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Stereocontrolled Addition Reaction of Organometallics to Chiral α-Keto Amides

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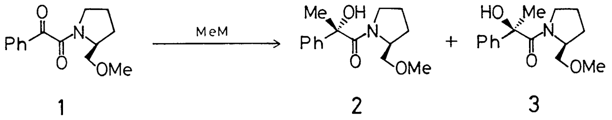
Complementary stereoselection in the addition reaction of several organometallics to chiral benzoylformamide, prepared from benzoylformic acid and (*S*)-2-(methoxymethyl)pyrrolidine, could be achieved using magnesium- and titanium-based reagents to give differeent diastereomers of atrolactamide. On the other hand, the reaction of phenyl metallics to the corresponding pyruvamide afforded (*S*)-atrolactamide.

In the field of asymmetric synthesis, the stereocontrolled addition of organometallics to carbonyl compounds possessing chiral auxiliary is one of the most important methods for asymmetric carbon-carbon bond formations.[1] Most of ever developed reactions, however, afforded only one of the possible two diastereomers. If the chiral auxiliaries were synthesized from naturally occurring compounds such as amino acids, preparation of the other diastereomer was very difficult, and there still remains the important problem to obtain both diastereomers in high diastereomeric excess from a same starting material.[2] In regard to obtaining either isomer, several successful chiral induction reactions in nucleophilic addition of organometallics to ketones were reported, such as 1,3-oxathianes,[3a] α-keto acetals,[3b] α-siloxy ketones,[3c] 3-acylisoxazolines,[3d] 14*β*-hydroxyandrostan-17-one,[3e] and hexopyranosiduloses.[3f] Being concerned with this matter, we have already reported that (*S*)-2-(methoxymethyl)pyrrolidine is efficient chiral auxiliary for either diastereoselection in the reaction with organometallics to afford both enantiomers depending on the metal used.[4] Now we wish to describe the diastereocontrolled reaction of organometallic reagents to chiral benzoylformamide or pyruvamide.[5]

Chiral benzoylformamide **1** was synthesized from benzoylformic acid and (*S*)-2-(methoxymethyl)pyrrolidine[6] using dicyclohexylcarbodiimide in 64% yield. The addition reaction of methyllithium to **1** in ether at −78 °C gave a mixture of the corresponding (*S*)-atrolactamide **2** and (*R*)-atrolactamide **3**. Separation of two diastereomers by TLC on silica gel afforded **2** and **3** in 53 and 40% yields, respectively (Entry 1). In the case of using methylmagnesium bromide, (*S*)-atrolactamide **2** was mainly obtained in 55% yield accompanied with 17% of **3** (Entry 2). The stereochemistry of **2** and **3** was confirmed by ^{1}H NMR spectra and the specific rotation by comparison with the reported data.[7] The effect of additives for the selectivity was examined and it was revealed that addition of divalent-metal salts greatly influenced the stereochemistry of the reaction to result in increasing the formation of **2** (Entries 3—5). The best selectivity (**2**:**3**=89:11) was realized when zinc chloride was utilized (Entry 4). Alkylation with dimethylzinc, prepared from zinc chloride and methylmagnesium bromide in situ,[8] proceeded less selectively (Entry 6).

On the other hand, (*R*)-atrolactamide **3** was mainly obtained when cerium reagent, derived from Grignard reagent and cerium trichloride,[9] was used (Entry 7). Furthermore, more Lewis acid titanium reagents, prepared from methyllithium and titanium tetra-



1 2 3

Fig. 1.

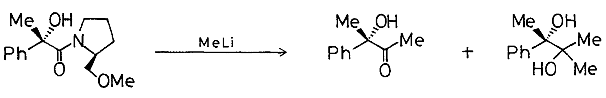
Table 1. Reaction of Chiral Benzoylformamide **1** with Organometallics

Entry	Me-Met	Solvent	Temp/°C	Yield/%	Ratio of **2** : **3**[a]
1	MeLi	Et_2O	−78	93	57:43
2	MeMgBr	Et_2O	−78	72	76:24
3	$MeMgBr-ZnBr_2$	Et_2O	−78	65	86:14
4	$MeMgBr-ZnCl_2$	Et_2O	−78	81	89:11
5	$MeMgBr-CdCl_2$	Et_2O	−78	79	82:18
6	Me_2Zn	Et_2O	−78→0	32	80:20
7	$MeMgBr-CeCl_3$	THF	−78	85	25:75
8	$MeTiCl_3$	Et_2O	−25	60	27:73
9	Me_2TiCl_2	Et_2O	−25	64	12:88
10	Me_2TiCl_2	CH_2Cl_2	−10	45	6:94

a) The ratios were determined by separation of the diastereomers by TLC on silica gel and/or HPLC analyses (Finepak SIL).

chloride in situ,[10] produced **3** predominantly (Entries 8—10), and dichlorodimethyltitanium realized better stereoselectivity than trichloromethyltitanium. Especially, the reaction of dichlorodimethyltitanium in CH_2Cl_2 afforded (*R*)-atrolactamide **3** in highly stereoselective manner (**2**:**3**=6:94).[11] These results were summarized in Table 1.

