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Toward a rational design of the assembly structure of polymetallic asymmetric catalysts: design, synthesis, and evaluation of new chiral ligands for catalytic asymmetric cyanation reactions

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Abstract—New chiral ligands (**4** and **5**) for polymetallic asymmetric catalysts were designed based on the hypothesis that the assembled structure should be stable when made from a stable module **8**. A metal–ligand=5:6+μ-oxo+OH complex was generated from $Gd(O^iPr)_3$ and **4** or **5**, and this complex was an improved asymmetric catalyst for the desymmetrization of *meso*-aziridines with TMSCN and conjugate addition of TMSCN to α,β-unsaturated *N*-acylpyrroles, compared to the previously reported catalysts derived from **1**–**3**. These two groups of catalysts produced opposing enantioselectivity even though the ligands had the same chirality. The functional difference in the asymmetric catalysts is derived from differences in the higher-order structure of the polymetallic catalysts.

1. Introduction

Chiral amino acids are important building blocks for natural products and pharmaceuticals. Although there are several catalytic asymmetric methods for the synthesis of chiral α-amino acids,[1] few methods exist that can produce chiral β-amino acids[2] and γ-amino acids.[3] Currently, these amino acids are of great interest; e.g., β-amino acids form a well-defined secondary structure by oligomerization,[4] and γ-amino acids are unique templates for pharmaceuticals targeting the nervous system. Thus, the development of new catalytic enantioselective methods for the synthesis of β-amino acids or γ-amino acids is in high demand. The catalytic asymmetric ring-opening of *meso*-aziridines with cyanide and the conjugate addition of cyanide to α,β-unsaturated carboxylic acid derivatives are two basic reactions that can produce direct precursors of such chiral building blocks.

We reported the first catalytic asymmetric ring-opening of *meso*-aziridines with TMSCN in 2005 (Scheme 1, Eq. 1).[5,6] A gadolinium complex prepared from $Gd(O^iPr)_3$, ligand **1**, and trifluoroacetic acid (TFA)[7] in a 1:2:0.5 ratio was used as the asymmetric catalyst. The ring-opening products were converted to chiral β-amino acids through simple acid hydrolysis. There remains room for improvement in this reaction because of its relatively high catalyst loading (10–20 mol %) requirement, and unsatisfactory enantioselectivity (80–93% ee). On the other hand, Jacobsen's group reported the first highly enantioselective catalytic conjugate addition of cyanide to β-aliphatic-substituted α,β-unsaturated imides using the chiral salen–Al complex as the catalyst.[8] The resulting β-cyano adducts were converted to chiral γ-amino acids under reducing conditions. Specifically, the anticonvulsant drug pregabalin[9] was synthesized using this methodology. β-Aromatic or β-alkenyl-substituted substrate, however, was unreactive under these conditions. More recently, we reported a more general catalytic enatioselective conjugate addition of cyanide to α,β-unsaturated *N*-acylpyrroles[10] using the chiral gadolinium complex derived from ligand **1** (Scheme 1, Eq. 2).[11] In addition to substrates containing β-aliphatic substituents, substrates containing β-aryl, β-alkenyl, and α,β-disubstituted derivatives produced excellent enantioselectivity. The long-reaction time (generally, 42–139 h), however, remains a drawback to our reaction.

To improve the utility and practicality of these two important reactions, we designed new ligands based on the mechanism and structure of the Gd catalyst derived from ligands **1**–**3**. The asymmetric catalysts derived from ligands **4** and **5**

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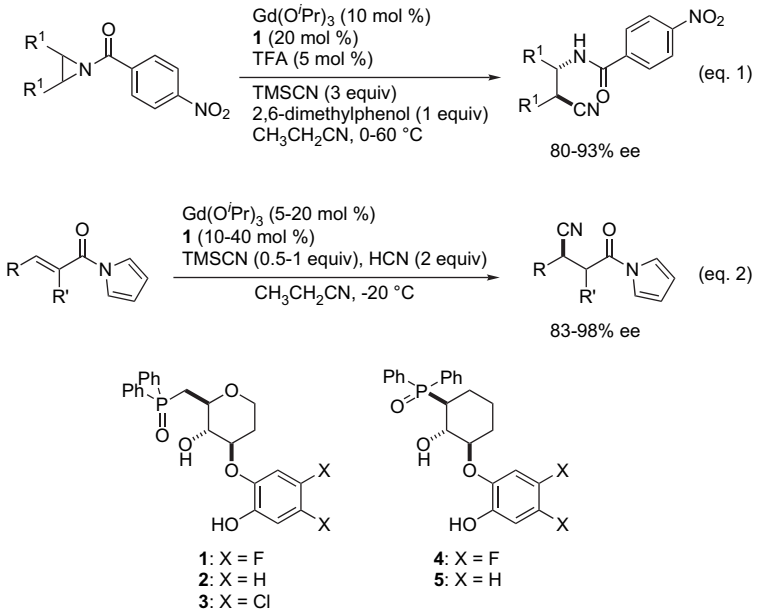


Scheme 1. Catalytic asymmetric ring-opening of *meso*-aziridines with TMSCN (Eq. 1) and conjugate addition of TMSCN (Eq. 2) using Gd catalysts derived from **1**–**3** (previous results), and structures of the chiral ligands.

produced a significantly improved function (enantioselectivity and catalyst activity) in the two reactions. In this paper, we describe the full account of the design and utility of the new catalysts.[12]

2. Results and discussion

2.1. Design and synthesis of new chiral ligands

Previous ESIMS studies indicated that the active asymmetric catalysts derived from **1**–**3** are polymetallic complexes. A catalyst solution prepared from Gd(O^{i}Pr)$_3$ and a ligand (**1**, **2** or **3**) in a 1:2 ratio (optimized procedure) contained two main species—a Gd–ligand=2:3 complex and a 4:5+μ-oxo complex.[13] These two species can be selectively obtained in pure forms either through a reaction of Gd(HMDS)$_3$ (HMDS=N(SiMe$_3$)$_2$) and the ligand in a 2:3 ratio for the 2:3 complex or through crystallization from a catalyst solution in propionitrile–hexane prepared from Gd(O^{i}Pr)$_3$ and **3** in a 2:3 ratio (crystal structure=**6** in Fig. 1, crystallization yield=ca. 80%).[14] Interestingly, the higher-order assembly structure of polymetallic catalysts has predominant effects on reactivity and enantioselectivity.[15] The catalytic species that mainly contributes to the outcome of each asymmetric reaction appeared to be different depending on the relative kinetics of the catalytic species in the reaction mixture. Therefore, stabilization of one specific assembled catalytic species should simplify the analysis of the results and further optimization of the reaction.

The three-dimensional crystal structure **6**[14] provided a clue for this approach. The crystal structure revealed a general module for construction of the self-assembled catalyst as depicted in Figure 1, **7**. In this module, the chiral ligand acts as a tetradentate ligand with each ligand bridging two metals, and a 7-, 5-, and 5-membered fused chelation ring system was observed.[16] This module structure prompted us to design a new asymmetric self-assembled polymetallic complex with a more stable higher-order structure. Our hypothesis was that the higher-order structure would be more stable when assembled from more stable modules. Thus, we

