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3-PHENYL-*l*-MENTHOPYRAZOLE [(4*R*,7*S*)-7-ISOPROPYL-4-METHYL-3-PHENYL-4,5,6,7-TETRAHYDROINDAZOLE]: A NEW TYPE OF CHIRAL AUXILIARY

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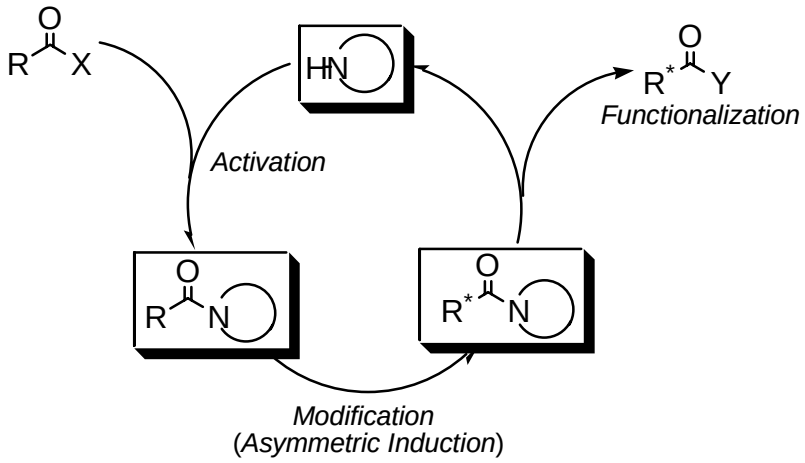
Abstract - The preparation and the utility of 3-phenyl-*l*-menthopyrazole [(4*R*,7*S*)-7-isopropyl-4-methyl-3-phenyl-4,5,6,7-tetrahydroindazole] as a new type of chiral auxiliary are outlined.

1 Introduction

The synthetic strategies using the auxiliary are summarized in the synthetic loop concept, in which three essential reaction steps are included, as illustrated in Scheme 1. First step (activation step) is the activation of the substrate by binding with an auxiliary compound. Next (modification step), the substrate moiety is modified under the influences of the auxiliary. The last step (functionalization step) is the conversion of the substrate moiety into the desired functionality accompanied by the recovery of the auxiliary compound. Moreover, the utility of an auxiliary compound should be raised by the stereoselective modification of substrate moiety under its chiral atmosphere.



Scheme 1 The Synthetic Loop

Many chiral auxiliaries for the synthesis of asymmetric carboxylic derivatives have been reported in the literature such as Oppolzer's sultams[1] and Evans's oxazolidinones.[2] Although the racemization on asymmetric α-position of carbonyl compounds generally occurs by basic catalyst, these conventional auxiliaries require the basic conditions using lithium hydroxide in the functionalization step, and removal of an auxiliary is much critical toward the racemization. Therefore, new type of chiral auxiliary, which

requires the acidic conditions for the functionalization, has long been desired for the synthesis of optically active carbonyl compounds.

In a meanwhile, imidazole has extensively been investigated as an activating agent for carboxylic acids by the formation of *N*-acylimidazole using carbonyldiimidazole.[3] By treatment with nucleophiles, *N*-acylimidazoles are converted into a large variety of carboxylic derivatives.[4] For example, the *N*-acylimidazoles derived from amino acids and/or peptides are used very often for the peptide bond formation. Moreover, these nucleophilic reactions of *N*-acylimidazoles are accelerated by acid catalyst.[5] For applying as an auxiliary, however, *N*-acylimidazoles are too labile to be isolated as a pure form, and to control the selective reactions in the modification step. On the contrary, *N*-acylpyrazoles are easily prepared by the action of acyl chloride on pyrazole. The chemical behaviors of *N*-acylpyrazoles toward the nucleophiles are shown to be analogous to those of *N*-acylimidazoles, but to be comparably less reactive.[6,7] Moreover, one of two adjacent nitrogen atoms on the pyrazole ring combines with acyl group, and the other should act as a ligand for Lewis acid. Namely, pyrazole compounds are presumed to be suitable as an auxiliary for the selective reactions of carboxylic derivatives.

Pyrazole ring is one of the heteroaromatic rings and has definitely planar structure. From this structural feature of pyrazole, the chiral pyrazoles are only expected by the introduction of optically active substituent groups on C3, C4 and/or C5 positions. For the convenient preparation of such optically active pyrazoles, we took three accounts as follows. 1) The chiral source must be easy to obtain. 2) The synthetic method must be convenient, efficient and applicable for a large scale preparation. 3) The resulting pyrazole must have no nucleophilic center other than pyrazole nitrogen for their easier acylation. Under these considerations, we designed 3-substituted 7-isopropyl-4-methyl-4,5,6,7-tetrahydroindazole (**1**) as the target for a chiral auxiliary. Due to retain the partial structure of *l*-menthone, this target compound was called “3-substituted *l*-menthopyrazole”. Here, I will review the preparation of *l*-menthopyrazoles, and their utility as a chiral auxiliary.

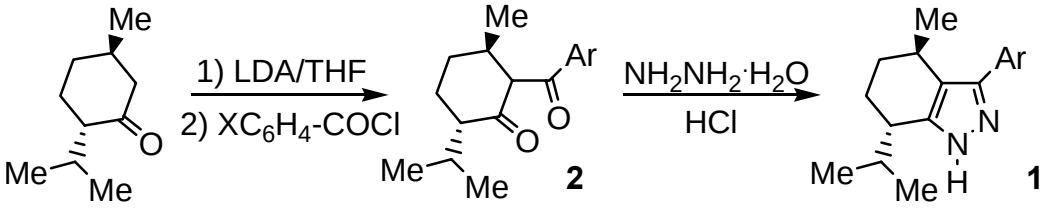
2 Preparation and *N*-Acylation

2.1 Preparation and Structure of 3-Phenyl-*l*-menthopyrazole (1a)[8]

Knorr pyrazole synthesis is acceptable as the most convenient and efficient preparative method, even in the large scale preparation of pyrazole derivatives.[9] Namely 1,3-dicarbonyl compounds, which are

prepared by the α-acylation of ketones, are regarded to be the key intermediates for Knorr pyrazole synthesis. From the viewpoints of the synthetic conveniences and the chemical stability, menthone and camphor are chosen as the chiral source, and 3-substituted (4*R*,7*S*)-7-isopropyl-4-methyl-4,5,6,7-tetrahydroindazole (**1**, *l*-menthopyrazole) is intended as the most attractive chiral pyrazole compound. When *l*-menthone was treated with benzoyl chloride in the presence of lithium diisopropylamide in dry THF, 2-benzoyl-*l*-menthone (**2a**) was obtained in good yield. By the action of hydrazine, **2a** was transformed into 3-phenyl-*l*-menthopyrazole (**1a**), which was easily purified by recrystallization from hexane in 65 % overall yield with high optical purity, illustrated in Scheme 2. The optical purity of **1a** was proved by the NMR spectroscopic method using the Mosher's MTPA derivative.[10]

The X-Ray structural analysis of 4-chlorophenyl derivative (**1b**, Ar=4-ClC_6H_4) showed that the aryl ring was twisted about 40° from the pyrazole ring and overlaid on one side of the *N*-2 nitrogen atom of



Scheme 2

a: Ar= Ph **c**: Ar= 1-Naph
b: Ar= 4-ClC_6H_4 **d**: Ar= 2-Anis

pyrazole (Figure 1). The steric hindrance between aryl and 4-methyl groups of 3-aryl-*l*-menthopyrazoles was relaxed by twisting the aryl ring, which transmitted the chirality of (4*R*)-methyl group onto *N*-2 nitrogen atom by the induction of the torsional asymmetry. This structural feature of 3-aryl-*l*-menthopyrazoles should be promising for the stereocontrolled reactions, and be emphasized by the introduction of *o*-substituent on aryl group. Although the preparations of 2-methylphenyl, 2-chlorophenyl (**1b**, Ar=4-ClC_6H_4), 2,6-disubstituted phenyl and 9-anthranyl derivatives

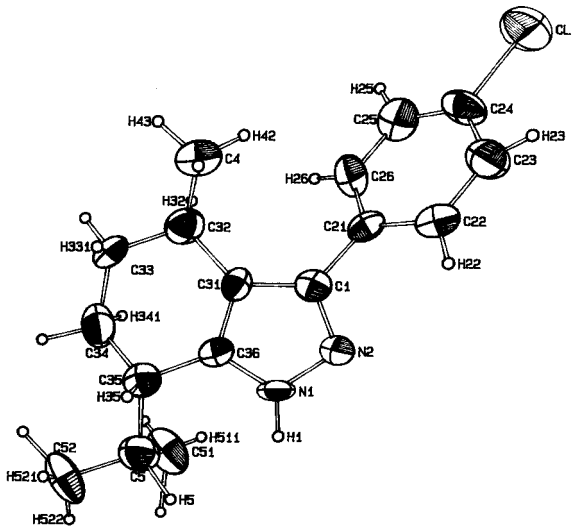
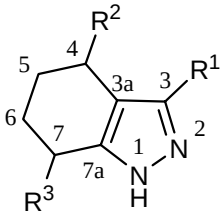


Figure 1. Molecular Structure of **1b** (Ar=4-ClC_6H_4)

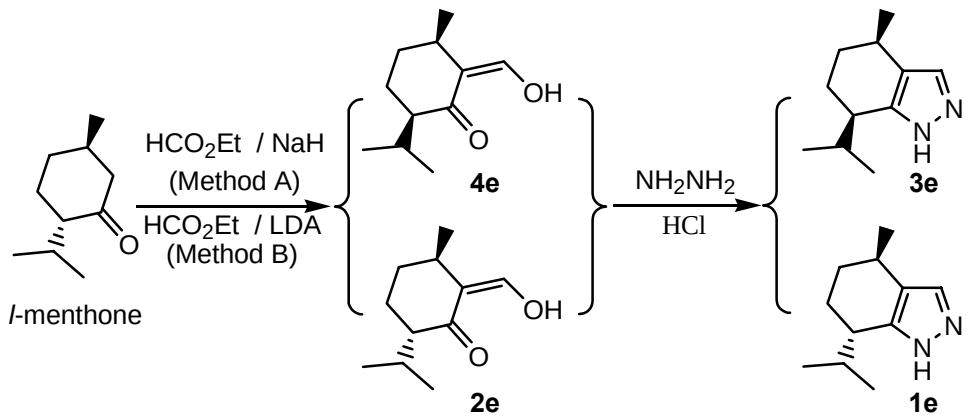
were unsuccessful owing to their severe steric hindrance, 3-(2-methoxyphenyl)- (**1d**, Ar=2-MeOC$_6$H$_4$) and 3-(1-naphthyl)-*l*-menthopyrazole (**1c**, Ar=1-Naph) were prepared in moderate yields. These *o*-substituted 3-aryl-*l*-menthopyrazoles (**1**) were found to be the complicated mixture including the atrop isomers due to the restricted rotation of aryl group. Therefore, the introduction of *o*-substituent on aryl group gave no practical advantage.

