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Tetrahedron Letters 47 (2006) 3453–3457
Tetrahedron Letters

Synthesis of optically active 2-hydroxy monoesters via-kinetic resolution and asymmetric cyclization catalyzed by heterometallic chiral (salen) Co complex

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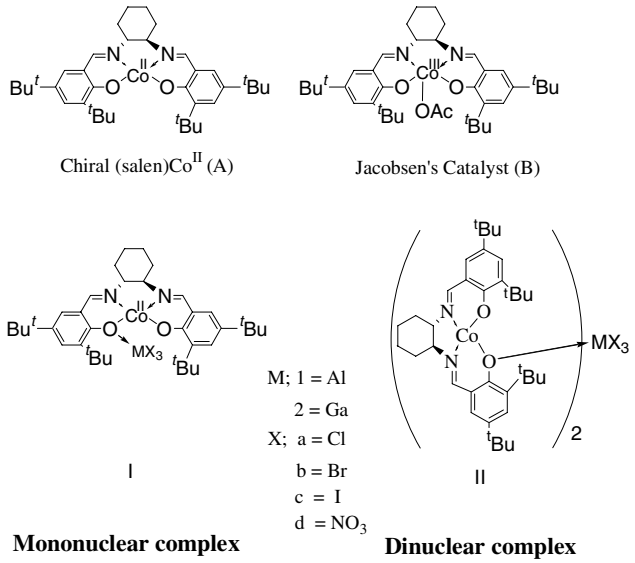
Received 12 September 2005; revised 6 March 2006; accepted 8 March 2006
Available online 3 April 2006

Abstract—The binuclear chiral (salen) Co complexes bearing Lewis acids of Al and Ga catalyze regio- and enantioselective ring opening of terminal epoxides with carboxylic acids. The ring opened product of epichlorohydrin with carboxylic acids followed by cyclization step in the presence of catalyst and base represent straightforward, efficient methods for the synthesis of enatiomerically enriched (>99% ee) valuable terminal epoxides. Strong synergistic effects of different Lewis acid of Co–Al and Co–Ga were exhibited in the catalytic process.

Among the myriad of nucleophiles that have been employed in epoxides ring openings catalyzed by chiral (salen) metal complexes,[1] carboxylic acids (which afford the corresponding 2-hydroxy monoesters) have been paid very less attention. In contrast to chemo- and regioselective ring openings of terminal epoxides with carboxylic acids,[2] only one literature is available for the enantioselective ring openings of *meso* epoxides using carboxylic acid as nucleophile.[3]

To broaden the application range of dinuclear chiral (salen) Co catalysts[1f,4] herein we report the catalytic enantioselective ring opening of terminal epoxides with carboxylic acids. Indeed, the Jacobsen's chiral (salen) Co complex and HKR catalyst[1a] showed low activity (<10% ee) in the present study. The coupled route of ARO/cyclization for epichlorohydrin (ECH) experienced to synthesize highly optically pure valuable terminal epoxides, for example, glycidyl butyrate.

We recently reported that dinuclear complexes bearing Lewis acids of B, Al, and Ga elements (Scheme 1) are highly efficient catalysts for the enantioselective ring opening of terminal epoxides with H_2O and HCl.[1f,4]



Scheme 1.

Encouraged with these results we have extended the applicability of these catalysts for enantioselective ring opening of terminal epoxides with carboxylic acids.

Keywords: Asymmetric catalysis; Dinuclear chiral catalyst; Asymmetric ring opening reactions; Cyclization.
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0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.042

Carboxylic acids are interesting candidates because of their low cost, ease of handling, and reaction with epoxides provide a direct route to 2-hydroxy monoesters.[3]

In a representative example of ARO of epichlorohydrin (ECH) with propionic acid, a series of chiral (salen) Co complexes (Scheme 1) were screened in order to identify the most enantioselective and reactive catalyst (Fig. 1). Complex II-1-d was proved to be most active and enantioselective (86% ee, 4 h). For a solvent choice in the present study, non-polar solvent *tert*-butyl methyl ether (TBME) dramatically increased the reactivity (Fig. 2) amongst CH_2Cl_2, CH_3CN, THF, and 1,4-dioxane. The catalyst loading amount depends on individual reaction (Table 1) and 2–4 mol % was optimum for the reaction to proceed (Fig. 3). Taking in to consideration all these parameters, the reactivity and enantioselectivity of the mono and dinuclear complexes were observed in the following order II-1-d > II-2-d ~ II-1-c ~ II-2-c ~ II-1-b ~ II-2-b ~ II-1-a > II-2-a > I-1-d > I-2-d ~ I-1-c ~ I-2-c ~ I-1-b ~ I-2-b ~ I-2-a > I-1-a. Furthermore, complex II-1-d was identified as the most effective of those evaluated, and it was selected for further study (Table 1).

