

Highly Enantio- and *s-trans* C=C Bond Selective Catalytic Hydrogenation of Cyclic Enones: Alternative Synthesis of (–)-Menthol

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Abstract: A highly enantioselective catalytic hydrogenation of cyclic enones was achieved by using the combination of a cationic Rh^I complex, (S)-5,5'-bis{di(3,5-di-*tert*-butyl-4-methoxyphenylphosphino)}-4,4'-bi-1,3-benzodioxole (DTBM-SEGPBOS), and (CH₂CH₂PPh₃Br)₂. The presence of an *s-cis* C=C bond isopropylidene moiety on the cyclic enone influenced the enantioselectivity of the hydrogenation. Thus, the hydrogenation of 3-alkyl-6-

isopropylidene-2-cyclohexen-1-one, which contains both *s-cis* and *s-trans* enones, proceeded in excellent enantioselectivity (up to 98 % *ee*). To obtain high enantio- and *s-trans* selectivities, the addition of a halogen source to the cationic Rh complex was the essential step. With the key step of the *s-trans*

selective asymmetric hydrogenation of piperitenone, we demonstrated a new synthetic method for optically pure (–)-menthol via three atom-economical hydrogenations. Moreover, we found that the complete *s-trans* and *s-cis* C=C bond selective reactions were also realized by the proper choice of both the chiral ligands and halides.

Keywords: asymmetric catalysis • enones • hydrogenation • rhodium

Introduction

Enantioselective hydrogenation is one of the most powerful and practical methods in asymmetric catalysis.^[1] A variety of chiral building blocks is synthesized by using chiral Rh^I or Ru^{II} complexes—some of them are used in the industrial production of enantiomerically-enriched compounds.^[1,2] Enantioselective hydrogenation of the enone C=C bond, however, has not been well studied, despite the usefulness of the resulting chiral ketones, and thus remains a challenging transformation. Toward this aim, efficient enantioselective hydrosilylations catalyzed by copper complexes were reported by Buchwald et al.^[3] and Lipshutz et al.^[4] In terms of atom-economy^[5] and environmental concerns, however, these catalyses still have much room for improvement, as

they require not only more than stoichiometric amounts of polymethylhydrosiloxane, but also more than stoichiometric amounts of reagents to cleave the Si–O bond of the enol silyl ether intermediate, which causes the formation of more than stoichiometric amounts of unwanted silicon waste. Thus, the development of an efficient catalytic asymmetric hydrogenation of enones is highly desirable. Successful results of catalytic asymmetric hydrogenation of enones, however, are limited to the following three Ru-catalyzed reactions. Takaya et al. reported the asymmetric hydrogenation of the *s-cis* (exocyclic) C=C bond of cyclopentanone catalyzed by an Ru-BINAP complex, providing α -substituted cyclopentanone in 98 % *ee* (one example).^[6] Simonneaux et al. reported that the [HRuCl(tbpc)₂] (TBPC = *trans*-1,2-bis(diphenylphosphinomethyl)cyclobutane) catalyzed the hydrogenation of *s-trans* (endocyclic) enones to afford chiral ketones in up to 62 % *ee* (four examples).^[7] Genêt et al. reported a practical synthesis of (+)-*cis*-methyl dihydrojasmonate (88 % *ee*) by catalytic hydrogenation using the Ru-JOSIPHOS complex (one example).^[8] The lower enantioselectivities of the *s-trans* enones might be due to the unfavorable *s-trans* coordination of cyclic enone to transition metals. These initial results clearly demonstrate the need for improved substrate generality, enantioselectivity, and catalyst activity for practical production of highly optically active chiral ketones. Herein, we report an enantioselective

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lective catalytic hydrogenation of various cyclic enones. The presence of an *s-cis* C=C bond isopropylidene moiety on the cyclic enone influenced the enantioselection of the hydrogenation. Thus, the reaction of 3-alkyl-6-isopropylidene-2-cyclohexen-1-one (**1**), which contains both *s-cis* and *s-trans* enones, proceeded in excellent enantioselectivity (up to 98% *ee*). Hydrogenation of **1** afforded 26 products via saturation of C=C and/or C=O double bonds [Eq. (1)].^[9] To obtain the C2–C3 saturated product **2** out of all the possible products in a highly selective manner, the addition of a halogen source to the cationic Rh complex was key. Using this asymmetric catalysis, piperitenone (**1a**; R=Me) was successfully converted to (+)-pulegone (**2a**; R=Me) in 98% *ee* with extremely high catalyst turnover (S/C 50000), allowing for an atom-economical synthesis of (–)-menthol by successive highly diastereoselective catalytic hydrogenations of (+)-**2a**. Moreover, complete *s-trans* (**1**→**2**) and *s-cis* (**1**→**3**) C=C bond selective reactions were realized by the proper choice of both the chiral ligands and halides.

