

## Lewis acid-mediated radical cyclization: stereocontrol in cascade radical addition–cyclization–trapping reactions†

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An efficient approach for achieving radical cyclizations by using hydroxamate ester as a coordination tether with Lewis acid was studied. The chiral Lewis acid-mediated cascade radical addition–cyclization–trapping reaction proceeded smoothly with good enantio- and diastereoselectivities, providing various chiral  $\gamma$ -lactams.

## Introduction

Free radical cyclization reactions have been extensively investigated as powerful and versatile methods for preparing cyclic compounds.<sup>1,2</sup> Particularly, the advantages of utilizing a radical cyclization in organic synthesis are the high functional group tolerance and the mild reaction conditions, because radical intermediates are not charged species. For an efficient cyclization process, the intramolecular radical cyclization must be faster than intermolecular trapping of the initially formed radical on a substrate. Therefore, the cyclization of a conformationally flexible substrate is sometimes difficult to achieve due to the competitive formation of undesired non-cyclic products by the intermolecular side reactions. In this context, we have been interested in developing a new and efficient approach for achieving radical cyclizations.

In radical reactions, the geometry of substrates plays an important role, because most radical reactions proceed through early transition states.<sup>3</sup> Particularly, the control of the rotamer population should be crucial for the efficiency of the cyclization process. The principal function of a Lewis acid is to control the rotamer population of substrates.<sup>4</sup> As a unique function of Lewis acid in radical cyclizations, Maruoka's group reported the template effect of aluminium tris(2,6-diphenylphenoxide) (ATPH), a Lewis acid receptor possessing a bowl-shaped reaction cavity.<sup>5</sup> We considered that the predominant formation of a single reactive rotamer **C** from **A** or **B** must be achieved by the introduction of a coordination tether into the middle of the substrates (Fig. 1). For this purpose, we paid attention to a hydroxamate ester as a

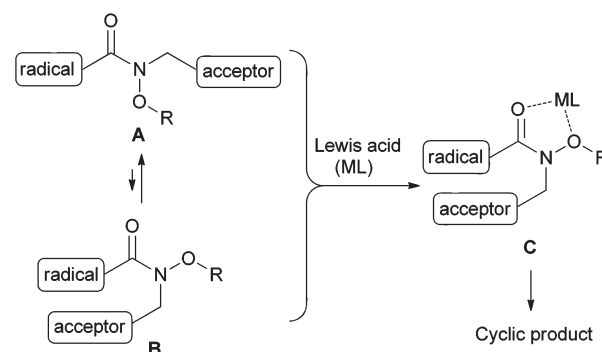


Fig. 1 Control of rotamer population using Lewis acid.

coordination tether with Lewis acid. Recently, hydroxamic acid derivatives have been shown to be useful achiral templates in enantioselective Diels–Alder reaction by Renaud and Corminboeuf.<sup>6</sup>

Strategies involving cascade, tandem or domino radical processes offer the advantage of multiple bond formations in a single operation to give highly functionalized compounds with multiple stereocenters.<sup>1,2</sup> In particular, our laboratory has been interested in enantioselective stereocontrol in cascade radical reactions involving a cyclization step. Recently, we have started investigating the cascade reaction of substrates containing a hydroxamate ester moiety and two radical acceptors.<sup>7</sup> In this study, it is important to control the regiochemical course as well as the stereochemistry (Fig. 2). (1) With the objective to control the enantioselectivity of the cyclization step, hydroxamate ester was used as a chiral Lewis acid-coordinating tether, which has the potential for the formation of a stable five-membered chelation **D** with chiral Lewis acid. (2) With the objective to control the regiochemical course, the substrate has two kinds of polarity-different radical acceptors. Additionally, we expected that the activation of electron-deficient acceptor (acceptor 1) by Lewis acid could enhance the regioselectivities and may suppress the

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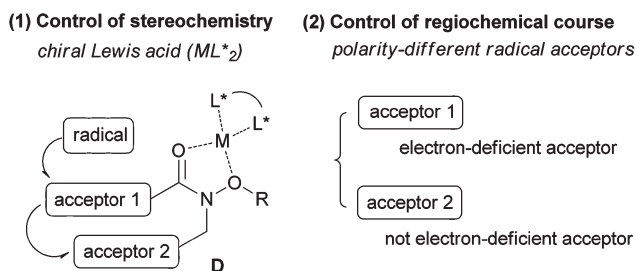
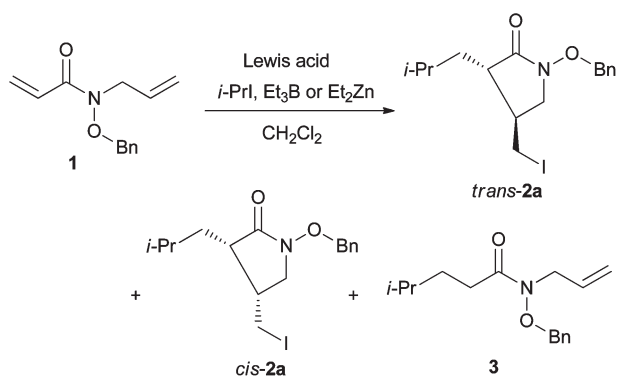


Fig. 2 Control of stereochemistry and regiochemical course.



Scheme 1 Reaction of substrate **1** having an acryloyl moiety.

non-catalyzed reaction giving racemic products. In this paper, we describe in detail the cascade addition–cyclization–trapping reactions on the basis of our cyclization strategy, together with the control of enantioselectivities.

## Results and discussion

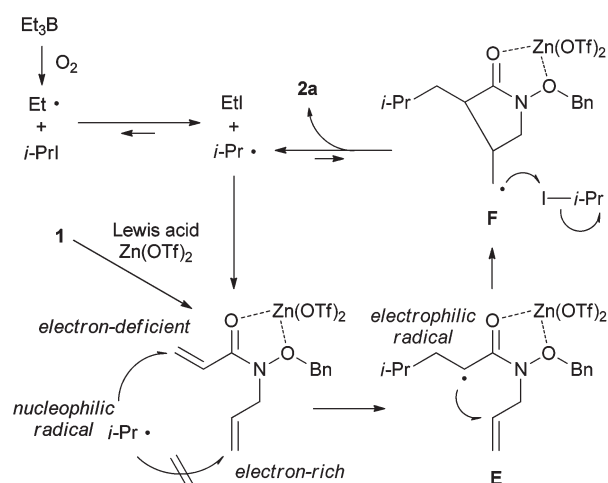
To study the geometry-control by Lewis acid in the absence of chiral ligands, our experiments began with an investigation of the radical reaction of hydroxamate ester **1** having an acryloyl moiety as an electron-deficient acceptor (Scheme 1). As another role of Lewis acid, we also expected that the desired cyclization would occur faster, owing to low-lying LUMO of electron-deficient acceptor, acryloyl group, arising from the complexation with Lewis acid. All reactions were evaluated in  $CH_2Cl_2$  under the tin-free iodine atom-transfer conditions using isopropyl iodide as a radical precursor and a radical initiator such as  $Et_3B$  or  $Et_2Zn$ .<sup>8,9</sup>

Several trends in Table 1 are noteworthy. The reaction of substrate **1** proceeded even in the absence of Lewis acid under mild reaction conditions using  $Et_3B$  (Table 1, entry 1). Two isomers *trans*-**2a** and *cis*-**2a** were isolated in 44% combined yield and 2 : 1 ratio after being stirred at 20 °C for 10 h. In contrast, the reaction using  $Et_2Zn$  as a radical initiator did not proceed effectively but gave a complex mixture (entry 2). With regard to the effect of Lewis acid, a stoichiometric amount of  $Zn(OTf)_2$  accelerated the present cascade sequence to form the products *trans*-**2a** and *cis*-**2a** in 54% combined yield and 9 : 4 ratio within 4 h, probably due to the expected geometry-control (entry 3), although the use of  $Mg(OTf)_2$  did not lead to an obvious enhancement of reaction rate (entry 4). Next, the reactions were

Table 1 Effect of Lewis acid on the reaction of **1**<sup>a</sup>

Entry	Lewis acid	<i>T</i> (°C)	Time (h)	Yield <sup>b</sup> (%)	
				<b>2a</b> ( <i>trans</i> : <i>cis</i> )	<b>3</b>
1 <sup>c</sup>	None	20	10	44 (2 : 1)	
2 <sup>d</sup>	None	20	10	Complex mixture	
3 <sup>c</sup>	$Zn(OTf)_2$	20	4	54 (9 : 4)	
4 <sup>c</sup>	$Mg(OTf)_2$	20	10	45 (2 : 1)	
5 <sup>e</sup>	None	0	10	21 (3 : 1)	
6 <sup>c</sup>	$Zn(OTf)_2$	0	10	42 (3 : 1)	
7 <sup>c</sup>	$Zn(OTf)_2$	−78	20	ND <sup>e</sup>	16
8 <sup>c</sup>	$Mg(OTf)_2$	−78	20	ND <sup>e</sup>	11

<sup>a</sup> Reactions were carried out using **1** (1 equiv) and isopropyl iodide (30 equiv) with Lewis acid (1 equiv). <sup>b</sup> Isolated yield. <sup>c</sup>  $Et_3B$  in hexane (1.0 M, 2.5 equiv) was used. <sup>d</sup>  $Et_2Zn$  in hexane (1.0 M, 2.5 equiv) was used. <sup>e</sup> Not detected.



Scheme 2 Reaction pathway.

conducted at 0 °C and −78 °C (entries 5–8). As expected, better chemical yield was observed in the reaction using  $Zn(OTf)_2$  at 0 °C (entries 5 and 6). In contrast, no cyclic product was obtained at −78 °C even in the presence of Lewis acid; instead, the formation of uncyclized simple adduct **3** was observed (entries 7 and 8). These results are important for stereocontrol using chiral ligands, because these observations indicate that the background reaction giving racemic products may be suppressed when the reactions are carried out at −78 °C.

