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Highly Stereoselective Titanium-Mediated Aldol Reaction from (*S*)-4-Benzyloxy-3-methyl-2-butanone†

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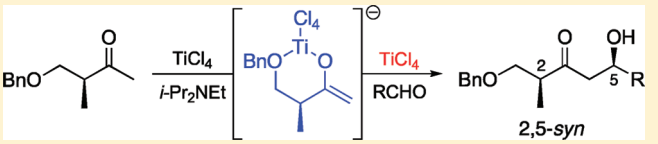
Supporting Information

ABSTRACT: Substrate-controlled titanium-mediated aldol reactions from (*S*)-4-benzyloxy-3-methyl-2-butanone provide satisfactory levels of 2,5-*syn* asymmetric induction if they are carried out in the presence of a second equivalent of $TiCl_4$. Such reactions give high yields and excellent diastereoselectivity with a wide array of achiral and chiral aldehydes without needing other sources of chirality. This procedure is thus of interest for the synthesis of natural products. Furthermore, spectroscopic studies and analyses of the reacting species have revealed a possible mechanism to account for the experimental results.

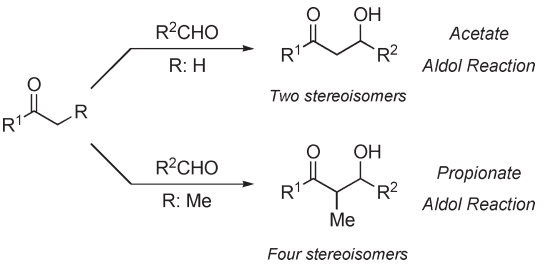


INTRODUCTION

Since pioneering studies in the 1970s, recent decades have witnessed the development of a large number of highly stereoselective aldol methodologies.[1] These have been used to synthesize structurally complex natural products, which have placed aldol reactions among the most important carbon−carbon bond-forming processes.[2] In spite of these accomplishments, some issues are still a matter of concern. One of them is the acetate aldol reaction.[3,4] Indeed, early reports by Evans[5] and Masamune[6] showed that the stereochemical control on the acetate aldol reaction was much more challenging than that on the apparently similar propionate counterpart (Scheme 1). This difference in behavior is due to the close energy of alternative transition state geometries for acetate aldol reactions, which hampers the differentiation of the two faces of the π C═O bond by the unsubstituted enolate.[7]

This challenge is usually countered by the use Mukaiyama-like[8] and organocatalytic approaches.[9] Unfortunately, some of these methodologies can only be applied to a narrow set of substrates, and for this reason, it has always been highly desirable to develop parallel transformations from metal enolates. Hence, it is not surprising that a large set of chiral auxiliaries,[10] stoichiometric and catalytic Lewis acids,[11,12] and catalytic Lewis bases[13] have been reported. This is particularly significant for aldol reactions of methyl ketones in the advanced steps of synthesis, where constraints are imposed by the structure of the reaction partners.[14] Therefore, a better understanding of the stereoselectivity imparted by chiral methyl ketones in substrate-controlled aldol reactions becomes crucial.[15] In this scenario, Paterson established that high diastereoselectivity could be achieved in boron-mediated aldol reactions with chiral ketones derived from Roche ester. Notably, the ethyl ketones give excellent levels of substrate-controlled 1,4-*syn* stereoinduction with cyclohexyl ligands on boron, which are reduced for the corresponding methyl ketone. In the latter case, chiral Ipc ligands on boron are then used to enhance the 1,4-*syn* stereoinduction to equally high levels.[1b,15a,16] Looking for a different approach, we envisaged that titanium(IV) Lewis acids might provide such levels of stereocontrol and offer an appealing alternative to chiral boron Lewis acids. Our previous experience in related processes indicated that the appropriate choice of the protecting group and the titanium Lewis acid might afford highly diastereoselective aldol reactions in a straightforward manner.[17,18] Herein, we document our studies on the titanium-mediated aldol reactions of protected (*S*)-4-hydroxy-3-methyl-2-butanone (Scheme 2) with achiral and chiral aldehydes, which give access to the corresponding 2,5-*syn* adducts in high yields and diastereoselectivity.

Scheme 1. Acetate and Propionate Aldol Reactions



Scheme 2. Titanium-Mediated Aldol Reactions from Protected (*S*)-4-Hydroxy-3-methyl-2-butanone

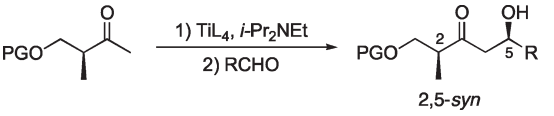


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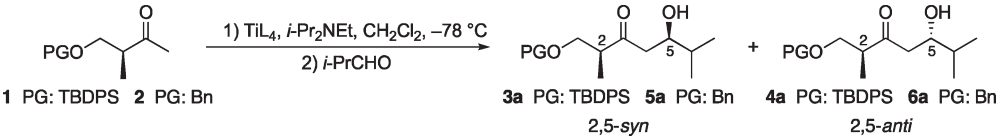
Table 1. Influence of the Hydroxyl Protecting Group and the Titanium(IV) Lewis Acid on the Aldol Reaction of Methyl Ketones 1 and 2



entry	ketone	PG	TiL_4	TiL_4 (equiv)	dr (*syn/anti*)[a]	yield[b] (%)
1	**1**	TBDPS	$TiCl_3$(*i*-PrO)	1	64:36	32
2	**1**	TBDPS	$TiCl_4$	1	64:36	77
3	**1**	TBDPS	$TiCl_4$	2	61:39	78
4	**2**	Bn	$TiCl_2$(*i*-PrO)$_2$	1	67:33	35
5	**2**	Bn	$TiCl_3$(*i*-PrO)	1	83:17	92
6	**2**	Bn	$TiCl_4$	1	68:32	81
7	**2**	Bn	$TiCl_3$(*i*-PrO)	2	77:23	67
8	**2**	Bn	$TiCl_4$	2	95:5	89

[a] Established by ^{1}H NMR analysis. [b] Overall isolated yield.

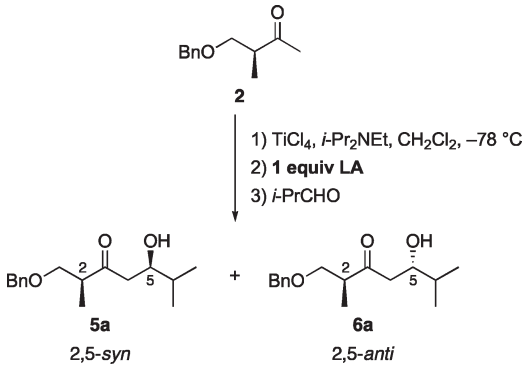
RESULTS AND DISCUSSION

Preliminary Experiments. Since the titanium-mediated aldol reactions from α- and β-hydroxy chiral ketones are sensitive to the hydroxyl protecting group and the titanium(IV) Lewis acid engaged in the enolization, we initially assessed the aldol additions of Roche ester-derived methyl ketones **1** and **2** possessing different protecting groups (PG = TBDPS and Bn respectively, see Table 1) to isobutyraldehyde (**a**) using several titanium Lewis acids. The results are summarized in Table 1.

The aldol reactions from TBDPS-ketone **1** proceeded in a low diastereomeric ratio irrespective of the titanium Lewis acid (see entries 1 and 2 in Table 1). Taking into account that bulky silicon protecting groups do not facilitate coordination to Lewis acids, the low stereocontrol provided by **1** may be attributable to the fact that the carbon substituents at the α-stereocenter are sterically too similar (Me versus CH_2OTBDPS) to permit effective π-facial differentiation of the C═O bond at the transition state. Otherwise, the chelating ability of the β-benzyl ether confirmed the strong influence of titanium Lewis acids on the substrate-controlled aldol reactions of methyl ketone **2**, being particularly remarkable the diastereoselectivity achieved with $TiCl_3$(*i*-PrO) (compare entries 4−6 in Table 1). Taking advantage of our experience with other benzyl-protected chiral ketones, we also examined the effect of an excess of Lewis acid on these reactions.[19] Such conditions were inappropriate for ketone **1** (see entry 3 in Table 1), but the use of two equivalents of $TiCl_4$ on ketone **2** provided 2,5-*syn* aldol **5a** in high yield and a high diastereomeric ratio (dr 95:5 and 89% yield, see entry 8 in Table 1). Interestingly, two equivalents of $TiCl_3$(*i*-PrO) were less suitable and aldol **5a** was isolated in a lower yield and in a lower diastereomeric ratio (compare entries 5, 7, and 8 in Table 1).

The data summarized in Table 1 show that the appropriate choice of the protecting group and the enolization conditions of chiral ketones derived from Roche ester secured highly stereoselective aldol transformations. In this context, the significant rise in the diastereoselectivity of the titanium-mediated aldol addition of ketone **2** to isobutyraldehyde due to the presence of a second equivalent of $TiCl_4$ led us to evaluate the influence of other Lewis acids. The results are summarized in Table 2.

Table 2. Influence of Lewis Acids on the Titanium-Mediated Aldol Reaction from 2



entry	Lewis acid, LA	dr (*syn/anti*)[a]	yield[b] (%)
1	$TiCl_4$	95:5	89
2	$TiCl_3$(*i*-PrO)	85:15	68 (6)
3	Ti(*i*-PrO)$_4$	68:32	36 (5)
4	$SnCl_4$	92:8	57 (18)
5	Et_2AlCl	92:8	79
6	$BF_3 \cdot OEt_2$	62:38	91

[a] Established by ^{1}H NMR analysis. [b] Overall isolated yield. Yield of recovered methyl ketone **2** is shown in parentheses.

