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Formal Enantioselective [4+3] Cycloaddition by a Tandem Diels–Alder Reaction/Ring Expansion

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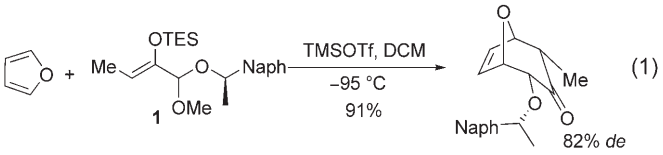
Abstract: The tandem Diels–Alder reaction/ring expansion between cyclopentadiene and unsaturated aldehydes is a highly stereoselective process for the synthesis of bicyclo[3.2.1]octenones, the formal products of a [4+3] cycloaddition. When the initial cycloaddition was conducted in the presence of the chiral Lewis acid catalyst **14**, the bicyclo[3.2.1]octenones were obtained in two steps in 72–85% yields with up to 96% *ee* and >98% *de*.

Keywords: asymmetric catalysis; asymmetric synthesis; cycloaddition; Diels–Alder reaction

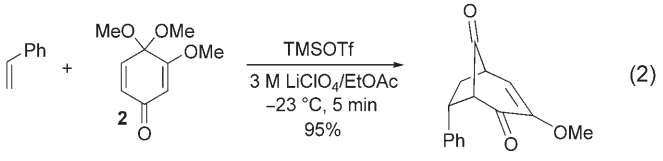
Introduction

The bicyclo[3.2.1]octane moiety is the basic framework of numerous natural products[1–3] and has been widely used as a strategic building block in natural product synthesis.[4] Appropriate modification of the bicyclic framework can lead to products containing multiple stereocenters. In order to fully exploit this chemistry, several methods for the stereoselective synthesis of this valuable bicyclic nucleus have been developed.[5] Among the most notable methods are the [4+3] cycloaddition of allyl cations with dienes [Eq. (1)],[6] the [5+2] cycloaddition between quinone

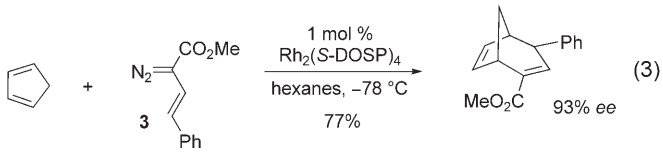


(1)

monoketals and alkenes [Eq. (2)],[7] and the tandem cyclopropanation/Cope rearrangement between vinylcarbenoids and dienes [Eq. (3)].[8] Even though the [4+3] cycloaddition between allyl cations and dienes is the most generally employed, it has suffered from



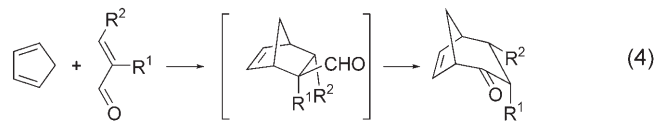
(2)



(3)

the lack of efficient enantioselective variants of this process. Recently, this situation has been addressed through the development of asymmetric cycloaddition protocols involving either the generation of chiral allyl cations and their external capture with π-facial selectivity by dienes[9–11] or asymmetric induction by chiral dienes in cycloadditions with achiral oxyallyl compounds.[12–15] However, very few examples of enantioselective [4+3] cycloadditions involving chiral catalysis have been developed.[16,17]

We have recently communicated an alternative approach for the synthesis of the bicyclo[3.2.1]octane system by the Lewis acid-catalyzed reaction of cyclopentadiene with 2-substituted acrolein derivatives.[18] Although the reaction has the overall appearance of a [4+3] cycloaddition, we have shown that the reaction is actually a Diels–Alder reaction followed by a ring expansion [Eq. (4)]. As numerous chiral Lewis acids are extremely effective in enantioselective Diels–Alder reactions,[19] this method has the potential of being a readily enantioselective synthesis of bicyclo-



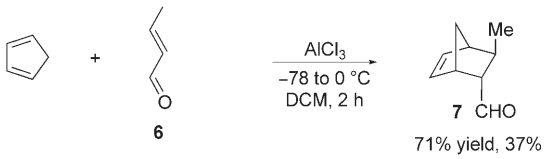
(4)

[3.2.1]octanes. In this paper we demonstrate the extension of this method to a broader range of 2-substituted acrolein derivatives, confirm the mechanistic hypothesis through deuterium labeling studies, and illustrate the scope of the enantioselective entry to bicyclo[3.2.1]octanes.

Results and Discussion

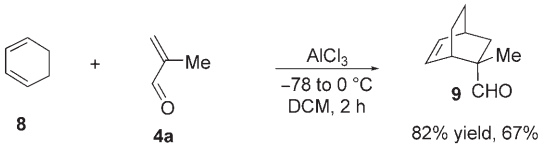
In our original communication of this work we demonstrated that these [4+3] cycloadditions occur on reaction of cyclopentadiene with α,β-unsaturated aldehydes in which the aldehydes are substituted with alkyl groups at the α position.[18] We have extended the reaction to a wider range of appropriate aldehydes and the results are summarized in Table 1. The optimized conditions for most substrates were found to be the use of 1.1 equivs. of aluminum trichloride as the Lewis acid with warming of the reaction mixture from −78 °C to 0 °C over the course of 2 h. This is very effective for the reactions between cyclopentadiene and 2-substituted and 2,3-disubstituted acrolein derivatives. In each case, the 3-*endo* diastereomer is formed with excellent diastereocontrol.

