Asymmetric Diels Alder Reaction using Pyrazole Derivatives as a Chiral Catalyst

Choji Kashima,* Yohei Miwa, Saori Shibata, and Hiroyuki Nakazono

Department of Chemistry, University of Tsukuba,
Ten-nodai, Tsukuba, Ibaraki 305-8571, Japan
(E-Mail: kashima@chac.tsukuba.ac.jp)
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N-Acylpyrazoles (**1**) were promising as good dienophiles, which were easily converted into the desired carboxylic derivatives. Bis(pyrazolyl)methanes, which were derived from chiral pyrazoles, showed the activity of chiral catalyst. Particularly 10 mol% of bis(isomenthopyrazol-1,1'-yl)methane (**8a**) catalyzed enantioselectively the Diels Alder reaction up to 40 % ee by the formation of complex with $Mg(ClO_4)_2$.

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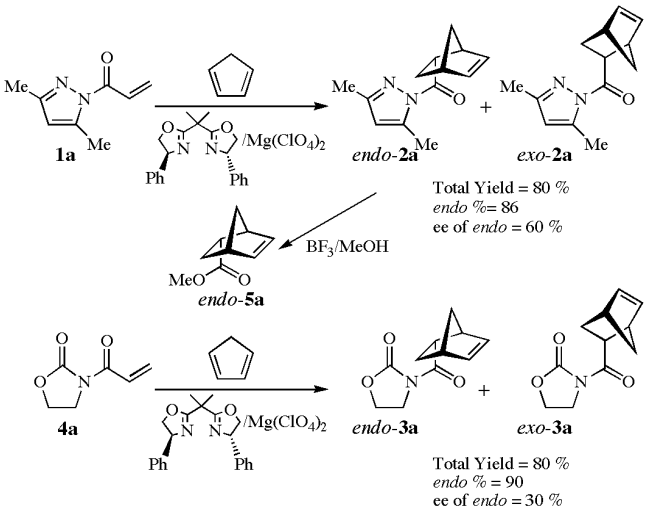
Recently we have reported the preparation and the utilities of the optically active pyrazoles as a new chiral auxiliary [1,2], which has unique structure and properties different from the conventional chiral auxiliaries [3]. Since Evans reported the enantioselective Diels Alder reactions using the chiral catalyst such as 2,2-bis[2-[4-(*S*)-phenyl-1,3-oxazolyl]]propane [(*S*,*S*)-Ph-box] [4], many papers concerning the analogous box derivatives have appeared in the literature [5]. From the fact that pyrazoles are good ligands for various Lewis acids [6], optically active pyrazoles are expected to show effective chiral catalytic activities for various enantioselective syntheses. These optically active pyrazoles have already exhibited chiral catalytic activities in borane mediated reductions and dialkylzinc addition on the prochiral carbonyl compounds [7]. As an extension of the diastereoselective Diels Alder reaction using 3-phenyl-*l*-menthopyrazole [10], we will report here the utilities of optically active pyrazole derivatives for either a convenient dienophile or a chiral catalyst in enantioselective Diels Alder reactions.

Results and Discussion.

Firstly, *N*-(α,β-unsaturated) acyl substituted pyrazoles were inspected using optically active box derivative as a chiral catalyst. When 1-acryloyl-3,5-dimethylpyrazole (**1a**) was treated with cyclopentadiene in the presence of Mg[(*R*,*R*)-Ph-box] complex, 1-(bicyclo[2.2.1]hept-5-ene-2-carbonyl)-3,5-dimethylpyrazole (**2a**) was afforded in 80 % yield with 86 % of *Endo* isomer ratio and 60 % ee of *Endo* isomer (Scheme 1). Under the same conditions from 3-acryloyloxazolidine-2-one (**4a**), 3-(bicyclo[2.2.1]hept-5-ene-2-carbonyl)oxazolidine-2-one (**3a**) was obtained in 80 % yield with 90 % of *Endo* isomer ratio and 30 % ee of *Endo* isomer. Moreover, the functionalization of **2a** into various carboxylic derivatives was easy to realize by the action of appropriate nucleophiles under acidic or basic conditions. By the action of sodium alkoxide, **2a** was converted into the corresponding bicyclo[2.2.1]hept-5-ene-2-carboxylic acid esters (**5a**) in 80 % ee. Alcoholysis of **2a** was also successful in the presence of boron trifluoride in 75 % yield with complete retention of its configuration.

Scheme 1

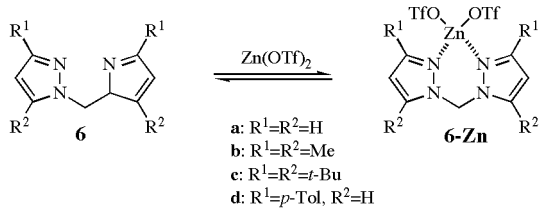


From these results, *N*-(α,β-unsaturated) acyl substituted pyrazoles were concluded to be convenient dienophiles for the asymmetric Diels Alder reactions.

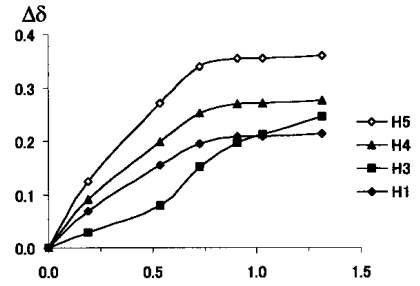
As part of a series of studies concerning optically active 3-phenyl-*l*-menthopyrazole, *l*-menthopyrazole, isomenthopyrazole, carvomenthopyrazole and carvoisomenthopyrazole were previously prepared by the formylation of menthone or carvomenthone using LDA [2]. The utility of these optically active pyrazoles as chiral catalyst was studied secondly. Many papers concerning poly(pyrazolyl)alkanes and their metal complexes were reported in the literature [8]. Some optically active bis(pyrazolyl)-methanes and borane analogues have already been prepared from terpenoids such as camphor and menthone [9]. Particularly the metal complexes of these optically active pyrazole compounds were applied as chiral Lewis acid catalysts for cyclopropanation and allylic alkylation [10].

