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Eco-friendly kinetic separation of *trans*-limonene and carvomenthene oxides

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Abstract. Kinetic separation of *trans*-limonene oxide and *trans*-carvomenthene oxide was achieved in high yield by selective ring opening of their *cis*-epoxides in the presence of $InCl_3$ catalyst in water. Catalytic activity of $InCl_3$ was conserved up to 10 cycles. Nucleophilic addition of methanol in presence of $InCl_3$ was also selective as *cis*-epoxides preferentially reacted leaving behind *trans*-epoxides, which were separated by fractional distillation.

Keywords. Eco-friendly; kinetic separation; indium chloride; *cis*-/*trans*-limonene oxide; *cis*-/*trans*-carvomenthene oxide; water.

1. Introduction

Chiral epoxides are versatile building blocks for the synthesis of biologically active, synthetically useful compounds such as fragrances, flavours, herbicides and fungicides.[1] They also serve as starting materials for the asymmetric synthesis of natural products.[2,3] Limonene, a cyclic monoterpene present in the essential oil of more than 300 plants and its (*R*)-(+)-enantiomer constitutes 90–96% of citrus peel oil. (*R*)-Limonene oxide is produced commercially as a *cis*- and *trans*-mixture (figure 1, **1a** and **1b**) in ~1:1 ratio. Due to its abundance availability and low cost, it is considered as bio-renewable source of epoxide for the preparation of biodegradable polymers such as polycarbonate and polyesters.[4]

Epoxidation of carvomenthene (**2**) also affords *cis*-/*trans*-epoxides (**2a** and **2b**) in ~1:1 ratio. Separation of *cis*- and *trans*-epoxides from both limonene and carvomenthe is very difficult because of their close boiling range. Also, separation by column chromatography is not practicable because they elute together without separation. They are either synthesized by chemical or biological methods.[5] The best way of separating individual epoxides is kinetic resolution method. Selective ring opening of epoxides has been effected by mercury salts, but requires an additional de-metallation step.[6] Base-induced cleavage of *cis*- or *trans*-epoxides affords separation of either of the epoxide depending upon choice of the base, but the reactions are usually effected at elevated temperatures.[7] Molybdenum complex has also been used for the kinetic resolution of monocyclic terpene epoxides.[8] Hydrolytic kinetic resolution gives pure epoxides but needs a specific catalyst and applicable to terminal epoxides.[9] Racemic chromium salen complex has been found to effect kinetic resolution in case of monocyclic terpene epoxides containing C-4 substituent.[10] We, earlier reported kinetic resolution of terpene oxides in methanol in the presence of Lewis acid catalysts.[11] In this photo-catalysed stereo-differentiation, *cis*-epoxides cleaved preferentially compared to *trans*-epoxides in the presence of Lewis acids catalysts. In order to develop an efficient eco-friendly kinetic separation of *cis*-/*trans*-limonene oxide, and *cis*-/*trans*-carvomenthene oxide, we checked the reactivity of these in water in the presence of Lewis acid catalyst such as $InCl_3$. This catalyst was chosen as many transition metal catalysts have low adaptability to water when compared to $InCl_3$, which on the other hand has a good tolerance of moisture.[12]

Firstly, the reaction of mixture of **1a** and **1b** in the presence of 10 mol% $InCl_3$ in water was carried out. It resulted in the cleavage of *cis*-epoxide leaving behind *trans*-epoxide (scheme 1). Upon fractional distillation of products, **1b** was separated from **1d**. Hence, a detail study was undertaken, which resulted in development of an efficient eco-friendly kinetic separation method for *trans*-limonene oxide. Scope of the reaction for

