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Asymmetric synthesis of isoquinuclidines by Diels–Alder reaction of 1,2-dihydropyridine utilizing a chiral Lewis acid catalyst

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ABSTRACT

The chiral isoquinuclidine derivative, 2-azabicyclo[2.2.2]octane ring system, *endo*-(7*R*)-**3** was obtained in good yield with excellent diastereoselectivity (up to 92% de) by Diels–Alder reaction of 1-(phenoxycarbonyl)-1,2-dihydropyridine **1** with *N*-acryloyl-(4*S*)-4-benzyloxazolidin-2-one (4*S*)-**2** using titanium-(2*R*,3*R*)-TADDOLate **4** as a chiral Lewis acid catalyst in toluene at 0 °C. On the other hand, *endo*-(7*S*)-**3** was obtained in good yield with excellent diastereoselectivity (up to 97% de) by Diels–Alder reaction of **1** with (4*R*)-**2** using $Cu(OTf)_2$/(4*S*,4′*S*)-bis(oxazoline) catalyst **8** as a chiral Lewis acid catalyst in dichloromethane at 0 °C. In these reactions, the choice of solvent and the combination of titanium-(2*R*,3*R*)-TADDOLate **4** {or Cu(II)/(4*S*,4′*S*)-bis(oxazoline) **8**} and dienophile (4*S*)-**2** {or (4*R*)-**2**} are very important. The stereochemistry of *endo*-(7*R*)-**3** has been established to be (1*R*,4*S*,7*R*) and the reaction mechanism is proposed.

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1. Introduction

Vinblastine extracted from the leaves of the Madagascar periwinkle plant (*Catharanthus roseus*), a natural product in the vinca alkaloid family, is used for several types of cancer.[1] A biosynthetic pathway of vinblastine is the nucleophilic addition of (−)-vindoline to (+)-catharanthine, which contains the isoquinuclidine ring system, 2-azabicyclo[2.2.2]octane ring system. (+)-Catharanthine is prototypical structure of *Iboga* family of alkaloid and (−)-ibogaine is the medicine for alcohol dependence.[1b,2d] Furthermore, isoquinuclidines are valuable intermediates in the synthesis of other alkaloid,[3] and in medicinal chemistry, such as oseltamivir.[4,5] The most promising method for the synthesis of isoquinuclidine derivatives is the Diels–Alder (D–A) reaction between 1,2-dihydropyridine and dienophiles. In the asymmetric synthesis of isoquinuclidines, the diastereoselective cycloadditions using 1,2-dihydropyridines or dienophiles having a chiral auxiliary have been reported.[6] The D–A reaction of 1,2-dihydropyridines and *N*-acryloyl-(1*S*)-2,10-camphorsultam in the presence of Lewis acid, such as titanium tetrachloride, zirconium tetrachloride, and hafnium tetrachloride, afforded the *endo*-cycloaddition product (chiral isoquinuclidine derivatives) in good yield with excellent diastereoselectivity (up to 98% de) in dichloromethane as a solvent.[6h] Recently, its catalytic enantioselective synthesis was also reported.[2] In order to synthesize the chiral isoquinuclidines, we adopted the asymmetric D–A reaction catalyzed by a chiral Lewis acid.[7] The commercial availability of optically pure oxazolidinones, and the ease of removal and recovery of these auxiliaries are valued characteristics in asymmetric synthesis. We report the study on synthesis of the chiral isoquinuclidine derivatives by D–A reaction of 1,2-dihydropyridine **1** with chiral dienophile **2** having a chiral auxiliary in the presence of Lewis acid. We investigated the two ways of the asymmetric D–A reactions. One is the reaction of 1-(phenoxycarbonyl)-1,2-dihydropyridine **1**[8] and *N*-acryloyl-(4*S*)-4-benzyloxazolidin-2-one (4*S*)-**2** {or *N*-acryloyl-(4*R*)-4-benzyloxazolidin-2-one (4*R*)-**2**}[9] using Lewis acid and the other is the reaction of **1** and (4*S*)-**2** {or (4*R*)-**2**} using Ti-(2*R*,3*R*)-TADDOLate **4** as a chiral Lewis acid catalyst. Though it is reported that 1,2-dihydropyridine is unstable for Lewis acid,[2c,6g] our reaction system afforded chiral isoquinuclidines in good yields with high diastereoselectivity (up to 92% de). The absolute stereochemistry of the cycloaddition product *endo*-(4′*S*)-**3** was determined to be (7*R*) by conversion of *endo*-(4′*S*)-**3** to the known benzyl ester (7*R*)-**7**. We describe the detail of the available method for the synthesis of the chiral isoquinuclidines (Fig. 1).

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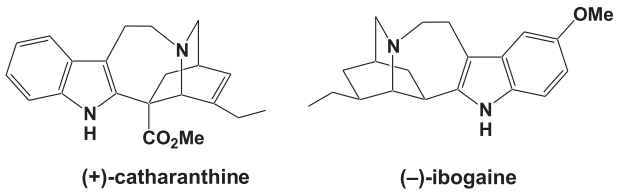
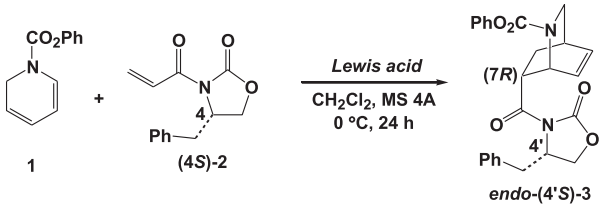


Fig. 1. Indole alkaloids.

2. Results and discussion

2.1. Diels–Alder reaction of 1-(phenoxycarbonyl)-1,2-dihydropyridine 1 with (4*S*)-2 {or (4*R*)-2} in the presence of Lewis acid

We first examined the D–A reaction of 1-(phenoxycarbonyl)-1,2-dihydropyridine **1** and *N*-acryloyl (4*S*)-4-benzyloxazolidin-2-one (4*S*)-**2** {or *N*-acryloyl (4*R*)-4-benzyloxazolidin-2-one (4*R*)-**2**} using Lewis acids, such as dichlorotitanium diisopropoxide, zirconium tetrachloride, hafnium tetrachloride, and scandium trifluoromethanesulfonate (Scheme 1). These D–A reactions were carried out in dichloromethane at 0 °C for 24 h in the presence of molecular sieves 4 Å, since Lewis acid, such as $ZrCl_4$, $HfCl_4$, and $Sc(OTf)_3$ could not be dissolved in toluene, and the results are summarized in Table 1.



Scheme 1. D–A reaction of **1** and (4*S*)-**2** in the presence of Lewis acid.

Table 1
D–A reaction of **1** and (4*S*)-**2** {or (4*R*)-**2**} in the presence of Lewis acid

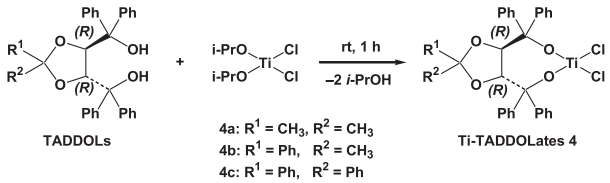
Entry	Diene (mol equiv)	Dienophile (mol equiv)	Lewis acid (mol equiv)	Yield[a]/% *endo*-**3**	% de of *endo*-**3**[b]
1	**1** (2)	(4*S*)-**2** (1)	$Ti(i\text{-}PrO)_2Cl_2$ (2)	99	63 (4′*S*)
2	**1** (2)	(4*S*)-**2** (1)	$ZrCl_4$ (1)	42 (24)	48 (4′*S*)
3	**1** (3)	(4*S*)-**2** (1)	$ZrCl_4$ (1)	72 (10)	57 (4′*S*)
4	**1** (2)	(4*S*)-**2** (1)	$HfCl_4$ (1)	73 (21)	59 (4′*S*)
5	**1** (3)	(4*S*)-**2** (1)	$HfCl_4$ (1)	94	43 (4′*S*)
6	**1** (2)	(4*S*)-**2** (1)	$Sc(OTf)_3$ (1)	99	52 (4′*S*)
7	**1** (2)	(4*R*)-**2** (1)	$Ti(i\text{-}PrO)_2Cl_2$ (2)	99	58 (4′*R*)
8	**1** (2)	(4*R*)-**2** (1)	$Sc(OTf)_3$ (1)	99	54 (4′*R*)

[a] Isolated yield. Recovery of (4*S*)-**2** is shown in parentheses.
[b] Diastereomeric excess (% de) was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 5% 2-propanol/*n*-hexane, flow rate 0.8 mL/min, 254 nm, t_R=18 min (minor), 28 min (major).

