Preparation of 2,6-Bis(*l*-menthopyrzol-3-yl)pyridines and their Catalytic Activity for Asymmetric Diels Alder Reaction

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3-Aryl-*l*-menthopyrazoles **1** and **2** and related compounds were prepared from *l*-menthone, and their enantioselective activities were discussed as chiral ligands. In this series of compounds, 2,6-bis(2-methyl-*l*-menthopyrazol-3-yl)pyridine (**8a**), which had both structural features of 3-phenyl-*l*-menthopyrazole (**1b**) and C_2 symmetric ligand in the molecule, should form the C_2 symmetric complex *in situ* with $Zn(OTf)_2$ or $Ni(ClO_4)_2 \cdot 6H_2O$. The subsequent complex catalyzed the Diels Alder reaction of 1-acryloyl-3,5-dimethylpyrazole (**11a**) with cyclopentadiene (**12**) enantioselectively up to 75 % ee.

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Introduction.

Recently we designed and prepared 3-phenyl-*l*-menthopyrazole (**1b**) and related compounds as chiral pyrazoles [1]. Moreover, we have investigated the excellent properties of these chiral pyrazoles as a new chiral auxiliary [2,3], which has unique structure and properties different from the conventional chiral auxiliaries [4]. The most important characteristics of this auxiliary are that the acyl substrate terminates to nitrogen atom of heteroaryl pyrazole ring, and that the chiral atmosphere surrounds the substrate. That is, the (4*R*)-methyl group of **1b** is located close to the 3-phenyl group and steric hindrance is relaxed by twisting of the benzene ring, which overlaps one side of the terminal nitrogen atom. These structural features cause the transmission of the chirality of the (4*R*)-methyl group into the terminal nitrogen atom through torsional asymmetry of phenyl group, and cause the diastereofacial effect in the reactions of the substrate moiety with alkyl halides [5], phenyldisulfide [6], acyl chloride [7], aldehydes [8], and compounds containing C=N bond [9]. The asymmetric addition of Grignard reagents [10], dienes [11] and 1,3-dipolar compounds [12] on *N*-(α,β-unsaturated)-acyl substituted pyrazoles have been reported as well. Otherwise, *N*-acylheteroaromatics such as *N*-acylimidazoles are utilized as the activated acyl moiety in a wide variety of organic syntheses [13]. As an analogue of these *N*-acylheteroaromatics, *N*-acylpyrazoles are easily converted into acyl derivatives by the action of nucleophiles such as alcohols [14], amines [15], Grignard reagents [16], and organozinc compounds [17] under basic or acidic conditions [18].

Since Evans reported the enantioselective Diels Alder reactions using the C_2 symmetric chiral catalyst such as 2,2-bis[2-(4-(*S*)-phenyl-1,3-oxazolyl)]propane [(*S*,*S*)-Phbox] [19], many papers concerning the analogous box derivatives have appeared in the literature [20]. Particularly the tridentate ligands in the box-series exhibited high stereoselective catalytic effects in various organic syntheses.

Pyrazoles are good ligands for various Lewis acids [21], and the optically active pyrazoles are expected to show effective chiral catalytic activities for various enantioselective syntheses. These optically active pyrazoles have already exhibited chiral catalytic activity in the borane reduction and the dialkylzinc addition on the prochiral carbonyl compounds [22]. Furthermore, bis(pyrazolyl)methanes, which were regarded as bidentate pyrazole ligand with C_2 symmetry, showed chiral catalytic activity for Diels Alder reaction by the formation of magnesium complex [23]. However, we have strongly desired to develop more effective catalyst of optically active pyrazole derivatives for a wide variety of synthetic reactions. Therefore, we designed the optically active 2,6-bis(*l*-menthopyrazol-3-yl)pyridine (**2a**), which had both structural features of 3-aryl-*l*-menthopyrazole (**1**) and tridentate ligand with C_2 symmetry in the molecule. Here we will report the preparation of **2a** and the related pyrazoles. Also, their chiral catalytic activities in the Diels Alder reaction will be discussed as the extension of the stereoselective Diels Alder reaction using menthopyrazoles [10,23].

Results and Discussion.

Since the coordination abilities depend on the properties of heteroaromatics, we undertook the preparation of 3-heteroaryl-*l*-menthopyrazoles (**1a**) as a structural analogue of **1b** summarized in Scheme 1. By the reaction of heteroaroyl chlorides (**3**) on *l*-menthone in the presence of lithium diisopropylamide, the corresponding 2-hetaroyl-*l*-menthones (**4**) were prepared. The subsequent diketones **4** were treated with hydrazine hydrate under the acidic conditions, 3-heteroaryl-*l*-menthopyrazoles (**1**) were prepared in good yields (Table 1). Similarly 3-heteroaryl-2-methyl-*l*-menthopyrazoles (**5**) were obtained by the treatment of **4** with methylhydrazine together with small portions of regioisomeric 3-hetrayl-1-methyl-*l*-menthopyrazoles (**6**). Otherwise, **6** can be synthesized by methylation of **1** with methyl iodide.

1,3-Bis(*l*-menthopyrazol-3-yl)benzene (**2b**) as a C_2 symmetric bidentate ligand was prepared from isoph-

Scheme 1

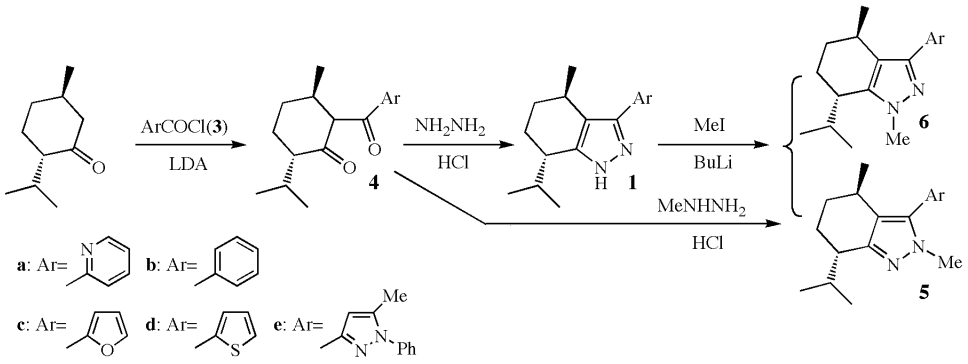


Table 1

Preparation of 3-Heteroaryl-*l*-menthopyrazoles and their *N*-Methyl Derivatives from **4**

Run	Aroyl-*l*-menthone[a]	Hydrazine	Product (Yield, %)
1	**4a** Py	NH_2NH_2	**1a** (27)
2	**4a** Py	$MeNHNH_2$	**5a** (65) + **6a** (17)
3	**4b** Ph	NH_2NH_2	**1b** (96)
4	**4b** Ph	$MeNHNH_2$	**5b** (83) + **6b** (12)
5	**4c** Fura	NH_2NH_2	**1c** (100)
6	**4c** Fura	$MeNHNH_2$	**5c** (78) + **6c** (10)
7	**4d** Thio	NH_2NH_2	**1d** (80)
8	**4d** Thio	$MeNHNH_2$	**5d** (82) + **6d** (trace)
9	**4e** Pyra	NH_2NH_2	**1e** (51)
10	**4e** Pyra	$MeNHNH_2$	**5e** (36) + **6e** (16)

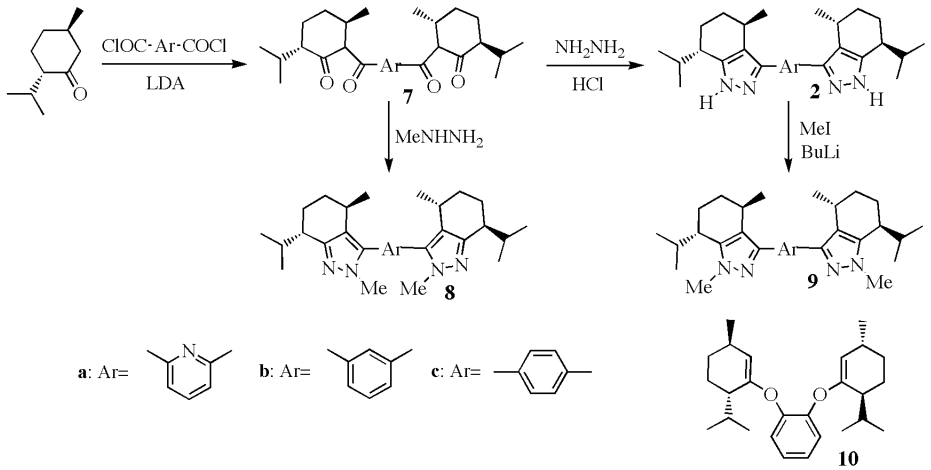
[a] 2-Pyridinyl, 2-furyl, 2-thienyl and 5-methyl-1-phenylpyrazol-3-yl groups were abbreviated as Py, Fura, Thio, and Pyra, respectively.

thaloyl chloride and *l*-menthone. By the action of lithium diisopropylamide, the corresponding tetraketone intermediate **7b** was afforded in moderate yield, then **7b** was treated with hydrazine hydrate to give **2b**. The treatment of **7b** with methylhydrazine afforded predominantly 1,3-bis(2-methyl-*l*-menthopyrazol-3-yl)benzene (**8b**). Alternatively, a regioisomer of **8b**, 1,3-bis(1-methyl-*l*-menthopyrazol-3-yl)benzene (**9b**) was regioselectively prepared by direct methylation of **2b** using methyl iodide and butyllithium. Although 1,4-bis(*l*-menthopyrazol-3-yl)benzene (**2c**) was obtained in good yield by similar reaction conditions, 1,2-analogue could not be prepared due to their steric hindrance and phthalic diester (**10**) of menthone enolate was afforded.

