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Resolution of secondary alcohols using 2-acyl-3-phenyl-*l*-menthopyrazoles as enantioselective acylating agents

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Abstract—The chelation of $AlCl_3$ with *N*-acylpyrazoles leads to structural fixation of the acyl moiety and an acceleration in the rate of acylation of secondary alcohols. The chiral environment of the fixed acyl moiety of 2-acyl-3-phenyl-*l*-menthopyrazole **2** causes diastereofacial selectivity in the reaction with secondary alcohols, and thus **2** behaves as an enantioselective acylating agent. By the use of 2.4 molar equivalents of racemic 1-phenylethanol **3a**, 2-acetyl-3-phenyl-*l*-menthopyrazole **2a** afforded (*S*)-1-phenylethyl acetate (*S*)-**4aa** enantioselectively and unreacted **3a** was recovered with (*R*)-configuration. Furthermore, the inverse configurational preferences were observed to give (*R*)-**4aa** and (*S*)-**3a** by the addition of strongly basic amines, which sometimes behaved as catalysts for enolate formation from **2** and $AlCl_3$. These dramatic changes in stereoselective preference should be useful properties of 2-acyl-3-phenyl-*l*-menthopyrazole **2** as an enantioselective acylating agent.

1. Introduction

The resolution of secondary alcohols has been investigated for a long time by enantioselective acylation using enzymes such as esterases, and this method has extended to the practical preparation of optically active alcohols and esters.[1] However, enzymatic reactions often have insufficient generality, and limitations in the substrates and the enantiopreference of the reaction often occur due to the high specificity of the enzyme. For example, secondary alcohols were preferentially acylated by a lipase to afford (*R*)-esters and the unreacted (*S*)-alcohols, but enantioselective acylation with the opposite enantiopreference is very difficult under enzymatic reaction conditions. In the mean time, some non-enzymatic resolutions by enantioselective acylation of secondary alcohols have appeared in the literature using artificial auxiliaries.[2] Also, alcohols and amines were enantioselectively acylated by acyl chlorides in the presence of a chiral catalyst.[3]

We have recently developed a method for the preparation for 3-phenyl-*l*-menthopyrazole **1** as a new chiral auxiliary,[4] which has a unique structure and properties, relative to other auxiliaries.[5] The most important characteristics of this auxiliary are that the substrate is bonded to a nitrogen atom of the heteroaromatic pyrazole ring in a chiral environment. The steric hindrance of **1** is especially relaxed by twisting of the benzene ring, which overlaps on one side of the terminal nitrogen atom.[4] These structural features cause a diastereofacial effect in the reactions of the substrate moiety. Moreover, the lone pair of electrons on the adjacent nitrogen acts as 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, fixing it in a *syn*-configuration. As a result, the chirality of the (4*R*)-methyl group of **1** causes a high level of asymmetric induction at the α-position of the acyl group of 2-acyl-3-phenyl-*l*-menthopyrazoles in their reactions with alkyl halides,[6] diphenyldisulfide,[7] acyl chloride,[8] aldehydes,[9] and C=N compounds.[10] A similar chelation of N···Mg···O=C, which is observed with *N*-acylpyrazoles and $MgBr_2{\cdot}OEt_2$,[11] induces the asymmetric Michael addition of Grignard reagents,[12] Diels–Alder cycloadditions,[13] and 1,3-dipolar cycloadditions[14] with *N*-(α,β-unsaturated acyl)pyrazoles.

N-Acylimidazoles are utilized as the activated acyl moiety in a wide variety of organic syntheses.[15] As analogues of these *N*-acylheteroaromatics, *N*-acylpyrazoles act as acyl donors on reaction with nucleophiles such as alcohols,[16] amines,[17] Grignard reagents,[18] and organo-

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zinc compounds[19] under basic or acidic conditions. As a further extension of the utility of **1** as a new chiral auxiliary, we report herein the reaction of 2-acyl-3-phenyl-*l*-menthopyrazoles **2** with racemic secondary alcohols, where diastereoselective attack of the secondary alcohol on the activated acyl carbonyl group was expected. Subsequently the resolution of racemic secondary alcohols should be possible by enantioselective acylation using **2**.

