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Highly stereoselective titanium-mediated addition of organocerium reagents to β-keto amides: an efficient synthesis of stereodefined β-hydroxy amides having a tertiary alcoholic fragment

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Abstract—A highly efficient and stereoselective protocol for the $TiCl_4$-mediated addition of organocerium reagents to β-keto amides is now available. The method allows the introduction of a large variety of carbon frameworks, including primary, secondary and tertiary alkyl chains, as well as aromatic, alkynylic and benzylic moieties, in high yields and with high stereoselection.

The construction of an alcoholic unit with stereodefined geometry represents an important target in organic synthesis.

A straightforward approach to this function consists in the conversion of a ketone into the corresponding alcohol by stereoselective reduction with hydrides or by addition of organometallic reagents.

One of the most common strategies utilizable in heterofunctionalized carbonylic systems having a stereogenic center near to the prochiral carbonylic function is based on the formation of a stable chelate complex between the bidentate substrate and an appropriate Lewis acid, followed by the selective attack of a hydride ion or a carbon nucleophile.

However, while these strategies have been successfully exploited in the reduction[1] of a large variety of functionalized ketones, less attention[2] has received their application to the addition of organometallic reagents. This is very likely due to the difficulty of avoiding undesired interferences between strong carbon nucleophiles and the Lewis acid moiety of the chelate complex.

Recently, we found that RMgX and RMgX–$CeCl_3$ reagents are able to add smoothly to a chloro Ti(IV)–alcoholate of a β-hydroxy ketone giving the expected tertiary alcohols in high yields and in high diastereomeric purity.[3] Nevertheless, this system should represent a particular and favorable case since the presence of the hydroxy group into the ketone framework allows the direct introduction of the Lewis acid functionality. Thus, the obtained trichloro–titanium alcoholate can organize itself into a very rigid and stable array having great stereofacial discrimination. At the same time a strong activation of the carbonyl function is generated through the internal Lewis acid coordinating action.

It seems, therefore, of great synthetic interest to investigate if this methodology can be applied to bidentate carbonylic substrates in which the formation of a covalent bond with the Lewis acid is not possible.

In this communication we report our preliminary results on titanium(IV)-mediated addition of organocerium compounds to *N,N,2*-trimethyl-3-oxo-3-phenylpropanamide (**1a**)[4] and to *N,N,2*-trimethyl-3-oxopentanamide (**1b**).[5]

Keywords: cerium reagents; diastereoselection; keto amides; hydroxy amides; tertiary alcohols.

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The chelate complex derived from the interaction between **1a** and $TiCl_4$ undergoes a smooth and stereoselective addition of R^1MgX–$CeCl_3$ reagents in THF at low temperature giving the expected hydroxy amide **3** in good to excellent yields. A typical procedure follows. To a solution of **1a** in CH_2Cl_2 at −30°C, $TiCl_4$ (1.05 equiv., 1 M solution in CH_2Cl_2) was added, under argon atmosphere. After 30 min, the reaction was cooled to −78°C and a large excess of organocerium reagent (8 equiv.) in THF was added. After 30 min the reaction was quenched with aqueous HCl (1 M); the usual work-up gave a crude product which was purified by chromatographic separation on a silica gel column (Et_2O/petroleum ether = 70/30).[6,7]

The reaction allows adding to the prochiral carbonylic group a large variety of carbon frameworks, including primary, secondary and tertiary alkyl chains, as well as alkynylic, allylic and benzylic moieties. Yields are generally high (see Table 1) except in the case of bulky carbon nucleophiles, such as *i*-Pr and *t*-Bu derivatives (60% yields in both cases). Moreover, some amounts of starting material were recovered (10–15%).[8] However, taking into account the difficulties in introducing secondary and tertiary fragments into a functionalized ketone, these results can be considered very satisfactory.