Analogously, C_2 symmetric tridentate ligands were prepared from pyridine-2,6-dicarbonyl chloride and *l*-menthone through the corresponding tetraketone intermediate (**7a**). Finally, **7a** was treated with hydrazine hydrate to give 2,6-bis(*l*-menthopyrazol-3-yl)pyridine (**2a**). Two regioisomeric derivatives 1,3-bis(2-methyl-*l*-menthopyrazol-3-yl)pyridine (**8a**) and 1,3-bis(1-methyl-*l*-menthopyrazol-3-yl)pyridine (**9a**) were prepared by treatment of **7a** with methylhydrazine and by the direct methylation of **2a**, respectively.

In order to reveal the capability of ligands as chiral catalysts, the asymmetric Diels Alder reaction of 1-acryloyl-3,5-dimethylpyrazoles (**11a**) with cyclopentadiene (**12**) was performed by using 3-heteroaryl-*l*-menthopyrazoles (**1**, **5** and **6**) in the presence of $Zn(OTf)_2$ as a catalyst. The

Scheme 2



main product was found to be 1-(*endo*-bicyclo[2.2.1]hept-5-ene-2-carbonyl)-3,5-dimethylpyrazole (**13a**) accompanied with small portions of *exo*-isomer **14a**. The enantiomeric mixture of **13a** was converted into methyl *endo*-bicyclo[2.2.1]hept-5-ene-2-carboxylate (**15**) by treatment with sodium methoxide in methanol, and the stereostructure and ratio of the predominant enantiomer was deduced by chiral gas chromatography.

Compared with the cases of 3-phenyl-*l*-menthopyrazoles (**1b**, **5b** and **6b**), similar enantioselectivities in the Diels Alder reactions were observed by the catalyst of *l*-menthopyrazoles having various heteroaryl groups other than pyridine as shown in Table 2. Methyl group on either *N*-1 or *N*-2 atom in compounds **5** and **6** did not affect the enantioselectivity in these reactions. In the cases of pyridine substituted analogues (**1a**), some enantioselective promotion under the neutral conditions were observed, while the deprotonation from **1a** by the addition of butyllithium set back to the similar activity to that of **1b**.

Table 2

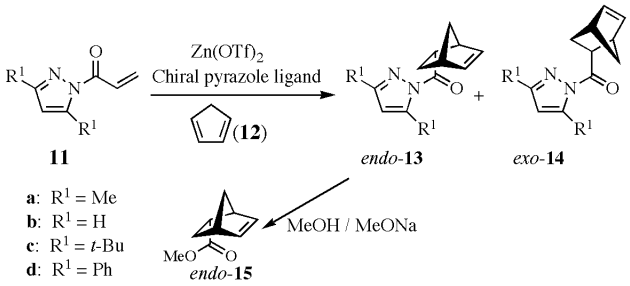
Catalytic Effect of 3-Heteroaryl-*l*-menthopyrazoles for Diels Alder Reaction

Run	Ligand	Ar[b]	R	Lewis Acid[a]	Additive	Yield	Endo %	ee %
1	**1b**	Ph	H	$Zn(OTf)_2$		79	92	24
2	**1b**	Ph	H	$Zn(OTf)_2$	BuLi	76	94	25
3	**5b**	Ph	2-Me	$Zn(OTf)_2$		89	93	40
4	**6b**	Ph	1-Me	$Zn(OTf)_2$		84	92	28
5	**1a**	Py	H	$Zn(OTf)_2$		92	93	32
6	**1a**	Py	H	$Zn(OTf)_2$	BuLi	79	95	25
7	**5a**	Py	2-Me	$Zn(OTf)_2$		90	94	26
8	**6a**	Py	1-Me	$Zn(OTf)_2$		91	92	23
9	**1c**	Fura	H	$Zn(OTf)_2$		63	93	23
10	**1c**	Fura	H	$Zn(OTf)_2$	BuLi	72	91	21
11	**5c**	Fura	2-Me	$Zn(OTf)_2$		77	91	21
12	**6c**	Fura	1-Me	$Zn(OTf)_2$		82	93	30
13	**1d**	Thio	H	$Zn(OTf)_2$		72	93	21
14	**1d**	Thio	H	$Zn(OTf)_2$	BuLi	80	94	20
15	**5d**	Thio	2-Me	$Zn(OTf)_2$		98	93	27
16	**6d**	Thio	1-Me	$Zn(OTf)_2$		76	93	25
17	**1e**	Pyra	H	$Zn(OTf)_2$		79	86	24
18	**1e**	Pyra	H	$Zn(OTf)_2$	BuLi	79	95	18
19	**5e**	Pyra	2-Me	$Zn(OTf)_2$		98	89	23
20	**6e**	Pyra	1-Me	$Zn(OTf)_2$		73	92	26

[a] The molar ratio between ligand and $Zn(OTf)_2$ was 1:1; [b]2-Pyridinyl, 2-furyl, 2-thienyl and 5-methyl-1-phenylpyrazol-3-yl groups were abbreviated as Py, Fura, Thio, and Pyra, respectively.

Since the complex formation of the heteroatoms was generally proportional to their basicity, the coordination abilities of heteroaryl group should be the order of pyrazolato anion > pyridine > pyrazole > thiophen or furan. By addition of strong base such as butyllithium, *N*-unsubstituted pyrazoles should be deprotonated to form the corresponding pyrazolato anion, and should perform as good ligands toward Lewis acid. Therefore, zinc atom should

Scheme 3



mainly coordinate with the nitrogen atom of pyridine ring in **1a**, **5a** and **6a**, while the other ligands should be coordinated on the nitrogen atom of menthopyrazole ring. Thus the enantioselectivity by these ligands was mainly dependent on the coordination site of the zinc atom.

Although 1,3-bis(*l*-menthopyrazol-3-yl)benzenes (**2b**, **8b**, and **9b**) seemed to be a bidentate ligand having C_2 symmetry, distinguishable enantioselectivity did not appear in the Diels Alder reaction using $Zn(OTf)_2$, as listed in Table 3. If nitrogen atom of one pyrazole on **2b** or **9b** approached to the other side of pyrazole nitrogen in the appropriate distance as a bidentate ligand, 2-H hydrogen atom on benzene ring should move to the hindered position for the complex formation. When these ligands were treated with equimolar amount of $Zn(OTf)_2$, one of two pyrazole moieties should chelate independently to the zinc atom to form a partially coordinated complex. These assumptions reasonably explained that these compounds exhibited similar enantioselectivities in the asymmetric Diels Alder reaction. Even though these ligands were

Table 3

Catalytic Effect of Bis(*l*-menthopyrazol-3-yl)arenes for Diels Alder Reaction

Run	Ligand	Ar[a]	R	Lewis Acid	Mole Ratio	Additive	Yield	Endo %	ee %
1	**2a**	Py	H	$Zn(OTf)_2$	1:1		95	92	27
2	**2a**	Py	H	$Zn(OTf)_2$	1:2		95	92	23
3	**2a**	Py	H	$Zn(OTf)_2$	1:1	BuLi	98	95	43
4	**2a**	Py	H	$Zn(OTf)_2$	1:2	BuLi	93	93	22
5	**2b**	Ph	H	$Zn(OTf)_2$	1:1		62	92	20
6	**2b**	Ph	H	$Zn(OTf)_2$	1:2		77	94	18
7	**2b**	Ph	H	$Zn(OTf)_2$	1:1	BuLi	92	93	27
8	**2b**	Ph	H	$Zn(OTf)_2$	1:2	BuLi	85	94	20
9	**8a**	Py	2-Me	$Zn(OTf)_2$	1:1		84	92	67
10	**8a**	Py	2-Me	$Zn(OTf)_2$	1:2		95	91	43
11	**8b**	Ph	2-Me	$Zn(OTf)_2$	1:1		98	95	33
12	**8b**	Ph	2-Me	$Zn(OTf)_2$	1:2		94	93	30
13	**9a**	Py	1-Me	$Zn(OTf)_2$	1:1		85	92	21
14	**9a**	Py	1-Me	$Zn(OTf)_2$	1:2		97	91	21
15	**9b**	Ph	1-Me	$Zn(OTf)_2$	1:1		89	96	31
16	**9b**	Ph	1-Me	$Zn(OTf)_2$	1:2		89	95	34

[a] 2,6-Disubstituted pyridine and 1,3-disubstituted benzene groups were abbreviated as Py and Ph, respectively.

treated with 2 molar amounts of $Zn(OTf)_2$ for the complete complex formation with all pyrazole moieties,any remarkable change was not observed in these Diels Alder reaction.