The D–A reaction of 1,2-dihydropyridine **1** (2 equiv) and (4*S*)-**2** (1 equiv) using 2 equiv of $Ti(i\text{-}PrO)_2Cl_2$ was carried out in dichloromethane at 0 °C for 24 h to afford the cycloaddition product *endo*-(4′*S*)-**3** in 99% yield with 63% de and the product was only *endo* isomer (Table 2, entry 1). In the D–A reaction of **1** and (4*S*)-**2** using 1 equiv of $ZrCl_4$, only *endo*-(4′*S*)-**3** was obtained in 42% yield with 48% de and the recovery of (4*S*)-**2** was 24% yield (entry 2). However, in the D–A reaction of **1** (3 equiv) and (4*S*)-**2** using 1 equiv of $ZrCl_4$, the yield of *endo*-(4′*S*)-**3** increased to 72% yield with 57% de (entry 3). As a result, the chemical yield of *endo*-(4′*S*)-**3** in the D–A reaction of **1** and (4*S*)-**2** was good to high, however, the diastereoselectivity of *endo*-(4′*S*)-**3** was moderate (from 43% de to 63% de). Next, the reaction of 1,2-dihydropyridine **1** and (4*R*)-**2**, which is the mirror image of (4*S*)-**2** was carried out. The D–A reaction of **1** (2 equiv) and (4*R*)-**2** (1 equiv) using 2 equiv of $Ti(i\text{-}PrO)_2Cl_2$ was carried out at 0 °C for 24 h to afford *endo*-(4′*R*)-**3** in 99% yield with 58% de (entry 7).

2.2. Preparation of Ti-(*R*,*R*)-TADDOLate 4 as a chiral Lewis acid catalyst

In order to investigate the additional effect of chiral Lewis acid, the chiral 1,4-diol (TADDOL)[11] {TADDOL: (2*R*,3*R*)-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol, (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol, and (4*R*,5*R*)-α,α,α′,α′,2,2-*O*-hexaphenyl-4,5-dimethanol-1,3-dioxalone[14,15]}, was employed as a chiral auxiliary (Scheme 2).[10,11]



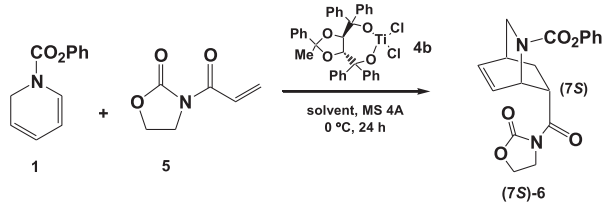
Scheme 2. Preparation of Ti-(2*R*,3*R*)-TADDOLate catalyst.

Chiral titanium complex Ti-(2*R*,3*R*)-TADDOLate **4** {**4a** (R^1=R^2=CH_3), **4b** (R^1=Ph, R^2=CH_3), and **4c** (R^1=R^2=Ph)} was prepared from TADDOL and dichlorotitanium diisopropoxide (ratio, 1:1) in the presence of molecular sieves 4 Å at room temperature (Scheme 2).[11]

2.3. Diels–Alder reaction of 1-(phenoxycarbonyl)-1,2-dihydropyridine 1 with *N*-acryloyloxazolidin-2-one 5 using chiral Lewis acid catalyst 4b

For the catalytic enantioselective version of the D–A reaction, we examined the reaction of 1-(phenoxycarbonyl)-1,2-dihydropyridine **1** and *N*-acryloyloxazolidin-2-one **5**[9] using chiral Lewis acid catalyst, Ti-(2*R*,3*R*)-TADDOLate **4b**.[11] The D–A reaction of diene **1** (2 equiv) with dienophile **2** (1 equiv) was carried out in dichloromethane at 0 °C for 24 h using 30 mol % of catalyst **4b** and molecular sieves 4 Å. A clean reaction proceeded to afford exclusively the *endo*-cycloadduct (7*S*)-**6** in 97% yield with 10% ee (Table 2,

Table 2
D–A reaction of **1** and **5** using chiral Lewis acid catalyst **4b**



Entry	Ti-TADDOLate **4b** (mol equiv)	Solvent	Yield[a]/% **6**	% ee of *endo*-**6**[b]
1	**4b** (0.3)	CH_2Cl_2	97	10 (7*S*)
2	**4b** (0.3)	Toluene	78	70 (7*S*)
3	**4b** (0.3)	Mesitylene	85	67 (7*S*)
4	**4b** (0.3)	Hexylbenzene	94	68 (7*S*)
5	**4b** (0.3)	Toluene/hexane (2:1)	98	73 (7*S*)

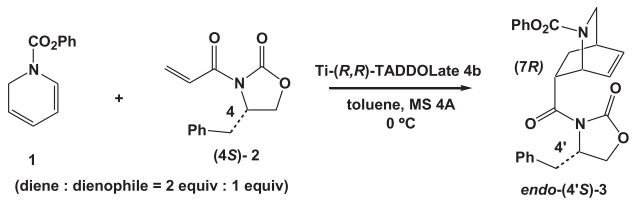
[a] Isolated yield.
[b] Enantiomeric excess (% ee) was determined by HPLC analysis using a Daicel CHRALPAK AD column; 25% 2-propanol/*n*-hexane, flow rate 0.5 mL/min, 254 nm, t_R=34.7 min (minor), 55.9 min (major).

entry 1). The preferable solvents for this cycloaddition were alkylbenzene, such as toluene. The D–A reaction of **1** (2 equiv) with **5** (1 equiv) using catalyst **4b** (0.3 equiv) in toluene was carried out at 0 °C for 24 h to give the cycloaddition product *endo*-(7*S*)-**6** in 78% yield with 70% ee (Table 2, entry 2).

We examined the above Diels–Alder reaction in several different solvents in order to see how the coordinating properties of the solvent would affect yield and enantioselectivity of *endo*-(7*S*)-**6** (Table 2). The Diels–Alder reaction was highly influenced by solvent as shown in Table 2; the chemical yield and enantioselectivity of *endo*-(7*S*)-**6** were as follows: in CH_2Cl_2 (97% yield, 10% ee) (Table 2, entry 1), in toluene (78% yield, 70% ee) (entry 2). The best result was obtained in the solvent of toluene/hexane (2:1) (98% yield, 73% ee) (entry 5). The absolute stereochemistry of the *endo*-**6** was established as (1*S*,4*R*,7*S*) by comparing the sign of the optical rotation with the literature value of (7*R*)-benzyl ester **7** {lit.,[2a] $[\alpha]_D^{24}$ −59.92 (*c* 2.52, $CHCl_3$), 97% ee} as follows: the reaction of the *endo*-**6** ($[\alpha]_D^{24}$ +76.7 (*c* 1.42, $CHCl_3$); 67% ee) with benzyl alcohol using *n*-BuLi as a base ($PhCH_2OLi$) in THF at 0 °C afforded the corresponding (7*S*)-benzyl ester **7** {$[\alpha]_D^{24}$ +63.9 (*c* 1.07, $CHCl_3$)} in good yield (83%) (see Experimental section).

2.4. Diels–Alder reaction of 1-(phenoxycarbonyl)-1,2-dihydropyridine 1 with chiral dienophile 2 using Ti-(2*R*,3*R*)-TADDOLate catalyst 4

As shown in Scheme 3, the D–A reaction of **1** (2 equiv) with (4*S*)-**2** (1 equiv) using 0.5 equiv of Ti-(2*R*,3*R*)-TADDOLate **4b** in toluene was carried out at 0 °C for 24 h to give the cycloaddition product *endo*-(4′*S*)-**3** in 99% yield with 90% de (Table 3, entry 3). Using of 0.3 equiv of **4b**, the yield of *endo*-(4′*S*)-**3** was 99% and the diastereomeric excess was 92% de {$[\alpha]_D^{24}$ −58.3 (*c* 0.50, $CHCl_3$)} (entry 2). Since the D–A reaction of **1** with (4*S*)-**2** using 0.1 equiv of **4b** proceeded slowly, the reaction time was extended to 48 h to give the product *endo*-(4′*S*)-**3** in 83% yield with 87% de and the recovery of (4*S*)-**2** was 14% yield (entry 1). In the case of using 0.1 equiv of **4b** the yield and the diastereoselectivity of (4′*S*)-**3** were decreased. Therefore, the best quantity of catalyst was 0.3 equiv.



Scheme 3. The D–A reaction of **1** and (4*S*)-**2** using Ti-(*R*,*R*)-TADDOLate catalyst **4b**.