However, the steric effects of substituent groups in the complex formation were still obscure. Accordingly the NMR spectra of various bis(pyrazolyl)methanes were studied in the presence of Lewis acid. When $Zn(OTf)_2$ was gradually added to bis(pyrazol-1,1'-yl)methane (**6a**) solu-

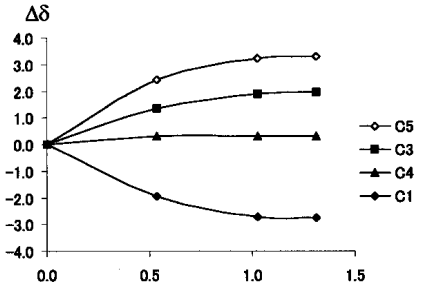
Scheme 2



tion (Scheme 2), the sharp ^{1}H- and ^{13}C-NMR signals were all shifted and saturated at the equimolar mixture, as shown in Figures 1 and 2. In the case of bis(3,5-dimethylpyrazol-1,1'-yl)methane (**6b**), similar shifts were observed in all signals, which were however broadened at room temperature. These signals were split at –40 °C, while sharp signals were observed at 60 °C. These remarkable peak shifts of bis(3,5-di-*t*-butylpyrazol-1,1'-yl)methane (**6c**) and bis(3-*p*-tolylpyrazol-1,1'-yl)methane (**6d**) were not observed by the addition of $Zn(OTf)_2$, even after the prolonged period of standing. These NMR observations suggested that the bulky substituent groups on the pyrazole ring of **6** retarded or prohibited the formation of zinc complexes. Furthermore, the catalytic activities of Mg and Zn complexes of **6b** were evaluated by the reaction rates of the Diels Alder reaction, as summarized in Table 1. The reaction of 1crotonoyl-3,5-dimethylpyrazole (**1b**) with cyclopentadiene was accelerated 6.2 times by the catalytic amounts of Mg complex of **6b**. From these facts, bis(menthopyrazolyl)methane and their analogues



Ratio of $Zn/OTf)_2$/**6a**
Figure 1. ^{1}H NMR Shifts of **6a**



Ratio of $Zn/OTf)_2$/**6a**
Figure 2. ^{13}C NMR Shifts of **6a**

seemed to be promising as a chiral catalysts for the asymmetric Diels Alder reaction.

Therefore bis(pyrazolyl)alkane derived from various optically active pyrazoles was designed as the ligand for

Table 1

Catalytic Effects of Metal Complex of **6b** in Diels Alder Reaction with Cyclopentadiene

Run		Dienophile	**6b** mol %	Lewis Acid	mol %	k_{cat}/k_0
1	**4b**	3-Crotonoyl-2-oxazolidinone	0	——	0	1
2	**4b**	3-Crotonoyl-2-oxazolidinone	0	$Zn(OTf)_2$	10	1.7
3	**4b**	3-Crotonoyl-2-oxazolidinone	12	$Zn(OTf)_2$	10	2.7
4	**1b**	1-Crotonoyl-3,5-dimethylpyrazole	0	——	0	1
5	**1b**	1-Crotonoyl-3,5-dimethylpyrazole	12	$Zn(OTf)_2$	10	1.9
6	**1b**	1-Crotonoyl-3,5-dimethylpyrazole	12	$Mg(ClO_4)_2$	10	6.2

Table 2

Preparation of Chiral Bis(pyrazolyl)alkane using Diiodomethane and NaH

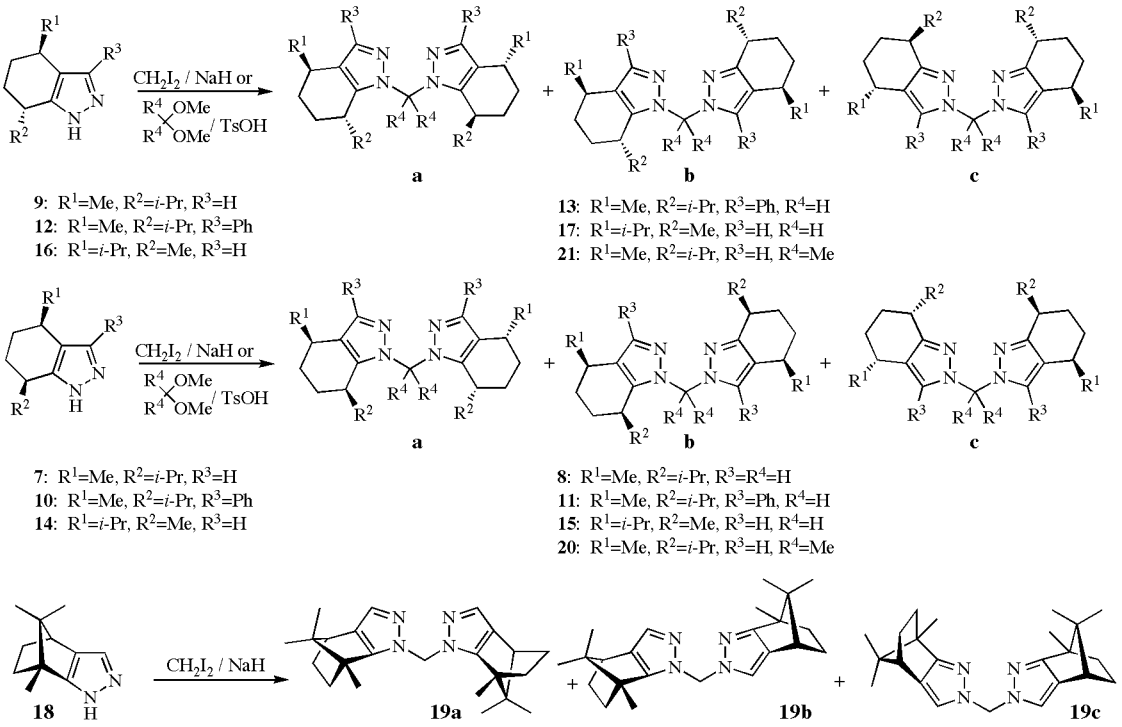
Run		Pyrazole R^1	Pyrazole R^2	Pyrazole R^3	Product	Yield **a**	Yield **b**	Yield **c**
1	**7**	(*R*)-Me	(*R*)-*i*-Pr	H	**8**	19	36	36
2	**10**	(*R*)-Me	(*R*)-*i*-Pr	Ph	**11**	23	43	13
3	**12**	(*R*)-Me	(*S*)-*i*-Pr	Ph	**13**	32	35	23
4	**14**	(*S*)-*i*-Pr	(*S*)-Me	H	**15**	10	33	32
5	**16**	(*S*)-*i*-Pr	(*R*)-Me	H	**17**	[a]	[a]	53
6	**18**	Bornyl			**19**	9	32	40
7	**7**	(*R*)-Me	(*R*)-*i*-Pr	H	**20**	0	0	26
8	**9**	(*R*)-Me	(*S*)-*i*-Pr	H	**21**	0	0	33