2. Results and discussion

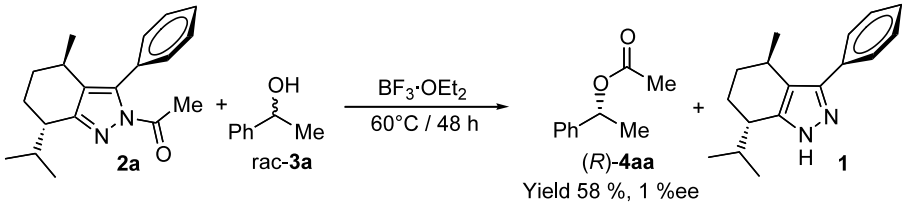
The phenyl group at the 3-position causes the chiral environment on the acyl moiety of 2-acyl-3-phenyl-*l*-menthopyrazoles **2**, and leads to diastereofacial attack of reagents on the α-position of the acyl moiety. These diastereofacial attacks might be allowed on the carbonyl carbon, which is much closer to the stereogenic center of **2**. Thus, we first attempted the reaction of 2-acetyl-3-phenyl-*l*-menthopyrazole **2a** with racemic 1-phenylethanol **3a** in the presence of $BF_3{\cdot}OEt_2$. When the reaction was carried out at 60°C for 48 h, 1-phenylethyl acetate **4aa** was obtained in 58% yield with 1% ee, as shown in Scheme 1. The low enantioselectivity of this reaction was thought to result from the drastic acylation conditions. Although $BF_3{\cdot}OEt_2$ acted as a Lewis acid on the pyrazole nitrogen atom to activate the carbonyl group toward nucleophiles, the chelating bond between B–O could not be formed and the rotation of the bond between the acyl group and the pyrazole ring could not be frozen. These properties of $BF_3{\cdot}OEt_2$ also caused the low selectivity of this reaction.

From the previous observations,[10,12] rotation about the bond between the acyl group and the pyrazole ring is known to be frozen by the chelation of acylpyrazoles with Lewis acids having high coordination number (Scheme 2) By using **3a** with 1-acetyl-3,5-dimethylpyrazole **5a**, which is the most convenient *N*-acylpyrazole, we optimized the acylation reaction in the presence of various kinds of Lewis acids having higher coordination number. In order to reveal the reaction profiles, the consumption of **5a** was traced by HPLC monitoring in the presence of various Lewis acids. The data in Table 1 showed that the reaction was accelerated more than 30 times by $TiCl_4$, $FeCl_3$ and $AlCl_3$, which usually behave as higher coordination number elements. These Lewis acids should enable acylation of secondary alcohols under mild conditions, and to freeze the C–N bond rotation between the acyl group and the pyrazole ring.

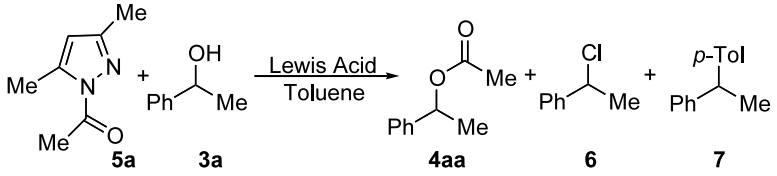
Further, the amount of $AlCl_3$ was optimized in the reaction of **5a** with **3a**, as summarized in Table 2. The acylated product was obtained in moderate yields even in the presence of less than 50 mol% of $AlCl_3$ (run 2), while reaction did not occur at all in the absence of $AlCl_3$ (run 1). Excess $AlCl_3$ inhibited the acylation and caused a Friedel–Crafts type side reaction, to form **6** and **7** (run 7). When the mixture of **3a** and $AlCl_3$ was treated with **5a**, no acylated product was obtained and **5a** was recovered (run 10). In the case of 1-benzoyl-3,5-dimethylpyrazole **5d**, the acylation also proceeded to give the corresponding benzoate ester **4da** in good yield. This shows that the intermediate from **5** and $AlCl_3$ was not the aluminum enolate but the chelated complex. By the treatment of an equimolar mixture of **5a** and $AlCl_3$ with 20 molar equiv. of **3a** at −5°C, half of **5a** was consumed in 15 min. In the case of 2.4 molar equiv. of **3a**, the half-life of **5a** was about 2 h, which suggests that the rate-determining step of this reaction was the attack of the alcohol on the acylpyrazole–$AlCl_3$ chelated species.

