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Highly Diastereoselective Addition of Organometallics to Novel Chiral α-Ketoamides of (*S*)-2-Methoxymethylindoline

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Abstract : The stereocontrolled nucleophilic addition of organometallics to novel chiral α-ketoamides which were synthesized from (*S*)-2-methoxymethylindoline as a chiral auxiliary was carried out to obtain α-hydroxyamides with extremely high diastereoselectivities (up to dr ≥ 99 : 1).

A number of diastereoselective nucleophilic additions of organometallic reagents to α-ketoamides[1] or α-ketoesters[2] bearing appropriate chiral auxiliaries have been reported as the useful methods for the synthesis of optically active α-hydroxyacid derivatives, which are valuable for the syntheses of optically active organic compounds and natural products.

There have been a number of reports concerning nucleophilic additions of organometallic reagents to chiral α-ketoamides, which have a pyrrolidine ring bearing an adjacent stereogenic centre as a chiral auxiliary.[1] In regard to the diastereoselectivities in the nucleophilic addition of organometallics to α-ketoamides of pyrrolidine derivatives, the chiral *trans*-2,5-disubstituted pyrrolidines[1c,d] afforded higher diastereofacial selectivities than 2-monosubstituted pyrrolidines.[1a,b] On the bases of these facts, we expected that a chiral pyrrolidine containing a benzene ring at the opposite side to the 2-position in (*S*)-2-methoxymethylindoline might play an important role and affect the diastereofacial selectivity in transition state ; a steric effect of the benzene ring of indoline[3] was expected to affect a high stereocontrolled selectivity by a modeling study on **1a** and **1b**. Recently, we reported that (*S*)-indoline derived catalysts resulted in high enantiomeric excess in asymmetric reductions of ketones to the corresponding secondary alcohols[4] and in asymmetric alkylations of the aldehydes to the alcohols.[5] (*S*)-2-Methoxymethylindoline (≥ 99% ee)[6] was easily prepared by reduction[3a] (80 %) of (*S*)-indoline-2-carboxylic acid with $LiAlH_4$ and then selective O-methylation (70 %) with NaH - MeI - HMPA. α-Ketoamides **1a** and **1b** were synthesized in high yields by condensation of the α-ketoacids and (*S*)-2-methoxymethylindoline using dicyclohexyl carbodiimide.

In this paper, we wish to describe that the chiral α-ketoamide **1a** reacted with Me_2TiCl_2 prepared from MeLi and $TiCl_4$[1b] to give (*R*)-α-hydroxyamide **2** in extremely high diastereoselectivity (Run 1 and 2 ; *R* : *S* ≥ 99 : 1) and that **1b** reacted with Ph_2TiCl_2 or $PhTiCl_3$[1b] to give (*S*)-α-hydroxyamide **2** in high diastereoselectivity (Run 10 and 11 ; *R* : *S* = 3 : 97). The degree of diastereoselectivity is highly dependent on the organometallics and solvents (Run 3 -9, Run 12). Grignard reagent or organolithium reagent afforded lower diastereoselectivities in comparison with alkyl or aryl titanium chloride. The ratios of *R*- and *S*-diastereomers of **2** were determined by HPLC analysis using a chiral column (Chiralcel OD column ; 25 cm

x 0.46 cm) and ^{1}H-NMR (300 MHz) analysis. The absolute configuration was determined by comparison of the specific rotation of atrolactic acid (Run 1 ; 84 %, $[\alpha]_D^{23}$ - 36.0 (c 0.76, EtOH), [lit.,[2b] $[\alpha]_D^{10.5}$ + 37.7 (c 3.5, EtOH)]) after hydrolysis (3M HCl in dioxane at reflux for 6 h) of **2**. (*S*)-2-Methoxymethylindoline used as a chiral auxiliary was recovered in 91 % without racemization. From the results described above, it can be concluded that the benzene ring of **1a** and **1b** plays an important role to affect the diastereofacial selectivity, although the detailed mechanism is not clear yet. Four conformers of α-ketoamides can be considered as shown in figure 1. Conformer **A** and **B** are destabilized by the repulsive interaction, and **D** is less stable than **C** because of the dipole-dipole repulsion[1c] between two carbonyl groups of **D**. However, in the presence of titanium reagent, **D** is more favorable than **C** due to the chelation of the strong oxophilic titanium with two carbonyl groups of **D**. Consequently, the **R'** may attack less hindered *si*-face to give *R*-configuration of α-hydroxyamide.

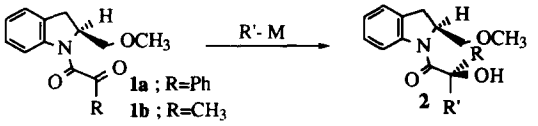
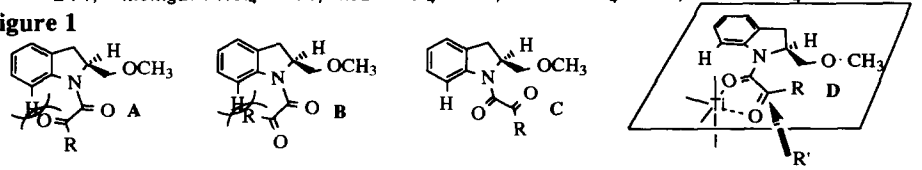


Table I. Diastereoselective Addition of Organometallics to α-Ketoamides

Run	α-Ketoamide	Organometal (eq)	Solvent	T (°C)	Time	Yield[a] (%)	Ratio[b] (*R*[c]:*S*)
1	**1a**	Me_2TiCl_2[d] (3 eq)	CH_2Cl_2	0	9 h	76	≥ 99 : 1
2	**1a**	$MeTiCl_3$[e] (3 eq)	CH_2Cl_2	0	9 h	60	≥ 99 : 1
3	**1a**	$MeTiCl_3$[f] (3 eq)	CH_2Cl_2	0	9 h	72	98 : 2
4	**1a**	MeMgI (6 eq)	THF	0	5 min	87	85 : 15
5	**1a**	MeMgI (6 eq)	THF	- 45	5 min	90	73 : 27
6	**1a**	MeMgI (6 eq)	THF	-78	5 min	82	66 : 34
7	**1a**	MeMgI (2 eq)	Toluene	0	5 min	90	54 : 46
8	**1a**	MeLi (2eq)	THF	- 45	1 h	43	38 : 62
9	**1a**	MeLi (2eq)	THF	- 78	1 h	66	31 : 69
10	**1b**	Ph_2TiCl_2[g] (3 eq)	CH_2Cl_2	- 78	5 h	60	3 : 97
11	**1b**	$PhTiCl_3$[h] (3 eq)	CH_2Cl_2	- 78	5 h	74	3 : 97
12	**1b**	PhLi (2 eq)	THF	- 78	1 h	62	35 : 65

[a] Isolated yield, [b] Determined by ^{1}H NMR and HPLC analysis (Daicel Chiralcel OD), [c] Determined from specific rotation of the hydrolysis product, atrolactic acid, [d] MeLi : $TiCl_4$ = 2 : 1, [e] MeMgBr : $TiCl_4$ = 1 : 1, [f] MeLi : $TiCl_4$ = 1 : 1, [g] PhLi : $TiCl_4$ = 2 : 1, [h] PhLi : $TiCl_4$ = 1 : 1

Figure 1



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6. The % ee was determined by ^{1}H NMR and HPLC analysis using (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (Mosher's reagent).

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