Review

Enantioselective Total Syntheses of Several Bioactive Natural Products Based on the Development of Practical Asymmetric Catalysis

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I present herewith enantioselective total syntheses of several bioactive natural products, such as (−)-strychnine, (+)-decursin, (−)-cryptocaryolone diacetate, (−)-fluoxetine, and aeruginosin 298-A, based on practical asymmetric catalyses (Michael reaction, epoxidation, and phase-transfer reaction) that I developed with coworkers in Prof. Shibasaki's group over the past 5 years. In the first part of this review, I discuss the great improvement of catalyst efficiency in an ALB-catalyzed asymmetric Michael reaction of malonate and application to the pre-manufacturing scale (greater than kilogram scale) and enantioselective total synthesis of (−)-strychnine with the development of novel domino cyclization. To broaden the substrate generality of the Michael reaction, we developed a highly stable, storable, and reusable La–O-linked-BINOL complex. Further extension of the reaction using β-keto ester as a Michael donor was achieved with the development of a La–NR-linked-BINOL complex, thereby improving indole alkaloid syntheses. In the second section, I discuss enantioselective total synthesis of (+)-decursin using catalytic asymmetric epoxidation. To achieve the synthesis, we developed a new La–BINOL–$Ph_3As{=}O$ (1 : 1 : 1) complex catalyst system, which has much higher reactivity and broader substrate generality than the previously developed catalyst systems. This allowed us to achieve catalytic asymmetric epoxidation of α,β-unsaturated carboxylic acid derivatives with high enantioselectivity and broad substrate generality for the first time by changing the lanthanide metal and reaction conditions. Among them, catalytic asymmetric epoxidation of α,β-unsaturated morpholinyl amides is quite useful in terms of synthetic utility of the corresponding α,β-epoxy morpholinyl amides. Highly catalyst-controlled enantio- or diastereoselective epoxidation of the α,β-unsaturated morpholinyl amides, coupled with diastereoselective reduction of β-hydroxy ketones, enabled the synthesis of all possible stereoisomers of 1,3-polyol arrays with successful enantioselective total synthesis of several 1,3-polyol natural products, such as (−)-cryptocaryolone diacetate. In addition, the development of a new regioselective epoxide-opening reaction of α,β-epoxy amides to the corresponding α- and β-hydroxy amides enhanced the usefulness of the present epoxidation and was applied to the enantioselective total synthesis of (−)-fluoxetine. In the final section, I report the development of a new asymmetric two-center organocatalyst (TaDiAS) and its application to the enantioselective synthesis of aeruginosin 298-A and its analogues. Because of the remarkable structural diversity of TaDiAS, a practical asymmetric phase-transfer reaction with broad substrate generality was achieved. As a result, we succeeded in developing a highly versatile synthetic method for aeruginosin 298-A and its analogues. Inhibitory activity studies of the compounds against the serine protease trypsin provided preliminary information about their structure–activity relations.

Key words enantioselective total synthesis; asymmetric catalysis; Michael reaction; epoxidation; phase-transfer reaction

1. Introduction

Biologic systems, in most cases, recognize various enantiomers as different substances, and therefore two enantiomers will elicit different responses. The importance and practicality of asymmetric synthesis as a tool to obtain enantiomerically pure or enriched compounds is fully acknowledged in synthetic organic chemistry, medicinal chemistry, agricultural chemistry, natural products chemistry, pharmaceutical industries, agricultural industries, *etc.*[1] Among the variety of asymmetric syntheses, the use of catalytic asymmetric reactions for the syntheses of chiral compounds is one of the most desirable methods in terms of atom economy, an increasingly important issue in organic chemistry and in industrial production.[1—3] The development of new catalytic asymmetric reactions enables more efficient syntheses of various highly potent chiral compounds, which allow for the development of new or more practical retrosynthetic analyses of complex natural products (arrow *a* in Fig. 1). Intensive efforts have been focused[1—8] on the development of a number of highly efficient asymmetric catalyses with successful applications for the syntheses of various complex natural products as well as industrial production.[1—3] Most asymmetric catalyses, however, especially catalytic asymmetric carbon–carbon forming reactions, are still limited in terms of substrate generality, catalyst efficiency, enantioselectivity, chemical yield, and reliability when applied to a large scale

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process, resulting in fewer synthetic applications and manufacturing scale processes. Evaluation from a synthetic point of view will facilitate further improvement of the present asymmetric catalyses (arrow *b*). In medicinal chemistry, product diversity and accessibility are highly important for high-throughput screening. Thus, to synthesize not only the natural product, but also a variety of its analogues for biologic studies, a much more reliable and versatile synthetic process is required (arrow *d*). The development of a practical synthetic process based on diversity-oriented retrosynthetic analysis makes it possible to supply very valuable product libraries that include the original natural products (arrow *c*). Finally, the feedback from biologic studies can lead to the development of a more desirable asymmetric catalysis and synthetic process (arrow *d* and *b*).

This review presents our enantioselective total syntheses of several bioactive natural products based on the development of practical asymmetric catalyses (Michael reaction, epoxidation, and phase-transfer reaction) and a discussion of the importance of the above-mentioned positive cooperation between "the development of new asymmetric catalyses," "enantioselective synthesis of the natural product," and "medicinal chemistry."

2. Catalytic Asymmetric Michael Reaction

2-1. Enantioselective Total Synthesis of (−)-Strychnine Using a Catalytic Asymmetric Michael Reaction of Malonate and Domino Cyclization[9—11] The catalytic asymmetric Michael reaction is an efficient method for enantioselective carbon–carbon bond formations because of the usefulness of the corresponding enantiomerically-enriched Michael adducts as an attractive chiral source.[12—32] Therefore, the development of a highly practical method to synthesize Michael adducts is very desirable. In 1996, the multifunctional asymmetric catalyst AlLibis(binaphthoxide) complex (ALB), which was prepared from $LiAlH_4$ and BINOL in a ratio of 1 : 2, was reported by Shibasaki *et al.* to be highly effective for the catalytic asymmetric Michael reaction of cyclic enones with malonates.[20] Later, this catalyst system was improved by using additional base (KO-*t*-Bu) and MS4A, which accelerated the reaction with a slight improvement in both chemical yield and enantioselectivity.[31] Although there are several efficient asymmetric catalysts for the asymmetric Michael reaction,[12—32] including the $LaNa_3$tris(binaphthoxide) complex,[19] GaNabis(binaphthoxide) complex,[21] and La–O-linked-BINOL complex,[22—24] ALB is the most effective catalyst for the present Michael reaction in terms of catalyst efficiency. In addition, all materials in the reaction, including each BINOL enantiomer, are inexpensive and commercially available. To apply this chemistry to a complex natural product synthesis as well as a manufacturing scale synthesis, we attempted to further improve not only catalyst efficiency, such as reducing catalyst loading and reaction time, but also the work-up procedure, such as eliminating the need for chromatographic separation. We examined the additive effects, solvent effects, and ligand tuning, and discovered that under highly concentrated conditions even 0.1 mol% of the catalyst induced the Michael reaction of dimethyl malonate (**2**) to 2-cyclohexen-1-one (**1**) to completion in 24 h (48 h with 0.05 mol% of ALB) without lowering the chemical yield or high enantiomeric excess (Chart 1).[9] We also examined the work-up procedure of the reaction. After an ordinary quenching procedure, the organic layer was half concentrated and treated with hexane with maintenance of the solvent ratio (EtOAc/hexane, 1 : 4) to afford a pure Michael adduct **3** as colorless crystals in greater

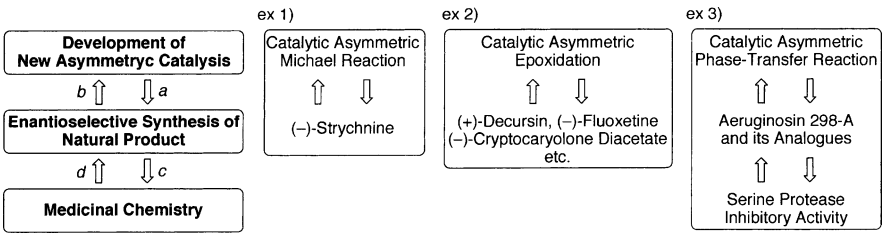


Fig. 1. Positive Cooperation between "Development of New Asymmetric Catalysis," "Enantioselective Synthesis of Natural Product," and "Medicinal Chemistry"

Takashi Ohshima was born in 1968 in Ehime, Japan. He received his bachelor's degree from The University of Tokyo in 1991 under the direction of Professor Masaji Ohno and received his Ph D. degree from The University of Tokyo in 1996 under the direction of Professor Masakatsu Shibasaki. On the following year, he joined Otsuka Pharmaceutical Co., Ltd. for one year. After two years as a postdoctoral fellow at The Scripps Research Institute with Professor K. C. Nicolaou (1997–1999), he returned to Japan and joined Professor Shibasaki's group in The University of Tokyo as an assistant professor. He has received the Fujisawa Award in Synthetic Organic Chemistry (2001) and The Pharmaceutical Society of Japan Award for Young Scientists (2004).

Takashi Ohshima

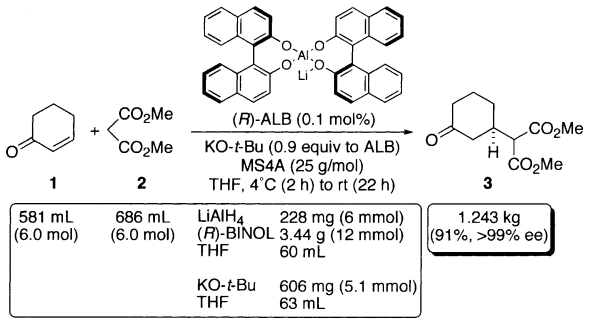


Chart 1. Catalytic Asymmetric Michael Reaction Promoted by ALB on a Greater than Kilogram Scale

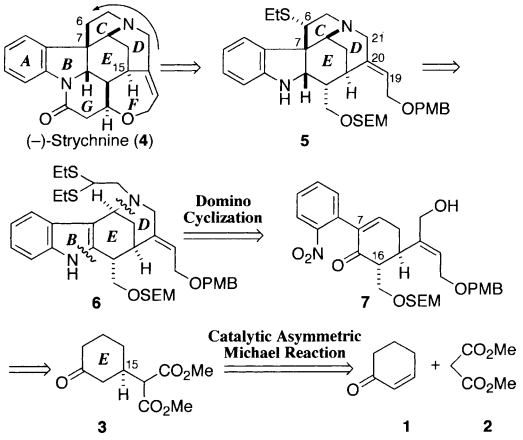


Fig. 2. Retrosynthetic Analysis of (−)-Strychnine (**4**)

than 90% yield. In addition, BINOL was recovered from the mother liquor in approximately 80% yield by subsequent fractional extraction. This process was successfully applied to a pre-manufacturing scale (greater than kilogram scale) synthesis. Enone **1** (581 ml, 6.0 mol) was added to a suspension of dried MS4A (150 g), malonate **2** (686 ml, 6.0 mol), 0.1 mol% of (*R*)-ALB in THF (containing only 3.4 g of BINOL), and 0.09 mol% of KO-*t*-Bu in THF at 4 °C (ice-water bath). After stirring at ambient temperature (20—25 °C) for 22 h, 1.24 kg of the desired product **3** was obtained as a white crystal in 91% combined yield following three successive crystallizations (1st: 76%, 2nd: 11%, 3rd: 4%). HPLC analysis revealed that the enantiomeric excess of the crude product and the crystal was 98% and greater than 99%, respectively. The purity of the crystals was estimated to be greater than 99% on the basis of elemental analysis and ^{1}H- and ^{13}C-NMR spectra. The described method is one of the most practical and efficient catalytic asymmetric carbon–carbon bond forming reactions with great enantioselectivity yet reported.[33] This greater than kilogram scale reaction can be performed with a conventional 2 l flask because of the very high concentration of the reaction.[9]

With the optically pure Michael product **3** in large quantities, we focused on the transformation of **3** to *Strychnos* alkaloid (−)-strychnine (**4**) (Fig. 2). Strychnine (**4**) is the flagship compound of the family of *Strychnos* alkaloids and, based on its molecular weight, is one of the most complex natural products.[34,35] Only 24 skeletal atoms are assembled into 7 rings and its structure contains 6 contiguous asymmetric carbon atoms, 5 of which are included within a single saturated 6-membered ring (E-ring).[36] The structural complexity of strychnine coupled with its biologic activity has served as the impetus for a number of synthetic investigations. The first total synthesis of strychnine, one of the most significant achievements in the history of organic synthesis, was reported by Woodward in 1954.[37,38] Nearly 40 years after Woodward's pioneering work, a number of groups reported the total synthesis,[37—52] four of which culminated in an enantioselective synthesis of the natural enantiomer.[41,42,44,45,47,48,52] As summarized in Bonjoch's excellent review,[34] the major stumbling blocks in the synthesis are the generation of the spirocenter at C7 and the assembly of the bridged framework (CDE core ring). In previous strategies, the C6–C7 bond was generated in the early stage of the synthesis, probably due to difficulties generating the C7 quaternary center; thus, in many cases, the CDE ring system was assembled in the direction of the C-ring to D-ring. Although an intramolecular alkylation strategy was applied for the construction of the C-ring in the synthesis of structurally simpler indole alkaloids,[34,35,54—56] this strategy has not been utilized for the synthesis of strychnine. The reason for this might be that intramolecular alkylation of dithioacetal is the only method that affords a cyclic product, thus desulfurization in the presence of exocyclic olefin is inevitable. To effectively utilize the above-mentioned optically pure Michael product **3** in our synthesis, we planned to assemble the CDE ring system from the D-ring to the C-ring and constructed the C7 spirocenter in the last stage using intramolecular alkylation.

