BINOL-Al Catalysed Asymmetric Cyclization and Amplification: Preparation of Optically Active Menthol Analogs

Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID:	OB-ART-03-2015-000433.R1
Article Type:	Paper
Date Submitted by the Author:	07-Apr-2015

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Organic and Biomolecular Chemistry RSCPublishing

ARTICLE

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Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2015,
Accepted 00th January 2015

DOI: 10.1039/x0xx00000x

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We report a highly selective asymmetric ring-closing ene reaction catalysed by aluminum complexes with chiral BINOL. This reaction yields optically active 6-membered cyclized alcohols from unsaturated aldehydes, with good diastereo- and enantioselectivities. Asymmetric amplification of this reaction was investigated by varying the *ee* of the BINOL employed in the catalyst.

Introduction

Optically active products are used in the preparation of organic materials, aroma compounds, and pharmaceuticals. A number of asymmetric intermolecular or intramolecular ene reactions have been reported for the synthesis of optically active products, the asymmetric intramolecular Heck reaction being a representative example.[1] In particular, asymmetric ene and Prins reactions between carbonyl and olefin compounds in the presence of Lewis or Brønsted acids have been reported.[2] For example, Overman *et al.* used the Prins reaction to synthesize Briarellin F,[3] and David *et al.* reported a leucascandrolide A synthesis by the Mukaiyama Aldol-Prins cyclization cascade reaction.[4]

Another common application of the ring-closing ene reaction is the synthesis of isopulegol from citronellal. Citronellal and isopulegol are not only important aroma compounds but also valuable intermediates for the synthesis of L-menthol.[5] A variety of methods have been reported for the cyclization of citronellal to isopulegol.[6-9] The stoichiometric ring-closing ene reaction of citronellal by alkylaluminum chloride has been reported previously,[10] while Williams *et al.* reported that methylaluminum chloride can catalyze the citronellal ring-closing ene reaction.[11] Various other aluminum complexes have also been applied to this reaction, giving excellent diastereoselectivity.[12-15] Furthermore, a variety of asymmetric cyclizations in which citronellal analogs were utilized as the substrate have been reported. For example, Sakane *et al.* reported a stoichiometric asymmetric cyclization of 3-methylcitronellal using an optically active zinc complex.[16]

Several catalysts bearing chiral ligands are also employed for asymmetric cyclization in other systems. Ding *et al.* reported that the 3,3'-Br_2-BINOL-Zn complex was found to be a highly efficient catalyst for enantioselective hetero-Diels-Alder reactions,[17] Mikami *et al.* reported an effective asymmetric cyclization and amplification of aldehydes with the BINOL-Ti catalyst,[18] and Jacobsen *et al.* found that Cr^{III} complexes of tridentate Schiff base ligands promote asymmetric hetero-ene reactions between electron rich enol ethers and electronically unactivated aldehydes.[19] Yang *et al.* reported intramolecular carbonyl-ene reaction with Cu^{II} complexes with chiral ligands.[20] Feng *et al.* reported a variety of catalysts bearing chiral *N*,*N*'-dioxide ligands and these utilities.[21] Chiral Pybox-Sc^{III} catalysts found by T.-P. Loh *et al.* show excellent performances for enantioselective cationic cyclizations and carbonyl-ene reactions.[22] Aluminium catalysts have also reported as a catalyst of a variety of asymmetric cyclizations.[2,23] However, to the best of our knowledge, asymmetric intramolecular carbonyl-ene reaction catalysed by aluminium complexes has not been reported.

We previously reported kinetic resolution of citronellal by aluminium catalysts bearing chiral ligands.[24] This work reports our further findings on the asymmetric cyclization of achiral substrates with the aluminum catalysts prepared from chiral BINOL. This catalyst yielded optically active ring-closed products with good diastereo- and enantioselectivities. Furthermore, asymmetric amplification of the cyclization was investigated by varying the *ee* of BINOL. As a result of the catalytic asymmetric cyclization, (+) and (-)-*trans*-menthol analogs were obtained.

Results and Discussion

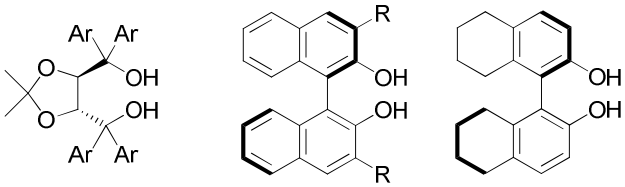
Optimization of Asymmetric Cyclization of 3-Methylcitronellal with Chiral Al Catalyst

We performed the ring-closing ene reaction of the achiral citronellal analog 3-methylcitronellal (**1**)[16] with chiral ligand-Al catalysts to afford 5-methylisopulegol (**2**) (Table 1). The steric structures of 5-methylisopulegol (**2**) were determined by comparison with the results from a previously reported synthesis employing BINOL-Zn.[16]

At the first, we selected TADDOL type compounds **3** as ligands of the asymmetric cyclization. The aluminum complex, bearing 5 mol % of triethylaluminum and 9 mol % of (*R*,*R*)-TADDOL ((*R*)-**3a**), afforded (-)-*trans*-**2** with 52% conversion, 59% selectivity and 64% *de* of (-)-*trans*-**2** (Table 1, entry 1). The enantioselectivity of (-)-*trans*-**2** was only 3% *ee*. The same reaction employing the aluminium complex with (*R,R*)-1-NaphtylTADDOL ((*R*)-**3b**) provided (-)-*trans*-**2** in 100% conversion with 96% *de*. The enantioselectivity of (-)-*trans*-**2** gained to 25% *ee*. We carried out the cyclization in the presence of a more bulky ligand, (*R,R*)-9-PhenanthrylTADDOL ((*R*)-**3c**).[25] The enantioselectivity of (-)-*trans*-**2** was higher than that with (*R*)-**3b** (Table 1, entry 3). However, the reactivity of the complex with (*R*)-**3c** was much lower than the case of (*R*)-**3b**. This is because the bulky 9-phenanthryl substituents, while making the catalyst less accessible to the substrate, promote a higher level of enantioselectivity.