The chiral sorce of atrolactamide **2**, (*S*)-2-(methoxymethyl)pyrrolidine, could be removed by transformation into (*S*)-3-hydroxy-3-phenyl-2-butanone (**4**) and (*S*)-3-methyl-2-phenyl-2,3-butanediol (**5**) using methyllithium.[7] The absolute configuration of **2** was also confirmed by the comparison of optical rotation values.[7]

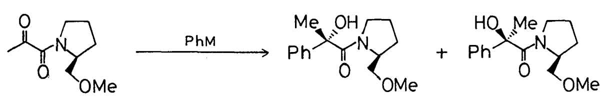


2 **4** **5**

Fig. 2.

On the other hand, when chiral pyruvamide **6**, derived from pyruvic acid and (*S*)-2-(methoxymethyl)-pyrrolidine, was used instead of **1**, the attack of several organometallics always proceeded from *si*-face to give **2**, and the phenomenon of reversal diastereoselection did not appear; i.e., the reaction **6** with phenylmagnesium bromide in the presence of zinc bromide afforded **2** and **3** in a ratio of 78:22 (Entry 4), and in the case of trichlorophenyltitanium compound **2** was also obtained mainly (**2**:**3**=74:26, Entry 6). The best selection of *si*-face addition to **6** occurred by using phenylmagnesium bromide in CH_2Cl_2 (Entry 3). These results were listed in Table 2.

Although the actual stereochemical course is still an open question, the diastereoselection might be rationalized using the models T_1—T_4. In the addition reaction of pyruvamide **6**, two carbonyl oxygens chelate to Lewis acid resulting *s-cis* conformation and organometallics, which coordinate to the ether oxygen of methoxymethyl group, attack from *si*-face (T_1). In the case of benzoylformamide **1**, *re*-facial attack of Grignard reagent occurred in the *s-trans* form of **1** (T_2) because steric interaction between large phenyl group and (*S*)-2-(methoxymethyl)-1-pyrrolidinyl group disfavored *s-cis* conformation of **1** (T_3). In contrast, a titanium reagent as highly strong Lewis acid is complexed with two carbonyl oxygens beyond steric interaction and reversal diastereoselection is realized by *si*-facial addition (T_4).



6 **2** **3**

Fig. 3.

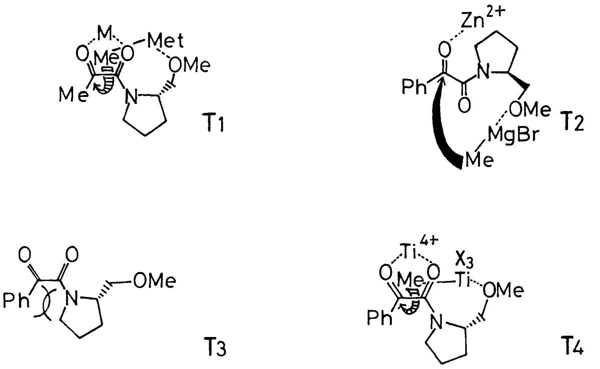


Fig. 4.

As described above, the different coordination states between chiral benzoylformamide and organometallics could control either diastereofacial differentiation.

Experimental

All the melting points and boiling point are uncorrected. The IR spectra were determined on JASCO IR 810 spectrometer. The ^1H NMR spectra were recorded with JEOL JNM—PMXC60si spectrometer in CCl_4 with tetramethylsilane as an internal standard. The MS spectra were taken on a JEOL JMS-D300 spectrometer. Optical rotations were measured with Union PM-101. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium diphenylketyl. Dichloromethane was distilled from CaH_2 and stored over Molecular Sieves 4A. Ethyl acetate was distilled before use in amidation reaction. Purification of products was performed by column chromatography on silica gel (Wako-

Table 2. Reaction of Chiral Pyruvamide **6** with Organometallics

Entry	Ph–Met	Solvent	Temp/°C	Yield/%	Ratio of **2** :**3**[a]
1	PhLi	THF	−78	70	53:47
2	PhMgBr	THF	−78	77	75:25
3	PhMgBr	CH_2Cl_2	−78→50	52	81:19
4	PhMgBr–$ZnBr_2$	Et_2O	−78	70	78:22
5	PhMgBr–$CeCl_3$	THF	−78	73	67:33
6	$PhTiCl_3$	Et_2O	−30	67	74:26

a) The ratios were determined by separation of the diastereomers by TLC on silica gel and/or HPLC analyses (Finepak SIL).

gel C-300) or preparative TLC on silica gel (Wakogel B-5F).

