

Dynamic Kinetic Resolution for the Catalytic Asymmetric Total Synthesis of Antithrombotic Agents M58163 and M58169

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In the honor of Professor Masakatsu Shibasaki on the occasion of his 60th birthday (Kanreki in Japanese).

Abstract: Dynamic kinetic resolution is one of the most synthetically useful phenomena for asymmetric synthesis. Dynamic kinetic resolution for the catalytic asymmetric synthesis of a spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4'-piperidin]-5(1*H*)-one scaffold with a lanthanum-linked BINOL complex is described. It is also clarified that starting materials, diamine **1** and keto ester **2**, play important roles not only as substrates but also as additives to modify an active spe-

cies of the lanthanum complex. The catalytic asymmetric total syntheses of our antithrombotic agents **M58163** and **M58169** have thus been achieved *via* dynamic kinetic resolution.

Keywords: antithrombotic agents; dynamic kinetic resolution; enantioselective acetal formation; M58163; M58169

Introduction

Factor Xa (FXa), a trypsin-like serine protease, occupies a central position in the blood coagulation cascade in linking the intrinsic and extrinsic mechanisms. FXa is known to activate prothrombin to thrombin. Compared to a thrombin inhibitor, an FXa inhibitor as an anticoagulant has been suggested to result in less risk of bleeding and, hence, to lead to a more favorable safety/efficacy ratio.^[1] Therefore the design of a new drug as an FXa inhibitor has been a challenge for the treatment and prevention of thrombosis diseases.^[2]

During the course of our development of an FXa inhibitor as an antithrombotic agent, we have reported the unique FXa inhibitor **M55529**, containing a cyclic *N,O*-acetal structure,^[3] and an asymmetric synthesis of **M55529** based on the enantioselective cyclic *N,O*-acetal formation using a chiral salen-manganese complex (Scheme 1).^[4]

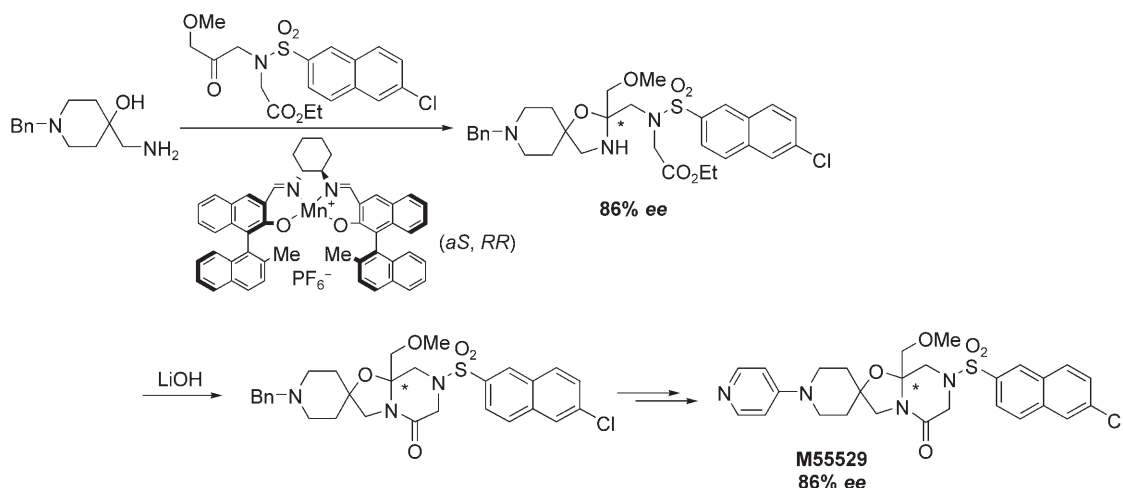
Quite recently, we also reported other oral FXa inhibitors **M58163** and **M58169**,^[5] with characteristic features of a spiro unit and an imidazopyrazinone as a cyclic *N,N*-acetal structure instead of the cyclic *N,O*-acetal of **M55529**. These compounds exhibit higher FXa inhibitory activity [**M58163** (IC₅₀ = 0.61 nM),

M58169 (IC₅₀ = 0.58 nM)] than **M55529** (IC₅₀ = 2.0 nM). Cyclic *N,N*-acetals are widely found in natural and unnatural products^[6] and are employed as a protective group for carbonyl compounds,^[7] as synthetic intermediates of *N*-containing heterocyclic compounds,^[8] or as chiral compounds prepared from chiral diamine and/or chiral carbonyl compounds, for a synthon, an optical resolution, an asymmetric catalyst, and so on.^[9] However, the enantioselective synthesis of cyclic *N,N*-acetals using achiral substrates has never been reported so far. We report here the full account of the dynamic kinetic resolution in the amide formation step following formation of a cyclic *N,N*-acetal leading to the tricyclic key intermediate of **M58163** and **M58169** (Scheme 2).^[10]

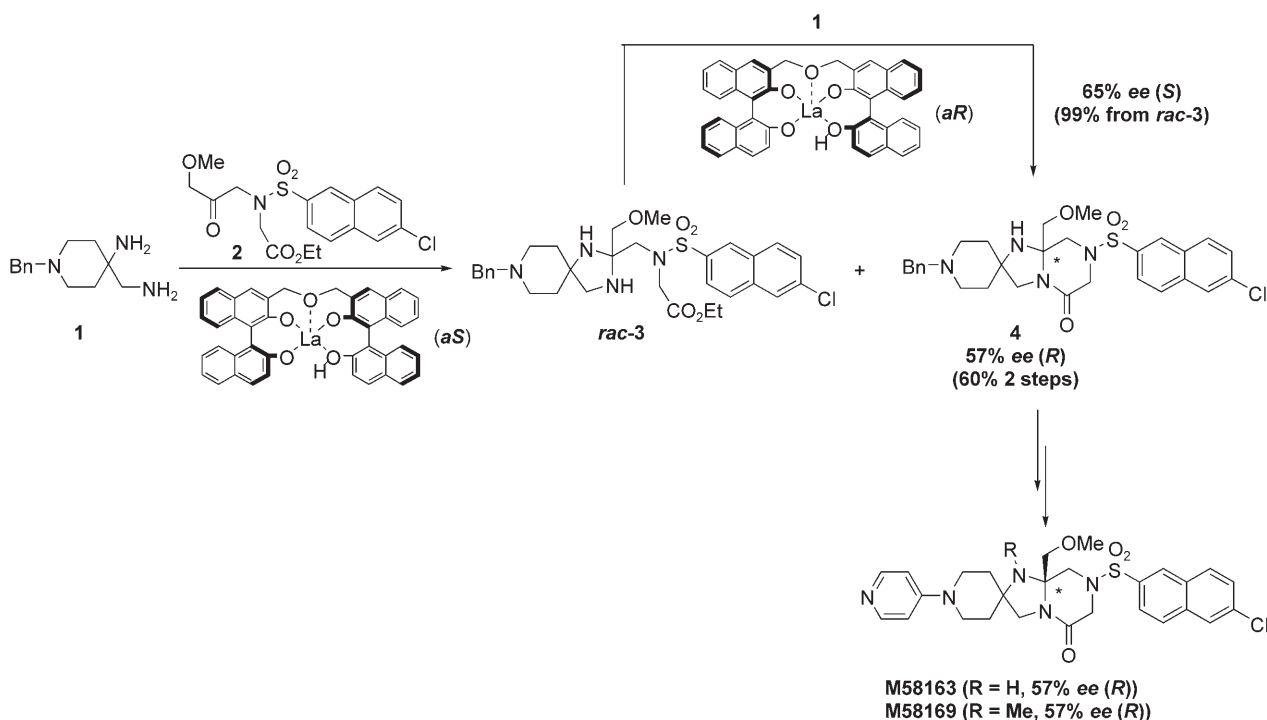
Results and Discussion

Enantioselective Cyclic *N,N*-Acetal Formation

First, the chiral Brønsted acids and salen-manganese complex, by which the cyclic *N,O*-acetal had been obtained enantioselectively,^[4] were examined. The results are summarized in Table 1. While the enantioenriched *N,O*-acetal was obtained with these chiral



Scheme 1. Enantioselective cyclic *N,O*-acetal formation and the asymmetric synthesis of the antithrombotic agent **M55529**.



