Review

Chiral poly-rare earth metal complexes in asymmetric catalysis

By Masakatsu SHIBASAKI*), †)

Graduate School of Pharmaceutical Sciences, The University of Tokyo,
Tokyo, Japan.
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Abstract: Asymmetric catalysis is a powerful component of modern synthetic organic chemistry. To further broaden the scope and utility of asymmetric catalysis, new basic concepts for the design of asymmetric catalysts are crucial. Because most chemical reactions involve bond-formation between two substrates or moieties, high enantioselectivity and catalyst activity should be realized if an asymmetric catalyst can activate two reacting substrates simultaneously at defined positions. Thus, we proposed the concept of bifunctional asymmetric catalysis, which led us to the design of new asymmetric catalysts containing two functionalities (e.g. a Lewis acid and a Brønsted base or a Lewis acid and a Lewis base). These catalysts demonstrated broad reaction applicability with excellent substrate generality. Using our catalytic asymmetric reactions as keys steps, efficient total syntheses of pharmaceuticals and their biologically active lead natural products were achieved.

Key words: Asymmetric catalyst; bifunctional; Lewis acid; Brønsted base; Lewis base; pharmaceutical synthesis.

1. Introduction. Asymmetric catalysis has received considerable attention over the past few decades, and its contribution in organic synthesis has become increasingly important.[1)] Various enantioselective chemical transformations are now performed with only catalytic amounts of chiral promoters. Some of these enantioselective transformations are applied to industrial production. The performance of most artificial asymmetric catalysts, however, is still far from satisfactory in terms of generality and reactivity. On the other hand, enzymes catalyze various organic transformations under mild conditions, even though they have often troubles in substrate generality. One advantage of enzymes over most artificial asymmetric catalysts is that they often contain two or more active sites for catalysis. The synergistic function of two active sites can make substrates more reactive in the transition state and control the relative positions of substrates. This concept of multifunctional catalysis is a key to increasing the scope of natural and artificial asymmetric catalysts.

The development of asymmetric catalysis has been, in many cases, accomplished by using various metal/chiral ligand complexes. While asymmetric catalysts containing p-block and/or d-block metal elements have been studied extensively, the use of f-block metal elements, such as lanthanides, for asymmetric catalysts have not been thoroughly investigated until recently. The utility of rare earth metals for asymmetric catalysis was first demonstrated by Danishefsky *et al*. in a hetero Diels-Alder reaction with $Eu(hfc)_3$.[2)] Successively, the utility of rare earth metal complexes as chiral Lewis acid catalysts was demonstrated in various reactions by several research groups.[3),4)] On the other hand, we were initially interested in using the Brønsted basic character of rare earth metal alkoxides for organic synthesis. Aldol reactions, cyanosilylations of aldehydes, and nitroaldol reactions proceeded smoothly with a catalytic amount of rare earth metal alkoxide.[5)] On the basis of the Lewis acidic and Brønsted basic properties of rare earth metals, we envisioned that rare earth metal complexes should be

*) Recipient of the Japan Academy Prize in 2005.

†) Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo, 113-0033, Japan (mshibasa@mol.f.u-tokyo.ac.jp).

suitable for use in multifunctional asymmetric catalysis. In this account, we briefly discuss the most recent advances in rare earth metal multifunctional asymmetric catalysis in our group. For more comprehensive reviews including details of our early work and the work of other groups, see other review articles.[6),7)]

2. Heterobimetallic rare earth-alkali metal-BINOL (REMB) complexes. *2.1. Use of REMB complexes as a Lewis acid-Brønsted Base catalyst.* Since our first report of a catalytic asymmetric nitroaldol reaction using rare earth metal complexes,[8)] we have continued to develop the concept of multifunctional catalysis wherein the catalyst exhibits both Lewis acidity and Brønsted basicity. In particular, heterobimetallic complexes that contain a rare earth metal, three alkali metals and three 1,1'-bi-2-naphthols (BINOLs) offer a versatile framework for asymmetric catalysts. The structure of such a rare earth-alkali metal-BINOL complex (abbreviated as REMB; RE: rare earth metal, M: alkali metal, B: BINOL) is shown in Fig. 1. The synergistic effect of the two functionalities enables various transformations that are otherwise difficult using conventional monometallic catalysts with only Lewis acidity. A variety of enantioselective transformations have been realized through the choice of appropriate combinations of metals, depending on the type of the reaction. The properties of REMB catalysts can be modified by varying the alkali metal and further refined by choosing the proper rare earth metal. REMB complexes can be prepared from several rare earth metal sources, such as RE(O-*i*-Pr)$_3$, RE{N(SiMe$_3$)$_2$}$_3$, RE(OTf)$_3$ and RECl$_3\cdot$7H$_2$O as shown in Scheme 1.[9)] For most of the transformations, REMB complexes prepared from RE(O-*i*-Pr)$_3$ were used. Among rare earth metal sources, RE(O-*i*-Pr)$_3$ and RE{N(SiMe$_3$)$_2$}$_3$ are most suitable for the preparation of pure REMB complex, because side products derived from catalyst preparation, such as *i*-PrOH, can be easily removed under reduced pressure. In the case of REMB complexes prepared from RE(OTf)$_3$ or RECl$_3\cdot$7H$_2$O, alkali metal salts, such as MOTf, remain in the catalyst solution, affecting asymmetric reactions either positively or negatively. Recently, we found that the La-Li-BINOL (LLB) complex prepared from La(OTf)$_3$ showed much better enantioselectivity in a direct aldol-Tishchenko reaction than the complex derived from La(O-*i*-Pr)$_3$ did. LiOTf in the catalyst mixture had positive effects on enantioselectivity in the Tishchenko reaction (eq. [1]).[10)] Mechanistic studies suggest that LiOTf changes the structure of LLB from monomeric to oligomeric.

