

Microwave-assisted asymmetric ring opening of *meso*-epoxides with aromatic amines catalyzed by a Ti-*S*-(–)-BINOL complex

Rukhsana I. Kureshy,* Surendra Singh, Noor-ul H. Khan, Sayed H. R. Abdi, Santosh Agrawal, Vishal J. Mayani and Raksh V. Jasra

Silicates and Catalysis Discipline, Central Salt and Marine Chemicals Research Institute (CSMCRI), Bhavnagar, 364 002 Gujarat, India

Received 12 March 2006; revised 18 May 2006; accepted 24 May 2006
Available online 13 June 2006

Abstract—Catalytic asymmetric ring opening of cyclohexene oxide and *meso*-stilbene oxide with anilines was catalyzed by a Ti-(*S*)-(–)-BINOL complex to afford β -amino alcohols in high yield (up to 95%) and good enantioselectivities (ee up to 55%) under microwave irradiation. The reaction using a microwave was found to be 10 times faster than traditional oil-bath heating with retention of enantioselectivity.

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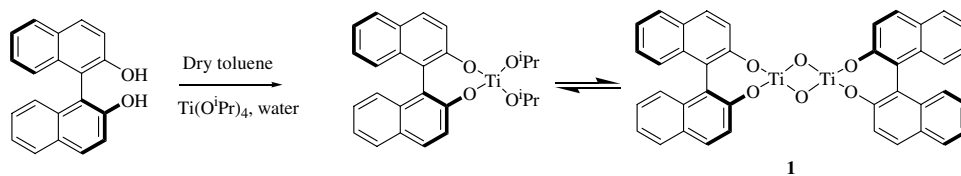
Chiral transition metal complex catalyzed asymmetric ring opening of *meso*-epoxides with aromatic amines^{1,2} is of particular interest because the chiral β -amino alcohol products have wide applications in the synthesis of pharmaceutically active compounds³ and chiral auxiliaries/ligands. In recent years, attempts have been made to ring open *meso*-epoxides with alkyl/aryl amines to generate β -amino alcohols using various lanthanides^{4–8} with (*R*)/(*S*)-BINOL, Cr(Salen)⁹ and Sc(bipyridine).¹⁰ Microwave irradiation is used for the ring opening of vinyl epoxides and terminal epoxides by NH₄OH,^{11,12} thiols,¹³ pyrazole and imidazole¹⁴ and amines;^{15–17} however, the area of transition metal catalyzed asymmetric epoxide ring opening reactions using microwaves¹⁸ has scarcely been studied, probably due to the difference in activation energy of the two enantiomers involved in the asymmetric reaction which is insignificant in comparison with the energy supplied by microwaves.¹⁹ Consequently, the enantioselectivity of the reactions could be affected in a negative way by the use of microwaves. Recently, Jacobs et al. reported the asymmetric ring opening of epoxides using TMSN₃ as the nucleophile under microwave irradiation.²⁰ As part of our continuing efforts towards asymmetric ring opening of

meso-epoxides with aromatic amines using Ti-(*S*)-BINOL at ambient temperature,²¹ we report for the first time asymmetric ring opening of *meso*-stilbene oxide and cyclohexene oxide with aniline and substituted anilines catalyzed by a Ti-(*S*)-BINOL complex to give enantioenriched *syn*- β -amino alcohols and *trans*- β -amino alcohols in high yields (up to 95%) with up to 55% enantiomeric excess under microwave (MW) irradiation at 60 °C. The enantiomeric excess (ee) was comparable with the values obtained at room temperature.

