Internal Lewis Acid Coordination as a Powerful Tool To Promote Highly Stereoselective Alkylation of α-Alkyl-β-Hydroxy Ketones with Grignard Reagents

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Abstract: An efficient and highly diastereoselective protocol is described for the alkylation of β-hydroxy ketones that contain an α-stereocenter. This method is based on the preliminary transformation of the β-hydroxy group into a titanium alcoholate by means of the facile transmetalation of the corresponding β-silyloxy derivative with $TiCl_4$ (Method A) or by reaction of the lithium alcoholate with $TiCl_4$ (Method B). On account of the strong internal coordinating action of the Lewis acid, this intermediate assumes a rigid half-chair conformation with the α-alkyl substituent in a pseudoaxial position. This geometrical arrangement facilitates the attack of the entering carbanion on the carbonylic function opposite to the α-substituent. The method uses simple Grignard reagents as the alkylating agents and allows the addition of a wide variety of carbon frameworks to the carbonyl function, including primary and secondary alkyl chains, arylic, alkynylic, vinylic, and benzylic moieties, with high efficiency and stereoselectivity.

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

Introduction

The stereoselective construction of 1,3-diols represents an important target in organic synthesis because this fragment appears in the structure of various natural products.[1] At present, several general protocols for their synthesis are available in literature. In particular, reductions of O-protected or unprotected β-hydroxy ketones that contain a stereogenic center in the α- or β-position have been extensively investigated.[2] In these reactions a high level of diastereoselectivity has been obtained by the exploitation of the ability of a proximal hydroxyl group to control the stereochemical outcome of organic reactions.[3]

On the contrary, in spite of their importance, no extensive studies have been reported on the alkylation of β-hydroxy carbonylic compounds. In fact these methodologies should represent a new entry to the synthesis of polyoxy natural products containing tertiary alcohol moieties.[4] Fujisawa et al.[5] reported that the treatment of β-hydroxy ketones, which have a stereocenter in the β-position, with $MeTiCl_3$ and $MeTi(OiPr)_3$ yielded mainly *anti*-diols, whereas reactions of the corresponding β-silyloxy ketones with lithium, magnesium, and titanium reagents afforded isomeric mixtures in which *syn*-diols were predominant. *Anti*-diols, as the prevalent diastereoisomers, were obtained by Ruano et al.[6] in the methylation of β-hydroxy ketones with MeLi in the presence of $ZnBr_2$, while formation of *syn*-diols was observed when Me_3Al was used as the methylating agent.

Much less attention has been paid to the alkylation of β-hydroxy ketones that contain an alkyl-substituted stereocenter in the α-position. In addition to a few old reports[7] on the reaction of α-alkyl-β-hydroxy ketones with Grignard reagents, only the alkylation of α-phenyl-β-alkoxy ketones with RMgX and RLi has been recently reported:[8] the reaction was found to proceed with high selectivity, but often in low yields, owing largely to the occurrence of enolization processes. In addition, there is no definite information given about the origin of the high stereocontrol observed; whether the reaction proceeds through a Cram-type[9] chelation mechanism or through an open-chain pathway (Felkin–Anh-type[10]), the same stereoisomer is obtained. However, on the basis of some experimental evidence, the latter mechanistic hypothesis appears to be more reasonable.

Furthermore, the formation of β-chelated intermediates in the reaction of protected L-erythrulose derivatives with various organometallic reagents has been challenged in a

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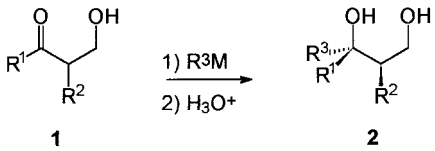
report[11] which appeared in the literature during the drafting of the present work. The authors affirm that the stereochemical results can be explained better in terms of an open-chain mechanism, despite the fact that β-chelates have often been invoked to explain the stereochemical outcome of nucleophilic addition in 1,3-difunctional compounds, such as β-oxo sulfoxides,[12] β-oxo amides,[13] β-oxygenated aldehydes,[14] β-oxophosphine oxides.[15]

Since the actual participation of β-hydroxyl groups in the nucleophilic addition to carbonylic compounds is still an object of discussion,[16] we decided to investigate the problem of 1,2-asymmetric induction in the reaction of β-oxygenated ketones, which contain an α-stereocenter, with organometallic species, starting from a simple system, such as **1** (Scheme 1).



Scheme 1. General 1,2-asymmetric induction reaction of β-oxygenated ketones, that contain an α-stereocenter, with an organometallic species.

We speculated that strong Lewis acids might form Cram-type chelates with bidentate compounds such as **1**, which would then lead to chelation-controlled products upon treatment with the appropriate alkylating reagent. We report herein on two very simple methodologies to alkylate **1** which proceed with high diastereoselectivity and with good-to-high efficiency.[17] These protocols are based on the use of $TiCl_4$, as the chelating agent,[18] and on common organometallic reagents, such as Grignard compounds, to transfer a wide variety of alkyl frameworks, including primary and secondary alkyl chains, aromatic, vinylic, benzylic, and alkynyl groups, to the carbonyl function of **1**.

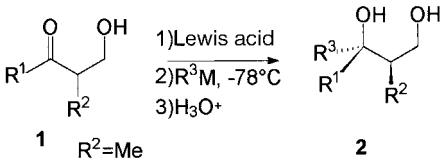
Abstract in Italian: *In questo lavoro viene riportato un protocollo efficiente nonché altamente diastereoselettivo per l'alchilazione di β-idrossichetoni contenenti uno stereocentro in α. Questo metodo si basa sulla trasformazione del gruppo idrossilico in un titanio-alcolato facilmente ottenibile per transmetallazione con $TiCl_4$ del corrispondente β-sililossi derivato (Metodo A) o per reazione di un Li-alcolato con $TiCl_4$ (Metodo B). Questo intermedio, grazie alla forte azione di coordinazione interna esercitata dall'acido di Lewis, assume una conformazione rigida a mezza sedia con il sostituente alchilico in α nella posizione pseudo-assiale. Questo arrangiamento obbliga il carbanione entrante ad attaccare il gruppo carbonilico dal lato opposto al sostituente in α. Questa procedura utilizza come agenti alchilanti i semplici reattivi di Grignard e consente di trasferire al gruppo carbonilico con elevata efficienza e diastereoselettività un'ampia varietà di gruppi saturi ed insaturi, quali catene alchiliche primarie e secondarie, residui arilici, alchinilici e vinilici.*

Results and Discussion

The papers published before 1966[7] on the alkylation of unprotected β-hydroxy ketones reported the prevalent formation of the chelation-controlled diastereoisomer, but did not give any information about the yield or the level of stereoselectivity. Therefore, we reexamined the reaction of some β-hydroxy ketones (**1aa**, **1ba**, **1ca**) with different Grignard reagents.

