Catalytic Asymmetric Synthesis of α,β-Epoxy Esters, Aldehydes, Amides, and γ,δ-Epoxy β-Keto Esters: Unique Reactivity of α,β-Unsaturated Carboxylic Acid Imidazolides

Tetsuhiro Nemoto, Takashi Ohshima, and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences
The University of Tokyo, Hongo
Bunkyo-ku, Tokyo 113-0033, Japan

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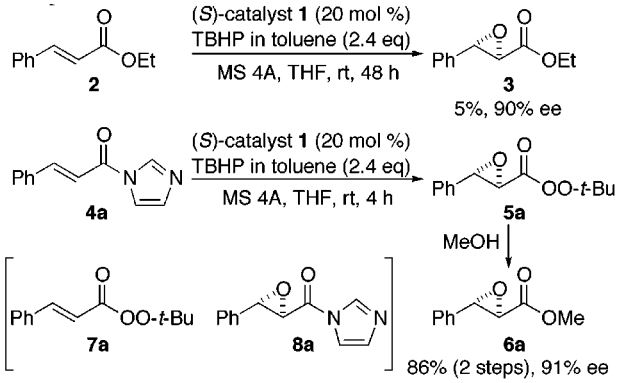
Asymmetric epoxidation of α,β-unsaturated carbonyl compounds remains one of the most important functional group manipulations in organic synthesis,[1] because of the usefulness of the corresponding enantiomerically enriched α,β-epoxy carbonyl compounds.[2] Although we[3] and others[1] have achieved efficient catalytic asymmetric epoxidation of α,β-unsaturated ketones, there are only a few reports of catalytic asymmetric epoxidation of α,β-unsaturated esters using a salen-manganese complex[4] or an optically active ketone[5] as a catalyst. In both cases, only cinnamic acid derivatives were utilized as a substrate. Substrates that have other functional groups, such as a C−C double bond or ketone, cannot be used for those asymmetric reactions due to poor chemoselectivity, indicating that there is still room for improvement in terms of substrate generality. We report the first example of a general catalytic asymmetric epoxidation of α,β-unsaturated carboxylic acid imidazolides via a 1,4-addition of peroxide to afford the corresponding α,β-epoxy carboxylic acid imidazolides, which were spontaneously converted into the α,β-epoxy peroxycarboxylic acid *tert*-butyl esters. In addition, efficient further transformations of α,β-epoxy peroxycarboxylic acid *tert*-butyl esters into α,β-epoxy esters, amides, aldehydes, and γ,δ-epoxy β-keto esters are reported.

We recently reported a general and practical catalytic asymmetric epoxidation of α,β-unsaturated ketones using the La−BINOL-Ph_3As═O complex **1** generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As═O in a ratio of 1:1:1.[3d] With this efficient catalyst, we examined a catalytic asymmetric epoxidation of ethyl (*E*)-cinnamate (**2**). As a result, 20 mol % of **1** promoted the epoxidation of **2** to afford **3** in 90% ee, even though the yield was only 5% after 48 h (Scheme 1). To enhance the reactivity of the substrate, we examined more reactive α,β-unsaturated esters, such as *p*-nitrophenyl ester, pentafluorophenyl ester, and so forth, as substrates. In these cases, however, only transesterification occurred to afford **7a**, which remained unchanged in the reaction medium. We then used an activated α,β-unsaturated amide as a substrate. Carboxylic acid imidazolides are widely used in organic synthesis, mainly as acylation reagents.[6] In contrast to the great success of *N*-acyloxazolidinones in asymmetric synthesis,[7] *N*-acylimidazoles (carboxylic acid imidazolides) have not yet been used in an asymmetric reaction as a substrate, perhaps because of their high reactivity at the carbonyl carbon toward nucleophiles. Despite the above-mentioned negative factors, on the basis of our preliminary molecular orbital calculations, we assumed that the exchange of alcohol for imidazole would decrease the energy of the lowest unoccupied molecular orbital (LUMO),[8] and a soft nucleophile might then attack at the β-carbon in preference to the carbonyl carbon. Thus, we investigated a catalytic asymmetric epoxidation using cinnamic acid imidazolide (**4a**) as a representative starting material. As we expected, the epoxidation of **4a** successfully proceeded by using the La−BINOL-Ph_3As═O complex **1** (20 mol %, rt, 4 h) to afford **5a** in high yield,[9] which was directly converted to **6a** (86%, 91% ee) by the addition of methanol to the reaction, with **7a** (5−10%). During the reaction, **8a** was not detected on thin-layer chromatography. In addition, **7a** was not converted to **5a** under the same conditions. These findings suggest that the epoxidation of **4** proceeded in preference to the transesterification to afford **8a**, which was spontaneously converted to **5a**.

