Asymmetric Borane Reduction of Ketones Promoted by Menthopyrazole-$ZnCl_2$ Complex

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The enantioselective reduction of ketones was accomplished by borane in the presence of pyrazole derivatives, particularly 2-methoxymethyl-3-phenyl-*l*-menthopyrazole (**8**). The catalysis of zinc chloride makes it possible to lower the reaction temperature below 0 °C, and to promote enantioselectivity.

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Recently we developed the preparation and the utilities of 3-phenyl-*l*-menthopyrazole (**1**) as a new chiral auxiliary [1], which has unique structure and properties different from conventional chiral auxiliaries [2]. The most important characteristics of this auxiliary are that the acyl substrate terminates to the nitrogen atom of heteroaromatic pyrazole ring, and that the substrate is surrounded by a chiral atmosphere. This structural feature causes the diastereofacial attack on the acyl moiety in reactions with alkyl halides [3], diphenyldisulfide [4], acyl chlorides [5], aldehydes [6], and C=N compounds [7]. Moreover, the asymmetric additions of Grignard reagents [8], dienes [9] and 1,3-dipolar compounds [10] on 2-(α,β-unsaturated)acyl-3-phenyl-*l*-menthopyrazoles have been reported. Otherwise, *N*-acylheteroaromatics such as *N*-acylimidazoles are utilized as the activated acyl moiety in a wide variety of organic syntheses [11]. As an analogue of these *N*-acylheteroaromatics, *N*-acylpyrazoles are easily converted into acyl derivatives by the action of nucleophiles such as alcohols [12], amines [13], Grignard reagents [14], or organozinc compounds [15] under basic or acidic conditions. As a part of these investigations, our goal was to develop a catalytic use for pyrazole derivatives in synthetic reactions, and particularly in asymmetric reactions.

In the literature, there are some papers of chiral amino alcohols, which are utilized as asymmetric catalysts for borane reduction of ketones. The hydroxyl moiety of these amino alcohols reacts with borane to form a boric esters, and the amino moiety takes the role of a Lewis base. Subsequently the rigid structure of the borane complex, such as oxazaborolidine, sterically regulates the reduction of ketones [16]. On these background, we examined the asymmetric borane reduction of ketones catalyzed by *N*-hydroxyalkyl-3-phenyl-*l*-menthopyrazoles [17]. This borane reduction however required long heating at 70 °C, which was rather drastic conditions for the stereo controlled reaction. Therefore milder reaction conditions are desired for the higher selective reactions. In serial study of the enantioselective synthesis of alcohols, we will report here the effects of *N*-alkyl-3-phenyl-*l*-menthopyrazoles and the co-effect of Lewis acids in the asymmetric borane reduction of ketones.

Results and Discussion.

In a previous paper [17], a ^{11}B-NMR study revealed that the diastereoselection is not caused by the formation of boric ester, but is regulated by chelation of the borane with the pyrazole nitrogen atom. This fact suggested that *N*-alkyl-3-phenyl-*l*-menthopyrazoles would satisfy the structural requirements necessary for a chiral catalyst in the borane reduction of ketones. As the typical *N*-substituted-3-phenyl-*l*-menthopyrazoles, *N*-methyl- (**2** and **3**), *N*-benzyl- (**4** and **5**), *N*-methoxymethyl- (**7** and **8**), *N*-ethoxymethyl- (**9** and **10**), and *N*-benzyloxymethyl-3-phenyl-*l*-pyrazoles (**11** and **12**) were provided by the alkylation of *N*-unsubstituted-3-phenyl-*l*-menthopyrazole (**1**). 2,3-Diphenyl-*l*-menthopyrazole (**6**) was prepared by the treatment of phenylhydrazine with benzoylmenthone. 2-(2'-Methoxyethyl)- (**14**) and (2'*S*)-2-(2'-phenyl-2'-methoxyethyl)-3-phenyl-*l*-menthopyrazoles (**16**) were prepared from the corresponding 2'-hydroxyethyl-derivatives (**13** and **15**).

The catalytic effects of these *N*-substituted-3-phenyl-*l*-menthopyrazoles were compared with that of 2-(2'-hydroxyethyl)-3-phenyl-*l*-menthopyrazole (**13**) in the

Table 1
Borane Reduction of *p*-Methylacetophenone (**18a**) Catalyzed by *N*-Substituted 3-Phenyl-*l*-menthopyrazoles

Entry		Catalyst R	Solvent [a]	Alcohols Yield (%)	Alcohols Ee (%)	Recovery [b] (%)
1	**2**	1-Me	Hexane	61	23(*S*)	92
2	**4**	1-Bn	Hexane	82	4(*S*)	73
3	**8**	2-CH_2OMe	Hexane	81	1(*R*)	87
4	**6**	2-Ph	Hexane-Toluene	69	13(*R*)	84
5	**13**	2-CH_2CH_2OH	Hexane	67	30(*S*)	89

[a] Borane reduction was carried out at 80°C for 24 hours; [b] Recovery of *N*-substituted-3-phenyl-*l*-menthopyrazoles.