We found that the reaction of **1aa** with a threefold excess of EtMgBr in THF at −78 °C (Table 1, entry 1) gave the

Table 1. Alkylation of **1** with different organometallic reagents in the presence of a Lewis acid.



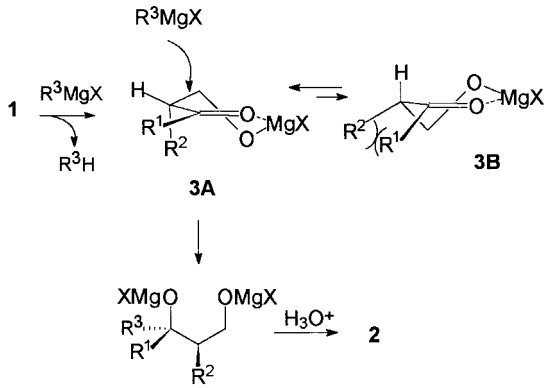
1 **2**

Entry	Starting material	R^1	Lewis acid	R^3M	Product	Yield [%][a,b]	*de* [%][a]
1	**1aa**	Me	–	EtMgBr	**2aab**	34	50
2	**1aa**	Me	–	PhMgBr	**2aac**	50[c]	80
3	**1ca**	Ph	–	MeMgCl	**2caa**	48[d]	70
4	**1aa**	Me	–	EtLi	**2aab**	50	2
5	**1aa**	Me	–	PhLi	**2aac**	70	34
6	**1aa**	Me	$TiCl_4$	EtMgBr	**2aab**	40	60
7	**1aa**	Me	$TiCl_4$	PhMgBr	**2aac**	64	90
8	**1aa**	Me	$TiCl_4$	PhCCMgBr	**2aac**	60	40
9	**1ba**	Et	$TiCl_4$	MeMgCl	**2baa**	48	86
10	**1aa**	Me	$CeCl_3$	EtMgBr	**2aab**	76	4
11	**1aa**	Me	–	$EtCeCl_2$	**2aab**	98	44

[a] Yields and diastereoselectivities [*de* %] were calculated from the ^1H NMR data of the mixture of diastereoisomers and starting material after chromatographic purification. [b] In all reactions an appreciable amount of starting material (10–30%) was recovered, except for the reaction of cerium derivatives (entries 10 and 11). [c] About 8% of benzyl alcohol was also recovered. [d] About 6% of propiophenone was also recovered

corresponding alcohol **2aab** in 34% yield and in 50% diastereoisomeric excess, as calculated from ^1H NMR data.[19]

The prevalent formation of the chelation-controlled diastereoisomer can be reasonably explained by the mechanism depicted in Scheme 2. In the first step, the Grignard reagent



Scheme 2. Chelation control in the reaction of β-hydroxy ketone **1** with Grignard reagents only.

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deprotonates the hydroxyl group: on account of the coordinating ability of Mg^{II}, the chelated alkoxy derivative **3** can assume a half-chair arrangement. Of the two possible conformers, the one with R^1 in the pseudoaxial position (**3A**) is more favorable as the steric interaction between the R^1 and R^2 groups is minimized.[15b]

If the operating mechanism is chelation-controlled, an increase in the stereoselectivity may be expected as the bulkiness of both the incoming nucleophile and the R^2 group increases. Indeed, in the reaction of **1aa** with PhMgBr and **1ca** with MeMgCl (Table 1, entries 2 and 3), compounds **2aac** and **2caa** were obtained in 80% and 70% *de*, respectively. The yields are very low again, due to an appreciable amount of enolization and retroaldolic side reactions.[20]

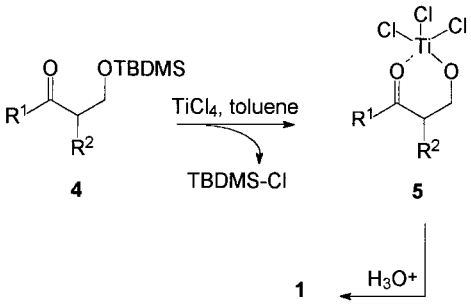
The attempt to use lithium derivatives was unsuccessful: the reaction of **1aa** with both EtLi and PhLi gave diols **2aab** and **2aac**, respectively, in better yields but with lower diastereoselectivity than with the Grignard reagents.

In order to increase the diastereoselectivity, we repeated the reactions in the presence of $TiCl_4$.[18] A slight improvement in the diastereoselectivity was observed; however, the extent of the enolization side reaction remained too high for a practical synthetic utility of this approach. Moreover, we noted a random variation of both diastereoselection and conversion yields, depending on the time of contact between **1** and $TiCl_4$ as well as on the time of addition of Grignard reagents and on the concentration of the reagents. The data reported in Table 1, entries 6–9, refer to the best results obtained.

Recently, we reported that alkylcerium reagents depress side reactions in the alkylation of β-hydroxy ketones.[21] Indeed, the use of alkylcerium reagents in the present system caused a dramatic increase in yields; however, it also led to unsatisfactory diastereoselectivity (Table 1, entries 10 and 11). On the other hand, the chelation ability claimed for cerium compounds[22] has been challenged in the $CeCl_3$-mediated reduction of α-alkyl-β-ketophosphine oxides; the observed stereochemical outcome is consistent with a nonchelated Felkin–Ahn pathway.[15b]

Undoubtedly, none of the aforementioned reactions can be of practical interest as the diastereoisomers cannot be separated by column chromatography. Moreover, it is extremely difficult to purify the mixture of diastereomers from large amounts of starting material. Therefore, it was necessary to find a new methodology that ensures high conversion yields and diastereoselectivity in order to avoid separation problems.

Diastereoselective alkylation of β-hydroxy ketones: Denmark and Almstead reported[23] direct spectroscopic evidence that alkyl silyl ethers, when treated with $TiCl_4$ in a polar solvent, can undergo a smooth transmetalation process to alkoxytitanium derivatives. Following these suggestions, we tried to synthesize a Ti derivative, **5** (Scheme 3), by the transmetalation of a β-*tert*-butyldimethylsilyloxy ketone **4** with $TiCl_4$ in toluene (Method A). The transmetalation process was monitored as follows: at particular time intervals, samples of the reaction mixture were poured into diluted aqueous HCl (5%), immediately extracted with Et_2O, and then analyzed by TLC and by GC–MS. Since β-silyloxy derivatives do not undergo deprotection under these acidic conditions, we considered the appearance of the unprotected ketone **1** as a proof of the formation of a pentacoordinate titanate[24] species, such as **5**, in the toluene solution.