Table 1. R^1MgCl–$CeCl_3$ addition to **1a** in THF

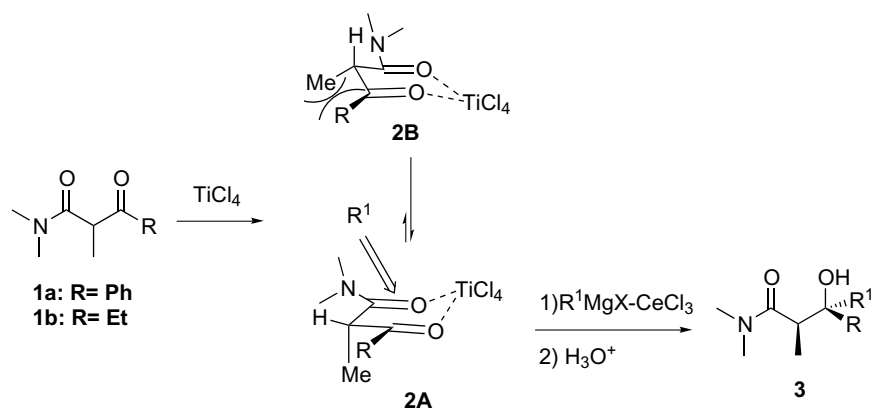
Entry	R^1 in R^1MgCl–$CeCl_3$	Product	Yields (%)[a]	de%[b]
1	Me	**3aa**	>99	>98
2	Et	**3ab**	65	>98
3	*n*-Bu	**3ac**	85	>98
4	$PhCH_2$	**3ad**	90	>98
5	PhC≡C	**3ae**	85	>98
6	CH_2=$CHCH_2$	**3af**	>99	>98
7	*i*-Pr	**3ag**	60[c]	>98
8	*t*-Bu	**3ah**	60[c]	>98

[a] Yields referred to pure isolated products.
[b] Determined on crude product.
[c] Together with small amounts of starting material (10–15%).

The reaction proceeds in all cases with very high diastereoselectivity;[9] 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 1.

More problems are present in the case of **1b**. Since this compound has an enolizable group bound to the carbonyl, proton abstraction can compete with addition when reagents containing non stabilized carbanionic moieties are used.[10] For example, the reaction of **1b** with $PhMgCl$–$CeCl_3$ gives the expected hydroxyamide **3bi** in 55% yield together with 30% of recovered starting material,[8] while the less basic benzyl and allyl reagents give the corresponding hydroxyamides **3bd** and **3bf** in 97 and 99% yield, respectively, (see Table 2). Carrying out the reaction in a less polar solvent such as Et_2O can lower the enolization process. This expedient allows increasing yields of the reaction with $PhMgCl$–$CeCl_3$ from 55 to 85%. In an analogous manner, diols **3ba** and **3bc** were obtained in 85 and 60% yield, respectively. 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. In fact in these cases 85 and 90% of starting material was, respectively, recovered after the acidic quenching.

The chelate complex **2** from **1b** (R = Et) suffers from an $A^{1,2}$ strain of lower entity with respect to that derived from **1a** (R = Ph). Therefore, the reaction between R^1MgX–$CeCl_3$ and **1b** may be expected to proceed with lower selectivity since the equilibrium is not completely shifted towards conformation **2A**, (see Scheme 1). Data reported in Table 2 are in good agreement with the above consideration. For example in the reaction with *n*-$BuMgCl$–$CeCl_3$, a de >98% and a de = 90% were found in the case of **1a** and **1b**, respectively, (see Table 1, entry 3 and Table 2, entry 2). A larger difference was observed in the case of alkynyl cerium reagents (Table 1 entry 5, Table 2 entry 6).



Scheme 1.

Table 2. $R^1MgCl–CeCl_3$ addition to **1b** in Et_2O or THF

Entry	R^1 in $R^1MgCl–CeCl_3$	Solvent	Product	Yields (%)[a]	de%[b]
1	Me	Et_2O	**3ba**	85	>98
2	*n*-Bu	Et_2O	**3bc**	60	94
3	Ph	Et_2O	**3bi**	85	>98
4	Ph	THF	**3bi**	55[c]	>98
5	$PhCH_2$	THF	**3bd**	97	>98
6	$PhC\equiv C$	THF	**3be**	60	40
7	$CH_2=CHCH_2$	THF	**3bf**	99	>98
8	*i*-Pr	Et_2O	**3bg**	0[d]	–
9	*t*-Bu	Et_2O	**3bh**	0[e]	–

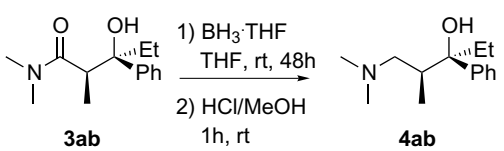
[a] Yields referred to pure isolated products.
[b] Determined on crude product.
[c] Together with 30% of starting material.
[d] 75% of starting material recovered.
[e] 60% of starting material recovered.

The addition of various organometallic reagents to 3-oxo-amides has been previously studied by Oshima, Utimoto and co-workers.[6] These authors reported that in order to obtain high stereoselectivity it is necessary to tune the choice of the reagent to the structure of the carbon chains to be introduced at the prochiral carbonylic group. For example, the best results in allylation were obtained using zinc derivatives, while PhMnI in ether was the best reagent for introducing a phenyl group.

