Diastereoselective Lewis Acid Mediated Reductions of α-Alkyl-β-Functionalized Carbonyl Compounds

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A high stereochemical induction has often been observed in the reduction of ketones with stereogenic centres close to the carbonyl function. The level of stereoselectivity is particularly high when "hard" donor groups such as nitrogen or oxygen atoms are present in the molecule. These results have been commonly explained in terms of a chelate-controlled process. However, this interpretation has recently been challenged, and in many cases an open-chain mechanism can better account for the observed results. Thus, Lewis-acid-mediated chelation and nonchelation control is one of the most fundamental and practical concepts in transferring a nucleophile moiety to carbonyl compounds. In order to clarify the role of a hard Lewis acid in controlling the stereochemical outcome of a given reaction, the Lewis acid mediated reduction of a series of α-alkyl-β-functionalized carbonyl compounds with metallic hydrides in various solvents was recently investigated. In particular, the results derived from the reductions in the presence of dry $CeCl_3$ were compared to those obtained under the same experimental conditions but in the presence of $TiCl_4$, whose ability to form chelation complexes is well established. These investigations show a stereochemical outcome that is fully consistent with a chelation-controlled pathway in the case of titanium, and an open-chain-controlled pathway in the case of $CeCl_3$. The strongly chelating $TiCl_4$ led to the *syn* isomer in high diastereomeric excess in noncoordinating solvents at –78 °C with borane–Lewis base complex reducing agents, while nonchelating $CeCl_3$ produced a high excess of the *anti* isomer in coordinating solvents at the same temperature with metal borohydrides as reducing agent. Therefore, our method based on the choice of $CeCl_3$ or $TiCl_4$ as a Lewis acid under the reported conditions represents a significant contribution to the development of new stereoselective reductions of α-alkyl-β-functionalized ketones. These procedures are one of the best known ways to obtain an alcoholic moiety.

1. Introduction

β-Hydroxy-functionalised compounds with a stereodefined geometry are an important target in organic chemistry since these units are present in various natural products.[1] Various strategies have therefore been developed for their synthesis. Among these, the most direct approaches are the aldolic condensation[2] between a functionalised enolate and an aldehyde, and the stereoselective addition of a reducing agent to the carbonyl moiety of a β-functionalized ketone carrying a stereocenter in the α-position. Since the stereochemical outcome of the aldol condensation is hardly controllable, the latter approach seems to be a more promising and practicable route. Thus, the diastereoselective reduction of α-substituted-β-functionalized carbonyl compounds remains an active, widespread area of organic chemistry, and the coordination with a complex metal hydride reagent in acyclic systems plays an important role in the stereochemical efficiency of the reaction.[3] The different reagents reported in the literature show characteristic advantages and disadvantages. Factors such as handling of reagents, strict reaction conditions, costs, and poor yields of the desired diastereomer product are some of the drawbacks associated with most of them. Therefore, the development of a mild and selective reducing agent for the diastereoselective reduction of a variety of carbonyl compounds still attracts a great deal of attention from organic chemists.

Lewis acids are useful reagents because they can bind complementary basic molecules and thereby modify their

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

reactivity.[4] Among the Lewis acid promoted reactions, those involving the formation of complexes between carbonyl compounds and Lewis acids are particularly important since these complexes play a fundamental role in organic and bioorganic chemistry. In fact, by reducing the electron density on the carbonyl carbon, enhancing the polarity of the carbon–oxygen double bond and lowering the energy of the lowest unoccupied molecular orbital, the complexation of carbonyl compounds by a Lewis acid can have dramatic kinetic effects.[5] Furthermore, Lewis acids can also have beneficial effects on regioselectivity and stereoselectivity.[6] For all of these reasons, the use of Lewis acids represents a valuable way to promote and control the reactivity of β-functionalised ketones toward metal hydrides. Since the most direct way to obtain complex alcohols containing stereodefined asymmetric centres is the Lewis acid mediated reduction of functionalised carbonyl compounds containing a chiral α-carbon, this organic transformation has been thoroughly described in numerous reviews and original papers. Herein, a brief overview of the most recent diastereoselective protocols for the Lewis acid promoted reduction of β-functionalised carbonyl compounds with an asymmetric α-carbon in their racemic form is presented (Scheme 1). A series of α-alkyl-β-functionalised ketones **1** were synthesized with varying bulkiness of the R^1 and R^2 groups. These compounds were reduced with hy-

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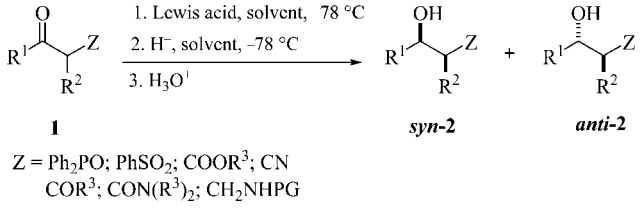
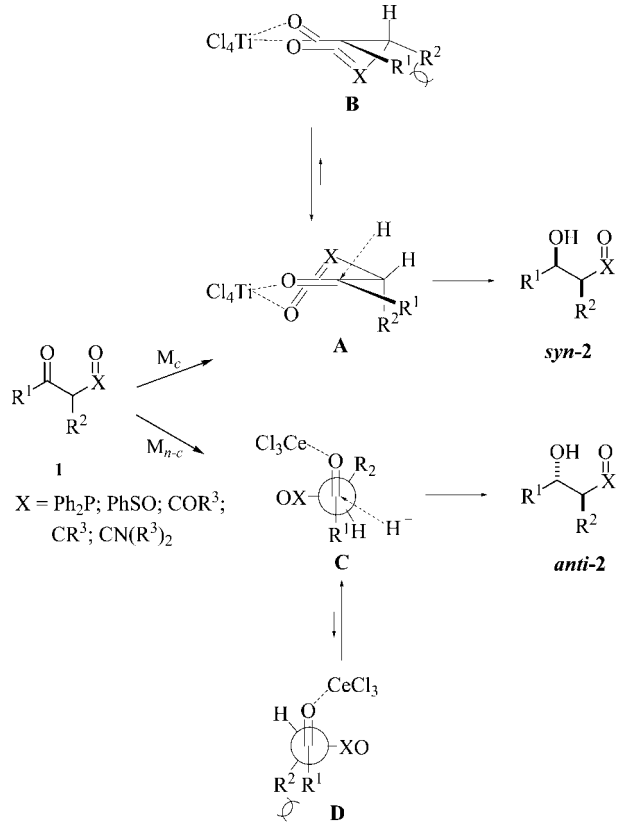
drides or borane–Lewis base complexes[7] in the presence of titanium tetrachloride or cerium trichloride as the Lewis acid. We found it convenient, thus, to gather the reduction into two distinct mechanisms, and, in fact, the correct choice of hydrides, solvent, and especially Lewis acid, has been found to be the switch for either chelation or nonchelation control in order to obtain high diastereomeric excess. Temperature is also an important factor in these reductions, and values higher than –78 °C considerably lower both selectivity and yields.



Scheme 1. Diastereoselective reduction of β-functionalised ketones **1**.

