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ASYMMETRIC 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZOMETHINE IMINES WITH ACROLEIN CATALYZED BY L-PROLINE AND ITS DERIVATIVES.

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Abstract – 1,3-Dipolar cycloadditions between acrolein and various *N*,*N*'-cyclic azomethine imines in the presence of L-proline and its derivatives as organocatalysts were investigated. Reactions that were catalyzed by (*S*)-indline-2-carboxylic acid (30 mol%) in $CHCl_3$/MeOH 97:3 (v/v) showed high *exo*-selectivities *(exo*/*endo* 91:9 ~ 99:1) and enantioselectivities (75 ~ 98% ee). In contrast, reactions catalyzed by L-proline (30 mol%) under similar conditions favored the *endo*-cycloadduct (83:27 ~ 99:1) with modest to good enantioselectivities (31 ~ 83% ee). Based on our studies, the diastereoselective mechanism of the L-proline-catalyzed reaction was found to involve the isomerization of the *exo*- to the *endo*-cycloadduct in the presence of L-proline.

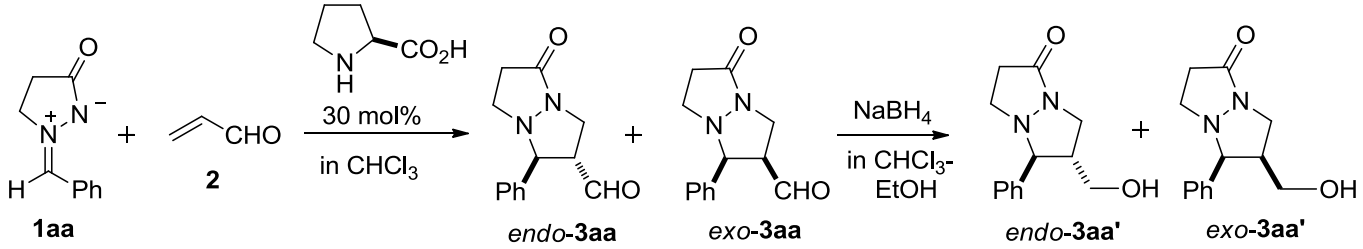
INTRODUCTION

1,3-Dipolar cycloadditions have served as powerful and effective reactions in the construction of five-membered heterocyclic compounds, commonly found within the fundamental frameworks of numerous biologically important natural products.[1, 2c] During the past two decades, various catalytic asymmetric 1,3-dipolar cycloadditions that are catalyzed by chiral Lewis acids and organocatalysts have been developed.[2] For the contribution of such asymmetric dipolar cycloaddition chemistry, we have recently reported on chiral Ni(II) complexes of binaphthyldiimine (BINIM) as highly effective catalysts for providing high levels of asymmetric induction for the cycloadditions of nitrones,[3] azomethine imines,[4]

nitrile oxides,[5] and carbonyl ylides.[6] For the reactions between *N*,*N*'-cyclic azomethine imines and 3-acryloyl-2-oxazolidinone, the catalytic effects of the BINIM-Ni(II) complexes were also evident in terms of rate acceleration with high *endo*- and enantioselectivity of the cycloadducts.[4] Upon further investigations using ^{1}H NMR, the BINIM-Ni(II) complex was found to be predominantly coordinated to the azomethine imine rather than 3-acryloyl-2-oxazolidinone during the reaction. In contrast to the BINIM-Ni(II)-catalyzed reactions, the use of aminoindanol-derived bis(oxazoline)-Cu(OTf)$_2$ as the catalyst resulted in high *exo*- and enantioselectivities for similar cycloadditions involving *N*,*N*'-cyclic azomethine imines and 2-acryloyl-3-pyrazolidinones.[7] However, for such chiral Lewis acid-catalyzed reactions, good reactivities with high enantioselectivities were limited to acrylic acid derivatives as the dipolarophiles, presumably due to the relatively basic nature of the *N*,*N*'-cyclic azomethine imines.[8] High levels of asymmetric induction have been reported for the organocatalytic [3+2] cycloadditions of *N*,*N*'-cyclic azomethine imines catalyzed by α,α-bis-[3,5-di(trifluoromethyl)phenyl]prolinol[9] (*exo*-selectivity) and 9-amino-9-deoxyepiquinine derivatives[10] (*endo*-selectivity). For these reactions, the disubstituted alkenes, which possess an aldehyde or ketone moiety, were effectively activated as the dipolarophiles – specifically, the above organocatalytic cycloadditions involve β-substituted-α,β-unsaturated aldehydes and cyclohexenone, respectively. Acrolein, however, remained to be employed as a dipolarophile for these organocatalytic cycloadditions of *N*,*N*'-cyclic azomethine imines. In this paper, we describe the cycloadditions between acrolein and *N*,*N*'-cyclic azomethine imines that are catalyzed by either **L**-proline to selectively give the corresponding *endo*-cycloadducts with good enantioselectivity, or by (*S*)-indoline-2-carboxylic acid to give the *exo*-cycloadducts with extremely high diastereo- and enantioselectivities.

RESULTS AND DISCUSSION

Cycloadditions of azomethine imines catalyzed by L-proline



Scheme 1

Initially, the cycloaddition between azomethine imine **1aa** and acrolein (**2**) was carried out in the presence

Table 1. **L**-proline-catalyzed cycloaddition reaction of azomethine imine **1aa** with acrolein (**2**)[a]

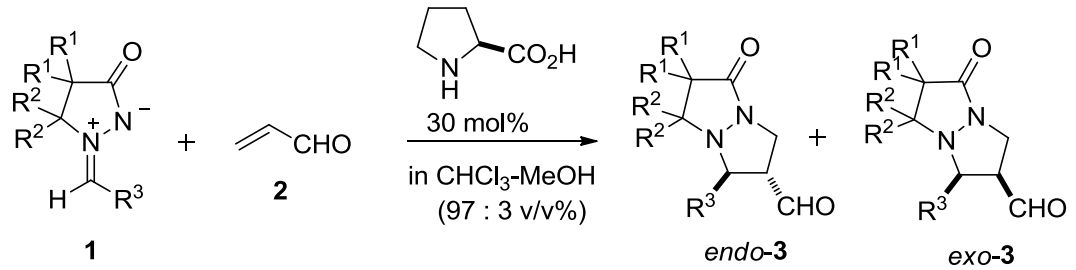
Entry	Purification of $CHCl_3$[b]	Additive (%, v/v)[c]	Time (h)	Yield (%)[d]	*endo*/*exo*[e]	% ee[f] *endo*	*exo*
1	No	None	17	93	88 : 12	78	74
2	Yes	None	5	66	57: 43	48	58
3	Yes	EtOH (0.1)	17	90	80 : 20	73	64
4	Yes	EtOH (1.0)	20	94	86 : 14	75	69
5	Yes	*i*-PrOH (1.0)	21	53	85 : 15	76	74
6	Yes	MeOH (0.1)	15	81	76 : 24	73	68
7	Yes	MeOH (0.5)	28	84	92 : 8	73	68
8	Yes	MeOH (1.0)	19	85	91 : 9	77	ND
9	Yes	MeOH (2.0)	28	93	95 : 5	79	77
10	Yes	MeOH (3.0)	24	87	94 : 6	83	84
11	Yes	MeOH (4.0)	24	83	89 : 11	83	88
12	Yes	MeOH (5.0)	19	86	78 : 22	76	84
13[g]	Yes	MeOH (3.0)	34	90	73 : 27	79	88

[a] The reaction was carried out in $CHCl_3$ in the presence of **L**-proline (30 mol%) at 25 ^oC. [b] No: commercial grade $CHCl_3$ (stabilized with EtOH, 0.3 ~ 1.0%, v/v; Kanto Kagaku) was used without further purifications, Yes: $CHCl_3$ purified by drying with $CaCl_2$ then distilled over P_2O_5. [c] Percent values (v/v) are based on the volume of $CHCl_3$. [d] The yield of the corresponding alcohols after reduction with $NaBH_4$. [e] Determined using ^1H NMR analysis. [f] Determined using chiral HPLC (Daicel Chiralpak AD-H) analysis after conversion to the corresponding alcohol via $NaBH_4$ reduction. [g] 10 mol% of **L**-proline was used.