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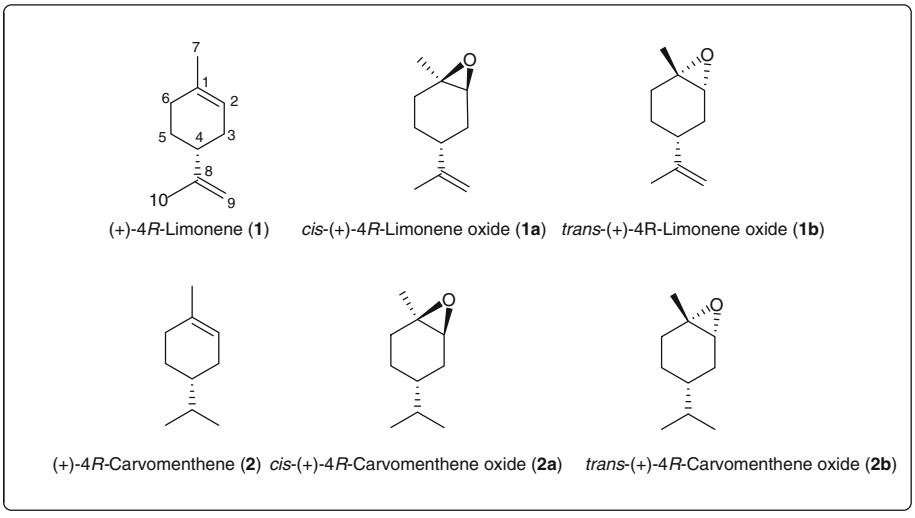
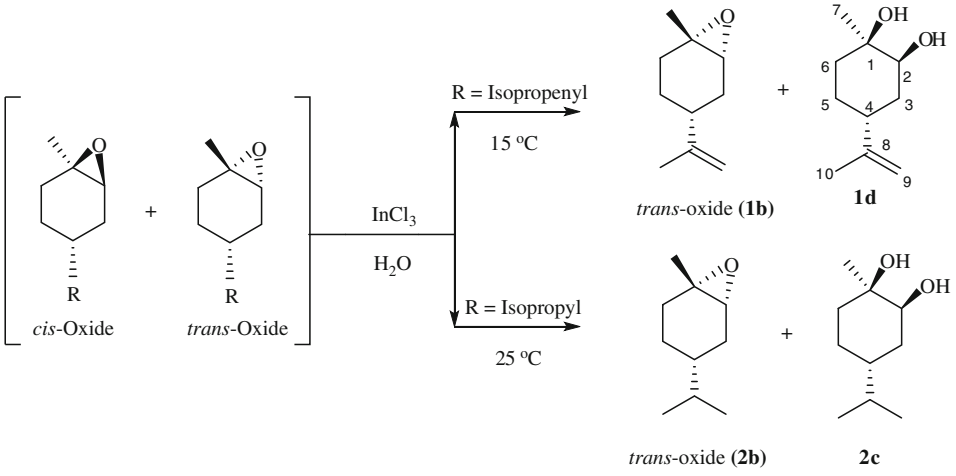


Figure 1. Structures of 4*R*-limonene, *cis-/trans*-limonene oxides, 4*R*-carvomenthene, and *cis-/trans*-carvomenthene oxides.



Scheme 1. Reaction of *cis/trans*-limonene and carvomenthene oxides in water in the presence of $InCl_3$.

kinetic separation of *trans*-carvomenthene oxide from *cis-/trans*-mixture (**2a** and **2b**) was also demonstrated.

2. Experimental

2.1 *Separation of trans-limonene and carvomenthene oxides in water*

In a two-necked RB flask, a mixture of *cis-/trans*-epoxide (30 mmol) in triple distilled water (50 ml) and $InCl_3$ (3 mmol) was stirred at 10–15°C in case of limonene oxide and 25°C in case of carvomenthene oxide. The mixture was similar to an emulsion at the beginning, which turned hazy during the reaction. Progress of reaction was checked by NMR for the complete disappearance of proton attached to epoxide ring at position 2 in **1a** and **2a**, respectively, at 3.06 and 3.01 ppm. After the complete reaction of *cis*-isomer, the mixture was extracted with CH_2Cl_2 (30 ml × 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to afford the crude product, which was purified by fractional distillation under reduced pressure. Physical and spectral data of the isolated compounds is presented here.