[a] Failed to be isolated because of poor yields.

chiral Lewis acid. Due to the different regioisomeric nitrogen atoms on menthopyrazole ring, 3 regioisomers, the pyrazol-1,1'-yl - (a), the pyrazol-1,2'-yl - (b) and the bis(pyrazol-2,2'-yl)methanes (c) were anticipated. Actually, the regioisomers of bis(isomenthopyrazolyl)-methanes (**8**) were prepared from isomenthopyrazole (**7**) by the action of dibromomethane under phase transfer conditions [23c]. Similarly optically active bis-(pyrazolyl)methanes (**11**, **13**, **15**, **17**, and **19**) were prepared from the corresponding pyrazoles (**10**, **12**, **14**, **16**, and **18**) [2a,4] under modified conditions using diiodomethane and NaH (Scheme 3), as listed in Table 2. According to the preparative method of 2,2-bis(pyrazol-1,1'-yl)propane [22], 2,2-bis(isomenthopyrazol-2,2'-yl)propane (**20c**) and 2,2-bis(*l*-menthopyrazol-2,2'-yl)propane (**21c**) were prepared from 2,2-dimethoxy-propane and the corresponding pyrazoles in the presence of *p*-toluenesulfonic acid.

Finally asymmetric Diels Alder reaction of 1-(α,β-unsaturated) acyl substituted pyrazoles with cyclopentadiene was performed in the presence of $Mg(ClO_4)_2$ and bis(pyrazolyl)alkanes (**8**, **11**, **13**, **15**, **17**, **20** and **21**) derived from optically active pyrazoles (Scheme 4). By the use of $Mg(ClO_4)_2$ and bis(isomenthopyrazol-1,1'-yl)methane (**8a**), the Diels Alder Reaction with cyclopentadiene was optimized and summarized in Table 3. The sufficient catalytic amount was estimated to be about 10 mol%. The reaction temperature was optimized to be 0 °C, as lower temperature retarded the reaction without any progression in enantioselectivity. The β-substituent group of (α,β-unsaturated) acyl pyrazoles retarded the Diels Alder reaction and required drastic reaction conditions. Substituent

Scheme 3



Scheme 4

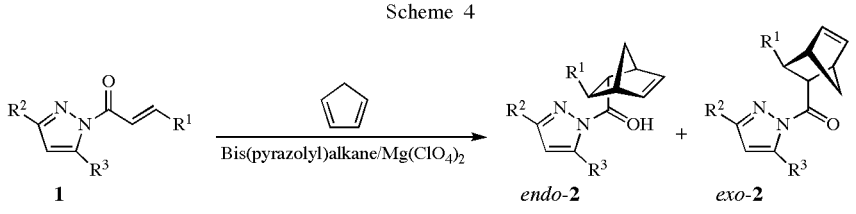


Table 3

Optimization of Diels Alder Reaction of **1** Catalyzed by **8a** and $Mg(ClO_4)_2$

Run[a]	$Mg(ClO_4)_2$ mol%	**8a** mol%		Dienophile R^1	R^2	R^3	Temp °C		Yield%	Product *Endo*%	%Ee
1	10	12	**1b**	Me	Me	Me	30	**2b**	9	78	26
2	10	12	**1b**	Me	Me	Me	30	**2b**	42	76	25
3	10	5	**1b**	Me	Me	Me	30	**2b**	5	74	15
4	10	15	**1b**	Me	Me	Me	30	**2b**	32	75	33
5	30	36	**1b**	Me	Me	Me	30	**2b**	58	88	28
6	50	60	**1b**	Me	Me	Me	30	**2b**	60	80	29
7	10	12	**1b**	Me	Me	Me	0	**2b**	2	91	—
8	10	12	**1a**	H	Me	Me	30	**2a**	92	76	29
9	10	12	**1a**	H	Me	Me	0	**2a**	81	84	40
10	10	12	**1a**	H	Me	Me	-5	**2a**	62	84	39
11	10	12	**1a**	H	Me	Me	-27	**2a**	57	94	39
12	10	12	**1c**	Ph	Me	Me	0	**2c**	7	85	15
13	10	12	**1d**	COOEt	Me	Me	0	**2d**	85	71	—
14	10	12	**1e**	Me	H	H	30	**2e**	62	73	12
17	10	12	**1f**	H	*t*-Bu	*t*-Bu	0	**2f**	40	91	21
18	10	12	**1g**	H	Ph	Ph	0	**2g**	51	87	35
19	10	12	**1h**	H	COOEt	Me	0	**2h**	77	97	34

[a] All data were obtained in the presence of MS4A, except run 1.