of **L**-proline (30 mol%) as the catalyst (Scheme 1, Table 1). Although the reaction in CH_2Cl_2 was unsuccessful,[11] presumably due to the insolubility of **L**-proline, the reaction in $CHCl_3$ (commercial grade) at 25 ^oC for 17 h gave the cycloadducts in high yield with an *endo*/*exo* ratio of 88:12 (entry 1).[12] The cycloadducts were isolated, after reduction with $NaBH_4$, as the corresponding alcohols. Enantiomeric excesses of the *endo*- (78% ee) and *exo*-cycloadducts (74% ee) were determined using HPLC analysis of the corresponding alcohols. Interestingly, under similar conditions, the use of purified $CHCl_3$ (dried over $CaCl_2$, followed by distillation over P_2O_5) resulted in a lower yield with decreased diastereo- and enantioselectivity (entry 2). Because commercial grade $CHCl_3$ contains 0.3 ~ 1.0% (v/v) EtOH as a

stabilizer, we decided to examine the inclusion of alcohols such as EtOH, *i*-PrOH, and MeOH as additives of dried and purified $CHCl_3$. Among the three alcohols (entries 4, 5, and 8), the addition of MeOH was found to give the highest diastereo- and enantioselectivity of the *endo*-cycloadduct (entry 8), in which an amount of 3.0% (v/v) MeOH gave the optimal diastereo- (*endo*/*exo* 94:6) and enantioselectivity (83% ee) (entry 10). Finally, a lower catalyst loading (10 mol%) resulted in slightly lower diastereo- (*endo*/*exo* 73:27) and enantioselectivity (79% ee) of the *endo*-cycloadduct (entry 13). Although a precise role of MeOH is not clear, an addition of MeOH presumably increases solubility of L-proline and accelerates the formation of an active iminium ion. An amount of the solvent ($CHCl_3$/MeOH 97:3 (v/v), 42 mL for 0.5 mmol scale) is also important factor for the reaction rate probably because of solubility of L-proline.

Table 2. **L**-proline-catalyzed reactions of azomethine imines with acrolein (**2**)[a]



Entry	R^1	R^2	R^3	**1**	Time (h)	**3**	Yield (%)[b]	*endo*/*exo*[c]	% ee[d], *endo*
1	H	H	Ph	**1aa**	24	**3aa**	87	94 : 6	83 (84)[e]
2	Me	H	Ph	**1ba**	14	**3ba**	89	87 : 13	78 (83)[e]
3	H	Me	Ph	**1ca**	39	**3ca**	50	90 : 10	79 (69)[e]
4	H	H	*p*-ClC_6H_4	**1ab**	24	**3ab**	68	99 : 1	74
5	H	H	*o*-ClC_6H_4	**1af**	48	**3af**	81	88 : 12	50
6	H	H	*p*-MeC_6H_4	**1ag**	24	**3ag**	88	99 : 1	74
7	H	H	2-Naphthyl	**1ai**	24	**3ai**	85	99 : 1	82
8	H	H	Cyclohexyl	**1aj**	52	**3aj**	78	> 99 : 1	31
9	H	H	Isobutyl	**1ak**	52	**3ak**	54	83 : 27	32

[a] The reactions were carried out in purified $CHCl_3$/MeOH 97:3 (v/v) in the presence of **L**-proline (30 mol%) at 25 °C. [b] The yield of the corresponding alcohols after reduction with $NaBH_4$. [c] Determined using ^1H NMR analysis. [d] Determined using chiral HPLC (Daicel Chiralpak AD-H or OD-H) analysis after conversion to the corresponding alcohol via $NaBH_4$ reduction. [e] Enantioselectivity of the *exo*-cycloadduct.

Next, the cycloadditions were carried out under the optimized conditions using azomethine imines **1ba** and **1ca**, which possess dimethyl substituents at their pyrazolidinone ring (Table 2, entries 2 and 3, respectively), to afford the corresponding *endo*-cycloadducts with relatively good enantioselectivities. The scope of the R^3-substituent was investigated using azomethine imines with *p*- and *o*-substituted phenyl, 2-naphthyl, and alkyl substituents. As shown in entries 4 – 9, the reactions exhibited good to high *endo*-selectivities. Although the imines with *p*-substituted phenyl and 2-naphthyl substituents showed relatively good enantioselectivities, the *o*-chlorophenyl- and alkyl-substituted imines resulted in merely moderate enantioselectivities.

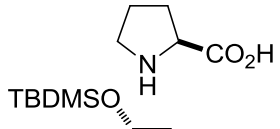
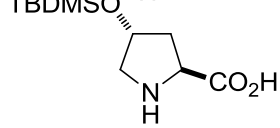
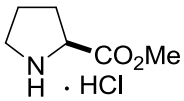
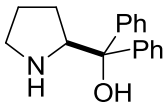
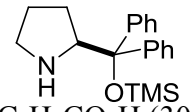
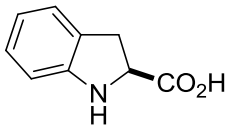
Cycloaddition of azomethine imine 1aa catalyzed by other L-proline derivatives

In attempts to improve the enantioselectivity, several other L-proline derivatives were evaluated as organocatalysts, as shown in Table 3 (Scheme 1). The use of L-proline derivative **4** (entry 2), which possesses a bulky TBDMSO-substituent at the 4-position of the pyrrolidine ring, failed to improve the enantioselectivity of the *endo*-cycloadduct. The use of L-proline methyl ester hydrochloride (**5**) resulted in a reversal of the facial selectivity, albeit with only slight asymmetric induction (entry 3). Although the combination of L-prolinol **6** and *p*-nitrobenzoic acid as catalysts resulted in a low-yielding reaction with only slight *exo*- and enantioselectivity (entry 4), the combination of TMS ether **7** and *p*-nitrobenzoic acid gave the *endo*-cycloadduct selectively in a high yield (entry 5), thus providing a complimentary enantioselectivity of the *endo*-cycloadduct to that of L-proline with the opposite facial selectivity. Surprisingly, the reaction catalyzed by (*S*)-indoline-2-carboxylic acid selectively gave the *exo*-cycloadduct in a high yield with good enantioselectivity (entry 6). Finally, although a longer reaction time was necessary, lowering the reaction temperature to 0 ^{o}C helped improve the *exo*/*endo*- (91:1) and enantioselectivity (94% ee) (entry 7).

Cycloadditions of azomethine imines catalyzed by (*S*)-indoline-2-carboxylic acid

The reaction of azomethine imine **1aa** with acrolein (**2**) in the presence of 10 mol% (*S*)-indoline-2-carboxylic acid under similar conditions resulted in decreased yield and *exo*-selectivity with good enantioselectivity of *exo*-adduct (Table 4, entry 2). The cycloadditions between acrolein (**2**) and dimethyl-substituted azomethine imines **1ba** and **1ca** proceeded smoothly in the presence of (*S*)-indoline-2-carboxylic acid (30 mol%) in $CHCl_3$/MeOH 97:3 (v/v) at 0 ^{o}C to selectively give the corresponding *exo*-cycloadducts in high yields with high enantioselectivities (entries 3 and 4, respectively). In particular, the highest *exo*- (> 99:1) and enantioselectivy (96% ee) were obtained using azomethine imine **1ca**. Subsequently, dimethyl-substituted azomethine imines **1cb** – **1ce** and **1cg** – **1ch**,

Table 3. Cycloadditions of azomethine imine **1aa** with acrolein (**2**) catalyzed by several organocatalysts[a]

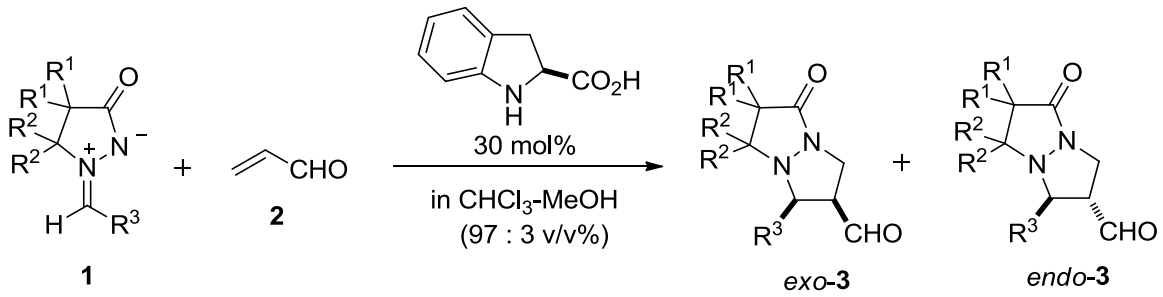
Entry	Organocatalyst		Time (h)	Yield (%)[b]	*endo*:*exo*[c]	% ee[d]	
						endo	*exo*
1			24	87	94 : 6	83	84
2		**4**	40	75	94 : 6	78	ND[e]
3		**5**	6	67	88 : 12	-14	17
4	 (p-$NO_2C_6H_4CO_2H$ (30 mol%))	**6**	2	< 18	44 : 56	1	0
5	 (p-$NO_2C_6H_4CO_2H$ (30 mol%))	**7**	6	87	95 : 5	-84	57
6		**8**	20	91	15 : 85	19	86
7[f]			70	94	9 : 91	20	94

[a] The reactions were carried out in purified $CHCl_3$/MeOH 97:3 (v/v) in the presence of an organocatalyst (30 mol%) at 25 °C. [b] The yield of the corresponding alcohols after reduction with $NaBH_4$. [c] Determined using ^1H NMR analysis. [d] Determined using chiral HPLC (Daicel Chiralpak AD-H) analysis after conversion to the corresponding alcohol via $NaBH_4$ reduction. [e] Not determined. [f] The reaction was carried out at 0 °C.

which possess *p*-substituted phenyl groups as the R^3–substituent, were examined under similar conditions. As shown in entries 5 – 10, relatively good to excellent enantioselectivies (98 ~ 75% ee) along with extremely high *exo*-selectivities (> 99:1) were observed, regardless of the electronic character of the *p*-susbstituents. However, in the case of *o*-chlorophenyl derivative **1cf** (R^1 = H, R^2 = Me, R^3 = *o*-ClC_6H_4), the reaction did not give cycloadducts under similar conditions. The use of 2-naphthyl derivative **1ci** (R^1 = H, R^2 = Me, R^3 = 2-naphthyl) also gave the *exo*-cycloadduct as the sole product with

high enantioselectivity (entry 11). Although the reaction of cyclohexyl derivative **1cj** (R^1 = H, R^2 = Me, R^3 = cyclohecyl) also showed good enantioselectivity with high *exo*-selectivity, the yield was unsatisfactory (entry 12).