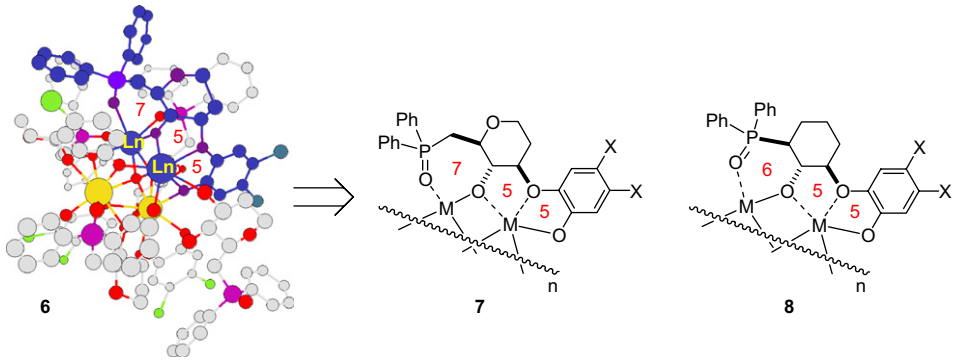
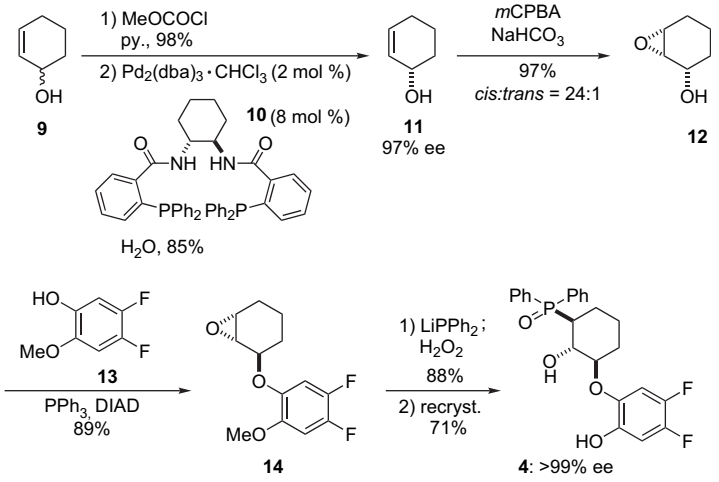


Figure 1. Crystal structure of the polymetallic 4:5+μ-oxo complex derived from ligand **3** (**6**: parts of the complex are deleted for clarity), observed modular unit of the polymetallic complex (**7**: a representative module in the polymetallic complex was colorized in blue in **6**), and an analogous module **8** derived from new ligands **4** and **5** designed to produce a more stable polymetallic complex.

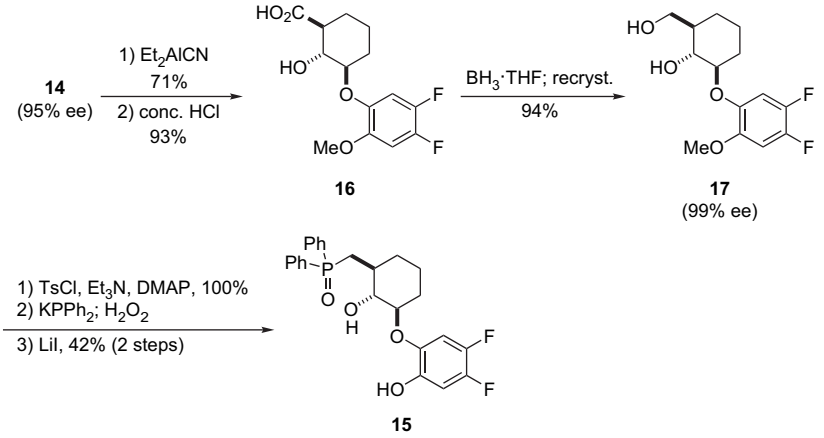
designed new ligands **4** and **5** with a truncated linker between the scaffolding cyclohexane ring and the Lewis base phosphine oxide. These ligands should form a 6-, 5-, and 5-membered fused chelation ring system in a module (Fig. 1, **8**), which is presumably more stable than the previous **7**.

We expected the designed ligands to be synthesized from a known chiral allylic alcohol **11**[17] via hydrogen bonding-assisted epoxidation, introduction of the catechol via Mitsunobu reaction, and regioselective epoxide opening with a phosphide as the key steps. Based on this plan, ligand synthesis began with deracemization of racemic allylic alcohol **9** using a palladium(0)-catalyzed allylic substitution (Scheme 2).[17] After conversion of racemic **9** to the corresponding methyl carbonate, allylic substitution using a Trost ligand (**10**)-modified palladium(0) catalyst afforded allylic alcohol **11** with 97% ee in 85% yield. The subsequent epoxidation of **11** with *m*CPBA proceeded with high diastereoselectivity through hydrogen bonding (cis–trans=24:1). Slow addition of *m*CPBA in CH_2Cl_2 to a solution of **11** for 1 h at 0 °C was necessary to produce high diastereoselectivity. Because epoxy alcohol **12** is water-soluble, the reaction mixture was directly filtered through a short pad of alumina to remove *m*-chlorobenzoic acid without an aqueous workup. The Mitsunobu reaction of **12** with **13** proceeded through complete inversion, and epoxy ether **14** was obtained in 89% yield.[18] Next, we investigated the site-selective epoxide opening reaction of **14** with a phosphide. First, commercially available potassium diphenylphosphide was used as a nucleophile. This reaction, however, provided many side products. One of the main by-products was derived through β-elimination of the phenoxy group, due to a strong basicity of potassium diphenylphosphide. To suppress such side reactions, lithium diphenylphosphide was used as a nucleophile.[19] The reaction then proceeded cleanly without any by-products. Moreover, cleavage of the phenolic methyl ether occurred simultaneously in this step, and **4** was produced from **14** in one-pot. Enantiomerically and diastereomerically pure **4** was obtained after one recrystallization from ^{i}PrOH. The related catechol-containing **5** was synthesized through the same route using 2-methoxyphenol instead of **13**.

To evaluate the effects of the oxygen atom of the core six-membered ring (pyran in **1**–**3** vs cyclohexane in **4** and **5**) on the catalytic enantioselective reactions, we synthesized control ligand **15**, which contains one methylene linker between the cyclohexane core and the phosphine oxide, as shown in Scheme 3. From the same synthetic intermediate **14** (95% ee), regioselective epoxide opening with Et_2AlCN,[20] followed by acidic hydrolysis of the cyanide



Scheme 2. Synthetic scheme of ligand **4**.



Scheme 3. Synthesis of control ligand **15**.

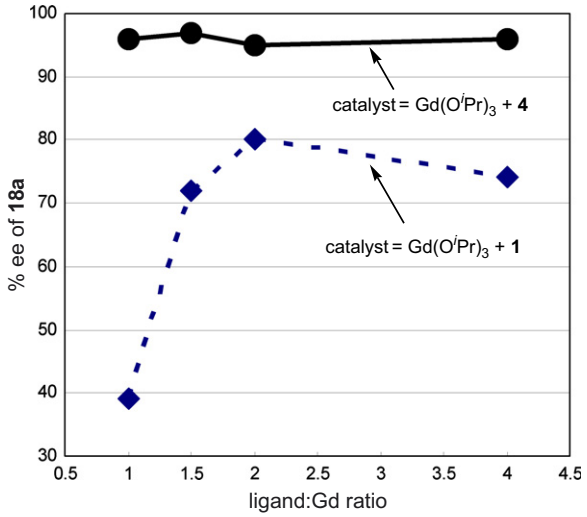


Figure 2. Dependency of enantioselectivity on ligand–Gd ratio in catalyst preparation.

produced carboxylic acid **16**. Reduction of the carboxylic acid with BH_3·THF complex furnished diol **17**, which was crystallized from CH_2Cl_2–hexane to afford enantiomerically pure **17** in 94% yield. The absolute and relative configuration of **17** was unequivocally determined by X-ray crystallography (Fig. 4 in Section 4). From **17**, selective tosylation, introduction of diphenylphosphine oxide, and deprotection of the phenol produced **15**. In this case, one-pot phosphine oxide introduction and deprotection with lithium phosphide did not proceed cleanly.