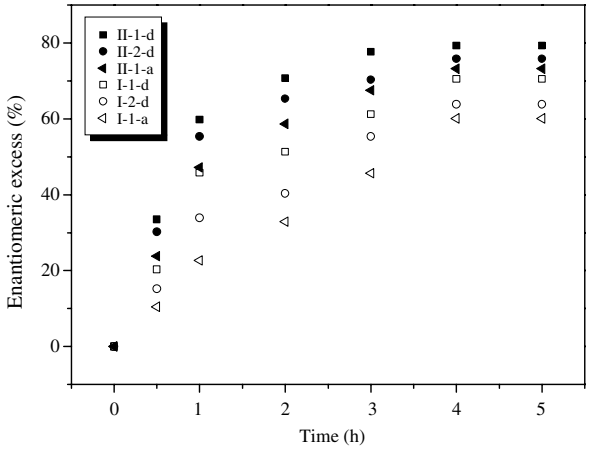


Figure 1. Comparison of the catalytic activity of the heterometallic mononuclear and dinuclear complexes for the ECH and propionic acid taking conditions according to Table 1 (ee % of recovered ECH).

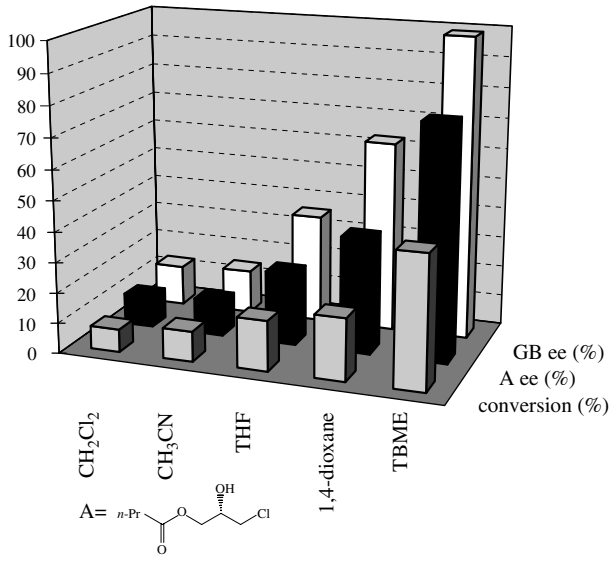


Figure 2. Conversions and enantioselectivities for the asymmetric ring opening of ECH with butyric acid in different solvents using catalyst II-1-d keeping other reaction conditions identical with that of Scheme 4.

Table 1 shows the optimized reaction conditions for various terminal epoxides with acetic, propionic, butyric, and propiolic acids. It is quite obvious from Table 1 that catalyst II-1-d showed mild (entry 1, 60% ee) to good (entry 14, 86% ee) enantioselectivity. In all the cases studied, the conversion of entries 1–25 to the corresponding 2-hydroxy monoesters underwent in one-pot within 4 h.

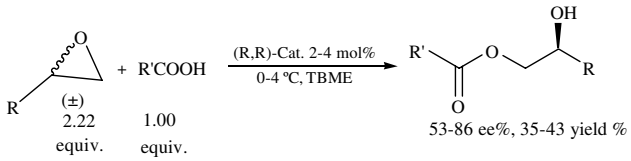
Complex II-1-d has also shown mild (45% ee) to good (66% ee) enantioselective ring opening for various terminal epoxides with aromatic carboxylic acid like benzoic acid and provides corresponding 2-hydroxy monoesters in a good yield (Table 2). The high selectivity factor ($k_{rel} = 60–70$) of ring opened product in the present study allowed to access optically active products in good ee % and useful yields.[5]

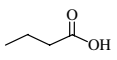
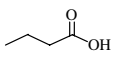
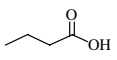
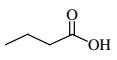
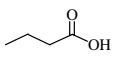
Unlikely asymmetric ring opening of terminal epoxides with H_2O (HKR), the mononuclear catalyst also showed good reactivity. It seems that Al and Ga Lewis acids coordinated to oxygen of chiral (salen) Co also play a crucial role to activate the reacting partners. In our present finding Co–Al/Co–Ga act as heterometallic complexes exhibiting two different Lewis acid centers and show strong synergistic effect. The proposed intramolecular pathway for the catalyst monomeric complex depicted in Scheme 2, which may be similar to enantioselective ring opening of epoxides with 4-methoxyphenol catalyzed by Ga heterobimetallic multifunctional catalysts was reported by Shibasaki et al.[6]