The stereochemical outcome of such an aldol reaction depends on the second Lewis acid. Thus, the bias imparted by titanium(IV) Lewis acids is enlightening: $TiCl_4$ furnishes an exceptional dr 95:5 (see entry 1 in Table 2) and the mildest Ti(*i*-PrO)$_4$ gives values (dr 68:32 and 36% yield, see entry 3 in Table 2) that are almost identical to those observed for $TiCl_2$(*i*-PrO)$_2$ (dr 67:33 and 35% yield, see entry 4 in Table 1), while $TiCl_3$(*i*-PrO) as a second Lewis acid affords better diastereoselectivities (dr 85:15, see entry 2 in Table 2) than the process that involves 1 or 2 equiv of $TiCl_3$(*i*-PrO) (dr 83:17 and 77:23, see entries 5 and 7 in Table 1 respectively). On the other hand, $SnCl_4$ and Et_2AlCl gave poorer yields than $TiCl_4$ but similar diastereoselectivities (compare entries 1, 4, and 5 in Table 2), while $BF_3 \cdot OEt_2$ seemed to have no influence and provided mixtures

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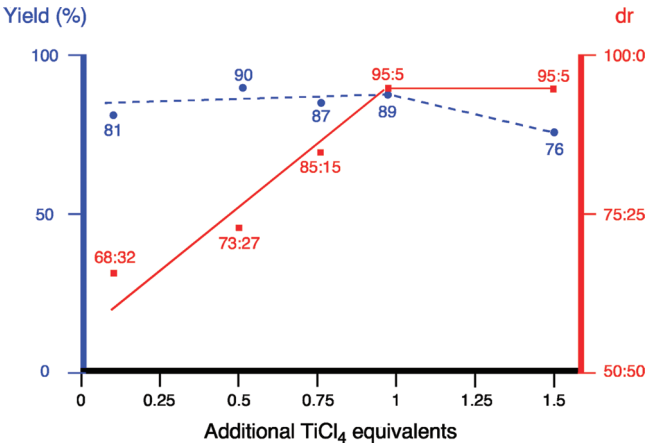


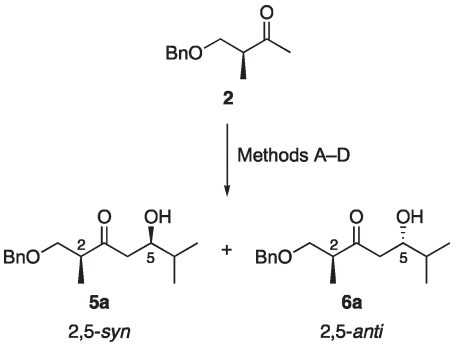
Figure 1. Influence of the additional equivalents of $TiCl_4$ on the yield and diastereoselectivity of the aldol addition of **2** to isobutyraldehyde.

of both aldols in good yields but poor diastereomeric ratios (see entry 6 in Table 2).

The enhanced diastereoselectivity observed in entry 1 of Table 2 raised the question of the amount of extra Lewis acid required to achieve such levels of stereocontrol, so the influence of $TiCl_4$ equivalents on the diastereoselectivity and yield of this transformation was next investigated. As shown in Figure 1, addition of increasing amounts of $TiCl_4$ to the reaction mixture did not significantly affect the yield (81−90%), but the diastereoselectivity was steadily improved from dr 68:32 to 95:5. Interestingly, the diastereoselectivity did not change but the yield dropped when more than 1 equiv of $TiCl_4$ was added (Figure 1). These results indicate that the additional 1 equiv of $TiCl_4$ is necessary for highly stereocontrolled aldol additions, which points to a dramatic change in the structure of the reacting species and the transition state involved in transformations of this sort.

Optimization. Once the ketone and the appropriate titanium(IV) Lewis acid required to achieve highly stereocontrolled aldol reactions had been ascertained, we examined some experimental aspects of the process. Initially, we focused on the way in which the second equivalent of $TiCl_4$ is added to the reaction mixture. Thus, four protocols were evaluated. In method A, the enolization of ketone **2** was carried out according to the procedure described in the preliminary experiments, and the second equivalent of $TiCl_4$ was then added, followed 10 min later by the aldehyde. In method B, 2 equiv of $TiCl_4$ were added simultaneously to ketone **2** at the beginning of the enolization, and the reaction was carried out according to the general procedure. In method C, the aldehyde was precomplexed with $TiCl_4$, and this mixture was added to the titanium enolate from **2**. Finally, in method D the enolate from **2** was added to a mixture containing the isobutyraldehyde precomplexed with $TiCl_4$ (inverse addition). The results summarized in Table 3 show that high levels of stereocontrol can be achieved irrespective of how the second equivalent of $TiCl_4$ is added to the reaction mixture. Importantly, the good results given by method B (see entry 2 in Table 3) show that the presence of a second equivalent of $TiCl_4$ does not prevent a proper enolization (no starting ketone was recovered), whereas the high diastereoselectivities provided by methods C and D (see entries 3 and 4 in Table 3) are more difficult to explain (see further comments).[20] The diastereoselectivity obtained in method D was particularly outstanding (dr 97:3, see entry 4 in Table 3), which illustrates how slight changes in the experimental procedure

Table 3. Different Methods for the Titanium-Mediated Aldol Addition of Ketone 2



entry	method[a]	dr (*syn*/*anti*)[b]	yield[c] (%)
1	A	95:5	89
2	B	94:6	75
3	C	93:7	33 (52)
4	D	97:3	86

[a]Method A: (i) $TiCl_4$ (1 equiv), *i*-Pr_2NEt (1.1 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $TiCl_4$ (1 equiv), 10 min c) *i*-PrCHO (1.5 equiv), −78 °C, 30 min. Method B: (i) $TiCl_4$ (2 equiv), *i*-Pr_2NEt (1.1 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) *i*-PrCHO (1.5 equiv), −78 °C, 30 min. Method C: (i) $TiCl_4$ (1 equiv), *i*-Pr_2NEt (1.1 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $TiCl_4$ (1.2 equiv)−*i*-PrCHO (1.2 equiv), −78 °C, 30 min. Method D: (i) $TiCl_4$ (1 equiv), *i*-Pr_2NEt (1.1 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $TiCl_4$ (1.2 equiv)−*i*-PrCHO (1.2 equiv), −78 °C, 30 min (inverse addition). [b] Established by HPLC analysis. [c] Overall isolated yield. The yield of recovered methyl ketone **2** is shown in parentheses.

can tune the diastereoselectivity. These findings prompted us to study methods A and D in more detail in order to identify the key features responsible for the greater stereocontrol.

We first examined method A. We assessed the influence of the enolization and reaction times (t_{enol} and t_{reac} respectively), as well as the time elapsed (t_{elap}) from the addition of the second equivalent of $TiCl_4$ and the aldehyde, on the outcome of the aldol reaction. The results (see Table 4) show that it is worth adding the second equivalent of $TiCl_4$ when the enolization is over and then the aldehyde some minutes later. This procedure does not affect the yield but increases the diastereoselectivity (compare entries 1−3 in Table 4). We then examined the enolization and the reaction times. These two variables seemed to have less influence on the reaction, but the yield decreased when the enolization time was reduced to 15 min (compare entries 4 and 5 in Table 4). Otherwise, the aldol addition to isobutyraldehyde turned out to be very fast, and the same yield was obtained when the reaction time was shortened to 15 min (compare entries 2 and 6 in Table 4). Finally, we also examined the use of fewer equivalents of the aldehyde, observing a loss of yield when just 1.2 equiv of isobutyraldehyde were added to the reaction mixture (compare entries 2 and 6 in Table 4).

In view of these results, we considered that the most appropriate conditions would involve enolization for 30 min, followed by the addition of a second equivalent of $TiCl_4$, stirring the reaction mixture for 10 min, addition of 1.5 equiv of aldehyde, and further reaction for 30 min at −78 °C (see entry 2 of Table 4).

Moreover, these enolization and reaction times optimized for method A were also deemed suitable for method D. Therefore, we recognized that the best conditions for method D would involve enolization for 30 min, followed by the

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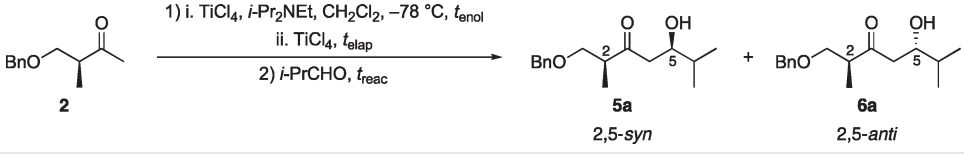
Table 4. Optimization of the Titanium-Mediated Aldol Addition of 2 to Isobutyraldehyde (a)



entry	t_{enol} (min)	t_{elap} (min)	t_{reac} (min)	*i*-PrCHO (equiv)	dr (*syn*/*anti*)[a]	yield[b] (%)
1	30	0	30	1.5	90:10	94
2	30	10	30	1.5	95:5	89
3	30	20	30	1.5	95:5	91
4	15	10	15	1.5	95:5	83
5	30	10	15	1.5	94:6	89
6	30	10	30	1.2	95:5	68

[a] Established by HPLC analysis. [b] Overall isolated yield.

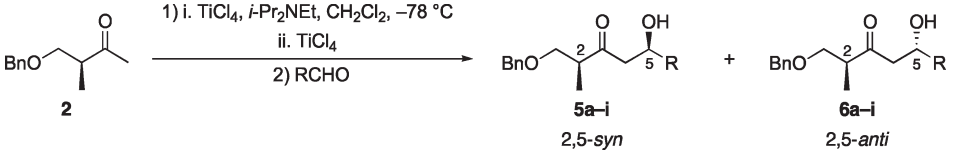
addition of the resulting solution to a mixture of 1.2 equiv of $TiCl_4$–aldehyde complex and further reaction for 30 min at −78 °C.

