The Role of the α-Stereogenic Center in the Control of Stereoselection in the Reduction of α-Alkyl-β-hydroxy Ketones: A Highly Diastereoselective Protocol for the Synthesis of 1,2-*syn*-2-Alkyl-1,3-diols

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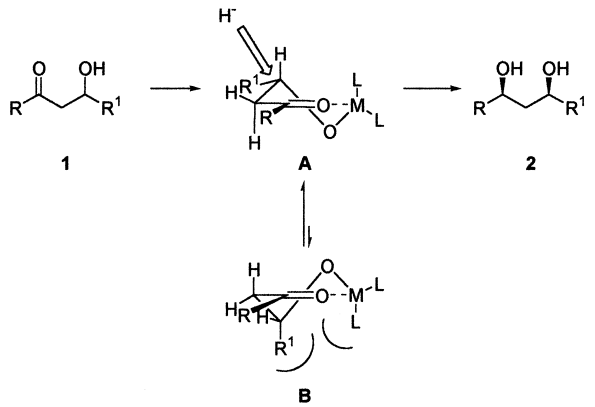
Abstract: Accurate investigations on the role played by an α-stereogenic center in controlling the reduction of various classes of β-hydroxy ketones allowed us to set up a general and highly diastereoselective protocol for the synthesis of 2-alkyl-1,3-diols with 1,2-*syn* relationship. This methodology is based on the conversion of a β-hydroxy ketone into the corresponding titanium alcoholate that permits us to organize the substrate in a stable and rigid structure, which stereofacially favors attacking hydride ions. The use of THF as solvent makes available a variety of hydride donors that cover a large spectrum of steric demand: the choice of the more appropriate one depends on the conformational stability of the cyclic intermediate. Excellent results are obtained also in the presence of an additional stereogenic center in the β-position, even if it exerts a concordant or an opposite steric effect with respect to the α-substituent.

Keywords: asymmetric synthesis · chelates · 1,3-diols · Lewis acids · reductions

Introduction

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.[1] Among the procedures to obtain 1,3-diols, the stereoselective reduction of β-hydroxy ketones has been the object of extensive investigations, as a result of the easy availability of the starting materials.

From the accumulated body of data, some generalizations can be made. *anti*-Diols are obtained either through a Tishchenko's reduction[2] or using reducing agents able to bind the hydroxyl function and then to intramolecularly transfer the hydride to the carbonyl group.[3] Conversely, *syn*-diols are generally obtained when a coordinating agent is added to build up a sufficiently rigid cyclic complex prior to intermolecular addition of the hydride ion from an external source.[4] Extensive studies on the latter method allowed further observations to be made. When only a β-stereocenter is present, two chair-like conformations **A** and **B** (Scheme 1)



Scheme 1. The origin of stereocontrol in the reduction of β-hydroxy ketone **1** via a cyclic intermediate followed by the attack of an external hydride ion source.

are considered to exist in the metal-chelated transition state. The conformation **B** is disfavored because of the 1,3-axial interaction between the R^1 group and the metal ligand L.[4g] The attack of the most populated conformation **A** must occur from the less hindered axial direction to give *syn*-diols.

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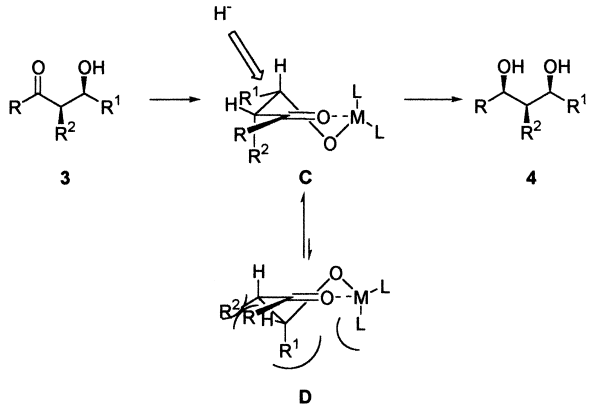
The presence of an additional stereocenter in the α-position adds a further complication. In a *syn* relationship between α- and β-substituents, their steric effects reinforce each other, since a further destabilizing 1,2-eclipsing interaction appears in conformation **D** (Scheme 2). Moreover, the higher steric

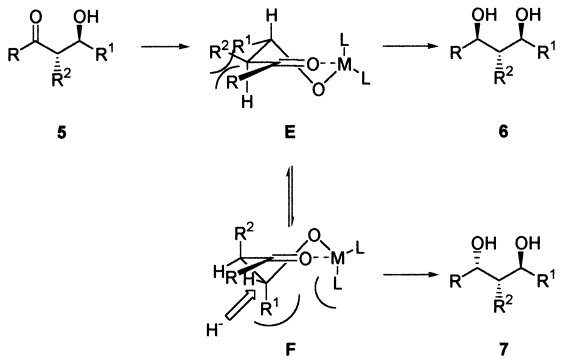


Scheme 2. Stereocontrol of the reduction via a chelated intermediate of β-hydroxy ketone **3** with a stereocenter both in the α- and β-position in a *syn* relationship.

hindrance offered by the encumbered R^2 axial group reinforces the preference for an attack at the top of conformation **C**.

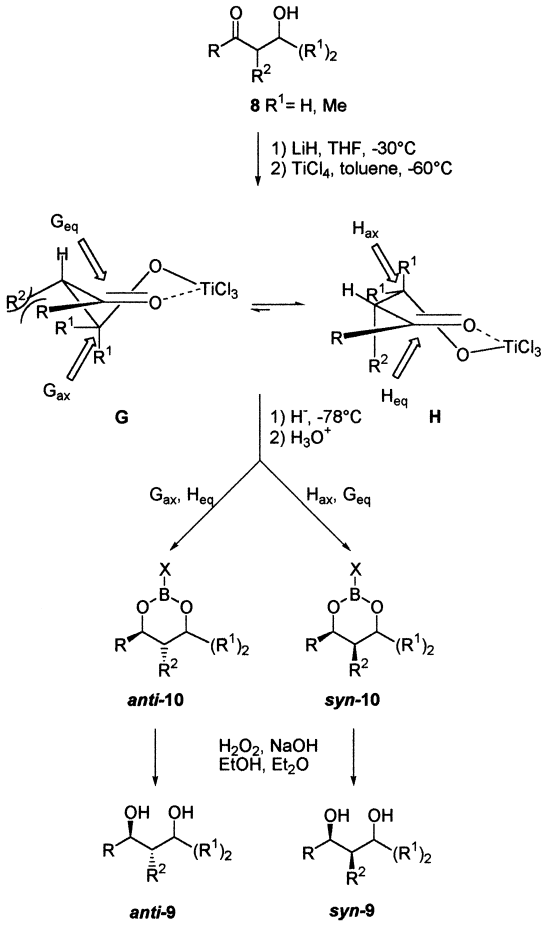
In the *anti*-isomer, both the possible chair-like conformations **E** and **F** suffer from strain (Scheme 3). The conformation **E** causes eclipsing interactions between R and R^2 alkyl groups; in the conformation **F**, the eclipsing interactions do not occur, but a 1,3-axial interaction is generated between R^1 and L. Therefore, the selectivity largely depends on the relative bulkiness of the substituents and the ligands at the coordinating metal. The intrinsic *syn* diastereoselectivity is diminished with the little methyl group in the α-position and it inverts to *anti* only with the larger butyl or ethyl groups.[4d, g] The use of sterically hindered boronic acids as the ligand L ensures a good *anti*, *anti*-selectivity when R^2 is ethyl, since the 1,3-axial interaction dominates the eclipsing interaction.[4a]

Abstract in Italian: *Studi approfonditi sul ruolo esercitato da uno stereocentro in posizione α nel controllo della riduzione di varie classi di β-idrossi chetoni hanno consentito di mettere a punto un protocollo generale ed altamente diastereoselettivo per la sintesi di 1,3-dioli sin 1,2-disostituiti. Questo metodo è basato sulla trasformazione, in THF, di un β-idrossi chetone nel corrispondente alcolato di Titanio che, attraverso un'azione di coordinazione interna, conferisce al substrato una struttura ciclica rigida caratterizzata da una notevole discriminazione stereofacciale verso lo ione idruro entrante. La possibilità di utilizzo del THF come solvente consente l'impiego di numerosi agenti riducenti a domanda sterica variabile, permettendo così di scegliere quello più appropriato, in funzione della stabilità conformazionale dell'intermedio ciclico. Abbiamo ottenuto eccellenti risultati anche quando in posizione β è presente un ulteriore centro sterogenico, sia nel caso che il sostituente in β eserciti un effetto stereochimico concorde rispetto al sostituente in α, sia che eserciti un effetto opposto.*



Scheme 3. Stereocontrol of the reduction via a chelated intermediate of β-hydroxy ketone **5** with a stereocenter both in the α- and β-position in an *anti* relationship.

