CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201200391

Asymmetric Brønsted Acid-Catalyzed Nazarov Cyclization of Acyclic α-Alkoxy Dienones

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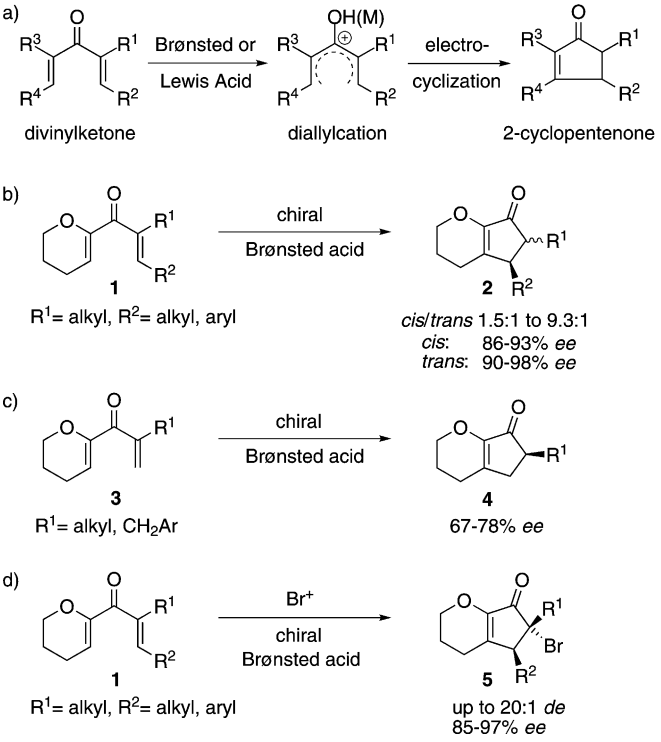
Abstract: A Brønsted acid-catalyzed asymmetric Nazarov cyclization of acyclic α-alkoxy dienones has been developed. The reaction offers access to chiral cyclopentenones in a highly enantioselective manner. The reaction is complementary to our previously reported Brønsted acid-catalyzed electrocyclization reactions, which provided differently substituted optically active cyclopentenones with a fused tetrahydropyrane ring in good yields and with excellent enantioselectivities.

Keywords: asymmetric synthesis · Brønsted acids · electrocyclizations · Nazarov reaction · organocatalysis

Introduction

Cyclopentenones are valuable building blocks in the synthesis of natural products and biologically active compounds. Important natural products such as jasmonoids, prostaglandins, and cyclopentanoid antibiotics contain these structural units.[1] Owing to the great importance of cyclopentenones in organic chemistry, different methods have been developed for their synthesis. Successful approaches include various intramolecular reactions such as aldol reactions, Wittig-type reactions, 1,5-C–H insertions, as well as intermolecular cyclization strategies using transition metals.[2] The Nazarov reaction is a 4π-electron conrotatory cyclization of a pentadienyl cation and is one of the most versatile methods for the synthesis of cyclopentenones.[3] Generally, the divinyl ketone involved in the transformation, is activated by a Brønsted or a Lewis acid (Scheme 1a). So far, only a few catalytic asymmetric versions have been described and they mainly rely on chiral metal complexes as catalysts.[4,5] Recently, we developed the first organocatalytic asymmetric version of the Nazarov cyclization.[6] The Brønsted acid-catalyzed reaction[7] developed by our research group provides access to optically active 2,3-disubstituted cyclopentenones **2** in good yields and high enantioselectivities (Scheme 1b). Furthermore, we have described a Brønsted acid-catalyzed electrocyclization/protonation reaction that yields cyclopentanones **4** in good yields and high enantioselectivities (Scheme 1c).[8] More recently, we succeeded in developing an organocatalyzed asymmetric domino electrocyclization/bromination reaction, which offers access to highly functionalized *trans*-4,5-substituted 5-bromocyclopentenone derivatives **5** with high to excellent enantioselectivities (Scheme 1d).[9]



Scheme 1. Enantioselective Brønsted acid-catalyzed Nazarov reactions.

Regarding the mechanism of the organocatalyzed Nazarov cyclization, the chiral 2,2'-dihydroxy-1,1'-binaphthyl (BINOL)-derived *N*-triflyl phosphoramide catalyst[10,11] activates the divinyl ketone **A** by a catalytic protonation. Subsequent conrotatory 4π electrocyclization gives the oxyallyl cation **C**, which leads to the enolate **D** after proton elimination. Protonation of the enolate results in the formation of

