Asymmetric Conjugate Addition Reaction Using Pyrazole Derivatives as a Chiral Catalyst

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The conjugate addition of Grignard reagent (**2**) onto 1-(α,β-unsaturated)acyl 3,5-dimethylpyrazole (**1**) was enantioselectively catalyzed by the copper complex from cuprous compounds and 3-phenyl-*l*-menthopyrazole (**3**).

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Recently we have reported the preparation and the utilities of the optically active pyrazoles as a new chiral auxiliary [1,2], which has unique structure and properties different from the conventional chiral auxiliaries [3]. The most important characteristics of this auxiliary are that the acyl substrate terminates to nitrogen atom of heteroaromatic pyrazole ring, and the substrate is surrounded by a chiral atmosphere [4]. This structural feature causes the diastereofacial attack on the enolate of *N*-acylpyrazoles in the reactions with alkyl halides [5], phenyldisulfide [6], acyl chlorides [7], aldehydes [8], and C=N compounds [9]. Moreover, the asymmetric cycloadditions of dienes [10] and 1,3-dipolar compounds [11] on *N*-(α,β-unsaturated)-acyl substituted pyrazoles have been reported. Subsequent *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 [16].

The optically active pyrazoles are also expected to show the effective chiral catalytic activities for various enantioselective syntheses. We have already exhibited the chiral catalytic activities of these optically active pyrazoles in the borane reduction and the dialkylzinc addition on the prochiral carbonyl compounds [17]. Furthermore, we have strongly desired to develop an effective catalyst of optically active pyrazole derivatives in the wide variety of synthetic reactions.

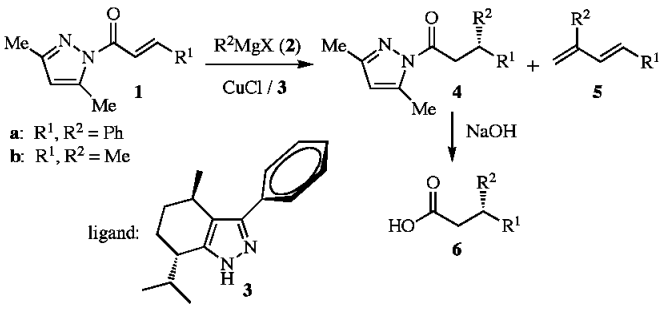
Recently, pyrazoles have been paid a great deal of attention because they are good ligands for various Lewis acids [18]. The complex formation of 3,5-Diphenylpyrazole with cuprous hydroxide was reported having 1 : 1 metal/pyrazole ratio [19]. We also revealed the complex formation of sodium salt of 3,5-diisopropylpyrazole with cuprous, silver and gold ions [20]. From the X-ray analysis, the structures of these complexes were found to be the cyclic trimer consisted of 3 pyrazoles and 3 cuprous ions or analogous tetramer. Otherwise, cuprous salts were widely applicable catalysts for the conjugate addition reaction. Previously we reported the diastereoselective conjugate addition of Grignard reagent on 2-(α,β-unsaturated)-acyl 3-phenyl-*l*-menthopyrazole [21], where cuprous iodide and magnesium bromide acted as the effective catalyst. Under these situation, the extensive utilities of the pyrazole derivatives as a chiral catalyst were investigated in the enantioselective conjugate addition of Grignard reagents on *N*-(α,β-unsaturated)acyl pyrazoles.