2.2 **Preparation of Menthopyrazole Analogues**[11]

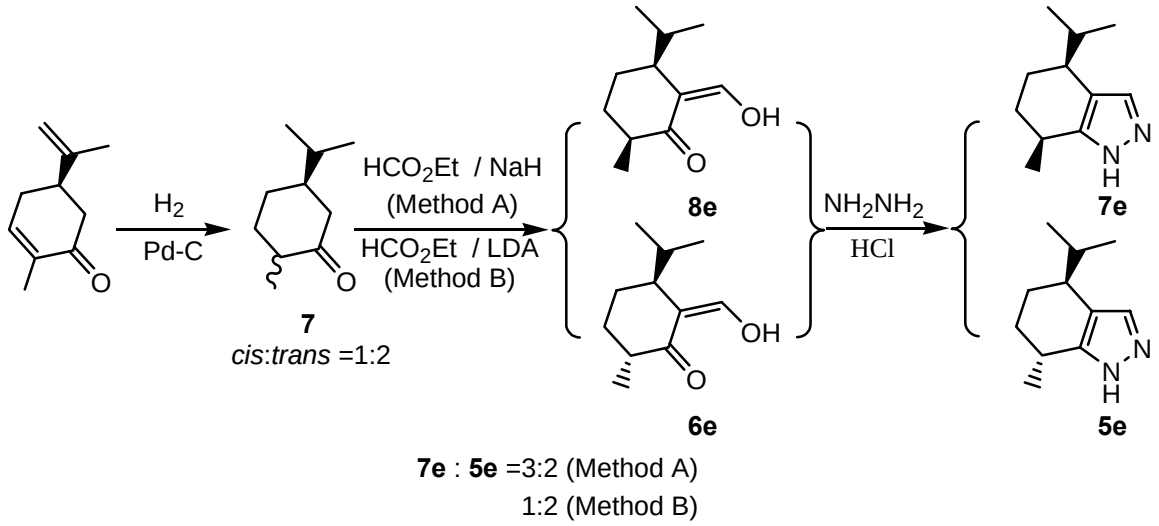


3-Phenyl-*l*-menthopyrazole (**1a**):	R^1= Ph, R^2= (*R*)-Me, R^3= (*S*)-*i*-Pr
3-Phenylisomenthopyrazole (**3a**):	R^1= Ph, R^2= (*R*)-Me, R^3= (*R*)-*i*-Pr
l-Menthopyrazole (**1e**):	R^1= H, R^2= (*R*)-Me, R^3= (*S*)-*i*-Pr
Isomenthopyrazole (**3e**):	R^1= H, R^2= (*R*)-Me, R^3= (*R*)-*i*-Pr
Carvomenthopyrazole (**5e**):	R^1= H, R^2= (*R*)-*i*-Pr, R^3= (*S*)-Me
Isocarvomenthopyrazole (**7e**):	R^1= H, R^2= (*R*)-*i*-Pr, R^3= (*R*)-Me

Similarly (2*R*,5*R*)-2-isopropyl-5-methylcyclohexanone (isomenthone) was derived into (4*R*,7*R*)-4-methyl-7-isopropyl-3-phenyl-4,5,6,7-tetrahydro-1*H*-indazole (3-phenyl-isomenthopyrazole; **3a**), which was a diastereomer of **1a**, and should perhaps have the different twisting angle of the 3-phenyl ring against the pyrazole ring. When *l*-menthone was formylated catalyzed by sodium ethoxide, the *l*-menthone skeleton was epimerized into isomenthone skeleton on *C*-2 carbon having 2*R* configuration, and (2*R*,5*R*)-6-hydroxymethylene-2-isopropyl-5-methylcyclohexanone (*cis*-**4e**) was predominantly formed with the ratio of 13:1.[12] On the contrary, *l*-menthone was formylated catalyzed by LDA to give the mixture of *cis*-**4e** and *trans*-**2e** with the ratio of 1:3. By Knorr pyrazole synthesis, the mixture of (4*R*,7*R*)-



Scheme 3. The syntheses of menthopyrazoles **1e** and **3e**.



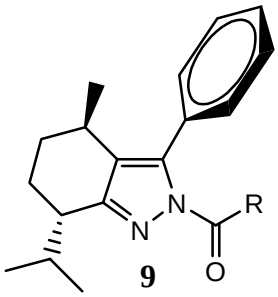
Scheme 4. The syntheses of carvomenthopyrazoles **5e** and **7e**

(isomenthopyrazole; **3e**) and (4*R*,7*S*)-7-isopropyl-4-methyl-4,5,6,7-tetrahydro-1*H*-indazole (*l*-menthopyrazole; **1e**) was formed (Scheme 3).

Moreover, the diastereomeric mixture of (4*S*,7*R*)-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-1*H*-indazole (carvomenthopyrazole; **5e**) and (4*S*,7*S*)-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-1*H*-indazole (isocarvo-menthopyrazole; **7e**), which has bulky isopropyl group not on 7-position but on 4-position, was prepared by hydrogenation of commercially available (*R*)-(-)-carvone, the formylation catalyzed by sodium hydride or LDA, and then Knorr pyrazole synthesis. These diasteromeric mixtures were regioselectively acetylated with acetyl chloride in the presence of triethylamine on the *N*-2 position. After the chromatographic separation of subsequent *N*-acetyl derivatives, optically pure menthopyrazole derivatives were obtained by the independent deacetylation by the action of sodium hydroxide (Scheme 4).

2.3 *N*-Acylation of 3-Phenyl-*l*-menthopyrazole[8]

The activation reaction in the synthetic loop (Scheme 1) was accomplished through the acylation of pyrazoles by the action of carboxylic acids or their acid chlorides.[13] The steric feature of **1a** affected regio- and stereoselectively to the *N*-acylation on pyrazole ring. When **1a** was treated with various acyl chlorides in the presence of triethylamine, the acyl group was introduced on the *N*-2 position to afford 2-acyl-3-phenyl-*l*-menthopyrazole (**10**) with a small portion of 1-acyl-3-phenyl-*l*-menthopyrazole (**9**), summarized in Scheme 5 and Table 1. The products (**9**) and (**10**) were able to be separated easily by chromatography, and to be distinguished with each other in their NMR spectra.



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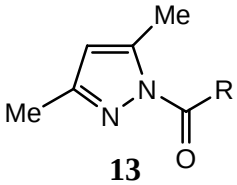
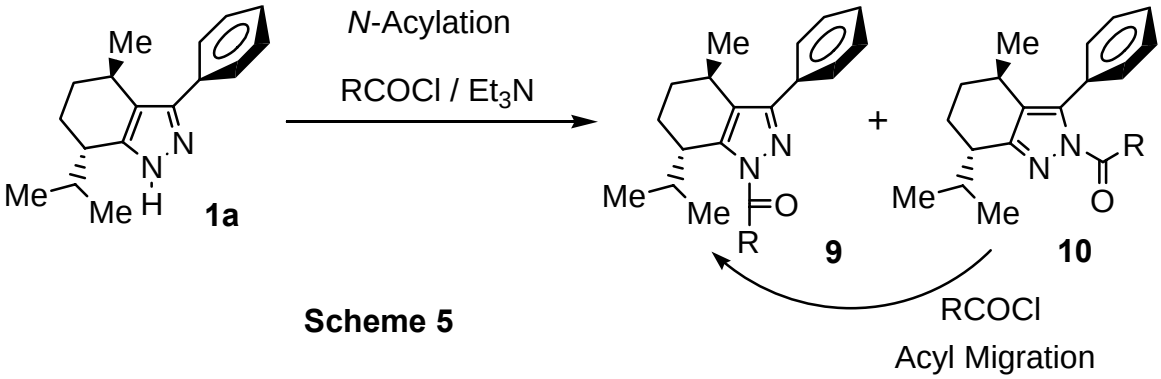


13

a: R= Me
b: R= Et
c: R= Pr
d: R= *i*-Pr
e: R= Bu
f: R= *s*-Bu
g: R= *i*-Bu
h: R= *t*-Bu
i: R= CH_2Ph
j: R= CH_2CH_2Ph
k: R= CH(Me)Ph
l: R= CH(Me)(*i*-Pr)
m: R= $CH(Me)CH_2Ph$
n: R= $CH(Me)CH_2COOEt$
o: R= $CH(Ph)CH_2COOEt$
p: R= $CH(CH_2Ph)CH_2COOEt$
q: R= $CH(Me)CH(Ph)_2$
r: R= CH(Me)CH(Me)Ph
s: R= CH(Me)CH(Et)Ph
t: R= CH(Me)CH(*i*-Pr)Ph
u: R= $CH_2CH(Me)Ph$
v: R= $CH_2CH(Et)Ph$
w: R= $CH_2CH(i\text{-}Pr)Ph$
x: R= $CH_2CH(t\text{-}Bu)Ph$
y: R= $CH_2CH(Me)(p\text{-}Tol)$
z: R= $CH_2CH(Me)(p\text{-}ClC_6H_4)$



Scheme 5

On the contrary, **9** was predominantly formed by the treatment of **10** with the same acyl chloride in the absence of triethylamine, where the acyl migration reaction proceeded. Table 1 showed that the product ratios (**9** : **10**) differed delicately by the bulkiness of acyl group in the *N*-acylation of **1a**. Also the ratios of **9** : **10** were dependent on the bulkiness of acyl group in the acyl migration reaction of **10**,. When the racemic acyl chloride was used, a little asymmetric induction was observed either in *N*-acylation of **1a** or in the acyl migration reaction of **10**. The de % and the configuration of acyl group were determined by the comparison of NMR spectra of the authentic samples, which were derived from (*S*)-2-methylbutyric and (*R*)-2-phenylpropionic acids. In the case of 3-phenyl-2-(2-phenylpropanoyl)-*l*-menthopyrazole (**10k**), the de % was evaluated by HPLC. Furthermore, the separation of the optical isomers of **10k** was accomplished by means of simple silica gel column chromatography, where **1a** acted as the chiral auxiliary.

Table 1. The Product Ratio (**9** : **10**) in the *N*-Acylation of **1a** and Acyl Migration Reaction of **10**

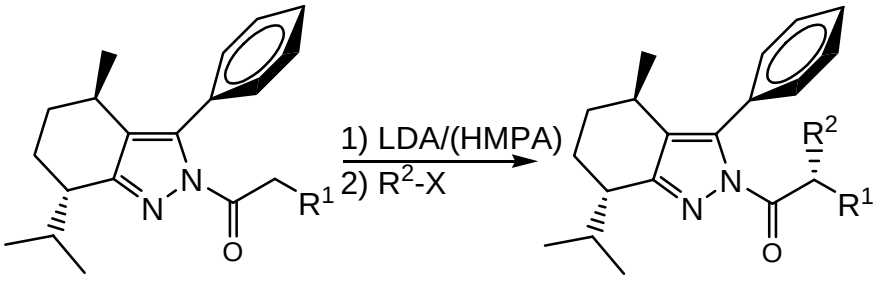
R	*N*-Acylation of **1a**		Acyl Migration of **10**	
	Yield (%)	**9** : **10** (de %, Conf.)	Yield (%)	**9** : **10** (de %, Conf.)
Me (**a**)	96	31 : 69	88	92 : 8
Et (**b**)	100	17 : 83	83	91 : 9
i-Pr (**d**)	100	5 : 95	85	90 : 10
s-Bu (**f**)	100	3 : 97 (1, *R*)	95	89 (8, *S*) : 11 (2, *S*)
t-Bu (**h**)	100	3 : 97	94	86 : 14
CH_2Ph (**i**)	97	37 : 63	78	90 : 10
CH(Me)Ph (**k**)	79	40 (16, *R*) : 60 (7, *R*)	74	80 (7, *R*) : 20 (19, *R*)
$CH_2CH(Me)Ph$ (**u**)	87	28 (16, *S*) : 72 (3, *R*)	86	90 (2, *S*) : 10 (6, *R*)

3 α-Replacement Reaction of 2-Acyl-3-phenyl-*l*-menthopyrazoles

As a new chiral auxiliary, 3-phenyl-*l*-menthopyrazole (**1*a***) has unique structure and properties that are different from the conventional chiral auxiliaries.[14] The most important characteristics of this auxiliary are that the substrate terminates in the nitrogen atom of a heteroaromatic pyrazole ring in a chiral environment. The serious steric interaction between 4-methyl and 3-phenyl group of **1a** is relaxed by the twisting of the benzene ring, which overlaps one side of the terminal nitrogen atom. This structural feature causes a diastereofacial effect in the reactions on the substrate moiety.[15] Moreover, the lone pair of electrons on the adjacent nitrogen play the role of a Lewis base, causing the chelation of N···Li-O in the lithium enolate derived from *N*-acylpyrazoles. These chelations must freeze the bond rotation of the acyl group so that it is fixed in a *Syn* configuration. Under these structural speculations, the chirality of the (4*R*)-methyl group of **1a** is expected to cause a highly asymmetric induction on the acyl group of 2-acyl-3-phenyl-*l*-menthopyrazoles (**10**).