Table 2

Borane Reduction Rates of *p*-Methylacetophenone (**18a**) with **17** and $ZnCl_2$ at -5 °C

Entry	BH_3•THF (eq.)	**17** (eq.)	$ZnCl_2$•Et_2O (eq.)	Rate ($l \cdot mol^{-1} \cdot s^{-1}$)
1	1.0	0	0	5.1×10^{-3}
2	1.0	1.0	0	7.0×10^{-6}
3	1.0	0	1.0	9.5×10^{-5}
4	1.0	1.0	1.0	1.8×10^{-3}
5	1.0	0.5	0.5	4.6×10^{-3}
6	1.0	1.3	1.3	1.7×10^{-3}
7	1.0	1.5	1.5	4.8×10^{-4}
8	1.0	2.0	2.0	2.7×10^{-4}
9	1.0	2.0	1.0	2.9×10^{-4}
10	1.0	1.0	2.0	3.7×10^{-4}

Table 3

Borane Reduction of *p*-Methylacetophenone (**18a**) in the Presence of **8** and Lewis Acids

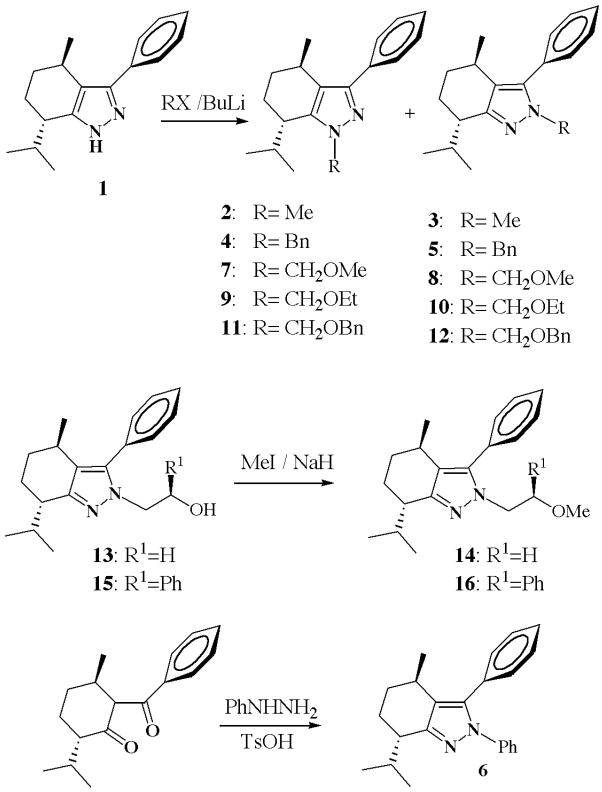
Entry	Lewis Acid	(eq.) [a]	Temp (°C)	Yield (%)	Ee (conf.) (%)	Recovery of **8** (%)
1	none		80	81	1 (*R*)	87
2	$ZnCl_2$	1.0	30	80	22 (*S*)	78
3	$ZnCl_2$	1.0	-5	54	46 (*S*)	79
4	$ZnCl_2$	1.0	-90	74	34 (*S*)	76
5	$ZnCl_2$	2.0	-5	34	47 (*S*)	96
6	$ZnCl_2$	0.1	-5	99	16 (*S*)	85
7	$BF_3 \cdot OEt_2$	1.0	-5	68	19 (*S*)	69
8	$CuBr_2$	1.0	-5	67	35 (*S*)	84
9	$MgBr_2$	1.0	-5	3	6 (*S*)	70
10	$AlEt_2Cl$	1.0	-5	64	19 (*S*)	60
11	$Al(i\text{-}PrO)_3$	1.0	-5	64	18 (*S*)	76
12	$TiCl_4$	1.0	-5	33	18 (*S*)	69

[a] The ratio of the equimolar mixture of **8** and Lewis acid versus borane.

asymmetric borane reduction of *p*-methylacetophenone (**18a**). As expected from ^{11}B-NMR, the data in Table 1 show the applicability of *N*-substituted-3-phenyl-*l*-menthopyrazoles for use as chiral catalysts in borane reduction reactions.