Next, BINOL type ligands **4** were used in this asymmetric cyclization. The reaction employing the (*R*)-BINOL ((*R*)-**4a**)-Al catalyst afforded (-)-*trans*-**2** with 98% conversion, 99% selectivity and over 99% *de* (Table1, entry 4). The enantioselectivity of (-)-*trans*-**2** reached nearly 90% *ee*. The reaction with 5 mol % of triethylaluminum and 5 mol % of (*R*)-**4a** gave (-)-*trans*-**2** in far lower selectivity (Table 1, entry 5). The reaction in toluene afforded (-)-*trans*-**2** with slightly lower selectivity and enantioselectivity (Table 1, entry 6). We investigated other BINOL type ligands for this reaction (Table 1, entries 7 to 9). The catalysts bearing the 3,3'-substituted analogues of BINOL such as, (*R*)-**4b** and (*R*)-**4c** afforded (+)-*trans*-**2** with lower enantioselective performance (Table 1, entries 7 and 8). The reaction in the presence of (*R*)-H8-BINOL ((*R*)-**4d**) afforded racemic *trans*-**2** with 48% selectivity (Table 1, entry 9). Interestingly, the optical rotation observed for the product from the reaction catalysed by BINOL-Al ((*R*)-**4a**-Al) is opposite to that seen in the product from the BINOL-Zn ((*R*)-**4a**-Zn) reaction. (*R*)-**4a**-Zn gave (+)-*trans*-**2** whereas (*R*)-**4a**-Al gave (-)-*trans*-**2** (Table 1, entry 1 vs entry 10) indicating that, although both catalysts work very well, the (*R*)-**4a**-Al catalyst structure is optically different from (*R*)-**4a**-Zn.

The optical rotation observed for *trans*-**2** depended on not only the steric structures of the catalysts but also the catalyst substituents. The aluminium catalysts bearing (*R*)-**4b** and (*R*)-**4c** afforded (+)-*trans*-**2** whereas the complex with (*R*)-**4a** afforded (-)-*trans*-**2** (Table 1, entry 4 vs entries 7 and 8), showing that the catalytic sites of Al metal BINOL complexes are fundamentally affected by the 3-position substituents on the naphthyl ring. Thus, tuning of these substituents can optimize the selectivity of the reactions.



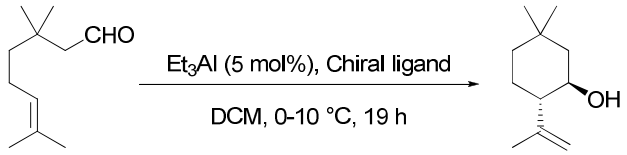
(*R*)-**3a:** Ar = Ph
(*R*)-**3b**: Ar = 1-Naph
(*R*)-**3c**: Ar = 9-Anth

(*R*)-**4a**: R = H
(*R*)-**4b**: R = Br
(*R*)-**4c**: R = $SiPh_3$

(*R*)-**4d**

Figure 1. Chiral ligands

Table 1. Asymmetric cyclization of 3-methylcitronellal (1) by chiral-Al catalysts



1 (-)-*trans*-**2**

Entry	Chiral ligand (mol %)	Conv. (%)[a]	Selectivity of (-)-*trans*-**2** (%)[a]	*de* of (-)-*trans*-**2** (%)[a]	*ee* of (-)-*trans*-**2** (%)[a]
1[b]	(*R*)-**3a** (9)	52	59	64	3
2[b]	(*R*)-**3b** (9)	100	88	96	25
3	(*R*)-**3c** (9)	6	40	97	49
4	(*R*)-**4a** (9)	98	99	>99	89
5	(*R*)-**4a** (5)	91	10	78	10
6[c]	(*R*)-**4a** (9)	99	91	>99	80
7	(*R*)-**4b** (9)	100	95	90	-11
8	(*R*)-**4c** (9)	96	87	>99	-41
9	(*R*)-**4d** (9)	51	48	70	0
10[d]	(*R*)-**4a** (300)	100	70	94	-75

[a]Determined by GC analysis. [b]This reaction was carried out for 5 h. [c]This reaction was carried out in PhMe instead of DCM. [d]This reaction was carried out using 300 mol % of Et_2Zn and (*R*)-**4a** at -78 °C to r.t. for 19 h.[16]

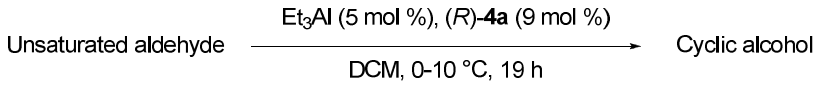
Scope and Limitation

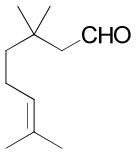
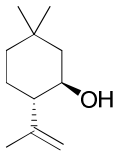
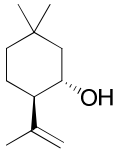
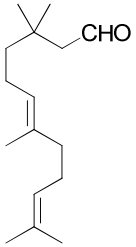
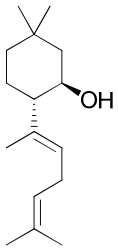
We used a variety of unsaturated aldehydes to obtain cyclization products with the aluminium complex bearing BINOL (**4a**) (Table 2). The reaction with (*S*)-BINOL ((*S*)-**4a**) afforded (+)-5-*trans*-methylisopulegol ((+)-*trans*-**2**) in 90% yield and 90% *ee* (Table 2, entry 2). This result demonstrates that the performance of the catalyst with (*S*)-**4a** was almost same as (*R*)-**4a** (Table 2, entry 1 vs entry 2). The asymmetric cyclization in the presence of (*R*)-**4a** afforded (-)-*trans*-**2** with same performance in large scale. Corresponding optically active *trans*-methylisopulegols ((-)-*trans*-**2**) were obtained with almost same yield and enantioselectivities (Table 2, entries 3 and 4 vs entries 1 and 2).