Results and Discussion

Catalyst discovery by using cationic Rh complexes: Despite the usefulness of optically active **2** as a chiral source, only a few catalysts that can selectively transform **1** to **2** have been reported. When a cationic Rh^I complex bearing chiral monodentate phosphine ligands was used, the highest enantioselectivity (**2a**, 38% *ee*) was obtained with moderate *s-trans* selectivity (**2a/3a/4a** 61:30:9).^[10] Because (+)-pulegone (**2a**) is an attractive intermediate for the synthesis of (–)-menthol, we first performed catalyst screening for the *s-trans* C=C bond selective hydrogenation of piperitenone (**1a**). To obtain high enantioselectivity, we used chiral diphosphine ligands, though diphosphine ligands are reported to dramatically de-

crease both enantio- and *s-trans* selectivities.^[10] Our catalyst screening for the hydrogenation of **1a** is summarized in Table 1. The catalytic activity of cationic Rh^I-diphosphine complexes in EtOAc^[11] was very high. After 18 h treatment under the conditions shown in Table 1, both C=C bonds of **1a** were saturated to give a diastereomixture of **4a** (R=Me; menthone/isomenthone ca. 4:1) as the sole detectable products (entries 1–3). Although shortening the reaction time partially prevented this over-reaction, in contrast to the pre-

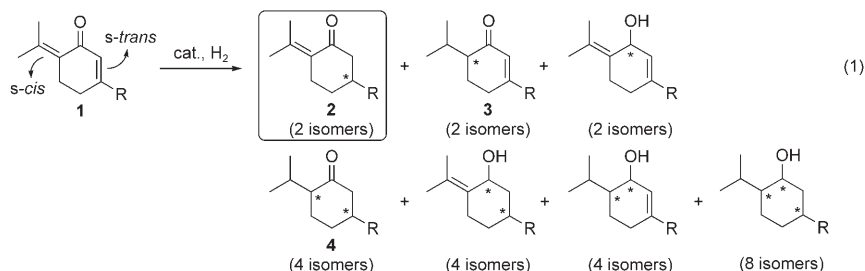
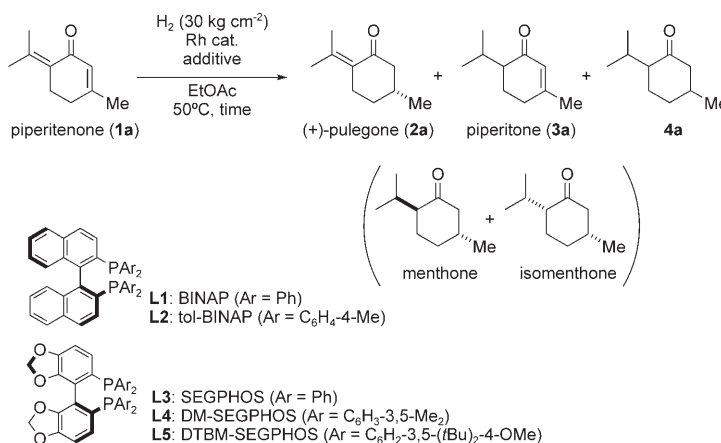


Table 1. Catalytic asymmetric hydrogenation of piperitenone (**1a**) by using cationic Rh^I-(*S*)-diphosphine complexes.



Entry	Catalyst	S/C ^[a]	<i>t</i> [h]	Conv. ^[b] [%]	Selectivity ^[c] 2a/3a/4a	<i>ee</i> 2a ^[d] [%]
1 ^[e]	[Rh(cod) ₂]OTf + L1	100	18	> 99	–:–: > 99	–
2 ^[e]	[Rh(cod) ₂]OTf + L2	100	18	> 99	–:–: > 99	–
3 ^[e]	[Rh(cod) ₂]OTf + L3	100	18	> 99	–:–: > 99	–
4	[Rh(cod)(L1)]BF ₄	100	1	91	4:83:13	10 ^[f]
5	[Rh(cod)(L1)]BF ₄	100	3	> 99	1:76:23	–
6	[Rh(cod)(L3)]BF ₄	100	3	> 99	–:80:20	–
7	[Rh(cod)(L5)]BF ₄	100	1	44	11:79:10	38
8	[Rh(cod)(L5)]BF ₄	100	3	> 99	–:14:86	–
9 ^[g]	[Rh(cod) ₂]OTf + L5 + Et ₄ NCl	1000	18	97	70:4:12	96
10 ^[g]	[Rh(cod) ₂]OTf + L5 + Et ₃ NBnCl	1000	18	89	79:4:7	96
11 ^[g]	[Rh(cod) ₂]OTf + L5 + HexPPh ₃ Br	1000	18	83	72:7:7	98
12 ^[g]	[Rh(cod) ₂]OTf + L5 + HexP[C ₆ H ₂ -2,4,6-(OMe) ₃] ₃ Br	1000	18	99	68:5:12	97
13 ^[g]	[Rh(cod) ₂]OTf + L5 + (CH ₂ CH ₂ PPh ₃) ₂	1000	18	97	77:5:9	98