The methodology reported in the present work appears to offer a more efficient and general solution since in all cases an organocerium derivative is used. In addition a large variety of carbon fragments can be inserted. It is in fact noteworthy, the possibility of adding secondary and tertiary organocerium reagents although this reaction is restricted to compounds having a non enolizable group bound to the carbonylic function.

β-Hydroxy amides with stereodefined geometry are important intermediates in organic synthesis. For example we found that compound **3ab** can be quantitatively converted into the *N*,*N*-dimethyl hydroxy amino derivative by treatment with BH_3–THF complex in THF at rt for 48 h (Scheme 2).

Studies are in progress in our laboratories to extend this protocol to other kinds of bidentate carbonylic compounds as well as to the introduction of functionalized carbon chains.



3ab **4ab**

Scheme 2.

Acknowledgements

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7. Spectroscopical data of unknown products follow:
(2*R,3*R**)-3-Hydroxy-*N*,*N*,2-trimethyl-3,4-diphenylbutanamide (3ad)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.93$ (d, 3H, CH_3, $J_{HH}=7.1$), 1.6 (bs, 1H, OH), 3.06 (bs, 5H, CH_2 and CH_3), 3.17 (s, 3H, CH_3), 3.19 (q, 1H, CH, $J_{HH}=7.1$), 7.05–7.40 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 12.7 (CH_3), 35.6 (CH_3), 37.6 (CH_3), 41.9 (CH), 48.7 (CH_2), 76.2 (C), 125.8 (CH), 125.9 (CH), 126.4 (CH), 127.3 (CH), 127.7 (CH), 130.5 (CH), 137.0 (C), 143.7 (C), 177.8 (C).
(2*R,3*R**)-3-Hydroxy-*N*,*N*,2-trimethyl-3,5-diphenyl-4-pentynamide (3ae)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.94$ (d, 3H, CH_3, $J_{HH}=6.9$), 1.6 (bs, 1H, OH), 3.09 (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 3.24 (q, 1H, CH, $J_{HH}=6.9$), 7.20–7.70 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=11.2$ (CH_3), 35.7 (CH_3), 37.8 (CH_3), 46.0 (CH), 72.7 (C), 83.8 (C), 92.8 (C), 122.7 (C), 125.9 (CH), 127.5 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 131.6 (CH), 141.7 (C), 177.0 (C).
(2*R,3*R**)-3-Hydroxy-*N*,*N*,2,4-tetramethyl-3-phenylpentanamide (3ag)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.69$ (d, 3H, CH_3, $J_{HH}=6.7$), 0.79 (d, 3H, CH_3, $J_{HH}=7.0$), 0.92 (d, 3H, CH_3, $J_{HH}=7.0$), 1.6 (bs, 1H, OH), 2.00–2.15 (m, 1H, CH), 3.02 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 3.40 (q, 1H, CH, $J_{HH}=7.0$), 7.15-7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=13.4$ (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*S**)-3-Hydroxy-*N*,*N*,2,4,4-pentamethyl-3-phenylpentanamide (3ah)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.86$ (s, 9H, CH_3), 0.88 (d, 3H, CH_3, $J_{HH}=7.0$), 1.6 (bs, 1H, OH), 3.01 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.47 (q, 1H, CH, $J_{HH}=7.0$), 7.15–7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=15.7$ (CH_3), 27.2 (CH_3), 35.1 (CH), 35.8 (CH_3), 37.6 (CH_3), 39.9 (C), 81.8 (C), 125.9 (CH), 126.1 (CH), 127.6 (CH), 128.2 (CH), 143.8 (C), 179.0 (C).
(2*R,3*R**)-3-Ethyl-3-hydroxy-*N*,*N*,2-trimethylheptanamide (3bc)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.80$ (t, 3H, CH_3, $J_{HH}=7.7$), 0.87 (t, 3H, CH_3, $J_{HH}=7.1$), 1.13 (d, 3H, CH_3, $J_{HH}=7.2$), 1.15–1.65 (m, 8H, CH_2), 2.70 (q, 1H, CH, $J_{HH}=7.2$), 2.97 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 3.1 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=7.6$ (CH_3), 11.4 (CH_3), 14.0 (CH_3), 23.2 (CH_2), 25.7 (CH_2), 26.6 (CH_2), 35.3 (CH_3), 36.8 (CH_2), 37.5 (CH_3), 38.9 (CH), 74.7 (C), 178.1 (C).