Scheme 1. Catalytic Asymmetric Epoxidation of Cinnamic Acid Ester **2** and Imidazolide **4** Using La−(*S*)-BINOL-Ph_3As═O Complex **1**



Next, we investigated the effect of different cinnamic acid amides **4a**−**h** in the reaction, again using 20 mol % of **1** as a catalyst. As shown in Table 1, 4-phenylimidazolide **4e**, which has a lower LUMO energy than that of imidazolide **4a**,[10] gave the best result in terms of reactivity, chemical yield, and enantiomeric excess (1 h, 91%, 94% ee). In this case, only a trace amount of **7a** was obtained. These results indicated that 4-phenylimidazolide effectively enhanced the reactivity at the β-carbon toward the soft nucleophile.

Having succeeded in developing an efficient catalytic asymmetric synthesis of **6a** from **4e**, we further examined the scope and limitation of different substrates.[11] This newly developed system had a broad generality for epoxidations of various α,β-unsaturated carboxylic acid 4-phenylimidazolides to afford the

(1) For a recent review, see: Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215.

(2) For recent examples, see: (a) Nemoto, T.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 9569. (b) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287. (c) Carde, L.; Davies, H.; Geller, T. P.; Roberts, S. M. *Tetrahedron Lett.* **1999**, *40*, 5421.

(3) (a) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329. (b) Watanabe, S.; Kobayashi, Y.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7353. (c) Watanabe, S.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 8090. (d) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725.

(4) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323.

(5) (a) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (b) Wang, Z. X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443. (c) Solladié-Cavallo, A.; Bouérat, L. *Org. Lett.* **2000**, *2*, 3531.

(6) For an example, see: Page, P. C. B.; Gareh, M. T.; Porter, R. A. *Tetrahedron Lett.* **1993**, *34*, 5159 and references therein.

(7) For a review, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3.

(8) Using semiempirical molecular orbital calculation (AM1), the energy of LUMO of **2** is calculated to be −0.64902 eV, whereas that of **4a** and **4h** is 8.9 and 5.0 kcal/mol lower, respectively.

(9) The peroxy ester **5a** can be isolated in 86% yield, which is stable for at least one month under air at room temperature.

(10) The energy of LUMO of the 4-phenylimidazolide**4e** is calculated to be 0.9 kcal/mol lower than that of the imidazolide **4a**.

(11) When 10 mol % of **1** was used, decane solution of TBHP gave a better result (Table 2, entry 1) than toluene solution (3.5 h, 90%, 89% ee) in terms of selectivity. Thus, decane solution of TBHP was used for further examinations.

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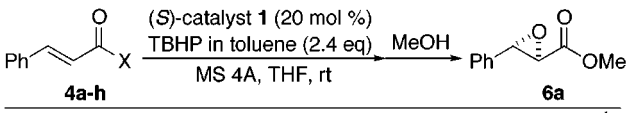
Table 1. Catalytic Asymmetric Epoxidation of Various Cinnamic Acid Amides **4a**−**h** Using La−(*S*)-BINOL-Ph_3As═O Complex **1**



entry	substrate		time (h)	yield (%)[a]	ee (%)[b]
1		**4a**	4	86	91
2		**4b**	12	70	77
3		**4c**	12	69	87
4		**4d**	3	85	92
5		**4e**	1	91	94
6		**4f**	24	80	63
7		**4g**	1	trace	–
8		**4h**	24	73	87

[a] Isolated yield. [b] Determined by HPLC analysis.

corresponding epoxides **6a**,**i**−**q** (Table 2). When 10 mol % of **1** was used at room temperature, all reactions proceeded to completion in reasonable reaction times (1−6 h). In the case of **4e**, even 5 mol % of **1** promoted the reaction efficiently to give **6a** (yield 73%, 85% ee, entry 2). Other cinnamic acid derivatives, which have an electron-withdrawing group (entry 3, 4) or an electron-donating group (entry 5) on the aromatic ring, were smoothly epoxidized to afford **6i**,**j** or **6k** in good enantiomeric excesses (89−93% ee). The epoxide **6k** is a key intermediate for one of the most potent calcium antagonists: diltiazem (Herbesser).[12] This asymmetric catalyst system was also effective for the β-alkyl-substituted α,β-unsaturated carboxylic acid-type substrates with higher reactivity than the cinnamic acid-type substrates (entry 6−11). Both primary (entry 6−10) and secondary (entry 11) alkyl-substituted substrates gave the products in high yields (72−93%) with good enantiomeric excesses (79−88% ee). Particularly noteworthy is that this reaction was applicable to substrates that were functionalized with a C−C double bond (entry 7−9) or a ketone (entry 10), without any overoxidation. To the best of our knowledge, this is the first example of a general catalytic asymmetric epoxidation of α,β-unsaturated carboxylic acid derivatives.