Table 3
Effect of catalyst quantity in the D–A reaction of **1** and (4*S*)-**2**

Entry	Ti-TADDOLate **4b** (mol equiv)	Time/h	Yield[a]/% **3**	% de of *endo*-**3**[b]
1	**4b** (0.1)	48	83 (14)	87 (4′*S*)
2	**4b** (0.3)	24	99	92 (4′*S*)
3	**4b** (0.5)	24	99	90 (4′*S*)

[a] Isolated yield. Recovery of (4*S*)-**2** is shown in parentheses.
[b] Diastereomeric excess (% de) was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 5% 2-propanol/*n*-hexane, flow rate 0.8 mL/min, 254 nm, t_R=18 min (minor), 28 min (major).

Then, we investigated the solvent effect of the D–A reaction of 1,2-dihydropyridine **1** (2 equiv) and (4*S*)-**2** (1 equiv) using 0.3 equiv of Ti-(2*R*,3*R*)-TADDOLate **4b** at 0 °C for 24 h (Table 4).

In order to improve the diastereoselectivity of the cycloaddition product *endo*-(4′*S*)-**3**, the D–A reaction of **1** with (4*S*)-**2** was examined in various solvents in the presence of 0.3 equiv of Ti-(2*R*,3*R*)-TADDOLate **4b** and molecular sieves 4 Å. The D–A reaction

Table 4
Solvent effect on diastereoselectivity of *endo*-**3** in the D–A reaction of **1** and (4*S*)-**2**

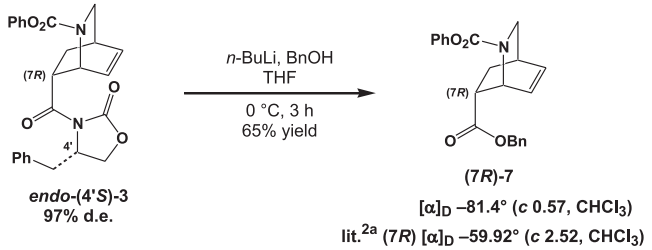
Entry	Ti-TADDOLate **4b** (mol equiv)	Solvent	Yield[a]/% **3**	% de of *endo*-**3**[b]
1	**4b** (0.3)	CH_2Cl_2	99	66 (4′*S*)
2	**4b** (0.3)	Toluene	99	92 (4′*S*)
3	**4b** (0.3)	Mesitylene	97	93 (4′*S*)
4	**4b** (0.3)	Toluene/hexane (1:1)	99	84 (4′*S*)
5	**4b** (0.3)	Toluene/hexane (2:1)	98	89 (4′*S*)

[a] Isolated yield.
[b] Diastereomeric excess (% de) was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 5% 2-propanol/*n*-hexane, flow rate 0.8 mL/min, 254 nm, t_R=18 min (minor), 28 min (major).

of **1** (2 equiv) with (4*S*)-**2** (1 equiv) using 0.3 equiv of Ti-(2*R*,3*R*)-TADDOLate **4b** was carried out in a solvent at 0 °C for 24 h to give the cycloaddition product *endo*-(4′*S*)-**3**. The reactivity of the D–A reaction was highly influenced by solvent as shown in Table 4; the chemical yields of *endo*-(4*S*′)-**3** were high (97–99%), however, there was a large difference in the diastereoselectivity of *endo*-(4′*S*)-**3** between dichloromethane (66% de) and toluene (92% de) (Table 4, entries 1 and 2). The best solvent was found in the Table 2 (toluene/hexane) and Table 4 (toluene and mesitylene), nevertheless, CH_2Cl_2 was used in Table 1. This solvent effect as shown in Table 4 is similar to the results as shown in Table 2. It was reported by Narasaka et al. that the enantioselectivity of cycloaddition product changes with solvent when the D–A reaction of *N*-acryloyl-1,3-oxazolidin-2-one derivatives and butadiene was investigated in the presence of Ti-(2*R*,3*R*)-TADDOLate **4b** as a catalyst.[11] As the reason of this solvent effect, it was estimated that the diastereoselectivity of this reaction is dependent on the donor and acceptor ability of the solvent.[12] In solvent having large acceptor number, such as dichloromethane, the diastereomeric excess of *endo*-(4′*S*)-**3** is lower (66% de) than that in toluene (92% de). That is, to attain high chemical yield and diastereoselectivity, it is necessary to carry out the reaction in a solvent having small donor and acceptor numbers, which means that the molecular interaction between the solvent and the titanium complex with a dienophile should be minimized. When the reaction of **1** and (4*S*)-**2** was investigated in mesitylene in the presence of Ti-(2*R*,3*R*)-TADDOLate **4b**, the diastereoselectivity of *endo*-(4′*S*)-**3** (93% de) was similar value as that of the reaction in toluene (92% de). For the aim of decreasing acceptor number of solvent, the reaction in mixed solvent, such as toluene and hexane was attempted, however, the diastereoselectivity of *endo*-(4′*S*)-**3** was 84% de or 89% de (entries 4 and 5).

2.5. Determination of absolute stereochemistry of cycloaddition product 3

The absolute stereochemistry of the *endo*-(4′*S*)-**3** was established as (1*R*,4*S*,7*R*) by comparing the sign of the optical rotation with the literature value of (7*R*)-benzyl ester **7** {lit.,[2a] $[\alpha]_D$ −59.92 (*c* 2.52, $CHCl_3$), 97% ee} as follows: the reaction of the *endo*-(4′*S*)-**3** ($[\alpha]_D^{24}$ −65.6 (*c* 1.00, $CHCl_3$); 97% de) with benzyl alcohol using *n*-BuLi as a base ($PhCH_2OLi$) in THF at 0 °C afforded the corresponding (7*R*)-benzyl ester **7** {$[\alpha]_D^{24}$ −81.4 (*c* 0.57, $CHCl_3$)} in moderate yield (65%) (Scheme 4).

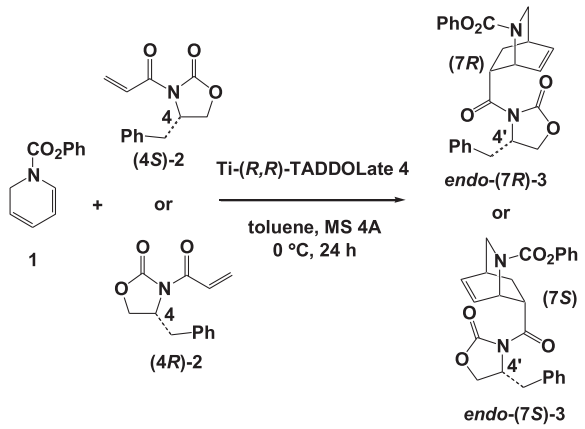


Scheme 4. Determination of absolute configuration of (4′*S*)-**3**.

On the other hand, the absolute configuration of isoquinuclidine derivative *endo*-(4′*R*)-**3**, which was obtained from the reaction of **1** and (4*R*)-**2** in the presence of Ti-TADDOLate **4**, has been established to be (1*S*,4*R*,7*S*).

2.6. Match–mismatch effect on diastereoselectivity of 3 in the D–A reaction of 1 and (4*S*)-2 {or (4*R*)-2} using Ti-(2*R*,3*R*)-TADDOLate catalyst 4 {or Cu(OTf)$_2$/(4*S*,4′*S*)-bisoxazoline catalyst 8}

As shown in Scheme 5, in order to test the possibility of match–mismatch effect on the diastereoselectivity of D–A cycloaddition product *endo*-**3**, the reaction of 1,2-dihydropyridine **1** and (4*S*)-**2** {or (4*R*)-**2**} in the presence of Ti-(2*R*,3*R*)-TADDOLate **4** was carried out in toluene at 0 °C for 24 h and the results are summarized in Table 5.



Scheme 5. Asymmetric D–A reaction of 1,2-dihydropyridine **1** with (4*S*)-**2** {or (4*R*)-**2**} using Ti-(2*R*,3*R*)-TADDOLate **4**.

Table 5
Match–mismatch effect on diastereoselectivity of **3** in the D–A reaction of **1** and (4*S*)-**2** {or (4*R*)-**2**} using Ti-TADDOLate **4**

Entry	Diene (mol equiv)	Dienophile (mol equiv)	Ti-TADDOLate **4** (mol equiv)	Product	Yield[a]/% *endo*-**3**	% de of *endo*-**3**[b]
1	**1** (2)	(4*S*)-**2** (1)	**4a** (0.3)	(7*R*)-**3**	96	87
2	**1** (2)	(4*S*)-**2** (1)	**4b** (0.3)	(7*R*)-**3**	99	92
3	**1** (2)	(4*S*)-**2** (1)	**4c** (0.3)	(7*R*)-**3**	99	88
4	**1** (2)	(4*R*)-**2** (1)	**4a** (0.3)	(7*S*)-**3**	55 (22)	70
5	**1** (2)	(4*R*)-**2** (1)	**4b** (0.3)	(7*S*)-**3**	73 (15)	68
6	**1** (2)	(4*R*)-**2** (1)	**4c** (0.3)	(7*S*)-**3**	51 (36)	68

[a] Isolated yield. Recovery of (4*R*)-**2** is shown in parentheses.
[b] Diastereomeric excess (% de) was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 5% 2-propanol/*n*-hexane, flow rate 0.8 mL/min, 254 nm, t_R=18 min (minor), 28 min (major).