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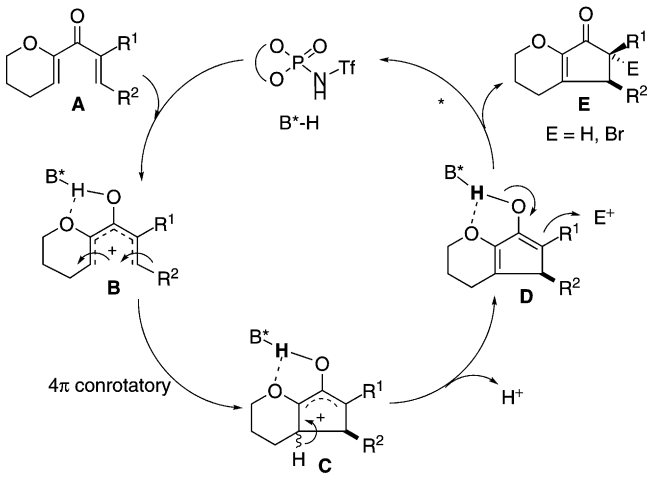
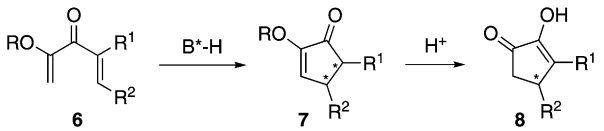
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201200391.



Scheme 2. Proposed mechanism for the Brønsted acid-catalyzed Nazarov cyclization.

the desired enantioenriched cyclopentenone **E** and regenerates the catalyst (Scheme 2). The stereodetermining step for the conversion of 2,3-substituted dienone derivatives **1** to cyclopentenones **2** (Scheme 1b) is the enantioselective electrocyclization reaction, a process followed by a diastereoselective kinetic protonation, which furnishes the *cis*-cyclopentenones **2** with high enantioselectivities. In contrast, the stereodetermining step for the generation of optically active 2-substituted cyclopentenones **4** (Scheme 1c) involves a Brønsted acid-catalyzed enantioselective protonation of intermediate **D**.

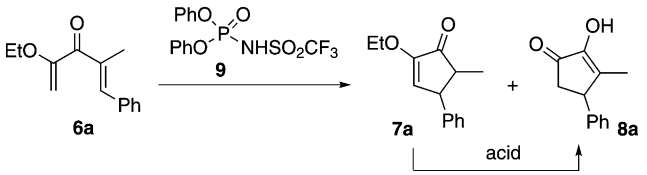
In our previous work, we focused on cyclic ethers as substrates of type **1** and **3**. Cyclopentenones fused with cyclic ethers are not particularly suitable as structural units for the synthesis of natural products. Therefore, we attempted to cleave the ether moiety after cyclization, but without success. Thus, we became interested in studying the Nazarov cyclization of divinyl ketones using acyclic ethers **6** (Scheme 3).[11]



Scheme 3. Brønsted acid-catalyzed Nazarov cyclization using acyclic ethers.

Results and Discussion

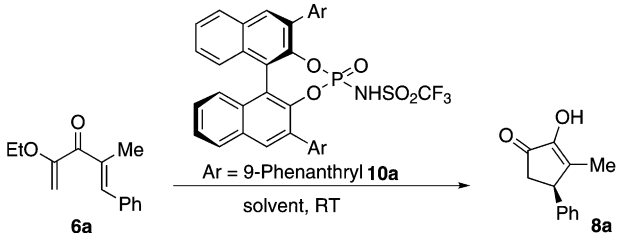
We started our experimental investigations by subjecting divinyl ketone **6a** to the cyclization reaction in the presence of strongly acidic achiral *N*-triflylphosphoramide **9** as a catalyst. Interestingly, in this case we observed the formation of two different cyclization products, cyclopentenone **7a** and α-hydroxyenone **8a**, in a 1:1 ratio (Scheme 4). However, when **7a** was treated with acid, the α-hydroxyenone **8a** was obtained. Therefore, we decided to isolate **8a** after acidic hydrolysis.



Scheme 4. Brønsted acid-catalyzed Nazarov cyclization using acyclic ether **6a**.

In our previous studies on asymmetric Nazarov cyclizations, the enantioselectivities were strongly dependent on the reaction media employed. Thus, our first examination focused on varying the solvent in the reaction of divinyl ketone **6a** to α-hydroxyenone **8a**. The best result with respect to selectivity was obtained when the reaction was performed in chloroform at room temperature (Table 1, entries 1–3). Comparable or slightly lower selectivities were observed in aromatic solvents, for example, benzene and toluene (Table 1, entries 5 and 6). In polar solvents, a very low level of stereocontrol was achieved. Accordingly, chloroform was the solvent of choice. With regard to the catalyst loading, the best result in terms of selectivity was achieved with 5 mol% of **10a**. Neither lower loadings (2 mol%) nor higher loadings (10 mol%) enhanced the enantioselectivity (Table 1, entries 1 and 3). A slightly better selectivity was observed with the H_8-BINOL-derived *N*-triflylphosphoramide derivative **11a** (Table 1, entry 11).

Table 1. Evaluation of different solvents and catalyst loadings.



Entry[a]	Solvent	*ee* [%][b]
1	$CHCl_3$	72
2[c]	$CHCl_3$	76
3[d]	$CHCl_3$	77
4	CH_2Cl_2	48
5	Benzene	72
6	Toluene	65
7	MeOH	6
8	nBu$_2$O	32
9	MeCN	Racemate
10	$ClCH_2CH_2Cl$	30
11[e]	$CHCl_3$	81

[a] Reaction conditions: **6a** (0.11 mmol), 2 mol% of **10a** in solvent at RT. Prior to treatment with conc. HCl. [b] Enantiomeric excess was determined by HPLC. [c] Using 5 mol% of **10a**. [d] Using 10 mol% of **10a**. [e] Using 5 mol% of the H_8 derivative **11a**.