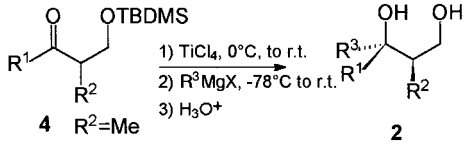


Scheme 3. Formation of titanium-alcoholate **5** by transmetalation of *O*-silyl-protected β-hydroxy ketone **4**.

The transmetalation process was found to be strongly dependent on the structure of the starting β-silyloxy ketone **4**. For compound **4aa**, the reaction at $-60\,^{\circ}C$ is complete within 2 h, while for ketone **4ca** the reaction at the same temperature is very sluggish and about 90% of the starting material was recovered after 2.5 h. At room temperature, the transmetalation of **4aa** and **4ca** requires a few minutes and 1 h, respectively, to go to completion.

Therefore the alkylation of β-silyloxy ketones **4** with Grignard reagents was carried out by performing the transmetalation process at room temperature and then cooling the titanium alcoholate solution at $-78\,^{\circ}C$, before R^3MgX in THF was added. After 1 h the temperature was allowed to rise to $20\,^{\circ}C$. The usual workup gave the expected diol **2** in good-to-high yields and with high diastereoselectivity (Table 2). The

Table 2. Synthesis of 1,3-diols **2** from β-silyloxy ketones **4** (Method A).



Entry	Starting material	R^1	R^3	Product	Yield [%][a]	*de* [%][b]
1	**4aa**	Me	Et	**2aab**	70	82[c]
2	**4aa**	Me	Ph	**2aac**	62	92[c]
3	**4aa**	Me	$PhCH_2$	**2aaf**	98	80[c]
4	**4aa**	Me	PhC≡C	**2aah**	89	75[c]
5	**4ba**	Et	Me	**2baa**	95	82[c]
6	**4ca**	Ph	Me	**2caa**	92	96

[a] Calculated for the mixture of diastereoisomers after chromatographic purification. [b] Calculated from ^1H NMR data. [c] Small amounts (<5%) of deprotected starting material were also recovered.

reaction works well both with nonstabilized (PhMgBr) and stabilized carbanions ($PhCH_2MgBr$). A comparison of entries 1 and 2 with 5 and 6 (Table 2), respectively, underlines the high flexibility of this methodology: both diastereoisomers of a given diol can be prepared with high purity just by exchanging the R^3 group in the Grignard reagent with the alkyl group R^1 in the β-silyloxy ketone **4**. The reaction requires a large excess of Grignard reagent, the amount of which depends on the nature of both substrate **4** and the

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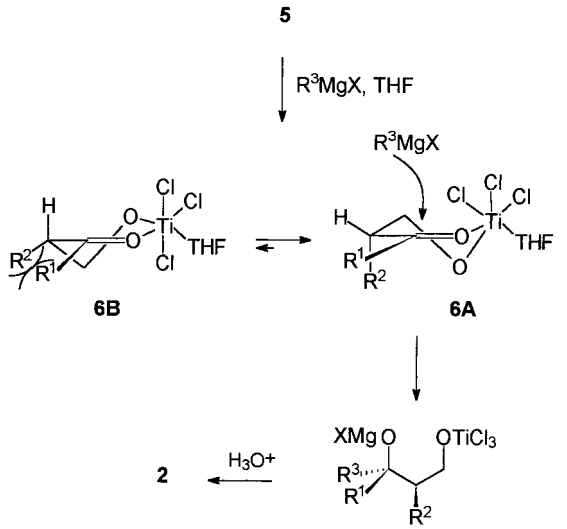
Grignard reagent itself. A fivefold excess of R^3MgX has been assumed as an optimum procedure, since these conditions ensure the high conversion of β-silyloxy ketones **4** in all cases. This waste of organometallic reagent is probably due to the interaction of R^3MgX with all the chlorotitanium species present in solution as well as with the TBDMS-Cl formed during the transmetalation process.

It is very likely that when the Grignard reagent in THF is added, five-coordinate complex **5** immediately rearranges to the preferred six-coordinate arrangement **6** (Scheme 4).[24]

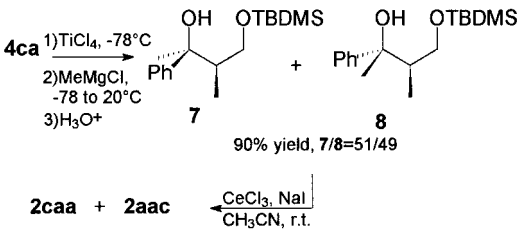


Scheme 4. Stereocontrol in the alkylation of titanium-alcoholate **5** with R^3MgX, (Method A).

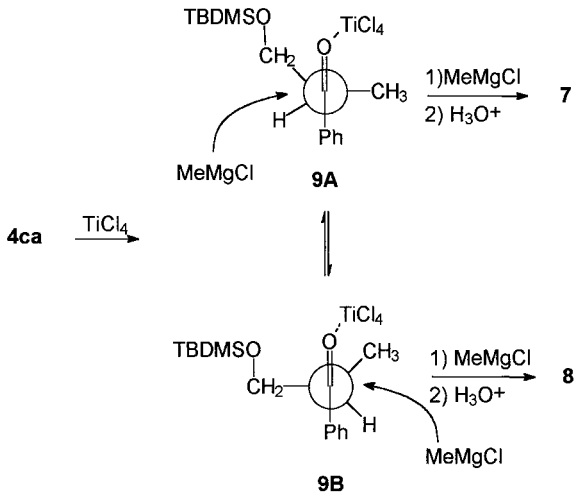
The reaction then proceeds by the direct attack of R^3MgX on **6**, rather than by the attack of an alkyltitanium derivative formed upon transmetalation of R^3MgX with chlorotitanium species. Evidence of this hypothesis is reported below.

In order to provide evidence that the formation of a titanium alcoholate is essential to gain high diastereoselectivity, compound **4ca** was treated with $TiCl_4$ in toluene at −78 °C for a few minutes only, and then an excess of CH_3MgCl was added at the same temperature. The usual workup gave β-silyloxy alcohols **7** and **8** in comparable amounts (90% total yield). The structures of **7** and **8** were confirmed by their conversion into the corresponding diols by treatment with $CeCl_3 \cdot 7H_2O$/NaI in CH_3CN at room temperature (Scheme 5).[25]

Since the transmetalation process does not occur at low temperatures, we can assume that the interaction between **4ca** and $TiCl_4$ gives an open-chain complex, such as **9** (Scheme 6),



Scheme 5. Alkylation of silyloxyketone **4ca** with MeMgCl in the presence of $TiCl_4$ at low temperature.