[a] Substrate catalyst ratio. [b] Conversion yield based on consumed starting material was determined by GC analysis. [c] Selectivity was determined by GC analysis. [d] The *ee* of **2a** was determined by chiral GC analysis. The absolute configuration of **2a** was determined by comparing the measured optical rotations with the reported one. [e] Rh/ligand 1:1. [f] (–)-Pulegone (**2a**) was obtained. [g] Rh/ligand/additive 1:1:1.

vious results using cationic Rh^I complexes bearing monodentate phosphine ligands as described above,^[10] cationic Rh^I-diphosphine complexes showed *s-cis* selectivity to afford piperitone (**3a**; R=Me) as a major product (entries 4–7) and a prolonged reaction time resulted in over-reaction (entry 8). Compound **3a** was racemic due to rapid epimerization of the α -stereocenter of the ketone. As compared with BINAP (**L1**) (entry 4), (*S*)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenylphosphino))-4,4'-bi-1,3-benzodioxole (DTBM-SEGPHOS, **L5**)^[12] showed higher enantioselectivity and slightly better *s-trans* selectivity (entry 7). Assuming that soft counteranions would appropriately adjust the reactivity,^[13] we next examined the effect of adding various halogen sources using DTBM-SEGPHOS as a chiral ligand. To our surprise, we observed drastic halogen effects. The addition of halogen sources to the cationic Rh complex reversed the selectivity to afford **2a** as a major product with high enantioselectivity (96–98% *ee*). Ammonium salts and phosphonium salts gave better selectivity and reproducibility than inorganic salts. Among the various halogen sources examined, (CH₂CH₂PPh₃Br)₂ was the best (entry 13).

As the second stage of the catalyst discovery, we further examined effects of a chiral diphosphine ligand on catalytic asymmetric hydrogenation by [Rh(cod)₂]OTf in the presence of (CH₂CH₂PPh₃Br)₂ (Table 2). DM-SEGPHOS (**L4**) (entries 4 and 5) and DTBM-SEGPHOS (**L5**) (entry 6) had significantly positive effects on catalyst activity as compared with BINAP (**L1**), tol-BINAP (**L2**), and SEGPHOS (**L3**), suggesting that the narrower dihedral angle in the chiral backbone and bulkier substituent on diarylphosphine moieties induce higher catalyst activity. In particular, when **L5** was used as a chiral ligand, the reaction completed within 1 h (S/C 100) (entry 6). When [Rh(cod)₂]BF₄ or [Rh(cod)-(**L5**)]BF₄ (entry 7) was used as an Rh source, almost the same result was obtained, while acetonitrile complexes, such as [Rh(cod)(MeCN)]BF₄, had lower reactivity and lower *s-trans* selectivity. Under the same conditions as entry 7, a high substrate catalyst ratio (S/C 20000) was realized with higher enantioselectivity (98% *ee*, entry 8). The reaction on a 2-mol scale (S/C 50000) also proceeded with similar efficiency (entry 9) and pure (+)-**2a** was isolated in 82% yield by distillation (70–75°C, 5 mm Hg).

Substrate scope: We then investigated the scope and limitations of different substrates. In the presence of 1 mol% of

Table 2. Ligand effects on catalytic asymmetric hydrogenation of piperitenone (**1a**) by using cationic Rh complexes with bromide source.

