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Asymmetric Synthesis of 1,2-Limonene Epoxides by Jacobsen Epoxidation

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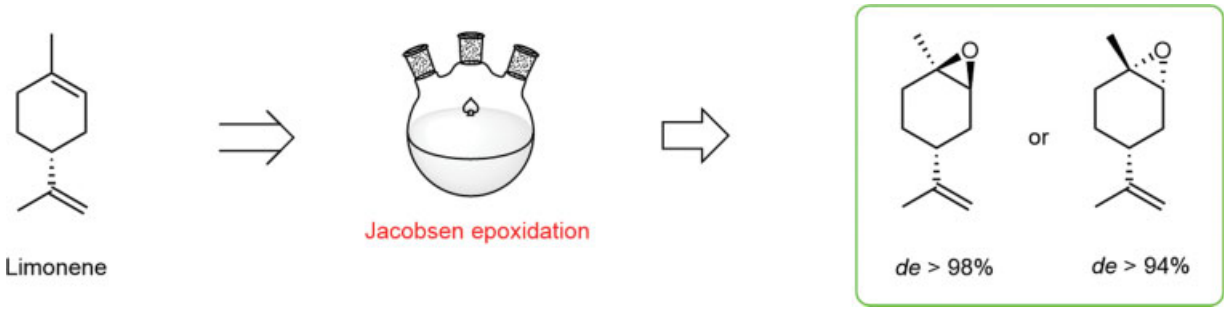

Abstract

This study reported an asymmetric synthesis of 1,2-limonene epoxides. The absolute stereochemistry was controlled by a Jacobsen epoxidation of *cis*-1,2-limonene epoxide (with diastereomeric excess of 98%) and *trans*-1,2-limonene epoxide (with diastereomeric excess of 94%), which could be used as important raw materials for the preparation of related cannabinoid drugs.

Keywords

- Jacobsen epoxidation
- 1,2 limonene epoxides
- asymmetric synthesis

Introduction

In recent years, cannabis and some of its bioactive components have received increasing attention in basic research and pharmaceutical applications.[1] Among these, cannabinoids including cannabidiol (CBD), tetrahydrocannabinol (THC), cannabichromene, and cannabigerol have shown extensive pharmacological effects. As early as the 1980s, Dronabinol (marketed as Marinol) was launched to prevent chemotherapy-induced nausea and vomiting, which was a synthetic form of delta-9-tetrahydrocannabinol (Δ^9-THC). In 2018, Epidiolex (CBD oral solution) was approved by the Food and Drug Administration to be the first CBD-based product available on the U.S. market for the treatment of two

