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Priority Communication

# Microwave-assisted Cr(salen)-catalysed asymmetric ring opening of epoxides

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**Abstract**

The effect of microwaves on the kinetics and the selectivity of the Cr(salen)-catalysed asymmetric ring opening of epoxides was investigated. It was found that the reaction rate of the Cr(salen)-catalysed kinetic resolution of terminal epoxides and the asymmetric ring opening (ARO) of *meso*-epoxides could be increased by three orders of magnitude without impairing the selectivity.


*Keywords:* Microwaves; Cr(salen); Asymmetric ring opening; Epoxides; Kinetic resolution

## 1. Introduction

Since the first reports on the use of microwaves in organic chemistry in 1986 [1,2], the number of publications on microwave-assisted chemistry has increased every year. Whereas many applications focus on uncatalysed organic synthesis reactions [3], only a minority of the articles have described the beneficial effect of microwaves on catalysed reactions. Furthermore, the area of transition metal-catalysed asymmetric reactions [4] has received little attention in the microwave research, probably because the difference in activation energy of the two enantiomers involved in the asymmetric reaction is insignificant in comparison with the energy supplied by the microwaves [5]. Consequently, the enantioselectivity of the reactions could be affected in a negative way by the use of microwaves.

The currently available microwave generators allow better control of reaction conditions such as irradiation power, temperature, and pressure. This enables fine-tuning of the microwave treatment to optimise the selectivity of even enantioselective reactions. In this context, the Cr(salen)-catalysed asymmetric ring opening of epoxides was tested under microwave irradiation.

The chiral Cr(salen) complex **1b** (Fig. 1) catalyses the kinetic resolution of racemic mixtures of terminal epoxides with high selectivity [6]. This yields a highly enantioenriched epoxide and a ring-opened product with high optical purity. In case of *meso*-epoxides, the symmetric epoxide can be opened to offer highly enantioenriched products (Fig. 2). In fact, the commercially available precatalyst **1a** is transformed into the catalytically active species **1b** under reaction conditions [7].

The Cr(salen)-catalysed asymmetric ring opening (ARO) of epoxides displays a second-order kinetic dependence on catalyst concentration [7]. Two catalyst molecules are involved in a simultaneous activation of both epoxide substrate

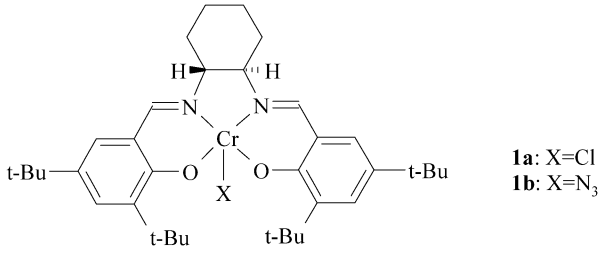


Fig. 1. The (R,R)-Cr(salen) complex.

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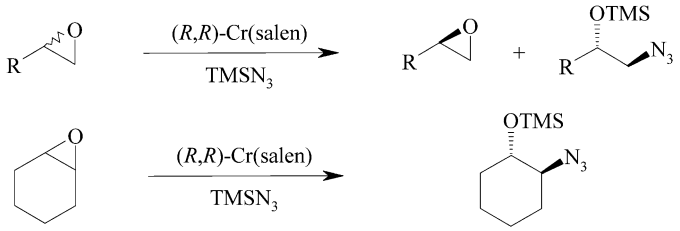



Fig. 2. ARO of terminal and *meso*-epoxides.

