Results of cyclization/rearrangement using a catalytic amount of a Cu^{II} complex. [a] Reaction conditions: substrate in CH_2Cl_2 (0.03 M) in the presence of $NaBAr^F$ (90 mol%) and $[(MeCN)_5Cu(SbF_6)_2]$ (10 mol%) at RT for 0.1–0.5 h. [b] Reaction carried out at 45 °C. All yields are of isolated product and the d.r. ratio is in parentheses. BAr^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).



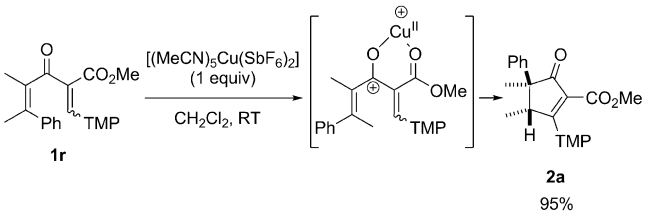
Scheme 6. Calculated free energies (ΔG, kcal mol^{-1}) for the copper(II)-mediated cyclization of dienone **1a**.

d1 is appreciably exergonic ($\Delta G_{298} = -11.33$ kcal mol^{-1}). 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 hydride 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 *E*/*Z* isomerization observed upon Cu^{II} mediation of the reaction in some of the tetrasubstituted substrates (Table 2), additional calculations were performed. The *E*/*Z* inversion shown in Scheme 6 could be modeled in four steps from **a1**: Complex **a1**, which is conformationally aligned for a 4π electrocyclization (*s-trans*/*s-trans*), readily rearranges though $\mathbf{TS_{a1\text{-}a2}}$ into the slightly more stable conformer **a2** ($\triangle G^{\ddagger}_{298} = 8.98$ kcal mol^{-1}, $\Delta G_{298} = -0.63$ kcal mol^{-1}). The diastereomutation then takes place to give **a3**, slightly less stable than **a1** ($\Delta G_{298} = 0.99$ kcal mol^{-1}). The corresponding transition state, $\mathbf{TS_{a2\text{-}a3}}$, is the lowest lying of this sequence at $\triangle G^{\ddagger}_{298} = 19.10$ kcal mol^{-1}. Then, **a3** isomerizes into the more stable complex **a4** in which copper coordinates to the phenyl group.[14] This coordination is appreciably exergonic ($\Delta G_{298} = -6.37$ kcal mol^{-1}), thus 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 $\mathbf{TS_{a4\text{-}a5}}$ ($\triangle G^{\ddagger}_{298} = 1.39$ kcal mol^{-1}), but is quite endergonic ($\Delta G_{298} = 2.04$ kcal mol^{-1}). Second, the electrocyclization of **a5** to give **b2** requires 25.70 kcal mol^{-1} of free energy of activation and is strongly endergonic ($\Delta G_{298} = 19.68$ kcal mol^{-1}). From **b2**, both shifts display high activation barriers (25.91 vs. 23.65 kcal mol^{-1}). Overall, as a result of the steric interaction between the phenyl and the TMP groups, the cyclization of **a1** to **b1** is more favorable 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 shown in Scheme 7: When the *Z*-isomer **1r** was subjected to the reaction conditions, product **2a** was isolated in 95% yield. Product **2a** was reported in Table 1, except the cyclization substrate was the *E*-isomer **1a**.

In summary, we have developed an efficient, chemoselective method for the 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-keto ester substrates led to the creation of adjacent stereogenic centers, including adjacent quaternary centers. It was found that partial *E*/*Z* isomerization of the enone moiety occurs in some cases, and it affects the selectivity of the reaction by compromising the stereochemical fidelity of the substrates. DFT computations support the possibility of a copper(II)-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 an asymmetric version of this reaction, and application of this strategy toward the synthesis of natural products.



Scheme 7. Copper-mediated cyclization of dienone **1r**.

Received: July 12, 2011
Revised: August 17, 2011
Published online: September 26, 2011

Keywords: copper · density functional calculations · homogeneous catalysis · Nazarov cyclization · Wagner–Meerwein rearrangement

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