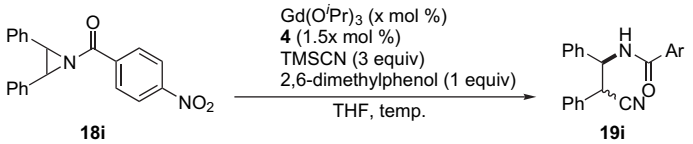
2.2. Catalytic asymmetric ring-opening reaction of *meso*-aziridines with TMSCN

We first examined the catalytic asymmetric aziridine-opening reaction of **18a** with TMSCN using new ligand **4** under the previously optimized conditions (10 mol % of Gd(O^{i}Pr)$_3$, 20 mol % of ligand, 5 mol % TFA, 3 equiv of TMSCN, and 1 equiv of 2,6-dimethylphenol in propionitrile at room temperature).[5] Product **19a** was obtained with only moderate enantioselectivity (52% ee, 99% yield for 15 h). The absolute configuration of the product was opposite to that obtained using previous ligand **1**. Speculating that the highly acidic TFA might have a detrimental effect in the present case, we investigated the reaction in the absence of TFA. The enantioselectivity and reactivity were dramatically increased (94% ee, >99% yield for 0.25 h). Screening of the solvent led to further improvement in enantioselectivity to 98% ee in THF.

Interestingly, there was a sharp contrast in the dependency of enantioselectivity on the Gd–ligand ratio between the catalysts prepared from ligands **1** and **4**. The enantioselectivity was dependent on the Gd–ligand ratio in the case of the catalyst prepared from **1**, and gradually increased according to the ratio to the maximum point at a 1:2 ratio (Fig. 2, dotted line). The enantioselectivity was constantly high (>95% ee) regardless of the Gd–ligand ratio, however, in the case of the catalyst prepared from **4** (Fig. 2, solid line). This tendency suggests that the active catalyst derived from **4** is stable irrespective of the mixed ratio of metal and ligand. This dependency is important information about the composition and stability of the active asymmetric catalyst. ESIMS studies suggest that the active catalyst derived from **4** is a Gd–**4**=5:6+μ-oxo+OH complex (see below). Therefore, we determined Gd–**4**=1:1.5 as the optimized ratio for further studies on substrate generality.

Another interesting phenomenon is the sharp temperature dependency of enantioselectivity, especially in the case of less reactive *cis*-stilbene-derived aziridine **18i** (Table 1).[21] A long-reaction time (136 h) was required for completion at 40 °C, and product **19i** (mixture of *anti* and *syn*) was obtained with low to moderate enantioselectivity (entry 1).[22] Enantioselectivity and reactivity dramatically improved when the reaction was conducted at higher temperatures (entries 3 and 4). When 5 mol % of catalyst was used under THF reflux (67 °C) conditions, the enantioselectivity and reactivity were at satisfactory levels (entry 5). This unusual temperature dependency might be due to the generation of a product-incorporated asymmetric catalyst of low enantioselectivity and activity during the course of the reaction. In fact, the initial reaction rate of **18i** was reasonably fast, even at 40 °C. The enantioselectivity of this initial phase was relatively high; product **19i** was obtained in 7% yield with 80% ee and 1% yield with 85% ee if the reaction at 40 °C was stopped in 1 h (entry 2). The reaction became very sluggish after ca. 40% conversion (on TLC analysis). Liberation of the product from the catalyst via protonolysis (or silylation) might be retarded in the case of **18i** due to both the relatively large size of the substrate[23] and the presumable compact reaction

Table 1. Catalytic asymmetric ring-opening of **18i** with TMSCN: temperature effects



18i **19i**

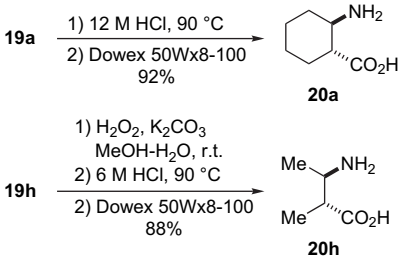
Entry	Loading (*x* mol %)	Temp (°C)	Time (h)	Yield[a] (%)	Ratio[b] (*anti–syn*)	ee[c] (%) (*anti–syn*)
1	2	40	136	95	1.9:1	11:52
2	2	40	1	8	6.7:1	80:85
3	2	60	18	98	0.9:1	80:82
4	2	Reflux	6	91	0.9:1	85:85
5	5	Reflux	4	95	0.9:1	93:93

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.

space generated by ligand **4**. Higher reaction temperature (>60 °C) should be required to regenerate a highly enantioselective catalyst that is free from the product.

Under the thus optimized conditions, substrate generality was studied (Table 2). Previous data using ligand **1** are shown in the same table.[5] In all the reactions, catalyst turnover number, turnover frequency, and enantioselectivity all markedly improved using the new ligand **4** compared to the previous ligand **1**. Simple catechol-containing ligand **5** demonstrated higher performance in the specific substrate **18a** (entry 2). Importantly, catalysts prepared from ligands **1** and **4** produced opposite enantioselectivity in all cases, despite the same chirality of the two ligands. This reversal in enantioselectivity was not due to the difference in the core six-membered ring structure (pyran vs cyclohexane). Thus, a catalyst prepared from $Gd(O^iPr)_3$ and control ligand **15** in a 1:2 ratio (10 mol %) produced the same enantiomer (with 44% ee) as was obtained using the catalyst prepared from **1**. Therefore, the reversed enantioselectivity between the catalysts generated from **1** and **4** is due to the one-carbon difference in the position of the phosphine oxide relative to Gd (for more detailed discussion, see Section 2.4).

It was previously demonstrated that the enantiomerically pure products can be obtained via one recrystallization with high efficiency.[5] The products were converted to enantiomerically pure β-amino acids in high yield through hydrolysis and purification by ion exchange chromatography (Scheme 4).

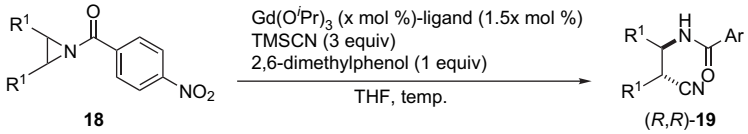


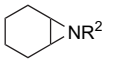
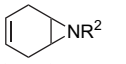
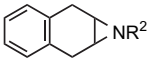
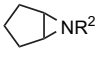
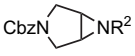
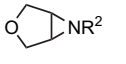
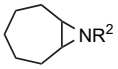
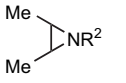
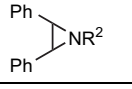
Scheme 4. Conversion to β-amino acids.

2.3. Catalytic enantioselective conjugate addition of TMSCN to α,β-unsaturated *N*-acylpyrroles

Initial studies to optimize the reaction conditions of a conjugate addition of TMSCN to α,β-unsaturated *N*-acylpyrroles

Table 2. Catalytic asymmetric aziridine-opening reaction with TMSCN



Entry	Substrate		Ligand	Loading (*x* mol %)	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1		**18a**	**4**	2	rt	13	98	98[f]
2[c]			**5**	1	rt	3	99	99[f]
3[d]			**1**	10	0	20	94	87[g]
4		**18b**	**4**	2	40	12	83	96
5[d]			**1**	10	rt	95	85	82
6		**18c**	**4**	2	40	14	98	95
7[d]			**1**	10	rt	42	91	83
8		**18d**	**4**	2	40	14	98	98[f]
9[d]			**1**	20	40	14	98	91[g]
10		**18e**	**4**	2	40	22	99	96
11[c]			**5**	2	rt	74	99	96
12[d]			**1**	20	60	23	89	84
13		**18f**	**4**	2	60	28	84	96
14[d]			**1**	20	60	96	92	84
15		**18g**	**4**	5	67	15	99	95
16[d]			**1**	10	60	64	92	80
17		**18h**	**4**	2	40	14	98	98[f]
18[d]			**1**	10	rt	39	93	85[g]
19		**18i**	**4**	5	67	4	95 (47:53)[e]	93:93
20[d]			**1**	10	rt	96	81 (54:46)[e]	90:80

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] In the presence of 10 mol % of 2,6-dimethylphenol.
[d] Using a catalyst generated from *x* mol % of $Gd(O^iPr)_3$ and 2*x* mol % of **1** (*x*=10 or 20) in the presence of 5 (or 2.5) mol % of TFA and 1 equiv of 2,6-dimethylphenol. See Ref. 5.
[e] Ratio of diastereomers determined by ^1H NMR.
[f] Absolute configuration was determined as (*R*,*R*).
[g] Absolute configuration was determined as (*S*,*S*). See Ref. 5.