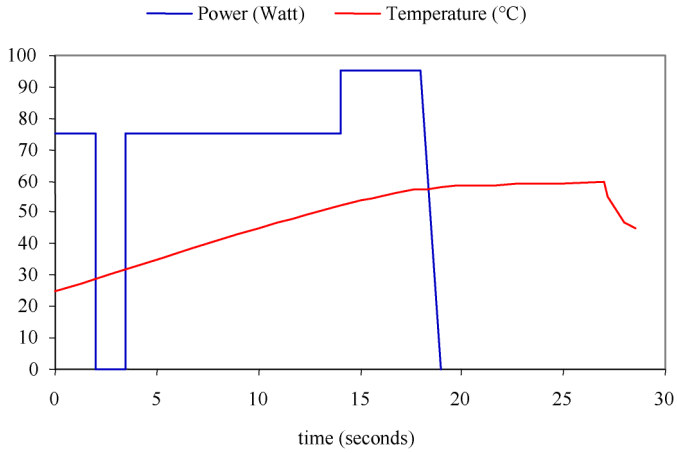



Fig. 3. Temperature and power profile of the microwave assisted ARO of cyclohexene oxide, using a hold time of 7 s at 60 °C.

and azide. To enforce this cooperative mechanism, Jacobsen and co-workers have prepared covalently linked dimeric complexes [8]. These dimeric Cr(salen) complexes were 1 to 2 orders of magnitude more reactive than the monomeric analogues, with no loss in enantioselectivity. The only drawback is the difficult and time-consuming synthesis of such special Cr(salen) complexes.

## 2. Experimental

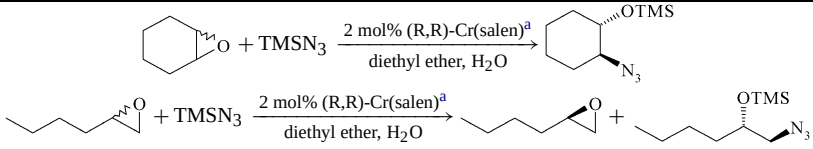
In this framework, commercially available monomeric Cr(salen) complex was tested under microwave irradiation (Table 1). Cyclohexene oxide and 1,2-epoxyhexane were chosen as representative substrates for the two major substrate classes (i.e., *meso*-epoxides and terminal epoxides).

The experiments were performed on a Biotage InitiatorTM Sixty microwave synthesizer. The ARO of cyclohexene oxide is described here as a representative procedure. In a 2- to 5-ml vial, 62.5 mg of Cr(salen) catalyst (2 mol%) was weighed. After addition of a stirring bar, 3 ml of diethyl ether, 500 µl of cyclohexene oxide, 100 µl of octane (internal standard), and 100 µl of water were added. This mixture was stirred for 60 s, and a reference gas chromatography (GC) sample was taken. Finally, 500 µl of $TMSN_3$ (1 eq.) was added to the reaction mixture, and the vial was capped. The reaction mixture was irradiated with microwaves (Fig. 3), and after a hold time of 7 s at 60 °C, was cooled with pressurised air. Ultimately, the reaction mixture was analysed by chiral GC, using a Chrompack-CHIRASIL-DEX CB column (0.32 mm × 0.25 mm × 25 m) using flame ionisation detection.

## 3. Results and discussion

For both epoxide substrates, the microwave-assisted ARO reactions displayed a very significant increase in reactivity of

Table 1
Microwave assisted ARO of epoxides at 60 °C versus traditional room temperature reactions




| Substrate | Temperature | Reaction time[b] | $TMSN_3$ (Eq.) | Hold time | Conversion (%) | EE (%) | | TON[c] | TOF[d] ($h^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Epox. | Prod. | | |
| Cyclohexene oxide[e] | Room temperature | 18 h | 1.05 | – | 83 | – | 84 | 41.5 | 2.3 |
| Cyclohexene oxide | 60 °C (microwave) | 30 s | 1.0 | 7 s | 84 | – | 78 | 42 | 5040 |
| Cyclohexene oxide | 60 °C (oil bath) | 3 m | 1.0 | – | 86 | – | 41 | 43 | 860 |
| 1,2-Epoxyhexane[f] | 0–2 °C | 27 h | 0.5 | – | 45.5 | – | 97 | 22.7 | 0.8 |
| 1,2-Epoxyhexane | 60 °C (microwave) | 30 s | 0.6 | 3 s | 59.5 | 99.5 | 76.5 | 29.7 | 3570 |
| 1,2-Epoxyhexane | 60 °C (microwave) | 30 s | 0.5 | 1 s | 57.9 | 98.6 | 89.8 | 28.9 | 3474 |
| 1,2-Epoxyhexane | 60 °C (microwave) | 30 s | 0.4 | 1 s | 45.3 | 70.6 | 93.5 | 22.6 | 2718 |
| 1,2-epoxyhexane | 60 °C (oil bath) | 3 m | 0.5 | – | 58.1 | 97.5 | 72.4 | 29.0 | 581 |

