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1,4-*syn*-Asymmetric induction in the titanium-mediated aldol reactions of chiral methyl α-silyloxy ketones

Adriana Lorente, Miquel Pellicena, Pedro Romea *, Fèlix Urpí *

Departament de Química Orgànica, Universitat de Barcelona, Martí i Franqués 1-11, 08028 Barcelona, Catalonia, Spain

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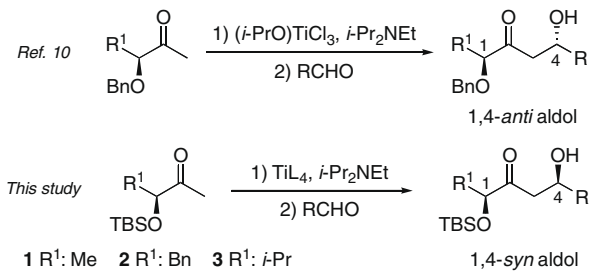
ABSTRACT

Good levels of 1,4-*syn* asymmetric induction are obtained in the $TiCl_4$-mediated aldol reaction of methyl α-silyloxy 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 syntheses of natural products.

In spite of the large number of highly stereoselective aldol methodologies[1] developed during the last decades and their successful application to the synthesis of natural products,[2] the *acetate* aldol reaction[3] is still a matter of concern.[1,4] Indeed, the lack of mechanistic models to understand the stereochemical outcome of these reactions[5,6] makes it difficult to use them for coupling large fragments in advanced steps of a synthesis.[7] Particularly, it is remarkable to note the scarce number of studies on aldol reactions from protected α-hydroxy methyl ketones.[8,9] In this context, we established that the titanium-mediated aldol reactions of chiral α-benzyloxy methyl ketones provide the corresponding 1,4-*anti* adducts in good yields and diastereomeric ratios.[10] More recently, Kalesse and co-workers reported that the enol borinates and the alkaline enolates from related α-silyloxy ketones show the same 1,4-*anti* asymmetric induction.[11,12] Thus, considering the importance of this transformation and taking advantage of our experience with chiral ethyl α-hydroxy ketones,[13] we envisaged that the appropriate choice of the titanium(IV) Lewis acid and the hydroxyl protecting group might give access to 1,4-*syn*-selective aldol reactions. Herein, we document that α-*tert*-butyldimethylsilyloxy methyl ketones **1–3** represented in Scheme 1 impart such asymmetric induction, which can be useful to design more flexible syntheses of structurally complex natural products.

At first, we surveyed the influence of the titanium Lewis acid on the stereochemical outcome of the aldol reactions from lactate-derived ketone **1**[14] and isobutyraldehyde (**a**). Disappointingly, preliminary experiments with mild $(i\text{-PrO})_2TiCl_2$ and $(i\text{-PrO})TiCl_3$ Lewis acids furnished low yields of the desired 1,4-*syn* aldol **4a**. Indeed, the experimental conditions optimized for related ethyl ketones[13c] afforded aldol **7** as the major component of the reaction mixtures (see entries 1 and 2 in Table 1). Such unexpected results suggest that the enolization step is slow enough to allow the resulting enolate to attack the activated ketone and deliver the self-condensation adduct **7**. Even the stronger $TiCl_4$ produced a significant amount of this adduct at −78 °C (see entry 3 in Table 1). Lowering the enolization temperature to −94 °C increased the overall yield (71%) of aldols **4** and **5** (1,4-*syn* and 1,4-*anti*, respectively) and minimized the formation of **7** (see entry 4 in Table 1).[15] However, it was then clear that tiny amounts of hemiacetal **6a** were also formed during the aldol reaction and could be isolated after chromatographic purification as a single diastereomer. Hence, assuming that **6a** arises from **4a**, the



Scheme 1. Asymmetric induction in titanium-mediated aldol reactions from chiral α-hydroxy methyl ketones.

* Corresponding authors. Tel.: +34 934039106; fax: +34 933397878 (P.R.); tel.: +34 934021247; fax: +34 933397878 (F.U.).
E-mail addresses: pedro.romea@ub.edu (P. Romea), felix.urpi@ub.edu (F. Urpí).