Our first step was the elaboration of the hydroxyethylidene substituent at C20 in an *E*-selective manner. The best result was achieved by an *anti*-selective reduction of β-keto ester **9** by $NaBH_3CN$ with $TiCl_4$ at −55 °C and subsequent *syn*-elimination by DCC-CuCl (Overman's method; 72% for 2 steps, $E:Z=15.7:1$).[41,42] After conversion of **10** (*E*, *Z* mixture) to pure (*E*)-**11**, regioselective enol silyl ether formation was facilitated by the action of a sterically hindered base to form the corresponding enol silyl ether regioselectively (C7 : C16 => 6 : 1). A subsequent Saegusa–Ito reaction using $Pd_2(dba)_3\cdot CHCl_3$ (5 mol%) in the absence of a phosphine ligand provided **12** in 90% yield.[57] To introduce one carbon unit at C16 prior to the indole formation, we next attempted methoxycarbonylation and hydroxymethylation using **12** or more advanced products. In most cases, however, aromatization of the corresponding cyclic β-keto ester and elimination of the corresponding β-hydroxyketone to the enone occurred. Instead, the mild aldol reaction of enol silyl ether in aqueous formaldehyde, which was developed by Kobayashi *et al.*,[58,59] was effective for the formation of **13** ($C16\alpha : C16\beta = ca.$ 3 : 1). Because of the instability of **13**$\boldsymbol{\beta}$ in the next iodination step, **13**$\boldsymbol{\beta}$ was converted to thermodynamically more stable **13**$\boldsymbol{\alpha}$ by treatment with DBU prior to iodination. Subsequent iodination with DMAP and a Stille coupling reaction[60—64] in the presence of CuI produced **14** efficiently, in contrast to the poor result (<5%) that occurred in the absence of CuI. Finally, protection of the primary alcohol with SEMCl and removal of the TIPS group provided the key intermediate **7** in excellent yield.

We then focused on construction of the BCDE-ring system. Initially, we examined a 1,4-addition of the secondary amine to the enone after introduction of the amine moiety at C21 of **7** for D-ring formation, however, it was very difficult

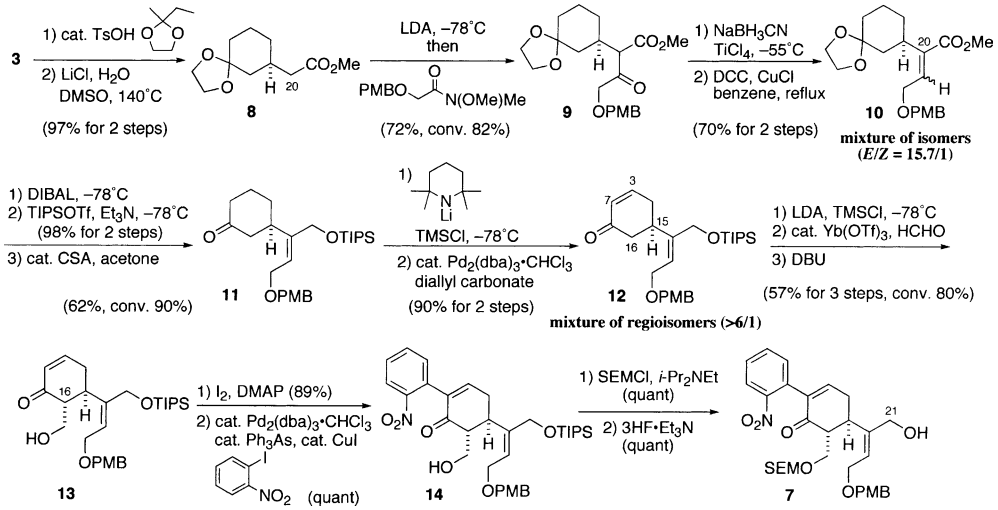


Chart 2. Preparation of the Key Intermediate **7**: Elaboration of the Hydroxyethylidene Substituent and Functionalization of the E-Ring

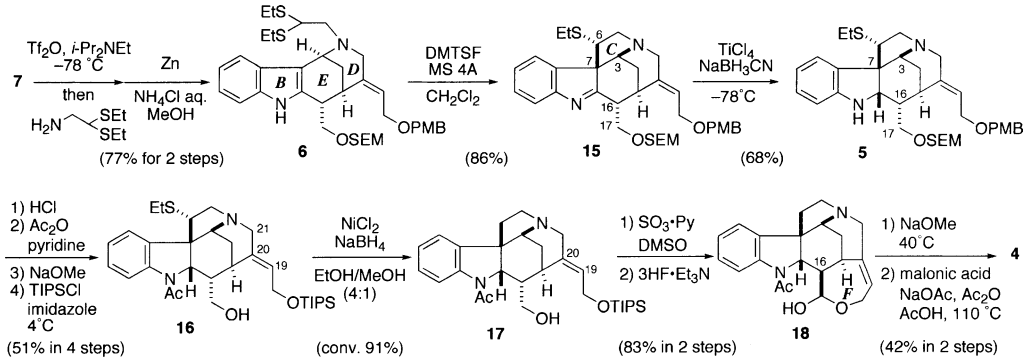
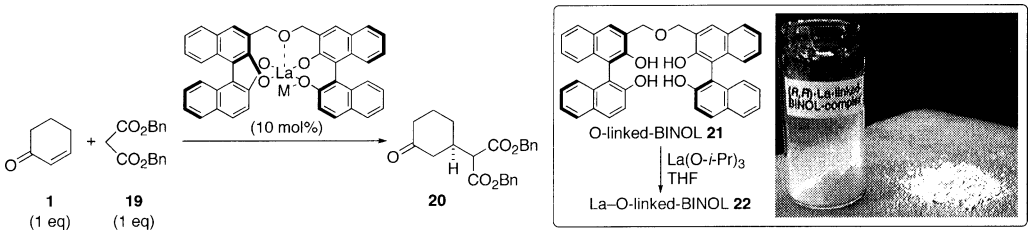


Chart 3. Completion of the Total Synthesis of (−)-Strychnine (**4**) through Domino Cyclization

due to the rapid retro reaction.[65] Numerous attempts[10,11] led us to examine a domino cyclization (Chart 3). After introduction of the amine moiety, the crude mixture was treated with Zn in MeOH–aq. NH_4Cl to provide **6** in 77% yield. This domino cyclization might proceed by one of the following sequences: (1) reduction of the nitro group to amine by Zn, (2) indole formation, and (3) 1,4-addition of the secondary amine or (1) reduction of the nitro group to amine by Zn, (2) 1,4-addition of the secondary amine, and (3) irreversible indole formation of the aniline moiety with the resulting ketone. Our next goal was to construct the C-ring. We examined the intramolecular electrophilic attack of a thionium ion to generate the C7 spirocenter. Unfortunately, the reported procedure using dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[31,32,54,66] provided unsatisfactory results (<20% yield), but the yield was improved (up to 86%) under the optimized conditions.[10,11] Reductions of imines in similar indole alkaloids under neutral conditions often result in cleavage of the C3–C7 bond, but using acidic conditions solved this problem. On the other hand, reduction of **15** under acidic conditions proceeded by elimination of the "SEMO" moiety to give C16–C17 exocyclic olefin. After testing numerous neutral or acidic conditions, we determined that treatment with 5 eq of $TiCl_4$ at −78 °C before the addition of $NaBH_3CN$ effectively prevented the ring opening reaction and accelerated reduction. As a result, **5** was obtained in 68% yield. The last major hurdle involved the chemoselective reduction of the thioether (desulfurization)[67] in the presence of exocyclic olefin. A Raney Ni (W-2) reduction was the first choice for this purpose. Even deactivated Raney Ni in acetone, however, promoted considerable migration of exocyclic olefin (C19–C20) to endocyclic olefin (C20–C21).[68] Eventually, Ni boride[69] emerged as a promising candidate. The conventional protocol caused over-reduction instead of migration. By changing the solvent (EtOH : MeOH = 4 : 1) and addition order, however, the desired product **17** was obtained in 91% yield, based on the consumed starting material, with high selectivity (>10 : 1). Consecutive $SO_3 \cdot Py$ oxidation of the primary alcohol and removal of the TIPS group afforded (+)-diaboline (**18**)[70—72] through epimerization of the C16 stereocenter. Finally, removal of the acetyl group provided the crude Wieland–Gumlich aldehyde, which was converted to (−)-strychnine (**4**) by the established method.[37—53]

2-2. Development of the Stable, Storable, and Reusable Asymmetric Catalyst La–O-linked-BINOL Complex for a Catalytic Asymmetric Michael Reaction[22—24] The ALB complex is a highly efficient catalyst for the Michael reaction of malonates to cyclic enones.[9—11,20,31,32] There is still a big demand for catalyst improvement, however, in terms of substrate generality and stability. Thus, we attempted to develop a new asymmetric catalyst. For preparation of an efficient catalyst, lanthanide and O-linked-BINOL **21**, which was previously developed by

Table 1. Catalytic Asymmetric Michael Reaction Promoted by (*R*,*R*)-La–M–O-Linked-BINOL Complexes



Entry	M	Solvent	Temp. (°C)	Time (h)	Yield (%)[a)]	ee (%)[b)]
1	Li	THF	0	24	21	35
2	Na	THF	0	24	41	43[c)]
3	K	THF	−20	24	16	54[c)]
4	H (**22**)	THF	0	45	53	85
5	H (**22**)	DME	rt	72	94	>99

a) Isolated yield. *b*) Determined by HPLC analysis. *c*) The mirror image enantiomer was formed.

Shibasaki, *et al.*,[73—76)] were chosen as a Lewis acidic center metal and chiral ligand based on the following properties: (1) the lanthanide (Ln) phenoxide complex is relatively stable against moisture[4—8)] and the oxygen in the linker is likely to coordinate to the lanthanide metal in an Ln–O-linked-BINOL complex, stabilizing the Ln complex as a pentadentate ligand[74)] and (2) the ionic radius and coordination number of lanthanides are larger than those of aluminum, making a relatively large chiral reaction pocket. First, the asymmetric Michael reaction of dibenzyl malonate (**19**) to **1** was examined with monometallic (La only) and heterobimetallic (*e.g.*, La–Li, La–Na, La–K) complexes. The results are summarized in Table 1. The best result was obtained using alkali-metal free La–O-linked-BINOL complex **22**[22)] (entry 4), in which the lanthanum metal functions as a Lewis acid and the lanthanum naphthoxide moiety functions as a Brønsted base to promote the reaction.[77)] After optimization of the reaction conditions, the use of DME as a solvent afforded **20** in 94% yield and >99% ee, even at room temperature (entry 5).[22)] The novel La–O-linked-BINOL complex **22** was very stable, even under air, and could be stored over a long time. Complex **22** was easily prepared from La(O-*i*-Pr)$_3$[78)] and 1.0 eq of O-linked-BINOL **21**, which were mixed in THF followed by removal of the solvent under reduced pressure to afford **22** as a pale-yellow powder.[79,80)] This air-stable complex **22** can be stored without any care at ambient temperature for at least 4 weeks, and there were no changes in catalytic activity, in terms of both chemical yield and enantiomeric excess.[22)] Furthermore, as we expected, the complex **22** was recovered from the reaction mixture due to the large difference in solubility between the complex **22** and product **20** and reused. This reaction is notable not only for its high enantioselectivity and the synthetic utility of its products, but also for the ease in handling the catalyst.

Having developed a novel, stable and storable catalyst, we examined the scope and limitations of different substrates. As shown in Fig. 3, La–O-linked-BINOL complex **22** promoted the Michael reaction of a variety of cyclic enones (n=0—4) with various malonates to afford Michael adducts with good to excellent enantiomeric excess (up to >99% ee) (condition A).[22)] Moreover, complex **22** was also effective for the catalytic asymmetric Michael reaction of various α-substituted malonates.[24)] Despite the greater utility of substituted Michael adducts compared to nonsubstituted adducts for complex molecule synthesis,[81)] especially when the substituent contains functional groups for further transformation,[82)] no catalytic asymmetric Michael reaction of α-substituted malonates, except for the α-methyl substituted malonate,[18—25)] has been reported because of their low reactivity. For example, the ALB complex (20 mol%) gave the Michael adduct **34** in only 36% yield and 19% ee and even La–O-linked-BINOL complex **22** (10 mol%) gave moderate chemical yield (67%), although the enantiomeric excess was excellent (99% ee) (condition A). After intensive optimization, concentration of the reaction was very important and the addition of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) very effectively enhanced reactivity. Under the best conditions (condition B), Michael adduct **34** was obtained in 93% yield and 99% ee.[24)] This condition was applicable to various α-substituted malonates and, in all cases, a higher yield was obtained than under condition A. In addition, HFIP effectively accelerated the Michael reaction of nonsubstituted malonates (condition C). Thus, only 5 mol% of catalyst forced the reaction to completion in approximately 24 h with 83 to 95% yield and greater than 99% ee.[24)] Although the role of HFIP is not yet clearly elucidated, we propose that this acidic (pK_a=17.9 in DMSO)[83)] and sterically-hindered additive acts as a proton source and assists in the dissociation of the product from the La complex. To the best of my knowledge, this is the first example of a Michael reaction of malonates in which the catalyst has such broad generality.