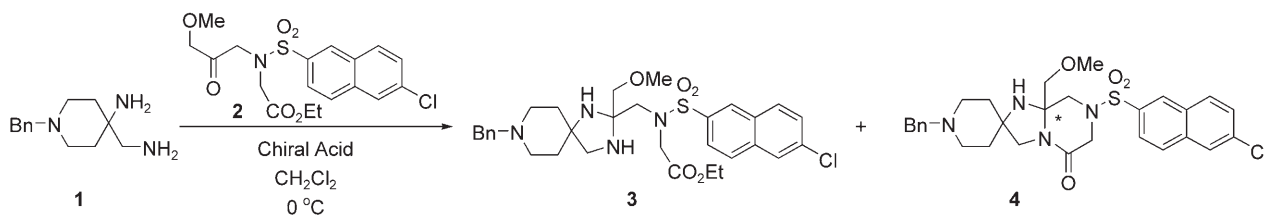
Scheme 2.

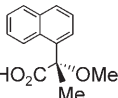
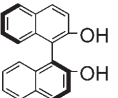
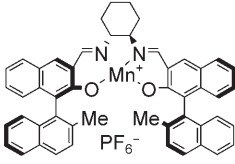
acids, the cyclic *N,N*-acetal **3** was also obtained, albeit in 0% *ee*. However, the tricyclic compound **4** was obtained *in situ* in up to 48% *ee* in low to moderate yield (entries 1, 3, and 5). The reaction time was thus prolonged until the *N,N*-acetal **3** disappeared and a sufficient amount of tricyclic compound **4** was observed on TLC; **4** was then obtained in moderate yield (up to 65%) and with the same enantioselectivity (up to 49% *ee*, entries 2, 4, and 6).

Unfortunately, these chiral Brønsted acids gave only low enantioselectivity although they could be

used in a catalytic amount. In contrast, the Lewis acidic salen-manganese complex gave moderate enantioselectivity. However, the amount could not be reduced to a catalytic level because the highly basic diamine **1** coordinated with the Lewis acidic salen-manganese complex.

In sharp contrast, a chiral base complex may efficiently catalyze the second amide formation step.^[4] Therefore, we next examined a commercially available, La-linked BINOL complex.^[11] As expected, the reaction could proceed with a catalytic amount of the

Table 1. The cyclic *N,N*-acetal formation with chiral Brønsted acids or a chiral salen-Mn complex.

Entry	Chiral Acid	Time [d]	3		4	
			Yield [%]	% ee ^[a]	Yield [%]	% ee ^[b]
1	 HO ₂ C ^{Me} OMe (S)	2	59	0	29	8 (S)
2	30 mol %	5	0	–	65	7 (S)
3	 (aS)	5	24	0	45	9 (R)
4	30 mol %	19	0	–	63	8 (R)
5	 (aS,RR)	5	32	0	8	48 (R)
6	130 mol %	32	0	–	46	49 (R)

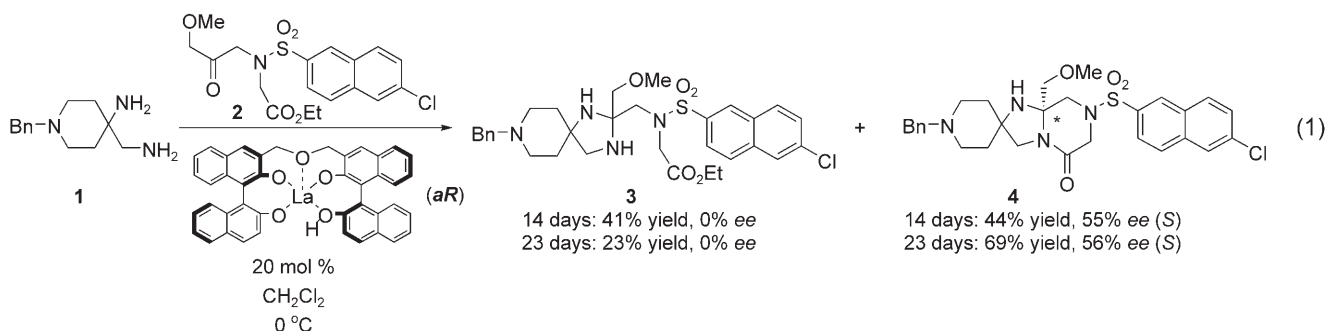
^[a] The % ee was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL min^{−1}; hexane/EtOH (diethylamine: 0.1 %) = 50/50; 10.6 and 16.0 min, respectively.

^[b] The % ee was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL min^{−1}; hexane/EtOH (diethylamine: 0.1 %) = 50/50; 20.5 and 46.9 min; the absolute configuration was correlated to **M58169**, of which the absolute configuration was determined by X-ray crystallographic analysis (see ref.^[5]).

La-linked BINOL complex and the enantioselectivity was increased up to 56 % ee [Eq. (1)]. Particularly, the tricyclic compound **4** was obtained in 69 % yield without reducing the enantioselectivity even after prolonged reaction time. In this case, the racemic *N,N*-acetal **3** was again obtained.

Dynamic Kinetic Resolution

The results shown in Eq. (1) suggest the following: 1) Since the *N,N*-acetal **3** could easily racemize, the *N,N*-acetal **3** was not obtained enantioselectively. 2) Dynamic kinetic resolution should take place in the



second amide formation step. We therefore proved the racemization of both enantiopure *N,N*-spiro-acetals, (+)- and (–)-**3** which were isolated by a chiral HPLC column chromatography [Daicel CHIRALCEL OJ-H column at 40 °C; flow rate: 0.5 mL min^{–1}; hexane/EtOH (diethylamine: 0.1 %) = 50/50; (+)-**3**: 10.6 min and (–)-**3**: 16.0 min]. Both enantiomers (+)- and (–)-**3** slowly racemized at 0 °C without catalyst. Racemization was indeed facilitated with the La-linked BINOL catalyst at 0 °C (Figure 1).

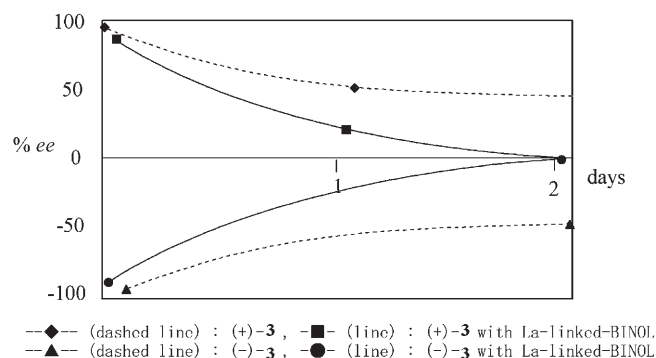


Figure 1. Racemization of (+)-**3**/(–)-**3** with La-linked BINOL.

On the basis of these results, this asymmetric induction in the second amide formation step from the racemic *N,N*-acetal **3** can be rationalized as a result of

dynamic kinetic resolution.^[12] The yield of **4** exceeded 50 % and racemic **3** was recovered, and both enantiomers of **3** racemized with La-linked BINOL complex at 0 °C within 2 days.

Dynamic kinetic resolution in the second amide formation step was then confirmed with *rac*-**3** and the La-linked BINOL complex. However, the amide **4** was obtained in lower yield and % *ee* (Table 2, entries 1–3; **4**: 10–21 % yield, 23–37 % *ee*), even with a shortened or prolonged reaction time. The reason for the lower enantioselectivity is that diamine **1** and/or keto ester **2** could play a significant role as an additive to assemble with the La-linked BINOL complex to give higher enantioselectivity. We thus examined these starting materials **1** and/or **2** as an additive in the stepwise reaction from *rac*-**3**. Diamine **1** led to higher enantioselectivity (65 % *ee*) than those in the one-pot reactions (entry 4). In sharp contrast, keto ester **2** gave the lowest enantioselectivity (21 % *ee*) (entry 5). Simultaneous addition of diamine **1** and keto ester **2** gave almost the same enantioselectivity as in the one-pot reactions (entries 6 and 7, 56–59 % *ee*).

These results clearly suggest that diamine **1** with the La-linked BINOL complex shows a positive effect and keto ester **2** exhibits a negative effect for this dynamic kinetic resolution. Therefore, it can be concluded that the enantioselectivity (56–59 % *ee*) in the one-pot reaction was the result of summation of these positive (65 % *ee*) and negative (21 % *ee*) effects of diamine **1** and keto ester **2**, respectively.

Table 2. Dynamic kinetic resolution in the second amide formation step.