The α-alkyl substituent is a requirement for this [4 + 3] cycloaddition process. The reaction of cyclopentadiene with crotonaldehyde (**6**) resulted in the clean formation of the Diels–Alder cycloadduct **7**, which showed no tendency towards ring expansion [Eq. (5)].[18] Ring strain in the Diels–Alder cycloadduct



(5)

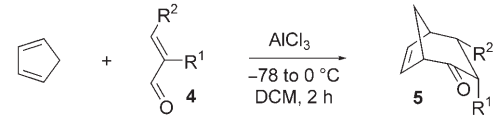
also appears to be a crucial factor as the reaction of **4a** with cyclohexadiene (**8**) gave only the Diels–Alder product **9** [Eq. (6)]. Furan (**10**), which has been extensively used in other types of [4+3] cycloadditions simply results in the formation of the bis-alkylation product **11** [Eq. (7)].[20]

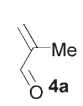
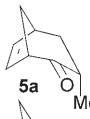
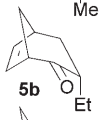
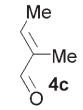
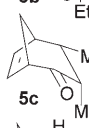
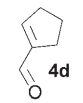
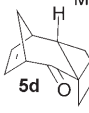
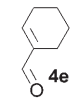
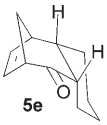
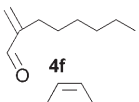
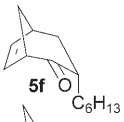
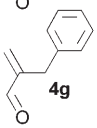
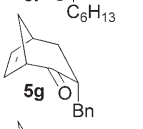
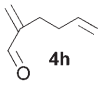
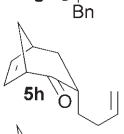
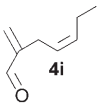
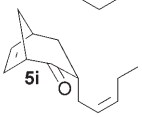


(6)

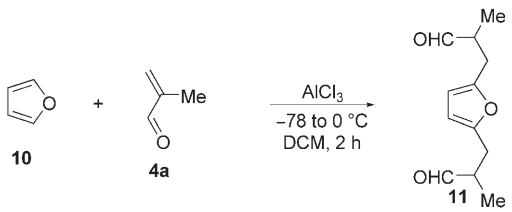
The mechanistic interpretation of this reaction has generated considerable interest. In our original com-

Table 1. [4+3] Cycloaddition of cyclopentadiene with α,β-unsaturated aldehydes.



Substrate	Product	Yield [%][a]	*de* [%][b]
 4a	 5a	90[c]	98[c]
 4b	 5b	80[c]	98[c]
 4c	 5c	75[c,d]	97[c]
 4d	 5d	86[c]	>98[c]
 4e	 5e	21[c]	>98[c]
 4f	 5f	93	>98
 4g	 5g	94	>98
 4h	 5h	83	>98
 4i	 5i	91	>98

[a] Isolated yield after chromatographic purification.
[b] The ratio was determined from a 500 MHz ^{1}H NMR spectrum of the crude reaction mixture.
[c] Ref.[18]
[d] Reaction time was 1 h.



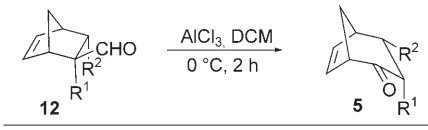
(7)

munication, we proposed that the reaction was a tandem Diels–Alder reaction/ring expansion.[18] The evidence in favor of this mechanistic hypothesis was the fact the Diels–Alder adducts were shown to undergo a Lewis acid-induced rearrangement to the formal [4+3] cycloadducts with the same diastereoselectivity as the direct formal [4+3] cycloaddition. A retro-Diels–Alder reaction followed by a [4+3] cycloaddition was ruled out because an enantioenriched Diels–Alder product rearranged without any stereochemical loss. This mechanistic interpretation is counter to the mechanism generally described for the related [4+3] cycloadditions of allyl cations or allyl cation equivalent with dienes, where the allyl cation is considered to act as a 2π system.[5] Most similar to our system is the Lewis acid-catalyzed [4+3] cycloaddition of 2-siloxyacroleins with dienes, which has been proposed to involve a stepwise process, in which the zwitterionic intermediate goes directly to the [4+3] cycloadduct.[21–23] Even though it has been shown that the Diels–Alder cycloadduct derived from cyclopentadiene and a 2-siloxyacrolein rearranges cleanly to the formal [4+3] cycloadduct,[18] computational studies suggest that this process occurs by a retro Diels–Alder reaction followed by a [4+3] cycloaddition.[24] Therefore, we decided to conduct further studies to understand how the [4+3] cycloadducts in the reaction of 2-alkylacroleins and cyclopentadiene are formed.