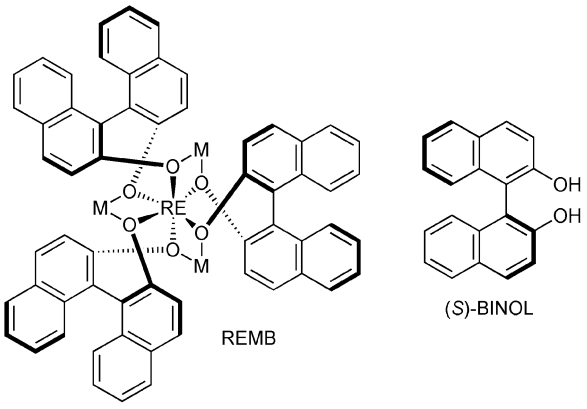
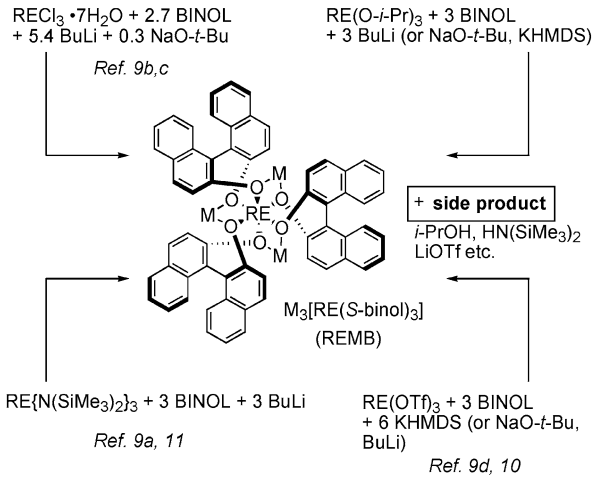
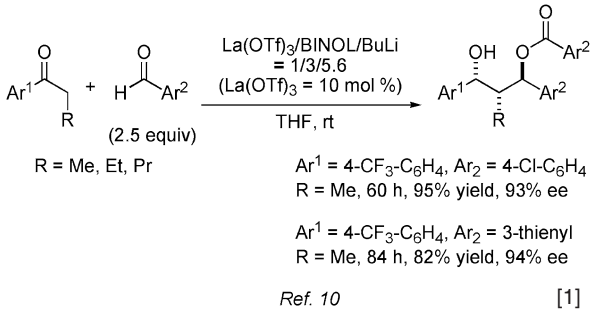


Fig. 1. Structure of RELi$_3$tris(binaphthoxide) heterobimetallic complexes (REMB).



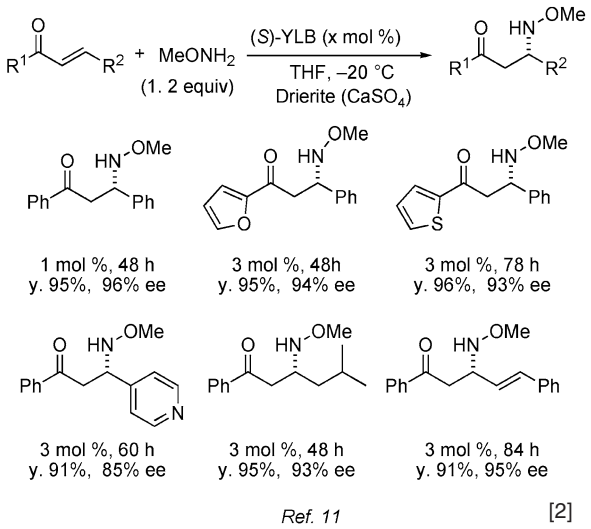
Scheme 1. Preparation methods of rare earth-alkali metal heterobimetallic complexes from various rare earth metal sources.



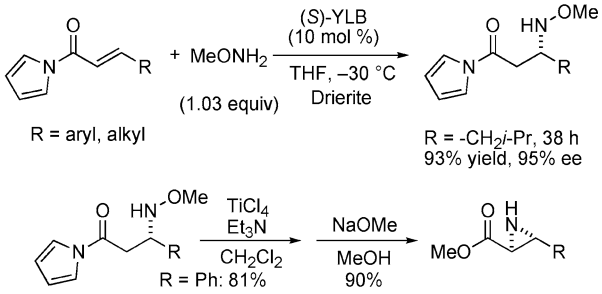
2.2. Use of REMB complexes as a Lewis acid-Lewis acid catalyst. In REMB heterobimetallic catalyzed reactions, only nucleophiles bearing protons with relatively low pK_a values (ca. 10-19 in H_2O), such as nitroalkanes, malonates, ketones, and thiols, were usable due to the limited Brønsted basicity of the catalysts. Nucleophiles with higher pK_a values were not applicable to REMB catalysis. Recently, however, we succeeded in broadening nucleophile scope by using the same REMB heterobimetallic catalysts, but in a different reaction mode. YLi_3tris(binaphthoxide) (YLB: RE = Y, M = Li) prepared from $Y\{N(SiMe_3)_2\}_3$ was shown to efficiently promote 1,4-addition of methoxylamine to enones, producing β-amino ketones in high ee (up to 97% ee, eq. [2]).[11),12)] α,β-Unsaturated *N*-acylpyrroles as carboxylic acid derivatives were also applicable, and β-amino acid derivatives were obtained in up to 94% ee (eq. [3]).[11c)] Mechanistic studies suggest that the rare earth metal functions as a Lewis acid to activate the enones and α,β-unsaturated *N*-acylpyrroles while the lithium ion functions as another Lewis acid to control the orientation of methoxylamine (Lewis acid-Lewis acid cooperative catalysis).[13)]