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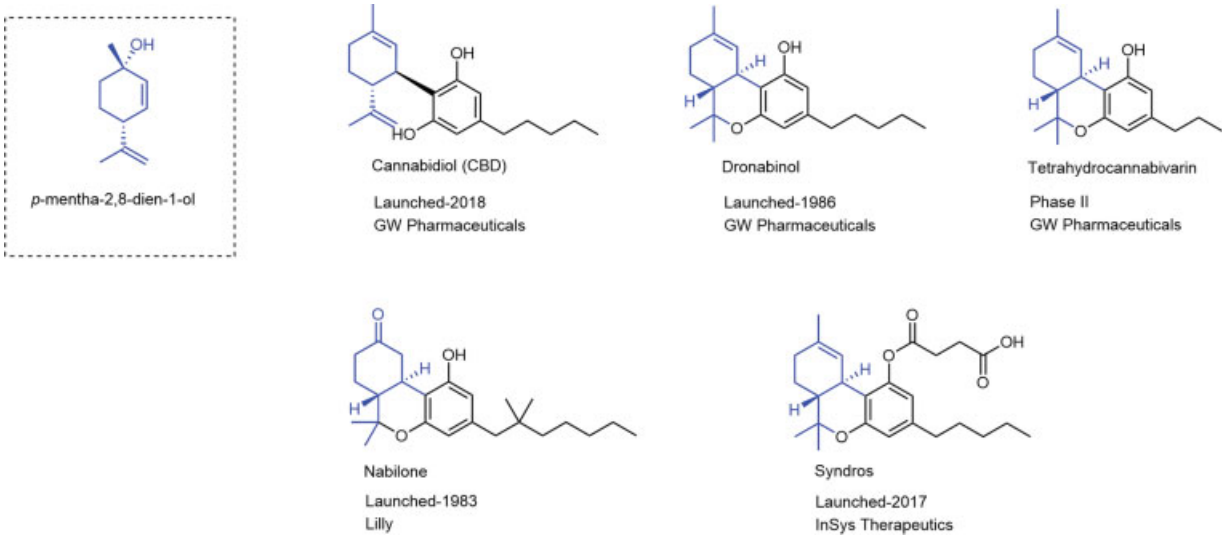
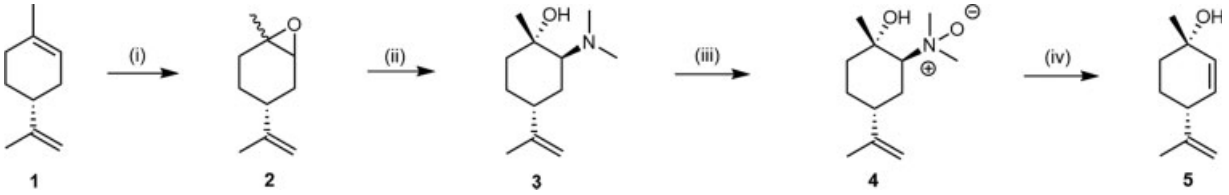


Scheme 1 *p*-Mentha-2,8-dien-1-ol as a common building block in bioactive cannabinoids.



Scheme 2 Synthesis of *p*-mentha-2,8-dien-1-ol (**5**). Reagents and conditions: (i) *m*-CPBA, $CHCl_3$, 0°C, 2 h, 62%; (ii) 40% $HNMe_2$ (aq), 80°C, 18 h, 88% based on the *trans*-isomer; (iii) 30% H_2O_2, 50% CH_3CN (aq), r.t., 2 h, 100%; (iv) 180°C, 1 mm Hg, 74%.

rare forms of epilepsy—Lennox–Gastaut syndrome and Dravet syndrome—which are among the two most difficult types of epilepsy to treat.[2] To date, THC and CBD have been the most studied cannabinoids.

The main way to obtain cannabinoids is to separate them from the dry substances and fresh cannabis leaves. Synthesizing cannabinoids by chemical synthesis instead of natural extraction has also become a research hotspot. In the reported total synthesis routes of CBD or THC, *p*-mentha-2,8-dien-1-ol (**5**) was used as an intermediate.[3] Among the listed cannabinoid drugs, compound **5** is also the key part of their structure (**Scheme 1**). Compound **5** is synthesized by four steps of epoxidation, ring opening, oxidation, and elimination from compound **1** (**Scheme 2**).[4] In the reported methods, compound **2** is a diastereomeric mixture (**Scheme 3**), which is difficult to obtain a single configuration by fractionation or column chromatography purification. In the ring-opening reaction of compound **2**, the *trans*-epoxide

Scheme 3 The structures of *cis*-**2** and *trans*-**2**.

was selectively opened with aqueous dimethylamine to generate **3**. The *cis*-**2** remained largely unreacted to affect the purity of the compound **3**, and so it is difficult to obtain compound **5** with high optical purity.[4] Therefore, it is necessary to explore the asymmetric oxidation synthesis of compound **1** to obtain *trans*-1,2-limonene epoxide with high optical purity for the synthesis of target cannabinoid drugs.

Jacobsen epoxidation is an asymmetric epoxidation of olefins without specified functional groups. The chiral salen–metal complexes are used as Jacobsen's enanitioselective epoxidation catalysts. The commonly used oxidants are iodosyl benzene (for organic solvents) and sodium hypochlorite (for water media).[5] In addition, hydrogen peroxide and *m*-CPBA can also be used as oxidants for this reaction, simultaneously additional ligands are required, such as 4-methylmorpholine *N*-oxide (NMO).[6] Despite the widespread application and the utility of the Jacobsen method, the optimum reaction conditions for its enantioselectivity have remained obscure.