			3		4	
Entry	Additive	Time [days]	Recovery [%]	% <i>ee</i> ^[a]	Yield [%]	% <i>ee</i> ^[b]
1	none	7	87	0	10	23 (S)
2	none	14	56	0	21	28 (S)
3	none	50	48	0	18	37 (S)
4	1 (20 mol %)	50	–	–	99	65 (S)
5	2 (20 mol %)	50	52	0	35	21 (S)
6	1 (20 mol %) + 2 (20 mol %)	50	–	–	70	59 (S)
7 ^[c]	–	50	–	–	70	56 (S)

^[a] The % *ee* was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL min^{–1}; hexane/EtOH (diethylamine: 0.1 %) = 50/50; 10.6 and 16.0 min, respectively.

^[b] The % *ee* was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL min^{–1}; hexane/EtOH (diethylamine: 0.1 %) = 50/50; 20.5 and 46.9 min; The absolute configuration was correlated to **M58169**, of which the absolute configuration was determined by X-ray crystallographic analysis (see ref.^[5]).

^[c] Entry 7 was carried out from diamine **1** and keto ester **2** for reference.

Chiral Diamine

Since these results gave us a charge, we next tried to add other typical chiral diamines as an additive for increasing selectivity in the one-pot reaction. These chiral diamines were selected from tetramethylated derivatives^[13] which could not react with keto ester **2**. The results are summarized in Table 3. In entry 3, (*R*)-*N,N,N',N'*-tetramethylcyclohexyldiamine gave slightly lower selectivity (42% *ee*). However, other diamines gave almost the same selectivity as in the one-pot reaction (entries 1–2 and 4–7).

Alkaline and Central Lanthanide Metals

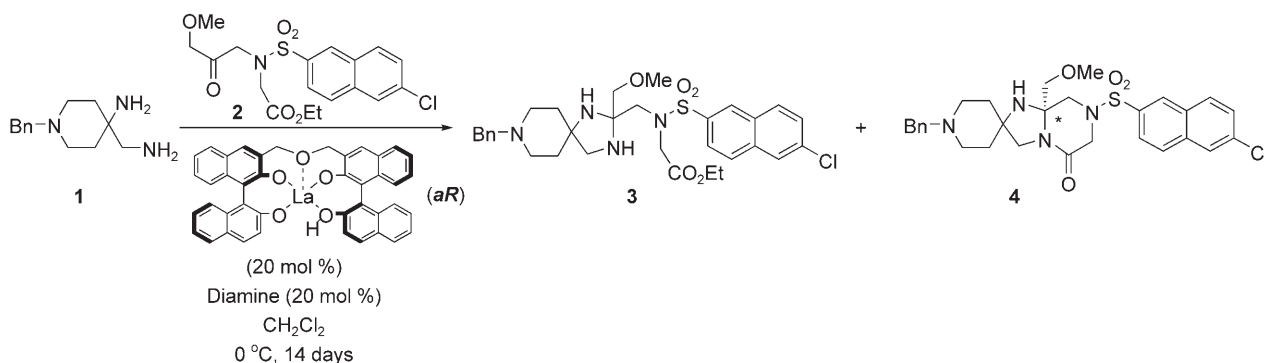
The alkaline and central lanthanide metals were then tuned (Table 4). Changing the alkaline metal in the La-linked BINOL complex from lithium *via* sodium

to potassium reduced the chemical yield and enantioselectivity of **4** (entries 1–3; **4**: 7–24% yield, 15–21% *ee*).^[11] When the central lanthanide metals have been changed to yttrium or gadolinium instead of lanthanum, chemical yield and enantioselectivity of **4** slightly decreased (entries 5 and 6; **4**: 38–44% yield, 51–52% *ee*). However, the ytterbium complex gave a low yield although with moderate selectivity (entry 7; **4**: 11% yield, 40% *ee*). A non-alkaline metal La-linked BINOL complex gave the best yield and enantioselectivity (entry 4; **4**: 44% yield, 55% *ee*).

Solvent Effects

Several solvents were then checked. According to Shibasaki's reports,^[11] tetrahydrofuran and dimethyl ether were advantageous to Michael reactions with the La-linked BINOL complex. However, dichloro-

Table 3. Comparison of chiral diamine effect as an additive in the one-pot reaction.



Entry	Diamine	3 % <i>ee</i> ^[a]	4 Yield [%]	4 % <i>ee</i> ^[b]
1	(<i>aR</i>)	0	49	56 (S)
2	(<i>aS</i>)	0	48	56 (S)
3	(<i>R,R</i>)	0	43	42 (S)
4	(<i>S,S</i>)	0	49	55 (S)
5	(<i>R,R</i>)	0	50	55 (S)
6	(<i>S,S</i>)	0	50	56 (S)
7	none	0	50	56 (S)

^[a] The % *ee* was determined by chiral HPLC (Daicel CHIRALPAK AD-H column) at 40 °C; flow rate: 0.5 mL min⁻¹; EtOH (diethylamine: 0.1%) = 100; 27.7 and 40.2 min, respectively.

^[b] Yield of **4** (based on **2**) and % *ee* were determined by chiral HPLC (Daicel CHIRALPAK AD-H column) at 40 °C; flow rate: 0.5 mL min⁻¹; EtOH (diethylamine: 0.1%) = 100; 36.2 and 55.1 min; The absolute configuration was correlated to **M58169**, of which the absolute configuration was determined by X-ray crystallographic analysis (see ref.^[5]).

Table 4. Comparison of alkaline metals or of central lanthanide metals.

Entry ^[a]	M ^[b]	Ln ^[b]	3		4	
			Yield [%]	% ee ^[c]	Yield [%]	% ee ^[d]
1	Li	La	26	0	24	21(S)
2	Na	La	23	0	14	15(S)
3	K	La	16	0	7	19(S)
4	H	La	41	0	44	55(S)
5	H	Y	34	0	44	52(S)
6	H	Gd	53	0	38	51(S)
7	H	Yb	30	0	11	40(S)

20 mol %

^[a] Each reaction was carried out at 0 °C for 14 days.

^[b] See ref.^[11]

^[c] The % ee was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL min⁻¹; hexane/EtOH (diethylamine: 0.1 %) = 50/50; 10.6 and 16.0 min, respectively.

^[d] The % ee was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL min⁻¹; hexane/EtOH (diethylamine: 0.1 %) = 50/50; 20.5 and 46.9 min; The absolute configuration was correlated to **M58169**, of which the absolute configuration was determined by X-ray crystallographic analysis (see ref.^[5]).

methane gave the best result in this dynamic kinetic resolution (Table 5).

Table 5. The solvent effects with La-linked BINOL.

Entry ^[a]	Solvent	3		4	
		Yield [%]	% ee ^[b]	Yield [%]	% ee ^[c]
1	CH ₂ Cl ₂	41	0	44	55 (S)
2 ^[d]	THF	N.R.	–	N.R.	–
3	DME	19	0	32	10 (S)

^[a] Each reaction with 20 mol % (*aR*)-La-linked BINOL was carried out at 0 °C for 14 days.

^[b] The % ee was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL min⁻¹; hexane/EtOH (diethylamine: 0.1 %) = 50/50; 10.6 and 16.0 min, respectively.

^[c] % ee was determined by chiral HPLC (Daicel CHIRALCEL OJ-H column) at 40 °C; flow rate: 0.5 mL min⁻¹; Hexane/EtOH (diethylamine: 0.1 %) = 50/50; 20.5 and 46.9 min; The absolute configuration was correlated with **M58169**, the absolute configuration of which was determined by X-ray crystallographic analysis (see ref.^[5]).

^[d] The reaction did not proceed. N.R. = no reaction.