2,6-Bis(*l*-menthopyrazol-3-yl)pyridines (**2a**, **8a** and **9a**) had a 2,6-disubstituted pyridine ring, which strongly preferred the complex formation rather than pyrazole moiety. Moreover, the absence of 1-H hydrogen atom on pyridine ring should avoid the steric inhibition of the complex formation differently from the cases of 1,3-bis(*l*-menthopyrazol-3-yl)benzenes. Particularly the structures of **2a** and **9a** were expected to be suitable for tridentate complex formation with the effective chiral surrounding.

The X-ray structural analysis gave the molecular structure of **1c**, in which the furan and pyrazole rings were bonded in *syn*-form and the heteroatoms of both rings were located in sufficiently near position for the bidentate chelation, as shown in Figure 1. On the contrary in structure **1a** and **9a**, pyridine ring and pyrazole rings were bonded in twisted *anti*-form, as shown in the ORTEP drawing in Figure 2 and Figure 3, respectively. Namely in crystal state, the Lewis basic nitrogen atoms of pyridine and pyrazoles were unfavorably located at far position, in spite of the expectation of the good tridentate ligand. In order to take a role of the bidentate or tridentate ligand, the bond rotation from the most stable conformer was required along the restricted bond between pyridine and pyrazole ring.

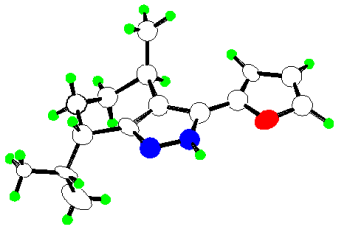


Figure 1. ORTEP of 3-(2-Furyl)-*l*-menthopyrazole (**1c**).

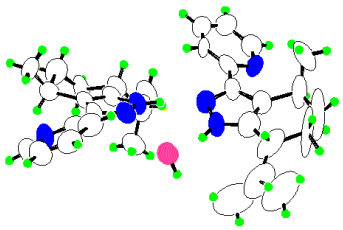


Figure 2. ORTEP of 3-(Pyridin-2'-yl)-*l*-menthopyrazole (**1a**).

When the Diels Alder reaction of **11a** was carried out in the presence of **9a** and $Zn(OTf)_2$, the enantioselectivity was found to be less than that of **9b**. Also the reaction proceeded with similar selectivity by the use of **2a** and

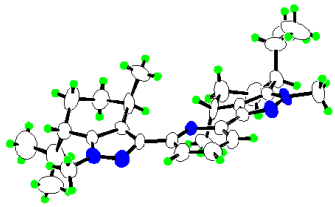


Figure 3. ORTEP of 2,6-Bis(1-methyl-*l*-menthopyrazol-3-yl)pyridine (**9a**).

$Zn(OTf)_2$, and the enantioselectivity increased up to 43 % ee under the forced conditions for tridentate complex formation by the deprotonation from the pyrazole ring of **2a** using butyllithium.

By the use of **8a** as a chiral ligand, the asymmetric Diels Alder reaction was observed with the good enantioselectivity up to 67 % ee, and the enantioselectivity fell down into 43 % ee when **8a** was used together with 2 molar equivalents of $Zn(OTf)_2$. These results can reasonably be explained by the following speculations. The central pyridine ring of **8a** should be surrounded by 4 methyl groups on 2-, 2'-, 4- and 4'-position, and the steric hindrance was relaxed by the twisted *anti*-form as an analogy of **9a**. Accordingly it was speculated that the basic nitrogen atoms of pyridine and pyrazoles are located far away from each other with their lone pairs of electrons directed in opposite directions. Thus the complex with $Zn(OTf)_2$ should be formed on the pyridine nitrogen keeping their C_2 symmetry. By the use of 2 molar amounts of Lewis acid, one Lewis acid should coordinate to pyridine and the other on the pyrazole nitrogen, and the subsequent complex should loose its C_2 symmetry.

For giving full play to the catalytic ability of these ligands, the reaction of various 3,5-disubstituted 1-acryloylpyrazoles (**11b**, **11c**, and **11d**) were carried out as listed in Table 4, and **11a** was the most preferable substrate for the asymmetric catalytic Diels Alder reaction.

Generally the catalytic activity of the complex molecule was affected by the stability, which depends on either the structure of ligand or the property of the Lewis acid. After attempting complex formation of these ligands with various Lewis acids, $Zn(OTf)_2$ was regarded as the most preferable activator for these Diels Alder reactions as listed in Table 5. Although the complex with $Ni(ClO_4)_2 \cdot 6H_2O$ did not show

Table 4

The Substituent Effect of Pyrazole in Diels Alder Reaction Catalyzed by **8b** and $Zn(OTf)_2$

Run	Substrate	R^1	Yield	Endo %	ee %
1	**11a**	Me	84	92	67
2	**11b**	H	60	95	48
3	**11c**	*t*-Bu	44	91	33
4	**11d**	Ph	62	85	23

Table 5

Catalytic Effect of Bis(*l*-menthopyrazol-3-yl)pyridine and Various Lewis Acid on Diels Alder Reaction

Run	Ligand	Ar[a]	R	Lewis Acid	Mole Ratio	Additive	Yield	Endo %	ee %
1	**2a**	Py	H	$Cu(OTf)_2$	1:1		63	89	6
2	**2a**	Py	H	$Mg(ClO_4)_2$	1:1		69	95	19
3	**2a**	Py	H	$Ni(ClO_4)_2$	1:1		59	94	17
4	**2a**	Py	H	$Zn(OTf)_2$	1:1		95	92	27
5	**2a**	Py	H	$Cu(OTf)_2$	1:1	BuLi	51	94	22
6	**2a**	Py	H	$Mg(ClO_4)_2$	1:1	BuLi	86	95	40
7	**2a**	Py	H	$Ni(ClO_4)_2$	1:1	BuLi	69	94	38
8	**2a**	Py	H	$Zn(OTf)_2$	1:1	BuLi	98	95	43
9	**8a**	Py	2-Me	$Cu(OTf)_2$	1:1		53	98	45
10	**8a**	Py	2-Me	$La(OTf)_3$	1:1		84	83	27
11	**8a**	Py	2-Me	$Mg(ClO_4)_2$	1:1		58	92	13
12	**8a**	Py	2-Me	$Ni(ClO_4)_2$	1:1		76	86	11
13	**8a**	Py	2-Me	$Ni(ClO_4)_2$	1:1	BuLi	82	94	75
14	**8a**	Py	2-Me	$RuCl_3$	1:1		68	93	21
15	**8a**	Py	2-Me	$Zn(OTf)_2$	1:1		84	92	67
16	**8a**	Py	2-Me	$Zn(SCN)_2$	1:1		79	91	28
17	**9a**	Py	1-Me	$Cu(OTf)_2$	1:1		43	92	12
18	**9a**	Py	1-Me	$Mg(ClO_4)_2$	1:1		74	95	12
19	**9a**	Py	1-Me	$Ni(ClO_4)_2$	1:1		89	94	8
20	**9a**	Py	1-Me	$Zn(OTf)_2$	1:1		85	92	21

[a] 2,6-Disubstituted pyridine was abbreviated as Py.

any remarkable enantioselectivity, the Diels Alder reaction of **11** with **12** succeeded with an enantioselectivity of 75 % ee using the complex catalyst which was formed *in situ* from **8a** and $Ni(ClO_4)_2 \cdot 6H_2O$ in the presence of equimolar amount of butyllithium.

Conclusion.

3-Heteroaryl-*l*-menthopyrazoles **1** and **2** and related compounds were prepared from *l*-menthone, and their enantioselective activities were discussed as chiral ligands. In this series of compounds, 2,6-bis(2-methyl-*l*-menthopyrazol-3-yl)pyridine (**8a**), which had both structural features of 3-phenyl-*l*-menthopyrazole (**1b**) and C_2 symmetric ligand in the molecule, should form the C_2 symmetric complex *in situ* with $Zn(OTf)_2$ or $Ni(ClO_4)_2 \cdot 6H_2O$. The catalytic amount of subsequent complex promoted the Diels Alder reaction of 1-acryloyl-3,5-dimethylpyrazole (**11a**) with cyclopentadiene (**12**) enantioselectively up to 75 % ee. From these facts, the utilities of chiral pyrazoles for asymmetric synthesis increased by the use as a catalyst rather than an auxiliary.

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 ir spectra were measured by Shimadzu IR-460 spectrometer. The enantiomer ratios were given 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 Diels Alder adducts 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. The X-ray structural analyses of the crystals were performed by the Rigaku R-AXIS RAPID-F X-Ray diffraction camera controlled with Rigaku R-AXIS RAPID AUTO program, and their data were analyzed by Rigaku Crystal Structure MFC Application (Ver. 1.0.0.1).

Materials.

3,5-Disubstituted 1-acryloylpyrazoles (**11**) were prepared from the corresponding pyrazoles and acryloyl chloride in the presence of triethylamine according to the method of the previous paper [9,13a], purified by silica gel column chromatography and distillation, and was stored in the refrigerator. During this protocol, the addition of hydroquinone was required to inhibit polymerization which could be effective during the concentration and the distillation procedure. Tetrahydrofuran was dried over sodium benzophenone ketyl radical and distilled just before use. Diisopropylamine and dichloromethane were distilled over calcium hydride under argon atmosphere. Anhydrous methanol was obtained by the distillation from the suspension of magnesium methoxide in methanol. Cyclopentadiene (**12**) was prepared by the pyrolysis of dicyclopentadiene at 160°, distilled and stored in the freezer. Molecular Sieves 4 Å were freshly dried at 250° under reduced pressure for 3 h.