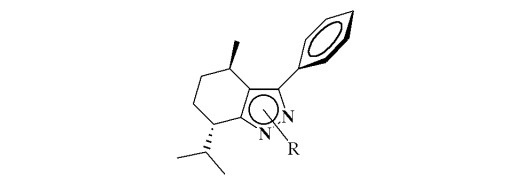
In the meantime, milder reaction conditions were desired in order to improve the borane reduction of ketones. Our experience has shown that derivatives of pyrazole such as *N*-acylpyrazoles exhibit a strong affinity with zinc salts [9]. Moreover borane reductions are accelerated by the addition of a Lewis acid [18]. Therefore the additive effects of Lewis acids were studied on the borane reduction catalyzed by *N*-substituted-3-phenyl-*l*-menthopyrazoles, particularly the effect of zinc chloride. For the experimental convenience, the reduction of *p*-methylacetophenone (**18a**) with borane was firstly surveyed in the presence of various amounts of 1-methoxymethyl-3,5-dimethylpyrazole (**17**) and zinc chloride. The data in Table 2 show that the addition of either **17** (entry 2) or zinc chloride (entry 3) retarded the

Scheme 1



borane reduction of ketones, and that drastic conditions with prolonged heating at 80 °C were required for the preparation of alcohols. Also the presence of excess amount of either **17** or zinc chloride depressed the reaction (entry 9 and 10), while the equimolar mixture of **17** and zinc chloride retained the reactivity of borane (entry 4-8). When taking into account the chiral catalytic effect, it was found that the use of equimolar amounts of the pyrazole derivative complex with zinc chloride resulted in the optimum conditions for the borane reduction (entry 4).

Scheme 2



a: R^2= *p*-Tol, R^3= Me
b: R^2= Ph, R^3= Me
c: R^2= *p*-Cl-Ph R^3= Me
d: R^2= *o*-Tol, R^3= Me
e: R^2= *p*-Anis, R^3= Me
f: R^2= Ph, R^3= Et
g: R^2= Ph, R^3= CH_2Br
h: R^2= 1-Naphth, R^3= Me
i: R^2, R^3= 2-C_6H_4-$(CH_2)_3$

Table 4

Chiral Catalytic Effects of 2-Substituted 3-Phenyl-*l*-menthopyrazole on Borane Reduction of *p*-Methylacetophenone (**18a**) at -5 °C

Entry	2-Substituted 3-Phenyl-*l*-menthopyrazole	R^1	$ZnCl_2$•OEt_2 Eq [a]	Yield (%)	Ee (Conf.) (%)	Pyrazole (Recovery) (%)
1	**13**	CH_2CH_2OH	0	73	30 (*S*)	89
2	**13**	CH_2CH_2OH	1.0	53	27 (*S*)	73
3	**8**	CH_2OMe	0	81	1 (*R*)	87
4	**8**	CH_2OMe	1.0	54	46 (*S*)	79
5	**10**	CH_2OEt	1.0	55	36 (*S*)	76
6	**12**	CH_2OBn	1.0	70	36 (*S*)	95
7	**14**	CH_2CH_2OMe	1.0	40	23 (*S*)	65
8	**15**	(2'*S*)-$CH_2CH(Ph)OH$	1.0	61	37 (*S*)	83
9	**16**	(2'*S*)-$CH_2CH(Ph)OMe$	1.0	48	8 (*S*)	89
10	**6**	Ph	0	84	13 (*S*)	84
11	**6**	Ph	1.0	62	13 (*R*)	96

[a] Amount of $ZnCl_2$•OEt_2 was used versus amount of 2-substituted-3-phenyl-*l*-menthopyrazoles.

Table 5

Enantioselective Borane Reduction of Ketones (**18**) in the Presence of **8** and $ZnCl_2$•OEt_2 at -5 °C

Entry	Ketones (**18**)	R^2	R^3	Product (**19**)	Yield (%)	Ee (Conf.)(%)	Recovery of **8** (%)
1	**18b**	Ph	Me	**19b**	48	36 (*S*)	98
2	**18c**	4-Cl-C_6H_4	Me	**19c**	74	39 (*S*)	78
3	**18a**	4-Me-C_6H_4	Me	**19a**	54	46 (*S*)	79
4	**18d**	2-Me-C_6H_4	Me	**19d**	51	12 (*S*)	92
5	**18e**	4-MeO-C_6H_4	Me	**19e**	61	46 (*S*)	99
6	**18f**	Ph	Et	**19f**	40	40 (*S*)	91
7	**18g**	Ph	CH_2Br	**19g**	77	4 (*S*)	73
8	**18h**	1-Naphth	Me	**19h**	59	3 (*R*)	99
9	**18i**	2-C_6H_4-$(CH_2)_3$		**19i**	66	12 (*R*)	91

Since the chilled reaction conditions generally brought a good stereo regulation, the borane reduction of **18a** was carried out in the presence of **8** under various temperatures, summarized in Table 3. The additive effects of various Lewis acids are also given in the Table 3. Moreover, the effects of *N*-substituted-3-phenyl-*l*-menthopyrazoles are shown in Table 4. These data show that the optimal conditions for the borane reduction of **8** is in the presence of an equimolar amount of zinc chloride at -5 °C. Under these optimal conditions, various ketones were reduced by borane THF complex in the presence of **8** and zinc chloride, and the results are listed in Table 5. In these reductions, the pyrazole derivative catalysts were recovered in high yield and reused.