A Possible Mechanism

A possible mechanism in this dynamic kinetic resolution can be exemplified as shown below (Figure 2 and Scheme 3). Shibasaki reported that the central lanthanum metal plays a role of Lewis acid and a lanthanum phenoxide (O-La) or an ammonium phenoxide (O < σππ > -N⁺H₃) coordinated with lanthanide metal acts as a Brønsted base (Figure 2).^[14] First, **rac-3** was formed with diamine **1** and keto ester **2** through complexation with Lewis acidic site of the La-linked BINOL complex. Then coordination of (+)- and (–)-**3** with the La-linked BINOL complex gave intermediates (*R*)- and (*S*)-**5**, respectively. The Lewis acid could activate the ester-carbonyl group and the Brønsted base part could activate the amino group in the *N,N*-acetal. Since these intermediates (*R*)- and (*S*)-**5** reacted to give the corresponding amides (*S*)- and (*R*)-**4** with unequal rate constants *k_S* and *k_R* (*k_S* > *k_R*; in this case), the kinetic resolution could take place. There was equilibrium between intermediates (*R*)- and (*S*)-**5** via an imino intermediate **6**, and both racemization

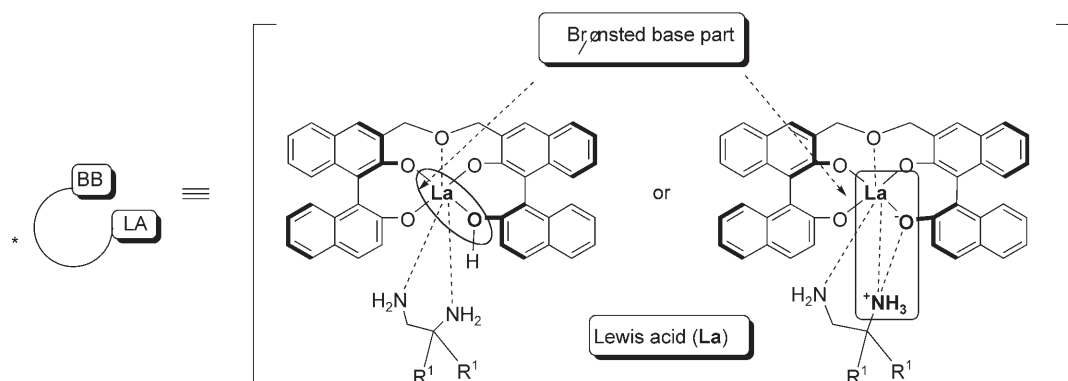
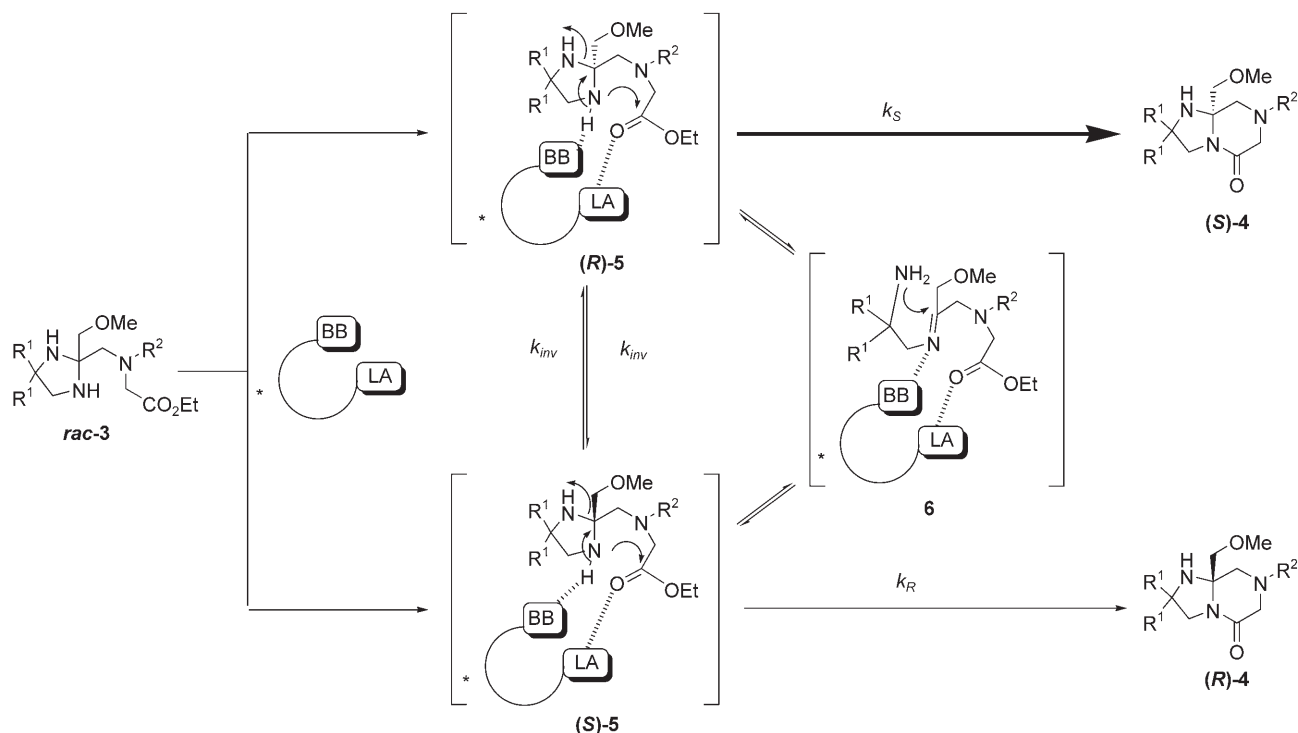


Figure 2.



Scheme 3.

rate constants (k_{inv}) were larger than k_S or k_R . Thus, this dynamic kinetic resolution could be achieved (Scheme 3).

Asymmetric Total Syntheses of M58163 and M58169 with the La-linked BINOL Complex

Finally, the target compounds **M58163** and **M58169** were synthesized (Scheme 4). The keto ester **2** was prepared from *N*-benzylglycine ethyl ester **7**. Compound **7** was allowed to react with glycidyl methyl ether, and the *N*-benzyl moiety was deprotected by catalytic hydrogenation under acidic conditions, then the deprotected compound was reacted with the corresponding sulfonyl chloride to give the hydroxy ester **8** (80% yield, 3 steps). The hydroxy ester **8** was oxidized by the 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl benzoate-NaClO oxidation method^[15] to obtain the desired keto ester **2** (89% yield).

Since the absolute configuration of **M58169** was determined to be *R* by X-ray crystallographic analysis,^[5] the commercially available (*aS*)-La-linked-BINOL complex was used with diamine **1**^[16] and keto ester **2** to obtain the desired compound **4** [60% yield, 57% *ee* (*R*)]. The compound **4** was deprotected by α -chloroethyl chloroformate in the presence of proton sponge^[17]. The deprotected compound **9** was coupled with 4-chloropyridine hydrochloride to afford **M58163**. The *N*-methyl moiety was created on

M58163 by a reductive amination to complete the synthesis of **M58169**. In these reaction sequences, racemization did not take place; **M58163** and **M58169** could be obtained in 57% *ee*.^[5]

