Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3143–3146

TETRAHEDRON
LETTERS

A new and efficient catalytic isomerization of *cis*- and *trans*-epoxides

Ching-Yu Lo, Sitaram Pal, Arjan Odedra and Rai-Shung Liu*

Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan 30043, ROC

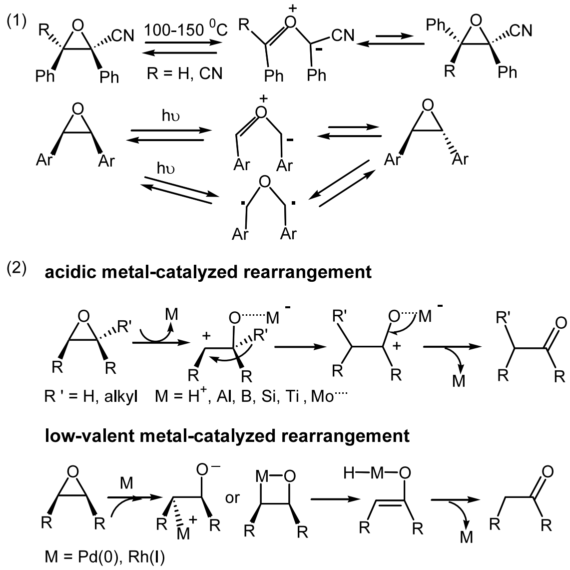
Received 18 February 2003; accepted 20 February 2003

Abstract—We report new ruthenium-catalyzed *cis–trans* isomerization of various functionalized epoxides. Enantiospecific isomerization of chiral epoxides is achieved without loss of enantiopurity, and epimerization occurs only at the epoxide carbon of the activating group. © 2003 Elsevier Science Ltd. All rights reserved.

Since epoxides (oxirane) are readily available intermediates, numerous reactions have been developed to make them useful in organic synthesis.[1,2] The stereoselective formation of a C–X bond (X = C, N, O, S) is readily achieved via the ring-opening of a *cis* or *trans* epoxide by a suitable nucleophile.[1,2] Despite the great popularity of epoxides in organic reactions, there has been little success in the isomerization of *cis* and *trans* epoxides.[1] The thermal isomerization of epoxides can be applied only to oxiranes of special types such as cyanostilbene oxide and α,β-dicyanostilbene oxide[3] (Scheme 1, Eq. (1)); the mechanism involves a carbonyl ylide intermediate. Photochemical isomerization of epoxides is only known for α,β-diaryloxirane derivatives, and the formation of the intermediate carbonyl ylide or diradical species depends on the presence of a suitable sensitizer.[4] This process is plagued by the formation of byproducts. Although some epoxyketones undergo isomerization catalyzed by sodium ethoxide, the recovery yields of epoxides are very low.[5] Common functionalized epoxides like aryl-, vinylepoxides or epoxyketones suffer homolysis of C–O and C–C bonds upon thermolysis or photolysis, to give complicated mixtures of products.[1,2]

Metal-catalyzed reaction is a powerful tool in organic synthesis. Most epoxides undergo catalytic rearrangement to ketones or aldehydes in the presence of either acidic or basic metal catalysts (Eq. (2)).[1,6–9] These rearrangement reactions have been intensively studied with the mechanisms depicted in Scheme 1. Isomerization of *cis* and *trans* epoxides was reported only for Ru(II)–porphyrin complexes, but the scope is limited to β-methyl-styrene oxide.[10] In this study, we report a new ruthenium-catalyzed *cis–trans* isomerization that is applicable to various epoxides comprising a phenyl, furanyl, alkynyl, alkenyl, ketone and aldehyde group.

We examined isomerization with various ruthenium catalysts, and found that $TpRuPy_2Cl$[11] (**1**) (Tp = trispyrazolylborate, Py = pyridine, 4.0 mol%, toluene, 100°C, 12 h) was the most active for the isomerization of *cis*-stilbene oxide (1.5 M) to its *trans*-isomer without formation of byproduct (96% recovery yield). The equilibrium ratio (*trans*/*cis* = 24.0) was confirmed by a reverse isomerization of *trans*-stilbene oxide using cata-



Scheme 1.