2. Opposite Stereochemical Effects Exerted by $CeCl_3$ and $TiCl_4$

Two methods of stereocontrol determine which diastereomer is obtained as the major product from the reduction of an α-alkyl-β-functionalised carbonyl compound. Chelation control,[8] where a Lewis acid coordinates to the carbonyl oxygen and the β-Lewis base group, enforces a *syn*-periplanar relationship between these two groups (Scheme 2), and can explain the *syn* diastereomer (***syn*-2**). Felkin–Anh control, where a dihedral angle of about 90° between the β-Lewis base and carbonyl groups maximizes stereoelectronic interactions in the transition state,[9] justifies the formation of the *anti* diastereomer (***anti*-2**), as shown, for example, in the results obtained by Yamada et al. for borohydride reductive desymmetrization of α-alkyl-1,3-dicarbonyl compounds.[10] Since the ability of titanium(IV) salts to give chelation complexes is well documented,[11] we first discuss the reduction mediated by $TiCl_4$. In the early results, we found that the reduction of **1** in dichloromethane at low temperature with a 2 M solution of lithium borohydride (1 equiv.) in the presence of $TiCl_4$ (1.2 equiv.) led to the prevalent formation of *syn* β-hydroxy compounds (***syn*-2**). This is clearly due to chelation by the metal atom, which creates a bridge between the oxygen atoms of the C=O and X=O groups. The resulting six-membered cyclic intermediate is then attacked by the incoming hydride, preferentially from the opposite, less-hindered, axial side of the most populated conformation **A** (Scheme 2). In 1995 DiMare et al. reported that the BH_3·py system efficiently reduces ketones in the presence of titanium tetrachloride.[12] As a consequence, aminoboranes reduce the carbonyl compounds **1** as efficiently as $LiBH_4$/THF, but with much higher stereoselectivity. From a practical point of view, the $LiBH_4$/THF method requires a simpler workup, but the use of a coordinating solvent, such as THF, which can compete with the substrate in coordinating the titanium atom, leads to loss of diastereoselectivity. Dichloromethane turned out to be a suitable solvent for the reduction.



Scheme 2. Expected stereochemical control in the reduction of α-substituted-β-functionalised ketones with hydrides (H^-) in the presence of chelating (Mc) or nonchelating (Mn-c) Lewis acids.

The most relevant finding from these diastereoselective $TiCl_4$-mediated reductions of α-alkyl-β-functionalised carbonyl compounds is that reactions with BH_3–Lewis base complexes always ensure a high stereoselectivity, regardless of the size of the R^1 and R^2 substituents. In a chelation-controlled reaction the minimum level of stereoselectivity should be observed when R^1 and R^2 are methyl groups, since this is the sterically least demanding alkyl group. Otherwise, from chelation control results achieved with $Zn(BH_4)_2$,[8a,13] CF_3COOH,[14] metal chlorides[15] and $R_3SnH/TiCl_4$,[16] a *syn*/*anti* ratio of 90:10 was obtained in this unfavourable case under the same experimental conditions as used for $TiCl_4/BH_3$–Lewis base complexes. The alternative method based on a Luche reduction[17] of α-alkyl-β-functionalised carbonyl compounds only gives good stereoselectivity when a secondary alkyl substituent is present in the α-position. In fact, straight-chain alkyl groups reverse the selectivity.[18] Thus, we first tested the reduction of carbonyl compounds **1** in the presence of dry $CeCl_3$[19] with the reducing system BH_3·py/CH_2Cl_2, which is highly efficient with $TiCl_4$. Unfortunately, no reaction was observed, even after prolonged reaction times and at high reaction temperature. A complex between cerium(III) chloride and the β-functionalised carbonyl compound was formed, since the addition of the substrate to a suspension of the

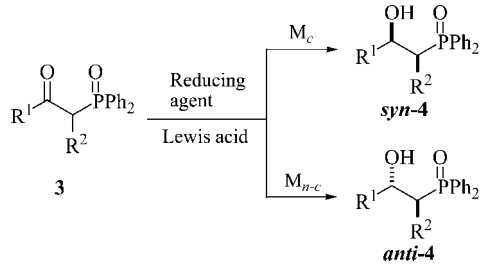
cerium salt resulted in a clear solution after about one hour. However, the paramagnetism of the cerium salt prevents the useful NMR information on the structure of this complex from being obtained.[20]

The reduction of the β-functionalised carbonyl compound **1** proceeded successfully when a 2 M THF solution of $LiBH_4$ was employed under the same experimental conditions as adopted with titanium tetrachloride. The reaction gave the expected α-substituted-β-functionalised hydroxy compounds **2** in almost quantitative yields, but with reversed stereoselectivity with respect to the BH_3·py/$TiCl_4$ system. These results strongly support an open-chain mechanism, and the *anti* selectivity may be explained by the Felkin–Anh model (Scheme 2). According to the Bürgi–Dunitz trajectory,[21] the attack at the **C** conformation should be directed by steric effects. Also, the use of coordinating solvents should give better results with a nonchelating Lewis acid mechanism. In fact, THF is the best solvent to ensure almost quantitative yields and high diastereoselectivities. Thus, although anhydrous $CeCl_3$ is highly hygroscopic[22] and a powerful Lewis acid, we believe no chelation occurs between the β-functionalised carbonyl compounds and $CeCl_3$; the results obtained with $TiCl_4$ support a mechanism involving a chelate intermediate. Moreover, since Greeves et al.[23] have shown quite clearly that cerium(III) can be chelated by 1,2-diols, we have considered the possibility that the real reducing agent of the carbonyl moiety is not the BH_4^- anion. It may be, however, that the hydride of boron can reduce the $CeCl_3$ to CeH_nCl_{3-n} in a polar solvent such as THF. However, ^{1}H NMR measurements demonstrated that, under these conditions, there was no generation of cerium hydride species by a transmetalation reaction between cerium trihalide and lithium borohydride.[24] Furthermore, Fukazawa et al.[25] have suggested that such hydride species are unlikely to be the reducing agent in the reduction reactions with $LiAlH_4$ in the presence of $CeCl_3$; therefore, a similar behaviour seems to be plausible in the $CeCl_3$-mediated reductions of α-alkyl-β-functionalised carbonyl compounds.

Dry cerium(III) chloride, then, is not able to give chelation with β-functionalised carbonyl compounds **1**, but its presence is essential to obtain high yields and diastereoselectivities; no reaction occurs at –78 °C in the absence of $CeCl_3$. Shorter reaction times could be obtained at 0 °C, but to the detriment of the diastereomeric ratio. Moreover, the yields were lower since an insoluble polymer was formed. At 0 °C in the presence of $CeCl_3$, high yields were obtained, but the same low stereoselectivity was observed. The presence of the cerium salt is essential to obtain both high yields and high stereochemical efficiency, since the reaction can then be carried out at lower temperatures. According to Boltzmann's law, the population of the more stable conformer increases as the temperature decreases.