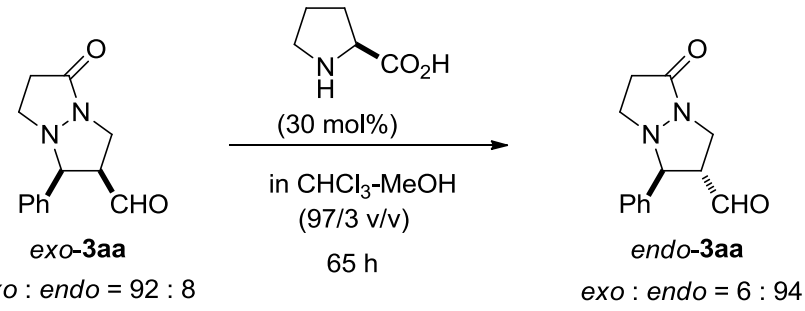
Table 4. (*S*)-Indoline-2-carboxylic acid-catalyzed cycloadditions of azomethine imines with acrolein (**2**)[a]



Entry	R^1	R^2	R^3	**1**	Time (h)	**3**	Yield (%)[b]	*exo*:*endo*[c]	% ee[d], *exo*
1	H	H	Ph	**1aa**	70	**3aa**	94	91 : 9	94 (20)[e]
2[f]	H	H	Ph	**1aa**	163	**3aa**	55	88 : 12	90 (30)[e]
3	Me	H	Ph	**1ba**	72	**3ba**	95	92 : 8	93 (6)[e]
4	H	Me	Ph	**1ca**	36	**3ca**	82	> 99 : 1	96
5	H	Me	*p*-ClC_6H_4	**1cb**	42	**3cb**	72	> 99 : 1	94
6	H	Me	*p*-BrC_6H_4	**1cc**	56	**3cc**	76	> 99 : 1	93
7	H	Me	*p*-CNC_6H_4	**1cd**	60	**3cd**	73	> 99 : 1	96
8	H	Me	*p*-$NO_2C_6H_4$	**1ce**	124	**3ce**	75	> 99 : 1	75
9	H	Me	*p*-MeC_6H_4	**1cg**	42	**3cg**	66	> 99 : 1	97
10	H	Me	*p*-$MeOC_6H_4$	**1ch**	56	**3ch**	77	> 99 : 1	98
11	H	Me	2-Naphthyl	**1ci**	60	**3ci**	83	> 99 : 1	95
12	H	Me	Cyclohexyl	**1cj**	149	**3cj**	< 29	> 99 : 1	88

[a] The reactions were carried out in purified $CHCl_3$/MeOH 97:3 (v/v) in the presence of (*S*)-indoline-2-carboxylic acid (30 mol%) at 0 °C. [b] The yield of the corresponding alcohols after reduction with $NaBH_4$. [c] Determined using ^1H NMR analysis. [d] Determined using chiral HPLC (Daicel Chiralpak AD-H or IA) analysis after conversion to the corresponding alcohol via $NaBH_4$ reduction. [e] Enantioselectivity of the *endo*-cycloadduct. [f] The reaction was carried out with 10 mol% of the catalyst.

Isomerization of the *exo*- to the *endo*-cycloadduct



Scheme 2

Table 5. Relationship between reaction time and the *endo*/*exo* ratio for **L**-proline-catalyzed cycloadditions between azomethine imine **1aa** and acrolein (**2**)[a]

Entry	Time (h)	Yield (%)[b]	*endo*:*exo*[c]	% ee,[d] *endo*	*exo*
1	1	27	47 : 53	82	88
2	3	73	60 : 40	73	82
3	6	87	81 : 19	72	88
4	12	92	92 : 8	79	88
5	24	87	94 : 6	83	84

[a] The reactions were carried out in purified $CHCl_3$/MeOH 97:3 (v/v) in the presence of **L**-proline (30 mol%) at 25 °C. [b] The yield of the corresponding alcohols after reduction with $NaBH_4$. [c] Determined using ^1H NMR analysis. [d] Determined using chiral HPLC (Daicel Chiralpak AD-H or OD-H) analysis after conversion to the corresponding alcohol via $NaBH_4$ reduction.

To gain insight into the reaction mechanisms causing opposite diastereoselectivities exhibited by the **L**-proline and the (*S*)-indoline-2-carboxylic acid catalyts, an *exo*-enriched (*exo*/*endo* 92:8) mixture of diastereomers **3aa** was treated with **L**-proline (30 mol%) in $CHCl_3$/MeOH 97:3 (v/v) at 25 °C (Scheme 2). Surprisingly, after stirring for 65 h, the *exo*/*endo* ratio indicated an *endo*-enriched (*exo*:*endo* 6:94) mixture, which strongly suggests that the *exo*-cycloadduct isomerizes to the *endo*-cycloadduct under our reaction conditions. To further investigate the *endo*-selectivity of the **L**-proline-catalyzed reactions, the rate of the *endo*/*exo*–isomerization was determined, under a catalyst loading of 30 mol% (Table 5, Scheme 1). After a reaction time of 1 h, the cycloadducts were obtained with an *endo*/*exo* ratio of 47:53 (27% yield,

entry 1). Longer reaction times resulted in higher *endo*/*exo* ratios (entries 2 – 5), ending with an *endo*/*exo* ratio of 94:4 after 24 h (87% yield, entry 5). The enantioselectivities of the *endo*- and *exo*-cycloadducts were 83% ee and 84% ee, respectively. These results indicate that the *exo*-cycloadduct isomerizes to the *endo*-cycloadduct in the presence of **L**-proline as the catalyst.

Absolute configuration of *exo*-3cc with reaction mechanism for the asymmetric induction

To gain insight into the mechanism behind the asymmetric induction, X-ray crystal analysis was carried out using the corresponding alcohol derived from *exo*-**3cc** via $NaBH_4$ reduction. For the (*S*)-indoline-2-carboxylic acid-catalyzed reaction, the resulting alcohol obtained via $NaBH_4$ reduction possesses a (5*S*,6*R*)-configuration (Figure 1). As shown in Scheme 3, the high *exo*-selectivity can be attributable to the selective formation of a sterically-favorable *Z*-iminium ion that is susceptible to the cycloaddition by the azomethine imine via an *exo*-approach. The selectivity is further assisted by favorable interactions between the negative charge of the carboxylate ion and the positive charge of the azomethine imine from the upper side of the olefin moiety. The configuration obtained from this facial selectivity (upper side approach) is consistent with that observed by X-ray analysis, as shown in Figure 1.