Ethyl 5-Methyl-1-phenylpyrazole-3-carboxylate.

To the toluene (10 ml) solution of ethyl 2,4-dioxovalerate (6.6 mmol, 1.05 g), phenylhydrazine (11 mmol, 1.2 g) in toluene (2 ml) was added drop by drop under refluxing. After continuous refluxing for 3.5 h, the reaction mixture was washed with dilute hydrochloric acid, aqueous sodium hydrogencarbonate and brine. The organic layer was dried over anhydrous magnesium sulfate, and concentrated to give the crude product. By silica gel column chromatography with hexane-ethyl acetate (3:1 v/v) mixture as eluent, ethyl 5-methyl-1-phenylpyrazole-3-carboxylate was obtained in 74 % yield; ^{1}H nmr: δ 1.40 (3H, t, *J*=6.9 Hz), 2.33 (3H, d, *J*=0.7 Hz), 4.42 (2H, q, *J*=6.9 Hz), 6.74 (1H, d, *J*=0.7 Hz), 7.41-7.49 (5H, m).

5-Methyl-1-phenylpyrazole-3-carboxylic Acid.

The mixture of ethyl 5-methyl-1-phenylpyrazole-2-carboxylate (4.8 mmol, 1.1 g), sodium hydroxide (1.2 g), ethanol (3 ml) and water (27 ml) was heated for 2.5 h at 90°. After acidified with dilute hydrochloric acid, the reaction mixture was extracted with ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. By recrystallization of the residue, 5-methyl-1-phenylpyrazole-3-carboxylic acid was obtained in 79 % yield; ^{1}H nmr: δ 2.35 (3H, d, *J*=0.7 Hz), 6.59 (1H, broad s), 6.80 (1H, d, *J*=0.7 Hz), 7.41-7.53 (5H, m); ir (chloroform): ν 3482, 1688, 1256 cm^{-1}.

Preparation of 2-Furoyl Chloride (**3c**) and 5-Methyl-1-phenylpyrazole-3-carbonyl Chloride (**3e**).

2-Furoyl chloride (**3c**) and 5-methyl-1-phenylpyrazole-3-carbonyl chloride (**3e**) were prepared from the corresponding carboxylic acid by refluxing with excess amount of thionyl chloride. After removal of the excess thionyl chloride under reduced pres-

sure, the residue was directly used for the acylation of *l*-menthone without purification.

5-Methyl-1-Phenylpyrazole-3-carbonyl Chloride (**3e**).

The title compound was obtained; bp 150°/ 10 mm Hg; ^{1}H nmr: δ 2.35 (3H, d, *J*=0.7 Hz), 6.84 (1H, d, *J*=0.7 Hz), 7.44-7.54 (5H, m); ^{13}C nmr: δ 12.4 (CH_3), 110.4 (CH), 125.3 (CH), 129.2 (CH), 129.4 (CH), 138.7 (C), 141.9 (C), 145.9 (C), 162.3 (C); ir (chloroform): ν 1762, 836 cm^{-1}.

(3*R*,6*S*)-2-Heteroaroyl-3-methyl-6-isopropylcyclohexanone (**4**).

According to the previously reported method [5], *l*-menthone (1.2 g, 7.9 mmol) in tetrahydrofuran (2 ml) was added at -5° under argon atmosphere to a tetrahydrofuran (10 ml) solution of lithium diisopropylamide, which was prepared from diisopropylamine (1 ml) and butyllithium in hexane solution (1.55 *M*, 5 ml, 7.75 mmol). After stirring for 30 min, heteroaroyl chloride (**3**) (8.5 mmol) in tetrahydrofuran (2 ml) was added at -5° and stirred for 5 h at room temperature. The reaction mixture was quenched with water, acidified with dilute hydrochloric acid and extracted with ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was removed. The product (**4**) was purified by silica gel column chromatography with hexane-ethyl acetate mixture as eluent.

(3*R*,6*S*)-6-Isopropyl-3-methyl-2-(2-pyridinecarbonyl)cyclohexanone (**4a**).

Compound **4a** was obtained in 37% yield; bp 130°/14mm Hg; ^{1}H nmr: δ 0.85 (3H, d, *J*=6.6 Hz), 0.91 (3H, d, *J*=6.6 Hz), 1.00 (3H, d, *J*=6.3 Hz), 1.23-1.46 (2H, m), 1.87-2.18 (4H, m), 2.31-2.38 (1H, m), 4.77 (1H, d, *J*=8.2 Hz), 7.40-7.45 (1H, m), 7.79-7.86 (1H, m), 8.06-8.10 (1H, m), 8.58-8.60 (1H, m); ^{13}C nmr: δ 18.5 (CH_3), 20.9 (CH_3), 22.1 (CH_3), 35.7 (CH), 27.7 (CH_2), 35.3 (CH), 50.7 (CH_2), 55.7 (CH), 64.0 (CH), 121.6 (CH), 126.9 (CH), 136.8 (CH), 148.5 (CH), 153.1 (C), 199.2 (C), 209.4 (C).

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.4. Found: C, 73.82; H, 8.07; N, 5.44.

(3*R*,6*S*)-2-(2-Furancarbonyl)-6-isopropyl-3-methylcyclohexanone (**4c**).

Compound **4c** was obtained in 37 % yield; mp 148-149° (hexane); ^{1}H nmr: δ 0.85 (3H, d, *J*=6.9 Hz), 0.92 (3H, d, *J*=6.9 Hz), 0.99 (3H, d, *J*=6.3 Hz), 1.46-1.59 (2H, m), 1.99-2.29 (4H, m), 2.45-2.55 (1H, m), 3.86 (1H, d, *J*=12.5 Hz), 6.53 (1H, d-d, *J*=3.6, 1.7 Hz), 7.19 (1H, d-d, *J*=3.6, 0.7 Hz), 7.53 (1H, d-d, *J*=1.7, 0.7 Hz); ^{13}C nmr: δ 18.5 (CH_3), 21.1 (CH_3), 26.0 (CH_2), 27.5 (CH_2), 33.4 (CH), 36.8 (CH), 26.6 (CH), 66.4 (CH), 112.5 (CH), 116.8 (CH), 146.1 (CH), 153.7 (C), 186.8 (C), 208.2 (C).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.24; H, 8.06.

(3*R*,6*S*)-6-Isopropyl-3-methyl-2-(2-thiophenecarbonyl)cyclohexanone (**4d**).

Compound **4d** was obtained in 35 % yield; mp 139-140° (hexane); ^{1}H nmr: δ 0.86 (3H, d, *J*=6.6 Hz), 0.92 (3H, d, *J*=6.6 Hz), 1.01 (3H, d, *J*=6.3 Hz), 1.48-1.65 (3H, m), 2.00-2.26 (3H, m), 2.50-2.55 (1H, m), 3.84 (1H, d, *J*=12.5 Hz), 7.11 (1H, d-d, *J*=5.0, 4.0 Hz), 7.58 (1H, d-d, *J*=3.6, 1.0 Hz), 7.63 (1H, d-d, *J*=5.0, 1.3 Hz); ^{13}C nmr: δ 18.5 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 26.0 (CH_2), 27.7 (CH_2), 33.4 (CH), 37.6 (CH), 56.8 (CH), 67.6 (CH), 128.1 (CH), 131.8 (CH), 133.8 (CH), 145.3 (C), 190.1 (C), 208.1 (C).

Anal. Calcd. for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.63; S, 12.13. Found: C, 68.24; H, 7.57; S, 11.72.

(3*R*,6*S*)-6-Isopropyl-3-methyl-2-(5-methyl-1-phenylpyrazole-3-carbonyl)cyclohexanone (**4e**).

Compound **4e** was obtained in 66 % yield; ^{1}H nmr: δ 0.84 (3H, d, *J*=6.6 Hz), 0.89 (3H, d, *J*=6.9 Hz), 1.00 (3H, d, *J*=6.3 Hz), 1.40-1.60 (1H, m), 1.62 (1H, s), 1.96-2.15 (2H, m), 2.25-2.33 (1H, m), 2.32 (3H, d, *J*=0.7 Hz), 2.40-2.60 (1H, m), 4.41 (1H, d, *J*=12.9 Hz), 6.77 (1H, d, *J*=0.7 Hz), 7.40-7.54 (5H, m); ^{13}C nmr: δ 12.4 (CH_3), 18.5 (CH_3), 21.0 (CH_3), 21.1 (CH_3), 26.0 (CH_2), 28.0 (CH_2), 33.4 (CH), 36.9 (CH), 56.5 (CH), 65.8 (CH), 107.0 (CH), 125.2 (CH), 128.5 (CH), 129.2 (CH), 139.1 (C), 141.1 (C), 151.9 (C), 193.8 (C), 209.2 (C).

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.20; H, 7.53; N, 8.14.

Preparation of 3-Heteroaryl-*l*-menthopyrazole (**1**).