2.3. Catalytic asymmetric cyanoethoxycarbonylation and cyanophosphorylation. YLB is also an effective catalyst for asymmetric cyanoethoxycarbonylation (eq. [4])[14)] and cyanophosphorylation.[15),16)] In these reactions, Ar_3P = O, H_2O, and BuLi were essential as additives in order to achieve high enantioselectivity. Mechanistic studies suggest that both Ar_3P= O and H_2O coordinate to YLB and modify its structure, affecting both enantioselectivity and reactivity. LiOH generated from H_2O and BuLi reacts with ethyl cyanoformate to generate a YLB-LiCN complex, which is the true active species. LiCN self-assembled with YLB functions as a nucleophile in these reactions.[14)]

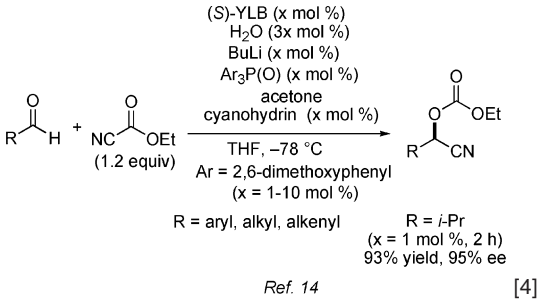
3. Rare earth metal/BINOL complexes. *3.1. Catalytic asymmetric epoxidation of electron deficient olefins.* Rare earth metal alkoxide complexes efficiently promote the catalytic asymmetric epoxidation[17)] of electron deficient olefins, such as enones, amides, and esters. Rare earth metal peroxides function as key active nucleophilic species in these reactions. The rare earth metal also functions as a Lewis acid to activate the electron deficient olefins. For best results it is important to select the rare earth metal alkoxide and chiral ligand suited to the substrate of interest. The addition of powdered MS 4 Å and either Ph_3P = O or Ph_3As = O is also critical in order to obtain high reactivity and enantioselectivity. For enones, La(O-*i*-Pr)$_3$/BINOL complex



Ref. 11 [2]



Ref. 11c [3]



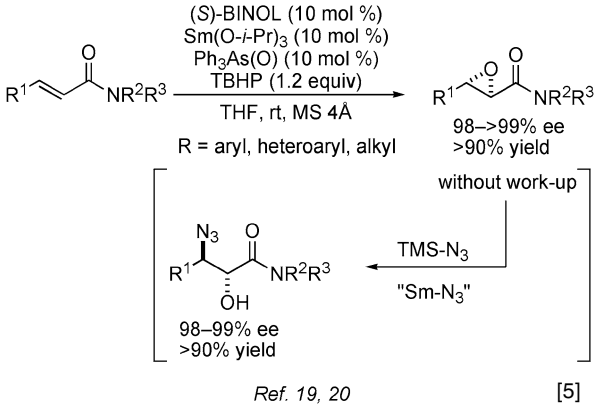
Ref. 14 [4]

gave the best results (up to 99% ee).[18)] Enolizable enones such as benzalacetone were applicable, producing the desired products in high yield and ee without any side adducts. For α,β-unsaturated amides, the Sm(O-*i*-Pr)$_3$/BINOL complex modified with Ph_3As = O was useful

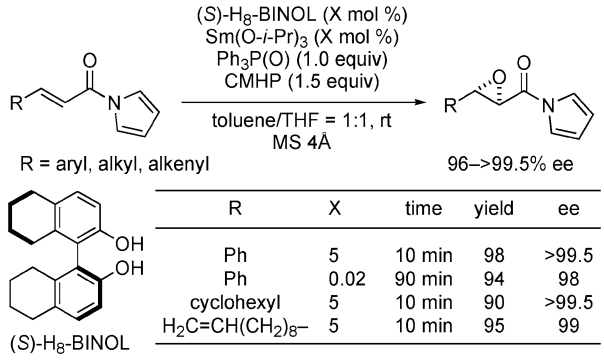
(up to 99% ee).[19] Sequential catalytic asymmetric epoxidation/regioselective epoxide opening reactions were also realized as shown in eq. [5].[20] In the regioselective epoxide opening reaction employing TMS-N_3, samarium azide was generated *in situ* as the active nucleophile. Returning to the epoxidation reaction, α,β-unsaturated *N*-acylpyrroles, which are activated, monodentate, ester equivalents, were also found to be competent acceptors (eq. [6]).[21),22)] $Sm(O\text{-}i\text{-}Pr)_3/H_8$-BINOL gives the best reactivity in this case; high TON (~4720) and high TOF (> 3000 h^{-1}) of the catalyst were realized.[21b)] The *N*-acylpyrrole moiety can be converted into various functional groups. It is also noteworthy that cumene hydroperoxide (CMHP), an oxidant with low explosion hazard, was applicable for the epoxidation of enones and α,β-unsaturated *N*-acylpyrroles. In the case of α,β-unsaturated esters, BINOL was not a suitable chiral ligand. Instead, a biphenyldiol ligand **1** was preferable, when used as its yttrium phenoxide complex (eq. [7]).[23)] Various β-substituents, including heteroaromatic rings, were tolerated in reactions catalyzed by the Y-biphenyldiol **1** complex.

3.2. Catalytic asymmetric Michael reactions of malonates. A complex prepared from $La(O\text{-}i\text{-}Pr)_3$ and linked-BINOL **2**[24)] is a good catalyst for the asymmetric Michael reaction[25)] between cyclic enones and malonates. The La-OAr moiety functions as a Brønsted base to generate La-enolates. La also acts as Lewis acid to activate enones. Reactions with various substituted and unsubstituted malonates gave products with high ee (99% ee, eq. [8]).[26)] Reactions proceeded in good yield using 1 equiv of malonate. The use of DME as solvent had drastic effects on enantioselectivity. With other ether solvents, ee was only modest to good. For less reactive malonates, the addition of hexafluoroisopropanol (HFIP) had beneficial effects on reactivity.