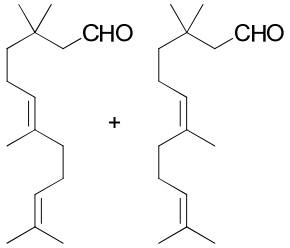
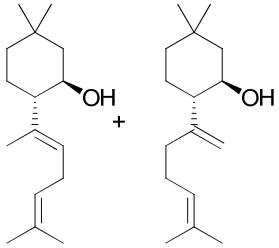
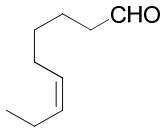
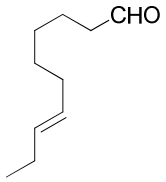
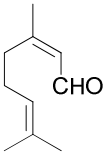
(*E*)-*3*-methyl-2,3-dihydrofarnesal ((*E*)-**5**) provided only (-)-*trans*-**6** in 86% yield with over 99% *de* (Table 2, entry 5). The cyclized product (-)-*trans*-**6** was obtained as exclusively (*E*)-isomer. The enantioselectivity of (-)-*trans*-**6** was over 60% *ee*, significantly lower than the *ee* seen for **2**. The isomeric mixture of (*E/Z*)-3-methyl-2,3-dihydrofarnesal ((*E/Z*)-**5**) was also investigated as an asymmetric cyclization substrate. The reactions of the (*E*/*Z*)-**5** in the presence of (*R*)-**4a** gave (-)-*trans*-**6** and (-)-*trans*-**7** respectively with high product yield (Table 2, entry 6). The diastereoselectivity and enantioselectivity are same as the (-)-*trans*-**6** in the result of (*E*)-**5** reaction. It indicates that (*E*)-**5** and (*Z*)-**5** independently gave the cyclization products (-)-*trans*-**6** and (-)-*trans*-**7** respectively without isomerization. By contrast of the low *ee* of (-)-*trans*-**6**, the enantioselectivity of (-)-*trans*-**7** reached 87% *ee*. The enantioselectivity seen in (-)-*trans*-**6** was lower than that for (-)-*trans*-**7**, indicating that the more bulky carbon chain of (*E*)-**5** hindered the interaction of the substrate with the chiral region of the catalyst. Interestingly, the optical rotation of *trans*-**6** and *trans*-**7** was the opposite of the result for the reaction using BINOL-Zn as well as the reaction of 3-methylcitronellal (**1**).

The reaction of *cis*-6-nonenal ((*Z*)-**9**) was gave no product (Table 2, entry 7). *trans*-7-Decenal ((*E*)-**10**), an aldehyde substrate resulting in a 7-membered ring product, gave complex mixture (Table 2, entry 8). The α,β−unsaturated aldehyde, such as (*Z*)-**12** also gave no product (Table 2, entry 9).

Table 2. Asymmetric cyclization of unsaturated aldehydes by BINOL (4a)-Al catalyst



Entry	Substrate	Product	Yield (%)	Ee (%)[a]
1	 **1**	 (-)-*trans*-**2**	85	89
2[b]		 (+)-*trans*-**2**	90	90
3[c]		(-)-*trans*-**2**	78	88
4[bc]		(+)-*trans*-**2**	84	85
5[e]	 (*E*)-**5**	 (-)-*trans*-**6**	86	61

6[e]	 (*E*/*Z*)-**5** (*E*/*Z* = 62/38)	 (-)-*trans*-**6** + (-)-*trans*-**7**	87 ((-)-*trans*-**6**/ (-)-*trans*-7 = 64/36)[a]	60 ((-)-*trans*-**6**) 87 ((-)-*trans*-7)
7[b]	 (*Z*)-**9**	N.R.	-	-
8[b]	 (*E*)-**10**	Complex mixture	-	-
9[b]	 (*Z*)-**12**	N.R.	-	-

[a]Determined by GC analysis. [b]This reaction was carried out using (*S*)-**4a**. [c]This reaction was carried out in 12 g scale. [d]This reaction was carried out in 10 g scale. [e]This reaction was carried out using 10 mol % of Et_3Al and 18 mol % of (*R*)-**4a**.

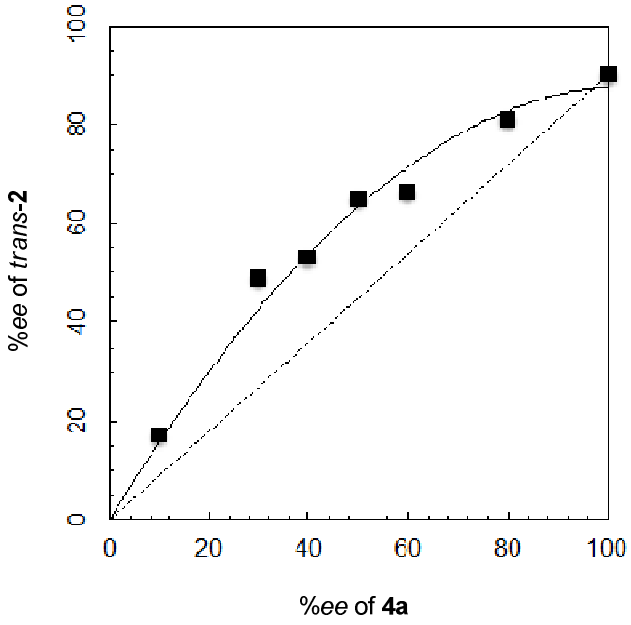


Figure 2. (+)-NLE in asymmetric cyclization in ene reaction by BINOL (4a)-Al.