To our knowledge, Montes de Correa and colleagues have engaged the challenge of asymmetric epoxidation of (*R*)-(+)-limonene with the salen–manganese complex as a catalyst to obtain 1,2-limonene epoxides by applying Jacobsen's epoxidation method. They found that the product stereochemistry was strongly dependent on the absolute configuration of both the catalyst and the limonene. The combination of *R*-(+)-limonene with (*R,R*)-Jacobsen catalyst or (*S*)-(−)-limonene with (*S,S*)-Jacobsen catalyst formed a

matched pair, giving rise to diastereomeric excess values of 56 and 45%, respectively.[7] Ratnasamy and colleagues have reported that Mn (salen) complexes immobilized on sulfonic acid-functionalized SBA-15 exhibited efficient catalytic activity for selective epoxidation of *R*-(+)-limonene with aerial oxygen. 1,2-Limonene epoxide was the major product. However, the diastereomeric excess for the endo-enantiomer was only 39.8%.[8] Bernardo-Gusma and colleagues have reported asymmetric epoxidation of *R*-(+)-limonene (**1**) using the Jacobsen catalysts in organic solvents and ionic liquids. *R*-(+)-Limonene (**1**) was selectively converted to 1,2-epoxi-*p*-ment-8-enes with a diastereoselectivity of 70% in organic solvents and 74% in ionic liquids.[9] Asymmetric epoxidation of limonene has been reported in many studies, but no high diastereomeric excess of 1,2-epoxides has been obtained.

In this article, *R*-(+)-limonene (**1**) was used as the substrate to screen the chiral salen-metal catalysts, oxidants, axial ligands, and dosage of ligands for asymmetric oxidation reactions. And we have successfully selected suitable conditions to prepare *cis*- and *trans*-epoxides with high optical purity, which can be used as important raw materials for the preparation of related cannabinoid drugs. The results provide a useful reference for the total synthesis of cannabinoids.

Methods and Experiments

Methods for (+)-1,2-Limonene Oxide Quantification

All reaction medium samples were diluted in methanol and analyzed in a gas chromatography–mass spectrometry (GC-MS; Agilent 7890B GC-5977A), equipped with a HP-5 column (30 m length × 0.25 mm internal diameter × 0.25 µm film thickness), and a mass (MS) detector (Agilent 5977A MSD). The samples were injected into the column initially at 50°C; after a holding time of 2 minutes, the temperature was increased to 15°C/min until 250°C, with a final holding time of 5 minutes.

Experiment for the Synthesis of 2 (a Diastereomeric Mixture)

A solution of *m*-CPBA (16 mmol) in DCM (30 mL) was added dropwise to a solution of *R*-(+)–limonene (**1**) (10 mmol) in DCM (30 mL) over 30 minutes in such a way that the temperature did not rise over 5°C. The solution was then stirred at 0° C for 30 minutes, and then at room temperature for 1 hour before the addition of sodium hydroxide (1 mol/L, 20 mL, 20 mmol). The organic phase was collected, washed with sodium carbonate and brine, and then dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (petroleum ether:ethyl acetate = 50:1) to obtain 1,2-epoxide (**2**) (yield: 62%) as a colorless oil. $[\alpha]^{20}_{D}$: +38.3 (0.1, $CHCl_3$); GC-MS (*m*/*z*): 152.1 (M^+); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.73–4.66 (m, 4H), 3.05 (s, 1H), 2.99 (d, *J* = 5.4 Hz, 1H), 2.15–2.07 (m, 2H), 2.05–2.01 (m, 2H), 1.91–1.78 (m, 4H), 1.71 (dd, *J* = 11.3, 3.8 Hz, 2H), 1.69 (s, 3H), 1.66 (s, 3H), 1.63 (s, 1H), 1.53 (dddd, *J* = 10.1, 5.4, 3.7, 2.0 Hz, 1H), 1.39–1.35 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H).

