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1,4-Asymmetric induction in the titanium-mediated aldol reactions of α-benzyloxy methyl ketones

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ABSTRACT

Good levels of 1,4-*anti* asymmetric induction are obtained in the $TiCl_3$(*i*-PrO)-mediated aldol reaction of α-benzyloxy methyl ketones with achiral aldehydes. Such methodology represents a new approach to the substrate-controlled acetate aldol reaction, which can be useful to design more efficient synthesis.

The ubiquitous presence of β-hydroxycarbonyl and 1,3-diol subunits in natural products has motivated the development of a plethora of synthetic strategies, being especially important those associated to the aldol reaction.[1] The intensive research carried out in this area during the last decades has given rise to a large number of highly stereoselective methodologies, which have been successfully applied to the construction of structurally complex molecular architectures.[2] Regardless of these advances, the *acetate* aldol reaction[3] is still a matter of concern.[1,4] Particularly, the lack of refined models to understand the mechanistic details of such reactions[5,6] makes difficult to use them for coupling large fragments in advanced steps of a synthesis.[7] Indeed, the lack of knowledge of the stereochemical bias imparted by α-alkoxy groups in titanium-mediated aldol reactions of methyl ketones is remarkable.[8] Considering the importance of such transformation, we have surveyed the reactivity of the chiral α-benzyloxy methyl ketones shown in Figure 1. Herein, we document the 1,4-*anti* induction provided by the titanium enolates from these ketones, which can be useful to design more efficient syntheses of complex natural products.

The significance of the titanium enolates has unceasingly increased since Evans established that they can be prepared by simple enolization with a titanium(IV) Lewis acid and a tertiary amine,[9] and they are nowadays recognized as one of the most useful tools for the stereoselective construction of carbon–carbon bonds. Unfortunately, the poor knowledge on their structure has hampered further synthetic advances. In this context, we have recently documented the structure of the titanium enolate from α-alkoxy ketones,[10] and have proved that the stereochemical outcome of the aldol reaction from chiral α-benzyloxy ethyl ketones relies on the titanium Lewis acid employed in the enolization step.[11] Bearing in mind these precedents, we speculated that the appropriate choice of the enolization conditions for the lactate-derived methyl ketone **1** would afford a well organized enolate that might provide the structural elements required to achieve a highly substrate-controlled reaction.

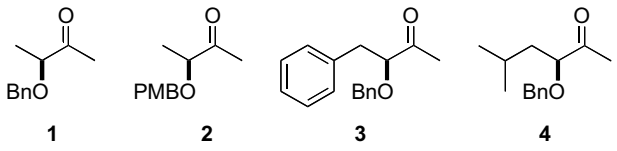

Figure 1.

Thus, we first evaluated the influence of the enolization conditions on the titanium-mediated aldol addition of ketone **1**[12] to isobutyraldehyde. The results are summarized in Table 1.

As expected, the stereochemical outcome of these reactions was highly dependent on the titanium Lewis acid used in the enolization. Thereby, almost no diastereoselectivity was observed with $TiCl_4$ (see entries 1 and 2 in Table 1), but better levels of stereocontrol favoring the *anti* adduct **5a** were achieved with 2 equiv of $TiCl_4$ (see Table 1, entry 3) or softer Lewis acids as $TiCl_3$(*i*-PrO) or $TiCl_2$-(*i*-PrO)$_2$ (see entries 4 and 5 in Table 1). The configuration of **5a** was established through conversion of an 85:15 mixture of diastereomers into the (*S*) 3-hydroxy-4-methylpentanoic acid, **7**[13] (Scheme 1).

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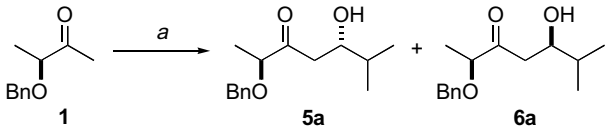
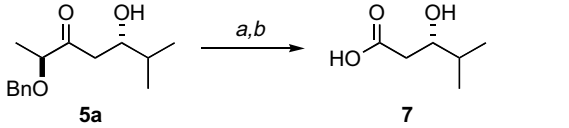
Table 1
Titanium-mediated aldol reaction of **1** and isobutyraldehyde



Entry	TiL_4	dr (**5a**:**6a**)[a]	Yield[b] (%)
1	TiC_4	57:43	90
2	$TiCl_4$ + THF	51:49	71
3	$TiCl_4$ + $TiCl_4$	71:29	77
4	$TiCl_3$(*i*-PrO)	85:15	80
5	$TiCl_2$(*i*-PrO)$_2$	73:27	80

[a] The diastereomeric ratio was established through HPLC analysis of the reaction mixture.
[b] Isolated yield of the aldol mixture.