Asymmetric Amplification

Figure 2 (Table S1, see also Supporting Information) depicts the asymmetric amplification of the reaction of 3-methylcitronellal (**1**). The *ee* value of the products was plotted against the *ee* of the BINOL used, giving a curve above the straight line (positive nonlinear effect, abbreviated as (+)-NLE).[26] This amplification behavior is similar to the glyoxylate-ene reaction when catalysed by the BINOL-Ti complex, which displays a very strong (+)-NLE relationship.[27-29]

This reaction, in the presence of lower *ee* of BINOL, displayed lower conversions in comparison with the conversions for **2**. The asymmetric amplification of the glyoxylate-ene reaction by BINOL-Ti was negatively affected by employing the *meso*-dimer of the catalyst.[27c] Based on this, we assume that the catalysts $[[(R)\text{-BINOL}]_2[(S)\text{-BINOL}]Al_2]_n$ and $[[(R)\text{-BINOL}]\ [(S)\text{-BINOL}]_2Al_2]_n$ exist in the reaction mixture and cause the low reactivity in the cyclization. The combination of BINOL ligands and aluminum is more complicated than for the BINOL-Ti complex. The BINOL/Al ratio in our catalyst is 3/2, which could lead to a variety of association combinations and therefore catalyst forms.[30,31]

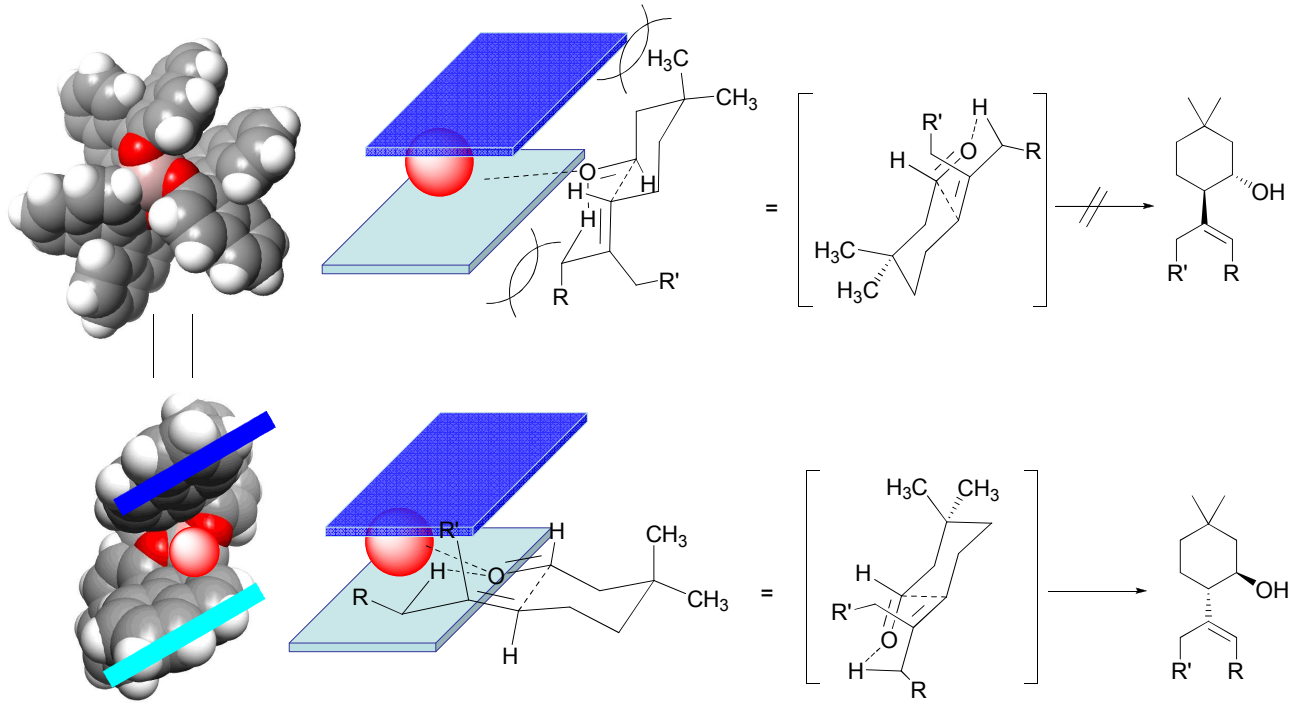


Figure 3. Proposed reaction mechanism of cyclization by (*R*)-4a-Al catalyst.

Reaction Mechanism

The reaction follows an intramolecular ene reaction mechanism catalysed by an aluminum complex as a Lewis acid. [15,16,24] The carbonyl group of 3-methylcitronellal (**1**) is coordinated to an aluminum active site, then a concerted reaction occurs to afford the 6-membered ring, affording 5-methylisopulegol (**2**).

The chiral recognition in these catalysts is a function of the TADDOL type ligands **3** or BINOL type ligands **4**. These complexes have a metal center between two parallel aromatic rings. During the *trans*ition state of the ring-closing ene reaction, the aromatic rings are in close proximity to citronellal, and this narrow space results in the excellent diastereo- and enantioselectivity seen in the reaction.

