VIP Vicinal Quaternary Stereocenters | Very Important Paper

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Catalytic Enantioselective Nazarov Cyclization: Construction of Vicinal All-Carbon-Atom Quaternary Stereocenters**

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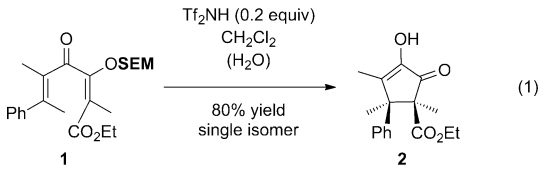
Dedicated to Professor E. J. Corey

Abstract: *The diastereoselective asymmetric synthesis of vicinal all-carbon-atom quaternary stereocenters is a challenging problem in organic synthesis for which only few solutions have been described. A catalytic asymmetric Nazarov cyclization of fully substituted dienones that provides cyclopentenone derivatives with vicinal quaternary stereocenters in high optical purity and as single diastereoisomers is now reported.*

The catalytic asymmetric synthesis of vicinal, all-carbon-atom quaternary stereocenters presents a difficult challenge for which only a small number of solutions, none of which are completely general, have been described to date.[1] The enantioselective version of the reaction that is shown in Equation (1) would constitute a new solution to this problem. None of the asymmetric Nazarov cyclizations that have been described thus far[2] form vicinal quaternary stereocenters. At best, vicinal quaternary and tertiary stereocenters could be generated.[3]



1 2 (1)

Polarization of the acyclic dienone precursor[4] accelerates the Nazarov cyclization.[5] We have previously disclosed the highly diastereoselective triflimide-catalyzed cyclization that converts dienone **1** into cyclopentenone **2** in 80% yield [Eq. (1)].[6] The stereochemistry of **2** reveals that a conrotatory process, which is required to conserve orbital symmetry, has occurred. The polarization of "push–pull" dienone **1** and the rapid termination process that is enabled through loss of the 2-(trimethylsilyl)ethoxymethyl (SEM) group contribute to the success of this cyclization, which results in the formation of vicinal all-carbon-atom quaternary stereocenters. Rapid termination is especially important in the case of Nazarov cyclizations that lead to sterically congested products as Wagner–Meerwein rearrangements of the intermediate cyclic cation, which would be driven by relief of steric compression, have to be suppressed.[7] Herein, we report the first catalytic asymmetric Nazarov cyclization of fully substituted dienones for the construction of vicinal all-carbon-atom stereocenters.

We had confidence that an asymmetric version of the cyclization that is shown in Equation (1) could be developed through systematic variation of the enol ether and ester groups, which could serve as recognition elements for a catalyst. The process could be optimized through iterative changes in catalyst, solvent, and additive(s). As the enol ether moiety must depart as a stable cation following the cyclization, its choice does not restrict the structural types of cyclopentenones that might be accessed by this reaction.

We chose the (*R*)-BINOL scaffold for our screen of chiral Brønsted acids.[8] The broad utility of this class of compounds for a variety of catalytic asymmetric reactions is related to the ease with which substituents at the C3 and C3′ positions can be introduced to quickly assemble a library of catalysts.[9] Catalyst optimization is summarized in Table 1. The phenyl ester group in **3** strongly influenced the enantioselectivity of the reaction. The ethyl ester analogue of **3** led to the desired product **5** with an enantioselectivity of 80:20 e.r. in the presence of catalyst **4e**, whereas the cyclization of **3** under the same conditions led to **5** in 90:10 e.r. (Table 1, entry 5). The cyclization of dienone **3** was subsequently used to evaluate all catalysts. The diphenylmethyl enol ether was chosen as a sterically demanding group that would be rapidly lost from the cyclic cation intermediate as a very stable cation.[10] Phosphoric acid **4a** was not an effective catalyst, presumably because of its weak acidity ($pK_a \approx 12$, CH_3CN), and no reaction took place.[11] Rueping and co-workers have demonstrated that *N*-triflyl phosphoramides are more acidic ($pK_a \approx 6$, CH_3CN) and have used these acids to catalyze asymmetric Nazarov cyclizations.[2b,i] Indeed, exposure of **3** to 10 mol% of *N*-triflyl phosphoramide **4b** (Ar = Ph) for 24 hours led to complete conversion of **3** into **5** in 85:15 e.r. A small improvement in the optical purity of **5** was observed with catalyst **4c** (Ar = 4-tolyl), and a much larger improvement to 96:4 e.r. was achieved with catalyst **4d** (Ar = 4-*tert*-butylphenyl). Phenyl (**4e**) or 9-phenanthryl (**4f**) substituents in the *para* position led to inferior catalyst performance.