3.1 α-Alkylation[16]

When 2-butanoyl-3-phenyl-*l*-menthopyrazole (**10c**) was treated with LDA in the presence of HMPA



Scheme 6

Table 2. Diastereoselective α-Alkylation of 2-Acyl-3-phenyl-*l*-menthopyrazoles (**10**)

Run		R^1	R^2-X	Base	Product	Yield (%)	De (%)	Confign
1	**10b**	Me	EtI	LDA	**10f**	69	61	2'*S*
2	**10c**	Et	MeI	LDA	**10f**	77	60	2'*R*
3	**10g**	*i*-Pr	MeI	LDA	**10*l***	42	>95	2'*R*
4	**10i**	Ph	MeI	LDA	**10k**	47	>95	2'*R*
5	**10j**	$PhCH_2$	MeI	LDA	**10m**	54	>95	2'*R*
6	**10b**	Me	$BrCH_2COOEt$	LDA	**10n**	69	72	2'*S*
7	**10i**	Ph	$BrCH_2COOEt$	LDA	**10o**	74	27	2'*R*
8	**10j**	$PhCH_2$	$BrCH_2COOEt$	LDA	**10p**	15	72	2'*S*
9	**10b**	Me	PhSSPh	LDA	**11b**	35	43	2'*R*
10	**10c**	Et	PhSSPh	LDA	**11c**	98	84	2'*R*
11	**10e**	Pr	PhSSPh	LDA	**11e**	84	80	2'*R*
15	**10g**	*i*-Pr	MeI	LiHMDS	**10*l***	78	>95	2'*R*
16	**10i**	Ph	MeI	LiHMDS	**10k**	65	>95	2'*R*
17	**10j**	$PhCH_2$	MeI	LiHMDS	**10m**	72	>95	2'*R*

followed by methyl iodide, the diastereomer mixture of 2-(2'-methyl)butanoyl-3-phenyl-*l*-menthopyrazole (**10f**) was obtained in 77 % yield. From the NMR spectrum, the major diastereomer was found to be (2'*R*)-**10f** with 60 % de. In the cases of bulky acyl derivatives such as 2-(3'-methyl)butanoyl-3-phenyl- (**10g**) and 3-phenyl-2-phenylacetyl-l-menthopyrazoles (**10i**), α-

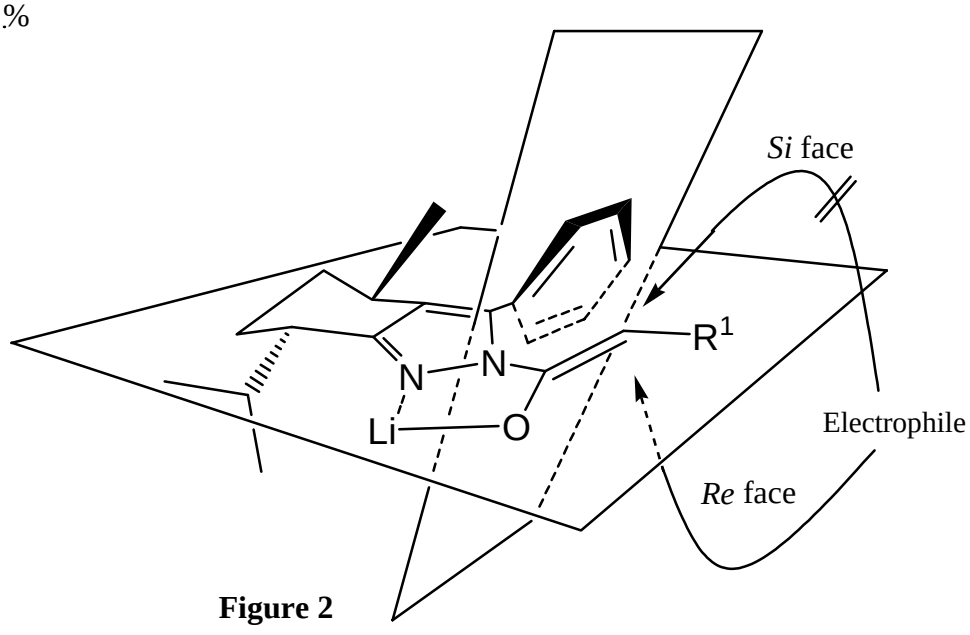


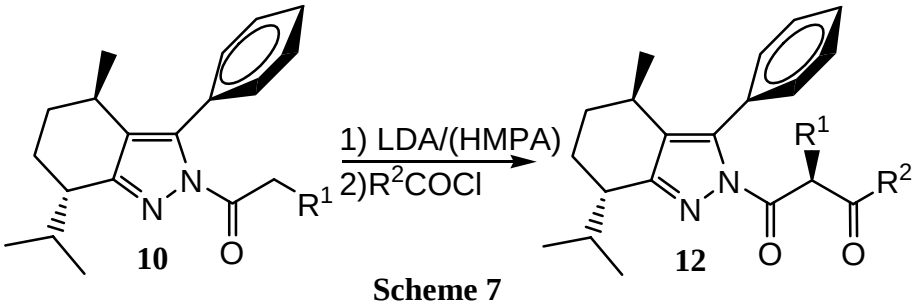
Figure 2

alkylation was accomplished with excellently high diastereoselectivities more than 95 % de. By the use of LiHMDS as a base, the yields and the diastereoselectivities were a little bit progressive, summarized in Scheme 6 and Table 2. Diastereoselective α-phenylthio derivatives (**11**) were also afforded by the treatment with phenyldisulfide under similar alkylation conditions.[17]

The asymmetric induction on α-alkylation may be reasonably explained by following reaction mechanism. In the first step, *N*-acylpyrazoles would be deprotonated with LDA to lead to thestereoselective formation of lithium *Z*-enolate by the allylic strain interaction. The subsequent lithium *Z*-enolate π plane was fixed to the pyrazole ring by the chelation between lithium and *N*-1 nitrogen atom of pyrazole as illustrated in Figure 2. On the basis of the X-Ray structural analysis of **1b**, the 3-phenyl ring was expected to be twisted about 40° against pyrazole ring. This twisted 3-phenyl ring would be somewhat overlaid on the lithium enolate plane. Through this atropic asymmetry of the 3-phenyl plane,the R-configuration on C-4 methyl group would cause the preferential attack of electrophiles from *Re* face of the Z-enolate plane.

3.2 α-Acylation[18]

As the diastereoselective α–acylation of *N*-acylpyrazoles, 3-phenyl-2-propanoyl-*l*-menthopyrazole (**10b**) was treated with benzoyl chloride in the presence of LDA, and the diastereomeric mixture of 2-(2'-methyl-3'-phenyl-3'-oxo)propanoyl-3-phenyl-*l*-menthopyrazole (**12ba**) was obtained in 73 % yield with 79 % de. Similarly, the reactions of various **10** with aliphatic and aromatic acyl chlorides were carried out as summarized in Scheme 7 and Table 3. The resulting α–acylated products (**12**), which were the *N*-(3-phenyl-*l*-menthopyrazolyl) derivatives of β–keto amides, were quite stable to the epimerization, even in the short contacts with weak acids and bases such as dilute hydrochloric acid and aqueous sodium hydrogen carbonate solution. Moreover, the separation of diastereomers was accomplished by the silica



Scheme 7

Table 3. α-Acylation of 2-Acyl-3-phenyl-*l*-menthopyrazole (**10**)

Run		R^1	Acylating Agent	Additive	Product	Yield (%)	De % (Conf.)
1	**10b**	Me	PhCOCl	none	**12ba**	96	84 (2'*S*)
2	**10b**	Me	PhCOCl	HMPA	**12ba**	73	79 (2'*S*)
3	**10c**	Et	PhCOCl	HMPA	**12ca**	82	80 (2'*S*)
4	**10g**	*i*-Pr	PhCOCl	HMPA	**12ga**	81	80 (2'*S*)
5	**10i**	Ph	PhCOCl	HMPA	**12ia**	85	54 (2'*S*)
6	**10j**	$PhCH_2$	PhCOCl	HMPA	**12ja**	94	68 (2'*S*)
7	**10b**	Me	MeCOCl	none	**12bb**	72	9 (2'*S*)
8	**10b**	Me	EtCOCl	none	**12bc**	84	58 (2'*S*)
9	**10c**	Et	EtCOCl	none	**12cc**	85	57 (2'*S*)
10	**10b**	Me	*i*-PrCOCl	none	**12bd**	80	50 (2'*S*)
11	**10b**	Me	*t*-BuCOCl	none	**12be**	87	>95 (2'*S*)
12	**10b**	Me	*p*-TolCOCl	none	**12bf**	75	87 (2'*S*)

gel column chromatography under ordinary conditions. The absolute configurations of the major α–acylated products (**12ja**) were determined to be (2'*S*) isomers by the X-Ray crystallographic analysis.

