Highly Diastereoselective Synthesis of β-Hydroxy Amides from β-Keto Amides

Giuseppe Bartoli,*[a] Marcella Bosco,[a] Enrico Marcantoni,[b] Massimo Massaccesi,[a] Samuele Rinaldi,[c] Letizia Sambri[a]

[a] Dipartimento di Chimica Organica 'A. Mangini', v. le Risorgimento 4, 40136 Bologna, Italy
Fax +39(51)2093654; E-mail: giuseppe.bartoli@unibo.it

[b] Dipartimento di Scienze Chimiche, Università di Camerino, v. S. Agostino 1, 62032 Camerino (MC), Italy

[c] Dipartimento di Scienze e Materiali della Terra, Università di Ancona, v. Brecce Bianche, 60131 Ancona, Italy

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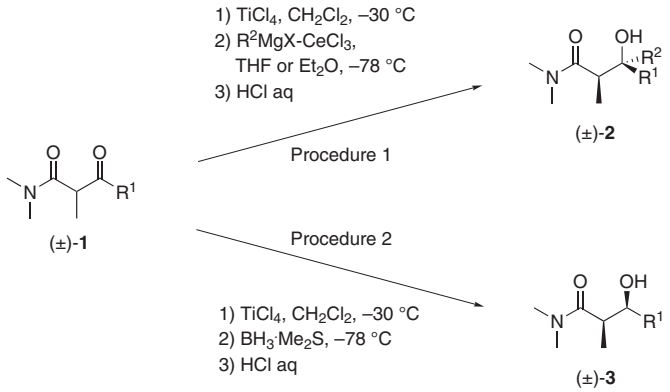
Abstract: β-Hydroxy amides with stereodefined geometry represent an important unit present in various natural products. The diastereoselective preparation of amides carrying a secondary or tertiary alcohol in β-position is described here.

Key words: diastereoselectivity, hydroxy amides, $TiCl_4$, organocerium reagents, boranes



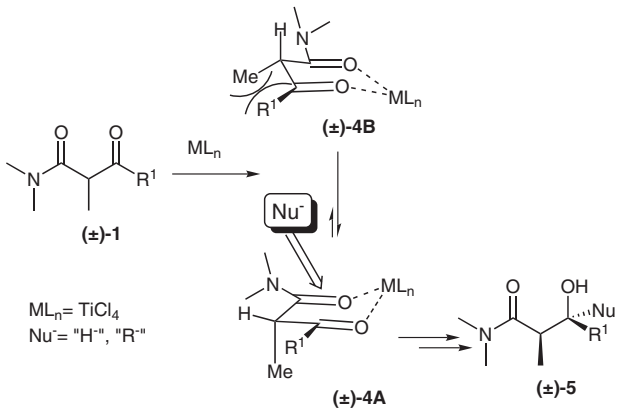
Scheme 1

Introduction

The construction of β-hydroxy amides with stereodefined geometry (Scheme 1) is an important target in organic synthesis since these units are present in various natural products. For instance, an amidic group carrying a tertiary alcohol in the β-position is a structural unit in a series of inhibitors of MMPs enzymes;[1] moreover, β-hydroxy amides can be used as useful building blocks for the synthesis of biologically active compounds.[2] Therefore, various strategies have been planned and developed for their synthesis.

Among these, the most direct approaches are the aldolic condensation[3] between an amide enolate and a ketone, or an aldehyde, and the stereoselective addition of an organometallic species[4] or of a reducing agent[5] to the carbonyl of a β-keto amide, carrying a stereocenter in α-position. Since the stereochemical outcome of the aldol condensation is hardly controllable, the latter approach seems to be a more promising and practicable tool.

In the design of a stereoselective process the formation of a cyclic metal-chelate intermediate is frequently planned.[6] In fact, the interaction of a bidentate system like **1** (Scheme 2) with an appropriate chelating agent leads to the formation of a cyclic complex, whose structure can be accounted for by an equilibrium between **4A** and **4B** conformations. Owing to the $A^{1,2}$ strain present in **4B**, the equilibrium should be shifted towards the most stable conformation **4A**.[7]



Scheme 2

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At variance with **4B**, **4A** presents a significant stereofacial discrimination. In fact the attack from the lower side of the molecule is prevented by the axial methyl group positioned in the same direction of the ideal trajectory of an incoming nucleophile. In conclusion, the winning strategy for a high stereocontrol of the process is, in principle, to pursue the most appropriate reaction conditions so as to favor the shift of the equilibrium towards the **4A** conformation.