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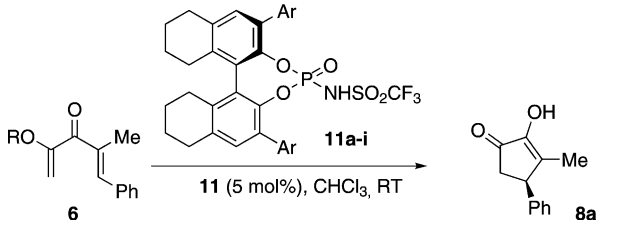
Table 2. Evaluation of different ether substrates and catalysts.



Entry[a]	6	R	11	Ar	*ee* [%][b]
1	**6a**	Et	**11a**	9-phenanthryl	81
2	**6b**	*n*Pr	**11a**	9-phenanthryl	82
3	**6c**	*i*Bu	**11a**	9-phenanthryl	89
4	**6c**	*i*Bu	**11b**	1-naphthyl	76
5	**6c**	*i*Bu	**11c**	2-naphthyl	72
6	**6c**	*i*Bu	**11d**	*p*-OMe-C_6H_4	50[c]
7	**6c**	*i*Bu	**11e**	9-anthracenyl	81
8	**6c**	*i*Bu	**11f**	phenyl	50
9	**6c**	*i*Bu	**11g**	3,5-$(CF_3)_2$-C_6H_3	60
10	**6c**	*i*Bu	**11h**	*p*-F-C_6H_4	56
11	**6c**	*i*Bu	**11i**	*p*-*t*Bu-C_6H_4	57

[a] Reaction conditions: **6** (0.123 mmol), 5 mol% **11** in $CHCl_3$ at RT. Prior to treatment with conc. HCl. [b] Enantiomeric excess was determined by HPLC. [c] Opposite enantiomer was obtained.

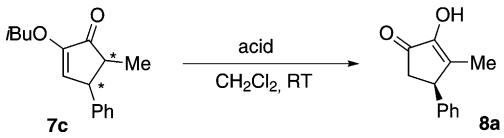
Next, we decided to prepare differently substituted enol ethers to establish which groups are suitable to improve the selectivity (Table 2 entries 1–3). We observed that the reaction proceeded with good enantiocontrol in all cases, with the best selectivity (89% *ee*) for **8a** being obtained with divinyl ketone **6c** that bears an *i*Bu group. In further experiments, we examined the Nazarov cyclization of **6c** in the presence of catalytic amounts of chiral *N*-triflylphosphoramides **11a–i** (Table 2, entries 3–11). The survey revealed that large aromatic substituents in the 3,3′-positions of the BINOL backbone provided better enantioselectivities. However, the best result was obtained with catalyst **11a** (Ar = 9-phenanthryl; Table 2, entry 3). Interestingly, the opposite enantiomer was obtained when the reaction was performed in the presence of catalyst **11d** (Ar = *p*-OMe-C_6H_4; Table 2, entry 6).

As previously mentioned, both products **7** and **8** are obtained in the asymmetric reaction. To isolate our desired product **8a** we concentrated on finding the appropriate reaction conditions for the conversion of chiral cyclopentenone **7c** into the corresponding α-hydroxyenone **8a** (Table 3).

Apart from various acids tested, the temperature and the acid concentration were also varied. These experiments revealed that both temperature and acid concentration have a considerable impact on the reactivity and enantioselectivity. While better selectivities for **8a** could be obtained at room temperature, higher yields were obtained when the reactions were run in the presence of strong acids at high temperatures. We observed that using concentrated acid caused a dramatic decrease in enantioselectivity (Table 3, entries 1 and 2).

Thus, the reaction was conducted using 6 N HCl at room temperature. Under these reaction conditions, the α-hydroxyenone **8a** was furnished in a good yield with high enantioselectivity (89% *ee*, Table 3, entry 6). Under the optimized reaction conditions we investigated the scope of the Brønsted acid-catalyzed enantioselective Nazarov cyclization of 4-aryl-substituted divinyl ketones **6c–k** (Table 4).

Table 3. Evaluation of acids for the transformation of cyclopentenone into diketone.



Entry[a]	Acid	*t* [h]	Yield [%][b]	*ee* [%][c]
1	HCl (conc.)[d]	4	91	31
2	HCl (conc.)[e]	2	59	27
3	HCl (conc.)[f]	36	42	71
4	HCl (conc.)	24	80	69
5	HCl (2 N)	24	–	–
6	HCl (6 N)	24	71	89

[a] Reaction conditions: **7c** in 0.5 mL CH_2Cl_2, 1 mL acid HCl (conc: 37%). [b] Yield of the isolated product after column chromatography. [c] Enantiomeric excess was determined by HPLC. [d] At 80 °C in microwave. [e] At 90 °C in microwave. [f] At 40 °C in microwave.

