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Diastereoselective Addition of Organometallics to N-(α-Ketoacyl)-trans-2,5-bis(methoxymethoxymethyl)pyrrolidine

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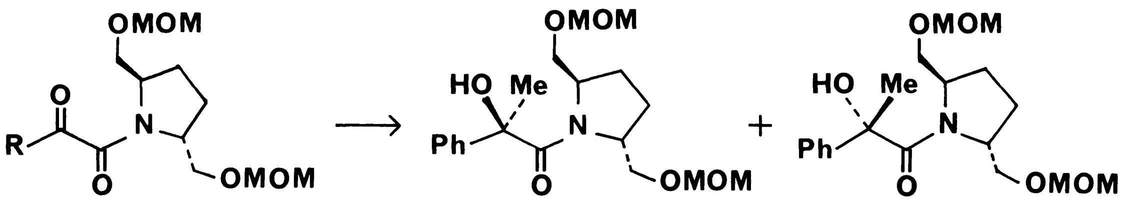
The nucleophilic addition of organometallics to α-keto amides having (2R,5R)-trans-2,5-bis(methoxymethoxymethyl)pyrrolidine as a chiral auxiliary was studied and it was found that the sense and degree of diastereoselection strongly depended on organometallics and the reaction conditions used and that the diastereomeric hydroxy amides was obtained with high stereoselectivity by the choice of appropriate reaction conditions.

Since the first study by McKenzie, alkylative addition reaction to chiral α-keto acid derivatives has been extensively investigated1) and the stereochemistry of this type of reactions has been rationalized as Prelog's rule.2) However, except for a few examples,3) the degree of their diastereoselectivity is not satisfactory from a synthetic point of view. In the course of our study on asymmetric synthesis using (2R,5R)-trans-2,5-bis(methoxymethoxymethyl)pyrrolidine [(R,R)-BMOMP] as a chiral auxiliary,4) we recently reported that the reduction of α-keto amide derived from (R,R)-BMOMP proceeded with high diastereoselectivity.5) In this communication, we wish to describe the asymmetric addition of some organometallic reagents to the same α-keto amides.

The starting α-keto amides (**1** and **2**) were prepared from (R,R)-BMOMP by N-acylation.5) The addition of organometallics to **1** and **2** was investigated in ethereal solvents and the ratio of resulting diastereomeric products (**3a** : **3b**) was dermined by ^{1}H NMR analysis. The results obtained are summarized in Table 1.

Addition of MeLi to **1** proceeded in low to moderate diastereoselectivity depending on the solvent used, to give the product **3a** preferentially (entries 1-3) and the use of THF-HMPA solvent system improved the stereoselectivity up to 81 : 19 (entry 4). In the case of MeMgBr, however, the interesting dependence of the stereoselectivity on the reaction temperature and solvent6) was observed as illustrated in Fig. 1. In THF, **3a** was obtained preferentially and the stereoselectivity increased as the temperature was raised (entries 5-7), while **3b** was the major isomer in ether and lower temperature enhanced the selectivity for **3b** (entries 8 and 9). Thus, either diastereomer (**3a** or **3b**) could be obtained selectively by the choice of appropriate reaction conditions. The high



1 R=Ph
2 R=Me

3a (2'R)

3b (2'S)

Table 1. Addition of Organometallics to Chiral α-Keto Amides

Entry	Amide R	Organometallics R'M (equiv.)	Solvent	Temp °C	Yield a) %	Ratio b,c) 3a : 3b
1	**1**	MeLi (1.2)	Et_2O	rt	68	42 : 58
2	**1**	MeLi (1.2)	Et_2O	-78	76	54 : 46
3	**1**	MeLi (1.2)	THF	-78	96	71 : 29
4	**1**	MeLi (1.2)	THF-HMPA d)	-78	75	81 : 19
5	**1**	MeMgBr (1.2)	THF	rt	94	19 : 81
6	**1**	MeMgBr (1.0)	THF	reflux	96	20 : 80
7	**1**	MeMgBr (1.1)	THF	-78	90	45 : 55
8	**1**	MeMgBr (3.0)	Et_2O	rt	89	52 : 48
9	**1**	MeMgBr (2.0)	Et_2O	-78	93	88 : 12
10	**1**	Me_2Mg (3.0)	Et_2O	0	98	60 : 40
11	**1**	$Me_2Cu(CN)Li_2$ (1.2)	THF	-78	74	85 : 15
12	**2**	PhLi (1.2)	Et_2O	-78	71	84 : 16
13	**2**	PhLi (1.2)	THF	-78	51	80 : 20
14	**2**	PhMgBr (2.0)	Et_2O	-78	70	74 : 26
15	**2**	PhMgBr (1.2)	THF	rt	91	84 : 16
16	**2**	PhMgBr (1.2)	THF	-78	85	94 : 6
17	**2**	$PhLi-TiCl_4$ e)	Et_2O	-78	40	95 : 5
18	**2**	$Ph_2Cu(CN)Li_2$ (1.2)	THF	-78	49	56 : 44