The mixture of **4** (2.0 mmol), hydrazine hydrate (16 mmol, 800 mg) and hydrazine hydrochloride (0.5 mmol, 34 mg) in methanol (15 ml) was refluxed for 7 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with dilute hydrochloric acid and brine, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed on silica gel column with benzene-ethyl acetate mixture as eluent.

3-(2-Pyridyl)-*l*-menthopyrazole (**1a**).

Compound **1a** was obtained in 27% yield; mp 96-101° (from Hexane); ^{1}H nmr: δ 0.89 (3H, d, *J*=6.9 Hz), 1.06 (3H, d, *J*=6.9 Hz), 1.14 (3H, d, *J*=6.6 Hz), 1.37-1.48 (1H, m), 1.64-1.73 (1H, m), 1.82-1.93 (1H, m), 2.64 (1H, q, *J*=5.9 Hz), 3.27 (1H, d-d, *J*=12.8, 6.3 Hz), 7.16-7.21 (1H, m), 7.65-7.76 (2H, m), 8.60-8.63 (1H,m); ^{13}C nmr: δ 19.0 (CH_3), 21.0 (CH_3), 21.2 (CH_3), 21.4 (CH_3), 26.8 (CH), 30.3 (CH_2), 30.8 (CH), 39.7 (CH), 120.0 (C), 121.1 (CH), 122.0 (CH), 136.4 (CH), 149.3 (CH), 151.1 (C).

Anal. Calcd. for $C_{16}H_{21}N_3 \cdot 1/4H_2O$: C, 73.95; H, 8.34; N, 16.17. Found: C, 73.70 H, 8.12; N, 16.03.

3-(2-Furyl)-*l*-menthopyrazole (**1c**).

Compound **1c** was obtained in 100 % yield; mp 129.5-130.5° (H_2O-MeOH); ^{1}H nmr: δ 0.86 (3H, d, *J*=6.6 Hz), 1.00 (3H, d, *J*=6.6 Hz), 1.14 (3H, d, *J*=6.9 Hz), 1.36-1.46 (1H, m), 1.60-1.71 (1H, m), 1.79-1.91 (1H, m), 1.95-2.10 (2H, m), 2.54-2.62 (1H, m), 3.02-3.10 (1H, m), 6.47 (1H, d-d, *J*=3.3, 2.0 Hz), 6.57 (1H, d-d, *J*=3.3, 0.7 Hz), 7.46 (1H, d-d, *J*=2.0, 0.7 Hz); ^{13}C nmr: δ 19.2 (CH_3), 20.7 (CH_3), 21.0 (CH_3), 21.2 (CH_2), 26.2 (CH_2), 29.9 (CH), 30.9 (CH), 39.0 (CH), 106.7 (CH), 111.2 (CH), 113.7 (C), 128.2 (C), 141.5 (CH).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.77; H, 8.03; N, 11.55.

3-(2-Thienyl)-*l*-menthopyrazole (**1d**).

Compound **1d** was obtained in 80 % yield; mp 118-119° (sublimation); ^{1}H nmr: δ 0.85 (3H, d, *J*=6.6 Hz), 0.97 (3H, d, *J*=6.9 Hz), 1.13 (3H, d, *J*=6.6 Hz), 1.38-1.46 (1H, m), 1.62-1.71 (1H, m), 1.80-1.86 (1H, m), 1.95-2.08 (2H, m), 2.52-2.60 (1H, m), 3.05-3.13 (1H, m), 7.06 (1H, d-d, *J*=4.9, 4.0 Hz), 7.24-7.27 (2H, m); ^{13}C nmr: δ 19.2 (CH_3), 20.4 (CH_2), 21.0 (CH_3), 26.2 (CH_2), 29.8 (CH), 30.8 (CH), 38.8 (CH), 118.5 (C), 124.3 (CH), 124.6 (CH), 127.2 (CH), 136.5 (C).

Anal. Calcd. for $C_{15}H_{20}N_2S$: C, 69.19; H, 7.74; N, 10.76; S, 12.31. Found: C, 68.50; H, 7.76; N, 10.68; S, 11.21.

3-(5-Methyl-1-phenylpyrazol-3-yl)-*l*-menthopyrazole (**1e**).

Compound **1e** was obtained in 51 % yield; ^{1}H nmr: δ 0.87 (3H, d, *J*=6.9 Hz), 1.04 (3H, d, *J*=6.6 Hz), 1.24 (3H, d, *J*=6.9 Hz), 1.37-1.43 (1H, m), 1.62-1.71 (1H, m), 1.84-1.88 (1H, m), 1.98-2.07 (1H, m), 2.11-2.17 (1H, m), 2.38 (3H, d, *J*=0.7 Hz), 2.58-2.64 (1H, m), 3.11-3.17 (1H, sex, *J*=6.3 Hz), 6.49 (1H, s), 7.44-7.53 (5H, m); ^{13}C nmr: δ 12.5 (CH_3), 19.0 (CH_3), 21.0 (CH_3), 21.5 (CH_2), 26.4 (CH_2), 30.3 (C), 30.7 (CH), 39.6 (CH), 105.6 (CH), 119.3 (C), 124.8 (CH), 127.5 (C), 128.3 (C), 129.0 (CH), 139.6 (C).

Anal. Calcd. for $C_{21}H_{26}N_4$: C, 75.41; H, 7.84; N, 16.75. Found: C, 74.71; H, 7.63; N, 16.53.

Preparation of 3-Heteroaryl-2-methyl-*l*-menthopyrazole (**5**).

The mixture of **4** (1.0 mmol), methylhydrazine (6.8 mmol, 313 mg) and hydrochloric acid (6 *M*, 60 mg) in methanol (7 ml) was refluxed for 7 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with dilute hydrochloric acid, aqueous sodium hydrogencarbonate and brine. It was dried over anhydrous magnesium sulfate, and the solvent was removed to obtain the product mixture. From the nmr spectrum of the mixture, the regioisomer ratio was estimated, summarized in Table 1. The product mixture was chromatographed on silica gel column with benzene-ethyl acetate mixture as eluent.

2-Methyl-3-(2-pyridyl)-*l*-menthopyrazole (**5a**).

Compound **5a** was obtained in 65% yield; bp 80°/14mm Hg; ^{1}H nmr: δ 0.79 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.6 Hz), 1.07 (3H, d, *J*=6.6 Hz), 1.23-1.28 (1H, m), 1.52-1.56 (1H, m), 1.82-1.86 (1H, m), 1.99-2.01 (1H, m), 2.40-2.47 (1H, m), 2.61-2.69 (1H, m), 2.94-2.97 (1H, m), 3.86 (3H, s), 7.24-7.29 (1H, m), 7.45 (1H, d, *J*=7.9 Hz), 7.73-7.79 (1H, m), 8.73 (1H, d, *J*=5.5 Hz).

Anal. Calcd. for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; N, 15.6. Found: C, 75.39; H, 8.23; N, 15.34.

3-(2-Furyl)-2-methyl-*l*-menthopyrazole (**5c**).

Compound **5c** was obtained in 78 % yield; ^{1}H nmr: δ 0.85 (3H, d, *J*=6.6 Hz), 0.94 (3H, d, *J*=6.9 Hz), 1.05 (3H, d, *J*=6.9 Hz), 1.25-1.36 (1H, m), 1.52-1.58 (1H, m), 1.81-1.87 (1H, m), 1.92-2.00 (1H, m), 2.29-2.37 (1H, m), 2.58-2.64 (1H, m), 2.86-2.92 (1H, m), 3.85 (3H, s), 6.46 (1H, d-d, *J*=3.3, 0.7 Hz), 6.51 (1H, d-d, *J*=3.3, 1.7 Hz), 7.53 (1H, d-d, *J*=2.0, 1.0 Hz); ^{13}C nmr: δ 18.2 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 22.0 (CH_2), 27.1 (CH_2), 30.2 (CH), 31.5 (CH), 37.7 (CH), 40.3 (CH_3), 110.0 (CH), 111.1 (CH), 122.0 (C), 129.9 (C), 142.4 (CH), 144.9 (C), 150.7 (C).

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84.?Found: C, 73.89; H, 8.51; N, 10.25.

2-Methyl-3-(2-thienyl)-*l*-menthopyrazole (**5d**).

Compound **5d** was obtained in 82 % yield; ^{1}H nmr: δ 0.86 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.6 Hz), 1.07 (3H, d, *J*=6.9 Hz), 1.23-1.33 (1H, m), 1.50-1.55 (1H, m), 1.81-1.98 (2H, m), 2.34-2.42 (1H, m), 2.59-2.67 (1H, m), 2.80-2.87 (1H, m), 3.74 (3H, s), 7.04 (1H, d-d, *J*=3.6, 1.3 Hz), 7.12 (1H, d-d, *J*=5.3, 3.6 Hz), 7.45 (1H, d-d, *J*=5.0, 1.0 Hz); ^{13}C nmr: δ 18.0 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 22.4 (CH_2), 27.3 (CH_2), 30.0 (CH), 32.1 (CH), 36.8 (CH), 40.6 (CH_3), 122.1 (C), 127.1 (CH), 127.2 (CH), 128.5 (CH), 131.8 (C), 132.2 (C), 150.7 (C).