It is assumed that these aromatic rings are horizontally aligned with respect to each other, so that the edge of the aromatic rings can interact with the 3-methyl group of **1** when the carbonyl group coordinates to the aluminum reaction site. 3-methylcitronellal (**1**) can be fitted between the two parallel aromatic rings of (*R*)-**4a**-Al. The narrow space between the aromatic rings results in the formation of **2** with high enantioselectivity. The narrow spacing of aromatic rings prohibits **1** from forming the *cis*-isomer of **2**.[24]

Proposed intermediate states for the reaction are shown in Figure 3. It is assumed that the dimethyl group in **1** forms a specific interaction confined by the narrowness of the aromatic rings. The dimethyl group and the propan-2-ylidene group in **1** can just fit into the narrow space of the aromatic rings when a carbonyl group of **1** approaches the aluminum reaction site. Thus the *trans*-isomers (-)-*trans*-**2** and (+)-*trans*-**2** were obtained with excellent diastereo- and enantioselectivity. When BINOL is substituted with triphenylsilyl groups (**4b**) or bromine (**4c**), the BINOL ring edges expand horizontally and become more spatially similar, thus affording less chiral recognition. (*R*)-H8-BINOL (**4d**) gives more bulky ring edges on its catalyst. The 3-dimethyl groups of **2** will not fit into the reaction site by the bulky obstacle and afforded far lower selectivity and enantioselectivity of **2**. 1-NaphTADDOL(**3a**)-Al also bears the same type of aromatic rings, consisting of 1-naphtyl groups. These rings are more flexible than those in BINOL-Al and thus afford **2** with lower enantioselectivity.

The reaction of 3-methyl-2,3-dihydrofarnesal (**5**) shows different enantioselectivity between the isomers (*E*)-**5** and (*Z*)-**5**. The (*Z*)-**5** yields *trans*-**7** with higher enantioselectivity than seen in the reaction of (*E*)-**5** to *trans*-**6**, with the differences between the *ee* of *trans*-**6** and *trans*-**7** reaching nearly 30%. It can be reasoned that the long and bulky aliphatic substituent of (*E*)-**5** is in a position to interact with the chiral recognition aromatic rings, whereas this is not the case for (*Z*)-**5**. (*Z*)-**5** can form the same interactions as 3-methylcitronellal (**1**) in the *trans*ition state as there are no bulky substituents around the olefin group in (*Z*)-**5**. Therefore (*Z*)-**5** gave *trans*-**7** with approximately the same enantioselectivity as seen in the 3-methylcitronellal (**1**).

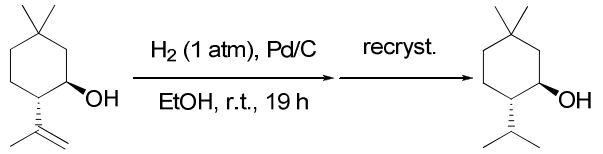
We previously reported the NMR spectra for all the catalysts indicated complex mixtures.[24] Based on this, we predict that the catalysts are associated.[30] (*R*)-BINOL ((*R*)-**4a**)-

Al was analyzed by ESI-MS in order to investigate the detail of the complex. In this result, not only mass spectra of the complex (calcd for $C_{60}H_{36}O_6Al_2$ (M^++Na^+) 929.2035, found 929.2118; see Supporting information), a variety of peaks of mass spectra were analyzed. This results also follows the association of the complex.

In order to increase enantioselectivity, we propose an expansion of the aromatic rings and their substituents to the opposite side of Aluminum metal center in order to keep the recognition space narrow. This will improve the chiral recognition of the substrate's 3-dimethyl group, improving the diastereoselectivity of these catalysts.

Synthesis of (-)-*trans*-5-Methylmenthol

As an application of this asymmetric cyclization, we prepared (-)-*trans*-5-methylmenthol ((-)-*trans*-**13**) from 3-methylcitronellal (**2**) as shown in Scheme 1. After the large scale procedure of synthesis of (-)-*trans*-**2** (Table 2, entry 2), hydrogenation of (-)-*trans*-**2** with Pd/C afforded (-)-*trans*-**13**, which is a novel compound. These menthol analogs could be purified chemoselectivity and enantioselectivity by recrystallization. The *ee* of (-)-*trans*-**13** reached 97%.



Scheme 1. Synthesis of (-)-*trans*-5-methylmenthol ((-)-*trans*-13).

Experimental

Gas liquid chromatography (GC) was performed with a GC-2010AF system (Shimadzu) using DB-WAX (30 m × 0.32 mm × 0.5 μm), IC-1 (30 m × 0.25 mm × 0.25 μm), Chirasil-DEX^{TM} 325 (30 m × 0.25 mm × 0.25 μm) columns. Gas chromatography-mass spectrometry (GC-MS) was performed on a GC-QP2010 system (Shimadzu) using Rtx-1 (30 m × 0.25 mm × 0.25 μm) columns. ^{1}H-NMR spectra were recorded on a Bruker 500 Hz spectrometer and Varian 300 Hz spectrometer. Chloroform-*d* was used as NMR solvent and chemical shifts are reported as δ values in parts per million relative to trimethylsilane (δ = 0). HRMS was performed on a JMS-T100GCV system (FI) or a LCMS-IT-TOF system (ESI) (JOEL). Optical rotations were determined on a JASCO P-1020 digital polarimeter (JASCO). SCIGRESS V2 powered by Fujitsu preceded molecular orbital calculation. Graphic drawings were performed with Excel.

(*Z*)-*trans*-3,7-Dimethylocta-2,6-dienal (neral) ((*Z*)-**12**) was obtained by isolation from citral by rectification (number of the theoretical stages were 60, bath 132 °C, bottom 111–113 °C, top 78–83 °C, press 2.0 mmHg, obtained 603 g from citral 2000 g).

Unsaturated aldehydes **1**,[16,32] (*E/Z*)-**5**,[16,33] (*E*)-**5**,[16,33] **10**[34,35] and ligand (*R*)-**4b**[20] were prepared according to literature procedures.