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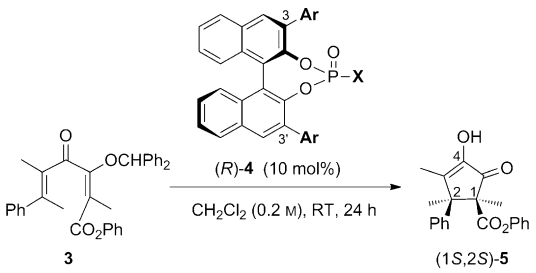
Table 1: Catalyst optimization.



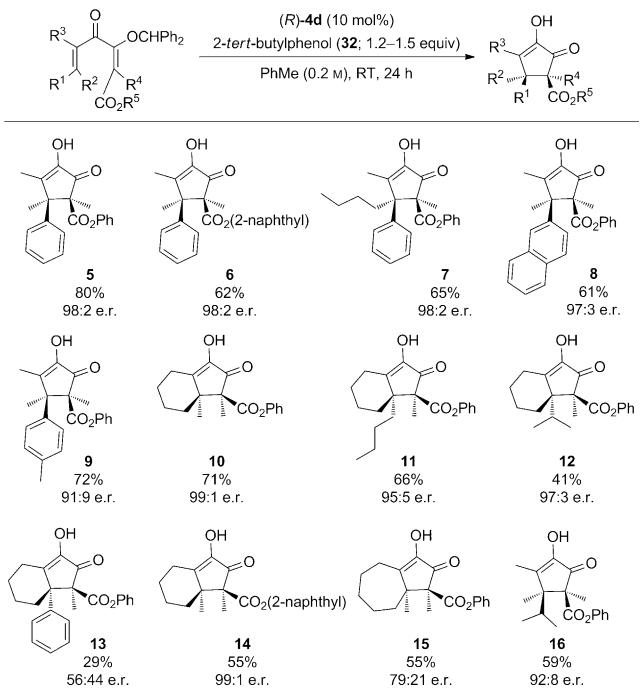
Entry	X	Catalyst	Ar	e.r. of **5**
1	OH	**4a**	3,5-$(CF_3)_2C_6H_3$	–[a]
2	NHTf	**4b**	C_6H_5	85:15
3	NHTf	**4c**	4-(Me)C_6H_4	88:12
4	**NHTf**	**4d**	**4-(*t*Bu)C_6H_4**	**96:4**
5	NHTf	**4e**	4-(Ph)C_6H_4	90:10
6	NHTf	**4f**	4-(9-phenanthryl)C_6H_4	74:26
7	NHTf	**4g**	4-(1-adamantyl)C_6H_4	–[b]

[a] **5** not formed. [b] < 5% conversion after five days. Tf = trifluoromethanesulfonyl.

Almost no reaction was observed in the case of catalyst **4g**, as the steric demand of the 4-(1-adamantyl) substituent seems to exclude **3** from the reaction pocket. Catalyst **4d** was thus chosen for all subsequent work.

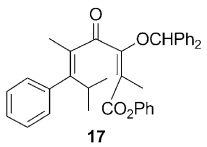
Next, a solvent screen was performed. No cyclization was observed in Brønsted basic solvents, such as THF or methanol, and the enantiomeric purity of **5** was highest in solvents with a low dielectric constant. This is consistent with the general trend of stronger ion pairing in such solvents, which leads to more efficient chirality transfer. The highest e.r. of 99:1 was observed in carbon tetrachloride. The results were almost as good in chloroform, benzene, and toluene (98:2 e.r. in all three solvents), so environmentally less problematic toluene was chosen. The configuration of **5** was determined to be (1*S*,2*S*) by single-crystal X-ray crystallographic analysis of the (1*S*)-(−)-camphanic acid derivative.[12] The relative stereochemistry was determined for each compound by nuclear Overhauser effect (NOE) studies. The absolute stereochemistry of all other compounds was assigned by analogy with **5**.