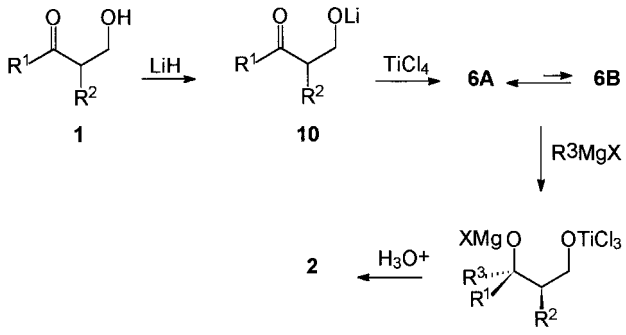


Scheme 6. Nonchelation control in the $TiCl_4$-mediated alkylation of **4ca** with MeMgCl.

due to the well-known weak ability of β-silyloxy ketones to chelate to Lewis acids.[26] With regard to the small difference in bulkiness between $CH_2OTBDMS$ and CH_3 groups, it is reasonable to assume that the structural arrangement of the complex can be described by an equilibrium between the almost equally populated conformers **9A** and **9B**. The attack of MeMgCl on **9A** and **9B**, followed by acidic quenching gave **7** and **8**, respectively.

The above results demonstrate that, when the reaction is forced to proceed through a Felkin–Ahn-type pathway, there is an almost complete collapse of the stereoselectivity.

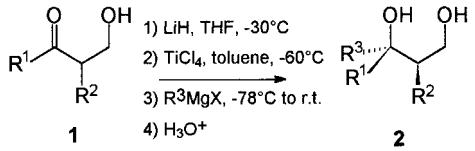
We developed an alternative procedure (Method B, Scheme 7) for the formation of titanium alcoholate **6**: treatment of **1** with LiH in THF below −30 °C, followed by



Scheme 7. Diastereoselective alkylation of titanium-alcoholate **6** formed from Li-alcoholate **10** and $TiCl_4$, (Method B).

addition of $TiCl_4$ in toluene at −78 °C gave the intermediate **6**. Addition of a Grignard reagent at −78 °C, following the same procedure adopted for Method A, gave the expected diols **2** in high yields and with high diastereomeric purity (Table 3). A comparison between results reported in Table 2 and in Table 3 shows that Methods A and B proceed with comparable efficiency. However, the latter is superior since it is based on a simpler and more convenient procedure. For these reasons, it was applied to a large variety of substrates and Grignard reagents R^3MgX.

Table 3. Synthesis of 1,3-diols **2** from **1** (Method B).



1 **2**

Entry	Starting material	R^1	R^2	R^3	Product	Yield [%][a]	*de* [%][b]
1	**1aa**	Me	Me	Et	**2aab**	92[d]	70
2	**1aa**	Me	Me	Ph	**2aac**	80[d]	82
3	**1aa**	Me	Me	*i*Pr	**2aae**	75[d]	90
4	**1aa**	Me	Me	$PhCH_2$	**2aaf**	88[d]	70
5	**1aa**	Me	Me	vinyl	**2aag**	75[c,d]	70
6	**1aa**	Me	Me	allyl	**2aai**	95[c,d]	0
7	**1ba**	Et	Me	Me	**2baa**	95[d]	70
8	**1ba**	Et	Me	Ph	**2bac**	85[d]	95
9	**1ca**	Ph	Me	Me	**2caa**	98	98
10	**1ca**	Ph	Me	Et	**2cab**	98	96
11	**1ca**	Ph	Me	Bu	**2cad**	94	96
12	**1ca**	Ph	Me	*i*Pr	**2cae**	95	98
13	**1ca**	Ph	Me	$PhCH_2$	**2caf**	98	98
14	**1ca**	Ph	Me	PhC≡C	**2cah**	85[c]	98
15	**1cb**	Ph	Et	Me	**2cba**	98	98
16	**1cb**	Ph	Et	Et	**2cbb**	92	96
17	**1cc**	Ph	Ph	Me	**2cca**	98	98
18	**1cc**	Ph	Ph	$PhCH_2$	**2ccf**	98	98
19	**1cc**	Ph	Ph	vinyl	**2ccg**	98[c]	98

[a] Calculated for the mixture of diastereoisomers after chromatographic purification. [b] Calculated from ^{1}H NMR data. [c] The Grignard reagent was added at $-50\,^\circ$C and the reaction allowed to warm to $-20\,^\circ$C. [d] Small amounts (<5%) of starting material were also recovered.

The data reported in Table 2 and 3 illustrate that, in both methods, stereoselectivity increases as the steric demand of both the R^1 and the R^2 substituents increases, due to a stronger destabilizing effect on conformer **6B**. Moreover, an improvement in the *de*% values was observed by increasing the steric hindrance of R^3MgX, in good agreement with the fact that the stereofacial selection in **6A** has to increase with bulkier attacking nucleophiles.

In both methods, the reaction always proceeds with good-to-high efficiency. In fact, the retroaldolic side reaction is completely suppressed due to the formation of a strong Ti–O covalent bond in alcoholate **6**. The enolization process occurs to a very negligible extent when R^1 (Me or Et) contains an acidic proton; the recovered starting material never exceeded 5%. Moreover, when R^1 is a not enolizable group (Ph), a complete conversion of ketone **1** was observed. The powerful activation exerted by the Ti-alcoholate through an internal coordinating action makes the carbonyl group highly reactive toward nucleophiles. As a consequence of this, the proton-abstraction process becomes less competitive with respect to carbonyl attack. In addition, the absence of these side reactions when an acidic hydrogen is present only in the α-position can be explained by the fact that in the most stable conformation of Ti-alcoholate **6A**, this hydrogen occupies an equatorial position from which the it can be abstracted only with difficulty due to stereoelectronic factors.[27]

As previously mentioned, the alkylation seems to proceed by the direct attack of R^3MgX on the alcoholate **6**. Convincing evidence of this assumption arises from results obtained in the alkylations with *i*PrMgBr. It is well known[28] that isopropylmagnesium bromide smoothly rearranges, even at low temperatures, to give *n*-propylmagnesium bromide in the presence of small amounts of $TiCl_4$. In the reaction of *i*PrMgX with **1aa** and **1ca** (Table 3, entries 3 and 12, respectively) we only found the incorporation of the α-branched chain in the final products **2aae** and **2cae**. Therefore, the attack of *i*PrMgBr on the carbonyl group has to occur before any interactions with chlorotitanium species.

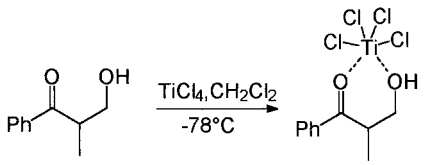
Moreover, chlorovinyl and alkynyltitanium derivatives are not stable, even at low temperatures,[29] and cannot be successfully employed in synthesis. The success of the reaction with vinyl and alkynyl frameworks can also be explained in terms of a direct attack of the Grignard reagent on the carbonyl group. However, for these unsaturated reagents a slight modification of the experimental conditions was necessary to avoid extensive decomposition phenomena[30] (see the Experimental Section).