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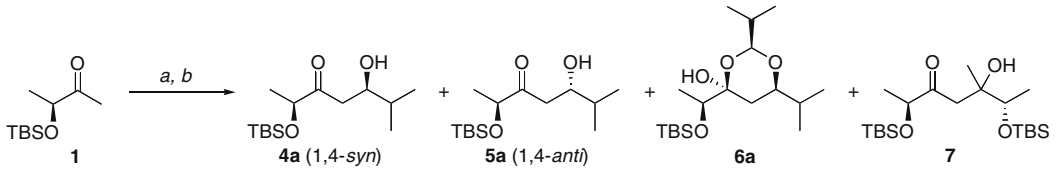
Table 1
Influence of the titanium Lewis acid on the aldol reaction of ketone **1** with isobutyraldehyde (**a**)



a) 1.1 eq TiL_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, T_{enol}, 30 min. *b)* 1.5 eq *i*-PrCHO (**a**), –78 °C, 30 min

Entry	TiL_4	T_{enol} (°C)	Yield **7**[a] (%)	Yield **6a**[a] (%)	Yield **4a** and **5a**[a] (%)	dr (**4a+6a**:**5a**)[b]
1	(*i*-PrO)$_2TiCl_2$	–78	68	—	5	75:25
2	(*i*-PrO)$TiCl_3$	–78	29	nd[c]	27	76:24
3	$TiCl_4$	–78	15	nd[c]	65	74:26
4	$TiCl_4$	–94	—	5	71	77:23

[a] Isolated yield.
[b] Determined by ^1H NMR analysis on isolated products.
[c] Not determined.

diastereoselectivity on the formation of **4a** was established as dr 77:23 (see entry 4 in Table 1).

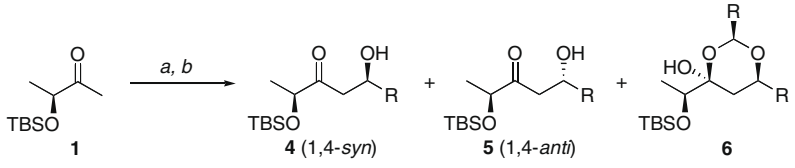
This optimized experimental procedure[16] was next applied to other aliphatic, aromatic, and α,β-unsaturated aldehydes. The results summarized in Table 2 prove that the $TiCl_4$-mediated aldol reactions of lactate-derived ketone **1** with aliphatic aldehydes **a–e** are fairly diastereoselective. Indeed, the desired 1,4-*syn* aldols **4** were isolated in good yields and diastereomeric ratios were close to 80:20 irrespective of the steric hindrance and the presence of other functional groups on the aldehyde (see entries 1–5 in Table 2). Interestingly, significant amounts of hemiacetals **6b** and **6c** from isovaleraldehyde and butanal (**b** and **c**, respectively, see entries 2 and 3 in Table 2) were isolated after chromatographic purification, but the corresponding hemiacetals from related aldehydes **d** and **e** were never observed (see entries 4 and 5 in Table 2). Conjugated aldehydes did not form such kind of hemiacetals either (see entries 6 and 7 in Table 2). Unfortunately, the diastereoselectivity for these aldehydes was rather poor, being particularly low with benzaldehyde (dr 55:45, see entry 6 in Table 2).

Having established the feasibility of this substrate-controlled methodology on lactate-derived ketone **1**, we were interested in gaining insight into the bias imparted by other α-silyloxy ketones containing more bulky chains. Hence, we studied the aldol reaction of methyl ketones **2** and **3**[14] (see Scheme 1) with some representative aldehydes as isobutyraldehyde (**a**), benzaldehyde (**f**), and methacrolein (**g**). The results are summarized in Table 3. Importantly, the potential hemiacetal from isobutyraldehyde was never observed and aldols **8–11** were isolated in excellent yields. On the other hand, the diastereoselectivity of these reactions turned out to be highly sensitive to the steric hindrance of the R^1 chain in such a way that the most bulky group produced the best diastereomeric ratios. Actually, aldol reactions from lactate- and phenylalanine-derived ketones (**1** and **2**, respectively) with isobutyraldehyde and methacrolein afford the same diastereoselectivities (compare entries 1 and 7 in Table 2 with entries 1 and 3 in Table 3), while the more bulky valine-derived ketone **3** produced a significant improvement on the corresponding diastereomeric ratios (see entries 4 and 6 in Table 3). In turn, benzaldehyde shows a closer dependence on the R^1 group and its diastereomeric ratios increase steadily from **1** to **3** (compare entry 6 in Table 2 with entries 2 and 5 in Table 3).

