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An efficient synthetic methodology of chiral isoquinuclidines by the enantioselective Diels–Alder reaction of 1,2-dihydropyridines using chiral cationic palladium–phosphinooxazolidine catalyst

Hiroto Nakano,* Natsumi Tsugawa, Kouichi Takahashi, Yuko Okuyama and Reiko Fujita

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan

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Abstract—High purity chiral isoquinuclidines (97% ee) were obtained from the enantioselective Diels–Alder reaction of 1-phenoxycarbonyl-1,2-dihydropyridine with 1-benzyl-2-acryloylpyrazolidin-3-one using chiral cationic palladium–phosphinooxazolidine (Pd–POZ) catalyst. The obtained DA adduct was easily converted to the chiral piperidine derivative bearing three stereogenetic centers in the structure.

1. Introduction

The 2-azabicyclo[2.2.2]octanes (isoquinuclidines) are found widely in natural products such as iboga-type indole alkaloids, which have varied and interesting biological properties (Fig. 1).[1] Typical iboga-alkaloids include catharanthine **1**, which is the precursor of pharmacologically important vinca alkaloids such as vinblastine **3a** and vincristine **3b**.[2] Most recently, it was also indicated that ibogaine **2** reduces cravings for alcohol and other drugs by means of its ability to boost the levels of a growth factor known as glial cell line-derived neurotrophic factor (GDNF).[3] Furthermore, isoquinuclidines are also valuable intermediates in the synthesis of other alkaloids[4] and in medicinal chemistry.[5] Therefore, it is important to establish an effective asymmetric synthetic methodology for chiral isoquinuclidines. A well-established route to this ring system is through the Diels–Alder (DA) reaction of 1,2-dihydropyridines with dienophiles. However, little research on the asymmetric version of this reaction has been reported, and most reports are of diastereoselective versions of the reaction, which used 1,2-dihydropyridines or dienophiles attached to a chiral auxiliary.[6] Despite the obvious advantages of its catalytic enantioselective version, to the best of our knowledge,

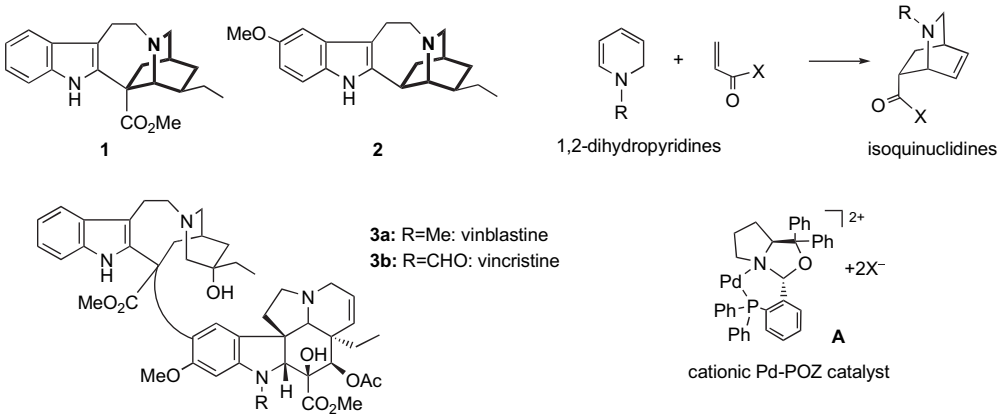

Figure 1.

Keywords: Enantioselective Diels–Alder reaction; 1,2-Dihydropyridine; Chiral cationic palladium–phosphinooxazolidine catalyst; Chiral isoquinuclidines; Chiral piperidines.
* Corresponding author. Tel.: +81 22 727 0147; fax: +81 22 275 2013; e-mail: hnakano@tohoku-pharm.ac.jp

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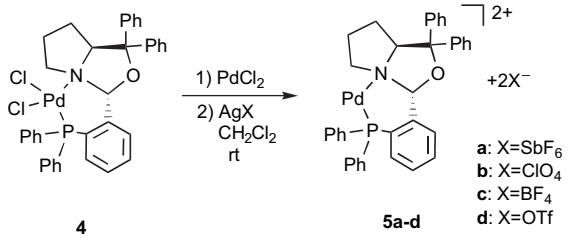
only one example employing a Cr–BINAM catalyst has been reported to date by Rawal et al. for the catalytic enantioselective version of the DA reaction. However, the reaction afforded only modest asymmetric induction (up to 85% ee).[7] Most recently, we have reported that the enantioselective DA reaction of 1,2-dihydropyridines with 1-substituted acryloylpyrazolidin-3-ones using a Pd–POZ catalyst is an efficient synthetic methodology for obtaining chiral isoquinuclidines at synthetically useful levels of enantiomeric excess (ee).[8]

In this paper, we describe the details of the first successful enantioselective DA reaction of 1,2-dihydropyridines with 1-substituted acryloylpyrazolidin-3-ones using a Pd–POZ catalyst,[8] and also the convenient transformation of the obtained DA adduct to the chiral piperidine derivative bearing three chiral carbon centers in the structure.

2. Results and discussion

2.1. Diels–Alder reaction with acryloyl-1,3-oxazolidine-2-one

We first tested the DA reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **6a** or 1-benzyloxycarbonyl-1,2-dihydropyridine **6b** with common 2-acryloyl-1,3-oxazolidine-2-one **7**. The reaction was carried out at 0 °C or −25 °C in CH_2Cl_2 in the presence of 10 mol % of the cationic Pd–POZ catalysts **5a–d** that were prepared by the reactions of $PdCl_2$–POZ complex **4** and the corresponding AgX (X=SbF_6, ClO_4, BF_4, OTf) using our previously reported procedure (Scheme 1).[9] As a result, antimonate catalyst **5a** at −25 °C and perchlorate catalyst **5b** at 0 °C gave the *endo*-DA adduct **8a** in good chemical yields and enantioselectivities (entries 2 and 5, Table 1). The other 1,2-dihydropyridine, 1-benzyloxycarbonyl-1,2-dihydropyridine **6b**, was also used in the same reaction. Although the reaction proceeded with an excellent chemical yield to afford **8b**, the enantioselectivity was moderate. In both reactions, enantioselectivity over 90% ee was not achieved as in the results of Rawal et al.[7]

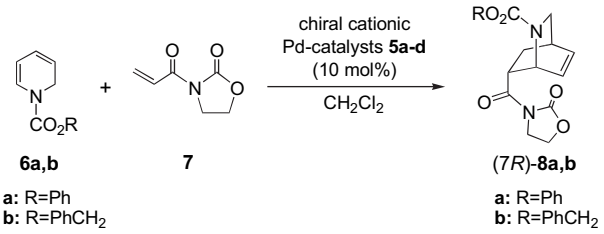


Scheme 1. Preparations of cationic POZ complexes **5a–d**.