It appears that central metal atom Co activates, control the orientation of epoxide, and stereoselectively activate only one enantiomer and the Al. Ga seems to bind and control the orientation of nucleophlie carboxylic acid by enabling an enantioselective ring opening of epoxides with nucleophiles. However binuclear complexes show higher reactivity and enantioselectivity than their monomeric analogues. The intermolecular mechanism for mono- and dimeric complexes may follow the earlier report.[7] Although the ARO reaction with carboxylic acids is easily carried out with Co^{II} complexes, it appears that the actual reactive species is in fact Co^{III}.

In an important and interesting reaction the optically active epichlorohydrin and glycidol were obtained in good ee with over 70% ee and 43% yield, respectively, catalyzed by the catalyst dimeric complex in the presence of equivalent amount base with respect to the substrate (Scheme 3). The asymmetric cyclization of 1,3-dichloro-2-propanol involves asymmetric elimination of hydrogen chloride with base potassium phosphate. The asymmetric cyclization of 1, 3-dichloro-2-propanol could proceed significantly only in the presence of the catalyst. In the absence of a catalyst the reaction

Table 1. Asymmetric ring opening of terminal epoxides with carboxylic acids catalyzed by heterometallic chiral (salen) Co complex



Entry	Terminal epoxide (R)	Carboxylic acid	Catalyst type	Catalyst amount[a]	Time (h)	Product[b] ee % (yield)[c]
1	CH_3		II-1-d	2.0	1.0	60.2 (41)
2	CH_3		II-1-a	2.0	1.0	53.7 (37)
3	CH_3		A	2.0	1.0	23.8 (15)
4	CH_3		B	2.0	1.0	27.3 (17)
5	C_2H_5		II-1-d	2.0	1.5	65.7 (40)
6	CH_2Br		II-1-d	2.0	3.0	67.1 (43)
7	CH_2Cl		II-1-d	2.0	3.0	61.5 (42)
8	$C_6H_5OCH_2$		II-1-d	4.0	6.0	55.8 (39)
9	CH_3		II-1-d	2.0	2.0	66.9 (40)
10	CH_3		II-1-a	2.0	2.0	43.8 (41)
11	CH_3		A	2.0	2.0	21.6 (14)
12	C_2H_5		II-1-d	3.0	2.0	67.5 (40)
13	CH_2Br		II-1-d	2.0	4.0	71.8 (43)
14	CH_2Cl		II-1-d	2.0	4.0	86.3 (41)
15	$C_6H_5OCH_2$		II-1-d	4.0	5.0	53.5 (36)
16	CH_3		II-1-d	2.0	3.0	68.2 (40)
17	C_2H_5		II-1-d	2.0	3.5	67.5 (41)
18	CH_2Br		II-1-d	2.0	4.0	69.3 (40)
19	CH_2Cl		II-1-d	2.0	4.0	76.7 (43)
20	$C_6H_5OCH_2$		II-1-d	4.0	5.0	53.2 (39)
21	CH_3		II-1-d	3.0	3.0	65.6 (42)
22	C_2H_5		II-1-d	3.0	3.0	67.2 (43)

(*continued on next page*)

Table 1 (*continued*)

Entry	Terminal epoxide (R)	Carboxylic acid	Catalyst type	Catalyst amount[a]	Time (h)	Product[b] ee % (yield)[c]
23	CH_2Br		II-1-d	4.0	4.0	73.3 (40)
24	CH_2Cl		II-1-d	4.0	4.0	75.1 (41)
25	$C_6H_5OCH_2$		II-1-d	4.0	4.5	52.8 (35)

[a] In mol % loading on a per [Co] basis w.r.t. racemic epoxides.
[b] The products obtained were characterized by ^1H, ^{13}C, and elemental analyses.
[c] Isolated yield is based on racemic epoxides (theoretical maximum = 45%). Ee % was determined by chiral GC or chiral HPLC.

