Synthetic Methods

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

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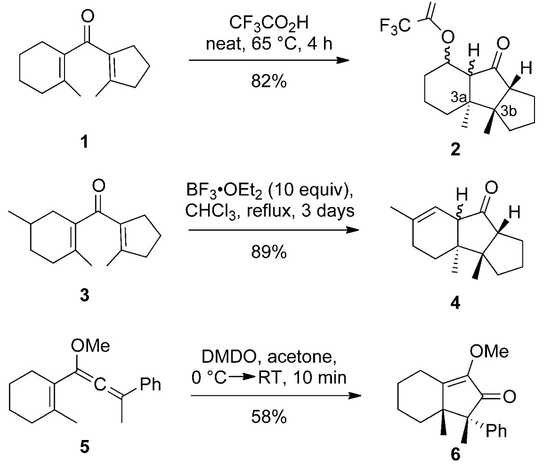
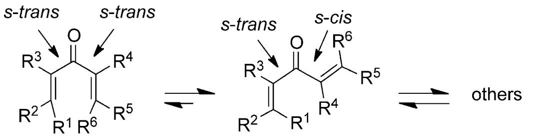
The joining of two carbon atoms through a σ bond so as to form vicinal all-carbon-atom quaternary centers remains a difficult challenge in organic synthesis.[1] An effective strategy to address the problem is to exploit an orbital-symmetry-controlled process.[2] We describe herein a diastereospecific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

We are aware of only three examples of Nazarov cyclizations that lead to two contiguous all-carbon-atom quaternary stereocenters during the ring-forming step (Scheme 1). The efforts of Harding and co-workers [Eqs. (1) and (2), Scheme 1] culminated in the total synthesis of DL-trichodiene.[4] The reaction conditions in both cases were harsh, but the yield of cyclic products **2** and **4**, which lack sensitive functionality, was high. In both reactions the C3a,C3b relative configuration (see compound **2**) was determined by the conrotation that is required by the selection rule governing the thermal 4π-electron process. The third example is the oxidative Nazarov cyclization of allenyl ether **5** that was reported by Frontier and co-workers in 2011 [Eq. (3) in Scheme 1].[5] The oxyallyl zwitterion that forms spontaneously from the allene oxide following the 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.



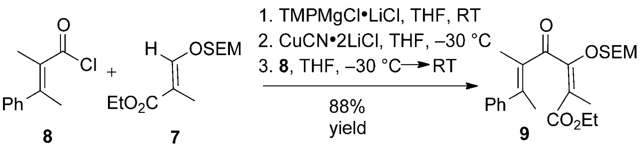
Scheme 1. Generation of vicinal all-carbon-atom quaternary stereocenters in the Nazarov cyclization.

Frontier and co-workers also described a diastereoselective tandem Nazarov–Wagner–Meerwein reaction that leads to cyclopentenones bearing vicinal all-carbon-atom stereocenters.[6] Finally, there are two reported examples of the Nazarov cyclization of 3,5-dibromo-2,6-dimethylhepta-2,5-dien-4-one; in each case the reaction led 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, R^1 and R^6 [Eq. (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, which cannot cyclize. Herein we will demonstrate how this problem can be overcome through judicious experimental design.



(4)

It has been shown that polarized dienones undergo accelerated Nazarov cyclizations.[9,10] An especially effective way to activate the dienone toward cyclization is to incorporate a "push–pull" vinylogous carbonate.[11] A synthesis of activated dienones that are ideally suited for the present application is shown in Scheme 2. Metalation of the 2-(trimethylsilyl)ethoxymethyl (SEM) enol ether **7** according to a procedure described by Knochel and Bresser[12] and



Scheme 2. Preparation of the dienone substrate. TMP = 2,2,6,6-tetramethylpiperidinyl.

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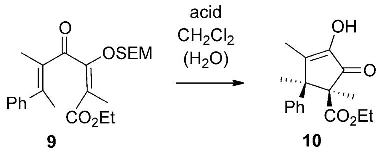
subsequent exposure to (*E*)-2-methyl-3-phenylbut-2-enoyl chloride (**8**) led to dienone **9** in 88 % yield from the carboxylic acid as a single (*E*,*E*) geometrical isomer. The isomeric purity of **9** is critical because contamination by the geometrical isomer of either double bond would erode the stereoisomeric purity of the derived cyclic product. The substituted acryloyl chlorides used in this study were synthesized according to reported procedures from the appropriate acetoacetate esters.[13]

We optimized the reaction conditions for the Nazarov cyclization by using dienone **9** (Table 1). No special effort was made to exclude traces of water from the reaction mixture.

Table 1: Optimization of the reaction conditions.