3.3. Direct catalytic asymmetric Mannich-type reactions of hydroxyketones. Recently, the catalytic, *in situ* generation of metal enolates from unmodified ketones and esters for application to asymmetric carbon-carbon bond-forming reactions has been intensively studied by several groups.[27)] REMB complexes catalyze catalytic asymmetric aldol reactions. We recently found that complexes of $Y\{N(SiMe_3)_2\}_3$ and linked-BINOL **2** or **3** are suitable for *syn*-selective direct catalytic asymmetric Mannich-type reactions of aromatic and heteroaromatic hydroxyketones with diphenylphosphinoyl-imines (Dpp-imines) (eq. [9]).[28)] In this reaction, rare earth metal alkoxides provided only modest reactivity and selectivity. The use of $Y\{N(SiMe_3)_2\}_3$ as a yttrium source

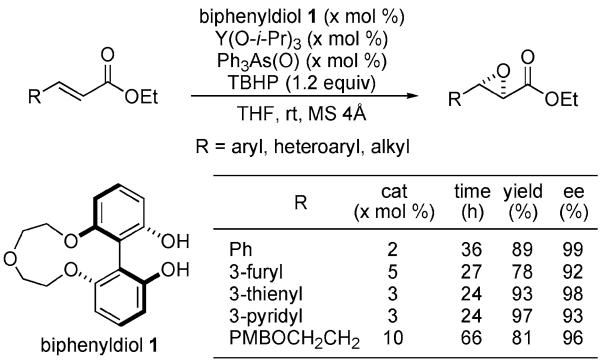


Ref. 19, 20 [5]



R	X	time	yield	ee
Ph	5	10 min	98	>99.5
Ph	0.02	90 min	94	98
cyclohexyl	5	10 min	90	>99.5
$H_2C{=}CH(CH_2)_8{-}$	5	10 min	95	99

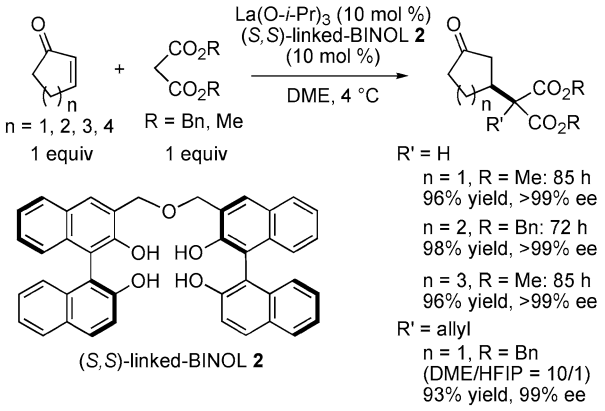
Ref. 21 [6]



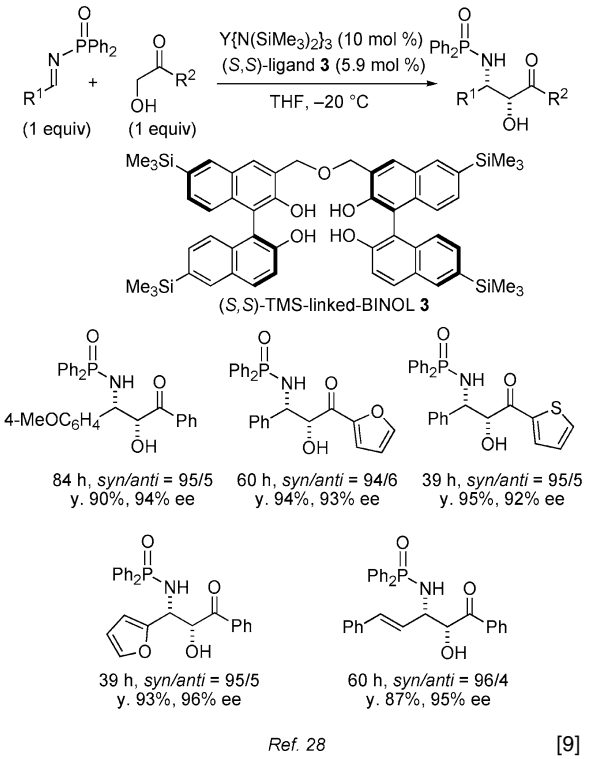
R	cat (x mol %)	time (h)	yield (%)	ee (%)
Ph	2	36	89	99
3-furyl	5	27	78	92
3-thienyl	3	24	93	98
3-pyridyl	3	24	97	93
$PMBOCH_2CH_2$	10	66	81	96

Ref. 23 [7]

was crucial. This tendency is opposite from that of asymmetric epoxidation, in which rare earth metal alkoxides were essential and $RE\{N(SiMe_3)_2\}_3$ gave only poor reactivity. Using $Y\{N(SiMe_3)_2\}_3$, β-amino-α-hydroxyketones were obtained in good yield and high ee.



Ref. 26 [8]



Ref. 28 [9]

Good yields were achieved using only equimolar amounts of hydroxyketones. For heteroaromatic hydroxyketones, TMS-linked-BINOL **3**[29] was necessary to achieve high ee. In the Mannich-type reaction, $Y\{N(SiMe_3)_2\}_3$/linked-BINOL complexes have sufficient Brønsted basicity to generate Y-enolate *in situ* from hydroxyketones.