All other reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., Nacalai Tesque, Inc., Takasago International Corporation, or Strem Chemicals Inc. and used without purification.

General Procedure of Asymmetric Cyclization of 3-Methylcitronellal (1) by Chiral-Al Catalysts (Table 1, Except Entry 10) (Figure 2)

A mixture of ligand **3** or **4** (5 mol % or 9 mol %), triethylaluminum toluene solution (1.0 mol/L, 0.30 mL, 0.297 mmol, 5 mol %), and solvent (3 mL) were added to a 50-mL schlenk tube under a N_2 atmosphere. After stirred at r.t. for over 1 h, the solution was cooled to less than 10 °C. 3-Methylcitrolellal (**1**) (1.00 g, 5.94 mmol) was dropwised slowly below 10 °C and stirred for 19 h. The reaction products were analyzed by GC.

Procedure of Asymmetric Cyclization of 3-Methylcitronellal (1) by Chiral-Zn Catalyst (Table 1, Entry 10)

A mixture of (*R*)-**4a** (5.10 g, 17.8 mmol) and dichloromethane (51 mL) were added to a 200 ml reactor with a dropping funnel under N_2 atmosphere. Diethyl zinc hexane solution (1.0 mol/L, 17.8 mL, 17.8 mmol) was dropwised into the reactor at r.t. Stirring for 3 h, 3-methylcitronellal (**1**) (1.00 g, 5.93 mmol) in dichloromethane (5 mL) was dropwised into the reactor at -78 °C and stirred at room temperature for 19 h. The reaction mixture was poured onto 2M NaOH aq. and extracted with dichrolomethane. The combined organic layer was analysed by GC and chiral-GC and used to determine the structures of (-)-*trans*-**2** and (+)-*trans*-**2** by BINOL-Al reaction.

General Procedure of Asymmetric Cyclization of 3-Methylcitronellal (1) by BINOL-Al Catalyst (Table 2, Entries 1 and 2)

A mixture of chiral BINOL ((*R*)-**4a** or (*S*)-**4a**) (153 mg, 9 mol %), triethylaluminium toluene solution (1.0 mol/L, 0.32 mL, 5 mol %), and dichrolomethane (3 mL) were added to a 50-mL schlenk tube under a N_2 atmosphere. After stirred at r.t. for over 1 h, the solution was cooled to less than 10 °C. 3-Methylcitronellal (**1**) (1.00 g, 5.94 mmol) was dropwised slowly below 10 °C and stirred for 19 h. The reaction products were analyzed by GC. After completion of the reaction, the mixture was quenched with *dil*HCl aq. The mixture was extracted with toluene/brine and dried on $MgSO_4$. After evaporation, the product was isolated by silica-gel column chromatography (heptane/AcOEt = 5/1, r/f = 0.4-0.5);

(-)-(1*R*,2*S*)-5,5-Dimethyl-2-(prop-1-en-2-yl)cyclohexanol ((-)-*trans*-5-methylisopulegol) ((-)-*trans*-2) (Table 2, Entry 1): 853 mg, 5.07 mmol, 85%, 89% *ee*; $[\alpha]^{20}_D$ = -9.4 (*c* 0.25, THF); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.14 (t, 1H, *J* = 11.7 Hz), 1.18-1.28 (m, 1H), 1.28-1.43 (m, 2H), 1.45-1.60 (m, 2H), 1.72 (br, 3H, C*H*$_3$-C=C), 1.74-1.89 (m, 2H), 3.59-3.69 (m, 1H, >C*H*-O), 4.87 (br, 1H, C=C*H*$_2$), 4.90-4.91 (m, 1H, C=C*H*$_2$).

(+)-(1*S*,2*R*)-5,5-Dimethyl-2-(prop-1-en-2-yl)cyclohexanol ((+)-*trans*-5-methylisopulegol) ((+)-*trans*-2) (Table 2, Entry 2):[16] 896 mg, 5.32 mmol, 90%, 90% *ee*; $[\alpha]^{20}_D$ = +7.1 (*c* 0.25, THF); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.14 (t, 1H, *J* = 11.7 Hz), 1.22 (td, 1H, *J* = 13.2, 4.7 Hz), 1.25-1.40 (m, 2H), 1.45-1.59 (m, 2H), 1.74 (m, 3H, C*H*$_3$-C=C), 1.76-1.88 (m, 2H), 3.64 (m, 1H, >C*H*-O), 4.85-4.87 (m, 1H, C=C*H*$_2$), 4.88-4.92 (m, 1H, C=C*H*$_2$).

Large Scale Procedure of Synthesis of (-)-*trans*-2 (Table 2, Entries 2)

A mixture of (*R*)-**4a** (1.63 g, 6.42 mmol, 9 mol %), triethylaluminium toluene solution (1.0 mol/L, 3.6 mL, 5 mol %), and dichloromethane (32 mL) were added to a 200-mL reactor a N_2 atmosphere. After stirred at r.t. for over 1 h, the solution was cooled to less than 10 °C. 3-Methylcitronellal (**1**) (12.0 g, 71.3 mmol) was dropwised slowly below 10 °C and stirred for 19 h. The reaction products were analyzed by GC. After completion of the reaction, the mixture was quenched with *dil*HCl aq. The mixture was extracted with toluene/brine and dried on $MgSO_4$. After evaporation, the residue was purified by distillation (bath 85 °C, top 45-55 °C, 0.3 torr) and the product (-)-*trans*-**2** was obtained as colorless oil: 9.36 g, 55.6 mmol, 78%, 89% *ee*; $[\alpha]^{20}_D$ = -6.6 (*c* 0.64, $CHCl_3$,); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.14 (t, 1H, *J* = 11.7 Hz), 1.22 (td, 1H, *J* = 13.0, 4.6 Hz), 1.26-1.41 (m, 2H), 1.45-1.57 (m, 2H), 1.74 (dd, 3H, *J* = 1.5, 0.9 Hz, C*H*$_3$-C=C), 1.75-1.87 (m, 2H), 3.61-3.66 (m, 1H, >C*H*-O), 4.85-4.86 (m, 1H, C=C*H*$_2$), 4.89-4.91(m, 1H, C=C*H*$_2$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 19.2 (CH_3), 25.1 (CH_3), 26.4 (CH_2), 32.2 (C), 33.0 (CH_3), 38.6 (CH_2), 46.8 (CH_2), 54.8 (CH), 67.6 (CH), 112.8 (CH_2), 146.7 (C); HRMS (FI) calcd for $C_{11}H_{20}O$ (M^+) 168.1519, found 168.1514; IR (neat) 3404m, 2956s, 2928s, 2865s, 2847m, 1645m, 1455m, 1364m, 1051m, 1027m, 885m.