---

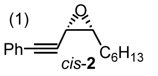
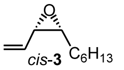
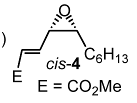
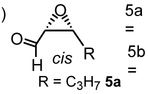
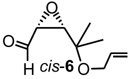
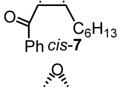
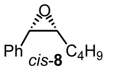
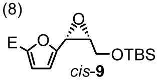
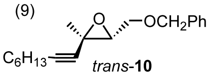
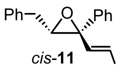
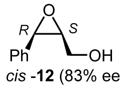
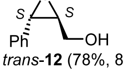
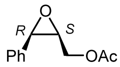
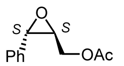
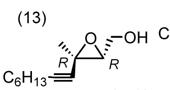
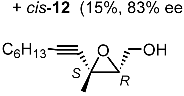
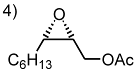
* Corresponding author. E-mail: rsliu@mx.nthu.edu.tw

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)00465-9

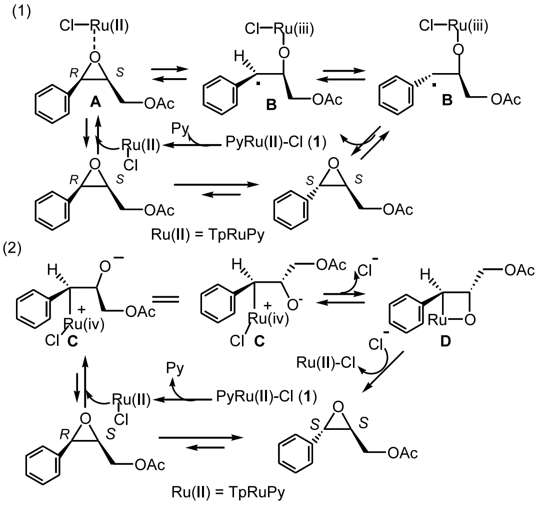
lyst **1** under the same conditions.[12] $C_5Me_5RuPy_2Cl$ (4 mol%) was less active for the isomerization of *cis*-stilbene oxide and give a *trans*/*cis* ratio of 0.68 after heating in toluene (100°C, 12 h). $CpRuPy_2Cl$ (10 mol%), pyridine alone (10 mol%) and many basic ruthenium complexes show no catalytic activity.[13]

Table 1 shows various *cis*-epoxides that can be isomerized by catalyst **1** (2–5 mol%) in toluene (100°C, 8–12 h). The resulting equilibrium ratios were verified by reverse isomerization of pure *trans*-isomers using catalyst **1**. Recovery yields exceeded 95%, with negligible amounts of byproduct. This isomerization is effective for diverse substrates including alkynyl epoxide **2**, and vinyl- and (2-methoxycarbonyl)vinyl epoxides **3** and **4**. It is also applicable to *cis*-epoxides **5**–**9**, bearing an aldehyde, ketone, phenyl and furanyl group, respectively (entries 4–8). Tertiary alkynyl epoxide **10** also underwent isomerization using catalyst **1**. Both the forward and reverse isomerization of *trans*- and *cis*-isomers of epoxide **10** confirm that *cis*-epoxide is more stable than its *trans*-isomer. This result is consistent with a calculation using the MM 2-program.[14] The acetylene group of **10** with a linear geometry is less bulky than a methyl group. A higher loading of catalyst **1** (5 mol%) is required for complete isomerization of tertiary epoxide *cis*-**11**. We also prepared chiral epoxides **12**–**14** to investigate the nature of the mechanism of isomerization. The *trans*-epoxides of **12** and **13** isolated from the reaction mixtures were determined to have a (2*S*,3*S*) configuration based on comparison of their [α]-values with those of authentic samples.[15,16] No decrease in ee values was seen either for the *trans*-isomers of **12** and **13** or for their recovered *cis* isomers. Epimerization clearly occurs at the epoxide carbon of the phenyl group of **12** and **13** during the catalytic reaction. Similar results were seen for chiral tertiary epoxide **14**, the tertiary epoxide carbon of which undergoes epimerization[15] to form its *cis*-isomer without any loss of its enantiopurity. Unfunctionalized *cis*-epoxide **15** fails to undergo isomerization even using a higher loading of **1** (10 mol%).

Table 1. Catalytic isomerization of epoxides and their isomeric rations

starting epoxides	isomeric ratios[a] (recovery yields)
(1)  *cis*-**2**	*trans* / *cis* = 1.3 (97%)[b]
(2)  *cis*-**3**	*trans* / *cis* = 5.8 (97%)
(3)  *cis*-**4** E = CO_2Me	*trans* / *cis* = 6.0 (97%)
(4)  *cis* R = C_3H_7 **5a** C_6H_{13} **5b**	**5a** *trans* / *cis* = 2.4 (95%) **5b** *trans* / *cis* = 5.0 (95%)
(5)  *cis*-**6**	*trans* / *cis* > 20 (98%)
(6)  *cis*-**7**	*trans* / *cis* = 3.1 (98%)
(7)  *cis*-**8**	*trans* / *cis* = 5.4 (96%)
(8)  *cis*-**9** E = CO_2Me	*trans* / *cis* = 5.8 (98%)
(9)  *trans*-**10**	*cis* / *trans* = 5.8 (98%)
(10)  *cis*-**11** E = CO_2Me	*trans* / *cis* = 1.2 (98%)
(11)  *cis*-**12** (83% ee)	 *trans*-**12** (78%, 82% ee)[c] + *cis*-**13** (15%, 83% ee)
(12)  *cis*-**13** (83% ee)	 *trans*-**13** (79%, 83% ee) + *cis*-**12** (15%, 83% ee)
(13)  *trans*-**14** (91% ee)	 *cis*-**14** (76%, 91%ee) *trans*-**14** (17%, 91% ee)
(14)  *cis*-**15**	only *cis*-**15**