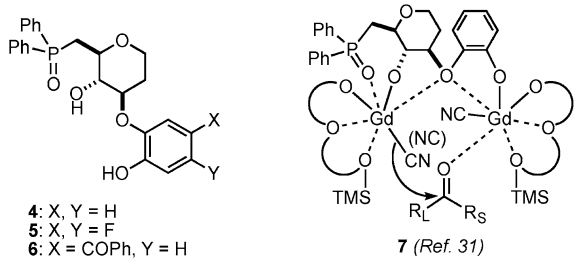
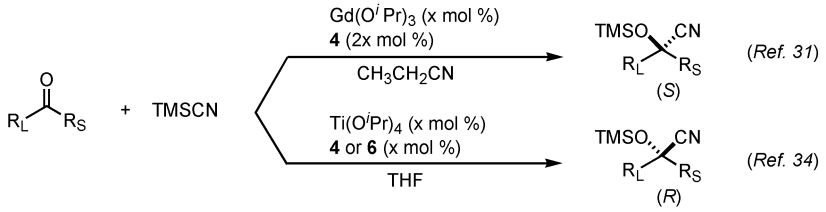


Fig. 2. D-Glucose derived ligands and proposed transition state for catalytic enantioselective cyanosilylation of ketones.

4. Catalytic enantioselective cyanosilylation of ketones. The chiral gadolinium complex prepared from $Gd(O\text{-}i\text{-}Pr)_3$ and D-glucose-derived ligand **4** or **5**[30] in a 1:2 ratio is a general enantioselective catalyst for the cyanosilylation of ketones (Fig. 2 and Table I).[31),32)] (*S*)–Ketone cyanohydrins are generally obtained with high enantioselectivity. Because the cyanide group can be easily converted to many other important functional groups, such as carboxylic acids or amines, this catalytic asymmetric reaction is a novel method for the production of a wide range of enantiomerically enriched chiral tertiary alcohols.[33)] The following results of mechanistic studies suggest a bimetallic transition state **7** for the enantioselective cyanosilylation of ketones. (1) The major species in the catalyst solution is a 2:3 complex of gadolinium and partially silylated **4**, according to the ^{1}H NMR and ESI-MS studies. (2) The 2:3 complex is likely to be a catalytically active species, based on the fact that enantioselectivity is dependent on the metal: ligand ratio used when the catalyst is prepared; enantioselectivity increases as the ligand/metal ratio increases, reaching a plateau at a 2:3 ratio (slightly higher enantioselectivity is obtained with a 1:2 ratio). (3) The actual nucleophile is a gadolinium cyanide (or isonitrile) generated through a facile transmetalation from TMSCN based on kinetic studies and labeling experiments. Previously, we developed a complementary (*R*)–selective catalytic cyanosilylation of ketones using a titanium complex of the same ligand **4** or **6**.[34)] Therefore, both ketone cyanohydrin enantiomers can be synthesized from a broad range of substrate ketones using one chiral source by appropriate choice of either titanium or gadolinium.

The utility of (*S*)–selective cyanosilylation of ketones catalyzed by the chiral lanthanide complexes was demonstrated by the following successful applica-