Typical Procedure for Jacobsen Asymmetric Oxidation Reaction

To a solution of *R*-(+)-limonene (**1**) (10 mmol), Jacobsen's catalyst (0.5 mmol), and axial ligand (30 mmol) in 30 mL DCM was added the *m*-CPBA (16 mmol, in 30 mL of DCM) drop by drop, and the resulting mixture was vigorously stirred at 0°C for 10 hours. After completion of the reaction, the mixture was detected by GC-MS. Saturated sodium bicarbonate solution was added to the reaction solution. The DCM layer was collected, washed with water, and dried over anhydrous sodium sulfate. The residue was purified by column chromatography to obtain 1,2-epoxide as a colorless oil.

Experiment for the Synthesis of *cis*-2

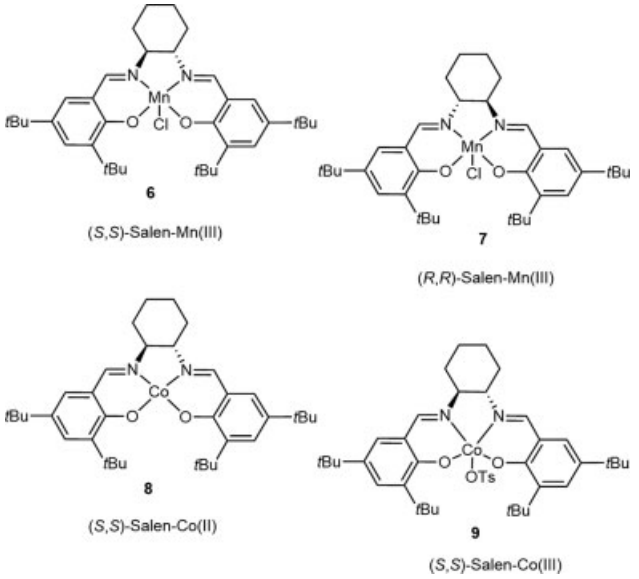
To a solution of *R*-(+)-limonene (**1**) (10 mmol), catalyst **7** (0.5 mmol), and NMO (50 mmol) in 30 mL DCM was added *m*-CPBA (16 mmol, in 30 mL of DCM) drop by drop, and the mixture was vigorously stirred at 0°C for 10 hours. After completion of the reaction, the mixture was detected by GC-MS. Saturated sodium bicarbonate solution was added to the reaction solution. The DCM layer was collected, washed with water, and dried over anhydrous sodium sulfate. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 50:1) to obtain *cis*-**2** (yield: 48.2%) as a colorless oil. $[\alpha]^{20}_{D}$: +70.7 (0.1, $CHCl_3$); GC-MS (*m*/*z*): 152.1 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (dd, *J* = 13.0, 11.5 Hz, 2H), 3.02 (d, *J* = 2.2 Hz, 1H), 2.16–1.97 (m, 2H), 1.89–1.76 (m, 2H), 1.69 (dd, *J* = 7.5, 5.1 Hz, 1H), 1.67 (s, 3H), 1.66–1.61 (m, 1H), 1.57–1.47 (m, 2H), 1.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.51 (s), 108.57 (s), 60.05 (s), 56.85 (s), 35.73 (s), 30.25 (s), 28.15 (s), 25.44 (s), 23.81 (s), 20.62 (s).