Table 4

Asymmetric Diels Alder Reaction of **1a** with Cyclopentadiene Catalyzed by $Mg(ClO_4)_2$ and Chiral Bis(pyrazolyl)alkanes

Run	Bis(pyrazolyl)methanes	R^1	R^2	R^3	Product (**2a**) Yield %	*Endo* %	% Ee	Conf.
1	**8a**	(*R*)-Me	(*R*)-*i*-Pr	H	81	84	40	*S*
2	**8b**	(*R*)-Me	(*R*)-*i*-Pr	H	75	91	23	*S*
3	**8c**	(*R*)-Me	(*R*)-*i*-Pr	H	91	92	17	*S*
4	**20c**	(*R*)-Me	(*R*)-*i*-Pr	H	63	94	18	*S*
5	**13a**	(*R*)-Me	(*S*)-*i*-Pr	Ph	85	83	1	*R*
6	**13b**	(*R*)-Me	(*S*)-*i*-Pr	Ph	86	82	2	*R*
7	**13c**	(*R*)-Me	(*S*)-*i*-Pr	Ph	98	79	11	*S*
8	**15a**	(*S*)-*i*-Pr	(*S*)-Me	H	75	87	15	*S*
9	**15b**	(*S*)-*i*-Pr	(*S*)-Me	H	75	92	30	*S*
10	**15c**	(*S*)-*i*-Pr	(*S*)-Me	H	74	93	19	*S*
11	**17b**	(*S*)-*i*-Pr	(*R*)-Me	H	93	87	17	*S*
12	**17c**	(*S*)-*i*-Pr	(*R*)-Me	H	95	83	1	*S*
13	**21c**	(*S*)-*i*-Pr	(*S*)-Me	H	87	95	23	*S*
14	**19a**	Bornyl	54	95	18	*S*		
15	**19b**	Bornyl	59	84	20	*S*		
16	**19c**	Bornyl	47	94	22	*S*		

[a] The Diels Alder reactions of **1a** were carried out at 0 °C in the presence of 10 mol% of $Mg(ClO_4)_2$, 12 mol% of bis(pyrazolyl)alkane, and MS4A.

groups on pyrazole ring were less effective sterically and/or electronically.

Under optimal conditions using **1a**, the catalytic effects of bis(pyrazolyl)methanes and $Mg(ClO_4)_2$ were revealed as summarized in Table 4. The bulky group substituted bis(pyrazolyl)methanes, which were hard to form the Mg-complex as discussed above, showed to be less effective for the enantioselective reaction. At this moment, bis(isomenthopyrazol-1,1'-yl)methane (**8a**) seemed to be the highest enantioselectivity of 40 % ee, but more effective chiral catalysts in this series of bis(pyrazolyl)methanes need to be found.

In conclusion, *N*-acylpyrazoles (**1**) were promising as good dienophiles, which were easily converted into the desired carboxylic derivatives by the action of nucleophiles. Bis(pyrazolyl)methanes, which were derived from the chiral pyrazoles, showed the activity of chiral catalyst. Particularly 10 mol% of bis(isomenthopyrazol-1,1'-yl)methane (**8a**) catalyzed enantioselectively the Diels Alder reaction up to 40 % ee by the formation of complex with $Mg(ClO_4)_2$.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL JNM-EX270 (270 MHz) spectrometer in deuterochloroform with tetramethylsilane as an internal standard. The enantiomer ratios were evaluated from the peak ratios of gas chromatography on SHIMADZU GC-14A gas chromatograph using Chrompack Chirasil DEX-CB capillary column (0.25 mm x 25 m). The yields of the products were evaluated by GL Science GC-353 gas chromatograph using dimethylsiloxane type capillary column (0.25 mm x 30 m) of GL Science TC-1.

Materials.

(*R*,*R*)-Ph-box was commercially available from Aldrich Chemical Co. *N*-(α,β-Unsaturated) acylpyrazoles (**1**) were prepared from the corresponding pyrazoles and (α,β-unsaturated) acyl chlorides in the presence of triethylamine according to the method of the previous paper [9,13a], and purified by silica gel column chromatography and distillation. In the cases of *N*-acryloylpyrazoles, the addition of hydroquinone was required to inhibit the polymerization in the procedures of concentration and the distillation. Moreover *N*-acryloylpyrazoles were stored in the refrigerator.

The optically active pyrazoles (**7**, **9**, **10**, **12**, **14**, and **16**) were prepared from *l*-menthone and carvone according to the previous paper [2a], and **18** was prepared by the method of House [23c].

1-Acryloyl-3,5-di(*t*-butyl)pyrazole (**1f**).

Compound **1f** was obtained in 72 %; ^{1}H NMR: δ 1.30 (9H, s), 1.44 (9H, s), 5.89 (1H, d, *J*=10.4 Hz), 6.15 (1H, s), 6.57 (1H, d, *J*=17.3 Hz), 7.64-75 (1H, dd, *J*=17.3, 10.4 Hz); ^{13}C NMR: δ 29.3 (CH_3), 29.7 (CH_3), 32.3 (C), 33.2 (C), 106.7 (CH_2), 130.3 (CH), 130.3 (CH), 157.4 (C), 163.1 (C), 164.7 (C).

Anal. Calcd. for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.35; H, 9.02; N, 11.99.

1-Acryloyl-3,5-diphenylpyrazole (**1g**).

Compound **1g** was obtained in 49 % yield; ^{1}H NMR: δ 6.01 (1H, d, *J*=10.2 Hz), 6.62 (1H, d, *J*=17.2 Hz), 6.75 (1H, s), 7.40-50 (8H, m), 7.71-7.81 (1H, dd, *J*=17.2, 10.2 Hz), 7.91 (2H, d, *J*=7.9 Hz); ^{13}C NMR: δ 110.1 (CH_2), 126.2 (CH), 127.9 (CH), 128.2 (CH), 128.8 (CH), 128.9 (CH), 129.2 (CH), 131.1 (C), 131.6 (C), 132.5 (CH), 147.7 (C), 153.6 (C), 164.1 (C).

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.41; H, 5.26; N, 10.20.

1-Acryloyl-3-ethoxycarbonyl-5-methylpyrazole (**1h**).

Compound **1h** was obtained in 93 % yield; bp 140 °C/5 mm Hg; ^{1}H NMR: δ 1.40 (3H, t, *J*=7.2 Hz), 2.65 (3H, d, *J*=1 Hz), 4.42 (2H, q, *J*=7.1 Hz), 6.05-6.11 (1H, m), 6.65-6.75 (2H, m), 7.62-7.75 (1.H, m); ^{13}C NMR: δ 14.2 (CH_3), 14.6 (CH_3), 61.5 (CH_2), 111.7 (CH), 127.5 (CH_2), 133.6 (CH), 145.2 (C), 145.8 (C), 161.7 (C), 165.3 (C).