2.2. Diels–Alder reaction with 1-substituted 2-acryloylpyrazolidin-3-ones

In order to improve the enantioselectivity of the reaction, we explored the possibilities presented in a report by Sibi et al.,[10] who examined a novel 1-substituted 2-crotonylpyrazolidin-3-one as a dienophile based on the concept of 'chiral relay', and reported that the combination of this dienophile and nonoptimized Cu–bis-oxazoline catalyst can bring about an excellent asymmetric induction in the DA reaction with cyclopentadiene as a diene. However, a fairly high level of catalytic loading (50 mol %) was needed for the achievement of satisfactory enantioselectivity in the reaction. We applied the 1-substituted 2-pyrazolidin-3-one dienophile to the DA reactions of 1,2-dihydropyridines **6a–c** using cationic Pd–POZ catalysts **5a–d**.

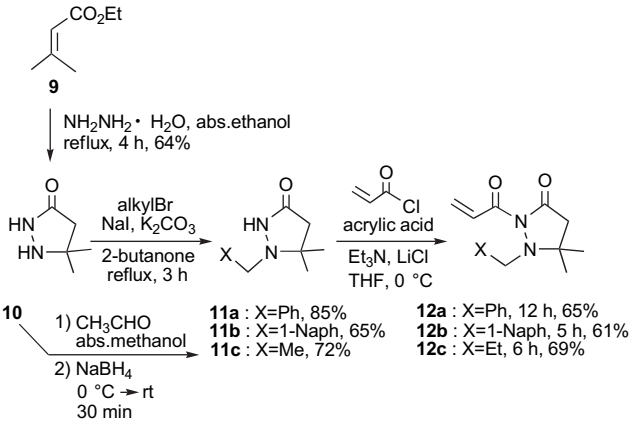
Table 1. Enantioselective DA reactions of 1,2-dihydropyridines **6a**,**b** with 2-acryloyl-1,3-oxazolidine-2-one **7**



Entry	Diene	Catalyst	Temp (°C)	Time (h)	DA adduct	Yield (%)[a]	ee (%)[b]
1	**6a**	**5a**	0	24	**8a**	98	76
2	**6a**	**5b**	0	24	**8a**	90	84
3	**6a**	**5c**	0	24	**8a**	46	88
4	**6a**	**5d**	0	24	**8a**	37	74
5	**6a**	**5a**	−25	48	**8a**	84	82
6	**6a**	**5b**	−25	48	**8a**	73	82
7	**6b**	**5a**	0	24	**8b**	90	74

[a] Isolated yields.
[b] Enantiomeric excess of *endo*-isomer was determined by chiral HPLC using a Daicel AD or AD-H column.

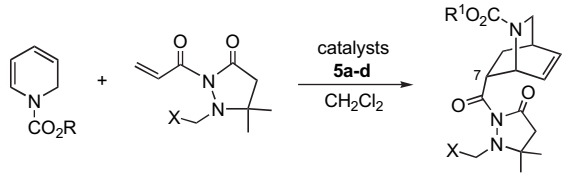
Although Sibi et al. used 1-substituted 2-crotonylpyrazolidin-3-ones as a dienophile, we applied the simplest 1-substituted 2-acryloylpyrazolidin-3-ones to our DA reaction. 2-Acryloylpyrazolidin-3-ones **12a–c** were prepared following the procedure reported by Sibi et al.[10] and Perri et al.[11] (Scheme 2). Thus, 3,3-dimethylacrylate **9** was converted to 5,5-dimethylpyrazolidin-3-one **10** by the reaction with hydrazine monohydrate. N-Alkylation of **10**, followed by the reactions of **11a**,**b** with acryloyl chloride, afforded the dienophiles **12a**[10] and **b** in moderate to good yields. On the other hand, dienophile **12c** was obtained from the condensation of **10** with acetaldehyde, followed by the reduction of the imino moiety and then the reaction of the obtained **11c** with acryloyl chloride in a moderate yield.



Scheme 2. Preparations of dienophiles **12a–c**.

First, we examined the effectiveness of dienophiles **12a–c** using superior antimonate catalyst **5a**. The reactions of diene **6a** with dienophiles **12a–c** were carried out at 0 °C in the presence of 10 mol % of the prepared Pd–POZ catalysts **5a–d** to give the corresponding *endo*-DA adducts **13a–c**. The results are summarized in Table 2. A significant difference was observed in chemical yield and enantioselectivity corresponding to the different substituent groups on the nitrogen at the 1-position. A dramatic increase in enantioselectivity to 97% ee was accomplished with good chemical yield when 1-benzyl substituted derivative **12a** was used as a dienophile (80%, entry 1). Despite our expectations, the bulkier 1-naphthylmethyl derivative **12b** brought about a decrease in both chemical yield and enantioselectivity (entry 2). Similarly, the reaction using the less bulky 1-ethyl substituted derivative **12c** was also sluggish, although the reasons for this remain unclear (entry 3). Next, we examined the effects of other counterions such as perchlorate, tetrafluoroborate, and triflate on the reaction with superior dienophile **12a**. As a result, cationic perchlorate catalyst **5b** and tetrafluoroborate catalyst **5c** afforded the DA adduct **13a** in high enantioselectivities with good chemical yields (entries 4 and 5). In particular, **5c** showed the best enantioselectivity (97% ee) with 76% yield (entry 5), the results are almost identical to those achieved with antimonate catalyst **5a**. However, triflate catalyst **5d** did not give satisfactory reactivity and enantioselectivity (60%, 89% ee, entry 6). The reactions with superior cationic catalysts **5a** and **c** at −25 °C did not afford better results for chemical yields and enantioselectivities than the results at 0 °C (entries 7 and 8). Furthermore, the effect of reducing the molar ratio of catalyst **5a** was examined. At low catalytic loading to 5 mol % of **5a**, equally satisfactory results (78%, 95% ee) were obtained, but the use of 2.5 mol % greatly decreased both the chemical yield and enantioselectivity (59 and 84% ee, entries 9 and 10). These results indicate that the antimonate POZ catalyst **5a** and 1-benzylpyrazolidin-3-one dienophile **12a** were most effective in obtaining chiral isoquinuclidines **13a** with excellent enantioselectivity. Other 1,2-dihydropyridines **6b**[6g] and **c**[6g] were also examined using superior antimonate catalyst **5a** and dienophile **12a** (entries 11 and 12). The reactions were carried out at 0 °C in the presence of 10 mol % of the prepared Pd–POZ catalysts **5a** to give the corresponding *endo*-DA adducts **13d** and **e**, respectively. However, the results of both reactions did not exceed the result of diene **6a**.