In conclusion, the enantioselective reduction of ketones was accomplished by borane in the presence of pyrazole derivatives, particularly 2-methoxymethyl-3-phenyl-*l*-menthopyrazole (**8**). The addition of zinc chloride accelerated the borane reduction, and made it possible to obtain enantioselectivity at a low reaction temperature.

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained on JEOL JNM-EX270 (270 MHz) or Varian GEMINI 2000 (200 MHz) spectrometers in deuterochloroform with tetramethylsilane as an internal standard. The enantiomer ratios were evaluated from the peak ratios of gas chromatography on SHIMADZU GC-14A gas chromatograph using Chrompack Chirasil DEX-CB capillary column (0.25 mm x 25 m). The yields of the products were evaluated by GL Science GC-353 gas chromatograph using dimethylsiloxane type capillary column (0.25 mm x 30 m) of GL Science TC-1.

General Procedure for *N*-Alkylation of Pyrazole

To a solution of 3-phenyl-*l*-menthopyrazole (or 3,5-dimethylpyrazole) (2.0 mmol) in THF (2 ml) was added a hexane solution (1.6 *M*) of butyllithium (1.25 ml, 2.0 mmol) at -5 °C. After stirring for 30 minutes, alkyl halide (2.2 mmol) was added to the mixture which was stirred for another 1.5 hours at room temperature. The mixture was quenched with water, and extracted with ether. The ether layer was washed with saturated

sodium hydrogen carbonate and sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel column eluting with hexane-ethyl acetate mixture (v/v 7 : 1).

1-Methyl-3-phenyl-*l*-menthopyrazole (**2**).

Compound **2** was obtained in 21% yield; ^{1}H NMR: δ 0.92 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.8 Hz), 1.02 (3H, d, *J* = 6.8 Hz), 1.37-1.47 (1H, m), 1.73-1.88 (2H, m), 1.97-2.16 (2H, m), 2.54-2.62 (1H, m), 3.19-3.28 (1H, m), 3.81 (3H, s), 7.23-7.42 (3H, m), 7.72 (2H, d, *J* = 6.8 Hz); ^{13}C NMR: δ 19.6 (CH_3), 20.5 (CH_2), 21.4 (CH_3), 21.4 (CH_3), 26.0 (CH_2), 27.9 (CH), 31.1 (CH), 37.1 (CH), 37.6 (CH_3), 119.0 (C), 126.9 (CH), 127.0 (CH), 128.2 (CH), 135.0 (C), 142.1 (C), 147.4 (C).

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.01; H, 8.90; N, 10.33.

2-Methyl-3-phenyl-*l*-menthopyrazole (**3**).

Compound **3** was obtained in 83% yield; ^{1}H NMR: δ 0.74 (3H, d, *J* = 6.60 Hz), 0.88 (3H, d, *J* = 6.6 Hz), 1.08 (3H, d, *J* = 6.9 Hz), 1.18-1.29 (1H, m), 1.45-1.54 (1H, m), 1.82-2.12 (2H, m), 2.41-2.50 (1H, m), 2.63-2.70 (1H, m), 2.77-2.85 (1H, m), 3.68 (3H, s), 7.27-7.46 (5H, m); ^{13}C NMR: δ 17.9 (CH_3), 20.8 (CH_3), 22.7 (CH_2), 27.5 (CH_2), 29.8 (CH), 32.7 (CH), 36.7 (CH), 40.9 (CH_3), 120.2 (C), 128.1 (CH), 128.4 (CH), 129.7 (CH), 132.1 (C), 139.5 (C), 150.7 (C).

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 79.95; H, 9.09; N, 10.36.

1-Benzyl-3-phenyl-*l*-menthopyrazole (**4**).