While the effects of the β-substituent on the steric induction on the carbonyl function are widely studied, much less attention has been paid to the influence exerted by the α-substituent on the conformational equilibrium between **E** and **F** (Scheme 3). The reduction of α-alkyl-β-hydroxy ketones with a stereocenter only in the α-position was reported to give excellent results only when R is a *tert*-butyl, a phenyl, or a sterically hindered vinyl group.[5] When R is a linear carbon chain a dramatic fall in selectivity is observed. However, in a preliminary communication we reported that the titanium alcoholate of **8** is able to undergo highly stereoselective reduction also in the presence of straight alkyl chains (Scheme 4).[6]



Scheme 4. Reduction of β-hydroxy ketones **8** via a titanium alcoholate.

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In this paper, we report a complete investigation on the reduction of a series of both α-alkyl substituted and α- and β-alkyl disubstituted β-hydroxy ketones via their titanium alcoholates in THF. We show that in most cases it is possible to enhance the influence of the stereogenic center in the α-position on the reaction stereocontrol.

Results and Discussion

Reduction of β-hydroxy ketones with only an α-stereocenter: We considered at first the reduction of β-hydroxy ketones **8a–g** (Table 1) with a stereocenter only in the α-position and adopted the same procedure reported for the alkylation with Grignard reagents via their titanium alcoholates.[7] In particular, a solution of the hydride ion source in THF was added at $-78\,^{\circ}C$ to a β-hydroxy ketone titanium alcoholate prepared in THF by transmetallation of the corresponding lithium alcoholate with $TiCl_4$. When the reduction was complete, the mixture was quenched with dilute HCl (1M). We noted that the acidic quenching gives at first the formation of cyclic boronates, whose structure and stability depend on the boron reducing agent. We isolated *syn*-**10a** from the reaction of **8a** with $LiBH_4$.[6] These boronates can be converted into the corresponding diols by treatment with aqueous HCl (10%) for prolonged periods of time (4–24 h). However, in some cases, especially when L-Selectride (lithium tri-*sec*-butylborohydride) or N-Selectride (sodium tri-*sec*-butylborohydride) is used as a reducing agent, boronates are so stable to acidic hydrolysis that an oxidative decomposition with H_2O_2 in basic medium is required to obtain the corresponding 1,3-diols.[8] For the sake of homogeneity, we adopted the last treatment in all cases (Scheme 4).

Table 1. *syn*-Reduction of α-alkyl-β-hydroxy ketones **8a–g** with an α-stereocenter via their titanium alcoholates in THF at $-78\,^{\circ}C$ with metal hydrides (H^-).

	Starting material	R	R^1	R^2	H^-	Product	Yields [%]	*de* [%]
1[a]	**8a**	Ph	H	Me	$LiBH_4$	*syn*-**9a**	95	98
2[a]	**8b**	Ph	H	Et	$LiBH_4$	*syn*-**9b**	95	98
3[a]	**8c**	Ph	H	Ph	$LiBH_4$	*syn*-**9c**	95	98
4[a]	**8d**	Et	H	Me	$LiBH_4$	*syn*-**9d**	90	30
5[a]	**8d**	Et	H	Me	L-Selectride	*syn*-**9d**	90	80
6[a]	**8d**	Et	H	Me	N-Selectride	*syn*-**9d**	92	86
7[a]	**8e**	Pr	H	Et	$LiBH_4$	*syn*-**9e**	90	40
8[a]	**8e**	Pr	H	Et	L-Selectride	*syn*-**9e**	91	90
9[a]	**8e**	Pr	H	Et	N-Selectride	*syn*-**9e**	93	98
10	**8f**	Ph	Me	Me	$LiBH_4$	*syn*-**9f**	92	98
11	**8g**	Et	Me	Me	$BH_3\cdot THF$	*syn*-**9g**	89	20
12	**8g**	Et	Me	Me	$LiBH_4$	*syn*-**9g**	91	40
13	**8g**	Et	Me	Me	L-Selectride	*syn*-**9g**	93	98

[a] See ref. [6].

The reduction with $LiBH_4$ of simple compounds **8a–g** gives the corresponding 1,3-diols in almost quantitative yields in all examined cases. However, the diastereoselectivity is excellent only when R is a phenyl group (Table 1, entries 1–3). When R and R^2 are straight alkyl chains, a significative drop in stereoselectivity is observed (Table 1, entries 4, 7).

Before these results are discussed, a careful consideration of the actual structure and nature of the species involved in the reduction process is required. In fact, since reaction products are obtained as boron cyclic derivatives, the question might arise whether cyclic boronates form by metal exchange between the alcoholate and the boron reducing agent so that a cyclic boron species rather than a titanium one is subjected to the hydride attack. Nevertheless, in our opinion this hypothesis is not probable, and the boronate formation occurs only at the end of the reducing process or during the quenching of the reaction with dilute HCl: later in the text, we will discuss this point and give our reasons for this statement.

If a cyclic chelate mechanism is in operation (Scheme 4), the population of conformation **G** may increase when the 1,2-strain weakens because of the presence of an unhindered straight alkyl chain in position 1 and 2.

The steric interactions exerted by the substituents on conformations **G** and **H** suggest the kinetic order of attack $\mathbf{H}_{ax} > \mathbf{G}_{ax} > \mathbf{G}_{eq} \gg \mathbf{H}_{eq}$. When the difference between $\mathbf{H}_{ax}$ and $\mathbf{G}_{ax}$ is not relevant, as expected with less hindered reducing agents like $LiBH_4$ or BH_3, the diastereoselectivity roughly reflects the conformational equilibrium composition. However, the magnitude of this difference can be enhanced, and the nature of the incoming reducing agent can be modified because the use of a very hindered hydride ion source can cause the $\mathbf{G}_{ax}$ attack to be much less favored than $\mathbf{H}_{ax}$ as a result of the steric hindrance exerted on the incoming hydride by the equatorial R^2 group. Actually, a dramatic increase in selectivity was observed in the reduction of both **8d** (R = Et, R^2 = Me) and **8e** (R = Pr, R^2 = Et) (Table 1, entries 4–6 and 7–9, respectively) using L-Selectride and N-Selectride. As expected, the bulkier N-Selectride afforded higher selectivity.[9]

The presence of two methyl groups in the β-position did not cause us to modify our stereochemical approach. High 1,2-eclipsing interactions like those in **8f** (R = Ph, R^2 = Me) ensure high *syn* diastereoselectivity with the small compound $LiBH_4$ (Table 1, entry 10). On the other hand, when strain does not produce a shift in the equilibrium, as in the case of **8g** (R = Et, R^2 = Me), facial stereoselectivity is obtained by using a bulkier reductant such as L-Selectride (Table 1, entries 12–13).

In conclusion, the α-stereocenter is able to strongly shape the selectivity in the reduction of titanium alcoholates of α-alkyl-β-hydroxy ketones. The R^2 group in the equatorial position of conformation **G** does not significatively hinder the $\mathbf{G}_{ax}$ attack of the $LiBH_4$, therefore it gives a stereochemical outcome which reflects the conformational equilibrium composition. This hypothesis is further verified by the use of the smaller $BH_3\cdot THF$, which makes the reaction less selective (Table 1, entry 11). On the other hand, Selectrides, largely influenced by steric interactions, must approach the carbonyl

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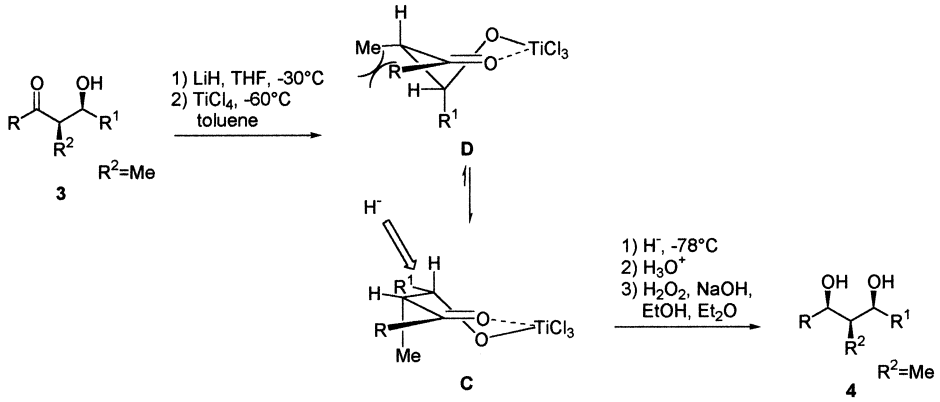
moiety from the $\mathbf{H}_{ax}$ direction, which is almost completely free from significative hindrance.

Reduction of α-alkyl-β-hydroxy ketones with stereocenters both in the α- and in the β-positions: We examined a series of α-alkyl-β-hydroxy ketones in which the hindrance of the substituents R and R^1 in the positions β and α′ varied. In the α-position, the methyl group was always present.

The *syn*-isomers **3a–d** always showed very high *syn*-selectivity and they gave the *syn*–*syn*-diols **4a–d** (Scheme 5, Table 2). These results are largely expected, since the



Scheme 5. Reduction of β-hydroxy ketones **3** via a titanium alcoholate.

Table 2. *syn*-Reduction of α-methyl-β-hydroxy ketones with two stereocenters in a *syn* relationship (**3a–d**, R^2 = Me) via their titanium alcoholates in THF at −78 °C with metal hydrides (H^-).