Results and Discussion

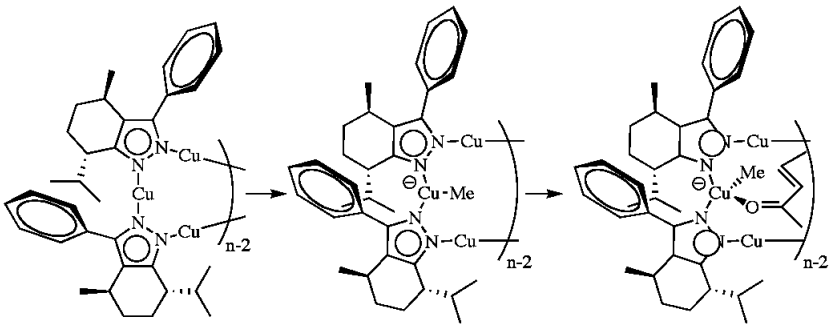
Previous paper [21] reported that the treatment of 1-cinnamoyl-3,5-dimethylpyrazole (**1a**) with methylmagnesium iodide (**2b**) afforded 1-(3-phenyl)butanoyl-3,5-dimethylpyrazole (**4ab**) and 3-methyl-1-phenyl-1,3-butadiene (**5ab**). The addition of cuprous iodide depressed the formation of **5ab**, and the yield of desired **4ab** was increased. By the addition of cuprous chloride and 3-phenyl-*l*-menthopyrazole (**3**), the reaction of **1a** with **2b** afforded **4ab** enantioselectively in good yield. For the confirmation of the stereostructure of the conjugate adduct, **4ab** was hydrolyzed into the corresponding carboxylic acid (**6ab**) by treatment with aqueous sodium hydroxide. By the HPLC of subsequent carboxylic acid, the stereostructure of the conjugate adduct was found to be 3'*S*-**4ab** by the comparison with authentic sample [21].

When **1a** was treated with **2b** in the presence of merely **3**, **4ab** was obtained in poor yield without any enantioselectivity. Even though cuprous chloride and **3** were added in catalytic amounts, enantioselective formation of **4ab** was observed in good yield. Further, **1a** was treated with **2b** after the formation of copper complex with **3** *in situ*.

Scheme 1



Scheme 2



As a result, the enantioselectivity of the conjugate adduct increased up to 33 % ee. From these facts, the copper complex with optically active pyrazole catalyzed the conjugate addition of Grignard reagent onto **1**, as summarized in the Table.

Since Grignard reagents were labile onto **1**, the conjugate addition was completed during 1 h, and the lower reaction temperature was preferred for the higher enantioselectivity. From the attempts using various cuprous salts as the Lewis acid, the yields and the enantioselectivities of these conjugate additions were independent of the kinds of cuprous salt, shown in Table.

N-Cu-N chelate bond independent from the structure of the substituent group on pyrazole ring. By the treatment with Grignard reagent, the copper atom was deformed into trigonal planar shape. The subsequent cuprate complex acted as the Lewis acid onto α,β-unsaturated carbonyl group to form the tetrahedral copper complex intermediate, and the conjugate addition proceeded intramolecularly. When the optically active pyrazole was provided for these reactions, the diastereofacial attack of α,β-unsaturated carbonyl compound occurred on the cuprate complex. Namely the *Si*-facial attack of **2b** was performed in the conjugate addition onto **1a**.

Table 1

Chiral Catalytic Effects of Cu Complex of **3** in the Conjugate Addition

Run	**3** eq	Cu Salt	eq	Base	eq	R^2MgX	eq	Temp °C	Yield %	Ee (Conf.) %	
1	1.0	CuCl	0.0	MeMgI	1.0	MeMgI	2.5	-28	33	1	(S)
2	0.1	CuCl	0.05	MeMgI	0.08	MeMgI	2.1	-28	92	12	(S)
3	1.0	CuCl	0.1	MeMgI	0.1	MeMgI	2.3	-28	43	17	(S)
4	1.0	CuCl	0.2	MeMgI	0.2	MeMgI	2.6	-28	52	15	(S)
5	1.0	CuCl	0.6	MeMgI	0.6	MeMgI	2.6	-5	22	7	(S)
6	1.0	CuCl	0.5	MeMgI	0.6	MeMgI	2.8	-28	60	33	(S)
7	1.0	CuCl	0.5	MeMgI	0.6	MeMgI	2.9	-90	11	3	(S)
8	1.0	CuCl	0.5	BuLi	0.8	MeMgI	2.9	-28	31	5	(S)
9	1.0	CuCl	1.0	MeMgI	1.0	MeMgI	2.1	-28	62	2	(R)
10	1.0	CuCl	0.5	MeMgI	1.1	MeMgI	2.8	-28	85	11	(S)
11	1.0	CuCl	0.6	MeMgI	1.7	MeMgI	2.3	-28	83	13	(S)
12	1.0	CuCl	1.0	PhMgBr	0.5	PhMgBr	2.8	-28	25	9	(S)
13	1.2	$CuCl+MgBr_2$	0.6	MeMgI	0.5	MeMgI	2.4	-28	34	8	(S)
14	1.0	CuBr	1.0	MeMgI	0.4	MeMgI	2.0	-28	67	7	(S)
15	1.0	CuBr(DMSO)	0.5	MeMgI	0.6	MeMgI	2.9	-28	91	16	(S)
16	1.0	CuI	0.5	MeMgI	0.5	MeMgI	2.5	-28	51	24	(S)
17	1.0	$Cu(OTf)_2$	0.5	MeMgI	0.6	MeMgI	2.5	-28	38	18	(S)
18	1.0	$ZnCl_2$	0.5	MeMgI	0.5	MeMgI	2.9	-28	16	[a]	?