In the D–A reaction of **1** (2 equiv) and (4*S*)-**2** (1 equiv) using 0.3 equiv of Ti-(*R*,*R*)-TADDOLate **4a** (R^1=R^2=CH_3), only *endo*-(7*R*)-**3** was obtained in 96% yield with 87% de (Table 5, entry 1). In the D–A reaction of **1** and (4*S*)-**2** using 0.3 equiv of **4b** (R^1=Ph, R^2=CH_3), *endo*-(7*R*)-**3** was obtained in 99% yield with 92% de {$[\alpha]_D^{24}$ −58.3 (*c* 0.50, $CHCl_3$)} (entry 2). The D–A reaction of **1** and (4*S*)-**2** using 0.3 equiv of **4c** (R^1=R^2=Ph) afforded *endo*-(7*R*)-**3** in 99% yield with 88% de (entry 3). However, in the D–A reactions of **1** (2 equiv) and (4*R*)-**2** (1 equiv) using 0.3 equiv of **4a**–**c**, both the chemical yield and the diastereoselectivity [70% de {$[\alpha]_D^{24}$ +40.9 (*c* 0.85, $CHCl_3$)}] of *endo*-(7*S*)-**3** are lower than those of *endo*-(7*R*)-**3** produced from the matched pair {(4*S*)-**2** and **4**} (entries 4–6). As a result, the combination of Ti-(2*R*,3*R*)-TADDOLate **4** and (4*S*)-**2** was a matched pair to give (7*R*)-**3** in high yield with 92% de (Table 2, entries 1–3), while the combination of Ti-(2*R*,3*R*)-TADDOLate **4** and (4*R*)-**2** was a mismatched pair to afford (7*S*)-**3** in moderate to good yield with 70% de (entries 4–6).

Based on the X-ray structure of complex of Ti-(2*R*,3*R*)-TADDOLate **4a** (R^1=R^2=CH_3) with *N*-[(*E*)-cinnamoyl]-1,3-oxazolidin-2-one reported by Jϕrgensen et al.,[13] we considered the reaction mechanism of the asymmetric D–A reaction of 1,2-dihydropyridine **1** and (4*S*)-**2** using Ti-(2*R*,3*R*)-TADDOLate **4b** (R^1=Ph, R^2=CH_3) (Fig. 2). As shown in Fig. 2, in the complex of matched pair {**4b** and (4*S*)-**2**} 1,2-dihydropyridine **1** can approach predominantly from the *si* face to give (7*R*)-**3** (up to 92% de) since the *re* face of the acryloyl group on the dienophile is shielded by the benzyl group of dienophile (4*S*)-**2** and the phenyl group at pseudoequatorial position of Ti-(2*R*,3*R*)-TADDOLate **4b**. On the other hand, in the complex of mismatched pair {**4b** and (4*R*)-**2**} 1,2-dihydropyridine **1** can approach from the *re* face to give (7*S*)-**3** (up to 70% de) since the *si* face of the acryloyl group on the dienophile is shielded by the benzyl group of dienophile (4*R*)-**2** in the complex of Ti-(2*R*,3*R*)-TADDOLate **4b**. In the complex of mismatched pair {**4b** and (4*R*)-**2**}, the *re* face of the acryloyl group on the dienophile is also shielded by phenyl group at pseudoequatorial position of Ti-(2*R*,3*R*)-TADDOLate **4b**. Consequently, it is assumed that both the chemical yield and the diastereoselectivity of (7*S*)-**3** are lower than those of (7*R*)-**3** produced from the matched pair {**4b** and (4*S*)-**2**}.

On the other hand, Cu(OTf)$_2$/(4*S*,4′*S*)-bis(oxazoline) catalysts **8** were chosen because of the abundance of literature data for their catalysis of Diels–Alder reactions involving oxazolidinones and related substrates.[14] Ready availability of various bis(oxazoline) ligands with differing steric volumes allowed for the possibility to assess the importance of the chiral ligand size relative to the dienophile (4*R*)-**2** in controlling diastereoselection. The D–A reaction of **1** (2 equiv) and (4*R*)-**2** (1 equiv) using 30 mol % of Cu(OTf)$_2$/(4*S*,4′*S*)-bisoxazoline catalyst (CH_3-box ligand) **8a** as a chiral Lewis acid catalyst afforded *endo*-(7*S*)-**3** in 89% yield with

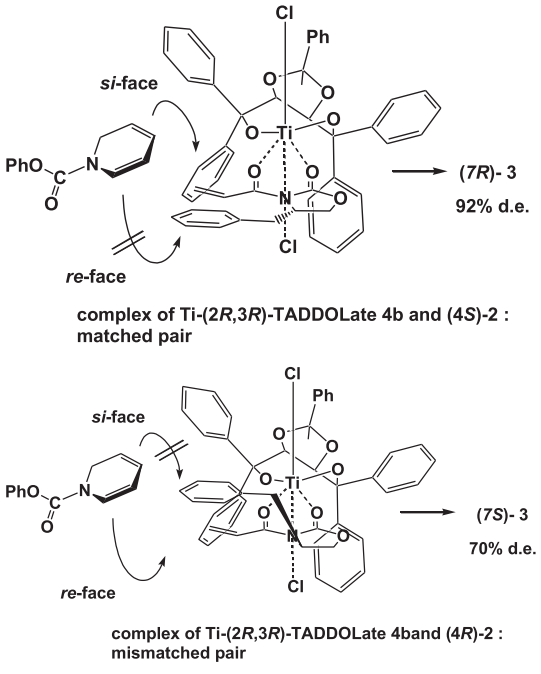


Fig. 2. Plausible complex formation of Ti-(2*R*,3*R*)-TADDOLate catalyst **4b** and (4*S*)-**2** {or (4R)-**2**}.

95% de in dichloromethane at 0 °C for 24 h (Fig. 3). The *endo*-(7*S*)-**3** was obtained in 87% yield with 97% de by Diels–Alder reaction of **1** (2 equiv) with (4*R*)-**2** (1 equiv) using 30 mol % of $Cu(OTf)_2$/(4*S*,4′*S*)-bis(oxazoline) catalyst (*i*-C_3H_7-box ligand) **8b** as a chiral catalyst.

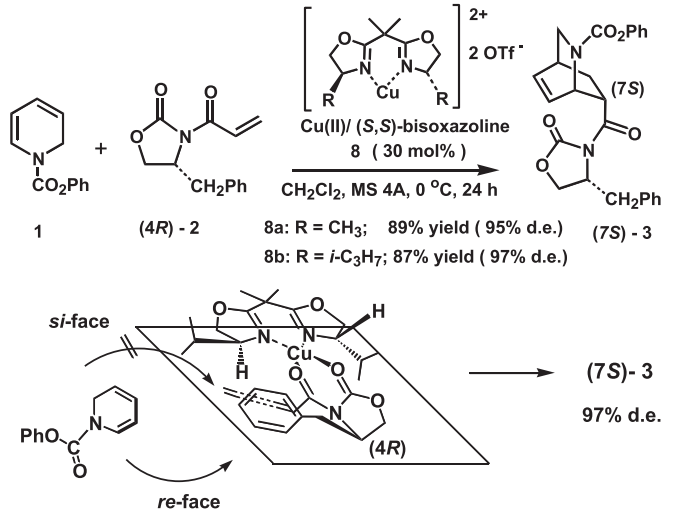


Fig. 3. Plausible complex formation of Cu(II)/(4*S*,4′*S*)-bis(oxazoline) catalyst **8b** and (4*R*)-**2**: matched pair.