All of the screening reactions were performed with 10 mg of **3** so that adventitious water had probably intercepted the diphenylmethyl cation that was generated during the course of the reaction. When the reaction was scaled up to 100 mg of **3**, a number of side products, which presumably arise from secondary reactions that involve the diphenylmethyl cation, were evident by TLC. Therefore, it was necessary to include 2-*tert*-butylphenol (**32**) as a cation scavenger. Control experiments showed that neither the rate nor the enantiomeric purity of **5** was affected by the presence of the scavenger. All of the reactions that are reported in Scheme 1 were performed at room temperature[13] for 24 hours in PhMe (0.2 M) in the presence of **4d** (10 mol%) and 2-*tert*-butylphenol (1.2–1.5 equiv). The catalyst was isolated from the reaction mixture, purified by column chromatography, and reused with no loss of activity.

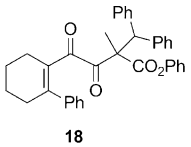


Scheme 1. Scope of the catalytic asymmetric Nazarov cyclization. All of the reactions were conducted for 24 hours at RT in PhMe (0.2 M) in the presence of **4d** (10 mol%) and **32** (1.2–1.5 equiv).

The scope of this Nazarov cyclisation is summarized in Scheme 1. Under the optimized reaction conditions, cyclopentenone **5** was formed in 80% yield and 98:2 e.r. Aliphatic cyclopentenone **10** was obtained in 71% yield and 99:1 e.r. All cyclopentenones that are depicted in Scheme 1 were formed as single diastereoisomers. The yield of 2-naphthyl ester **6** (62%) was lower than for phenyl ester **5**, probably because placing the larger naphthyl group on the "inside" of the U-shaped reactive conformer of the acyclic dienone suppresses cyclization. Nevertheless, the optical purity of **6** (98:2 e.r.) was as high as that of **5**. The cyclization tolerates an inside *n*-butyl group, as shown by the successful synthesis of **7** (65%, 98:2 e.r.). The β-aryl group is not necessary to activate the dienone towards cyclization as indicated by the formation of compounds **10**–**12** and **14**–**16**. Remarkably, cyclization of an aliphatic dienone with an inside isopropyl group was also successful and led to cyclopentenone **12** in 97:3 e.r., albeit in 41% yield. Substrate **17**, which also bears an inside isopropyl group, failed to cyclize. Cyclopentenone **13**, which incorporates an inside phenyl group, was formed in only 29% yield and as a nearly racemic mixture. These two examples define the current limits of this method. The cyclizations of less reactive substrates were accompanied by the formation of substantial amounts of a yellow side product, which was isolated from the reaction mixture that led to cyclopentenone **13**. The side product was shown to be α-diketone **18**.



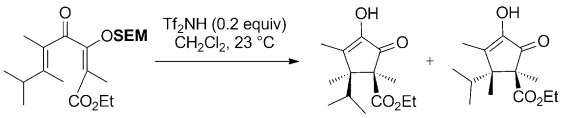
17



18

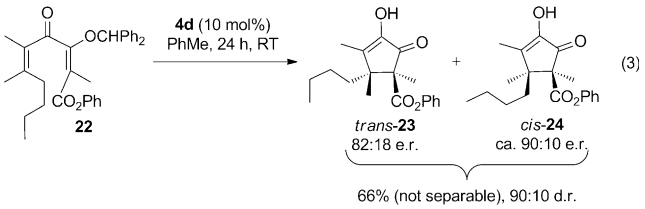
As the cyclization is slow, protonation of the oxygen atom of the enol ether leads to the loss of the diphenylmethyl cation, which is subsequently trapped by the carbon atom of the enol ether to give side product **18**. All cyclizations led to a small quantity of the yellow α-diketone side product, which could be detected by TLC.