Table 2. Enantioselective DA reactions of dienes **6a–c** with **12a–c**



6a-c
a: R=Ph
b: R=CH_2Ph
c: R=Bu^t

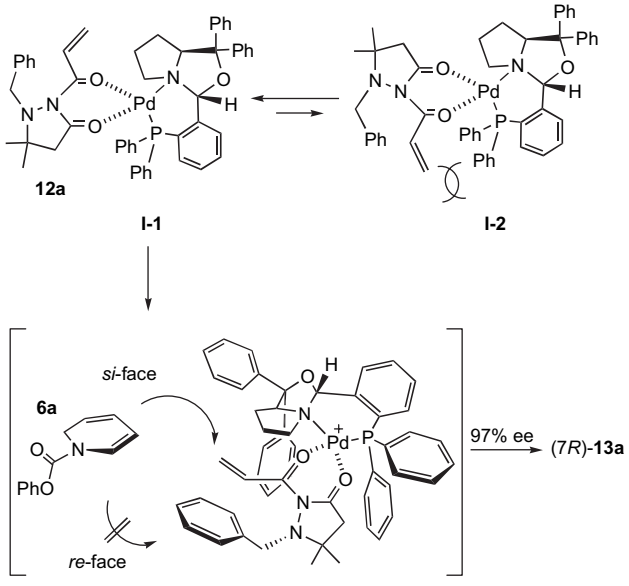
12a-c
a: X=Ph
b: X=1-Naph
c: X=Me

[7*R*]-**13a-e**
a: R=Ph, X=Ph
b: R=Ph, X=1-Naph
c: R=Ph, X=Me
d: R=CH_2Ph, X=Ph
e: R=Bu^t, X=Ph

Entry	Diene	Dienophile	Cat. (mol %)	Temp (°C)	Time (h)	DA adduct	Yield[a] (%)	ee[b] (%)
1	**6a**	**12a**	**5a** (10)	0	24	**13a**	80	97
2	**6a**	**12b**	**5a** (10)	0	72	**13b**	47	33
3	**6a**	**12c**	**5a** (10)	0	72	**13c**	44	43
4	**6a**	**12a**	**5b** (10)	0	24	**13a**	87	94
5	**6a**	**12a**	**5c** (10)	0	24	**13a**	76	97
6	**6a**	**12a**	**5d** (10)	0	24	**13a**	60	89
7	**6a**	**12a**	**5a** (10)	−25	48	**13a**	76	95
8	**6a**	**12a**	**5c** (10)	−25	48	**13a**	76	89
9	**6a**	**12a**	**5a** (5)	0	24	**13a**	78	95
10	**6a**	**12a**	**5a** (2.5)	0	24	**13a**	59	84
11	**6b**	**12a**	**5a** (10)	0	24	**13d**	74	89
12	**6c**	**12a**	**5a** (10)	0	24	**13e**	85	67

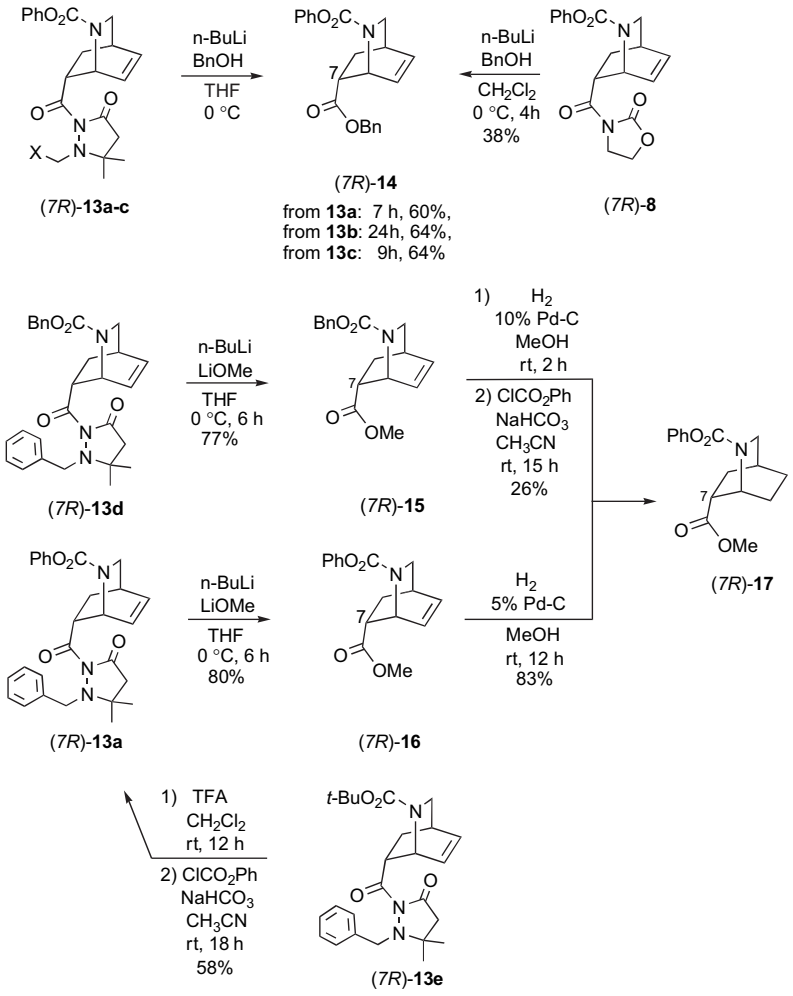
[a] Isolated yields.
[b] Enantiomeric excess of *endo*-isomer was determined by HPLC analysis using a DAICEL Chiralcel AD-H column.

Based on the X-ray structure of $PdCl_2$–POZ complex **4**[9a] and the high enantiopurity (97% ee) of the chiral DA adduct (7*R*)-**13a** that was obtained from the reaction of diene **6a** with dienophile **12a**, a model of the enantioselective reaction course was proposed as follows (Scheme 3). Thus, the reaction might be through the intermediate **I-1** that has a less steric interaction between the diphenylphosphino substituent on the phenyl group in the catalyst and the olefin part of the dienophile. Then, the diene might attack from the *si*-face of the acryloyl group on the dienophile rather than the *re*-face that was masked by the 1-benzyl group on the dienophile to afford (7*R*)-**13a**.



Scheme 3. Plausible reaction course for DA reaction of **6a** with **12a**.

The absolute stereochemistry assignments of the new DA adducts **13a–e** were carried out as follows (Scheme 4). For the assignments of **13a–c**, both **13a–c** and the known (7*R*)-**8a** were converted to benzyl ester **14**. Thus, the reactions of **13a–c** or (7*R*)-**8** with BnOH using *n*-BuLi as a base in THF afforded (7*R*)-benzyl ester **14** in moderate yields (**13a**: 60%; **13b**: 64%; **13c**: 64%; **7**: 38%). Furthermore, both the DA adducts **13d** and (7*R*)-**13a** were converted to methyl esters **15** and (7*R*)-**16**, respectively, by the reactions with LiOMe for the assignment of **13d**. And then, the reduction of the olefin moiety in **15**, followed by the exchange from the benzyloxycarbonyl group to the phenoxycarbonyl



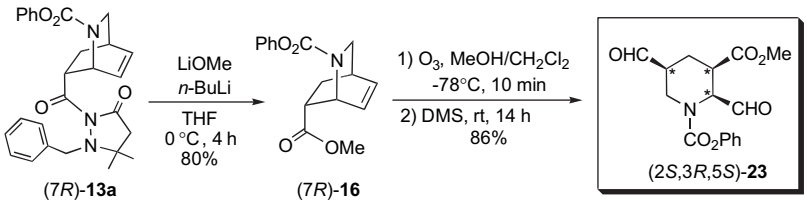
Scheme 4. Absolute configurations of DA adducts **13a**–**e**.

group on nitrogen at the 2-position afforded the compound (7*R*)-**17** in 26% yield. Similarly, (7*R*)-**16** was also transformed to (7*R*)-**17** in a good yield. In addition, the DA adduct **13e** was converted to (7*R*)-**13a** by the decarboxylation and the phenoxycarboxylation on nitrogen at the 2-position in a moderate yield.