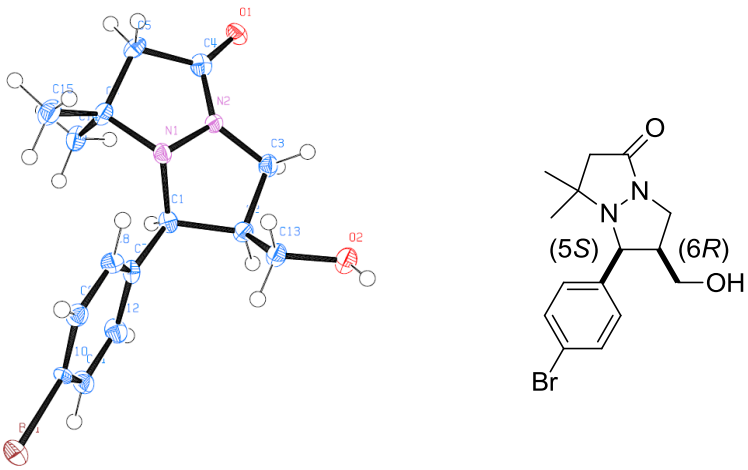
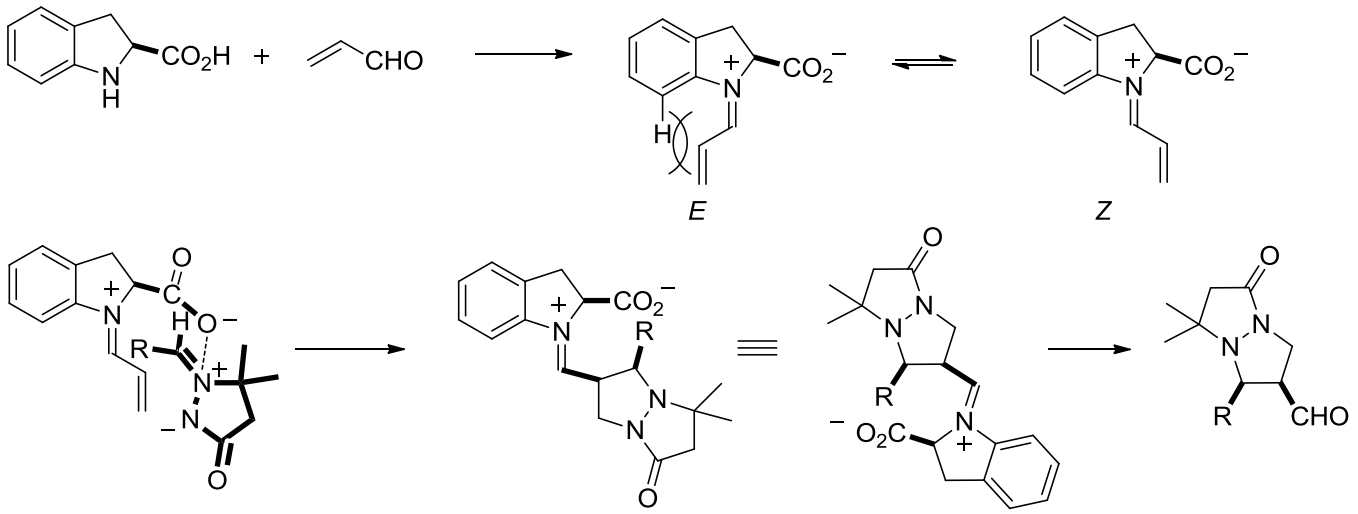


Figure 1. ORTEP drawing of the corresponding alcohol obtained from *exo*-**3cc**

On the other hand, for the **L**-proline-catalyzed reactions, although the initial diastereoselectivity remains unclear, the *exo*-cycloadduct readily epimerizes at the aldehyde-substituted stereogenic center, under the reaction conditions, to the more thermodynamically stable *endo*-cycloadduct. The facial selectivity during the asymmetric induction would be similar to that of the (*S*)-indoline-2-carboxylic acid-catalyzed reactions. In contrast to these organocatalysts that possess a carboxylic acid moiety, the

L-prolininol-derived TMS ether catalyst **7** exhibited the opposite facial selectivity (Table 3, entry 4), which can be attributed to the effective shielding of the upper side by the sterically hindered TMS ether moiety thus blocking the interactions of the positive charge of azomethine imine.



Scheme 3

CONCLUSION

We have demonstrated that (*S*)-indoline-2-carboxylic acid (30 mol%) can serve as an efficient organocatalyst for the asymmetric cycloadditions between *N*,*N*'-cyclic azomethine imines and acrolein to afford the corresponding *exo*-cycloadducts with high diastereo- (91:1 ~ > 99:1) and enantioselectivities (75 ~ 98% ee). In contrast, the **L**-proline catalyst (30 mol%) afforded the *endo*-cycloadducts selectively (83:27 ~ > 99:1) with modest to good enantioselectivities (31 ~ 83% ee). The contrasting diastereoselectivites can be explained based on our studies that showed the isomerization of the *exo*-cycloadduc into the *endo*-cycloadduct in the presence of **L**-proline. The solvent system of $CHCl_3$/MeOH 97:3 (v/v) was also essential for optimizing the cycloadditions.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were taken with FT/IR spectrophotometer. ^{1}H NMR spectra were run at 400 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 100 MHz using broadband proton decoupling. Chemical shifts are expressed in parts per million downfield from tetramethylsilane, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. For preparative column

chromatography, Wakogel C-300HG was employed. All reactions were carried out under an argon atmosphere in dried glassware. *L*-Proline, *L*-proline methyl ester hydrochloride (**5**), (*S*)-indoline-2-carboxylic acid (**8**), and acrolein (**2**) are commercially available and used without further purification. (4*R*)-4-(*t*-Butyldimethylsilyloxy)-*L*-proline (**4**),[13] *L*-prolinol **6**,[14] and TMS ether **7**[15] were prepared according to the procedure reported previously. Azomethine imines were prepared according to the procedure reported by Fu.[16] Chloroform was purified by distillation first from $CaCl_2$ and then P_2O_5 under argon. Dichloromethane was purified by distillation first from $CaCl_2$ and then CaH_2 under argon. Methanol and ethanol were purified by distillation from the corresponding magnesium alkoxide.

General procedure for the asymmetric cycloaddition reaction of azomethine imine with acrolein was exemplified by the reaction of azomethine imine 1ca in the presence of (*S*)-indoline-2-carboxylic acid.

Azomethine imine **1ca** (101.1 mg, 0.50 mmol) was added to a solution of acrolein (66.7 μl, 1.0 mmol) and (*S*)-indoline-2-carboxylic acid (24.5 mg, 0.15 mmol) in $CHCl_3$ (40.7 mL) and MeOH (1.3 mL) at 0 ^oC. After stirring the mixture for 36 h at the same temperature, a solution of $NaBH_4$ (75.7 mg, 2.0 mmol) in EtOH (5.0 mL) was added, and then the stirring was continued for 1 h. The reaction was quenched with saturated NH_4Cl solution (5.0 mL) and water (10.0 mL), and then the mixture was extracted with chloroform (10.0 mL x 3). The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate and ethyl acetate-MeOH (30 : 1 v/v) as an eluent to give the corresponding alcohol derived from *exo*-**3ca'** (*exo* : *endo* = >99 : 1, 106.4 mg, 82%). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 ^oC, t_{major} = 47.0 min (*exo*), t_{minor} = 62.4 min (*exo*)).

(5*R*,6*R*)-6-Hydroxymethyl-3,3-dimethyl-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3ca'): Colorless plates; mp 223-224 ^oC (MeOH-Et_2O); $[\alpha]_D^{26}$ -60.5 ^{o} (*c* 1.0, MeOH, *exo* : *endo* = >99 : 1, 96% ee).; IR (KBr) 3367, 2964, 2926, 2879, 2359, 1678, 1601, 1473, 1432, 1398, 1370, 1296, 1222, 1177, 1113, 1047, 970, 912, 868, 758, 707, 683, 625, 507 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.06 (3H, s), 1.26 (3H, s), 1.60 (1H, brs), 2.46 (1H, d, *J* = 16.1 Hz), 2.68 (1H, d, *J* = 16.1 Hz), 2.83 (1H, m), 3.30 (1H, ddd, *J* = 1.2 Hz, 3.9 Hz, 11.7 Hz), 3.35-3.47 (2H, m), 4.00 (1H, dd, *J* = 8.5, 11.7 Hz), 4.17 (1H, d, *J* = 7.3 Hz), 7.30-7.45 (5H, m); ^{13}C NMR ($CDCl_3$) δ = 22.5 (CH_3), 29.1 (CH_3), 43.2 (CH_2), 47.7 (CH_2), 48.2 (CH), 60.2 (C), 62.6 (CH_2), 64.5 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 136.7 (C), 168.7 (C); Mass

(EI) m/z 260 (M^+), 201, 91, 77, 56. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76%. Found: C, 69.17; H, 7.82; N, 10.72%.