Table I. Catalytic enantioselective cyanosilylation of ketones

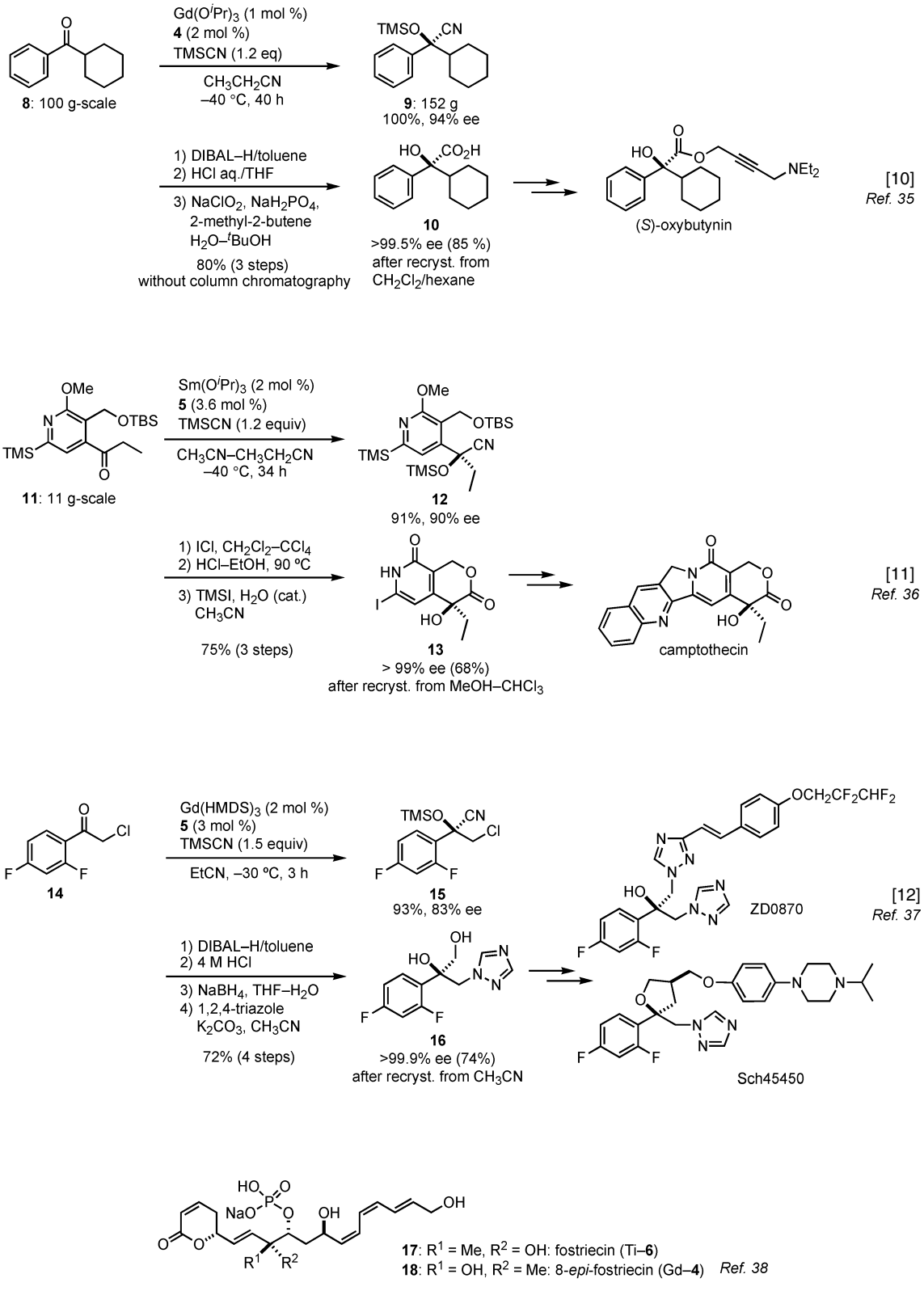


entry	ketone	metal source	ligand	loading (x mol %)	temp (°C)	time (h)	yield (%)	ee (%)
1	R = H	Gd(O^{i}Pr)$_3$	**4**	1	−40	16	93	91
2		Ti(O^{i}Pr)$_4$	**6**	1	−20	88	92	94
3	R = Cl	Gd(O^{i}Pr)$_3$	**4**	5	−60	55	89	89
4		Ti(O^{i}Pr)$_4$	**6**	1	−25	92	72	90
5		Gd(O^{i}Pr)$_3$	**4**	5	−60	14	93	97
6		Ti(O^{i}Pr)$_4$	**6**	1	−10	92	90	92
7		Gd(O^{i}Pr)$_3$	**4**	5	−60	6.5	94	87
8		Ti(O^{i}Pr)$_4$	**4**	10	−50	88	72	91
9		Gd(O^{i}Pr)$_3$	**4**	5	−60	19	96	76
10		Ti(O^{i}Pr)$_4$	**6**	2.5	−30	92	72	90
11		Gd(O^{i}Pr)$_3$	**4**	5	−60	1	97	66
12		Ti(O^{i}Pr)$_4$	**6**	10	−50	36	92	85
13		Gd(O^{i}Pr)$_3$	**4**	5	−60	0.5	79	47
14		Ti(O^{i}Pr)$_4$	**6**	2.5	−45	92	80	82

tions to pharmaceutical synthesis (Scheme 2). First, key synthetic intermediate **10** for (*S*)-oxybutynin, a muscarinic receptor antagonist and a drug for treatment of urinary urgency, frequency, and incontinence, was synthesized in 4 steps from commercially available ketone **8** (eq. [10]).[35] The key catalytic enantioselective cyanosilylation proceeded using 1 mol % of catalyst, and the product **9** was obtained in quantitative yield with 94% ee. This reaction was conducted on a 100 g-scale. Enantiomerically pure **10** was produced from **9** through reduction, deprotection, oxidation, and, finally, recrystallization.

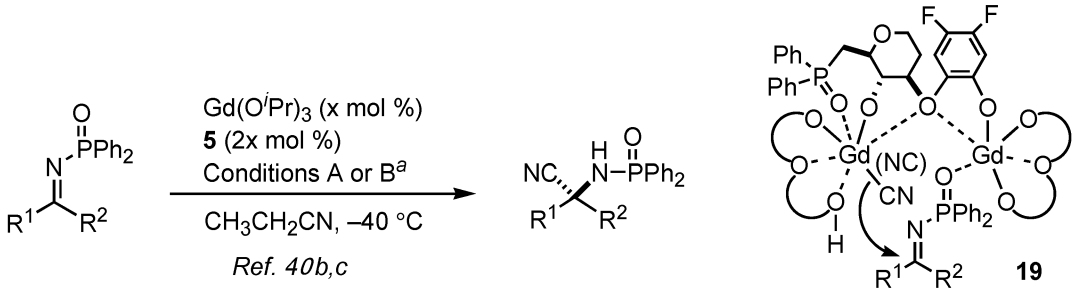
Second, catalytic enantioselective synthesis of Curran's precursor (**13**) to the anticancer drug, camptothecin, was achieved (eq. [11]).[36] When ketone **11** was used as a starting material, catalyst generated from Sm(O-*i*-Pr)$_3$ and **5** in a 1:1.8 ratio gave the best enantioselectivity. Using 2 mol % catalyst, product cyanohydrin **12** was obtained in 91% yield with 90% ee. The reaction was conducted on an 11 g-scale. After iododesilylation of **12**, lactone formation, methyl ether cleavage, and recrystallization from MeOH-$CHCl_3$, enantiomerically pure **13** was afforded.

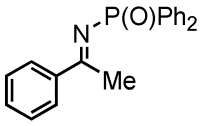
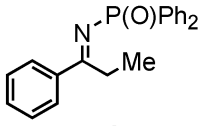
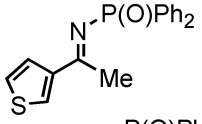
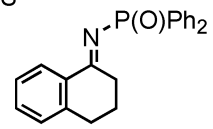
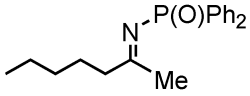
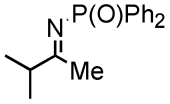
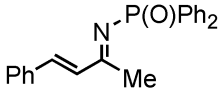
Third, a rapid synthesis of versatile key intermediate **16** of triazole antifungal agents such as ZD0870 and Sch45450, was achieved (eq. [12]).[37] When electron-deficient ketone **14** was used as a substrate, catalyst prepared from Gd(HMDS)$_3$ and ligand **5** in a 2:3 ratio exhibited superior enantioselectivity to catalyst prepared by the conventional method using Gd(O-*i*-Pr)$_3$ and ligand in a 1:2 ratio. Thus, product **15** was obtained in 93% yield with 83% ee using 2 mol % of catalyst. Catalyst prepared from Gd(O-*i*-Pr)$_3$ in the conventional method gave only 68% ee from **14**. Based on ESI-MS studies, the sharp difference in enantioselectivity depending on the gadolinium source was attributed to the existence of a less enantioselective catalytic species containing Gd/chiral ligand/μ-oxo in a 4/5/1 ratio when catalyst was prepared from Gd(O-*i*-Pr)$_3$. Only the desired 2:3 complex was observed in ESI-MS when the catalyst was prepared from Gd(HMDS)$_3$. The 4:5:1 μ-oxo complex is problematic only in the case of reactive ketones such as **14**, probably because it is less active than the 2:3 complex. Cyanohydrin **15** was converted to **16** in 4 steps with high yield. Recrystallization of **16** afforded enantiomerically pure target compound.