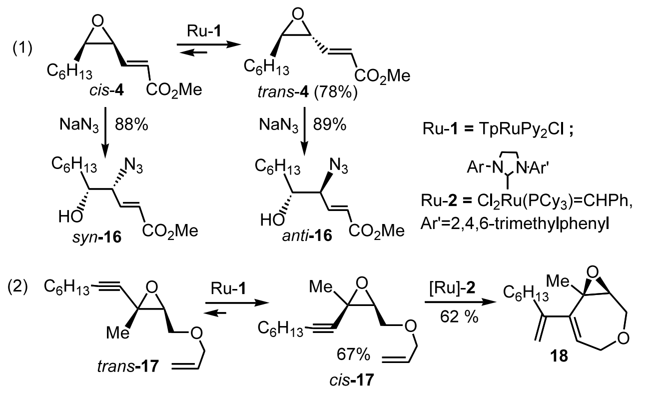
Conditions: (a) 2 mol% catalyst for entries 1-6, 8-9, 11-13, 5 mol% for entries 7 and 10, 10 mol% for entry 14; toluene 100 °C, 12 h (b) the combined yields of cis and trans-epoxides after column chromatography (entries 1-10) (c) the isolated yields after separation from silica column (entries 11-13).



Scheme 2.

Scheme 2 shows two possible mechanisms for isomerization of *cis*–*trans* epoxides. Similar to Ru(II)–porphyrin complexes,[10] epoxide may coordinate to TpRuPyCl to form species **A** which subsequently undergoes C–O bond cleavage to form Ru(III)-radical intermediate **B**. This radical species is stabilized by a phenyl or other unsaturated functionalities. An alternative pathway involves an initial attack of the epoxide by ruthenium metal (Scheme 2), to give Ru(IV)-intermediate species **C**, and Ru(IV)–oxetane **D** is obtained via formation of a Ru(IV)–O bond. Species **D** may be prone to irreversible reductive elimination to complete the reaction. Both processes rationalize the enantiospecific isomerization of chiral epoxides **12**–**14**. The success of this process relies on the Tp group of catalyst **1**, which shows one crucial feature[17,18]—it increases the basicity of Ru(II) to facilitate Ru(II)–Ru(III) or Ru(II)–Ru(IV) interconversion. Further clarification of the reaction mechanism requires additional work.

The ease of the isomerizations of epoxides provides new routes in organic synthesis. As shown in Scheme 3, *cis*-epoxide **4** provides access not only to *syn*-alcohol **16** (88% yield) but also to *anti*-alcohol **16**. *trans*-Epoxide **4** was isolated in 80% yield using this approach (entry 3, Table 1), and further gave *anti*-alcohol **16** (89%) upon treatment with NaN_3 and NH_4Cl in $MeOH/H_2O$. Catalyst **1** (2 mol%) also effected the



Scheme 3.

transformation of *trans*-epoxide **17** into its *cis*-isomer (*cis*/*trans* = 4.3) in 67% yield. Enyne metathesis of *cis*-isomer of **17** using Grubbs catalyst[19] afforded functionalized diene **18** in 62% yield.

In summary, we found that the isomerization of *cis*-*trans* epoxides can be achieved efficiently with ruthenium catalyst **1** (2–5 mol%) under mild conditions. The method is applicable to diverse functionalized epoxides. The mechanism of isomerization involves cleavage of the C–O bond at the epoxide carbon of the activating group. S_N2 attack of the epoxide by ruthenium is proposed as the key step. This isomerization enhances the usefulness of epoxides in organic synthesis.

Supplementary material

Experimental procedures for catalytic reactions and spectral data of new compounds **1**–**18**.

Acknowledgements

The authors wish to thank National Science Council, Taiwan for support of this work.