The 1,4-*syn* asymmetric induction provided by these ketones was initially proved by conversion of aldol **4a** into (*R*)-3-hydroxy-4-methylpentanoic acid (see Eq. 1 in Scheme 2). Later, the same strategy was applied to aldols **10a** and **10f** obtained from the aldol reactions of ketone **3** with isobutyraldehyde (**a**) and benzaldehyde (**f**), respectively (see Eq. 2 in Scheme 2).

The asymmetric induction imparted by the titanium enolates of the α-*tert*-butyldimethylsilyloxy methyl ketones **1–3** can be

Table 2
Titanium-mediated aldol reaction from lactate-derived ketone **1**

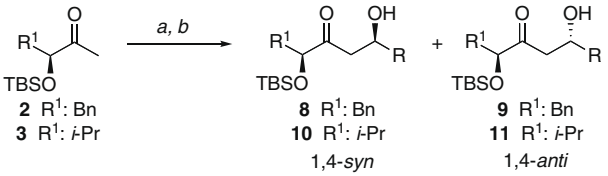


a) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –94 °C, 30 min. *b)* 1.5 eq RCHO, –78 °C, 30 min

Entry	Aldehyde	R	Yield **6**[a] (%)	Yield **4** and **5**[a] (%)	dr (**4+6**:**5**)
1	**a**	*i*-Pr	5	71	77:23[b]
2	**b**	*i*-Bu	19	63	76:24[b]
3	**c**	Pr	18	65	76:24[b]
4	**d**	CH_2CH_2OTIPS	—	72	77:23[c]
5	**e**	CH_2CH_2NPhth	—	68	80:20[c]
6	**f**	Ph	—	75	55:45[c]
7	**g**	$C(CH_3)=CH_2$	—	80	65:35[c]

[a] Overall isolated yield.
[b] Determined by ^1H NMR analysis on isolated products.
[c] Determined by ^1H NMR analysis of the reaction mixture.

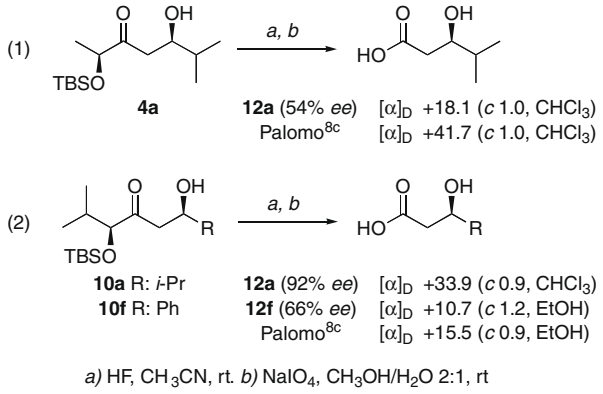
Table 3
Titanium-mediated aldol reactions from ketones **2** and **3**



a) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –94 °C, 30 min. *b)* 1.5 eq RCHO, –78 °C, 30 min

Entry	Ketone	R^1	Aldehyde	R	dr (**8**:**9**)[a]	dr (**10**:**11**)[a]	Yield[b] (%)
1	**2**	Bn	**a**	*i*-Pr	77:23		95
2	**2**	Bn	**f**	Ph	75:25		94
3	**2**	Bn	**g**	$C(CH_3)=CH_2$	68:32		93
4	**3**	*i*-Pr	**a**	*i*-Pr		96:4	85
5	**3**	*i*-Pr	**f**	Ph		83:17	84
6	**3**	*i*-Pr	**g**	$C(CH_3)=CH_2$		90:10	83