(2*R,3*R**)-3-Benzyl-3-hydroxy-*N*,*N*,2-trimethylpentanamide (3bd)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.99$ (t, 3H, CH_3, $J_{HH}=7.7$), 1.15 (d, 3H, CH_3, $J_{HH}=7.2$), 1.30–1.55 (m, 2H, CH_2), 1.6 (bs, 1H, OH), 2.57 (q, 1H, CH, $J_{HH}=7.2$), 2.67 (d, 1H, CH_2, $J_{HH}=13.7$), 2.93 (s, 3H, CH_3), 2.96 (d, 1H, CH_2, $J_{HH}=13.7$), 2.99 (s, 3H, CH_3), 7.15–7.30 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=7.5$ (CH_3), 11.3 (CH_3), 26.6 (CH_2), 35.0 (CH_3), 37.0 (CH_3), 38.5 (CH), 42.7 (CH_2), 75.5 (C), 125.7 (CH), 127.0 (CH), 129.8 (CH), 137.6 (C), 177.7 (C).
(2*R,3*S**)-3-Ethyl-3-hydroxy-*N*,*N*,2-trimethyl-5-phenyl-4-pentynamide (3be)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=1.12$ (t, 3H, CH_3, $J_{HH}=7.6$), 1.20 (d, 3H, CH_3, $J_{HH}=7.0$), 1.60–1.75 (m, 1H, CH_2), 1.85–1.95 (m, 1H, CH_2), 1.9 (bs, 1H, OH), 3.02 (s, 3H, CH_3), 3.07 (q, 1H, CH, $J_{HH}=7.0$), 3.13 (s, 3H, CH_3), 7.25–7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=8.6$ (CH_3), 10.7 (CH_3), 31.1 (CH_2), 35.5 (CH_3), 37.7 (CH_3), 41.5 (CH), 71.8 (C), 83.3 (C), 92.0 (C), 122.8 (C), 128.1 (CH), 131.5 (CH), 131.7 (CH), 177.2 (C).
(2*R,3*R**)-3-Ethyl-3-hydroxy-*N*,*N*,2-trimethyl-5-hexenamide (3bf)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.89$ (t, 3H, CH_3, $J_{HH}=7.5$), 1.15 (d, 3H, CH_3, $J_{HH}=7.0$), 1.30–1.45 (m, 1H, CH_2), 1.55–1.75 (m, 1H, CH_2), 2.15 (dd, 1H, CH_2, $J_{HH}=8.6$, $J_{HH}=14.0$), 2.38 (tdd, 1H, CH_2, $J_{HH}<1$, $J_{HH}=8.6$, $J_{HH}=14.0$), 2.67 (q, 1H, CH, $J_{HH}=7.0$), 2.97 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 3.3 (bs, 1H, OH), 4.90–5.10 (m, 2H, CH_2), 5.70–5.90 (m, 1H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=7.3$ (CH_3), 11.5 (CH_3), 27.6 (CH_2), 35.3 (CH_3), 37.4 (CH_3), 39.0 (CH), 42.3 (CH_2), 74.9 (C), 116.9 (CH_2), 134.7 (C), 178.0 (C).
(2*S,3*R**)-1-(Dimethylamino)-2-methyl-3-phenyl-3-pentanol (4ab)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.78$ (t, 3H, CH_3, $J_{HH}=7.2$), 0.84 (d, 3H, CH_3, $J_{HH}=7.2$), 1.70–1.85 (m, 1H, CH_2), 1.85–2.10 (m, 3H, OH, CH and CH_2), 2.21 (dd, 1H, CH_2, $J_{HH}=3.9$, $J_{HH}=13.2$), 2.26 (s, 6H, CH_3), 2.59 (dd, 1H, CH_2, $J_{HH}=8.9$, $J_{HH}=13.2$), 7.20–7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=7.8$ (CH_3), 14.7 (CH_3), 27.0 (CH_2), 41.0 (CH), 46.1 (CH_3), 63.8 (CH_2), 79.9 (C), 125.9 (CH), 126.5 (CH), 127.6 (CH), 146.7 (C).
8. Starting material can be easily separated from the product by column chromatography.
9. Diastereomeric excesses were calculated by ^{13}C NMR experiments using long delay times. Values obtained from experiments on the crude of the reaction were identical to those calculated for the mixture of diastereoisomers recovered after column chromatographic purification. Structural assignments were made by comparison of spectroscopic data with those reported in literature (see Ref. 6). Structural assignments of unknown compounds were made on the basis of NOE NMR experiments.
10. Owing to stereoelectronic reasons, the α-hydrogen which is in pseudo–equatorial position in the chelated complex **2** is not easily abstracted as a proton.