(5*R*,6*R*)-6-Hydroxymethyl-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3aa'): Colorless plates; mp 111.5-112.5 ^oC (benzene); $[\alpha]_D^{26}$ -147.3 ^{o} (*c* 1.0, $CHCl_3$, *exo* : *endo* = 94 : 6, 94% ee (*exo*), 20% ee (*endo*)).; IR (KBr) 3424, 2947, 2847, 2360, 1664, 1470, 1426, 1213, 1139, 1041, 990, 749, 704, 601, 551 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.79 (1H, brs), 2.69 (1H, ddd, *J* = 6.3 Hz, 9.3 Hz, 16.6 Hz), 2.80 (1H, m), 2.85-2.95 (2H, m), 3.33 (1H, m), 3.37-3.43 (2H, m), 3.63 (1H, ddd, *J* = 6.3 Hz, 9.3 Hz, 11.0 Hz), 3.79 (1H, d, *J* = 7.1 Hz), 4.05 (1H, dd, *J* = 8.5 Hz, 11.7 Hz), 7.29-7.55 (5H, m); ^{13}C NMR ($CDCl_3$) δ = 32.8 (CH_2), 43.9 (CH_2), 47.7 (CH), 48.0 (CH_2), 62.2 (CH_2), 71.6 (CH), 127.1 (CH), 127.9 (CH), 128.7 (CH), 134.7 (C), 170.5 (C).; MS (EI) m/z 232 (M^+), 173, 117, 91, 78, 49; HRMS (EI) Calcd for $C_{13}H_{16}N_2O_2$: (M^+), 232.1236. Found: 232.1236. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.04%. Found: C, 67.46; H, 6.95; N, 11.82%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, Flow rate = 0.5 mL/min, 35 °C, t_{minor} = 36.8 min (*endo*), t_{major} = 44.1 min (*endo*), t_{major} = 88.6 min (*exo*), tminor = 136.5 min (*exo*)).

(5*R*,6*R*)-6-Hydroxymethyl-2,2-dimethyl-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3ba'): Colorless prisms; mp 57.5-59.0 ^oC (CH_2Cl_2-hexane); $[\alpha]_D^{26}$ -117.7 ^{o} (*c* 1.0, $CHCl_3$, *exo* : *endo* = 92 : 8, 93% ee (*exo*), 6% ee (*endo*)); IR (KBr) 3423, 2965, 2362, 1670, 1457, 136,5 1047, 757, 705, 498 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.21 (3H, s), 1.34 (3H, s), 2.04 (1H, brs), 2.55 (1H, d, *J* = 9.5 Hz), 2.94 (1H, m), 3.31-3.42 (3H, m), 3.45 (1H, dd, *J* = 2.7 Hz, 11.6 Hz), 3.66 (1H, d, *J* = 6.6 Hz), 4.00 (1H, dd, *J* = 8.3 Hz, 11.6 Hz), 7.28-7.48 (5H, m); ^{13}C NMR ($CDCl_3$) δ = 23.7 (CH_3), 24.1 (CH_3), 42.9 (CH_2), 46.0 (C), 47.7 (CH), 61.8 (CH_2), 64.9 (CH_2), 72.7 (CH), 126.9 (CH), 127.7 (CH), 128.4 (CH), 134.5 (C), 170.7 (C); Mass (EI) m/z 260 (M^+), 201, 117, 92, 78. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76%. Found: C, 69.21; H, 7.78; N, 10.72%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, Flow rate = 1.0 mL/min, 35 °C, t_{minor} = 16.3 min (*endo*), t_{major} = 19.0 min (*endo*), t_{major} = 29.1 min (*exo*), t_{minor} = 39.1 min (*exo*)).

(5*R*,6*R*)-6-Hydroxymethyl-3,3-dimethyl-5-(4-chlorophenyl)tetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3cb'): Colorless prisms.; mp. 184-184.5 ^oC (benzene); $[\alpha]_D^{25}$ -67.6 ^{o} (*c* 1.0, MeOH, *exo* : *endo* = >99 : 1, 94% ee (*exo*)).; IR (KBr) 3396, 2974, 2927, 2854, 1670, 1488, 1469, 1411, 1399, 1382, 1372, 1325, 1289, 1250, 1225, 1198, 1173, 1123, 1104, 1086 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.05 (3H, s), 1.23 (3H, s), 1.68 (1H, brs), 2.47 (1H, d, *J* = 16.3 Hz), 2.67 (1H, d, *J* = 16.3 Hz), 2.80 (1H, m), 3.26-3.36 (2H, m), 3.41 (1H, dd, *J* = 6.6, 11.0 Hz), 4.00 (1H, dd, *J* = 8.2, 11.0 Hz), 4.14 (1H, d, *J* = 7.6 Hz), 7.30-7.43 (4H,

m); ^{13}C NMR ($CDCl_3$) δ = 22.3 (CH_3), 28.9 (CH_3), 43.3 (CH_2), 47.7 (CH_2), 47.8 (CH), 60.3 (C), 62.2 (CH_2), 63.3 (CH), 128.6 (CH), 129.0 (CH), 133.5 (C), 135.4 (C), 168.4 (C); Mass (EI) m/z 294 (M^+), 151, 126, 111, 92, 83, 56. Anal. Calcd for $C_{15}H_{19}ClN_2O_2$: C, 61.12; H, 6.50; N, 9.72%. Found: C, 60.83; H, 6.57; N, 9.72%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, flow rate = 1.0 mL/min, 35 °C, t_{minor} = 24.7 min (*endo*), t_{major} = 27.5 min (*endo*), t_{major} = 52.0 min (*exo*), t_{minor} = 67.3 min (*exo*)).

(5*R*,6*R*)-6-Hydroxymethyl-3,3-dimethyl-5-(4-bromophenyl)tetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3cc'): Colorless plates; mp 202-203 °C (benzene); $[\alpha]_D^{23}$ -63.6 ° (*c* 0.80, MeOH, *exo* : *endo* = >99 : 1, 93% ee (*exo*)); IR (KBr) 3370, 2967, 2941, 2910, 2876, 1665, 1486, 1449, 1427, 1407, 1387, 1370, 1351, 1294, 1220, 1205, 1177, 1162, 1122, 1111, 1072, 1049, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.05 (3H, s), 1.24 (3H, s), 1.58 (1H, brs), 2.45 (1H, d, *J* = 16.3 Hz), 2.66 (1H, d, *J* = 16.3 Hz), 2.80 (1H, m), 3.29 (1H, ddd, *J* = 1.5 Hz, 4.4 Hz, 11.7 Hz), 3.31-3.47 (2H, m), 4.01 (1H, dd, *J* = 8.5, 11.7 Hz), 4.13 (1H, d, *J* = 7.3 Hz), 7.27-7.33 (2H, m), 7.46-7.54 (2H, m); ^{13}C NMR ($CDCl_3$) δ = 22.5 (CH_3), 29.0 (CH_3), 43.3 (CH_2), 47.6 (CH_2), 47.8 (CH), 60.4 (C), 62.4 (CH_2), 63.6 (CH), 121.7 (C), 129.4 (CH), 131.5 (CH), 136.0 (C), 168.7 (C); Mass (EI) m/z 338 (M^+), 138, 126, 111, 83, 56. Anal. Calcd for $C_{15}H_{19}BrN_2O_2$: C, 53.11; H, 5.65; N, 8.26%. Found: C, 53.03; H, 5.65; N, 8.26%.; The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, flow rate = 1.0 mL/min, 35 °C, t_{minor} = 9.1 min (*endo*), t_{major} = 11.4 min (*endo*), t_{major} = 20.3 min (*exo*), t_{minor} = 26.9 min (*exo*)).

(5*R*,6*R*)-6-Hydroxymethyl-3,3-dimethyl-5-(4-cyanophenyl)tetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3cd'): Colorless needles; mp 163-164.5 °C (benzene); $[\alpha]_D^{23}$ -98.4 ° (*c* 1.0, MeOH, *exo* : *endo* = >99 : 1, 96% ee (*exo*)); IR (KBr) 3379, 2976, 2953, 2934, 2911, 2892, 2225, 1671, 1605, 1504, 1474, 1443, 1421, 1371, 1294, 1252, 1229, 1181, 1157, 1122, 1111, 1075, 1051, 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.04 (3H, s), 1.25 (3H, s), 1.68 (1H, brs), 2.46 (1H, d, *J* = 16.4 Hz), 2.66 (1H, d, *J* = 16.4 Hz), 2.87 (1H, m), 3.24 (1H, m), 3.28 (1H, ddd, *J* = 1.2, 4.6, 11.7 Hz), 3.36 (1H, dd, *J* = 7.5 Hz, 10.7 Hz), 4.05 (1H, dd, *J* = 8.5 Hz, 11.7 Hz), 4.21 (1H, d, *J* = 7.8 Hz), 7.50 – 7.61 (2H, m), 7.63 – 7.73 (2H, m); ^{13}C NMR ($CDCl_3$) δ = 22.3 (CH_3), 28.7 (CH_3), 43.4 (CH_2), 47.2 (CH_2), 47.5 (CH), 60.4 (C), 61.7 (CH_2), 63.0 (CH), 111.3 (C), 118.2 (C), 128.4 (CH), 131.8 (CH), 142.9 (C), 168.7 (C).; Mass (EI) m/z 285 (M^+), 111, 83, 56. Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73%. Found: C, 67.15; H, 6.89; N, 14.75%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA, hexane : 2-PrOH = 5 : 1 v/v%, detector: UV 254 nm, flow rate = 0.4 mL/min, 35 °C, t_{minor} = 22.4 min (*endo*), t_{major} = 25.0 min (*endo*), t_{major} = 37.0 min (*exo*), t_{minor} = 46.0 min (*exo*)).