We also examined the effectiveness of six kinds of chiral catalysts (Pd–hydroxyPOZ-**18a** and **18b**,[9b] 2-azanorbornane-based Pd–POZ-**19**,[9b] Cu–bis-oxazoline-**20**,[10] Pd–BINAP-**21**,[12] and phosphinooxazoline-**22**[13] catalysts) in the DA reaction of superior diene **6a** with dienophile **12a**. The reactions were carried out at 0 °C in the presence of 10 mol % of catalysts **18**–**22** to give the corresponding DA adduct **13a**. The results are shown in Table 3. The catalytic abilities of our developed 7-hydroxy-POZ catalysts **18a** and **b** in this reaction were contrastive. Thus, the reaction using the 2,7-*cis*-catalyst **18a** proceeded with 82% yield and 91% ee (entry 1). On the other hand, 2,7-*trans*-catalyst **18b** gave only low chemical and moderate enantioselectivity (44%, 79% ee, entry 2). The contrast of the results between **18a** and **b** might be due to the steric factor of the 7-hydroxy group. The more conformationally constrained cationic POZ catalyst **19**, fusing the 2-azanorbornane ring system, was applied in this reaction. Unfortunately, the catalyst **19** did not afford a better result than the result of **5a** in fusing the pyrrolidine ring system (entry 3). The effective catalyst **20** in Sibi's experiment[10] did not show catalytic activity when 10 mol % of **20** was used (entry 4). Catalyst **21**, acting as a superior catalyst in many reactions, had low reactivity and afforded only moderate chemical yield (57%) even at 72 h of reaction time, although it gave excellent enantioselectivity (96% ee, entry 5). Furthermore, catalyst **22** gave DA adduct **13a** in a low chemical yield (31%), but with 85% ee (entry 6). These results indicated that the combination of the POZ catalyst **8a** and dienophile **12a** was the most effective combination for this reaction.

2.3. Transformation from isoquinuclidines to piperidines

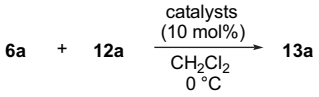
Many medicines and biologically active compounds include a piperidine skeleton[14] in their structures. Therefore, it is important to develop an effective and convenient synthetic methodology for chiral piperidines bearing two or more chiral carbon centers in the structure. In order to develop such a methodology, we attempted to obtain the chiral piperidine derivative bearing three carbon centers by means of the ozonolysis of DA adduct **16** converted from **13a** (Scheme 5). The desired chiral piperidine derivative **23** bearing three chiral carbon centers at 2,3,5-positions was obtained with good yield, as well as we expected.



(7*R*)-**13a** (7*R*)-**16** (2*S*,3*R*,5*S*)-**23**

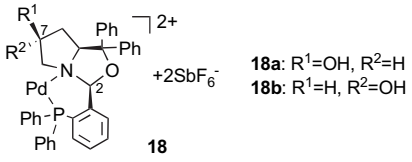
Scheme 5. Transformation from **13a** to piperidine **23**.

Table 3. Catalyst screen



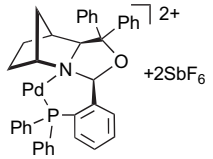
Entry	Catalyst	Time (h)	Yield[a] (%)	ee[b] (%)	Config.[c]
1	**18a**	24	82	91	7*R*
2	**18b**	24	44	79	7*R*
3	**19**	24	54	10	7*S*
4	**20**	72	No reaction	—	—
5	**21**	72	57	96	7*S*
6	**22**	24	31	85	7*S*

[a] Isolated yields.
[b] Enantiomeric excess of *endo*-isomer was determined by HPLC analysis using a DAICEL Chiralcel AD column.
[c] After conversion to benzyl ester [7*R*]-**14**, the absolute configuration was determined.



18a: R^1=OH, R^2=H
18b: R^1=H, R^2=OH

18



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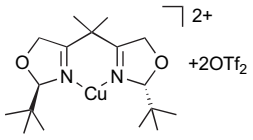

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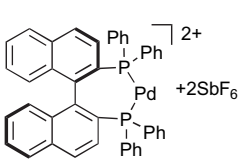

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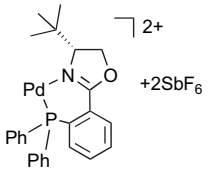

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3. Conclusion

In conclusion, we have developed an efficient methodology for obtaining the chiral isoquinuclidines that are the precursor of pharmacologically important compounds. Thus, the DA reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **6a** with 1-benzyl-2-acryloylpyrazolidin-3-one **12a** as a dienophile using cationic antimonate Pd–POZ catalyst **5a** afforded the corresponding DA adduct **13a** at 97% ee with good chemical yield. Furthermore, the obtained DA adduct **13a** was easily transformed to the chiral piperidine **23** that bears three chiral carbon centers in the structure. Compound **23** might have a high potential utility as the synthetic intermediate of the pharmacologically important chiral piperidines and other alkaloids. In addition, these results indicate that the combination of Pd–POZ catalyst **5** with 1-substituted pyrazolidin-3-one dienophile **12** is useful not only in the DA reaction of 1,2-dihydropyridine but also in other asymmetric processes.

4. Experimental

4.1. General information

Melting points are uncorrected. IR spectra were recorded as KBr pellets (solids) or thin films (liquids). ^{1}H NMR spectra were recorded at 270 and 400 MHz. ^{13}C NMR spectra were recorded at 67.5 and 100 MHz. The chemical shifts are reported in parts per million downfield to TMS (δ=0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.0) for ^{13}C NMR. Mass spectra were obtained by EI. The enantiomeric excess (ee) of the products was determined by chiral HPLC. Optical rotations were recorded at the sodium D line with a polarimeter at room temperature. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Chromatography refers to flash chromatography on silica gel (230–400 mesh), unless otherwise noted.