a) Isolated Yield. b) Determined by ^1H NMR (400MHz or 90MHz using $Eu(fod)_3$). c) Configuration of the predominant isomer was determined by the optical rotation of the corresponding acid after hydrolysis (6 mol dm^{-3} HCl and then K_2CO_3 in MeOH). d) THF:HMPA ratio was 50:1. e) Reagents molar ratio; 2:PhLi:$TiCl_4$=1:1.1:1.1.

selectivity toward **3a** was also observed in addition of higher order cuprate (entry 11).

In the reaction of **2**, however, both PhLi and PhMgBr gave the compound (**3a**) preferentially in either ether or THF and maximum diastereoselectivity (**3a** : **3b** =

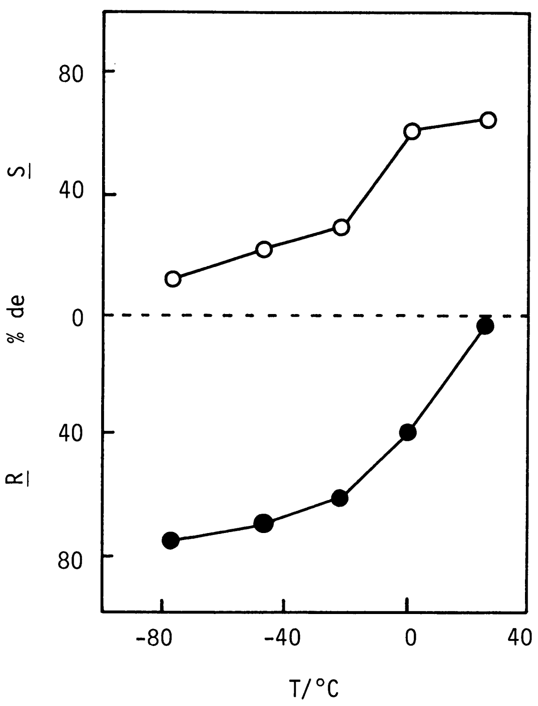


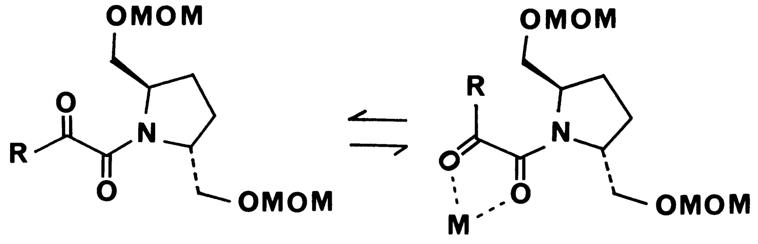
Fig. 1. The effect of temperature on diastereomeric excess (% de) in the addition of MeMgBr to **1** ; (○) THF, (●) ether.

94 : 6) was obtained by using PhMgBr in THF at -78 °C (entry 16). PhLi-TiCl$_4$ system7) also showed the high stereoselectivity of 95 : 5 (entry 17) but higher order cuprate exhibited the poor selectivity (entry 18).