Experiment for the Synthesis of *trans*-2

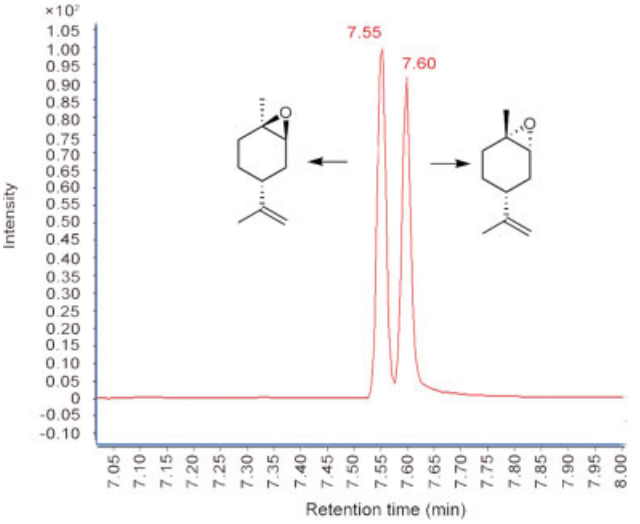
To a solution of *R*-(+)-limonene (**1**) (10 mmol), catalyst **6** (0.5 mmol), and 2-pyridinol-1-oxide (30 mmol) in 30 mL DCM was added *m*-CPBA (16 mmol, in 30 mL of DCM) drop by drop, and the mixture was vigorously stirred at 0°C for 10 hours. After completion of the reaction, the mixture was detected by GC-MS. Saturated sodium bicarbonate solution was added to the reaction solution. The DCM layer was collected, washed with water, and dried over anhydrous sodium sulfate. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 60:1) to obtain *trans*-**2** (yield: 36.3%) as a colorless oil. $[\alpha]^{20}_{D}$: +79.1 (0.1, $CHCl_3$); GC-MS (*m*/*z*): 152.2 (M^+); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.65 (s, 2H), 2.97 (d, *J* = 5.4 Hz, 1H), 2.01 (ddd, *J* = 15.0, 7.2, 4.3 Hz, 2H), 1.86 (ddd, *J* = 14.8, 12.0, 6.1 Hz, 1H), 1.72–1.65 (m, 5H), 1.36 (ddd, *J* = 12.2, 8.2, 3.8 Hz, 2H), 1.30 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.21 (s), 109.08 (s), 59.27 (s), 57.50 (s), 40.74 (s), 30.75 (s), 29.88 (s), 24.34 (s), 23.09 (s), 20.22 (s).

Results and Discussion

R-(+)-Limonene (**1**) was used as the substrate, and first, the oxidants and catalysts used in Jacobsen asymmetric epoxidation (**Scheme 4**) were screened (the results are shown



Scheme 4 The catalysts used in the Jacobsen method.

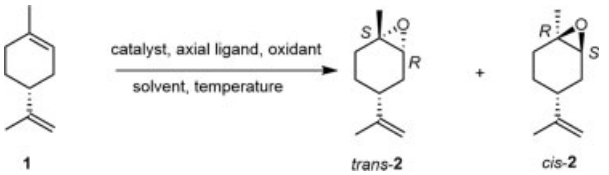


Scheme 5 GC-MS chromatogram showing the direct epoxidation by *m*-CPBA. GC-MS, gas chromatography–mass spectrometry.

in ►**Table 1**). Initially, when **1** reacted with 3 equiv. of H_2O_2, epoxidation did not occur with or without the axial ligand NMO and catalyst (►**Table 1**, entries 1 and 2). By replacing H_2O_2 with *m*-CPBA as oxidants, the reaction could be performed, and a mixture of isomers with *cis*- to *trans*- ratios close to 1:1 was obtained (►**Table 1**, entry 3, **Scheme 5**). When *m*-CPBA was used as the oxidant, **7**, **8**, **9** as the catalyst, and NMO as the axial ligand, excess *cis*-isomer epoxides (►**Table 1**, entries 5–7) were obtained, and the highest diastereoselectivity was found with **7** as the catalyst, and the diastereomeric excess was up to 98% (►**Table 1**, entry 5, **Scheme 6**). And when **6** was used as the catalyst, excess *trans*-isomer epoxides were obtained with diastereomeric excess of 52% (►**Table 1**, entry 4).

