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Diastereospecific Nazarov Cyclization of Fully Substituted Dienones: Vicinal All-Carbon Atom Quaternary Stereocenters**

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The joining of two carbon atoms through a σ bond so as to form vicinal all-carbon atom quaternary centers remains a difficult challenge in organic synthesis.^[1] An effective strategy to address the problem is to exploit an orbital symmetry controlled process.^[2] We describe herein a diastereospecific Nazarov cyclization^[3] that leads to cyclopentenones bearing adjacent all-carbon atom quaternary centers.

We are aware of only the three examples of Nazarov cyclizations that lead to two contiguous all-carbon atom quaternary stereocenters during the ring forming step that are shown in Scheme 1. The first two examples in Scheme 1 describe Harding and coworkers' efforts that culminated in the total synthesis of (*d,l*)-trichodiene.^[4] Reaction conditions in both cases were harsh but the yield of cyclic products **2** and **4** that lack sensitive functionality was high. Both reactions were diastereospecific, with the C3a,C3b relative stereochemistry (see compound **2**) determined by the conrotation that is required by the selection rule governing the thermal 4π electron process. The third example in Scheme 1 is the oxidative Nazarov cyclization of allenyl ether **5** that was reported by Frontier and coworkers in 2011.^[5] The oxyallyl zwitterion that forms spontaneously from the allene oxide following treatment of **5** with dimethyldioxirane (DMDO) underwent stereospecific cyclization to **6** in moderate yield. The zwitterion intermediate is strongly polarized, hence the mild reaction conditions.

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Frontier and coworkers have also described a diastereoselective tandem Nazarov-Wagner-Meerwein reaction that leads to cyclopentenones bearing vicinal all-carbon atom stereocenters.^[6] Finally, there are two published examples of the Nazarov cyclization of 3,5-dibromo-2,6-dimethylhepta-2,5-dien-4-one that lead in each case to vicinal *gem*-dimethyl groups in the cyclic product.^{[7],[8]} To the best of our knowledge the formation of adjacent quaternary carbon atoms during the Nazarov cyclization is limited to this very small number of examples. These cyclizations represent a special challenge because the two “inside” substituents, R¹ and R⁶ (Equation 4) destabilize the U-shaped *s-trans/s-trans* conformer of the dienone that is able to form a ring, thereby displacing the equilibrium to the *s-cis* conformers that cannot cyclize. In what follows we will demonstrate how this problem can be overcome through judicious experimental design.

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Frontier^[9] and others^[10] have shown that polarized dienones undergo accelerated Nazarov cyclizations. An especially effective way to activate the dienone toward cyclization is to incorporate a “push-pull” vinylogous carbonate.^[11] Scheme 2 illustrates a synthesis of activated dienones that are ideally suited for the present application. Metalation of 2-(trimethylsilyl)ethoxymethyl (SEM) enol ether **7** according to Knochel’s procedure^[12] followed by exposure to (*E*)-2-methyl-3-phenylbut-2-enoyl chloride **8** led to dienone **9** in 88% yield from the carboxylic acid as a single (*E,E*) geometrical isomer. The isomeric purity of **9** is critical because contamination by the geometrical isomer of either double bond would erode the stereoisomeric purity of the derived cyclic product. The synthesis of the substituted acryloyl chlorides was performed according to published procedures starting from the appropriate acetoacetate esters.^[13]