2-3. Development of a Catalytic Asymmetric Michael Reaction of β-Keto Esters Using the La–NR-linked-BINOL Complexes[25)] Structurally-related β-keto esters were also studied as Michael donors because of the higher potential of the corresponding Michael products to be useful in further transformations.[84)] In this case, appropriate substituents can be introduced in the ketone unit prior to the Michael reaction, while one of the ester units in the Michael product of malonate is often removed by decarboxylation during the synthetic process (Chart 2, **3**→**8**).[10,11,31,32)] In spite of the usefulness of the above-mentioned reactions, we mainly studied the catalytic asymmetric Michael reaction of α-substituted β-keto esters to methyl vinyl ketone; thus, the

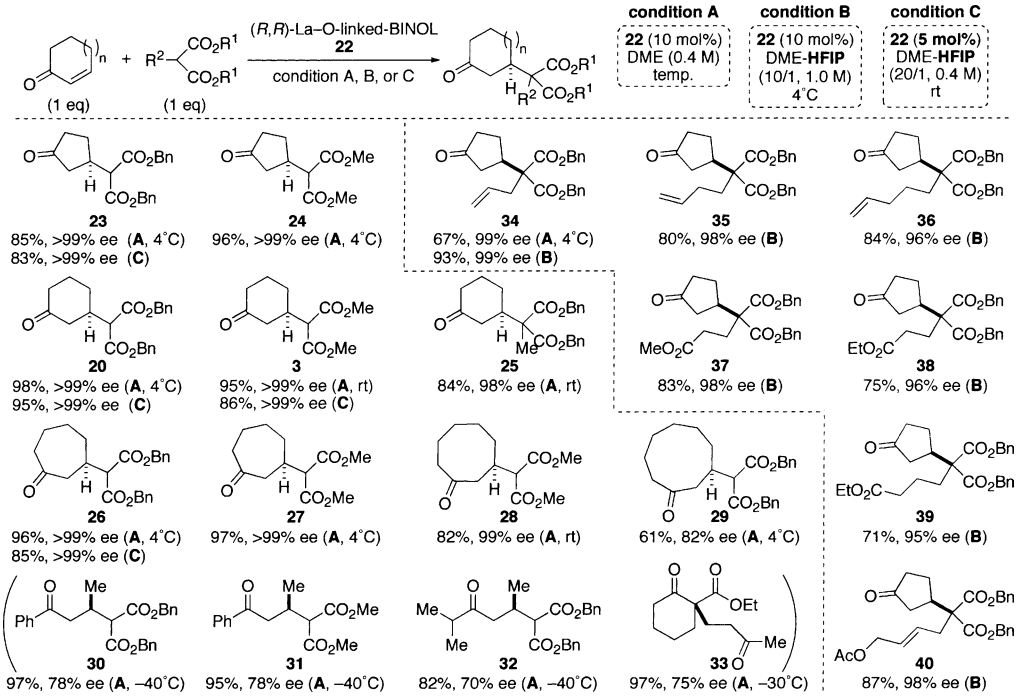
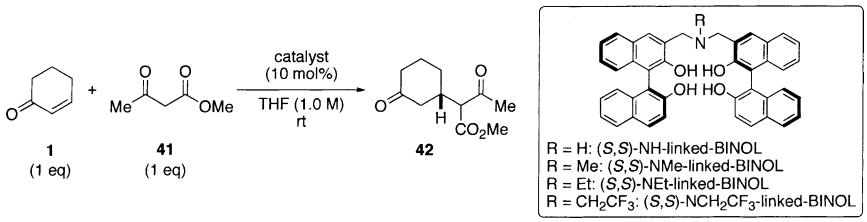


Fig. 3. Catalytic Asymmetric Michael Reactions of Malonates to Enones Promoted by La–O-linked-BINOL Complex **22**

Table 2. Catalyst Screening for the Catalytic Asymmetric Michael Reaction of β-Keto Ester[a)]

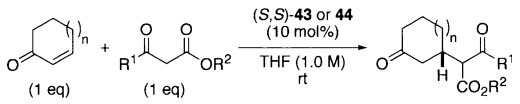


Entry	Catalyst	Time (h)	Yield (%)[b)]	ee (%)[c)]
1	(*S*)-LSB	39	72	6
2	(*S*)-ALB	94	24	0
3	(*S*,*S*)-La–O-linked-BINOL (**22**)	60	66	74
4	(*S*,*S*)-Pr–O-linked-BINOL	42	19	51
5	(*S*,*S*)-Sm–O-linked-BINOL	36	NR	—
6	(*S*,*S*)-La–S-linked-BINOL	24	24	58
7	(*S*,*S*)-La–NH-linked-BINOL (**43**)	24	65	90
8	(*S*,*S*)-La–NMe-linked-BINOL (**44**)	24	77	92
9	(*S*,*S*)-La–NEt-linked-BINOL	24	60	88
10	(*S*,*S*)-La–NCH_2CF_3-linked-BINOL	24	11	24

a) Product was obtained as a 1 : 1 mixture of diastereomers. *b*) Isolated yield. *c*) Enantiomeric excess was determined by GC analysis after conversion to the appropriate derivatives.[25)]

chiral center was constructed at the α-position of the β-keto esters.[85—94)] In contrast, only a few asymmetric Michael reactions of β-keto esters to β-substituted enones, such as cyclic enones, achieved asymmetric induction at the β-position of the acceptor.[95—99)] In our preliminary studies, asymmetric induction in the Michael reaction of β-keto ester **41** to **1** was not observed, even when using excellent catalysts for the Michael reaction of malonates, such as the LSB[19)] and ALB[9,20,31)] complexes (Table 2, entries 1, 2). Only La–O-linked-BINOL complex **22**[22—24)] afforded **42** in moderate yield and enantiomeric excess (entry 3). Other more Lewis-acidic lanthanide metals gave unsatisfactory results (entries 4, 5). These findings suggested that the use of β-keto esters prevents dissociation of the product from the complex or form undesired complexes with more Lewis-acidic Ln-catalysts. Thus, a less Lewis-acidic metal was expected to be more suitable for the reaction of β-keto esters. Because La is the weakest Lewis acid of the lanthanide metals, we expected that a linker heteroatom on linked-BINOL would electronically tune the properties of the La-catalyst. We examined S-linked-BINOL[75)] (entry 6) and NR-linked-BINOL (R=H, Me)[25)] (entries 7, 8) and found that nitrogen on the linker accelerates the reaction with high selectivity (up to 92% ee). Coordination of the electron-rich amine moiety to the central

Table 3. Catalytic Asymmetric Michael Reaction of β-Keto Esters Promoted by (*S*,*S*)-La–NR-linked-BINOL Complexes[a)]



Entry	Enone (n)	β-Keto ester		Catalyst	Co-solvent	Time (h)	Yield[b)] (%)	ee[c)] (%)
		R^1	R^2					
1	0	Me	Me	**44**	DME (1/9)	24	94	73
2	0	Et	Me	**44**	DME (1/9)	24	85	80
3	0	Pr	Me	**43**	—	24	75	75
4[d)]	0	$CH_2=CH(CH_2)_2$–	Me	**43**	—	48	84	72
5	1	Me	Me	**44**	DME (1/9)	24	82	92
6	1	Me	Et	**44**	DME (1/9)	42	71	88
7	1	Et	Me	**44**	DME (1/9)	24	71	91
8	1	Pr	Me	**44**	DME (1/9)	36	81	87
9[d)]	1	$CH_2=CH(CH_2)_2$–	Me	**43**	—	48	73	80
10[d)]	1	$CH\equiv C(CH_2)_2$–	Me	**43**	HFIP (1/19)	48	65	73
11[d)]	1	*c*-Hex–CH_2–	Me	**43**	—	48	67	73
12	2	Me	Me	**44**	DME (1/9)	42	83	92
13[e)]	2	Me	Et	**43**	HFIP (1/19)	24	88	89
14[e)]	2	Et	Me	**43**	HFIP (1/19)	24	91	90
15[e)]	2	Pr	Me	**43**	HFIP (1/19)	24	87	88
16	2	$CH_2=CH(CH_2)_2$–	Me	**43**	HFIP (1/19)	48	83	83
17	2	$CH\equiv C(CH_2)_2$–	Me	**43**	—	48	74	77
18	2	*c*-Hex–CH_2–	Me	**43**	—	48	66	69

a) Product was obtained as a 1 : 1 mixture of diastereomers. *b*) Isolated yield. *c*) Enantiomeric excess was determined by GC analysis after conversion to the appropriate derivatives.[25)] *d*) 1.2 eq of enone was used. *e*) Concentration of the reaction was 2.0 M.

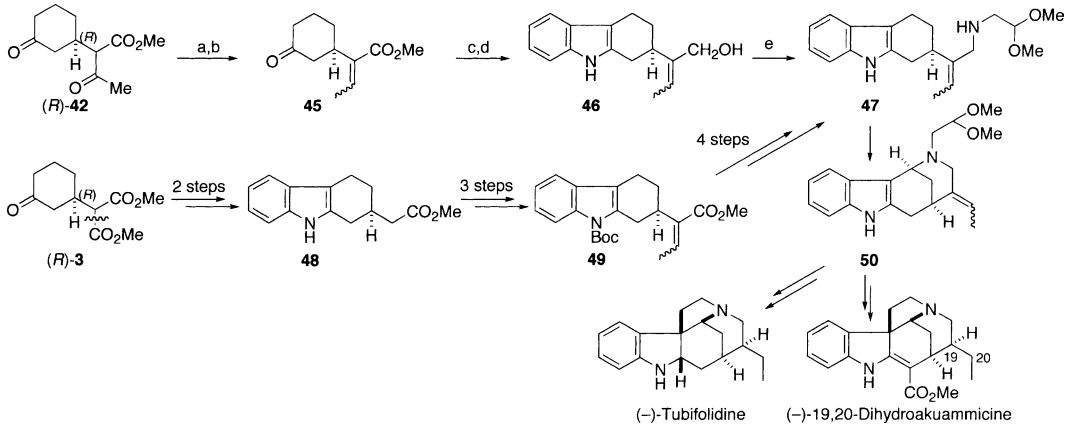
metal might decrease the Lewis acidity of the central metal. The electronic effects of the NR moiety were demonstrated by comparing the NEt ligand with the NCH_2CF_3 ligand. As we presumed, the NCH_2CF_3 ligand had much lower reactivity and selectivity (entry 10) than the NEt ligand (entry 9). These results directly support our hypothesis that the amine moiety of NR-linked-BINOL can tune the Lewis acidity of the central metal. This hypothesis was also supported by B3LYP[100,101)] density functional studies.[25)] Based on the results of further mechanistic studies,[25)] we propose that a β-keto ester serves as a ligand as well as a substrate and at least one β-keto ester should be included in the active catalyst complex.

One advantage of the NR-linked-BINOL ligand is its versatility; the ligand can be readily synthesized from the corresponding primary amine, making possible electronic as well as steric fine-tuning of the catalyst. The selectivity of this reaction is highly dependent on the bulkiness of the β-keto esters, and high reactivity and selectivity were accomplished by the appropriate choice of the substituent (R) in the NR-linked-BINOL ligand. In general, the NMe-ligand was suitable for the combination of small enones and small β-keto esters and the NH-ligand was suitable for bulkier substrates. After optimizing the reaction conditions, *e.g.*, solvent composition and concentration, we investigated the scope and limitations of several substrates. For the reaction using the NMe ligand, the addition of DME (THF/DME=9/1) often improved reactivity while maintaining the enantioselectivity. On the other hand, when the NH ligand was used, the addition of HFIP[24)] sometimes had positive effects in terms of reactivity while maintaining selectivity. The Michael reaction of a variety of acyclic β-keto esters to cyclic enones was promoted by the La–NR-linked-BINOL complexes **43** (R=H) and **44** (R=Me) to afford Michael adducts with moderate to good enantiomeric excess (Table 3). This is the first example of a general catalytic asymmetric Michael reaction of acyclic β-keto esters to cyclic enones, in which asymmetric induction occurs at the β-position of the enones.

The usefulness of the Michael product of β-keto esters was demonstrated (Chart 4). Indole **47** is the key intermediate of indole alkaloid (−)-tubifolidine[31)] and (−)-19,20-dihydroakuammicine,[32)] which were previously synthesized by Shibasaki *et al.* from the Michael product of malonate (*R*)-**3** through a C–C bond cleavage (decarboxylation) and formation (aldol reaction). Using (*R*)-**42** as a starting material, which was prepared using the (*R*,*R*)-La–NMe-linked-BINOL complex **44** (82%, 92% ee), the key intermediate **47** was synthesized more efficiently in terms of atom economy.[25)] Compared with the previous synthesis using the Michael adduct of malonate as a starting material (**3**→**47**), the present synthesis requires fewer steps (5 steps *vs.* 9 steps) and all the carbon atoms of the Michael donor were efficiently utilized for the construction of the carbon skeleton of **47** without C–C bond cleavage.