2.1. Diastereoselective Reduction of α-Alkyl-β-keto Phosphane Oxides

A general, highly efficient methodology[26] for obtaining both *syn* and *anti* β-hydroxy phosphane oxides by reduction of the corresponding β-keto phosphane oxides has been described (Scheme 3). Strongly chelating $TiCl_4$ led to the *syn* isomer in high diastereomeric excess in noncoordinating solvents (CH_2Cl_2) at –78 °C with BH_3·py as reducing agent, while nonchelating $CeCl_3$ gave a high excess of the *anti* isomer in coordinating solvents (THF) at the same temperature with $LiBH_4$ as reducing agent (Table 1). The most relevant finding from the data reported in Table 1 is that when R^2 is an α-branched alkyl group such as cyclohexyl, the *syn* isomer prevails even in the presence of $CeCl_3$ (Table 1, entry 6); this demonstrates that the steric demand of this group is higher than that of the diphenylphosphinoyl moiety. In the nonchelated model, the cyclohexyl becomes the largest group and **E** is the most populated conformation (Scheme 4). Moreover, the steric effect prevails over the



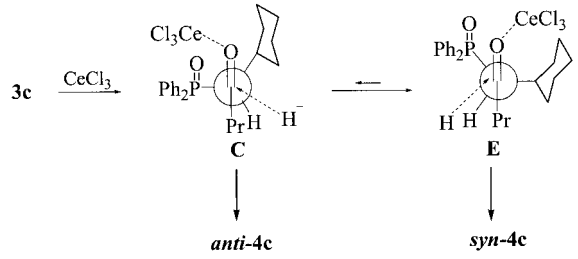
Scheme 3. Diastereoselective reduction of α-alkyl-β-keto phosphane oxides.

Table 1. Stereoselective reduction of β-keto phosphane oxides **3** to β-hydroxy phosphane oxides **4**.

Entry	**3**	R^1	R^2	Reducing agent	Lewis acid[a]	Product **4**	*syn*:*anti*[b]	Yield [%][c]
1	**3a**	Me	Me	BH_3·py	$TiCl_4$	**4a**	90:10	>98
2	**3a**	Me	Me	$LiBH_4$	$CeCl_3$	**4a**	25:75	>98
3	**3b**	Me	Ph	BH_3·py	$TiCl_4$	**4b**	>99:01	>98
4	**3b**	Me	Ph	$LiBH_4$	$CeCl_3$	**4b**	02:98	>98
5	**3c**	c-C_6H_{11}	*n*-Pr	$LiBH_4$	$TiCl_4$	**4c**	97:03	95
6	**3c**	c-C_6H_{11}	*n*-Pr	$LiBH_4$	$CeCl_3$	**4c**	80:20	80
7	**3d**	*n*-Pr	–C≡C–Ph	$LiBH_4$	$TiCl_4$	**4d**	98:02	90
8	**3d**	*n*-Pr	–C≡C–Ph	$LiBH_4$	$CeCl_3$	**4d**	50:50	95
9	**3e**	CH_2Ph	Me	BH_3·py	$TiCl_4$	**4e**	97:03	>98
10	**3e**	CH_2Ph	Et	$LiBH_4$	$CeCl_3$	**4e**	04:96	>98

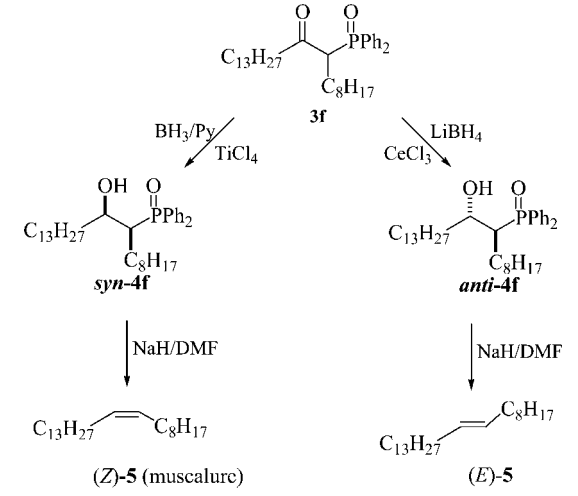
[a] Noncoordinating solvents (CH_2Cl_2) for $TiCl_4$ and coordinating solvents (THF) for $CeCl_3$. [b] Determined by ^{1}H and ^{13}C NMR spectroscopy. [c] Calculated for the mixture of diastereomers isolated by column chromatography.

Coulombic repulsion between the electronegative Ph_2PO and the incoming hydride in conformation **E**.[9d,27] It should be noted that the cylindrical symmetry of alkynyl groups in the R^1 position reduces the unfavourable steric interactions between the two substituents R^1 and R^2 (Table 1, entry 8).



Scheme 4.

The highly stereoselective synthesis of *syn* and *anti* β-hydroxy phosphane oxides would open up the way to stereoselective Horner olefination. Thus, we have modified the previously reported procedure[28] to prepare a large variety of α-alkyl-β-keto phosphane oxides, which can undergo facile stereospecific elimination of diphenylphosphinoate anion in basic media. The system proposed by Warren (KH in DMF)[29] for the synthesis of disubstituted alkenes was very efficient in most cases. Thus, a particular attention has been focused on the synthesis of muscalure,[30] the pheromone of the domestic fly, from ***syn*-4f** and its (*E*)-isomer from ***anti*-4f** (Scheme 5). For this purpose, the reaction mixtures obtained from reduction of **3f** with $TiCl_4/BH_3$·py and $CeCl_3/LiBH_4$, respectively, were submitted, without purification, to elimination according to Warren's procedure. Muscalure (*Z*)-**5** was obtained in 95% yield, and with 93:7 diastereomeric purity; the corresponding values for (*E*)-**5** were 98% and 92:8, respectively.



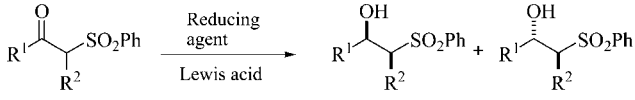
Scheme 5. Synthesis of muscalure and its (*E*)-isomer.

2.2. Diastereoselective Reduction of α-Alkyl-β-keto Sulfones

In the last few years organic sulphur compounds have become increasingly important in organic synthesis. In this field, the benzenesulfonyl group is a versatile and flexible functionality that enjoys increasing popularity as a temporary control element and activating group in organic synthesis.[31] In particular, β-hydroxy sulfones are versatile intermediates for the synthesis of 2,5-disubstituted tetrahydrofurans.[32] These units are found in many natural products, including polyether antibiotics[33] and furanoterpenes.[34] For this reason, we have reported[35] an extremely simple and effective alternative procedure for the highly stereoselective synthesis of *syn*- or *anti*-α-alkyl-β-hydroxy sulfones by the reduction of the corresponding β-keto sulfones[36] with BH_3·py or lithium triethylborohydride ($LiEt_3BH$) in the presence of $TiCl_4$ or dry $CeCl_3$, respectively (Table 2). The reduction of β-keto sulfones **6** with a THF solution of hydride in the presence of dry $CeCl_3$ proceeds with higher diastereoselectivity than the $TiCl_4$ Lewis acid promoted reaction (Table 2, entries 1 and 2).

