ORGANIC LETTERS

2005
Vol. 7, No. 10
1927−1930

Enantioselective Ring-Opening Reaction of *meso*-Epoxides with ArSeH Catalyzed by Heterometallic Ti–Ga–Salen System

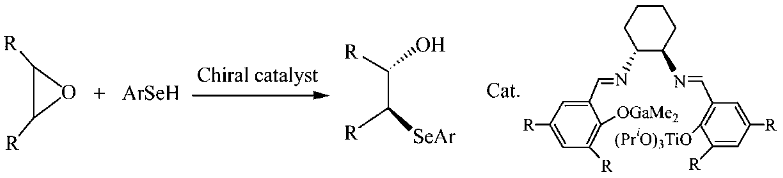
Minghua Yang,[†] Chengjian Zhu,*[,†,‡] Fang Yuan,[†] Yijun Huang,[†] and Yi Pan[†]

State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

cjzhu@netra.nju.edu.cn

Received February 14, 2005

ABSTRACT



The first example of enantioselective ring-opening reaction of *meso*-epoxides with aryl selenols to give optically active β-arylseleno alcohol in up to 97% ee was realized, using a chiral Ti–Ga–Salen heterometallic catalyst. A strong synergistic effect of different Lewis acids in the system was exhibited in the catalytic process.

Selenium-based methods have developed rapidly over the past few years and are now a very important tool in organic synthesis.[1] Chiral organoselenium compounds have been employed as useful ligands, catalysts, or intermediates in various asymmetric transformations such as diethylzinc addition to aldehydes, asymmetric hydrosilylation, and 1,4-addition of Grignard reagents to enones.[2] β-Arylseleno alcohols are used as starting materials for several interesting synthetic applications.[3] Tiecco et al. recently described mild and convenient methods for the synthesis of enantiomerically pure substituted 1,3-oxazolidin-2-ones and tetrahydrofurans starting from chiral β-arylseleno alcohols.[4] It is of interest to obtain the optically active β-arylseleno alcohols by the catalytic asymmetric desymmetrization of *meso*-epoxides with selenols, which has the advantage of simultaneously establishing two contiguous stereogenic centers.

The design and use of chiral homo- and heterobimetallic complexes for asymmetric catalysis have seen significant progress and are emerging as a rapidly developing area.[5] Inspired by the advantage of enzymes that contain two or more active sites, chemists have succeeded in developing some kinds of multifunctional catalysts for asymmetric synthesis.[6] For example, Shibasaki et al. developed a series of heterobimetallic, two-center Lewis acid−Brönsted base asymmetric catalysts, in which the Brönsted basicity promotes the reactions, while the Lewis acidity simultaneously

---

[†] Nanjing University.

[‡] Chinese Academy of Sciences.

(1) (a) Pandey, G.; Gadre, S. R. *Acc. Chem. Res.* **2004**, *37*, 201. (b) Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3740. (c) Khokhar, S. S.; Wirth, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 631. (d) Devan, N.; Sirdhar, P. R.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2002**, *67*, 9417. (e) Engman, L.; Gupta, V. *J. Org. Chem.* **1997**, *62*, 157. (f) Nakamura, S.; Aoki, T.; Ogura, T.; Wang, L. B.; Toru, T. *J. Org. Chem.* **2004**, *69*, 8916.

(2) (a) Tiecco, M.; Testaferri, L.; Santi, C. *Org. Lett.* **2004**, *6*, 4751. (b) Wirth, T. *Tetrahedron Lett.* **1995**, *36*, 7849. (c) Hiroi, K.; Suzuki, Y.; Abe, I. *Tetrahedron: Asymmetry* **1999**, *10*, 1173. (d) Fukuzawa, S. I.; Tsudzuki, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1039. (e) Kazuki, O.; Yoshiaki, N.; Sakae, U.; Akio, T. *Tetrahedron Lett.* **2004**, *45*, 6137.

(3) (a) Tomoda, S.; Iwaoka, M. In *Topics in Current Chemistry*; Wirth, T., Ed.; Springer: Berlin, 2000; p 55. (b) Tiecco, M. In *Topics in Current Chemistry*; Wirth, T., Ed.; Springer: Berlin, 2000; p 7. (c) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3131.

(4) (a) Tiecco, M.; Testferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Chem. Eur. J.* **2004**, *10*, 1752. (b) Tiecco, M.; Testferri, L.; Bagnoli, L.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2004**, *15*, 405.