The first stage of this study was directed towards expanding the evaluation of the rearrangement chemistry of the Diels–Alder cycloadducts. The Diels–Alder cycloadducts **12** were readily prepared using low temperature Lewis acid-catalyzed reactions and then the rearrangement chemistry was explored using a slight excess of aluminum chloride at 0 °C for 2 h. In the case of the Diels–Alder cycloadducts **12a**, **12b** and **12d**, very effective ring expansion to the [4+3] cycloadducts was observed; over 90% isolated yields were obtained (Table 2). However, **12c** and **12e** gave low yields of the formal [4+3] cycloadducts as they preferentially underwent the retro-Diels–Alder reaction under the reaction conditions. Better yield (80%) of **5c** was achieved when the reaction time was decreased to 1 h. The diastereoselectivity in the rearrangement of **12** to **5** was very high in all cases, following the trend seen in the direct reactions. These results are consistent with the [4+2] cycloadducts being intermediates in the formation of the Diels–Alder cycloadducts. The observation of a retro-Diels–Alder reaction with at least two of the substrates, indicates that such a retro Diels-Ader reaction followed by a [4+3] cycloaddition cannot yet be discounted as a possible mechanism.

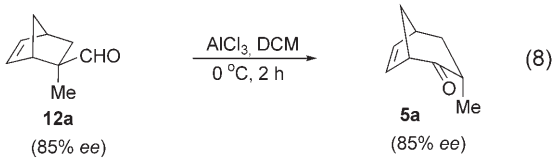
The most convincing piece of evidence for the tandem Diels–Alder reaction/ring expansion mechanism was the discovery that an enantioenriched Diels–Alder cycloadduct rearranged to the [4+3] cycloadduct without change in enantioinduction. The Diels–Alder cycloadduct **12a**, prepared using Faller's catalyst[25] in 85% *ee*, rearranged to **5a** with the same enantioenrichment [Eq. (8)].[18]

Table 2. Ring expansion of [4 + 2] adduct **12** to [4 + 3] adduct **5.**



Substrate	Product	Yield [%]	*de* [%]
12a	**5a**	91	98
12b	**5b**	92	98
12c	**5c**	25(80)[a]	>98
12d	**5d**	92	>98
12e	**5e**	14	>98

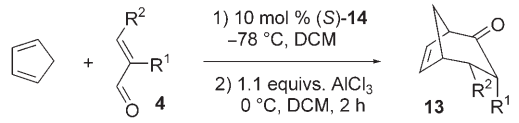
[a] Reaction time was 1 h.

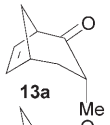
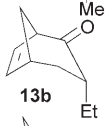
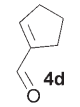
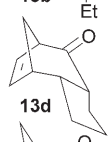
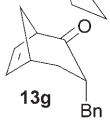


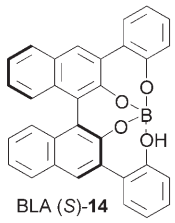
(8)

Since these preliminary studies, we have developed an improved method for the enantioselective synthesis of the [4+3] cycloadducts using Yamamoto's Brønsted acid-assisted chiral Lewis acid (BLA) catalyst **14**.[26] Due to the fact that a stoichiometric amount of Lewis acid is required to efficiently induce the formation of the formal [4+3] cycloadducts, the use of chiral Lewis acids for the direct transformation would not be practical. The asymmetric synthesis of the formal [4+3] cycloadducts, however, can be readily achieved in a two-step process beginning with a chiral Lewis acid-catalyzed asymmetric Diels–Alder

Table 3. Asymmetric [4 + 3] cycloaddition of cyclopentadiene with α,β-unsaturated aldehydes.

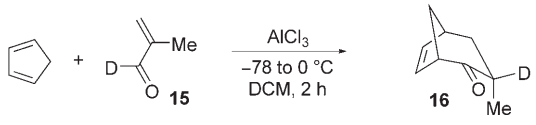


Substrate	Product	Yield [%]	*ee* [%]
 **4a**	 **13a**	72	96
 **4b**	 **13b**	82	90
 **4d**	 **13d**	78	96
 **4g**	 **13g**	85	46


BLA (*S*)-**14**

reaction followed by aluminum chloride-induced rearrangement.[18] The principle is that the aluminum chloride-induced rearrangement of [4 + 2] adducts generated from [4 + 3] adducts proceeds without change in the enantiomeric ratio. Taking advantage of this concept, we developed a one-pot reaction to chiral [4+3] adducts (Table 3). Good yields and up to 96% *ee* were achieved with several substrates. The asymmetric induction, however, is sensitive to the substrate as the [4+3] adduct **13g** was obtained in only 46% *ee*.

In order to probe the stereochemical outcome, the reaction of the deuterated methacrolein **15** with cyclopentadiene was examined. A clean transfer of the deuterium to the 3β position of the [4+3] adduct **16** was observed [Eq. (9)]. The assignment was readily determined by ^{1}H NMR as the signal for the 3β proton at 2.6 ppm is absent in **16** (Figure 1).