[a] Enantiomer ratio could not be measured.

The reaction mechanism of these stereo controlled conjugate additions onto **1** is illustrated in Scheme 2. From the previous discussions [19,20], the structure of 1:1 cuprous complex with pyrazolato anion was found to be a triangle trimer or a square tetramer, having the straight

If the substituent group on γ-position of **1** was exchanged for the group of Grignard reagent (**2**), the product should have the reverse stereo structure. However, the conjugate addition of phenylmagnesium bromide (**2a**) onto 1-crotonoyl-3,5-dimethylpyrazole (**1b**) afforded preferably

3'*S*-**4ab** with different diastereoselection. Previously such an inverse diastereoselectivity was observed in the conjugate addition of Grignard reagent onto 2-(α,β-unsaturated)acyl 3-phenyl-*l*-menthopyrazole due to the geometric structural change of the N-acyl moiety [21].

After all, the conjugate addition of Grignard reagent (**2**) onto 1-(α,β-unsaturated)acyl 3,5-dimethylpyrazole (**1**) was enantioselectively catalyzed by the copper complex from cuprous chloride and 3-phenyl-*l*-menthopyrazole (**3**).

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL JNM-EX270 (270 MHz) spectrometer in deuterochloroform with tetramethylsilane as an internal standard. The enantiomer ratios of 3-phenylbutanoic acid were evaluated from the peak ratios of HPLC by CHIRALCEL OD-R (Daicel Chemical Industries) column on JASCO GULLIVER chromatograph series using acetonitrile-perchlorate buffer (pH 3.0, 0.5 M) mixture (v/v 3:7). The yields of the products were evaluated by GL Science GC-353 gas chromatograph using dimethylsiloxane type capillary column (0.25 mm x 30 m) of GL Science TC-1.

Materials

1-(α,β-Unsaturated)acyl 3,5-dimethylpyrazoles (**1**) were prepared from 3,5-dimethylpyrazole and (α,β-unsaturated)acyl chlorides in the presence of triethylamine according to the method of the previous paper [11], and purified by silica gel column chromatography and distillation. 3-Phenyl-*l*-menthopyrazole (**3**) was prepared from *l*-menthone according to the previous paper [1,2]. Cuprous salts were commercially available from Wako Pure Chemical Industries Ltd., and purified cuprous chloride was prepared by washing with acetic acid and with ethanol, and then heating in the casserole until acetic acid was not detected, and stored under nitrogen atmosphere. THF and ether were dried over benzophenone ketyl radical prepared *in situ* from sodium metal and benzophenone, and freshly distilled just before use.

General Procedure of Asymmetric Conjugate Addition.

To the mixture of cuprous salt (0.08 mmol), **3** (0.16 mmol) and biphenyl (internal standarad, ca 20 mg) in THF (1 ml) was added Grignard reagent (ca 1 M, 0.16 mmol), and stirred for 20 min at room temperature. The THF (2 ml) solution of 1-(α,β-unsaturated)acyl 3,5-dimethylpyrazole (**1**) (0.16 mmol) was added to the subsequent mixture at room temperature and stirred another 20min. After the mixture was chilled at –28 ºC, the Grignard solution(ca 2M, 0.35 mmol) was again added and stirred for 1 h. The reaction mixture was quenched with acetic acid, and diluted with water. By the GC measurement of the ether extract, the yields of the conjugate adduct were evaluated. Aqueous sodium hydroxide (3M, 0.5 ml) and methanol (4 ml) was added to this ether extract, and refluxed for 1 h. The subsequent mixture was washed with ether, and the aqueous layer was directly injected to HPLC for determining the enantiomer ratio of the conjugate adduct.

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