The results with the copper Lewis acid catalyst **8** suggested that amplification of diastereoselectivity of (7*S*)-**3** was excellent for Lewis acid with square planar geometry. It is well established that Cu(II)/(4*S*,4′*S*)-bis(oxazoline) catalysts **8** react via distorted square planar geometries upon complexation to bidentate substrates.[15] In the reaction, the choice of the combination of Cu(II)/(4*S*,4′*S*)-bis(oxazoline) **8** and dienophile (4*S*)-**2** {or (4*R*)-**2**} is also important. In the complex of a matched pair {**8b** and (4*R*)-**2**} 1,2-dihydropyridine **1** can approach from the *re* face to give (7*S*)-**3** (up to 97% de) since the *si* face of the acryloyl group on the dienophile is shielded by the benzyl group of dienophile (4*R*)-**2** and C-4 *iso*-propyl substituents of bisoxazoline in the complex of Cu(II)/(4*S*,4′*S*)-bis(oxazoline) **8b** (Fig. 3).

3. Conclusion

In conclusion, we have accomplished the synthesis of chiral isoquinuclidine derivative *endo*-(7*R*)-**3** (up to 92% de) {or *endo*-(7*S*)-**3** (up to 97% de)} by Diels–Alder reaction of 1,2-dihydropyridine **1** with chiral oxazolidinone dienophile (4*S*)-**2** {or (4*R*)-**2**} using Ti-(2*R*,3*R*)-TADDOLate **4** {or Cu(II)/(4*S*,4′*S*)-bis(oxazoline) **8**} as a chiral Lewis acid catalyst, respectively. In the D–A reaction, the combination of Ti-(2*R*,3*R*)-TADDOLate **4** {or Cu(II)/(4*S*,4′*S*)-bis(oxazoline) **8**} and chiral dienophile (4*S*)-**2** {or (4*R*)-**2**} affected the chemical yield and the diastereoselectivity of the chiral isoquinuclidine derivative *endo*-(7*R*)-**3** {or *endo*-(7*S*)-**3**}.

4. Experimental section

4.1. General information

(4*S*)-4-Benzyl-2-oxazolidin-2-one, (4*R*)-4-benzyl-2-oxazolidin-2-one, (2*R*,3*R*)-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol, (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol, dichlorotitanium diisopropoxide, acrylic acid, acryloyl chloride, dimethyl L-(+)-tartrate, trimethyl *ortho*-formate, and copper(II) trifluoromethanesulfonate were purchased from Tokyo Chemical Ind. Co. Hafnium tetrachloride, scandium trifluoromethanesulfonate, indium chloride, phenyl chloroformate, toluene, and mesitylene were purchased from Wako Pure Chemical Ind. Pyridine, tetrahydrofuran, dichloromethane, hexane, ethanol, 2-propanol, diethyl ether, triethylamine, and sodium borohydride were purchased from Kanto Kagaku Reagent Division. Zirconium tetrachloride and molecular sieves 4 Å were purchased from Merck Co. Chiral (*S*,*S*)-bis(oxazoline) ligands **8a** (CH_3-box) and **8b** (*i*-C_3H_7-box) were prepared according to method described by Ishihara et al.[16] ^1H NMR spectra and ^{13}C NMR spectra were recorded at 270 MHz and 67.8 MHz on a JEOL JNM-EX 270 FT NMR SYSTEM and 500 MHz and 125 MHz on a JEOL JNM-ECA in $CDCl_3$ using tetramethylsilane as an internal standard. Specific rotations were recorded at the sodium D line with a polarimeter at room temperature. The enantiomeric excess (ee) or diastereomeric excess (de) of the cycloaddition products was determined by high performance liquid chromatography (HPLC) using the CHIRALPAK AD-H (25 cm) or TOSOH TSK-GEL Silica-60 (25 cm).

4.2. General procedure for asymmetric cycloaddition of 1-(phenoxycarbonyl)-1,2-dihydropyridine 1 with dienophile 2 in the presence of Lewis acid (Table 1)

An oven-dried round-bottom flask containing a stir bar were charged dichloromethane (3 mL) solution of (4*S*)-**2** (116 mg, 0.50 mmol), molecular sieves 4 Å (200 mg) and Ti(*i*-PrO)$_2$Cl$_2$ (237 mg, 1.0 mmol) at room temperature and the solution was stirred for 30 min under nitrogen. Then the solution was cooled to 0 °C, and the dichloromethane (3 mL) solution of 1-(phenoxycarbonyl)-1,2-dihydropyridine **1** (201 mg, 1.0 mmol) was added and the solution was stirred at 0 °C for 24 h. The reaction was stopped by addition of saturated $NaHCO_3$ solution and water and the product was extracted with chloroform. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane), and *endo*-(4′*S*)-**3** was obtained in 99% yield (214 mg, 0.49 mmol) with 63% de Diastereomeric excess (% de) of *endo*-(4′*S*)-**3** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; eluent, 5% 2-propanol/*n*-hexane; flow rate, 0.8 mL/min: 254 nm, retention time, t_R (minor)=18 min, t_R (major)=28 min. The reaction conditions, chemical yields, and optical yields are shown in Table 1.

*4.2.1. Chiral isoquinuclidine derivative endo-(4′S)-**3** (63% de).* Yield 214 mg, 99%; $[\alpha]_D^{24}$ −42.6 (*c* 0.50, $CHCl_3$). ^1H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 1.54–1.59 (0.5H, m), 1.72–1.77 (0.5H, m), 2.14–2.19 (0.5H, m), 2.31–2.36 (0.5H, m), 2.71 (1H, dd, *J*=13.3, 9.8 Hz), 2.89–2.93 (1H, m), 3.09 (0.5H, td, *J*=10.63, 2.6 Hz), 3.22 (0.5H, td, *J*=10.4, 2.5 Hz), 3.29 (1H, d, *J*=13.3 Hz), 3.40 (1H, dd, *J*=10.6, 1.9 Hz), 3.56 (1H, dd, *J*=10.3, 1.9 Hz), 4.13–4.16 (2H, m), 4.21–4.29 (1H, m), 4.52–4.60 (1H, m), 5.17–5.19 (0.5H, m), 5.24–5.26 (0.5H, m), 6.48–6.51 (1H, m), 6.54–6.62 (1H, m), 7.12–7.14 (1H, m), 7.16–7.21 (4H, m), 7.24–7.28 (1H, m), 7.30–7.37 (4H, m); ^{13}C NMR [ppm] (125 MHz, $CDCl_3$, 20 °C): δ 28.58, 30.84, 37.79, 45.17, 46.66, 47.75, 55.60, 66.32, 121.81, 125.22, 127.42, 129.04, 129.23, 129.26, 129.38, 129.42, 130.73, 132.45, 133.57, 134.86, 135.20, 151.32, 152.65, 153.44, 173.01.

*4.2.2. Chiral isoquinuclidine derivative endo-(4′R)-**3** (58% de).* Yield 214 mg, 99%; $[\alpha]_D^{24}$ +30.6 (*c* 0.57, $CHCl_3$). ^1H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 1.54–1.59 (0.5H, m), 1.72–1.77 (0.5H, m), 2.14–2.19 (0.5H, m), 2.31–2.36 (0.5H, m), 2.71 (1H, dd, *J*=13.3, 9.8 Hz), 2.89–2.93 (1H, m), 3.09 (0.5H, td, *J*=10.63, 2.6 Hz), 3.22 (0.5H, td, *J*=10.4, 2.5 Hz), 3.29 (1H, d, *J*=13.3 Hz), 340 (1H, dd, *J*=10.6, 1.9 Hz), 3.56 (1H, dd, *J*=10.3, 1.9 Hz), 4.13–4.16 (2H, m), 4.21–4.29 (1H, m), 4.52–4.60 (1H, m), 5.17–5.19 (0.5H, m), 5.24–5.26 (0.5H, m), 6.48–6.51 (1H, m), 6.54–6.62 (1H, m), 7.12–7.14 (1H, m), 7.16–7.21 (4H, m), 7.24–7.28 (1H, m), 7.30–7.37 (4H, m); ^{13}C NMR [ppm]

(125 MHz, $CDCl_3$, 20 °C): δ 28.58, 30.84, 37.79, 45.17, 46.66, 47.75, 55.60, 66.32, 121.81, 125.22, 127.42, 129.04, 129.23, 129.26, 129.38, 129.42, 130.73, 132.45, 133.57, 134.86, 135.20, 151.32, 152.65, 153.44, 173.01.