2.1a *trans-Limonene-oxide (**1b**)*: Yield 2.40 g, (97%); b.p. 78–80°C/1.33 kPa, (ref.[13]): 57–59°C/0.33 kPa; $[\alpha]_{20}^{D} = +74°$ (c = 1, MeOH), (ref.[14]): +82° ; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.66 (s, 2H, -CH_2), 2.98 (d, 1H, J = 5.3 Hz, -CH), 2.00–2.05 (m, 2H, -CH_2), 1.84–1.89 (m, 1H), 1.68–1.72 (m, 2H, -CH_2), 1.66 (s, 3H, -CH_3), 1.35–1.39 (m, 2H, -CH_2), 1.31 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.8, 108.7, 58.9, 57.1, 40.4, 30.4, 29.5, 24.02, 22.7,

19.8; MS (*m/z*) :152(2), 137(8), 119(9), 108(76), 94(89), 79(51), 67(93), 43(100)

2.1b *trans-Carvomenthene-oxide (**2b**)*: Yield 2.45 g, (96.4%); b.p. 73–75°C/0.66 kPa, $[\alpha]_{20}^{D} = +48°$ ($c = 1$, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.96$ (d, 1H, $J = 5.3$ Hz, -CH), 1.91–2.00 (m, 2H, -CH_2), 1.61 (ddd, 1H, $J_1 = 14.51$ Hz,$J_2 = 12.21$ Hz, $J_3 = 4.8$ Hz) 1.51 (dd, 1H, $J_1 = 15.0$, $J_2 = 11.62$, -CH_2), 1.37 (sept, 1H, $J = 6.73$ Hz, -CH), 1.29 (s, 3H, -CH_3), 1.10 (dq, 2H, $J_1 = 12.46$ Hz, $J_2 = 4.16$ Hz, -CH_2), 1.01 (ds, 1H, $J_1 = 6.15$ Hz, $J_2 = 2.05$ Hz, -CH), 0.82 (d, 6H, $J = 6.92$ Hz, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 59.2, 57.4, 38.9, 31.9, 30.6, 27.5, 22.7, 22.1, 19.3, 18.9; MS(*m/z*): 154(2), 139(20), 125(13), 111(46), 97(9), 83(20), 69(24), 55(32), 43(100).

2.1c *(1S,2S,4R)-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (**1d**)*: b.p. 115–117°C/0.46 kPa; $[\alpha]_{20}^{D} = +42°$ ($c = 1$, MeOH); Yield: 2.1 g (90 %); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.72$ (s, 2H, -CH_2), 3.61 (t, 1H, $J = 3.12$ Hz, -CH), 2.21–2.29 (m, 1H, -CH), 1.91 (ddd, 1H, $J_1 = 13.99$ Hz,$J_2 = 11.47$ Hz, $J_3 =$ 2.84 Hz, -CH_2), 1.72–1.77 (m, 1H, -CH_2), 1.71 (s, 3H), 1.61–1.66 (m, 1H, -CH_2), 1.52–1.56 (m, 2H, -CH_2), 1.47–1.52 (m, 1H, -CH_2), 1.24 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 148.9$, 108.6, 73.5, 71.1, 37.1, 33.6, 33.3, 26.1, 25.8, 20.7; MS (*m/z*): 170(2), 152(34), 137(21), 111(21), 108(46), 93(40),82(35), 71(80), 67(46), 55(32), 43(100).

2.1d *(1S,2S,4R)-4-isopropyl-1-methylcyclohexane-1,2-diol (**2c**)*: b.p. 123–125° C/0.46 kPa; $[\alpha]_{20}^{D} = +43°$ ($c = 1$, MeOH); Yield 2 g, (85%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.59$ (t, 1H, $J = 3.45$ Hz, -CH), 1.93 (br, 2H, -OH confirmed by D exchange), 1.64–1.74 (m, 2H, -CH_2), 1.56–1.61 (m, 1H, -CH_2), 1.50–1.53 (m, 1H, -CH_2), 1.46–1.50 (m, 2H,-CH_2)**,** 1.33–1.38 (m, 2H, -C(4)H and –C(5)H_2), 1.24 (s, 3H, -CH_3), 0.88 (t, 6H, $J = 7.54$ Hz, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 73.7$, 36.4, 33.4, 32.3, 31.0, 29.3, 25.8, 23.9, 19.7, 19.6; MS (*m/z*): 172(8), 154(4), 139(11), 111(52), 97(13), 83(28), 71(100), 55(48), 43(91).