4.2. General procedure for the DA reaction of 1,2-dihydropyridines 6a,b with 2-acryloyl-1,3-oxazolidine-2-one 7 catalyzed by cationic Pd–POZ complexes 5a–d

A suspension of $PdCl_2$–POZ complex **4** (0.07 mmol) and AgX (X=SbF_6, ClO_4, BF_4, OTf) (2 equiv) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h under Ar. The suspension was cooled to 0 °C and diene **6a** or **b** (3.5 mmol) and dienophile **7** (0.7 mmol) were added. The reaction mixture was stirred under Ar. The mixture was then quenched with satd $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtrated, and concentrated under a reduced pressure. The residue was purified by flash chromatography (hexane/AcOEt, 1/1) to afford **8**. The reaction conditions, chemical yields, and optical yields are shown in Table 1.

4.2.1. (1*R*,4*R*,7*R*)-7-(2′-Oxo-oxazolidine-3′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid benzyl ester (8b). Yield 118 mg, 90%; white solid (*n*-hexane), mp 37–38 °C; IR (KBr) 2929, 2342, 1781, 1694, 697 cm^{-1}; ^{1}H NMR (DMSO-d_6, 100 °C) δ 1.54–1.63 (m, 1H), 2.05 (ddd, *J*=2.6, 9.8, 12.6 Hz, 1H), 2.84 (m, 1H), 2.92 (dt, *J*=2.7, 10.2 Hz, 1H), 3.28 (d, *J*=10.1 Hz, 1H), 3.80–3.89 (m, 2H), 4.00 (ddd, *J*=2.7, 5.4, 9.8 Hz, 1H), 4.32–4.38 (m, 2H),

4.92 (m, 1H), 5.08 (s, 2H), 6.32–6.44 (m, 2H), 7.28–7.36 (m, 5H); ^{13}C NMR (DMSO-d_6, 100 °C) δ 26.88, 29.72, 42.13, 43.33, 46.24, 46.37, 61.84, 65.54, 126.80 (2C), 127.06, 127.73 (2C), 130.66, 133.44, 152.50, 153.69, 163.65, 171.59; MS *m/z* 356 (M^+); HRMS (EI) calcd for $C_{19}H_{20}N_2O_5$ (M^+) 356.1372, found 356.1365. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.12, H, 5.70; N, 7.72. The enantiomeric excess (ee) was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=28.5 min, t_R (major)=35.4 min).

4.3. General procedure for the preparation of pyrazolidin-3-ones 12b,c

To a solution of acrylic acid (1.53 mmol) and Et_3N (2.95 mmol) in THF (10 mL) was added acryloyl chloride (1.60 mmol) at −25 °C and the mixture was stirred for 1 h under Ar. Lithium chloride (1.30 mmol) was added, followed by the pyrazolidin-3-ones, **11b** (1.18 mmol) or **11c** (1.18 mmol). The mixture was allowed to warm to room temperature and stirred for 6 h. The reaction was quenched by satd NaCl and THF was removed under a reduced pressure. The residue was partitioned between AcOEt and satd NaCl. The organic layer was washed with satd Na_2CO_3. The organic layers were then dried over anhydrous $MgSO_4$, filtrated, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford **12b** and **12c**, respectively.

4.3.1. 2-Acryloyl-1-(1-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one (12b). Yield 223 mg, 61%; white solid (*n*-hexane), mp 120–122 °C; IR (KBr) 1599, 1669, 1766 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6H), 2.75 (s, 2H), 4.45 (br s, 2H), 5.01 (m, 1H), 5.84 (d, *J*=15.9 Hz, 1H), 6.36 (m, 1H), 7.36 (t, *J*=4.2 Hz, 1H), 7.48 (t, *J*=1.2 Hz, 2H), 7.56 (t, *J*=1.5 Hz, 1H), 7.77 (d, *J*=8.3 Hz, 1H), 7.82 (d, *J*=8.3 Hz, 1H), 8.17 (d, *J*=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.93, 30.89, 43.00, 55.20, 61.45, 123.22, 125.33, 125.59, 126.29, 127.54, 128.72, 128.74, 129.31, 129.41, 133.63, 163.38, 173.96; MS *m/z* 308 (M^+); HRMS (EI) calcd for $C_{19}H_{20}N_2O_2$ (M^+) 308.1525, found 308.1539. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.12; H, 6.51; N, 8.87.

4.3.2. 2-Acryloyl-1-ethyl-5,5-dimethylpyrazolidin-3-one (12c). Yield 158 mg, 72%; pale yellow oil; IR (NaCl) 1694, 1749 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J*=7.2 Hz, 3H), 1.33 (s, 6H), 2.60 (s, 2H), 3.01 (q, *J*=7.1 Hz, 2H), 5.86 (d, *J*=12.2 Hz, 1H), 6.55 (d, *J*=17.1 Hz, 1H), 7.27 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.79, 25.75, 43.79, 47.31, 60.67, 128.57, 131.30, 163.76, 175.11; MS *m/z* 196 (M^+); HRMS (EI) calcd for $C_{10}H_{16}N_2O_2$ (M^+) 196.1212, found 196.1226. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.28; H, 8.31; N, 14.16.

4.4. General procedure for the DA reaction of 1,2-dihydropyridine 6a with 2-acryloylpyrazolidin-3-ones 12a–c using cationic Pd–POZ complexes 5a–d

A suspension of $PdCl_2$–POZ complex **4** (10 mol %: 28 mg, 5 mol %: 14 mg, 2.5 mol %: 7 mg) and AgX (X=SbF_6, ClO_4, BF_4, OTf) (2 equiv) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h under Ar. The suspension was cooled to 0 °C and diene **6a** (402 mg, 2.0 mmol) and pyrrazolidin-3-ones **12a–c** (0.4 mmol) in CH_2Cl_2 (1 mL) were added under Ar. The reaction mixture was stirred under Ar. The reaction was then quenched with satd $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford **13a–c**. The reaction conditions, chemical yields, and optical yields are shown in Table 2.

4.4.1. (1*R*,4*R*,7*R*)-7-(1′-Benzyl-5′,5′-dimethyl-3′-oxo-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid phenyl ester (13a). White solid (AcOEt/*n*-hexane), mp 165–168 °C; $[\alpha]_D^{20}$ −52.94 (*c* 0.68, $CHCl_3$); IR (KBr) 1216, 1524, 1644, 3020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12–1.24 (m, 6H), 1.59 (m, 1H), 2.06 (m, 1H), 2.58 (m, 1H), 2.67 (m, 1H), 2.84 (br s, 1H), 3.06 (d, *J*=10.6 Hz, 0.5H), 3.18 (d, *J*=10.3 Hz, 0.5H), 3.35 (d, *J*=10.6 Hz, 0.5H), 3.50 (d, *J*=10.3 Hz, 0.5H), 4.00 (br s, 1H), 4.03 (br s, 2H), 5.07 (br s, 1H), 6.39–6.44 (m, 2H), 7.13 (m, 1H), 7.13–7.38 (m, 7H), 7.43–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.80, 26.65, 27.51, 30.76, 43.50, 45.54, 46.79, 47.20, 57.10, 60.93, 121.78, 121.83, 125.13, 127.45, 127.50, 128.37, 128.88, 128.99, 129.18, 129.23, 130.84, 133.65, 137.58, 151.36, 153.38, 169.68, 173.91; MS *m/z* 459 (M^+); HRMS (EI) calcd for $C_{27}H_{29}N_3O_4$ (M^+) 459.2158, found 459.2176. Anal. Calcd for $C_{27}H_{29}N_3O_4$: C, 70.57; H, 6.36; N, 9.14. Found: C, 70.62; H, 6.21; N, 9.25. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=12.70 min, t_R (major)=14.38 min).