The fact that $CeCl_3/LiEt_3BH$ gave essentially opposite stereoselectivity with respect to the $TiCl_4/BH_3$·py system indicates that the β-chelate pathway does not participate in these cases to a noticeable extent. We have proposed that

Table 2. Stereoselective reduction of β-keto sulfones **6** to β-hydroxy sulfones **7** with hydride (H^-) in the presence of Lewis acids at –78 °C.



6 ***syn*-7** ***anti*-8**

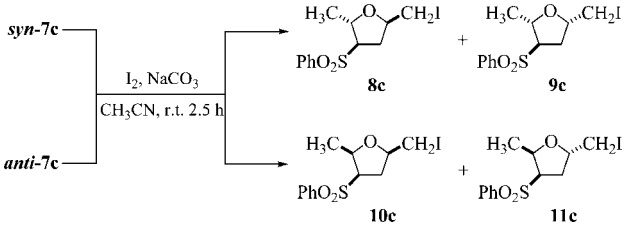
Entry	**6**	R^1	R^2	Reducing agent	Lewis acid	Product **7**	*syn*:*anti*[a]	Yield [%][b]
1	**6a**	Me	Me	BH_3·py	$TiCl_4$	**7a**	87:13	85
2	**6a**	Me	Me	$LiEt_3BH$	$CeCl_3$	**7a**	01:99	85
3	**6b**	Me	Et	BH_3·py	$TiCl_4$	**7b**	90:10	90
4	**6b**	Me	Et	$LiEt_3BH$	$CeCl_3$	**7b**	03:97	88
5	**6c**	c-C_6H_{11}	allyl	BH_3·py	$TiCl_4$	**7c**	93:07	87
6	**6c**	c-C_6H_{11}	allyl	$LiEt_3BH$	$CeCl_3$	**7c**	02:98	88
7	**6d**	4-MeOPh	Et	BH_3·py	$TiCl_4$	**7d**	94:06	88
8	**6d**	4-MeOPh	Et	$LiEt_3BH$	$CeCl_3$	**7d**	01:99	81
9	**6e**	4-NO_2Ph	Et	BH_3·py	$TiCl_4$	**7e**	93:07	83
10	**6e**	4-NO_2Ph	Et	$LiEt_3BH$	$CeCl_3$	**7e**	01:99	82

[a] Determined by ^1H and ^{13}C NMR spectroscopy. [b] Calculated for the mixture of diastereomers isolated by column chromatography.

the former system reacts mainly under nonchelation control due to the weak donor ability of the sulfonyl group.[37]

Furthermore, the parent compound of $LiEt_3BH$, lithium borohydride,[25] does not work at –78 °C either with or without $CeCl_3$. To eliminate complexity due to the disproportion of the reducing species, those having complex hydride anions of a less dissociative nature should have been the choice. After examination of various types of metal hydride complex, $LiEt_3BH$ was found to be among the best. The data clearly reveal that lithium triethylborohydride is an exceptionally powerful hydride reducing agent,[38] far more powerful than lithium borohydride. Nonetheless, $LiEt_3BH$ exhibits a remarkable selectivity, a property normally considered to be characteristic of relatively mild reducing agents such as lithium borohydride.

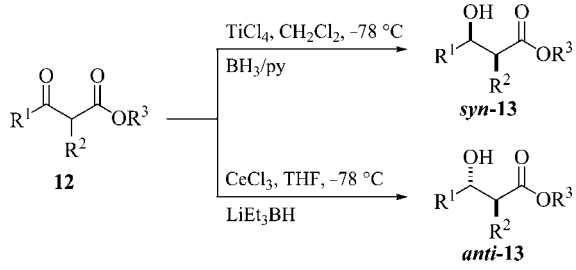
In order to extend this procedure to obtain both *syn*- and *anti*-α-alkyl-β-hydroxy sulfones by reduction of the corresponding β-keto sulfones, the stereoselectivity of this reaction was examined (Table 2, entries 5 and 6). The adducts are key intermediates in the synthesis of 2,5-disubstituted tetrahydrofurans with high regioselectivity, since they can undergo easy electrophilic cyclization.[39] For this purpose, the reaction mixtures obtained from reduction of **6c** with $TiCl_4/BH_3$·py and $CeCl_3/LiEt_3BH$, respectively, were separated (Table 2, entries 5 and 6, respectively). These compounds, when submitted to iodocyclization,[40] gave the 2,5-disubstituted tetrahydrofurans in high yields; no formation of a six-membered cyclic product was observed (Scheme 6). To elucidate the stereochemical outcome of these two reactions, the four possible isomeric products generated (**8c**–**11c**) were isolated and characterized by ^1H and ^{13}C NMR spectroscopy. In the products (**10c** and **11c**), the methyl group must be *cis* to the sulfonyl group because its proton signal appears at lower field (δ = 1.53 and 1.61 ppm). Moreover, in the *trans* 2,5-disubstituted tetrahydrofurans (**8c** and **11c**), one of the proton signals of the methylene group in the ring appears at lower field owing to the deshielding effects of both sulfonyl and iodomethyl groups *cis* to the proton.[41] These findings suggest that the introduction of a sulfonyl group facilitates the separation and the identification of the products. Since a sulfonyl and iodine can be replaced by other functional groups, this strategy may be applicable to organic synthesis.



Scheme 6. Synthesis of 2,5-disubstituted tetrahydrofuran units.

2.3. Diastereoselective Reduction of α-Alkyl-β-keto Esters

There is a continuing need for a new direct reduction of the carbonyl group of ketones with an adjacent asymmetric α-carbon in their racemic form to the corresponding alcohols.[42] Particular interest has been focused on two strategies (chelation and nonchelation) that enable the achievement of an opposite sense of diastereoselectivity by the appropriate choice of reducing systems. We have found that a simple and effective strategy[23] for a highly diastereoselective synthesis of *syn*- or *anti*-α-alkyl-β-hydroxy esters is represented by the reduction of the corresponding β-keto esters by BH_3·py or $LiEt_3BH$[34] in the presence of $TiCl_4$ or dry $CeCl_3$, respectively (Scheme 7). These methods can be successfully applied to a variety of natural product syntheses,[32] including β-lactams[43] and β-lactone antibiotics.[44] Thus, this diastereoselective reduction represents an attractive alternative to stereoselective aldol condensation of various metal enolates, which has been successfully employed for such a purpose.[45]



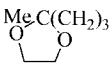
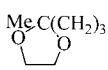
Scheme 7. Diastereoselective reduction of β-keto esters.

The high diastereoselectivity observed in the reduction with the $TiCl_4/BH_3$·py system (Table 3) is probably a consequence of the generally strong ability of titanium(IV) compounds to engage in chelation-controlled carbonyl addition.[46] It is obvious that every increase in the bulkiness of R^2 shifts the conformational equilibrium toward the **A** conformation (Scheme 2) and increases the *syn*/*anti* ratio.