Although the exact steric course of the reaction is not clear at present, the results described above suggest that the α-keto amide (**1**) mostly exists as *s-trans* conformer (**A**) due to the unfavorable dipole-dipole repulsion of two carbonyl groups and the interference of α-phenyl group and pyrrolidine moiety in *s-cis* conformer (**B**) and that organometallics such as MeMgBr in ether or higher order cuprate preferentially attacks the less hindered bottom face (*si*-face) to afford **3a**. In contrast, an organometallic reagent such as Grignard reagent in THF having the high ability of chelate formation, makes *s-cis* conformer (**B**) preferable and therefore affords **3b** preferentially. This is in accord with the observation that the reaction of Grignard reagent with α-heterosubstituted ketone in THF exhibits higher stereoselectivity based on chelation control than that in ether.6,8) This chelation control mechanism is considered to play a much important role in the addition reaction to **2** because of the decrease of steric interference which destabilizes *s-cis* conformer (**B**), giving rise to the preferential formation of **3a**, even when Ph$_2$Cu(CN)Li$_2$ or ethereal PhMgBr is used.

The following experimental procedure is representative.

A solution of the α-keto amide (**2**, 38.2 mg, 0.132 mmol) in THF (0.6 ml) was added to 2 ml of a THF solution of PhMgBr (0.158 mmol) at -78 °C. After stirring 3 h at the same temperature, the reaction mixture was quenched with saturated



(**A**) (**B**)

aqueous NH_4Cl, extracted with dichloromethane three times, and dried over $MgSO_4$. Concentration of the solvent gave a mixture of **3a** and **3b** as a colorless oil (41.2 mg, 85%). ^1H NMR analysis showed that the ratio of **3a** and **3b** was 94 : 6.

The amides thus obtained could be hydrolyzed in conventional manners[4f)] to give the corresponding hydroxy acid.

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References

1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, New Jersey (1971), Chap. 2.

2) V. Prelog, Helv. Chim. Acta, 36, 308 (1953); Bull. Soc. Chim. Fr., 1956, 987.

3) a) J. A. Berson and M. A. Greenbaum, J. Am. Chem. Soc., 80, 445, 653 (1958); b) Y. Tamai et al., reported that reinvestigation of Berson's procedure showed much lower diastereoselectivity (3-17% de) than that (85% de) reported in Ref. 3a; Y. Tamai, T. Nakano, S. Koike, K. Kawahara, and S. Miyano, Chem. Lett., 1989, 1135; c) J. K. Whitesell, A. Bhattacharya, and K. Henke, J. Chem. Soc., Chem. Commun., 1982, 988; J. K. Whitesell, D. Deyo, and A. Bhattacharya, J. Chem. Soc., Chem. Commun., 1983, 802; d) G. Boireau, A. Korenova, A. Deberly, and D. Abenhaim, Tetrahedron Lett., 26, 4181 (1985); e) K. Soai and M. Ishizaki, J. Org. Chem., 51, 3290 (1986).

4) a) Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., 25, 857 (1984); b) Y. Ito, T. Katsuki, and M. Yamaguchi, ibid., 25, 6015 (1984); 26, 4643 (1985); c) T. Katsuki and M. Yamaguchi, ibid., 26, 5807 (1985); d) M. Enomoto, Y. Ito, T. Katsuki, and M. Yamaguchi, ibid., 26, 1343 (1985); e) S. Ikegami, T. Hayama, T. Katsuki, and M. Yamaguchi, ibid., 27, 3403 (1986); f) T. Hanamoto, T. Katsuki, and M. Yamaguchi, ibid., 27, 2463 (1986); g) M. Uchikawa, T. Hanamoto, T. Katsuki, and M. Yamaguchi, ibid., 27, 4577 (1986); h) Y. Kawanami, T. Katsuki, and M. Yamaguchi, Bull. Chem. Soc. Jpn., 60, 4190 (1987).

5) Y. Kawanami, I. Fujita, Y. Taniguchi, T. Katsuki, and M. Yamaguchi, Chem. Lett., 1987, 2021.

6) Similar observations were reported in addition to chiral ketones; E. L. Eliel, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Orlando, Florida (1983), Vol. 2, Chap. 5; E. L. Eliel and S. Morris-Natschke, J. Am. Chem. Soc., 106, 2937 (1984).

7) M. T. Reetz, Angew. Chem., Int. Ed. Engl., 23, 556 (1984); M. T. Reetz, S. H. Kyung, and M. Hullann, Tetrahedron, 42, 2931 (1986).

8) The higher ability of chelate formation of Grignard reagent in THF than in ether is suggested to be attributed to the change in the position of the Schlenk equilibrium ($2RMgX \rightleftarrows R_2Mg + MgX_2$) or in the degree of association of the reagent. See Ref. 6.

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