	Starting material	R	R^1	R^2	H^-	Product	Yields [%]	*de* [%]
1	**3a**	Ph	Et	Me	$LiBH_4$	**4a**	92	>98
2	**3b**	Et	Et	Me	L-Selectride	**4b**	88	>98
3	**3b**	Et	Et	Me	$BH_3\cdot THF$	**4b**	90	>98
4	**3c**	Ph	Ph	Me	$LiBH_4$	**4c**	94	>98
5	**3c**	Ph	Ph	Me	$BH_3\cdot THF$	**4c**	92	>98
6	**3d**	Ph	*i*Pr	Me	$LiBH_4$	**4d**	92	>98

influence of the substituents determines selectivity in the same manner, and the **D** conformation is disfavored (Scheme 5) as previously established for boron derivatives.[4a]

It is noteworthy that diastereomeric excesses higher than 98% were always obtained; these results were independent of the shape and the hindrance of both substituents and the reducing agent employed. In conclusion, our methodology based on the formation of a titanium alcoholate that leads to a rigid intermediate, even in a coordinating solvent such as THF, has a high degree of selectivity, which is comparable and in some cases superior to the reported procedures.[4]

The reduction of the *anti*-isomers was more complex due to the discordant influences of the substituents. The 1,2-eclipsing interactions disfavor the **E** conformation, while 1,3-axial interactions disfavor the **F** conformation (Scheme 6). After examination of the *anti* compound **11** (R = R^1 = Et, Table 3), we found that $BH_3\cdot THF$ and $LiBH_4$ lead mainly to the formation of the *anti*,*anti* product **13** (*anti*,*anti*:*syn*,*anti* ratio 3:1 and 7:3, respectively - Table 3, entries 1 and 2). These data are in good agreement with the interpretation described above. In fact, in the present case, it is expected that the conformer **E** becomes predominant, as a result of the 1,3-axial strain between R^1 = Et and the metal ligand (Scheme 6), and so the use of small reducing agents must reflect the conformational equilibrium. However, the use of L-Selectride upsets the stereochemistry. In fact, a high *syn*-selectivity is observed again, and the *syn*,*anti*-isomer **12** is obtained in a 94:6 ratio (Table 3, entry 3). Notwithstanding a conformational equilibrium largely shifted towards **E**, the sterically bulky L-Selectride prevents an attack on the most populated conformation.

In the case of **14** (R = Ph, R^1 = Et) and **17** (R = Ph, R^1 = *i*Pr), a very high *syn*-selectivity is obtained with $BH_3\cdot THF$ (97:3 and 98:2, Table 3, entries 4 and 7). According to the proposed mechanistic interpretation, these results suggest that the conformational equilibrium is completely shifted towards the **F** conformation. In other words, when an aromatic substituent is bound to the carbonyl group, the resulting strong 1,2-eclipsing interaction completely overcomes the 1,3-axial strain between R^1 and the chlorine atoms, even when the R^1 group is an α-branched chain (*i*Pr). Moreover, these features are not in disagreement with those previously reported,[4a] since the chlorine atoms are closer to titanium and more polarizable than boron ligands, and thus there is lower strain on the axial β-substituent.

$LiBH_4$ behaves in a similar way to $BH_3\cdot THF$, but with lower selectivity (77:23 and 70:30, Table 3, entries 5 and 8). Very likely, these differences can be ascribed to the higher steric demand of $LiBH_4$, which suffers from the repulsion of the axial alkyl substituent in position 3.

On the other hand, when the sterically bulky L-Selectride is used, the formation of the *anti*,*anti*-isomers **16** and **19** prevails (Table 3, entries 6 and 9). The stereochemical outcome of **14** with L-Selectride seems to be in disagreement with the analogous result obtained in the reduction of **11**, when a complete *syn*,*anti*-selectivity was observed: since both **11** and **14** carry an ethyl group in the β-position, repulsions towards the approaching Selectride are expected to be comparable. However, when one considers that the aromatic ketone **14** is much less reactive than the aliphatic ketone **11**, the bond between the approaching hydride ion and the electrophilic carbon in the transition state is highly formed for **14**. In other words, L-Selectride must come closer to the carbonyl function, and this dramatically increases the steric "sensitivity" of the *sec*-butyl groups to the axial β-substituent.

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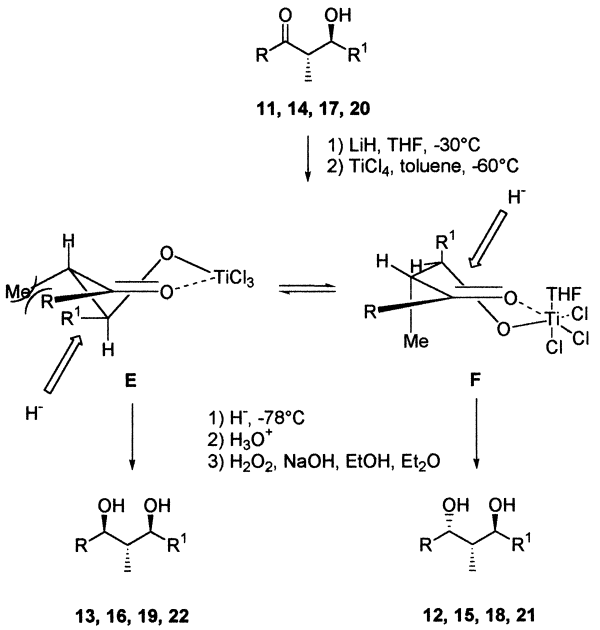
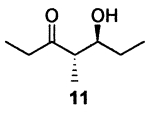
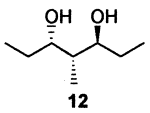
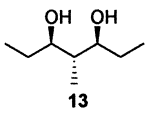
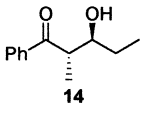
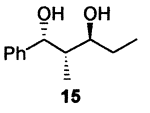
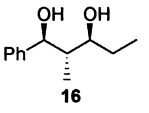
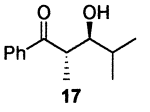
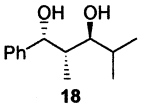
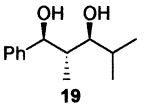
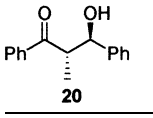
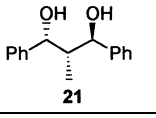
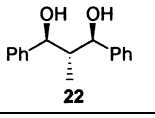


Scheme 6. Reduction of β-hydroxy ketones **11**, **14**, **17**, and **20** via a titanium alcoholate.

Table 3. Reduction of α-alkyl-β-hydroxy ketones with two stereocenters in an *anti* relationship via their titanium alcoholates in THF at $-78\,^{\circ}C$ with metal hydrides (H^-).

Starting material	Products	Entry	H^-	Yields [%]	Isomer ratio
 **11**	 **12**  **13**	1	$BH_3\cdot THF$	90	25:75 (**12:13**)
		2	$LiBH_4$	90	30:70 (**12:13**)
		3	L-Selectride	86	94:6 (**12:13**)
 **14**	 **15**  **16**	4	$BH_3\cdot THF$	94	97:3 (**15:16**)
		5	$LiBH_4$	89	77:23 (**15:16**)
		6	L-Selectride	85	20:80 (**15:16**)
 **17**	 **18**  **19**	7	$BH_3\cdot THF$	90	98:2 (**18:19**)
		8	$LiBH_4$	90	70:30 (**18:19**)
		9	L-Selectride	90	15:85 (**18:19**)
 **20**	 **21**  **22**	10	$BH_3\cdot THF$[a]	92	55:45 (**21:22**)
		11	$LiBH_4$	91	1:99 (**21:22**)

[a] Reaction time 11 h.

We examined the reactivity of compound **20**, in which both R and R^1 groups are phenyl frameworks. We observed that the reduction is very slow to complete (11 h) with both $BH_3\cdot THF$ and $LiBH_4$. The reaction with $BH_3\cdot THF$ gives a negligible *syn*-selectivity (Table 3, entry 10), and this indicates that the two conformations **E** and **F** have equal populations as a result of the disfavoring interactions between the phenyl groups and both the α-methyl group and the titanium ligands. While $BH_3\cdot THF$ is not influenced by the steric crowding of the axial β-substituents in the direction of attack on conformations **E** and **F**, the larger $LiBH_4$ chooses to attack conformation **E**, in which the hydrogen is present, rather than conformation **F**, which is crowded by the phenyl group. Actually, $LiBH_4$ reduction of **20** afforded almost exclusively the *anti*,*anti*-diol **22** (99:1, Table 3, entry 11).

Finally, we will discuss the reasons why it is unlikely that a transmetallation process between the Ti-alcoholate and the boron reducing agent to form a cyclic boron alcoholate can occur prior to the reduction. In fact such boron cyclic compounds may be formed when a β-hydroxy ketone is treated with a boron reducing agent alone.[4d] However, the presence of $TiCl_4$ is essential for the reaction. In fact it has been reported[10] that the use of $LiBH_4$ alone gives 1,3-diols with low selectivity. In addition, we found that the reaction carried out with $BH_3\cdot THF$ alone does not work at low temperature. Finally, the stereochemical picture shown in the reduction is quite similar to that observed for the alkylation process,[7] in which experimental evidence proved that the attack of the carbanion on the carbonyl group occurs before any interaction with titanium.