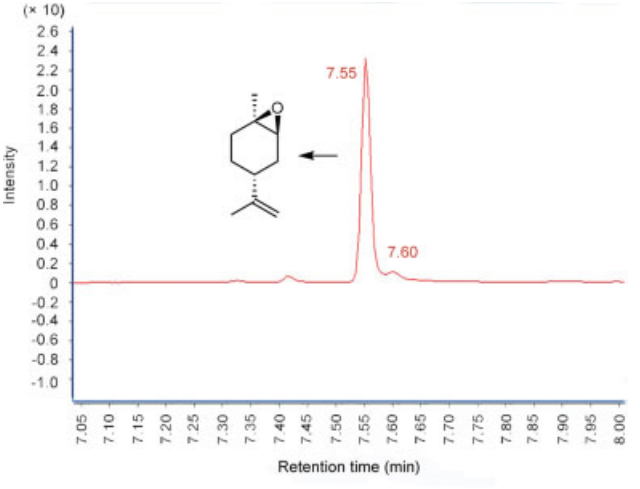
The disparate results in asymmetric induction can be understood in terms of the common model proposed by Jacobsen epoxidation. Olefins attack from the side of the metal–oxygen bond in the Jacobsen asymmetric oxidation reaction.[10,11] When metal atoms are complexed with axial ligands, they are closer to the salen plane, and the interaction between olefins and substituents on salen ligands is stronger. The complexation of axial ligands can also reduce the reactivity of oxygenated salen complexes to improve the selectivity.[12]

Table 1 Screening of catalysts and oxidants[a]



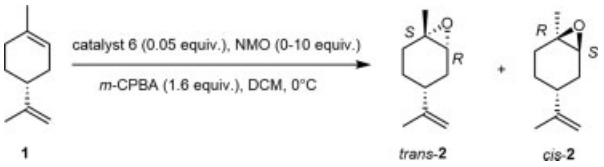
Entry	Catalyst	Oxidant	Axial ligands	de %[b]
1	–	H_2O_2[c]	–	–
2	**6**	H_2O_2[c]	NMO	–
3	–	*m*-CPBA	–	7[d]
4	**6**	*m*-CPBA	NMO	52[e]
5	**7**	*m*-CPBA	NMO	98[d]
6	**8**	*m*-CPBA	NMO	41[d]
7	**9**	*m*-CPBA	NMO	37[d]

Abbreviation: de, diastereomeric excess.
[a]All the reactions were performed at 0°C in DCM (60 mL) with alkene (10 mmol), NMO (50 mmol, if necessary), catalysts (0.5 mmol, 5.0 mmol%) and oxidants (16 mmol), unless otherwise.
[b]Determined by GC-MS. The order of peaks of *cis*-**2** and *trans*-**2** referred to Mccue et al[14] and Melchiors et al[15].
[c]3 equiv. of H_2O_2 was used.
[d]Referred to *cis*-1,2-limonene oxide (predominant epoxide).
[e]Referred to *trans*-1,2-limonene oxide (predominant epoxide).



Scheme 6 GC-MS chromatogram showing epoxide products starting from *R*-(+)-limonene (**1**) using **7** as the catalyst. GC-MS, gas chromatography–mass spectrometry.

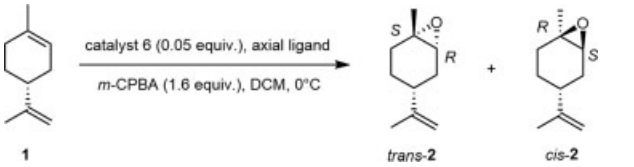
Table 2 Screening of NMO dosage[a]



Entry	NMO (equiv.)	de %[b]
1	0	18[c]
2	0.5	0
3	1	24[d]
4	2	49[d]
5	3	53[d]
6	5	52[d]
7	10	48[d]

Abbreviation: de, diastereomeric excess.
[a]All the reactions were performed at 0°C in DCM (60 mL) with alkene (10 mmol), catalyst **6** (0.5 mmol, 5.0 mmol%), and *m*-CPBA (16 mmol).
[b]Determined by GC-MS. The order of peaks of *cis*-**2** and *trans*-**2** referred to Mccue et al[14] and Melchiors et al[15].
[c]Referred to *cis*-1,2-limonene oxide (predominant epoxide).
[d]Referred to *trans*-1,2-limonene oxide (predominant epoxide).