2.2 *General procedure for separation of trans-limonene and carvomenthene oxides in methanol*

In a two-necked RB flask, a solution of *cis-/trans*-epoxide (30 mmol) in methanol (50 ml) and $InCl_3$ (3 mmol) was taken. The solution was stirred at room temperature. Progress of the reaction was checked by NMR for the complete disappearance of proton attached to epoxide ring at position 2 in **1a** and **2a**, respectively, at 3.06 and 3.01 ppm. After the reaction was complete (4 h), methanol was evaporated and the products were extracted into CH_2Cl_2 (30 ml × 3) by aqueous work-up. The combined organic extracts was dried over Na_2SO_4 and concentrated to afford the crude product. It was then purified by fractional distillation under reduced pressure to afford pure products. Physical and spectral data of isolated compounds is presented here.

2.2a *(1S,2S,4R)−2-hydroxy-1-methoxy-p-menthan-8(9)-ene (**1c**)*: Yield 2.16 g, (85%); b.p. 115–117 ° C/0.66 kPa; $[\alpha]_{20}^{D} = +39°$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.72$ (br s, 2H, CH_2), 3.68 (s, 1H, CH), 3.19 (s, 3H, OCH_3), 2.24 (tt, 1H, $J_1 = 11.70$ Hz, $J_2 = 3.52$ Hz, CH), 1.91 (ddd, 1H, $J_1 = 13.64$ Hz,$J_2 = 12.29$ Hz, $J_3 = 2.69$ Hz, CH_2), 1.80 (br, 1H, OH), 1.72 (s, 3H, CH_3), 1.70 (dt, 1H,$J_1 = 3.72$ Hz,$J_2 =$ 1.35 Hz, CH_2), 1.62 (m, 1H, CH_2), 1.56 (dt, 1H, $J_1 =$ 13.64 Hz,$J_2 = 1.77$ Hz, CH_2), 1.37-1.51 (m, 2H, CH_2), 1.18 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 149.4$, 108.4, 74.8, 72.0, 48.0, 37.1, 33.5, 28.5, 25.7, 20.6, 19.9; MS (*m/z*): 184(2), 169(4), 152(10), 108(15), 85(100), 72(21), 55(19), 43(16).

2.2b *(1S,2S,4R)−2-hydroxy-1-methoxy-p-menthane (**2d**)*: Yield 2.17 g, (86.8%); b.p. 102–104°C/0.33 kPa; $[\alpha]_{20}^{D} = 33°$ ($c = 1$, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.62$ (s, 1H, CH), 3.17 (s, 3H, CH_3), 2.40 (br, 1H, OH), 1.63–1.72 (m, 2H, -C(3)H_2 and -C(6)H_2), 1.52–1.59 (m, 1H, -CH_2), 1.50 (dd, 1H, $J_1 = 12.95$ Hz,$J_2 = 3.59$ Hz, -CH_2), 1.43–1.47 (m, 1H, -CH), 1.40–1.43 (m, 1H, -CH_2), 1.32–1.38 (m, 1H, -CH), 1.18–1.22 (m, 1H, -CH_2), 1.15 (s, 3H, -CH_3), 0.87 (t, 6H, $J = 6.67$ Hz, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 75.2$, 72.2, 48.0, 36.2, 32.0, 31.5, 28.6, 23.7, 19.8, 19.7, 19.5; MS (*m/z*): 186(6), 171(4), 154(4), 143(4), 136(11), 125(2), 111(10), 97(2), 85(100), 83(4), 72(20), 55(17), 43(13).

2.3 *Catalyst reusability test*

Retention of catalytic activity of $InCl_3$ was checked by carrying out reaction over 10 cycles. Under each cycle, the reaction was carried out on 10 mmol scale, after completion of the reaction, the usual work-up afforded the mixture of *trans*-epoxide and **1d**. The aqueous layer obtained at work-up stage, was separated and utilized for succeeding reactions. The sequence of operation was followed in every subsequent cycle

and repeated for 10 times. The data of distribution of *cis*- and *trans*-epoxides over 10 cycles is presented in table 1. It was observed that in every cycle, stereo-differentiation between the *cis*- and *trans*-epoxides was observed which indicates the catalytic role of $InCl_3$ in water. It was seen that the rate of reactions for initial cycles was within 5 h and further it gradually reduced from 3rd to 10th cycle.