The lower yield of the 2-naphthyl ester **14** parallels what was observed for 2-naphthyl ester **6**. The formation of cyclopentenone **16**, which only bears aliphatic substituents, as a single diastereoisomer (59%, 92:8 e.r.) underscores an important difference between this organocatalyzed asymmetric version of the Nazarov cyclization and our earlier results. Whereas the triflimide-catalyzed cyclization of **19** led to a nearly equimolar mixture of **20** and **21** [Eq. (2)],[6] indicating competitive *E* to *Z* isomerization of the trimethylbutenyl



(2)

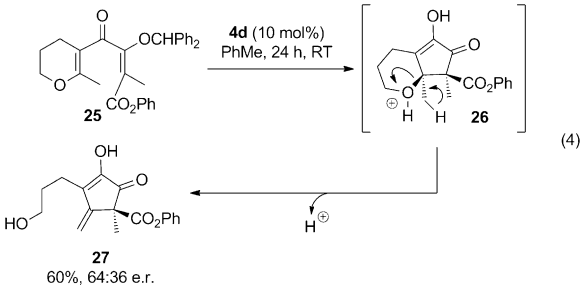
group in **19**, **16** was formed as a single diastereoisomer, which suggests that one role of catalyst **4d** may be to restrict the conformational freedom of the acyclic dienone. Even in the case of dienone **22**, which has an inside *n*-butyl group, only partial double bond isomerization took place in the presence of **4d**, and the anticipated isomer **23** was isolated as the major product [90:10 d.r.; Eq. (3)]. With the exception of **22**, all



(3)

other substrates gave the corresponding cyclic products as single diastereoisomers.

When dihydropyranyl dienone **25** was subjected to the optimized reaction conditions, cyclopentenone **27** was isolated in only 60% yield [Eq. (4)]. This may be due to the



(4)

formation of a secondary product through the acid-catalyzed fragmentation of the primary product **26** in a facile process that is driven by a release of steric compression. The lower optical purity of **27** compared to **10** may indicate a change of mechanism from a conrotatory ring closure to a 5-*exo*-*trig*

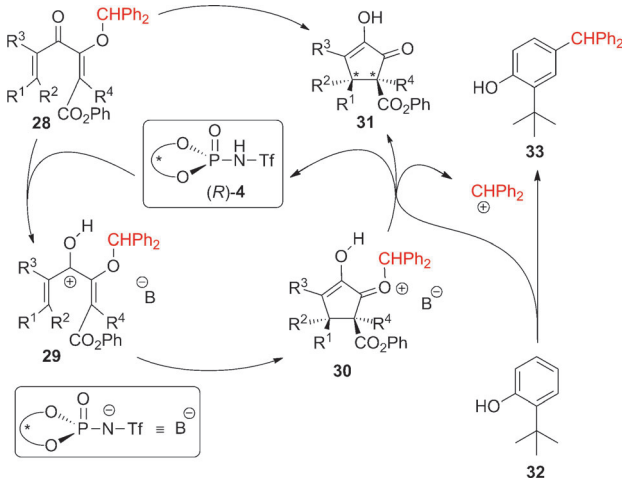


Figure 1. Mechanistic hypothesis.

aldol-like process, which is initiated by the formation of a cyclic oxonium ion.

Our mechanistic hypothesis is summarized in Figure 1. Protonation of dienone **28** leads to pentadienyl cation **29** in the first step. Only the reactive U-shaped conformer of **29** is shown. Sterically demanding internal substituents, such as R^2, favor extended conformers that are unable to undergo cyclization. Conrotatory electrocyclization of **29** leads to a single diastereomer of **30**. Ion pairing between **29** and the conjugate base of (*R*)-**4** biases the absolute sense of the conrotatory ring closure; in this case, clockwise ring closure, as viewed within the plane of the page from the bottom of structure **29**, occurred. Cyclopentenone product **31** is formed following the loss of the diphenylmethyl carbocation from **30**. The diphenylmethyl carbocation is subsequently trapped by 2-*tert*-butylphenol (**32**), which presumably leads to byproduct **33** and regeneration of the catalyst.