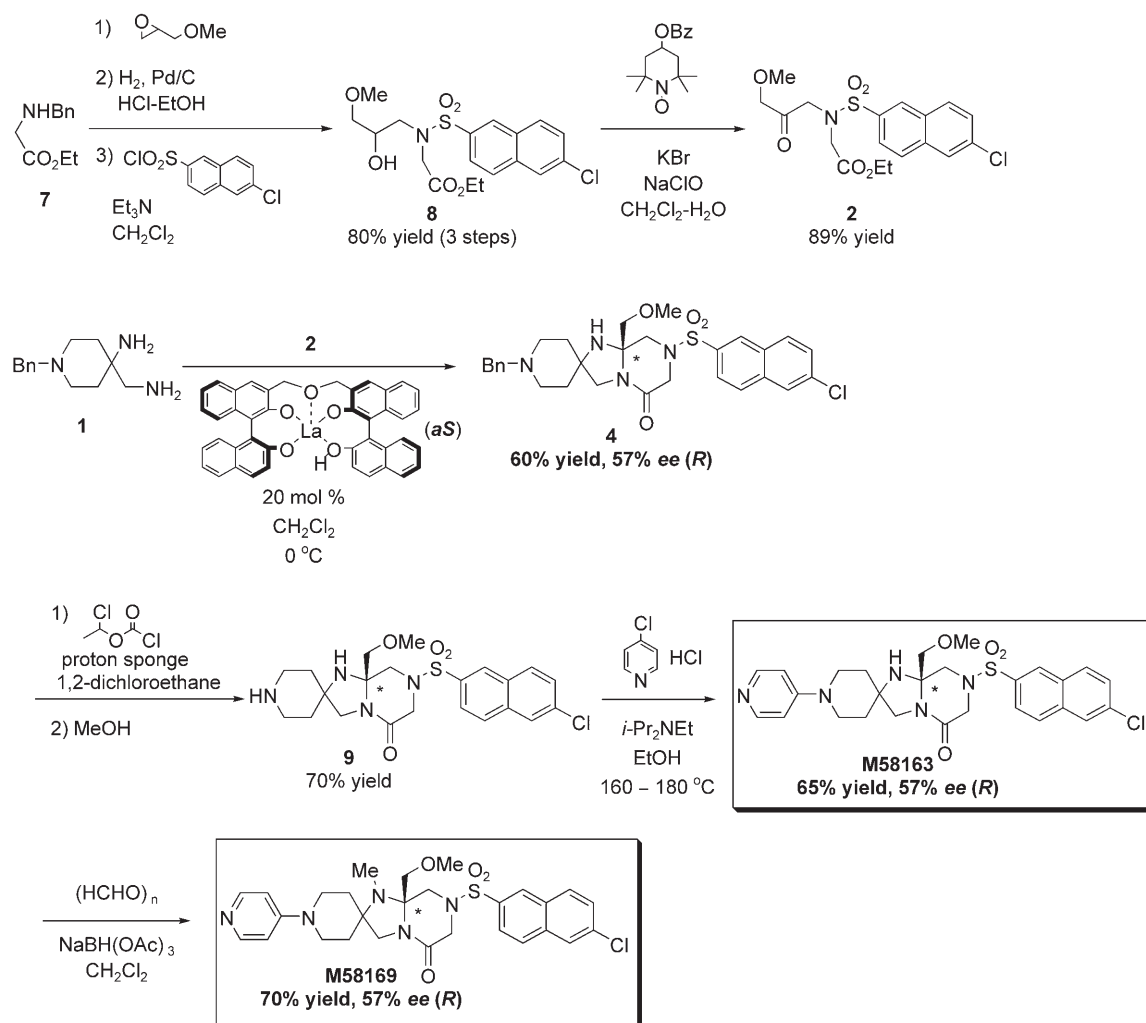
Conclusions

In summary, we have reported the asymmetric cyclic *N,N*-acetal formation and the following dynamic kinetic resolution in the second amide formation step using an La-linked BINOL complex. The dynamic kinetic resolution is further clarified by a racemization experiment on an enantiopure (+)- or (–)-cyclic *N,N*-acetal **3** and by the enantiomer-selective amide formation step. Interestingly, diamine **1** plays a key role not only as a substrate but also as an additive to modify the La catalyst. We have thus accomplished the catalytic asymmetric total synthesis of our antithrombotic agents **M58163** and **M58169**.

Experimental Section

General Remarks

Nuclear magnetic resonance (NMR) spectra were taken with JEOL JNM-LA300 and Varian GEMINI 300 spectrometers, in CDCl₃ using tetramethylsilane as the internal reference. High-resolution mass spectra (HR-MS) were obtained



Scheme 4. Asymmetric synthesis of **M58163** and **M58169**.

using JEOL JMS-GCMATE or BRUKER Auto FLEX TOF/TOF instruments. Infrared absorption spectra (IR) were run using a HORIBA FT-720 FT-IR spectrometer. High performance liquid chromatography (HPLC) was conducted by using Shimadzu LC-10 A and JASCO PU-980 systems. Optical rotations were measured with a JASCO DIP-1000 digital polarimeter.

Cyclic *N,N*-Acetal Formation with a Chiral Brønsted Acid

To a solution of keto ester **2** (30 mg, 0.072 mmol) in CH_2Cl_2 (1.0 mL) was added a chiral Brønsted acid (30 mol%) at 0°C . After stirring for 30 min at 0°C , a solution of diamine **1** (15.8 mg, 0.072 mmol) in CH_2Cl_2 (1.0 mL) was added to the above mixture. The reaction mixture was stirred at 0°C for 2–19 days, then was purified by silica gel column chromatography (eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}=97/3\text{--}95/5\text{--}93/7\text{--}90/10$) to afford the *N,N*-acetal **3** in 0–59% yield (0% ee) and the tricyclic compound **4** in 29–65% yield (7–9% ee), respectively. Enantiomeric excess of **3** and **4** were measured by

HPLC [Daicel CHIRALCEL OJ-H column (0.46×25 cm) at 40°C , flow rate: 0.5 mL min^{-1} with hexane/EtOH (containing 0.1% diethylamine)=50/50, retention times: **3** 10.6 min and 16.0 min, **4** 20.5 min (*S*)-form and 46.9 min (*R*)-form].

Cyclic *N,N*-Acetal and Amide Formation with a Salen-Manganese Complex

Method A: To a suspension of dried MS 4 Å (120 mg) in CH_2Cl_2 (1.0 mL) were added a chiral salen-manganese complex (84.3 mg, 0.094 mmol) and a solution of keto ester **2** (30.0 mg, 0.072 mmol) in CH_2Cl_2 (0.5 mL) at 0°C . After stirring for 30 min at 0°C , a solution of diamine **1** (15.8 mg, 0.072 mmol) in CH_2Cl_2 (0.5 mL) was added at 0°C to the above mixture. The reaction mixture was stirred for 5 days at 0°C , then MS 4 Å was filtered off and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (eluant: $\text{CH}_2\text{Cl}_2/\text{MeOH}=95/5\text{--}93/7\text{--}90/10\text{--}80/20$) to afford the *N,N*-acetal **3** as a colorless amorphous solid (yield: 19.5 mg, 32%, 0% ee) and the tricyclic intermediate **4**-manganese complex. Then this man-

ganese complex was once more purified for isolating **4** by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH[®], eluant: Hex/CH₂Cl₂ = 4/1–1/1) to afford **4** as a colorless amorphous solid [yield: 4.8 mg, 8%, 48% *ee* (*S*)]. The enantiomeric excesses of **3** and **4** were measured by HPLC under the above conditions.

Method B: To a suspension of dried MS 4 Å (120 mg) in CH₂Cl₂ (1.0 mL) were added a chiral salen-manganese complex (84.3 mg, 0.094 mmol) and a solution of keto ester **2** (30.0 mg, 0.072 mmol) in CH₂Cl₂ (0.5 mL) at 0°C. After stirring for 30 min at 0°C, a solution of diamine **1** (15.8 mg, 0.072 mmol) in CH₂Cl₂ (0.5 mL) was added at 0°C to the above mixture. The reaction mixture was stirred for 32 days at 0°C until the *N,N*-acetal **3** had disappeared on TLC. Then MS 4 Å was filtered off and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (eluant: CH₂Cl₂/MeOH = 95/5–93/7–90/10) to afford **4**-manganese complex. Then this complex was dissolved in CH₂Cl₂ (2.0 mL) and Et₃N (0.26 mL, 1.88 mmol) was added into the solution for isolating **4**. The mixture was once more purified by silica gel column chromatography (eluant: CH₂Cl₂/MeOH = 97/3–95/5–93/7–90/10) to afford **4** as a colorless amorphous solid [yield: 18.9 mg, 46%, 49% *ee* (*S*)]. Enantiomeric excesses of **3** and **4** were measured by HPLC under the above conditions.

Cyclic *N,N*-Acetal and Amide Formation with a Lanthanum-Linked BINOL Complex

To a solution of keto ester **2** (30.0 mg, 0.072 mmol) in CH₂Cl₂ (2.0 mL) was added the (*aR*)-La-linked BINOL complex (11.8 mg, 0.0014 mmol) at 0°C. After stirring for 30 min at 0°C, a solution of diamine **1** (15.8 mg, 0.072 mmol) in CH₂Cl₂ (1.0 mL) was added at 0°C to the above mixture and the reaction mixture was stirred for 14–23 days at 0°C. After the reaction, the mixture was purified by silica gel column chromatography (eluant: CH₂Cl₂/MeOH = 100/1–50/1–25/1–20/1) to afford **3** as a colorless amorphous solid (yield: 41–23%, 0% *ee*) and **4** as a colorless amorphous solid [yield: 44–69%, 56% *ee* (*S*)]. Enantiomeric excesses of **3** and **4** were measured by HPLC under the above conditions.

***rac*-Ethyl *N*-[8-phenylmethyl-2-(methoxymethyl)-1,3,8-triazaspiro[4.5]dec-2-yl]methyl-*N*-[(6-chloro-2-naphthalenyl)sulfonyl]glycinate (**3**):** ¹H NMR (300 MHz, CDCl₃): δ = 8.32 (1H, s), 7.95–7.75 (4H, m), 7.54 (1H, dd, *J* = 1.8, 9.0 Hz), 7.35–7.20 (5H, m), 4.62 (1H, d, *J* = 18.5 Hz), 4.55 (1H, d, *J* = 18.5 Hz), 3.94–3.80 (2H, m), 3.55–3.25 (6H, m), 3.34 (3H, s), 2.82 (1H, d, *J* = 11.7 Hz), 2.73 (1H, d, *J* = 11.7 Hz), 2.65–2.10 (4H, m), 1.75–1.45 (4H, m), 1.05 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 169.12, 136.72, 135.37 (2C), 134.77, 130.69, 130.33, 129.11 (2C), 128.58, 128.49, 128.19 (2C), 126.98, 126.70, 124.16, 81.02, 76.81, 75.13, 63.16, 60.91, 60.77, 59.15, 52.38, 51.45, 51.26, 49.98, 38.13, 37.55, 13.98.