3.3 **Aldol Reaction with 2-Acyl-3-phenyl-*l*-menthopyrazole**[19]

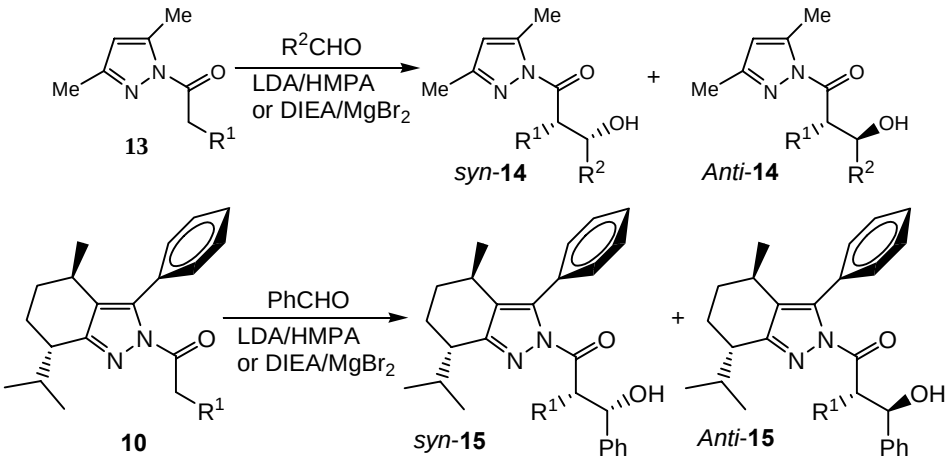
When 1-acyl-3,5-dimethylpyrazole (**13**) was treated with aromatic aldehydes in the presence of LDA, 1-(3'-aryl-3'-hydroxy) acyl-3,5-dimethylpyrazoles (**14**) were obtained in good yield as the *syn*/*anti* isomeric mixture. The Table 4 showed that every aldol reaction proceeded with the *syn* stereoselectivity,especially bulky aldehydes such as isobutyraldehyde and pivalaldehyde gave predominantly *syn* isomers. The *syn* selectivity of this reaction was speculated by the formation of *Z*-lithium enolate and following aldehyde attack through the chair like cyclic transition structure with R^1 group on pseudo equatorial position.[20]

Table 4. The Aldol Reaction of 1-Acyl-3,5-dimethylpyrazole (**13**)

Run	Substrate		Aldehyde	Product	With LDA		With $MgBr_2$-DIEA	
		R^1	R^2CHO		Yield (%)	*Syn*/*Anti*	Yield (%)	*Syn*/*Anti*
1	**13b**	Me	Ph-CHO	**14ba**	69	85 : 15	91	31 : 69
2	**13b**	Me	Et-CHO	**14bb**	27	67 : 33	37	32 : 68
3	**13b**	Me	*i*-Pr-CHO	**14bc**	37	90 : 10	47	32 : 68
4	**13b**	Me	*t*-Bu-CHO	**14bd**	13	>95 : 5	37	13 : 87
5	**13b**	Me	*p*-Tol-CHO	**14be**	76	78 : 22	76	28 : 72
6	**13b**	Me	*o*-Tol-CHO	**14bf**	71	55 : 45	74	29 : 71
7	**13b**	Me	*p*-Anis-CHO	**14bg**	65	78 : 22	70	28 : 72
8	**13a**	H	Ph-CHO	**14aa**			64	
9	**13a**	H	Et-CHO	**14ab**			51	
10	**13a**	H	*t*-Bu-CHO	**14ad**			57	
11	**13c**	Et	Ph-CHO	**14ca**	50	69 : 31	83	14 : 86
12	**13g**	*i*-Pr	Ph-CHO	**14ga**	78	16 : 84	50	0 : 100
13	**13j**	$PhCH_2$	Ph-CHO	**14ja**	68	63 : 37	57	23 : 77

Otherwise, *N*-acylpyrazole formed the 5-membered C=O¨Mg¨*N*-2 chelate complexes with $MgBr_2$ which afforded the dimeric Claisen condensation products, 1-(2'-methyl-3'-oxo)pentanoyl-3,5-dimethylpyrazole, by the action of tertiary amine through the corresponding enolate.[21] The aldol reaction of various 1-acyl-3,5-dimethylpyrazoles (**13**) was carried out with either aromatic or aliphatic aldehydes catalyzed by $MgBr_2$ in the presence of *N,N*-diisopropylethylamine (DIEA), as summarized in Table 4. The *syn*/*anti* ratios in this reaction of **13a** were found to be about 30 : 70 independent from the structures of aldehyde, except the reaction with pivalaldehyde. Further, the structure of acyl moiety of **13** was much affected to the *syn/anti* ratios. When *syn*-1-(3'-hydroxy-2'-methyl-3'-phenyl)propanoyl-3,5-dimethylpyrazole (*syn*-**14ba**) was treated with $MgBr_2$ and DIEA in CH_2Cl_2, isomerization into *anti*-**14ba** was observed with the *syn-anti* ratio of 35 : 65 accompanying with small amount of 1-propanoyl-3,5-dimethylpyrazole (**13b**). By the treatment of **14ba** with $MgBr_2$ and DIEA in the presence of 1-acetyl-3,5-dimethylpyrazole (**13a**), the formation of **13b** and 1-(3'-hydroxy-3'-phenyl)propanoyl-3,5-dimethylpyrazole (**14aa**) was detected as well as the *syn-anti* isomerization of **14ba**. These facts suggested that the aldol reaction was equilibrated with retro aldol reaction catalyzed by $MgBr_2$ and DIEA, and that the product ratio was dependent on the stabilities of the products.

The reaction of 2-acyl-3-phenyl-*l*-menthopyrazoles (**10**) with aldehydes was performed under the conditions using either LDA to form lithium enolate or DIEA in the presence of $MgBr_2$, summarized in



Scheme 8

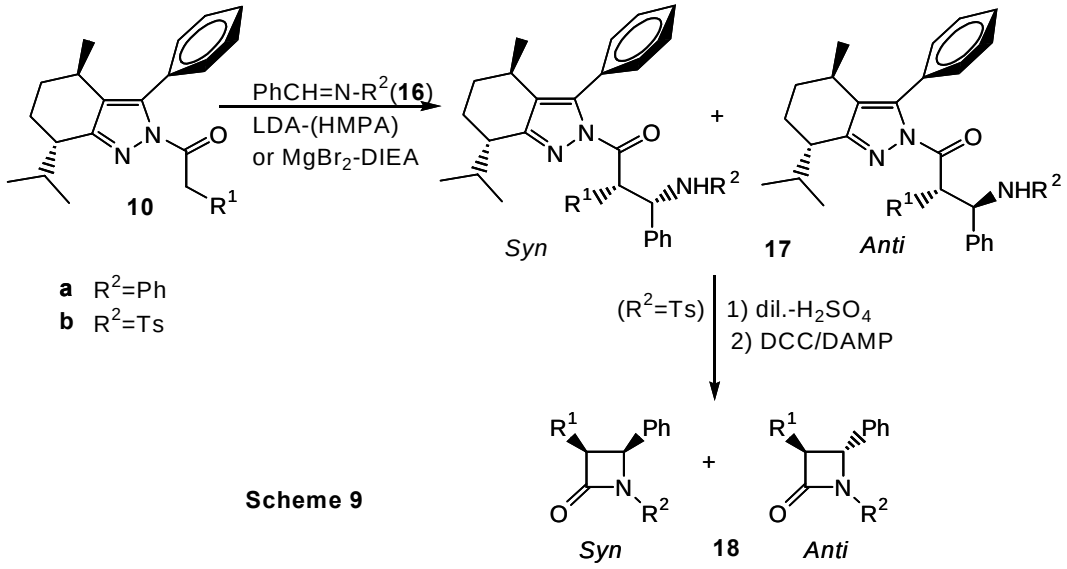
Table 5. Aldol Reaction of 2-Acyl-3-phenyl-*l*-menthopyrazoles (**10**) with Benzaldehyde

Run	Substrate	R^1	Product	With LDA					with $MgBr_2$-DIEA				
				Yield	*Syn*	De %	*Anti*	de%	Yield	*Syn*	de%	*Anti*	de%
1	**10b**	Me	**15b**	38	69	51	31	24	80	32	30	68	43
2	**10a**	H	**15a**	0					70	—		—	
3	**10c**	Et	**15c**	53	65	52	35	55	80	11	28	89	29
4	**10g**	*i*-Pr	**15g**	0					69	0		100	15
5	**10j**	$PhCH_2$	**15j**	58	32	81	68	52	67	7		93	8

Scheme 8 and Table 5. Under the conditions using LDA, 2-propanoyl-3-phenyl-*l*-menthopyrazole (**10b**) reacted with benzaldehyde to give the aldol mixture of 4 isomers. From the NMR spectrum, these isomers were assigned to be the diastereomeric pairs of *syn* (*syn*-**15ba**) and *anti* isomers (*anti*-**15ba**) with the *syn*/*anti* ratio of 69 : 31. The diastereomer ratios of *syn*-**15ba** and *anti*-**15ba** were found to be 51 and 24 % de, respectively. On the contrary, *anti*-**15ba** was the major aldol product from **10b** and benzaldehyde with the *syn*/*anti* ratio of 32 : 68 by the action of DIEA in the presence of $MgBr_2$. The diastereomer ratios of *syn*-**15ba** and *anti*-**15ba** were found to be 30 and 43 % de with the predominance of 2'*S* configuration, respectively. Namely, the aldol reaction of *N*-acylpyrazoles was kinetically controlled with *syn* stereoselectivity under the conditions using LDA. On the contrary, the *anti* stereoselective aldol reaction of *N*-acylpyrazoles was caused by the action of DIEA in the presence of $MgBr_2$ under the thermodynamic control.

3.4 **Formation of β-Lactams**[22]

As analogs to the aldehydes described in previous section, C=N compounds were expected to react with *N*-acylpyrazoles to afford *N*-(β-amino)acylpyrazoles, which should be the good precursor for β-lactams through the intramolecular cyclization. By the use of LDA-HMPA at 0°C, β-lactam (*syn*-**18**) was preferably obtained in moderate yield from 2-acyl-3-phenyl-*l*-menthopyrazoles (**10**) and benzylideneaniline (**16a),** summarized in Table 6 and Scheme 9. By lowering the reaction temperature, the stereoselectivity to *syn* isomer was improved with drop of the yield of **18**. The preferable structure of *syn*-**18** was deduced to be *3R,4S* configuration from the comparison of specific rotation.[23]



Scheme 9

Table 6. The Reaction of 2-Acyl-3-phenyl-*l*-menthopyrazoles (**10**) with C=N Compounds.

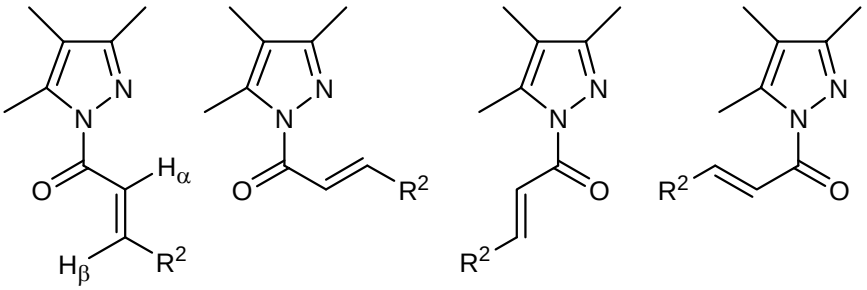
Run	Substrate		Product		With LDA-HMPA(-78°C)					With DIEA-$MgBr_2$ (0°C)				
		R^1		R_2	Yield	*Syn*	de	*Anti*	de	Yield	*Syn*	de	*Anti*	de
1	**10b**	Me	**18ba**	Ph	45	>98	8	2						
2	**10c**	Et	**18ca**	Ph	18	>98	14	2						
3	**10e**	Pr	**18ea**	Ph	19	>98	14	2						
4	**10j**	$PhCH_2$	**18ja**	Ph	20	>98	26	2						
5	**10b**	Me	**17bb**	Ts	92	80	91	20	76	94	4	91	96	15
6	**10a**	H	**17ab**	Ts						98				
7	**10c**	Et	**17cb**	Ts	85	64	95	36	85	93	3	15	97	12
8	**10e**	Pr	**17eb**	Ts	77	57	93	43	91	97	4	7	96	17
9	**10j**	$PhCH_2$	**17jb**	Ts	79	53	85	47	76	98	4	21	96	8

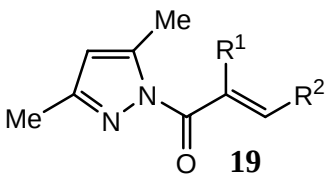
When **10** was treated with *N*-benzylidene-4-toluenesulfonamide (**16b)** by using LDA-HMPA at 0°C, *syn*-β-aminoacyl-3-phenyl-*l*-menthopyrazole derivatives (*syn*-**17**) were predominantly formed summarized in Table 6, where high chemical and optical yields were observed and *syn*/*anti* stereoselectivities were dependent on the bulkiness of acyl moiety. After separation of *syn* and *anti* isomers by column chromatography, both isomers were derived into the corresponding β-lactams (*syn*-**18b** and *anti*-**18b**). On the DIEA catalyzed reaction of **16b** in the presence of $MgBr_2$, **10** gave *anti*-**17** having *2'S,3'R* configuration in low diastereoselectivity listed in Table 6.