While the reducing system BH_3·py is highly efficient with $TiCl_4$, no reaction with $CeCl_3$ was observed, and at –78 °C the starting material was recovered quantitatively. On the other hand, the reaction of **12** with a solution of $LiEt_3BH$ in the presence of dry $CeCl_3$ gave the α-alkyl-β-hydroxy esters **13**, but with lower and reversed stereoselectivity to the $TiCl_4/BH_3$·py system. The *anti* selectivity for the system $CeCl_3/LiEt_3BH$ may be explained by a Felkin–Anh model, and this explanation was further supported by the fact that the *anti*-diastereoselectivity was enhanced in the reduction of the more bulky *tert*-butyl esters (Table 3, entries 12 and 14). It is known that in the nonchelation control mechanism the diastereoselectivity (*syn*/*anti* ratio) varies widely depending on the chemical structure of the α-alkyl substituent other than with the size of the alkoxy ester.[47]

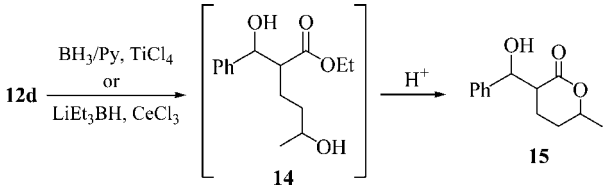
On extending the procedure to obtain both *syn*- and *anti*-α-alkyl-β-hydroxy esters, the stereoselectivity of the reduction of **12** in the presence of other functionalities was examined. The isolated ester function was stable under these reaction conditions (Table 3, entries 5 and 6). In addition, when the substrate contains an acetal moiety (**12e**), the carbonyl group can be selectively reduced with $CeCl_3/LiEt_3BH$ (Table 3, entry 10). However, no selectivity was obtained, and the acetal moiety was also cleaved when the

Table 3. Stereoselective reduction of β-keto esters **12** mediated by a Lewis acid.

Entry	12	R^1	R^2	R^3	Method[a]	Product 13	*syn*:*anti*[b]	Yield (%)[c]
1	**12a**	Me	$PhCH_2$	Et	A	**13a**	99:01	93
2	**12a**	Me	$PhCH_2$	Et	B	**13a**	13:87	92
3	**12b**	Ph	allyl	Et	A	**13b**	99:01	92
4	**12b**	Ph	allyl	Et	B	**13b**	10:90	90
5	**12c**	Me	$EtO_2C(CH_2)_3$	Et	A	**13c**	95:05	89[d]
6	**12c**	Me	$EtO_2C(CH_2)_3$	Et	B	**13c**	13:87	85
7	**12d**	Ph	$MeOC(CH_2)_3$	Et	A	**15**[e]		57[d]
8	**12d**	Ph	$MeOC(CH_2)_3$	Et	B	**15**[e]		55[d]
9	**12e**	Ph		Et	A	**13e**[f]		
10	**12e**	Ph		Et	B	**13e**	36:64	90
11	**12f**	Me	$PhCH_2$	*t*Bu	A	**13f**	99:01	94
12	**12f**	Me	$PhCH_2$	*t*Bu	B	**13f**	01:99	94
13	**12g**	Ph	allyl	*t*Bu	A	**13g**	99:01	93
14	**12g**	Ph	allyl	*t*Bu	B	**13g**	03:97	83

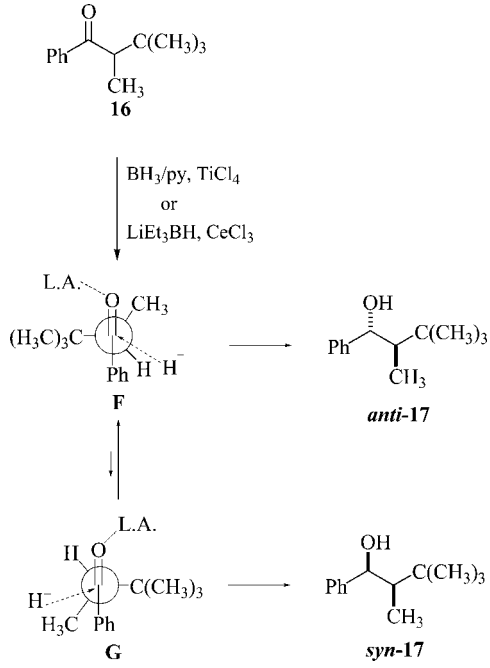
[a] Method A: $TiCl_4$ in CH_2Cl_2 at –78 °C, then BH_3·py; Method B: $CeCl_3$ in THF at –78 °C, then $LiEt_3BH$. [b] Determined by ^1H and ^{13}C NMR spectroscopy. [c] Calculated for the mixture of diastereomers isolated by column chromatography. [d] 2.5 equivalents of $TiCl_4$. [e] The 3,6-disubstituted δ-lactone was isolated. [f] Cleavage of the acetal moiety.

$TiCl_4/BH_3$·py system was used (Table 3, entry 9).[48] Unfortunately, both reducing systems are unsuccessful when the α-alkyl chain of the β-keto esters **12** contains another isolated carbonyl moiety (**12d**), and the reduction of both carbonyl groups provides dihydroxycarboxylates **14** (Scheme 8); no attempt to isolate this intermediate was undertaken. Treatment with acid during workup directly afforded the 3,6-disubstituted δ-lactone **15** as a mixture of diastereomers.



Scheme 8. Reduction of β-keto esters that also contain an isolated carbonyl group.

We have also examined the stereochemical effects exerted by $CeCl_3$ and $TiCl_4$ on the Lewis acid mediated reduction of α-substituted carbonyl compounds that have no ability to chelate with metals. Our choice was ketone **16** because the *tert*-butyl group should be bulky enough to cause strong differentiation between conformations **F** and **G** (Scheme 9). The high diastereoselectivity (***syn*-17**/***anti*-17** = 2:98 and 5:95 by ^1H NMR spectroscopy[49]) can be qualitatively understood by a nonchelating open-chain mechanism, and the *anti* selectivity may be explained by the Felkin–Anh model. With substrate **16**, therefore, both $TiCl_4$ and $CeCl_3$ are un-



Scheme 9.

able to chelate, and they give a high excess of the *anti* isomer with BH_3·py and $LiEt_3BH$ as reducing agent, respectively.

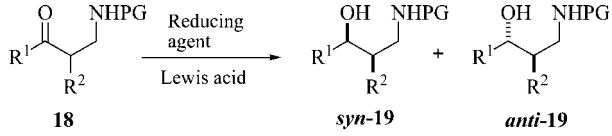
2.4. Diastereoselective Reduction of N-Protected α-Alkyl-β-Amino Ketones

To date we have noted that the influence of Lewis acid promoters on the stereochemical selectivities in the addition of hydrides to carbonyl compounds is instrumental in determining the stereochemical outcome. In particular, Lewis acids that possess two empty coordination sites ($TiCl_4$) usually form chelates when a second basic site is present in the carbonyl ligand.[4,50] In contrast, rare-earth element Lewis acids (such as $CeCl_3$) tend, in several circumstances, to be incapable of chelation because the resulting large coordination number leads to long and therefore unstable metal–ligand bonds.[51] Chelation and nonchelation control have been proposed by us to justify the diastereofacial selectivity obtained in the reduction of α-alkyl-β-functionalised carbonyl compounds. On the basis of this, we have studied the reduction of N-protected α-alkyl-β-amino ketones **18** leading to the formation of *syn*- and *anti*-1-amino-3-hydroxy compounds (***syn*-19** and ***anti*-19**; Table 4).[52] An important conclusion to be drawn from the results in Table 4 is that the nature of the protecting group significantly influences the diastereoselectivity of the reduction of **18**.[53] Although the number of examples is limited, it may be safely said that with these N-protected substrates the procedure for hydride addition is less diastereoselective than with the corresponding β-functionalised keto compound O-derivatives.