Identification of compounds: The *syn*-:*anti*-isomer ratio was determined by NMR analysis of the mixture and based on the vicinal coupling constants among the two hydrogen atoms bound to the carbon atom with the hydroxyl function and the hydrogen atom bound to the internal carbon atom.[11] In most cases assignment was ambiguous, since the conformations are not rigid enough to give rise to definite axial – axial, equatorial – equatorial, and axial – equatorial coupling constants. Furthermore, Hoffman[12] criteria based on the comparison between ^{13}C chemical shifts of the *syn*- and the *anti*-isomer can not be applied because in several cases only one isomer is available as the reduction is completely diastereoselective. Thus, diols were transformed into cyclic phenylboronates, (Scheme 7), whose well-defined cyclic structure makes it possible for vicinal coupling constants based on the related stereochemistry of the starting diols to be confidently predicted, and these provide an unambiguous stereochemical assignment.[13] The conversion into phenylboronates can be synthetically useful when the reaction is not selective since, in contrast to 1,3-diols, the mixture of boronates is separable by column chromatography. For example, in the reduction of **20** with $BH_3\cdot THF$ we obtained a 1:1 mixture of **21** and **22**. Our attempts to separate these compounds by chromatography were unsuccessful. However, the corresponding boronates **25d** and **26d** were easily separated by chromatography and quantitatively converted into diols **21** and **22** respectively by oxidation with H_2O_2 in basic medium. This two-step procedure allowed us to obtain pure **21**.

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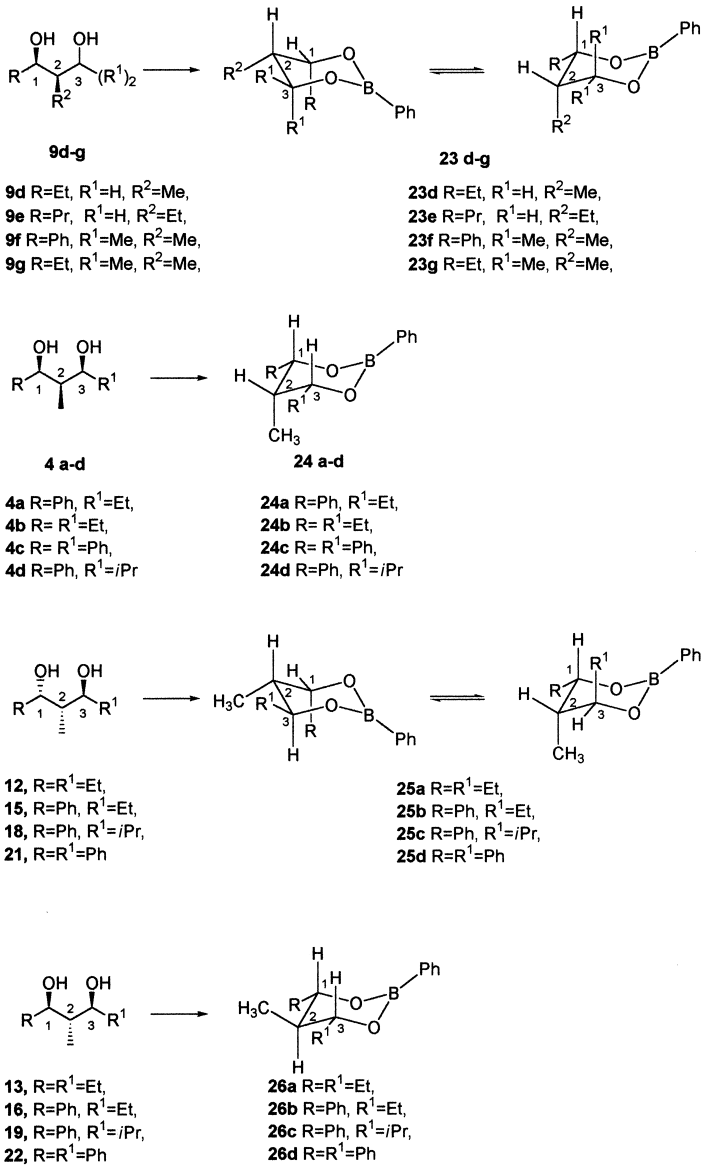

Scheme 7. Transformation of diols into cyclic phenylboronates.

Conclusion

A general and highly efficient method for the *syn*-selective reduction of β-hydroxy ketones with an α-stereocenter is now available. This methodology, which is efficient as a result of the stereocontrol exerted by the α-substituent, also works if an additional stereocenter is present in the β-position in either a *syn* or *anti* relationship with respect to the α-substituent.

This result is important: in fact, all previously reported studies concerned with the stereocontrolled reduction of β-hydroxy ketones focused on the intensification of the effect of the β-substituent.

Our methodology is based on the conversion of an α-alkyl-β-hydroxy ketone into the corresponding Ti-alcoholate; the powerful internal Lewis acid coordination exerted by titanium allows the alcoholate to assume a stable cyclic conformation, which has a high stereofacial selectivity towards the approaching external hydride source. The novelty of this methodology is expressed by two crucial statements.

1) The use of $TiCl_4$ ensures small and polarizable substituents are linked to the metal in the cyclic intermediate, so that the 1,3-strain between metal ligands and the β-substituent is lowered. The 1,2-strain between the α-substituent and the substituent to the carbonyl group can dominate the control of the stereoselectivity.
2) The stability of the Ti-alcoholate in a cyclic conformation and in highly coordinating solvents such as THF allowed us to choose the most suitable reducing agent from an entire range of boranes with different steric requirements that depended on the conformational stability of the Ti-alcoholate.

Finally, we want to outline how significant the quantitative conversion of 1,3-diols into phenylboronate derivatives is.[13] This is not only because the structure can be unambiguously assigned, but also because one can obtain the pure *syn* derivative in cases of low diastereoselectivity of the reaction. In fact the mixture of *syn*- and *anti*-phenylboronates can be easily resolved by column chromatography and reconverted into the corresponding pure *syn*- and *anti*-diols by a simple methodology.[8]

Experimental Section

General: Flash chromatography was performed on silica gel (Merck, 0.040–0.063 nm). THF was dried under reflux over sodium wire until the blue color of benzophenone ketyl persisted and then distilled into a dry receiver in a nitrogen atmosphere. Hexane was dried on calcium hydride and then distilled into a dry receiver in a nitrogen atmosphere. All reactions were carried out in oven-dried glassware in a dry argon atmosphere.

For ^{1}H NMR, *J*-resolved and decoupling experiments were recorded at 300 MHz and 25 °C in $CDCl_3$ with a Varian Gemini instrument. ^{13}C NMR spectroscopy and DEPT experiments were carried out at 75 MHz and 25 °C in $CDCl_3$ with a Varian Gemini instrument. The relative proportions between the two diastereoisomers were measured by integration of some ^{13}C peaks using long delay times. Chemical shifts have been given in δ from Me_4Si and coupling constants given in Hertz.

Compounds **3a–d** were obtained in excellent diastereomeric purity (>99%) following the procedure reported by Masamura.[14] Compounds **8a–e** were synthesized by a standard procedure.[15] Compounds **8f–g** were prepared according to standard methodology.[16] *anti*-β-Hydroxy ketones **11**, **14**, **17**, and **20** were prepared in excellent diastereomeric purity (>99%) following the procedure reported by Brown.[17] Spectroscopic data of known compounds **3a**,[18] **3b**,[19] **3c**,[20] **3d**,[21] **8a**,[22] **8d**,[22] **8e**,[23] **8f**,[24] **8g**,[25] **11**,[26] **14**,[18] **17**,[27] and **20**[27] were identical to those reported in the literature. Spectroscopic data of unknown compounds **8b** and **8c** follow.

2-(Hydroxymethyl)-1-phenyl-1-butanone (8b): ^{1}H NMR (300 MHz): δ = 0.97 (t, *J*(H,H) = 7.4 Hz, 3H; CH_3), 1.60–1.85 (m, 2H; CH_2), 2.3 (br s, 1H; OH), 3.45–3.60 (m, 1H; EtCH), 3.80–3.90 (m, 1H; CH_2OH), 3.90–4.00 (m, 1H; CH_2OH), 7.40–7.50 (m, 2H; Ph), 7.50–7.60 (m, 1H; Ph), 7.90–8.00 (m, 2H; Ph); ^{13}C NMR (75 MHz): δ = 12.0 (CH_3), 22.5 (CH_2), 49.7 (CH), 62.8 (CH_2), 204.4 (C); $C_{11}H_{14}O_2$ (178.23): calcd C 74.12, H 7.92; found C 74.18, H 7.86.

3-Hydroxy-1,2-diphenyl-1-propanone (8c): ^{1}H NMR (300 MHz): δ = 2.3 (br s, 1H; OH), 3.88 (dd, *J*(H,H) = 5.1, *J*(H,H) = 11.3 Hz, 1H; CH_2OH), 4.28 (dd, *J*(H,H) = 8.7, *J*(H,H) = 11.3 Hz, 1H; CH_2OH), 4.79 (dd, *J*(H,H) = 5.1, *J*(H,H) = 8.7 Hz, 1H; CH), 7.20–7.50 (m, 8H; Ph), 7.90–8.00 (m, 2H; Ph); ^{13}C NMR (75 MHz): δ = 56.4 (CH), 65.1 (CH_2), 127.5 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 129.1 (CH), 133.2 (C), 136.1 (C), 200.0 (C); $C_{15}H_{14}O_2$ (226.27): calcd C 79.61, H 6.24; found C 79.53, H 6.30.