(9)

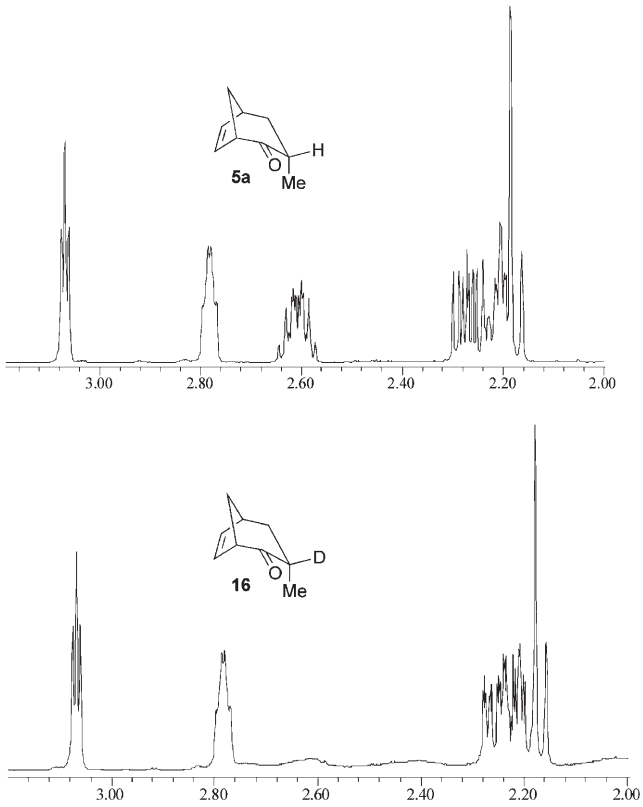
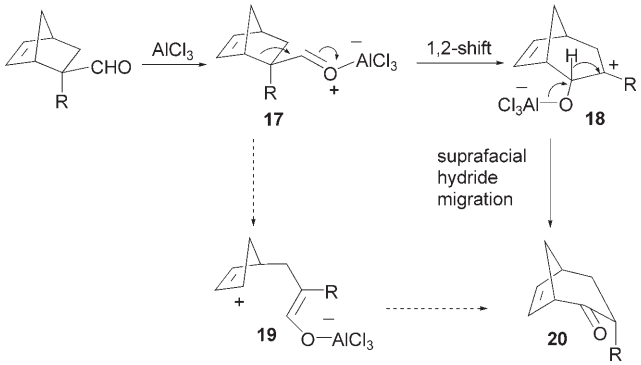


Figure 1. ^{1}H NMR spectra (2.0–3.2 ppm) of **5a** and **16**.

The studies described above offer insights into the likely mechanism of the [4+3] cycloaddition of 2-alkylacroleins with cyclopentadiene. The conversion of the Diels–Alder cycloadducts to the the [4+3] cycloadducts by a retro-Diels–Alder reaction followed by a [4+3] cycloaddition is highly unlikely because there is no loss of enantioselectivity during this process. The most likely mechanism is a Lewis acid-induced 1,2-alkyl shift to form the tertiary carbocation **18** with the alkoxide in the *endo* position (Scheme 1). A suprafacial hydride migration in **18** would then generate the observed *endo* [4+3] cycloadduct **20**. This mechanism is consistent with the deuterium isotope study and



Scheme 1.

would explain why crotonaldehyde (**6**) fails to form the [4+3] cycloadduct because a less favorable secondary carbocation would be the intermediate in this case. A third possibility involving ring opening to the zwitterionic intermediate **19** followed by ring closure to the [4+3] cycloadduct **20** would also result in retention of enantioselectivity but such a mechanism is not likely when R is alkyl because the closure would involve electrophilic attack at the central carbon of an enolate. Such a ring closure of **19** would be much more reasonable when R is siloxy, especially if it is also accompanied by a silyl migration.[21–23]

Conclusions

In summary, we demonstrated a novel and useful tandem Diels–Alder reaction/ring expansion between cyclopentadiene and unsaturated aldehydes. An efficient synthesis of bicyclo[3.2.1]octenones has been achieved by this formal [4+3] cycloaddition. In particular, the enantioselective construction of bicyclo-[3.2.1]octenones was achieved by a two step reaction using a chiral Lewis acid catalyst.

Experimental Section

2-Methylenehex-5-enal (4h)

To a stirred solution of hex-5-enal (378 mg, 3.8 mmol) and triethylamine (1.61 mL, 11.5 mmol) in CH_2Cl_2 (5 mL) was added Eschenmoser's salt (1.43 g, 7.71 mmol) at ambient temperature, and the resulting mixture was stirred for further 15 h. After addition of saturated aqueous $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using pentane-diethyl ether (98:2) as eluent to afford compound **4h** as a colorless oil; yield: 191 mg (45%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.54 (s, CHO, 1H), 6.27 (br s, 1H), 6.03 (br s, 1H), 5.78 (m, 1H), 5.02 (dd, J=17.5, 2.0 Hz, 1H), 4.98 (br d, J=10.5 Hz, 1H), 2.36 (t, J=7.5 Hz, 2H), 2.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=194.6, 149.4, 137.4, 134.6, 115.3, 31.7, 27.1; HR-MS (EI): m/z= 109.0648, calcd. for $C_7H_{10}O$ $[M]^+$: 109.0648.