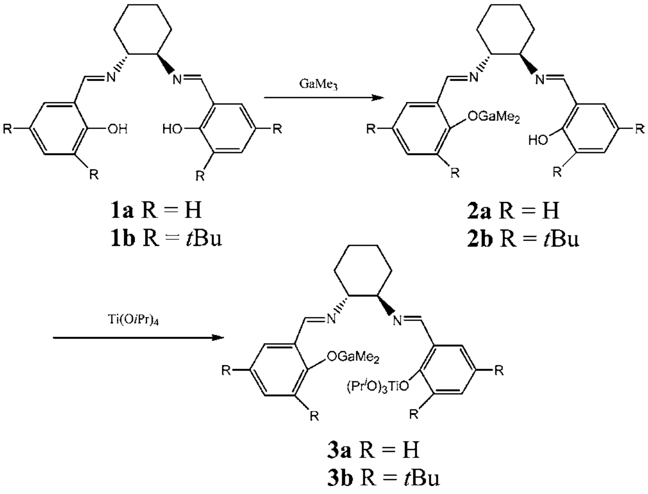
(5) (a) Ma, J. A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566 and references therein. (b) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928. (c) Ohno, K.; Kataoka, Y.; Mashima, K. *Org. Lett.* **2004**, *6*, 4695. (d) Luo, Z.; Liu, Q.; Gong, L.; Cui, X.; Mi, A.; Jiang, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4532.

10.1021/ol0503034 CCC: $30.25

assists the catalysis by controlling the position of the electrophiles as well as activating them, and successfully applied them to a variety of enantioselective transformations with excellent selectivities.[7] Very recently, Belcokon and Kagan showed that a mixture of two chiral V^{V} and Ti^{IV} complexes resulted in the formation of a mixed complex that exhibited catalytic properties derived from both homometallic species.[8]

Herein we wish to report the enantioselective ring-opening reaction of *meso*-epoxides[9] with aryl selenols catalyzed by a novel heterobimetallic system, Ti−Ga−Salen catalyst system, in which two different Lewis acids activate and/or direct the substrate and nucleophile, respectively, and promote the asymmetric reaction synergistically.

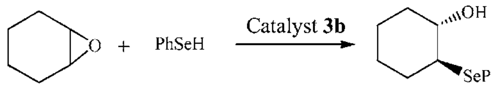
Scheme 1. Formation of Ti−Ga−Salen Heterobimetallic Catalysts



The readily obtainable Salen compounds (*R*,*R*)-**1** were chosen as the requisite ligands. As shown in Scheme 1, treatment of **1** with an equivalence of $GaMe_3$ provided monometallic "open" complexes **2** in high yields.[10] Reactions of **2** with another equivalent of Ti(O*i*Pr)$_4$ gave the heterobimetallic complexes **3**, which were directly used as chiral catalysts. Using hexane as the solvent, we initially tested the asymmetric ring-opening reaction of cyclohexene oxide with selenophenol at 20 °C with **3a** and **3b** as the catalysts (10 mol %), respectively. To our delight, the reaction gave the β-phenylseleno alcohol in 85% ee and 96% chemical yield with **3b** as the catalyst, while only 9% ee was obtained with **3a** as the catalyst. To the best of our knowledge, this is the first example of catalytic enantioselective ring-opening reaction of *meso*-epoxide with selenol.

The reaction conditions were then optimized as shown in Table 1 with **3b** as a catalyst. From the results, we could see that all of the solvents gave excellent chemical yields; toluene and hexane provided good enantioselectivities (entries 3 and 4), while Et_2O and CH_2Cl_2 showed only mediocre ee values (entries 1 and 2). Among the solvents tested, hexane was proven to be the best solvent in terms of both the chemical yield and enantioselectivity. A variation of the reaction temperature from 20 to −40 °C caused a significant increase in the ee value to 97% (entry 6), but there was a small decrease when the reaction was carried out at −78 °C (entry 7). We were pleased to find that there was no significant change in enantioselectivity and chemical yield when the catalyst amount was decreased to 5 mol % (entry 8). The reaction still showed good results even with only 2 mol % catalyst used (entry 9). Those results demonstrated that the Ti−Ga−Salen heterobimetallic catalyst was very efficient for the reaction. By the way, the addition of 4 Å molecular sieves did not improve the reactivity and enantioselectivity for the reaction.

