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Diastereoselective Addition of Organometallics to Chiral α-Keto Amides Having *trans*-2,5-Disubstituted Pyrrolidine

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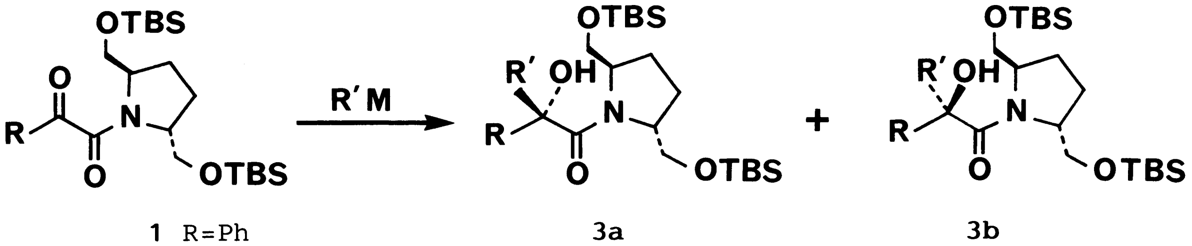
The nucleophilic addition of organotitanium reagents to α-keto amides derived from (2*R*,5*R*)-*trans*-2,5-bis(*t*-butyldimethylsiloxymethyl)pyrrolidine [(*R*,*R*)-BTBSP] afforded the corresponding α-hydroxy amides with very high diastereofacial selectivity.

In the course of our study on asymmetric synthesis using *trans*-2,5-disubstituted pyrrolidine with C_2-axis of symmetry as a chiral auxiliary, we have recently reported the diastereoselective addition of organometallics to α-keto amide derived from (2*R*,5*R*)-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine [(*R*,*R*)-BMOMP], where the sense and degree of the stereoselectivity strongly depended on the organometallic reagent, the solvent, and the temperature.[1] In order to improve the selectivity, we have studied the reaction of α-keto amide having (*R*,*R*)-BTBSP, since its *t*-butyldimethylsilyl group is expected to provide larger steric hindrance and could inhibit the chelation of organometallics to the alkoxy group on the pyrrolidine ring.[2] In this communication, we wish to describe high diastereoselective addition of organotitanium reagents to α-keto amides bearing (*R*,*R*)-BTBSP.

The α-keto amides (**1** and **2**) were prepared from (*R*,*R*)-BTBSP by N-acylation.[1] The ratios of the resulting diastereomeric products (**3a** : **3b**) were determined by HPLC analysis.



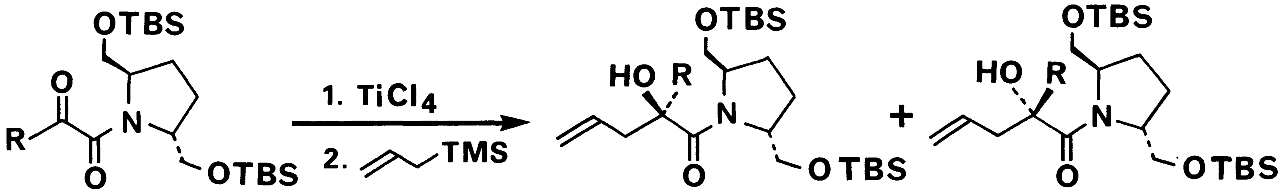
1 R=Ph
2 R=Me

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

Entry	Amide R	Organometallics[a)] R'M	Solvent	Temp °C	Yield[b)] %	Ratio[c,d)] **3a** : **3b**
1	**1**	MeLi	Et_2O	-78	84	31 : 69
2	**1**	MeLi	THF	-78	77	37 : 63
3	**1**	MeLi	THF-HMPA[f)]	-78	75	24 : 76
4	**1**	MeMgBr	Et_2O	rt	94	56 : 44
5	**1**	MeMgBr	Et_2O	-78	87	30 : 70
6	**1**	MeMgBr	THF	rt	89	81 : 19
7	**1**	MeMgBr	THF	-78	67	48 : 52
8	**1**	MeMgBr-$TiCl_4$[e)]	CH_2Cl_2	-23	72	>99 : <1
9	**2**	PhLi	Et_2O	-78	62	90 : 10
10	**2**	PhLi	THF	-78	72	91 : 9
11	**2**	PhMgBr	Et_2O	-78	74	77 : 23
12	**2**	PhMgBr	THF	rt	83	74 : 26
13	**2**	PhMgBr	THF	-78	83	78 : 22
14	**2**	PhMgBr-$TiCl_4$[e)]	CH_2Cl_2	-78	72	95 : 5