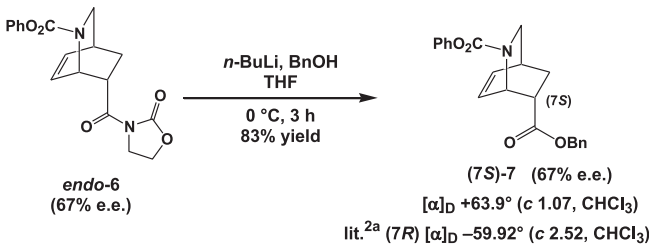
4.3. General procedure for asymmetric cycloaddition of 1-(phenoxycarbonyl)-1,2-dihydropyridine 1 with *N*-acryloyloxazolidin-2-one 5 using chiral titanium complex Ti-(2*R*,3*R*)-TADDOLate 4b (Table 2)

An oven-dried round-bottom flask containing a stir bar were charged toluene/hexane (2:1) (6 mL) solution, powdered molecular sieves 4 Å (230 mg), Ti(*i*-PrO)$_2$Cl$_2$ (35.5 mg, 0.15 mmol), and (2*R*,3*R*)-TADDOL (R^1=Ph, R^2=CH_3) (79.3 mg, 0.15 mmol) at room temperature and the solution was stirred for 30 min under nitrogen. When to the solution was added dienophile **5** (116 mg, 0.50 mmol) the color of the solution changed into yellow and the solution cooled to 0 °C. Then 1-(phenoxycarbonyl)-1,2-dihydropyridine **1** (201 mg, 1.00 mmol) was added and the solution was stirred at 0 °C for 24 h. The reaction was stopped by addition of saturated $NaHCO_3$ solution and the product was extracted with chloroform. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane), and *endo*-**6** was obtained in 98% yield (173 mg, 0.49 mmol) with 73% ee. Enantiomeric excess (% ee) was determined by HPLC analysis using a Daicel CHIRALPAK AD-H column; eluent, 25% 2-propanol/*n*-hexane; flow rate, 0.8 mL/min; 254 nm; retention time, t_R (minor)=34.7 min, t_R (major)=55.9 min. The reaction conditions, chemical yields, and optical yields are shown in Table 2.

*4.3.1. Chiral isoquinuclidine derivative endo-(7S)-**6** (73% ee).* Yield 173 mg, 98%; $[\alpha]_D^{24}$ +86.2 (*c* 1.00, $CHCl_3$). ^{1}H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 1.56 (0.5H, ttd, *J*=13.0, 5.6, 2.8 Hz), 1.71 (0.5H, ttd, *J*=13.0, 5.3, 2.8 Hz), 2.23 (0.5H, ddd, *J*=12.9, 10.1, 2.7 Hz), 2.39 (0.5H, ddd, *J*=13.0, 10.3, 2.6 Hz), 2.89–2.92 (1H, m), 3.09 (0.5H, td, *J*=10.7, 2.6 Hz), 3.22 (0.5H, td, *J*=10.4, 2.6 Hz), 3.41 (0.5H, dd, *J*=10.6, 2.0 Hz), 3.56 (0.5H, dd, *J*=10.3, 1.9 Hz), 3.90–4.03 (2H, m), 4.15–4.19 (0.5H, m), 4.23–4.27 (0.5H, m), 4.37–4.46 (2H, m), 5.10–5.12 (0.5H, m), 5.18–5.20 (0.5H, m), 6.46–6.50 (1H, m), 6.52–6.60 (1H, m), 7.11–7.13 (1H, m), 7.15–7.20 (2H, m), 7.33–7.37 (2H, m); ^{13}C NMR [ppm] (125 MHz, $CDCl_3$, 20 °C): δ 27.66, 28.60, 30.47, 30.75, 42.55, 42.69, 44.60, 44.78, 46.54, 47.09, 47.15, 62.12, 62.19, 121.75, 121.84, 125.16, 125.20, 129.18, 129.21, 130.89, 132.45, 133.43, 134.61, 151.24, 151.25, 152.85, 152.87, 152.89, 153.37, 154.85, 166.19, 172.87, 173.01.

4.4. Conversion of *endo*-(4′*S*)-6 to benzyl ester (7*S*)-7

An oven-dried round-bottom flask containing a stir bar was charged THF (4 mL) solution of benzyl alcohol (0.10 mL, 1.00 mmol) and to the solution was added *n*-BuLi (1.57 M in hexane, 0.50 mL, 0.78 mmol) at −78 °C under nitrogen and the solution was stirred for 5 min. Then to this solution was added the solution of *endo*-**6** {$[\alpha]_D^{24}$ +76.7 (*c* 1.42, $CHCl_3$), 67% ee; 178 mg, 0.52 mmol} in THF (2 mL), and the solution was warmed to 0 °C and stirred for 3 h. The reaction was quenched with 5 mL of saturated NH_4Cl solution and the product was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane), and benzyl ester *endo*-(7*S*)-**7** was obtained in 83% yield (162.2 mg, 0.43 mmol). The enantiomeric excess (67% ee) of (7*S*)-benzyl ester **7** {$[\alpha]_D^{24}$ +63.9 (*c* 1.07, $CHCl_3$)} as shown in the following Scheme was determined by HPLC analysis using a DAICEL CHIRALPAK AD-H column; eluent, 5% 2-propanol/hexane; flow rate, 0.8 mL/min; 254 nm; retention time, t_R (minor)=21.1 min, t_R (major)=23.8 min.



endo-6 (67% e.e.)

(7*S*)-7 (67% e.e.)

$[\alpha]_D$ +63.9° (*c* 1.07, $CHCl_3$)

lit.[2a] (7*R*) $[\alpha]_D$ −59.92° (*c* 2.52, $CHCl_3$)

*4.4.1. Benzyl ester endo-(7S)-**7**.* Yield 162.2 mg, 83%; $[\alpha]_D^{24}$ +63.9 (*c* 1.07, $CHCl_3$; 67% ee); lit.[2a] benzyl ester *endo*-(7*R*)-**7**: $[\alpha]_D^{24}$ −59.92 (*c* 2.52, $CHCl_3$; 97% ee). ^{1}H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 1.92–1.99 (2H, m), 2.91 (1H, br s), 3.04 (0.5H, td, *J*=10.6, 2.4 Hz), 3.16 (0.5H, d, *J*=10.2 Hz), 3.22–3.26 (1H, m), 3.35 (0.5H, dd, *J*=10.6, 2.1 Hz), 3.49 (0.5H, dd, *J*=10.2, 2.1 Hz), 5.06–5.16 (2H, m), 5.23–5.28 (1H, m), 6.33–6.38 (1H, m), 6.47–6.52 (1H, m), 7.09–7.17 (2H, m), 7.18–7.21 (1H, m), 7.29–7.37 (7H, m); ^{13}C NMR [ppm] (125 MHz, $CDCl_3$, 20 °C): δ 25.93, 30.60, 43.81, 46.91, 47.52, 66.56, 121.65, 121.72, 125.25, 128.07, 128.16, 128.21, 128.51, 128.55, 129.17, 129.21, 130.54, 135.69, 151.22, 153.58, 153.61, 172.33.

4.5. General procedure for cycloaddition of 1-(phenoxycarbonyl)-1,2-dihydropyridine 1 with chiral dienophile 2 in the presence of Ti-(2*R*,3*R*)-TADDOLate 4 (Tables 3–5)

An oven-dried round-bottom flask containing a stir bar was charged with toluene (3 mL) solution of (2*R*,3*R*)-TADDOL (R^1=Ph, R^2=Me) (79 mg, 0.15 mmol), dry powdered molecular sieves 4 Å (200 mg), and Ti(*i*-PrO)$_2$Cl$_2$ (36 mg, 0.15 mmol) at room temperature and the solution was stirred for 1 h under nitrogen. Then (4*S*)-**2** (116 mg, 0.50 mmol) was added and the solution was stirred at room temperature for 30 min, and the solution was cooled to 0 °C. To this solution was added the toluene (2 mL) solution of 1-(phenoxycarbonyl)-1,2-dihydropyridine **1** (201 mg, 1.0 mmol) and the solution was stirred at 0 °C for 24 h. Then saturated $NaHCO_3$ solution and water were added and the product was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane), and *endo*-(4′*S*)-**3** was obtained in 99% yield (214 mg, 0.49 mmol) with 92% de Diastereomeric excess (% de) of *endo*-(4′*S*)-**3** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 5% 2-propanol/hexane; flow rate, 0.8 mL/min, 254 nm; retention time, t_R (minor)=18 min, t_R (major)=28 min. The reaction conditions, chemical yields, and optical yields are shown in Tables 3–5.