4 Addition Reaction to 2-(α,β-Unsaturated) Acyl-3-phenyl-*l*-menthopyrqazoles

4.1 Structure of 2-(α,β-Unsaturated) Acyl-3-phenyl-*l*-menthopyrazoles[24,25]

Generally diastereoselectivity of conjugate addition to α,β-unsaturated carbonyl compounds is known to be dependent on their geometric structure and their facial attack by nucleophiles. The α-proton signals of α,β-unsaturated acyl groups appeared at 1.3~1.5 ppm lower field than that of α,β-unsaturated acid methyl esters, while the lower shifts less than 0.35 ppm were observed in β-proton peaks (Table 7). Analogous low field shifts were reported in the cases of α,β-unsaturated phenyl ketones, where α-proton was deshielded by the anisotropic effect of the proximate phenyl group of s-*cis* form.[26] Moreover, the C-N bond between pyrazole ring and acyl carbonyl was previously found to be *anti* form.[27] These facts





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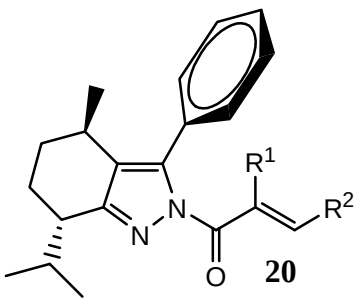


20

a: R^1=R^2= H
b: R^1= H, R^2= Ph
c: R^1= H, R^2= *p*-Tol
d: R^1= H, R^2= *p*-ClPh
e: R^1= H, R^2= Me
f: R^1= H, R^2= Et
g: R^1= H, R^2= *i*-Pr
h: R^1= H, R^2= *t*-Bu
i: R^1= H, R^2= COOEt
j: R^1= Me, R^2= H
k: R^1= Me, R^2= Ph
l: R^1= Me, R^2= Me
m: R^1= Me, R^2= Et
n: R^1= Me, R^2= *i*-Pr

suggested that *N*-(α,β-unsaturated) acylpyrazoles (**19a**-**b**, **19e**, **20a**-**b**, and **20e**) preferred the *anti*-s-*cis* form and α-proton was deshielded, showing down field shift by the anisotropic effect of the pyrazole ring. In the cases of *N*-(α-methyl-α,β-unsaturated) acylpyrazoles (**19j**-***l*** and **20j**-***l***), β-proton signals appeared rather high field compared with those of the corresponding methyl esters. From these spectral evidences, *N*-(α-methyl-α,β-unsaturated) acylpyrazoles (**19j**-***l*** and **20j**-***l***) were also supposed to be preferably the *anti*-s-*trans* form.

Table 7. The ^{1}H NMR Data of *N*-(α,β-Unsaturated) Acylpyrazoles Compared with the Corresponding Me Esters

Run	*N*-(α,β-Unsaturated) Acylpyrazoles				$\delta^{acylpyrazole}$		$\delta^{Me\ Ester}$-$\delta^{acylpyrazole}$	
		R^1	R^2	Pyrazole	α	β	α	β
1	**19b**	H	Ph	3,5-dimethylpyrazolyl-	7.88	7.96	-1.43	-0.26
2	**20b**	H	Ph	2-(3-phenyl-*l*-menthopyrazolyl)-	7.78	8.03	-1.33	-0.33
3	**19a**	H	H	3,5-dimethylpyrazolyl-	7.59	6.62	-1.46	-0.20
4	**20a**	H	H	2-(3-phenyl-*l*-menthopyrazolyl)-	7.63	6.50	-1.50	-0.08
5	**19e**	H	Me	3,5-dimethylpyrazolyl-	7.32	7.20	-1.47	-0.20
6	**20e**	H	Me	2-(3-phenyl-*l*-menthopyrazolyl)-	7.33	7.10	-1.48	-0.10
7	**19k**	Me	Ph	3,5-dimethylpyrazolyl-		7.33		+0.37
8	**20k**	Me	Ph	2-(3-phenyl-*l*-menthopyrazolyl)-		7.30		+0.40
9	**19j**	Me	H	3,5-dimethylpyrazolyl-		5.82		+0.25
10	**20j**	Me	H	2-(3-phenyl-*l*-menthopyrazolyl)-		5.87		+0.25
11	**19*l***	Me	Me	3,5-dimethylpyrazolyl-		6.58		+0.27
12	**20*l***	Me	Me	2-(3-phenyl-*l*-menthopyrazolyl)-		6.53		+0.32

In order to reveal the diastereofacial properties of **20** in more detail, a rational explanation of the diastereoselection of **20** was attempted through the use of PM3 calculations. When *N*-acylpyrazoles were treated with $MgBr_2 \cdot OEt_2$, the structure changed into *syn*-s-*cis* form, and the bond rotation between the acyl group and the pyrazole ring was fixed by the chelation of N···Mg···O=C. Similar structural change was anticipated with the addition of $ZnCl_2$. These structural aspects based on NMR spectra were supported by the PM3 calculation of **20a**. The electron densities of 2'- and 3'-carbon atoms decreased, and the double bond of the acrylic moiety was more polarized by Mg or Zn chelation, as summarized in Table 8. The bond features of the acrylic moiety were proved by following conjugate addition and Diels-Alder

cycloaddition, where confirm previous results showing that the reaction rate is accelerated by the addition of $MgBr_2 \cdot OEt_2$ or $ZnCl_2$.

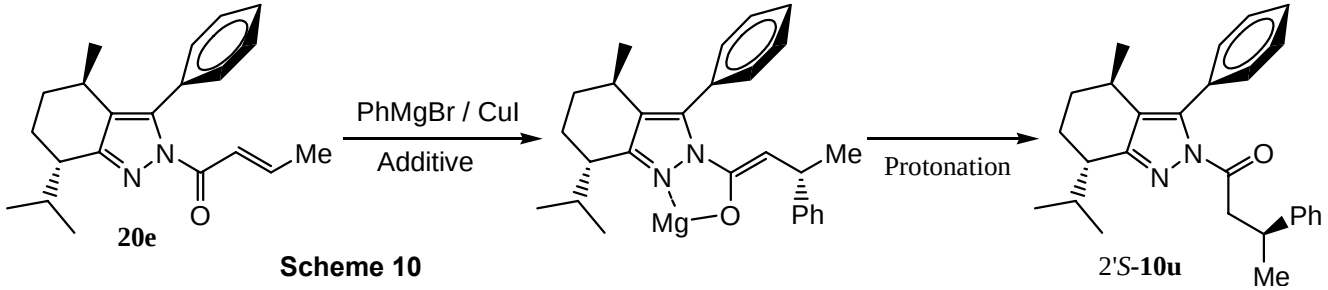
Table 8. The Charges and Electron Densities of the Acrylic Moiety and the Heat of Formation (ΔHf) on 2-Acryloyl-3-phenyl-*l*-menthopyrazoles (**20a**).

	Density		Charge		ΔHf [a]
	2'-C	3'-C	2'-C	3'-C	(kcal/mol)
20a	3.945	3.950	-0.213	0.023	55.43
20a + $MgBr_2$	3.930	3.926	-0.357	0.098	-49.18
20a + $ZnCl_2$	3.938	3.938	-0.384	0.053	2.15

a: ΔHf presented the heat of formation of the starting mixture of **20a** and **5** with catalyst.

4.2 **Conjugate Addition**[23,16a]

Grignard reagent was expected to be the promising carbon nucleophiles for the conjugate addition to the *N*-(α,β-unsaturated) acylpyrazoles having the *syn*-form. When 2-cinnamoyl-3-phenyl-*l*-menthopyrazole (**20b**) was treated with either methylmagnesium iodide in the presence of a cuprous catalyst, the conjugate adduct (**10u**) was obtained in good yield with 5 % de. Similarly the conjugate addition of phenylmagnesium bromide on 2-crotonoyl-3-phenyl-*l*-menthopyrazoles (**20e**) was performed, and the higher diastereoselectivity with the *S*-configuration on β-position was shown on the formation of **10u** in the Scheme 10 and Table 9. The diastereoselectivity of this conjugate addition was rationally explained by the *Re*-facial attack of Grignard reagent on the *syn*-s-*cis* form of **20**, which was fixed by the chelation



Scheme 10

Table 9. Asymmetric Conjugate Addition to 2-(α,β-Unsaturated) Acyl-3-phenyl-*l*-menthopyrazoles.

Run	Acylpyrazole			Nucleophile (equiv.)	Product		
		R^1	R^2			Yield	De % (conf.)
1	**20b**	H	Ph	MeMgI(2)+CuI(1)	**10u**	78	5 (*R*)
2	**20b**	H	Ph	MeMgI(2)+CuI(1)+$MgBr_2$(2)	**10u**	97	66 (*S*)
3	**20b**	H	Ph	MeMgI(2)+CuBr(1)+$MgBr_2$(1)	**10u**	92	68 (*S*)
4	**20b**	H	Ph	EtMgI(2)+CuI(1)+$MgBr_2$(2)	**10v**	67	30 (*S*)
5	**20b**	H	Ph	*i*-PrMgBr(2)+CuI(1)+$MgBr_2$(2)	**10w**	67	10 (*R*)
6	**20b**	H	Ph	*t*-BuMgBr(2)+CuI(1)+$MgBr_2$(2)	**10x**	53	6 (*R*)
7	**20c**	H	*p*-Tol	MeMgI(2)+CuI(1)+$MgBr_2$(2)	**10y**	49	69 (*S*)
8	**20d**	H	*p*-ClC_6H_4	MeMgI(2)+CuI(1)+$MgBr_2$(2)	**10x**	100	54 (*S*)
9	**20e**	H	Me	PhMgBr(2)+CuI(1)	**10u**	75	80 (*S*)
10	**20e**	H	Me	PhMgBr(2)+CuI(1)+$MgBr_2$(2)	**10u**	96	49 (*S*)
11	**20e**	H	Me	*p*-TolMgBr(2)+CuI(1)+$MgBr_2$(2)	**10y**	78	58 (*S*)
12	**20f**	H	Et	PhMgBr(2)+CuBr(1)+$MgBr_2$(2)	**10v**	91	62 (*S*)
13	**20g**	H	*i*-Pr	PhMgBr(2)+CuI(1)+$MgBr_2$(2)	**10w**	88	58 (*R*)
14	**20h**	H	*t*-Bu	PhMgBr(2)+CuBr(1)+$MgBr_2$(2)	**10x**	88	69 (*R*)

with metal halides such as cuprous iodide and magnesium iodide.