(*Z*)-2-Methylenehept-4-enal (4i)

To a stirred solution of (*Z*)-hept-4-enal (500 mg, 4.45 mmol) and triethylamine (1.86 mL, 13.35 mmol) in CH_2Cl_2 (15 mL) was added Eschenmoser's salt (1.65 g, 8.92 mmol) at ambient temperature, and the resulting mixture was stirred for further 15 h. After addition of saturated aqueous $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using pentane-diethyl ether (98:2 to 93:7) as eluent to afford compound **4i** as a colorless oil; yield: 442 mg (80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.59 (s, CHO, 1H), 6.26 (br s, 1H), 6.02 (br s, 1H), 5.56 (m, 1H), 5.37 (m, 1H), 2.98 (d, J=7.5 Hz, 2H), 2.06 (m, 2H), 0.97 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=194.4, 149.0, 134.5, 134.1, 123.9, 25.4, 20.4, 14.1; IR (neat): ν= 2694, 1694 (C=O) cm^{-1}; HR-MS (EI): m/z=124.0885, calcd. for $C_8H_{12}O$ $[M]^+$: 124.0883.

3-Hexylbicyclo[3.2.1]oct-6-en-2-one (5f)

Aluminum chloride powder (87 mg, 1.1 equivs.) was added in one portion to a stirred solution of 2-methyleneoctanal (**4f**) (83 mg, 0.59 mmol) in dry CH_2Cl_2 (5 mL) in a 25-mL round-bottom flask at −78 °C. Freshly distilled and precooled cyclopentadiene (98 mg, 1.48 mmol) was then added dropwise by syringe to the reaction mixture. After 30 min at −78 °C, the reaction was gradually warmed to 0 °C in 30 min. Then the reaction was kept at the same temperature for another 1 h. The reaction was then quenched with saturated sodium bicarbonate solution (10 mL) and extracted with ether (2×), and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel using pentane-diethyl ether (93:7) as eluent to give **5f** as a colorless oil; yield: 113 mg (93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.25 (dd, J=5.5, 3.0 Hz, 1H), 5.80 (dd, J=5.5, 3.0 Hz, 1H), 3.05 (t, J=4.0 Hz, 1H), 2.78 (m, 1H), 2.47 (m, 1H), 2.24–2.13 (m, 2H), 2.12 (d, J=11.5 Hz, 1H), 1.78 (m, 1H), 1.35–1.13 (m, 10H), 0.87 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=208.9, 140.7, 129.8, 54.6, 45.5, 37.7, 37.4, 34.9, 31.7, 30.4, 29.2, 26.6, 22.6, 14.0; IR (neat): ν=2927, 2856, 1705 (C=O), 749 cm^{-1}; HR-MS (EI): m/z=206.1672, calcd for $C_{14}H_{22}O$ $[M]^+$. 206.1665.

3-Benzylbicyclo[3.2.1]oct-6-en-2-one (5g)

Aluminum chloride powder (85 mg, 1.1 equivs.) was added in one portion to a stirred solution of 2-benzylacrylaldehyde (**4g**) (90 mg, 0.61 mmol) in dry CH_2Cl_2 (3 mL) in a 10-mL round-bottom flask at −78 °C. Freshly distilled and precooled cyclopentadiene (102 mg, 1.54 mmol) was then added dropwise by syringe to the reaction mixture. After 30 min at −78 °C, the reaction was gradually warmed to 0 °C in 30 min. Then the mixture was kept at the same temperature for another 1 h. The reaction was then quenched with saturated sodium bicarbonate solution (5 mL) and extracted with ether (2×), and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel using pentane-diethyl ether (93:7) as eluent to give **5g** as a colorless oil; yield: 122 mg (94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26 (t, J=7.0 Hz, 2H), 7.18 (t, J= 7.0 Hz, 1H), 7.12 (d, J=7.0 Hz, 2H), 6.21 (dd, J=5.5, 3.0 Hz, 1H), 5.81 (dd, J=5.5, 3.0 Hz, 1H), 3.34 (dd, J=14.0, 4.0 Hz, 1H), 3.12 (t, J=4.0 Hz, 1H), 2.82 (m, 1H), 2.73 (m, 1H), 2.49 (dd, J=14.0, 10.5 Hz, 1H), 2.18 (m, 1H), 2.13 (d, J=10.5 Hz, 1H), 1.93 (ddd, J=16.0, 10.0, 6.5 Hz, 1H), 1.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=207.6, 140.9, 139.9, 129.7, 129.2 (2C), 128.3 (2C), 126.1, 54.5, 47.0, 40.4, 37.5, 37.0, 29.6; IR (neat): ν=2943, 1704 (C=O), 1495, 1453, 1222, 912 cm^{-1}; HR-MS (EI): m/z=212.1204, calcd. for $C_{15}H_{16}O$ $[M]^+$: 212.1196.