7 (70% *ee*) $[\alpha]_D$ –25.3 (*c* 1.2, $CHCl_3$)
Evans[13a] $[\alpha]_D$ –42.1 (*c* 1.8, $CHCl_3$)
Yan[13b] $[\alpha]_D$ –40.7 (*c* 3.0, $CHCl_3$)

Scheme 1. Reagents and conditions: (a) H_2, Pd/C, EtOH, rt; (b) $NaIO_4$, MeOH/H_2O 2:1, rt; 50% overall yield.

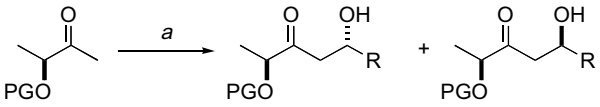
As the most promising result was obtained with $TiCl_3$(*i*-PrO), we carried out an exhaustive evaluation on the reaction conditions with this Lewis acid. Unfortunately, attempts to improve the diastereoselectivity by lowering the reaction temperature and by altering times were unsuccessful, but we were pleased to observe that the amount of aldehyde could be safely reduced to 1.2 equiv without a significant erosion of the yield.[14] Next, these experimentally simple conditions were applied to the reaction of lactate-derived methyl ketones **1** and **2**[12] with a broad array of aldehydes. The results are summarized in Table 2.

These results prove that the lactate-derived methyl ketone **1** affords the 1,4-*anti* aldol adducts **5** from aliphatic, aromatic, and α,β-unsaturated aldehydes in good yields and diastereomeric ratios (see entries 1–6 in Table 1).[15] Significantly, the steric bulk dictates the diastereoselectivity for aliphatic aldehydes **a**–**d** (compare entries 1–4 in Table 2), which ranges from dr 93:7 for pivalaldehyde (**b**) to dr 80:20 for butanal (**d**). The level of stereocontrol was evenly high for benzaldehyde, but became poorer for the α,β-unsaturated methacrolein (see entries 5–6 in Table 2). Moreover, the PMB-protected ketone **2** delivered parallel results with model aldehydes (see entries 7–10 in Table 2). Eventually, the *anti* configuration of the major diastereomer was confirmed through analysis of the spectroscopic data for **5e**[8c] and chemical correlation of aldol **8a**.[16]

Since structurally simple ketones **1** and **2** enable highly stereocontrolled reactions, we were interested in gaining insight into the bias imparted by related α-benzyloxy methyl ketones containing more bulky chains. Therefore, we tried the aldol reaction of ketones **3** and **4**[12] (see Fig. 1) with some representative aldehydes. The results are summarized in Table 3.

These results confirm that the titanium aldol chemistry optimized for lactate-derived ketones can be safely expanded to other

Table 2
$TiCl_3$(*i*-PrO)-Mediated aldol reaction of lactate-derived ketones **1** and **2**



1 PG: Bn **5** PG: Bn **6** PG: Bn
2 PG: PMB **8** PG: PMB **9** PG: PMB

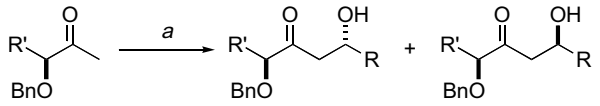
Entry	Ketone	PG	Aldehyde	R	dr (**5**:**6**)[a]	dr (**8**:**9**)[a]	Yield[b] (%)
1	**1**	Bn	**a**	*i*-Pr	85:15		77
2	**1**	Bn	**b**	*t*-Bu	93:7		72
3	**1**	Bn	**c**	*i*-Bu	85:15		76
4	**1**	Bn	**d**	Pr	80:20		67
5	**1**	Bn	**e**	Ph	83:17		66
6	**1**	Bn	**f**	$H_2C{=}C(CH_3)$	69:31		58
7	**2**	PMB	**a**	*i*-Pr		86:14	80
8	**2**	PMB	**c**	*i*-Bu		83:17	81
9	**2**	PMB	**e**	Ph		82:18	70
10	**2**	PMB	**f**	$H_2C{=}C(CH_3)$		75:25	65

[a] The diastereomeric ratio was established through NMR analysis of the reaction mixture.
[b] Isolated yield of the aldol mixture.