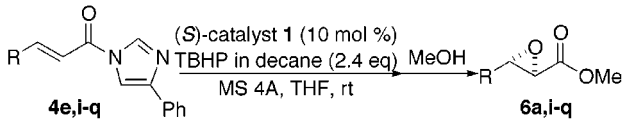
Finally, the usefulness of the intermediate **5** was further demonstrated (Scheme 2). The isolated peroxy ester **5a**[9] was converted not only to the α,β-epoxy ester **6a** (89%) but also to the α,β-epoxy amide **9** (92%), the aldehyde **10** (70%), and the γ,δ-epoxy β-keto ester **11** (77%) by addition of lithium methoxide, lithium amide, Red-Al, and lithium ester enolate, respectively, without any epoxide ring-opening reactions.[13]

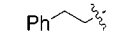
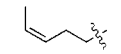
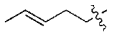
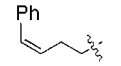
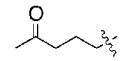
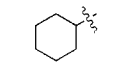
In conclusion, we developed the first catalytic enantioselective synthesis of α,β-unsaturated carboxylic acid derivatives with broad generality via a 1,4-addition of peroxide using the α,β-unsaturated carboxylic acid 4-phenylimidazolide as a substrate

(12) For a recent example, see: Imashiro, R.; Kuroda, T. *Tetrahedron Lett.* **2001**, *42*, 1313 and references therein.

(13) Isolation of **5** is essential for the synthesis of **9**, **10**, and **11**.

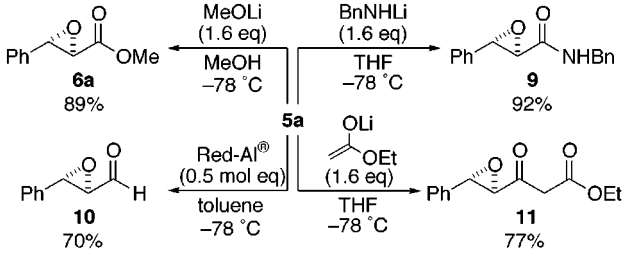
Table 2. Catalytic Asymmetric Epoxidation of Various α,β-Unsaturated Carboxylic Acid 4-Phenylimidazolides



entry	R	substrate	product	time (h)	yield (%)[a]	ee (%)[b]
1	Ph-	**4e**	**6a**	3.5	86	92
2[c]	Ph-	**4e**	**6a**	12	73	85
3	4-Cl-C_6H_4-	**4l**	**6l**	5	91	93
4[d]	4-Br-C_6H_4-	**4j**	**6j**	4	86	89
5	4-MeO-C_6H_4-	**4k**	**6k**	6	80	91
6		**4l**	**6l**	1	86	83
7		**4m**	**6m**	2	93[e]	86[f]
8		**4n**	**6n**	1.5	92[e]	79[f]
9		**4o**	**6o**	2	85	82
10		**4p**	**6p**	4	81[e]	81[f]
11		**4q**	**6q**	4	72[e]	88[f]

[a] Isolated yield. [b] Determined by HPLC analysis. [c] 5 mol % of the catalyst was used. [d] 4-Methylimidazolide was used due to the low solubility of the corresponding 4-phenylimidazolide. [e] Isolated yield of the corresponding peroxycarboxylic acid *tert*-butyl ester. Addition of methanol to the reaction gave the corresponding methyl ester in similar yield. [f] ee was determined after conversion to the corresponding 4-methoxybenzyl ester.

Scheme 2. Conversion of **5a** to α,β-Epoxy Ester **6a**, Amide **9**, Aldehyde **10**, and γ,δ-Epoxy β-Keto Ester **11**



and the novel La−BINOL-Ph_3As═O complex **1** as a catalyst. The intermediates: the α,β-epoxy peroxycarboxylic acid *tert*-butyl esters **5** were efficiently converted to the chiral α,β-epoxy esters, the amide, the aldehyde, and the γ,δ-epoxy β-keto ester. The described method renders functionalized enantiomerically enriched α,β-epoxy carboxylic acid derivatives readily available. Further investigation concerning the development of a catalyst with higher activity, the clarification of the reaction mechanism, and applications to a catalytic asymmetric synthesis of biologically active compounds is ongoing.

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

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