focused on the choice of solvent. Propionitrile was the optimum solvent for both the aziridine-opening reaction and the conjugate addition reaction using ligands **1**–**3**.[11] In the case of the aziridine-opening reaction using **4** and **5**, however, THF was a better solvent than propionitrile with regard to enantioselectivity and reactivity (see Section 2.2). To define the optimum solvent in the conjugate addition reaction using the new catalyst, reactions of *N*-acylpyrrole **21a** in THF and propionitrile were performed using 5 mol % of catalyst prepared from **4**, 1.5 equiv of TMSCN, and 1 equiv of 2,6-dimethylphenol as a protic additive at −20 °C. A much higher reactivity and enantioselectivity were produced in propionitrile than in THF (99% yield with 60% ee for 18 h in THF vs 99% yield with 93% ee for 5.5 h in propionitrile). Next, we investigated the effects of a protic additive.[24] In the previous system, the addition of hydrogen cyanide produced markedly higher enantioselectivity than 2,6-dimethylphenol. In the present case, however, 2,6-dimethylphenol produced slightly better results than hydrogen cyanide. Therefore, we determined the optimized conditions using 2,6-dimethylphenol as an additive in propionitrile solvent.

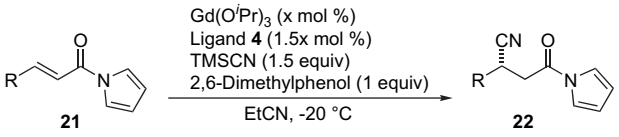
Substrate generality was investigated under the optimized conditions (Table 3). High enantioselectivity was produced from both β-aryl and β-aliphatic-substituted substrates. The catalyst activity was significantly higher in the present case using ligand **4** than when using the previous catalyst prepared from **1**. In addition, enantioselectivity was again reversed. With regard to β-alkenyl and α-substituted substrates, the enantioselectivity was less satisfactory (entry 14). Thus, the new catalyst was more active and comparably enantioselective, but demonstrated slightly narrower substrate generality than the previous catalyst in asymmetric conjugate addition of TMSCN.

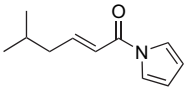
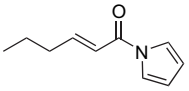
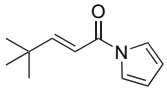
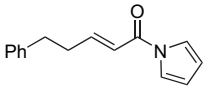
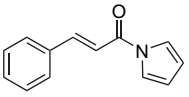
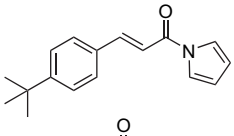
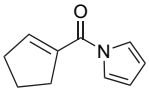
The products obtained in those reactions are useful precursors for chiral γ-amino acids (Scheme 5), e.g., a β-phenyl-substituted γ-amino butyric acid (GABA) analog, which has inhibitory activity in the nervous system,[25] can be synthesized in three steps from **22e** (Scheme 5, Eq. 1). In addition, known intermediate of pregabalin (**24**) was synthesized from **22a**.

2.4. Structural studies of the asymmetric catalyst

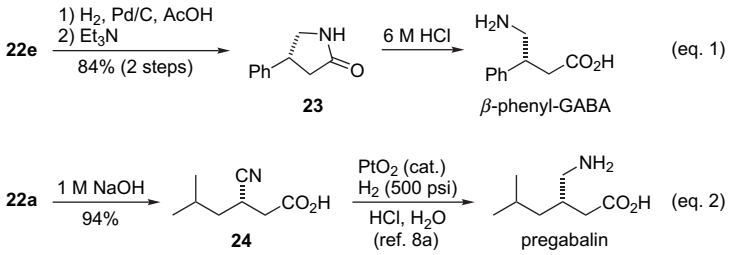
There are two main contrasting characteristics between the catalysts prepared from ligands **1**–**3** and new ligands **4** and **5**; (1) the opposing enantioselectivity (Tables 2 and 3) and

Table 3. Catalytic asymmetric conjugate addition of TMSCN to α,β-unsaturated *N*-acylpyrroles



Entry	Substrate		Ligand	*x* (mol %)	Time (h)	Yield[a] (%)	ee[b] (%)
1		**21a**	**4**	5	5.5	99	93[d]
2			**4**	2	14	99	93[d]
3[c]			**1**	5	42	89	97[e]
4		**21b**	**4**	5	2.5	93	93[d]
5[c]			**1**	5	42	91	98[e]
6		**21c**	**4**	5	2.5	95	96
7[c]			**1**	5	88	87	90
8		**21d**	**4**	5	24	96	86
9[c]			**1**	5	43	92	96
10		**21e**	**4**	5	38	91	88[d]
11[c]			**1**	10	98	90	91[e]
12		**21f**	**4**	10	20	89	95
13[c]			**1**	10	88	91	89
14		**21h**	**4**	5	1	92 (5.7:1)	76:12
15[c]			**1**	5	8	99 (1.1:1)	88:83

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] Using a catalyst generated from Gd(O^{i}Pr)$_3$ and **1** in a 1:2 ratio with 0.5 equiv of TMSCN and 2 equiv of HCN. See Ref. 11.
[d] Absolute configuration was determined as shown in the scheme.
[e] Absolute configuration was opposite to the one shown in the scheme.



Scheme 5.

(2) the contrasting dependency of enantioselectivity on the Gd–ligand ratio in catalyst preparation (Fig. 2). These differences might be due to the dramatic switching of the higher-order catalyst structure depending on the position of the phosphine oxide. To support this hypothesis, we conducted structural studies on the new catalyst.

First, ESIQFTMS studies on the catalyst indicated that the Gd–**4**=5:6+μ-oxo+OH complex is the sole species in the catalyst solution (Fig. 3a). The isotope distribution pattern precisely matched the calculated pattern. This composition was constant with Gd–**4** ratios of 1:1.2–1:4, which was consistent with the observed constant enantioselectivity independent of the Gd–**4** ratio in the catalyst preparation. Therefore, the active catalyst composition is different between the catalysts prepared from **1**–**3** (2:3 or 4:5+μ-oxo) and **4**, and this difference in the higher-order assembly structure should be the origin of the improved, opposing enantioselectivity, and the enhanced activity of the new catalyst. The fact that the catalyst composition and enantioselectivity were constant regardless of the Gd–ligand ratio supports the idea that the active catalyst structure is more stable in the new catalyst prepared from **4** than the previous catalyst derived from **1**–**3**.

To obtain three-dimensional information of the polymetallic structure, we next attempted crystallization of the catalyst. After intensive effort, we succeeded in obtaining colorless prisms from a solution of Gd(O^iPr)$_3$ and **4** mixed in a 1:2 ratio in propionitrile (77% yield). Crystallographic analysis revealed that the crystal was a Gd–ligand=3:4+2OH complex (Fig. 3b),[26] which is different from the observed species using ESIMS (Fig. 3a). The composition of the crystal was stable after dissolving in a solvent, and the peak corresponding to the 3:4+2OH complex was the sole observed peak in ESIMS. The 3:4+2OH complex is not the actual catalyst in the asymmetric cyanation reaction; using the crystal as a catalyst (Gd=12.5 mol %), aziridine-opening product **18a** was obtained with only 62% ee (24 h, >99% yield). The crystal, however, can function as a pre-catalyst of the highly enantioselective catalyst (5:6+μ-oxo+OH complex). Thus, when Gd(O^iPr)$_3$ was added to the crystal to adjust the Gd–**4** ratio to 5:6 and the solution was heated at 50 °C for 1 h, the enantioselectivity recovered to 94% ee (Gd=12.5 mol %, 12 h, >99% yield). Therefore, the assembly state conversion from the 5:6+μ-oxo+OH complex to the 3:4+2OH complex in the crystallization process was reversible under appropriate conditions. This result again supports the hypothesis that the 5:6+μ-oxo+OH structure of the new catalyst is stable. Moreover, it is noteworthy that the crystal structure was in accord with our initial design concept that the polymetallic complex module would contain a tricyclic 6-, 5-, and 5-membered fused chelation ring system (Fig. 3c).