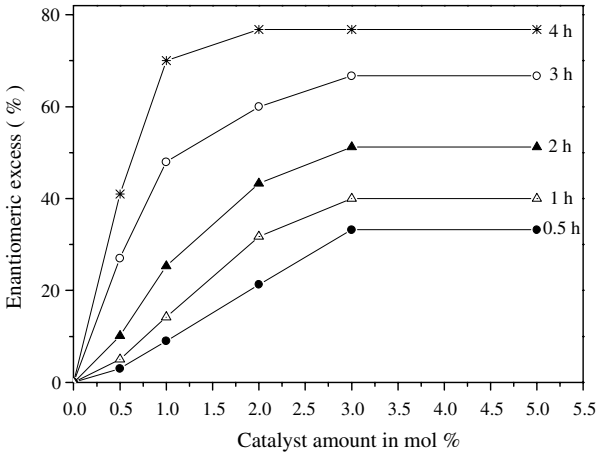
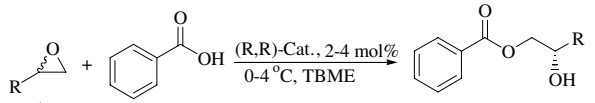


Figure 3. Effect of catalyst (II-1-d) loading amount on enantioselectivity of the asymmetric ring opening of ECH with butyric acid, keeping other reaction conditions identical with Table 1 (entry 19) (ee % of recovered ECH).

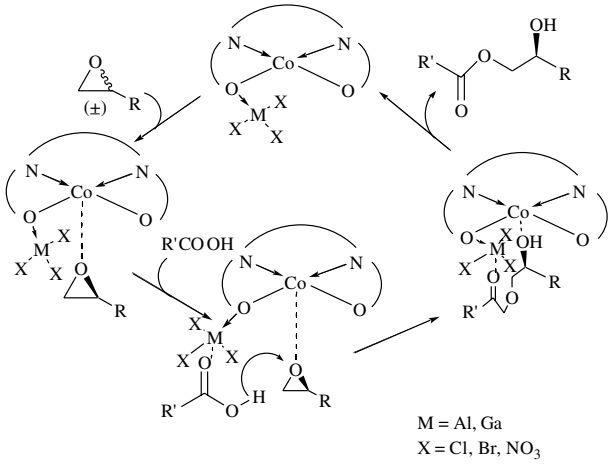
Table 2. Asymmetric ring opening of terminal epoxides with carboxylic acids catalyzed by heterometallic chiral (salen) Co complex



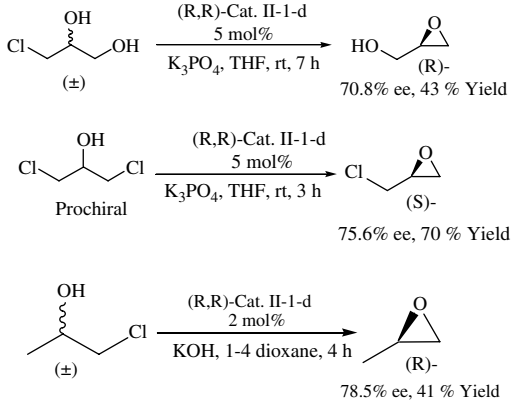
Entry	R	Catalyst	Catalyst loading[a]	Time (h)	Yield (%)[b]	ee (%)[c]
1	CH_3	II-1-d	4.0	2.0	41	56.2
2	CH_3	II-1-a	4.0	2.0	33	45.3
3	CH_3	A	4.0	2.0	14	23.2
4	CH_3	B	4.0	2.0	18	25.5
5	C_2H_5	II-1-d	2.0	2.5	40	65.5
6	CH_2Br	II-1-d	4.0	3.0	42	59.3
7	CH_2Cl	II-1-d	3.0	4.0	43	66.7

[a] In mol % loading on a per [Co] basis w.r.t. racemic epoxides.
[b] Isolated yield is based on racemic epoxides (theoretical maximum = 45%).
[c] Ee % was determined by chiral HPLC and the products obtained were characterized by ^1H, ^{13}C, and elemental analyses.

proceeded slowly and formed racemic mixture. Similarly optically active glycidol was synthesized from asymmetric cyclization of 3-chloro-propane-1,2-diol via kinetic



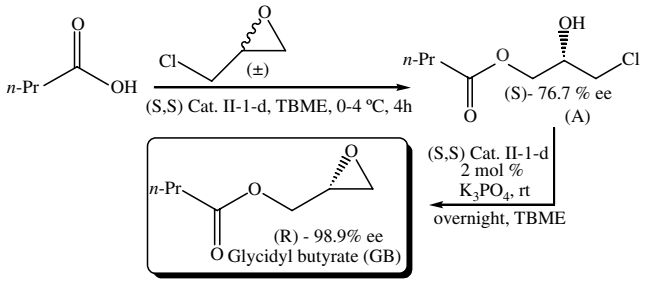
Scheme 2.