Scope. The experimental procedures optimized for the titanium-mediated aldol addition of ketone **2** to isobutyraldehyde (**a**) were next applied to other achiral aliphatic, α,β-unsaturated and aromatic aldehydes. The results summarized in Table 5 demonstrate the excellent stereocontrol achieved by this transformation using method A. Remarkably, aliphatic aldehydes **a**–**c** gave the corresponding 2,5-*syn* aldols **5a**–**c** in high yields and diastereomeric ratios depending on their steric hindrance. Indeed, isobutyraldehyde furnished **5a** almost as a single diastereomer (dr 95:5) in 89% yield (see entry 1 in Table 5), while *n*-butanal afforded **5c** in a somewhat less stereoselective way (dr 90:10 and 78% yield, see entry 3 in Table 5). In turn, α,β-unsaturated aldehydes as methacrolein, crotonaldehyde, or cinnamaldehyde (**d**–**f** respectively) provided comparable results, and 2,5-*syn* aldols **5d**–**f** were obtained in 77–80% yield and diastereomeric ratios ranging from 90:10 to 95:5 (compare entries 4–6 in Table 5). Finally, aromatic aldehydes **g**–**i** afforded 2,5-*syn* aldols **5g**–**i** in high yields and diastereomeric ratios irrespective of the electronic character of the aldehyde (compare entries 8–10 in Table 5).

Having established that method A provided highly diastereoselective aldol additions of methyl ketone **2** to a broad range of aldehydes (dr ≥90:10), we turned our attention to method D. Although preliminary experiments with isobutyraldehyde had shown that it furnished slightly better diastereoselectivities than method A (compare entries 1 and 4 in Table 3), we were concerned that the inverse addition required by the former could jeopardize the generality of our approach. Thus, we decided to test the scope of this methodology with the same aldehydes **a**–**i**. The results of this study are summarized in Table 6.

These reactions show an improved diastereoselectivity. Remarkably, aliphatic aldehydes **a**–**c** afforded excellent diastereomeric ratios, and even the sterically unhindered butanal delivered 2,5-*syn* aldol **5c** in dr 96:4 and 88% yield (see entry 3 in Table 6). Among the α,β-unsaturated aldehydes, reactions of methacrolein (**d**) and crotonaldehyde (**e**) were also successful and provided the 2,5-*syn* aldols **5d** and **5e**, respectively, in high yields and as a single diastereomer (dr 97:3, see entries 4 and 5 in Table 6). Parallel additions to highly conjugated aldehydes such as cinnamaldehyde (**f**) or aromatic aldehydes **h**–**i** also proceeded in excellent diastereomeric ratios but in somewhat lower yields (see entries 6–9 in Table 6). The reasons for these low yields are still unclear, but they may be attributable to the formation of

Table 5. Titanium-Mediated Aldol Reactions of 2 (Method A)



entry	aldehyde	R	dr (*syn*/*anti*)[a]	yield (%)[b]
1	**a**	*i*-Pr	95:5	89
2	**b**	*i*-Bu	92:8	86
3	**c**	*n*-Pr	90:10	78
4	**d**	$H_2C{=}C(CH_3)$	95:5	78
5	**e**	(*E*) $CH_3CH{=}CH$	93:7	80
6	**f**	(*E*) $PhCH{=}CH$	90:10[c]	77
7[d]	**g**	Ph	92:8	93
8[d]	**h**	4-NO_2Ph	94:6	81
9[d]	**i**	4-MeOPh	90:10	91

[a] Established by HPLC analysis. [b] Overall isolated yield. [c] Established by ^1H NMR analysis [d] 1.2 equiv of aldehyde were used.

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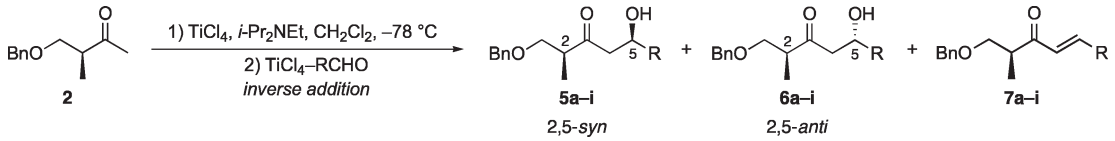
Table 6. Titanium-Mediated Aldol Reactions of 2 (Method D)



entry	aldehyde[a]	R	yield of 7 (%)	dr (*syn*/*anti*)[b]	yield of 5[c] (%)
1	**a**	*i*-Pr		97:3	86
2	**b**	*i*-Bu		96:4	86
3	**c**	*n*-Pr		96:4	88
4	**d**	$H_2C{=}C(CH_3)$	<5	97:3	81
5	**e**	(*E*) $CH_3CH{=}CH$	<5	97:3	80
6	**f**	(*E*) PhCH=CH	22	95:5[d]	22 (43)
7	**g**	Ph	21	97:3	68
8	**h**	4-NO_2Ph	34	96:4	60
9	**i**	4-MeOPh	<5	91:9	35 (40)

[a] 1.2 equiv of aldehyde were used. [b] Established by HPLC analysis. [c] Overall isolated yield. The yield of recovered methyl ketone **2** is shown in parentheses. [d] Established by ^{1}H NMR analysis.

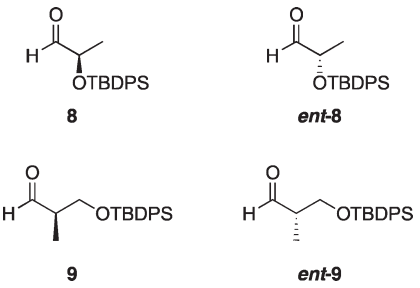


Figure 2. Chiral aldehydes.

nonproductive aldehyde-Lewis acid complexes and the conversion of the putative titanium aldolate to α,β-unsaturated ketone **7** (see entries 6–8 in Table 6).

In spite of such failures, the scope of this procedure is not seriously affected, and we conclude that the titanium-mediated acetate aldol reactions of ketone **2** and achiral aldehydes through method A or D proceed in high yields and excellent diastereomeric ratios.

Double-Stereodifferentiating Reactions. Once the feasibility of the substrate-controlled aldol addition of ketone **2** to a wide set of achiral aldehydes **a**–**i** had been demonstrated, we proceeded to test such reactions with protected chiral α- and β-hydroxy aldehydes represented in Figure 2.[21,22]

Current models of double-stereodifferentiating reactions predict that one of the enantiomers should reinforce the stereochemical bias imparted by the chiral ketone, while the other would act in the opposite sense.[23] Therefore, we expected the former to deliver the 2,5-*syn* aldol as a single diastereomer and the latter to reduce the stereocontrol. Surprisingly, the diastereoselectivities observed for the four aldehydes shown in Figure 2 were similar.

Indeed, the double-stereodifferentiating titanium-mediated aldol additions of ketone **2** gave high yields (77–90%) and excellent diastereomeric ratios (from dr 92:8 to 94:6) of 2,5-*syn* aldols **10**–**13** irrespective of the configuration of the chiral aldehyde (Scheme 3). The lack of influence of chiral α- and β-hydroxy aldehydes on the diastereoselectivity of such aldol reactions hints at a mechanism in which the new carbon–carbon bond is not formed in the stereochemical-determining step. From a synthetic point of view, these results bear out the high levels of 2,5-*syn* asymmetric induction provided by the methyl ketone **2** on the titanium-mediated acetate aldol reaction with a broad array of achiral and chiral aldehydes in a simple and reliable manner.

Stereochemistry. The *syn* asymmetric induction imparted by ketone **2** was initially established by reduction of aldols **5a** and **5g** to the corresponding diols **14a** and **14g** (Scheme 4). The relative configuration of these diols was secured through conversion into acetonides **15**, which were studied by 1D and 2D NMR experiments.[24] The configuration of the new stereocenter C3 was pivotal in our strategy, since it was connected with the original C2 stereocenter to establish the absolute configuration of aldols **5**. Indeed, DDQ oxidation of diols **14** delivered benzylidene acetals **16** as a single diastereomer.

Then, comprehensive analyses of diagnostic geminal ($^2J_{1-1'}$, see Figure 3) and vicinal coupling constants ($^3J_{1-2}$ and $^3J_{1'-2}$, see Figure 3) on their ^{1}H NMR spectra and key NOE experiments made clear the 2,5-*syn* configuration of aldols **5**. Importantly, such stereochemistry was later confirmed by comparison of spectroscopic features of aldol **5a** with those reported in the literature.[1b]

Mechanistic Hypothesis. The experimental evidence presented so far demonstrates that the second Lewis acid plays a key role in the stereochemical outcome of the titanium-mediated aldol reaction from benzyl-protected methyl ketone **2**. Indeed, it wholly determines the diastereoselectivity.

From a mechanistic point of view, we first envisaged that the titanium-mediated aldol reactions from **2** in the presence of a second Lewis acid might proceed through an open transition state. This assumption was inspired by Heathcock's seminal report on the preparation of *syn*- and *anti*-aldols by addition of boron enolates from chiral *N*-propanoyl-1,3-oxazolidinones to aldehydes in the presence of different Lewis acids.[25] The rationale for the observed diastereoselectivity relied on the steric bulk of Lewis acids: small Lewis acids prefer transition state A because it minimizes gauche interactions about the forming bond, whereas transition state B becomes competitive for large Lewis acids in order to avoid methyl–Lewis acid interactions (Scheme 5).