The choices of the carbanionic moiety and the hydride ion sources are also a crucial point. These reagents in fact should have a high nucleophilic character associated with a low basicity, so as to minimize proton abstraction phenomena at the α-position.[8] Although this undesirable side reaction should easily occur only at the axial hydrogen of the minor conformer **4B**, however, it could become competitive when the addition process is slow on account of steric factors and/or the equilibrium is not appreciably shifted towards **4A** (small $A^{1,2}$ strain).[9]

In this 'Practical Synthetic Procedure' we present the best reaction conditions for the stereocontrolled synthesis of β-hydroxy amides.

Scope and Limitations

Our first goal was to set up a general and efficient protocol (Procedure 1) to obtain β-hydroxy amides having a tertiary alcoholic fragment by addition of the appropriate organometallic species to a metal complex of the starting β-keto amide **1** (Scheme 1).

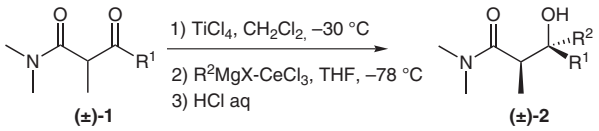
Although the addition of organometallic reagents to oxoamides had been previously studied, the few methods present in the literature did not supply general conditions.[4] In these works, in order to obtain high stereoselectivity it was indeed necessary to tune the choice of the reagent to the structure of the carbon chain to be introduced at the prostereogenic carbonylic group. We were looking for an organometallic species able to transfer to the carbonyl various carbon frameworks, independently from the nature of the substrate, in order to furnish general applicability to the proposed protocol.[10]

Organocerium reagents completely fulfill these requirements.[11] In fact, a large variety of carbon frameworks is available since they can be easily prepared from the corresponding RMgX derivatives. Moreover, they generally exhibit a high nucleophilicity, in some cases superior to that of the parent compounds. At the same time, their low basic character avoids the occurrence of extensive enolization processes.

The high nucleophilicity of the organometallic species is crucial for the success of the reaction since it allows the addition to be carried out at low temperature. In fact, according to the Boltzmann law, the population of the most stable conformer **4A** increases with lowering of the temperature.

Organocerium derivatives, however, can be prepared only in ethereal solvents. Hence, to form a cyclic intermediate, we needed a Lewis acid able to chelate even in coordinating solvents (THF, Et_2O). Between various Lewis acids, $TiCl_4$ proved to be the best choice. In fact we found that it is strong enough to ensure the formation of a stable and rigid chelate with β-keto amides **1** even in the presence of ethereal cosolvents. The reaction was tested on two substrates **1a** (R^1 = Ph) and **1b** (R^2 = Et), carrying a phenyl group and an ethyl group bound to the carbonyl, respectively. Our results are reported in Table 1.[12]

Table 1 Diastereoselective Addition of Organocerium Reagents to β-Keto Amides **1** in THF at –78 °C, Unless Otherwise Mentioned



Entry	R^1	R^2 in R^2MgX-$CeCl_3$	Product	Yield (%)[a]	de (%)[b]
1	Ph	Me	**2aa**	>99	>98
2	Ph	Et	**2ab**	65	>98
3	Ph	*n*-Bu	**2ac**	85	>98
4	Ph	$PhCH_2$	**2ad**	90	>98
5	Ph	PhC≡C	**2ae**	85	>98
6	Ph	CH_2=$CHCH_2$	**2af**	>99	>98
7	Ph	*i*-Pr	**2ag**	60[c]	>98
8	Ph	*t*-Bu	**2ah**	60[c]	>98
9	Et	Me[d]	**2ba**	85	>98
10	Et	*n*-Bu[d]	**2bc**	60	94
11	Et	Ph[d]	**2bi**	85	>98
12	Et	$PhCH_2$	**2bd**	97	>98
13	Et	CH_2=$CHCH_2$	**2be**	99	>98
14	Et	*i*-Pr[d]	**2bf**	0[e]	–
15	Et	*t*-Bu[d]	**2bg**	0[f]	–

[a] Yields refer to pure isolated products.
[b] Determined on the crude product.
[c] Together with small amounts of starting material.
[d] Reaction carried out in Et_2O.
[e] 85% of starting material recovered.
[f] 90% of starting material recovered.

When R^1 = Ph, the reaction shows in all cases a high stereochemical control. Yields vary from good to excellent. In addition the protocol has a general applicability, in fact a large variety of carbon frameworks can be introduced, including saturated alkyl chains, as well as alkynylic, allylic and benzylic moieties (Table 1, entries 1–6). Moreover, we wish to outline that this is the first methodology that allows bulky alkyl chains, such as *i*-Pr and *t*-Bu, to be

introduced with very satisfactory yields (Table 1, entries 7 and 8).