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.59; H, 5.85; N, 13.48.

General Preparation of Bis(pyrazolyl)methanes.

The corresponding pyrazole (50 mmol) in DMF (20 ml) was added to a suspension of NaH (60 % in oil, 1.5 g, 37.5 mmol) in DMF (10 ml). After stirring for 15 min at room temperature, diiodomethane (8.3 ml, 31 mmol) was added and refluxed for 12 h. The resulting mixture was quenched with water and extracted with Et_2O. The organic layer was washed with water and aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated. Compounds **8** and **19** were identical with the authentic data [24c,23c].

Bis(3-phenylisomenthopyrazol-1,1'-yl)methane (**11a**).

Compound **11a** was obtained in 14 % yield; mp 71-72 °C (Sublimation); ^{1}H NMR: δ 0.82 (6H, d, *J*=6.9 Hz), 0.99 (6H, d, *J*=6.9 Hz), 1.16 (6H, d, *J*=6.6 Hz), 1.50-1.80 (8H, m), 2.43-2.51 (2H, m), 2.55-2.68 (2H, m), 3.01-3.12 (2H, m), 6.49 (2H, s), 7.29-7.41 (6H, m), 7.36 (4H, dd, *J*=8.4, 1.3 Hz); ^{13}C NMR: δ 17.4 (CH_3), 19.3 (CH_2), 20.5 (CH_3), 21.0 (CH_3), 26.2 (CH), 29.3 (CH), 29.7 (CH_2), 36.9 (CH), 65.4 (CH_2), 121.8 (C), 127.0 (CH), 127.2 (CH), 128.3 (CH), 134.5 (C), 143.1 (C), 147.5 (C).

Anal. Calcd. for $C_{35}H_{44}N_4$: C, 80.72; H, 8.52; N, 10.76. Found: C, 80.81; H, 8.46; N, 10.24.

Bis(3-phenylisomenthopyrazol-1,2'-yl)methane (**11b**).

Compound **11b** was obtained in 23 % yield; mp 49-50 °C (Sublimation); ^{1}H NMR: δ 0.80 (3H, d, *J*=6.9 Hz), 0.83 (3H, d, *J*=6.9 Hz), 0.85 (3H, d, *J*=6.9 Hz), 1.01 (3H, d, *J*=6.9 Hz), 1.04 (3H, d, *J*=6.8 Hz), 1.15 (3H, d, *J*=6.8 Hz), 1.26-1.30 (1H, m), 1.54-1.67 (4H, m), 1.72-1.77 (2H, m), 1.80-1.86 (1H, m), 2.27-2.31 (1H, m), 2.35-2.38 (1H, m), 2.59-2.62 (1H, m), 2.79-2.81 (1H, m), 3.07-3.12 (1H, m), 3.15-3.18 (1H, m), 6.07 (2H, d, *J*=14.1 Hz), 6.17 (2H, d, *J*=14.1 Hz), 7.25-7.42 (6H, m), 7.50 (2H, d, *J*=6.8 Hz), 7.69 (2H, d, *J*=7.4 Hz); ^{13}C NMR: δ 18.1 (CH_3), 18.6 (CH_3), 20.1 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 20.7 (CH_3), 20.8 (CH_2), 21.1 (CH_2), 21.5 (CH), 25.3 (CH), 26.5 (CH), 29.3 (CH), 30.2 (CH_2), 36.9 (CH_2), 40.7 (CH), 61.8 (CH_2), 120.7 (C), 121.5 (C), 126.9 (CH), 127.0 (CH), 128.13 (CH), 128.19 (CH), 128.28 (CH), 128.31 (C), 130.5 (CH), 134.9 (C), 140.0 (C), 143.8 (C), 147.7 (C), 151.6 (C).

Anal. Calcd. for $C_{35}H_{44}N_4$: C, 80.72; H, 8.52; N, 10.76. Found: C, 80.71; H, 8.36; N, 10.11.

Bis(3-phenylisomenthopyrazol-2,2'-yl)methane (**11c**).

Compound **11c** was obtained in 43 % yield; mp 69-70 °C (Sublimation); ^{1}H NMR: δ 0.80 (6H, d, *J*=6.6 Hz), 0.88 (6H, d, *J*=6.9 Hz), 0.95 (6H, d, *J*=6.9 Hz), 1.52-1.74 (8H, m), 2.23-2.30 (2H, m), 2.55-2.61 (2H, m), 2.74-2.80 (2H, m), 5.82 (2H, s), 7.37-7.46 (6H, m), 7.63 (4H, dd, *J*=7.6, 1.3 Hz); ^{13}C NMR: δ 18.3 (CH_3), 20.0 (CH_2), 20.1 (CH_3), 22.0 (CH_3), 25.2 (CH), 30.2 (CH), 30.4 (CH_2), 40.8 (CH), 59.4 (CH_2), 121.3 (C), 128.18 (CH), 128.23 (CH), 130.6 (CH), 131.0 (C), 140.6 (C), 151.7 (C).

Anal. Calcd. for $C_{35}H_{44}N_4$: C, 80.72; H, 8.52; N, 10.76. Found: C, 80.67; H, 8.41; N, 10.63.

Bis(3-phenyl-*l*-menthopyrazol-1,1'-yl)methane (**13a**).

Compound **13a** was obtained in 32 % yield; mp 62 °C (from MeOH); ^{1}H NMR: δ 0.90 (6H, d, *J*=6.9 Hz), 0.94 (6H, d, *J*=6.9 Hz), 1.09 (6H, d, *J*=6.9 Hz), 1.30-38 (2H, m), 1.63-80 (4H, m), 1.98-2.10 (2H, m), 2.16-28 (2H, m), 2.51-55 (2H, m), 3.17-21 (2H, m), 6.45 (2H, s), 7.28-41 (6H, m), 7.71 (4H, d, *J*=7.3 Hz); ^{13}C NMR: δ 19.5 (CH_3), 20.4 (CH_3), 21.4 (CH_3), 21.5 (CH_2), 26.3 (CH), 27.7 (CH), 31.0 (CH_2), 36.7 (CH), 64.7 (CH_2), 120.8 (C), 127.1 (CH), 127.3 (CH), 128.4 (CH), 134.7 (C), 143.5 (C), 148.5 (C).

