

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 (2R,5R)-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 C₂-axis of symmetry as a chiral auxiliary, we have recently reported the diastereoselective addition of organometallics to α -keto amide derived from (2R,5R)-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.

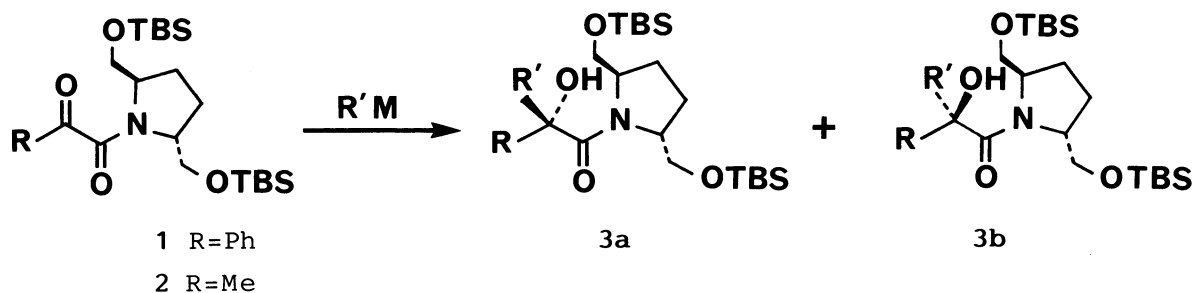
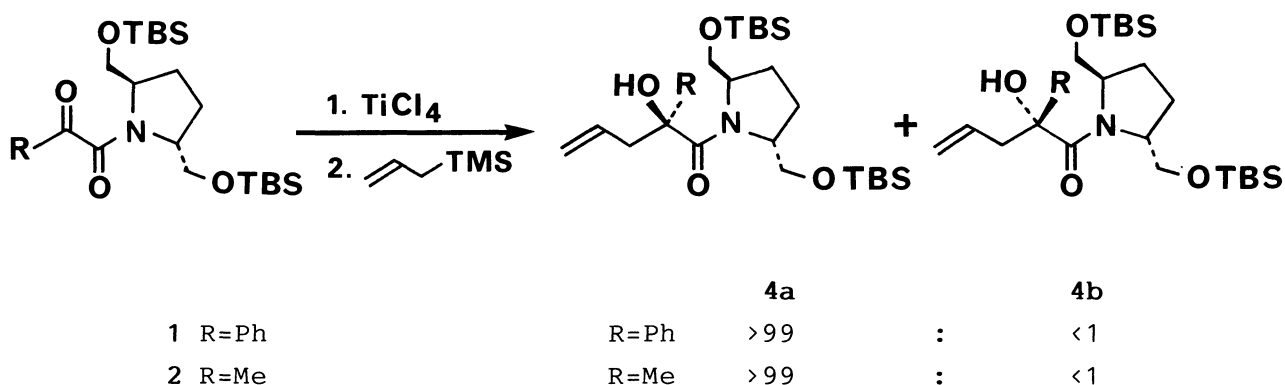


Table 1. Addition of Organometallics to Chiral α -Keto Amides

Entry	Amide R	Organometallics ^{a)} R'M	Solvent	Temp °C	Yield ^{b)} %	Ratio ^{c,d)} 3a : 3b
1	1	MeLi	Et ₂ O	-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 ₂ O	rt	94	56 : 44
5	1	MeMgBr	Et ₂ O	-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 ₂ Cl ₂	-23	72	>99 : <1
9	2	PhLi	Et ₂ O	-78	62	90 : 10
10	2	PhLi	THF	-78	72	91 : 9
11	2	PhMgBr	Et ₂ O	-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 ₂ Cl 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 K₂CO₃ in MeOH) without any detectable epimerization (Ref. 3). e) 3 equiv. of organometallic reagent and TiCl₄ 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 TiCl₄^{4,5)} in CH₂Cl₂ 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 TiCl₄ afforded the alcohol **3a** and **3b** in the ratio of 95 : 5 (entry 14). These results



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 hindered 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⁾

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

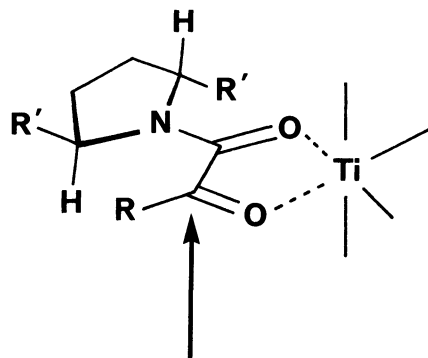


Fig. 1.

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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References

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