Compound **4** was obtained in 65% yield; ^{1}H NMR: δ 0.81 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 6.8 Hz), 1.21-1.63 (1H, m), 1.65-1.86 (1H, m), 1.89-2.23 (2H, m), 2.46-2.53 (1H, m), 2.67-2.80 (1H, m), 3.18-3.30 (1H, m), 5.35 (2H, AB-q, *J* = 16.6, 19.2 Hz), 6.86-7.41 (8H, m), 7.75-7.80 (2H, m); ^{13}C NMR: δ 19.3 (CH_3), 19.9 (CH_2), 21.3 (CH_3), 21.5 (CH_3), 26.1 (CH_2), 28.1 (CH), 31.1 (CH), 37.2 (CH), 53.4 (CH_2), 120.2 (C), 126.4 (CH), 127.0 (CH), 127.2 (CH), 128.2 (CH), 128.5 (CH), 135.0 (C), 137.9 (C), 142.3 (C), 148.4 (C).

Anal. Calcd. for $C_{24}H_{28}N_2$: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.60; H, 8.41; N, 7.95.

2-Benzyl-3-phenyl-*l*-menthopyrazole (**5**).

Compound **5** was obtained in 31% yield; ^{1}H NMR: δ 0.75 (3H, d, *J* = 6.6 Hz), 0.87 (3H, d, *J* = 6.8 Hz), 1.06 (3H, d, *J* = 7.0 Hz), 1.21-1.63 (1H, m), 1.65-1.86 (1H, m), 1.89-2.23 (2H, m), 2.46-2.53 (1H, m), 2.67-2.80 (1H, m), 3.18-3.30 (1H, m), 5.16 (2H, broad), 6.86-7.41 (10H, m); ^{13}C NMR: δ 17.8 (CH_3), 20.6 (CH_3), 20.9 (CH_3), 22.7 (CH_2), 27.5 (CH_2), 29.9 (CH), 32.7 (CH), 40.9 (CH), 52.7 (CH_2), 120.9 (C), 126.8 (CH), 127.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 129.8 (CH), 132.0 (C), 138.3 (C), 140.0 (C), 151.3 (C).

Anal. Calcd. for $C_{24}H_{28}N_2$: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.15; H, 8.15; N, 8.19.

1-Methoxymethyl-3-phenyl-*l*-menthopyrazole (**7**).

Compound **7** has bp 225-235 °C/ 5 mmHg; yield 25%; ^{1}H NMR: δ 0.87 (3H, d, *J* = 7.0 Hz), 0.96 (3H, d, *J* = 7.0 Hz), 1.03 (3H, d, *J* = 7.0 Hz), 1.36-1.47 (1H, m), 1.75-1.84 (2H, m), 1.97-2.10 (1H, m), 2.21-2.31 (1H, m), 2.73-2.80 (1H, m), 3.15-3.23 (1H, m), 3.37 (3H, s), 5.40 (2H, AB-q, *J* = 10.8, 22.4 Hz), 7.25-7.43 (3H, m), 7.71-7.76 (2H, m).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.11; H, 8.78; N, 9.27.

2-Methoxymethyl-3-phenyl-*l*-menthopyrazole (**8**).

Compound **8** has bp 225-235 °C/ 5 mmHg; yield 61%; ^{1}H NMR: δ 0.79 (3H, d, *J* = 6.6 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 1.09 (3H, d, *J* = 7.0 Hz), 1.23-1.35 (1H, m), 1.44-1.61 (1H, m), 1.81-2.05 (2H, m), 2.44-2.60 (1H, m), 2.66-2.77 (1H, m), 2.80-2.91 (1H, m), 3.34 (3H, s), 5.21 (2H, AB-q, *J* = 10.6, 27.2 Hz), 7.42 (5H, s).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.27; H, 8.56; N, 9.43.

1-Ethoxymethyl-3-phenyl-*l*-menthopyrazole (**9**).

Compound **9** has Bp 120 °C/ 8 mmHg; yield 22; ^{1}H NMR: δ 0.86 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 6.8 Hz), 1.04 (3H, d, *J* = 6.8 Hz), 1.15 (3H, t, *J* = 6.8 Hz), 1.33-1.46 (1H, m), 1.75-1.91 (2H, m), 1.96-2.10 (1H, m), 2.13-2.39 (1H, m), 2.75-2.83 (1H, m), 3.14 (1H, m), 3.60 (2H, quint, *J* = 7.0 Hz), 5.45 (2H, AB-q, *J* = 11.0, 23.0 Hz), 7.26-7.42 (3H, m), 7.70-7.74 (2H, m); ^{13}C NMR: δ 14.9 (CH_3), 17.8 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 22.6 (CH_2), 27.5 (CH_2), 29.7 (CH), 29.8 (CH), 32.6 (CH), 40.9 (CH_2), 64.0 (CH_2), 121.5 (C), 127.9 (CH), 128.2 (CH), 128.3 (CH), 129.8 (CH), 131.5 (C), 140.2 (C), 151.8 (C).

Anal. Calcd. for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.71; H, 8.81; N, 9.18.