Table 3 Screening of axial ligands[a]

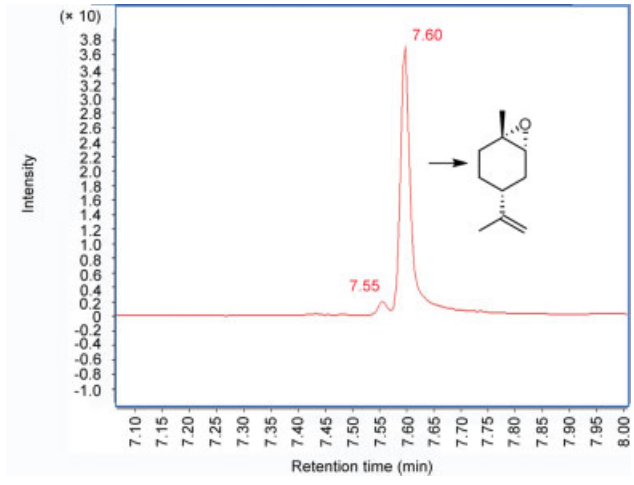


Entry	Axial ligands	de %[b]
1	NMO	53
2	Imidazole	20
3	2-Methylimidazole	1
4	1-Methylimidazole	23
5	2-Hydroxypyridine-*N*-oxide (HOPO)	94
6	Piperidine	8
7	*N*-Methyl piperazine	10
8	Pyridine-1-oxide	35
9	4-*tert*-Butylpyridine	15

Abbreviation: de, diastereomeric excess.
[a]All the reactions were performed at 0°C in DCM (60 mL) with alkene (10 mmol), catalyst **6** (0.5 mmol, 5.0 mmol%), *m*-CPBA (16 mmol), and axial ligands (30 mmol).
[b]Determined by GC-MS. The order of peaks of *cis*-**2** and *trans*-**2** referred to Mccue et al[14] and Melchiors et al[15]; Referred to *trans*-1,2-limonene oxide (predominant epoxide).

According to the above epoxidation mechanism analysis, to obtain the *trans*-**2** with higher diastereomeric excess, we screened the amount of NMO (►**Table 2**). However, GC-MS showed that the diastereomeric excess value of *trans*-epoxide was not significantly increased by increasing the amount of NMO. When the ligand dosage was 3 equiv., the diastereomeric excess value was only 53% (►**Table 2**, entry 5), indicating that NMO was not the best ligand for the oxidation system.

Considering the importance of axial ligands in the epoxidation systems, to obtain *trans*-**2** with higher diastereomeric excess value, we further performed a series of screening of axial ligands reported in the epoxidation systems (►**Table 3**).[13] It was found that high purity *trans*-epoxides with a diastereomeric excess of 94% could be obtained successfully when 2-hydroxypyridine-*N*-oxide (HOPO) was used as the axial ligand (►**Table 3**, entry 5; **Scheme 7**).



Scheme 7 GC-MS chromatogram showing epoxide products starting from *R*-(+)-limonene (**1**) using **6** as the catalyst, 2-pyridinol-1-oxide (HOPO) as the axial ligand. GC-MS, gas chromatography–mass spectrometry.

Conclusion

In summary, we have successfully found an effective method of catalytic asymmetric epoxidation to synthesize *cis*-1,2-limonene epoxide and *trans*-1,2-limonene with high diastereomeric excess values, respectively. *cis*-1,2-Limonene epoxide with a diastereomeric excess of 98% was synthesized by asymmetric oxidation of **7** as the catalyst, NMO as the axial ligand and *m*-CPBA as the oxidant. Using **6** as the catalyst, 2-pyridinol-*N*-oxide as the axial ligand, and *m*-CPBA as the oxidant, the *trans*-**2** could be obtained with a diastereomeric excess of 94%. In this study, we reported for the first time that 1,2-limonene epoxides in rather high diastereoselectivity (>90%) were obtained by Jacobsen epoxidation, which will provide an effective preparation method of key intermediates for the chemical synthesis of cannabinoid drugs.

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Conflict of Interest
None.

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