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Cr^{III}(salen) catalysed asymmetric ring opening of monocyclic terpene-epoxides

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Abstract—The racemic Cr^{III}(salen) complex was found to be an efficient catalyst for the asymmetric ring opening (ARO) with $TMSN_3$ of cyclic 1,2-epoxy-terpenes bearing C_4-substituents. © 2003 Elsevier Science Ltd. All rights reserved.

The chiral Cr^{III}(salen) complex **1** (Fig. 1) proved to be an efficient catalyst for the enantioselective ring opening of epoxides with trimethylsilylazide ($TMSN_3$). The reaction was first examined with terminal epoxides[1] as substrates, but also *meso*-epoxides[2], 1,2-[3] and 2,2-disubstituted[4] epoxides have been successfully subjected to the asymmetric ring opening reaction with $TMSN_3$. In a search for other and more complex substrates for the ARO reaction, a range of trisubstituted epoxides, in particular epoxides of monocyclic terpenes were screened.

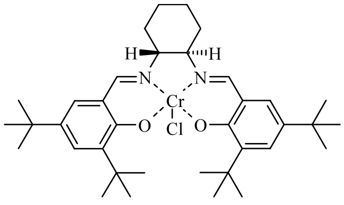
Terpenes are widely distributed in nature, in particular as essential oils in higher plants. Epoxy-terpenes often serve as starting materials for the synthesis of fragrances, flavours, herbicides, fungicides and biologically or therapeutically active substances.[5] In this perspective enantiopure epoxy-terpenes are valuable building blocks.[6]

Starting from the corresponding terpenes, the epoxy-terpenes (Fig. 2) were synthesised by epoxidation with *m*-chloroperbenzoic acid[7] (*m*-CPBA) or with an H_2O_2–phosphorous–tungsten phase transfer system.[8] Both types of epoxidations are rapid and result in high epoxide yields.

(−)-Carvomenthene epoxide **4** was synthesised by hydrogenation of (−)-limonene 1,2-epoxide **2** using Raney nickel as catalyst.[9]

The ARO reactions were performed at room temperature and at atmospheric pressure. The temperature affects the selectivity of the resolution: if the reaction mixture is heated (in order to speed up the reaction) the selectivity diminishes. If the reaction mixture is cooled, the selectivity slightly improves, but the reaction slows down significantly. A reaction temperature of about 20°C (rt) proved to be a good compromise.

Diethyl ether was used as solvent, since it offered superior results compared to other ethereal solvents like



(R,R)-**1**

Figure 1. The chromium^{III}(salen) complex.

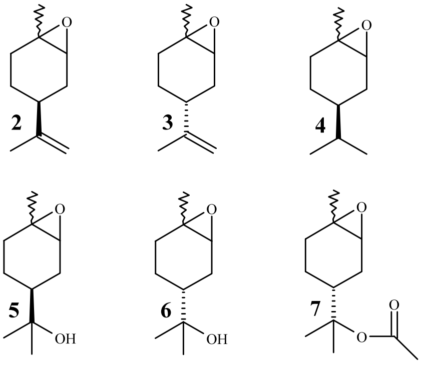


Figure 2. The epoxy-terpene substrates.

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THF or TBME.[10] Though it can be expected that some of these reactions can be performed without solvent, most of these substrates however need to be dissolved in a solvent because of their relatively high melting point (M_p >20°C).

Although a slight excess of $TMSN_3$, (0.55 equiv.) suffices, a larger excess of 0.7 to 1.0 equiv. is used to shorten the reaction time. Since the trisubstituted epoxides are not easily accessible for coordination with the catalytic complex due to steric effects, a fairly high catalyst/substrate ratio was required in order to reduce the reaction time. A catalyst/substrate ratio of 5 mol% was preferred.

First of all, it is important to stipulate that the Jacobsen kinetic resolution of internal epoxides has not been demonstrated.[12] This was confirmed by the ARO of 1-methyl-1,2-epoxy-cyclohexene, for which an enantiomeric excess of barely 5% was reached (Fig. 3).

Regarding the catalytic results summarised in Table 1, a racemic Cr^{III}(salen) catalyst[13] was used and for all substrates, D.E. values of over 85% were obtained at conversions of 42–62%.[14]

Therefore, the selectivity for the asymmetric ring opening of the epoxy-terpenes is not due to the chiral properties of the Cr^{III}(salen) catalyst, but is caused by the presence of the C_4-substituent. It is likely that the C_4-substituent forces the substrate molecules into the most stable conformation, orienting the substituents into an equatorial position. Consequently blocking the approach of the $Cr–N_3$ species from one side, and thereby allowing only a specific coordination of the epoxide with the catalytic complex resulting in a diastereoselective ARO reaction. Furthermore, the selectivity of the ARO for all tested substrates was the same, the *cis*-diastereomers were selectively transformed and all remaining epoxides were *trans*-epoxides (Fig. 4).