3. Conclusion

We developed new asymmetric polymetallic catalysts that are useful for a ring-opening reaction of *meso*-aziridines with TMSCN and conjugate addition of TMSCN to α,β-unsaturated *N*-acylpyrroles. In most cases, the new catalysts derived from **4** and **5**, whose phosphine oxide is directly attached to the core six-membered cyclohexane ring, produced significantly improved activity and enantioselectivity compared to the previous catalysts derived from **1**–**3**. Although these two groups of chiral ligands contain the same chirality, asymmetric catalysts derived from these ligands demonstrated opposite enantioselectivity. The origin of the functional difference of the two asymmetric catalysts is the difference in their higher-order assembled structure: the

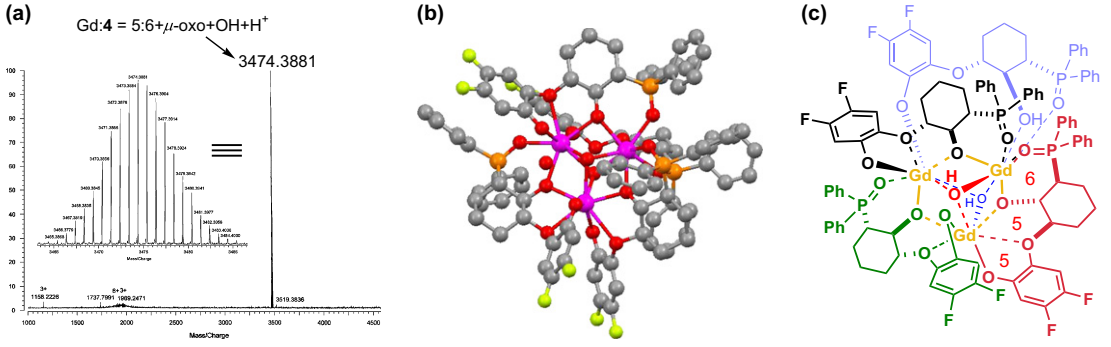


Figure 3. (a) ESI-QFT-MS chart of the catalyst prepared from Gd(O^iPr)$_3$ and **4** (the optimized catalyst). (b) X-ray structure of Gd–**4**=3:4+2OH. (c) Chemical depiction of Gd–**4**=3:4+2OH.

active catalysts derived from **1**–**3** were Gd–ligand=2:3 complexes or 4:5+μ-oxo complexes; the active catalysts derived from **4** and **5**, however, were Gd–ligand=5:6+μ-oxo+OH complexes. Thus, a minor structural (one carbon) difference in the module was amplified in the higher-order structure of a polymetallic catalyst, and caused a dramatic difference in the asymmetric catalyst function. The results of this study clearly demonstrate the importance of the higher-order structure of the asymmetric polymetallic catalyst. Elucidation of the enantio-differentiation mechanism and extension of the utility of the new catalyst is currently ongoing in our group.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 126.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported in the scale relative to $CHCl_3$ (7.24 ppm) for ^{1}H NMR, and to $CDCl_3$ (77.0 ppm) for ^{13}C NMR, as internal references. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI-Q mass spectra were measured on Water-ZQ4000. EI Mass spectra were measured on JEOL JMS-BU20 GCmate. ESI-QFT mass spectra were measured on IonSpec QFT-7 (JASCO International Co., Ltd.). X-ray data were collected on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo Kα radiation. The enantiomeric excesses (ee's) were determined by HPLC. HPLC analysis was performed on JASCO HPLC systems containing of following: pump, PU-980; detector, UV-970, measured at 254 nm; column, Daicel Chiralpak AD-H, AS-H, or Daicel Chiralcel OD-H; mobile phase, 2-propanol–hexane. In general, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Dry solvents of tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Kanto Chemical Co., Inc. Propionitrile was distilled from calcium hydride. Other reagents were purified by usual methods. $Gd(O^iPr)_3$ was purchased from Kojundo Chemical Laboratory Co., Ltd. (fax: +81 492 84 1351, sales@kojundo.co.jp). *Caution!* TMSCN is very toxic, and experiments should be carried out in a well-ventilated hood.

4.2. Syntheses of 4 and 5

4.2.1. (1*S*,2*S*,3*R*)-*cis*-2,3-Epoxycyclohexan-1-ol (12).[27] To a suspension of **11**[17] (2.86 g, 29.1 mmol) and $NaHCO_3$ (2.50 g, 29.1 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL), *m*CPBA (60% purity, 8.4 g, 29.1 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added dropwise over 1.5 h with cooling in an ice bath. After stirring for 5 h at 0 °C, about a half of the solvent was removed under reduced pressure. The mixture was purified by short pad column chromatography (alumina, CH_2Cl_2–EtOAc) and flash column chromatography (silica gel, hexane–EtOAc, 3:1–3:2) to afford **12** (3.21 g, 28.1 mmol) as a pale yellow oil in 97% yield (cis–trans=96:4).

4.2.2. (1*R*,2*R*,6*R*)-2-(4′,5′-Difluoro-2′-methoxyphenoxy)-7-oxabicyclo[4.1.0]heptane (14). To a solution of PPh_3 (1.12 g, 4.27 mmol, 1.5 equiv) and 4,5-difluoro-2-methoxyphenol (**13**: 684 mg, 4.27 mmol, 1.5 equiv), DIAD (diisopropyl azodicarboxylate, 840 μL, 4.27 mmol, 1.5 equiv) was added dropwise with cooling in an ice bath. Epoxy alcohol **12** in THF was added dropwise to the mixture, and the mixture was warmed to room temperature. After stirring for 22 h, water was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane–EtOAc, 5:1) to afford **14** (649 mg, 2.53 mmol) as a colorless solid in 89% yield with 93% ee. IR (KBr): 2846, 1519, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=6.86 (dd, J=12.0, 7.7 Hz, 1H), 6.73 (dd, J=12.0, 7.7 Hz, 1H), 4.36 (dd, J=9.0, 5.5 Hz, 1H), 3.82 (s, 3H), 3.28–3.26 (m, 1H), 3.22 (d, J=3.5 Hz, 1H), 2.10–2.04 (m, 1H), 1.95–1.89 (m, 1H), 1.85–1.78 (m, 1H), 1.57–1.51 (m, 1H), 1.48–1.40 (m, 1H), 1.33–1.24 (m, 1H); ^{13}C NMR ($CDCl_3$): δ=145.2–141.0 (multiple peaks due to coupling with ^{19}F), 104.8 (d, J=21.7 Hz), 100.5 (d, J=21.7 Hz), 72.8, 55.0, 52.3, 51.7, 25.0, 22.6, 13.1; MS (ESI): m/z 279 [M+Na$^+$]; HRMS (EI): m/z calcd for $C_{13}H_{14}F_2O_3$ [M$^+$]: 256.0906. Found: 256.0931; $[\alpha]_D^{25}$ +4.26 (c 1.00, $CHCl_3$) (93% ee), HPLC (Chiralpak AD-H, 2-propanol–hexane 1:99, flow 1.0 mL min^{-1}, detection at 254 nm): t_R 12.6 min (minor) and 20.4 min (major).