Scheme 2. Catalytic asymmetric synthesis of key intermediates of pharmaceuticals.

Table II. Catalytic enantioselective Strecker reaction of ketoimines



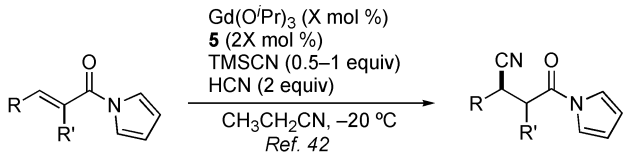
entry	substrate	conditions (x = loading)	time (h)	yield (%)	ee (%)
1		A (1)	30	94	92
2		B (0.1)	19	97	90
3		A (1)	31	97	95
4		A (1)	21	93	93
5		B (1)	3	99	99
6		A (1)	22	92	92
7		A (1)	43	73	90
8		A (2.5)	2.5	91	80
9		A (1)	38	93	96

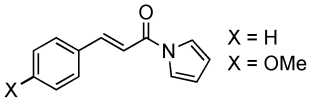
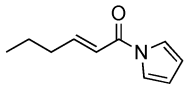
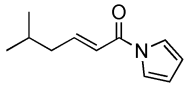
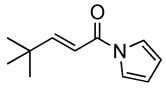
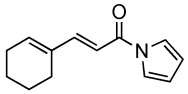
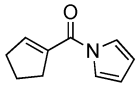
[a] Conditions A = TMSCN (1.5 equiv) + 2,6-dimethylphenol (1 equiv). Conditions B = TMSCN (2.5~5 mol %) + HCN (150 mol %).

Finally, we recently succeeded in the catalytic asymmetric synthesis of 8-*epi*-fostriecin (**18**), an analogue of naturally-occurring anticancer compound, fostriecin (**17**), using the Gd-**4**-catalyzed (*S*)-selective cyanosilylation of a ketone.[38]

5. Catalytic enantioselective Strecker reaction of ketoimines. Chiral α,α-disubstituted α-amino acids are important building blocks for pharmaceuticals and artificially designed peptides. The catalytic enantioselective Strecker reaction of ketoimines is one of the most direct and practical methods for the synthesis of this class of compounds.[39] The gadolinium complex prepared from Gd(O-*i*-Pr)$_3$ and **5** is an excellent catalyst for the enantioselective Strecker reaction of *N*-phophinoylketoimines (Table II).[40),41] In this reaction, protic additives such as 2,6-dimethylphenol or HCN greatly

Table III. Catalytic enantioselective conjugate addition of cyanide



entry	substrate	catalyst (x mol %)	time (h)	yield (%)	ee (%)
1[a]	 X = H	10	98	90	91
2[a]	X = OMe	10	98	85	90
3[b]		5	42	91	98
4[b]		5	42	89	97
5[b]		5	88	87	90
6[a]		20	139	78	93
7[a,c]		5	8	99 (1.1/1)[d]	88/83

β-phenyl-GABA

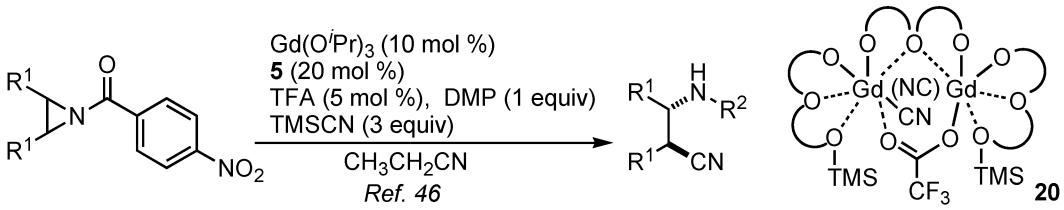
(*ent.*)-pregabalin

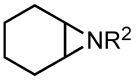
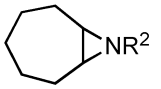
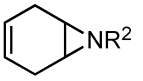
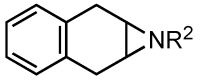
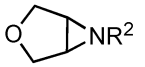
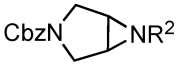
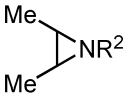
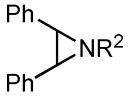
[a] 1 equiv of TMSCN was used. [b] 0.5 equiv of TMSCN was used. [c] The reaction was performed at room temperature. [d] Diastereomer ratio.

improved enantioselectivity, substrate generality, and catalyst activity. Excellent enantioselectivity was obtained from a wide range of substrates, including aromatic, heteroaromatic, cyclic, α,β-unsaturated, and aliphatic ketoimines. In the optimum case, the reaction was performed using 0.1 mol % catalyst in the presence of 2.5 mol % TMSCN and 150 mol % HCN (entry 2). This method is the most general catalytic enantioselective Strecker reaction of ketoimines reported to date. Based on ESI-MS studies, the protic additive functions by changing the active catalyst to a proton-containing 2:3 complex (**19**), which is more active and enantioselective than trimethylsilylated 2:3 complex **7** in the Strecker reaction. The internal proton of **19** might act to facilitate product dissociation from the catalyst, promoting regeneration of the active catalyst.