The regiochemical course of the cascade reaction of **1** was controlled well even in the absence of Lewis acid. The rationale of the reaction pathway is that the nucleophilic isopropyl radical initially reacted with the electron-deficient acryloyl moiety of **1** to form carbonyl-stabilized radical **E** (Scheme 2). The competitive attack of isopropyl radical on the electron-rich acceptor of **1** was completely suppressed. Since the intermediate radical **E** is an electrophilic radical, it attacked intramolecularly the electron-rich olefin moiety in a 5-*exo* radical cyclization manner owing to better orbital overlap in the chair-like *exo* transition state.<sup>10</sup> The cyclic product **2a** was obtained *via* iodine atom-transfer reaction from isopropyl iodide to the primary radical **F**. The success of this reaction reflects the overall difference in the stability of the

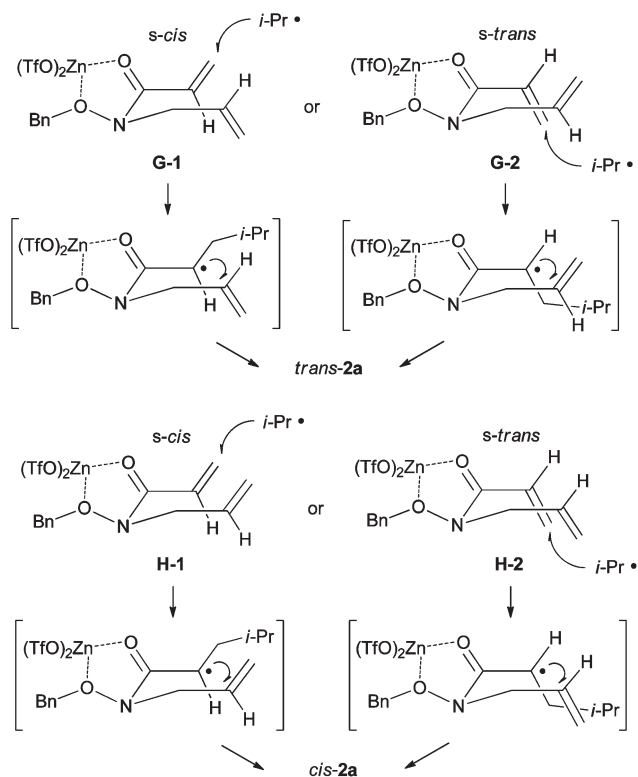


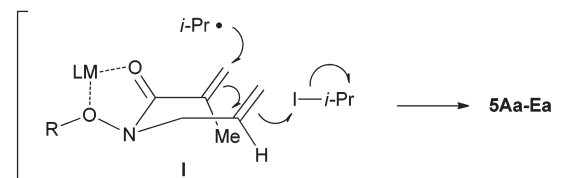
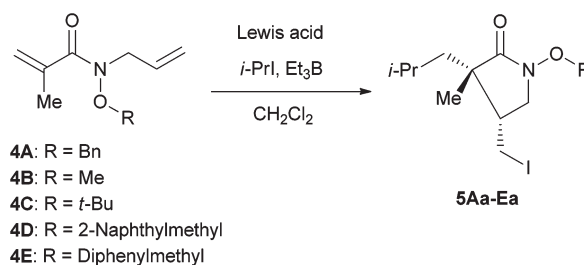
Fig. 3 Diastereoselectivity in the cascade radical reaction of **1**.

isopropyl radical and an intermediate radical **F**. In other words, a key step of the cascade sequence is the iodine atom-transfer process from secondary alkyl iodide to unstable primary intermediate radical **F** giving the stable secondary isopropyl radical.<sup>11</sup>

The *trans/cis* diastereoselectivity can be assumed to be controlled by two factors: the steric factor around the two olefin moieties (factor 1) and the effect of orbital symmetry (factor 2) reported by Beckwith and Houk.<sup>12</sup> With regard to factor 1, the steric repulsion between the two olefin units promotes the cyclization leading to the *trans* diastereomer *via* the conformers **G-1** or **G-2** (Fig. 3). With regard to factor 2, the better orbital overlap leads to the *cis* diastereomer *via* the chair-like conformers **H-1** or **H-2**, in which the two olefin units adopt a *cis* arrangement. These two disparate interactions would direct the diastereoselectivity.

To probe the utility of the hydroxamate ester functionality, the cascade reaction was next studied by employing the substrates **4A–E** having a methacryloyl moiety (Scheme 3). In this study, we also investigated the effect of the fluxional substituent **R** of the hydroxamate ester moiety on chemical efficiency or regio- and diastereoselectivities.<sup>13</sup>

Representative results are shown in Table 2. In marked contrast to the substrate **1** having an acryloyl moiety, the cyclization of **4A** having the benzyl (**R** = Bn) group did not proceed without the geometry-control by Lewis acid (entry 1). The addition of Zn(OTf)<sub>2</sub> remarkably promoted the reaction at 20 °C to give the 5-*exo* cyclization product **5Aa** in 41% yield accompanied by the recovered starting material **4A** in 42% yield, because the equilibrium population of reactive rotamer would be increased by coordination of Zn(OTf)<sub>2</sub> (entry 2). The chemical yield



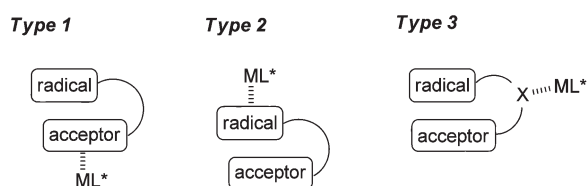
Scheme 3 Reaction of substrates **4A–E**.

Table 2 Reaction of **4A–E** in the absence of chiral ligand<sup>a</sup>

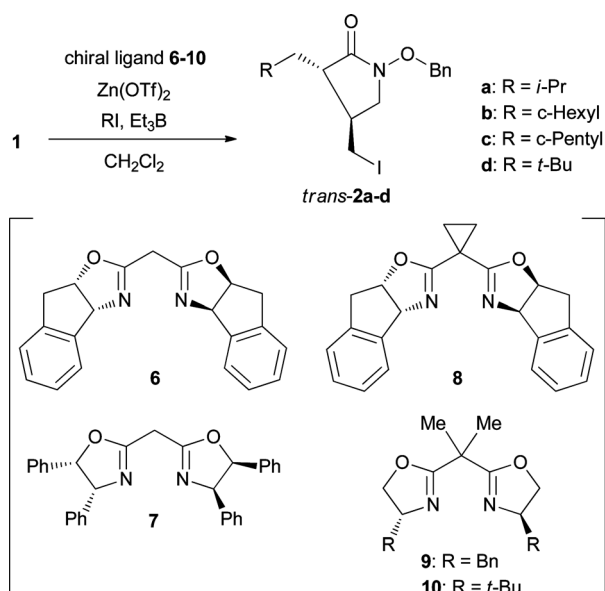
Entry	Substrate	Lewis acid	<i>T</i> (°C)	Yield <sup>b</sup> (%)	<i>trans</i> : <i>cis</i>
1	<b>4A</b>	None	20	NR <sup>c</sup>	—
2	<b>4A</b>	Zn(OTf) <sub>2</sub>	20	41 (42)	>98 : 2
3	<b>4A</b>	Mg(OTf) <sub>2</sub>	20	23 (69)	>98 : 2
4	<b>4A</b>	Zn(OTf) <sub>2</sub>	−78	NR <sup>c</sup>	—
5	<b>4B</b>	Zn(OTf) <sub>2</sub>	20	42 (33)	>98 : 2
6	<b>4C</b>	Zn(OTf) <sub>2</sub>	20	13 (75)	>98 : 2
7	<b>4D</b>	Zn(OTf) <sub>2</sub>	20	41 (20)	>98 : 2
8	<b>4E</b>	Zn(OTf) <sub>2</sub>	20	31 (25)	>98 : 2

<sup>a</sup> Reactions were carried out using **1** (1 equiv), isopropyl iodide (30 equiv) and Et<sub>3</sub>B in hexane (1.0 M, 2.5 equiv) with Lewis acid (1 equiv) for 10 h. <sup>b</sup> Isolated yield; The yield in parentheses is for the recovered starting material **4A–E**. <sup>c</sup> No reaction.

decreased to 23% by changing Zn(OTf)<sub>2</sub> into Mg(OTf)<sub>2</sub>; instead, the recovered starting material **4A** increased to 69% yield (entry 3). In the case of the substrate **1** having the labile acryloyl moiety, the starting material was not recovered, probably due to the side reactions such as competitive radical polymerization. In contrast, stable substrate **4A** was recovered in reasonable yields under similar reaction conditions. Again, the reaction did not proceed at −78 °C even with Lewis acid (entry 4). The steric factor of the fluxional substituent **R** affected the chemical efficiency (entries 5–8). Although the substrate **4B** having the small methyl group and the substrate **4D** having a 2-naphthylmethyl group showed similar reactivities to substrate **4A** (entries 5 and 7), the use of **4C** having a *t*-butyl group and **4E** having a diphenylmethyl group led to a decrease in the chemical yields, probably because of the dissociation of Lewis acid by bulky substituents (entries 6 and 8). In contrast, the substituent **R** did not affect the regio- and diastereoselectivities, giving the products **5Aa–Ea** as a single isomer. Interestingly, high *cis* selectivities were observed in the reaction of all substrates **4A–E** (>98 : 2 dr). Cyclization leading to the *cis* diastereomers *cis*-**5Aa–Ea** occurred *via* the conformer **I** mainly by the effect of orbital symmetry (factor 2). In contrast to substrate **1** having an acryloyl moiety, the steric factor (factor 1) was not a dominant factor for the diastereoselectivity of **5Aa–Ea**, because steric repulsion between a methyl group and olefin unit as well as the repulsion between two olefin units are in existence.



**Fig. 4** Stereocontrol using chiral Lewis acids (ML\*: chiral Lewis acid).



**Scheme 4** Enantioselective reaction of substrate **1**.

Over the last fifteen years, enantioselective radical reactions, particularly intermolecular radical reactions have made great advances.<sup>1,14–16</sup> However, enantiocontrol in radical cyclizations still remains a major challenge,<sup>2,17–22</sup> although significant progress has been made recently by chiral complexing reagent,<sup>17</sup> organocatalyst,<sup>18</sup> and chiral titanocene.<sup>19</sup> Stereocontrol using chiral Lewis acids is a general method. The reported studies on chiral Lewis acids-mediated radical cyclizations can be classified into two types by the nature of the coordination with a Lewis acid (Types 1 and 2 in Fig. 4). In Type 1 cyclization, the radical acceptor works as a coordination site with a chiral Lewis acid,<sup>20</sup> whereas, the radical center works as a coordination site in Type 2 cyclization.<sup>21</sup> Therefore, we have been interested in exploring an alternative approach to control the stereochemistry using a coordination tether (X) as new Type 3 cyclization.

The stereocontrol in the radical addition–cyclization–trapping reaction of substrate **1** was studied (Scheme 4). The results of an experiment to explore the proper combination of chiral ligand, Lewis acid and hydroxamate ester are shown in Table 3. At first, the effect of chiral ligand **6** was evaluated by using isopropyl iodide as a radical precursor in the presence of Zn(OTf)<sub>2</sub> (entries 1–3). A stoichiometric amount of chiral Lewis acid promoted the reaction at –20 °C to form the products *trans*-**2a** and *cis*-**2a** in 41% combined yield and 82 : 18 ratio (entry 1). Two isomers *trans*-**2a** and *cis*-**2a** were isolated with 69% ee and 32% ee,

**Table 3** Reaction of **1** in the presence of chiral ligand<sup>a</sup>

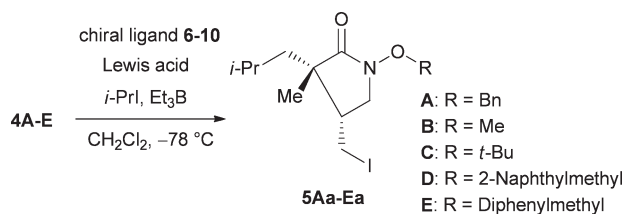
Entry	Ligand	RI	<i>T</i> (°C)	Yield <sup>b</sup> (%)	<i>dr</i> <sup>c</sup>	ee (%)	
						<i>trans</i> - <b>2</b>	<i>cis</i> - <b>2</b>
1	<b>6</b>	<i>i</i> -PrI	–20	41	82 : 18	69	32
2	<b>6</b>	<i>i</i> -PrI	–60	38	90 : 10	86	42
3	<b>6</b>	<i>i</i> -PrI	–78	38	91 : 9	89	–61
4	<b>7</b>	<i>i</i> -PrI	20	68	73 : 23	–45	
5	<b>7</b>	<i>i</i> -PrI	–20	40	82 : 18	–58	
6	<b>7</b>	<i>i</i> -PrI	–60	30	89 : 11	–65	–47
7	<b>7</b>	<i>i</i> -PrI	–78	24	91 : 9	–70	–52
8	<b>8</b>	<i>i</i> -PrI	–78	52	92 : 8	92	71
9	<b>8</b>	<i>c</i> -HexylI	–78	57	94 : 6	92	
10	<b>8</b>	<i>c</i> -PentylI	–78	35	94 : 6	91	
11	<b>8</b>	<i>t</i> -BuI	–78	19	89 : 11	83	
12 <sup>d</sup>	<b>8</b>	<i>i</i> -PrI	–78	18	92 : 8	92	
13	<b>9</b>	<i>i</i> -PrI	–78	31	90 : 10	51	21

<sup>a</sup> Reactions were carried out using **1** (1 equiv), RI (30 equiv) and Et<sub>3</sub>B in hexane (1.0 M, 2.5 equiv) with Zn(OTf)<sub>2</sub> (1 equiv) and ligand **6–9** (1 equiv). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis. <sup>d</sup> Zn(OTf)<sub>2</sub> (0.5 equiv) and ligand **8** (0.5 equiv) were used.

respectively. The enantiomeric purities of the products were checked by chiral high performance liquid chromatography analysis.