4.2.3. (1*S*,2*S*,6*R*)-2-Diphenylphosphinyl-6-(4′,5′-difluoro-2′-phenoxy)cyclohexanol (4). To a solution of **14** (1.50 g, 5.85 mmol) and Ph_2PH (3 mL, 17.6 mmol, 3.0 equiv) in THF (20 mL), BuLi (1.6 M in hexane, 11 mL, 17.6 mmol, 3.0 equiv) was added dropwise at −78 °C, and the mixture was stirred at room temperature for 6 h. Saturated aqueous NH_4Cl was added. Then, 30% H_2O_2 was added dropwise to the mixture with cooling in an ice bath, and the mixture was stirred at room temperature for 12 h. Saturated aqueous $Na_2S_2O_3$ was added at 0 °C. The mixture was diluted with EtOAc, and the organic layer was washed with water twice. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine before being dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 1:1–1:2) to afford **4** (2.29 g, 5.16 mmol) as a colorless solid in 88% yield. The compound **4** was recrystallized from ^{i}PrOH to afford enantiomerically and diastereomerically pure **4** in 71% yield. IR (KBr): 3334, 1515, 1173, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=9.10 (br s, 1H), 7.78–7.71 (m, 4H), 7.66–7.58 (m, 2H), 7.57–7.50 (m, 4H), 6.88 (br s, 1H), 6.79–6.73 (m, 2H), 4.10 (dd, J=18.0, 8.6 Hz, 1H), 3.71 (ddd, J=9.8, 9.8, 4.6 Hz, 1H), 2.67–2.61 (m, 1H), 2.22 (d, J=10.4 Hz, 1H), 1.81–1.72 (m, 2H), 1.46–1.41 (m, 1H), 1.38–1.30 (m, 1H), 1.30–1.26 (m, 1H) (chemical shift depends on the substrate concentration); ^{13}C NMR ($CDCl_3$): δ=147.5–142.0 (multiplet, coupled with fluoride), 132.5–128.9 (multiplet, coupled with phosphorus), 108.1 (d, J=20.7 Hz), 105.7 (d, J=21.7 Hz), 86.6 (d, J=14.5 Hz), 72.5 (d, J=5.2 Hz), 41.8, 41.2, 30.0, 25.5, 23.8, 23.7 (d, J=15.5 Hz); MS (ESI): m/z 467 [M+Na$^+$]; HRMS (EI): m/z calcd for $C_{24}H_{23}F_2O_4P$[M$^+$]: 444.1297. Found: 444.1283;

$[\alpha]_D^{25}$ +58.2 (*c* 1.00, $CHCl_3$) (>99% ee), HPLC (Chiralcel OD-H, 2-propanol–hexane 1:9, flow 1.0 mL min^{-1}, detection at 254 nm): t_R 6.9 min (minor) and 10.2 min (major).

4.2.4. (1*S*,2*S*,6*R*)-2-Diphenylphosphinyl-6-(2′-phenoxy)-cyclohexanol (5). Prepared via the same procedure as described above using guaiacol instead of **13**. IR (KBr): 3312, 1499, 1179, 1154 cm^{-1}; ^1H NMR ($CDCl_3$): δ=8.88 (br s, 1H), 7.74–7.71 (m, 4H), 7.53–7.45 (m, 4H), 6.96–6.88 (m, 3H), 6.73–6.70 (m, 1H), 6.61 (br s, 1H), 4.14 (dd, *J*=18.0, 8.3 Hz, 1H), 3.81–3.76 (m, 1H), 2.65 (ddd, *J*=22.0, 10.0, 3.4 Hz, 1H), 2.27 (d, *J*=10.0 Hz, 1H), 1.79–1.75 (m, 1H), 1.62 (d, *J*=12.8 Hz, 1H), 1.49–1.41 (m, 1H), 1.38–1.32 (m, 1H), 1.26–1.16 (m, 1H); ^{13}C NMR ($CDCl_3$): δ=149.4, 146.4, 132.4–128.8 (multiple peaks due to coupling with phosphorus), 124.1, 119.4, 119.3, 117.1, 85.8 (d, *J*=11.2 Hz), 72.6 (d, *J*=5.2 Hz), 41.9, 41.4, 30.1, 25.6, 23.7 (d, *J*=15.5 Hz); MS (ESI): *m*/*z* 431 [M+Na^+]; HRMS (EI): *m*/*z* calcd for $C_{24}H_{25}O_4P[M^+]$: 408.1485. Found: 408.1461; $[\alpha]_D^{26}$ +58.4 (*c* 1.00, $CHCl_3$) (>99% ee), HPLC (Chiralcel OD-H, 2-propanol–hexane 1:9, flow 1.0 mL min^{-1}, detection at 254 nm): t_R 11.8 min (major) and 19.0 min (minor).

4.3. Synthesis of 15

4.3.1. (1*R*,2*R*,3*R*)-3-(4′,5′-Difluoro-2′-methoxyphenoxy)-2-hydroxycyclohexanecarbonitrile. To a solution of **14** (100 mg, 0.390 mmol) in Et_2O (2 mL), Et_2AlCN (470 μL, 0.468 mmol, 1.2 equiv) was added dropwise with cooling in an ice bath. After stirring for 15 min, saturated aqueous Rochelle salt was added to the mixture and stirred for 1 h. The organic layer was separated and washed with water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 5:2) to afford the product (80 mg, 0.281 mmol) as a pale yellow oil in 72% yield. ^1H NMR ($CDCl_3$): δ=6.85 (dd, *J*=12.0, 7.6 Hz, 1H), 6.75 (dd, *J*=12.0, 7.6 Hz, 1H), 4.02 (br s, 1H), 3.83 (s, 3H), 3.82–3.78 (m, 1H), 3.60 (ddd, *J*=12.5, 8.5, 4.6 Hz, 1H), 2.50 (ddd, *J*=12.5, 10.0, 3.7 Hz, 1H), 2.18–2.07 (m, 2H), 1.88–1.82 (m, 1H), 1.68–1.59 (m, 1H), 1.56–1.48 (m, 1H), 1.34–1.24 (m, 1H); ^{13}C NMR ($CDCl_3$): δ=147.6–142.7 (multiple peaks due to coupling with ^{19}F), 120.2, 110.4 (d, *J*=19.7 Hz), 102.1 (d, *J*=22.7 Hz), 86.2, 73.9, 56.8, 35.3, 30.0, 28.3, 22.8; MS (ESI): *m*/*z* 306 [M+Na^+]; HRMS (EI): *m*/*z* calcd for $C_{14}H_{16}F_2NO_3$: 284.1098. Found: 284.1096.

4.3.2. (1*S*,2*R*,3*R*)-3-(4′,5′-Difluoro-2′-methoxyphenoxy)-2-hydroxycyclohexanecarboxylic acid (16). To a solution of the nitrile (350 mg, 1.236 mmol) synthesized in Section 4.3.1 in DME (15 mL), 12 N HCl was added and the mixture was stirred at 90 °C for 24 h. The mixture was diluted with EtOAc, and the organic layer was separated and washed with water twice. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine before being dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was dissolved in 3 N NaOH, and diluted with water. The aqueous layer was washed with Et_2O four times. After 1 N HCl was added to acidify, the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford **16** (303 mg, 1.00 mmol) in 81% yield. ^1H NMR ($CDCl_3$): δ=6.89 (dd, *J*=10.7, 7.9 Hz, 1H), 6.76 (dd, *J*=11.3, 7.7 Hz, 1H), 3.93 (dd, *J*=10.6, 8.8 Hz, 1H), 3.85 (s, 3H), 3.68 (ddd, *J*=11.3, 8.8, 4.9 Hz, 1H), 2.43 (ddd, *J*=12.5, 10.6, 4.3 Hz, 1H), 2.21–2.15 (m, 1H), 2.14–2.08 (m, 1H), 1.90–1.84 (m, 1H), 1.60–1.46 (m, 3H), 1.37–1.28 (m, 1H); MS (ESI): *m*/*z* 325 [M+Na^+]; HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}F_2O_5$: 303.1044. Found: 303.1049.