3. Catalytic Asymmetric Epoxidation

3-1. Catalytic Asymmetric Epoxidation of Enones Using Lanthanide–BINOL Complexes: Enantioselective Total Syntheses of (+)-Decursin and Related Natural Compounds[102—104)] Protein kinase C (PKC) is thought to have a principal role in cellular signal transduction and is a target of anticancer drug screening.[105,106)] (+)-Decursin (**51**) (Fig. 4) (a dihydropyranocoumarin originally isolated from *Angelica decursiva* Fr. *et* Sav.[107—109)]) was recently reported to be cytotoxic against several human cancer cell lines with relatively low cytotoxicity against normal fibroblasts.[110—112)] Other related natural dihydropyranocoumarins, (+)-decursinol angelate (**52**), (−)-prantschimgin (**53**), (+)-decursinol



Reagents and conditions: (a) cat. $RuCl_3$, cat. DPPB, MeOH, H_2 (30 atm), 50 °C, 84%; (b) CuCl, DCC, benzene, reflux, 81%; (c) $PhNHNH_2 \cdot HCl$, AcOH, reflux; (d) DIBAL-H, toluene, −78 °C, 72% (2 steps); (e) Ms_2O, *i*-Pr_2NEt, CH_2Cl_2, −20 °C, then $H_2NCH_2CH(OMe)_2$, 4 °C, 60%.

Chart 4. Synthesis of the Key Intermediate of (−)-Tubifolidine and (−)-19,20-Dihydroakuammicine

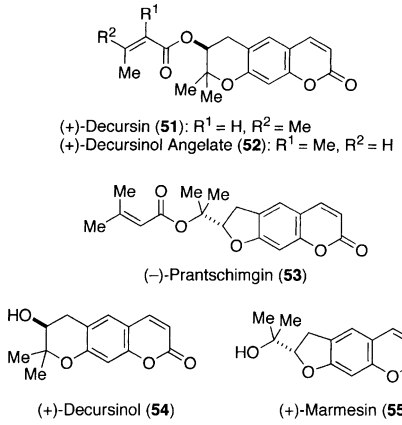


Fig. 4. Structures of (+)-Decursin (**51**), (+)-Decursinol Angelate (**52**), (−)-Prantschimgin (**53**), (+)-Decursinol (**54**), and (+)-Marmesin (**55**)

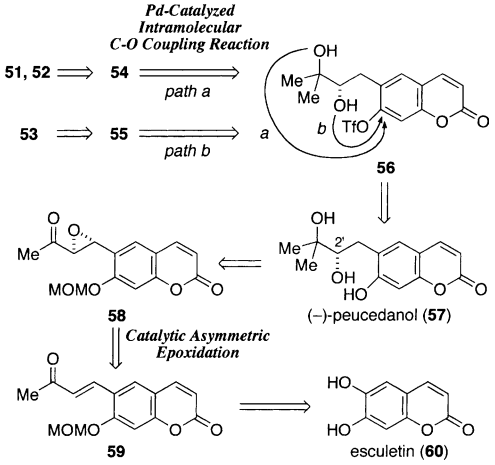


Fig. 5. Retrosynthetic Analysis

(**54**), and (−)-marmesin (**55**), were also identified in *A. gigas*.[107—109] The cytotoxic activity of decursin is related to PKC activation,[110,111] however, the mechanism is not yet clear. Moreover, decursin has a simple structure among the exogenous PKC activators reported so far. These profiles have made decursin quite attractive as a lead compound for drug discovery and as a biologic tool for clarification of the mechanism of PKC activation. Racemic syntheses of **51** and related dihydropyranocoumarins were reported by Steck[113] and by Murray *et al.*[114] In 2000, we achieved enantioselective total syntheses of **51**, **53**, **54**, and **55** using catalytic asymmetric epoxidation of an enone (96% ee) as the key step.[102,104] Later, enantioselective total syntheses using Jacobsen's epoxidation as the key step were reported independently by Han *et al.* (92% ee for **51**, **52**, and **54**)[115] and Kim *et al.* (97% ee for **51**).[116]

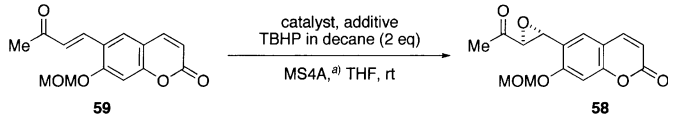
For synthesis, we chose a strategy based on the regioselective palladium-catalyzed intramolecular C–O coupling reaction[117,118] to construct the dihydropyran ring for **51**, **52**, and **54** (path a) and the dihydrofuran ring for **3** and **5** (path b) (Fig. 5). This strategy allowed us to synthesize all the natural compounds from the same intermediate, (−)-peucedanol (**57**). The triol **57** can be synthesized by catalytic asymmetric epoxidation[119,120] of enone **59** followed by methylation. Asymmetric epoxidation of olefins is one of the most important functional group manipulations in organic synthesis[1—3] due to the fact that enantiomerically enriched epoxides can be converted into various useful optically active synthetic intermediates. Catalytic asymmetric epoxidations of allylic alcohols using a Ti–tartrate complex[121,122] and unfunctionalized olefins using salen-manganese complexes[123] are well established. On the other hand, since the initial report by Juliá and coworkers,[124] the catalytic asymmetric epoxidation of enones has been studied using several other methodologies such as ligand-metal catalysts, phase-transfer catalysts, and polyamino acid catalysts.[119,120] Previously, Shibasaki *et al.* reported a general catalytic asymmetric epoxidation of enones using alkali-metal free lanthanide-BINOL complexes.[125—127] Thus, we planned to utilize this reaction for the synthesis of epoxy ketone **58**. Although there are many methods for constructing the chiral center at the C-2′ position, this method is the most effective. For example, Sharpless asymmetric epoxidation of *tert*-allylic alcohol[121,122] and asymmetric hydrogenation of α-substituted enone[128] do not proceed very well.

After preparing enone **59** from commercially available esculetin (**60**) in 5 steps,[102,104] we focused on the catalytic asymmetric epoxidation of **59**.[119,120] Preliminary experi-

ments using several general conditions, such as TBHP–Triton B, H_2O_2–NaOH, and TBHP–La(O-*i*-Pr)$_3$ with or without MS4A, produced undesirable results (almost no reaction). Despite the above-mentioned negative factors in epoxidation, we expected that the use of a multifunctional asymmetric catalyst[125—127] would overcome these problems. The unique feature of the catalyst is believed to be a result of a synergistic cooperation of metals and ligands.[4—8] Although the original catalyst [La–BINOL (1 : 1)] had low to moderate reactivity and selectivity (28% yield, 20% ee for La–BINOL and 88% yield, 83% ee for Yb–BINOL) (Table 4, entries 3, 4),[125—127] after optimization of the reaction conditions, the La–BINOL complex with triphenylphosphine oxide ($Ph_3P{=}O$)[129,130] or triphenylarsine oxide ($Ph_3As{=}O$)[102—104] was highly effective for catalytic asymmetric epoxidation.[131] In terms of atom economy, the best result was obtained using 1 eq of $Ph_3As{=}O$ to La(O-*i*-Pr)$_3$[78]–BINOL (94%, 96% ee, entry 12). A single recrystallization of 96% ee epoxide **58** from hexane–acetone afforded epoxide **58** in 76% purified yield with greater than 99% ee. Although several methodologies for catalytic asymmetric epoxidation of enones have been developed, only a few applications to total syntheses have been reported.[119,120] There are no examples of the use of an enolizable enone as a substrate. To my knowledge, this is the first application of this chemistry.

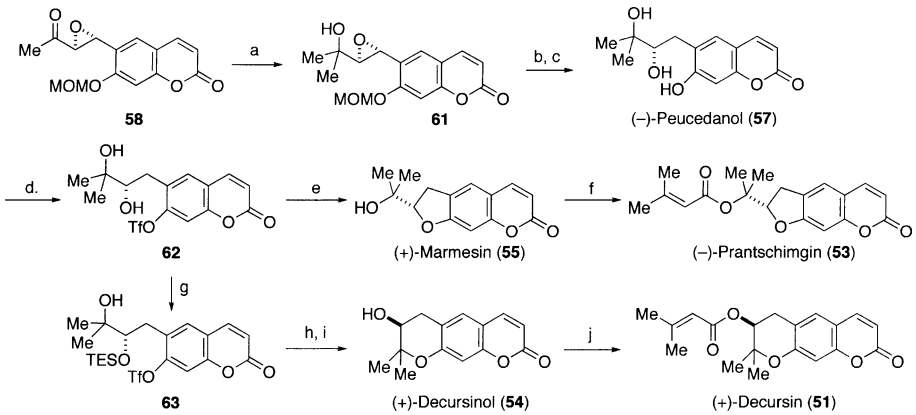
With the nearly optically pure advanced intermediate **58** in hand, the stage was set for completion of the total synthesis (Chart 5). Methylation of epoxyketone **58** afforded epoxyalcohol **61** (76%, conv. 91%), and subsequent regioselective reduction[132] (74%) followed by removal of the MOM group (92%) produced the common intermediate (−)-peucedanol (**57**). Selective transformation of the phenolic hydroxyl group to the triflate produced substrate **62**. With the use of 10 mol% $Pd(OAc)_2$, 20 mol% DPPF, and NaO-*t*-Bu, the 5-membered ring product (+)-marmesin (**55**) was obtained exclusively (80%). The Pd-catalyzed direct 6-membered ring formation was then examined using diol **62** under a variety of reaction conditions. In all cases, however, we obtained only the 5-membered ring product. Thus, the secondary hydroxyl group was first protected with a TES group. Cycliza-

Table 4. Catalytic Asymmetric Epoxidation of Enone **59** Using Ln–BINOL Complexes



Entry	Catalyst (mol%)	Additives (mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1	La(O-*i*-Pr)$_3$ (10)	—	24	Trace	—
2	La(O-*i*-Pr)$_3$ (10)	$Ph_3As{=}O$ (10)	18	Trace	—
3[d]	Yb–(*R*)-BINOL (1 : 1) (25)	—	15	88	83
4	La–(*R*)-BINOL (1 : 1) (25)	—	25	28	20
5	La–(*R*)-BINOL (1 : 1) (25)	$Ph_3P{=}O$ (100)	2.5	98	97
6	La–(*R*)-BINOL (1 : 1) (25)	$Ph_3P{=}O$ (75)	4	91	97
7	La–(*R*)-BINOL (1 : 1) (25)	$Ph_3P{=}O$ (50)	4	82	93
8	La–(*R*)-BINOL (1 : 1) (25)	$Ph_3P{=}O$ (25)	4	89	91
9	La–(*R*)-BINOL (1 : 1) (25)	$Ph_3As{=}O$ (100)	25	55	75
10	La–(*R*)-BINOL (1 : 1) (25)	$Ph_3As{=}O$ (75)	12	56	91
11	La–(*R*)-BINOL (1 : 1) (25)	$Ph_3As{=}O$ (50)	6	88	95
12	La–(*R*)-BINOL (1 : 1) (25)	$Ph_3As{=}O$ (25)	2	94	96
13	La–(*R*)-BINOL (1 : 1) (10)	$Ph_3As{=}O$ (10)	5	90	93

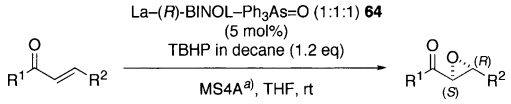
a) MS4A was not dried (1.0 g/mmol). *b*) Isolated yield. *c*) Determined by HPLC analysis. *d*) MS4A was dried for 3 h at 180 °C under reduced pressure before use (200 mg/mmol) and TBHP in toluene was used.



Reagents and conditions: (a) MeMgBr, THF, −78 °C, conv. 91%. (b) $NaBH_4$, $BH_3{\cdot}$THF, THF, 0 °C, 74%. (c) conc. HCl–H_2O–THF (1 : 3 : 4), 40 °C, 92%. (d) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 92%. (e) $Pd(OAc)_2$ (10 mol%), DPPF (20 mol%), NaO-*t*-Bu, toluene, 90 °C, 80%. (f) senecioyl chloride, DMAP, LHMDS, THF, −40 to 0 °C, 72%. (g) TESCl, imidazole, CH_2Cl_2, rt, 92%. (h) $Pd(OAc)_2$ (10 mol%), (*S*)-tol-BINAP (12 mol%), K_2CO_3, toluene, 90 °C, 91%. (i) TBAF, THF, rt, 95%. (j) senecioyl chloride, DMAP, LHMDS, THF, −40 to 0 °C, 83%.