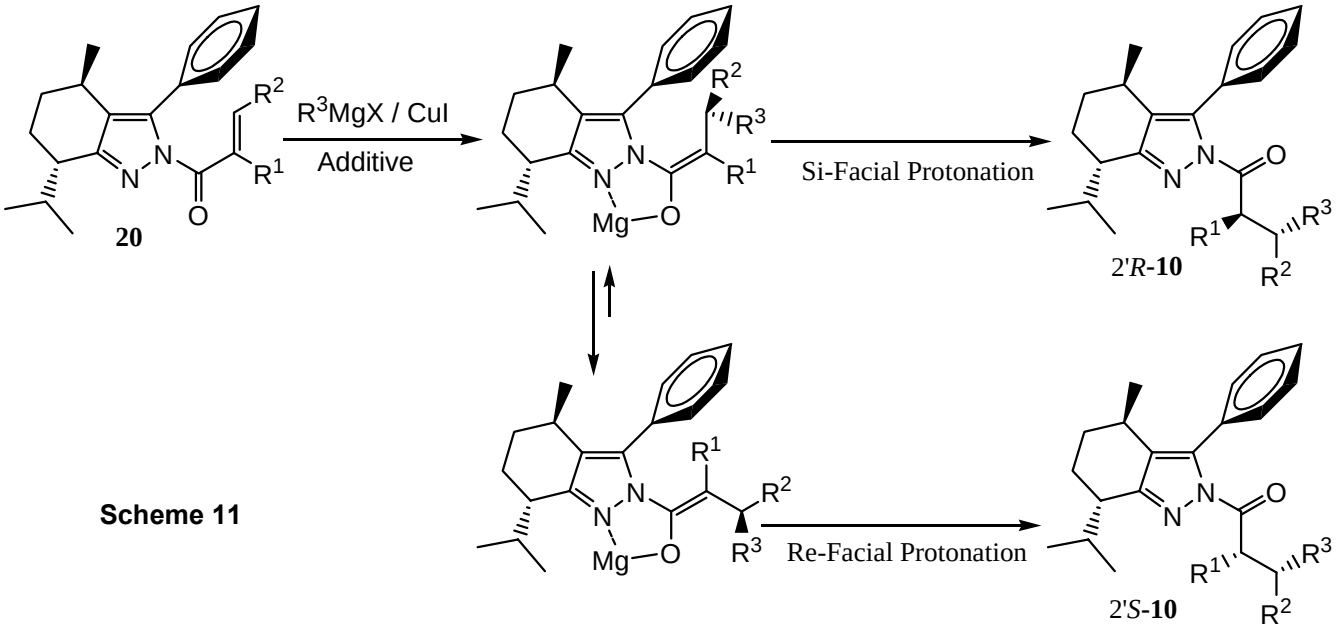
By the treatment of *N*-acylpyrazoles with excess amount of Lewis acid, the open transition form was expected rather than the cyclic C=O···Mg···N chelated intermediate.[28] Namely, the addition of excess amounts of magnesium bromide allowed to change the geometric structure, and to affect to the diastereoselectivity in the conjugate addition of **20** with Grignard reagents in the presence of cuprous iodide. When 2 equiv. of magnesium bromide were added to the suspension of cuprous iodide in the THF solution of **20b**, the mixture changed to a clear orange solution. This homogeneous solution was treated with methylmagnesium iodide to give **10u** in good yield with higher diastereoselectivity of *S*-configuration on β-position, listed in Table 9. The yields and the diastereoselectivities dropped down in

the reactions with more bulky Grignard reagents. In the cases of **20g** and **20h**, the conjugate addition in the presence of $MgBr_2$ proceeded in satisfactory yields, but preferences on β-position were changed into *R*-selectivities.

Next the asymmetric induction on α-position was attempted by the conjugate additions of α-methylated 2-(α,β-unsaturated) acyl-3-phenyl-*l*-menthopyrazoles (**20j**-**n**) with Grignard reagents. Since the conjugate addition of unsaturated acylpyrazoles was completed by the final protonation of metal enolate intermediate with an acid, the asymmetric induction on α-position was dependent on the structure of metal enolates. When 2-methacryloyl-3-phenyl-*l*-menthopyrazole (**20j**) was treated with Grignard reagents in the presence of cuprous halides, **10f** was formed in good yields with optical yields changing widely as

Table 10. Asymmetric Conjugate Addition to 2-(α-Methyl-α,β-unsaturated) Acyl-3-phenyl-*l*-menthopyrazoles.

Run	Acylpyrazole			Nucleophile (equiv.)	Time		Yield	De % (conf.)	
		R^1	R^2		h		(%)	α	β
1	**20k**	Me	Ph	PhMgBr(1)+CuI(1)	2	**10q**	18	87 (*S*)	
2	**20k**	Me	Ph	PhMgBr(1)+CuI(1)+$MgBr_2$(2)	2	**10q**	54	97 (*S*)	
3	**20j**	Me	H	MeMgI(1)+CuI(1)	2	**10f**	70	47 (*R*)	
4	**20j**	Me	H	MeMgI(1)+CuI(1)	12	**10f**	25	22 (*S*)	
5	**20j**	Me	H	MeMgI(1)+CuI(1)+$MgBr_2$(2)	2	**10f**	70	6 (*S*)	
6	**20j**	Me	H	PhMgBr(1)+CuI(1)	2	**10m**	71	0	
7	**20*l***	Me	Me	MeMgI(1)+CuBr(1)	2	**10*l***	74	88 (*S*)	
8	**20k**	Me	Ph	MeMgI(1)+CuI(1)	2	**10r**	70	>95 (*S*)	30 (*R*)
9	**20k**	Me	Ph	MeMgI(1)+CuI(1)+$MgBr_2$(2)	2	**10r**	25	>95 (*S*)	20 (*R*)
10	**20*l***	Me	Me	PhMgBr(1)+CuI(1)	2	**10r**	84	>95 (*S*)	92 (*S*)
11	**20m**	Me	Et	PhMgBr(1)+CuI(1)	2	**10s**	82	>95 (*S*)	92 (*S*)
12	**20n**	Me	*i*-Pr	PhMgBr(1)+CuI(1)	2		0		
13	**20n**	Me	*i*-Pr	PhMgBr(1)+CuI(1)+$MgBr_2$(2)	2	**10t**	26	>95 (*S*)	63 (*S*)

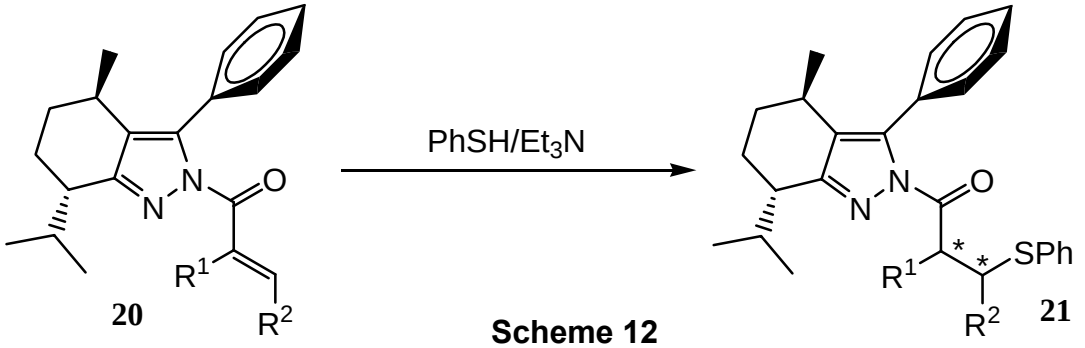


Scheme 11

summarized in Table 10. The preferable structure of **10f** was found to be *R*-configuration on α-position in the short reaction time, whereas *S*-preference was observed by the prolonged reaction. This inversion was reasonably interpreted by the slow conversion into *Z*-enolate from *E*-enolate, which was first formed by the conjugate addition of Grignard reagent on s-*trans* form of **20j**, as shown in Scheme 11. In the case of **20*l***, metal enolate was rapidly isomerized into the thermally stable *Z*-enolate, and subsequent protonation from *Re*-face afforded the conjugate adduct (**10*l***) with *S*-configuration on α-position.

Finally the conjugate additions of **20j-n** with Grignard reagents were performed for the double asymmetric induction on the α- and β-positions. The treatment of **20*l*** with phenylmagnesium bromide in the presence of cuprous halide afforded (2'*S*,3'*S*)-2-(2'-methyl-3'-phenyl)butanoyl-3-phenyl-*l*-menthopyrazole (**10r**) with the excellent diastereoselectivities on either α- and β-position. The stereostructure of **10r** was supported by the derivatization into (2*S*,3*S*)-2-(2-methyl-3-phenyl)butanoic acid. Similar asymmetric induction on α- and β-positions was simultaneously accomplished by the conjugate addition of Grignard reagent to **20m** and **20n** summarized in Table 10.

In the case of **20k** with methylmagnesium iodide, the excellent diastereoselectivity of α-position was



Scheme 12

observed with a low *R*-selectivity on β-position. By the addition of $MgBr_2$, the selectivity on the β-position was reversed like the conjugate addition to **20b**.

Next, the conjugate addition of thiophenol to *N*-(α,β−unsaturated) acylpyrazoles was attempted for the introduction of phenylthio group on β−position of *N*-acylpyrazoles.[29] When 2-(α,β−unsaturated) acyl-3-phenyl-*l*-menthopyrazoles (**20**) was treated with an excess amount of thiophenol in the presence of weaker base such as triethylamine (TEA), β−phenylthio substituted product (**21**) was formed, summarized in Scheme 12 and Table 11. In the case of 2-methacryloyl-3-phenyl-*l*-menthopyrazole (**20j**), an asymmetric center was newly formed on the α-position. From the NMR data, the diastereomer ratio of **21j** was deduced to be 30 % de. When 2-(2'-methyl-2'-butenoyl)-3-phenyl-*l*-menthopyrazole (**20*l***) was treated with thiophenol in the presence of TEA, two pairs of diastereomeric mixture of 2-(3'-phenylthio-2'-methyl)butanoyl-3-phenyl-*l*-menthopyrazole (**21*l***) was obtained complicatedly. The NMR spectrum of

Table 11. Conjugate Addition of Thiophenol on 2-(α,β-Unsaturated) Acyl-3-phenyl-*l*-menthopyrazole (**20**)

