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Highly Stereoselective Aldol Reactions of Titanium Enolates from Ethyl α-Silyloxyalkyl Ketones

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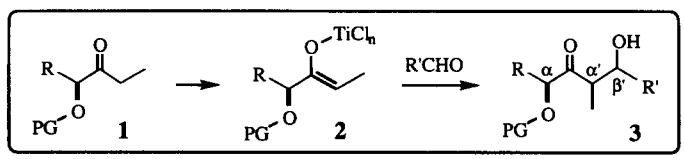
Abstract: Aldol-like reactions of titanium enolates derived from α-OH, α-OBn, and α-OTBS ketones with a series of aldehydes have been studied. In sharp contrast to the *O*-benzyl derivatives, the TBS-protected ketones lead to excellent yields and selectivities (*syn-syn/anti-syn* ratios from 30:1 to >95:1) even for the lactate-derived substrate (2-*tert*-butyldimethylsilyloxy-3-pentanone).

Chiral enolates derived from α- and β-hydroxy ketones have proved to be very useful in acyclic stereocontrol and for the assembly of polypropionate-like natural products[1] since the effect of the enolisation conditions and protecting groups on the stereochemical outcome of the aldol-like reactions was established.[1–3]

Regarding the asymmetric aldol reactions involving *titanium enolates generated directly from α-hydroxy ketones* (**1** → **2**), there is only one example, described by Evans et al.:[4] that of **2** (in which R = cyclohexyl and PG = TBS = Bu^tMe_2Si) with PhCHO. The selectivity noted in this case is implicitly associated to the large bulk of R. Since, as shown in the preceding communication,[5] we had disclosed an easy route to compounds of general formula **1**, we decided to study in depth the reactions of their titanium enolates with a few representative aldehydes. To our surprise, we have observed that **any titanium enolate of type 1z**, ie when PG = TBS, but not those of type **1y**, **afford aldols with high diastereoselectivity**. We also account here for a plausible cause of these differences.

Scheme 1



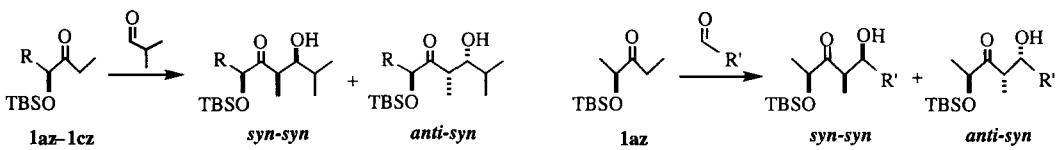
a, R = CH_3 **x**, PG = H
b, R = CH_2Ph = Bn **y**, PG = Bn
c, R = $CH(CH_3)_2$ **z**, PG = TBS

We have first checked the aldol reaction of α-hydroxy ketones *without any protecting group* (type **1x**). Luke and Morris have reported[3b] that the titanium-mediated reaction of a β-hydroxy ketone, (*S*)-1-hydroxy-2-methyl-3-pentanone, with isobutyraldehyde, $(CH_3)_2CHCHO$, gives the *syn-syn* aldol in excellent yield and with an acceptable diastereoselectivity (88:12). However, we have been unable to extend this reaction to α-hydroxy ketones. In fact, in all attempted cases we have obtained low yields and erratic stereoselectivities.

We have achieved better results with *O-benzyl-protected* ketones (**1ay**, **1by**, and **1cy**). Thus, by using the enolisation conditions described by Evans et al.[4] and isobutyraldehyde as the aldehyde, the yields could be improved (62–88%). Nevertheless, the diastereoselectivities were disappointing: a 5:1 *syn(α,α')-syn(α',β')/anti-syn* ratio of **3ay**, R' = isopropyl, from **1ay**; a 4:1 ratio of **3by**, R' = isopropyl, from **1by**; and a 1:1 ratio of **3cy**, R' = isopropyl, from **1cy**.

As this trend could rely upon the well-known coordinating ability of alkoxy (ether) groups, we have focused our attention *on the TBS group*, since the strength of silyl ethers as Lewis bases is generally assumed to be lower.[5,6] In this way we have obtained high yields and stereoselectivities in favour of the *syn-syn* isomers of **3**[7] from the titanium enolates of α-OTBS ketones **1az**, **1bz**, and **1cz** with isobutyraldehyde (see Table 1, left side); moreover, from **1az** and other three types of aldehydes excellent results are also reached (Table 1, right side). Apparently, the stereoselectivity of these aldol reactions depends only moderately on the R chain, as the *syn-syn* adducts predominate in all cases.