Lower temperature led not only to an enhancement in enantioselectivity but also an improvement in *trans/cis* diastereoselectivity (entries 2 and 3). The isomer *trans*-**2a** was formed even at –78 °C with 89% ee and good diastereoselectivity. As mentioned above, the non-catalyzed background reaction giving racemic products was suppressed at –78 °C (see: entry 7 in Table 1). These results suggest that the chelation with chiral Lewis acid led to reduced conformation flexibility and the expected chiral Lewis acid-coordinating rotamer was present to a significant extent to enhance the cyclization rates. The moderate chemical yields of products were attributed to competitive polymerization of **1** having the labile acrylamide moiety. Similar trends were observed in the reactions using ligand **7**, surprisingly resulting in antipode adducts *ent*-**2a** (entries 4–7). The best result was obtained when ligand **8** was employed at –78 °C (entry 8). The product *trans*-**2a** was obtained with 92% ee along with *cis*-**2a** with 71% ee. The improved *trans*-selectivity suggests that the steric factor can be assumed to be more significant than the orbital symmetry under the enantioselective reaction conditions. Under analogous reaction conditions, outstanding levels of enantio- and diastereoselectivities were obtained by employing cyclohexyl iodide or cyclopentyl iodide as a radical precursor (entries 9 and 10). The products *trans*-**2b** and *trans*-**2c** were obtained with 92% ee and 91% ee, respectively. In contrast, the bulky *tert*-butyl radical showed lower reactivity leading to the cyclic product *trans*-**2d** in 19% yield with 83% ee and 89 : 11 ratio (entry 11). Because the non-catalyzed background reaction was suppressed at –78 °C, decreasing the amount of chiral Lewis acid to 0.5 equivalents did not affect both enantio- and diastereoselectivities, although chemical yield diminished to 18% (entry 12). The use of ligand **9** attenuated enantioselectivity (entry 13). Additionally, the combination of ligand **10** and Zn(OTf)<sub>2</sub> or Mg(OTf)<sub>2</sub> was also less effective for the present cascade reaction.<sup>23</sup>

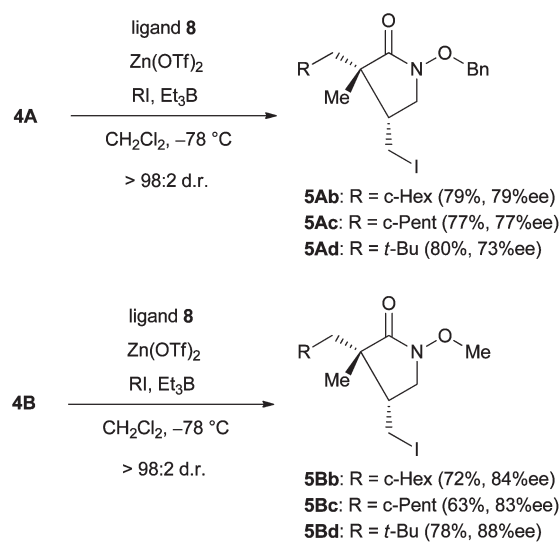
Having identified a promising chiral Lewis acid for this reaction, the cascade reaction of the substrates **4A–E** having a methacryloyl moiety and the fluxional substituent R was next studied (Scheme 5). The addition of chiral Lewis acid, prepared from ligand **6** and Zn(OTf)<sub>2</sub>, promoted the reaction of **4A** with isopropyl iodide even at  $-78\text{ }^{\circ}\text{C}$  to give the product **5Aa** in 76% yield with 71% ee and high *cis* diastereoselectivity (Table 4, entry 1), although the combination of ligand **6** and Cu(OTf)<sub>2</sub> did not promote the reaction (entry 2). The ligand **7** also worked well (entry 3). Again, the higher enantioselectivity was obtained by employing ligand **8** to form the product **5Aa** in 81% yield with 76% ee (entry 4). In general, the use of ligand led to an improvement in chemical yield (see: entry 2 in Table 2). With regard to the solvent effect, the replacement of CH<sub>2</sub>Cl<sub>2</sub> with toluene was not suitable for the present reaction (entry 5), although somewhat better enantioselectivity was obtained when the reaction was carried out in toluene–CH<sub>2</sub>Cl<sub>2</sub> (4 : 1, v/v) (entry 6). Surprisingly, decreasing the amount of chiral Lewis acid to 0.2 equivalents resulted in a low enantioselectivity and good chemical yield, owing to the unexpected background reaction at  $-78\text{ }^{\circ}\text{C}$  giving racemic products (entry 7). In contrast, the reactions using ligands **9** or **10** and Mg(OTf)<sub>2</sub> gave the nearly racemic product with low chemical efficiencies (entries 8 and 9).<sup>23</sup> Next, we were interested in probing the effect of the fluxional substituent R of the hydroxamate ester moiety on enantioselectivity and chemical yield (entries 10–13). High enantioselectivity and good yield were obtained in the reaction of **4B** having the small methyl group (entry 10). Increasing the size of R affected the



**Scheme 5** Enantioselective reaction of substrates **4A–E**.

enantioselectivities. The introduction of bulky groups such as **4C** and **4D** led to slightly lower enantioselectivities (entries 11 and 12). More interestingly, the use of substrate **4E** having a diphenylmethyl group gave the nearly racemic product **5Ea** in 52% yield, probably due to dissociation between chiral Lewis acid and the bulky diphenylmethyl group (entry 13). These observations clearly indicate that rigid conformation of the ternary complex of substrate, Zn(OTf)<sub>2</sub> and ligand was required for both high stereocontrol and good chemical efficiency. In the presence of chiral Lewis acid prepared from ligand **6** and Zn(OTf)<sub>2</sub>, the reaction of **4B** having the small methyl group also took place with good chemical efficiency to give the product **5Ba** with 73% ee (entry 14).

On the basis of the above results, we next studied the reaction of substrates **4A** having a benzyl group and **4B** having a methyl group with other radical precursors (Scheme 6). Under similar reaction conditions, substrates **4A** and **4B** reacted well with

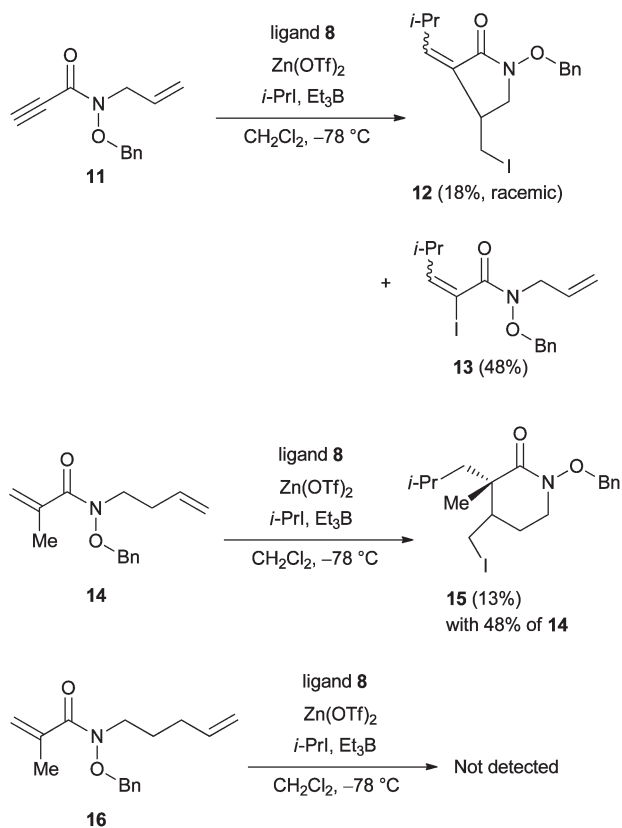


**Scheme 6** Enantioselective reaction of **4A** and **4B**.

**Table 4** Reaction of **4A–E** in the presence of chiral ligand<sup>a</sup>

Entry	Substrate	Ligand	Lewis acid	Solvent	% Yield <sup>b</sup> (dr)	ee <sup>c</sup> (%)
1	<b>4A</b>	<b>6</b>	Zn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	76 (>98 : 2)	71
2 <sup>d</sup>	<b>4A</b>	<b>6</b>	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	NR <sup>e</sup>	
3	<b>4A</b>	<b>7</b>	Zn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	81 (>98 : 2)	–69
4	<b>4A</b>	<b>8</b>	Zn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	81 (>98 : 2)	76
5	<b>4A</b>	<b>8</b>	Zn(OTf) <sub>2</sub>	toluene	NR <sup>e</sup>	
6 <sup>f</sup>	<b>4A</b>	<b>8</b>	Zn(OTf) <sub>2</sub>	toluene–CH <sub>2</sub> Cl <sub>2</sub>	71 (>98 : 2)	77
7 <sup>g</sup>	<b>4A</b>	<b>8</b>	Zn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	73 (>98 : 2)	30
8 <sup>h</sup>	<b>4A</b>	<b>9</b>	Mg(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	16 (>98 : 2)	racemic
9 <sup>i</sup>	<b>4A</b>	<b>10</b>	Mg(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	18 (>98 : 2)	racemic
10	<b>4B</b>	<b>8</b>	Zn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	75 (>98 : 2)	82
11	<b>4C</b>	<b>8</b>	Zn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	71 (>98 : 2)	75
12	<b>4D</b>	<b>8</b>	Zn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	75 (>98 : 2)	73
13	<b>4E</b>	<b>8</b>	Zn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	52 (>98 : 2)	racemic
14	<b>4B</b>	<b>6</b>	Zn(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	77 (>98 : 2)	73

<sup>a</sup> Reactions were carried out using **4A–E** (1 equiv), isopropyl iodide (30 equiv) and Et<sub>3</sub>B in hexane (1.0 M, 2.5 equiv) with Zn(OTf)<sub>2</sub> (1 equiv) and ligand **6–10** (1 equiv). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis. <sup>d</sup> Starting material **4A** was recovered in 99%. <sup>e</sup> No reaction. <sup>f</sup> In toluene–CH<sub>2</sub>Cl<sub>2</sub> (4 : 1, v/v). <sup>g</sup> Zn(OTf)<sub>2</sub> (0.2 equiv) and ligand **8** (0.2 equiv) were used. <sup>h</sup> Starting material **4A** was recovered in 79%. <sup>i</sup> Starting material **4A** was recovered in 81%.