3-(But-3-enyl)bicyclo[3.2.1]oct-6-en-2-one (5h)

Aluminum chloride powder (49 mg, 1.1 equivs.) was added in one portion to a stirred solution of 2-methylenehex-5-enal (**4h**) (37 mg, 0.33 mmol) in dry CH_2Cl_2 (3 mL) in a 10-mL round-bottom flask at −78 °C. Freshly distilled and pre-cooled cyclopentadiene (56 mg, 0.84 mmol) was then added dropwise by syringe to the reaction mixture. After 60 min at −78 °C, the reaction was gradually warmed to 0 °C in 10 min. Then the mixture was kept at the same temperature for 50 min. The reaction was then quenched with saturated sodium bicarbonate solution (5 mL) and extracted with ether (2×), and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel using pentane-diethyl ether (98:2 to 93:7) as eluent to give **5h** as a colorless oil; yield: 49 mg (83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.25$ (dd, $J = 5.5$, 3.0 Hz, 1H), 5.81 (dd, $J = 5.5$, 3.0 Hz, 1H), 5.76 (m, 1H), 5.00 (m, 1H), 4.95 (m, 1H), 3.07 (t, $J = 3.5$ Hz, 1H), 2.79 (m, 1H), 2.51 (m, 1H), 2.24–2.16 (m, 2H), 2.13 (d, $J = 11.5$ Hz, 1H), 2.09–2.03 (m, 1H), 1.99–1.89 (m, 2H), 1.45–1.37 (m, 1H), 1.31–1.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 208.5$, 140.8, 138.2, 129.9, 114.9, 54.6, 44.6, 37.7, 37.2, 33.9, 30.8, 30.4; IR (neat). $\nu = 2943$, 1705 (C=O) cm^{-1}; HR-MS (EI): $m/z = 176.1196$, calcd. for $C_{12}H_{16}O$ $[M]^+$: 176.1196.

3-[(*Z*)-Pent-2-enyl]bicyclo[3.2.1]oct-6-en-2-one (5i)

Aluminum chloride powder (71 mg, 1.1 equivs.) was added in one portion to a stirred solution of (*Z*)-2-methyleneheptenal (**4i**) (60 mg, 0.48 mmol) in dry CH_2Cl_2 (4 mL) in a 10-mL round-bottom flask at −78 °C. Freshly distilled and pre-cooled cyclopentadiene (160 mg, 2.42 mmol) was then added dropwise by syringe to the reaction mixture. After 60 min at −78 °C, the reaction was gradually warmed to 0 °C in 15 min. Then at the reaction was kept at the same temperature for 45 min. The reaction was then quenched with saturated sodium bicarbonate solution (5 mL) and extracted with ether (2×), and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel using pentane-diethyl ether (98:2 to 93:7) as eluent to give **5i** as a colorless oil; yield: 83 mg (91%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.26$ (dd, $J = 5.5$, 3.0 Hz, 1H), 5.81 (dd, $J = 5.5$, 3.0 Hz, 1H), 5.43 (m, 1H), 5.17 (m, 1H), 3.08 (t, $J = 4.0$ Hz, 1H), 2.77 (m, 1H), 2.57 (m, 1H), 2.47 (m, 1H), 2.24–2.09 (m, 3H), 2.15 (d, $J = 11.0$ Hz, 1H), 2.00 (dt, $J = 7.5$, 7.5 Hz, 2H), 1.30 (m, 1H), 0.94 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 207.9$, 140.8, 133.4, 129.7, 126.1, 54.5, 45.3, 37.6, 37.2, 31.8, 29.6, 20.6, 14.2; IR (neat): $\nu = 2960$, 1707 (C=O), 1451 cm^{-1}; HR-MS (EI): m/z: 190.1355, calcd. for $C_{13}H_{18}O$ $[M]^+$: 190.1352.

Revised Synthesis of (*S*)-3,3′-Di(2-hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl [Precursor to the Catalyst (*S*)-14]

In a 500-mL, flame-dried, three-necked, round-bottomed flask equipped with an argon inlet were placed dry Et_2O (150 mL) and TMEDA (3.2 g, 27 mmol). To this solution was added 1.6 M *n*-BuLi in hexane (18 mL, 29 mmol). The solution was stirred for 30 min at room temperature, solid (*S*)-2,2′-dimethoxy-1,1′dinaphthyl (3.0 g, 9.5 mmol) was added in one portion, and the reaction mixture was stirred for 3 h. The resulting light brown suspension was cooled to −78 °C, and $B(OEt)_3$ (8.6 g, 59 mmol) was added via syringe over a period of 10 min. The solution was allowed to warm to room temperature and was left stirring overnight. The reaction mixture was cooled to 0 °C, 1 M HCl (75 mL) was added, and the reaction mixture was stirred for 2 h. The phases were separated, and the organic phase was washed twice with 1 M HCl (50 mL) and saturated aqueous NaCl (50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting white solid was recrystallized from toluene to give (*S*)-3,3′-bis(dihydroxyborane)-2,2′-dimethoxy-1,1′-dinaphthyl as white crystals; yield: 2.84 g (76%). The physical and spectral data were identical to those previously reported for this compound.[27] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.62$ (s, 2H), 7.99 (d, $J = 8.0$ Hz, 2H), 7.44 (t, $J = 7.5$ Hz, 2H), 7.32 (td, $J = 7.5$, 1.0 Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 6.00 (s, 4H, OH), 3.31 (s, 6H).