Preparation of (*S*)-*N*-Benzoylformyl-2-(methoxymethyl)-pyrrolidine (1). To an ethyl acetate (10 mL) solution of benzoylformic acid (666 mg, 4.44 mmol) was added an ethyl acetate (3 mL) solution of (*S*)-2-(methoxymethyl)pyrrolidine⁶⁾ (467 mg, 4.05 mmol) at −16 °C under an argon atmosphere. After being stirred for 30 min at that temperature, an ethyl acetate (3 mL) solution of dicylohexylcarbodiimide (882 mg, 4.28 mmol) was added and then the solution was gradually warmed to room temperature for 12 h.¹²⁾ The resulting precipitate was filtered off and the condensed filtrate was dissolved in CH_2Cl_2 and washed with 1 M hydrochloric acid, sat. aq $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4 and condensed under reduced pressure. Purification by column chromatography on silica gel (hexane:ethyl acetate=1:1 v/v) gave (*S*)-*N*-benzoylformyl-2-(methoxymethyl)pyrrolidine (**1**) (641 mg, 64%). $[\alpha]_D^{23}$ −108.5 ° (*c* 1.03, CH_2Cl_2). IR (neat) 1685, 1640 cm^{-1}. ^{1}H NMR δ=1.53—2.32 (4H, m), 2,87 and 3.37 (total 3H, s, CH_3), 2.98—3.77 (4H, m), 4.01—4.47 (1H, m), 7.18—7.62 (3H, m), 7.62—8.12 (2H, m). Found: *m/z* 247.1160. Calcd for $C_{14}H_{17}NO_3$:M, 247.1206.

Stereoselective Reaction of Chiral Benzoylformamide 1 with MeMgBr-ZnCl$_2$ in Ether (Table 1, Entry 4). To an ether solution (8 mL) of $ZnCl_2$ (151 mg, 1.10 mmol) was added an ether (5 mL) solution of benzoylformamide **1** (204 mg, 0.83 mmol) at 0 °C under an argon atmosphere and stirred for 1 h at 0 °C. After being cooled to −78 °C, methylmagnesium bromide (4.7 mL of a 0.71 M solution in ether (1M=1 mol dm^{-3})) was added and the solution was stirred at that temperature for 7 h. The reaction was quenched with sat. aq NH_4Cl and was extracted with CH_2Cl_2. The separated organic layer was dried over Na_2SO_4 and condensed under reduced pressure. Purification by preparative TLC on silica gel (hexane:ethyl acetate=3:2, v/v) to give (*S*)-[*N*-(*S*)-2-hydroxy-2-phenylpropionyl]-2--(methoxymethyl)pyrrolidine (**2**) (157 mg, 72%), and (*S*)-[*N*-(*R*)-2-hydroxy-2-phenylpropionyl]-2-(methoxymethyl)pyrrolidine (**3**) (20 mg, 9%). The ratio of **2**/**3** was also determined by HPLC analysis after isolation of the mixture of **2** and **3** (Finepak SIL, hexane:ethyl acetate :2-propanol=90:10:3, v/v; Rt_2=30 min, Rt_3=24 min). **2**; $[\alpha]_D^{23}$ −15.3 ° (*c* 0.90, C_6H_6), mp 82—83 °C (hexane) (lit,⁶⁾ $[\alpha]_D^{23}$ −15.5 ° (*c* 2.3, C_6H_6), mp 82—83 °C), IR ($CHCl_3$) 3400, 1625 cm^{-1}. ^{1}H NMR δ=1.33—2.03 (4H, m), 1.69 (3H, s), 2.73—3.60 (4H, m), 3.28 (3H, s), 4.00—4.41 (1H, m), 4.61 (1H, br s), 7.29 (5H, s). Found: *m/z* 263.1511. Calcd for $C_{15}H_{21}NO_3$:M, 263.1520. **3**; $[\alpha]_D^{23}$ −106.9° (*c* 0.34, C_6H_6), mp 108.5—109.5 °C (hexane) (lit,⁶⁾ $[\alpha]_D^{23}$ −103.2 ° (*c* 2.2, C_6H_6), mp 108.5—109 °C), IR ($CHCl_3$) 3400, 1625 cm^{-1}. ^{1}H NMR δ=1.20—2.02 (4H, m), 1.69 (3H, s), 2.67—3.68 (4H, m), 3.28 (3H, s), 3.93—4.43 (1H, m), 4.81 (1H, br s), 7,29 (5H, s). Found: *m/z* 263.1513. Calcd for $C_{15}H_{21}NO_3$:M, 263.1520.