Anal. Calcd. for $C_{35}H_{44}N_4$: C, 80.72; H, 8.52; N, 10.76. Found: C, 80.81; H, 8.59; N, 10.68.

Bis(3-phenyl-*l*-menthopyrazol-1,2'-yl)methane (**13b**).

Compound **13b** was obtained in 35 % yield; mp 144 °C (from MeOH); ^{1}H NMR: δ 0.72 (3H, d, *J*=6.7 Hz), 0.81 (3H, d, *J*=6.8Hz), 0.90 (3H, d, *J*=6.9 Hz), 0.92 (3H, d, *J*=6.8 Hz), 0.98 (3H, d, *J*=6.9 Hz), 1.03 (3H, d, *J*=6.9 Hz), 1.19-21 (1H, m), 1.35-38 (1H, m), 1.45-47 (1H, m), 1.70-74 (1H, m), 1.77-83 (2H, m), 1.89-92 (1H, m), 2.02-04 (1H, m), 2.13-17 (1H, m), 2.31-34 (1H, m), 2.62-65 (1H, m), 2.73-76 (1H, m), 3.00-03 (1H, m), 3.14-17 (1H, m), 6.18 (2H, s), 7.22-46 (8H, m), 7.10 (2H, d, *J*=7.5 Hz); ^{13}C NMR: δ 18.7 (CH_3), 19.8 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 20.7 (CH_3), 21.3 (CH_3), 21.4 (CH_2), 23.2 (CH_2), 26.2 (CH), 27.4 (CH), 27.5 (CH), 30.2 (CH), 31.3 (CH_2), 32.7 (CH_2), 36.6 (CH), 40.9 (CH), 61.7 (CH_2), 119.7 (C), 121.6 (C), 126.9 (CH), 126.9 (CH), 128.0 (CH), 128.3 (CH), 128.3 (CH), 130.0 (CH), 131.4 (C), 134.7 (C), 140.4 (C), 143.0 (C), 147.9 (C), 152.0 (C).

Anal. Calcd. for $C_{35}H_{44}N_4$: C, 80.72; H, 8.52; N, 10.76. Found: C, 80.71; H, 8.55; N, 10.76.

Bis(3-phenyl-*l*-menthopyrazol-2,2'-yl)methane (**13c**).

Compound **13c** was obtained in 23 % yield; mp 153 °C (from MeOH); ^{1}H NMR: δ 0.72 (6H, d, *J*=6.9 Hz), 0.87 (6H, d, *J*=6.9 Hz), 1.04 (6H, d, *J*=6.9 Hz), 1.18 (2H, q, *J*=12.5 Hz), 1.44 (2H, q, *J*=12.5 Hz), 1.76-86 (2H, m), 1.89-99 (2H, m), 2.28-43 (2H, m), 2.52-2.63 (2H, m), 2.77-89 (2H, m), 5.76 (2H, s), 7.31-45 (6H, m), 7.66 (4H, d, *J*=7.9 Hz); ^{13}C NMR: δ 18.4 (CH_3), 20.4 (CH_3), 20.6 (CH_3), 23.5 (CH_2), 27.5 (CH), 29.9 (CH), 32.8 (CH_2), 41.2 (CH), 59.5 (CH_2), 120.5 (C), 128.1 (CH), 128.14 (CH), 130.5 (CH), 131.5 (C), 141.2 (C), 152.7 (C).

Anal. Calcd. for $C_{35}H_{44}N_4$: C, 80.72; H, 8.52; N, 10.76. Found: C, 80.57; H, 8.63; N, 10.69.

Bis(isocarvomenthopyrazol-1,1'-yl)methane (**15a**).

Compound **15a** was obtained in 10 % yield; mp 82-83 °C (Sublimation); ^{1}H NMR: δ 0.80 (6H, d, *J*=6.9 Hz), 0.97 (6H, d, *J*=6.9 Hz), 1.12 (6H, d, *J*=6.9 Hz), 1.43-1.80 (8H, m), 2.02-2.11 (2H, m), 2.51-2.61 (2H, m), 3.29-3.26 (2H, m), 6.19 (2H, s), 7.29 (2H, s); ^{13}C NMR: δ 17.6 (CH_3), 18.7 (CH_3), 20.0 (CH_3), 25.0 (CH_2), 30.1 (CH), 30.8 (CH_2), 38.7 (CH_2), 61.5 (CH_2), 119.8 (C), 137.4 (CH), 144.4 (C).

Anal. Calcd. for $C_{23}H_{36}N_4$: C, 74.95; H, 9.85; N, 15.2. Found: C, 74.77; H, 9.58; N, 15.05.

Bis(isocarvomenthopyrazole-1,2'-yl)methane (**15b**).

Compound **15b** was obtained in 33 % yield; ^{1}H NMR: δ 0.81 (3H, d, *J*=6.9 Hz), 0.81 (3H, d, *J*=6.6 Hz), 0.93 (3H, d, *J*=6.9 Hz), 0.98 (3H, d, *J*=6.9 Hz), 1.17 (3H, d, *J*=6.9 Hz), 1.23 (3H, d, *J*=6.9 Hz), 1.55-1.63 (5H, m), 1.70-1.83 (4H, m), 2.00-2.12 (1H, m), 2.41-2.48 (1H, m), 2.55-2.60 (1H, m), 2.84-2.92 (2H, m), 3.04-3.15 (2H, m), 6.14 (2H, s), 7.22 (1H, s), 7.35 (1H, s); ^{13}C NMR: δ 17.7 (CH_3), 18.7 (CH_3), 18.8 (CH_3), 20.1 (CH_3), 20.2 (CH_3), 20.7 (CH_3), 21.1 (CH_2), 21.5 (CH_2), 25.2 (CH), 28.1 (CH), 29.6 (CH), 30.1 (CH), 30.8 (CH_2), 31.4 (CH_2), 38.6 (CH), 38.7 (CH), 63.1 (CH_2), 119.8 (C), 120.5 (C), 125.9 (CH), 137.9 (CH), 144.1 (C), 154.6 (C).