Entry	Ligand	S/C ^[a]	<i>t</i> [h]	Conv. ^[b] [%]	Selectivity ^[c] 2a/3a/4a	<i>ee</i> 2a ^[d] [%]
1	(<i>S</i>)-BINAP (L1)	100	3	26	85:12:3	94
2	(<i>S</i>)-tol-BINAP (L2)	100	3	57	91:6:3	96
3	(<i>S</i>)-SEGPHOS (L3)	100	3	56	92:5:3	91
4	(<i>S</i>)-DM-SEGPHOS (L4)	100	3	92	71:3:26	94
5	(<i>S</i>)-DM-SEGPHOS (L4)	100	1	15	43:31:26	81
6	(<i>S</i>)-DTBM-SEGPHOS (L5)	100	1	99	86:3:11	97
7 ^[e]	(<i>S</i>)-DTBM-SEGPHOS (L5)	100	1	> 99	88:2:10	97
8 ^[e]	(<i>S</i>)-DTBM-SEGPHOS (L5)	20000	18	98	85:3:6 ^[f]	98
9 ^[e,g]	(<i>S</i>)-DTBM-SEGPHOS (L5)	50000	47	98	87:2:5 ^[f]	98

[a] Substrate catalyst ratio. [b] Conversion yield based on consumed starting material was determined by GC analysis. [c] Selectivity was determined by GC analysis. [d] The *ee* of **2a** was determined by chiral GC analysis. The absolute configuration of **2a** was determined by comparing the measured optical rotations with the reported one. [e] [Rh(cod)(**L5**)]BF₄ was used as a catalyst instead of the combination of [Rh(cod)₂]OTf and **L5**. [f] Cyclohexanol derivatives were also observed. [g] 2-mol scale.

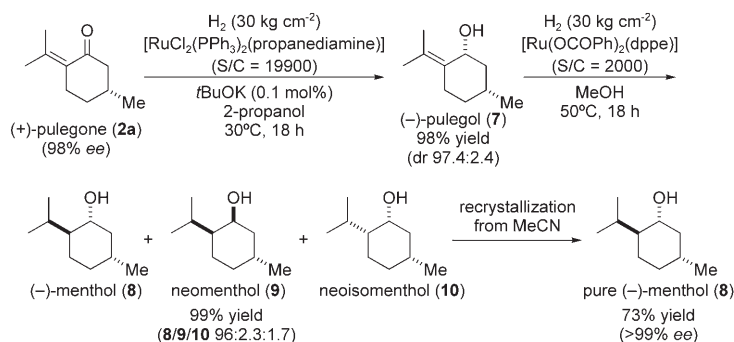
the best catalyst, [Rh(cod)₂]OTf/**L5**/(CH₂CH₂PPh₃Br)₂, the hydrogenation of β -alkyl substituted cyclic enones **5a–d** proceeded efficiently to afford the corresponding ketones **6a–d** in up to 88% *ee* (Table 3, entries 1–4), which is the same level as the highest enantioselectivity of catalytic hydrogenation of cyclic enone.^[8] The introduction of a sterically congested substituent (R = *i*Pr, entry 4) at the β -position did not have negative effects on either reactivity (99% yield) or selectivity (85% *ee*). On the other hand, the reaction of β -phenyl substituted cyclic enone **5e** proceeded sluggishly and a mixture of **6e** and an over reduction product, 3-phenyl-2-cyclohexanol, was obtained, though the enantiomeric excess of **6e** was quite high (entry 5). The addition of a bromide source was essential for the hydrogenation of simple cyclic enones **5** as well. In the absence of a bromide source, the hydrogenation of **5** proceeded in lower yield with lower enantioselectivity. Next, to determine the effect of the isopropylidene moiety on cyclic enone, we performed the reaction using several 3-alkyl-6-isopropylidene-2-cyclohexen-1-ones **1a–c** as substrates (entries 6–8). In all cases, catalytic hydrogenation proceeded smoothly with high enantio- and *s-trans* selectivities. As compared with the results using simple β -substituted cyclic enones **5**, the obtained enantioselectivities using **1** were markedly improved (97–98% *ee*), indicating the importance of the isopropylidene moiety in the enantioface selection. Coupled with the fact that the isopropylidene moiety of **2** was easily removed via a retro-aldol reaction to give the corresponding β -substituted ketone **6**,^[14] a variety of highly optically active 3-substituted-cyclic ketones can be synthesized using this catalytic asymmetric hydrogenation of cyclic enones. To the best of our knowledge, this is the first example of a highly enantioselective catalytic hydrogenation of a C=C bond of a cyclic enone with substrate generality.

Table 3. Catalytic asymmetric hydrogenation of various cyclic enones.