Table 1. The effect of Lewis acid on the reaction of **5a** with **3a**

Lewis acid	Half life of **5a** (min)
p-TsOH	384
$BF_3{\cdot}OEt_2$	191
$ZnCl_2$	188
$CuBr_2$	88
$TiCl_4$	13
$FeCl_3$	7
$AlCl_3$	6



Scheme 1.



Scheme 2.

Table 2. Catalytic effect of $AlCl_3$ in the reaction of **5a** with **3a**

Run	**3a** (equiv.)	$AlCl_3$ (equiv.)	Yield (%)[c]				
			5a	**4aa**	**3a**	**6**	**7**
1	2.4	0	100	0	60	0	0
2	2.4	1.0	0	87	35	0	0
3	2.4	1.9	0	79	38	0	0
4	2.4	2.7	0	68	32	3	7
5	2.4	3.7	100	4	0	19	39
6	2.4	4.7	72	0	0	12	72
7	2.4	6.9	41	0	0	0	84
8	0	2.5	–	–	0	0	84
9[a]	2.4	2.5	0	84	23	0	5
10[b]	2.4	2.3	58	0	0	0	76

[a] Compound **3a** (1.2 equiv.) was treated with **5a** and $AlCl_3$ for 30 min, and then further **3a** (1.2 equiv.) was added to the mixture.
[b] **5a** was added to the mixture of **3a** and $AlCl_3$ and stirred.
[c] The yields of **5a** and **4aa** were determined by GC based on **5a** and those of **3a**, **6** and **7** were determined based on **3a**.

From these basic experiments, a catalytic amount of Lewis acid such as $AlCl_3$ was revealed to promote the acylation of secondary alcohols with *N*-acylpyrazoles even under mild conditions. Moreover, the results indicated that reaction of secondary alcohols with the chelated complex derived from **2** and $AlCl_3$ is the rate determining step and diastereofacial attack occurs due to the chiral environment around the carbonyl carbon.

When **2a** was treated with 20 molar equiv. of **3a** in the presence of equimolar $AlCl_3$ at room temperature for 3 h, (*S*)-**4aa** was obtained in 87% yield with 48% ee. The reaction was completed practically at −5°C for 17 h, but the reaction was too slow at −20°C, affording **4aa** in only 50% yield after 17 h. After optimization of the reaction in various solvents with a number of Lewis acids, as summarized in Table 3, (*S*)-**4aa** was predominantly obtained in 94% yield with 71% ee in a toluene–hexane mixture at −5°C. The selectivity factor(s) under various conditions are also listed in Table 3. Here, the enantioselective acylation of **3a** was accomplished by the use of **2a** in the presence of $AlCl_3$ (Scheme 3).

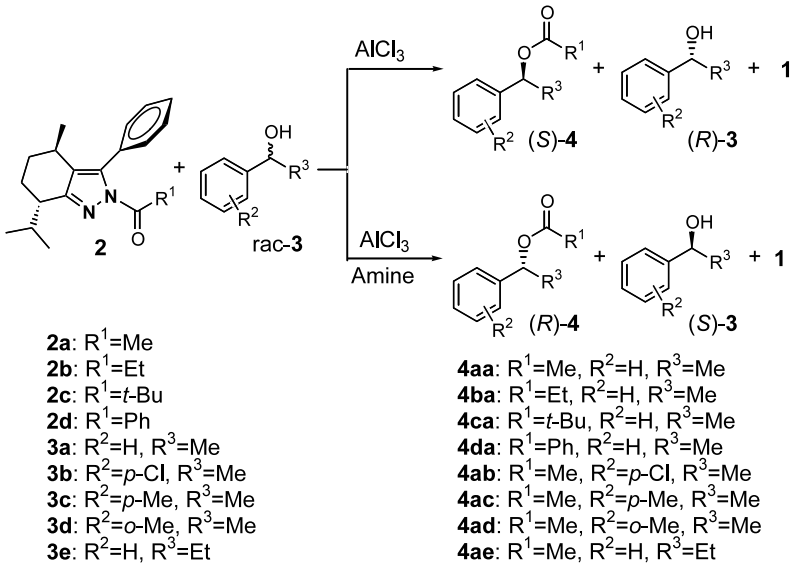
By the use of 2.4 molar equiv. of racemic **3a** under optimal conditions, (*S*)-**4aa** was obtained in 99% yield with 66% ee. In this reaction, unreacted (*R*)-**3a** was recovered in 93% yield with 46% ee as well as the chiral auxiliary **1** in 64% yield. Similarly some secondary alcohols were enantioselectively acetylated by the use of **2a** in good yields, as summarized in Table 4. Also (*S*)-1-phenylethyl propanoate **4ba** was obtained by the use of 2-propanoyl-3-phenyl-*l*-menthopyrazole **2b**. However, bulky acyl substituted 3-phenyl-*l*-menthopyrazoles **2c** and **2d** did not give the corresponding esters and were hydrolyzed to **1** during workup. These results show that the structure of the acyl moiety of **2** strongly affects the approach of the alcohol molecule.