4.3.3. (1*R*,2*R*,6*R*)-2-(4′,5′-Difluoro-2′-methoxyphenoxy)-6-(hydroxymethyl)cyclohexanol (17). To a solution of **16** (119 mg, 0.394 mmol) in THF (4.0 mL), $BH_3 \cdot THF$ (1.35 mL, 1.575 mmol, 4.0 equiv) was added, and the mixture was stirred at room temperature for 1.5 h. After adding 1 N HCl, the mixture was diluted with EtOAc. The organic layer was separated and washed twice with saturated aqueous $NaHCO_3$ and water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine before being dried over Na_2SO_4. The solvent was removed under reduced pressure to afford diol **17** (114 mg, 0.394 mmol) as a colorless solid in quantitative yield. The compound **17** was recrystallized from CH_2Cl_2–hexane to afford optically enriched **17** in 55% yield with 99% ee. ^1H NMR ($CDCl_3$): δ=6.87 (dd, *J*=11.0, 8.0 Hz, 1H), 6.74 (dd, *J*=11.9, 7.6 Hz, 1H), 3.91 (br s, 1H), 3.84 (s, 3H), 3.75–3.62 (m, 4H), 2.17–2.11 (m, 1H), 1.82–1.77 (m, 1H), 1.74–1.60 (m, 2H), 1.51–1.42 (m, 1H), 1.38–1.28 (m, 1H), 1.10–1.01 (m, 1H); MS (ESI): *m*/*z* 311 [M+Na^+]; HRMS (EI): *m*/*z* calcd for $C_{14}H_{19}F_2O_4$: 289.1251. Found: 289.1246; $[\alpha]_D^{22}$ −42.9 (*c* 0.87, $CHCl_3$) (99% ee). HPLC (Chiralpak AD-H, 2-propanol–hexane 1:9, flow 1.0 mL min^{-1}, detection at 254 nm): t_R 12.2 min (major) and 14.1 min (minor). The absolute and relative configurations were unequivocally determined at this stage by X-ray crystallography (Fig. 4, R^2 value=7%).[26] The absolute configuration was determined based on the Flack parameter (0.01(13)). This X-ray structure also confirmed the absolute configuration of ligands **4** and **5**.

4.3.4. ((1*R*,2*R*,3*R*)-3-(4′,5′-Difluoro-2′-methoxyphenoxy)-2-hydroxycyclohexyl)methyl-4″-benzene sulfonate. To a solution of **17** (38 mg, 0.132 mmol), Et_3N (37 μL, 0.264 mmol, 2.0 equiv), and DMAP (1.6 mg, 13.3 μmol, 10 mol %) in CH_2Cl_2 (1.3 mL), TsCl (51 mg, 0.265 mmol, 2.0 equiv) was added, and the mixture was stirred at room temperature for 6 h. The mixture was diluted with EtOAc, and washed twice with 1 N HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine before being dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 3:1) to afford the tosylate (59.6 mg, 0.135 mmol) as a pale yellow oil in quantitative yield. ^1H NMR ($CDCl_3$): δ=7.81 (d, *J*=8.1 Hz, 2H), 7.34 (d, *J*=8.1 Hz, 2H), 6.84 (dd, *J*=11.0, 7.9 Hz, 1H), 6.73 (dd, *J*=11.0, 7.3 Hz, 1H), 4.22 (dd, *J*=9.5, 3.1 Hz, 1H), 4.16 (dd, *J*=9.5, 6.1 Hz, 1H), 3.81 (s, 3H), 3.66–3.61 (m, 1H), 3.50 (t, *J*=9.5 Hz, 1H), 3.40 (s, 1H), 2.45 (s, 3H), 2.13–2.07 (m, 1H), 1.80–1.70 (m, 3H), 1.48–1.41 (m, 1H), 1.26–1.21 (m, 2H); MS (ESI): *m*/*z* 465 [M+Na^+]; HRMS

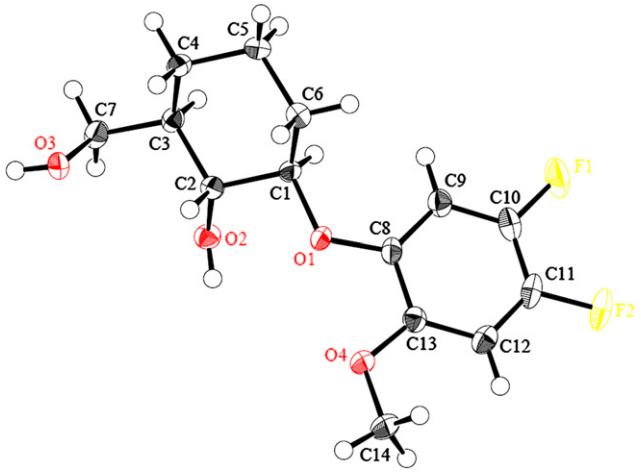


Figure 4. X-ray crystal structure of **17**.

(EI): *m/z* calcd for $C_{21}H_{25}F_2O_6S$ [M+H$^+$]: 443.1334. Found: 443.1335; $[\alpha]_D^{19}$ −0.47 (*c* 0.88, $CHCl_3$) (99% ee).

4.3.5. (1*R*,2*R*,6*S*)-6-Diphenylphosphinylmethyl-2-(4′,5′-difluoro-2-phenoxy)cyclohexanol (15). The tosylate (86 mg, 0.195 mmol) was dissolved in THF (1 mL), and $KPPh_2$ (0.5 M solution in THF, 858 μL, 0.429 mmol, 2.2 equiv) was added dropwise to the solution with cooling in an ice bath. After stirring for 15 min, 30% H_2O_2 was added and stirred for 6 h. The saturated aqueous $Na_2S_2O_3$ was added, and the solution was diluted with EtOAc. The organic layer was separated, and washed with water and brine before being dried over Na_2SO_4. The solvent was removed under reduced pressure. Without purification, the resulting crude oil was dissolved in DMF (1 mL). LiI (157 mg, 1.17 mmol, 6.0 equiv) was added, and the mixture was stirred at 180 °C for 19 h. Water and EtOAc were added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine before being dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 1:2) to afford **15** (74 mg, 0.162 mmol) as a colorless solid in 83% yield. IR (KBr): 3216, 1512, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=9.59 (s, 1H), 7.78–7.69 (m, 5H), 7.60–7.46 (m, 6H), 6.78 (dd, *J*=10.7, 8.3 Hz, 1H), 6.72 (dd, *J*=11.6, 8.0 Hz, 1H), 3.56 (t, *J*=9.0 Hz, 1H), 3.34 (ddd, *J*=11.3, 9.0, 4.9 Hz, 1H), 2.44–2.39 (m, 2H), 2.18–2.13 (m, 1H), 1.80–1.67 (m, 2H), 1.57–1.48 (m, 1H), 1.35–1.26 (m, 2H), 1.19–1.10 (m, 1H); ^{13}C NMR ($CDCl_3$): δ=148.2–141.4 (multiple peaks due to coupling with fluoride), 132.5–128.8 (multiple peaks due to coupling with phosphorus), 111.1 (d, *J*=18.6 Hz), 105.2 (d, *J*=21.7 Hz), 88.3, 76.7, 38.9 (d, *J*=4.1 Hz), 36.8, 36.2, 34.2 (d, *J*=13.4 Hz), 30.5, 22.9; MS (ESI): *m/z* 481 [M+Na$^+$]; HRMS (EI): *m/z* calcd for $C_{24}H_{25}O_4P$[M$^+$]: 458.1453. Found: 458.1472; $[\alpha]_D^{25}$ −35.4 (*c* 0.70, $CHCl_3$) (99% ee).

4.4. General procedure for the catalytic asymmetric ring-opening reaction of *meso*-aziridines with TMSCN (Table 2, entry 1)

To a solution of ligand **4** (13.3 mg, 0.03 mmol) in THF (0.6 mL), Gd(O^{i}Pr)$_3$ (0.2 M in THF, 100 μL, 0.02 mmol) was added at room temperature. The mixture was stirred at 54 °C for 1 h, and then the solvent was evaporated. After drying the resulting pre-catalyst under reduced pressure (<5 mmHg) for 2 h, **18a** (246 mg, 1.0 mmol), 2,6-dimethylphenol (122 mg, 1.0 mmol, 1.0 equiv), and THF (5.0 mL) were added at room temperature. TMSCN (40 μL, 0.30 mmol, 3.0 equiv) was added to start the reaction. After 13 h, water and EtOAc were added. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane–AcOEt, 3:1–3:2) to afford **19a** (269 mg, 0.99 mmol) in 99% yield as a colorless solid. The enantiomeric excess of the product was determined by HPLC analysis to be 98% ee. Characterization of the products and ee determination methods were described in Ref. 5.