(+)-(8*aS*)-7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-8*a*-(methoxymethyl)-1'-[(phenylmethyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4'-piperidin]-5(1*H*)-one (4**):** MALDI-TOF-HR-MS: *m/z* = 569.1960, (*M* + *H*), calcd. for C₂₉H₃₄³⁵ClN₄O₄S: 569.1989; ¹H NMR (300 MHz, CDCl₃): δ = 8.32 (1H, s), 7.97–7.87 (3H, m), 7.80–7.73 (1H, m), 7.62–7.55 (1H, m), 7.35–7.17 (5H, m), 4.31 (1H, d, *J* = 16.9 Hz),

4.22–4.08 (2H, m), 3.70 (1H, d, *J* = 9.5 Hz), 3.50–3.35 (3H, m), 3.42 (3H, s), 3.27 (1H, d, *J* = 16.9 Hz), 2.87 (1H, d, *J* = 11.4 Hz), 2.65–2.05 (5H, m), 2.20 (1H, d, *J* = 11.7 Hz), 1.80–1.65 (2H, m), 1.40–1.20 (2H, m); ¹³C NMR (75 MHz, CDCl₃): δ = 163.19, 138.15, 135.65, 135.38, 132.90, 130.79, 130.45, 129.05 (2C), 128.99, 128.93, 128.90, 128.22 (2C), 127.07, 126.81, 123.56, 77.05, 74.49, 62.94, 59.52, 58.41, 53.09, 51.39, 50.80, 50.52, 47.61, 37.97, 36.72; IR (film): ν = 1653, 1348, 1167, 698 cm^{−1}; [α]_D^{28.0}: +50.7° (*c* 1.120, MeOH, 56% *ee*).

Racemization of (+)-/(−)-**3**

(+)-**3** and (−)-**3** were isolated by chiral HPLC [Daicel CHIRALCEL OJ-H column (0.46 × 25 cm) at 40°C; flow rate: 0.5 mL min^{−1}; hexane/EtOH (diethylamine: 0.1%) = 50/50; (+)-**3**: 10.6 min and (−)-**3**: 16.0 min, respectively]. To both enantiomers (+)-**3** and (−)-**3** in the above eluent, was added La-linked BINOL, respectively. These solutions with/without (*aR*)-La-linked BINOL were stirred at 0°C and a chiral HPLC time course analysis was carried out.

From *rac*-**3** to Amide **4** with La-Linked BINOL and Diamine **1** and/or Keto Ester **2**

To a suspension of (*aR*)-La-linked-BINOL (8.0 mg, 0.0098 mmol) in CH₂Cl₂ (0.5 mL), diamine **1** (2.1 mg, 0.0098 mmol) and/or keto ester **2** (4.0 mg, 0.0098 mmol) were added at 0°C. Then the solution of *rac*-**3** (30 mg, 0.049 mmol) in CH₂Cl₂ (0.5 mL) was added into the reaction mixture at 0°C. The reaction mixture was stirred at 0°C for 50 days. After the reaction, the mixture was purified by silica gel column chromatography (eluant: CH₂Cl₂/MeOH = 100/1–50/1–25/1–20/1) to obtain the amide **4** [yield: 18–99%, 21–59% *ee* (*S*)] as a colorless amorphous solid and to recover *rac*-**3** as a colorless amorphous solid (yield: 0–52%, 0% *ee*). Enantiomeric excesses of **3** and **4** were measured by HPLC under the above conditions.

Procedure for Adding a Chiral Diamine

To a suspension of (*aR*)-La-linked BINOL (5.9 mg, 0.0072 mmol) in CH₂Cl₂ (0.2 mL), a chiral diamine [e.g., (*aR*)-*N,N,N',N'*-tetramethyl-(1,1'-binaphthalene)-2,2'-diamine; 2.5 mg, 0.0072 mmol] was added at 0°C. Then a solution of keto ester **2** (15.0 mg, 0.036 mmol) in CH₂Cl₂ (0.5 mL) and a solution of diamine **1** (7.9 mg, 0.036 mmol) in CH₂Cl₂ (0.5 mL) were added at 0°C, respectively. The reaction mixture was stirred at 0°C for 14 days.

Enantiomeric excesses of **3** and **4** were measured and the yield of **4** (based on keto ester **2**) was calculated by HPLC analysis [Daicel CHIRALPAK AD-H column (0.46 × 25 cm) at 40°C, flow rate: 0.5 mL min^{−1} with EtOH (containing 0.1% diethylamine) = 100, retention time: **2** 25.2 min; **3** 27.7 min, and 40.2 min; **4** 36.2 min (*S*)-form and 55.1 min (*R*)-form].

Asymmetric Synthesis of M58163 and M58169

***N*-[(6-Chloro-2-naphthalenyl)sulfonyl]-*N*-(2-hydroxy-3-methoxypropyl)glycine ethyl ester (**8**)** [Step 1]: *N*-Benzylglycine ethyl ester **7** (35 g, 0.181 mol) and glycidyl methyl ether (21.1 mL, 0.181 mol) were mixed and the reaction mixture

was stirred at 120°C for 3 h. After cooling, it was concentrated under vacuo to afford the crude *N*-(2-hydroxy-3-methoxypropyl)-*N*-(phenylmethyl)glycine ethyl ester (47.3 g, quant.) as a yellow oil.

[Step 2]: To an EtOH (360 mL) solution of the crude compound (47.3 g) which was obtained in Step 1, 4.6 N HCl-EtOH (100 mL) and 10% Pd/C (4.37 g) were added under an argon atmosphere. The atmosphere was changed to hydrogen gas and the reaction mixture was stirred at room temperature overnight. Then it was filtered through Celite® pad to remove Pd/C and filtrate was concentrated under reduced pressure to afford *N*-(2-hydroxy-3-methoxypropyl)-glycine ethyl ester hydrochloride (47.8 g, quant.) as a yellow oil.

[Step 3]: To a CH₂Cl₂ (520 mL) solution of the compound (47.8 g) which was obtained in Step 2, 6-chloronaphthalene-2-sulfonyl chloride (47.3 g, 0.181 mol) was added. Then triethylamine (55.5 mL, 0.398 mol) was slowly added into the above mixture at 0°C. The reaction mixture was stirred at room temperature for 1 hour. Then water was added into the reaction mixture at 0°C and it was extracted with CH₂Cl₂. The organic layer was washed with 1 N aqueous HCl, H₂O, saturated aqueous NaHCO₃, and brine, respectively. After drying the organic layer with anhydrous Na₂SO₄, the solvent was removed under reduced pressure and the resulting residue was purified by silica gel flash column chromatography (eluant: hexane/AcOEt=2/1–4/3) to obtain compound **8** as a colorless amorphous solid; yield: 80% (3 steps). EI-HR-MS: *m/z*=415.0858 (M⁺), calcd. for C₁₈H₂₂³⁵ClNO₆S: 415.0856; ¹H NMR (300 MHz, CDCl₃): δ=8.39 (1H, s), 7.95–7.83 (3H, m), 7.84 (1H, dd, *J*=1.7, 8.8 Hz), 7.56 (1H, dd, *J*=2.2, 8.8 Hz), 4.19 (2H, s), 4.07 (2H, q, *J*=7.2 Hz), 4.05–3.95 (1H, m), 3.48–3.29 (2H, m), 3.44 (2H, d, *J*=5.1 Hz), 3.35 (3H, s), 1.17 (3H, t, *J*=7.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ=169.77, 136.49, 135.47, 134.98, 130.74, 130.36, 128.65, 128.64, 128.51, 126.75, 123.85, 73.89, 69.22, 61.70, 59.24, 52.62, 50.30, 13.99; IR (KBr): ν=3483, 1732, 1344, 1153, 694 cm^{−1}.