Reduction of β-hydroxy ketones to the corresponding 1,3-diols

General procedure: LiH (1.3 mmol) was added to a solution of the β-hydroxy ketone (1 mmol) in dry THF at −30 °C. After 10 min, the reaction was cooled at −78 °C, and $TiCl_4$ (1.3 mmol, 1M solution in CH_2Cl_2) was

added. The reaction mixture turned orange. After 30 min, the appropriate reducing agent (Tables 1, 2, and 3) was added, the mixture was stirred at this temperature for a time that varied from 2 h to 11 h; the time depended on the nature of both the β-hydroxy ketone and the reducing agent. The reaction was then quenched with aqueous HCl (1M), and finally the organic layer was extracted with diethyl ether. The organic layer with a stable cyclic boron derivative was concentrated in vacuo, dissolved in a 1/1 ethanol:Et_2O mixture, and treated with NaOH (10%, pH 8), and then H_2O_2 (1.5 mmol, 30%) was added at 0 °C.[8] Stirring was continued at room temperature for 36 h. Then the mixture was diluted with water, extracted with Et_2O, dried over $MgSO_4$, and purified by flash chromatography on a silica gel column. Product yields and isomer ratios have been collected in Tables 1, 2, and 3. When the reaction gave a mixture of two diastereoisomers, the separation of both diols could not be accomplished by chromatography.

As a result of the overlap of the signals in the ^{1}H NMR spectrum of the mixture of many *syn*–*anti*-isomers, ^{1}H chemical shifts relative to the minor isomer could not be assigned, and only ^{13}C NMR signals have been reported.

Reduction of *syn*-β-hydroxy ketones 3a–d to 1,3-diols 4a–d: The reduction of compounds **3a** and **3d** was carried out according to the general procedure with $LiBH_4$. In the reduction of **3b**, both $BH_3\cdot$THF and L-Selectride were employed. The reduction of **3c** was carried out with both $LiBH_4$ and $BH_3\cdot$THF. In all cases, the reduction gave the corresponding diols **4a–d** in high yields (Table 2) and in very excellent diastereomeric purity (*de* > 98%).

^{1}H NMR and ^{13}C NMR spectroscopic data of (*1R**, *2R**, *3R**)-2,4-dimethyl-1-phenyl-pentan-1,3-diol **4d** were identical to those reported in the literature.[5a, 28] Spectroscopic data for unknown compounds **4a–c** follow.

(*1R**, *2R**, *3R**)-*2-Methyl-1-phenyl-pentan-1,3-diol* (***4a***): ^{1}H NMR (300 MHz): $\delta = 0.80$ (d, J(H,H) = 7.0 Hz, 3H; CH_3), 0.95 (t, J(H,H) = 7.4 Hz, 3H; CH_3), 1.40–1.85 (m, 3H; CH_2 and CH), 2.5 (brs, 1H; OH), 3.2 (brs, 1H; OH), 3.85–3.95 (m, 1H; C*H*OH), 5.04 (d, J(H,H) = 2.8 Hz, 1H; PhC*H*OH), 7.15–7.40 (m, 5H; Ph); ^{13}C NMR (75 MHz): $\delta = 4.2$ (CH_3), 10.4 (CH_3), 28.4 (CH_2), 43.2 (CH), 78.1 (CH), 78.7 (CH), 125.6 (CH), 126.9 (CH), 128.1 (CH), 143.9 (C); $C_{12}H_{18}O_2$ (194.27): calcd C 74.19, H 9.34; found C 74.26, H 9.30.

(*3R**, *4r**, *5S**)-*4-Methylheptan-3,5-diol* (***4b***): ^{1}H NMR (300 MHz): $\delta = 0.88$ (d, J(H,H) = 7.2 Hz, 3H; CH_3), 0.93 (t, J(H,H) = 7.5 Hz, 6H; $2CH_3$), 1.40–1.65 (m, 5H; $2CH_2$ and CH), 2.9 (brs, 2H; 2OH), 3.70–3.80 (m, 2H; 2C*H*OH); ^{13}C NMR (75 MHz): $\delta = 3.9$ (CH_3), 10.4 (CH_3), 28.0 (CH_2), 39.1 (CH), 78.9 (CH); $C_8H_{18}O_2$ (146.23): calcd C 65.69, H 12.14; found C 65.75, H 12.08.

(*1S**, *2r**, *3R**)-*2-Methyl-1,3-diphenyl-propan-1,3-diol* (***4c***): ^{1}H NMR (300 MHz): $\delta = 0.72$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 2.00–2.10 (m, 1H; CH), 2.8 (brs, 2H; OH), 5.14 (d, J(H,H) = 2.9 Hz, 2H; 2C*H*OH), 7.20–7.45 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 4.6$ (CH_3), 46.8 (CH), 77.9 (CH), 125.6 (CH), 127.2 (CH), 128.2 (CH), 143.2 (C); $C_{16}H_{18}O_2$ (242.32): calcd C 79.30, H 7.49; found C 79.41, H 7.55.

Reduction of β-hydroxy ketones 8a–e to the corresponding 1,3-diols *syn*-9a–e: The reduction of compounds **8a–c** was carried out according to the general procedure using $LiBH_4$ as the reducing agent, and the corresponding 1,3-diols **9a–c** were obtained in high yields and in high diastereomeric purity (> 98%). Spectroscopic data of compounds *syn*-**9a**[5a] and *syn*-**9c**[13] were identical to literature data. Spectroscopic data of unknown *syn*-**9b** follow.

(*1S**, *2R**)-*2-Ethyl-1-phenyl-propan-1,3-diol* (*syn-**9b***): ^{1}H NMR (300 MHz): $\delta = 0.89$ (t, J(H,H) = 7.6 Hz, 3H; CH_3), 1.25–1.35 (m, 2H; CH_2CH$_3$), 1.80–1.90 (m, 1H; CH), 2.5 (brs, 2H; 2OH), 3.74 (d, J(H,H) = 5.0 Hz, 2H; CH_2OH), 5.02 (d, J(H,H) = 3.8 Hz, 1H; C*H*OH), 7.20–7.40 (m, 5H; Ph); ^{13}C NMR (75 MHz): $\delta = 12.0$ (CH_3), 17.9 (CH_2), 47.9 (CH), 63.7 (CH_2), 77.1 (CH), 126.2 (CH), 127.3 (CH), 128.2 (CH), 142.5 (C); $C_{11}H_{16}O_2$ (180.25): calcd C 73.29, H 8.95; found C 73.20, H 9.06.

The reduction of **8d** was carried out using various reducing agents, and high yields were obtained in all cases, but different diastereoselectivity ratios were obtained according to the nature of the reducing agent employed: with $LiBH_4$ *syn*-**9d**/*anti*-**9d** = 65:35, with L-Selectride *syn*-**9d**/*anti*-**9d** = 90:10, and with N-Selectride *syn*-**9d**/*anti*-**9d** = 93:7. Our attempts to separate the two diastereoisomers by chromatography were unsuccessful in all cases. Spectroscopic data of unknown *syn*-**9d** follow.

(*2R**, *3R**)-*2-Methyl-pentan-1,3-diol* (*syn-**9d***): ^{1}H NMR (300 MHz): $\delta = 0.93$ (d, J(H,H) = 7.2 Hz, 3H; CH_3), 0.97 (t, J(H,H) = 7.4 Hz, 3H; CH_3), 1.40–1.60 (m, 2H; CH_2CH$_3$), 1.75–1.90 (m, 1H; C*H*CH$_3$), 2.3 (brs, 1H; OH), 2.4 (brs, 1H; OH), 3.70–3.85 (m, 3H; CH_2OH and C*H*OH); ^{13}C NMR (75 MHz): $\delta = 9.9$ (CH_3), 10.6 (CH_3), 27.0 (CH_2), 38.7 (CH), 67.3 (CH_2), 76.2 (CH); $C_6H_{14}O_2$ (118.18): calcd C 60.97, H 11.95; found C 61.08, H 11.88.

(*2R**, *3S**)-*2-Methyl-pentan-1,3-diol* (***anti-9d***): ^{13}C NMR (75 MHz): $\delta = 9.4$ (CH_3), 13.9 (CH_3), 28.0 (CH_2), 39.4 (CH), 67.7 (CH_2), 78.6 (CH).

The reduction of **8e** to *syn*-**9e** carried out with $LiBH_4$, L-Selectride, and N-Selectride gave the expected *syn*-**9e** in high yields and in 40, 90, and 98% diastereomeric excess, respectively.