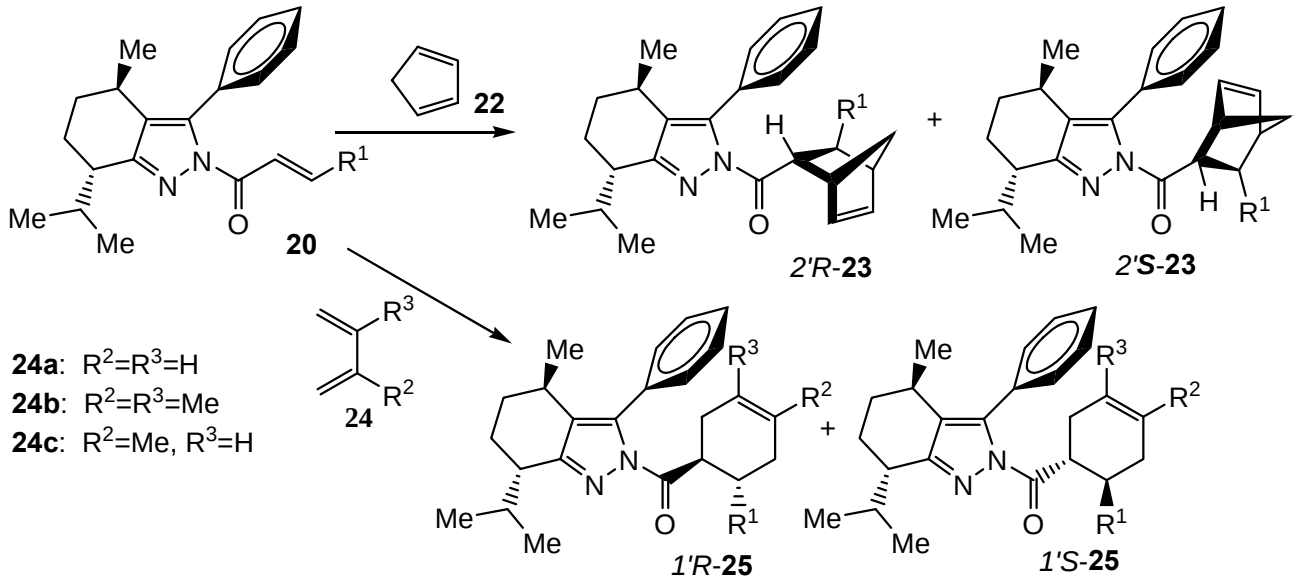
Run	Substrate			Base	Conditions	Product		
		R^1	R^2				Yield	De
1	**20b**	H	Ph	NaH	0°C, 2.5 h	**21b**	99	23
2	**20b**	H	Ph	TEA	20°C, 1 h	**21b**	85	19
3	**20b**	H	Ph	TEA	-78° to 0°C, 4 h	**21b**	98	22
4	**20e**	H	Me	TEA	20°C, 1 h	**21e**	100	43
5	**20f**	H	Et	TEA	20°C, 2.5 h	**21f**	94	38
6	**20g**	H	*i*-Pr	TEA	20°C, 1.5 h	**21g**	84	33
7	**20h**	H	*t*-Bu	TEA	20°C, 2 h	**21h**	76	38
8	**20j**	Me	H	TEA	20°C, 1 h	**21j**	85	30
9	**20*l***	Me	Me	TEA	20°C, 1 h	**21*l***	78	a

a: The de % of *syn* and *anti* isomers were 33 and 32 % respectively, while the *syn*/*anti* ratio was 8.4:1.

α−proton showed that *syn* isomers (*syn*-**21*l***) were predominant with the *syn*/*anti* ratio of 8.4 : 1. The diastereomeric excesses of *syn*-**21*l*** and *anti*-**21*l*** were found to be 33 and 32 % de, respectively.

4.3 **Diels-Alder Cycloaddition**[24]

The reaction rate of 1-acryloyl-3,5-dimethylpyrazole (**19a**) and cyclopentadiene (**22**) at 0°C was evaluated to be about 4 x 10^{-5} *l*/mol·s, and acceleration of the reaction rates was observed with the addition of Lewis



Scheme 13

Table 12. Diels-Alder Reaction of 2-(α,β-Unsaturated) Acyl-3-phenyl-*l*-menthopyrazole (**20**) with Cyclopentadiene (**22**).

Run	Substrate	R^1	Lewis Acid	Time (h)	Product	Yield (%)	Ratio *Endo* : *Exo*	De(*Endo*) (Conf.)	De(*Exo*) (Conf)
1	**20a**	H	none	17	**23a**	98	96 : 4	15 (2'*R*)	
2	**20a**	H	$BF_3{\cdot}OEt_2$	1.5	**23a**	90	94 : 6	12 (2'*R*)	
3	**20a**	H	$MgBr_2{\cdot}OEt_2$	2	**23a**	98	96 : 4	84 (2'*S*)	
4	**20a**	H	$ZnCl_2$	1	**23a**	98	>99 : 1	85 (2'*S*)	
5	**20e**	Me	none	17	**23e**	56	60 : 40	12 (2'*S*)	27 (2'*S*)
6	**20e**	Me	$MgBr_2{\cdot}OEt_2$	8	**23e**	90	79 : 21	86 (2'*S*)	27 (2'*S*)
7	**20e**	Me	$ZnCl_2$	4	**23e**	91	96 : 4	83 (2'*S*)	

acids such as BF_3·OEt_2, $MgBr_2$·OEt_2, and $ZnCl_2$, but LiBr was not effective. Strong Lewis acids such as $TiCl_4$ and $AlCl_3$ depressed the formation of Diels-Alder adducts due to the C-N bond cleavage of *N*-acylpyrazoles. Also the Diels-Alder reaction of 1-cinnamoyl-3,5-dimethylpyrazole (**19b**) is very slow and the high-pressure conditions are necessary to produce the adduct in moderate yield.

When 2-acryloyl-3-phenyl-*l*-menthopyrazole (**20a**) was treated with **22** for 17 h, the mixture of 4 diastereoisomers was afforded in high yield, as shown in Scheme 13 and Table 12. The major product was found to be the *endo*-cycloadduct having a 2'*R*- conformation (1'*S*,2'*R*,4'*R*-**23a**). The formation of **23a** was catalyzed 10 times faster through the use of BF_3·OEt_2 without any promotion of diastereoselectivity. The $MgBr_2$·OEt_2 catalyst exhibited the reversed diastereoselectivity of an *endo*-cycloadduct (1'*R*,2'*S*,4'*S*-**23a**)[30] with high 2'*S*-preference. By the addition of $ZnCl_2$, the *endo*-cycloadduct was formed exclusively with high diastereoselectivity.

As shown in Table 13, either $MgBr_2$·OEt_2 or $ZnCl_2$ can catalyze the diastereoselective Diels-Alder reaction

Table 13. Reaction of 2-(α,β-Unsaturated) Acyl-3-phenyl-*l*-menthopyrazoles (**20**) with 1,3-Butadienes (**24**).

Dienophile		1,3-Butadiene			Lewis Acid	Time	Product	Yield	% De
	R^1		R^2	R^3		(h)		(%)	(Conf.)
20a	H	**24a**	H	H	None	42	**25aa**	2	20(1'*R*)
20a	H	**24a**	H	H	$MgBr_2$·OEt_2	17	**25aa**	98	80(1'*S*)
20a	H	**24a**	H	H	$ZnCl_2$	4	**25aa**	97	90(1'*S*)
20a	H	**24c**	Me	H	$ZnCl_2$	10	**25ac**	95[a]	>95(1'*S*)
20a	H	**24b**	Me	Me	None	80	**25ab**	17	28(1'*R*)
20a	H	**24b**	Me	Me	BF_3·OEt_2	12	**25ab**	67	3(1'*S*)
20a	H	**24b**	Me	Me	$MgBr_2$·OEt_2	15	**25ab**	99	>95(1'*S*)
20a	H	**24b**	Me	Me	$ZnCl_2$	7	**25ab**	90	>95(1'*S*)
20i	CO_2Et	**24a**	H	H	$ZnCl_2$	20	**25ia**	90	75(1'*R*)
20i	CO_2Et	**24a**	Me	Me	$MgBr_2$·OEt_2	3	**25ib**	97	33(1'*S*)
20i	CO_2Et	**24a**	Me	Me	$ZnCl_2$	2	**25ib**	98	72(1'*R*)

a: The regioisomer ratio was found to be 100 : 0.

of **20** with 1,3-butadienes (**24**) with 1'*S*-preference, while the alternate diastereoisomers are formed in the reactions without a catalyst. In the case of **24c**, the $ZnCl_2$-catalyzed reaction of **20a** afforded only one diastereoisomer of 2-(4'-methyl-3'-cyclohexene-1'-carbonyl)-3-phenyl-*l*-menthopyrazole (1'*S*-**25ac**) in 95 % yield.