In general, differently substituted α-hydroxyenones **8** were obtained in moderate to good yields and with excellent enantioselectivities of up to 99% *ee* (Table 4). With regard to the mechanism, we assume that the highly enantioselective cyclization starts with activation of divinyl ketone **6** by the Brønsted acid catalyst. The oxyallyl cation, which is formed during the conrotatory 4π electrocyclization is stabilized by the *i*Bu group. A subsequent protonation of the generated enolate leads to the corresponding cyclopentenone **7**, which isomerizes in the presence of acid into α-hydroxyenone **8**.

Conclusions

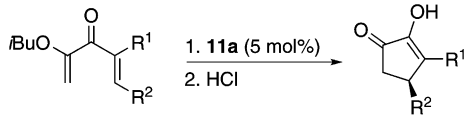
In summary, we have presented a new Brønsted acid-catalyzed asymmetric Nazarov cyclization of α-alkoxy divinyl ketones to afford optically active cyclopentenones. This efficient electrocyclization reaction proceeds under mild reaction conditions and leads to various substituted aromatic α-hydroxyenones with excellent enantioselectivities (88–99% *ee*). Further studies to expand the generality of asymmetric Brønsted acid-catalyzed Nazarov reactions are in progress.[12]

Experimental Section

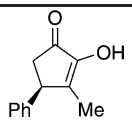
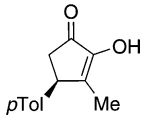
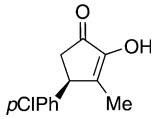
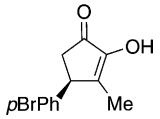
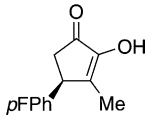
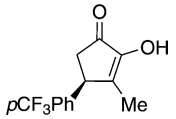
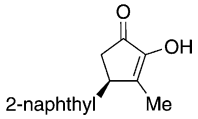
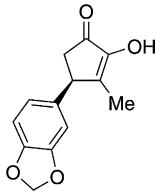
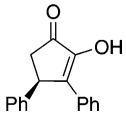
General procedure for preparation of divinyl ketone ***6***

*t*BuLi (20.5 mL, 1.6 M in pentane, 33 mmol) was slowly added to a solution of isobutyl vinyl ether (4.5 mL, 34.6 mmol) in tetrahydrofuran (THF; 30 mL) at −78 °C and the resulting reaction mixture was allowed to warm to 0 °C over 1 h. Afterwards, a solution of morpholine enamide (4 g, 17.3 mmol) in THF (50 mL) was added dropwise and the mixture was stirred at −78 °C for 1 h. The reaction mixture was quenched with brine and the aqueous phase was extracted with ethyl acetate (3×

Table 4. Scope of the Nazarov cyclization.



6c-k 8a-i

Entry[a]	Product		Yield[b]	*ee* [c]
1		**8a**	71	89
2		**8b**	48	93
3		**8c**	43	92
4		**8d**	63	91
5		**8e**	40	91
6		**8f**	43	99
7		**8g**	44	92
8		**8h**	42	99
9		**8i**	53	88

[a] Reaction conditions: 1) substrates **6c–k**, 5 mol% **11a** in $CHCl_3$ at RT for 48 h; 2) 6 N HCl, 0 °C→RT in CH_2Cl_2. [b] Yield of the isolated product after column chromatography. [c] Enantiomeric excess was determined by HPLC.

20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by column chromatography on silca gel to afford the divinyl ketone **6**.

(E)-4-Isobutoxy-2-methyl-1-phenyl-penta-1,4-dien-3-one

The product was purified by column chromatography (EtOAc/cyclohexane 1:40). Yield: 44%; yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.29–7.17 (m, 5H), 4.68 (d, J=2.5 Hz, 1H), 4.39 (d, J=2.4 Hz, 1H), 3.42 (d, J=6.5 Hz, 2H), 1.97 (d, J=1.1 Hz, 3H), 1.94–1.87 (m, 1H), 0.85 ppm (d, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=194.2, 158.9, 141.3, 135.9, 135.6, 129.7, 128.5, 128.3, 91.5, 74.5, 27.9, 19.3, 13.9 ppm; IR (KBr): $\tilde{\nu}$=3058, 2961, 1736, 1660, 1467, 1383, 1290, 1193, 1050, 776, 697 cm^{-1}; MS-EI: m/z (%): 244.3 (2), 188.1 (100), 173.1 (48), 145 (85).

(E)-4-Isobutoxy-2-methyl-1-p-tolyl-penta-1,4-dien-3-one

The product was purified by column chromatography (EtOAc/cyclohexane 1:40). Yield: 42%; yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.29–7.17 (m, 5H), 4.68 (d, J=2.5 Hz, 1H), 4.39 (d, J=2.4 Hz, 1H), 3.42(d, J=6.5 Hz, 2H), 1.97 (d, J=1.1 Hz, 3H), 1.94–1.87 (m, 1H), 0.85 ppm (d, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=193.1, 159.9, 141.3, 138.5, 135.4, 133.7, 130.1, 129.3, 90.7, 74.4, 28.3, 21.4, 19.5, 14.3 ppm; IR (KBr): $\tilde{\nu}$=3025, 2961, 1735, 1607, 1469, 1384, 1292, 1192, 816 cm^{-1}; MS-EI m/z (%): 159.2 (96), 145.2 (100), 131.2 (45).