Table 1. Asymmetry Ring Opening of Cyclohexene Oxide with Selenophenol under Different Conditions



entry	**3b** (mol %)	solvent	*T* (°C)	time (h)	yield[a] %	ee[b] %
1	10	Et_2O	20	2	96	69
2	10	CH_2Cl_2	20	2	90	35
3	10	toluene	20	2	93	83
4	10	hexane	20	2	96	85
5	10	hexane	0	3	96	90
6	10	hexane	−40	5	94	97
7	10	hexane	−78	5	83	91
8	5	hexane	−40	5	93	97
9	2	hexane	−40	5	92	95
10	0.5	hexane	−40	5	62	89

[a] Isolated yield after purification by prepared TLC. [b] Determined by HPLC analysis on a Chiracel OD-H chiral column.

Asymmetric ring openings of a variety of *meso*-epoxides with selenophenol and 1-selenonaphthol were investigated

---

(6) (a) Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782. (b) Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410. (c) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (d) Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Ohnoto, K.; Maruok, K. *J. Am. Chem. Soc.* **2004**, *126*, 1150.

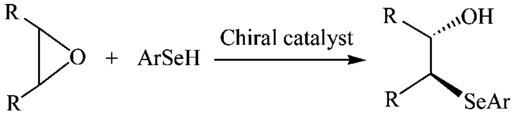
(7) (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (b) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (c) Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int., Ed.* **2003**, *42*, 5489. (d) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.*, **2004**, *126*, 8777.

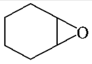
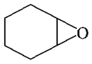
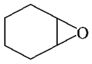
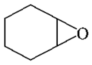
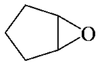
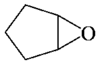
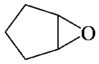
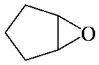
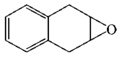
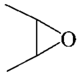
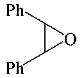
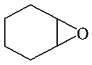
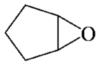
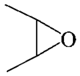
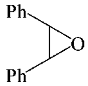
(8) Belokon, Y. N.; North, M.; Maleev, V. I.; Voskoboev, N. V.; Moskalenko, M. A.; Peregudov, A. S.; Dmitriev, A. V.; Ikonnikov, N. S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 4085.

(9) (a) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 1. (b) Zhou, H. Y.; Campbell, E. J.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 2229. (c) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252. (d) Denmark, S. E.; Barsanti, P. A.; Wang, K. T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428. (e) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J.; Snapper, M. L.; Hoveyda, A. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668. (f) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (g) Schneider, C.; Sreekanth, A. R.; Mai, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5691. (h) Zhao L. S.; Han, B.; Huang, Z. L.; Miller, M.; Huang, H. J.; Malashock, D. S.; Zhu, Z. L.; Milan, A.; Robertson, D. E.; Weiner, D. P.; Burk, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 11156. (i) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 2173.

(10) Hill, M. S.; Wei, P.; Atwood, D. A. *Polyhedron* **1998**, *17*, 811.

Table 2. Ring-Opening Reactions of Different *meso*-Epoxides with Selenophenol and Selenonaphthol Catalyzed by Different Types of Catalysts[a]

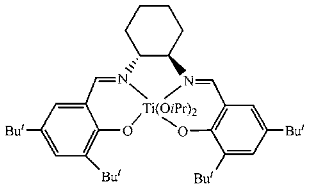


entry	epoxide	Ar	cat.	yield[b] %	ee % (config)[c]
1		Ph	**3b**	94	97 (*S*, *S*)
2		Ph	**2b**	75	32 (*S*, *S*)
3		Ph	**4**	85	59 (*S*, *S*)
4		Ph	**5**	75	35 (*S*, *S*)
5		Ph	**3b**	85	94 (*S*, *S*)
6		Ph	**2b**	70	35 (*S*, *S*)
7		Ph	**4**	74	55 (*S*, *S*)
8		Ph	**5**	72	39 (*S*, *S*)
9		Ph	**3b**	92	90
10		Ph	**3b**	87	87
11		Ph	**3b**	70	72
12		1-Naphthyl	**3b**	93	78
13		1-Naphthyl	**3b**	80	70
14		1-Naphthyl	**3b**	73	75
15		1-Nap-h-thyl	**3b**	70	55