We have previously reported that magnesium enolates of *N*-acylpyrazoles were formed by treatment with $MgBr_2$ in the presence of diisopropylethylamine.[11] Otherwise, *N*-acylpyrazoles reacted readily with primary and secondary amines to afford the corresponding amides.[17] Since the nucleophilic attack of amines is mainly seen with sterically unhindered amines such as

Table 3. Enantioselective acetylation of **3a** with **2a**

Run	Solvent	Lewis acid	Time (h)	Temp. (°C)	Product (**4aa**)			
					Yield (%)[a]	Ee (%)[b]	Conf.	*s*[c]
1	CH_2Cl_2	$AlCl_3$	3	20	87	48	(*S*)	2.8
2	CH_2Cl_2	$AlCl_3$	17	−5	91	51	(*S*)	3.1
3	CH_2Cl_2	$AlCl_3$	17	−20	50	31	(*S*)	1.9
4	CH_2Cl_2	$FeCl_3$	17	−5	21	19	(*S*)	1.5
5	CH_2Cl_2	$TiCl_4$	17	−5	63	32	(*S*)	1.9
6	CH_2Cl_2	$CuBr_2$	17	−5	13	41	(*S*)	2.4
7	THF	$AlCl_3$	17	−5	3	10	(*R*)	1.2
8	Et_2O	$AlCl_3$	17	−5	57	52	(*S*)	3.2
9	Toluene	$AlCl_3$	17	−5	87	67	(*S*)	5.1
10	Toluene–hexane (3:1)	$AlCl_3$	17	−5	94	71	(*S*)	5.9
11	Toluene–hexane (1:1)	$AlCl_3$	17	−5	90	65	(*S*)	4.7
12	Toluene–hexane (1:3)	$AlCl_3$	17	−5	64	51	(*S*)	3.1
13	Hexane	$AlCl_3$	17	−5	67	37	(*S*)	2.2

[a] Yields were determined by GC.
[b] Enantiomeric ratios were determined by chiral GC (Chirasil-DEX CB).
[c] Selectivity factor.



Scheme 3.

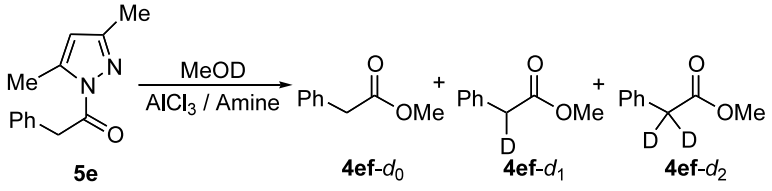
methylamine and pyrrolidine, the formation of the aluminum enolate (rather than the formation of amides) from *N*-acylpyrazoles and $AlCl_3$ could be effected by the use of bulky amines. Thus, the structural change caused by the formation of the aluminum enolate of **2** perhaps leads to different steric effects toward the attack of the alcohol. When 1-phenylacetyl-3,5-dimethylpyrazole **5e** was treated with MeOD in the presence of $AlCl_3$, product ratio of undeuterated **4ef**-d_0, mono- **4ef**-d_1 and dideuterated methyl phenylacetates **4ef**-d_2 was shown to be 25:49:26. A similar ratio of 26:45:29 was observed in the reaction of **5e** with MeOD in the presence of $AlCl_3$ and pyridine. On the contrary, **4ef**-d_1 and **4ef**-d_2 were exclusively formed in the ratio of 65:35 in the presence of diisopropylethylamine. These results using MeOD showed that the reaction proceeded through the enolate in the presence of strongly basic bulky amines (Scheme 4).