Entry	Substrate	<i>t</i> [h]	Conv. ^[a] [%]	Selectivity ^[b] 2/3/4	<i>ee</i> 6 ^[c] or 2 ^[d] [%]
1	R = Me (5a)	1.5	> 99	–	88
2	R = Et (5b)	3	> 99	–	83
3	R = Pr (5c)	3	> 99	–	85
4	R = <i>i</i> Pr (5d)	3	99	–	85
5	R = Ph (5e)	6	48	28 ^[e] :72 ^[f]	96
6	R = Me (1a)	1	99	86:3:11	97
7	R = Et (1b)	1	99	84:1:15	98
8	R = Pr (1c)	1	99	82:5:13	98

[a] Conversion yield based on consumed starting material was determined by GC analysis. [b] Selectivity was determined by GC analysis. [c] The *ee* of **6** was determined by chiral LC analysis after conversion to the corresponding acetal compound. [d] The *ee* of **2** was determined by chiral GC analysis. [e] Selectivity of **6e**. [f] Selectivity of 3-phenyl-1-cyclohexanol.

Synthetic application: With the new synthetic method of highly optically active ketones at hand, we next undertook transformation of (+)-pulegone (**2a**) to (–)-menthol (**8**) (Scheme 1). (–)-Menthol (**8**) is a major constituent of pep-



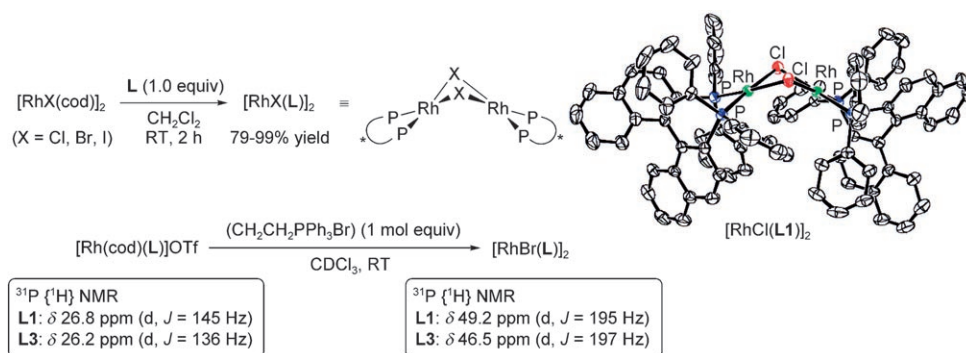
Scheme 1. Highly atom-economical synthesis of (–)-menthol (**8**) by successive catalytic hydrogenations of (+)-pulegone (**2a**).

permint and other mint oils and is widely used in confections, perfume, liqueurs, cough drops, cigarettes, toothpaste, and nasal inhalers.^[15] In industrial production, (–)-**8** was synthesized from β-pinene via catalytic asymmetric isomerization of geranylamine to the corresponding enamine as a key step.^[1,2,16] Although this process is fairly efficient and practical, the development of an alternative efficient process for the production of a constant supply of this mass product (3500 tons per year)^[15] is still in high demand. Thus, an alternative, atom-economical approach to (–)-**8** is presented in Scheme 1. Our synthesis was accomplished by three succes-

sive catalytic hydrogenations, including the first enantioselective hydrogenation described above. To prevent epimerization of the α'-stereocenter of the ketone as described above, the ketone in pulegone (**2a**) was hydrogenated prior to hydrogenation of the isopropylidene moiety. Thus, the second catalytic hydrogenation using an RuCl₂(PPh₃)₂(propanediamine) complex^[17,18] selectively saturated the C=O bond of **2a** in a highly diastereoselective manner to afford (–)-pulegol (**7**) (98% yield, dr: 97.4:2.6). The diastereomixture of **7** was hydrogenated using an Ru(OCOPh)₂(dppe) complex^[19,20] to afford (–)-menthol (**8**) together with small amounts of neomenthol (**9**) and neoisomenthol (**10**) (99% yield, **8/9/10** 96:2.3:1.7). Finally, optically

and chemically pure (–)-menthol (**8**) was obtained in 73% yield by recrystallization of the mixture. Based on the high catalyst turnover, high atom-economy, and ease of scale-up, this process is a potential industrial process for producing (–)-**8**, and demonstrates the efficiency of homogeneous catalytic hydrogenation.^[1]