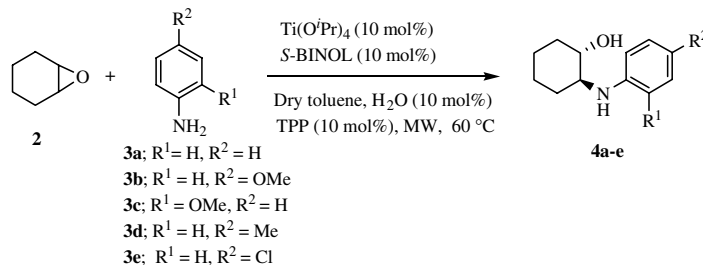
Complex **1** was generated in situ by the reaction of equimolar quantities of (*S*)-BINOL, Ti(O^{*i*}Pr)₄ and water in dry toluene (Scheme 1). NMR and MS data for complex **1** suggested the existence of a catalytically active dimeric species, which was in equilibrium with the corresponding monomeric species and this observation was in agreement with previous reports.^{22,23} In our earlier report on asymmetric ring opening of *meso*-stilbene oxide with aniline at room temperature, we observed that complex **1** was superior in performance to other Ti(IV) complexes and toluene was the solvent of choice.²¹ The asymmetric ring opening (ARO) of *meso*-cyclohexene oxide with aniline was carried out using 10 mol % of complex **1** under microwave irradiation as a test reaction in toluene. The asymmetric ring opening under microwave irradiation at 60 °C showed a comparable enantiomeric excess (49% ee, Table 1, entry 3) to that of the reaction conducted at 60 °C in an oil bath (54% ee, Table 1, entry 5). The turnover frequency

Keywords: Microwave irradiation; Ring opening; Epoxides; Aniline; Ti-BINOL complex.

* Corresponding author. Tel.: +91 278 567760; fax: +91 0278 2566970; e-mail: rukhsana93@yahoo.co.in



Scheme 1. Preparation of complex 1.

Table 1. Asymmetric ring opening of cyclohexene oxide with anilines catalyzed by complex 1 under microwave irradiation^a

Entry	Amine	Temperature	Reaction time	Isolated yield 4a-e (%) ^b	ee (%) ^c	TON ^d	TOF ^e
1	3a	27 (RT)	2 h	92	39	9.2	4.6
2	3a	40 (MW)	30 s	80	50	8.0	960
3	3a	60 (MW)	30 s	90	49	9.0	1080
4	3a	60 (MW) ^f	30 s	85	17	8.5	1020
5	3a	60 (oil-bath heating)	6 min	93	54	9.3	93
6	3a	70 (MW)	30 s	95	26	9.5	1140
7	3a	70 (oil-bath heating)	5 min	94	55	9.4	112
8	3b	60 (MW)	30 s	90	46	9.0	1080
9	3c	60 (MW)	30 s	92	50	9.2	1104
10	3d	60 (MW)	30 s	95	47	9.5	1140
11	3e	60 (MW)	30 s	94	48	9.4	1128

^a A mixture of complex **1** (generated in situ using 10 mol% *S*-(-)-BINOL and 10 mol% Ti(O^{*i*}Pr)₄ in 150 μL toluene), 10 mol% TPP, epoxide (0.5 mmol) and aniline (0.5 mmol) was irradiated for 30 s in a microwave oven at 60 °C.

^b Isolated yield after chromatographic separation.

^c Determined by HPLC using OJ and OD columns. The absolute configuration was found to be 1*S*,2*S* by comparison with the literature.^{8,21}

^d TON, turnover number (number of substrate molecules converted to product per catalyst molecule).

^e TOF, turnover frequency (TON per unit of time) h⁻¹.

^f Reaction carried out in the absence of TPP.

(TOF) of complex **1** was also increased 10-fold under microwave irradiation (Table 1, entry 3) compared to traditional heating at 60 °C (Table 1, entry 5) and was 235 times that of the reaction conducted at room temperature (Table 1, entry 1).

Further it has been reported in the literature^{3,21} that the use of additives improves the ee of the amino alcohols. We conducted similar experiments in the presence of triphenylphosphine (TPP) and in the absence of TPP (Table 1, entry 4), and the results showed that TPP (Table 1, entry 3) increased the ee of *trans*-β-amino alcohol **4a** probably due to the weak interaction of TPP with complex **1**. These results are significantly superior compared to those obtained using the previously reported lanthanide iodo binaphtholate⁸ (yield 55%, ee 20%, 18 h) and the enantiomeric excess was comparable with Sc(Bipyridine),¹⁰ but the reactivity was found to be better in the case of complex **1** than both the other systems.^{8,10} The absolute configuration was determined by comparing the optical rotation (found to be 1*S*,2*S*)

and the HPLC profile with the literature, and details are given in the Supplementary data.