The reaction of **2a** with **3a** was performed by the addition of various amines in the presence of $AlCl_3$, as summarized in Table 5. When strongly basic amines were added, the configuration of **4aa** was dramatically changed (runs 4–6). On the other hand, the reaction profile using pyridine (run 9) was similar to that seen in the reaction of **2a** with **3a** in the absence of amine (run

Table 4. Resolution of **3** by enantioselective acylation with **2** in toluene–hexane (3:1)

Run	**2**		*rac*-**3**			Product (*S*)-**4**			Unreacted (*R*)-**3**		**1**
		R^1		R^2	R^3		Yield (%)[a]	Ee (%)[b]	Yield (%)[c]	Ee (%)[b]	Yield (%)[a]
1	**2a**	Me	**3a**	H	Me	**4aa**	99	66	64	46	93
2	**2b**	Et	**3a**	H	Me	**4ba**	54	66	40	57	88
3	**2c**	*t*-Bu	**3a**	H	Me	**4ca**	3	1	58	1	51
4	**2d**	Ph	**3a**	H	Me	**4da**	Trace[d]	–	22[d]	–	95
5	**2a**	Me	**3b**	*p*-Cl	Me	**4ab**	85	60	81	30	86
6	**2a**	Me	**3c**	*p*-Me	Me	**4ac**	79	53	24	13	83
7	**2a**	Me	**3d**	*o*-Me	Me	**4ad**	29	69	58	16	37
8	**2a**	Me	**3e**	H	Et	**4ae**	89	66	65	42	90

[a] Yields were determined by GC.
[b] Enantiomeric ratios were determined by chiral GC (Chirasil-DEX CB).
[c] Yields were determined by HPLC.
[d] Yields were determined by NMR.



Scheme 4.

Table 5. Resolution of **3a** with **2a** in the presence of $AlCl_3$ and amines in toluene

Run	Amine	equiv.[a]	Temp. (°C)	Product **4aa**			Unreacted **3a**			**1**
				Yield[b]	Ee[c]	Conf.	Yield[b]	Ee[c]	Conf.	Yield[d]
1	None[e]	0	−5	99	66	(*S*)	64	46	(*R*)	93
2	*i*-Pr_2NEt[e]	1.0	40	8	12	(*R*)	26	5	(*S*)	16
3	None	0	40	77	13	(*S*)	31	7	(*R*)	84
4	*i*-Pr_2NH	1.0	40	99	15	(*R*)	56	7	(*S*)	87
5	$BnNH_2$	1.0	40	100	18	(*R*)	72	8	(*S*)	91
6	*i*-Pr_2NEt	1.0	40	26	38	(*R*)	31	11	(*S*)	32
7	Pyrrolidine	1.0	40	33	6	(*S*)	65	4	(*R*)	91
8	*t*-$BuNH_2$	1.0	40	58	6	(*R*)	57	3	(*S*)	93
9	Pyridine	1.0	40	100	4	(*S*)	75	2	(*R*)	86
10	DMAP	1.0	40	5	0		69	0		9
11	DBU	1.0	40	5	0		73	0		8
12	None	0	−5	90	49	(*S*)	58	30	(*R*)	94
13	*i*-Pr_2NH	0.5	−5	98	5	(*R*)	70	9	(*S*)	89
14	*i*-Pr_2NH	1.0	−5	89	64	(*R*)	60	41	(*S*)	83
15	*i*-Pr_2NH	1.2	−5	69	61	(*R*)	76	23	(*S*)	67
16	*i*-Pr_2NH	1.5	−5	100	64	(*R*)	77	38	(*S*)	82
17	*i*-Pr_2NH	2.0	−5	82	61	(*R*)	58	24	(*S*)	58
18	$BnNH_2$	1.0	−5	69	2	(*R*)	79	0		64
19	*i*-$PrNH_2$	1.0	−5	68	65	(*R*)	85	26	(*S*)	70

[a] Amount of amine against **2a** and $AlCl_3$.
[b] Yields (%) were determined by GC.
[c] Enantiomeric excesses (%) were determined by chiral GC (Chirasil-DEX CB).
[d] Yields (%) were determined by HPLC.
[e] The solvent was a toluene–hexane mixture (3:1).