a) 1.1-2 equiv. of reagents were used. b) Isolated Yield. c) Determined by HPLC (ZOBAX-SIL, 4.6 x 250, hexane/EtOH). d) Configuration was determined by the optical rotations of the corresponding acid after hydrolysis (1 mol dm^{-3} HCl and then K_2CO_3 in MeOH) without any detectable epimerization (Ref. 3). e) 3 equiv. of organometallic reagent and $TiCl_4$ was mixed at -23 °C for 30 min and then used. f) 1.1 equiv. of HMPA was used.

The results obtained are summarized in Table 1. Addition of MeLi proceeded with moderate diastereoselectivity to give the alcohol **3b** preferentially (entries 1-3). Although MeMgBr in ether at -78 °C gave the alcohol **3b** as a major diastereomer, the addition in THF at room temperature afforded the opposite diastereomeric alcohol **3a** preferentially (entries 4-7). Thus, in addition of MeMgBr the strong dependence of the stereoselectivity on the solvent and the temperature was observed as in the reaction of α-keto amides derived from (R,R)-BMOMP.[1)] Finally, excellent diastereoselectivity (**3a** : **3b** = >99 : <1) was obtained in the addition of the titanium reagent prepared *in situ* from MeMgBr and $TiCl_4$[4,5)] in CH_2Cl_2 at -23 °C (entry 8). On the other hand, the reaction of **2** with PhLi or PhMgBr in either ether or THF produced the alcohol **3a** predominantly (entries 9-13). Again, the titanium reagent prepared from PhMgBr and $TiCl_4$ afforded the alcohol **3a** and **3b** in the ratio of 95 : 5 (entry 14). These results



			4a		4b
1 R=Ph		R=Ph	>99	:	<1
2 R=Me		R=Me	>99	:	<1

suggest that the reaction of **2** may proceed via a chelation-control mechanism because of the small steric interference of methyl group in **2** compared to phenyl group in **1**.

Furthermore, complexation of **1** and **2** with $TiCl_4$ followed by addition of allylsilane at -78 °C in CH_2Cl_2 also afforded almost complete stereoselection.[6] These results apparently indicate that stronger Lewis acidic organometallics such as titanium reagents chelate the two carbonyl group in s-cis conformation (5-membered chelate ring)[7] and would attack less hidered back face (re-face) to give the alcohol **3a** and **4a** exclusively as shown in Fig. 1.

Thus, using the Lewis acidic organometallics which have the high ability of chelation and the chiral auxiliary (R,R)-BTBSP bearing larger steric hindrance resulted in almost complete diastereoselection.[8]

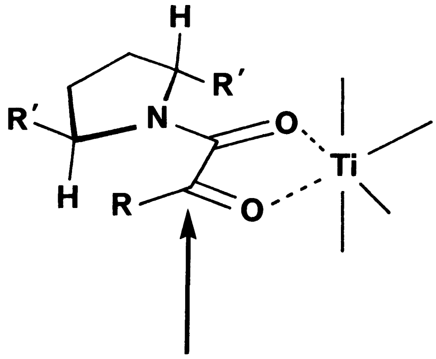


Fig. 1.

The following experimental procedure is representative.

MeMgBr in ether (1.10 mmol) was added slowly to a solution of $TiCl_4$ (0.120 ml, 1.10 mmol) in CH_2Cl_2 (4 ml) at -23 °C (CCl_4-dry ice), which caused a color change to dark black-brown. The mixture was stirred for 10 min and then a solution of α-keto amide (**1**, 179 mg, 0.365 mmol) in CH_2Cl_2 (1 ml) was added. After stirring for 3 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with dichloromethane three times, washed with water, and dried over $MgSO_4$. Concentration of the solvent gave α-hydroxy amide as a colorless oil (133 mg, 72%). HPLC analysis showed that the selectivity was more than 99 : 1.

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