Anal. Calcd. for $C_{16}H_{22}N_2S$: C, 70.03; H, 8.08; N, 10.21; S, 11.68. Found: C, 69.90; H, 8.12; N, 10.09; S, 11.06.

2-Methyl-3-(5-methyl-1-phenylpyrazol-3-yl)-*l*-menthopyrazole (**5e**).

Compound **5e** was obtained in 36 % yield; ^{1}H nmr: δ 0.84 (3H, d, *J*=6.6 Hz), 1.03 (3H, d, *J*=6.9 Hz), 1.05 (3H, d, *J*=7.3 Hz), 1.49-1.59 (1H, m), 1.67-1.87 (2H, m), 1.95-2.01 (1H, m), 2.32-2.40 (1H, m), 2.42 (3H, s), 2.59-2.65 (1H, m), 2.96-3.00 (1H, m), 3.93 (3H, s), 6.33 (1H, d, *J*=0.7 Hz), 7.35-7.51 (5H, m); ^{13}C nmr: δ 12.6 (CH_3), 18.2 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 22.0 (CH_2), 27.2 (CH_2), 30.2 (CH), 31.8 (CH), 37.8 (CH), 40.4 (C), 107.9 (CH), 121.4 (C), 124.5 (C), 124.7 (CH), 127.7 (C), 129.1 (CH), 139.3 (C), 139.7 (C), 143.3 (C), 150.5 (C).

Anal. Calcd. for $C_{22}H_{28}N_4$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.58; H, 7.56; N, 16.26.

Preparation of 3-Heteroaryl-1-methyl-*l*-menthopyrazole (**6**).

Butyllithium in hexane solution (1.55 *M*, 0.56 ml, 0.87 mmol) was added to a tetrahydrofuran solution of **1** (0.8 mmol) at -5° and kept for 30 min with stirring under argon atmosphere. To the reaction mixture was added methyl iodide (6.7 mmol, 958 mg) in tetrahydrofuran (1 ml) at -5°, and then stirred for 6 h at room temperature. The reaction mixture was quenched with water, acidified with dilute hydrochloric acid, and extracted with ether. The organic layer was washed with dilute hydrochloric acid, aqueous sodium hydrogencarbonate and brine. It was dried over anhydrous magnesium sulfate, and the solvent was removed to obtain the product mixture. From the nmr spectrum of the mixture, the regioisomer ratio was estimated, summarized in Table 1. The product mixture was chromatographed on silica gel column with benzene-ethyl acetate mixture as eluent to obtained **6**.

1-Methyl-3-(2-pyridyl)-*l*-menthopyrazole (**6a**).

Compound **6a** was obtained in 67% yield; 80°/14mm Hg; ^{1}H nmr: δ 0.84 (3H, d, *J*=6.6 Hz), 1.04 (3H, d, *J*=6.6 Hz), 1.19 (3H, d, *J*=6.6 Hz), 1.57-1.88 (4H, m), 2.26-2.33 (1H, m), 2.71 (1H, q, *J*=6.3 Hz), 3.40-3.46 (1H, m), 3.85 (3H, s), 7.10-7.15 (1H, m), 7.63-7.69 (1H, m), 7.80-7.84 (1H, m), 8.60-8.63 (1H, m), ^{13}C nmr: δ 17.6 (CH_3), 20.5 (CH_2), 20.7 (CH_3), 21.2 (CH_3), 26.4 (CH), 29.2 (CH_2), 29.8 (CH), 37.8 (CH_3), 38.1 (CH), 121.0 (CH), 121.3 (CH), 121.8 (C), 135.9 (CH), 142.6 (C), 146.3 (C), 149.0 (CH), 154.1 (C).

Anal. Calcd. for $C_{17}H_{23}N_3$: C, 75.8; H, 8.61; N, 15.6. Found: C, 75.30; H, 8.58; N,15.23.

3-(2-Furyl)-1-methyl-*l*-menthopyrazole (**6c**).

Compound **6c** was obtained in 76 % yield; ^{1}H nmr: δ 0.90 (3H, d, *J*=6.9 Hz), 1.01 (3H, d, *J*=6.9 Hz), 1.11 (3H, d, *J*=6.6 Hz), 1.43-1.52 (1H, m), 1.76-1.91 (2H, m), 1.93-2.08 (2H, m), 2.53-2.59 (1H, m), 3.10-3.17 (1H, m), 3.79 (3H, s), 6.46 (1H, d-d, *J*=3.3, 2.0 Hz), 6.57 (1H, d-d, *J*=3.3, 0.7 Hz), 7.45 (1H, d-d, *J*=2.0, 0.7 Hz); ^{13}C nmr: δ 19.8 (CH_3), 19.9 (CH_3), 21.1 (CH_3), 21.4 (CH_2), 25.4 (CH_2), 27.0 (CH), 31.5 (CH), 37.0 (CH), 37.0 (CH_3), 105.8 (CH), 110.9 (CH), 119.0 (C), 139.5 (C), 141.1 (CH), 141.7 (C), 149.3 (C).

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 73.85; H, 8.43; N, 10.54.

1-Methyl-3-(2-thienyl)-*l*-menthopyrazole (**6d**).

Compound **6d** was obtained in 61 % yield; ^{1}H nmr: δ 0.91 (3H, d, *J*=6.9 Hz), 1.01 (3H, d, *J*=6.9 Hz), 1.11 (3H, d, *J*=6.9 Hz),

1.45-1.52 (1H, m), 1.76-1.87 (2H, m), 1.97-2.08 (2H, m), 2.52-2.58 (1H, m), 3.15-3.21 (1H, m), 3.77 (3H, s), 7.05 (1H, d-d, *J*=5.3, 3.6 Hz), 7.21 (1H, d-d, *J*=5.3, 1.0 Hz), 7.28 (1H, d-d, *J*=3.6, 1.0 Hz); ^{13}C nmr: δ 19.8 (CH_3), 19.9 (CH_3), 20.8 (CH_3), 21.4 (CH_2), 25.5 (CH_2), 27.0 (CH), 31.5 (CH), 37.0 (CH), 37.1 (CH_3), 118.8 (C), 123.4 (CH), 123.6 (CH), 127.2 (CH), 137.3 (C), 142.1 (C), 142.3 (C).

Anal. Calcd. for $C_{16}H_{22}N_2S$: C, 70.03; H, 8.08; N, 10.21; S, 11.68. Found: C, 70.23; H, 7.97; N, 10.21; S, 11.82.

1-Methyl-3-(5-methyl-1-phenylpyrazol-3-yl)-*l*-menthopyrazole (**6e**).

Compound **6e** was obtained in 87% yield; ^{1}H nmr: δ 0.89 (3H, d, *J*=6.9 Hz), 1.00 (3H, d, *J*=6.9 Hz), 1.19 (3H, d, *J*=6.9 Hz), 1.43-1.49 (1H, m), 1.78-1.86 (2H, m), 1.96-2.09 (2H, m), 2.39 (3H, s), 2.54-2.60 (1H, m), 3.30-3.35 (1H, m), 3.80 (3H, s), 6.57 (1H, s), 7.31-7.55 (5H, m); ^{13}C nmr: δ 12.7 (CH_3), 19.9 (CH_3), 20.2 (CH_2), 21.4 (CH_3), 25.7 (CH_2), 27.4 (CH), 31.5 (CH), 37.0 (CH), 37.3 (CH_3), 105.5 (CH), 120.0 (C), 124.6 (CH), 127.0 (CH), 128.8 (CH), 139.0 (C), 140.3 (C), 141.7 (C), 141.8 (C), 147.1 (C).

Anal. Calcd. for $C_{22}H_{28}N_4$: C, 75.82; H, 8.1; N, 16.08. Found: C, 75.29; H, 7.81; N, 15.59.

Reaction of Phthaloyl Chlorides with *l*-Menthone.

According to the previously reported method [5], *l*-menthone (620 mg, 4.0 mmol) in tetrahydrofuran (2 ml) was added at -5° under argon atmosphere to a tetrahydrofuran (5 ml) solution of lithium diisopropylamide, which was prepared from diisopropylamine (0.6 ml) and butyllithium in hexane solution (1.55 *M*, 2.6 ml, 4.0 mmol). After stirring for 30 min, isophthaloyl, terephthaloyl or phthaloyl chloride (406 mg, 2.0 mmol) in tetrahydrofuran (2 ml) was added at -5° and stirred for 3 h at room temperature. The reaction mixture was quenched with water, acidified with dilute hydrochloric acid and extracted with ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was removed. The product (**7b** or **7c**) was roughly purified by silica gel column chromatography with hexane-ethyl acetate mixture as eluent, and was provided to the preparation of **2** and **8**. In the case of phthaloyl chloride, tetraketone **7** could not be obtained and di[(3*S*,6*R*)-6-isopropyl-3-methyl]cyclohex-1-enyl phthalate (**10**) was isolated by recrylstallization from methanol.

1,3-Bis-[(3*S*,6*R*)-3-isopropyl-6-methyl-2-oxocyclohexanecarbonyl]benzene (**7b**).