4.5. Conversion of the aziridine-opening products to β-amino acids

The following conversions were conducted using the corresponding enantiomeric products.

4.5.1. (1*S*,2*S*)-2-Amino-cyclohexanecarboxylic acid (*ent*-20a).[28] Amido nitrile *ent*-**19a** (>99% ee; recrystallized from 1-butanol) (201.0 mg, 0.735 mmol) was treated with 12 M HCl (20 mL) at 90 °C for 5 days. The mixture was concentrated under reduced pressure and the residue was dissolved in 1 M HCl. The solution was washed with CH_2Cl_2 three times and the aqueous phase was concentrated. The residue was purified through ion exchange chromatography (Dowex 50W×8-100 (acidic) (10 g)) to afford *ent*-**20a** (97.1 mg) as a white solid in 92% yield. The absolute configuration was determined based on the comparison of the optical rotation with the reported value. $[\alpha]_D^{23}$ +78.8 (*c* 0.246, MeOH).

4.5.2. (2*S*,3*S*)-3-Amino-2-methyl butyric acid (*ent*-20h).[29] To a solution of amido nitrile *ent*-**19h** (80% ee) (14.6 mg, 0.059 mmol) in MeOH–H_2O (2 mL), H_2O_2 (1 mL), and saturated aqueous Na_2CO_3 (1 mL) were added and the mixture was stirred at room temperature for 3 h. $Na_2S_2O_6$ and CH_2Cl_2 were added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 twice and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was treated with 6 M HCl (2 mL) at 90 °C. After 62 h, the mixture was diluted with water and washed twice with CH_2Cl_2. The aqueous phase was concentrated and the residue was purified through ion exchange chromatography (Dowex 50W×8-100 (acidic) (2.2 g)) to afford *ent*-**20h** (6.1 mg) as a white solid in 88% yield. The absolute configuration was determined based on the comparison of the optical rotation with the reported value. $[\alpha]_D^{23}$ +6.5 (*c* 0.270, H_2O).

4.6. General procedure for the catalytic asymmetric conjugate addition of TMSCN to α,β-unsaturated *N*-acylpyrroles (Table 3, entry 1)

To a solution of ligand **4** (6.7 mg, 0.015 mmol) in THF (0.3 mL), Gd(O^{i}Pr)$_3$ (0.2 M in THF, 50 μL, 0.01 mmol)

was added at room temperature. The mixture was stirred at 54 °C for 1 h, and then the solvent was evaporated. After drying the resulting pre-catalyst under reduced pressure (<5 mmHg) for 2 h, 2,6-dimethylphenol (24.4 mg, 0.2 mmol, 1.0 equiv) was added, followed by addition of **21a** (35.4 mg, 0.2 mmol) in THF (0.2 mL). The mixture was cooled down to −20 °C, and then TMSCN (40 μL, 0.30 mmol, 1.5 equiv) was added to start the reaction. After 5.5 h, silica gel was added. The slurry was directly loaded on silica gel column, and purified by flash column chromatography (silica gel, hexane–AcOEt, 10:1–4:1) to afford **22a** (40.5 mg) in 99% yield as a colorless solid. The enantiomeric excess of the product was determined by HPLC analysis to be 93% ee. Characterization of the products and ee determination methods were described in Ref. 11.

4.7. Conversion of the conjugate adducts to γ-amino acids

The following conversions were conducted using the corresponding enantiomeric products.

4.7.1. (4*S*)-4-Phenyl-2-pyrrolidinone (*ent*-23).[30] To a solution of *ent*-**22e** (>99% ee; recrystallized from 2-propanol) (9.7 mg, 0.0067 mmol) in MeOH (0.5 mL) and AcOEt (0.5 mL), AcOH (25 μL) and 10% Pd–C (7.1 mg, 0.0067 mmol) were added, and the mixture was stirred under 20 atm pressure of hydrogen at room temperature. After 20 h, catalyst was filtered off through Celite, and the solvent was removed under reduced pressure. To this residue, toluene (2 mL) and Et_3N (500 μL) were added. The mixture was heated at 100 °C for 2 h, and 1 M HCl and CH_2Cl_2 were added and the organic layer was separated. The water layer was extracted twice with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 20:1) to afford *ent*-**23** (5.9 mg) in 84% yield as white solid. IR (KBr): 3244, 2905, 2796, 1684, 1495, 1444, 1259, 1052, 746, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.38–7.31 (m, 2H), 7.29–7.21 (m, 3H), 6.65 (br s, 1H), 3.80–3.77 (m, 1H), 3.72–3.66 (m, 1H), 3.42 (dd, *J*=7.4, 9.7 Hz, 1H), 2.73 (dd, *J*=9.1, 17.0 Hz, 1H), 2.51 (dd, *J*=8.5, 17.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=177.9, 142.1, 128.8, 127.0, 126.7, 49.5, 40.2, 38.0; MS (ESI): *m*/*z* 161 [M^+]; HRMS (EI): *m*/*z* calcd for $C_{10}H_{11}NO$ [M^+]: 161.0841. Found: 161.0836; $[\alpha]_D^{21}$ +35.2 (*c* 0.590, MeOH). The absolute configuration was determined based on the comparison of the optical rotation with the reported value.[30] To determine the enatiomeric excess by HPLC, the lactam was converted to its *N*-Boc derivative (90% yield).[31] The ee of the carbamate was determined to be 98%. HPLC (Chiralpak AS-H, 2-propanol–hexane 1:20, flow 1.0 mL min^{-1}, detection at 210 nm): t_R 24.8 min (major) and 28.3 min (minor). Compound **23** can be converted to β-phenyl-GABA via acid hydrolysis.[32]

4.7.2. (3*R*)-3-Cyano-5-methylhexanoic acid (*ent*-24).[8a] To a solution of *ent*-**22a** (90% ee) (44.8 mg, 0.219 mmol) in THF (440 μL), 1 M NaOH (440 μL, 0.440 mmol) was added at room temperature. After 1 h, THF was removed, and saturated $NaHCO_3$ was added. The aqueous phase was washed with CH_2Cl_2 three times, acidified to pH 1, and extracted with CH_2Cl_2 three times. The combined organic layers were dried over Na_2SO_4 and concentrated to afford *ent*-**24** (31.8 mg) in 94% yield as colorless oil. IR (neat): 2961, 2244, 1714, 1469, 1414, 1371, 1175, 924, 619 cm^{-1}; ^1H NMR ($CDCl_3$): δ=9.29 (br s, 1H), 3.12–2.96 (m, 1H), 2.76 (dd, *J*=7.5, 17.0 Hz, 1H), 2.62 (dd, *J*=6.1, 17.0 Hz, 1H), 1.95–1.78 (m, 1H), 1.74–1.57 (m, 1H), 1.43–1.30 (m, 1H), 0.98 (d, *J*=6.7 Hz, 3H), 0.96 (d, *J*=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=175.5, 120.8, 40.6, 36.8, 26.1, 25.5, 22.8, 21.2; MS (ESI): *m*/*z* 155 [M^+]; HRMS (EI): *m*/*z* calcd for $C_8H_{14}NO_2$ [M+H^+]: 156.1025. Found: 156.1026; $[\alpha]_D^{21}$ +15.0 (*c* 0.590, $CHCl_3$). Compound **24** was converted to pregabalin via PtO_2-catalyzed hydrogenation.[8a]

4.8. Preparation of crystal from catalyst solution

To a solution of ligand **4** (89.0 mg, 0.20 mmol) in THF (3.0 mL), $Gd(O^iPr)_3$ (0.2 M in THF, 500 μL, 0.10 mmol) was added at room temperature. The mixture was stirred at 54 °C for 1 h, and then the solvent was evaporated at 0 °C. After drying the residue under reduced pressure (<5 mmHg) for 2 h, propionitrile (350 μL) was added to dissolve the residue. After 1 day, colorless prisms appeared. The solvent was removed with a syringe, and the crystals were washed twice with propionitrile. The resulting colorless prisms were dried under vacuum to afford the 3:4+2OH crystal (68 mg) in 77% yield.

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