2-Ethoxymethyl-3-phenyl-*l*-menthopyrazole (**10**).

Compound **10** was obtained in 54% yield; ^{1}H NMR: δ 0.77 (3H, d, *J* = 6.6 Hz), 0.87 (3H, d, *J* = 6.8 Hz), 1.07 (3H, d, *J* = 7.0 Hz), 1.13 (3H, t, *J* = 7.2 Hz), 1.21-1.25 (1H, m), 1.27-1.43 (1H, m), 1.49-1.60 (1H, m), 1.80-2.03 (2H, m), 2.42-2.58 (1H, m), 2.64-2.75 (1H, m), 2.79-2.90 (1H, m), 3.54 (2H, quint, *J* = 7.0 Hz), 5.24 (2H, quint, *J* = 10.6, 30.4 Hz), 7.36-7.44 (5H, m).

Anal. Calcd. for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.75; H, 9.29; N, 8.96.

1-Benzyloxymethyl-3-phenyl-*l*-menthopyrazole (**11**).

Compound **11** was obtained in 20% yield; ^{1}H NMR: δ 0.85 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 8.0 Hz), 1.00 (3H, d, *J* = 7.0 Hz), 1.27-1.45 (1H, m), 1.77-1.88 (2H, m), 1.99-2.13 (1H, m), 2.22-2.35 (1H, m), 2.71-2.79 (1H, m), 3.11-3.23 (1H, m), 4.61 (2H, AB-q, *J* = 12.0, 17.4 Hz), 5.53 (2H, AB-q, *J* = 11.0, 24.2 Hz), 7.23-7.44 (8H, *m)*, 7.73 7 7 (2H, m).

Anal. Calcd. for $C_{25}H_{30}N_2O$: C, 80.17*;* H, 8.07**;** N, 7.**4**8. Found: C, 80.00; H, 8.08; N, 7.44.

2-Benzyloxymethyl-3-phenyl-l-menthopyrazole (**12**).

Compound **12** was obtained in 51% yield; 1H NMR: δ 0.78 (3H, d, *J* = 6.6 Hz), 0.91 (3H, d, *J* = 6.6 Hz), 1.10 (3H, d, *J* = 7.0 Hz), 1.22-1.34 (1H, m), 1.44-1.63 (1H, m), 1.81-2.02 (1H, m), 2.44-2.59 (1H, m), 2.65-2.75 (1H, m), 2.80-2.90 (1H, m), 4.57 (2H, AB-q, *J* = 12.2, 16.6 Hz), 5.32 (2H, AB-q, *J* = 10.8, 30.2 Hz), 7.20-7.41 (10H, m); ^{13}C NMR: δ 18.0 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 22.8 (CH_2), 27.6 (CH_2), 29.9 (CH), 32.7 (CH), 41.0 (CH_2), 70.3 (CH_2), 121.8 (C), 127.6 (CH), 127.9 (CH), 128.3 (CH), 128.3 (CH), 129.8 (CH), 131.4 (C), 137.7 (C), 140.3 (C), 152.0 (C).

Anal. Calcd. for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 80.08; H, 8.07; N, 7.47.

1-Methoxymethyl-3,5-dimethylpyrazole (**17**).

Compound **17** has bp 75-85 °C/ 5 mmHg; yield 87%; ^{1}H NMR: δ 2.22 (3H, s), 2.29 (3H, d, *J* = 0.6 Hz), 2.29 (3H, d, *J* = 0.6 Hz), 3.31 (3H, s), 5.28 (2H, s), 5.87 (1H, s); MS (m/e,% Int.); 140 (11.3), 110 (71.0), 109 (100), 95 (10), 82 (12.9), 68 (30.6).

Anal. Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.78; H, 8.58; N, 19.85.

2,3-Diphenyl-*l*-menthopyrazole (**6**).

A toluene (5 ml) solution of phenylhydrazine (254 mg, 2.4 mmol), *p*-toluenesulfonic acid (76 mg, 0.4 mmol) and benzoylmenthone (536 mg, 2.1 mmol), which was prepared from benzoyl chloride and *l*-menthone according to the previously reported method [3], was refluxed for 18 hours. The reaction mixture was washed with saturated sodium hydrogen carbonate and sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The reaction residue was purified by recrystallization from benzene-hexane; mp 111-112 °C; yield 43%; ^{1}H NMR: δ 0.80 (3H, d, *J* = 6.6 Hz), 0.89 (3H, d, J = 6.9 Hz), 1.09 (3 Hz, d, J = 6.9 Hz), 1.24-1.37 (1H, m), 1.52-1.65 (1H, m), 1.85-2.06 (2H, m), 2.46-2.53 (1H, m), 2.55-2.77 (1H, m), 2.90-2.97 (1H, m), 7.15-7.31 (5H, m); ^{13}C NMR: δ 18.1 (CH_3), 20.8 (CH_3), 22.6 (CH_2), 27.5 (CH_2), 30.0 (CH), 32.5 (CH), 40.6 (CH), 122.0 (C), 125.0 (CH), 126.3 (CH), 127.8 (CH), 128.2 (CH), 128.5 (CH), 130.0 (CH), 132.2 (C), 138.9 (C), 140.6 (C), 152.7 (C).