In a 50-mL, two-necked flask equipped with a condenser were placed (*S*)-3,3′-bis(dihydroxyborane)-2,2′-dimethoxy-1,1′-dinaphthyl (950 mg, 2.40 mmol), $Ba(OH)_2{\cdot}8H_2O$ (2.28 g, 7.22 mmol), and $Pd(PPh_3)_4$ (278 mg, 0.24 mmol), and the flask was evacuated and filled with argon three times. 1,4-Dioxane (15 mL), H_2O (5 mL), and 1-bromo-2-methoxybenzene (1.80 g, 9.62 mmol) were added. The reaction mixture was refluxed for 24 h under argon and cooled to room temperature. The dioxane was removed, and the resulting phase was redissolved in CH_2Cl_2 (75 mL), washed with 1 M HCl (2×50 mL) and saturated aqueous NaCl (75 mL), and dried over Na_2SO_4. The solvent was removed to give the crude product as a yellow semicrystalline oil. The crude product was purified by column chromatography on silica gel using 1/12 to 1/8 EtOAc/hexanes as eluent to give (*S*)-3,3′-bis(2-methoxy-phenyl)-2,2′-dimethoxy-1,1′-binaphthyl as pale white solid; yield: 703 mg (56%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.89$ (s, 2H), 7.87 (d, $J = 8.0$ Hz, 2H), 7.47 (dd, $J = 7.5$, 2.0 Hz, 2H), 7.40–7.35 (m, 4H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.26 (m, 2H), 7.05 (t, $J = 8.0$ Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 3.77 (s, 6H), 3.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 157.2$, 154.9, 133.8, 132.5, 131.3, 130.8, 130.5, 128.8, 128.4, 127.9, 125.9, 125.8, 124.8, 124.5, 120.4, 110.9, 60.5, 55.7; HR-MS (ESI): m/z: 549.2052, calcd. for $C_{36}H_{30}O_4Na$ $[M+Na]^+$: 549.2036.

To a solution of (*S*)-3,3′-bis(2-methoxy-phenyl)-2,2′-dimethoxy-1,1′-binaphthyl (703 mg, 1.33 mmol) in DCM (10 mL) at −78 °C, was added BBr_3 (10.7 mL. 1.0 M in DCM) dropwise. The reaction was allowed to warm to 0 °C over 2 h. After stirring at 0 °C for 30 min, the reaction was poured into 50 mL ice/water. The mixture was extracted with ether (2×), and the combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The resulting yellow solid was chromatographed on silica to give (*S*)-3,3′-di(2-hydroxyphenyl)-2,2′- dihydroxy-1,1′-binaphthyl as white crystalline solid; yield: 375 mg (60%). The physical and spectral data were identical to those previously reported for this compound.[26] $[\alpha]_D^{23}$: 153.6 (*c* 2.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.82$ (br s, 2H), 6.65 (br s, 2H), 6.86 (t, $J = 7.5$ Hz, 2H), 7.14 (m, 2H), 7.26 (m, 4H), 7.33 (d, $J = 7.5$ Hz, 2H), 7.57 (d, $J = 7.0$ Hz, 2H), 7.70 (s, 2H), 7.73 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 114.77$, 115.96, 120.77, 124.05, 124.36, 124.92, 126.83, 128.04, 128.34, 129.19,

129.85, 131.46, 131.95, 133.58, 149.77, 151.98; HR-MS: $m/z=$ 470.1513, calcd. for $[C_{32}H_{22}O_4]$: 470.1513.

Representative Example of Sequential Asymmetric Diels–Alder Reaction/Ring Expansion, 3-Methylbicyclo[3.2.1]oct-6-en-2-one (13a)

A dry 25-mL, round-bottom flask fitted with a stir bar and a 25-mL pressure-equalized addition funnel (containing a cotton plug and *ca.* 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with (*S*)-3,3′-di(2-hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl (25 mg, 0.05 mmol), trimethyl borate (0.5 mL, 0.1 M solution in dichloromethane, 0.05 mmol), and dichloromethane (3 mL). An argon atmosphere was secured and the solution was brought to reflux (bath temperature 50–60 °C). After 2 h the reaction mixture was cooled to 25 °C and the addition funnel and condenser were quickly removed and replaced with a septum. To the white precipitate in dichloromethane was added dry THF (50 μL) at 25 °C and after 2 h the precipitate was completely dissolved. After the colorless solution of the catalyst (*S*)-**14** had been cooled to −78 °C, 2-methylacrolein (41 μL, 0.5 mmol) and cyclopentadiene (134 μL, 2.0 mmol) were added dropwise. After 4 h, 50 μL of H_2O were added and the mixture was warmed to 25 °C, extracted with ether, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was passed through a short column washed with 3% ether/pentane to afford the crude Diels–Alder adduct and then washed with 33% EtOAc/hexanes to recover the ligand (*S*)-3,3′-di(2-hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl.