Catalyst discovery using neutral Rh complexes: The addition of a bromide to a cationic Rh complex might form a neutral dimeric Rh–phosphine complex. To investigate the formation of neutral Rh complexes under the conditions shown in Table 2, we first synthesized various halogen-bridged dimeric Rh–phosphine complexes [RhX(L)]₂ (X = Cl, Br, I). After mixing [RhX(cod)]₂ and chiral diphosphine ligand (*S*)-BINAP (**L1**), (*S*)-tol-BINAP (**L2**), and (*S*)-SEGPHOS (**L3**) in CH₂Cl₂, the color of the solution immediately turned deep red. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure and the obtained residue was washed with hexane to afford [RhX(L)]₂ in good yield (77–99% yield) as a deep red solid. The syntheses of [RhX(L4)]₂ and [RhX(L5)]₂ complexes were unsuccessful due to the high steric hindrance of DM-SEGPHOS (**L4**) and DTBM-SEGPHOS (**L5**). The structure of [RhCl(L1)]₂ was determined by X-ray crystallographic analysis (Scheme 2), and was identical to the reported data.^[21] The addition of (CH₂CH₂PPh₃Br)₂ to a [Rh(cod)(L1)]OTf complex changed the chemical shift of ³¹P{¹H} NMR from δ 26.8 (d, *J* = 145 Hz) to δ 49.2 (d, *J* = 195 Hz). The latter signal was identical to that of the [RhBr(L1)]₂ complex. Similarly, the addition of (CH₂CH₂PPh₃Br)₂ to the [Rh(cod)(L3)]OTf complex moved the chemical shift of ³¹P{¹H} NMR from δ 26.2 ppm (d, *J* =



Scheme 2. Preparation of halogen-bridged dimeric Rh-phosphine complexes $[RhX(L)]_2$.

136 Hz) to δ 46.5 ppm (d, $J = 197$ Hz), which was identical to that of the $[RhBr(L3)]_2$ complex.

It is likely that the neutral dimeric Rh-phosphine complex $[RhX(L)]_2$ acts as a stable pre-catalyst and a monomeric complex might act as the active species. Thus, we next examined the use of neutral halogen-bridged Rh complexes as catalysts using **1a** as a representative substrate. The neutral complex $[RhBr(L1)]_2$ showed comparable selectivity (Table 4, entry 2) to the combination of $[Rh(cod)_2]OTf$, **L1**,

while maintaining high selectivity. In the presence of the Rh-SEGPHOS complex $[RhCl(L3)]_2$ or $[RhBr(L3)]_2$, the reaction proceeded with quite low selectivity (entries 10 and 11). In sharp contrast with those results, iodo complex $[RhI(L3)]_2$ selectively saturated only the *s-cis* C=C bond to afford piperitone (**3a**) as the sole product (entry 12). It is noteworthy that the complete *s-trans* (entry 9) and *s-cis* (entry 12) C=C bond selective reactions were realized by the proper choice of both the chiral ligands and halides.^[12]

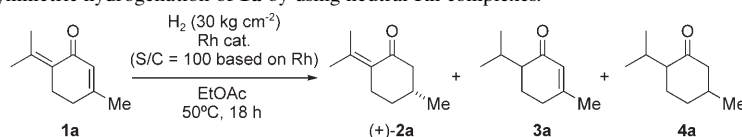
Having obtained surprising results using Rh-SEGPHOS iodo complex $[RhI(L3)]_2$, we further examined ligand effects of the combination of $[Rh(cod)_2]OTf$, chiral ligand **L**, and iodide source $EtPPh_3I$. In the same manner as the $[RhI(L3)]_2$ complex (entry 12), the catalyst in situ prepared from $[Rh(cod)_2]OTf$, SEGPHOS (**L3**), and $EtPPh_3I$ also selectively saturated the *s-cis* C=C bond, suggesting the formation of similar active species, presumably neutral $RhI(L3)$ complex (entry 13). Unlike SEGPHOS ligand (**L3**), the reaction using DTBM-SEGPHOS (**L5**) had quite high *s-trans* selectivity, even in the presence of an iodide source (entry 14).

Conclusion

We developed a highly enantioselective catalytic hydrogenation of cyclic enones promoted by the combination of a cationic Rh^I complex, DTBM-SEGPHOS, and $(CH_2CH_2PPh_3)_2$ with substrate generality. The presence of an *s-cis* C=C bond isopropylidene moiety on cyclic enone influenced the enantioselection of the hydrogenation. Thus, the reaction of 3-alkyl-6-isopropylidene-2-cy-

and $(CH_2CH_2PPh_3)_2$ (Table 2, entry 1), and $[RhI(L1)]_2$ improved both enantio- and *s-trans* selectivities, though the reactivity was decreased (entry 3). This low reactivity was slightly improved by changing the solvent from EtOAc to CH_2Cl_2 (entry 6) and greatly improved by changing the chiral ligand from BINAP (**L1**) to tol-BINAP (**L2**) (entry 9),

Table 4. Asymmetric hydrogenation of **1a** by using neutral Rh complexes.