4.4.2. (1*R*,4*R*,7*R*)-7-(1′-Naphthylmethyl-5′,5′-dimethyl-3′-oxo-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid phenyl ester (13b). White solid (AcOEt/*n*-hexane), mp 170–172 °C; $[\alpha]_D^{20}$ −20.13 (*c* 1.49, $CHCl_3$); IR (KBr) 1238, 1596, 1717, 2969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35–1.41 (m, 6H), 1.58 (m, 1H), 2.18 (m, 1H), 2.63–2.71 (m, 2H), 2.83 (m, 1H), 3.00–3.13 (m, 2H), 3.54 (m, 1H), 4.32 (m, 1H), 4.57 (m, 1H), 4.87 (m, 1H), 6.10 (t, *J*=6.5 Hz, 0.5H), 6.18 (t, *J*=6.7 Hz, 0.5H), 6.28 (m, 1H), 7.12 (d, *J*=7.6 Hz, 1H), 7.17–7.22 (m, 2H), 7.35–7.40 (m, 3H), 7.42–7.58 (m, 2H), 7.65 (m, 1H), 7.78 (t, *J*=7.4 Hz, 1H), 7.86 (t, *J*=7.9 Hz, 1H), 8.21 (t, *J*=9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.92, 27.22, 30.33, 30.58, 43.22, 46.50, 46.90, 47.44, 54.98, 55.18, 121.72, 121.74, 123.25, 123.33, 125.13, 125.15, 125.35, 125.45, 125.74, 125.85, 126.39, 128.48, 128.76, 129.23, 129.27, 131.77, 133.71, 151.40, 151.43, 153.15, 173.85; MS *m/z* 509 (M^+); HRMS (EI) calcd for $C_{31}H_{31}N_3O_4$ (M^+) 509.2315, found 509.2336. Anal. Calcd for $C_{31}H_{31}N_3O_4$: C, 73.06; H, 6.13; N, 8.25. Found: C, 73.11; H, 6.01; N, 8.36. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=15.00 min, t_R (major)=17.98 min).

4.4.3. (1*R*,4*R*,7*R*)-7-(1′-Ethyl-5′,5′-dimethyl-3′-oxo-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid phenyl ester (13c). White solid (AcOEt/*n*-hexane), mp 130–133 °C; $[\alpha]_D^{20}$ −33.98 (*c* 1.53, $CHCl_3$); IR (KBr) 1207, 1596, 1711, 2979 cm^{-1}; ^{1}H NMR ($CDCl_3$)

δ 1.02–1.07 (m, 3H), 1.24–1.31 (m, 6H), 1.70 (m, 1H), 2.21 (m, 1H), 2.53–2.64 (m, 2H), 2.89 (br s, 1H), 2.90–3.01 (m, 2H), 3.09 (d, J=10.5 Hz, 0.5H), 3.22 (d, J=10.2 Hz, 0.5H), 3.40 (d, J=10.5 Hz, 0.5H), 3.55 (d, J=10.2 Hz, 0.5H), 4.12 (m, 1H), 5.17 (m, 0.5H), 5.19 (m, 0.5H), 6.44–6.54 (m, 2H), 7.11–7.21 (m, 3H), 7.31–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.95, 25.77, 25.99, 30.84, 44.04, 45.70, 45.87, 47.03, 47.94, 121.78, 121.90, 125.09, 125.18, 129.15, 129.22, 132.19, 133.53, 134.36, 151.40, 152.96, 153.37; MS m/z 397 (M^+); HRMS (EI) calcd for $C_{22}H_{27}N_3O_4$ (M^+) 397.2002, found 397.1996. Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.57; H, 6.94; N, 10.38. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=9.96 min, t_R (major)=11.75 min).

4.5. General procedure for the DA reaction of 1,2-dihydropyridines 6b,c with 2-acryloylpyrazolidin-3-one 12a

A suspension of $PdCl_2$–POZ complex **4** (0.03 mmol) and $AgSbF_6$ (0.06 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h under Ar. The suspension was cooled to 0 °C and the solution of dienophile **12a** (0.26 mmol) in CH_2Cl_2 (1 mL) and **6b** (1.30 mmol) or **6c** (1.30 mmol) was added at that temperature. The reaction mixture was stirred under Ar for 24 h. The mixture was then quenched with satd $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford the corresponding DA adducts **13d** and **13e**, respectively. The reaction conditions, chemical yields, and optical yields are shown in Table 2.

4.5.1. (1*R*,4*R*,7*R*)-7-(1′-Benzyl-5′,5′-dimethyl-3′-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid benzyl ester (13d). White solid (AcOEt/*n*-hexane), mp 158–162 °C; $[\alpha]_D^{20}$ −25.20 (*c* 1.23, $CHCl_3$); IR (KBr) 1232, 1495, 1689, 1755, 2957 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.81–1.27 (m, 6H), 1.54 (m, 1H), 2.05 (br s, 1H), 2.52–2.67 (m, 2H), 2.77 (m, 1H), 3.01 (m, 1H), 3.31 (m, 1H), 3.99 (d, J=6.6 Hz, 1H), 4.01–4.08 (m, 2H), 5.05 (m, 1H), 5.11–5.17 (m, 2H), 6.28–6.37 (m, 2H), 7.21–7.33 (m, 4H), 7.35–7.39 (m, 5H), 7.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.87, 26.60, 26.63, 27.55, 30.73, 43.52, 45.57, 46.65, 46.78, 57.00, 66.81, 127.39, 127.47, 127.66, 127.83, 127.89, 127.94, 128.01, 128.34, 128.36, 128.45, 128.84, 128.91, 131.65, 133.67, 136.91, 137.69, 154.96; MS m/z 473 (M^+); HRMS (EI) calcd for $C_{28}H_{31}N_3O_4$ (M^+) 473.2315, found 473.2320. Anal. Calcd for $C_{28}H_{31}N_3O_4$: C, 71.01; H, 6.60; N, 8.87. Found: C, 71.18; H, 6.72; N, 8.98. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=12.97 min, t_R (major)=14.55 min).