(E)-1-(4-Fluoro-phenyl)-4-isobutoxy-2-methyl-penta-1,4-dien-3-one

The product was purified by column chromatography (EtOAc/cyclohexane 1:40). Yield: 54%; yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.29–7.17 (m, 5H), 4.68 (d, J=2.5 Hz, 1H), 4.39 (d, J=2.4 Hz, 1H), 3.42 (d, J=6.5 Hz, 2H), 1.97 (d, J=1.1 Hz, 3H), 1.94–1.87 (m, 1H), 0.85 ppm (d, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=194.0, 164.2,158.9, 140.1, 131.6, 131.5, 115.6, 115.4, 91.5, 74.5, 27.8, 19.3, 13.9 ppm; IR (KBr): $\tilde{\nu}$=2926, 2852, 1743, 1600, 1449, 1235, 1154, 902, 835 cm^{-1}; MS-EI m/z (%): 262.3 (3), 206.2 (63), 178 (90), 135 (93).

(E)-1-(4-Bromo-phenyl)-4-isobutoxy-2-methyl-penta-1,4-dien-3-one

The product was purified by column chromatography (EtOAc/cyclohexane 1:40). Yield: 62%; yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.29–7.17 (m, 5H), 4.68 (d, J=2.5 Hz, 1H), 4.39 (d, J=2.4 Hz, 1H), 3.42(d, J=6.5 Hz, 2H), 1.97 (d, J=1.1 Hz, 3H), 1.94–1.87 (m, 1H), 0.85 ppm (d, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=159.4, 138.7, 138.2, 137.4, 134.6, 129.8, 91.4, 74.5, 28.3, 19.4, 14.2 ppm; IR (KBr): $\tilde{\nu}$=3469, 2962, 2874, 1716, 1586, 1486, 1385, 1290, 1193, 1071, 948, 820, 516 cm^{-1}; MS-EI m/z (%): 225.1(36), 185.1 (35), 116.2 (35), 57.4 (100).

(E)-1-(4-Chloro-phenyl)-4-isobutoxy-2-methyl-penta-1,4-dien-3-one

The product was purified by column chromatography (EtOAc/cyclohexane 1:40). Yield: 58%; yellowish oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.28–7.23 (m, 5H), 4.74 (s, 1H), 4.44 (s, 1H), 3.47(d, J=6.4 Hz, 2H), 2.00 (s, 3H), 1.98–1.93 (m, 1H), 0.85 ppm (d, J=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=193.8, 158.7, 139.5, 136.1, 134.4, 134.2, 130.9, 128.6, 91.7, 74.6, 28.0, 19.5, 14.2 ppm; IR (KBr): $\tilde{\nu}$=3459, 2958, 1741, 1651, 1489, 1386, 1312, 1188, 1090, 823, 699 cm^{-1}; MS-EI m/z (%): 179.2 (13), 115 (36), 57.5 (100).

(E)-4-Isobutoxy-2-methyl-1-(4-trifluoromethyl-phenyl)-penta-1,4-dien-3-one

The product was purified by column chromatography (EtOAc/cyclohexane 1:40). Yield: 38%; yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.71 (d, J=7.8 Hz, 1H), 7.61–7.32 (m, 4H), 4.93 (d, J=2.7 Hz, 1H), 4.6 (d, J=2.7 Hz, 1H), 3.57 (d, J=6.6 Hz, 2H), 2.14–2.03 (m, 1H), 1.91 (d, J=1.4 Hz, 3H), 0.98 ppm (d, J=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=158.1, 137.2, 131.6, 130.3, 127.9, 125.9, 92.8, 74.7, 29.1, 27.8, 19.3, 13.9 ppm; IR (KBr): $\tilde{\nu}$=3446, 2966, 1740, 1670, 1469, 1382, 1315, 1165, 1061, 951, 771 cm^{-1}; MS-EI m/z(%): 255.2 (13), 213.2 (99), 199.2 (95), 185 (36), 145 (19).

(E)-4-Isobutoxy-2-methyl-1-naphthalen-2-yl-penta-1,4-dien-3-one

The product was purified by column chromatography (EtOAc/cyclohexane 1:60). Yield: 46%; yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.29–7.17 (m, 5H), 4.68 (d, J=2.5 Hz, 1H), 4.39 (d, J=2.4 Hz, 1H), 3.42 (d, J=6.5 Hz, 2H), 1.97 (d, J=1.1 Hz, 3H), 1.94–1.87 (m, 1H), 0.85 ppm (d, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=193.2, 159.8, 144.5, 141.2, 136.5, 133.9, 133.6, 133.4, 131.3, 129.9, 127.3, 126.9, 126.6, 123.7, 121.1, 90.9, 74.5, 28.2, 19.3, 14.3 ppm; IR (KBr): $\tilde{\nu}$=3490, 2961, 1736, 1660, 1466, 1382, 1292, 1192, 1050, 821, 747 477 cm^{-1}; MS-EI m/z (%): 294.2 (43), 238.2 (98), 195.1 (100), 167 (61).