(*2R**, *3R**)-*2-Ethylhexan-1,3-diol* (*syn-**9e***): ^{1}H NMR (300 MHz): $\delta = 0.95$ (t, J(H,H) = 7.4 Hz, 6H; $2CH_3$), 1.25–1.70 (m, 7H; $3CH_2$ and CH), 2.8 (brs, 1H; OH), 2.9 (brs, 1H; OH), 3.70–3.95 (m, 3H; CH_2OH and C*H*OH); ^{13}C NMR (75 MHz): $\delta = 12.3$ (CH_3), 14.1 (CH_3), 18.0 (CH_2), 19.5 (CH_2), 35.3 (CH_2), 46.0 (CH), 64.4 (CH_2), 75.1 (CH); $C_8H_{18}O_2$ (146.23): calcd C 65.69, H 12.41; found C 65.59, H 12.50.

(*2R**, *3S**)-*2-Ethylhexan-1,3-diol* (*anti-**9e**, minor*): ^{13}C NMR (75 MHz): $\delta = 11.8$ (CH_3), 15.1 (CH_3), 18.9 (CH_2), 21.5 (CH_2), 37.8 (CH_2), 45.8 (CH), 65.7 (CH_2), 75.4 (CH).

Reduction of 8f to (*1R, *2R**)-2,3-dimethyl-1-phenyl-butan-1,3-diol (*syn*-9f)**: The reduction of **8f** with $LiBH_4$ gave the expected *syn*-**9f** in high yield (92%) and in excellent diastereomeric excess (98%).

(*1R**, *2R**)-*2,3-Dimethyl-1-phenyl-butan-1,3-diol* (*syn-**9f***): ^{1}H NMR (300 MHz): $\delta = 0.82$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.28 (s, 3H; CH_3), 1.52 (s, 3H; CH_3), 1.60–1.70 (m, 1H; CH), 2.8 (brs, 2H; OH), 5.38 (d, J(H,H) = 1.9 Hz, 1H; CH), 7.15–7.50 (m, 5H; Ph); ^{13}C NMR (75 MHz): $\delta = 6.4$ (CH_3), 28.9 (CH_3), 29.3 (CH_3), 47.9 (CH), 73.4 (CH), 73.8 (C), 125.5 (CH), 126.5 (CH), 127.9 (CH), 143.9 (C); $C_{12}H_{18}O_2$ (194.27): calcd C 74.18, H 9.34; found C 74.30, H 9.28.

Reduction of 8g to (3*R, 4*R**)-2,3-dimethylhexan-2,4-diol (*syn*-9g)**: The reduction of **8g** to *syn*-**9g** was carried out with $LiBH_4$, $BH_3\cdot$THF, and L-Selectride, and the expected *syn*-**9g** was obtained in high yields (89%, 91%, and 93%, respectively) and in 20%, 40%, and 98% diastereomeric excess, respectively.

(*3R**, *4R**)-*2,3-Dimethyl-hexan-2,4-diol* (*syn-**9g***): ^{1}H NMR (300 MHz): $\delta = 0.93$ (t, J(H,H) = 7.5 Hz, 3H; CH_3), 0.98 (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.25 (s, 3H; CH_3), 1.36 (s, 3H; CH_3), 1.35–1.65 (m, 3H; CH and CH_2), 2.4 (brs, 1H; OH), 2.6 (brs, 1H; OH), 4.06 (brt, J(H,H) = 6.5 Hz, 1H; C*H*OH); ^{13}C NMR (75 MHz): $\delta = 6.5$ (CH_3), 10.5 (CH_3), 28.3 (CH_2), 28.9 (CH_3), 29.2 (CH_3), 44.1 (CH), 73.4 (CH), 73.9 (C); $C_8H_{18}O_2$ (146.23): calcd C 65.69, H 12.41; found C 65.74, H 12.48.

(*3R**, *4S**)-*2,3-Dimethyl-hexan-2,4-diol* (*anti-**9g**, minor*): ^{13}C NMR (75 MHz): $\delta = 8.7$ (CH_3), 13.7 (CH_3), 23.0 (CH_3), 28.1 (CH_2), 30.6 (CH_3), 46.8 (CH), 75.2 (C), 75.7 (CH).

Reduction of 11 to (3*R, 5*R**)-4-methyl-heptan-3,5-diol (12)**: The reduction of **11** with L-Selectride gave **12** in high yields and in excellent diastereomeric purity (**12**/**13** = 96:4).

(*3R**, *5R**)-*4-Methyl-heptan-3,5-diol* (***12***): ^{1}H NMR (300 MHz): $\delta = 0.90$–1.00 (m, 9H; CH_3), 1.40–1.65 (m, 5H; 2CH_2CH$_3$ and C*H*CH$_3$), 2.8 (brs, 2H; 2OH), 3.50–3.60 (m, 1H; C*H*OH), 3.80–3.90 (m, 1H; C*H*OH); ^{13}C NMR (75 MHz): $\delta = 10.0$ (CH_3), 10.7 (CH_3), 11.3 (CH_3), 26.8 (CH_2), 28.2 (CH_2), 40.2 (CH), 74.0 (CH), 77.3 (CH); $C_8H_{18}O_2$ (146.23): calcd C 65.69, H 12.41; found C 65.61, H 12.35.

The reduction of **11** with $LiBH_4$ and $BH_3\cdot$THF gave a mixture of **12** and **13**, and the latter dominated (**12**/**13** = 25:75 and 30:70, respectively).

(*3R**, *4S**, *5R**)-*4-Methylheptan-3,5-diol* (***13***): ^{13}C NMR (75 MHz): $\delta = 9.0$ (CH_3), 13.1 (CH_3), 27.6 (CH_2), 42.8 (CH), 77.6 (CH).

Reduction of 14 to (*1S, *2R**, *3R**)-2-methyl-1-phenyl-pentan-1,3-diol (15)**: The reduction of **14** with $BH_3\cdot$THF gave the expected diol **15** in high yield (94%) and in high diastereomeric purity (94%).

(*1S**, *2R**, *3R**)-*2-Methyl-1-phenyl-pentan-1,3-diol* (***15***): ^{1}H NMR (300 MHz): $\delta = 0.83$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.00 (t, J(H,H) = 7.5 Hz, 3H; CH_3), 1.60–1.70 (m, 2H; CH_2), 1.80–1.95 (m, J(H,H) = 1.9, J(H,H) = 2.8, J(H,H) = 7.1 Hz, 1H; CHMe), 2.66 (d, J(H,H) = 4.6 Hz, 1H; OH), 3.36 (d, J(H,H) = 3.3 Hz, 1H; OH), 3.50–3.65 (m, 1H; C*H*Et), 5.14 (brt, J(H,H) = 2.8 Hz, 1H; CHPh), 7.10–7.45 (m, 5H; Ph); ^{13}C NMR

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(75 MHz): $\delta = 10.0$ (CH_3), 11.1 (CH_3), 28.4 (CH_2), 43.2 (CH), 74.3 (CH), 76.7 (CH), 125.9 (CH), 126.9 (CH), 128.0 (CH), 143.0 (C); $C_{12}H_{18}O_2$ (194.27): calcd C 74.18, H 9.34; found C 74.26, H 9.40.

The reduction of **14** with $LiBH_4$ gave the diol **15** in high yields but with moderate diastereoselectivity (**15**/**16** = 77:23), conversely the reduction with L-Selectride gave mainly the diol **16** (**15**/**16** = 20:80).

(*1R**, *2R**, *3R**)-*2-Methyl-1-phenyl-pentan-1,3-diol* (***16***): ^{13}C NMR (75 MHz): $\delta = 8.9$ (CH_3), 13.4 (CH_3), 27.5 (CH_2), 44.0 (CH), 77.9 (CH), 80.8 (CH), 127.1 (CH), 127.7 (CH), 128.3 (CH), 143.3 (C).

Reduction of 17 to (*1S, *2R**, *3R**)-2,4-dimethyl-1-phenyl-pentan-1,3-diol (18)**: The reduction of **17** with $BH_3 \cdot THF$ gave the expected diol **18** in high yield (90%) and in high diastereomeric purity (96%).

(*1S**, *2R**, *3R**)-*2,4-Dimethyl-1-phenyl-pentan-1,3-diol* (***18***): ^{1}H NMR (300 MHz): $\delta = 0.78$ (d, J(H,H) = 7.2 Hz, 3H; CH_3), 0.96 (d, J(H,H) = 7.4 Hz, 3H; CH_3), 0.98 (d, J(H,H) = 6.7 Hz, 3H; CH_3), 1.80–2.00 (m, 2H; C*H*Me and C*H*(Me)$_2$), 3.1 (brs, 2H; OH), 3.29 (t, J(H,H) = 6.0 Hz, 1H; C*H*CH(Me)$_2$), 5.11 (d, J(H,H) = 2.4 Hz, 1H; CHPh), 7.20–7.40 (m, 5H; Ph); ^{13}C NMR (75 MHz): $\delta = 11.0$ (CH_3), 17.2 (CH_3), 19.6 (CH_3), 30.7 (CH), 40.7 (CH), 74.4 (CH), 80.3 (CH), 125.9 (CH), 126.7 (CH), 127.9 (CH), 143.1 (C); $C_{13}H_{20}O_2$ (208.30): calcd C 74.96, H 9.68; found C 74.88, H 9.60.