(5*R*,6*R*)-6-Hydroxymethyl-3,3-dimethyl-5-(4-nitrophenyl)tetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3ce'): Pale yellow leaflets; mp 161.5-163 ^{o}C (benzene); $[\alpha]_D^{23}$ -55.3 ^{o} (*c* 0.80, MeOH, *exo* : *endo* = >99 : 1, 75% ee (*exo*)).; IR (KBr) 3384, 2976, 2963, 2944, 2897, 1646, 1597, 1525, 1465, 1421, 1385, 1370, 1345, 1314, 1296, 1228, 1108, 1074, 1053, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.05 (3H, s), 1.25 (3H, s), 2.20 (1H, brs), 2.46 (1H, d, *J* = 16.8 Hz), 2.67 (1H, d, *J* = 16.3 Hz), 2.90 (1H, m), 3.20 (1H, dd, *J* = 5.4, 10.5 Hz), 3.29 (1H, ddd, *J* = 1.2, 4.6, 12.0 Hz), 3.37 (1H, dd, *J* = 7.8, 10.5 Hz), 4.04 (1H, dd, *J* = 8.3, 12.0 Hz), 4.27 (1H, d, *J* = 8.1 Hz), 7.56-7.71 (2H, m), 8.14-8.34 (2H, m); ^{13}C NMR ($CDCl_3$) δ = 22.8 (CH_3), 29.1 (CH_3), 43.5 (CH_2), 47.1 (CH_2), 47.8 (CH), 60.4 (C), 62.1 (CH_2), 63.4 (CH), 123.5 (CH), 128.7 (CH), 145.1 (C), 147.3 (C), 169.6 (C); Mass (EI) m/z 305 (M^+), 111, 78. Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76%. Found: C, 59.21; H, 6.17; N, 13.66%.; The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, flow rate = 1.0 mL/min, 35 ^{o}C, t_{minor} = 18.1 min (*endo*), t_{major} = 24.8 min (*endo*), t_{major} = 37.3 min (*exo*), t_{minor} = 64.1 min (*exo*)).

(5*R*,6*R*)-6-Hydroxymethyl-3,3-dimethyl-5-p-toyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3cg'): Colorless needles; mp 187-187.5 ^{o}C (benzene); $[\alpha]_D^{23}$ -67.7 ^{o} (c 0.80, MeOH, *exo* : *endo* = >99 : 1, 97% ee (*exo*)); IR (KBr) 3368, 3094, 3060, 3028, 3010, 2963, 2926, 2875, 1685, 1632, 1515, 1474, 1449, 1431, 1398, 1371, 1297, 1256, 1222, 1205, 1182, 1167, 1125, 1078, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.06 (3H, s), 1.23 (3H, s), 1.71 (1H, brs), 2.35 (3H, s), 2.46 (1H, d, *J* = 16.3 Hz), 2.68 (1H, d, *J* = 16.3 Hz), 2.79 (1H, m), 3.28 (1H, dd, *J* = 3.7 Hz, 11.7 Hz), 3.38 – 3.46 (2H, m), 3.97 (1H, dd, *J* = 8.5 Hz, 11.7 Hz), 4.14 (1H, d, *J* = 7.3 Hz), 7.14 – 7.20 (2H, m), 7.27 – 7.34 (2H, m); ^{13}C NMR ($CDCl_3$) δ = 21.2 (CH_3), 22.1 (CH_3), 28.7 (CH_3), 42.9 (CH_2), 47.9 (CH_2), 47.9 (CH), 60.3 (C), 62.5 (CH_2), 64.1 (CH), 127.5 (CH), 129.0 (CH), 133.3 (C), 137.4 (C), 167.9 (C); Mass (EI) m/z 274 (M^+), 131, 111, 83, 56; Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21%. Found: C, 70.04; H, 8.07; N, 10.23%.; The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 ^{o}C, t_{minor} = 21.5 min (*endo*), t_{major} = 23.7 min (*endo*), t_{major} = 39.6 min (*exo*), t_{minor} = 47.3 min (*exo*)).

(5*R*,6*R*)-6-Hydroxymethyl-5-(4-methoxyphenyl)-3,3-dimethyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3ch'): Colorless needles; mp 192 ^{o}C (benzene); $[\alpha]_D^{26}$ -70.5 ^{o} (c 0.80, MeOH, *exo* : *endo* = >99 : 1, 98% ee (*exo*)).; IR (KBr) 3344, 2989, 2972, 2951, 2892, 2878, 2834, 1683, 1632, 1615, 1583, 1516, 1473, 1465, 1443, 1431, 1402, 1369, 1296, 1256, 1221, 1204, 1170, 1126, 1109, 1078, 1053, 1036, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.07 (3H, s), 1.21 (3H, s), 1.77 (1H, brs), 2.44 (1H, d, *J* = 16.3 Hz), 2.68 (1H, d, *J* = 16.3 Hz), 2.77 (1H, m), 3.29 (1H, dd, *J* = 3.7 Hz, 11.7 Hz), 3.39 – 3.50 (2H, m), 3.82 (3H, s), 3.97

(1H, dd, J = 8.5 Hz, 11.7 Hz), 4.13 (1H, d, J = 7.3 Hz), 6.84 – 6.96 (2H, m), 7.28–7.38 (2H, m); ^{13}C NMR ($CDCl_3$) δ = 22.0 (CH_3), 28.7 (CH_3), 43.0 (CH_2), 48.0 (CH_2), 47.8 (CH), 55.1 (CH_3), 60.2 (C), 62.2 (CH_2), 63.3 (CH), 113.6 (CH), 128.0 (C), 128.7 (CH), 158.8 (C), 167.5 (C); Mass (EI) m/z 290 (M^+), 147, 111, 83, 56. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65%. Found: C, 66.07; H, 7.99; N, 9.41%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 ^oC, t_{minor} = 30.8 min (*endo*), t_{major} = 33.5 min (*endo*), t_{major} = 60.4 min (*exo*), t_{minor} = 70.6 min (*exo*)).

(5*R*,6*R*)-6-Hydroxymethyl-3,3-dimethyl-5-(2-naphthyl)tetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3ci'): Pale red prisms; mp 260-261 ^oC (MeOH); $[\alpha]_D^{26}$ -43.7 ^{o} (c 0.40, MeOH, *exo* : *endo* = >99 : 1, 95% ee (*exo*)).; IR (KBr) 3351, 2990, 2970, 2925, 2877, 1671, 1632, 1599, 1507, 1473, 1446, 1428, 1402, 1388, 1365, 1306, 1294, 1252, 1221, 1202, 1174, 1124, 1109, 1079, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.09 (3H, s), 1.27 (3H, s), 1.60 (1H, brs), 2.49 (1H, d, J = 16.4 Hz), 2.71 (1H, d, J = 16.4 Hz), 2.90 (1H, m), 3.36 (1H, m), 3.39 (1H, dd, J = 5.6 Hz, 11.2 Hz), 3.46 (1H, dd, J = 6.3 Hz, 11.2 Hz), 4.05 (1H, dd, J = 8.1 Hz, 11.2 Hz), 4.35 (1H, d, J = 7.3 Hz), 7.46 – 7.61 (3H, m), 7.77 – 7.96 (4H, m); ^{13}C NMR ($CDCl_3$) δ = 22.8 (CH_3), 29.2 (CH_3), 43.2 (CH_2), 47.7 (CH_2), 48.3 (CH), 60.3 (C), 62.7 (CH_2), 64.7 (CH), 125.3 (CH), 126.2 (CH), 126.4 (CH), 126.8 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 132.9 (C), 133.0 (C), 134.3 (C); Mass (EI) m/z 310 (M^+), 167, 111, 83, 56. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03%. Found: C, 73.39; H, 7.33; N, 8.97%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 ^oC, t_{minor} = 26.2 min (*endo*), t_{major} = 31.1 min (*endo*), t_{major} = 55.2 min (*exo*), t_{minor} = 74.1 min (*exo*)).

(5*R*,6*R*)-5-Cyclohexyl-6-hydroxymethyl-3,3-dimethyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*exo*-3cj'): Pale yellow oil; $[\alpha]_D^{23}$ +40.6 ^{o} (c 0.60, MeOH, *exo* : *endo* = >99 : 1, 88% ee (*exo*)).; IR (neat) 2984, 2932, 2856, 2361, 1680, 1452, 1371, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.15 – 1.70 (11H, m), 1.26 (6H, s), 2.17 (1H, d, J = 14.9 Hz), 2.62 (1H, m), 2.79 (1H, d, J = 14.9 Hz), 2.99 – 3.09 (2H, m), 3.81-3.84 (2H, m), 3.99 (1H, dd, J = 8.3 Hz, 11.2 Hz), The signal of OH could not be identified; Mass (EI) m/z 266 (M^+), 141; HRMS (EI) Found: m/z 266.1950. Calcd for $C_{15}H_{26}N_2O_2$ (M^+): 266.1994. Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52%. Found: C, 68.21; H, 9.85; N, 9.93% (Satisfactory elemental analysis was not obtained). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 ^oC, t_{minor} = 19.6 min (*endo*), t_{major} = 20.1 min (*endo*), t_{major} = 31.2 min (*exo*), t_{minor} = 34.0 min (*exo*)).