The reduction of *N*-(*p*-methoxybenzyl)amino ketones **18e–g** with $TiCl_4/BH_3$·py gave the corresponding *N*-(*p*-methoxybenzyl)-1,3-amino alcohols **19e–g** in excellent yields and with better diastereoselectivity than with *N*-carbamate protecting groups[54] (Table 4, entries 9 and 11). The presence of a strongly electron-withdrawing group probably causes a decrease in the electron density on the nitrogen atom of the carbamate group, thereby weakening the interaction between the lone pair of electrons of nitrogen and titanium(IV). N-Substitution by an electron-donating protecting group therefore seems to be required to realize major levels of diastereoselectivity in these $TiCl_4/BH_3$·py reductions. The reversed diastereoselectivity obtained with $CeCl_3/LiBH_4$ supports a nonchelation mechanism. The sterically demanding alkyl chains favour conformation **C** over **D** in Scheme 2, and the hydride anion attacks the carbonyl at the opposite side to the N-protected amino group leading to *anti* diastereomers (Table 4). This mechanism was further supported by the fact that in the $TiCl_4$ system the relative diastereoselectivity decreases in the order PMB > Cbz > Boc, whereas in the $CeCl_3$ system the *anti*-diastereoselectivity is enhanced with a more-bulky N-protecting group (Table 4, entries 1, 3 and 10). Differently to α-alkyl-β-keto sulfones and esters, the reduction of N-protected substrates with a powerful hydride reducing agent such as $LiEt_3BH$ occurs with no diastereoselectivity (Table 4, entry 5). Thus, although several types of metal hydride complexes are available for this reduction in the presence of $CeCl_3$, lithium borohydride is still among the best.[55]

Given that 1,3-amino alcohol structures have been discovered to play a crucial role in the preparation of important alkaloids,[56] as well as drugs for therapeutic purposes,[57] we obtained a new, straightforward method for the synthesis of *syn*-1,3-amino alcohols.[58] The diastereoselective double reduction of β-ketoamides **20** to obtain *syn*-γ-amino-β-alkyl alcohols **21** was examined (Table 5).

Table 4. Stereoselective reduction of β-amino ketones **18** to 1,3-amino alcohols **19** with hydride (H^-) in the presence of Lewis acids.[a]



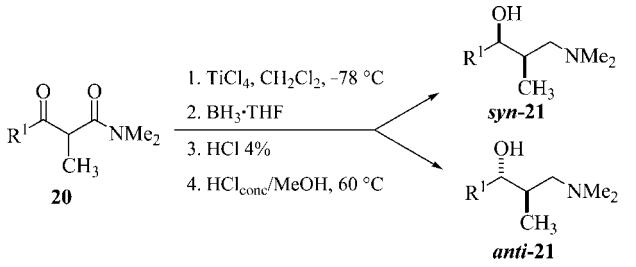
18 ***syn*-19** ***anti*-19**

PG = Protecting Group

Entry	**18**	R	R	P	Reducing agent	Lewis acid	Product	*syn*:*anti*[a]	Yield [%][b]
1	**18a**	*n*Pr	Bn	Boc	$LiBH_4$	$CeCl_3$	**19a**	15:85	98
2	**18a**	*n*Pr	Bn	Boc	BH_3·py	$TiCl_4$	**19a**	62:38	97
3	**18b**	*n*Pr	Bn	Cbz	$LiBH_4$	$CeCl_3$	**19b**	22:78	91
4	**18b**	*n*Pr	Bn	Cbz	BH_3·py	$TiCl_4$	**19b**	80:20	98
5	**18b**	*n*Pr	Bn	Cbz	$LiEt_3BH$	$CeCl_3$	**19b**	50:50	98
6	**18c**	Me	Bn	Boc	BH_3·py	$TiCl_4$	**19c**	60:40	92
7	**18c**	Me	Bn	Boc	$LiBH_4$	$CeCl_3$	**19c**	18:82	93
8	**18d**	Me	Bn	Cbz	BH_3·py	$TiCl_4$	**19d**	80:20	98
9	**18e**	Ph	Et	PMB	BH_3·py	$TiCl_4$	**19e**	93:07	96
10	**18e**	Ph	Et	PMB	$LiBH_4$	$CeCl_3$	**19e**	33:67	91
11	**18f**	*n*Bu	Et	PMB	BH_3·py	$TiCl_4$	**19f**	90:10[c]	90
12	**18f**	*n*Bu	Et	PMB	$Me_2S{\cdot}BH_3$	$TiCl_4$	**19f**	90:10[c]	95
13	**18f**	*n*Bu	Et	PMB	$LiBH_4$	$CeCl_3$	**19f**	30:70[c]	90
14	**18g**	Ph	*n*Pr	PMB	$LiBH_4$	$CeCl_3$	**19g**	30:70	90

[a] Determined by ^1H and ^{13}C NMR spectroscopy. [b] Calculated for the mixture of diastereomers isolated by column chromatography. [c] Assignment of configuration from the ^1H NMR spectra of the corresponding cyclic carbamates.

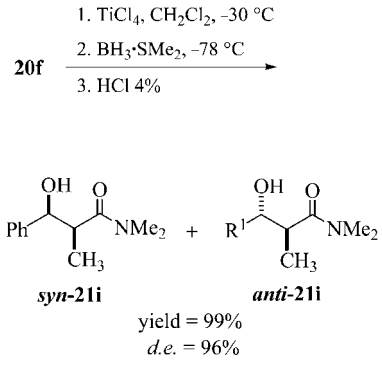
Table 5. Diastereoselective one-pot reduction of α-methyl-β-keto amides **20** to the corresponding *syn*-amino alcohols **21**.



Entry	**20**	R^1	Product	*syn*:*anti*[a]	Yield [%][b]
1	**20a**	Me	**21a**	96:04	65
2	**20b**	*i*Pr	**21b**	90:10	60
3	**20c**	*n*-C_5H_{11}	**21c**	99:01	98
4	**20d**	*t*Bu	**21d**	98:02	83
5	**20e**	c-C_6H_{11}	**21e**	95:05	72
6	**20f**	Ph	**21f**	99:01	87
7	**20g**	4-NO_2Ph	**21g**	90:10	62
8	**20h**	4-BrPh	**21h**	94:06	63

[a] Determined by ^1H and ^{13}C NMR spectroscopy. [b] Calculated for the mixture of diastereomers isolated by column chromatography.