References

1. For review of oxirane chemistry, see: Erden, I. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 1A, pp. 97–1369; (b) Sainsbury, M. In *Three-, Four-, and Five-membered Monoheterocyclic Compounds*. Rodds' Chemistry of Carbon Compounds, 2nd ed.; Second Supplement to Volume IV, Heterocyclic Compounds; Part A, Elsevier: Amsterdam, 1997.
2. For representative examples, see: (a) Lautens, M.; Fagnou, K. *Org. Lett.* **2000**, *2*, 2319; (b) Sodergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760; (c) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557; (d) Lin, K.-Q.; Li, Y.-M.; Chan, A. S. C. In *Principles and Applications of Asymmetric Synthesis*; Wiley: London, 2001; Chapter 4, pp. 159–220; (e) Paterson, I.; Berrisford, D. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1179.
3. (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 572; (b) Mukaiyama, T.; Kuwajima, J.; Ohno, K. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 54; (c) McDonald, H. H. J.; Crawford, R. J. *Can. J. Chem.* **1972**, *50*, 428.
4. (a) Rau, H. *Chem. Rev.* **1983**, *83*, 535; (b) Inoue, Y.; Yamasaki, N.; Shimoyama, H.; Tai, A. *J. Org. Chem.* **1993**, *58*, 1785; (c) Manring, L. E.; Peters, K. S. *J. Am. Chem. Soc.* **1984**, *106*, 8077; (d) Griffin, G. W. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 537.
5. House, H. O.; Reif, D. J. *J. Am. Chem. Soc.* **1957**, *79*, 6491.
6. The term 'isomerization reaction' is often misused in the literature.[1,9a,b] Many so-called isomerization reactions are actually rearrangement reactions. For instance, the base-catalyzed isomerization of epoxide in Ref. 1a involves the rearrangement of epoxide to allylic alcohol in the presence of a strong base.
7. For reviews on acid-mediated rearrangement of epoxides: (a) Rickborn, B. In *Comprehensive Organic Synthesis, Carbon–Carbon σ-Bond Formation*; Trost, B. M.; Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 3.3, pp. 733–775; (b) Parker, R. E.; Issacs, N. S. *Chem. Rev.* **1959**, *59*, 737.
8. For representative examples of acid-catalyzed rearrangement of epoxides, see: (a) Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* **2001**, *66*, 8779 and references cited therein; (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379 and references cited therein; (c) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
9. The mechanism appears to vary for low-valence metal catalysts, see: (a) Milstein, D.; Buchman, O.; Blum, J. *J. Org. Chem.* **1977**, *42*, 2299; (b) Kulawiec, R. J. *J. Org. Chem.* **1994**, *59*, 7195; (c) Alper, H.; Des Roches, D.; Durst, T.; Legault, R. *J. Org. Chem.* **1976**, *41*, 3611; (d) Suzuki, M.; Dda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623; (e) Eisenmann, J. L. *J. Org. Chem.* **1962**, *27*, 2706.
10. Groves, J. T.; Ahn, K.-H.; Quinn, R. *J. Am. Chem. Soc.* **1988**, *110*, 4217.
11. Gemel, C.; Trimmel, G.; Slugovc, C.; Kremel, S.; Mereiter, K.; Schmid, R.; Kirchner, K. *Organometallics* **1996**, *15*, 3998.
12. The *trans*/*cis* equilibrium ratio of stilbene oxide was found to be 31 upon photolysis at 23°C in pentane. See Ref. 4b.
13. No catalytic activity was found for ruthenium catalysts including TpRu(PPh$_3$)$_2$Cl, C$_5$M$_5$Ru(PPh$_3$)$_2$Cl, TpRu(COD)Cl, Cl$_2$Ru(PPh$_3$)$_3$ and C$_5$M$_5$Ru(COD)Cl.
14. The *cis* form of alkynylepoxide **10a** has 0.89 kcal/mol less in energy than its *trans* isomer based on MM2 program (Pro 6.0 edition).
15. The *trans*-epoxide **12** given from isomerization of (2*S*,3*R*)-*cis*-epoxide has [α] value −45.6 (83% ee, CHCl$_3$, *c* = 0.50) consistent to that of authentic (2*S*,3*S*)-*trans*-epoxide ([α] = −49.5, 89% ee, CHCl$_3$, *c* = 0.50) reported in literature.[16] We also prepared authentic (2*S*,3*S*)-*trans*-epoxides **13** and (2*S*,3*R*)-*cis*-epoxide **14**, the [α] values of which are used to identify absolute configurations of products isomerized from (2*S*,3*R*)-*trans*-epoxides **13** and (2*S*,3*S*)-*cis*-epoxide **14**. For the details, see Supporting information.

16. Wang, Z.-M.; Zhou, W. S. *Tetrahedron* **1987**, *43*, 2935.
17. For the stereoelectronic effect of the Tp group on coordination and reaction chemistry, see Ref. 10 and Trofimenko, S. In *Scorpinoates: Polypyrazolylborate Ligands and Their Coordination Chemistry*; Imperial Press, 1999.
18. (a) Yeh, K.-L.; Liu, B.; Lo, C.-Y.; Huang, H.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2002**, *124*, 6510; (b) Lo, C.-Y.; Guo, H.; Lian, J.-J.; Shen, F.-M.; Liu, R.-S. *J. Org. Chem.* **2002**, *67*, 3930.
19. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.