When R^1 is a linear alkyl group, as in **1b**, some problems arise in the organometallic addition to the carbonyl. Owing to the presence of a less hindered group bound to the carbonyl, the $A^{1,2}$ strain decreases with a consequent increased amount of **4B** at the equilibrium. Yields are excellent with benzylic and allylic derivatives (Table 1, entries 12 and 13), but they remarkably decrease with nonstabilized carbanionic moieties. In these cases, yields can be improved using a less coordinating and less polar solvent, such as Et_2O instead of THF, (Table 1, entries 9–11). However, when highly sterically hindered and highly basic carbanionic moieties, such as *i*-Pr and *t*-Bu, are present in the organocerium reagents the enolization process largely prevails even carrying out the reaction in Et_2O, (Table 1, entries 14 and 15).

The reaction proceeds in all cases with very high diastereoselectivity; indeed the exclusive formation of the diastereoisomer derived from the attack of the carbanionic moiety opposite to the α-methyl group was observed according to the mechanism depicted in Scheme 2. An important feature of this methodology is the opportunity to obtain both diastereoisomers of a certain β-hydroxy amide simply by exchanging the residue R^1 on the β-keto amide with R^2 in the organometallic reagent (Table 1, entry 1 and entry 9).

Organocerium reagents are frequently employed in large amount, and also in our procedure an excess of $R^2MgX{\cdot}CeCl_3$ is required. This can be partially due to interactions of the organocerium reagents with $TiCl_4$ present in the reaction mixture to give organotitanium species. However, the addition to the carbonyl proceeds through a direct attack of $R^2MgX{\cdot}CeCl_3$ on the intermediate **4**. A convincing evidence for this assumption arises from results obtained in the reaction with *i*-$PrMgCl{\cdot}CeCl_3$.[13] It is well known that *i*-propylmagnesium bromide smoothly rearranges, even at low temperatures, to *n*-propylmagnesium chloride in the presence of small amounts of $TiCl_4$.[14] In the reaction of *i*-$PrMgCl{\cdot}CeCl_3$ with **1a** (Table 1, entry 7) the exclusive incorporation of the α-branched chain was found in the final product **2ag**. Then the productive attack of *i*-$PrMgCl{\cdot}CeCl_3$ on the carbonyl group has to occur before any interactions with chlorotitanium species.

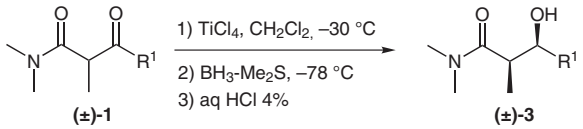
Moreover, alkynyltitanium derivatives are not stable even at low temperatures and cannot be successfully employed in synthesis.[15] The success of the reaction with the alkynyl framework can be explained again in terms of direct attack of the organocerium reagent at the carbonyl group.

The same concepts can be applied to the synthesis of functionalized amides carrying a secondary alcohol in β-position. This target can be achieved by developing an appropriate procedure for the reduction of the same intermediate **4**. In fact, the addition of an appropriate hydride ion source to the less hindered side of the metal chelate **4** will lead to *syn*-β-hydroxy amides **3**.

We tested various hydride donors. The best choice was the $BH_3{\cdot}Me_2S$ complex[16] since it can act at low temperatures in poorly coordinating solvents, such as CH_2Cl_2. The reasons of this choice are as follows: the small hydride ion is less sensitive, with respect to bulky carbanionic nucleophiles, to the stereofacial discrimination exerted by the axial methyl group in **4A** conformation. It was therefore necessary to increase the stability and rigidity of the chelate complex by carrying out the reaction in poorly coordinating solvents which cannot compete with the substrate in the coordination of Ti(IV).[17]

The results reported in Table 2 show that the reaction proceeds with high diastereoselectivity and in almost quantitative yields. It is interesting to note that, contrary to other borane complexes,[16] the reduction with $BH_3{\cdot}Me_2S$ does not proceed on to γ-aminols, but it stops at β-hydroxy amides.

Table 2 Diastereoselective Reduction of β-Keto Amides **1** with $BH_3{\cdot}Me_2S$, in CH_2Cl_2 at –78 °C



Entry	R^1	Product	Yield (%)[a]	de (%)[b]
1	Ph	**3a**	>99	96
2	Et	**3b**	>99	90
3	*i*-Pr	**3c**	>99	>98
4	C_5H_{11}	**3d**	>99	96
5	*t*-Bu	**3e**	>99	80
6	*c*-C_6H_{11}	**3f**	>99	>98
7	*p*-BrC_6H_4	**3g**	>99	>98

[a] Yields refer to pure isolated products.
[b] Determined on the crude product.

Due to the efficiency and the high diastereoselectivity observed, the $TiCl_4$-$BH_3{\cdot}Me_2S$ method represents a very useful alternative to previously reported procedures.[5]

Experimental Procedures

Herein we describe the typical practical synthetic procedures for the synthesis of β-hydroxy amides. Depending on the nature of the desired hydroxy amide, the addition or the reduction procedure should be chosen.