Finally, there is a complete lack of diastereoselectivity in the case of allyl reagents. This may be due to the fact that many allyl-type organometallic reagents react in most instances with allylic inversion through cyclic transition states of metallo-ene type,[31] which leads to different reaction intermediates. An analogous behavior has recently been observed in the allylation of protected erythrulose derivatives.[11]

In conclusion, we attributed the origin of the observed diastereoselectivity to the formation of a rigid and stable β-chelated intermediate **6A** in which the α-substituent in pseudoaxial position produces an high stereofacial discrimination towards the incoming nucleophile.

The lower efficiency observed in the reaction of **1** with R^3MgX alone can be ascribed to the more polar character of the Mg–O bond compared to the Ti–O bond in coordinating solvents, such as THF. This situation makes the cyclic structure of the complex more flexible, and thus less stable and more prone to undergo enolization and/or retroaldolic reactions. The same explanation accounts for the lower selectivity observed. Further support of this interpretation was provided by the results obtained in the reaction of **1** with Li derivatives (Table 1, entries 3 and 4): the more enhanced ionic character of the Li–O bond caused a dramatic decrease in the stereoselectivity.

The failure in the attempts to form a rigid β-chelate, such as **6**, by addition of R^3MgX to a 1:1 mixture of $TiCl_4$ and **1** in toluene can be explained on the basis of recently reported results on the reduction of β-hydroxy ketones: DiMare[2d] found evidence that the interaction between $TiCl_4$ and β-hydroxy ketone **1ca** (Scheme 8) does not give a titanium alcoholate with elimination of HCl, but rather the complex **11**.



4ca **11**

Scheme 8. Reaction between $TiCl_4$ and β-hydroxy ketone **1ca**.

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As the use of toluene instead of CH_2Cl_2 as the solvent does not modify the nature of the interaction between **1ca** and $TiCl_4$, we can assume the formation of an analogous complex, even in our system. The addition of a Grignard reagent in THF to **11** can produce **6**, but an alternative direct carbonylic attack cannot be excluded, as well as enolization phenomena, since the complex **11** is obviously much less rigid than **6**.

Our interpretations do not disagree with previously reported studies on the formation of β-chelates in closely related systems, such as β-alkoxyaldehydes and β-alkoxy ketones. Conformational spectroscopic investigations on the interaction between 2-methyl-3-(benzyloxy)propanals and $TiCl_4$ and $MgBr_2$ show that a rigid 1:1 complex is formed with either of these Lewis acids and that the methyl group occupies a pseudoequatorial position in a flattened half-chair arrangement.[32] This preferred conformation is allowed by the absence of 1,2-strain between the α-methyl group and the aldehydic hydrogen, in order to minimize steric interactions of the O-benzyl substituent with both the α-methyl group and the ligands at the chelating metal.

On the other hand, the ability of β-alkoxy ketones to form stable β-chelates with Lewis acids has been challenged recently, because in these systems the presence of all the aforementioned steric strains has a destabilizing effect on both possible conformations.[8, 11]

There are substantial differences in the steric factors governing the conformational stability of β-alkoxyaldehydes and β-alkoxy ketones and our system: the absence of an O-substituent in the titanium alcoholate **6** means that the conformational arrangement is governed mainly by the 1,2-interaction between R^1 and R^2 groups, with the formation of a stable and rigid **6A** structure.

On the other hand, a lot of convincing experimental evidence on the formation of stable β-chelates has been reported for systems having similar structural features, such as β-ketophosphine oxides[15b] and β-ketosulfones.[33]

In conclusion, a new efficient protocol for stereoselective alkylation of β-hydroxy ketones is now available. The present method is characterized by the following features:

1) The reaction proceeds with high efficiency in the presence of a coordinating cosolvent, such as THF, whose use is generally discouraged, owing to its destabilizing effect on chelated complexes.[15b, 34] The tolerance of THF permits the employment of simple Grignard compounds as the alkylating agents.

2) A large variety of carbon frameworks can be introduced, including primary and secondary alkyl chains, arylic, alkynylic, vinylic, and benzylic moieties, with high efficiency and selectivity, the only exception is the allyl group.

We applied this methodology to simple systems, such as **1**, in order to exclude other relevant steric interferences. Studies are in progress to extend this protocol to more complex systems, as well as to rationalize the abnormal reactivity showed by allyl Grignard reagents.

Experimental Section

Flash chromatography was performed on Merck silica gel (0.040–0.063 mm). THF was refluxed over sodium until the blue color of benzophenone ketyl persisted and then distilled into a receiver under nitrogen atmosphere. ^{1}H NMR spectra were acquired at 300 MHz in $CDCl_3$ and referenced to Me_4Si as the internal standard. ^{13}C and DEPT NMR spectra were acquired at 75 MHz in $CDCl_3$ and referenced to Me_4Si as the internal standard. All reactions were conducted in oven-dried glassware under an atmosphere of dry argon. Compound **1aa** is commercially available and it was distilled twice before use. The starting β-hydroxy ketones **1ba**, **1ca**, **1cb**, and **1cc** were synthesized according to standard procedures.[35]

General workup procedure for alkylation of β-hydroxy ketones 1: All the reactions were quenched following a standard procedure: aqueous HCl (10%) was added to the reaction mixture, which was then extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on a short silica gel column (petroleum ether/ethyl acetate 7:3). Yields and *de* % are reported in the Tables and are calculated from ^{1}H NMR data. Configurations were assigned by analogy with the ^{1}H and ^{13}C NMR spectra of known products.

Alkylation of 1 with R^3MgBr and R^3Li: R^3MgBr (6 mmol, 3 equiv, 1.0 M solution in THF) was added to a solution of **1** (2 mmol) in THF at −78 °C. The reaction mixture was kept at this temperature for 3 h and was then allowed to warm to 0 °C. The usual work-up gave the mixture of diastereoisomers and starting material that could not be separated by chromatography. The same procedure was followed using R^3Li instead of R^3MgBr.

Alkylation of 1aa with EtMgBr in the presence of $CeCl_3$: Compound **1aa** (2 mmol) was added at 0 °C to a THF suspension of $CeCl_3$ (6 mmol, 3 equiv), prepared according to the standard methodology.[22a] After 1 h, EtMgBr (6 mmol, 3 equiv, 1.0 M solution in THF) was added to the gray suspension at −78 °C. The reaction mixture was kept at this temperature for 3 h and was then allowed to warm to 0 °C. The usual work-up gave the mixture of diastereoisomers.