*4.5.1. Chiral isoquinuclidine derivative endo-(4′S)-**3** (92% de).* Yield 214 mg, 99%; $[\alpha]_D^{24}$ −58.3 (*c* 0.50, $CHCl_3$). ^{1}H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 1.54–1.59 (0.5H, m), 1.72–1.77 (0.5H, m), 2.14–2.19 (0.5H, m), 2.31–2.36 (0.5H, m), 2.71 (1H, dd, *J*=13.3, 9.8 Hz), 2.89–2.93 (1H, m), 3.09 (0.5H, td, *J*=10.63, 2.6 Hz), 3.22 (0.5H, td, *J*=10.4, 2.5 Hz), 3.29 (1H, d, *J*=13.3 Hz), 3.40 (1H, dd, *J*=10.6, 1.9 Hz), 3.56 (1H, dd, *J*=10.3, 1.9 Hz), 4.13–4.16 (2H, m), 4.21–4.29 (1H, m), 4.52–4.60 (1H, m), 5.17–5.19 (0.5H, m), 5.24–5.26 (0.5H, m), 6.48–6.51 (1H, m), 6.54–6.62 (1H, m), 7.12–7.14 (1H, m), 7.16–7.21 (4H, m), 7.24–7.28 (1H, m), 7.30–7.37 (4H, m); ^{13}C NMR [ppm] (125 MHz, $CDCl_3$, 20 °C): δ 28.58, 30.84, 37.79, 45.17, 46.66, 47.75, 55.60, 66.32, 121.81, 125.22, 127.42, 129.04, 129.23, 129.26, 129.38, 129.42, 130.73, 132.45, 133.57, 134.86, 135.20, 151.32, 152.65, 153.44, 173.01.

*4.5.2. Chiral isoquinuclidine derivative endo-(4′R)-**3** (70% de).* Yield 119 mg, 55%; $[\alpha]_D^{24}$ +40.9 (*c* 0.85, $CHCl_3$). ^{1}H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 1.54–1.59 (0.5H, m), 1.72–1.77 (0.5H, m), 2.14–2.19

(0.5H, m), 2.31–2.36 (0.5H, m), 2.71 (1H, dd, J=13.3, 9.8 Hz), 2.89–2.93 (1H, m), 3.09 (0.5H, td, J=10.63, 2.6 Hz), 3.22 (0.5H, td, J=10.4, 2.5 Hz), 3.29 (1H, d, J=13.3 Hz), 3.40 (1H, dd, J=10.6, 1.9 Hz), 3.56 (1H, dd, J=10.3, 1.9 Hz), 4.13–4.16 (2H, m), 4.21–4.29 (1H, m), 4.52–4.60 (1H, m), 5.17–5.19 (0.5H, m), 5.24–5.26 (0.5H, m), 6.48–6.51 (1H, m), 6.54–6.62 (1H, m), 7.12–7.14 (1H, m), 7.16–7.21 (4H, m), 7.24–7.28 (1H, m), 7.30–7.37 (4H, m); ^{13}C NMR [ppm] (125 MHz, $CDCl_3$, 20 °C): δ 28.58, 30.84, 37.79, 45.17, 46.66, 47.75, 55.60, 66.32, 121.81, 125.22, 127.42, 129.04, 129.23, 129.26, 129.38, 129.42, 130.73, 132.45, 133.57, 134.86, 135.20, 151.32, 152.65, 153.44, 173.01.

4.6. Conversion of *endo*-(4′*S*)-3 to benzyl ester (7*R*)-7

An oven-dried round-bottom flask containing a stir bar was charged with THF (2 mL) solution of benzyl alcohol (0.08 mL, 0.8 mmol) and to this solution was added *n*-BuLi (1.57 M in hexane, 0.4 mL, 0.63 mmol) at −78 °C under nitrogen and the solution was stirred for 5 min. Then to this solution was added the solution of *endo*-(4′*S*)-**3** {$[\alpha]_D^{24}$ −65.6 (*c* 1.00, $CHCl_3$), 97% de; 121 mg, 0.28 mmol} in THF (4 mL), and the solution was warmed to 0 °C and stirred for 3 h. The reaction was quenched with 10 mL of saturated NH_4Cl solution and the product was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (25% ethyl acetate in hexane), and *endo*-(7*R*)-**7** was obtained in 78% yield (78.6 mg, 0.22 mmol). The enantiomeric excess (97% ee) of (7*R*)-benzyl ester **7** {$[\alpha]_D^{24}$ −81.4 (*c* 0.57, $CHCl_3$)} as shown in Scheme 4 was determined by HPLC analysis using a DAICEL CHIRALPAK AD-H column; eluent, 5% 2-propanol/hexane; flow rate, 0.8 mL/min, 254 nm; retention time, t_R (minor)=28.7 min, t_R (major)=32.0 min.

*4.6.1. Benzyl ester endo-(7R)-**7**.* $[\alpha]_D^{24}$ −81.4 (*c* 0.57, $CHCl_3$; 97% ee); Yield 78.6 mg, 78%; lit.[2a] $[\alpha]_D^{24}$ −59.92 (*c* 2.52, $CHCl_3$; 97% ee). ^{1}H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 1.92–1.99 (2H, m), 2.91 (1H, br s), 3.04 (0.5H, td, J=10.6, 2.4 Hz), 3.16 (0.5H, d, J=10.2 Hz), 3.22–3.26 (1H, m), 3.35 (0.5H, dd, J=10.6, 2.1 Hz), 3.49 (0.5H, dd, J=10.2, 2.1 Hz), 5.06–5.16 (2H, m), 5.23–5.28 (1H, m), 6.33–6.38 (1H, m), 6.47–6.52 (1H, m), 7.09–7.17 (2H, m), 7.18–7.21 (1H, m), 7.29–7.37 (7H, m); ^{13}C NMR [ppm] (125 MHz, $CDCl_3$, 20 °C): δ 25.93, 30.60, 43.81, 46.91, 47.52, 66.56, 121.65, 121.72, 125.25, 128.07, 128.16, 128.21, 128.51, 128.55, 129.17, 129.21, 130.54, 135.69, 151.22, 153.58, 153.61, 172.33. (7*S*)-benzyl ester **7** (99% ee): $[\alpha]_D^{24}$ +90.4 (*c* 0.71, $CHCl_3$); $[\alpha]_D^{24}$ +74.46 (*c* 0.39, DMSO); (7*R*)-benzyl ester **7** (97% ee): lit.[2b] $[\alpha]_D$ −59.92 (*c* 2.52, DMSO).

4.7. General procedure for cycloaddition of 1-(phenoxycarbonyl)-1,2-dihydropyridine 1 with chiral dienophile 2 in the presence of Cu(OTf)$_2$/(4*S*,4′*S*)-bis(oxazoline) 8 (Fig. 3)

An oven-dried round-bottom flask containing a stir bar was charged with dichloromethane (3 mL) solution of (4*S*,4′*S*)-bis(oxazoline) (*i*-C_3H_7-box ligand) **8b** (40 mg, 0.15 mmol), dry activated molecular sieves 4 Å (230 mg), and $Cu(OTf)_2$ (54 mg, 0.15 mmol) at room temperature and the solution was stirred for 1 h under nitrogen. Then (4*R*)-**2** (116 mg, 0.50 mmol) was added and the solution was stirred at room temperature for 30 min, and the solution was cooled to 0 °C. To this solution was added the dichloromethane (2 mL) solution of 1-(phenoxycarbonyl)-1,2-dihydropyridine **1** (201 mg, 1.0 mmol) and the solution was stirred at 0 °C for 24 h. Then saturated $NaHCO_3$ solution and water were added and the product was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexane), and *endo*-(7*S*)-**3** was obtained in 87% yield (188 mg, 0.435 mmol) with 97% de Diastereomeric excess (% de) of *endo*-(7*S*)-**3** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 5% 2-propanol/*n*-hexane; flow rate, 0.8 mL/min, 254 nm; retention time, t_R (minor)=20 min, t_R (major)=30 min.

*4.7.1. Chiral isoquinuclidine derivative endo-(7S)-**3** (97% de).* Yield 188 mg, 87%; $[\alpha]_D^{24}$ −65.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 1.54–1.59 (0.5H, m), 1.72–1.77 (0.5H, m), 2.14–2.19 (0.5H, m), 2.31–2.36 (0.5H, m), 2.71 (1H, dd, J=13.3, 9.8 Hz), 2.89–2.93 (1H, m), 3.09 (0.5H, td, J=10.63, 2.6 Hz), 3.22 (0.5H, td, J=10.4, 2.5 Hz), 3.29 (1H, d, J=13.3 Hz), 3.40 (1H, dd, J=10.6, 1.9 Hz), 3.56 (1H, dd, J=10.3, 1.9 Hz), 4.13–4.16 (2H, m), 4.21–4.29 (1H, m), 4.52–4.60 (1H, m), 5.17–5.19 (0.5H, m), 5.24–5.26 (0.5H, m), 6.48–6.51 (1H, m), 6.54–6.62 (1H, m), 7.12–7.14 (1H, m), 7.16–7.21 (4H, m), 7.24–7.28 (1H, m), 7.30–7.37 (4H, m); ^{13}C NMR [ppm] (125 MHz, $CDCl_3$, 20 °C): δ 28.58, 30.84, 37.79, 45.17, 46.66, 47.75, 55.60, 66.32, 121.81, 125.22, 127.42, 129.04, 129.23, 129.26, 129.38, 129.42, 130.73, 132.45, 133.57, 134.86, 135.20, 151.32, 152.65, 153.44, 173.01.