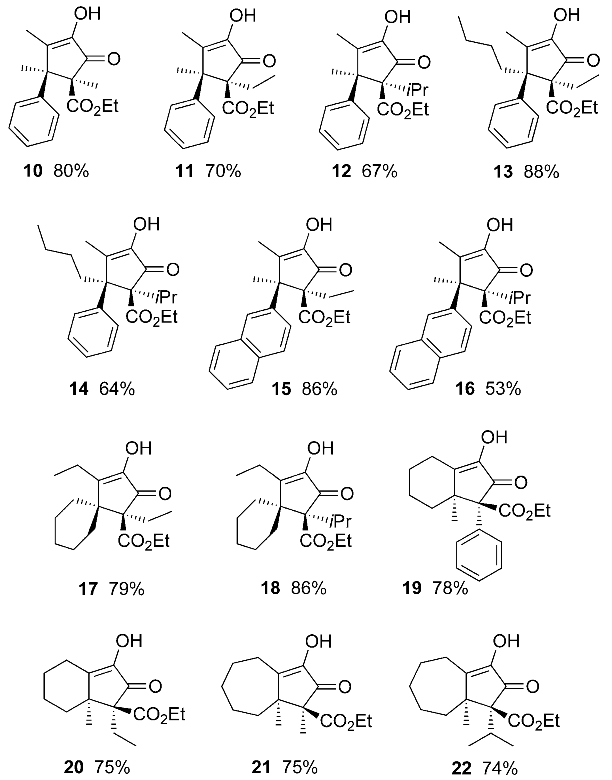


Entry	Acid (equiv)	*T* [°C]	*t* [min][a]	Yield [%][b]
1[c]	TFA (90)	0	1	63
2[c]	TFA (4)	0	10	–
3[c]	Tf_2NH (4)	0	2	81
4[c]	Tf_2NH (1)	0	2	–
5[d]	Tf_2NH (0.2)	0	2	–
6[e]	**Tf_2NH (0.2)**	**23**	**60**	**80**
7[f]	Tf_2NH (0.1)	23	180	78

[a] Total reaction time. [b] Yield of isolated **10**. [c] The acid was added neat. [d] Triflimide was added as a 0.27 M solution in CH_2Cl_2. [e] Inverse addition at 5 μL min^{-1} of a 1 M solution of **9** to a 1 M solution of triflimide. [f] Inverse addition at 1.7 μL min^{-1} of a 1 M solution of **9** to a 1 M solution of triflimide. Tf = trifluoromethanesulfonyl.

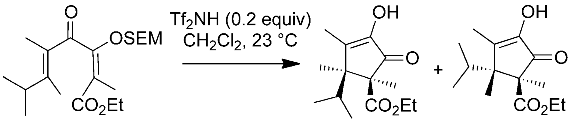
The first conditions that were examined, trifluoroacetic acid (TFA; 90 equiv) in dichloromethane at 0 °C, were successful and led to the α-hydroxycyclopentenone **10** as a single diastereomer in 63 % yield after a reaction time of 1 min (Table 1, entry 1). A reduction in the amount of acid used to 4 equivalents resulted in a slower reaction that led to a mixture in which **10** was a minor product (Table 1, entry 2). One of the by-products appeared to be the acyclic α-diketone resulting from loss of the SEM group. We reasoned that a Brønsted acid with a less nucleophilic counterion would suppress this unwanted reaction. Support for this hypothesis was obtained by the exposure of **9** to triflimide (4 equiv), which led to the production of **10** in 81 % yield as a single diastereomer (Table 1, entry 3). In an effort to reduce the amount of acid required, the reaction was conducted in the presence of 1 and 0.2 equivalents of triflimide (Table 1, 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. When a solution of **9** was added with a syringe pump to a concentrated solution of triflimide (0.2 equiv; Table 1, entry 6), **10** was produced in 80 % yield by the time the transfer was complete. When even less triflimide was used (0.1 equiv), it was necessary to increase the addition time, and the yield of **10** was 78 % (Table 1, entry 7). For all subsequent investigations we used the conditions described in entry 6 of Table 1. The requirement of a high acid concentration is consistent with the cyclization of a diprotonated intermediate of the type that West and co-workers postulated for certain Nazarov cyclizations.[14,15]

The reaction scope is indicated by the examples in Scheme 3 of compounds obtained under the optimized reaction conditions (Table 1, entry 6). All compounds were formed as single diastereomers, and their configuration was determined by NMR spectroscopy on the basis of NOE data. The configuration of **10** was confirmed by single-crystal X-ray crystallographic analysis.[16] The yield of the cyclic products varied from 53 to 88 %. The cyclization is surprisingly tolerant of sterically demanding substrates. For example, even cyclopentenone **16**, which 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 demonstrated by examples **17**–**22**.



Scheme 3. Products formed with vicinal quaternary carbon atoms in the Nazarov cyclization.