Chart 5. Enantioselective Total Syntheses of (+)-Decursin (**51**) and Related Natural Compounds

Table 5. Catalytic Asymmetric Epoxidation of Various Enones Promoted by La–(*R*)-BINOL–Ph_3As=O (1 : 1 : 1) Complex **64**



Entry	R^1	R^2	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph	Ph	0.25	99	96
2[d]	Ph	Ph	3	97	89
3	2-MOMO–C_6H_4–	Ph	4	91	95
4	Ph	*i*-Pr	1.5	95	94
5	*t*-Bu	Ph	7	94	98
6	*i*-Pr	Ph	8	72	95
7	Me	Ph	6	92	>99
8	Me	$-(CH_2)_2Ph$	1.5	98	92
9	Me	C_5H_{11}	1.5	89	95
10	Ph	$-(E)$-CH=CHC_3H_7	3	95	96

a) MS4A was not dried (1.0 g/mmol). *b*) Isolated yield. *c*) Determined by HPLC analysis. *d*) 1 mol% of the catalyst was used.

tion of the mono-protected substrate **63** proceeded in 91% yield using 10 mol% $Pd(OAc)_2$, 12 mol% (*S*)-tol-BINAP, and K_2CO_3.[133] (+)-Decursinol (**54**) was obtained after removal of the TES group. Finally, esterification of (+)-marmesin (**55**) and (+)-decursinol (**54**) resulted in the first asymmetric total syntheses of (−)-prantschimgin (**53**) and (+)-decursin (**51**), respectively.[102,104]

The new asymmetric catalyst system consisting of La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in a ratio of 1 : 1 : 1 [La–BINOL–Ph_3As=O (1 : 1 : 1) complex **64**] had a broad generality for enones, affording the products in excellent yield and up to greater than 99% ee, even at room temperature.[103] Almost all reactions proceeded to completion in reasonable reaction times using 5 mol% of the catalyst **64** (Table 5). Epoxidation of both aryl (entries 1—4) and alkyl (entries 5—9) ketone-type substrates proceeded smoothly and afforded the corresponding epoxy ketones in excellent yield (up to 99% yield) and enantiomeric excess (up to >99% ee). Particularly, epoxidation of chalcone proceeded quite efficiently and the reaction completed in 3 h, even with 1 mol% of the catalyst (entry 2). This asymmetric catalyst system was also effective for the enolizable enones (entries 6—9), which are generally difficult to epoxidize.[119,120] Furthermore, the epoxidation of dienone also proceeded to afford α,β-epoxy-γ,δ-unsaturated ketone in 95% yield and 96% ee with complete regioselectivity (entry 10). Reactions that proceed at room temperature clearly have significant practical advantages compared to those that require low temperature for the induction of higher selectivity. Additionally, the simple chiral ligand, unmodified BINOL, makes this process more accessible.

The structure of the active catalyst and reaction mechanism was established by X-ray analysis, which is the first X-ray crystal structure analysis of an alkali-metal free lanthanide–BINOL complex (Fig. 6), laser desorption/ionization time-of-flight mass spectrometry (LDI-TOF-MS), kinetic studies, and asymmetric amplification studies.[103,104] The proposed mechanism of the epoxidation is shown in Fig. 7. Our observation suggests that the alkali-metal-free La–BINOL complex exists as an oligomer and oxygen-containing ligands such as Ph_3As=O make it a monomeric complex. In the complex solution generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in the best ratio (1 : 1 : 1), the monomeric

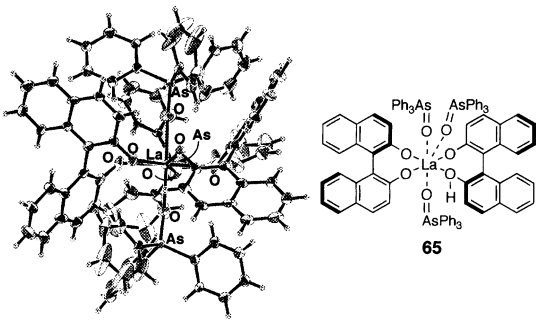


Fig. 6. X-Ray Structure of La(binaphthoxide)$_2$(Ph_3As=O)$_3$ **65**

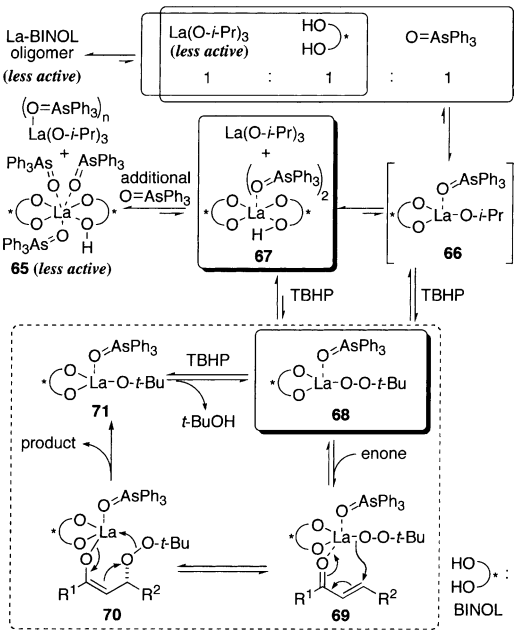


Fig. 7. Proposed Mechanism for the Epoxidation of Enones Catalyzed by La–BINOL–Ph_3As=O (1 : 1 : 1) Complex **64**

La–BINOL–Ph_3As=O (1 : 2 : 2) complex **67** was formed as the major complex with 1 eq of excess La(O-*i*-Pr)$_3$. The excess La(O-*i*-Pr)$_3$ reacts with TBHP and **67** to afford the most active and effective catalyst La–BINOL–Ph_3As=O–TBHP (1 : 1 : 1 : 1) **68**. Excess La(O-*i*-Pr)$_3$ might facilitate the trans-

formation of **67** to **68**.[103,104)]

3-2. Catalytic Asymmetric Epoxidation of α,β-Unsaturated Carboxylic Acid Imidazolides[134—136)] As described above, efficient catalytic asymmetric epoxidation of α,β-unsaturated ketones have been realized by several groups.[102—104,119,120,125—127,129,130)] There are only a few reports, however, of α,β-unsaturated carboxylic acid derivatives. A salen–manganese complex[137)] or an optically-active ketone[138—141)] was used for catalytic asymmetric epoxidation of α,β-unsaturated esters. 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. Our strategy relies on a Weitz–Scheffer-type epoxidation[142)] using 1,4-addition of hydroperoxide as an initial step; thus, chemoselective epoxidation of electron-deficient alkenes in the presence of other olefins would be realized.

To address this issue, we first examined catalytic asymmetric epoxidation of α,β-unsaturated ester **72** using the La–BINOL–$Ph_3As{=}O$ (1 : 1 : 1) complex **64**. As a result, 20 mol% of **64** promoted the epoxidation of **72** to afford α,β-epoxy ester **73** in 90% ee, even though the yield was only 5% after 48 h (Chart 6). To enhance the reactivity of the substrate, we examined more reactive α,β-unsaturated esters, such as *p*-nitrophenyl ester, pentafluorophenyl ester, *etc.*, as substrates. In these cases, however, only transesterification occurred to afford **77**, which remained unchanged in the reaction medium. We then used an activated α,β-unsaturated amide as a substrate. Although *N*-acylimidazoles (carboxylic acid imidazolides) have not yet been used in an asymmetric reaction as substrates, our preliminary molecular orbital calculations[134—136)] led us to hypothesize that the exchange of alcohol for imidazole would decrease the energy of the lowest unoccupied molecular orbital (LUMO) and a soft nucleophile might then attack at the β-carbon in preference to the carbonyl carbon. As expected, epoxidation of imidazolide **74** successfully proceeded using complex **64** (20 mol%, rt, 4 h) to afford α,β-epoxy peroxy ester **75** in high yield, which was directly converted to α,β-epoxy ester **76** (86%, 91% ee) by the addition of methanol to the reaction mixture, with **77** (5—10%). During the reaction, **78** was not detected on thin-layer chromatography. In addition, **77** was not converted to **75** under the same conditions. These findings suggest that the epoxidation of **74** proceeded in preference to the transesterification to afford **78**, which was spontaneously converted to **75**. Next, we investigated the effect of active amides in the reaction and found that 4-phenylimidazolide **79**, which has a lower LUMO energy than that of imidazolide **74**, gave the best result in terms of reactivity, chemical yield, and enantiomeric excess (1 h, 91%, 94% ee).[134—136)] In this case, only a trace amount of **77** was obtained. These results indicated that 4-phenylimidazolide effectively enhanced the reactivity at the β-carbon toward the soft nucleophile.

Having developed an efficient catalytic asymmetric synthesis of α,β-epoxy ester **76** from α,β-unsaturated 4-phenylimidazolide **79**, we examined the scope and limitations of different substrates. This newly developed system had broad generality for epoxidations of various α,β-unsaturated 4-phenylimidazolides to afford the corresponding α,β-epoxy esters (Table 6).[134—136)] When 10 mol% of **64** was used at room temperature, all reactions proceeded to completion in reasonable reaction times (1—6 h). Other cinnamic acid derivatives, which have an electron withdrawing group (entries 3, 4) or an electron donating group (entry 5) on the aromatic ring, as well as β-alkyl derivatives (entries 6—11) were smoothly epoxidized in good enantiomeric excess (79—93% ee). The epoxide (R = 4-MeO–C_6H_4, entry 5) is a key intermediate for one of the most potent calcium antagonists: diltiazem (Herbesser).[143,144)] Particularly noteworthy is that this reaction was applicable to substrates that were functionalized with a C–C double bond (entries 7—9) or a ketone (entry 10), without overoxidation. This is the first example of a general catalytic asymmetric epoxidation of α,β-unsaturated carboxylic acid derivatives.

The usefulness of the intermediate, α,β-epoxy peroxy ester **75**, was further demonstrated (Chart 7). The α,β-epoxy peroxy ester **75** is a stable compound, which was isolated using common flash column chromatography and can be

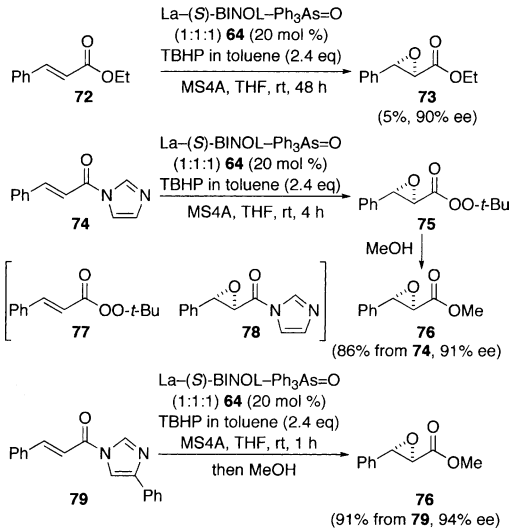
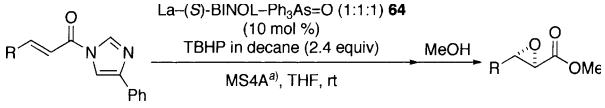


Chart 6. Preliminary Studies on Catalytic Asymmetric Epoxidation of α,β-Unsaturated Ester and α,β-Unsaturated Active Amide

Table 6. Catalytic Asymmetric Epoxidation of Various α,β-Unsaturated 4-Phenylimidazolide Promoted by La–(*S*)-BINOL–$Ph_3As{=}O$ (1 : 1 : 1) Complex **64**



Entry	R	Time (h)	Yield (%)[b)]	ee (%)[c)]
1	Ph	3.5	86	92
2[d)]	Ph	12	73	85
3	4-Cl–C_6H_4–	5	91	93
4[e)]	4-Br–C_6H_4–	4	86	89
5	4-MeO–C_6H_4–	6	80	91
6	$Ph(CH_2)_2$–	1	86	83
7	(*Z*)-$CH_3CH{=}CH(CH_2)_2$–	2	93[f)]	86
8	(*E*)-$CH_3CH{=}CH(CH_2)_2$–	1.5	92[f)]	79
9	(*Z*)-$PhCH{=}CH(CH_2)_2$–	2	85	82
10	$CH_3C(O)(CH_2)_3$–	4	81[f)]	81
11	*c*-Hex	4	72[f)]	88

a) MS4A was not dried (1.0 g/mmol). *b*) Isolated yield. *c*) Determined by HPLC analysis. *d*) 5 mol% of the catalyst was used. *e*) 4-Methylimidazolide was used due to the low solubility of the corresponding 4-phenylimidazolide. *f*) Isolated yield of the corresponding peroxycarboxylic acid *tert*-butyl ester. Addition of methanol to the reaction gave the corresponding methyl ester in similar yield.

stored for at least 2 months at 4 °C. On the other hand, it is a so-called active-ester, thus many kinds of nucleophiles can react very easily at the carbonyl carbon in preference to the epoxide. In fact, they were converted to the corresponding α,β-epoxy amides **80** (92%), the γ,δ-epoxy β-keto esters **81** (77%), and the α,β-epoxy aldehydes **82** (70%) by the addition of amine, lithium ester enolate, and aluminum hydrides (Red-Al), respectively, without any epoxide ring opening reactions.[134—136] Further application of this process is discussed below.

3-3. Catalytic Asymmetric Epoxidation of α,β-Unsaturated Simple Amides: Enantioselective Syntheses of Several 1,3-Polyol Natural Products[145—147] Chiral α,β-epoxy amides are very important compounds because they can be converted into useful chiral building blocks such as α- and β-hydroxy amides. Many chiral α,β-epoxy amides can be synthesized from the corresponding α,β-epoxy peroxy esters (Chart 7). Catalytic asymmetric epoxidation of α,β-unsaturated amides should be a more direct and efficient method for the preparation of chiral α,β-epoxy amides. There are no reports, however, of catalytic asymmetric epoxidation of α,β-unsaturated amides,[148] perhaps due to the lower reactivity, based on LUMO energy level, than that of α,β-unsaturated ester.[136] While catalytic asymmetric epoxidation of α,β-unsaturated esters proceeded very sluggishly with the use of the La-complex **64**, surprisingly, α,β-unsaturated amides were epoxidized more smoothly under the same conditions. This result prompted us to optimize the reaction conditions. The effect of the central metal and the amount of TBHP were investigated using β-alkyl substituted α,β-unsaturated amide [*N*-methyl-5-phenyl-2-pentenamide (**83**)] as a representative substrate.[136,145] The amount of TBHP strongly affected reactivity and 1.2 eq of TBHP to the substrate was optimal. Sm–(*S*)-BINOL–$Ph_3As{=}O$ (1 : 1 : 1) complex **84**, generated from Sm(O-*i*-Pr)$_3$, (*S*)-BINOL, and $Ph_3As{=}O$ in a ratio of 1 : 1 : 1, was the best catalyst for this reaction (condition A). This condition promoted the epoxidation of β-aryl-substituted α,β-unsaturated amide with lower reactivity. To enhance reactivity, the reaction was optimized. In the case of β-aryl, activation of MS4A was necessary to improve the reactivity (condition B). The scope and limitations using numerous substrates were examined under these conditions (condition A or B). As shown in Table 7, this catalytic system had a broad generality for epoxidations of various β-alkyl (entries 1—12) and β-aryl (entryies 13—17)-substituted α,β-unsaturated amides with high yield (94—>99%) and selectivity (up to >99% ee).[136,145] This is the first example of a general catalytic asymmetric epoxidation of α,β-unsaturated simple amides.