3), where no evidence of an enolate intermediate was observed in the reaction of **5e** with MeOD. Because of the quantitative formation of **4aa**, the reaction of **2a** with **3a** was optimized in the cases of benzylamine and diisopropylamine. When **2a** was treated with **3a** in the presence of equimolar amounts of $AlCl_3$ and diisopropylamine in toluene at −5°C, (*R*)-**4aa** was optimally obtained in 89% yield with 64% ee, and unreacted (*S*)-**3a** was recovered in 60% yield with 41% ee.

Finally the effect of diisopropylamine as an additive was demonstrated by changing the amount added to the reaction, as summarized in Table 5 (runs 13–17), compared to the reaction without additive (run 12). Increasing the amount of additive depressed the enantioselectivity of the product, and the enantiopreference was changed to the inverse configuration to give (*R*)-**4aa** on addition of an equimolar amount of diisopropylamine.

In summary, the chelation of $AlCl_3$ with an *N*-acylpyrazole brings about the structural fixation of the acyl moiety and an acceleration in the rate of acylation of secondary alcohols with *N*-acylpyrazoles. The chiral environment of the fixed acyl moiety of 2-acyl-3-phenyl-*l*-menthopyrazole **2** leads to diastereofacial selectivity in the attack of secondary alcohols, and thus **2** behaves as an enantioselective acylating agent. By the use of 2.4 molar equiv. of racemic **3a**, 2-acetyl-3-phenyl-*l*-menthopyrazole **2a** afforded (*S*)-**4aa** enantioselectively, and unreacted **3a** was recovered with (*R*)-configuration. Furthermore, the inverse configurational preferences were observed to give (*R*)-**4aa** and (*S*)-**3a** by the addition of strongly basic amines, which sometimes performed as catalysts for enolate formation from **2** and $AlCl_3$. These dramatic changes in enantiopreference show 2-acyl-3-phenyl-*l*-menthopyrazole **2** to be a very useful enantioselective acylating agent.

3. Experimental

^1H NMR data were collected on a JEOL NMR JNM-EX270 (270 MHz) spectrometer or a Varian NMR Gemini-200 (200 MHz) spectrometer in deuteriochloroform with tetramethylsilane used as an internal standard. The yields of **3** and **4** were evaluated from their chromatogram of GL-Science GC353 Gas Chromatograph through capillary column (0.25 mm ϕ×25 m) coated with Silicon oil (TC-1) using naphthalene as an internal standard. The enantiomer ratios of **3** and **4** were obtained from the peak intensities of gas-chromatogram using Shimadzu GC14A gas chromatograph through CHROMPACK capillary (0.25 mm ϕ×25 m) column coated with Chirasil DEX-CB. For the determination of the contents of **1** and **2**, HPLC analysis was carried out by SIL-C18 column on a JASCO BIP-I chromatograph using an aqueous methanol solvent. Optical rotations were observed using a JASCO DIP-370 digital polarimeter at 21°C. The melting points are uncorrected.

3.1. Materials

Toluene and diisopropylamine were distilled over calcium hydride under an argon atmosphere. Hexane and CH_2Cl_2 were dried over calcium chloride under an argon atmosphere. $AlCl_3$ and another Lewis acids were commercially available from Wako Pure Chemical Industries, Ltd. 1-Phenylpropanol, 1-(*o*-methylphenyl)-, 1-(*p*-methylphenyl)- and 1-(*p*-chlorophenyl)ethanol were prepared by the $NaBH_4$ reduction of the corresponding ketones. (*S*)-1-Phenylethanol ((*S*)-**3a**) was commercially available from Tokyo Chemical Industry Co. Ltd., and was derived into the corresponding ester ((*S*)-**4aa**) by the treatment with acetyl chloride in the presence of Et_3N. By the gas chromatographic comparison with these authentic samples, the absolute configuration of the products was determined. According to the method described previously,[6] 2-acyl-3-phenyl-*l*-menthopyrazoles (**2**) and 1-acyl-3,5-dimethylpyrazole (**5**) were prepared from the corresponding acyl chloride and pyrazoles in the presence of Et_3N, and purified by column chromatography on silica gel using benzene/hexane mixture.