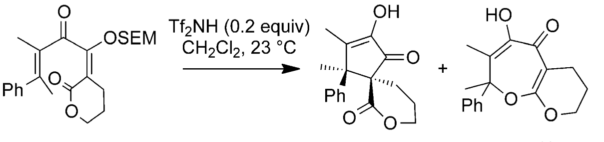
The success of these Nazarov reactions rests in a delicate balance, as the following examples demonstrate. Exposure of dienone **23**, which differs from **9** only in the presence of an isopropyl group in place of the phenyl group, to the optimized cyclization conditions led to an approximately 1.5 : 1 mixture of the anticipated product **24** and its diastereomer **25** in 81 % yield [Eq. (5)]. The appearance of **25** is evidence of the occurrence of double-bond isomerization in **23** in competition with cyclization. It is unlikely that isomerization of the enol ether took place, because this isomerization would then have



23 **24** ca. 1.5:1 **25** (5)

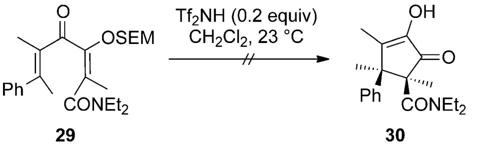
been observed for some of the compounds in Scheme 3 under the identical reaction conditions. Furthermore, double-bond isomerization was observed during the preparation of (*E*)-2,3,4-trimethylpent-2-enoyl chloride in the presence of an acid.[17] There is a higher barrier to the isomerization of **9** because it requires the 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 Eq. (4)].

The use of lactone **26** as a substrate revealed an unanticipated process [Eq. (6)]. Cyclization according to the predicted pathway led to nearly equal amounts of a single diastereomer of **27** and by-product **28**. The ketene acetal **28** may have been formed by means of an intramolecular Michael addition of the oxygen atom of the lactone carbonyl group. This process 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]



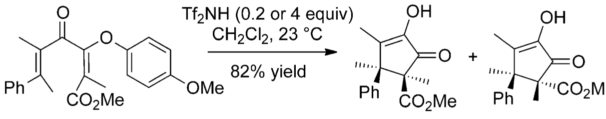
26 **27** 43% **28** 39% (6)

Diethylamide **29** failed to undergo cyclization even upon exposure to triflimide (4 equiv) for 24 h and was recovered from the reaction mixture [Eq. (7)]. This result demonstrates the effect of double-bond polarization on the rate of cyclization. The amide group, which is less electron withdrawing than the ester, apparently does not enable the cyclization under the same conditions.



29 **30** (7)

In dienone **31**, the SEM group has been replaced with a 4-methoxyphenyl group [Eq. (8)]. Cyclization proceeded in good yield but led to an approximately 1:3 mixture of diastereomers **32** and **33**. This result underscores 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 provide an opportunity for enol ether isomerization in **31** to compete with cyclization.



31 **32** ca. 1:3 **33** (8)

On the basis of these results, it appears that the Nazarov cyclization to produce 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 the loss of ethylene and formaldehyde to suppress processes that lead to erosion of the stereochemical integrity of the cyclic product. Inverse addition of the dienone to the 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 study greatly expands the scope of the Nazarov reaction by making highly congested cyclopentenones readily available. An 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, 1 M). 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, 1 M) was added dropwise with a syringe pump (5 μL min^{-1}) to the solution of Tf_2NH at room temperature. The reaction mixture was placed on a vortex stirrer during the addition. The reaction mixture was then diluted with CH_2Cl_2 (2 mL) and quenched with 5% aqueous $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2. The combined layers were washed with water and brine and then dried over Na_2SO_4. Evaporation of the solvent and column chromatography (silica gel, 2% Et_2O/CH_2Cl_2) afforded **10** (61 mg, 80%) as a white solid. M.p.: 141–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.28$–7.06 (m, 5 H), 5.31 (s, 1 H, OH), 3.49–3.39 (m, 1 H), 3.32–3.18 (m, 1 H), 1.90 (s, 3 H), 1.61 (s, 3 H), 1.46 (s, 3 H), 0.83 ppm (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 200.4$, 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 ppm; IR (neat): $\tilde{\nu} = 3366$, 2982, 1708, 1661, 1445, 1404, 1363, 1249, 1193, 1083, 777, 733 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{17}H_{20}O_4$: 311.1260 $[M+Na]^+$; found: 311.1253.

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[20] Optically enriched **11** (e.r. 74:26) has been formed with a chiral Brønsted acid catalyst.

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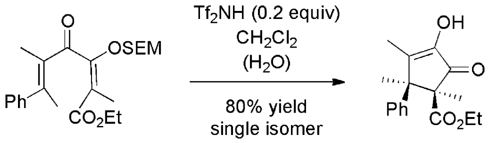
Diastereospecific Nazarov Cyclization of Fully Substituted Dienones: Generation of Vicinal All-Carbon-Atom Quaternary Stereocenters



No vacancy: Fully substituted dienones that are highly polarized by a vinylogous carbonate group were found to undergo a remarkably rapid and diastereospecific Nazarov cyclization that led to cyclopentenones with vicinal all-carbon-atom quaternary centers (see example; SEM = 2-(trimethylsilyl)ethoxymethyl, Tf = trifluoromethanesulfonyl).