Aluminum chloride powder (58 mg, 0.44 mmol) was added in one portion to a stirred solution of the above crude [4+2] adduct in dry CH_2Cl_2 (2 mL) in a 10-mL round-bottom flask at 0 °C and the reaction mixture was then stirred for 2 h. The reaction was quenched with saturated sodium bicarbonate solution (3 mL) and extracted with ether (2×), and the combined extracts were washed with water and brine, dried over $MgSO_4$, and carefully concentrated due to the volatility of the product. The crude product was purified by column chromatography on silica gel using pentane-diethyl ether (93:7) as eluent to give desired product as a colorless oil; yield: 48 mg (72%, 96% *ee*, >98% *de*); The physical and spectral data were identical to those previously reported for this compound.[18a] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.24$ (dd, $J=5.0$, 4.0 Hz, 1H), 5.81 (dd, $J=5.0$, 4.0 Hz, 1H), 3.06 (t, $J=3.5$ Hz, 1H), 2.77 (m, 1H), 2.57–2.62 (m, 1H), 2.15–2.29 (m, 3H), 1.17–1.21 (m, 1H), 1.13 (d, $J=7.5$ Hz, 3H). $[\alpha]_D^{25}$: 488° (*c* 2.5, $CHCl_3$). The enantiomeric excess was determined by GC using a Chiraldex B-DM column [flow 1 mL min^{-1}, 105 °C/30 min, 30 m × 0.25 mm, 1 mg mL^{-1}; $t_r=22.6$ and 23.5 min; 96% *ee*].

3-Ethylbicyclo[3.2.1]oct-6-en-2-one (13b)

Compound **13b** was prepared in the same manner as **13a**. The crude product was purified by column chromatography on silica gel using pentane-diethyl ether (93:7) as eluent to give desired product as a colorless oil; yield: 74 mg (82% for two steps, 90% *ee*, >98% *de*); The physical and spectral data were identical to those previously reported for this compound.[18a] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.25$ (dd, $J=$ 6.5, 4.0 Hz, 1H), 5.79 (dd, $J=6.5$, 4.0 Hz, 1H), 3.05 (t, $J=$ 4.5 Hz, 1H), 2.79 (m, 1H), 2.41–2.48 (m, 1H), 2.12–2.24 (m, 2H), 1.71–1.80 (m, 1H), 1.40–1.48 (m, 1H), 1.27–1.33 (m, 1H), 0.86–0.91 (m, 1H), 0.82 (t, $J=9.0$ Hz, 3H). $[\alpha]_D^{25}$: 594° (*c* 0.28, $CHCl_3$). The enantiomeric excess was determined by GC using a Chiraldex B-DM column [flow 1 mL min^{-1}, 105 °C/30 min, 30 m × 0.25 mm, 1 mg mL^{-1}; $t_r=33.0$ and 33.8 min; 90% *ee*].

2,3,3a,4,7,8a-Hexahydro-*1H*-4,7-methanoazulen-8-one (13d)

Compound **13d** was prepared in the same manner as **13a**. The crude product was purified by column chromatography on silica gel using pentane-diethyl ether (93:7) as eluent to give desired product as a colorless oil: 57 mg (78% yield for two steps, 96% *ee*, >98% *de*); The physical and spectral data were identical to those previously reported for this compound.[18a] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.26$ (dd, $J=$ 5.8, 3.0 Hz, 1H), 5.87 (dd, $J=5.8$, 3.0 Hz, 1H), 3.04 (t, $J=$ 4.0 Hz, 1H), 2.83–2.86 (td, $J=5.0$, 2.5 Hz, 1H), 2.72 (dd, $J=$ 19.5, 9.5 Hz, 1H), 2.52–2.59 (m, 1H), 2.29–2.34 (m, 1H), 2.12 (d, $J=11.5$ Hz, 1H), 2.07–2.13 (m, 1H), 1.77–1.83 (m, 1H), 1.63–1.68 (m, 1H), 1.42–1.51 (m, 1H), 1.31–1.39 (m, 2H). $[\alpha]_D^{25}$: 883° (*c* 1.25, $CHCl_3$). The enantiomeric excess was determined by GC using a Chiraldex B-DM column [flow 1 mL min^{-1}, 105 °C/30 min, 30 m × 0.25 mm, 1 mg mL^{-1}; $t_r=95.4$ and 96.1 min; 96% *ee*].

3-Benzylbicyclo[3.2.1]oct-6-en-2-one (13g)

Compound **13g** was prepared in the same manner as **13a**. The crude product was purified by column chromatography on silica gel using pentane-diethyl ether (93:7) as eluent to give desired product as colorless oil; yield: 180 mg (85% for two steps, 46% *ee*, >98% *de*). The enantioselective excess of **13g** was determined by HPLC (Daicel Chiralcel OJ, hexanes/*i*-PrOH = 99:1, flow rate = 0.9 mL min^{-1}) $t_r=17.6$ min (minor), $t_r=21.9$ min (major).

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