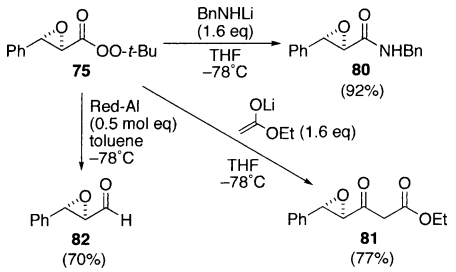
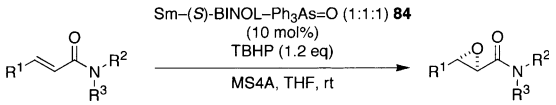


Chart 7. Further Transformations of α,β-Epoxy Peroxy Ester **75** to α,β-Epoxy Amide **80**, γ,δ-Epoxy β-Keto Ester **81**, and α,β-Epoxy Aldehyde **82**

The nearly optically pure α,β-epoxy amides were successfully transformed into several useful chiral compounds.[145—147] From a synthetic point of view, we examined the catalytic asymmetric epoxidation of α,β-unsaturated Weinreb amide[149] **85** using 10 mol% of the Sm complex **84** (Chart 8). Although the reaction proceeded smoothly, it had exceptionally lower enantioselectivity (64% ee) than that with methyl amide **83** (>99% ee). Thus, we explored other synthetically useful substrates that can take the place of Weinreb amides. Morpholinyl amides are as useful as Weinreb amides.[150—152] A variety of organometallic reagents, such as Grignard

Table 7. Catalytic Asymmetric Epoxidation of Various α,β-Unsaturated Simple Amides Promoted by Sm–(*S*)-BINOL–$Ph_3As{=}O$ (1 : 1 : 1) Complex **84**



Entry	R^1	R^2NR^3	Conditions[a]	Time (h)	Yield (%)[b]	ee (%)[c]
1	$Ph(CH_2)_2$–	MeNH	A	8	99	>99
2[d]	$Ph(CH_2)_2$–	MeNH	A	24	94	>99
3	$Ph(CH_2)_2$–	BnNH	A	6	97	>99
4[d]	$Ph(CH_2)_2$–	BnNH	A	24	82	99
5	$Ph(CH_2)_2$–	AllylNH	A	4	95	98
6	$Ph(CH_2)_2$–	*c*-HexNH	A	11	97	>99
7	$Ph(CH_2)_2$–	*t*-BuNH	A	22	91	99
8	$Ph(CH_2)_2$–	MeNMe	A	3	96	99
9	$Ph(CH_2)_2$–	*N*-pyrrolidinyl	A	4	94	>99
10	$Ph(CH_2)_4$–	MeNH	A	8	81	>99
11	Pr	BnNH	A	9	94	94
12	*c*-Hex	BnNH	A	12	90	>99
13	Ph	MeNH	B	18	95	99
14	Ph	BnNH	B	18	91	>99
15	Ph	MeNMe	B	9	96	>99
16	4-F–C_6H_4–	MeNH	B	20	94	99
17	4-Me–C_6H_4–	MeNH	B	21	89	>99

a) Conditions A: TBHP in decane was used. MS4A was not dried. Conditions B: TBHP in toluene was used. MS4A was dried for 3 h at 180 °C under reduced pressure. *b*) Isolated yield. *c*) Determined by HPLC analysis. *d*) 5 mol% of the catalyst was used.

reagents, alkyllithiums, and metal hydrides, react with morpholinyl amide through a reaction mechanism similar to that of the Weinreb amide, affording the corresponding ketone or aldehyde in good yield. When α,β-unsaturated morpholinyl amide **87** was used as a substrate, in stark contrast to the Weinreb amide **85**, 10 mol% of **85** afforded the corresponding α,β-epoxy morpholinyl amide **86** in quantitative yield and excellent enantiomeric excess (99% ee).[147] In a multigram scale reaction, the use of 5 mol% of the catalyst also gave satisfactory results (quant., 98% ee). When using Weinreb amide **85**, there was an unfavorable *anti* coordination **89**, and this bidentate coordination might disturb the favorable manner of the reaction, resulting in unsatisfactory selectivity. On the other hand, asymmetric epoxidation of morpholinyl amide **87** should proceed in the favorable *syn-s-cis* coordination manner **90** because rotation of the C–N bond to form a bidentate coordination (**90**→**91**) would be prevented by unfavorable energetics, such as orthogonality of the *N*-lone pair and the carbonyl π-orbitals.[136,147]

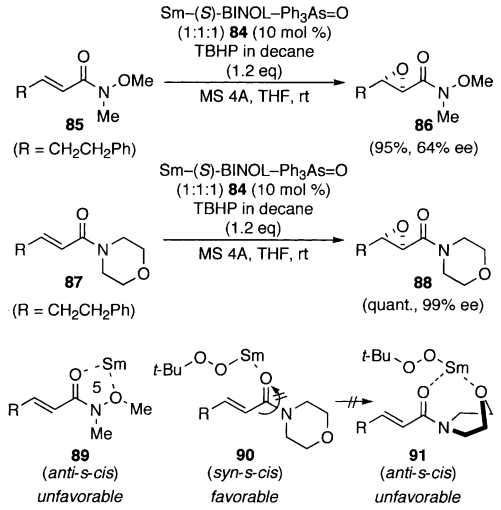


Chart 8. Catalytic Asymmetric Epoxidation of α,β-Unsaturated Weinreb Amide (**85**) and Morpholinyl Amide (**87**)

The resulting chiral α,β-epoxy morpholinyl amides are synthetically very useful and versatile intermediates that react with a variety of nucleophiles to afford the corresponding chiral carbonyl compounds such as γ,δ-epoxy β-keto esters. The following regioselective epoxide-opening reaction and *syn*- or *anti*-selective ketone reduction allows for a highly stereoselective 1,3-diol synthesis (Chart 9).[146,147] Stereoselective elongation of 1,3-polyol arrays, which often exist in various biologically active natural products and drugs such as polyene macrolide antibiotics,[153—156] was realized by repeating these processes. A new strategy for the stereoselective syntheses of all possible stereoisomers of 1,3-polyol arrays was achieved using the Sm–BINOL–Ph_3As=O (1 : 1 : 1) complex **84**, which promoted highly enantioselective as well as diastereoselective epoxidation of α,β-unsaturated morpholinyl amides. Even when there is chirality in the vicinity of the β-carbon of an α,β-unsaturated morpholinyl amide, stereoselectivity of the epoxidation can be controlled by the chirality of BINOL with overwhelming inherent diastereofacial preference for the substrate (**92**→**93**, **92**→**94**).[147] The present strategy allows for highly stereoselective syntheses of all possible stereoisomers of 1,3-polyol arrays, and eight possible stereoisomers of 1,3,5,7-tetraol arrays were successfully demonstrated for the first time.[147] Using this strategy, enantioselective syntheses of several 1,3-polyol natural products such as (−)-cryptocaryolone diacetate (**98**)[157—159] were achieved.[146,147]

3-4. Regioselective Epoxide-Opening Reaction of α,β-Epoxy Amides: Enantioselective Syntheses of Chiral α-

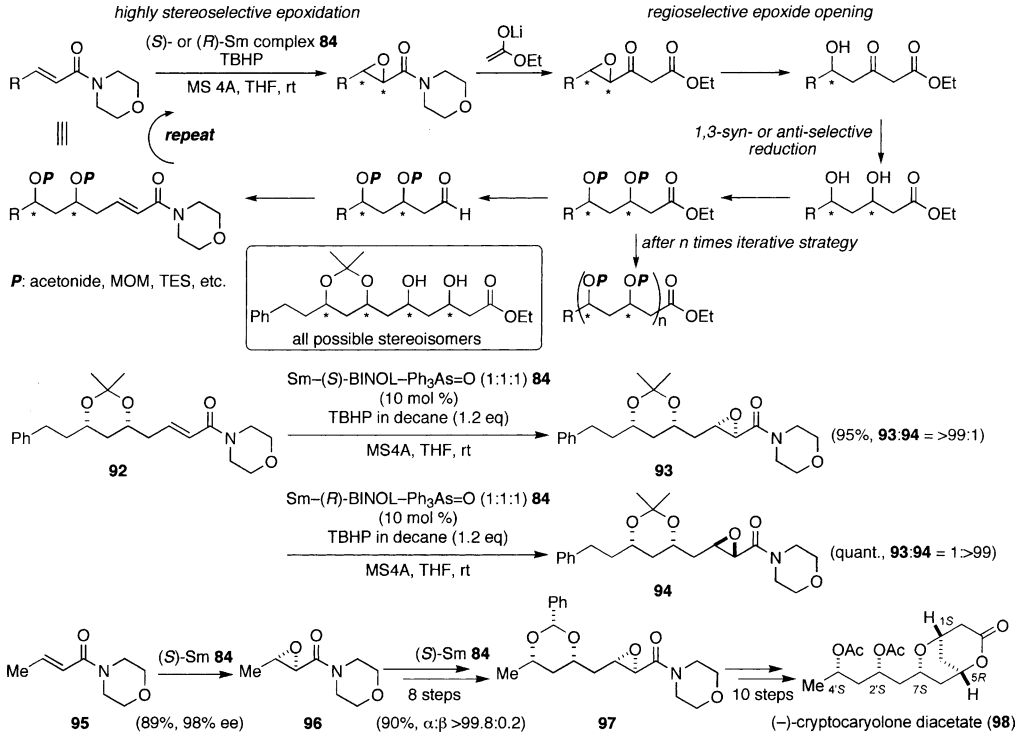


Chart 9. Strategy for Enantio- and Diastereoselective Syntheses of All Possible Stereoisomers of 1,3-Polyol Array Based on a Highly Catalyst-Controlled Epoxidation of α,β-Unsaturated Morpholinyl Amides: Application to 1,3-Polyol Natural Product Synthesis

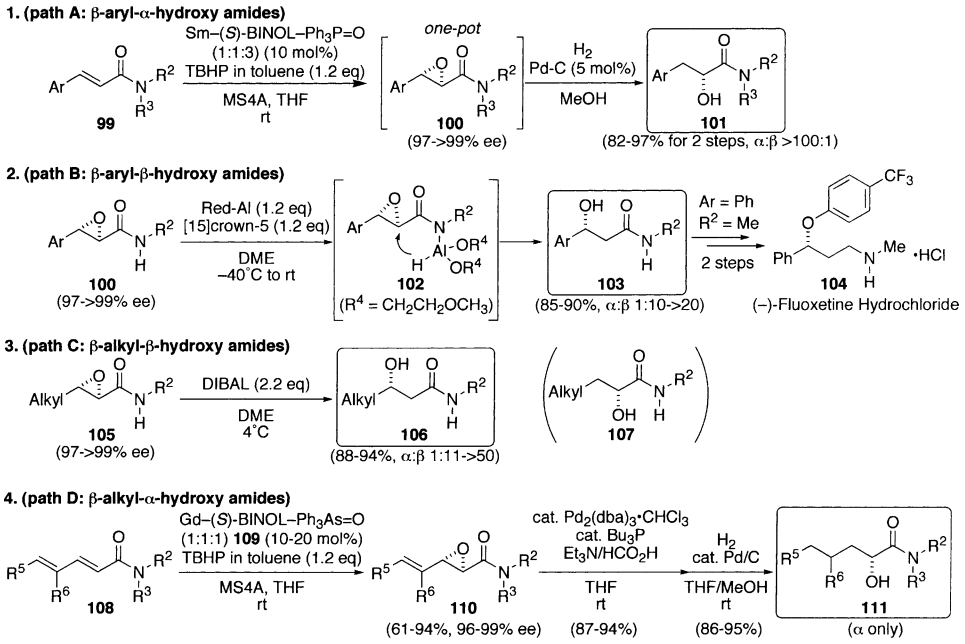


Chart 10. Syntheses of α- and β-Hydroxy Amides from α,β-Epoxy Amides by Regioselective Epoxide-Opening Reactions