The reduction of **17** with $LiBH_4$ gave the diol **18** in high yield (90%) but with moderate diastereoselectivity (**18**/**19** = 70:30), conversely the reduction with L-Selectride mainly gave the diol **19** (**18**/**19** = 15:85).

(*1R**, *2R**, *3R**)-*2,4-Dimethyl-1-phenyl-pentan-1,3-diol* (***19***): ^{13}C NMR (75 MHz): $\delta = 13.4$ (CH_3), 13.7 (CH_3), 20.1 (CH_3), 29.9 (CH), 42.4 (CH), 81.0 (CH), 81.4 (CH), 127.2 (CH), 127.7 (CH), 128.3 (CH), 143.3 (C).

Reduction of 20: The reduction of **20** with $LiBH_4$ gave the diol **22** in high yield (91%) and with excellent diastereomeric purity (98%).

(*1R**, *2R**, *3S**)-*2-Methyl-1,3-diphenyl-propan-1,3-diol* (***22***): ^{1}H NMR (300 MHz): $\delta = 0.19$ (d, J(H,H) = 7.0 Hz, 3H; CH_3), 2.05–2.20 (m, 1H; CH), 3.7 (brs, 2H; 2OH), 4.56 (d, J(H,H) = 9.1 Hz, 2H; 2C*H*OH), 7.20–7.45 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 13.9$ (CH_3), 45.9 (CH), 80.9 (CH), 127.2 (CH), 127.9 (CH), 128.4 (CH), 143.0 (C); $C_{16}H_{18}O_2$ (242.32): calcd C 79.30, H 7.49; found C 79.48, H 7.56.

The reduction of **20** with $BH_3 \cdot THF$ gave a mixture of **21** and **22** isomers (92% yield, **21**/**22** = 55:45).

(*1R**, *3R**)-*2-Methyl-1,3-diphenyl-propan-1,3-diol*) (***21***): ^{1}H NMR (300 MHz): $\delta = 0.67$ (d, J(H,H) = 7.2 Hz, 3H; CH_3), 2.05–2.20 (m, 1H; CH), 3.1 (brs, 1H; OH), 3.2 (brs, 1H; OH), 4.63 (d, J(H,H) = 6.5 Hz, 1H; C*H*OH), 4.95 (brs, 1H; C*H*OH), 7.15–7.30 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 11.3$ (CH_3), 45.9 (CH), 74.4 (CH), 77.8 (CH), 126.1 (CH), 126.3 (CH), 127.0 (CH), 127.7 (CH), 128.0 (CH), 128.5 (CH), 142.7 (C), 143.2 (C).

Cyclization of 1,3-diols 4a–d, *syn*-9d–g, 12, 15, and 18 into the corresponding phenylboronate derivatives

General procedure: According to the Pelter[13] methodology, the 1,3-diol (1 mmol), dissolved in dry CH_2Cl_2 (10 mL), was added to $PhB(OH)_2$ (1.1 mmol) and molecular sieves (4 Å, 5 g), and the mixture was stirred for 18 h at room temperature. The solution was filtered, evaporated, and purified by chromatography on a short silica gel column and gave the corresponding cyclic boronates. In all cases, almost quantitative yields were obtained (> 98%).

(*4R, *5R**, *6R**)-4-Ethyl-5-methyl-2,6-diphenyl-1,3,2-dioxaborinane (24a)**: ^{1}H NMR (300 MHz): $\delta = 0.50$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.01 (t, J(H,H) = 7.4 Hz, 3H; CH_3), 1.40–1.50 (m, 1H; CH_2CH$_3$), 1.65–1.80 (m, 1H; CH_2CH$_3$), 2.10–2.20 (m, J(H,H) = 7.1, J(H,H) = 2.6, J(H,H) = 2.8 Hz, 1H; C*H*CH$_3$), 4.20–4.35 (m, J(H,H) = 2.6, J(H,H) = 6.5, J(H,H) = 8.2 Hz, 1H; C*H*Et), 5.36 (d, J(H,H) = 2.8 Hz, 1H; CH), 7.15–7.90 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 4.0$ (CH_3), 10.1 (CH_3), 27.0 (CH_2), 38.0 (CH), 77.2 (CH), 77.5 (CH), 125.3 (CH), 127.0 (CH), 127.6 (CH), 128.2 (CH), 130.7 (CH), 134.0 (CH), 141.3 (C); $C_{18}H_{21}BO_2$ (280.17): calcd C 77.10, H 7.55; found C 76.96, H 7.63.

(*4R, *5r**, *6S**)-4,6-Diethyl-5-methyl-2-phenyl-1,3,2-dioxaborinane (24b)**: ^{1}H NMR (300 MHz): $\delta = 0.80$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.04 (t, J(H,H) = 7.4 Hz, 6H; 2CH_3), 1.40–1.60 (m, 2H; 2CH_2CH$_3$), 1.65–1.85 (m, 2H; 2CH_2CH$_3$), 1.85–1.95 (m, 1H; C*H*CH$_3$), 4.05–4.15 (m, J(H,H) = 2.7, J(H,H) = 5.7, J(H,H) = 7.4 Hz, 2H; 2C*H*O), 7.30–7.90 (m, 5H; Ph); ^{13}C NMR (75 MHz): $\delta = 3.6$ (CH_3), 10.1 (CH_3), 26.8 (CH_2), 34.9 (CH), 77.7 (CH), 127.4 (CH), 130.4 (CH), 133.8 (CH); $C_{14}H_{21}BO_2$ (232.13): calcd C 72.36, H 9.12; found C 72.44, H 9.06.

(*4R, *5r**, *6S**)-5-Methyl-2,4,6-triphenyl-1,3,2-dioxaborinane (24c)**: ^{1}H NMR (300 MHz): $\delta = 1.18$ (d, J(H,H) = 7.2 Hz, 3H; CH_3), 3.70 (dq, J(H,H) = 3.1, J(H,H) = 7.2 Hz, 1H; CHMe), 5.24 (d, J(H,H) = 2.7 Hz, 2H; CHPh); ^{13}C NMR (75 MHz): $\delta = 4.2$ (CH_3), 40.8 (CH), 76.8 (CH), 125.2 (CH), 127.1 (CH), 127.7 (CH), 128.3 (CH), 131.1 (CH), 134.1 (CH), 141.0 (C); $C_{22}H_{21}BO_2$ (328.22): calcd C 80.45, H 6.45; found C 80.28, H 6.54.

(*4R, *5R**, *6R**)-4-Isopropyl-5-methyl-2,6-diphenyl-1,3,2-dioxaborinane (24d)**: ^{1}H NMR (300 MHz): $\delta = 0.58$ (d, J(H,H) = 7.2 Hz, 3H; CH_3), 0.92 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 1.24 (d, J(H,H) = 6.4 Hz, 3H; CH_3), 1.70–1.90 (m, 1H; C*H*(Me)$_2$), 2.25–2.40 (m, J(H,H) = 7.2, J(H,H) = 2.7, J(H,H) = 2.5 Hz, 1H; C*H*CH$_3$), 3.91 (dd, J(H,H) = 2.5, J(H,H) = 9.8 Hz, 1H; CH*i*Pr), 5.41 (d, J(H,H) = 2.7 Hz, 1H; CH), 7.30–8.00 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 3.9$ (CH_3), 17.8 (CH_3), 19.8 (CH_3), 31.0 (CH), 36.5 (CH), 77.3 (CH), 81.8 (CH), 125.3 (CH), 127.0 (CH), 127.5 (CH), 128.2 (CH), 130.7 (CH), 134.0 (CH), 141.7 (C); $C_{19}H_{23}BO_2$ (294.20): calcd C 77.57, H 7.88; found C 77.49, H 7.83.

(*4R, *5R**)-4-Ethyl-5-methyl-2-phenyl-1,3,2-dioxaborinane (23d)**: ^{1}H NMR (300 MHz): $\delta = 0.97$ (d, J(H,H) = 7.2 Hz, 3H; CH_3), 1.07 (t, J(H,H) = 7.3 Hz, 3H; CH_3), 1.45–1.70 (m, 2H; CH_2CH$_3$), 2.10–2.25 (m, 1H; C*H*CH$_3$), 3.91 (dd, J(H,H) = 5.4, J(H,H) = 11.1 Hz, 1H; CH_2O), 4.00–4.10 (m, J(H,H) = 3.4, J(H,H) = 4.9, J(H,H) = 8.5 Hz, 1H; C*H*O), 4.14 (dd, J(H,H) = 3.8, J(H,H) = 11.1 Hz, 1H; CH_2O), 7.30–7.80 (m, 5H; Ph); ^{13}C NMR (75 MHz): $\delta = 10.3$ (CH_3), 10.7 (CH_3), 25.7 (CH_2), 33.4 (CH), 67.4 (CH_2), 75.8 (CH), 127.6 (CH), 130.6 (CH), 133.8 (CH); $C_{12}H_{17}BO_2$ (204.08): calcd C 70.63, H 8.40; found C 70.72, H 8.48.