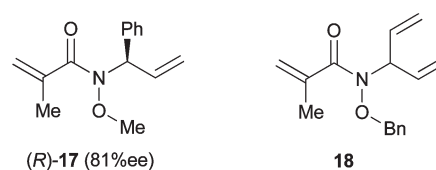
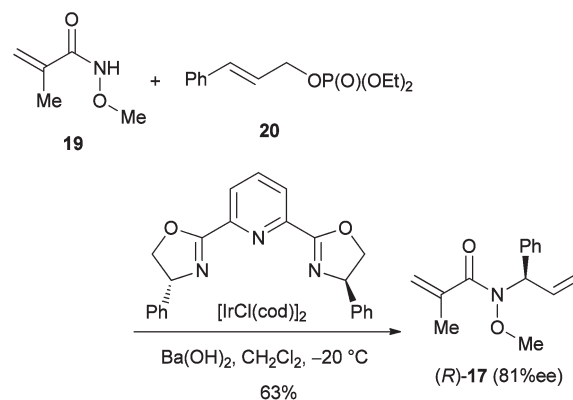


Scheme 7 Reaction of substrates 11, 14 and 16.

cyclohexyl, cyclopentyl, and *tert*-butyl radicals. In general, substrate **4B** having a small substituent gave better enantioselectivities. Particularly, the difference between **4A** and **4B** was clearly observed in the reactions with bulky *tert*-butyl radical. The reaction of **4B** with *tert*-butyl radical gave the desired product **5Bd** with 88% ee, while **5Ad** was obtained only with 73% ee from **4A**.

To understand the limitations of the present cascade reaction, the next substrates of choice were substrates **11**, **14** and **16** (Scheme 7). The introduction of a carbon–carbon triple bond into an electron-deficient acceptor apparently inhibited the cyclization step. The reaction of substrate **11** with an isopropyl radical predominantly gave the simple adduct **13** due to the fast iodine atom-transfer from isopropyl iodide to reactive intermediate vinyl radical, which would direct the reaction course. Thus, the cyclic compound **12** was formed only in 18% yield as a nearly racemic product. Under analogous reaction conditions, the 6-*exo* cyclization product **15** could be obtained from substrate **14** in 13% yield, accompanied by 48% yield of the recovered starting material **14**. However, the formation of 7-*exo* cyclization product from substrate **16** was not observed.

The introduction of additional substituents on the electron-rich acceptor of the substrates leads to the synthesis of highly functionalized compounds with three stereocenters (Fig. 5). At first, we studied the reaction of the chiral substrate (*R*)-**17** (81% ee) having a phenyl group at an allyl position to determine the absolute configuration of the cyclic products derived from the present cascade radical reaction. Next, the desymmetrization reaction of

Fig. 5 Substrates (*R*)-17 and 18.Scheme 8 Preparation of substrate (*R*)-17.

substrate **18** having a symmetric substituent was investigated for the synthesis of  $\gamma$ -lactams having three chiral centers.

The chiral substrate (*R*)-**17** was prepared by a regio- and enantioselective allylic substitution based on our recent studies (Scheme 8).<sup>24</sup> The iridium complex, derived from [IrCl(cod)]<sub>2</sub> and chiral pybox ligand, was employed as a catalyst under basic reaction conditions. In the presence of Ba(OH)<sub>2</sub> as base, the iridium-catalyzed reaction of nucleophile **19** with phosphate **20** proceeded smoothly to give (*R*)-**17** with 81% ee, which was determined by chiral HPLC analysis. The absolute configuration of **17** was confirmed to be *R* configuration from our previously reported studies.<sup>24</sup>

Initially, the reaction of chiral substrate (*R*)-**17** (81% ee) with an isopropyl radical was tested in the presence of ligand **8** (Scheme 9). The cascade reaction proceeded smoothly at -40 °C by using 2.5 equivalents of Et<sub>3</sub>B, although the reaction was fairly slow at -78 °C. As the major product, *cis*-**21** was obtained in 63% yield with 99% ee. At the same time, a small amount of *trans*-**22** was formed with low ee. The relative configuration of the substituents on *cis*-**21** and *trans*-**22** was determined by NOE interaction experiments.<sup>25</sup> A similar trend was also observed in the reaction of (*R*)-**17** (81% ee) with *tert*-butyl iodide. The reaction with a bulky *tert*-butyl radical proceeded well to give a 59% yield of *cis*-**23** with 99% ee, accompanied by a 10% yield of nearly racemic *trans*-**24**. A remarkable feature of this reaction is the construction of three bonds and three chiral centers *via* a cascade process.

The enhanced enantioselectivity of *cis*-diastereomers *cis*-**21** and *cis*-**23** can be explained by kinetic resolution (Fig. 6). Apparently, the major cyclization leading to *cis*-diastereomers proceeded *via* a more stable conformer **J** minimizing A<sup>1,3</sup>-strain effect, in which two olefin units adopt a *cis* arrangement and the Ph group is in the equatorial direction. In other words, the chirality-enriched products *cis*-**21** and *cis*-**23** (99% ee) were

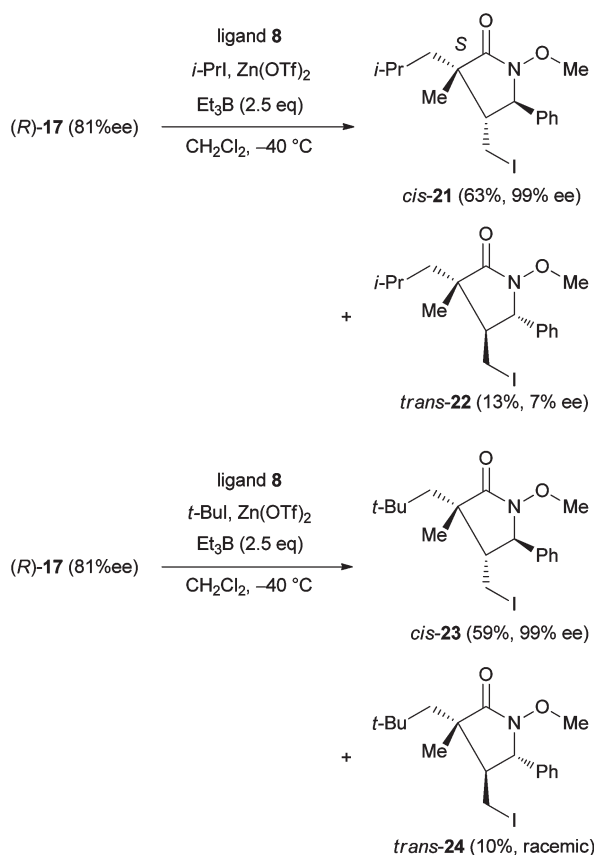
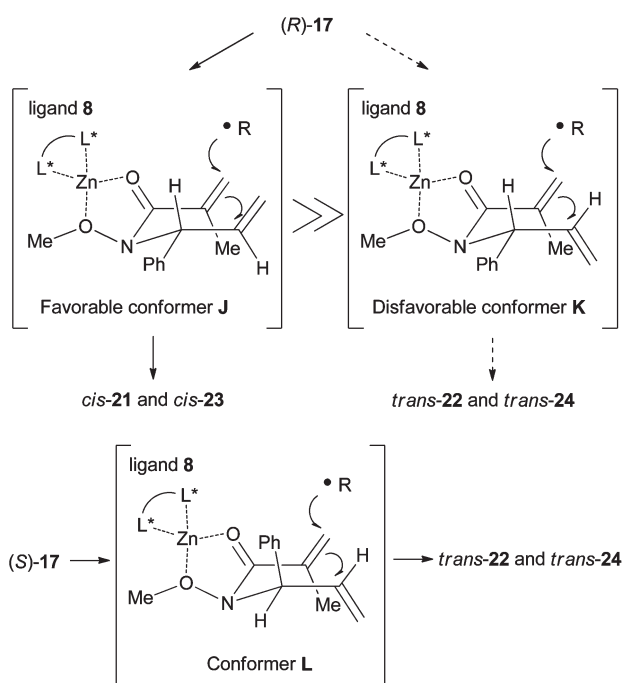
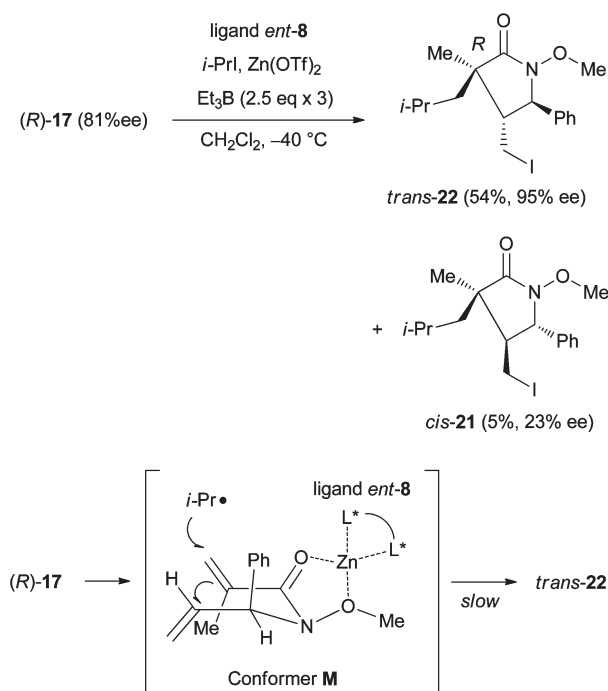
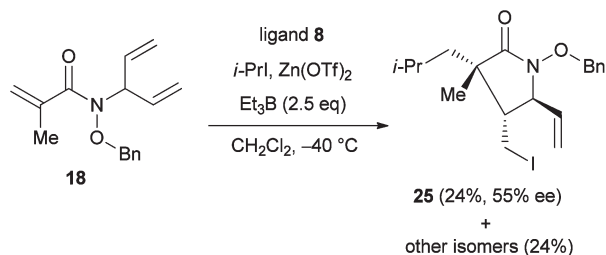
Scheme 9 Reaction of chiral substrate (*R*)-**17**.

Fig. 6 Kinetic resolution.

predominantly obtained from (*R*)-**17** via the favorable conformer **J** over the disfavorable conformer **K** giving *trans*-**22** and *trans*-**24**. The cyclization of (*S*)-**17** predominantly gave *trans*-

Scheme 10 Reaction using ligand *ent*-**8**.Scheme 11 Reaction of substrate **18**.

diastereomers via the conformer **L** carrying an axial Ph group, in which two olefin units adopt a *trans* arrangement due to minimizing A<sup>1,3</sup>-strain effect.