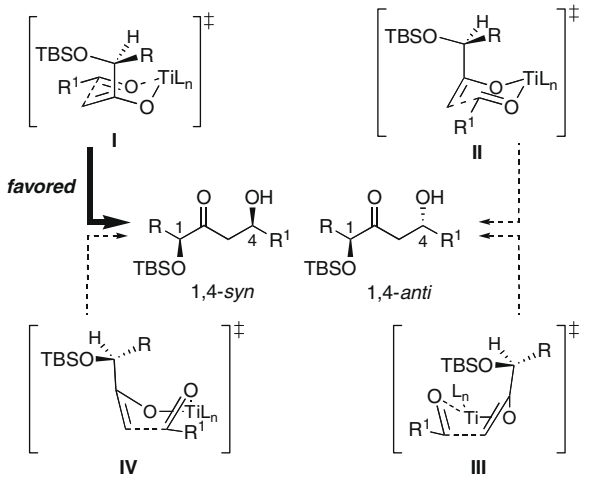
[a] Determined by ^1H NMR analysis of the reaction mixture.
[b] Overall isolated yield of aldols **8**–**9** or **10**–**11**.



a) HF, CH_3CN, rt. *b)* $NaIO_4$, CH_3OH/H_2O 2:1, rt

Scheme 2. Proof of the 1,4-*syn* asymmetric induction.

rationalized invoking the six-membered chair-like transition state **I** represented in Scheme 3. In such scenario, the antiperiplanar distribution of both TBSO–C and C–OTi bonds would act as the key element that determines the configuration of the major 1,4-*syn* diastereomer since the preferred transition state places the less sterically demanding substituent (H vs Me, Bn, *i*-Pr) of the α-stereocenter pointing toward the inside of the ring (compare transition states **I** and **II** in Scheme 3). We are aware that other boat-like transition states (as **III** and **IV** in Scheme 3) might also be suggested to explain the stereochemical outcome of such *acetate* aldol reactions. However, transition state **IV** leading to 1,4-*syn* diastereomers should be particularly irrelevant for the most hindered ketone **3**. Hence, these boat-like transition states probably do not play a significant role in the titanium-mediated aldol reactions of the aforementioned α-silyloxy ketones **1**–**3**.[17]



Scheme 3. Transition states for acetate aldol reactions from chiral α-*tert*-butyldimethylsilyloxy methyl ketones.

In summary, the substrate-controlled titanium-mediated aldol reactions from chiral α-*tert*-butyldimethylsilyloxy methyl ketones with aliphatic, aromatic, and α,β-unsaturated aldehydes furnish the corresponding 1,4-*syn* aldols in high yields. Remarkably, the diastereoselectivity is very sensitive to the steric hindrance of the starting ketone, particularly important being the stereochemical control achieved with the valine-derived ketone **3**. In any case, these results complement the 1,4-*anti* asymmetric induction observed for related α-benzyloxy methyl ketones[10] and can be helpful to design more efficient syntheses of natural products.

Acknowledgments

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15. The aldol reaction was also carried out at −94 °C. However, it turned out to be too sluggish and required longer reaction times.
16. *Typical procedure*: $TiCl_4$ (120 μL, 1.1 mmol) was added dropwise to a solution of methyl ketone **1** (202 mg, 1 mmol) in CH_2Cl_2 (5 mL) at −94 °C under N_2, followed by *i*-Pr_2NEt (190 μL, 1.1 mmol). The resulting dark red solution was stirred for 30 min at −94 °C. After dropwise addition of the aldehyde (1.5 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 (50 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).
17. At this point, it is worth mentioning that the boron-mediated aldol reactions from mandelic-derived tert-butyldimethylsilyloxy methyl ketone provided a roughly equimolar mixture of two diastereomeric aldol adducts, which was assumed to be due to the competition between two boat-like transition states, see: Masamune, S.; Sato, T.; Kim, B.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279–8281. Therefore, it is clear the crucial role of the metal on the transition states and the stereochemical outcome of such reactions.