3. Results and discussion

Commercial limonene oxide containing **1a** and **1b** in ~1:1 ratio was taken for the reaction in presence of 10 mol% of $InCl_3$ in water (scheme 1). Progress of reaction was monitored by NMR. The reaction at 25°C was found to be fast as both *cis*-oxide and *trans*-oxide underwent cleavage and afforded a mixture of diaxial diols as products. Hence, under these conditions, the kinetic diastereo-differentiation was not apparent. However, at a lower temperature of 10–15°C, the reaction was found to proceed towards selective cleavage of *cis*-oxide and *trans*-oxide remained un-reactive. The *trans*-epoxide **1b** did not react upon prolonged agitation for up to 24 h. Hence, the reaction under said conditions was diastereo-differentiating between *cis*- and *trans*-epoxides. In the course of the reaction at 5 h, components of the system were *trans*-diaxial diol **(1d)** formed by cleavage of *cis*-oxide and un-reacted *trans*-oxide. Since these products have different in boiling ranges, they were separated by fractional distillation under reduced pressure. After the separation, the *trans*-epoxide was confirmed by comparison with standard *trans*-limonene oxide (NMR). The standard *trans*-limonene oxide was synthesized *via* β-bromo-*tert*-alcohol intermediate, by reacting limonene with *N*-bromosuccinimide (NBS) in aqueous acetone followed by treatment with Na_2CO_3 in aqueous ethanol.[15] The characteristic doublet signal for the proton attached to epoxide at 2.98 ppm in *trans*-epoxide (**1b**) was confirmed with standard *trans*-epoxide by NMR experiment. Kinetics of the reaction of *cis*-/*trans*-limonene oxide and *cis*-/*trans*-carvomenthene oxide with respect to time is presented in figure 2.

Next, the reaction of *cis*-/*trans*-limonene oxide in the presence of $InCl_3$ (10 mol%) in methanol was carried out (scheme 2). It was found that **1a** reacted faster and afforded the ring cleaved product **1c** leaving behind **1b** unaffected. Easy separation of *trans*-epoxide was accomplished by fractional distillation under reduced pressure as **1b** and **1c** had different boiling ranges. Graphical representation of progress of the reaction of mixture *cis*-/*trans*-limonene oxide and *cis*-/*trans*-carvomenthene oxide in methanol is presented in figure 3.

Further, the reaction was checked with *cis*-/*trans*-carvomenthene oxide (schemes 1 and 2). Carvomenthene was prepared by hydrogenation of *R*-(+)-limonene using Raney nickel catalyst. It was then distilled to afford pure carvomenthene. Its epoxide was prepared using peracetic acid (30%) oxidation. The *cis*-/*trans*-carvomenthene oxides were not well-resolved by GC analysis. The *cis*-/*trans* ratio was checked by NMR. Integration of proton attached to oxirane ring at 2nd position in *cis*-epoxide appeared as broad singlet at 3.01 ppm integrated to 0.45 units, whereas *trans*-epoxide appeared as doublet at 2.95 ppm integrated to 0.55 units, hence, the ratio of *cis*- to *trans*-oxide was taken as 45:55. Pure *trans*-epoxide of carvomenthene

Table 1. Reaction of *cis*/*trans*-limonene oxide in water in presence of 10% $InCl_3$.

Cycle No.	% oxide in 5 h		Time (h)[a]
	cis-oxide	*trans*-oxide	
1	0	54	5.0
2	0	54	5.0
3	2	54	5.5
4	7	54	6.0
5	12	54	7.5
6	17	54	8.5
7	22	54	10.0
8	27	54	13.0
9	30	54	16.0
10	33	54	18.0