(5*R*,6*S*)-6-Hydroxymethyl-5-phenyl-tetrahydropyrazolo[1,2-a]pyrazol-1-one (*endo*-3aa'): Pale orange leaflets; mp 142-143 ^{o}C (benzene-hexane); $[\alpha]_D^{26}$ -14.1 ^{o} (*c* 1.0, $CHCl_3$, *endo* : *exo* = 94 : 6, 83% ee (*endo*), 84% ee (*exo*)).; IR (KBr) 3387, 3028, 2935, 2852, 2356, 1680, 1471, 1411, 1306, 1251, 1200, 1160, 1129, 1060, 1019, 837, 797, 754, 699, 610, 581 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.52 (1H, brs), 2.69–2.77 (3H, m), 2.93 (1H, dt, *J* = 11.2 Hz, 8.8 Hz), 3.41 (1H, d, *J* = 9.3 Hz), 3.45 (1H, dt, *J* = 11.2 Hz, 7.8 Hz), 3.52 (1H, dd, *J* = 9.8 Hz, 11.2 Hz), 3.61 (1H, dd, *J* = 5.0 Hz, 11.5 Hz), 3.71 (1H, dd, *J* = 3.8 Hz, 11.5 Hz), 3.82 (1H, dd, *J* = 6.6 Hz, 11.2 Hz), 7.32-7.41 (5H, m); ^{13}C NMR ($CDCl_3$) δ = 32.8 (CH_2), 43.2 (CH_2), 47.5 (CH_2), 52.7 (CH), 60.0 (CH_2), 71.0 (CH), 127.6 (CH), 128.0 (CH), 128.8 (CH), 137.1 (C), 170.3 (C); MS (EI) m/z 232 (M^+), 173, 117, 91, 78, 56; HRMS (EI) Calcd for $C_{13}H_{16}N_2O_2$: (M^+), 232.1212. Found: 232.1236. Anal. Calcd for $C_{19}H_{20}N_4O_4$: C, 67.22; H, 6.94; N, 12.04%. Found: C, 67.99; H, 7.39; N, 10.61% (Satisfactory elemental analysis was not obtained). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, Flow rate = 0.5 mL/min, 35 ^{o}C, t_{minor} = 35.0 min (*endo*), t_{major} = 41.9 min (*endo*), t_{major} = 84.3 min (*exo*), tminor = 130.0 min (*exo*)).

(5*R*,6*S*)-6-Hydroxymethyl-2,2-dimethyl-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*endo*-3ba'): Colorless prisms; mp 129-130.5 ^{o}C (CH_2Cl_2-hexane); $[\alpha]_D^{26}$ -27.6 ^{o} (*c* 0.80, $CHCl_3$, *endo* : *exo* = 87 : 13, 78% ee (*endo*), 83% ee (*exo*)).; IR (KBr) 3440, 3031, 2971, 2927, 2838, 2360, 1694, 1469, 1405, 1367, 1345, 1306, 1254, 1191, 1127, 1074, 1038, 995, 949, 839, 775, 744, 697, 602, 556 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.21 (3H, s), 1.29 (3H, s), 2.59 (1H, brs), 2.62 (1H, d, *J* = 9.5 Hz), 2.75 (1H, m), 3.21 (1H, d, *J* = 9.5 Hz), 3.37 (1H, d, *J* = 9.3 Hz), 3.53-3.65 (2H, m), 3.72 (1H, dd, *J* = 3.6 Hz, 11.2 Hz), 3.83 (1H, dd, *J* = 8.0 Hz, 11.2 Hz), 7.23-7.45 (5H, m); ^{13}C NMR ($CDCl_3$) δ = 23.8 (CH_3), 24.1 (CH_3), 42.4 (CH_2), 52.6 (CH), 59.8 (CH_2), 64.5 (CH_2), 72.4 (CH), 127.6 (CH), 128.0 (CH), 128.5 (CH), 137.0 (C), 170.7 (C); Mass (EI) m/z 260 (M^+), 201, 117, 91, 56. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76%. Found: C, 68.88; H, 7.97; N, 10.86%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, Flow rate = 0.5 mL/min, 35 ^{o}C, t_{minor} = 16.4 min (*endo*), t_{major} = 18.9 min (*endo*), t_{major} = 29.1 min (*exo*), t_{minor} = 39.2 min (*exo*).

(5*R*,6*S*)-6-Hydroxymethyl-3,3-dimethyl-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*endo*-3ca'): Colorless leaflets; mp 142-143 ^{o}C (CH_2Cl_2-hexane); $[\alpha]_D^{26}$ +23.6 ^{o} (*c* 1.0, $CHCl_3$, *endo* : *exo* = 90 : 10, 79% ee (*endo*), 69% ee (*exo*)); IR (KBr) 3437, 3029, 2970, 2935, 2872, 2360, 1687, 1461, 1379, 1292, 1252, 1229, 1177, 1060, 817, 753, 701, 594, 543 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.01 (6H, s), 1.97 (1H, brs), 2.47 (1H, d, *J* = 16.6 Hz), 2.63 (1H, d, *J* = 16.6 Hz), 2.67 (1H, m), 3.50-3.63 (2H, m), 3.64-3.76 (2H,

m), 3.78 (1H, d, *J* = 9.3 Hz), 7.27-7.44 (5H, m); ^{13}C NMR ($CDCl_3$) δ = 22.7 (CH_3), 28.6 (CH_3), 42.5 (CH_2), 47.8 (CH_2), 53.7 (CH), 59.9 (CH_2), 63.2 (CH), 127.6 (CH), 127.7 (CH), 128.4 (CH), 139.4 (C), 168.1 (C); Mass (EI) m/z 260 (M^+), 201, 138, 117, 91, 56. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76%. Found: C, 69.17; H, 7.82; N, 10.72%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak IA, CH_2Cl_2 : hexane : 2-PrOH = 20 : 10 : 1 v/v%, detector: UV 254 nm, flow rate = 0.3 mL/min, 25 °C, t_{major} and t_{minor} = 40.5 min (*exo*), t_{major} = 44.0 min (*endo*), t_{minor} = 47.4 min (*endo*)).

(5*R*,6*S*)-5-(4-Chlorophenyl)-6-hydroxymethyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*endo*-3ab'): Colorless needles; mp 200.5-201 °C (benzene); $[\alpha]_D^{26}$ -17.5 ° (c 0.80, MeOH, *endo* : *exo* = 99 : 1, 74% ee (*endo*)); IR (KBr) 3289, 3041, 2972, 2945, 2928, 2888, 2865, 1645, 1498, 1460, 1419, 1380, 1347, 1303, 1204, 1182, 1119, 1090 cm-1; ^{1}H NMR ($CDCl_3$) δ = 2.22 (1H, brs), 2.60-2.79 (3H, m), 2.92 (1H, dt, *J* = 11.2, 8.4 Hz), 3.40 (1H, d, *J* = 8.8 Hz), 3.43-3.56 (2H, m), 3.60 (1H, dd, *J* = 5.4, 11.2 Hz), 3.70 (1H, dd, *J* = 3.9, 11.2 Hz), 3.81 (1H, dd, *J* = 6.1, 11.2 Hz), 7.35 (5H, brs); ^{13}C NMR ($CDCl_3$) δ = 32.8 (CH_2), 43.2 (CH_2), 47.4 (CH_2), 53.0 (CH), 59.9 (CH_2), 70.3 (CH), 128.8 (CH), 129.0 (CH), 133.9 (C), 135.9 (C), 170.9 (C); Mass (EI) m/z 266 (M^+), 151, 115, 98, 56. Anal. Calcd for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50%. Found: C, 58.61; H, 5.63; N, 10.47%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 20 : 1 v/v%, detector: UV 254 nm, Flow rate = 0.5 mL/min, 35 °C, t_{minor} = 65.0 min (*endo*), t_{major} = 70.2 min (*endo*)).