Large Scale Procedure of Synthesis of (+)-*trans*-2 (Table 2, Entry 4)

(+)-trans-5-methylisopulegol ((+)-*trans*-**2**) was synthesized in the same manner as the synthesis of (-)-*trans*-**2** using (*S*)-BINOL ((*S*)-**4a**) in 10 g scale: 8.38 g, 49.8 mmol, 84%, 85% *ee*; $[\alpha]^{20}_D$ = +5.8 (*c* 0.30, $CHCl_3$,); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.14 (t, 1H, *J* = 11.7 Hz), 1.22 (td, 1H, *J* = 13.0, 4.7 Hz), 1.25-1.42 (m, 2H), 1.45-1.59 (m, 2H), 1.74 (br, 3H, C*H*$_3$-C=C), 1.76-1.88 (m, 2H), 3.61-3.66 (m, 1H, >C*H*-O), 4.85-4.87 (m, 1H, C=C*H*$_2$), 4.89-4.92 (m, 1H, C=C*H*$_2$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 19.3 (CH_3), 25.1 (CH_3), 26.4 (CH_2), 32.2 (C), 33.0 (CH_3), 38.5 (CH_2), 46.8 (CH_2), 54.8 (CH), 67.6 (CH), 112.8 (CH_2), 146.6 (C).

Procedure of Asymmetric Cyclization of (*E*)-3-Methyl-2,3-dihydrofarnesal ((*E*)-5) by BINOL-Al Catalyst (Table 2, Entry 5)

A mixture of (*R*)-BINOL ((*R*)-**4a**) (59 mg, 18 mol %), triethylaluminium toluene solution (1.0 mol/L, 0.12 mL, 10 mol %), and dichrolomethane (3 mL) were added to a 50-mL schlenk tube under a N_2 atmosphere. After stirred at r.t. for over 1 h, the solution was cooled to less than 10 °C. (*E*)-3-Methyl-2,3-dihydrofarnesal ((*E*)-**5**) (150 mg, 0.635 mmol) was dropwised slowly below 10 °C and stirred for 19 h. The reaction products were analyzed by GC. After completion of the reaction, the mixture was quenched with *dil*HCl aq. The mixture was extracted with toluene/brine and dried on $MgSO_4$. After evaporation, the product was isolated by preparative TLC (heptane/AcOEt = 5/1, r/f = 0.4)**:** 129 mg, 0.545 mmol, 86%, 61% *ee*; $[\alpha]^{20}_D$ = -5.0 (*c* 0.24, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.94 (d, 6H, *J* = 10.0 Hz, C*H*$_3$-C-C*H*$_3$), 1.07 (t, 1H, *J* = 12.0 Hz), 1.20 (td, 1H, *J* = 13.0, 5.3 Hz), 1.37 (dq, 1H, *J* = 13.2, 2.9 Hz), 1.48-1.53 (m, 1H), 1.60 (s, 3H), 1.62 (d, 3H, *J* = 4.2 Hz), 1.69 (br, 3H), 1.72-2.20 (m, 4H), 2.74 (t, 2H, *J* = 7.1 Hz, =CH-C*H*$_2$-CH=), 3.58-3.65 (m, 1H, C*H*-OH), 5.08-5.12 (m, 1H, C=C*H*), 5.30 (td, 1H, *J* = 7.0, 1.2 Hz, C=C*H*); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 12.8 (CH_3), 17.7 (CH_3), 25.1 (CH_3), 25.7 (CH_3), 26.1 (CH_2), 26.9 (CH_2), 32.1 (C), 33.0 (CH_3), 38.6 (CH_2), 46.7 (CH_2), 56.5 (CH), 67.2 (CH), 122.8 (CH), 127.0 (CH), 131.9 (C), 135.3 (C); HRMS (FI) calcd for $C_{16}H_{28}O$ (M^+) 236.2140, found 236.2101; IR (neat) 3435m, 2951s, 2926s, 1452s, 1384m, 1364m, 1256w, 1139m, 1046m, 921w.

Procedure of Asymmetric Cyclization of (*E*/*Z*)-3-Methyl-2,3-dihydrofarnesal ((*E*/*Z*)-5) by BINOL-Al Catalyst (Table 2, Entry 6)