Stereoselective Reaction of Chiral Benzoylformamide 1 with Me$_2$TiCl$_2$ in CH$_2$Cl$_2$ (Table 1, Entry 10). To a CH_2Cl_2 (3 mL) solution of $TiCl_4$ (171 mg, 0.90 mmol) was added methyllithium (1.73 mL of a 1.04 M solution in ether) at −78 °C under an argon atmosphere and stirred for 1 h.¹⁰⁾ Then a CH_2Cl_2 (3 mL) solution of benzoylformamide **1** (110 mg, 0.44 mmol) was added and stirred for 1.5 h at −78 °C. The mixture was gradually warmed to −10 °C during 10 h and stirred overnight at that temperature. The reaction was quenched with pH 7 buffer and the resulting precipitate was filtered off. The filtrate was extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. After the solvent was removed in vacuo, the residue was chromatographed on silica gel by using hexane–ethyl acetate (3:2, v/v) to give **2** and **3** (total 53 mg, 45%) in the ratio of 6:94, respectively.

Removal of Chiral Source of 2 with Methyllithium. To a THF (4 mL) solution of **2** (66 mg, 0.75 mmol) was added methyllithium (0.55 ml of a 1.37 M solution in ether) at −10 °C under an argon atmosphere, and stirred at 0 °C for 12 h.⁷⁾ The reaction was quenched with sat. aq NH_4Cl, extracted with ether, and dried over Na_2SO_4. The ethereal solution was concentrated in vacuo and the residue was purified by preparative TLC on silica gel (hexane:ether=1:1, v/v) to furnish (*S*)-3-hydroxy-3-phenyl-2-butanone (**4**) (28 mg, 69%) accompanied with (*S*)-3-methyl-2-phenyl-2,3-butanediol (8 mg, 18%). **4**; $[\alpha]_D^{23}$ −149.7 ° (*c* 0.33, EtOH) (lit,⁷⁾ $[\alpha]_D^{23}$ −150.6 ° (*c* 2.1, EtOH)). IR (neat) 3450 cm^{-1}. ^{1}H NMR δ=1.66 (3H, s), 2.02 (3H, s), 4.15 (1H, br s), 7.13—7.53 (5H, m).

Preparation of (*S*)-*N*-Pyruvoyl-2-(methoxymethyl)pyrrolidine (6). To an ethyl acetate (3 mL) solution of *N*-hydroxysuccinimide (353 mg, 3.06 mmol) were added an ethyl acetate (2 mL) solution of pyruvic acid (295 mg, 3.35 mmol) and an ethyl acetate (2 mL) solution of (*S*)-2-(methoxymethyl)pyrrolidine (353 mg, 3.06 mmol) at 0 °C under an argon atmosthere, and stirred for 2 h. Being cooled to −13 °C, an ethyl acetate (2 mL) solution of dicyclohexylcarbodiimide (704 mg, 3.41 mmol) was slowly added to the mixture and gradually warmed to room temperatute.¹³⁾ After being stirred for 64 h, the resulting precipitate was filtered off. The condensed filtrate was dissolved in CH_2Cl_2, washed with 1 M hydrochloric acid, sat. aq $NaHCO_3$, and water, dried over Na_2SO_4, and condensed under reduced pressure. The residue was purified by preparative TLC on silica gel (hexane:ethyl acetate=2:1, v/v) gave (*S*)-*N*-pyruvoyl-2-(methoxymethyl)pyrrolidine (**6**) (383 mg, 68%). $[\alpha]_D^{23}$ −56.6 ° (*c* 0.94, $CHCl_3$). bp 134 °C/2 mmHg (bath temp) (1 mmHg=133.322 Pa). IR (neat) 1720, 1650, 1635 cm^{-1}. ^{1}H NMR δ=1.43—2.23 (4H, m), 2.25 and 2.33 (total 3H, s, CH_3C), 2.90—3.75 (4H, m), 3.25 and 3.27 (total 3H, s, CH_3O), 3.90—4.67 (1H, m). Found: *m/z* 185.1023. Calcd for $C_9H_{15}NO_3$:M, 185.1050.

Reaction of Chiral Pyruvamide 6 with PhMgBr in CH$_2$Cl$_2$ (Table 2, Entry 3). Tetrahydrofuran, as a solvent of phenylmagnesium bromide (9.2 mL of 0.70 M solution in THF), was evaporated in vacuo and the residual Grignard reagent was dissolved in CH_2Cl_2 (6.5 mL) under an argon atmosphere. The phenylmagnesium bromide was added to a CH_2Cl_2 (7 mL) solution of pyruvamide **6** (198 mg, 1.07 mmol) at −78 °C under an argon atmosphere. After being stirred at −78 °C for 6 h and at −50 °C for 30 min, the reaction was quenched with sat. aq NH_4Cl extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by preparative TLC on silica gel (hexane:ethyl acetate=3:2, v/v) to give **2** (119 mg, 42%) and **3** (29 mg, 10%).

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