4.5.2. (1*R*,4*R*,7*R*)-7-(1′-Benzyl-5′,5′-dimethyl-3′-oxo-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid-*tert*-butyl ester (13e). White solid (AcOEt/*n*-hexane), mp 155–158 °C; $[\alpha]_D^{20}$ −30.98 (*c* 1.42, $CHCl_3$); IR (KBr) 1236, 1496, 1688, 1756, 2981 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19–1.23 (m, 6H), 1.45–1.48 (m, 9H), 1.53 (m, 1H), 2.01 (m, 1H), 2.54–2.66 (m, 2H), 2.72 (d, J=1.8 Hz, 1H), 2.90 (d, J=10.3 Hz, 0.5H), 2.94 (d, J=10.6 Hz, 0.5H), 3.23 (t, J=5.1 Hz, 1H), 3.90 (br s, 1H), 4.03 (d, J=1.7 Hz, 2H), 4.80 (br s, 0.5H), 5.00 (br s, 0.5H), 6.28–6.37 (m, 2H), 7.22–7.31 (m, 3H), 7.45 (d, J=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.99, 26.50, 27.63, 28.50, 28.54, 30.63, 30.90, 31.23, 43.54, 45.84, 46.58, 47.10, 60.81, 127.34, 128.31, 128.35, 128.77, 128.82, 131.23, 133.42, 134.00, 137.80, 154.23, 154.46; MS m/z 439 (M^+); HRMS (EI) calcd for $C_{25}H_{33}N_3O_4$ (M^+) 439.2471, found 439.2452. Anal. Calcd for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 70.48; H, 7.65; N, 9.78. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=7.89 min, t_R (major)=12.97 min).

4.6. Determinations of the absolute stereochemistries of 13a–c, d, and e

4.6.1. General procedure for the conversion of DA adducts 8 or 13a–c to benzyl ester 14. To a stirred solution of benzyl alcohol (0.1 mL, 1.0 mmol) in anhydrous THF (6 mL) was added *n*-BuLi (1.0 M in *n*-hexane, 0.73 mL, 0.78 mmol) at −78 °C under Ar. The reaction mixture was stirred for 5 min and then the solution of (7*R*)-**8** or **13a–c** (0.52 mmol) in THF was added to the mixture at 0 °C. After being stirred for 3 h, the reaction was quenched by satd NH_4Cl and the solvent was removed under a reduced pressure, diluted with water, and extracted with $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under a reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/AcOEt, 1/3) to afford (7*R*)-**14** (**8**: 75 mg, 38%; **13a**: 113 mg, 57%; **13b**: 121 mg, 61%; **13c**: 127 mg, 64%). The absolute stereochemistries of **13a–c** were determined in comparison with the optical rotation of (7*R*)-**14** derived from (7*R*)-**8**.

4.6.2. (1*R*,4*R*,7*R*)-1-Phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-benzylcarboxylate (14). Colorless oil [**14** (from **8**, 76% ee): $[\alpha]_D^{21}$ −47.77 (*c* 0.90, $CHCl_3$); **14** (from **13a**, 97% ee): $[\alpha]_D^{21}$ −59.92 (*c* 2.52, $CHCl_3$); **14** (from **13b**, 33% ee): $[\alpha]_D^{21}$ −12.50 (*c* 0.64, $CHCl_3$); **14** (from **13c**, 43% ee): $[\alpha]_D^{21}$ −33.33 (*c* 0.75, $CHCl_3$)]; IR (NaCl) 1216, 1595, 1713, 3019 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.91–2.07 (m, 2H), 2.91 (br s, 1H), 3.05 (d, J=10.6 Hz, 0.5H), 3.16 (d, J=10.3 Hz, 0.5H), 3.24 (m, 1H), 3.35 (d, J=10.6 Hz, 0.5H), 3.49 (d, J=10.3 Hz, 0.5H), 5.07–5.16 (m, 2H), 5.26 (m, 1H), 6.36 (m, 1H), 6.52 (m, 1H), 7.04–7.13 (m, 2H), 7.19 (m, 1H), 7.30–7.41 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 26.00, 30.67, 43.87, 46.96, 47.58, 66.61, 121.69, 121.76, 125.22, 128.11, 128.20, 128.25, 128.55, 128.59, 129.21, 129.25, 130.15, 135.26, 151.27, 153.06, 153.62, 172.36; MS m/z 363 (M^+); HRMS (EI) calcd for $C_{22}H_{21}NO_4$ (M^+) 363.1471, found 363.1471.

4.6.3. (1*R*,4*R*,7*R*)-1-Benzyloxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-methylcarboxylate (15). To the solution of lithium methoxide (1.0 M in methanol, 0.6 mL, 0.6 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (1.0 M in *n*-hexane, 0.42 mL, 0.45 mmol) and the solution of **13d** (89% ee, 140 mg, 0.3 mmol) in THF (8 mL) was added at that temperature. The mixture was stirred at 0 °C

for 6 h. The reaction was quenched by satd NH_4Cl and extracted with $CHCl_3$. The organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under a reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/AcOEt, 3/1) to afford (7*R*)-**15** (70 mg, 77% yield). Colorless oil; $[\alpha]_D^{20}$ −74.75 (*c* 1.03, $CHCl_3$); IR (NaCl) 1216, 1587, 1692, 1732, 3019 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85–1.87 (m, 2H), 2.84 (m, 1H), 3.00 (m, 1H), 3.09 (m, 1H), 3.31 (m, 1H), 3.66 (s, 3H), 5.09 (m, 1H), 5.12–5.20 (m, 2H), 6.35 (m, 1H), 6.45 (m, 1H), 7.28–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.98, 30.61, 43.73, 46.73, 47.09, 51.95, 66.88, 127.84, 127.91, 127.95, 127.99, 128.46, 128.50, 130.23, 130.63, 135.14, 135.45; MS *m*/*z* 301 (M^+); HRMS (EI) calcd for $C_{17}H_{19}NO_4$ (M^+) 301.1314, found 301.1288.

4.6.4. (1*R*,4*R*,7*R*)-1-Phenoxycarbonyl-2-azabicyclo-[2.2.2]octane-7-methylcarboxylate (17). A suspension of **15** (50 mg, 0.17 mmol) and 10% Pd–C (18 mg, 0.17 mmol) in methanol (5 mL) was stirred under H_2 at room temperature for 2 h. Pd–C (10%) was filtered off and the filtrate was concentrated under a reduced pressure. The obtained residue without purification was dissolved in CH_3CN (1.5 mL). To the solution, phenyl chloroformate (0.02 mL, 0.17 mmol) and $NaHCO_3$ (43 mg, 0.51 mmol) were added and the mixture was stirred at room temperature for 15 h under Ar. The reaction was quenched by satd NH_4Cl and extracted with $CHCl_3$. The organic layers were dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 3/2) to afford (7*R*)-**17** (13 mg, 26% yield). White solid (AcOEt/*n*-hexane), mp 68–70 °C; $[\alpha]_D^{20}$ −56.80 (*c* 1.02, $CHCl_3$); IR (KBr) 1202, 1591, 1704, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59–1.79 (m, 3H), 1.85–2.09 (m, 2H), 2.22 (m, 1H), 3.07 (m, 1H), 3.45 (s, 1H), 3.58 (m, 1H), 3.68–3.74 (m, 3H), 4.47 (br s, 0.5H), 4.53 (br s, 0.5H), 7.09–7.21 (m, 3H), 7.32–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.0, 23.3, 23.7, 25.9, 42.7, 45.5, 46.5, 49.2, 121.7, 121.8, 125.1, 129.2 (2C), 129.3, 151.4, 153.6; MS *m*/*z* 289 (M^+); HRMS (EI) calcd for $C_{16}H_{19}NO_4$ (M^+) 289.1314, found 289.1290.