The reaction conditions for the Nazarov cyclization were optimized using dienone **9** (Table 1). No special effort was made to exclude traces of water from the reaction mixture. The first conditions that were examined, 90 equiv trifluoroacetic acid (TFA) in dichloromethane at 0 °C, were successful and led to α -hydroxycyclopentenone **10** as a single diastereomer in 63% yield after a reaction time of 1 min (entry 1). Reducing the amount of acid to 4 equiv (entry 2) resulted in a slower reaction that led to a mixture in which **10** was the minor product. One of the byproducts appeared to be the acyclic α -diketone resulting from loss of the SEM group. We reasoned that a Bronsted acid with a less nucleophilic counterion would suppress this unwanted reaction. Support for this hypothesis was obtained by exposing **9** to 4 equiv triflimide (entry 3) which led to the production of **10** in 81% yield as a single diastereomer. In an effort to reduce the amount of acid being used, the reaction was conducted in the presence of 1 equiv and 0.2 equiv triflimide (entries 4 and 5) but in each case mixtures of products were observed. Because the reaction was only successful when excess acid was used, the mode of addition was changed. A solution of **9** was added via syringe pump to a concentrated solution of 0.2 equiv triflimide (entry 6). This led to the production of **10** in 80% yield by the time the transfer was complete. When 0.1 equiv triflimide was used (entry 7) it was necessary to increase the addition time and the yield of **10** was 78%. For all subsequent work we used the conditions of entry 6 in Table 1. The requirement of high acid concentration is consistent with the cyclization of a diprotonated

intermediate of the type that West and coworkers have postulated in certain Nazarov cyclizations.^{[14],[15]}

The reaction scope is indicated by the examples of Scheme 3. All compounds were prepared according to the optimized conditions represented by entry 6 of Table 1 and were formed as single diastereomers. The stereochemistry of all products was determined by NOE NMR and in the case of **10** was confirmed by single crystal X-ray crystallographic analysis.^[16] The yield of cyclic products varied from 53% to 88%. The cyclization is surprisingly tolerant of sterically demanding substrates. For example even cyclopentenone **16** that bears isopropyl and 2-naphthyl groups on adjacent carbon atoms was formed in 53% yield. Significantly, there is no requirement for a β -aryl group to activate the dienone as examples **17–22** demonstrate.

The success of these Nazarov reactions rests in a delicate balance, as the following examples will demonstrate. Exposure of dienone **23**, that differs from **9** only in having an isopropyl in place of phenyl, to the optimized cyclization conditions led to a *ca.* 1/1 mixture of the anticipated product **24** and its diastereomer **25** in 81% yield (Equation 5). The appearance of **25** is evidence of double bond isomerization in **23** taking place in competition with cyclization. It is unlikely that isomerization of the enol ether took place, because this would then have been observed for some of the compounds of Scheme 3 that were treated under the identical reaction conditions. Furthermore, double bond isomerization was observed during the preparation of (*E*)-2,3,4-trimethylpent-2-enoyl chloride in the presence of acid.^[17] There is a higher barrier to the isomerization of **9** because it requires disruption of conjugation to the phenyl group. The formation of **25** is remarkable, because it demonstrates that cyclization can even take place efficiently with an “inside” isopropyl group (see Equation 4).

Lactone **26** revealed an unanticipated process (Equation 6). Cyclization according to the predicted pathway led to nearly equal amounts of a single diastereomer of **27** and byproduct **28**. Ketene acetal **28** may have been formed by means of an intramolecular

(5)

Michael addition of the lactone carbonyl group oxygen atom that is facile in this example because of the enforced coplanarity of the lactone carbonyl group with the dienone. It is also possible that **28** was formed through an electrocyclization.^[18]

Diethylamide **29** failed to cyclize even after exposure to 4 equiv triflimide for 24 h and was recovered intact from the reaction

mixture (Equation 7). This result demonstrates the effect of double bond polarization on the rate of cyclization. The amide group that is less electron withdrawing than the ester apparently does not enable

(7)

the cyclization under the same conditions.

In dienone **31** the SEM has been replaced by 4-methoxyphenyl (Equation 8). Cyclization proceeded in good yield but led to a *ca.* 1/3 mixture of diastereomers **32** and **33**, underscoring the critical role that the SEM group plays in the successful cyclization. Favorably polarized **31** is expected to cyclize as fast as **9**, but the hydrolytic loss of the 4-methoxyphenyl group is probably slower than SEM cleavage, which does not require the participation of water. A slow termination step leading to a reversible Nazarov-*retro*-Nazarov^[19] process might allow an opportunity for enol ether isomerization in **31** to compete with cyclization.