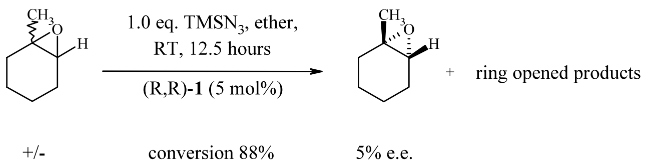


Figure 3. ARO of 1-methyl-1,2-epoxy-cyclohexene.

The Cr^{III}(salen) catalyst merely acts as an activating agent for the azide-transfer, not as a stereogenic environment for the ARO.

The selectivity of the ARO reactions can be tuned for both epoxide and product by adjusting the amount of $TMSN_3$. All ARO reactions in Table 1 (except entry 1) were optimised for the recuperation of the optically pure epoxides. Therefore larger amounts of $TMSN_3$ (0.7 or 1.0 equiv.) were added. The reaction can also be adapted for the synthesis of ring-opened products, hence 0.5 equiv. of $TMSN_3$ should be added and considerably longer reaction times are required (entry 1).

Both *trans*-epoxide and ring-opened product can be isolated from the reaction mixture by rotatory evaporation followed by a column chromatography work-up. The obtained azido products can be transformed into the corresponding amino alcohols by a desilylation/reduction sequence.[16]

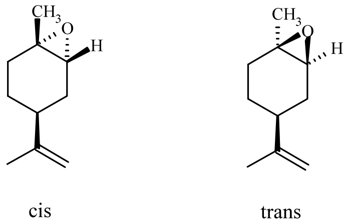
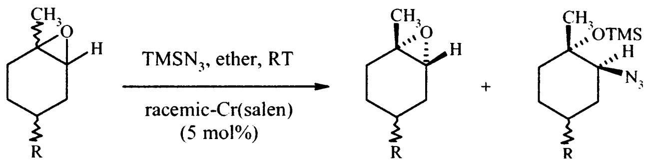


Figure 4. *cis*- And *trans*-diastereomers of (–)-limonene 1,2-epoxide.[15]

Table 1. Catalytic results of asymmetric ring opening of cyclic 1,2-epoxy-terpenes



Entry	Substrate	$TMSN_3$ (equiv.)	Reaction time (h)	Conversion (%)	Initial D.E.[a] (%)	Final D.E.[a] (%)	Remaining epoxide	Product D.E.[a] (%)
1	**2**	0.5	182	50	13	85	*trans*	83
2	**2**	0.7	42	56	9	92	*trans*	36
3	**3**	1.0	48	56	17	88	*trans*	27
4	**4**	1.0	25	55	14	90	*trans*	52
5	**5**	0.7	19.5	53	20	92	*trans*	N.d.[b]
6	**6**	0.7	9	42	18	96	*trans*	N.d.
7	**7**	0.7	23	62	20	94	*trans*	N.d.

[a] D.E.: diastereomeric excess.[11]

[b] N.d.: not determined.

The technique here proposed is thus a practical strategy for the synthesis of both optically pure *trans*-1,2-epoxyterpenes and the corresponding *cis*-azido-products that can serve as chiral auxiliaries or be derivatised to biologically active compounds.[6]

Acknowledgements

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11. All diastereomeric excesses were determined by chiral GC on a Chrompack-CHIRASIL-DEX CB column (0.32 mm×0.25 μm×25 m) using FID detection. The D.E.'s listed in Table 1 correspond to the composition of the reaction mixture and consequently do not reflect to the isolated products.
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13. Initially some introductory experiments using (*R*,*R*)-Cr^{III}(salen) proved the capacities of the complex for ARO reactions of terpene-epoxides. In later experiments, the (*S*,*S*)-Cr^{III}(salen) exhibited identical selectivity and reactivity. Therefore the final experiments (listed in Table 1) were carried out with a racemic Cr^{III}(salen) catalyst.
14. As a representative procedure, the experimental details and work-up for the ARO of (−) limonene 1,2-epoxide are described:
    In a glass vial with a magnetic stirrer, the Cr^{III}(salen) complex (5 mol%) was dissolved in diethyl ether (5 ml). Toluene was added as internal standard. (−)-Limonene 1,2-epoxide (1.5 mmol) was added and the solution was allowed to stir for 10 min before adding 0.7 equiv. of $TMSN_3$. The glass vial was then sealed and the reaction mixture was stirred at room temperature for 72 h. A conversion of 50% was observed (measured by GC analysis). Diethyl ether and an excess of $TMSN_3$ were removed from the reaction mixture by rotary evaporation. By adding a small amount of diethyl ether/hexane (5/95) to the residue, the catalyst precipitates and can easily be separated and recycled. The remaining mixture was purified by column chromatography (silica gel; diethyl ether/hexane: 5/95) and (−)-*trans*-limonene 1,2-epoxide (43% yield on epoxide, 89% D.E.) and azido product (36% yield, 90% D.E.) were recovered (not listed in Table 1). During the chromatographic work-up, desilylation of the azido compound already occurred due to the mild acidity of the silica combined with traces of water in the stationary phase.
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