3.1.1. 2-Acetyl-3-phenyl-*l*-menthopyrazole, 2a. Yield: 62%; $[\alpha]_D$ −268.5 (*c* 0.46, $CHCl_3$); ^{1}H NMR: δ 0.69 (3H, d, $J=7$ Hz), 0.94 (3H, d, $J=7$ Hz), 1.09 (3H, d, $J=7$ Hz), 1.18–1.31 (1H, m), 1.46–1.55 (1H, m), 1.83–2.00 (2H, m), 2.36–2.44 (1H, m), 2.59–2.79 (2H, m), 2.63 (3H, s), 7.27–7.41 (5H, m); ^{13}C NMR: δ 18.6 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 23.0 (CH_2), 23.6 (CH_2), 27.3 (CH), 30.0 (CH), 32.1 (CH), 41.3 (CH_3), 126.2 (C), 127.9 (CH), 128.1 (CH), 129.3 (CH), 132.6 (C), 140.8 (C), 155.9 (C), 170.5 (C). Anal. calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45; found: C, 76.75; H, 8.07; N, 9.42%.

3.1.2. 2-Propanoyl-3-phenyl-*l*-menthopyrazole, 2b. Yield 83%; $[\alpha]_D$ −243.3 (*c* 0.48, $CHCl_3$); ^{1}H NMR: δ 0.69 (3H, d, $J=7$ Hz), 0.94 (3H, d, $J=7$ Hz), 1.08 (3H, d, $J=7$ Hz), 1.16 (3H, t, $J=7$ Hz), 1.20–1.31 (1H, m), 1.36–1.65 (1H, m), 1.76–2.06 (2H, m), 2.20–2.48 (1H, m), 2.54–2.68 (1H, m), 2.70–2.83 (1H, m), 3.04–3.24 (2H, m), 7.25–7.46 (5H, m); ^{13}C NMR: δ 8.52 (CH_3), 18.61 (CH_3), 20.27 (CH_3), 20.44 (CH_3), 23.07 (CH_2), 27.40 (CH_2), 28.92 (CH), 30.05 (CH), 32.23 (CH), 41.40 (CH_2), 126.06 (C), 128.25 (CH), 128.48 (CH), 129.40 (CH), 132.93 (C), 155.92 (C), 174.12 (C). Anal. calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02; found: C, 77.43; H, 8.40; N, 9.10%.

3.1.3. 2-Pivaloyl-3-phenyl-*l*-menthopyrazole, 2c. Bp 160–170°C/5 mmHg; yield 99%; $[\alpha]_D$ −244.9 (*c* 0.39, $CHCl_3$); ^{1}H NMR: δ 0.67 (3H, d, $J=7$ Hz), 0.96 (3H, d, $J=7$ Hz), 1.09 (3H, d, $J=7$ Hz), 1.18–1.34 (1H, m), 1.41–1.56 (1H, m), 1.46 (9H, s), 1.85–1.98 (2H, m), 2.38–2.45 (1H, m), 2.59–2.77 (2H, m), 7.26–7.42 (5H, m); ^{13}C NMR: δ 18.6 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 23.5 (CH_2), 27.4 (CH_2), 28.1 (CH_3), 30.0 (CH), 32.6 (CH), 41.6 (CH), 42.2 (C), 124.7 (C), 127.8 (CH), 127.9 (CH), 129.0 (CH), 133.5 (C), 141.8 (C), 154.5 (C), 177.4 (C). Anal. calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28; found: C, 78.02; H, 8.96; N, 8.26%.