Compound **7b** was obtained in 41% yield; 105-107° (methanol) ^{1}H nmr: δ 0.87 (3H, d, *J*=6.6 Hz), 0.93 (3H, d, *J*=6.6 Hz), 0.98 (3H, d, *J*=6.3 Hz), 1.50-1.66 (3H, m), 2.04-2.20 (2H, m), 2.25-2.33 (1H, m), 2.51-2.57 (1H, m), 4.04 (1H, d, *J*=11.5 Hz), 7.55 (1H, t, *J*=7.8 Hz), 7.99 (2H, d, *J*=7.8 Hz), 8.27 (1H, s); ^{13}C nmr: δ 18.5 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 26.0 (CH), 27.8 (CH_2), 33.4 (CH_2), 37.6 (CH), 57.0 (CH), 66.3 (CH), 127.5 (CH), 129.1 (CH), 132.2 (CH), 138.3 (C), 197.6 (C), 208.8 (C).

Anal. Calcd. for $C_{22}H_{28}N_4$: C, 76.68; H, 8.73. Found: C, 76.32; H, 8.27.

1,4-Bis-[(3*S*,6*R*)-3-isopropyl-6-methyl-2-oxocyclohexanecarbonyl]benzene (**7c**).

Compound **7c** was obtained in 44 % yield; mp 172-173° (methanol); ^{1}H nmr: δ 0.83 (3H, d, *J*=6.6 Hz), 0.85 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.9 Hz), 0.92 (3H, d, *J*=6.6 Hz), 0.98 (3H, d, *J*=6.3 Hz), 0.99 (3H, d, *J*=6.6 Hz), 1.41-2.00 (6H, m), 2.03-2.34 (6H, m), 2.53-2.60 (2H, m), 4.00 (1H, d, *J*=11.6 Hz), 4.63 (1H, d, *J*=4.6 Hz), 7.88 (2H, d, *J*=8.6 Hz), 8.06 (2H, d, *J*=8.6 Hz); ^{13}C nmr: δ 18.5 (CH_3), 18.7 (CH_3), 20.9 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 26.0 (CH_2), 27.8 (CH_2), 28.0 (CH_2), 29.1 (CH), 33.4 (CH), 37.4 (CH), 39.5 (CH), 53.1 (CH), 57.0 (CH), 66.1 (CH), 66.5 (CH), 128.2 (CH), 128.9 (CH), 141.1 (C), 196.2 (C), 197.9 (C), 208.3 (C), 209.2 (C).

Di[(3*S*,6*R*)-6-isopropyl-3-methyl]cyclohex-1-enyl Phthalate (**10**).

Compound **10** was obtained in 56 % yield; mp 106-107° (methanol); ^{1}H nmr: δ 0.81 (6H, d, *J*=6.6 Hz), 0.90 (6H, d, *J*=6.9 Hz), 1.04 (6H, d, *J*=7.3 Hz), 1.16-1.30 (2H, m), 1.35-1.49 (2H, m), 1.74-1.85 (4H, m), 1.95-2.05 (2H, m), 2.28-2.34 (2H, m), 2.58-2.64 (2H, m), 5.49 (2H, s), 7.56 (2H, d-d, *J*=5.9, 3.3 Hz), 7.78 (2H, d-d, *J*=5.6, 3.3 Hz); ^{13}C nmr: δ 16.8 (CH_3), 20.1 (CH_3), 21.7 (CH_3), 22.3 (CH_2), 27.4 (CH_2), 30.2 (CH), 30.7 (CH), 41.7 (CH), 122.4 (CH), 129.1 (CH), 131.1 (CH), 132.1 (C), 150.3 (C), 165.4 (C); ir (chloroform): ν 3019, 1735, 1286, 1271 cm^{-1}.

Anal. Calcd. for $C_{28}H_{38}O_4$: C, 76.68; H, 8.73. Found: C, 75.92; H, 8.69.

2,6-Bis[(3*S*,6*R*)-3-isopropyl-6-methyl-2-oxocyclohexanecarbonyl]pyridine (**7a**).

According to the previously reported method [5], *l*-menthone (620 mg, 4.0 mmol) in tetrahydrofuran (2 ml) was added at -5° under argon atmosphere to the tetrahydrofuran (5 ml) solution of lithium diisopropylamide, which was prepared from diisopropylamine (0.6 ml) and butyllithium in hexane solution (1.55 *M*, 2.6 ml, 4.0 mmol). After stirring for 30 min, powder of pyridine-2,6-dicarbonyl chloride hydrochloride (480 mg, 2.0 mmol) was directly added at -5° and stirred for 3 h at room temperature. The reaction mixture was quenched with water, acidified with dilute hydrochloric acid and extracted with ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was removed. The product (**7a**) was purified by silica gel column chromatography with hexane-ethyl acetate (7:1 v/v) mixture in 55 % yield; ^{1}H nmr: δ 0.92 (6H, d, *J*=6.9 Hz), 0.95 (6H, d, *J*=6.3 Hz), 0.99 (6H, d, *J*=6.6 Hz), 1.47-1.64 (4H, m), 2.02-2.14 (4H, m), 2.19-2.36 (4H, m), 2.48-2.54 (2H, m), 4.58 (2H, d, *J*=11.9 Hz), 8.01 (1H, q, *J*=7.9 Hz), 8.25 (2H, d, *J*=7.9 Hz); ^{13}C nmr: δ 19.0 (CH_3), 21.0 (CH_3), 21.9 (CH_3), 27.1 (CH), 29.3 (CH_2), 33.7 (CH_2), 36.7 (CH), 57.8 (CH), 64.3 (CH), 125.0 (CH), 138.2 (CH), 152.1 (C), 197.6 (C), 209.3 (C).

Anal. Calcd. for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48; N, 3.19. Found: C, 73.86; H, 8.50; N, 3.08.

2,6-Bis(*l*-menthopyrazol-3-yl)pyridine (**2a**) and 1,3-Bis(*l*-menthopyrazol-3-yl)benzene (**2b**).

The mixture of **7** (14.0 mmol), hydrazine hydrate (160 mmol, 8.0 g) and hydrazine hydrochloride (8.2 mmol, 562 mg) in methanol (20 ml) was refluxed for 19 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with dilute hydrochloric acid and brine, dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed on silica gel column with benzene-ethyl acetate mixture or recrystallized from aqueous methanol.

2,6-Bis(*l*-menthopyrazol-3-yl)pyridine (**2a**).

Compound **2a** was obtained in 62% yield; mp 124-134°; ^{1}H nmr: δ 0.92 (6H, d, *J*=5.9 Hz), 1.06 (6H, d, *J*=6.9 Hz), 1.45-1.50 (1H, m), 1.69-1.76 (1H, m), 1.86-1.96 (1H, m), 2.03-2.18 (2H, m), 2.63 (1H, q, *J*=5.6 Hz), 3.33 (1H, d-d, *J*=12.2, 5.6 Hz), 7.59 (2H, d, *J*=7.6 Hz), 7.76 (1H, d-d, *J*=8.6, 7.3 Hz); ^{13}C nmr: δ 19.2 (CH_3), 21.0 (CH_2), 21.1 (CH_3), 26.8 (CH), 29.7 (CH_2), 30.9 (CH), 39.5 (CH), 118.9 (CH), 120.0 (C), 136.9 (CH), 141.1 (C), 149.3 (C), 150.2 (C).

Anal. Calcd. for $C_{27}H_{37}N_5$: C, 75.13; H, 8.64; N, 16.23. Found: C, 75.78; H, 8.55; N, 15.43

1,3-Bis(*l*-menthopyrazol-3-yl)benzene (**2b**).

Compound **2b** was obtained in 39% yield; ^{1}H nmr: δ 0.84 (3H, d, *J*=6.6 Hz), 0.90 (3H, d, *J*=6.9 Hz), 1.00 (3H, d, *J*=6.6 Hz), 1.25 (2H,m, 1.54 (2H, m), 1.79 (2H, m), 2.00 (2H,m), 2.21 (2H, m), 2.62 (2H, m), 2.99 (2H, m), 7.22 (1H,t, *J*=7.8 Hz), 7.38 (2H, d *J*=7.6 Hz), 7.64 (1H, s); ^{13}C nmr: δ 18.2 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 21.9 (CH_2), 26.9 (CH), 30.0 (CH), 31.7 (CH_2), 39.9 (CH), 118.4 (C), 126.7 (CH), 128.1 (CH), 133.5 (CH), 144.8 (C), 146.8 (C).

Anal. Calcd. for $C_{28}H_{38}N_4$: C, 78.09; H, 8.89; N, 13.01. Found: C, 78.31; H, 9.22; N, 12.82.

1,4-Bis(*l*-menthopyrazol-3-yl)benzene (**2c**).

Compound **2c** was obtained in 54 % yield; mp 268-269° (methanol); ^{1}H nmr: δ 0.89 (6H, d, *J*=6.8 Hz), 1.01 (6H, d, *J*=6.7 Hz), 1.06 (6H, d, *J*=6.8 Hz), 1.25-1.36 (2H, m), 1.56-1.62 (2H, m), 1.83-1.89 (2H, m), 2.02-2.08 (2H, m), 2.17-2.24 (2H, m), 2.64-2.68 (2H, m), 3.07-3.11 (2H, m), 7.61 (4H, s); ^{13}C nmr: δ 18.6 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 22.1 (CH_2), 27.2 (CH_2), 30.4 (CH), 31.7 (CH), 39.9 (CH), 118.9 (C), 127.5 (CH).