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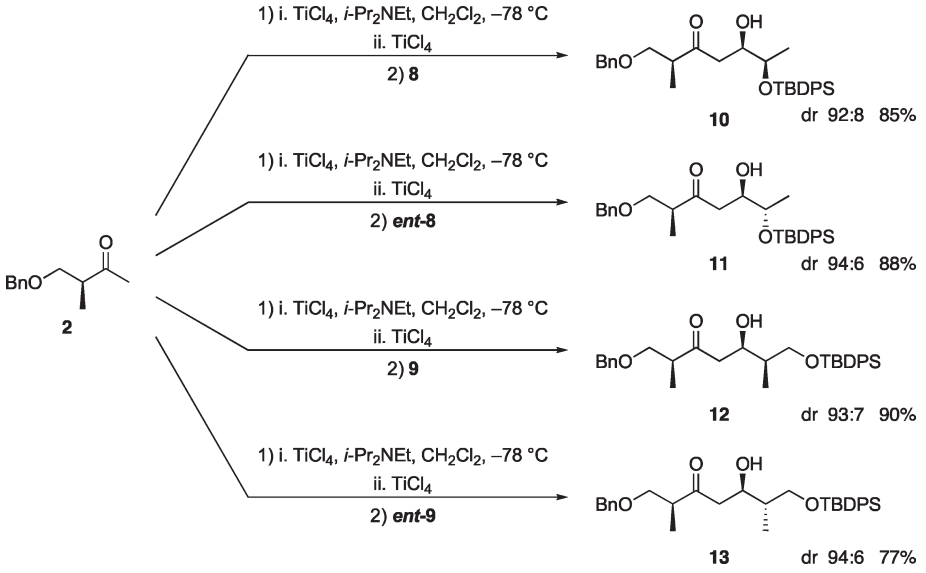
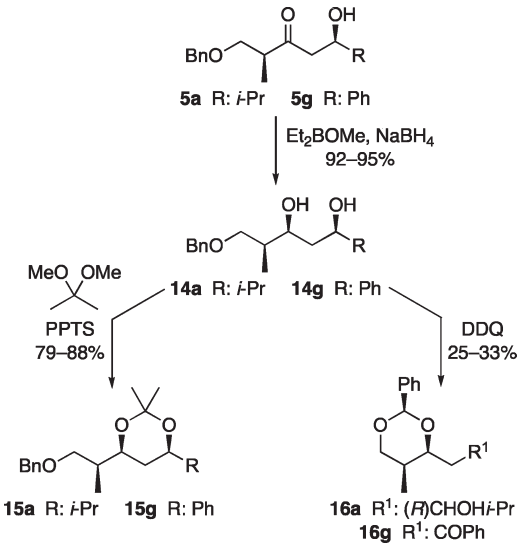
Scheme 3. Double-Stereodifferentiating Aldol Reactions



Scheme 4. Elucidation of the Configuration of Aldols 5



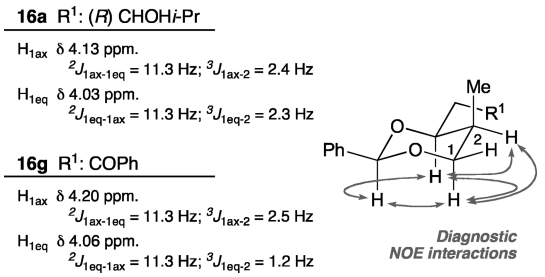
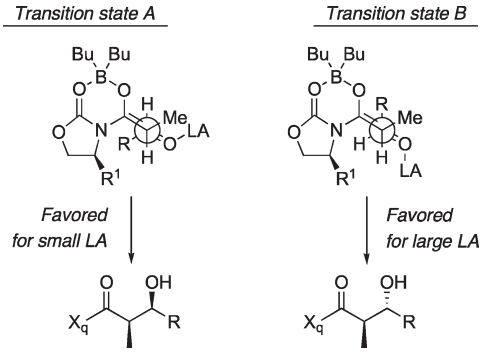
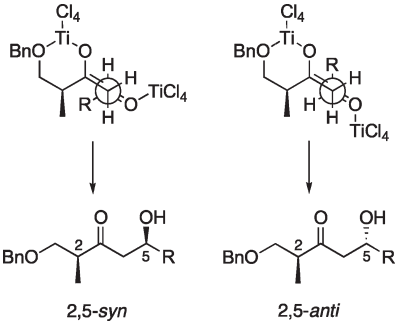


Figure 3. NMR diagnostic features of benzylidene acetals **16**.

Scheme 5. Heathcock's Proposal for Transition States in Lewis Acid Mediated Propionate Aldol Reactions



Scheme 6. Hypothetical Open Transition States for the Titanium-Mediated Acetate Aldol Reactions from 2



However, this model does not account for the stereochemical outcome of titanium-mediated aldol reactions from **2** carried out in the presence of a second equivalent of $TiCl_4$ (Scheme 6). Indeed, the lack of a methyl on the enolate should have produced similar diastereoselectivities in Table 2 irrespective of the Lewis

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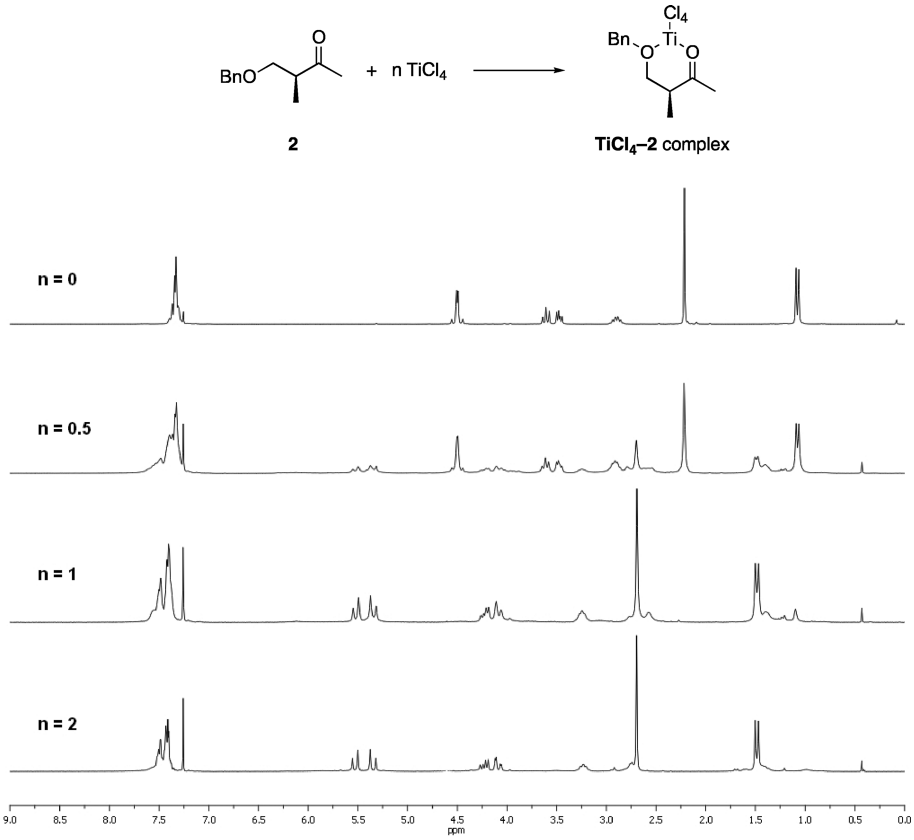

Figure 4. Titration of **2**. ^{1}H NMR spectra (250 MHz, $CDCl_3$, −10 °C) of $TiCl_4$−**2** complex.

acid used because the same H−LA interactions appear in transition states leading to *syn* or *anti* aldol adducts. Furthermore, these open transition states fail to explain why chiral aldehydes do not affect the stereochemical outcome of double-stereodifferentiating reactions represented in Scheme 3.

Alternatively, other authors reporting on titanium-mediated aldol reactions claim that the presence of a second equivalent of $TiCl_4$ modifies the structure of the titanium enolate. For instance, Crimmins suggested that the second molecule of $TiCl_4$ acts as a chlorine scavenger from the hexacoordinated titanium enolate of a *N*-propanoyl-1,3-oxazolidine-2-thione,[26] while Ghosh assumed that it binds to other centers of the enolate and changes the geometry of the transition state.[27] In an attempt to test such hypotheses in our system and to gain insight into the structure of the titanium enolate from ketone **2**, we carried out NMR experiments on $TiCl_4$−**2** complexes and the ensuing enolate. The corresponding ^{1}H NMR spectra are shown in Figures 4 and 5.

As expected, the titration of **2** with increasing amounts of $TiCl_4$ revealed the formation of a 1:1 chelated $TiCl_4$−**2** complex (see, for instance, the dramatic low field shifts of $PhCH_2OCH_2$ protons from δ 4.5 to 5.5 ppm, in Figure 4), which was the only species observed in the presence of 1 equiv of $TiCl_4$.[28] Moreover, we did not observe significant changes in these chemical shifts after the addition of a second equivalent of $TiCl_4$, so the position of this additional $TiCl_4$ remained unclear.

Otherwise, the behavior of the titanium enolate was surprising. Clear NMR spectra registered for this intermediate (for ^{1}H NMR, see Figure 5) also pointed to a chelated structure that adopts a half-chair-like conformation in which the methyl group is placed in a pseudoequatorial position. However, significant changes were observed in the ^{1}H NMR spectrum when the titanium enolate was prepared with 2 equiv of $TiCl_4$ or when the second one was added to the titanium enolate. Indeed, the clear ^{1}H NMR spectrum collapsed, and we only observed broad bands which we could not easily explain. Thus, the enolate underwent a change upon addition of a second Lewis acid, but it is still unknown what sort of intermediate results from such interaction.

Trying to shed light on this issue, we carried out some aldol reactions involving benzyl-protected α- and *β*-hydroxy aldehydes **17** and **18** (Scheme 7). These aldehydes are structurally akin to **8** (and ***ent*-8**) and **9** (and ***ent*-9**) represented in Figure 2, but the higher chelating ability of OBn group should alter the structure of the reacting species and affect the stereochemical outcome of the aldol reaction. This hypothesis was confirmed, since the diastereoselectivity of the aldol reactions involving these aldehydes was dramatically eroded to such an extent that almost equimolecular mixtures of diastereomers were obtained in high yields (Scheme 7).