Furthermore, we have studied the ARO of cyclohexene oxide with aniline under microwave irradiation whilst varying the temperature (Table 1, entries 2, 3 and 6). The TOF and ee were highest at 60 °C as shown in Figure 1. On increasing the temperature up to 70 °C, the TOF was increased but the enantioselectivity was decreased (Table 1, entry 6). On the other hand, when the temperature was decreased to 40 °C, there was a decrease in TOF along with a slight improvement in enantioselectivity (entry 2).

The ARO of cyclohexene oxide with different anilines under microwave irradiation at 60 °C was also studied. The isolated yields and ee's of the products **4b-e** were in the range of 90–95% and 46–50%, respectively (entries 8–11). The ARO of cyclohexene oxide with 4-methoxyaniline gave product **4b** (ee 46%, yield 90%, TON = 9 and TOF = 1080 h⁻¹), which is an improvement on that

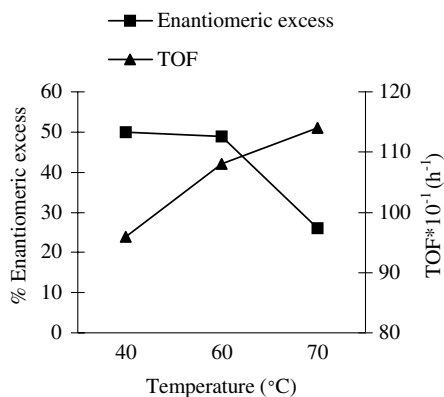
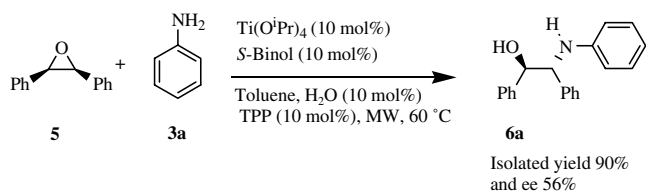


Figure 1. Effect of temperature on the enantiomeric excess and TOF of the asymmetric ring opening of cyclohexene oxide with aniline.

reported in the literature using Pr-(*R*)-BINOL-Ph₃P=O (ee 35%, yield 87%, TON = 8.7 and TOF = 0.725 h⁻¹)³ and BINOL/Yb(OTf)₂ (ee 37%, yield 64% and TON = 6.4).⁵ We also investigated the asymmetric ring opening of *meso*-stilbene oxide with aniline under microwave irradiation and obtained *syn*-β-amino alcohol **6a** in 90% isolated yield and 56% ee (Scheme 2). These results are comparable with our previous report²¹ and superior to that of the system reported by Hou et al.⁵ using BINOL/Yb(OTf)₂ (ee 17%, 92% isolated yield).

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.¹⁹ In contrast, enhancement of the polarity from the ground state to the transition state can result in an additional acceleration of the reaction.²⁴ Hence, microwave flash heating is superior to traditional heating, because it combines increased reaction rates with optimal selectivity.

In summary, we have developed a regio-, diastereo-, and enantioselective ring opening reaction of *meso*-cyclohexene oxide and *meso*-stilbene oxide with anilines under microwave irradiation at 60 °C catalyzed by a Ti-(*S*)-(-)-BINOL complex to give the respective *trans*-β-amino alcohols **4a–e** and *syn*-β-amino alcohol **6a** in 80–95% isolated yields with 49–56% ee. The asymmetric ring opening of other epoxides with anilines and the mechanistic aspects of the reaction are under study in our research laboratory.



Acknowledgements

S.S., CSIR (SRF) and R.I.K. are thankful to DST and CSIR Network on catalysis for financial assistance and are also thankful to Dr. P. K. Ghosh, the Director of the Institute, for providing instrumentation facilities.

Supplementary data

A typical experimental procedure for the asymmetric ring opening of an epoxide by an aromatic amine, ¹H and ¹³C NMR data and a HPLC chromatogram are provided as supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.150.

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