4.6.5. (1*R*,4*R*,7*R*)-1-Phenoxycarbonyl-2-azabicyclo-[2.2.2]oct-5-ene-7-methylcarboxylate (16). To a solution of lithium methoxide (1.0 M in methanol, 1.70 mL, 1.70 mmol) in THF (10 mL) were added *n*-BuLi (1.0 M in *n*-hexane, 1.20 mL, 1.30 mmol) and the solution of **13a** (>99% ee, 400 mg, 0.87 mmol) in THF (23 mL) at −78 °C. The mixture was stirred at 0 °C for 4 h. The reaction was quenched by satd NH_4Cl and extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The residue was purified by flash chromatography (AcOEt/$CHCl_3$, 1/3) to afford (7*R*)-**16** (199 mg, 80% yield). White solid (AcOEt/*n*-hexane), mp 76–78 °C; $[\alpha]_D^{20}$ −68.18 (*c* 1.98, $CHCl_3$); IR (KBr) 1204, 1570, 1703, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90–1.98 (m, 2H), 2.92 (br s, 1H), 3.05 (d, *J*=10.6 Hz, 0.5H), 3.16–3.22 (m, 1.5H), 3.5 (d, *J*=10.3 Hz, 0.5H), 3.48 (m, 0.5H), 3.67–3.71 (m, 3H), 5.21 (m, 0.5H), 5.27 (m, 0.5H), 6.42 (m, 1H), 6.52 (m, 1H), 7.07–7.14 (m, 2H), 7.19 (m, 1H), 7.31–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.96, 30.61, 30.87, 43.61, 46.85, 47.50, 51.95, 121.64, 121.69, 125.15, 125.22, 129.16, 129.21, 135.19, 135.69, 151.23; MS *m*/*z* 287 (M^+); HRMS (EI) calcd for $C_{16}H_{17}NO_4$ (M^+) 287.1158, found 287.1176.

4.6.6. Conversion of 16 to 17. The suspension of **16** (103 mg, 0.36 mmol) and 5% Pd–C (8 mg, 0.36 mmol) in methanol (12 mL) was stirred under H_2 at room temperature for 12 h. Pd–C (5%) was filtered off and the solvent was removed under a reduced pressure to give the (7*R*)-**17** [86 mg, 83% yield, $[\alpha]_D^{20}$ −61.03 (*c* 1.00, $CHCl_3$)].

4.6.7. Conversion of 13e to 13a. To the solution of **13e** (67% ee, 33 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (TFA) (0.01 mL, 0.11 mmol), and the mixture was stirred at room temperature for 12 h. The reaction was quenched by 1 N HCl and extracted with $CHCl_3$. The organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under a reduced pressure. The obtained residue was dissolved in CH_3CN, phenyl chloroformate (0.01 mL, 0.08 mmol) and $NaHCO_3$ (21 mg, 0.25 mmol) were added to the solution. The solution was stirred at room temperature for 18 h. The reaction was quenched by satd NH_4Cl and extracted with $CHCl_3$. The organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 2/1) to afford (7*R*)-**13a** [23 mg, 38% yield, $[\alpha]_D^{20}$ −24.99 (*c* 1.36, $CHCl_3$)].

4.7. General procedure for the DA reaction of 1,2-dihydropyridine 6a with 2-acryloylpyrazolidin-3-one 12a using cationic Pd–POZ complexes 18a,b and 19

A suspension of $PdCl_2$–POZ complexes (0.04 mmol) and $AgSbF_6$ (0.08 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h under Ar. To the suspension of the obtained catalysts **18a**,**b** or **19** was added the solution of **12a** (0.4 mmol) in CH_2Cl_2 (1 mL) and **6a** (2.0 mmol) at 0 °C. The reaction was stirred at that temperature for 24 h under Ar. The mixture was then quenched with satd $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford **13a**. The reaction conditions, chemical yields, and optical yields are shown in Table 3.

4.8. General procedure for the DA reaction of 1,2-dihydropyridine 6a with 2-acryloyl-1,3-oxazolidine-2-one 12a using cationic Pd–POZ complexes 20–22

To a suspension of chiral catalysts **20**–**22** (0.04 mmol) prepared by the previous reported methods[6g,12,13] in CH_2Cl_2 (1 mL) was added the solution of **12a** (0.4 mmol) in CH_2Cl_2 (1 mL) and **6a** (2.0 mmol) at 0 °C and the suspension was stirred at that temperature under Ar. The reaction conditions are shown in Table 3. The mixture was then quenched with satd $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford **13a**. The reaction conditions, chemical yields, and optical yields are shown in Table 3.

4.9. Transformation of 16 to chiral piperidine derivative 23

4.9.1. (2*S*,3*R*,5*S*)-2,5-Diformyl-1-phenoxycarbonyl-piperidin-3-methylcarboxylate (23). O_3 was bubbled through a MeOH/CH_2Cl_2 (1/1) (6 mL) of DA adduct **16** (115 mg, 0.4 mmol) at −78 °C. After 10 min, the ozone stream from the blue solution was immediately removed from the mixture, which was then purged with N_2 for 5 min. Excess dimethyl sulfide (1 mL) was quickly added and the solution was allowed to reach room temperature slowly (12 h), and then quenched with brine and extracted with AcOEt. The organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 2/1) to give the product **23** (110 mg, 86%). Pale yellow solid (AcOEt/*n*-hexane), mp 63–65 °C; $[\alpha]_D^{20}$ −54.37 (*c* 1.84, $CHCl_3$); IR (KBr) 1413, 1594, 1719, 2954, 3446 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61–1.71 (m, 1H), 2.57–2.60 (m, 2H), 2.63–3.00 (m, 2H), 3.78–3.81 (m, 3H), 4.63 (m, 1H), 5.51 (d, J=5.1 Hz, 1H), 7.12–7.16 (m, 2H), 7.25 (m, 1H), 7.38–7.42 (m, 2H), 9.68 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 23.28, 42.03, 47.78, 52.44, 60.40, 60.63, 121.45, 121.52, 125.93, 125.99, 128.70, 129.50, 129.78, 197.97, 199.77; MS *m*/*z* 319 (M^+); HRMS (EI) calcd for $C_{16}H_{17}NO_6$ (M^+) 319.1056, found 319.1049.

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