Alkylation of 1aa with $EtCeCl_2$: EtLi (6 mmol, 3 equiv, 1.0 M solution in THF) was added at −78 °C to a THF suspension of $CeCl_3$ (6 mmol, 3 equiv), prepared according to standard methodology.[22a] After 1 h, **1aa** (2 mmol) was added to the red suspension at −78 °C. The reaction mixture was kept at this temperature for 3 h and was then allowed to warm to 0 °C. The usual work-up gave the mixture of diastereoisomers.

Alkylation of 1aa and 1ba with RMgBr in the presence of $TiCl_4$: $TiCl_4$ (6 mmol, 3 equiv) was added at −78 °C to a solution of **1** (2 mmol) in toluene. After 10 min, RMgBr (6 mmol, 3 equiv, 1.0 M solution in THF) was added at −78 °C. The reaction mixture was kept at this temperature for 3 h and was then allowed to warm to 0 °C. The usual work-up gave a mixture of diastereoisomers and starting material that could not be separated.

Method A: General procedure: α-Methyl-β-hydroxy ketones **1aa**, **1ba**, and **1ca** were converted into their TBDMS derivatives **4aa**, **4ba**, and **4ca** by a standard methodology[36] in 72, 62, and 68% yields, respectively. To a toluene solution of the α-methyl-β-silyloxy ketone **4** (2 mmol, 1 equiv) was added $TiCl_4$ (2.6 mmol, 1.3 equiv, 1.0 M solution in toluene) at room temperature. The mixture was stirred until transmetalation was complete, (10–15 min for **4aa** and **4ba**, 1 h for **4ca**). The mixture was then cooled to −78 °C and the appropriate Grignard reagent (5 mmol, 3 equiv) was added dropwise. After stirring for 1 h at −78 °C, the mixture was allowed to warm to room temperature and then quenched with diluted aqueous HCl. The usual work-up gave the crude product. Diastereomeric purity, determined by NMR analysis, and yields are reported in Table 2.

Alkylation of 4ca with MeMgBr at −78 °C in the presence of $TiCl_4$: $TiCl_4$ (2.6 mmol, 1.3 equiv, 1.0 M solution in toluene) was added to a solution of **4ca** (2 mmol, 1 equiv) in toluene at −78 °C. After 15 min, MeMgBr (5 mmol, 3 equiv) was added dropwise. The mixture was stirred for 3 h at −78 °C and then quenched with diluted aqueous HCl. The usual work-up gave the crude product as a 1:1 mixture of monosylilated 1,3-diols **7** and **8**. Compounds **7** and **8** were converted into the corresponding 1,3-diols **2caa** and **2aac** by treatment with $CeCl_3 \cdot 7H_2O$ (1 equiv) and $NaI \cdot 2H_2O$ (0.1 equiv) in commercial CH_3CN for 48 h at room temperature.[25]

Method B: General procedure: LiH (1.3 mmol, 1.3 equiv), was added to a solution of **1** (1 mmol) in dry toluene at −30 °C. After 10 min the reaction was cooled to −78 °C and $TiCl_4$ (1.3 mmol, 1 M solution in toluene) was added. The reaction mixture turned orange. After 30 min the appropriate Grignard reagent was added, the mixture was allowed to warm to room temperature, and was then quenched. The vinyl and alkynyl reagents were added at −50 °C in order to increase the rate of reaction, and then the

mixture was allowed to warm to $-20\,^{\circ}C$ to complete the alkylation, since, if the reaction temperature rises over $-20\,^{\circ}C$, extensive decomposition phenomena may occur. The usual work-up gave the mixture of diastereoisomers. Diastereomeric purity, determined by NMR analysis, and yields are reported in Table 3.

The compounds[37] (2*R**,3*S**)-2,3-dimethyl-1,3-pentanediol (**2aab**), (2*R**,3*R**)-2-methyl-3-phenyl-1,3-butanediol (**2aac**), (2*R**,3*R**)-2,3-dimethyl-1,3-pentanediol (**2baa**), and (2*R**,3*S**)-2-methyl-3-phenyl-1,3-butanediol (**2caa**) were identified by comparison with literature data.[38]

(2*R,3*S**)-2,3,4-Trimethyl-1,3-pentanediol** (**2aae**): ^{1}H NMR: $\delta = 3.65-3.80$ (m, 2H, CH_2OH), 3.1 (brs, 2H, OH), 1.95–2.05 (m, 1H, CH_3CH), 1.75–1.90 (m, 1H, $CHMe_2$), 1.10 (s, 3H, CH_3), 0.95 (d, 3H, CH_3, J(H,H) = 6.8 Hz), 0.91 (d, 3H, CH_3, J(H,H) = 6.8 Hz), 0.85 (d, 3H, CH_3, J(H,H) = 7.0 Hz); ^{13}C NMR: $\delta = 77.7$ (C), 65.8 (CH_2), 39.2 (CH), 34.6 (CH), 19.1 (CH_3), 16.9 (CH_3), 16.3 (CH_3), 12.6 (CH_3); elemental analysis calcd for $C_8H_{18}O_2$: C 65.71, H 12.41; found: C 65.64, H 12.43.

(2*R,3*S**)-4-Phenyl-2,3-dimethyl-1,3-butanediol** (**2aaf**): ^{1}H NMR: $\delta = 7.15-7.40$ (m, 5H, Ph), 3.75 (dd, 1H, CH_2OH, J(H,H) = 8.6 Hz, J(H,H) = 11.0 Hz), 3.59 (dd, 1H, CH_2OH, J(H,H) = 4.0 Hz, J(H,H) = 11.0 Hz), 2.79 (dd, 2H, CH_2Ph, J(H,H) = 2 Hz), 2.7 (brs, 2H, OH), 1.80–1.95 (m, 1H, CH), 1.10 (s, 3H, CH_3), 0.90 (d, 3H, CH_3CH, J(H,H) = 7.1 Hz); ^{13}C NMR: $\delta = 76.2$ (C), 65.7 (CH_2), 47.3 (CH_2), 42.2 (CH), 21.6 (CH_3), 13.1 (CH_3); elemental analysis calcd for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 74.24, H 9.36.

(2*R,3*S**)-2,3-Dimethyl-4-pentene-1,3-diol** (**2aag**): ^{1}H NMR: $\delta = 5.80-5.95$ (m, 1H, $CH{=}CH_2$), 5.00–5.40 (m, 2H, $CH{=}CH_2$), 3.55–3.75 (m, 2H, CH_2OH), 2.8 (brs, 1H, OH), 2.7 (brs, 1H, OH), 1.65–1.85 (m, 1H, CH_3CH), 1.25 (s, 3H, CH_3), 0.95 (d, 3H, CH_3, J(H,H) = 6.9 Hz); ^{13}C NMR: $\delta = 145.1$ (CH), 112.3 (CH_2), 76.7 (C), 66.0 (CH_2), 42.7 (CH), 19.1 (CH_3), 23.6 (CH_3), 12.1 (CH_3); elemental analysis calcd for $C_7H_{14}O_2$: C 64.58, H 10.84; found: C 64.70, H 10.69.