(8)

On the basis of these results it appears that the Nazarov cyclization that produces vicinal all-carbon atom quaternary centers is successful and diastereospecific within a carefully defined range of reaction parameters. The strongly polarized “push-pull” vinylogous carbonate is required to lower the barrier to cyclization. The SEM group also plays a critical role by collapsing rapidly through loss of ethylene and formaldehyde to suppress processes that lead to erosion of the stereochemical integrity of the cyclic product. Inverse addition of dienone to acid leads to a rapid cyclization that suppresses undesired competing acid catalyzed processes. The examples described in Scheme 3 suggest broad synthetic utility, and it is also likely that other “push-pull” alkenes can be used in place of the vinylogous carbonates that have been described herein. This work greatly expands the scope of the Nazarov reaction by making highly congested cyclopentenones easily available. The asymmetric version of this cyclization is under investigation.^[20]

Experimental Section

A reaction vial equipped with a membrane cap was loaded with Tf_2NH (15 mg, 0.054 mmol, 0.2 equiv) in dry CH_2Cl_2 (0.05 mL, 1M). A small needle was inserted through the cap to relieve pressure. A solution of dienone **9** (112 mg, 0.268 mmol, 1 equiv) in dry CH_2Cl_2 (0.27 mL, 1M) was added dropwise via a syringe pump (5 $\mu\text{L}/\text{min}$) into the solution of Tf_2NH at room temperature. The reaction mixture was placed on a vortex stirrer during the addition. The reaction mixture was diluted with 2 mL of CH_2Cl_2 and quenched with 5% aq.

NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ (2x). The combined layer was washed with water, brine and dried over Na₂SO₄. Evaporation and column chromatography (silica gel, 2% Et₂O/CH₂Cl₂) afforded **10** as a white solid (61 mg, 80% yield): mp 141–145 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.28–7.06 (m, 5H), 5.31 (s, 1H, OH), 3.49–3.39 (m, 1H), 3.32–3.18 (m, 1H), 1.90 (s, 3H), 1.61 (s, 3H), 1.46 (s, 3H), 0.83 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 200.4, 170.8, 148.2, 147.5, 141.5, 128.0 (2C), 127.8 (2C), 127.1, 61.5, 60.8, 52.7, 21.3, 18.4, 13.4, 10.9; IR (neat, cm⁻¹) 3366, 2982, 1708, 1661, 1445, 1404, 1363, 1249, 1193, 1083, 777, 733; HRMS (ESI⁺) calculated for C₁₇H₂₀O₄ ([M+Na]⁺): 311.1260, found 311.1253.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Crystallographic data for **10**. CCDC 949925 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif
- To suppress isomerization, the acid chloride in this case was prepared through the sodium carboxylate.
- The authors thank a referee for pointing this out.

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20. Optically enriched **11** (74/26 er) has been formed with a chiral Bronsted acid catalyst.

Scheme 1.

Vicinal all-carbon atom quaternary stereocenters from the Nazarov cyclization.

Scheme 2.
Preparation of dienones.

Scheme 3.
Vicinal Quaternary Carbons from the Nazarov Cyclization

Table 1

Optimization of reaction conditions.

Entry	Acid [equiv]	Temp [°C]	Time [min] ^[a]	Yield [%] ^[b]
1 ^[c]	TFA [90]	0	1	63
2 ^[c]	TFA [4]	0	10	-
3 ^[c]	Tf ₂ NH [4]	0	2	81
4 ^[c]	Tf ₂ NH [1]	0	2	-
5 ^[d]	Tf ₂ NH [0.2]	0	2	-
6 ^[e]	Tf₂NH [0.2]	23	60	80
7 ^[f]	Tf ₂ NH [0.1]	23	180	78

^[a]Total reaction time.^[b]Yield of isolated **10**.^[c]Acid was added neat.^[d]Triflimide was added as a 0.27M solution in CH_2Cl_2 .^[e]Inverse addition at 5 $\mu\text{L}/\text{min}$ of a 1M solution of **9** to 1M triflimide.^[f]Inverse addition at 1.7 $\mu\text{L}/\text{min}$ of a 1M solution of **9** to 1M triflimide.