(E)-1-Benzo[1,3]dioxol-5-yl-4-isobutoxy-2-methyl-penta-1,4-dien-3-one

The product was purified by column chromatography (EtOAc/cyclohexane 1:60). Yield: 52%; yellowish oil; ^{1}H NMR (C_6D_6, 400 MHz): δ=7.46 (s, 1H), 6.84 (s, 1H), 6.69–6.66 (m, 1H), 6.54 (d, J=8.1 Hz, 1H), 5.23 (s, 2H), 4.91 (d, J=2.3 Hz, 1H), 4.27 (d, J=2.3 Hz, 1H), 3.24 (d, J=6.3 Hz, 2H), 2.07 (d, J=1.3 Hz, 3H), 1.79 (m, 1H), 0.79 ppm (d, J=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=193.0, 159.9, 148.3, 141.1, 134.7, 130.5, 125.2, 110.0, 108.6, 101.3, 90.6, 74.5, 28.3, 19.5, 14.3 ppm; IR (KBr): $\tilde{\nu}$= 2965, 1640, 1600, 1488, 1317, 1250, 1060, 929, 830, 761 cm^{-1}; MS-EI m/z (%): 288.3 (27), 232.3 (64), 189.2 (65), 159.2 (60), 103.3 (100).

(E)-4-Isobutoxy-1,2-diphenyl-penta-1,4-dien-3-one

The product was purified by column chromatography (EtOAc/cyclohexane 1:60). Yield: 48%; yellowish oil; ^{1}H NMR (C_6D_6, 400 MHz): δ= 7.28–7.25 (m, 2H), 7.07–7.02 (m, 5H), 6.87–6.85 (m, 3H), 5.17 (d, J= 2.4 Hz, 1H), 4.26 (d, J=2.4 Hz, 1H), 3.10 (d, J=6.4 Hz, 2H), 1.69–1.61 (m, 1H), 0.72 ppm (d, J=6.7 Hz, 6H); ^{13}C NMR (C_6D_6, 75 MHz): δ= 191.7, 159.5, 140.7, 138.8, 136.9, 135.5, 130.7, 129.9, 128.8, 92.2, 74.6, 28.2, 19.4 ppm; IR (KBr): $\tilde{\nu}$=3475, 3058, 2961, 1732, 1670, 1492, 1383, 1292, 1200, 1123, 697 cm^{-1}; MS-EI m/z (%): 306.2 (52), 250.3 (22), 232.3 (13), 178.2 (65), 131.3 (91), 105 (100).

General procedure for Nazarov cyclization

A mixture of catalyst **11a** (5 mol%) and divinylketone **6** (0.24 mmol) in $CHCl_3$ (1.2 mL) was placed in a screw-capped test tube equipped with a stirring bar. The resulting solution was stirred for 48 h at room temperature. The solvent was then exchanged to CH_2Cl_2 and at 0°C 6 N HCl (1 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 48 h. The crude reaction mixture was directly charged on silica gel and purified by column chromatography to afford the cyclopentenone **8**.

*(R)-2-Hydroxy-3-methyl-4-phenyl-cyclopent-2-enone (**8a**)[5b]*

White solid, m.p.: 104–107°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.34–7.12 (m, 5H), 5.68 (brs, 1H), 3.80 (d, J=6.5, 1H), 2.93 (dd, J=19.2, 6.5 Hz, 1H), 2.35 (d, J=20.0 Hz, 1H), 1.80 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ=202.2, 149.5, 145.9, 141.7, 128.9, 127.3, 127.1, 44.9, 42.3, 12.6 ppm; IR (KBr): $\tilde{\nu}$=3332, 2918, 2853, 1693, 1511, 1403, 1351, 1122, 928, 814 cm^{-1}; MS-EI m/z (%): 188.2 (100); $[\alpha]_D^{25}$=−8.6 (c=1.2 in MeOH); HPLC conditions: AD-H column, n-hexane/2-propanol=90:10, flow rate=1.0 mL min^{-1}, major enantiomer: t_R=30.84 min; minor enantiomer: t_R=25.91 min.

*(R)-2-Hydroxy-3-methyl-4-p-tolyl-cyclopent-2-enone (**8b**)*

White solid, m.p.: 119–121°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.13 (d, J=7.8 Hz, 2H), 7.00 (d, J=8.0 Hz, 2H), 5.68 (brs, 1H), 3.75 (d, J= 6.4 Hz, 1H), 2.90 (dd, J=19.2, 6.5 Hz, 1H), 2.35–2.30 (m, 4H), 1.80 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ=202.1, 149.2, 145.8, 138.6, 136.8, 129.6, 127.1, 44.5, 42.3, 21.0, 12.6 ppm; IR (KBr): $\tilde{\nu}$=3330, 2920, 2853, 1693, 1511, 1403, 1353, 1120, 928, 815, 668 cm^{-1}; MS-EI m/z (%): 202.1 (100), 187.1 (76), 159.1 (72); $[\alpha]_D^{25}$=−14.4 (c=0.7 in MeOH); HPLC conditions: AD-H column, n-hexane/2-propanol=95:5, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=21.25 min; minor enantiomer: t_R=25.07 min.