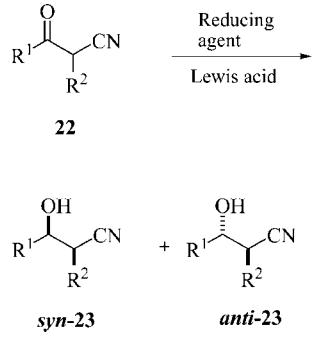
Such a diastereoselective conversion was accomplished in a one-pot procedure by using an excess of the BH_3·THF complex in the presence of $TiCl_4$. In order to obtain a complete reduction of **20** to **21** and to promote the further reduction of the amide to the amino function, the mixture needed to reach room temperature. Subsequent treatment with dilute HCl gave amino alcohols as their cyclic borane complexes. Further treatment with methanolic HCl at 60 °C gave the *syn*-amino alcohol **21** in a pure form. This decomposition procedure was adopted since the usual oxidative method (H_2O_2, NaOH, MeOH) failed due to the presence of a trivalent nitrogen in the substrate.[59] Other boron complexes were also tested. The BH_3·py complex works quite well, although the use of this reagent leads to serious problems in the purification of final compounds. However, contrary to other borane–Lewis base complexes, the reduction of β-keto amides **20** with BH_3·Me_2S complex does not gives γ-aminols but stops at the β-hydroxy amides.[60] Due to the efficiency and the high diastereoselectivity observed (Scheme 10), the $TiCl_4/BH_3$·Me_2S system is therefore a very useful alternative to previously reported procedures.[14]



Scheme 10. Diastereoselctive reduction of β-keto amides to β-hydroxy amides.

2.5. Diastereoselective Reduction of α-Alkyl-β-keto Carbonitriles

β-Hydroxy nitriles[61] are suitable synthons for the preparation of 1,3-amino alcohols, and an easy access for their preparation seems to be the direct reduction of β-keto carbonitriles. Gotor and co-workers, after trying different reagents [K-Selectride®, $Zn(BH_4)_2$, $CeCl_3/NaBH_4$], found that $TiCl_4/BH_3$·py and $CeCl_3/LiEt_3BH$ gave the best results in the reduction of cyclic β-keto carbonitriles.[62] *trans* Diastereomers were obtained when $TiCl_4$ was used as the chelating Lewis acid, whereas in reductions with boron hydrides and anhydrous $CeCl_3$ as the nonchelating reagent the *cis* diastereomers were predominantly obtained. Several years ago, it was reported[63] that acyclic α-alkyl-β-keto carbonitriles can be reduced stereoselectively to *syn*- and *anti*-α-alkyl-β-hydroxy carbonitriles, and that the stereoselectivity is affected by the properties of the Lewis acid promoter employed (Scheme 11). The chelating ability of titanium led to the *syn*-diastereomer **23**, and the $TiCl_4/BH_3$·py procedure was found to be efficient for the reduction of a large variety of keto carbonitriles (Table 6). Under these conditions the cyano group is also reduced, but this process is much slower than the reduction of the carbonyl function. Thus, the methodology is not efficient for the preparation of *syn*-amino alcohols, since decomposition phenomena occur in the presence of the required excess of the BH_3·py complex.



Scheme 11. Reduction of an α-alkyl-β-keto carbonitrile at low temperature.

It should be noted (Table 6, entry 5) that the β-keto carbonitriles are reduced with a lower level of diastereoselectivity than the β-functionalised keto compound O-derivatives, probably because the linear nature of the nitrile function prevents it from assuming the rigid, half-chair structure of conformer **A** in Scheme 2. However, this $TiCl_4/BH_3$·py reducing system is the first general preparation of *syn*-α-alkyl-β-hydroxy carbonitriles. Previous protocols in the literature proceed with only poor to moderate *syn*-selectivity depending on the structure of the α-alkyl group.[64] The interpretation of the stereochemical outcome of $CeCl_3$-mediated reduction of a large variety of bidentate compounds in terms of nonchelation control suggested to us a methodol-

Table 6. Reduction of **22** at –78 °C in the presence of a Lewis acid.

Entry	**22**	R^1	R^2	Reducing agent	Lewis acid	Product	*syn*:*anti*[a]	Yield [%][b]
1	**22a**	Me	Ph	BH_3·py	$TiCl_4$	**23a**	94:06	69
2	**22a**	Me	Ph	$LiBH_4$	$CeCl_3$	**23a**	15:85	75
3	**22b**	*i*Pr	Ph	BH_3·py	$TiCl_4$	**23b**	98:02	67
4	**22b**	*i*Pr	Ph	$LiBH_4$	$CeCl_3$	**23b**	02:98	79
5	**22c**	Ph	*i*Pr	BH_3·py	$TiCl_4$	**23c**	89:11	70
6	**22c**	Ph	*i*Pr	$LiBH_4$	$CeCl_3$	**23c**	48:52	68

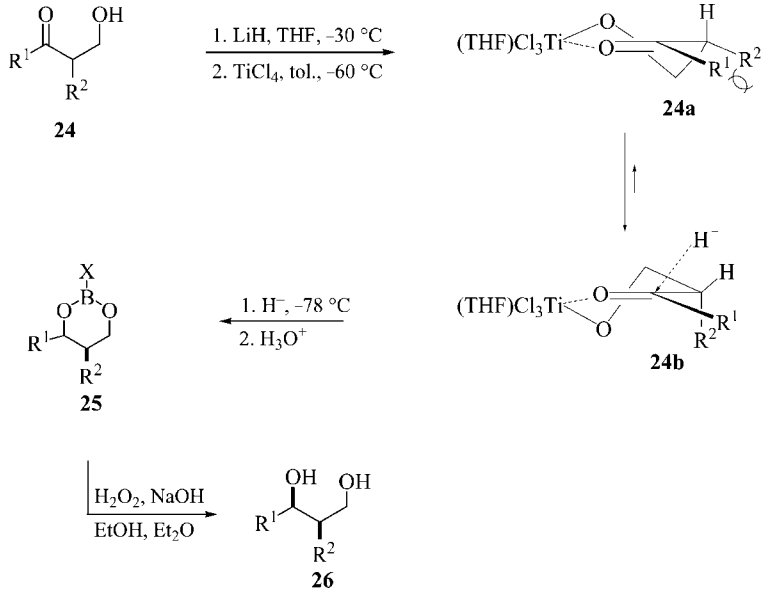
[a] Determined by ^{1}H and ^{13}C NMR spectroscopy. [b] Calculated for the mixture of diastereomers isolated by column chromatography.

ogy leading to *anti*-α-alkyl-β-keto carbonitriles (Table 6). The $CeCl_3/LiBH_4$ system led to good diastereoselectivity except when the α-alkyl substituent was an α-branched framework. Other reducing agents such as L-Selectride® or $LiEt_3BH$ were employed in conjunction with $CeCl_3$, but a retro-aldol process rather than a reduction was observed.