3.1.4. 2-Benzoyl-3-phenyl-*l*-menthopyrazole, 2d. Mp 110–111°C (from hexane); yield 75%; $[\alpha]_D$ −225.3 (*c* 0.35, $CHCl_3$); ^{1}H NMR: δ 0.80 (3H, d, $J=7$ Hz), 0.89 (3H, d, $J=7$ Hz), 1.04 (3H, d, $J=7$ Hz), 1.35–1.18 (1H, m), 1.52–1.60 (1H, m), 1.87–2.01 (2H, m), 2.34–2.41 (1H, m), 2.66 (1H, quint, $J=5$ Hz), 2.79–2.86 (1H, m), 7.36–7.56 (8H, m), 7.97–8.01 (2H, m); ^{13}C NMR: δ 18.3 (CH_3), 20.4 (CH_3), 22.8 (CH_2), 27.5 (CH_2), 29.9 (CH), 32.3 (CH), 41.3 (CH), 125.8 (C), 127.5 (C), 127.6 (CH), 127.9 (CH), 128.1 (CH), 129.3 (CH), 131.7 (CH), 132.3 (CH), 133.3 (C), 142.1 (C), 155.9 (C), 167.4 (C). Anal. calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.22; H, 7.39; N, 7.88%.

3.2. The reaction of 2a with 3a in the presence of $BF_3{\cdot}OEt_2$

A mixture of **2a** (30 mg, 0.1 mmol), **3a** (249 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (0.015 mL) in THF (2 mL) was heated at 60°C for 48 h under an argon atmosphere. The reaction mixture was quenched with dil. hydrochloric acid and extracted with ether. The organic layer was washed with aq. $NaHCO_3$ and aq. NaCl, and dried over anhydrous $MgSO_4$. After the addition of biphenyl as an internal standard, the yield of **4aa** was found to be 58% by GC. The ether solution was concentrated and **4aa** was distilled by cold finger distillator. From the GC of the distillate on chiral column, **4aa** was found have ee of <1%.

3.3. Evaluation of the catalytic effect of Lewis acids

To the powdered Lewis acid (0.01 mmol), a mixture of **5a** (138 mg, 0.1 mmol) and **3a** (244 mg, 2.0 mmol) in CH_2Cl_2 (2.0 mL) was added at room temperature under an argon atmosphere. At regular intervals, a small portion of the reaction mixture was taken and quenched with dil. hydrochloric acid. The resulting solution was monitored for content of **5a** by GC analysis to allow the evaluation of catalytic effect of Lewis acid (as summarized in Table 1).

3.4. Optimization of conditions for the reaction 2a with 3a

To the appropriate Lewis acid (0.1 mmol), a solution (2 mL) of **2a** (30 mg, 0.1 mmol) and **3a** (244 mg, 2.0 mmol) was added under an argon atmosphere. After stirring, the reaction mixture was quenched with dil. hydrochloric acid and extracted with ether. The organic layer was washed with aq. $NaHCO_3$ and aq. NaCl, and dried over anhydrous $MgSO_4$. After addition of biphenyl as an internal standard, the yield of **4aa** was evaluated by means of GC. The ether solution was concentrated and **4aa** was distilled by cold finger distillator, and the enantiomer ratios of **4aa** were obtained from the GC of the distillate on chiral column. The results are summarized in Table 3.

3.5. General procedure for enantioselective acylation for the resolution

3.5.1. In the absence of amines. To the freshly powdered $AlCl_3$ (0.5 mmol), a mixture of **2** (0.5 mmol) and **3** (1.2 mmol) in toluene (3 mL) and hexane (1 mL) was added at −5°C under an argon atmosphere. After stirring was continued for 17 h at −5°C, the subsequent mixture was quenched with dil. hydrochloric acid and extracted with two portions of ether. The organic layer was washed with aq. NaCl, and dried over anhydrous $MgSO_4$. After the addition of biphenyl as an internal standard, the yields of **4** and unreacted **3** were evaluated by means of GC. The ether solution was concentrated. Compounds **3** and **4** were roughly purified by cold finger distillation of the residue. The enantiomeric ratios of **4** and unreacted **3** were obtained by means of GC analysis on a chiral column. The results are summarized in Table 4.

3.5.2. In the presence of amines. To freshly powdered $AlCl_3$ (0.5 mmol), a solution of the appropriate amine (0.5 mmol) in toluene (2 mL) was added. A mixture of **2a** (150 mg, 0.5 mmol) and **3a** (146 mg, 1.2 mmol) in toluene (3 mL) was added at −5°C under an argon atmosphere. After stirring was continued at −5°C for 17 h, the mixture was quenched with dil. hydrochloric acid and extracted with two portions of ether. The organic layer was worked up as the method described above, and the results are summarized in Table 5.

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