Anal. Calcd. for $C_{28}H_{38}N_4$: $C_{28}H_{38}N_4 \bullet CH_3OH$: C, 75.28; H, 9.15; N, 12.11. Found: C, 75.46; H, 8.96; N, 12.50.

2,6-Bis(2-methyl-*l*-menthopyrazol-3-yl)pyridine (**8a**) and 1,3-Bis(2-methyl-*l*-menthopyrazol-3-yl)benzene (**8b**).

The mixture of **7** (2.3 mmol), methylhydrazine (9.6 mmol, 440 mg) and *p*-toluenesulfonic acid (2.0 mmol, 387 mg) in methanol (50 ml) was refluxed for 9 h. The reaction mixture was diluted with water and extracted with toluene. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The product mixture was chromatographed on silica gel column with benzene-ethyl acetate mixture as eluent.

2,6-Bis(2-methyl-*l*-menthopyrazol-3-yl)pyridine (**8a**).

Compound **8a** was obtained in 25% yield; mp 68-71°; ^{1}H nmr: δ 0.85 (3H, d, *J*=6.6 Hz), 0.87 (6H, d, *J*=6.6 Hz), 1.08 (6H, d, *J*=6.9 Hz), 1.25-1.30 (2H, m), 1.53-1.57 (2H, m), 1.83-1.88 (2H, m), 1.98-2.03 (2H, m), 2.38-2.45 (2H, m), 2.61-2.67 (2H, m), 2.96-2.99 (2H, m), 3.86 (6H, s), 7.40 (2H, d, *J*=7.6 Hz), 7.81 (1H, t, *J*=7.6 Hz); ^{13}C nmr: δ 28.0 (CH_3), 20.8 (CH_3), 21.2 (CH_3), 22.4 (CH_2), 27.4 (CH), 29.9 (CH), 32.2 (CH_2), 37.8 (CH_3), 40.7 (CH), 121.3 (C), 123.3 (CH), 136.3 (CH), 137.7 (C), 150.5 (C), 151.0 (C).

Anal. Calcd. for $C_{29}H_{41}N_5$: C, 75.77; H, 8.99; N, 15.24. Found: C, 75.37; H, 8.59; N, 14.85.

1,3-Bis(2-methyl-*l*-menthopyrazol-3-yl)benzene (**8b**).

Compound **8b** was obtained in 7 % yield; mp 202-203° (benzene-hexane); ^{1}H nmr: δ 0.75 (6H, d, *J*=6.9 Hz), 0.87 (6H, d, *J*=6.9 Hz), 1.08 (6H, d, *J*=6.9 Hz), 1.20-30 (2H, q, *J*=12.5 Hz), 1.44-58 (2H, q, *J*=12.2 Hz), 1.82-98 (4H, m), 2.40-46 (2H, m), 2.62-67 (2H, m), 2.76-86 (2H, m), 3.70 (6H, s), 7.29-37 (3H, m), 7.49 (1H, t, *J*=6.9 Hz); ^{13}C nmr: δ 17.9 (CH_3), 20.8 (CH_3), 22.7 (CH_2), 27.4 (CH), 29.9 (CH), 32.6 (CH_2), 36.8 (CH_3), 40.9 (CH), 120.6 (C), 128.6 (CH), 129.5 (CH), 130.8 (CH), 132.5 (C), 138.8 (C), 150.9 (C).

Anal. Calcd. for $C_{30}H_{42}N_4$: C, 78.56; H, 9.23; N, 12.21. Found: C, 78.56; H, 9.26; N, 11.81.

2,6-Bis(1-methyl-*l*-menthopyrazol-3-yl)pyridine (**9a**) and 1,3-Bis(1-methyl-*l*-menthopyrazol-3-yl)benzene (**9b**).

Under argon atmosphere, butyllithium in hexane solution (1.55 *M*, 1.28 ml, 2.0 mmol) was added to the tetrahydrofuran (5 ml) solution of **2** (1.1 mmol) at -5° and kept for 30 min with stirring. To the reaction mixture was added methyl iodide (2.2 mmol, 318 mg) in tetrahydrofuran (3 ml) at -5°, and then stirred for 2 h at room temperature. The reaction mixture was quenched with water, acidified with dilute hydrochloric acid, and extracted with ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The product (**9**) was purified from the residual mixture by recrystallization or by silica gel column chromatography with benzene-ethyl acetate mixture as eluent.

2,6-Bis(1-methyl-*l*-menthopyrazol-3-yl)pyridine (**9a**).

Compound **9a** was obtained in 81% yield; mp 260-270° (MeOH-AcOEt); ^{1}H nmr: δ 0.92 (6H, d, *J*=6.6 Hz), 1.04 (6H, d, *J*=6.9 Hz), 1.04 (6H, d, *J*=6.6 Hz), 1.40-1.47 (2H, m), 1.77-1.85 (4H, m), 1.99-2.15 (4H, m), 2.57-2.62 (2H, m), 3.52-3.58 (2H, m), 3.83 (6H, s), 7.66 (1H, dd, *J*=8.6, 7.3 Hz), 7.81 (2H, d, *J*=7.3 Hz); ^{13}C nmr: δ 19.7 (CH_3), 20.4 (CH_2), 21.5 (CH_3), 22.0 (CH_3), 25.8 (CH), 27.7 (CH_2), 31.4 (CH), 37.3 (CH_3), 37.5 (CH), 119.1 (CH), 121.3 (C), 136.1 (CH), 142.1 (C), 147.4 (C), 153.4 (C).

Anal. Calcd. for $C_{29}H_{41}N_5$: C, 75.77; H, 8.99; N, 15.24. Found: C, 75.71; H, 8.57; N, 15.07.

1,3-Bis(1-methyl-*l*-menthopyrazol-3-yl)benzene (**9b**).

Compound **9b** was obtained in 7% yield; mp 217-219° (methanol); ^{1}H nmr: δ 0.93 (3H, d, *J*=6.3 Hz), 0.94 (3H, d, *J*=6.3 Hz), 1.02 (3H, d, *J*=6.9 Hz), 1.36-1.42 (1H, m), 1.74-1.81 (2H, m), 2.01-2.16 (2H, m), 2.57 (1H, dd, *J*=5.6, 4.3 Hz), 3.21-3.26 (1H, m), 3.81 (3H, s), 7.38 (1H, t, *J*=7.6 Hz), 7.62 (2H, d, *J*=7.6 Hz), 8.02 (1H, s); ^{13}C nmr: δ 19.6 (CH_3), 20.6 (CH_2), 21.4 (CH_3), 21.5 (CH_3), 26.0 (CH), 27.9 (CH_2), 31.1 (CH), 37.1 (CH_3), 37.7 (CH), 119.1 (C), 126.0 (CH), 128.3 (CH), 135.1 (C), 142.0 (C), 147.8 (C).

Anal. Calcd. for $C_{30}H_{42}N_4$: C, 78.56; H, 9.23; N, 12.21. Found: C, 78.16; H, 8.82; N, 11.98.

Diels Alder Reaction of 3,5-Disubstituted-1-acryloylpyrazole (**11**) with Cyclopentadiene (**12**).

Under argon atmosphere, the mixture of 3-heteroaryl-*l*-menthopyrazole ligand (**1**, **2**, **5**, **6**, **8**, or **9**) (0.03 mmol), Lewis acid (0.025 mmol) and Molecular Sieves 4 Å (*ca*. 100 mg) in dichloromethane (0.5 ml) was stirred for 30 min at 0°. In some cases, 0.03 mmol of Lewis acid was used toward the ligand (**2**, **8**, or **9**) (0.015 mmol). 3,5-Disubstituted-1-acryloylpyrazole (**11**) (0.25 mmol) in dichloromethane (1 ml) was added to the reaction mixture, and stirred for another 30 min at 0°. Cyclopentadiene (**12**) (2.4 mmol, 0.2 ml) was added and the mixture was kept stir-

ring for 5 h at 0°. The reaction mixture was washed with dilute hydrochloric acid, saturated sodium hydrogencarbonate, aqueous NaCl, dried over anhydrous magnesium sulfate, and concentrated. After addition of appropriate amount of phenanthrene as an internal standard, the reaction residue was injected to the gas chromatography to determine the product yields.

Further the reaction residue was dissolved in methanol solution of sodium methoxide, which was prepared from sodium (5 mg) and methanol (1 ml). The subsequent methanol solution was stirred for 45 min at room temperature, diluted with water, and extracted with ether. After washing with dilute hydrochloric acid, the ether extract was directly injected to the chiral column gas chromatography to evaluate the *endo*-*exo* isomer ratio and the enantiomer ratio of *endo*-adduct (**13**). The results are summarized in Table 2 and Table 3.

Formation of **2a** under Forced Conditions.

Under argon atmosphere, butyllithium in hexane solution (1.55 *M*, 0.03 mmol) was added to the mixture of 2,6-bis(*l*-menthopyrazol-3-yl)pyridine (**2a**) (0.03 mmol), Lewis acid (0.025 mmol) and Molecular Sieves 4 Å (*ca*. 100 mg) in dichloromethane (0.5 ml), and stirred for 30 min at 0°. The reaction mixture was applied for the Diels Alder reaction catalyst described as above, and the results were summarized in Table 2 and Table 3.

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