We next employed the enantiomer of ligand *ent*-**8** for the reaction of (*R*)-**17** (81% ee) with an isopropyl radical (Scheme 10). The reaction using ligand *ent*-**8** required the large amount of Et<sub>3</sub>B (2.5 eq × 3). The major product *trans*-**22** was obtained with 95% ee as a result of kinetic resolution, accompanied by a 5% yield of *cis*-**21** with 23% ee. The chirality-enriched *trans*-**22** was formed via conformer **M** carrying an axial Ph group to avoid steric interaction with the allylic substituent.

The absolute configuration of products was deduced from the NOESY experimental of *cis*-**21** and *trans*-**22** having three chiral centers on the basis of (*R*)-Ph group (see: *S* configuration of *cis*-**21** in Scheme 9 and *R* configuration of *trans*-**22** in Scheme 10).<sup>25</sup> Therefore, the absolute configuration at the quaternary carbon derived from substrates **4A–E** and ligand **8** was also assumed to be *S* configuration.

Finally, we investigated the cascade reaction of substrate **18** involving a desymmetrization process (Scheme 11). The reaction of **18** with isopropyl iodide was run at -40 °C by using 2.5

equivalents of Et<sub>3</sub>B. As expected, the desired cyclic product **25** was obtained in 24% yield, accompanied by other isomers. Although this desymmetrization was moderately selective (55% ee), a  $\gamma$ -lactam having three chiral centers was able to be synthesized by the new approach using hydroxamate ester moiety as a chiral Lewis acid-coordinating tether.

## Conclusions

We have shown that the cascade radical reaction involving a cyclization process generally proceeds with moderate efficiency, but in certain cases they proceed with good chemical efficiency based on a new strategy using hydroxamate ester as a coordination site with Lewis acid. The present new approach offers opportunities for further exploration with intriguing possibilities in enantioselective radical cyclization.

## Experimental

### General

Melting points were taken on a YANAGIMOTO micromelting point apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 500 MHz and at 125 MHz, respectively. IR spectra were recorded on a JASCO FT/IR-410 Fourier-transfer infrared spectrometer. Low and high resolution mass spectra were obtained by EI, CI or FAB method. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck 60F<sub>254</sub>). Optical rotations were recorded on a JASCO DIP-360 polarimeter. As the O<sub>2</sub> source for reacting with Et<sub>3</sub>B, undegassed CH<sub>2</sub>Cl<sub>2</sub> was used which was contaminated with a trace of O<sub>2</sub>. The experimental procedure and the characterization data for substrates **1**, **4A–E**, **11**, **14**, **16**, **18**, and corresponding synthetic intermediates are provided in the ESI.†

**Preparation of (R)-17.** A mixture of amide **19** (576 mg, 5.0 mmol) and Ba(OH)<sub>2</sub>·H<sub>2</sub>O (947 mg, 5.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was stirred under argon atmosphere at 20 °C for 10 min. To the reaction mixture was added a solution of phosphate **20** (2.02 g, 7.5 mmol), pybox ligand (296 mg, 0.80 mmol) and [IrCl(cod)]<sub>2</sub> (269 mg, 0.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at –20 °C. After being stirred at the same temperature for 20 h, the reaction mixture was diluted with saturated NH<sub>4</sub>Cl and then extracted with AcOEt. The organic phase was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt–hexane = 1:10–1:5) afforded the product (*R*)-**17** (728 mg, 63%).

**N-Methoxy-2-methyl-N-[(1*R*)-1-phenyl-2-propen-1-yl]-2-propenamide ((*R*)-17).** A colorless oil. IR (CHCl<sub>3</sub>) 1652 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.43–7.28 (5H, m), 6.24 (1H, m), 5.96 (1H, br d, *J* = 6.7 Hz), 5.38 (1H, br d, *J* = 10.4 Hz), 5.35 (1H, s), 5.35–5.28 (2H, m), 3.44 (3H, s), 1.99 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  172.0, 140.6, 138.0, 134.3, 128.5, 128.3, 127.9, 118.5, 117.3, 64.2, 19.7. One carbon peak was missing due to overlapping. MS (EI<sup>+</sup>) *m/z* 231 (M<sup>+</sup>, 2), 117 (100). HRMS (EI<sup>+</sup>) calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub> (M<sup>+</sup>) 231.1259, found 231.1264. HPLC (Chiralcel AD-H, hexane–2-propanol = 95:5, 0.5 mL min<sup>-1</sup>,

254 nm) *t*<sub>r</sub> (major) = 12.8 min, *t*<sub>r</sub> (minor) = 15.1 min. A sample of 81% ee by HPLC analysis gave  $[\alpha]_D^{25} + 51.0$  (*c* 1.1, CHCl<sub>3</sub>).

**General experimental procedure for radical reaction in the absence of ligand.** A solution of substrate **1** or **4A–E** (0.5 mmol) and Zn(OTf)<sub>2</sub> or Mg(OTf)<sub>2</sub> (0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was stirred for 10 min under a nitrogen atmosphere at 20 °C. To the reaction mixture were added isopropyl iodide (1.5 mL, 15 mmol) and Et<sub>3</sub>B (1.0 M in hexane, 1.25 mL, 1.25 mmol) at 20, 0, or –78 °C. After being stirred at the same temperature for 4–20 h, the reaction mixture was diluted with saturated NaHCO<sub>3</sub> and then extracted with AcOEt. The organic phase was dried over MgSO<sub>4</sub> and concentrated at reduced pressure. Purification of the residue by column chromatography (hexane–AcOEt = 4:1) afforded product *trans*-**2a**, *cis*-**2a**, **3**, **5Aa**, **5Ba**, **5Ca**, **5Da** or **5Ea**.

**General experimental procedure for enantioselective radical reaction.** A solution of substrate **1**, **4A–E**, **11**, **14**, **16**, (*R*)-**17**, or **18** (0.5 mmol), Lewis acid (0.5 mmol) and ligand **6–10** (0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was stirred for 30 min under a nitrogen atmosphere at 20 °C. To the reaction mixture were added RI (15 mmol) and Et<sub>3</sub>B (1.0 M in hexane, 1.25 mL, 1.25 mmol) at –40 or –78 °C. After being stirred at the same temperature for 3–10 h, the reaction mixture was diluted with saturated NaHCO<sub>3</sub> and then extracted with AcOEt. The organic phase was dried over MgSO<sub>4</sub> and concentrated at reduced pressure. Purification of the residue by column chromatography (hexane–AcOEt = 4:1) afforded product **2a–d**, **5Aa–5Bd**, **12**, **13**, **15**, *cis*-**21**, *trans*-**22**, *cis*-**23**, *trans*-**24**, or **25**. In the case of the reaction using ligand *ent*-**8**, the reaction of (*R*)-**17** was carried out with Et<sub>3</sub>B (1.0 M in hexane, 1.25 mL  $\times$  3, 3.75 mmol).

**(3*S*,4*S*)-4-(Iodomethyl)-3-(2-methylpropyl)-1-(phenylmethoxy)-2-pyrrolidinone (*trans*-2a).** A colorless oil. IR (CHCl<sub>3</sub>) 1707 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.47–7.35 (5H, m), 5.01 (1H, d, *J* = 10.9 Hz), 4.98 (1H, d, *J* = 10.9 Hz), 3.37 (1H, dd, *J* = 8.8, 7.6 Hz), 3.22 (1H, dd, *J* = 10.1, 4.6 Hz), 3.06–2.97 (2H, m), 2.14 (1H, m), 2.09 (1H, m), 1.80 (1H, m), 1.66 (1H, m), 1.29 (1H, m), 0.94 (3H, d, *J* = 6.7 Hz), 0.93 (3H, d, *J* = 6.7 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  172.3, 135.2, 129.6, 129.0, 128.6, 76.8, 52.4, 44.3, 40.0, 38.4, 25.4, 22.9, 22.1, 9.0. MS (CI<sup>+</sup>) *m/z* 388 (M + H<sup>+</sup>, 12), 91 (100). HRMS (CI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>23</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 388.0774, found 388.0776. HPLC (Chiralcel AD-H, hexane–2-propanol = 95:5, 0.5 mL min<sup>-1</sup>, 254 nm) *t*<sub>r</sub> (minor) = 49.9 min, *t*<sub>r</sub> (major) = 73.4 min. A sample of 92% ee by HPLC analysis gave  $[\alpha]_D^{25} + 31.7$  (*c* 0.5, CHCl<sub>3</sub>).

**(3*S*,4*R*)-4-(Iodomethyl)-3-(2-methylpropyl)-1-(phenylmethoxy)-2-pyrrolidinone (*cis*-2a).** A colorless oil. IR (CHCl<sub>3</sub>) 1711 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.46–7.35 (5H, m), 5.00 (2H, s), 3.38 (1H, dd, *J* = 9.2, 6.7 Hz), 3.15 (2H, m), 2.77 (1H, dd, *J* = 10.9, 9.9 Hz), 2.61 (1H, m), 2.47 (1H, m), 1.76 (1H, m), 1.52 (1H, m), 1.24 (1H, m), 0.95 (3H, d, *J* = 6.8 Hz), 0.91 (3H, d, *J* = 6.8 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  171.7, 135.2, 129.6, 129.1, 128.7, 76.9, 52.2, 41.8, 37.4, 33.5, 25.3, 22.6, 22.1, 4.7. MS (CI<sup>+</sup>) *m/z* 388 (M + H<sup>+</sup>, 6), 91 (100). HRMS (CI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>23</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 388.0774, found 388.0779. HPLC (Chiralcel AD-H,



hexane–2-propanol = 95 : 5, 0.5 mL min<sup>-1</sup>, 254 nm) *t<sub>r</sub>* (minor) = 30.5 min, *t<sub>r</sub>* (major) = 53.8 min.

**(3*S*,4*S*)-3-(Cyclohexylmethyl)-4-(iodomethyl)-1-(phenylmethoxy)-2-pyrrolidinone (trans-2b).** A colorless oil. IR (CHCl<sub>3</sub>) 1706 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.48–7.33 (5H, m), 5.01 (1H, d, *J* = 10.9 Hz), 4.98 (1H, d, *J* = 10.9 Hz), 3.36 (1H, t, *J* = 8.9 Hz), 3.21 (1H, dd, *J* = 10.1, 4.9 Hz), 3.06–2.96 (2H, m), 2.18 (1H, m), 2.10 (1H, m), 1.60–1.10 (11H, m), 0.95–0.85 (2H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 172.5, 135.2, 129.6, 129.0, 128.6, 76.9, 52.4, 43.6, 38.4, 38.3, 34.8, 33.6, 32.8, 26.4, 26.1, 26.0, 9.1. MS (CI<sup>+</sup>) *m/z* 428 (M + H<sup>+</sup>, 34), 302 (100). HRMS (CI<sup>+</sup>) calcd for C<sub>19</sub>H<sub>27</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 428.1086, found 428.1094. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL min<sup>-1</sup>, 254 nm) *t<sub>r</sub>* (minor) = 55.6 min, *t<sub>r</sub>* (major) = 98.4 min. A sample of 92% ee by HPLC analysis gave [α]<sub>D</sub><sup>29</sup> + 13.3 (*c* 0.2, CHCl<sub>3</sub>).