The data presented so far suggest that a complex mechanism operates in this aldol reaction. Unfortunately, studies on the structure of the titanium enolates are scarce, which makes it difficult to offer explanations for their reactions.[29]

However, it is well-known that RR′C═O−$TiCl_4$ complexes exist as octahedral 2:1 RR′C═O−$TiCl_4$ adducts or centrosymmetric dimeric species resulting from the formation of chlorine bridges in the case of 1:1 stoichiometry (**I** in Figure 6).[30] In turn, Sharpless epoxidation is thought to be governed by a catalytic species containing a four-membered ring with two titanium atoms connected by bridging oxygens (**II** in Figure 6).[31] Hence, bimetallic

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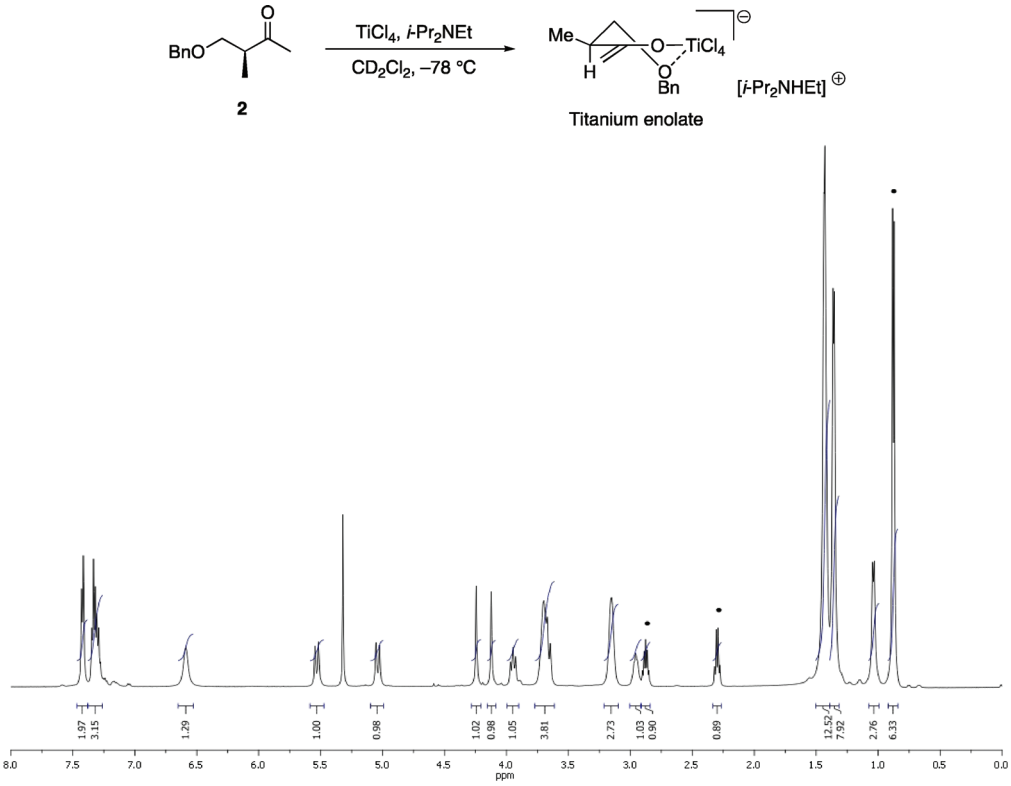
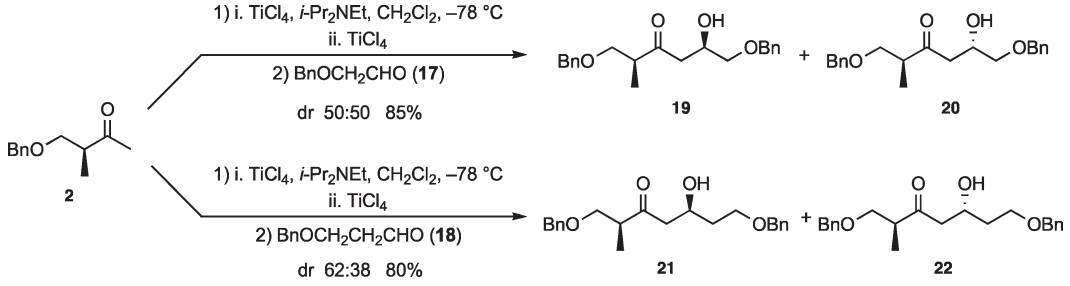


Figure 5. ^{1}H NMR (500 MHz, CD_2Cl_2, −78 °C) of the titanium enolate of **2** (●, *i*-Pr_2NEt peaks).

Scheme 7. Titanium-Mediated Aldol Reactions of 2 with α- and β-Benzyloxy Aldehydes



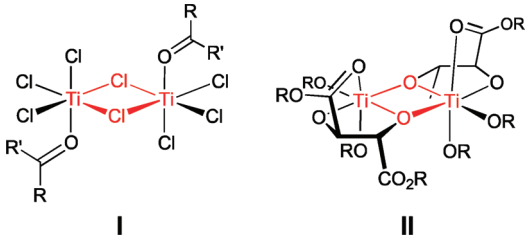


Figure 6. Bimetallic titanium complexes.

four-membered cyclic structures with two titanium atoms connected through a chlorine and an oxygen atom are often invoked to explain the structure of this sort of reacting species.

Moreover, several mechanistic proposals to account for the stereochemical outcome of different processes based on titanium enolates also involve *bimetallic-like* species. For instance, Trost invoked an eight-membered cyclic transition state with a chlorine bridge between titanium and silicon atoms to account for the high selectivity observed in a Mukaiyama-like aldol reaction of a lactate-derived methyl ketone (see eq 1 in Scheme 8).[32] More recently, Wang speculated that a complex with two chlorine atoms bridging two titanium atoms could be responsible of the highly regioselective 1,4-addition of a titanium enolate to an activated enone (see eq 2 in Scheme 8).[33] Finally, Liotta depicted a transition state that involves a chlorine bridge to rationalize the stereoselective formation of a carbon−carbon bond through the addition of a titanium enolate to *O*-methyl oximes activated by $TiCl_4$ (see eq 3 in Scheme 8).[34]

Keeping all these models in mind, the observation that the second equivalent of $TiCl_4$ affects the structure of the titanium enolate and it is required to achieve high stereocontrol suggests that these aldol reactions proceed through a bimetallic enolate. It is likely that the titanium enolate is a hexacoordinated species and

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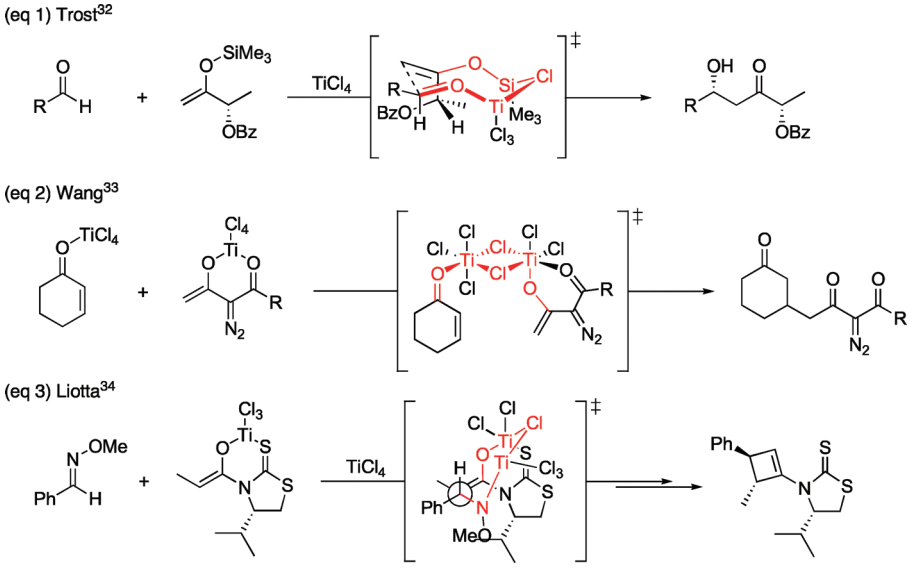
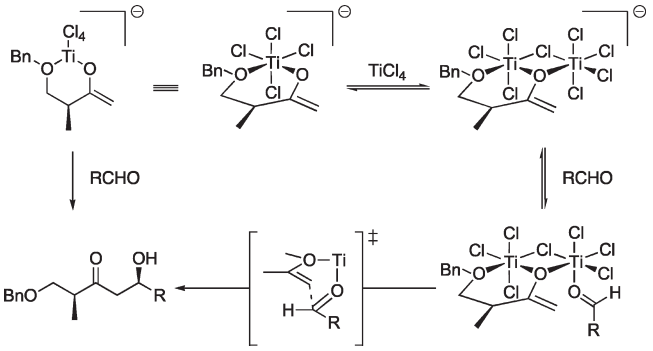
Scheme 8. Transition States Involving Titanium Enolates Proposed for Different Carbon−Carbon Bond-Forming Reactions



Scheme 9. Proposed Mechanism for the Titanium-Mediated Aldol Reaction from Ketone 2



the second $TiCl_4$ equivalent binds to this enolate to give a more complex one containing two titanium atoms. Then, the interaction of this bimetallic enolate and an aldehyde could take advantage of the higher reactivity of the outer titanium atom to produce an intermediate, which would evolve through a cyclic six-membered transition state shown in Scheme 9. According to this mechanism, the stereochemical-determining step of the titanium-mediated aldol addition of methyl ketone **2** to aldehydes in the presence of a second equivalent of $TiCl_4$ would not involve the carbon-forming step but instead the coordination of the aldehyde to the bimetallic enolate complex. Such an approach is compatible with the stereochemistry of the resulting adducts obtained in methods A and D and explains the indifference toward the configuration of chiral aldehydes. Furthermore, aldehydes possessing α- and β-benzyloxy groups like **17** and **18** prevent this sort of interaction because they favor the formation of a hexacoordinated chelated RCHO−$TiCl_4$ complex, which would react through less stereoselective pathways.

This rationale is based on the structure of titanium complexes and has precedents in related processes involving titanium enolates, although we are aware that it is just a working hypothesis. It obviously requires much more experimental and theoretical support, but we consider that this proposal may be useful to guide further advances in this field.