N-[(6-Chloronaphthalen-2-yl)sulfonyl]-*N*-(3-methoxy-2-oxopropyl)glycine Ethyl Ester (**2**)

To a solution of compound **8** (60.4 g, 0.145 mol) in CH₂Cl₂ (560 mL) were added an aqueous solution of potassium bromide (3.46 g, 0.291 mol) in H₂O (58.2 mL) and 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl benzoate free radical (0.454 g, 0.291 mol). Then within 5°C, an alkaline aqueous NaClO solution, which was prepared with 5 wt% aqueous NaClO solution (281 mL, 0.189 mol), water (280 mL) and sodium hydrogen carbonate (28.1 g, 0.338 mol), was added dropwise into the above mixture. This oxidation reaction ended almost as soon as dropping the NaClO solution was completed. Then the reaction mixture was extracted with CH₂Cl₂ and the organic layer was washed with 10% aqueous Na₂S₂O₃ solution and brine and was dried with anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel flash column chromatography (eluant: hexane/AcOEt=2/1) to obtain compound **2** as a pale yellow amorphous solid; yield: 53.8 g (89%). EI-HR-MS: *m/z*=413.0701 (M⁺), calcd. for C₁₈H₂₀³⁵ClNO₆S: 413.0700; ¹H NMR (300 MHz, CDCl₃): δ=8.42–8.38 (1H, m), 7.95–7.85 (3H, m), 7.81 (1H, dd, *J*=

2.0, 8.8 Hz), 7.56 (1H, dd, *J*=2.0, 8.8 Hz), 4.43 (2H, s), 4.19 (2H, s), 4.11 (2H, s), 4.04 (2H, q, *J*=7.2 Hz), 3.41 (3H, s), 1.15 (3H, t, *J*=7.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ=202.85, 168.67, 136.46, 135.48, 134.97, 130.72, 130.28, 128.60, 128.55, 128.47, 126.74, 123.78, 76.42, 61.50, 59.49, 54.00, 48.74, 13.95; IR (film): ν=1743, 1338, 1157, 955, 696 cm^{−1}.

(−)-(8*aR*)-7-[(6-Chloronaphthalen-2-yl)sulfonyl]-tetrahydro-8*a*-(methoxymethyl)-1'-(phenylmethyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4'-piperidin]-5(1*H*)-one (**4**)

To a solution of keto ester **2** (125 mg, 0.302 mmol) in CH₂Cl₂ (16 mL) was added the (*aS*)-La-linked BINOL complex (49.7 mg, 0.0604 mmol) at 0°C. After stirring for 30 min at 0°C, a solution of diamine **1** (66.2 mg, 0.302 mmol) in CH₂Cl₂ (8.0 mL) was added at 0°C to the above mixture and the reaction mixture was stirred for 30 days at 0°C. After the reaction, the mixture was purified by silica gel column chromatography (eluant: CH₂Cl₂/MeOH=97/3–95/5–93/7–90/10) to afford **3** as a colorless amorphous solid (yield: 38.3 mg, 21%, 0% *ee*) and **4** as a colorless amorphous solid [yield: 99.5 mg, 60%, 57% *ee*, (*R*)]. Enantiomeric excesses of **3** and of **4** were measured by HPLC under the above conditions. [α]_D²⁰: −51.5° (c 0.953, MeOH, 57% *ee*).

(−)-(8*aR*)-7-[(6-Chloronaphthalen-2-yl)sulfonyl]-tetrahydro-8*a*-(methoxymethyl)-spiro[imidazo-1,2-*a*]pyrazine-2(3*H*),4'-piperidin]-5(1*H*)-one (**9**)

To a solution of **4** (90.0 mg, 0.158 mmol) in CH₂Cl₂ (1.5 mL) were added proton sponge® [1,8-bis(*N,N*-dimethylamino)-naphthalene, 40.7 mg, 0.19 mmol] and α-chloroethyl chloroformate (0.043 mL, 0.395 mmol) at 0°C. The reaction mixture was stirred at room temperature for 5 min and then was refluxed for 2 h. After cooling, the reaction mixture was concentrated under vacuum. Then MeOH (1.5 mL) was added to the residue, and the reaction mixture was refluxed for 2 h. After cooling, the mixture was concentrated under vacuum and 1 N HCl was added to the residue and the mixture was washed with Et₂O to remove benzyl chloride that was generated in this reaction. Then 1 N NaOH was added to the water layer at 0°C (pH > 11). The water layer was extracted with CH₂Cl₂, washed with brine and dried with anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by amino-silica gel column chromatography (Moritex Corporation, Purif-pack NH₂, eluant: hexane/CH₂Cl₂=50/50–CH₂Cl₂–CH₂Cl₂/MeOH=99/1–98/2–97/3) to afford **9** as a colorless amorphous solid; yield: 52.7 mg (70%), 57% *ee* (*R*). MALDI-TOF-HR-MS: *m/z*=479.1526 (M+H), calcd. for C₂₂H₂₈³⁵ClN₄O₄S: 479.1520. ¹H NMR (300 MHz, CDCl₃): δ=8.33 (1H, s), 8.00–7.85 (3H, m), 7.78 (1H, dd, *J*=1.8, 8.6 Hz), 7.60 (1H, dd, *J*=1.8, 8.8 Hz), 4.32 (1H, d, *J*=16.7 Hz), 4.24–4.10 (2H, m), 3.71 (1H, d, *J*=9.4 Hz), 3.43 (1H, d, *J*=9.4 Hz), 3.43 (3H, s), 3.29 (1H, d, *J*=16.7 Hz), 3.00–2.80 (2H, m), 2.88 (1H, d, *J*=11.4 Hz), 2.75–2.28 (3H, m), 2.23 (1H, d, *J*=11.9 Hz), 1.80–1.60 (2H, m), 1.35–1.15 (2H, m); ¹³C NMR (75 MHz, CDCl₃): δ=163.26, 135.66, 135.41, 132.92, 130.81, 130.46, 129.02, 128.94, 128.93, 126.82, 123.56, 77.08, 74.60, 59.52, 58.77, 53.20, 51.47, 47.61, 43.96,

43.50, 38.92, 37.56; IR (film): ν =2920, 1655, 1456, 1348, 1167, 698 cm^{-1} . $[\alpha]_{\text{D}}^{28.0}$: -52.3° (c =1.090, MeOH, 57% *ee*).

(–)-(8*aR*)-7-[(6-Chloronaphthalen-2-yl)sulfonyl]-tetrahydro-8*a*-(methoxymethyl)-1'-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4'-piperidin]-5(1*H*)-one (M58163)

To the solution of **9** (40 mg, 0.084 mmol) in EtOH (2.0 mL) was added 4-chloropyridine hydrochloride (18.9 mg, 0.126 mmol) and *i*-Pr₂NEt (0.073 mL, 0.42 mmol). The reaction mixture was heated at 160–180 °C in sealed tube for 4 h. After cooling, the mixture was concentrated under vacuum. Then the residue was purified by amino-silica gel column chromatography (Moritex Corporation, Purif-pack NH[®], eluant: CH₂Cl₂/MeOH=99.5/0.5–99.3/0.7–99/1–98.5/1.5) to afford **M58163** as a colorless amorphous solid; yield: 30.3 mg (65%), 57% *ee* (*R*)-form.^[5] The enantiomeric excess of **M58163** was measured by HPLC [Daicel CHIRALCEL AS-H column (0.46×25 cm) at 40 °C, flow rate: 1.0 mL min^{–1} with MeOH (containing 0.1% diethylamine), retention time: 8.7 min (*S*)-form, 11.4 min (*R*)-form]. $[\alpha]_{\text{D}}^{28.6}$: -59.1° (c 0.580, MeOH, 57% *ee*) (lit. $[\alpha]_{\text{D}}^{26}$: -111° (c 0.320, MeOH), 98.6% *ee*).^[5]

(–)-(8*aR*)-[(6-Chloronaphthalen-2-yl)sulfonyl]-tetrahydro-8*a*-(methoxymethyl)-1-methyl-1'-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4'-piperidin]-5(1*H*)-one (M58169)