**(3*S*,4*S*)-3-(Cyclopentylmethyl)-4-(iodomethyl)-1-(phenylmethoxy)-2-pyrrolidinone (trans-2c).** A colorless oil. IR (CHCl<sub>3</sub>) 1706 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.39–7.27 (5H, m), 4.93 (1H, d, *J* = 11.0 Hz), 4.90 (1H, d, *J* = 11.0 Hz), 3.30 (1H, t, *J* = 8.6 Hz), 3.15 (1H, dd, *J* = 9.8, 4.3 Hz), 2.99–2.89 (2H, m), 2.11–2.01 (2H, m), 1.89 (1H, m), 1.75–1.36 (8H, m), 1.12–0.98 (2H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 172.2, 135.1, 129.5, 129.0, 128.6, 76.7, 52.3, 45.5, 38.0, 37.2, 36.9, 33.0, 32.3, 25.1, 25.0, 9.2. MS (CI<sup>+</sup>) *m/z* 414 (M + H<sup>+</sup>, 23), 288 (100). HRMS (CI<sup>+</sup>) calcd for C<sub>18</sub>H<sub>25</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 414.0930, found 414.0934. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL min<sup>-1</sup>, 254 nm) *t<sub>r</sub>* (minor) = 56.5 min, *t<sub>r</sub>* (major) = 99.1 min. A sample of 91% ee by HPLC analysis gave [α]<sub>D</sub><sup>29</sup> + 19.6 (*c* 1.0, CHCl<sub>3</sub>).

**(3*S*,4*S*)-3-(2,2-Dimethylpropyl)-4-(iodomethyl)-1-(phenylmethoxy)-2-pyrrolidinone (trans-2d).** A colorless oil. IR (CHCl<sub>3</sub>) 1709 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.46–7.33 (5H, m), 5.01 (1H, d, *J* = 10.7 Hz), 4.98 (1H, d, *J* = 10.7 Hz), 3.38 (1H, t, *J* = 8.0 Hz), 3.29 (1H, dd, *J* = 10.0, 3.9 Hz), 3.08–2.97 (2H, m), 2.10 (1H, br m), 2.02 (1H, br m), 1.83 (1H, dd, *J* = 14.3, 4.3 Hz), 1.18 (1H, dd, *J* = 14.3, 5.8 Hz), 0.96 (9H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 172.8, 135.1, 129.5, 129.0, 128.6, 76.7, 52.1, 44.5, 43.2, 40.2, 30.9, 29.6, 8.4. MS (CI<sup>+</sup>) *m/z* 402 (M + H<sup>+</sup>, 52), 276 (100). HRMS (CI<sup>+</sup>) calcd for C<sub>17</sub>H<sub>25</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 402.0930, found 402.0928. HPLC (Chiralcel OD-H, hexane–2-propanol = 95 : 5, 0.5 mL min<sup>-1</sup>, 254 nm) *t<sub>r</sub>* (minor) = 31.8 min, *t<sub>r</sub>* (major) = 36.3 min. A sample of 83% ee by HPLC analysis gave [α]<sub>D</sub><sup>29</sup> + 26.3 (*c* 1.0, CHCl<sub>3</sub>).

**4-Methyl-*N*-phenylmethoxy-*N*-(2-propen-1-yl)-2-pentanamide (3).** A colorless oil. IR (CHCl<sub>3</sub>) 1654 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.42–7.34 (5H, m), 5.87 (1H, m), 5.25 (1H, dd, *J* = 17.1, 1.5 Hz), 5.21 (1H, dd, *J* = 10.1, 1.5 Hz), 4.84 (2H, s), 4.25 (2H, br d, *J* = 5.2 Hz), 2.39 (2H, t, *J* = 7.9 Hz), 1.60–1.48 (3H, m), 0.88 (6H, d, *J* = 6.4 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 175.6, 134.6, 132.5, 129.2, 128.9, 128.7, 118.2, 76.9, 49.1, 33.3, 30.4, 27.8, 22.2. MS (EI<sup>+</sup>) *m/z* 261 (M<sup>+</sup>, 12), 130 (100). HRMS (CI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>23</sub>NO<sub>2</sub> (M<sup>+</sup>) 261.1729, found 261.1736.

**(3*S*,4*R*)-4-(Iodomethyl)-3-methyl-3-(2-methylpropyl)-1-(phenylmethoxy)-2-pyrrolidinone (5Aa).** A colorless oil. IR (CHCl<sub>3</sub>) 1700 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.46–7.33 (5H, m), 4.99 (2H, s), 3.41 (1H, dd, *J* = 8.8, 7.6 Hz), 3.24 (1H, dd, *J* = 9.8, 4.3 Hz), 3.05 (1H, br t, *J* = 8.8 Hz), 2.95 (1H, dd, *J* = 11.9, 9.8 Hz), 2.32

(1H, m), 1.82 (1H, m), 1.38 (1H, dd, *J* = 14.3, 4.3 Hz), 1.20 (3H, s), 1.67 (1H, dd, *J* = 14.3, 7.0 Hz), 0.93 (3H, d, *J* = 6.7 Hz), 0.90 (3H, d, *J* = 6.7 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.8, 135.2, 129.5, 129.0, 128.6, 76.8, 51.6, 46.9, 45.8, 41.0, 25.1, 24.2, 24.0, 22.6, 2.6. MS (FAB<sup>+</sup>) *m/z* 402 (M + H<sup>+</sup>, 36), 91 (100). HRMS (FAB<sup>+</sup>) calcd for C<sub>17</sub>H<sub>25</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 402.0930, found 402.0921. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 1.0 mL min<sup>-1</sup>, 254 nm) *t<sub>r</sub>* (major) = 9.9 min, *t<sub>r</sub>* (minor) = 13.6 min. A sample of 76% ee by HPLC analysis gave [α]<sub>D</sub><sup>25</sup> + 36.9 (*c* 0.7, CHCl<sub>3</sub>).

**(3*S*,4*R*)-4-(Iodomethyl)-1-methoxy-3-methyl-3-(2-methylpropyl)-2-pyrrolidinone (5Ba).** A colorless oil. IR (CHCl<sub>3</sub>) 1705 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.79 (3H, s), 3.72 (1H, br t, *J* = 8.8 Hz), 3.33 (1H, dd, *J* = 9.7, 4.0 Hz), 3.28 (1H, t, *J* = 8.8 Hz), 3.12 (1H, dd, *J* = 11.6, 9.7 Hz), 2.45 (1H, m), 1.85 (1H, m), 1.42 (1H, dd, *J* = 14.4, 4.3 Hz), 1.23 (1H, dd, *J* = 14.4, 7.6 Hz), 1.22 (3H, s), 0.94 (3H, d, *J* = 6.7 Hz), 0.90 (3H, d, *J* = 6.7 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.3, 61.9, 49.8, 46.6, 45.8, 41.4, 25.1, 24.2, 24.0, 22.8, 2.3. MS (FAB<sup>+</sup>) *m/z* 326 (M + H<sup>+</sup>, 100). HRMS (FAB<sup>+</sup>) calcd for C<sub>11</sub>H<sub>21</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 326.0617, found 326.0623. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 1.0 mL min<sup>-1</sup>, 254 nm) *t<sub>r</sub>* (major) = 7.6 min, *t<sub>r</sub>* (minor) = 8.9 min. A sample of 82% ee by HPLC analysis gave [α]<sub>D</sub><sup>27</sup> + 55.7 (*c* 1.0, CHCl<sub>3</sub>).

**(3*S*,4*R*)-1-(1,1-Dimethylethoxy)-4-(iodomethyl)-3-methyl-3-(2-methylpropyl)-2-pyrrolidinone (5Ca).** A colorless oil. IR (CHCl<sub>3</sub>) 1714 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.66 (1H, dd, *J* = 9.2, 7.6 Hz), 3.38–3.31 (2H, m), 3.13 (1H, dd, *J* = 11.9, 10.1 Hz), 2.46 (1H, m), 1.87 (1H, m), 1.47 (1H, dd, *J* = 14.3, 4.3 Hz), 1.31 (9H, s), 1.23 (3H, s), 1.22 (1H, dd, *J* = 14.3, 7.0 Hz), 0.95 (3H, d, *J* = 6.4 Hz), 0.92 (3H, d, *J* = 6.4 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 177.4, 83.4, 54.7, 47.1, 45.9, 41.0, 27.4, 25.2, 24.2, 24.0, 22.6, 3.0. MS (FAB<sup>+</sup>) *m/z* 368 (M + H<sup>+</sup>, 55), 312 (100). HRMS (FAB<sup>+</sup>) calcd for C<sub>14</sub>H<sub>27</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 368.1086, found 368.1089. HPLC (Chiralcel AD-H, hexane–2-propanol = 98 : 2, 1.0 mL min<sup>-1</sup>, 254 nm) *t<sub>r</sub>* (major) = 6.3 min, *t<sub>r</sub>* (minor) = 7.2 min. A sample of 75% ee by HPLC analysis gave [α]<sub>D</sub><sup>27</sup> + 53.4 (*c* 1.0, CHCl<sub>3</sub>).

**(3*S*,4*R*)-4-(Iodomethyl)-3-methyl-3-(2-methylpropyl)-1-(2-naphthalenylmethoxy)-2-pyrrolidinone (5Da).** A colorless oil. IR (CHCl<sub>3</sub>) 1704 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.90–7.83 (4H, m), 7.60 (1H, d, *J* = 8.2 Hz), 7.54–7.48 (2H, m), 5.16 (2H, s), 3.45 (1H, dd, *J* = 8.8, 7.6 Hz), 3.20 (1H, dd, *J* = 9.8, 4.0 Hz), 3.06 (1H, br t, *J* = 8.8 Hz), 2.91 (1H, dd, *J* = 11.9, 9.8 Hz), 2.30 (1H, m), 1.81 (1H, m), 1.37 (1H, dd, *J* = 14.3, 4.5 Hz), 1.20 (3H, s), 1.15 (1H, dd, *J* = 14.3, 7.0 Hz), 0.92 (3H, d, *J* = 6.7 Hz), 0.88 (3H, d, *J* = 6.7 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.8, 133.5, 133.1, 132.6, 128.8, 128.5, 128.1, 127.8, 126.7, 126.6, 126.4, 76.9, 51.5, 46.9, 45.8, 40.9, 25.1, 24.2, 24.0, 22.5, 2.5. MS (FAB<sup>+</sup>) *m/z* 452 (M + H<sup>+</sup>, 11), 141 (100). HRMS (FAB<sup>+</sup>) calcd for C<sub>21</sub>H<sub>27</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 452.1087, found 452.1096. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 1.0 mL min<sup>-1</sup>, 254 nm) *t<sub>r</sub>* (major) = 14.8 min, *t<sub>r</sub>* (minor) = 23.4 min. A sample of 73% ee by HPLC analysis gave [α]<sub>D</sub><sup>25</sup> + 40.9 (*c* 1.2, CHCl<sub>3</sub>).