[a]Time taken for complete conversion of *cis*-oxide

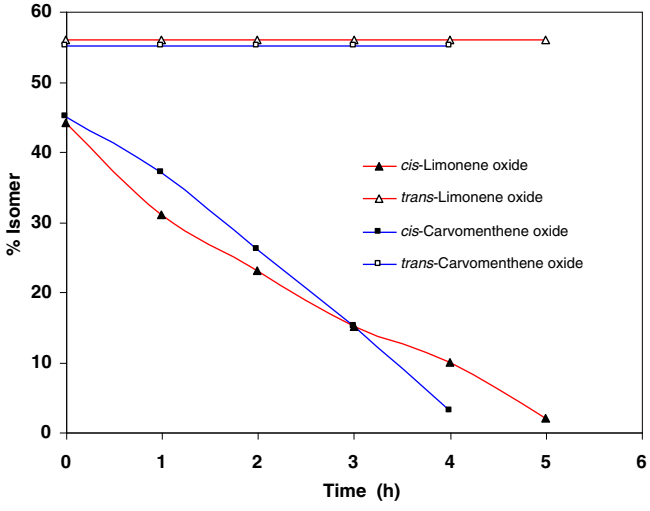
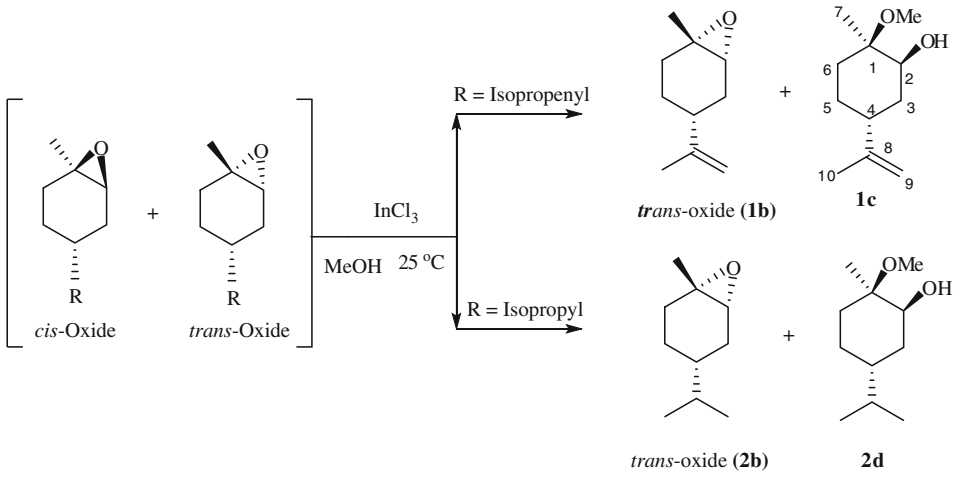


Figure 2. Kinetics of the reaction of *cis*/*trans*-limonene and carvomenthene oxides in water in the presence of $InCl_3$.



Scheme 2. Reaction of *cis/trans*-limonene and carvomenthene oxides in methanol in the presence of $InCl_3$.

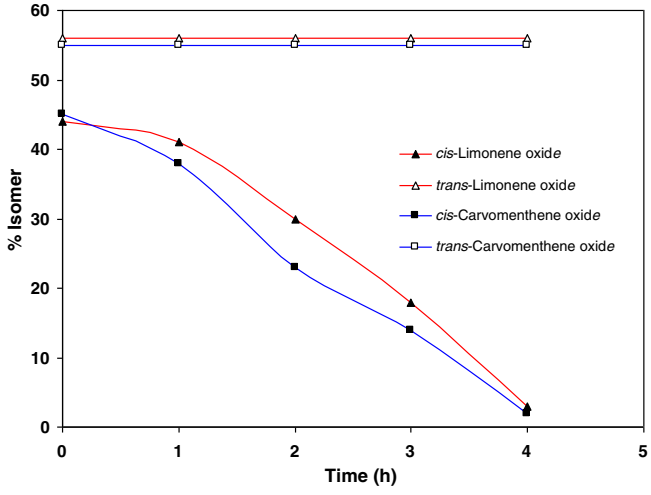
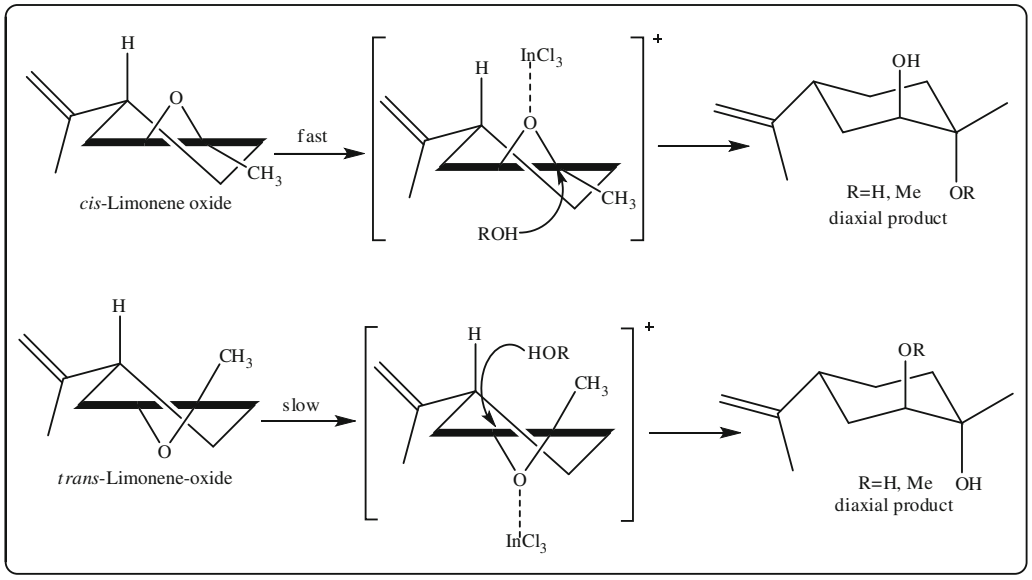