To the solution of **M58163** (25 mg, 0.045 mmol) in CH₂Cl₂ (1 mL) were added paraformaldehyde (8.1 mg, 0.27 mmol) and NaBH(OAc)₃ (28.6 mg, 0.135 mmol). The reaction mixture was refluxed for 10 h. After cooling, 10% HCl-MeOH (1 mL) was added into the reaction mixture. Then the mixture was refluxed again for 1 hour to degrade the product-borane complex. At the end of reaction, saturated aqueous NaHCO₃ solution was added into the mixture to adjust the pH to more than 11. The mixture was extracted with CH₂Cl₂ and the organic solvent was washed with brine and dried with anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the resulting residue was purified by amino-silica gel column chromatography (Moritex Corporation, Purif-pack NH[®], eluant: hexane/AcOEt=50/50–0/100) to afford **M58169** as a colorless amorphous solid; yield: 18.0 mg (70%), 57% *ee*, (*R*)-form.^[5] The enantiomeric excess of **M58169** was measured by HPLC [Daicel CHIRALCEL AS-H column (0.46×25 cm) at 40 °C, flow rate: 1.0 mL min^{–1} with MeOH (containing 0.1% diethylamine), retention time: 11.9 min (*R*)-form, 17.8 min (*S*)-form]. $[\alpha]_{\text{D}}^{27.3}$: -79.7° (c 0.455, MeOH, 57% *ee*) (lit. $[\alpha]_{\text{D}}^{29}$: -129° (c 0.560, MeOH), >99% *ee*).^[5]

References

[1] a) M. Ragosta, L. W. Gimple, D. Gertz, C. T. Dunwiddie, G. P. Vlasuk, H. L. Haber, E. R. Powers, W. C. Roberts, I. J. Sarembock, *Circulation* **1994**, *89*, 1262–1271; b) J. M. Fevig, R. R. Wexler, *Ann. Rep. Med. Chem.* **1999**, *34*, 81–100; c) P. E. J. Sanderson, *Med. Res. Rev.* **1999**, *19*, 179–197; d) J. Hauptmann, J. Stur-

zebecher, *Thromb. Res.* **1999**, *93*, 203–241; e) J. I. Weitz, J. Hirsh, *Chest* **2001**, *119*, 95S–107S.

[2] a) H. Van Aken, C. Bode, H. Darius, C. Diehm, A. Encke, D. C. Gulba, S. Haas, W. Hacke, W. Puhl, M. Quante, H. Riees, R. Scharf, S. Schellong, K. Schror, K.-L. Schulte, U. Tebbe, *Clinic. Appl. Thromb./Hemost.* **2001**, *7*, 195–204; b) J. J. Sixma, P. G. De Groot, *Thromb. Res.* **1992**, *68*, 507–512.

[3] H. Nishida, T. Mukaihira, F. Saitoh, K. Harada, M. Fukui, T. Matsusue, A. Okamoto, Y. Hosaka, M. Matsumoto, I. Shiromizu, S. Ohnishi, H. Mochizuki, *Chem. Pharm. Bull.* **2004**, *52*, 406–412, and references cited therein.

[4] F. Saitoh, H. Nishida, T. Mukaihira, K. Aikawa, K. Mikami, *Eur. J. Org. Chem.* **2006**, 2269–2272.

[5] F. Saitoh, T. Mukaihira, H. Nishida, T. Satoh, A. Okano, Y. Yumiya, M. Ohkouchi, R. Johka, T. Matsusue, I. Shiromizu, Y. Hosaka, M. Matsumoto, S. Ohnishi, *Chem. Pharm. Bull.* **2006**, *54*, 1535–1544, and references cited therein.

[6] a) A. J. Moreno-Vargas, P. Vogel, *Tetrahedron: Asymmetry* **2003**, *14*, 3173–3176; b) R. Deprez-Poulain, N. Willand, C. Boutillon, G. Nowogrocki, N. Azaroual, B. Deprez, *Tetrahedron Lett.* **2004**, *45*, 5287–5290; c) P. Boffelli, A. Brouillard, C. Colladant, S. Droux, M. Elter, D. Ferroud, G. Lemaître, J. Paladino, World Patent WO2003/054001 A3, **2003**.

[7] a) W. T. Green, P. G. Wuts, *Protecting Groups in Organic Synthesis*, 3rd. edn., Wiley, New York, **1999**; b) H. Sharghi, N. M. Ali, *Phosphorus, Sulfur and Silicon and the Related Elements* **2003**, *178*, 1353–1359.

[8] a) S. M. Sondhi, N. Singh, M. Johar, A. Kumar, *Bioorg. Med. Chem.* **2005**, *13*, 6158–6166; b) G. Claudon, N. Le Bris, H. Bernard, H. Handel, *Eur. J. Org. Chem.* **2004**, 5027–5030; c) F. Chanteau, B. Didier, B. Dondy, P. Doussot, R. Plantier-Royon, C. Portella, *Eur. J. Org. Chem.* **2004**, 1444–1454; d) P. Sohar, A. Csampa, G. Magyarfalvi, A. E. Szabo, G. Stajer, *Monatsh. Chem.* **2004**, *135*, 1519–1527; e) F. Miklos, A. Hetenyi, P. Sohar, G. Stajer, *Montsh. Chem.* **2004**, *135*, 839–847; f) Y. V. Sosnovskikh, A. M. Barabanov, I. B. Usachev, *Russian Chem. Bull.* **2003**, *52*, 1758–1767; g) E. Malamidou-Xenikaki, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2523–2529.

[9] a) A. J. Moreno-Vargas, I. Robina, E. Petricci, P. Vogel, *J. Org. Chem.* **2004**, *69*, 4487–4491; b) G. Verardo, P. Geatti, M. Merli, E. E. Castellarin, *Eur. J. Org. Chem.* **2004**, 2833–2939; c) F. Miklos, I. Kanizsai, S. Thomas, E. Kleinpeter, R. Sllianpaeae, G. Stajer, *Heterocycles* **2004**, *63*, 63–74; d) D. Tepfenhart, L. Moisan, P. I. Dalko, J. Cossy, *Tetrahedron Lett.* **2004**, *45*, 1781–1784; e) A. J. Moreno-Vargas, P. Vogel, *Tetrahedron: Asymmetry* **2003**, *14*, 3173–3176; f) N. Halland, R. G. Hazell, K. A. Jorgensen, *J. Org. Chem.* **2002**, *67*, 8331–8338; g) A. Forster, T. Kovac, H. Mosimann, P. Renaud, P. Vogel, *Tetrahedron: Asymmetry* **1999**, *10*, 567–572; h) N. Mase, Y. Watanabe, Y. Ueno, T. Toru, *J. Org. Chem.* **1997**, *62*, 7794–7800.

[10] For our preliminary report: F. Saitoh, H. Nishida, T. Mukaihira, K. Aikawa, K. Mikami, *Eur. J. Org. Chem.* **2006**, 5454–5457.

- [11] Shibasaki et al. have already developed bifunctional lanthanide basic catalysts: a) Y. S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6506–6507, and references cited therein; recent reviews: b) M. Shibasaki, M. Kanai, S. Matsunaga, *Aldrichimica Acta* **2006**, *39*, 31–39; c) M. Shibasaki, S. Matsunaga, *J. Organometallic Chem.* **2006**, *691*, 2089–2100; d) M. Shibasaki, S. Matsunaga, *Chem. Soc. Rev.* **2006**, *35*, 269–279.
- [12] Dynamic kinetic resolution is one of the most synthetically useful phenomena for asymmetric synthesis: For reviews, see: a) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490; b) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56; c) F. F. Huerta, A. B. E. Minidis, J.-E. Backvall, *Chem. Soc. Rev.* **2001**, *30*, 321–331; d) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291–8327; e) D. E. J. E. Robinson, S. D. Bull, *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446.
- [13] a) C. Rosini, L. Franzini, P. Salvadori, G. P. Spada, *J. Org. Chem.* **1992**, *57*, 6820–6824; b) P. Muller, C. Bolea, *Helvetica Chim. Acta* **2001**, *84*, 1093–1111; c) J.-C. Kizirian, J.-C. Caille, A. Alexakis, *Tetrahedron Lett.* **2003**, *44*, 8893–8895; d) T. A. Whitney, A. W. Langer Jr., *Advances in Chemistry Series* **1974**, *130*, 270–280; e) P. Gamez, F. Fache, M. Lemaire, *Tetrahedron: Asymmetry* **1995**, *6*, 705–718; f) K. Tomioka, M. Shindo, K. Koga, *J. Am. Chem. Soc.* **1989**, *111*, 8266–8268.
- [14] a) T. Nemoto, T. Ohshima, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2725–2732; b) K. Majima, R. Takita, A. Okada, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 15837–15845.
- [15] P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559–2662.
- [16] K. Araki, T. Kuroda, K. Tsutsumi, H. Isoshima, World Patent WO1993/13101 A1, **1993**.
- [17] R. A. Olofson, J. T. Marts, J.-P. Senet, M. Piteau, T. Malfroot, *J. Org. Chem.* **1984**, *49*, 2081–2082.