6. Catalytic enantioselective conjugate addition of cyanide. Recently, we developed a catalytic enantioselective conjugate addition of cyanide to α,β-unsaturated *N*-acylpyrroles using the Gd–**5** complex.[42] This type of reaction is useful for the synthesis of a wide variety of chiral building blocks including chiral γ-amino acids. Prior to our contribution, Jacobsen's group reported the first catalytic enantioselective conjugate addition of cyanide using the chiral salen–Al complex.[43] Although excellent enantioselectivity was realized from β-aliphatic-substituted substrates, substrates with a β-aryl or vinyl substituents were unreactive. Our catalyst has overcome this limitation: products were obtained with high enantioselectivity from a wide range of substrates including β-aliphatic, aromatic, and alkenyl *N*-acyl pyrroles in the presence of TMSCN and

Table IV. Catalytic enantioselective ring-opening of aziridines with TMSCN

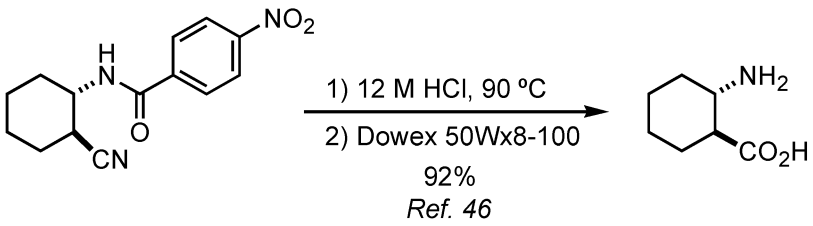


entry	substrate (R^2 = p-NO_2-Bz)	temp (°C)	time (h)	yield (%)	ee (%)
1		0	20	94 (79)[a]	87 (>99)[a]
2[b]		r.t.	69	81	93
3[c]		60	64	92 (58)[a]	80 (>99)[a]
4		r.t.	95	85 (66)[a]	82 (>99)[a]
5[d]		r.t.	42	91	83
6[b]		60	96	92	88
7[b]		60	23	89	84
8		r.t.	39	93	85
9		r.t.	96	44/37	90/89

[a] After recrystallization. Recrystallization yield and its ee are shown in parentheses. [b] With 20 mol % Gd(O-*i*-Pr)$_3$ and 40 mol % **5**. [c] 2.5 mol % TFA was used. [d] CH_3CH_2CN/CH_2Cl_2 = 1/2 was used as solvent.

HCN (Table III). Due to the versatility of cyanides and *N*-acyl pyrroles, pharmaceuticals and their lead compounds such as pregabalin, an anticonvulsant drug, and β-phenyl-GABA, an inhibitor in the nervous system, were synthesized using this reaction as the key step.

7. Catalytic enantioselective ring-opening of meso-aziridines with TMSCN. Chiral β-amino acids are important building blocks for the synthesis of natural products and pharmaceuticals. Among them, chiral cyclic β-amino acids are currently of great interest due to the recent finding that peptides composed of these amino acids can act as foldamers with well-defined secondary structure.[44] Despite their emerging importance, diastereoselective reactions relying on stoichiometric amounts of chiral amines were formally the only methods available for the synthesis of chiral cyclic β-amino acids.[45] Recently, we reported the first catalytic enantioselective ring-opening reaction of *meso*-aziridines by cyanide using the Gd–**5** complex (Table IV).[46] The addition of a catalytic amount of trifluoroacetic acid (TFA) reproducibly improved the enantioselectivity of this reaction. Based on ESI-MS studies, TFA was shown



Scheme 4. Conversion to cyclic β-Amino acid.

to be involved in the catalyst metal/ligand 2:3 complex. TFA is believed to bridge the two gadolinium atoms of the catalyst and stabilize the enantioselective 2:3 complex (**20**). In addition, enhancement of the Lewis acidity of gadolinium, and fine-tuning of the relative positions of the two gadolinium atoms, might well contribute to the improved enantioselectivity. The ring-opened products of cyanide addition were easily converted to chiral cyclic β-amino acids through acid hydrolysis (Scheme 4).

8. Conclusions. The recent development of enantioselective reactions catalyzed by chiral poly-rare earth metal complexes is reviewed. Broad substrate generality and excellent enantioselectivity stem from dual activation of both electrophiles and nucleophiles, at defined positions, by the bifunctional asymmetric catalysts. These catalytic enantioselective reactions are practical, and can be utilized for preparative scale synthesis of pharmaceuticals and their lead compounds. The characteristics of rare earth metal alkoxides (or phenoxides) such as mild Lewis acidity, significant Brønsted basicity, rapid ligand-exchange rates, and facile formation of aggregates are essential properties that allow these new asymmetric catalysts to function. Investigations are ongoing in our group toward broadening the applicability of chiral poly-rare earth metal complexes to asymmetric catalysis.

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Profile

Masakatsu Shibasaki was born in 1947 in Saitama, Japan, and received his Ph. D. from the University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977 he returned to Japan and joined Teikyo University as an associate professor. In 1983 he moved to Sagami Chemical Research Center as a group leader, and in 1986 took up a professorship at Hokkaido University, before returning to the University of Tokyo as a professor in 1991. He was a visiting professor at Philipps-Universität Marburg during 1995. He has received the Pharmaceutical Society of Japan Award for Young scientists (1981), Inoue Prize for Science (1994), Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (1998), the Pharmaceutical Society of Japan Award (1999), the Molecular Chirality Award (1999), the Naito Foundation Research Prize for 2001 (2002), ACS Award (Arthur C. Cope Senior Scholar Award) (2002), the National Prize of Purple Ribbon (2003), the Toray Science Award (2004) and The Japan Academy Prize (2005). Moreover, he has been selected as a Fellow of the Royal Society of Chemistry (1997) and a Honorary Fellow of Chemical Research Society of India in 2003. His research interests include asymmetric catalysis, including asymmetric Heck reactions and reactions promoted by asymmetric bifunctional complexes, and also the medicinal chemistry of biologically significant compounds.