Figure 3. Kinetics of the reaction of *cis/trans*-limonene oxide and *cis/trans*-carvomenthene oxide in methanol in the presence of $InCl_3$.

was also prepared *via* β-bromo-*tert*-alcohol intermediate by reacting carvomenthene with NBS followed by treatment with Na_2CO_3 in aqueous ethanol.[15] Reaction of *cis-/trans*-carvomenthene oxides in presence of $InCl_3$ in water occurred at a similar rate and was completed in 4 h leaving behind un-reacted *trans*-carvomenthene oxide **2b** (scheme 1). The reaction was checked at 25°C with 10% $InCl_3$. T*rans*-carvomenthene oxide remained un-reactive during the time in which *cis*-carvomenthene oxide completely reacted affords resolution of *trans*-epoxide. The rate of reaction versus percent *cis-/trans*-oxide is plotted (figure 2). The reaction when performed at 5–10°C and 10–15°C was also found to be selective but rate of reaction was slow.

In the reaction using methanol as a solvent, *cis*-carvomenthene oxide reacted selectively to give 1-methoxy-2-hydroxy-*p*-menthane as the product, while



Scheme 3. $InCl_3$-catalysed solvolysis of *cis-/trans*-limonene oxide.

trans-oxide remain un-reacted (scheme 2). The mixture of un-reacted *trans*-oxide and chiral product **2d** were separated by fractional distillation. The rate of reaction versus time is presented in figure 3.

A plausible explanation for the kinetic separation of *trans*-limonene oxide and *trans*-carvomenthene oxide in water and methanol in presence of $InCl_3$ is presented in scheme 3. The isopropenyl group occupies equatorial position in both *cis*- and *trans*-oxides due to inherent conformational differences.[7] Interaction of indium chloride with oxirane oxygen followed by its opening takes place fast in case of *cis*-oxide. Nucleophilic substitution takes place at more substituted carbon (C-1) due to more S_N1 character. Interaction of indium chloride with oxirane oxygen in case of *trans*-oxide is relatively slower and its opening with nucleophile leading to diaxial product takes place with nucleophile sitting on C-2 according to Furst–Plattner rule.[7] Hence, this difference in reactivity between *cis*- and *trans*-oxide with Lewis acid towards nucleophilic substitution facilitates kinetic separation of *trans*-oxide over *cis*-oxide by stopping the reaction at appropriate time.

4. Conclusions

In summary, we report a new and environment-friendly kinetic separation protocol for *trans*-limonene and carvomenthene oxides. An easily available and inexpensive $InCl_3$ was employed to achieve kinetic separation in a simple experimental protocol. Catalytic activity of $InCl_3$ was found to be effective up to 10 cycles. When compared to existing methods for kinetic separation, the method is superior in affording separation of terpene-epoxides in quantitative yield. The present methodology also works well in the presence of an alcoholic solvent such as methanol.

Supplementary information

The electronic supplementary material contains ^1H NMR, ^{13}C NMR and mass spectra of compounds **1b**, **1c**, **1d**, **2b**, **2c** and **2d**, which can be seen in www.ias.as.in/chemsci.

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