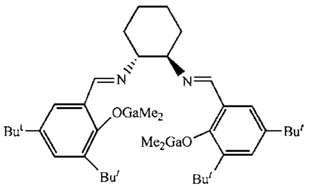
[a] Reaction conditions: epoxide (1.0 mmol), ArSeH (1.2 mmol), catalyst (5 mol %), hexane (3 mL), −40 °C, 5 h. [b] Isolated yields. [c] Enantiomeric purity was determined by HPLC analysis on a Chiracel OD-H column. The determination of absolute configuration was based on the comparison of CD spectroscopy of the product with that of sulfur analogue with known absolute configuration.[12]

under the optimized reaction conditions as in Table 1, entry 8. For comparison, Salen titanium complex **4**,[11] monogallium complex **2b**, and homobimetallic gallium complex **5**[10] were also examined as the catalysts for the ring-opening reactions of cyclohexene oxide and cyclopentene oxide with selenophenol under identical conditions. The results are shown in Table 2.

From Table 2, it can be found that all reactions proceeded smoothly to afford the *β*-arylseleno alcohols in high yields for both cyclic and acyclic *meso*-epoxides, with catalyst **3b** giving the best chemical yields. In terms of enantioselectivity, the open-chain mono- and homobigallium catalysts **2b** (entries 2 and 6) and **5** (entries 4 and 8) gave poor results, while the cyclic titanium complex **4** provided moderate selectivity (entries 3 and 7). As anticipated, the heterobimetallic catalyst **3b** gave the highest ee values with the substrates examined. The selectivity of catalyst **3b** showed significant margins over that of catalysts **2b**, **4**, and **5**. In other aspects, cyclic *meso*-epoxides provided better selectivities compared to acyclic ones, while the nucleophile selenophenol gave better results than selenonaphthol. It is also worth noting that the results represent a considerable improvement with respect to the reaction promoted by thiols and catalyzed by complex **4**.[12]



4



5

Although the complete reaction mechanism is not clear at this moment, the results shown above manifest that the two different Lewis acids Ti and Ga should work synergistically in the heterometallic catalyst system. A possible working model is depicted in Figure 1. It is likely that the epoxide coordinates to the hard Lewis acid titanium metal and is activated, while the nucleophile selenophenol coordinates to the relatively soft Lewis acid gallium, which directs the attack of the selenophenol to the epoxide more efficiently and selectively. The coordination of the oxygen in the isopropoxyl group to the gallium is supported by ^{1}H NMR study. The chemical shifts of the dimethylgallium hydrogens of complex **3b** appear at a higher field (*δ* −0.25 and −0.36 ppm) in comparison with that of complex **2b** (*δ* −0.22 and

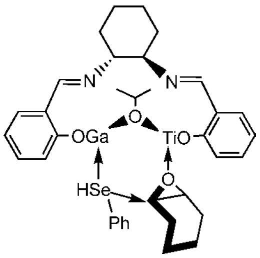


Figure 1. Possible working model for the synergistic effect (other groups omitted for clarity).

---

(11) (a) Belokon, Y.; Ikonnikov, N.; Moscalenko, M.; North, M.; Orlova, S.; Yashkina, L. *Tetrahedron: Asymmetry* **1996**, *7*, 851. (b) Jiang, Y.; Gong, L.; Feng, X.; Hu, W.; Pan, W.; Li, Z.; Mi, A. *Tetrahedron* **1997**, *53*, 14327.

(12) Wu, J.; Hou, X. L.; Dai, L. X.; Xia, L. J.; Tang, M. H. *Tetrahedron: Asymmetry* **1998**, *9*, 3431.

−0.31 ppm). The coordination of the oxygen in the isopropoxyl group to the gallium, which results in the close distance between the titanium and the gallium and the formation of a six-member transition state as well, is possible a crucial factor.

In conclusion, the enantioselective ring-opening reaction of *meso*-epoxides with aryl selenols to give the optically active *β*-arylseleno alcohols was realized in up to 97% ee, employing a novel type of chiral Ti−Ga−Salen heterometallic system that contains two different Lewis acids. A strong synergistic effect of different Lewis acids was exhibited in the catalysis process. In this catalyst system, the two Lewis acids activate and/or direct the substrate and nucleophile, respectively, and work synergistically. Other reactions catalyzed by these kinds of heterometallic catalysts are now under investigation in our group.

Acknowledgment. We gratefully acknowledge the National Natural Science Foundation of China (20332050, 20472028) and the Science Foundation of Zhejiang Province (M203052) for their financial support.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0503034