and β-Hydroxy Amides[145,160] To further enhance the utility of the α,β-epoxy amides in organic synthesis, new regioselective epoxide-opening processes for α,β-epoxy amides to give both α- and β-hydroxy amides were developed (Chart 10). Chiral α- and β-hydroxy amides are useful building blocks for the synthesis of biologically active compounds.[161—163] There are no reports, however, of regioselective epoxide-opening reactions of α,β-epoxy amides,[164,165] in contrast to the success with α,β-epoxy ketones.[166—172] To realize highly regioselective epoxide-opening reactions of α,β-epoxy amides, it is important to control the relative reactivity of the α- and β-positions. α,β-Epoxy amides have completely different reactivity depending on the β-substituents. Thus, we developed separate regioselective epoxide-opening processes for both the β-aryl substituted amides **100** (path A, B) and the β-alkyl substituted amides **105** (path C, D). (1) Because of the higher reactivity of the β-position (benzyl position) than the α-position, the C_β–O bond of β-aryl substituted α,β-epoxy amides **100** can be selectively cleaved by Pd–C catalyzed hydrogenolysis conditions to afford β-aryl α-hydroxy amides **101**. An epoxide-opening reaction of isolated β-aryl α,β-epoxy amides **100** with Pd–C, however, afforded a mixture of desired α-hydroxy amide **101**, α,β-saturated amide, and α-keto amide in a ratio of 100 : 6 : 3. On the other hand, we achieved the highly enantio- and regioselective synthesis of β-aryl α-hydroxy amides **101** using a one-pot sequential catalytic asymmetric epoxidation–Pd-catalyzed epoxide-opening process (path A).[145] The formation of those by-products was successfully retarded in the reaction conditions including all of the reagents for the first epoxidation, affording **101** with excellent selectivity (100 : 0 : 1). Thus, the one-pot sequential catalytic asymmetric epoxidation–Pd-catalyzed epoxide-opening process (**99**→**101**) has a beneficial effects and functioned efficiently to provide **101** in excellent overall yield (82—97%) and enantiomeric excess (97—>99% ee) with almost no regioisomers and by-products. (2) The higher reactivity of the β-position of β-aryl α,β-epoxy amides **100**, however, makes it difficult to obtain β-hydroxy amides **103** through C_α–O bond cleavage (path B). Indeed, general conditions for selective C_β–O bond cleavage of α,β-epoxy ketones, such as SmI_2 and Cp_2TiCl_2–Zn,[166—172] produced unsatisfactory results (trace amounts) with α,β-unsaturated and saturated amides as major products. To overcome this difficulty, we examined the so-called intramolecular hydride transfer using Red-Al,[163,173—175] which might react with N–H first to produce N–Al species **102** and the remaining hydride attacks the α-position of the epoxy amide. As expected, the reduction of **100** with Red-Al gave β-hydroxy amides **103** as a major product in moderate yield (*ca.* 70%) and selectivity ($\alpha:\beta=1:2$). The reactivity and selectivity were further improved by the addition of 15-crown-5 as an additive to trap sodium cations, which might coordinate to oxygen in both the epoxide and carbonyl and weaken the C_β–O bond more effectively than the C_α–O bond,[176] resulting in higher yield of **103** (85—90%) with much higher selectivity ($\alpha:\beta=1:10$—>20).[160] To demonstrate the usefulness of this methodology, a catalytic asymmetric synthesis of (−)-fluoxetine hydrochloride (**104**), which is an anti-depressant drug and marketed as a racemate from Eli Lilly Co., was executed on a multi-gram scale.[160,177—182] (3) The Red-Al–crown ether strategy was also applicable to a regioselective epoxide-opening reaction of *β-alkyl* substituted amides **105** (path C). Because these substrates have higher reactivity at the α-position than the β-position, in contrast to *β-aryl* substituted amides **100**, satisfactory selectivity was obtained using even simple reaction conditions, such as DIBAL.[160] When 2 eq of DIBAL were used, *β-alkyl* α,β-epoxy amides **105** were successfully converted to the corresponding β-hydroxy amides **106** in excellent yield (88—94%) and selectivity ($\alpha:\beta=1:11$—>50). (4) Transformation of *β-alkyl* substituted α,β-epoxy amides **105** into α-hydroxy amides **107** (path D) is extremely challenging because there is much less reactivity at the β-position than at the α-position. After in-

tensive examination, α-hydroxy amide **107** was obtained using $LiAlH_4$ with moderate selectivity ($\alpha:\beta=2.7:1$). To obtain α-hydroxy amides efficiently, we used a new synthetic strategy with $\alpha,\beta,\gamma,\delta$-unsaturated amides **108**.[160] For the first catalytic asymmetric epoxidation of $\alpha,\beta,\gamma,\delta$-unsaturated amides **108**, Gd–(*S*)-BINOL–$Ph_3As{=}O$ complex **109** was determined to function best, affording γ,δ-unsaturated α,β-epoxy amides **110** as a sole product in good yield (61—94%) and excellent selectivity (96—99% ee). These γ,δ-unsaturated α,β-epoxy amides **110** were easily and efficiently converted to β-*alkyl* α-hydroxy amides **111** *via* γ,δ-unsaturated α-hydroxy amides. In this way, the syntheses of all types of hydroxy amides were realized by catalytic asymmetric epoxidation and subsequent regioselective epoxide-opening reactions.[160]

4. Catalytic Asymmetric Phase-Transfer Reaction

4-1. Development of New Asymmetric Two-Center Organocatalysts (TaDiAS) for Phase-Transfer Reactions[183,184] A wide variety of metal-mediated asymmetric two-center catalyses based on the multifunctional catalyst concept has been developed in Shibasaki's group.[4—8] To extend this concept to asymmetric organocatalysis, we developed a new versatile asymmetric phase-transfer catalysis (PTC).[183] In recent years, asymmetric organocatalysis has become of great interest as a new catalytic method to introduce chirality into a molecule.[185—189] Among them, PTC is one of the most important and useful methods in synthetic organic chemistry because of its preparative advantages, such as simple reaction procedures, mild conditions, inexpensive and environmentally benign reagents, and the ease in scaling-up the reaction.[190—194] An asymmetric version of PTC utilizing chiral phase-transfer catalysts is a highly attractive method in terms of atom economy; however, it has not been as extensively studied as metal-mediated asymmetric catalysis. The pioneering studies of O'Donnell and co-workers in 1989 led to the development of a highly practical enantioselective alkylation of a prochiral-protected glycine derivative using *Cinchona* alkaloid ammonium salts to produce chiral α-amino acids.[195—200] Later, Corey[201—203] and Lygo[204—207] independently greatly improved this catalyst system.[208—210] Although many types of chiral phase-transfer catalysts have been developed, *Cinchona* alkaloid derivatives give more impressive enantioselectivity for a range of reactions than do other catalysts, with few exceptions,[213—222] such as *N*-spiro binaphtyl derivatives.[213—217] The major drawback of these catalysts is the difficulty in modifying the catalyst structure for further improvement of selectivity and reactivity or further application to other types of catalytic asymmetric reaction systems. To address this issue, we developed a novel two-center catalyst: tartrate-derived diammonium salt (TaDiAS **112**) (Fig. 8).[183,184,223] The new asymmetric catalyst design was based on a two-center catalyst, in which two ammonium salt moieties maintain an appropriate distance and the substrate can be fixed in a chiral environment by two cationic moieties, and structural diversity. To achieve ideal complexation of the two-center catalyst and the substrate (glycine Schiff base **113**), we selected a 1,4-diammonium salt, rather than a 1,2- or 1,3-diammonium salt, considering the spatial environment created by two cationic moieties based on several preliminary investigations.[183,184] Thus, we designed a new two-center catalyst, TaDiAS **112**, both enantiomers of which can be synthesized from commercially available and relatively inexpensive[224] L- or D-tartrate in 5 steps using only common and inexpensive reagents under operationally simple reaction conditions (Chart 11).[183,184] Although we examined other candidates during preliminary catalyst screening of *N*-substituents,[183,184] based on several preliminary studies, we hypothesized that the combination of two large *N*-substituents and one small *N*-substituent like TaDiAS **112** would be best for the phase-transfer alkylation of **113**. TaDiAS **112** has remarkable structural diversity because a wide variety of catalysts can be easily synthesized by changing acetal moieties (R^1, R^2), aromatic parts (Ar), and counter anions (X^-), making it possible to three-dimensionally fine-tune the catalyst (*vide infra*).

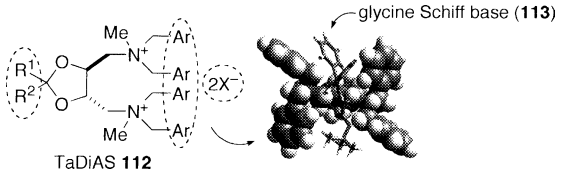


Fig. 8. Structure of TaDiAS **112** (Left) and the Result of Molecular Mechanics Simulation (Right)

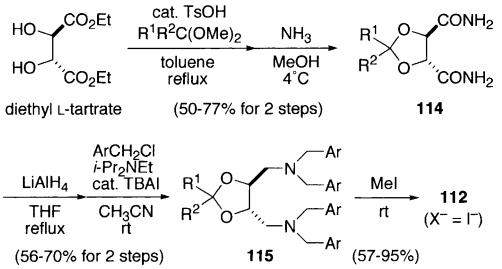


Chart 11. Preparation of TaDiAS **112** ($X^-=I^-$) from Diethyl Tartrate

We then examined a variety of TaDiAS **112** in phase-transfer alkylation. Starting from the original TaDiAS **112a**, the effect of an acetal moiety was examined. Contrary to our expectation, better phase-transfer alkylation was obtained when un-C_2-symmetric catalysts (*i.e.*, $R^1\neq R^2$) were used. Among them, the catalyst having *tert*-butyl methyl acetal had the highest selectivity. Keeping the acetal moiety as a *tert*-butyl methyl acetal, the effect of the aromatic part was examined. Screening of the aromatic part revealed that TaDiAS **112b** (Ar=4-methoxyphenyl) gave the best result. After optimization of the reaction conditions, we examined the scope and limitations of different electrophiles (Fig. 9). When 10 mol% of TaDiAS **112b** was used with cesium hydroxide, all phase-transfer alkylations of **113** with benzyl, allyl, and propargyl reagents proceeded at $-70\,^{\circ}C$ in good to high enantiomeric excess.[184,185] In addition, the reaction with 4-bromo- and 4-fluorobenzyl bromide, allyl bromide, propargyl bromide, *etc.*, afforded the corresponding protected synthetic α-amino acids, which can be a versatile intermediate of various synthetic α-amino acids. In all cases, when (*S*,*S*)-TaDiAS **112** was used as a catalyst, the absolute configurations were *R*.

Catalytic asymmetric phase-transfer Michael reaction of **113** to acrylate was investigated next. The results of catalyst screening for phase-transfer Michael reaction revealed that, in contrast to the above-mentioned phase-transfer alkylation,

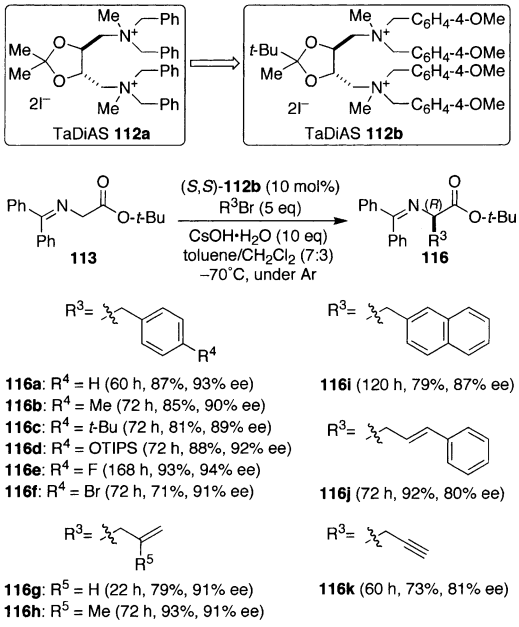


Fig. 9. Catalytic Asymmetric Phase-Transfer Alkylation of Various Electrophiles under Optimized Conditions

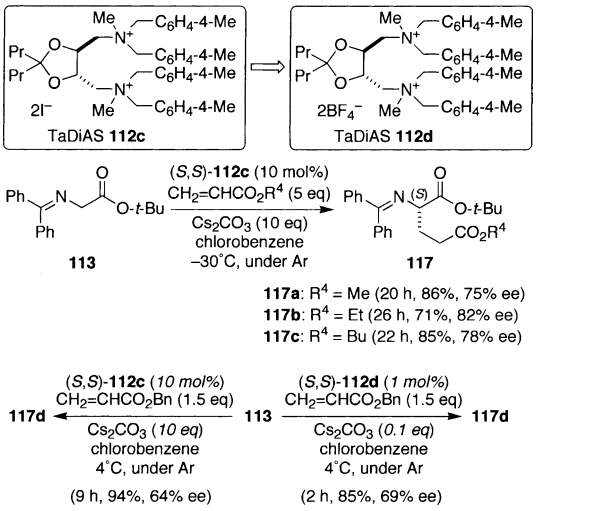


Fig. 10. Catalytic Asymmetric Phase-Transfer Michael Reaction and Counter Anion Effects

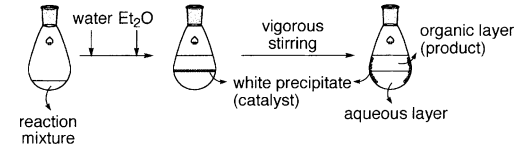


Fig. 11. General Procedure for Recovery of the Catalyst **112**

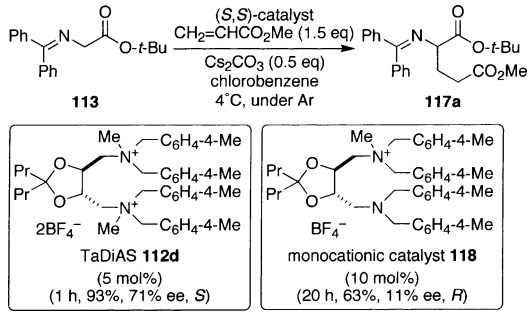


Fig. 12. Catalytic Asymmetric Phase-Transfer Michael Reaction Using TaDiAS **112d** and Monocationic Catalyst **118**

a C_2-symmetric catalyst gave better results than an un-C_2-symmetric catalyst. In this reaction, 4-methylphenyl was the best aromatic substituent and **112c** (R^1=R^2=Pr) gave the highest enantiomeric excess (75—82% ee) (Fig.10).[183,184] Although the phase-transfer Michael reaction, in principle, requires only a catalytic amount of base, most reported phase-transfer Michael reactions are performed in the presence of excess base.[190—194] In the case of our catalyst system for the Michael reaction, a decrease in Cs_2CO_3 from 10 to 0.5 eq decreased selectivity, although reactivity was maintained. At this stage, we expected that the counter anion of TaDiAS **112** would affect the reactivity in the catalytic base system. Thus, we examined counter anion effects of **112** in the present Michael reaction system. A variety of new types of TaDiAS **112** with hard counter anions instead of iodide were prepared and hard counter anions dramatically accelerated the phase-transfer Michael reaction. Among the examined counter anions, tetrafluoroborate catalyst **112d** had the highest reactivity with improved enantioselectivity. Moreover, using only 1 mol% of the catalyst **112d** with catalytic amount of Cs_2CO_3 (0.1 eq) gave much higher reactivity (2 h, 85%, 69% ee) than 10 mol% of **112c** with excess Cs_2CO_3 (10 eq) (9 h, 94%, 64% ee) at 4 °C. The counter anion effects were also observed under optimized conditions (−30 °C) to provide **117d** in 81% ee.[183,184] To the best of my knowledge, this is the first example of such dramatic counter anion effects in PTC. Surprisingly, using (*S*,*S*)-TaDiAS **112**, the obtained Michael product **117** had an *S* configuration in all cases.