*(R)-4-(4-Chloro-phenyl)-2-hydroxy-3-methyl-cyclopent-2-enone (**8c**)*

White solid, m.p.: 163–166°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.45 (d, J=8.4 Hz, 2H), 7.00 (d, J=8.4 Hz, 2H), 5.58 (brs, 1H), 3.76 (d, J= 6.5 Hz, 1H), 2.93 (dd, J=19.3, 6.6 Hz, 1H), 2.28 (d, J=19.2 Hz, 1H), 1.79 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ=201.6, 149.6, 144.8, 140.2, 132.9, 129.1, 128.6, 44.3, 42.0, 12.5 ppm; IR (NaCl): $\tilde{\nu}$=cm^{-1}; MS-EI m/z (%): 323.7 (21) $[M]^{+\cdot}$, 321.7 (14) $[M]^{+\cdot}$, 20 9.8 (25), 207.8 (25), 129.0 (100), 85.9 (90); $[\alpha]_D^{25}$=−19.5 (c=0.5 in MeOH); HPLC conditions: AD-H column, n-hexane/2-propanol=98:2, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=70.49 min; minor enantiomer: t_R=56.98 min.

*(R)-4-(4-Bromo-phenyl)-2-hydroxy-3-methyl-cyclopent-2-enone (**8d**)*

The product was purified by column chromatography (EtOAc/cyclohexane 1:5). White solid; m.p.: 133–135°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.30 (d, J=8.4 Hz, 2H), 7.05 (d, J=8.4 Hz, 2H), 5.48 (brs, 1H), 3.77 (d, J=6.4 Hz, 1H), 2.93 (dd, J=19.2, 6.6 Hz, 1H), 2.29 (d, J=19.2 Hz, 1H), 1.79 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ=201.5, 149.5, 144.8, 140.3, 133.0, 129.1, 128.6, 44.324, 42.1, 12.6 ppm; IR (KBr): $\tilde{\nu}$=3335, 2924, 2854, 1697,1652, 1461, 1215, 759 cm-1; MS-EI m/z(%): 289.0 (23) $[M]^{+\cdot}$, 271.0 (45) $[M\text{-}H_2O]^{+\cdot}$, 261.0 (74), 211.0 (100); $[\alpha]_D^{25}$=−11.4 (c=0.5 in MeOH); HPLC conditions: OD-H column, n-hexane/2-propanol= 98:2, flow rate=0.5 mL min-1, major enantiomer: t_R=53.76 min; minor enantiomer: t_R=44.91 min

*(R)-4-(4-Fluoro-phenyl)-2-hydroxy-3-methyl-cyclopent-2-enone (**8e**)*

White solid, m.p.: 174–176°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.10–6.99 (m, 4H), 5.49 (brs, 1H), 3.78 (d, J=6.46 Hz, 1H), 2.93 (dd, J=19.2, 6.5 Hz, 1H), 2.29 (d, J=19.3 Hz, 1H), 1.78 ppm (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=201.6, 149.8, 144.9, 143.9, 134.8, 130.3, 127.5, 125.4, 44.6, 41.9, 12.6 ppm; IR (KBr): $\tilde{\nu}$=3330, 2922, 1697, 1507, 1401, 1358, 1226, 1122, 927, 825, 669 cm^{-1}; MS-EI m/z (%): 206.1 (100), 191.1 (49), 177.1 (75), 163.1 (47); $[\alpha]_D^{25}$=−4.3 (c=0.2 in MeOH); HPLC conditions: AD-H column, n-hexane/2-propanol=95:5, flow rate= 0.5 mL min^{-1}, major enantiomer: t_R=26.49 min, minor enantiomer: t_R= 24.56 min.

*(R)-2-Hydroxy-3-methyl-4-(4-trifluoromethyl-phenyl)-cyclopent-2-enone (**8f**)*

White solid; m.p.: 182–185°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.68 (d, J=7.9 Hz, 1H), 7.51 (t, J=15.1, 7.5 Hz, 1H), 7.36 (t, J=15.2, 7.6 Hz, 1H), 7.12 (d, J=7.8 Hz, 1H), 5.50 (brs, 1H), 4.30 (d, J=6.9 Hz, 1H), 2.97 (dd, J=18.2, 6.2 Hz, 1H), 2.23 (d, J=19.2 Hz, 1H), 1.81 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ=201.4, 150.1, 144.0, 132.7, 127.4, 126.0, 125.9, 42.7, 39.8, 12.5 ppm; IR (KBr): $\tilde{\nu}$=3325, 2923, 1700, 1653, 1399, 1153, 1107, 1035, 932, 772, 659 cm^{-1}; MS-EI m/z (%): 256.0 (100), 159.1 (60); $[\alpha]_D^{25}$=−15.2 (c=0.2 in MeOH); HPLC conditions: OD-H column, n-hexane/2-propanol=90:10, flow rate=1.0 mL min^{-1}, major enantiomer: t_R=57.89 min; minor enantiomer: t_R=38.22 min.