Anal. Calcd. for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48. Found: C, 83.31; H, 7.98; N, 8.46.

General Procedure for Alkylation of **13** and **15**.

To a dispersion (60%) of sodium hydride (54 mg, 1.4 mmol) in mineral oil was added a tetrahydrofuran (THF) solution (1 ml) of **13** (or **15**) (0.6 mmol) and stirred for 30 minutes. Methyl iodide (0.06 ml, 1.0 mmol) was added to the mixture, which was stirred for another 1 hour at room temperature. The mixture was quenched with water, and extracted with ether. The ether layer was washed with saturated sodium hydrogen carbonate and sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography eluting with hexane-ethyl acetate mixture.

2-(2'-Methoxyethyl)-3-phenyl-*l*-menthopyrazole (**14**).

Compound **14** was obtained in 51% yield; ^{1}H NMR: δ 0.73 (3H, d, *J* = 6.6 Hz), 0.87 (3H, d, *J* = 6.6 Hz), 1.07 (3H, d, *J* = 6.9 Hz), 1.17-1.30 (1H, m), 1.42-1.57 (1H, m), 1.80-1.86 (1H, m), 1.89-1.97 (1H, m), 2.39-2.51 (1H, m), 2.64-2.69 (1H, m), 2.73-2.83 (1H, m), 3.18 (3H, s), 3.59-3.73 (2H, m), 4.06-4.11 (2H, m), 7.34-7.44 (5H, m); ^{13}C NMR: δ 18.2 (CH_3), 20.9 (CH_3), 21.2 (CH_3), 23.0 (CH_2), 27.7 (CH_2), 30.2 (CH), 32.9 (CH), 41.1 (CH), 48.5 (CH_3), 59.0 (CH_2), 71.8 (CH_2), 120.4 (C), 128.4 (CH), 128.6 (CH), 130.2 (CH), 132.3 (C), 140.4 (C), 151.5 (C).

Anal. Calcd. for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.03; H, 9.10; N, 8.90.

(2'*S*)-2-(2'-Phenyl-2'-methoxyethyl)-3-phenyl-*l*-menthopyrazole (**16**).

Compound **16** was obtained in 66% yield; ^{1}H NMR: δ 0.72 (3H, d, *J* = 6.6 Hz), 0.85 (3H, d, *J* = 6.8 Hz), 1.06 (3H, d, *J* = 6.8 Hz), 1.16-1.39 (1H, m), 1.42-1.61 (1H, m), 1.80-1.96 (2H, m), 2.40-2.49 (1H, m), 2.66-2.81 (2H, m), 3.09 (3H, s), 3.98 (1H, ABX, *J* = 13.6, 5.2 Hz), 4.15 (1H, ABX, *J* = 8.2,13.6 Hz), 4.67 (1H, ABX, *J* = 8.0, 5.4 Hz), 7.07-7.37 (10H, m); ^{13}C NMR; δ 17.9 (CH_3), 20.6 (CH_3), 21.1 (CH_3), 22.5 (CH_2), 27.3 (CH_2), 30.2 (CH), 32.4 (CH), 40.6 (CH), 54.8 (CH_3), 57.2 (CH_2), 82.4 (CH), 120.2 (C), 126.7 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 130.1 (CH), 132.0 (C), 139.5 (C), 140.7 (C), 151.1 (C).

Anal. Calcd for $C_{26}H_{32}N_2O$: C, 80.37; H, 8.3; N, 7.21. Found: C, 79.99; H, 8.48; N, 7.06.

Borane Reduction of Ketone (**18**) using *N*-Substituted-3-Phenyl-*l*-menthopyrazoles.

Under argon atmosphere, Lewis acid (0.3 mmol) was stirred with *N*-substituted 3-phenyl-*l*-menthopyrazoles (0.3 mmol) in ether (3 ml) for 30 minutes at -5 °C. After the addition of borane THF solution (1.0 *M*, 0.3 ml, 0.3 mmol) with 30 minutes stirring, ketone (**18**, 0.3 mmol) was added at -5 °C and the mixture was stirred for 24 hours at -5 °C. The mixture was quenched with water and extracted with ether. The organic layer was washed with dilute hydrochloric acid, water, saturated sodium hydrogen carbonate, and saturated sodium chloride, and dried over anhydrous magnesium sulfate. After removal of the solvent, the yields of the products were evaluated by gas chromatography. By silica gel column chromatography of the residue, the fraction of the corresponding alcohol (**19**) was collected and the enantiomer ratio were measured by the gas chromatography using a chiral column. The absolute configuration of the product was deduced by comparison of the optical rotation with authentic data [19].