**(3*S*,4*R*)-1-(Diphenylmethoxy)-4-(iodomethyl)-3-methyl-3-(2-methylpropyl)-2-pyrrolidinone (5Ea).** A colorless oil. IR

(CHCl<sub>3</sub>) 1704 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.50–7.30 (10H, m), 6.24 (1H, s), 3.34 (1H, br t, *J* = 8.3 Hz), 3.59 (1H, dd, *J* = 9.7, 4.0 Hz), 2.93 (1H, br t, *J* = 8.3 Hz), 2.78 (1H, dd, *J* = 11.6, 9.7 Hz), 2.23 (1H, m), 1.78 (1H, m), 1.31 (1H, dd, *J* = 14.4, 4.6 Hz), 1.16 (3H, s), 1.09 (1H, dd, *J* = 14.4, 7.0 Hz), 0.92 (3H, d, *J* = 6.4 Hz), 0.88 (3H, d, *J* = 6.7 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.8, 139.1, 139.0, 128.5 (2C), 128.4, 128.1, 87.3, 52.1, 47.1, 45.8, 40.6, 25.2, 24.2, 24.0, 22.2, 2.9. Two peaks of <sup>13</sup>C NMR were missing due to overlap. MS (FAB<sup>+</sup>) *m/z* 478 (M + H<sup>+</sup>, 1.1), 167 (100). HRMS (FAB<sup>+</sup>) calcd for C<sub>23</sub>H<sub>29</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 478.1243, found 478.1241. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 1.0 mL min<sup>-1</sup>, 254 nm) *t*<sub>r</sub> (racemic) = 10.5 and 12.4 min.

**(3*S*,4*R*)-3-(Cyclohexylmethyl)-4-(iodomethyl)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (5Ab).** A colorless oil. IR (CHCl<sub>3</sub>) 1703 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.46–7.34 (5H, m), 5.00 (1H, d, *J* = 11.0 Hz), 4.97 (1H, d, *J* = 11.0 Hz), 3.39 (1H, dd, *J* = 8.9, 7.6 Hz), 3.23 (1H, dd, *J* = 9.7, 3.9 Hz), 3.05 (1H, br t, *J* = 8.9 Hz), 2.94 (1H, dd, *J* = 11.9, 9.7 Hz), 2.30 (1H, m), 1.73–0.85 (13H, m), 1.18 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.8, 135.1, 129.5, 129.0, 128.6, 76.7, 51.5, 46.8, 45.6, 39.6, 35.4, 35.0, 33.1, 26.3, 26.0, 22.5, 2.8. One peak of <sup>13</sup>C NMR was missing due to overlap. MS (FAB<sup>+</sup>) *m/z* 442 (M + H<sup>+</sup>, 28), 91 (100). HRMS (FAB<sup>+</sup>) calcd for C<sub>20</sub>H<sub>29</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 442.1243, found 442.1234. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL min<sup>-1</sup>, 254 nm) *t*<sub>r</sub> (major) = 24.0 min, *t*<sub>r</sub> (minor) = 30.6 min. A sample of 79% ee by HPLC analysis gave [α]<sub>D</sub><sup>27</sup> + 48.5 (*c* 1.3, CHCl<sub>3</sub>).

**(3*S*,4*R*)-3-(Cyclopentylmethyl)-4-(iodomethyl)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (5Ac).** A colorless oil. IR (CHCl<sub>3</sub>) 1704 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.46–7.35 (5H, m), 5.00 (1H, d, *J* = 11.9 Hz), 4.99 (1H, d, *J* = 11.9 Hz), 3.40 (1H, dd, *J* = 8.8, 7.6 Hz), 3.24 (1H, dd, *J* = 9.8, 4.3 Hz), 3.02 (1H, br t, *J* = 8.8 Hz), 2.99 (1H, dd, *J* = 11.6, 9.8 Hz), 2.32 (1H, m), 1.90–1.76 (3H, m), 1.65–1.40 (5H, m), 1.29 (1H, dd, *J* = 14.4, 7.0 Hz), 1.19 (3H, s), 1.12–0.97 (2H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.8, 135.1, 129.6, 129.0, 128.6, 76.7, 51.6, 46.7, 46.0, 38.7, 36.0, 35.1, 34.1, 25.3, 24.6, 22.8, 2.5. MS (FAB<sup>+</sup>) *m/z* 428 (M + H<sup>+</sup>, 61), 91 (100). HRMS (FAB<sup>+</sup>) calcd for C<sub>19</sub>H<sub>27</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 428.1087, found 428.1091. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL min<sup>-1</sup>, 254 nm) *t*<sub>r</sub> (major) = 23.0 min, *t*<sub>r</sub> (minor) = 32.8 min. A sample of 77% ee by HPLC analysis gave [α]<sub>D</sub><sup>27</sup> + 51.0 (*c* 1.0, CHCl<sub>3</sub>).

**(3*S*,4*R*)-3-(2,2-Dimethylpropyl)-4-(iodomethyl)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (5Ad).** A colorless oil. IR (CHCl<sub>3</sub>) 1706 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.46–7.35 (5H, m), 5.03 (1H, d, *J* = 11.0 Hz), 4.94 (1H, d, *J* = 11.0 Hz), 3.40 (1H, dd, *J* = 9.5, 7.4 Hz), 3.23 (1H, dd, *J* = 9.8, 3.7 Hz), 3.13 (1H, br t, *J* = 9.5 Hz), 2.97 (1H, dd, *J* = 11.9, 9.8 Hz), 2.28 (1H, m), 1.47 (1H, d, *J* = 14.4 Hz), 1.29 (3H, s), 1.17 (1H, d, *J* = 14.4 Hz), 1.01 (9H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.8, 135.2, 129.4, 129.0, 128.6, 76.7, 51.0, 49.7, 46.3, 43.9, 31.3, 31.0, 22.8, 2.7. MS (FAB<sup>+</sup>) *m/z* 416 (M + H<sup>+</sup>, 42), 91 (100). HRMS (FAB<sup>+</sup>) calcd for C<sub>18</sub>H<sub>27</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 416.1087, found 416.1094. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL min<sup>-1</sup>, 254 nm) *t*<sub>r</sub> (major) = 18.4 min, *t*<sub>r</sub> (minor) = 30.0 min. A sample of 73% ee by HPLC analysis gave [α]<sub>D</sub><sup>27</sup> + 39.5 (*c* 1.1, CHCl<sub>3</sub>).

**(3*S*,4*R*)-3-(Cyclohexylmethyl)-4-(iodomethyl)-1-methoxy-3-methyl-2-pyrrolidinone (5Bb).** A colorless oil. IR (CHCl<sub>3</sub>) 1704 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.79 (3H, s), 3.72 (1H, dd, *J* = 8.8, 7.6 Hz), 3.33 (1H, dd, *J* = 9.8, 4.0 Hz), 3.27 (1H, br t, *J* = 8.8 Hz), 3.11 (1H, dd, *J* = 11.9, 9.8 Hz), 2.45 (1H, m), 1.76–1.57 (5H, m), 1.50 (1H, m), 1.35 (1H, dd, *J* = 14.3, 4.0 Hz), 1.30–0.85 (6H, m), 1.21 (3H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.4, 61.9, 49.7, 46.5, 45.6, 40.0, 35.4, 35.0, 33.2, 26.3, 26.0, 22.6, 2.5. One peak of <sup>13</sup>C NMR was missing due to overlap. MS (FAB<sup>+</sup>) *m/z* 366 (M + H<sup>+</sup>, 100). HRMS (FAB<sup>+</sup>) calcd for C<sub>14</sub>H<sub>25</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 366.0930, found 366.0936. HPLC (Chiralcel OD-H, hexane–2-propanol = 95 : 5, 0.5 mL min<sup>-1</sup>, 254 nm) *t*<sub>r</sub> (major) = 14.8 min, *t*<sub>r</sub> (minor) = 21.7 min. A sample of 84% ee by HPLC analysis gave [α]<sub>D</sub><sup>26</sup> + 50.6 (*c* 1.3, CHCl<sub>3</sub>).

**(3*S*,4*R*)-3-(Cyclopentylmethyl)-4-(iodomethyl)-1-methoxy-3-methyl-2-pyrrolidinone (5Bc).** A colorless oil. IR (CHCl<sub>3</sub>) 1704 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.80 (3H, s), 3.74 (1H, dd, *J* = 8.9, 7.6 Hz), 3.34 (1H, dd, *J* = 9.8, 4.0 Hz), 3.26 (1H, br t, *J* = 8.9 Hz), 3.16 (1H, dd, *J* = 11.9, 9.8 Hz), 2.47 (1H, m), 1.88 (1H, m), 1.86–1.79 (2H, m), 1.70–1.42 (4H, m), 1.61 (1H, dd, *J* = 14.1, 4.6 Hz), 1.37 (1H, dd, *J* = 14.1, 7.4 Hz), 1.22 (3H, s), 1.14–0.98 (2H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.5, 62.0, 49.9, 46.4, 46.0, 39.2, 36.1, 35.0, 34.0, 25.3, 24.6, 23.0, 2.4. MS (FAB<sup>+</sup>) *m/z* 352 (M + H<sup>+</sup>, 100). HRMS (FAB<sup>+</sup>) calcd for C<sub>13</sub>H<sub>23</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 352.0773, found 352.0768. HPLC (Chiralcel OD-H, hexane–2-propanol = 95 : 5, 0.5 mL min<sup>-1</sup>, 254 nm) *t*<sub>r</sub> (major) = 16.0 min, *t*<sub>r</sub> (minor) = 22.4 min. A sample of 83% ee by HPLC analysis gave [α]<sub>D</sub><sup>29</sup> + 41.3 (*c* 1.2, CHCl<sub>3</sub>).

**(3*S*,4*R*)-3-(2,2-Dimethylpropyl)-4-(iodomethyl)-1-methoxy-3-methyl-2-pyrrolidinone (5Bd).** A colorless oil. IR (CHCl<sub>3</sub>) 1708 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.78 (3H, s), 3.65 (1H, dd, *J* = 9.2, 7.4 Hz), 3.37 (1H, br t, *J* = 9.2 Hz), 3.31 (1H, dd, *J* = 9.8, 3.6 Hz), 3.16 (1H, dd, *J* = 11.9, 9.8 Hz), 2.40 (1H, m), 1.51 (1H, d, *J* = 14.4 Hz), 1.32 (3H, s), 1.19 (1H, d, *J* = 14.4 Hz), 1.02 (9H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.1, 61.8, 49.8, 49.1, 46.1, 44.2, 31.4, 31.0, 22.9, 2.3. MS (FAB<sup>+</sup>) *m/z* 340 (M + H<sup>+</sup>, 100). HRMS (FAB<sup>+</sup>) calcd for C<sub>12</sub>H<sub>23</sub>INO<sub>2</sub> (M + H<sup>+</sup>) 340.0773, found 340.0780. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 1.0 mL min<sup>-1</sup>, 254 nm) *t*<sub>r</sub> (major) = 6.8 min, *t*<sub>r</sub> (minor) = 8.3 min. A sample of 88% ee by HPLC analysis gave [α]<sub>D</sub><sup>29</sup> + 44.4 (*c* 1.4, CHCl<sub>3</sub>).