(2*R,3*R**)-5-Phenyl-2,3-dimethyl-4-pentyne-1,3-diol** (**2aah**): ^{1}H NMR: $\delta = 7.25-7.50$ (m, 5H, Ph), 4.00–4.10 (m, 1H, CH_2OH), 3.75–3.85 (m, 1H, CH_2OH), 3.2 (brs, 1H, OH), 2.5 (brs, 1H, OH), 2.00–2.15 (m, 1H, CH_3CH), 1.58 (s, 3H, CH_3C), 1.13 (d, 3H, CH_3CH, J(H,H) = 7.1 Hz); ^{13}C NMR: $\delta = 122.6$ (C), 92.9 (C), 83.7 (C), 71.8 (C), 65.7 (CH_2), 44.0 (CH), 26.0 (CH_3), 12.2 (CH_3); elemental analysis calcd for $C_{13}H_{16}O_2$: C 65.71, H 12.41; found: C 65.64, H 12.43.

(2*R,3*R**)-2-Methyl-3-phenyl-1,3-pentanediol** (**2bac**): ^{1}H NMR: $\delta = 7.10-7.45$ (m, 5H, Ph), 3.50 (d, 2H, CH_2OH, J(H,H) = 3.8 Hz), 2.5 (brs, 2H, OH), 1.95–2.05 (m, 2H, CH_3CH_2), 1.70–1.90 (m, 1H, $CHCH_3$), 1.16 (d, 3H, CH_3, J(H,H) = 7.3 Hz), 0.75 (t, 3H, CH_2CH_3, J(H,H) = 7.4 Hz); ^{13}C NMR: $\delta = 80.6$ (C), 66.3 (CH_2), 43.4 (CH), 31.6 (CH_2), 11.8 (CH_3), 7.6 (CH_3); elemental analysis calcd for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 73.95, H 9.43.

(2*R,3*S**)-2-Methyl-3-phenyl-1,3-pentanediol** (**2cab**): ^{1}H NMR: $\delta = 7.20-7.45$ (m, 5H, Ph), 3.82 (dd, 1H, CH_2OH, J(H,H) = 3.4 Hz, J(H,H) = 11.0 Hz), 3.53 (dd, 1H, CH_2OH, J(H,H) = 6.2 Hz, J(H,H) = 11.0 Hz), 2.5 (brs, 2H, OH), 2.05–2.15 (m, 1H, $CHCH_3$), 2.00 (q, 2H, CH_3CH_2, J(H,H) = 7.4 Hz), 0.80 (d, 3H, CH_3, J(H,H) = 7.2 Hz), 0.76 (t, 3H, CH_2CH_3, J(H,H) = 7.4 Hz); ^{13}C NMR: $\delta = 80.7$ (C), 65.6 (CH_2), 43.1 (CH), 33.0 (CH_2), 12.6 (CH_3), 7.6 (CH_3); elemental analysis calcd for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 74.25, H 9.38.

(2*R,3*S**)-2-Methyl-3-phenyl-1,3-heptanediol** (**2cad**): ^{1}H NMR: $\delta = 7.20-7.40$ (m, 5H, Ph), 3.80–3.90 (m, 1H, CH_2OH), 3.45–3.55 (m, 1H, CH_2OH), 3.3 (brs, 2H, OH), 2.05–2.15 (m, 1H, $CHCH_3$), 1.85–2.00 (m, 2H, CH_2), 1.15–1.35 (m, 4H, $2CH_2$), 0.84 (t, 3H, CH_3, J(H,H) = 7.4 Hz), 0.79 (d, 3H, CH_3, J(H,H) = 7.2 Hz); ^{13}C NMR: $\delta = 80.4$ (C), 65.4 (CH_2), 43.2 (CH), 40.3 (CH_2), 25.3 (CH_2), 23.1 (CH_2), 14.0 (CH_3), 12.6 (CH_3); elemental analysis calcd for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.55, H 9.92.

(2*R,3*S**)-2,4-Dimethyl-3-phenyl-1,3-pentanediol** (**2cae**): ^{1}H NMR: $\delta = 7.20-7.45$ (m, 5H, Ph), 3.49 (dd, 1H, CH_2OH, J(H,H) = 3.7 Hz, J(H,H) = 10.8 Hz), 3.28 (dd, 1H, CH_2OH, J(H,H) = 8.2 Hz, J(H,H) = 10.8 Hz), 2.30–2.45 (m, 2H, 2CH), 1.02 (d, 3H, CH_3, J(H,H) = 6.6 Hz), 0.81 (d, 3H, CH_3, J(H,H) = 7.0 Hz), 0.70 (d, 3H, CH_3, J(H,H) = 7.0 Hz); ^{13}C NMR: $\delta = 82.5$ (C), 66.1 (CH_2), 40.4 (CH), 33.8 (CH), 17.0 (CH_3), 16.1 (CH_3), 12.6 (CH_3); elemental analysis calcd for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 75.00, H 9.61.

(2*R,3*S**)-2-Methyl-3,4-diphenyl-1,3-butanediol** (**2caf**): ^{1}H NMR: $\delta = 6.80-7.45$ (m, 10H, 2Ph), 3.84 (dd, 1H, CH_2OH, J(H,H) = 3.3 Hz, J(H,H) = 11.2 Hz), 3.56 (dd, 1H, CH_2OH, J(H,H) = 6.3 Hz, J(H,H) = 11.2 Hz), 3.31 (d, 2H, CH_2Ph, J(H,H) = 2.2 Hz), 2.4 (brs, 2H, OH), 2.25–2.15 (m, 1H, $CHCH_3$), 0.89 (d, 3H, CH_3, J(H,H) = 7.2 Hz); ^{13}C NMR: $\delta = 80.4$ (C), 65.4 (CH_2), 46.3 (CH_2), 43.1 (CH), 12.9 (CH_3); elemental analysis calcd for $C_{17}H_{20}O_2$: C 79.65, H 7.86; found: C 79.58, H 7.91.

(2*R,3*S**)-2-Methyl-3,5-diphenyl-4-pentyne-1,3-diol** (**2cah**): ^{1}H NMR: $\delta = 7.10-7.70$ (m, 10H, 2Ph), 4.89 (dd, 1H, CH_2OH, J(H,H) = 3.9 Hz, J(H,H) = 11.0 Hz), 3.70 (dd, 1H, CH_2OH, J(H,H) = 5.1 Hz, J(H,H) = 11.0 Hz), 3.20–3.35 (m, 1H, $CHCH_3$), 3.6 (brs, 2H, OH), 0.97 (d, 3H, CH_3, J(H,H) = 7.1 Hz); ^{13}C NMR: $\delta = 91.8$ (C), 86.0 (C), 76.5 (C), 65.8 (CH_2), 46.1 (CH), 11.8 (CH_3); elemental analysis calcd for $C_{18}H_{18}O_2$: C 81.17, H 6.81; found: C 81.34, H 6.83.