α-benzyloxy methyl ketones. Indeed, the diastereoselectivity and the yields achieved with ketones **3** and **4** are much better to that obtained from **1** and **2** (compare, for instance, the data corresponding to methacrolein in entries 6 and 10 in Table 2, and entries 3 and 6 in Table 3),[15,17] so, although a theoretical model is still elusive, the stereocontrol imparted by model ketones **1**–**4** can be used for coupling large fragments in advanced steps of a synthesis.

In summary, the titanium-mediated aldol reaction from chiral α-benzyloxy methyl ketones is highly sensitive to the titanium Lewis acid used in the enolization step. High yields and a remarkable 1,4-*anti* induction have been obtained for aliphatic, aromatic, and α,β-unsaturated aldehydes when the reaction is carried out with $TiCl_3$(*i*-PrO). Thus, the titanium-based methodology disclosed herein represents a new approach to the substrate-controlled acetate aldol reaction, which can be helpful to design more efficient synthesis.

Table 3
$TiCl_3$(*i*-PrO)-mediated aldol reaction of α-benzyloxy methyl ketones **3** and **4**



3 R': Bn **10** R': Bn **11** R': Bn
4 R': *i*-Bu **12** R': *i*-Bu **13** R': *i*-Bu

Entry	Ketone	R′	Aldehyde	R	dr (**10**:**11**)[a]	dr (**12**:**13**)[a]	Yield[b] (%)
1	**3**	Bn	**a**	*i*-Pr	85:15		92
2	**3**	Bn	**e**	Ph	88:12		96
3	**3**	Bn	**f**	$H_2C{=}C(CH_3)$	83:17		78
4	**4**	*i*-Bu	**a**	*i*-Pr		85:15	93
5	**4**	*i*-Bu	**e**	Ph		75:25	94
6	**4**	*i*-Bu	**f**	$H_2C{=}C(CH_3)$		81:19	85

[a] The diastereomeric ratio was established through NMR analysis of the reaction mixture.
[b] Isolated yield of the aldol mixture.

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14. *Typical experimental procedure*: Freshly distilled Ti(*i*-PrO)$_4$ (80 μL, 0.27 mmol) was added dropwise to a solution of $TiCl_4$ (90 μL, 0.82 mmol) in CH_2Cl_2 (1 mL) at 0 °C under N_2. The white mixture was stirred for 15 min at 0 °C and 10 min at room temperature. It was diluted with CH_2Cl_2 (1 mL), and the resulting colorless solution was added dropwise (it was rinsed with 2 × 0.5 mL) to a solution of **1** (178 mg, 1 mmol) in CH_2Cl_2 (2 mL) at −78 °C under N_2, followed by *i*-Pr_2NEt (0.19 mL, 1.1 mmol). The resulting dark red solution was stirred for 30 min at −78 °C. After the dropwise addition of the aldehyde (1.2 mmol), stirring was continued for 30 min at −78 °C. The reaction was quenched by the addition of saturated NH_4Cl (5 mL), diluted with Et_2O (80 mL) and washed with H_2O (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oil was analyzed by NMR and purified by flash chromatography (hexanes/EtOAc).
15. Unfortunately, the separation of aldol adducts by column chromatography turns out to be painful and they are isolated as a mixture of diastereomers.
16. The configuration of aldol **8a** was secured through conversion into (*S*) 5-hydroxy-6-methyl-3-heptanone, see: Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260.
17. The single exception of this trend has been observed for the aldol reaction of **4** and benzaldehyde (see entry 5 in Table 3). The reasons of the low diastereoselectivity (dr 75:25) obtained in this case are still unclear and warrants further investigation on the structural issues that determine the stereochemical outcome of such transformations.