3. Diastereoselectivity in the Reduction of α-Alkyl-β-Hydroxy Ketones

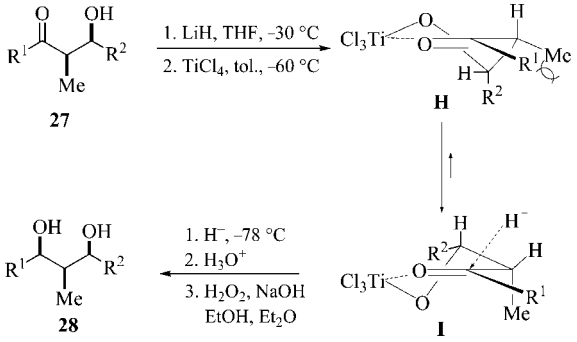
The diastereoselective synthesis of acyclic 1,3-diols is an important target in organic chemistry, since these units are present either in a *syn* or an *anti* relationship in the structures of a large variety of natural products.[65] In the case of 1,3-induction for the stereoselective reduction of β-hydroxy ketones it is possible to obtain *anti*-diols by a Tishchenko reduction[66] or by using reducing agents that are able to bind the hydroxyl function and then to intramolecularly transfer the hydride to the carbonyl group.[67] To obtain *syn*-diols it is necessary to add a coordinating agent that is able to build up a sufficiently rigid cyclic complex prior to intramolecular addition of the hydride ion from an external source.[68] Following these suggestions, it seemed very useful to investigate the possibility of applying the $TiCl_4/BH_3$·py chelation control to the reduction of β-hydroxy ketones when only a β-stereocentre is present.[69] Excellent results were obtained and 1,3-diols units with stereodefined geometry were isolated. Analogous procedures for the reduction of simple α-alkyl-β-hydroxy ketones like **24** give excellent stereochemical results only when R^1 is a bulky group such as *tert*-butyl or an sp^2-hybridized centre such as a phenyl or a sterically hindered vinyl fragment. When R^1 is a linear carbon chain, a dramatic decrease in selectivity was observed. Highly diastereoselective reduction of **24** (Scheme 12) was accomplished by treating the corresponding titanium alkoxide[70] with a variety of reducing agents.[67] The steric hindrance of boron hydrides such as L-Selectride® (lithium tri-*sec*-butylborohydride) and N-Selectride (sodium tri-*sec*-butylborohydride) has been advantageously exploited to ensure highly stereoselective reduction. It should be noted that acidic quenching gave the cyclic boronates **25** which, in some cases, are so stable to acidic hydrolysis that an oxidative decomposition with H_2O_2 in basic medium was required to obtain the corresponding 1,3-diols.[58]

The presence of an additional stereocentre in the α-position adds a further complication.[71] In a *syn* relationship between the α- and β-substituents, their steric effects reinforce each other, whereas in the *anti*-isomers the selectivity largely depends on the relative bulkiness of the substituents and on the ligands at the titanium metal. We examined a



Scheme 12. *syn*-Reduction of α-alkyl-β-hydroxy ketones with only an α-stereocentre via their titanium alkoxides..

series of α-alkyl-β-hydroxy ketones where the methyl group is always present in the α-position. The *syn*-isomers **27** always showed very high *syn*-selectivity and they gave *syn*-*syn*-diols **28** (Scheme 13). The **H** conformation is disfavoured, as previously established for boron derivatives.[67]



Scheme 13. Reduction of *syn*-β-hydroxy ketones **27** via a titanium alkoxide.

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The reduction of the *anti*-isomers **29** was more complex due to the discordant influences of the substituents. The 1,2-eclipsing interactions disfavour the **L** conformation, while 1,3-axial interactions disfavour the **M** conformation (Scheme 14). The data obtained (Table 7) are in good agreement with the interpretation described above.

Furthermore, it is unlikely that a transmetallation process can occur between the Ti-alkoxide and the boron reducing agent to form a cyclic boron alkoxide prior to the reduction. Such boron cyclic compounds may be formed when a β-hydroxy ketone is treated with a boron reducing agent alone,[1e] however the presence of $TiCl_4$ is essential for the reaction. It has been reported[73] that the use of $LiBH_4$ alone gives 1,3-diols with low diastereoselectivity. In addition, the stereochemical picture shown in Table 7 is quite similar to that observed for the alkylation process,[69b] in which experimental evidence proved that the attack of the carbanion on the carbonyl group occurs before any interaction with titanium.

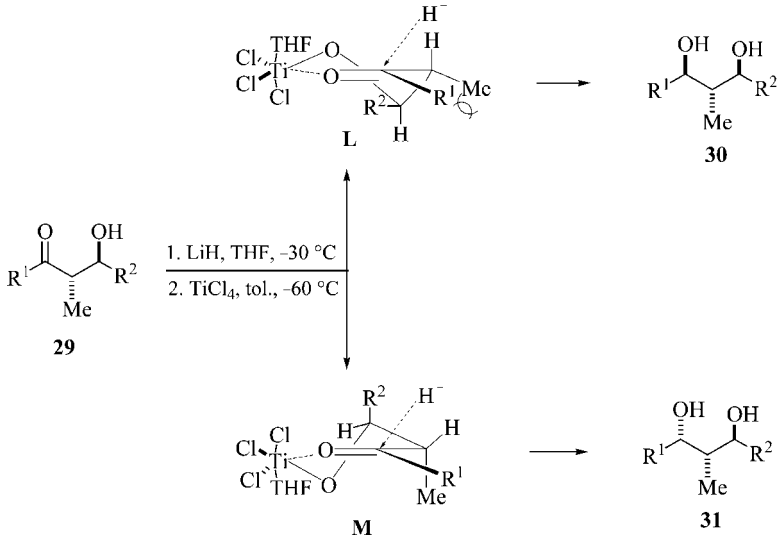
Table 7. Reduction of α-methyl-β-hydroxy ketones with two stereocentres in an *anti* relationship via their titanium alkoxides in THF at –78 °C with metal hydrides (H^-).

Entry	**29**	R^1	R^2	Reducing agent	Ratio **30**:**31**[a]	Yield [%][b]
1	**29a**	Et	Et	BH_3·THF	75:25	90
2	**29a**	Et	Et	$LiBH_4$	70:30	90
3	**29a**	Et	Et	L-Selectride	6:94	86
4	**29b**	Ph	Et	BH_3·THF	3:97	94
5	**29b**	Ph	Et	$LiBH_4$	23:77	89
6	**29c**	Ph	Et	L-Selectride	0:20	85
7	**29d**	Ph	*i*Pr	BH_3·THF	2:98	90
8	**29d**	Ph	*i*Pr	L-Selectride	5:15	90
9	**29e**	Ph	Ph	BH_3·THF	45:55	92
10	**29e**	Ph	Ph	$LiBH_4$	01:99	91

[a] The isomeric ratio was determined by NMR analysis of their cyclic phenylboronate derivatives, which provide an unambiguous stereochemical assignment.[72] [b] Calculated for the mixture of diastereomers isolated by column chromatography.

Summary and Outlook

As we have seen in this review, the design and development of new Lewis acid based diastereoselective strategies for the reduction of α-alkyl-β-functionalised carbonyl compounds have received a great deal of attention in recent years. These strategies, which overcome the historical drawbacks of the lack of regio-, chemo-, and stereoselectivity associated with metal hydride reductions, should allow easy access to several classes of polyfunctionalised enantiomerically enriched compounds, which are valuable building blocks in organic synthesis. Thus, these reactions are undergoing continuous development. The attempt to extend the applicability of Lewis acid stereoselective protocols to non-racemic substrates is only one of the challenges that engage



Scheme 14. Reduction of *anti*-β-hydroxy ketones **29** via a titanium alkoxide.

researchers on a daily basis in one of the most important transformations in modern organic chemistry.

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