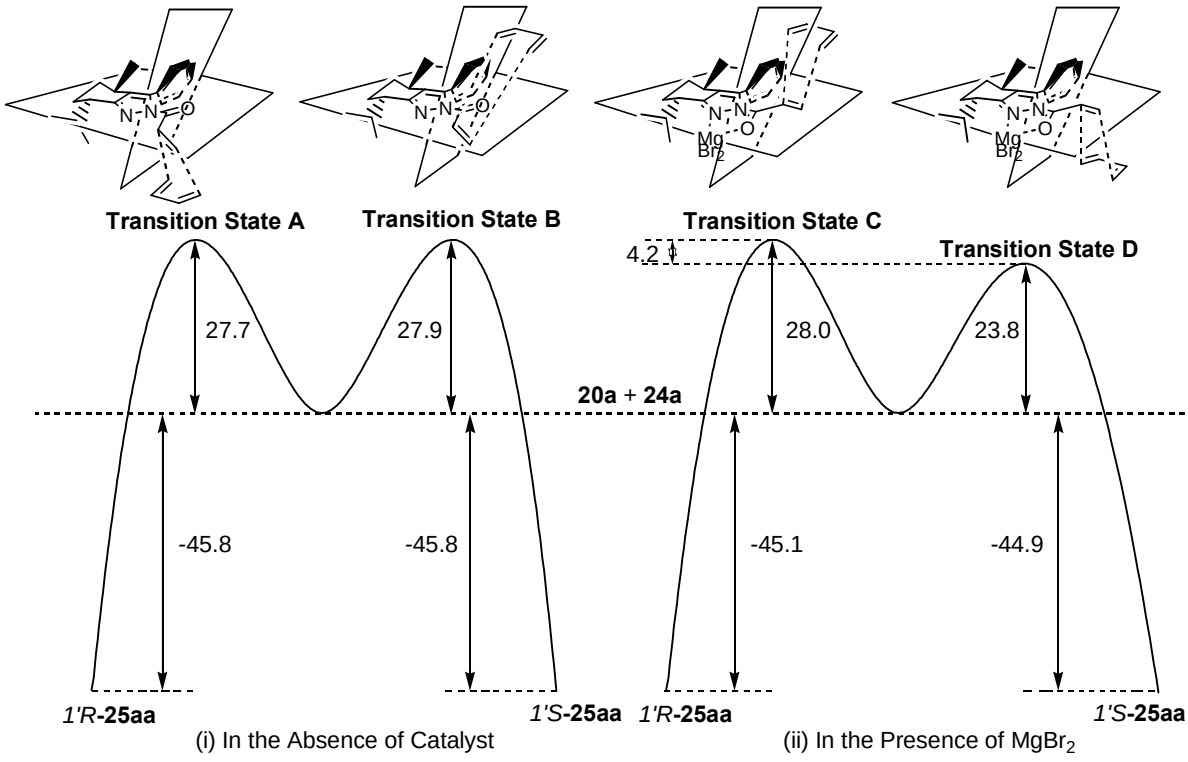


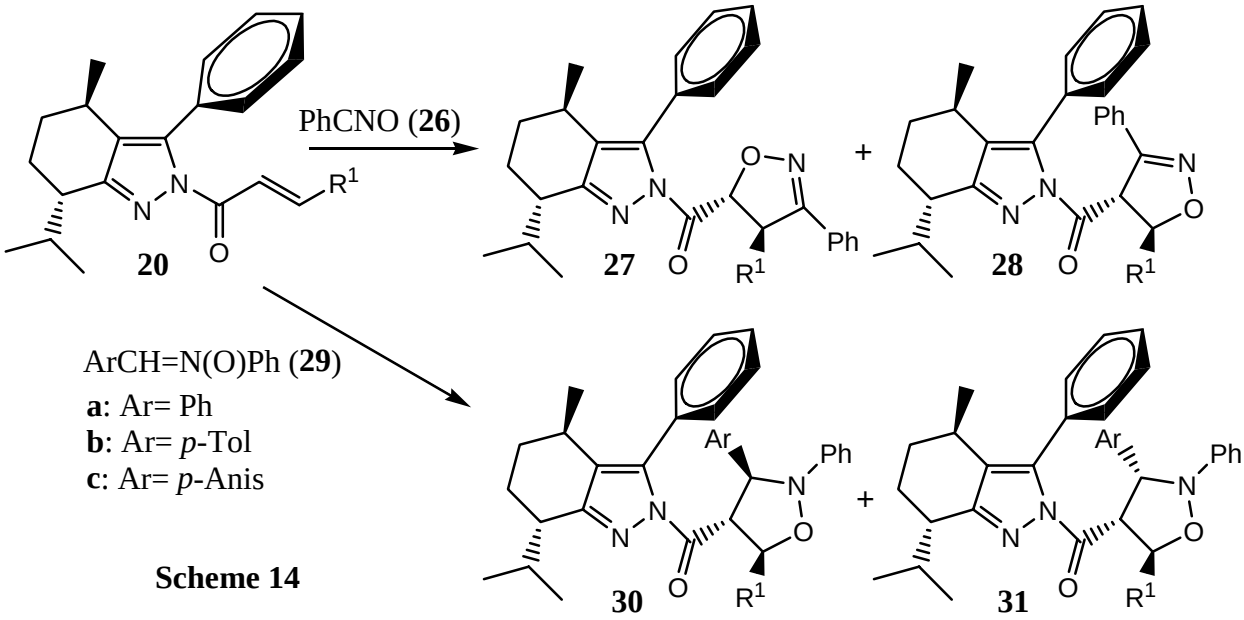
Figure 3 The Reaction Profile of **20a** with **24a** (kcal/mol)

In order to reveal the diastereofacial properties of 3-phenyl-*l*-menthopyrazole in more detail, a rational explanation of the diastereoselection in the Diels-Alder reaction of **20a** was attempted through the use of PM3 calculations. The calculation of the heats of formation (ΔHf) was performed for the mixture of **24a** and the *anti*-s-*cis* form of **20a**. The ΔHf of the product (**25aa**) was also obtained by the PM3 calculation**.** Moreover, four transition states were calculated dependent on two facial attacks of **24a**, which included two transition state geometries of *endo*- and *exo*-approach due to the orientation of **24a**. The energy differences among these four transition states suggest that the diastereoselection is ineffective, and the reaction profile is shown in Figure 3 (i). These calculations anticipated the actual experimental fact that the reaction of **20a** and **24a** in the absence of catalyst afforded (1'*R*)-2-(3'-cyclohexene-1'-carbonyl)-3-phenyl-*l*-menthopyrazole (1'*R*-**25aa**) with low diastereoselectivity.

Similarly, the reaction profile of **20a** with **24a** was obtained by calculations based on the starting mixture, the transition state, and the product, including the chelating bond of N···Mg···O=C and N···Zn···O=C. The case of $MgBr_2$ shown in Figure 3 (ii) indicates that the transition barrier of the *Re*-face attack was 4.2 kcal/mol lower than that of the *Si*-face attack. The difference of the transition barriers supported a diastereoselective reaction. Moreover, this reaction profile suggested that the diastereoselective reaction of **20a** with **24a** is governed by kinetic control rather than thermodynamic control. Compared with the A and B transition states, the lower reaction barrier of transition state D could explain the acceleration of the reaction by the addition of $MgBr_2{\cdot}OEt_2$. The reaction profile of **20a** and **24a** in the presence of $ZnCl_2$ was supported by the corresponding results of the PM3 transition-states calculation.

4.4 **1,3-Dipolar Cycloaddition**[31]

As the diastereofacial 1,3-dipolar cycloaddition to 2-(α,β-unsaturated) acyl-3-phenyl-*l*-menthopyrazoles (**20**), the reaction of 2-acryloyl-3-phenyl-*l*-menthopyrazole (**20a**) with benzonitrile oxide (**26**) afforded predominantly 1,3-dipolar cycloadduct (**27a**), while 2-cinnamoyl-3-phenyl-*l*-menthopyrazole (**20b**) gave the regioisomeric mixture of **27b** and **28b**. The diastereoselectivities in these reactions of 3-phenyl-*l*-menthopyrazole derivatives were observed in some extent, summarized in Scheme 14 and Table 14. Any remarkable promotion of the diastereoselectivity in the 1,3-dipolar cycloaddition of benzonitrile oxide was not observed in the addition of $MgBr_2$.



Scheme 14

Table 14. 1,3-Dipolar Cycloaddition of 2-(α,β-Unsaturated) Acyl-3-phenyl-*l*-menthopyrazole (**20**) with Benzonitrile Oxide (**26**).

Run	Substrate		Yield	Product				Ratio
		R^1	(%)		De		De	27 : 28
1	**20a**	H	85	(5'*R*)-**27a**	24	(4'*R*)-**28a**		100 : 0
2	**20e**	Me	84	(5'*R*)-**27e**	12	(4'*R*)-**28e**	31	52 : 48
3	**20b**	Ph	78	(5'*R*)-**27b**	1	(4'*R*)-**28b**	29	21 : 79

Table 15. 1,3-Dipolar Cycloaddition of 2-(α,β-Unsaturated) Acyl-3-phenyl-*l*-menthopyrazoles (**20**) with Nitrones (**29**).

Run	Substrate		Nitrone		Lewis Acid	Yield	Product				ratio
		R^1		Ar		(%)		De		De	**30** : **31**
1	**20a**	H	**29a**	Ph	$MgBr_2$	79	(4'*R*)-**30aa**	>95	(4'*R*)-**31aa**	22	83 : 17
2	**20e**	Me	**29a**	Ph	None	93	(4'*R*)-**30ea**	34	(4'*R*)-**31ea**	10	86 : 16
3	**20e**	Me	**29a**	Ph	$MgBr_2$	94	(4'*R*)-**30ea**	>95	(4'*R*)-**31ea**	48	91 : 9
4	**20e**	Me	**29b**	*p*-Tol	$MgBr_2$	99	(4'*R*)-**30eb**	>95	(4'*R*)-**31eb**	50	86 : 14
5	**20e**	Me	**29c**	*p*-Anis	$MgBr_2$	85	(4'*R*)-**30ec**	>95	(4'*R*)-**31ec**	25	89 : 11
6	**20e**	Me	**29a**	Ph	LiBr	85	(4'*R*)-**30ea**	29	(4'*R*)-**31ea**	19	87 : 13
7	**20e**	Me	**29a**	Ph	$ZnBr_2$	100	(4'*R*)-**30ea**	66	(4'*R*)-**31ea**	27	47 : 53
8	**20b**	Ph	**29a**	Ph	none	32	(4'*R*)-**30ba**	37	(4'*R*)-**31ba**	a	a

a: Product ratio and de cannot be evaluated due to the complicated reaction mixture.

When **20a** was treated with diphenylnitrone (**29a**) at refluxing temperature in THF, the mixture of 4 cycloadduct isomers (**30a**, and **31a**) was obtained along the regio- and stereoisomerism. As shown in Table 15, the addition of some Lewis acid accelerated the rate of 1,3-dipolar cycloaddition reaction with diphenylnitrone. The 1,3-cycloaddition of β-substituted *N*-(α,β-unsaturated) acylpyrazoles (**20b** and **20e**) occurred regioselectively to afford **30** and **31** summarized in Table 15. Moreover, the addition of divalent Lewis acids such as $MgBr_2$ and $ZnBr_2$ caused the change in the stereoselectivity, while no change in stereoselectivity was observed in the presence of tributylborane. The promotion of the stereoselectivity was reasonably interpreted by the formation of chelate complex, in which the bond rotation between pyrazole and acyl group of *N*-acylpyrazole was frozen.

The predominant isomers (**30**) was converted into azetidinones, which were paid much attention as the antibiotics. In the first step, isoxazolidine ring of **30** was cleaved by hydrogenation to afford aminoalcohol

derivative. After the protection of hydroxyl group with tert-butyldimethylsilyl chloride (TBDMS-Cl), the intramolecular aminolysis led to azetidinone derivative catalyzed by ethylmagnesium bromide. The TBDMS derivative of 3-*cis*-(1'-*anti*-hydroxyethyl)-1,4-diphenyl-2-azetidinone, which was identified by the comparison with the authentic data,[32] was obtained in 29 % overall yield from **30**.

5 Conclusion

We have recently developed a method for the preparation of 3-phenyl-*l*-menthopyrazole (**1**, (4*R*,7*S*)-7-isopropyl-4-methyl-3-phenyl-4,5,6,7-tetrahydroindazole) as a new chiral auxiliary, which has unique structure and properties that are different from the conventional chiral auxiliaries. The most important characteristics of this auxiliary are that the acyl substrate terminates in the nitrogen atom of a heteroaromatic pyrazole ring in a chiral environment. The steric hindrance of **1** is relaxed by the twisting of the benzene ring, which overlaps one side of the terminal nitrogen atom. This structural feature causes a diastereofacial effect in the reactions on the substrate moiety. Moreover, the lone pair of electrons on the adjacent nitrogen plays the role of a Lewis base, causing the chelation of N···Li-O in the lithium enolate derived from *N*-acylpyrazoles. These chelations freeze the bond rotation of the acyl group so that it is fixed in a *syn* configuration. As a result, the chirality of the (4*R*)-methyl group of **1** causes a highly asymmetric induction on the acyl group of 2-acyl-3-phenyl-*l*-menthopyrazoles in the reactions with alkyl halides, phenyldisulfide, acyl chloride, aldehydes, and C=N compounds. A similar chelation of N···Mg···O=C, which is observed in the mixture of *N*-acylpyrazoles and $MgBr_2 \cdot OEt_2$, induces the asymmetric addition of Grignard reagents, 1,3-dipolar compounds, and dienes on *N*-(α,β-unsaturated) acylpyrazoles. As an analogue of the *N*-acylheteroaromatics, *N*-acylpyrazoles are easily converted into acyl derivatives by the action of nucleophiles such as alcohols, amines, Grignard reagents, or organozinc compounds under basic or acidic conditions.[7] This 3-phenyl-*l*-menthopyrazole is regarded as an excellent chiral auxiliary, which induces the asymmetric reactions with high stereoselectivity and converts easily into the wide variety of functionalities.

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