Borane Reduction Rates of *p*-Methylacetophenone (**18a**) in the Presence of Zinc Chloride and **17**.

Under argon atmosphere, zinc chloride etherate (1.0 *M*, 0.3 ml, 0.3 mmol) was added to a ether solution (3 ml) of 1-methoxymethyl-3,5-dimethylpyrazole (**17**, 42 mg, 0.30 mmol) with 30 minutes stirring at -5 °C, and then borane THF solution (1.0 *M*, 0.3 ml, 0.3 mmol) was added and stirred at -5 °C. After 30 minutes, *p*-methylacetophenone (**18a**, 0.04 ml, 0.31 mmol) was added to the mixture. Small portions of the solution were sucked each hour, quenched with hydrochloric acid, and diluted with dichloromethane. The contents of **18a** mixture was monitored by HPLC and the evaluated reaction rates are summarized in Table 2.

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REFERENCES AND NOTES

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[1] C. Kashima, I. Fukuchi, K. Takahashi, and A. Hosomi, *Tetrahedron Lett.*, **34**, 8305 (1993).

[2] For recent reviews, see: [a] 'Asymmetric Synthesis', Vol. **1-5**, ed. by D. J. Morrison, Academic Press Inc., New York, 1983-1985; [b] B. H. Kim and D. P. Curran, *Tetrahedron*, **49**, 294 (1993); [c] L. Deloux and M. Srebnik, *Chem. Rev.*, **93**, 763 (1993); [d] T. G. Gant and A. I. Meyers, *Tetrahedron*, **50**, 2297 (1994).

[3] C. Kashima, I. Fukuchi, and A. Hosomi, *J. Org. Chem.*, **59**, 7821 (1994).

[4] C. Kashima, K. Takahashi, and A. Hosomi, *Heterocycles*, **42**, 241 (1996).

[5] C. Kashima, I. Fukuchi, K. Takahashi, and A. Hosomi, *Tetrahedron*, **52**, 10335 (1996).

[6] C. Kashima, I. Fukuchi, K. Takahashi, K. Fukusaka, and A. Hosomi, *Heterocycles*, **47**, 357 (1998).

[7] C. Kashima, K. Fukusaka, and K. Takahashi, *J. Heterocyclic Chem*., **34**, 1559 (1997).

[8] C. Kashima, K. Takahashi, K. Fukusaka, and A. Hosomi, *J. Heterocyclic Chem*., **35**, 503 (1998).

[9] C. Kashima, K. Fukusaka, K. Takahashi, and Y. Yokoyama, *J. Org. Chem.*, **64**, 1108 (1999).

[10] C. Kashima, K. Takahashi, I. Fukuchi, and K. Fukusaka, *Heterocycles*, **44**, 289 (1997).

[11a] H. A. Staab, *Angew. Chem*., **74**, 407 (1962); [b] T. Kamijo, H. Harada, and K. Iizuka, *Chem. Pharm. Bull*., **32**, 5044 (1984); [c] T. Kitagawa, M. Kawaguchi, S. Inoue, and S. Katayama, *Chem. Pharm. Bull*., **39**, 3030 (1991).

[12] C. Kashima, H. Harada, I. Kita, I. Fukuchi, and A. Hosomi, *Synthesis*, 61 (1994).

[13] C. Kashima, I. Fukuchi, K. Takahashi, and A. Hosomi, *Heterocycles*, **38**, 1407 (1994).

[14] C. Kashima, I. Kita, K. Takahashi, and A. Hosomi, *J. Heterocyclic Chem.*, **32**, 25 (1995).

[15] C. Kashima, I. Kita, K. Takahashi, and A. Hosomi, *J. Heterocyclic Chem.*, **32**, 723 (1995).

[16] E. J. Corey and C. J. Helal, *Angew. Chem. Int. Ed.*, **37**, 1986 (1998).

[17] C. Kashima, Y. Tsukamoto, and K. Higashide, *J. Heterocyclic Chem.*, in press.

[18] W. M. Jones, *J. Am. Chem. Soc*., **82**, 2528 (1960).

[19] K. Naemura, M. Murata, R. Tanaka, M. Yano, K. Hirose, and Y. Tobe, *Tetrahedron Asym.*, **7**, 3285 (1996).