Anal. Calcd. for $C_{23}H_{36}N_4$: C, 74.95; H, 9.85; N, 15.2. Found: C, 74.52; H, 9.43; N, 14.13.

Bis(isocarvomenthopyrazol-2,2'-yl)methane (**15c**).

Compound **15c** was obtained in 32 % yield; ^{1}H NMR: δ 0.77 (6H, d, *J*=6.9 Hz), 0.94 (6H, d, *J*=6.6 Hz), 1.30 (6H, d, *J*=6.6 Hz), 1.24-1.40 (4H, m), 1.75-2.01 (2H, m), 1.88-2.01 (2H, m), 2.53-2.57 (2H, m), 2.68-2.73 (2H, m), 6.15 (2H, s), 7.25 (2H, s); ^{13}C NMR: δ 18.6 (CH_3), 20.5 (CH_3), 21.1 (CH_3), 21.2 (CH_2), 28.1 (CH), 29.7 (CH_2), 31.5 (CH_2), 38.5 (CH), 65.5 (CH_2), 120.6 (C), 126.5 (CH), 155.4 (C).

Anal. Calcd. for $C_{23}H_{36}N_4$: C, 74.95; H, 9.85; N, 15.2. Found: C, 74.51; H, 9.32; N, 15.14.

Bis(carvomenthopyrazol-2,2'-yl)methane (**17c**).

Compound **17c** was obtained in 53 % yield; mp 106-107 °C (from MeOH-H_2O); ^{1}H NMR: δ 0.77 (6H, d, *J*=6.9 Hz), 0.94 (6H, d, *J*=6.6 Hz), 1.30 (6H, d, *J*=6.6 Hz), 1.75-1.80 (2H, m), 1.88-2.02 (4H, m), 1.88-2.01 (2H, m), 2.53-2.57 (2H, m), 2.68-2.73 (2H, m), 6.15 (2H, s), 7.25 (2H, s); ^{13}C NMR: δ 17.9 (CH_3), 19.9 (CH_3), 20.1 (CH_3), 24.0 (CH_2), 29.9 (CH), 31.4 (CH_2), 32.5 (CH_2), 39.2 (CH), 65.6 (CH_2), 121.1 (C), 125.9 (CH), 155.3 (C).

Anal. Calcd. for $C_{23}H_{36}N_4$: C, 74.95; H, 9.85; N, 15.2. Found: C, 74.20; H, 9.21; N, 15.13.

The General Preparation of 2,2-Bis(pyrazolyl)propanes.

A toluene (4 ml) solution of pyrazole (**7** or **9**, 356 mg, 2.0 mmol) and 2,2-dimethoxypropane (129 mg, 1.24 mmol) was refluxed for 20 h in the presence of *p*-toluenesulfonic acid (15.5 mg, 0.08 mmol) under argon atmosphere. The mixture was quenched with water and extracted with Et_2O. The organic layer was washed with dilute hydrochloric acid, saturated $NaHCO_3$ and saturated NaCl solutions. After dried over anhydrous $MgSO_4$, the solvent was removed. The residue was purified by silica gel chromatography with hexane-ethyl acetate mixture.

2,2-Bis(isomenthopyrazol-2,2'-yl)propane (**20c**).

Compound **20c** was obtained in 26 % yield; mp 95 °C; ^{1}H NMR: δ 0.83 (6H, d, *J*=6.9 Hz), 0.97 (6H, d, *J*=6.9 Hz), 1.09 (6H, d, *J*=6.9 Hz), 1.39-1.46 (2H, m), 1.62-1.82 (6H, m), 2.11 (2H, oct, *J*=6.6 Hz), 2.20 (6H, s), 2.55 (2H, q, *J*=5.9 Hz), 2.70 (2H, sext, *J*=5.9 Hz), 7.06 (2H, s); ^{13}C NMR: δ 19.0 (CH_3), 20.7 (CH_3), 22.2 (CH_3), 22.4 (CH_3), 26.5 (CH_2), 27.6 (CH), 29.7 (CH_2), 31.0 (CH), 39.6 (CH), 76.2 (C), 122.7 (C), 123.6 (CH), 151.4 (C).

Anal. Calcd. for $C_{25}H_{40}N_4$: C, 75.71; H, 10.17; N, 14.13. Found: C, 75.52; H, 9.75; N, 14.12.

2,2-Bis(*l*-menthopyrazol-2,2'-yl)propane (**21c**).

Compound **21c** was obtained in 33 % yield; mp 74 °C; ^{1}H NMR: δ 0.79 (6H, d, *J*=6.9 Hz), 0.98 (6H, d, *J*=6.9 Hz), 1.10 (6H, d, *J*=6.9 Hz), 1.16 (2H, q, *J*=12.2 Hz), 1.40 (2H, q, *J*=12.9 Hz), 1.82-1.89 (4H, m), 2.17 (6H, s), 2.34-2.42 (2H, m), 2.52-2.58 (2H, m), 2.61-2.72 (2H, m), 6.92 (2H, d, *J*=1.0 Hz); ^{13}C NMR: δ 18.7 (CH_3), 20.9 (CH_3), 22.5 (CH_3), 24.8 (CH_3), 28.8 (CH_2), 29.0 (CH), 31.2 (CH_2), 33.7 (CH), 41.5 (CH), 77.7 (C), 124.3 (CH), 124.6 (C), 152.4 (C).

Anal. Calcd. for $C_{25}H_{40}N_4$: C, 75.71; H, 10.17; N, 14.13. Found: C, 75.59; H, 9.47; N, 14.16.

Detection of Zn-Complexation of **6** by NMR Spectroscopy.

Appropriate amounts of $Zn(OTf)_2$ were added to the solution of **6** in $CDCl_3$-CD_3OD mixture (1:1 v/v), and ^{1}H and ^{13}C NMR spectra were measured. The complexation of **6** with $Zn(OTf)_2$ was observed by the shifts of all signals. When more than equimolar amounts of $Zn(OTf)_2$ were added, the shifts of signals were saturated. The result of **6a** was plotted in Figure 1 and 2, where the down field shifts were defined to be positive Δδ values.