A mixture of (*R*)-BINOL ((*R*)-**4a**) (117 mg, 18 mol %), triethylaluminium toluene solution (1.0 mol/L, 0.23 mL, 10 mol %), and dichrolomethane (3 mL) were added to a 50-mL schlenk tube under a N_2 atmosphere. After stirred at r.t. for over 1 h, the solution was cooled to less than 10 °C. (*E*/*Z*)-3-Methyl-2,3-dihydrofarnesal ((*E*/*Z*)-**5**) (300 mg, 1.14 mmol) was dropwised slowly below 10 °C and stirred for 19 h. The reaction products were analyzed by GC. After completion of the reaction, the mixture was quenched with *dil*HCl aq. The mixture was extracted with toluene/brine and dried on $MgSO_4$. After evaporation, the product was isolated by silica-gel column chromatography (heptane/AcOEt = 5/1, r/f = 0.4)**:** 261 mg, 0.992 mmol (mixture of (-)-*trans*-**6** and (-)-*trans*-**7**), 86% (total isolated yield), 61% *ee* ((-)-*trans*-**6**) and 87% *ee* ((-)-*trans*-**7**); $[\alpha]^{20}_D$ = -11.3 (*c* 0.20, $CHCl_3$, mixture of (-)-*trans*-**6** and (-)-*trans*-7); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.935 (s, 3H, C*H*$_3$-C-C*H*$_3$), 0.944 (s, 3H, C*H*$_3$-C-C*H*$_3$), 1.10-1.52 (m, 4H), 1.61 (s, 3H, C*H*$_3$-C=), 1.69 (s, 3H, C*H*$_3$-C=), 1.72-2.20 (m, 4H), 2.35 (s, 3H, =C-C*H*$_3$), 2.74 (t, 2H, *J* = 6.9 Hz, =CH-C*H*$_2$-CH=), 3.61 (dt, 1H, *J* = 10.8, 4.4 Hz, C*H*-OH), 5.05-5.12 (m, 1H, C=C*H*), 5.30 (br, 1H, C=C*H*) (major); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.955 (s, 3H, C*H*$_3$-C-C*H*$_3$), 0.964 (s, 3H, C*H*$_3$-C-C*H*$_3$), 1.09-1.52 (m, 6H), 1.62 (s, 3H, C*H*$_3$-C=), 1.69 (s, 3H, C*H*$_3$-C=), 1.71-1.85 (m, 4H), 2.03-2.20 (m, 2H), 3.64-3.73 (m, 1H, C*H*-OH), 4.91 (br, 2H, C=C*H*$_2$), 5.12 (br, 1H, C=C*H*) (minor); ^{13}C-NMR (125 MHz, $CDCl_3$): 12.8 (CH_3), 17.8 (CH_3), 25.1 (CH_3), 25.7 (CH_3), 26.1 (CH_2), 26.9 (CH_2), 32.2 (C), 33.1 (CH_3), 38.6 (CH_2), 46.7 (CH_2), 56.5 (CH), 67.2 (CH), 122.8 (CH), 127.0 (CH), 131.9 (C), 135.3 (C) (major); ^{13}C-NMR (125 MHz, $CDCl_3$): 17.8 (CH_3), 25.2 (CH_3), 25.7 (CH_3), 26.5 (CH_2), 27.3 (CH_2), 32.1 (C), 33.0 (CH_3), 33.7 (CH_2), 38.8 (CH_2), 46.8 (CH_2), 54.3 (CH), 68.4 (CH), 110.6 (CH_2), 124.0 (CH), 132.0 (C), 150.8 (C) (minor); HRMS (FI) calcd for $C_{16}H_{28}O$ (M^+) 236.2140, found 236.2116; IR (neat) 3396s, 2920s, 1716m, 1455s, 1386m, 1365s, 1171m, 1049s, 923m (mixture of (-)-*trans*-**6** and (-)-*trans*-**7**).

Synthesis of (-)-*trans*-2-Isopropyl-5,5-dimethylcyclohexanol ((-)-*trans*-5-Methylmenthol) ((-)-*trans*-13) (Scheme 1)

A mixture of (-)-*trans*-**2** (6.32 g, 37.5 mmol), ethanol (19 mL) and Pd/C(10 wt.%) (316 mg, 5 wt.% of (-)-*trans*-**2**) were added into 100 mL reactor with condenser. The solution was stirred under H_2 atmosphere at r.t. for 19 h. the reaction mixture was filtered by celite and concentrated. Crystallization with hexane and ethanol gave (-)-*trans*-5-methylmenthol ((-)-*trans*-**13**) as white solid: 3.29 g, 19.3 mmol, 52%, 97% *ee*; $[\alpha]^{20}_D$ = -36.7 (*c* 0.05, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.84 (d, 3H, *J* = 7.0 Hz), 0.89 (s, 3H, >C-C*H*$_3$), 0.93-0.95 (m, 6H), 1.04-1.21 (m, 5H), 1.37 (dt, 1H, *J* = 9.6, 2.6 Hz), 1.46-1.50 (m, 1H), 1.68-1.73 (m, 1H), 2.12-2.21 (m, 1H), 3.57 (sep, 1H, *J* = 4.7 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 16.2 (CH_3), 19.8 (CH_2), 21.0 (CH_3), 25.1 (CH_3), 25.9 (CH), 32.2 (C), 32.9 (CH_3), 38.7 (CH_2), 49.1 (CH_2), 50.9 (CH), 68.8 (CH); HRMS (FI) calcd for $C_{11}H_{22}O$ (M^+) 170.1671, found 170.1671; IR (neat) 3265s,

2957s, 2870s, 2843s, 1466m, 1453m, 1383m, 1363m, 1348m, 1215m, 1038s.

Conclusions

We utilized aluminium complexes with chiral ligands to asymmetric cyclization. 3-methylcitronellal (**1**) afforded optically active *trans*-5-menthylisopulegols (*trans*-**2**) with BINOL-Al catalyst in excellent yield, diastereoselectivity and up to 90% *ee*. Asymmetric amplification of 3-methylcitronellal (**1**) also occurred in the presence of a variety of *ee* of BINOL. As a utility of asymmetric cyclization, optically active (-)-5-*trans*-methylmenthol ((-)-*trans*-**13**) were synthesized with BINOL-Al catalysts. In the future, we investigate utilities of optically active *trans*-5- methylmenthols.

Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/c000000x/

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