In contrast to commonly used *Cinchona* alkaloid-derived catalysts,[190—212] TaDiAS **112** is extremely stable under strongly basic conditions. In spite of the existence of β-hydrogen to the ammonium cation, catalyst decomposition, such as that due to Hoffman elimination, has not been observed under phase-transfer reaction conditions. As a result, TaDiAS **112** can be recovered from the reaction mixture in a high recovery yield (80—90%).[183,184] After quenching the reaction with water and diethyl ether, the catalyst appeared as a white solid between two layers. Vigorous stirring for 5 to 10 min resulted in the white solid sticking to the glass walls. Thus, the solid was easily separated from the product by simple decantation (Fig. 11). The residual solid was dissolved with 30% MeOH in CH_2Cl_2 and filtered through a paper filter to remove inorganic salts, resulting in recovered catalyst after the solvent evaporated. The recovered catalyst was reused in the phase-transfer alkylation without further purification, and had the same catalyst efficiency.

The precise reaction mechanism, especially the reason for opposite facial selectivity between alkylation and Michael reaction, remains unclear. Thus, we performed several preliminary mechanistic investigations. Molecular mechanics simulations suggested that the existence of two cationic moieties in the catalyst is essential for obtaining high enantioselectivity (Fig. 8). The monocationic catalyst **118** (10 mol%) had much lower reactivity and selectivity than the dicationic catalyst **112d** (5 mol%) in the phase-transfer Michael addition

(Fig. 12).[184] Although bis- and tris-*Cinchona* alkaloid ammonium salt catalysts were reported,[225—228] similar reactivity and selectivity were observed, compared with standard *Cinchona* alkaloid catalysts, even with the same catalyst loading. These results suggest that, as expected, substrate **113** is fixed in a chiral environment by two cationic moieties. Moreover, based on previous reports[229—232] and our preliminary *ab initio* calculation,[184] the *Z*-enolate of **113** might be fixed with the catalyst **112** through several hydrogen bonds between the α-methylene or methyne unit of the ammonium cation units and the enolate oxygen atom and imine nitrogen atom of **113**.

4-2. Enantioselective Syntheses of Aeruginosin 298-A and Its Analogues Using Catalytic Asymmetric Phase-Transfer Reaction and Epoxidation[233,234] With the practical asymmetric PTC using TaDiAS **112** with broad substrate generality in hand, we next examined the synthetic application of this asymmetric PTC to produce complex natural products because of its easy accessibility to a variety of optically active natural and unnatural α-amino acids. First, we chose aeruginosin 298-A (**119**) as a target compound based on its unique serine protease inhibitor activity and the existence of nonstandard amino acids such as 2-carboxy-6-hydroxyoctahydroindole (Choi) in the molecule (Fig. 13).[235,237,238] To gain insight into the structure–activity relations, we developed a highly versatile synthetic method for aeruginosin 298-A as well as its analogues, using the above-mentioned catalytic asymmetric phase-transfer alkylation[183,184] for the syntheses of the D-Leu, L-Choi, and L-Algol portions and the above-mentioned catalytic asymmetric epoxidation of α,β-unsaturated imidazolide[134—136] for the synthesis of the (*R*)-3-(4-hydroxyphenyl)lactic acid (D-Hpla) portion.[233,234] Because most of the aeruginosin families contain a D-Hpla portion, an L-Choi portion, and a guanidine unit,[235,236] we synthesized a variety of analogues by altering the second amino acid portion from the *N*-terminus (R^5) and arginine portion (R^6, R^7 as well as their enantiomers).

The syntheses of aeruginosin 298-A and its analogues are summarized in Chart 12.[233,234] The D-Hpla portion was prepared based on catalytic asymmetric epoxidation of α,β-unsaturated imidazolide **120** using 10 mol% of the La–(*S*)-BINOL–$Ph_3P{=}O$ (1 : 1 : 3) complex[129,130,134—136] to afford epoxy peroxy ester **121** in 95% yield and 94% ee, which was directly used for the next coupling reaction with the second amino acid portions from the *N*-terminus (D-Leu portion). The second amino acid portion was synthesized using catalytic asymmetric phase-transfer alkylation with (*S*,*S*)-TaDiAS **112b** (91—94% ee; Fig. 9). Synthesis of the L-Choi portion began with catalytic asymmetric phase-transfer alkylation of **113** to **122** using (*R*,*R*)-TaDiAS **112b** (80%, 88% ee). The following transformation, including five one-pot reactions (deprotection of the benzophenone imine and acetal,

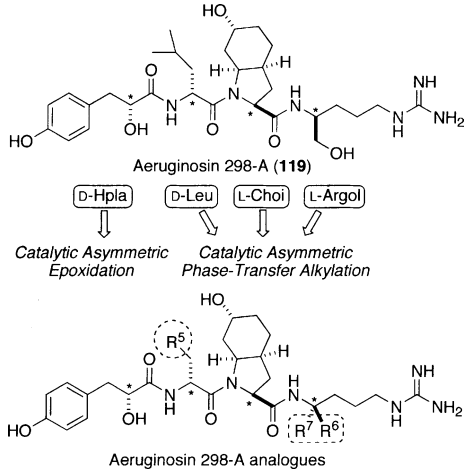


Fig. 13. Structures of Aeruginosin 298-A (**119**) and Its Analogues

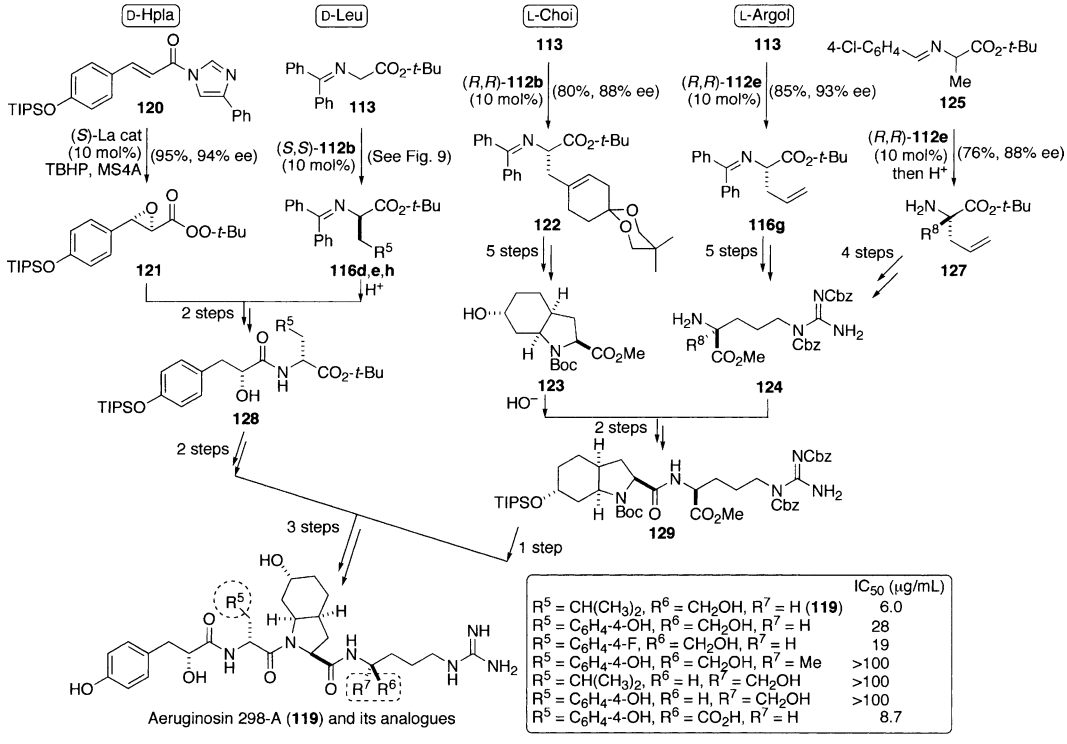


Chart 12. Syntheses of Aeruginosin 298-A (**119**) and Its Analogues

transesterification, migration of the C–C double bond to form enone, and 1,4-addition of the resulting amine to enone), afforded unusual bicyclic amino ester **123**. Synthesis of the L-Argol portion was achieved by the phase-transfer alkylation of **113** using the tetrafluoroborate catalyst (*R*,*R*)-**112e** (R^1=*t*-Bu, R^2=Me, Ar=C_6H_4-4-OMe, X^-=BF_4^-). Even in the alkylation conditions (in the presence of excess hydroxide), the tetrafluoroborate catalyst **112e** had positive effects and gave higher reactivity (85%, 93% ee) than the iodide catalyst **112b** (79%, 91% ee). Then, **116g** was converted to **124** (R^8=H) through introduction of the guanidine moiety. In a similar way, the enantiomer of **124** was prepared using (*S*,*S*)-**112e** as a catalyst. Moreover, the α-methyl analogue (R^8=Me) was also synthesized through catalytic asymmetric phase-transfer alkylation of **125** (76%, 88% ee) using the tetrafluoroborate catalyst **112e**. With all the amino acid portions and their derivatives in hand, each amino acid portion was assembled. Coupling of the α,β-epoxy peroxy ester **121** with amino ester (D-Leu portion) proceeded smoothly by simply mixing both portions (see Chart 7) and a subsequent regioselective one-pot epoxide-opening reaction with Pd–C (see Chart 10, path A) furnished the left dipeptide **128** in high yield (88—91% for 2 steps). Other coupling reactions were conducted using EDC–HOBt (L-Choi, L-Argol) and HATU[239] (D-Hpla–D-Leu, L-Choi–L-Argol). In the latter case, HATU gave superior results, preventing epimerization of the D-Leu portion. Through the reduction of methyl ester and removal of the protecting group (TIPS, Cbz), enantioselective syntheses of aeruginosin 298-A (**119**) and its six analogues were then accomplished and all stereocenters were controlled by asymmetric catalysis. Furthermore, inhibitory activity studies against the serine protease trypsin were performed. The biologic activity studies of the newly synthesized aeruginosin analogues suggest that conformation of the Argol portion, especially the guanidine side-chain, is extremely important for the inhibitory activity. Access to additional derivatives and closer investigation are now possible through molecular design and chemical synthesis.

5. Conclusion

As presented here, we developed several highly enantioselective and practical catalytic asymmetric catalyses (Michael reaction, epoxidation, and phase-transfer reaction), which allow enantioselective total synthesis of a variety of biologically active natural products (strychnine, decursin, cryptocaryolone diacetate, fluoxetine, aeruginosin 298-A, *etc.*). During the studies on total syntheses, we often faced severe problems in the key asymmetric catalysis; for example, quite low reactivity and selectivity in the catalytic asymmetric epoxidation in decursin synthesis using the previously developed catalyst system. From a different standpoint, this kind of difficulty provides us with a great opportunity to improve the present asymmetric catalysis. In fact, to meet the demands of total synthesis, we intensively investigated the reaction and many times succeeded in further improvement of the reaction in terms of substrate generality, catalyst efficiency, and practicality. As a result, we developed a more versatile and efficient synthetic process, such as aeruginosin 298-A synthesis (Chart 12), 1,3-polyol synthesis (Chart 9) and improved indole alkaloid syntheses (Chart 4, β-keto ester route), with a successful application to medicinal chemistry (Chart 12). I believe that total synthesis of complex natural products is a very powerful tool, not only for supplying highly potent compounds, but also for developing highly practical and very useful asymmetric catalysis through positive cooperation as shown in Fig. 1. I hope that the findings discussed herein will facilitate the development of the field of asymmetric catalysis as well as total synthesis.

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