4.8. Preparation of 1-(phenoxycarbonyl)-1,2-dihydropyridine 1[8]

An oven-dried three necked round-bottom flask containing a stir bar was charged with pyridine (24.0 g, 303 mmol), ethanol (180 mL), and $NaBH_4$ (6.0 g,159 mmol) and the mixture were stirred together at −78 °C, and then phenyl chloroformate (32.0 g, 204 mmol) was added slowly to the solution by a dropping funnel for 1 h. The mixture was stirred at −78 °C for 24 h. The solution was poured into ice-water, and the mixture was stirred until the H_2 bubble stopped. The mixture was extracted with diethyl ether (100 mL×3) and the ether solution was dried over anhydrous sodium sulfate. The organic layer was filtered and the diethyl ether was removed in vacuo. The residue was recrystallized from ethanol to give the product **1** as a white solid in 67% yield (27.50 g, 136.7 mmol). The ratio of 1,2-dihydropyridine and 1,4-dihydropyridine (97:3) was measured by ^{1}H NMR (δ 4.44–4.59 and 2.89 ppm).

*4.8.1. 1-(Phenoxycarbonyl)-1,2-dihydropyridine **1**.* Yield 27.50 g, 67%; white solid (ethanol), mp 64–66 °C; ^{1}H NMR [ppm] (270 MHz, $CDCl_3$, 25 °C): δ 4.45 (1H, q, J=3.8, 2.0 Hz), 4.59 (1H, br s), 5.22–5.31 (1H, m), 5.59–5.62 (1H, m), 5.88–5.93 (1H, m), 6.84 (1H, dd, J=20.0, 7.7 Hz), 7.13 (2H, d, J=7.6 Hz), 7.22 (1H, t, J=8.2 Hz), 7.38 (2H, t, J=7.8 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz, 25 °C): δ 43.78, 105.82, 119.47, 121.54 (2C), 121.82, 125.35, 125.67, 126.06, 129.36 (2C), 150.81.

4.9. Preparation of *N*-acryloyl-4-benzyloxazolidin-2-one 2[9]

An oven-dried three necked round-bottom flask containing a stir bar was charged with solution of acrylic acid (1.88 g, 26 mmol), triethylamine (5.06 g, 50 mmol), and THF (100 mL) and to this solution was added acryloyl chloride (2.17 g, 24 mmol) at −20 °C. A white solid was formed instantaneously. The mixture was stirred at −20 °C for 1 h. Lithium chloride (1.06 g, 25 mmol) was added, followed by 4-benzyloxazolidin-2-one (3.540 g, 20 mmol). The mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched by addition of 0.2 M HCl (240 mL), and THF was removed in vacuo. The residue was partitioned between ethyl acetate and 0.2 M HCl (60 mL). The organic layer was washed subsequently with 0.2 M HCl (60 mL), brine (60 mL), 1 M sodium bicarbonate (60 mL, two times), and brine (60 mL). The organic solution was then dried over sodium sulfate and filtered. Ethyl acetate was removed in vacuo, and the white solid was dissolved in toluene. The toluene solution was filtered through a silica gel bed, and the white solid was washed with

toluene. Concentration of toluene solution to dryness afforded the *N*-acryloyl-4-oxazolidin-2-one **2**, which was recrystallized from hexane as a white crystalline solid (2.914 g, 63% yield).

*4.9.1. N-Acryloyl (4S)-4-benzyloxazolidin-2-one (4S)-**2**.* Yield 2.914 g, 63%; white solid (recrystallized from hexane), mp 72–73 °C; lit.[9a] mp 72–73 °C; $[\alpha]_D^{24}$ +85.0 (*c* 1.00, $CHCl_3$); lit.[9b] $[\alpha]_D^{24}$ +80.1 (*c* 2.41, $CHCl_3$). ^{1}H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 2.82 (1H, dd, *J*=13.5, 9.6 Hz), 3.36 (1H, dd, *J*=13.5, 3.3 Hz), 4.19–4.26 (2H, m), 4.72–4.77 (1H, m), 5.95 (1H, dd, *J*=10.5, 1.8 Hz), 6.62 (1H, dd, *J*=17.0, 1.8 Hz), 7.23 (2H, d, *J*=6.8 Hz), 7.29 (1H, t, *J*=7.3 Hz), 7.35 (2H, t, *J*=7.0 Hz), 7.52 (1H, dd, *J*=17.0, 10.5 Hz); ^{13}C NMR [ppm] (125 MHz, $CDCl_3$, 20 °C): δ 37.80, 55.32, 66.28, 127.38, 127.41, 129.01 (2C), 129.46 (2C), 132.00, 135.22, 153.35, 164.92.

*4.9.2. N-Acryloyl (4R)-4-benzyloxazolidin-2-one (4R)-**2**.* Yield 2.035 g, 44%; white solid (recrystallized from hexane), mp 71–72 °C; lit.[9a] mp 72–73 °C; $[\alpha]_D^{24}$ −83.4 (*c* 1.0, $CHCl_3$); lit.[9a] $[\alpha]_D^{24}$ −74.2 (*c* 0.84, $CHCl_3$). ^{1}H NMR [ppm] (500 MHz, $CDCl_3$, 20 °C): δ 2.82 (1H, dd, *J*=13.5, 9.6 Hz), 3.36 (1H, dd, *J*=13.5, 3.3 Hz), 4.19–4.26 (2H, m), 4.72–4.77 (1H, m), 5.95 (1H, dd, *J*=10.5, 1.8 Hz), 6.62 (1H, dd, *J*=17.0, 1.8 Hz), 7.23 (2H, d, *J*=6.8 Hz), 7.29 (1H, t, *J*=7.3 Hz), 7.35 (2H, t, *J*=7.0 Hz), 7.52 (1H, dd, *J*=17.0, 10.5 Hz); ^{13}C NMR [ppm] (125 MHz, $CDCl_3$, 20 °C): δ 37.80, 55.32, 66.28, 127.38, 127.41, 129.01 (2C), 129.46 (2C), 132.00, 135.22, 153.35, 164.92.

4.10. Preparation of (4*R*,5*R*)-α,α,α′,α′-2,2-hexaphenyl-4,5-dimethanol-1,3-dioxalone (TADDOL 4c, R^1=Ph, R^2=Ph)[11,17,18]

An oven-dried round-bottom flask containing a stir bar and reflux condenser was charged with a mixture of benzophenone (3.64 g, 20 mmol), dimethyl L-(+)-tartrate (7.13 g, 40 mmol), and trimethyl orthoformate (4.25 g, 40 mmol), acetonitrile (20 mL), and indium trichloride (0.22 g, 1 mmol) and the solution was refluxed for 7 days. The solution was cooled to room temperature, and the solution was concentrated under reduced pressure. Then the residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to give the acetal in 23% yield. An oven-dried three necked round-bottom flask containing a stir bar was charged with THF (4 mL) solution of 2 M PhMgBr/THF (12 mL, 24 mmol) and to this solution was added the THF (8 mL) solution of the acetal (1.37 g, 4.0 mmol) under nitrogen at 0 °C, and the solution was stirred at room temperature for 1 day. The reaction was quenched with saturated NH_4Cl solution (15 mL). The product was extracted with ethyl acetate and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. After the removal of ethyl acetate, the residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to give the TADDOL **4c** (R^1=Ph, R^2=Ph) in 77% yield.

*4.10.1. TADDOL **4c**.* White solid, mp 77–80 °C; $[\alpha]_D^{24}$ +150.6 (*c* 1.00, $CHCl_3$), lit.[18] $[\alpha]_D^{20}$ +187.7 (*c* 0.505, $CHCl_3$). ^{1}H NMR [ppm] (270 MHz, $CDCl_3$, 25 °C): δ 2.08 (2H, s), 5.53 (2H, s), 6.75–7.73 (30H, m); ^{13}C NMR [ppm] (97.8 MHz, $CDCl_3$, 25 °C): δ 79.49 (2C), 83.64 (2C), 112.06, 115.26, 124.94, 125.68, 126.18, 126.43, 126.57, 126.75, 127.08, 127.75, 127.94. 128.02, 128.20, 128.52, 129.16, 129.57, 142.32, 144.56, 145.69.

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