■ CONCLUSIONS

A systematic study of the substrate-controlled titanium-mediated aldol reactions of methyl ketones derived from Roche esters has established that this transformation is sensitive to the hydroxyl protecting group, the titanium Lewis acid engaged in the enolization step, and the addition of another Lewis acid to the reacting mixture. The best results were obtained when the $TiCl_4$-mediated aldol reaction of (*S*)-4-benzyloxy-3-methyl-2-butanone was carried out in the presence of a second equivalent of $TiCl_4$. Then, high yields (77−93%) and diastereomeric ratios up to 98:2 were obtained with a wide array of achiral aliphatic, α,β-unsaturated, and aromatic aldehydes, as well as chiral α- and β-OTBDPS aldehydes. The mechanism of this highly stereocontrolled reaction is still unclear, but experimental and spectroscopic evidence suggests that it might proceed through a cyclic transition state in which an oxygen and a chlorine act as bridges between two titanium atoms. Irrespective of the theoretical background of such a process, the reported transformation is simple and does not need other sources of chirality, and both enatiomeric starting methyl ketones are easily available from the corresponding Roche esters.

In summary, these features and the above-mentioned high levels of stereocontrol achieved with a wide array of aldehydes, provided that they are not sensitive to Lewis acids or they do not contain chelating groups, confer to the reported methodology an appealing interest to the synthesis of natural products.

■ EXPERIMENTAL SECTION

1. General Experimental Methods. Specific rotations were determined at 20 °C. IR data only show the most representative frequencies (cm^{-1}). Chemical shifts (δ are quoted in ppm and referenced to internal TMS (δ 0 for ^1H NMR, and $CDCl_3$ (δ 77.0) for ^{13}C

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NMR; data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Where appropriate, 2D techniques were also used to assist in structure elucidation. Flash chromatography was performed on 35−70 μm silica gel. Analytical thin-layer chromatography was carried out on silica gel 60 F_{254} plates. HPLC analyses of aldols products were carried out with a Chiralcel OD-H column at 0.9 mL min^{-1} flow.

All reactions were conducted in oven-dried glassware under inert atmosphere of nitrogen with anhydrous solvents. The solvents and reagents were purified and dried according to standard procedures.

Chiral ketone **2** and aldehydes (**8**, ***ent*-8**, **9**, ***ent*-9**) were prepared according to reported procedures.[15a,21,22]

2. General Procedure for Aldol Reactions from Ketone 2 (Method A). Neat $TiCl_4$ (110 μL, 1.0 mmol) was added dropwise to a solution of ketone **2** (1.0 mmol) in CH_2Cl_2 (5 mL) at −78 °C under N_2, and the resulting yellow mixture was stirred for 2−3 min. Then, *i*-Pr_2NEt (190 μL, 1.1 mmol) was carefully added, and the ensuing dark red solution was stirred for 30 min at −78 °C followed by addition of neat $TiCl_4$ (110 μL, 1.0 mmol). After the solution was stirred for 10 min, aldehyde (1.5 mmol) was added, and the reaction mixture was stirred for 30 min at −78 °C.

The mixture was quenched by addition of saturated NH_4Cl (5 mL), diluted with Et_2O (50 mL), and washed with H_2O (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The aqueous layers were extracted with Et_2O (2 × 30 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oil was analyzed by HPLC and NMR and purified by column chromatography.

3. General Procedure for Aldol Reactions from Ketone 2 (Method D). Neat $TiCl_4$ (120 μL, 1.1 mmol) was added dropwise to a solution of ketone **2** (1.0 mmol) in CH_2Cl_2 (2 mL) at −78 °C under N_2, and the resulting yellow mixture was stirred for 2−3 min. *i*-Pr_2NEt (190 μL, 1.1 mmol) was carefully added, and the dark red solution was stirred for 30 min at −78 °C.

At the same time, neat $TiCl_4$ (130 μL, 1.2 mmol) was added dropwise to a solution of aldehyde (1.2 mmol) in CH_2Cl_2 (2 mL) in another round-bottom flask at −78 °C under N_2. The resulting mixture was stirred for 10 min at −78 °C, and then the enolate solution was added dropwise to the solution of precomplexed aldehyde via cannula. The resulting solution was stirred for 30 min at −78 °C, quenched, and purified as in the former method.

4. Physical and Spectroscopic Data of Aldols 5 and 10−13. *(2S,5R)-1-Benzyloxy-5-hydroxy-2,6-dimethyl-3-heptanone (**5a**):* yellowish oil; R_f = 0.50 (hexane/EtOAc 7:3); HPLC (hexane/*i*-PrOH 95:5) t_R = 13.1 min; $[\alpha]_D$ +56.5 (*c* 1.0, $CHCl_3$) [lit.[1b] ***ent*-3a** $[\alpha]_D$ −50.5 (*c* 0.27, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 3.83 (ddd, *J* = 9.7, 5.7, 2.3 Hz, 1H), 3.62 (dd, *J* = 9.0, 8.3 Hz, 1H), 3.49 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.06 (s, 1H), 2.96−2.88 (m, 1H), 2.69 (dd, *J* = 17.4, 2.3 Hz, 1H), 2.54 (dd, *J* = 17.4, 9.7 Hz, 1H), 1.73−1.61 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.9, 137.8, 128.4, 127.7, 127.6, 73.3, 72.2, 72.1, 46.8, 46.0, 33.0, 18.4, 17.8, 13.2; IR (film) ν 3491, 2962, 1708, 1454, 1367, 1098; HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{24}NaO_3$ $[M + Na]^+$ 287.1618, found 287.1623.

*(2S,5S)-1-Benzyloxy-5-hydroxy-2,7-dimethyl-3-octanone (**5b**):* yellowish oil; R_f = 0.50 (hexane/EtOAc 7:3); HPLC (hexane/*i*-PrOH 95:5) t_R = 10.0 min; $[\alpha]_D$ +35.4 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.17−4.11 (m, 1H), 3.62 (dd, *J* = 9.0, 8.3 Hz, 1H), 3.49 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.07 (s, 1H), 2.91−2.88 (m, 1H), 2.68 (dd, *J* = 17.5, 2.7 Hz, 1H), 2.53 (dd, *J* = 17.5, 9.1 Hz, 1H), 1.82−1.72 (m, 1H), 1.45 (ddd, *J* = 13.7, 8.9, 5.6 Hz, 1H), 1.12 (ddd, *J* = 13.7, 8.5, 4.5 Hz, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.9, 138.0, 128.6, 128.0, 127.9, 73.6, 72.4, 65.8, 49.7, 47.0, 45.7, 24.6, 23.5, 22.3, 13.4; IR (film) ν 3472, 2955, 2869, 1708, 1454, 1367, 1099, 1028. HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{26}NaO_3$ $[M + Na]^+$ 301.1774, found 301.1779.

*(2S,5S)-1-Benzyloxy-5-hydroxy-2-methyl-3-octanone (**5c**):* yellowish oil; R_f = 0.40 (hexane/EtOAc 7:3); HPLC (hexane/*i*-PrOH 95:5) t_R = 12.2 min; $[\alpha]_D$ +41.0 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.10−4.04 (m, 1H), 3.62 (dd, *J* = 9.0, 8.2 Hz, 1H), 3.49 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.09 (s, 1H), 2.94−2.85 (m, 1H), 2.70 (dd, *J* = 17.5, 2.6 Hz, 1H), 2.54 (dd, *J* = 17.5, 9.2 Hz, 1H), 1.53−1.41 (m, 2H), 1.39−1.30 (m, 2H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.9, 138.0, 128.6, 128.0, 127.9, 73.6, 72.4, 67.4, 49.2, 47.0, 38.7, 18.9, 14.2, 13.4; IR (film) ν 3471, 3031, 2959, 2932, 2872, 1708, 1454, 1375, 1099, 1028; HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{24}NaO_3$ $[M + Na]^+$ 287.1618, found 287.1621.

*(2S,5R)-1-Benzyloxy-5-hydroxy-2,6-dimethyl-6-hepten-3-one (**5d**):* yellowish oil; R_f = 0.30 (hexane/EtOAc 7:3); HPLC (hexane/*i*-PrOH 95:5) t_R = 19.2 min; $[\alpha]_D$ +51.6 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.01−4.99 (m, 1H), 4.86−4.84 (m, 1H), 4.52 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 3.62 (dd, *J* = 9.0, 8.3 Hz, 1H), 3.50 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.11 (s, 1H), 2.96−2.87 (m, 1H), 2.77 (dd, *J* = 17.4, 3.1 Hz, 1H), 2.69 (dd, *J* = 17.4, 9.1 Hz, 1H), 1.72 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.2, 145.9, 138.0, 128.6, 128.0, 127.9, 111.2, 73.6, 72.4, 71.1, 47.8, 47.1, 18.6, 13.3; IR (film) ν 3462, 3030, 2972, 2862, 1710, 1652, 1496, 1454, 1370, 1092; HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{22}NaO_3$ $[M + Na]^+$ 285.1461, found 285.1460.

*(2S,5R,6E)-1-Benzyloxy-5-hydroxy-2-methyl-6-octen-3-one (**5e**):* yellowish oil; R_f = 0.30 (hexane/EtOAc 7:3); HPLC (hexane/*i*-PrOH 95:5) t_R = 15.6 min; $[\alpha]_D$ +33.5 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.70 (dqd, *J* = 15.3, 6.5, 1.1 Hz, 1H), 5.48 (ddq, *J* = 15.3, 6.5, 1.6 Hz, 1H), 4.55−4.52 (m, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 3.62 (dd, *J* = 9.0, 8.1 Hz, 1H), 3.49 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.06 (s, 1H), 2.93−2.85 (m, 1H), 2.73 (dd, *J* = 17.4, 3.7 Hz, 1H), 2.66 (dd, *J* = 17.4, 8.3 Hz, 1H), 1.68 (ddd, *J* = 6.5, 1.6, 0.9 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.9, 137.8, 131.9, 128.4, 127.7, 127.6, 126.9, 73.3, 72.1, 68.4, 48.8, 46.9, 17.7, 13.1; IR (film) ν 3454, 3030, 2858, 1709, 1496, 1454, 1376, 1098, 1028; HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{22}NaO_3$ $[M + Na]^+$ 285.1461, found 285.1459.