(*4R, *5R**)-5-Ethyl-2-phenyl-4-propyl-1,3,2-dioxaborinane (23e)**: ^{1}H NMR (300 MHz): $\delta = 0.85–1.05$ (m, 6H; 2CH_3), 1.20–1.75 (m, 6H; 3CH_2), 1.90–2.05 (m, 1H; C*H*Et), 3.96 (dd, J(H,H) = 7.9, J(H,H) = 11.3 Hz, 1H; CH_2O), 4.06 (dd, J(H,H) = 4.3, J(H,H) = 11.3 Hz, 1H; CH_2O), 4.15–4.20 (m, J(H,H) = 3.9, J(H,H) = 9.1, J(H,H) = 3.8 Hz, 1H; C*H*O), 7.30–7.85 (m, 5H; Ph); ^{13}C NMR (75 MHz): $\delta = 11.8$ (CH_3), 14.1 (CH_3), 18.8 (CH_2), 19.1 (CH_2), 33.8 (CH_2), 41.2 (CH), 63.8 (CH_2), 73.6 (CH), 127.5 (CH), 130.5 (CH), 133.7 (CH); $C_{14}H_{21}BO_2$ (232.13): calcd C 72.44, H 9.12; found C 72.55, H 9.18.

(*5R, *6R**)-4,4,5-Trimethyl-2,6-diphenyl-1,3,2-dioxaborinane (23f)**: ^{1}H NMR (300 MHz): $\delta = 0.64$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.38 (s, 3H; CH_3), 1.62 (s, 3H; CH_3) 2.00–2.10 (dq, J(H,H) = 3.1, J(H,H) = 7.2 Hz, 1H; C*H*CH$_3$), 5.65 (d, J(H,H) = 3.1 Hz, 1H; CHO), 7.25–8.00 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 7.2$ (CH_3), 28.0 (CH_3), 30.3 (CH_3), 42.9 (CH), 72.8 (CH), 125.3 (CH), 126.8 (CH), 127.6 (CH), 128.2 (CH), 130.7 (CH), 134.0 (CH), 141.5 (C); $C_{18}H_{21}BO_2$ (280.17): calcd C 77.17, H 7.55; found C 76.95, H 7.65.

(*5R, *6R**)-6-Ethyl-4,4,5-trimethyl-2-phenyl-1,3,2-dioxaborinane (23g)**: ^{1}H NMR (300 MHz): $\delta = 0.88$ (d, J(H,H) = 7.2 Hz, 3H; CH_3), 1.05 (t, J(H,H) = 7.4 Hz, 3H; CH_3), 1.33 (s, 3H; CH_3), 1.43 (s, 3H; CH_3), 1.45–1.60 (m, 1H; CH_2CH$_3$), 1.65–1.75 (m, J(H,H) = 3.0, J(H,H) = 7.2 Hz, 1H; C*H*CH$_3$), 1.75–1.90 (m, 1H; CH_2CH$_3$), 4.20–4.30 (m, J(H,H) = 3.0, J(H,H) = 5.5, J(H,H) = 8.5 Hz, 1H; C*H*O), 7.25–7.80 (m, 5H; Ph); ^{13}C NMR (75 MHz): $\delta = 6.7$ (CH_3), 10.3 (CH_3), 27.0 (CH_2), 28.0 (CH_3), 30.1 (CH_3), 40.2 (CH), 73.0 (CH), 127.4 (CH), 130.3 (CH), 133.8 (CH); $C_{13}H_{21}BO_2$ (220.12): calcd C 70.94, H 9.62; found C 71.10, H 9.66.

(*4R, *6R**)-4,6-Diethyl-5-methyl-2-phenyl-1,3,2-dioxaborinane (25a)**: ^{1}H NMR (300 MHz): $\delta = 0.95$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.06 (t, J(H,H) = 7.5 Hz, 3H; CH_3), 1.08 (t, J(H,H) = 7.4 Hz, 3H; CH_3), 1.45–1.65 (m, 2H; CH_2CH$_3$), 1.65–1.85 (m, 2H; CH_2CH$_3$), 1.85–2.00 (m, 1H; C*H*CH$_3$), 3.75–3.85 (m, J(H,H) = 7.9, J(H,H) = 6.1, J(H,H) = 4.5 Hz, 1H; CHO), 3.90–4.00 (m, J(H,H) = 7.0, J(H,H) = 6.5, J(H,H) = 3.9 Hz, 1H; CHO), 7.30–7.45 (m, 3H; Ph), 7.80–7.95 (m, 2H; Ph); ^{13}C NMR (75 MHz): $\delta = 9.6$ (CH_3), 10.5 (CH_3), 12.6 (CH_3), 25.3 (CH_2), 28.4 (CH_2), 37.0 (CH), 74.0 (CH), 76.4 (CH), 127.4 (CH), 130.4 (CH), 133.9 (CH); $C_{14}H_{21}BO_2$ (232.13): calcd C 72.44, H 9.12; found C 72.26, H 9.21.

(*4R, *5R**, *6S**)-4-Ethyl-5-methyl-2,6-diphenyl-1,3,2-dioxaborinane (25b)**: ^{1}H NMR (300 MHz): $\delta = 0.74$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 1.10 (t, J(H,H) = 7.3 Hz, 3H; CH_3), 1.60–1.80 (m, 1H; CH_2CH$_3$), 2.10–2.25 (m, 1H; C*H*CH$_3$), 3.75–3.85 (m, J(H,H) = 5.3, J(H,H) = 7.5 Hz, 1H; CHEt), 5.27 (d, J(H,H) = 4.1 Hz, 1H; CH), 7.25–7.95 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 9.6$ (CH_3), 12.6 (CH_3), 28.2 (CH_2), 38.5 (CH), 74.4 (CH), 75.6

(CH), 126.2 (CH), 127.3 (CH), 127.6 (CH), 128.1 (CH), 130.7 (CH), 134.0 (CH), 140.0 (C); $C_{18}H_{21}BO_2$ (280.17): calcd C 77.17, H 7.55; found C 76.96, H 7.44.

(*4R, *5R**, *6S**)-4-Isopropyl-5-methyl-2,6-diphenyl-1,3,2-dioxaborinane (25c)**: ^{1}H NMR (300 MHz): $\delta = 0.66$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 0.97 (d, J(H,H) = 6.6 Hz, 3H; CH_3), 1.02 (d, J(H,H) = 6.8 Hz, 3H; CH_3), 1.75–1.90 (m, 1H; C*H*(Me)$_2$), 2.20–2.35 (m, 1H; C*H*CH_3), 3.48 (t, J(H,H) = 6.0 Hz, 1H; CH*i*Pr), 5.18 (d, J(H,H) = 4.1 Hz, 1H; CH), 7.25–7.95 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 12.5$ (CH_3), 16.9 (CH_3), 19.5 (CH_3), 31.0 (CH), 36.3 (CH), 74.6 (CH), 79.0 (CH), 126.2 (CH), 127.3 (CH), 127.6 (CH), 128.1 (CH), 130.7 (CH), 134.0 (CH), 140.0 (C); $C_{19}H_{23}BO_2$ (294.20): calcd C 77.57, H 7.88; found C 77.62, H 7.76.

Conversion of a mixture of 21 and 22 to a mixture of the corresponding cyclic boronate diastereoisomers as a route to obtain pure 21: The mixture of **21** and **22** was converted, according to the reported general procedure above, into the corresponding mixture of **25d** and **26d** boronates. These compounds were easily separated by chromatography on a silica gel column (petroleum ether: Et_2O = 80:20). Both pure **25d** and **26d** were converted into pure **21** and **22**, respectively, in almost quantitative yields by treatment with H_2O_2 in EtOH and Et_2O in basic medium (pH 8).[8]

(*4R**, *6R**)-*5-Methyl-2,4,6-triphenyl-1,3,2-dioxaborinane* (***25d***): ^{1}H NMR (300 MHz): $\delta = 0.36$ (d, J(H,H) = 7.1 Hz, 3H; CH_3), 2.45–2.60 (m, 1H; CH), 5.68 (br d, J(H,H) = 2.8 Hz, 2H; 2CH), 7.25–7.95 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 12.9$ (CH_3), 40.9 (CH), 73.6 (CH), 77.2 (CH), 125.8 (CH), 126.0 (CH), 127.4 (CH), 128.2 (CH), 128.5 (CH), 134.2 (CH), 141.7 (C); $C_{22}H_{21}BO_2$ (328.22): calcd C 80.51, H 6.45; found C 80.39, H 6.49.

(*4R**, *5R**, *6S**)-*5-Methyl-2,4,6-triphenyl-1,3,2-dioxaborinane* (***26d***): ^{1}H NMR (300 MHz): $\delta = 0.60$ (d, J(H,H) = 6.6 Hz, 3H; CH_3), 1.55–2.00 (m, J(H,H) = 6.6, J(H,H) = 10.2 Hz, 1H; CH), 4.90 (d, J(H,H) = 10.2 Hz, 2H; 2CH), 7.25–7.95 (m, 10H; Ph); ^{13}C NMR (75 MHz): $\delta = 13.5$ (CH_3), 45.2 (CH), 80.4 (CH), 127.2 (CH), 127.6 (CH), 128.1 (CH), 128.4 (CH), 130.9 (CH), 134.2 (CH), 141.2 (C); $C_{22}H_{21}BO_2$ (328.22): calcd C 80.51, H 6.45; found C 80.58, H 6.40.

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