Entry	Catalyst	Solvent	Conv. ^[a] [%]	Selectivity ^[b] 2a/3a/4a	ee 2a ^[c] [%]
1	$[RhCl(L1)]_2$	EtOAc	92	84:3:13	81
2	$[RhBr(L1)]_2$	EtOAc	96	84:3:13	87
3	$[RhI(L1)]_2$	EtOAc	46	91:5:4	98
4	$[RhCl(L1)]_2$	CH_2Cl_2	90	90:3:7	90
5	$[RhBr(L1)]_2$	CH_2Cl_2	96	96:2:2	96
6	$[RhI(L1)]_2$	CH_2Cl_2	56	96:3:1	97
7	$[RhCl(L2)]_2$	CH_2Cl_2	99	94:-:6	94
8	$[RhBr(L2)]_2$	CH_2Cl_2	> 99	92:-:8	97
9	$[RhI(L2)]_2$	CH_2Cl_2	96	98:-:2	97
10	$[RhCl(L3)]_2$	CH_2Cl_2	69	10:15:75	–
11	$[RhBr(L3)]_2$	CH_2Cl_2	> 99	39:3:58	–
12	$[RhI(L3)]_2$	CH_2Cl_2	> 99	–: > 99:–	–
13 ^[d]	$[Rh(cod)_2]OTf + L3 + EtPPh_3I$	EtOAc	98	–:98:2	–
14 ^[d]	$[Rh(cod)_2]OTf + L5 + EtPPh_3I$	EtOAc	> 99	85:3:12	98

[a] Conversion yield based on consumed starting material was determined by GC analysis. [b] Selectivity was determined by GC analysis. [c] The ee of **2a** was determined by chiral GC analysis. The absolute configuration of **2a** was determined by comparing the measured optical rotations with the reported one. [d] Rh/ligand/additive 1:1:2.

clohexen-1-ones containing both *s-cis* and *s-trans* enone moieties proceeded in excellent enantioselectivity (up to 98% *ee*). To obtain high enantio- and *s-trans* selectivities, the addition of a halogen source to a cationic Rh complex was essential. With the key step of *s-trans* selective asymmetric hydrogenation of piperitenone, we demonstrated a new synthetic method for optically pure (–)-menthol via three atom-economical hydrogenations. Moreover, *s-trans* and *s-cis* C=C bond selective reactions were accomplished by the proper choice of both the chiral ligands and halides. Further applications and mechanistic studies for understanding the effects of the isopropylidene moiety and the exceptional reactivity of the Rh-SEGPHOS iodo complex are ongoing in our group.

Experimental Section

General: All reactions and manipulations were performed under argon by use of standard vacuum line and Schlenk tube techniques. ^1H NMR spectra were recorded on a Varian MERCURY 300 or Bruker DRX500, and chemical shifts are reported in ppm (δ) relative to tetramethylsilane or referenced to the chemical shifts of residual solvent resonances (CHCl_3 and C_6H_6 were used as internal standards, δ 7.26 and 7.20 ppm, respectively). $^{31}\text{P}\{^1\text{H}\}$ NMR spectra were recorded on a Varian MERCURY 300 at 121 MHz or Bruker DRX500 at 202 MHz, and chemical shifts were referenced to external 85% H_3PO_4 . Infrared spectra were recorded on a JASCO FT/IR-230; mass spectra on a JEOL JMS DX-303HF spectrometer; GC analyses on a Shimadzu GC-14 A and Shimadzu GC-2014 gas chromatograph with a Shimadzu C-R3 A Chromatopac; HPLC Jasco UV-970 and PU-980 with Shimadzu C-R16 A Chromatopac. Elemental analyses were recorded on a Perkin Elmer 2400. All melting points were recorded on a Yanaco MP-52982 and are not corrected. Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification. Dichloromethane ($\text{H}_2\text{O} < 0.003\%$) was degassed. Tetrahydrofuran, toluene, hexane, and diethyl ether were distilled over sodium/benzophenone under argon prior to use. Degassed ethyl acetate ($\text{H}_2\text{O} < 0.003\%$) was used. $[\text{Rh}(\mu\text{-X})(\text{cod})_2]_2^{[22]}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) (COD: 1,5-cyclooctadiene), $[\text{Rh}(\text{cod})_2]\text{OTf}^{[23]}$, $[\text{Rh}(\text{cod})_2]\text{BF}_4^{[23]}$, $[\text{Rh}(\text{cod})]\{(\text{S})\text{-binap}\}\text{BF}_4^{[16b]}$, $[\text{Rh}(\mu\text{-Cl})\{(\text{S})\text{-binap}\}]_2^{[24]}$, $[\text{Ru}(\text{OCOPh})_2(\text{dppe})]^{[19]}$ and $[\text{RuCl}_2(\text{PPh}_3)_2(\text{propanediamine})]^{[17]}$ were prepared according to the literature methods.