General Procedure of Asymmetric Diels Alder Reaction Catalyzed by (*R*,*R*)-Ph-box or Bis(pyrazolyl)alkanes.

A mixture of chiral ligand (0.03 mmol) of (*S*,*S*)-Ph-box or bis(pyrazolyl)alkanes, Lewis acid (0.025 mmol) and MS4A (*ca*. 80 mg) in CH_2Cl_2 (0.5 ml) was stirred for 30 min at room temperature under an argon atmosphere. Subsequently dienophile (**4b** or **1**, 0.25 mmol) in CH_2Cl_2 (1 ml) was added and stirred for another half an hour. Cyclopentadiene (0.2 ml, 2.43 mmol) was then added and stirred for 5 h at appropriate temperature. The reaction was monitored from time to time by GC and HPLC using phenanthrene as an internal standard. After the reaction was complete, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with dilute hydrochloric acid, saturated $NaHCO_3$ and saturated NaCl solution. After drying over anhydrous $MgSO_4$, the solvent was removed. The separation of *Endo* and *Exo* isomers was performed by silica gel column chromatography with benzene-hexane mixture. The products **2a**, **2b**, **2c** and **2d** were identified with authentic samples [10].

The *Endo* isomer (0.06 mmol) dissolved in MeOH solution (1 ml) of sodium methoxide (0.2 mmol), and stirred for 1 h at room temperature. The resulting mixture was quenched with water and extracted with Et_2O. The organic layer was washed with dilute hydrochloric acid, saturated $NaHCO_3$ and saturated NaCl solutions. After drying over anhydrous $MgSO_4$, the solvent was removed. From the GC measurement on the chiral phase column, the enantiomer excess of the residual methyl ester of the cycloadduct was evaluated.

Endo-1-(3-Methylbicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-pyrazole (**2e**).

Compound **2e** was obtained; ^{1}H NMR: δ 1.23 (3H, d, *J*=6.9 Hz), 1.51 (1H, d, *J*=8.6 Hz), 1.78 (1H, d, *J*=8.9 Hz), 2.12 (1H, sext, *J*=6.6 Hz), 2.59 (1H, s), 3.37 (1H, s), 3.63 (1H, t, *J*=3.9 Hz), 5.88 (1H, m), 6.39 (1H, m), 6.43 (1H, s), 7.73 (1H, s), 8.22 (1H, d, *J*=2.9 Hz); ^{13}C NMR: δ 20.4 (CH_3), 37.2 (CH_2), 47.0 (CH), 48.6 (CH), 49.6 (CH), 51.1 (CH), 109.0 (CH), 128.3 (CH), 131.7 (CH), 139.2 (CH), 143.5 (CH), 173.0 (C).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.19; H, 7.11; N, 13.74.

Endo-1-(Bicyclo[2.2.1]heptene-4-carbonyl)-3,5-di(*t*-butyl)pyrazole (**2f**).

Compound **2f** was obtained; ^{1}H NMR: δ 1.31 (9H, s), 1.36 (9H, s), 1.45 (2H, s), 1.52-1.57 (1H, m), 1.98 (1H, t-d, *J*=10.4, 3.6 Hz), 2.94 (1H, broad s), 3.36 (1H, broad s), 4.20-4.27 (1H, m), 5.86-5.89 (1H, m), 6.08 (1H, s), 6.22-6.25 (1H, m); ^{13}C NMR: δ 29.3 (CH_3), 29.7 (CH_2), 29.9 (CH_3), 32.3 (C), 33.1 (C), 43.0 (CH), 45.3 (CH), 47.4 (CH), 50.1 (CH_2), 105.6 (CH), 132.0 (C), 137.5 (CH), 156.7 (C), 162.3 (C), 174.9 (C).

Anal. Calcd. for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.32. Found: C, 75.63; H, 9.41; N, 9.14.

Endo-1-(Bicyclo[2.2.1]heptene-4-carbonyl)-3,5-diphenylpyrazole (**2g**).

Compound **2g** was obtained; ^{1}H NMR: δ 1.52 (1H, s), 1.52 (1H, s), 1.59 (1H, dd, *J*=10.4 ,3.6 Hz), 2.05 (1H, t-d, *J*=10.4, 3.6 Hz), 2.98 (1H, broad s), 3.57 (1H, broad s), 4.25-34 (1H, m), 5.94-97 (1H, m), 6.23-26 (1H, m), 6.69 (1H, s), 7.39-49 (8H, m), 7.93 (2H, d, *J*=8.1 Hz); ^{13}C NMR: δ 29.8 (CH_2), 43.0 (CH), 44.3 (CH), 47.6 (CH), 50.3 (CH_2), 109.3 (CH), 126.2 (CH), 127.9 (CH_2), 128.6 (CH), 128.77 (CH), 128.84 (CH), 129.0 (CH), 131.4 (C), 131.7 (CH), 132.1 (C), 138.0 (CH), 147.3 (C), 153.0 (C), 174.0 (C).

Anal. Calcd. for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 80.94; H, 5,95; N, 8.20.

Endo-1-(Bicyclo[2.2.1]hept-5-ene-2-carbonyl)-3-ethoxycarbonyl-5-methylpyrazole (**2h**).

Compound **2h** was obtained; ^{1}H NMR: δ 1.41 (3H, t, *J*=7.3 Hz), 1.50 (2H, br s), 1.49-57 (2H, m), 2.04 (1H, t-d, *J*=10.4, 3.6 Hz), 2.54 (3H, s), 2.99 (1H, broad s), 3.42 (1H, broad s), 4.22-28 (1H, m), 4.41 (2H, q, *J*=7.3 Hz), 5.86-89 (1H, m), 6.27-30 (1H, m), 6.59 (1H, s); ^{13}C NMR: δ 14.3 (CH_3), 14.5 (CH_3), 29.8 (CH_2), 43.0 (CH), 43.7 (CH), 47.5 (CH), 50.3 (CH_2), 61.3 (CH_2), 111.0 (CH), 131.5 (CH), 138.2 (CH), 144.5 (C), 145.3 (C), 162.0 (C), 175.7 (C).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.37; H, 6.65; N, 10.03.

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