*(R)-2-Hydroxy-3-methyl-4-naphthalen-1-yl-cyclopent-2-enone (**8g**)*

White solid, m.p.: 127–130°C; ^{1}H NMR($CDCl_3$, 400 MHz): δ=7.83–7.79 (m, 3H), 7.61 (s, 1H), 7.52–7.45 (m, 2H), 7.17 (dd, J=8.4, 1.7 Hz, 1H), 3.94 (d, J=6.4 Hz, 1H), 2.97 (dd, J=19.2, 6.6 Hz, 1H), 2.41 (d, J= 19.3 Hz, 1H), 1.80 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ=202.4, 149.7, 146.4, 139.0, 133.4, 132.6, 128.9, 127.6, 127.5, 126.3, 125.8, 124.6, 45.0, 42.2, 12.7 ppm; IR (KBr): $\tilde{\nu}$=3339, 2921, 2852, 1739, 1653, 1440, 1360, 1227, 1117, 858, 750, 675 cm^{-1}; MS-EI m/z (%): 238.0 (100); $[\alpha]_D^{25}$= −8.6 (c=0.4 in MeOH); HPLC conditions: AD-H column, n-hexane/2-propanol=98:2, flow rate=0.5 mL min^{-1}, major enantiomer: t_R= 57.94 min; minor enantiomer: t_R=47.91 min.

*(R)-4-Benzo[1,3]dioxol-4-yl-2-hydroxy-3-methyl-cyclopent-2-enone (**8h**)*

White solid, m.p.: 125–127°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=6.75 (d, J=7.9 Hz, 1H), 6.61 (dd, J=7.8 and 1.6 Hz, 1H), 6.55 (d, J=1.6 Hz, 1H), 5.95 (s, 2H), 5.67 (brs, 1H), 3.71 (d, J=6.4 Hz, 1H), 2.90 (dd, J= 19.2, 6.5 Hz, 1H), 2.29 (d, J=19.3 Hz, 1H), 1.80 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ=201.8, 149.2, 148.3, 146.7, 145.3, 135.5, 120.6, 108.5, 107.1, 101.1, 44.7, 42.2, 12.5 ppm; IR (KBr): $\tilde{\nu}$=3319, 2924, 2855, 1701, 1652, 1450, 1216, 759 cm^{-1}; MS-EI m/z (%): 232.1 (100); $[\alpha]_D^{25}$= −48.3 (c=0.45 in MeOH); HPLC conditions: OJ-H column, n-hexane/2-propanol=90:10, flow rate=0.5 mL min^{-1}, major enantiomer: t_R= 38.39 min; minor enantiomer: t_R=62.13 min.

*(R)-2-Hydroxy-3,4-diphenyl-cyclopent-2-enone (**8i**)[5b]*

White solid, m.p.: 145–147°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.75 (m, 2H), 7.33–7.24 (m, 4H), 7.20–7.16 (m, 4H), 6.10 (brs, 1H), 4.49 (d, J= 6.9 Hz, 1H), 3.09 (dd, J=19.3, 6.9 Hz, 1H), 2.38 ppm (d, J=19.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ=201.9, 149.1, 143.3, 139.4, 132.8,

129.1 129.0, 128.8, 128.4, 127.0, 126.9, 42.5, 41.6 ppm; IR (KBr): $\tilde{\nu}$ = 3293, 2921, 2853, 1682, 1624, 1451, 1389, 1281, 1134, 740, 690 cm^{-1}; MS-EI *m*/*z* (%): 250.1 (100), 221.1 (35); $[\alpha]_D^{25} = -19.2$ (*c* = 0.6 in MeOH); HPLC conditions: AD-H column, *n*-hexane/2-propanol = 95:5, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 24.72 min; minor enantiomer: t_R = 42.76 min.

Acknowledgements

The authors acknowledge the DFG (Programme Organocatalysis) for financial support.

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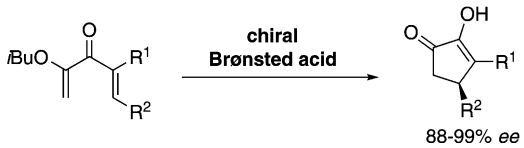
Received: May 1, 2012
Published online: ■■ ■■, 0000



I've got 5 on it! An enantioselective Brønsted acid-catalyzed Nazarov cyclization of acyclic α-alkoxy dienones that affords optically active cyclopentenones in good yields and excellent enantiomeric excess has been developed.

Organocatalysis

Sadiya Raja, Winai Ieawsuwan, Vadim Korotkov, Magnus Rueping** _____ ▮▮▮▮–▮▮▮▮

Asymmetric Brønsted Acid-Catalyzed Nazarov Cyclization of Acyclic α-Alkoxy Dienones