(2*R,3*S**)-2-Ethyl-3-phenyl-1,3-butanediol** (**2cba**): ^{1}H NMR: $\delta = 7.20-7.50$ (m, 5H, Ph), 3.90–4.00 (m, 1H, CH_2OH), 3.65–3.80 (m, 1H, CH_2OH), 3.50–3.60 (m, 1H, CH), 3.3 (brs, 2H, OH), 1.65 (s, 3H, CH_3C), 1.20–1.30 (m, 2H, CH_3CH_2), 0.82 (t, 3H, CH_3CH_2, J(H,H) = 7.3 Hz); ^{13}C NMR: $\delta = 78.7$ (C), 61.4 (CH_2), 51.0 (CH), 29.6 (CH_3), 18.9 (CH_2), 12.7 (CH_3); elemental analysis calcd for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 74.31, H 9.31.

(2*R,3*S**)-2-Ethyl-3-phenyl-1,3-pentanediol** (**2cbb**): ^{1}H NMR: $\delta = 7.20-7.40$ (m, 5H, Ph), 4.04 (dd, 1H, CH_2OH, J(H,H) = 2.5 Hz, J(H,H) = 11.2 Hz), 3.70 (m, 2H, CH_2OH, J(H,H) = 5.2 Hz, J(H,H) = 11.2 Hz), 3.2 (brs, 1H, OH), 2.6 (bt, 1H, OH), 1.90–2.15 (m, 2H, CH_3CH_2), 1.70–1.80 (m, 1H, CH_3CH_2CH), 1.20–1.35 (m, 2H, CH_3CH_2), 0.84 (t, 3H, CH_3, J(H,H) = 7.4 Hz), 0.72 (t, 3H, CH_3, J(H,H) = 7.4 Hz); ^{13}C NMR: $\delta = 81.3$ (C), 61.4 (CH_2), 49.9 (CH), 33.3 (CH_2), 18.7 (CH_2), 12.6 (CH_3), 7.7 (CH_3); elemental analysis calcd for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 74.82, H 9.72.

(2*R,3*S**)-2,3-Diphenyl-1,3-butanediol** (**2cca**): ^{1}H NMR: $\delta = 7.15-7.35$ (m, 12H, Ph), 6.80–6.90 (m, 2H, Ph), 4.04 (dd, 1H, CH_2OH, J(H,H) = 7.3 Hz, J(H,H) = 11.0 Hz), 3.89 (m, 1H, CH_2OH, J(H,H) = 5.6 Hz, J(H,H) = 11.0 Hz), 3.41 (dd, 1H, CH_2OH, J(H,H) = 5.0 Hz, J(H,H) = 7.3 Hz), 3.26 (dd, 1H, CHPh, J(H,H) = 5.6 Hz, J(H,H) = 7.3 Hz), 2.9 (brs, 1H, OH), 2.4 (brs, 1H, OH), 1.63 (s, 1H, CH_3); ^{13}C NMR: $\delta = 77.7$ (C), 63.8 (CH_2), 57.8 (CH), 28.9 (CH_3); elemental analysis calcd for $C_{16}H_{18}O_2$: C 79.31, H 7.49; found: C 79.45, H 7.47.

(2*R,3*S**)-2,3,4-Triphenyl-1,3-butanediol** (**2ccf**): ^{1}H NMR: $\delta = 6.80-7.30$ (m, 15H, Ph), 4.09 (dd, 1H, CH_2OH, J(H,H) = 7.3 Hz, J(H,H) = 11.3 Hz), 3.87 (m, 1H, CH_2OH, J(H,H) = 5.0 Hz, J(H,H) = 11.3 Hz), 3.41 (dd, 1H, CHPh, J(H,H) = 5.0 Hz, J(H,H) = 7.3 Hz), 3.32 and 3.28 (*AB* system, 2H, CH_2Ph, J(H,H) = 13.2 Hz), 3.0 (brs, 1H, OH), 2.9 (brs, 1H, OH); ^{13}C NMR: $\delta = 80.2$ (C), 64.2 (CH_2), 57.5 (CH), 46.9 (CH); elemental analysis calcd for $C_{22}H_{22}O_2$: C 82.99, H 6.96; found: C 82.80, H 6.99.

(2*R,3*S**)-2,3-Diphenyl-4-pentene-1,3-diol** (**2ccg**): ^{1}H NMR: $\delta = 7.00-7.35$ (m, 10H, Ph), 6.39 (dd, 1H, $CH{=}CH_2$, J(H,H) = 17.1 Hz, J(H,H) = 10.5 Hz), 5.42 (dd, 1H, $CH{=}CH_2$, J(H,H) = 17.1 Hz, J(H,H) = 1.1 Hz), 5.19 (dd, 1H, $CH{=}CH_2$, J(H,H) = 10.5 Hz, J(H,H) = 1.1 Hz), 3.95–4.10 (m, 2H, CH_2OH, *ABX* system, $J_{AB} = 5.6$ Hz, $J_{AX} = J_{BX} = 11.3$ Hz), 3.24 (bt, 1H, CHPh, J(H,H) = 5.6 Hz), 2.0 (brs, 2H, OH); ^{13}C NMR: $\delta = 113.2$ (CH_2), 79.7 (C), 64.1 (CH_2), 56.9 (CH); elemental analysis calcd for $C_{17}H_{18}O_2$: C 80.28, H 7.13; found: C 80.42, H 7.15.

The reaction of **1aa** with allyl Grignard gave a 1:1 mixture of diastereomeric **(2*R**,3*S**)-** and **(2*R**,3*S**)-2,3-dimethylhex-5-ene-1,3-diols** (**2aai**). As a consequence, we were not able to reach an unequivocal assignment of the various peaks. Therefore, we only report shifts for pairs of signals. Since most of the ^{1}H NMR signals are overlapped, only selected data are reported. ^{1}H NMR: $\delta = 1.24$ and 1.16 (s, 3H, CH_3COH), 0.95 and 0.85 (d, 3H, CH_3CH, J(H,H) = 7.1 Hz); ^{13}C NMR: $\delta = 133.8$ and 133.5 (CH), 118.8 and 118.6 (CH_2), 75.8 and 75.4 (C), 65.8 and 65.7 (CH_2), 46.0 and 42.0 (CH_2), 43.1 and 41.8 (CH), 26.4 and 21.9 (CH_3), 12.6 and 12.4 (CH_3).

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