*(2S,5R,6E)-1-Benzyloxy-5-hydroxy-2-methyl-7-phenyl-6-hepten-3-one (**5f**):* yellowish solid; mp = 70−72 °C; R_f = 0.30 (hexane/EtOAc 7:3); $[\alpha]_D$ +21.0 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.21 (m, 10H), 6.62 (dd, *J* = 15.9, 1.1 Hz, 1H), 6.19 (dd, *J* = 15.9, 5.9 Hz, 1H), 4.81−4.75 (m, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.47 (d, *J* = 12.1 Hz, 1H), 3.63 (dd, *J* = 9.0, 8.2 Hz, 1H), 3.52 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.24 (d, *J* = 3.5 Hz, 1H), 2.97−2.89 (m, 1H), 2.85 (dd, *J* = 17.5, 3.4 Hz, 1H), 2.76 (dd, *J* = 17.5, 8.6 Hz, 1H), 1.09 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.6, 137.8, 136.6, 130.2, 130.2, 128.5, 128.4, 127.8, 127.7, 126.5, 73.4, 72.1, 68.3, 48.8, 46.9, 13.1; IR (film) ν 3494, 3030, 2978, 2933, 2861, 1705, 1684, 1653, 1496, 1420, 1118; HRMS (+ESI) *m*/*z* calcd for $C_{21}H_{24}NaO_3$ $[M + Na]^+$ 347.1618, found 347.1621.

*(1R,4S)-5-Benzyloxy-1-hydroxy-4-methyl-1-phenyl-3-pentanone (**5g**):* yellowish oil; R_f = 0.30 (hexane/EtOAc 7:3); HPLC (hexane/*i*-PrOH 85:15) t_R = 10.5 min; $[\alpha]_D$ +42.0 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.24 (m, 10H), 5.16 (dd, *J* = 7.9, 4.4 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 3.61 (dd, *J* = 9.1, 8.1 Hz, 1H), 3.50 (dd, *J* = 9.1, 5.1 Hz, 1H), 3.47 (s, 1H), 2.98−2.82 (m, 3H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.7, 142.9, 137.8, 128.9, 128.4, 127.7, 127.6, 127.5, 125.6, 73.3, 72.1, 69.7, 50.9, 46.8, 13.0; IR (film) ν 3460, 3062, 3030, 2972, 2862, 1709, 1495, 1454, 1365, 1094, 1028; HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{22}NaO_3$ $[M + Na]^+$ 321.1461, found 321.1467.

*(1R,4S)-5-Benzyloxy-1-hydroxy-4-methyl-1-(4-nitrophenyl)-3-pentanone (**5h**):* yellowish oil; R_f = 0.25 (hexane/EtOAc 6:4); HPLC (hexane/*i*-PrOH 85:15) t_R = 28.1 min; $[\alpha]_D$ +28.4 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.16−8.14 (m, 2H), 7.45−7.43 (m, 2H), 7.37−7.26 (m, 5H), 5.24 (dt, *J* = 9.4, 2.8 Hz, 1H), 4.48 (s, 2H), 3.78−3.69 (m, 1H), 3.64−3.51 (m, 2H), 2.95 (dd, *J* = 17.7, 2.8 Hz, 1H), 2.95−2.87 (m, 1H), 2.80 (dd, *J* = 17.7, 9.4 Hz, 1H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.4, 150.2, 147.2, 137.6, 128.5, 127.9, 127.7, 126.4, 126.3, 123.6, 73.4, 72.3, 68.8, 50.7, 46.7, 12.8; IR (film) ν 3469, 2862, 1710, 1604, 1519, 1347, 1078; HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{21}NNaO_5$ $[M + Na]^+$ 366.1312, found 366.1316.

*(1R,4S)-5-Benzyloxy-1-hydroxy-1-(4-methoxyphenyl)-4-methyl-3-pentanone (**5i**):* yellowish oil; R_f (hexane/EtOAc 6:4) = 0.35; HPLC (hexane/*i*-PrOH 85:15) t_R = 18.2 min; $[\alpha]_D$ +25.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 7H), 6.87−6.85 (m, 2H), 5.11 (td, *J* = 6.2, 2.6 Hz, 1H), 4.49 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 12.3 Hz, 1H), 3.79 (s, 3H), 3.61 (dd, *J* = 9.0, 8.2 Hz, 1H), 3.50 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.38 (d, *J* = 2.6 Hz, 1H), 2.95−2.80 (m, 3H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.8, 159.0, 137.8, 135.0, 128.4, 127.7, 127.6, 126.9, 126.9, 113.8, 73.3, 72.1, 69.3, 55.3, 50.9, 46.9, 29.7, 13.1; IR (film) ν 3462, 2924, 2854, 1709, 1612, 1514, 1248, 1034; HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{24}NaO_4$ $[M + Na]^+$ 351.1567, found 351.1559.

*(2S,5R,6R)-1-Benzyloxy-6-tert-butyldiphenylsilyloxy-5-hydroxy-2-methyl-3-heptanone (**10**):* colorless oil; R_f = 0.50 (hexane/EtOAc 7:3); HPLC (hexane/*i*-PrOH 95:5) t_R = 8.9 min; $[\alpha]_D$ +21.3 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 5H), 7.45−7.25 (m, 10H), 4.48 (d, *J* = 12.3 Hz, 1H), 4.44 (d, *J* = 12.3 Hz, 1H), 4.04−3.99 (m, 1H), 3.84 (qd, *J* = 6.3, 4.6 Hz, 1H), 3.61 (dd, *J* = 9.1, 7.7 Hz, 1H), 3.45 (dd, *J* = 9.1, 5.4 Hz, 1H), 2.91−2.85 (m, 1H), 2.85 (d, *J* = 4.3 Hz, 1H), 2.69 (dd, *J* = 17.2, 3.9 Hz, 1H), 2.63 (dd, *J* = 17.2, 8.7 Hz, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 9H), 1.02 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.3, 137.9, 135.8, 135.8, 134.0, 133.5, 129.8, 129.7, 128.4, 127.7, 127.7, 127.6, 127.5, 73.2, 72.0, 71.5, 71.1, 47.0, 44.1, 27.0, 19.3, 18.4, 13.3; IR (film) ν 3491, 3070, 2932, 2858, 1710, 1472, 1454, 1428, 1375, 1111; HRMS (+ESI) *m*/*z* calcd for $C_{31}H_{44}NO_4Si$ $[M + NH_4]^+$ 522.3034, found 522.3025.

*(2S,5R,6S)-1-Benzyloxy-6-tert-butyldiphenylsilyloxy-5-hydroxy-2-methyl-3-heptanone (**11**):* colorless oil; R_f = 0.55 (hexane/EtOAc 7:3); $[\alpha]_D$ +9.5 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.64 (m, 5H), 7.45−7.24 (m, 10H), 4.47 (d, *J* = 12.1 Hz, 1H), 4.43 (d, *J* = 12.1 Hz, 1H), 4.04−3.98 (m, 1H), 3.82 (qd, *J* = 6.3, 4.6 Hz, 1H), 3.58 (dd, *J* = 9.1, 7.9 Hz, 1H), 3.46 (dd, *J* = 9.1, 5.3 Hz, 1H), 2.90−2.82 (m, 1H), 2.85 (d, *J* = 3.3 Hz, 1H), 2.70 (dd, *J* = 17.2, 3.2 Hz, 1H), 2.58 (dd, *J* = 17.2, 9.0 Hz, 1H), 1.06 (s, 9H), 1.04 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.3, 137.9, 135.9, 134.2, 133.6, 129.8, 129.6, 128.4, 127.7, 127.6, 127.5, 73.3, 72.1, 72.0, 71.6, 46.9, 44.6, 27.0, 19.3, 18.5, 13.2; IR (film) ν 3499, 3070, 2932, 2857, 1710, 1472, 1454, 1428, 1375, 1111; HRMS (+ESI) *m*/*z* calcd for $C_{31}H_{44}NO_4Si$ $[M + NH_4]^+$ 522.3034, found 522.3029.

*(2S,5R,6R)-1-Benzyloxy-7-tert-butyldiphenylsilyloxy-5-hydroxy-2,6-dimethyl-3-heptanone (**12**):* colorless oil; R_f = 0.55 (hexane/EtOAc 7:3); HPLC (hexane/*i*-PrOH 95:5) t_R = 8.3 min; $[\alpha]_D$ +11.4 (*c* 1.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 5H), 7.45−7.24 (m, 10H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 4.35−4.30 (m, 1H), 3.68 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.65 (dd, *J* = 9.3, 5.2 Hz, 1H), 3.62 (dd, *J* = 9.0, 8.0 Hz, 1H), 3.47 (dd, *J* = 9.0, 5.3 Hz, 1H), 3.15 (d, *J* = 3.3 Hz, 1H), 2.94−2.85 (m, 1H), 2.71 (dd, *J* = 17.1, 9.1 Hz, 1H), 2.61 (dd, *J* = 17.1, 3.4 Hz, 1H), 1.78−1.70 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.06−1.05 (s, 9H), 0.91 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.7, 137.9, 135.6, 135.6, 133.4, 133.3, 129.7, 128.4, 127.7, 127.6, 73.3, 72.1, 68.9, 67.1, 46.9, 46.8, 39.7, 26.9, 19.2, 13.2, 11.0; IR (film) ν 3512, 3070, 2931, 2858, 1709, 1472, 1454, 1428, 1362, 1112; HRMS (+ESI) *m*/*z* calcd for $C_{32}H_{42}O_4Si$ $[M + H]^+$ 519.2925, found 519.2922.