(5*R*,6*S*)-5-(2-Chlorophenyl)-6-hydroxymethyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*endo*-3af'): Pale yellow oil; $[\alpha]_D^{24}$ +1.1 ° (*c* 0.80, MeOH, *endo* : *exo* = 88 : 12, 50% ee (*endo*)).; IR (KBr) 3354, 2990, 2943, 2916, 2884, 1653, 1569, 1471, 1422, 1373, 1312, 1272, 1200, 1161, 1139, 1115, 1091, 1053, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.17 (1H, brs), 2.63-2.83 (3H, m), 3.00 (1H, ddd, *J* = 7.8. 9.0, 11.2 Hz), 3.43 (1H, ddd, *J* = 7.3, 9.3, 11.2 Hz), 3.54 (1H, m), 3.68 (1H, dd, *J* = 5.4, 11.2 Hz), 3.74 (1H, dd, *J* = 4.4, 11.2 Hz), 3.85 (1H, dd, *J* = 6.1, 11.2 Hz), 4.02 (1H, d, *J* = 9.0 Hz), 7.20-7.40 (3H, m), 7.63-7.71 (1H, m); ^{13}C NMR ($CDCl_3$) δ = 32.5 (CH_2), 44.0 (CH_2), 47.3 (CH_2), 53.4 (CH), 60.9 (CH_2), 66.4 (CH), 127.2 (CH), 128.9 (CH), 129.0 (CH), 129.3 (CH), 133.9 (C), 135.0 (C), 171.3 (C); Mass (EI) m/z 266 (M^+), 151, 125, 84, 77, 56. Anal. Calcd for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50%. Found: C, 58.66; H, 5.76; N, 10.30%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 12 : 1 v/v%, detector: UV 254 nm, Flow rate = 1.0 mL/min, 35 °C, t_{minor} = 20.4 min (*endo*), t_{major} = 35.4 min (*endo*)).

(5*R*,6*S*)-6-Hydroxymethyl-5-*p*-tolyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*endo*-3ag'): Colorless needles; mp 189-190 °C (benzene); $[\alpha]_D^{27}$ -6.6 ° (*c* 0.80, MeOH, *endo* : *exo* = 99 : 1, 74% ee (*endo*)); IR

(KBr) 3343, 3026, 2949, 2926, 2889, 2868, 1661, 1518, 1458, 1418, 1381, 1303, 1256, 1215, 1205, 1186, 1108, 1086, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.90 (1H, brs), 2.36 (3H, s), 2.65-2.79 (3H, m), 2.93 (1H, dt, *J* = 11.2, 8.4 Hz), 3.33 (1H, d, *J* = 9.5 Hz), 3.43 (1H, dt, *J* = 11.2, 7.7 Hz), 3.53 (1H, m), 3.61 (1H, m), 3.70 (1H, m), 3.78 (1H, dd, *J* = 6.8, 9.0 Hz), 7.16-7.21 (2H, m), 7.26-7.32 (2H, m); ^{13}C NMR ($CDCl_3$) δ = 21.2 (CH_3), 32.8 (CH_2), 43.2 (CH_2), 47.5 (CH_2), 52.7 (CH), 60.0 (CH_2), 70.9 (CH), 127.5 (CH), 129.2 (CH), 133.9 (C), 137.7 (C), 170.3 (C); Mass (EI) m/z 246 (M^+), 131, 98, 56. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37%. Found: C, 68.35; H, 7.41; N, 11.25%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 20 : 1 v/v%, detector: UV 254 nm, Flow rate = 0.5 mL/min, 35 °C, t_{minor} = 51.3 min (*endo*), t_{major} = 55.9 min (*endo*)).

(5*R*,6*S*)-6-Hydroxymethyl-5-(2-naphthyl)tetrahydropyrazolo[1,2-a]pyrazol-1-one (*endo*-3ai'): Pale yellow prisms; mp 196-197 °C (benzene-MeOH); $[\alpha]_D^{24}$ -13.7 ° (*c* 0.80, MeOH, *endo* : *exo* = 99 : 1, 82% ee (*endo*)).; IR (KBr) 3463, 3402, 3384, 2932, 2888, 2853, 2811, 1671, 1598, 1509, 1472, 1408, 1380, 1349, 1247, 1205, 1127, 1097, 1085, 1064, 1041, 1019 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.96 (1H, brs), 2.70-2.83 (2H, m), 2.85 (1H, m), 2.99 (1H, dt, J = 11.2, 8.5 Hz), 3.47 (1H, ddd, *J* = 7.3, 8.5, 11.2 Hz), 3.59 (1H, m), 3.65 (1H, m), 3.75 (1H, m), 3.85 (1H, dd, *J* = 6.6, 11.2 Hz), 7.43-7.63 (3H, m), 7.78-7.92 (4H, m); ^{13}C NMR ($CDCl_3$) δ = 32.8 (CH_2), 43.4 (CH_2), 47.5 (CH_2), 52.8 (CH), 60.2 (CH_2), 71.3 (CH), 124.9 (CH), 126.1 (CH), 126.2 (CH), 127.3 (CH), 127.5 (CH), 127.6 (CH), 128.5 (CH), 133.0 (C), 133.1 (C), 134.6 (C), 171.0 (C); Mass (EI) m/z 282 (M^+), 167, 78, 56. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92%. Found: C, 72.52; H, 6.20; N, 9.95%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane : 2-PrOH = 20 : 1 v/v%, detector: UV 254 nm, Flow rate = 1.0 mL/min, 35 °C, t_{minor} = 72.9 min (*endo*), t_{major} = 85.7 min (*endo*)).

(5*R*,6*S*)-5-Cyclohexyl-6-hydroxymethyltetrahydropyrazolo[1,2-a]pyrazol-1-one (*endo*-3aj'): Colorless oil; $[\alpha]_D^{23}$ -12.4 ° (c 0.60, MeOH, *endo* : *exo* = 99 : 1, 31% ee (*endo*)); IR (neat) 3374, 3018, 2930, 2856, 2401, 2361, 2339, 1669, 1451, 1426, 1215, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.87-1.82 (11H, m), 1.86 (1H, brs), 2.18 (1H, m), 2.51 (1H, m), 2.65 (1H, ddd, *J* = 4.9, 9.5, 14.4 Hz), 2.77 (1H, m), 2.94 (1H, m), 3.15 (1H, m), 3.46 (1H, dd, *J* = 7.8, 10.7 Hz), 3.56-3.70 (2H, m), 3.84 (1H, m); ^{13}C NMR ($CDCl_3$) δ = 26.2 (CH_2), 26.4 (CH_2), 29.79 (CH_2), 29.85 (CH_2), 34.0 (CH_2), 41.2 (CH), 42.5 (CH_2), 46.9 (CH), 52.0 (CH_2), 63.6 (CH_2), 73.4 (CH), 167.6 (C); Mass (EI) m/z 238 (M^+), 156, 55. Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75%. Found: C, 65.27; H, 9.52; N, 11.71%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane : 2-PrOH = 20 : 1 v/v%, detector: UV 254 nm, Flow rate = 1.0 mL/min, 35 °C, t_{major} = 22.2 min (*endo*), t_{minor} = 27.6 min (*endo*)).

(5*R*,6*S*)-6-hydroxymethyl-5-Isobutyltetrahydropyrazolo[1,2-a]pyrazol-1-one *(endo*-3ak'): Colorless oil; $[\alpha]_D^{23}$ -18.4 ^{o} (*c* 0.80, MeOH, *endo* : *exo* = 83 : 17, 32% ee (*endo*)); IR (KBr) 3282, 3000, 2954, 2913, 2905, 2866, 1671, 1470, 1426, 1377, 1366, 1328, 1319, 1253, 1226, 1191, 1165, 1150, 1109, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.94 (3H, d, *J* = 6.6 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 1.33-1.58 (2H, m), 1.61-1.83 (2H, m), 2.43 (1H, m), 2.50 (1H, m), 2.66 (1H, ddd, *J* = 5.1, 9.3, 14.4 Hz), 2.77 (1H, m), 2.99 (1H, q, *J* = 9.3 Hz), 3.32 (1H, m), 3.54-3.65 (2H, m), 3.66-3.77 (2H, m); ^{13}C NMR ($CDCl_3$) δ = 22.7 (CH_3), 23.4 (CH_3), 25.4 (CH), 33.9 (CH_2), 34.0 (CH_2), 42.5 (CH_2), 42.5 (CH_2), 50.4 (CH), 62.2 (CH_2), 65.4 (CH), 167.9 (C).; Mass (EI) m/z 212 (M^+), 156, 125, 81, 55; HRMS (EI) Calcd for $C_{11}H_{20}N_2O_2$: (M^+), 212.1215. Found: 212.1551. Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20%. Found: C, 61.92; H, 9.90; N, 13.11%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane : 2-PrOH = 20 : 1 v/v%, detector: UV 254 nm, Flow rate = 1.0 mL/min, 35 ^{o}C, t_{major} = 17.3 min (*endo*), t_{minor} = 21.2 min (*endo*), t_{mimor} = 36.2 min (*exo*), t_{major} = 41.0 min (*exo*)).

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