In fact, **Procedure 1**, carried out by addition of organocerium reagents to β-keto amides pretreated with $TiCl_4$, is used for the stereocontrolled preparation of amides having a tertiary alcohol in β-position. The described typical procedure employs THF as the solvent for the preparation of organocerium compounds. When a less coordinating solvent is required, the anhydrous $CeCl_3$ is suspended in Et_2O and a Et_2O solution of Grignard reagent is added.

On the other hand, when a secondary alcohol is required, **Procedure 2** can be used to successfully reduce the β-keto amides **1** with $BH_3{\cdot}Me_2S$ in CH_2Cl_2.

(2*R,3*R**)-3-Hydroxy-*N*,*N*,2,4-tetramethyl-3-phenylpentanamide (2ag); Typical Procedure 1**

The organocerium reagent should be prepared[8] separately.

$CeCl_3{\cdot}7H_2O$ (2.98 g, 8.0 mmol) was quickly and finely ground in a mortar and placed in a three-necked flask equipped with a stirrer bar and a three-way cock. The flask was immersed in an oil bath and gradually heated to 135–140 °C under vacuum (<0.5 mmHg). After 1 h at this temperature, the cerium chloride was completely dried in vacuo by stirring at the same temperature for an additional hour. While the flask was still hot, argon gas was introduced and the flask then cooled in an ice bath. THF (10 mL) freshly distilled from sodium/benzophenone was added all at once with vigorous stirring. The ice bath was removed and the suspension left to stir overnight under argon at r.t. Then, a 2 M THF solution of *i*-PrMgCl (4 mL, 8 mmol) was added dropwise to the stirring suspension of anhyd $CeCl_3$ at 0 °C under argon and the stirring was continued for 1.5 h. The reaction mixture resulted in a dark grey suspension. Meanwhile, an oven dried 100 mL three necked flask, equipped with a stirring bar, was charged with a solution of *N*,*N*,2-trimethyl-3-oxo-3-phenylpropanamide (**1a**, R^1 = Ph; 205 mg, 1.0 mmol) in anhyd CH_2Cl_2 (10 mL) under argon and cooled at –30 °C. Then a 1 M CH_2Cl_2 solution of $TiCl_4$ (1.05 mL, 1.05 mmol) was added. After 30 min at –30 °C, the reaction mixture was cooled to –78 °C and the previously prepared suspension of *i*-PrMgCl-$CeCl_3$ (8 mmol) in THF was added with a syringe. The mixture was left to stir at –78 °C for 30 min, and then quenched with aq HCl (ca. 1 M, 20 mL). The aqueous layer was separated and washed with additional Et_2O (20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated by rotary evaporation. The crude product was purified by silica gel column chromatography using a Et_2O–petroleum ether (80:20) mixture as eluent affording **2ag** (150 mg, 60%) as a yellow solid; mp 102.3–102.5 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.69 (d, 3 H, CH_3, $J_{H,H}$ = 6.7), 0.79 (d, 3 H, CH_3, $J_{H,H}$ = 7.0), 0.92 (d, 3 H, CH_3, $J_{H,H}$ = 7.0), 1.6 (br s, 1 H, OH), 2.00–2.15 (m, 1 H, CH), 3.02 (s, 3 H, CH_3), 3.20 (s, 3 H, CH_3), 3.40 (q, 1 H, CH, $J_{H,H}$ = 7.0), 7.15–7.40 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.4 (CH_3), 17.5 (CH_3), 18.4 (CH_3), 35.6 (CH_3), 37.5 (CH_3), 37.7 (CH), 38.9 (CH), 80.0 (C), 126.2 (CH), 127.4(CH), 141.7 (C), 178.0 (C).

(2*R,3*R**)-3-Hydroxy-*N*,*N*,2,-Trimethyl-3-phenylpropionamide (3a); Typical Procedure 2**

An oven dried 100 mL three necked flask, equipped with a stirring bar, was charged with a solution of *N*,*N*,2-trimethyl-3-oxo-3-phenylpropanamide (**1a**, R^1 = Ph; 205 mg, 1.0 mmol) in anhyd CH_2Cl_2 (10 mL) under argon and cooled at –30 °C. Then a 1 M CH_2Cl_2 solution of $TiCl_4$ (1.1 mL, 1.1 mmol) was added. After 30 min at –30 °C, the reaction was cooled to –78 °C and a 10 M solution of $BH_3{\cdot}Me_2S$ complex in Me_2S (0.5 mL, 5 mmol) was added dropwise. The mixture was left to stir at –78 °C for 3 h, and then quenched with aq HCl (ca. 1 M, 20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated by rotary evaporation. The crude product was purified by flash column chromatography on aluminum oxide using a Et_2O–petroleum ether (80:20) mixture as eluent affording **3a**[5] (205 mg, >99%) as a white solid.

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