[a] For all reactions precatalyst **1a** was used, except for the ARO of 1,2-epoxyhexane at 0–2 °C, which was performed with catalyst **1b**.
[b] For the microwave assisted ARO reactions, the reaction time is considered to be 30 s. For the reference reactions at 60 °C, the glass vials were put in an oil bath for 3 m.
[c] TON, turnover number (number of substrate molecules converted to product per catalyst molecule).
[d] TOF, turnover frequency (TON per unit of time).
[e] Homogeneous reaction at room temperature, optimised for product selectivity, data from Ref. [9].
[f] Homogeneous reaction at 0–2 °C, optimised for product selectivity, data from Ref. [10].

the Cr(salen) catalyst with no significant loss in enantioselectivity. The turnover frequencies (TOFs) for the microwave-assisted ARO reactions were increased by 3 orders of magnitude over those for the reactions at room temperature.

For the ARO of cyclohexene oxide at room temperature, the enantiomeric excess for the ring-opened product amounted to 84% [9]. The TOF was 2.3 $h^{-1}$, compared with $>5000\,h^{-1}$ for the microwave-assisted system. The ring-opened product for the microwave-assisted reaction was present in an enantiomeric excess of 78%.

For the kinetic resolution of terminal epoxides, the selectivities of both the epoxide and ring-opened products were equal to the reported values for the room temperature reactions [10]. As shown in Table 1, the reaction can be tuned for the recovery of highly enantioenriched epoxide or highly pure ring-opened product by simply adjusting the amount of $TMSN_3$ used. Again, a TOF of $>3500\,h^{-1}$ can be calculated for the microwave-assisted reaction, whereas at room temperature the TOF is limited to $0.84\,h^{-1}$.

In fact, the selectivity of the kinetic resolution is temperature-dependent; an increase in reaction temperature causes an important decrease in the enantiomeric excess of the product. The reference reactions, optimised for product selectivity, were performed at 0–2 °C and room temperature, respectively. The impact of heating on selectivity is illustrated by the reactions performed at 60 °C using an oil bath as heating apparatus, which provided enantioselectivities of 41 and 72% for the ring-opened products.

The rapid homogeneous heating offered by microwave irradiation can eliminate wall effects caused by temperature gradients, whereas with oil-bath heating, the reaction mixture in contact with the vessel wall is heated first [5]. Rapid cooling of the reaction mixture is necessary to halt the reaction, because for the kinetic resolution, the enantiomeric excess of the ring-opened product decreases with increasing conversion. In contrast, enhancement of the polarity from the ground state to the transition state can result in an additional acceleration of the reaction [11]. Hence, the microwave flash-heating is superior to traditional heating, because it can combine an increased reaction rate with optimal selectivity.

## 4. Conclusion

The reaction rate of the Cr(salen)-catalysed ARO of epoxides can be improved by increasing the reaction temperature, but because the product selectivity is temperature dependent, this increase in temperature has a negative impact on the enantiomeric excess of the product. In this context, the use of microwaves offers an alternative. This is the first report of a kinetic resolution enhanced by microwave irradiation. The reaction rate can be enhanced by 3 orders of magnitude over the reaction at room temperature. At the same time, because of rapid homogeneous heating, the selectivity of the reaction is not impaired. Therefore, the commercially available Cr(salen) complex under microwave irradiation can replace the synthesis of dimeric Cr(salen) complexes as a method of increasing the reactivity of the catalyst.

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