In summary, we have described the first asymmetric organocatalytic Nazarov cyclization that leads to cyclic products with vicinal all-carbon-atom quaternary stereocenters. The reaction does not require an activating β-aryl substituent in the acyclic dienone and proceeds well for cyclic (e.g., **10**) and acyclic (e.g., **16**) aliphatic compounds. Remarkably, even highly congested products such as **12** could be obtained by this cyclization in excellent optical purity. This Nazarov cyclization represents a new solution to a vexing problem in organic synthesis, the asymmetric formation of vicinal all-carbon-atom quaternary stereocenters.

Experimental Section

After the addition of 2-*tert*-butylphenol (45 mg, 0.3 mmol, 1.5 equiv) to a solution of **3** (100 mg, 0.2 mmol, 1 equiv) in toluene (1 mL, 0.2 M) at room temperature, catalyst (*R*)-**4d** (14 mg, 0.02 mmol, 0.1 equiv) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with 1 mL of a saturated aqueous $NaHCO_3$ solution, and the organic layer was separated. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2/Et_2O, 98:2) afforded (1*S*,2*S*)-**5** (54 mg, 80%, 98:2 e.r.) as a white solid.

The enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase (Chiralpak OD-H column, 4.6×250 mm, UV detection at 261 nm, eluent: hexane/*i*PrOH (90:10), 1 mL min^{-1}, t_{R1} (minor) = 8.5 min, t_{R2} (major) = 10.1 min). $[\alpha]_D^{25} = +34.1$ ($c = 1.0$, $CHCl_3$, 98:2 e.r.); m.p. 82.5–83.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.28 (m, 5H), 7.17–6.98 (m, 3H), 6.19 (d, $J = 8.2$ Hz, 2H), 6.16–6.03 (bs, 1H, OH), 1.95 (s, 3H), 1.69 (s, 3H), 1.62 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.8$, 169.3, 149.7, 148.1, 148.0, 141.6, 128.8 (2C), 128.3 (2C), 128.2 (2C), 127.3, 125.6, 121.0 (2C), 61.4, 52.8, 21.6, 19.1, 11.0 ppm; IR (neat): $\tilde{\nu}$ =3344, 2983, 1751, 1705, 1659, 1594, 1492, 1446, 1405, 1362, 1235, 1190, 1091, 911, 732 cm^{-1}; HRMS (ESI$^+$) calculated for $C_{21}H_{20}O_4$ ([*M*+Na]$^+$): 359.1254; found: 359.1230.

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Keywords: asymmetric catalysis · chiral Brønsted acids · Nazarov cyclization · quaternary stereocenters

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[10] The diphenylmethyl ether and phenyl ester groups were chosen through an iterative optimization process that will be described in a future disclosure.

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[12] CCDC 991275 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] Compound **10** was also prepared in 73% yield and 99:1 e.r. at 75 °C in 3.5 hours using a catalyst loading of 5 mol%.

Communications

VIP

Vicinal Quaternary Stereocenters

A. Jolit, P. M. Walleser, G. P. A. Yap, M. A. Tius* ——— ■■■■–■■■■

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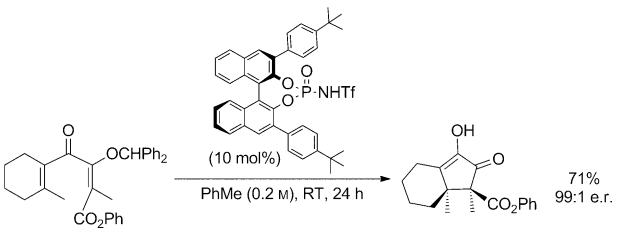

Nazarov cyclization: The diastereoselective asymmetric synthesis of vicinal all-carbon-atom quaternary stereocenters is a challenging problem in organic synthesis. A catalytic asymmetric Nazarov cyclization of fully substituted dienones now provides cyclopentenone derivatives with vicinal quaternary stereocenters in high optical purity and as single diastereoisomers.