**4-(Iodomethyl)-3-(2-methylpropylidene)-1-(phenylmethoxy)-2-pyrrolidinone (12).** A colorless oil. IR (CHCl<sub>3</sub>) 1711 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.48–7.35 (5H, m), 6.48 (1H, dd, *J* = 10.7, 1.6 Hz), 5.06 (2H, s), 3.44 (1H, br t, *J* = 7.2 Hz), 3.20–3.04 (3H, m), 2.81 (1H, t, *J* = 7.2 Hz), 2.27 (1H, m), 1.08 (3H, d, *J* = 6.7 Hz), 1.03 (3H, d, *J* = 6.7 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 164.8, 144.4, 135.2, 129.7, 129.1, 128.7, 128.4, 76.7, 52.1, 36.1, 28.5, 22.3, 22.1, 8.6. MS (EI<sup>+</sup>) *m/z* 385 (M<sup>+</sup>, 0.3), 91 (100). HRMS (EI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>20</sub>INO<sub>2</sub> (M<sup>+</sup>) 285.0539, found 285.0548. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 1.0 mL min<sup>-1</sup>, 254 nm) *t*<sub>r</sub> (racemic) = 17.3 and 31.7 min.

**1-Iodo-*N*-phenylmethoxy-*N*-(2-propen-1-yl)-2-pentenamide (13).** Major isomer: A colorless oil. IR (CHCl<sub>3</sub>) 1645 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.42–7.35 (5H, m), 5.92 (1H, d, *J* = 8.8 Hz), 5.88 (1H, m), 5.30 (1H, dd, *J* = 17.1, 1.2 Hz), 5.25 (1H, dd, *J* = 10.0,

1.2 Hz), 4.85 (2H, s), 4.19 (2H, br d,  $J = 5.8$  Hz), 2.62 (1H, m), 1.04 (6H, d,  $J = 6.7$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  167.2, 148.5, 134.4, 131.5, 129.3, 128.9, 128.6, 118.9, 89.4, 76.7, 51.4, 35.7, 20.9. MS ( $\text{EI}^+$ )  $m/z$  385 ( $\text{M}^+$ , 2), 91 (100). HRMS ( $\text{EI}^+$ ) calcd for  $\text{C}_{16}\text{H}_{20}\text{INO}_2$  ( $\text{M}^+$ ) 285.0539, found 285.0558.

**4-(Iodomethyl)-3-methyl-3-(2-methylpropyl)-1-(phenylmethoxy)-2-piperidinone (15).** A colorless oil. IR ( $\text{CHCl}_3$ ) 1650  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.46–7.41 (2H, m), 7.39–7.33 (3H, m), 4.97 (1H, d,  $J = 10.4$  Hz), 4.86 (1H, d,  $J = 10.4$  Hz), 3.48–3.37 (3H, m), 2.87 (1H, t,  $J = 10.1$  Hz), 2.25 (1H, m), 1.92–1.79 (3H, m), 1.53 (1H, dd,  $J = 14.0, 5.2$  Hz), 1.36 (3H, s), 1.28 (1H, dd,  $J = 14.0, 6.1$  Hz), 0.96 (3H, d,  $J = 6.7$  Hz), 0.92 (3H, d,  $J = 6.5$  Hz). MS ( $\text{CI}^+$ )  $m/z$  416 ( $\text{M} + \text{H}^+$ , 0.1), 91 (100). HRMS ( $\text{CI}^+$ ) calcd for  $\text{C}_{18}\text{H}_{27}\text{INO}_2$  ( $\text{M} + \text{H}^+$ ) 416.1085, found 416.1071.

**(3S,4R,5R)-4-(Iodomethyl)-1-methoxy-3-methyl-3-(2-methylpropyl)-5-phenyl-2-pyrrolidinone (cis-21).** A colorless oil. IR ( $\text{CHCl}_3$ ) 1707  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.44–7.36 (5H, m), 4.31 (1H, d,  $J = 9.0$  Hz), 3.60 (3H, s), 3.23 (1H, dd,  $J = 11.0, 9.5$  Hz), 3.11 (1H, dd,  $J = 11.0, 5.5$  Hz), 2.48 (1H, m), 1.99 (1H, m), 1.62 (1H, dd,  $J = 14.5, 4.0$  Hz), 1.48 (1H, dd,  $J = 14.5, 7.5$  Hz), 1.46 (3H, s), 1.00 (3H, d,  $J = 6.5$  Hz), 0.96 (3H, d,  $J = 6.5$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  174.6, 137.3, 129.0, 128.8, 128.0, 66.2, 63.0, 54.0, 44.6, 41.8, 25.5, 24.8, 24.3, 24.2, 21.5. MS ( $\text{EI}^+$ )  $m/z$  401 ( $\text{M}^+$ , 2), 378 (100). HRMS ( $\text{EI}^+$ ) calcd for  $\text{C}_{17}\text{H}_{24}\text{INO}_2$  ( $\text{M}^+$ ) 401.0852, found 401.0871. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL  $\text{min}^{-1}$ , 254 nm)  $t_r$  (major) = 16.1 min,  $t_r$  (minor) = 17.8 min. A sample of 99% ee by HPLC analysis gave  $[\alpha]_{\text{D}}^{25} + 29.0$  ( $c$  1.0,  $\text{CHCl}_3$ ).

**(3R,4R,5R)-4-(Iodomethyl)-1-methoxy-3-methyl-3-(2-methylpropyl)-5-phenyl-2-pyrrolidinone (trans-22).** A colorless oil. IR ( $\text{CHCl}_3$ ) 1714  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.46–7.38 (5H, m), 4.13 (1H, d,  $J = 9.5$  Hz), 3.57 (3H, s), 3.11–3.06 (2H, m), 2.74 (1H, m), 1.92 (1H, m), 1.83 (1H, dd,  $J = 14.5, 3.5$  Hz), 1.73 (1H, dd,  $J = 14.5, 10.0$  Hz), 1.16 (3H, s), 1.02 (3H, d,  $J = 6.5$  Hz), 0.99 (3H, d,  $J = 6.5$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  176.7, 137.6, 129.3, 129.2, 128.2, 66.4, 63.0, 46.0, 45.0, 44.3, 24.9, 24.7, 21.8, 19.2. One carbon peak was missing due to overlapping. MS ( $\text{EI}^+$ )  $m/z$  401 ( $\text{M}^+$ , 1), 345 (100). HRMS ( $\text{EI}^+$ ) calcd for  $\text{C}_{17}\text{H}_{24}\text{INO}_2$  ( $\text{M}^+$ ) 401.0852, found 401.0869. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL  $\text{min}^{-1}$ , 254 nm)  $t_r$  (minor) = 11.7 min,  $t_r$  (major) = 15.0 min. A sample of 95% ee by HPLC analysis gave  $[\alpha]_{\text{D}}^{25} + 28.9$  ( $c$  1.2,  $\text{CHCl}_3$ ).

**(3S,4R,5R)-3-(2,2-Dimethylpropyl)-4-(iodomethyl)-1-methoxy-3-methyl-5-phenyl-2-pyrrolidinone (cis-23).** A white solid. IR ( $\text{CHCl}_3$ ) 1708  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.44–7.33 (5H, m), 4.41 (1H, d,  $J = 8.9$  Hz), 3.60 (3H, s), 3.26 (1H, dd,  $J = 10.7, 8.8$  Hz), 3.07 (1H, dd,  $J = 10.7, 5.8$  Hz), 2.37 (1H, m), 1.62 (1H, d,  $J = 14.4$  Hz), 1.55 (3H, s), 1.50 (1H, d,  $J = 14.4$  Hz), 1.08 (9H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  173.6, 136.6, 129.0, 128.8, 128.2, 64.8, 62.5, 57.2, 45.0, 44.7, 31.5, 31.2, 24.7, –3.2. MS ( $\text{EI}^+$ )  $m/z$  415 ( $\text{M}^+$ , 5), 136 (100). HRMS ( $\text{EI}^+$ ) calcd for  $\text{C}_{18}\text{H}_{26}\text{INO}_2$  ( $\text{M}^+$ ) 415.1008, found 415.0999. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL  $\text{min}^{-1}$ , 254 nm)  $t_r$  (major) = 16.8 min,  $t_r$  (minor) = 21.0 min. A sample of 99% ee by HPLC analysis gave  $[\alpha]_{\text{D}}^{28} + 20.1$  ( $c$  1.6,  $\text{CHCl}_3$ ).

**(3RS,4RS,5RS)-3-(2,2-Dimethylpropyl)-4-(iodomethyl)-1-methoxy-3-methyl-5-phenyl-2-pyrrolidinone (trans-24).** A white solid. IR ( $\text{CHCl}_3$ ) 1716  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.47–7.39 (5H, m), 4.22 (1H, d,  $J = 9.1$  Hz), 3.57 (3H, s), 3.17 (1H, dd,  $J = 10.4, 6.7$  Hz), 3.12–3.01 (2H, m), 1.94 (1H, d,  $J = 15.0$  Hz), 1.68 (1H, d,  $J = 15.0$  Hz), 1.12 (3H, s), 1.10 (9H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  176.4, 137.6, 129.1, 128.9, 128.4, 66.8, 62.8, 47.2, 45.8, 45.5, 31.7, 31.4, 20.2, –2.4. MS ( $\text{EI}^+$ )  $m/z$  415 ( $\text{M}^+$ , 3), 136 (100). HRMS ( $\text{EI}^+$ ) calcd for  $\text{C}_{18}\text{H}_{26}\text{INO}_2$  ( $\text{M}^+$ ) 415.1008, found 415.1016. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL  $\text{min}^{-1}$ , 254 nm)  $t_r$  (racemic) = 21.0 and 22.2 min.

**(3S,4R,5R)-5-Ethenyl-4-(iodomethyl)-1-methoxy-3-methyl-3-(2-methylpropyl)-2-pyrrolidinone (25).** A colorless oil. IR ( $\text{CHCl}_3$ ) 1705  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45–7.33 (5H, m), 5.56 (1H, m), 5.35 (1H, d,  $J = 9.8$  Hz), 5.32 (1H, d,  $J = 16.8$  Hz), 5.04 (1H, d,  $J = 10.4$  Hz), 4.90 (1H, d,  $J = 10.4$  Hz), 3.58 (1H, t,  $J = 8.5$  Hz), 3.15–3.03 (2H, m), 2.16 (1H, m), 1.90 (1H, m), 1.48 (1H, dd,  $J = 14.3, 3.6$  Hz), 1.40 (3H, s), 1.35 (1H, dd,  $J = 14.3, 7.4$  Hz), 0.97 (3H, d,  $J = 6.4$  Hz), 0.92 (3H, d,  $J = 6.7$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  174.1, 135.8, 135.1, 129.7, 129.0, 128.5, 121.7, 77.6, 66.1, 51.7, 44.3, 41.5, 29.7, 25.4, 24.5, 24.3, 24.2. MS ( $\text{FAB}^+$ )  $m/z$  428 ( $\text{M} + \text{H}^+$ , 32), 91 (100). HRMS ( $\text{FAB}^+$ ) calcd for  $\text{C}_{19}\text{H}_{27}\text{INO}_2$  ( $\text{M} + \text{H}^+$ ) 428.1087, found 428.1078. HPLC (Chiralcel AD-H, hexane–2-propanol = 95 : 5, 0.5 mL  $\text{min}^{-1}$ , 254 nm)  $t_r$  (major) = 18.3 min,  $t_r$  (minor) = 21.4 min. A sample of 53% ee by HPLC analysis gave  $[\alpha]_{\text{D}}^{25} - 10.7$  ( $c$  0.4,  $\text{CHCl}_3$ ).

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