*(2S,5R,6S)-1-Benzyloxy-7-tert-butyldiphenylsilyloxy-5-hydroxy-2,6-dimethyl-3-heptanone (**13**):* colorless oil; R_f = 0.50 (hexane/EtOAc 7:3); HPLC (hexane/*i*-PrOH 95:5) t_R = 8.7 min; $[\alpha]_D$ +24.0 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 5H), 7.44−7.25 (m, 10H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 4.17−4.11 (m, 1H), 3.71 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.66 (dd, *J* = 10.2, 6.1 Hz, 1H), 3.62 (dd, *J* = 9.0, 8.0 Hz, 1H), 3.51 (d, *J* = 3.3 Hz, 1H), 3.47 (dd, *J* = 9.0, 5.3 Hz, 1H), 2.95−2.87 (m, 1H), 2.73−2.62 (m, 1H), 1.85−1.75 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 9H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.9, 137.9, 135.6, 133.3, 129.7, 128.4, 127.7, 127.6, 73.3, 72.1, 70.3, 66.7, 46.9, 46.8, 40.2, 26.9, 19.2, 13.3, 13.3; IR (film) ν 3497, 3070, 2961, 2931, 2858, 1709, 1472, 1428, 1112; HRMS (+ESI) *m*/*z* calcd for $C_{32}H_{42}O_4Si$ $[M + H]^+$ 519.2925, found 519.2925.

5. PROOF OF THE STEREOCHEMISTRY FOR ALDOLS 5

5.1. Stereoselective Reduction of Aldols 5. A 1 M solution of Et_2BOMe (1.7 mL, 1.7 mmol) in THF was added dropwise to a 0.15 M solution of aldol **5a** or **5g** (1 mmol) in THF at −78 °C under N_2, and the resulting mixture was stirred for 20 min at −78 °C. $NaBH_4$ (46 mg, 1.2 equiv) was quickly added, and the reaction mixture was further stirred for 3 h at −78 °C under N_2.

The reaction was quenched by addition of AcOH (2 mL), and the mixture was allowed to warm to room temperature. The mixture was partitioned with CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 1 M NaOH, dried ($MgSO_4$), and concentrated. The residue was diluted in a 1 M solution of NaOAc in 9:1 MeOH/H_2O (25 mL) and treated with 33% w/v H_2O_2 (4 mL) at room temperature for 1 h.

The reaction mixture was partitioned with CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The resultant oil was purified by column chromatography (hexane/EtOAc) to afford *syn* 1,3-diols **14a** and **14g** in 92−95% yield.

*(2S,3S,5R)-1-Benzyloxy-2,6-dimethyl-3,5-heptanediol (**14a**):* colorless oil; R_f = 0.20 (hexane/EtOAc 7:3); $[\alpha]_D$ +30.3 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.01 (dt, *J* = 9.7, 2.7 Hz, 1H), 3.63 (ddd, *J* = 9.0, 5.0, 2.6 Hz, 1H), 3.54 (dd, *J* = 9.1, 5.0 Hz, 1H), 3.51 (dd, *J* = 9.1, 6.5 Hz, 1H), 1.97−1.90 (m, 1H), 1.71−1.60 (m, 1H), 1.53−1.44 (m, 2H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.0, 128.7, 128.1, 127.9, 77.9, 76.2, 74.5, 73.8, 38.9, 36.0, 34.3, 18.5, 17.8, 11.6; IR (film) ν 3410, 2950, 2874, 1450, 1410, 1384, 1365, 1329, 1098, 1028; HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{26}NaO_3$ $[M + Na]^+$ 289.1774, found 289.1767.

*(2S,3S,5R)-1-Benzyloxy-2-methyl-5-phenyl-3,5-pentanediol (**14g**):* colorless oil; R_f = 0.30 (hexane/EtOAc 7:3); $[\alpha]_D$ +22.6 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.407.27 (m, 10H), 4.95 (dd, *J* = 10.0, 2.6 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.14 (dt, *J* = 10.83, 2.17 Hz, 1H), 3.56 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.51 (dd, *J* = 9.1, 6.9 Hz, 1H), 1.99−1.92 (m, 1H), 1.88 (ddd, *J* = 14.3, 10.8, 10.0 Hz, 1H), 1.66 (ddd, *J* = 14.3, 2.7, 2.0 Hz, 1H), 0.92 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.9, 128.8, 128.6, 128.1, 127.9, 127.6, 125.9, 75.9, 75.5, 74.5, 73.8, 42.5, 38.7, 11.7; IR (film) ν 3396, 2916, 2857, 1454, 1100, 1061; HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{24}NaO_3$ $[M + Na]^+$ 323.1618, found 323.1612.

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5.2. Protection of Diols 14. A mixture of a *syn* 1,3-diol **14** (0.2 mmol) and a catalytic amount of PPTS in 1:1 CH_2Cl_2/$(MeO)_2CMe_2$ (5 mL) was stirred at room temperature for 24 h under N_2. The solvent was removed in vacuo, and the resultant white residue was purified by column chromatography (hexane/EtOAc) to afford isopropylidene ketals **15a** and **15g** as a colorless oil in 95% and 88% yield, respectively.

*(2S,3S,5R)-1-Benzyloxy-3,5-isopropylidenedioxy-2,6-dimethylheptane (**15a**):* colorless oil; R_f = 0.80 (hexane/EtOAc 7:3); $[\alpha]_D$ +24.6 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 3.88 (ddd, *J* = 11.7, 4.8, 2.5 Hz, 1H), 3.47 (dd, *J* = 9.1, 6.5 Hz, 1H), 3.44 (dd, *J* = 9.1, 4.7 Hz, 1H), 3.34 (dd, *J* = 9.1, 5.8 Hz, 1H), 1.84−1.73 (m, 1H), 1.65−1.55 (m, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.37−1.33 (m, 1H), 1.26−1.16 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.9, 128.5, 127.8, 127.7, 98.4, 74.4, 73.3, 72.5, 69.8, 38.9, 33.3, 31.1, 30.4, 20.1, 18.7, 17.9, 12.4; IR (film) ν 2990, 2959, 2872, 1378, 1257, 1201, 1171, 1098; HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{30}NaO_3$ $[M + Na]^+$ 329.2087, found 329.2084.

*(1R,3S,4S)-5-Benzyloxy-1,3-isopropylidenedioxy-4-methyl-1-phenylpentane (**15g**):* colorless oil; R_f = 0.80 (hexane/EtOAc 7:3); $[\alpha]_D$ +22.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 10H), 4.88 (dd, *J* = 11.3, 2.9 Hz, 1H), 4.49 (s, 2H), 4.08 (ddd, *J* = 11.3, 4.9, 2.5 Hz, 1H), 3.49 (dd, *J* = 9.1, 6.4 Hz, 1H), 3.35 (dd, *J* = 9.1, 5.6 Hz, 1H), 1.87−1.77 (m, 1H), 1.63 (dt, *J* = 12.9, 2.8 Hz, 1H), 1.59−1.50 (m, 1H), 1.53 (s, 3H), 1.47 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.9, 138.8, 128.6, 128.6, 127.8, 127.7, 127.7, 126.1, 99.2, 73.4, 72.2, 71.9, 69.9, 38.8, 36.9, 30.5, 20.1, 12.4; IR (film) ν 3029, 2991, 2919, 2856, 1453, 1379, 1254, 1201, 1169, 1098; HRMS (+ESI) *m*/*z* calcd for $C_{22}H_{28}NaO_3$ $[M + Na]^+$ 363.1931, found 363.1927.

5.3. Oxidation of Diols 14. A mixture of diol **14** (0.2 mmol), DDQ (179 mg, 0.75 mmol), and 4 Å molecular sieves in CH_2Cl_2 (5 mL) was stirred under N_2 at room temperature for 24 h. The mixture was then filtered through Celite, eluted with CH_2Cl_2, and washed with H_2O. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with H_2O and dried ($MgSO_4$), and the solvent was removed in vacuo. The resultant oil was purified by column chromatography (hexane/EtOAc) to afford benzylidene acetals **16a** and **16g** as a colorless oil in 23% and 33% yield, respectively.

*(2R,4S,5S)-4-[(2R)-2-Hydroxy-3-methyl-1-butyl]-5-methyl-2-phenyl-1,3-dioxane (**16a**):* orange oil; R_f = 0.50 (hexane/EtOAc 6:4); $[\alpha]_D$ −10.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.26 (m, 5H), 5.56 (s, 1H), 4.24 (ddd, *J* = 9.74, 3.43, 2.35 Hz, 1H), 4.13 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.03 (dd, *J* = 11.2, 1.3 Hz, 1H), 3.63 (ddd, *J* = 10.1, 5.3, 1.8 Hz, 1H), 1.82−1.52 (m, 4H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.4, 129.2, 128.5, 126.3, 102.1, 81.4, 76.7, 74.1, 36.5, 34.1, 32.5, 18.6, 17.8, 11.7; IR (film) ν 3525, 2961, 2929, 2873, 1466, 1389, 1375, 1165, 1113, 1003; HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{23}O_2$ $[M - OH]^+$ 247.1693, found 247.1693.

*(2R,4S,5S)-5-Methyl-2-phenyl-4-(2-phenyl-2-oxoethyl)-1,3-dioxane (**16g**):* colorless oil; R_f = 0.60 (hexane/EtOAc 7:3); $[\alpha]_D$ +2.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.27 (m, 10H), 5.59 (s, 1H), 4.70 (td, *J* = 6.5, 2.4 Hz, 1H), 4.20 (dd, *J* = 11.3, 2.5 Hz, 1H), 4.06 (dd, *J* = 11.3, 1.2 Hz, 1H), 3.41 (dd, *J* = 16.9, 6.7 Hz, 1H), 3.06 (dd, *J* = 16.9, 6.3 Hz, 1H), 1.80−1.85 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.9, 138.8, 137.3, 133.5, 129.0, 128.8, 128.4, 128.4, 126.3, 102.1, 76.3, 73.8, 41.8, 31.7, 11.7; IR (film) ν 2965, 2918, 2850, 1686, 1597, 1449, 1374, 1213, 1119, 1001; HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{20}NaO_3$ $[M + Na]^+$ 319.1305, found 319.1296.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of aldols adducts **5** and **10**−**13** and acetals **15** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

†This paper is dedicated to Professor Carmen Nájera on the occasion of her 60th birthday.

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