General procedure for the Rh-catalyzed asymmetric hydrogenation of enones (1) (Table 2, entry 6): A Schlenk flask was charged with $[\text{Rh}(\text{cod})_2]\text{OTf}$ (15.1 mg, 0.0322 mmol), (S)-DTBM-SEGPHOS (38.0 mg, 0.0322 mmol), and $(\text{CH}_2\text{CH}_2\text{PPh}_3)_2$ (23.8 mg, 0.0322 mmol) under argon. To the mixture, ethyl acetate (1.0 mL) and piperitenone (**1a**) (484 mg, 3.22 mmol) were added. After stirring at 50°C for 2 h, the resulting deep red solution was transferred to a stainless steel autoclave. The autoclave was charged five times with H_2 to displace the argon, and subsequently the pressure was increased to 30 kg cm^{-2} . After stirring at 50°C for 1 h, H_2 was released, and the conversion yield and the enantiomeric excesses were determined by ^1H NMR and GC analysis of the crude products.

Large scale reaction (2-mol scale) (Table 2, entry 9): The crystal coated with paratone-N was mounted on glass fiber. The crystal structure was solved by using SHELXS 97 (Sheldrick, 1997). Refinement was carried out by full-matrix least squares (on F^2) with anisotropic temperature factors for non-H atoms after omission of redundant and space group forbidden data. In all of the structures H atoms were included as their calculated positions. For refinement of the structure and structure analysis, the program package SHELXTL was used.

CCDC 269103 (**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cam-

bridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Two-step conversion of (+)-pulegone (**2a**) to (–)-menthol (**8**)

Diastereoselective hydrogenation of (+)-pulegone (2a**) to (–)-pulegol (**7**):** A stainless steel autoclave (500 mL) was charged with (+)-pulegone (**2a**) (200 g, 1.316 mol), $[\text{RuCl}_2(\text{PPh}_3)_2(\text{propanediamine})]$ (50.9 mg, 0.066 mmol), *t*BuOK (148.1 mg, 1.32 mmol), and 2-propanol (40 mL). The autoclave was charged with H_2 (30 kg cm^{-2}) to displace the argon and then stirred for 18 h at 30°C. After H_2 was released, the reaction mixture was concentrated and distilled (70–72°C, 2 mmHg) to afford a diastereomeric mixture of (–)-pulegol (**7**) (198.6 g, 98%) as a colorless oil. The diastereoselectivity was determined to be 97.4:2.4 by GC analysis. GC analysis [Neutrabond-1 (0.25 mm $\times$ 30 m), column temperature 10°C up per 1 min from 80 to 220°C, injection temperature 250°C, detection temperature 250°C, t_R = 7.9 min (pulegone), 8.7 min (pulegol)].

Diastereoselective hydrogenation of (–)-pulegol (7**) to (–)-menthol (**8**):** A stainless steel autoclave (100 mL) was charged with the diastereomixture of (–)-pulegol (**7**) (3.09 g, 20 mmol, dr: 97.4:2.4), $[\text{Ru}(\text{OCOPh})_2(\text{dppe})]$ (6.2 mg, 0.01 mmol), and methanol (3 mL). The autoclave was charged with H_2 (30 kg cm^{-2}) to displace the argon and then stirred for 18 h at 50°C. After H_2 was released, the reaction mixture was concentrated to afford a diastereomixture of (–)-menthol (**8**) (3.11 g, 99%, menthol (**8**)/neomenthol (**9**)/neoisomenthol (**10**) 96:1.7:2.3). This mixture was recrystallized from acetonitrile to give pure menthol (2.28 g, 73%) with chemical purity of >99% (either neomenthol or neoisomenthol was not detected) and with enantiomeric excess of 99.6% *ee*. Chemical purity of the product was determined by GC analysis and optical purity of the product was determined by chiral GC analysis. GC analysis [Neutrabond-1 (0.25 mm $\times$ 30 m), column temperature 10°C up per 1 min from 80 to 220°C, injection temperature 250°C, detection temperature 250°C, t_R = 7.1 (neomenthol), 7.5 (neoisomenthol), 7.6 (menthol), 8.7 min (pulegol)]; Chiral GC analysis [β -DEX225 (0.25 mm $\times$ 30 m), column temperature 1°C up per 1 min from 70 to 130°C, injection temperature 230°C, detection temperature 230°C, t_R = 34.6 min ((+)-menthol), 34.9 min ((–)-menthol)].

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