Scheme 3.

resolution. The result shows that (*S*)-3-chloro-propane-1,2-diol is preferentially cyclized to give (*S*)-glycidol. Similarly these asymmetric cyclization may also follow the mechanism reported by Takeichi et al.[8]

The practical utility of the present study is synthesis of optically pure (*R*)-glycidyl butyrate (Scheme 4). Butyric acid and (±) epichlorohydrin were catalyzed by II-1-d with complete regioselectivity along with 76% ee and in a 46% yield (50% theoretical yield). The resolved ring opened product followed by ring closing in the presence



Scheme 4.

of base and catalyst afforded glycidyl butyrate in high 98.9% ee and 40% yield. In the absence of catalyst II-1-d, the reaction proceeded slowly and formed racemic mixture. The role of the catalyst II-1-d for asymmetric cyclization may be understood by a similar report of Takeichi et al.[8]

(*R*)-Glycidyl butyrate is a very important compound and has been used to introduce a stereogenic center in the synthesis of Linezolid,[9] which is currently marketed for the treatment of multidrug resistant Gram-positive infections such as nosocomial, community-acquired pneumonia, and skin infections.

In summary, the chiral (salen) Co bearing Lewis acids of Al and Ga were not only able to activate the enantioselective ring opening of terminal epoxide with carboxylic acids, it also catalyze asymmetric cyclization reaction too. Currently we are looking at the synergistic effect of Co–Al and Co–Ga on other asymmetric catalytic reaction for a multifunctional characteristic of the catalyst.

References and notes

1. H_2O: (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776; $TMSN_3$: (b) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897; Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197; Thiols: (c) Wu, M.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 5252; Phenols: (d) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086; ArSeH: (e) Yang, M.; Zhu, C.; Yuan, F.; Huang, Y.; Pan, Y. *Org. Lett.* **2005**, *7*, 1927; HCl: (f) Thakur, S. S.; Li, W.; Kim, S. J.; Kim, G.-J. *Tetrahedron Lett.* **2005**, *46*, 2263; NH_2Boc: (g) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973; Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 2173.
2. Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Shaibani, R. *Tetrahedron* **2004**, *60*, 6105, and references cited therein; Bukowska, A.; Bukowski, W.; Leszczak, B. M. *J. Chem. Technol. Biotechnol.* **1999**, *74*, 1145; Baum, K.; Berkowitz, P. T.; Grakauskas, V.; Archibald, T. G. *J. Org. Chem.* **1983**, *48*, 2953; Mirkhani, V.; Tangestaninejada, S.; Yadollahib, B.; Alipanaha, L. *Tetrahedron* **2003**, *59*, 8213; Junzo, O.; Shinjiro, M. *Synthesis* **1986**, *12*, 1019; Khalafi-Nezhad, A.; Soltani Rad, M. N.; Khoshnood, A. *Synthesis* **2003**, *16*, 2552.
3. Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773, and references cited therein.
4. (a) Shin, C. K.; Kim, S. J.; Kim, G.-J. *Tetrahedron Lett.* **2004**, *45*, 7429; (b) Thakur, S. S.; Li, W.; Shin, C. K.; Kim, G.-J. *Catal. Lett.* **2005**, *104*, 151.
5. The selectivity factor (k_{rel}) was calculated using the equation $= \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$ where ee is the enantiomeric excess of the ring opened product and c is the conversion (set to equal the isolated yield).
6. Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223.
7. Nielson, L. P. C.; Stevenson, C. P.; Backmond, D. G.; Jacobson, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360.
8. Takeichi, T.; Arihara, M.; Ishimori, M.; Tsuruta, T. *Tetrahedron* **1980**, *36*, 3391.
9. (a) Brickner, S.; Hutchinson, D.; Barbachyn, M.; Manninen, P.; Ulanowicz, D.; Garmon, S.; Grega, K.; Hendges, S.; Toops, D.; Ford, C.; Zurenko, G. *J. Med. Chem.* **1996**, *39*, 673; (b) Weidner-Wells, M. A.; Boggs, C. M.; Foleno, B. D.; Melton, J.; Bush, K.; Goldschmidt, R. M.; Hlasta, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 2345.