Table 1. Ti-mediated aldol reactions of **1az–1cz** with isobutyraldehyde and of **1az** with other aldehydes[a]



ketone	*yield*[b]	*syn-syn/anti-syn*[c]
1az	**90%**	**30 : 1**
1bz	**85%**	**35 : 1**
1cz	**70%**	**> 95 : 1**

R'	*yield*[b]	*syn-syn/anti-syn*[c]
$CH_2CH_2CH_3$	**85%**	ca. **30 : 1**[d]
$C(CH_3)=CH_2$	**86%**	**45 : 1**
Ph	**90%**	**50 : 1**

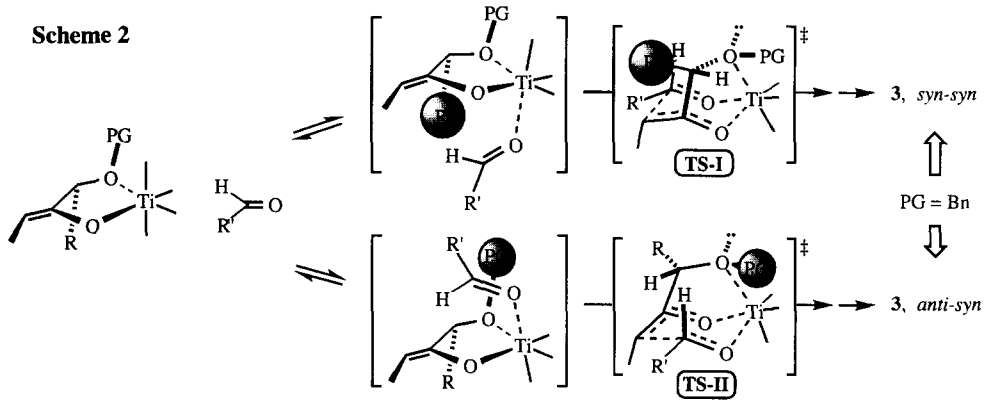
[a] 1 mmol of ketone (0.2 M), 1.1 equiv $TiCl_4$, 1.1 equiv $EtPr^i_2N$ (DIPEA), –78 °C, 1.5 h; addition of 1.5 equiv of aldehyde; stirring at –78 °C for 1–2 h; work-up as in ref. 4. [b] Isolated yield (column chromatography) of the aldol mixture. [c] From 500 MHz ^1H NMR spectra and GC analyses; see ref. 8. [d] This ratio could not be exactly established (partial overlap).

The remarkable stereoselectivity differences between the α-OBn and α-OTBS cases, as well as the fact that the more crowded substrates (R = isopropyl, ie **1cy** and **1cz**) give rise to the lowest selectivity in the former case and the highest in the latter, suggest different transition states.

Our explanation is that when PG = Bn, as the titanium chelate is expected to predominate largely in the equilibrium,[6] the reaction takes chiefly place through this chelate, in which R and Bn are placed in *trans* position.[9] Two main pathways may be then involved (see Scheme 2): in the first one, with the aldehyde

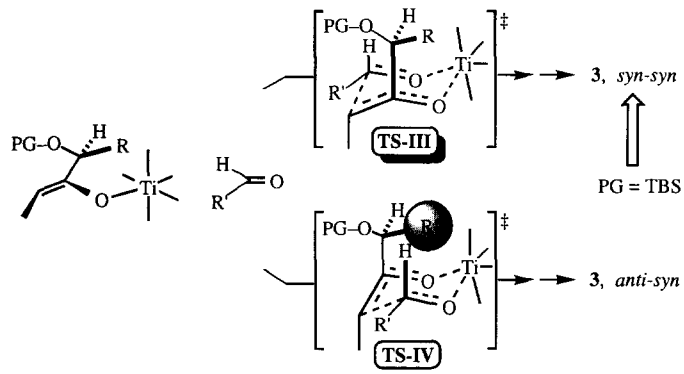
approaching to the chelate from the bottom, steric interactions between the aldehyde and Bn are avoided, but transition state **TS-I** may be seriously disfavoured when the bulk of R increases; in the second approach and in **TS-II**, the steric interactions may be just the opposite. This explains the above-mentioned decrease of diastereoselectivity showed by the *O*-benzyl-protected ketones in going from **1ay** to **1cy**.

Scheme 2



On the other hand, in the α-OTBS case, since the 5-membered chelate is likely not so abundant in the equilibrium,[5,10] the non-chelated transition states should also be taken into account. Our results may be rationalised if the standard 6-membered TS,[4,11] **TS-III**, is favoured over **TS-IV** (as expected, see Scheme 3), as well as in relation to the more crowded bicyclic systems, especially when R and R' become bulkier.

Scheme 3



In summary, the titanium-mediated aldol reactions of ketones **1** proceed in high yields and with high stereoselectivities (which are rather independent of the R and R' chains) if they are protected with TBS. This is not the case for the Bn-protected analogues. The differences are rationalised on the basis of TS models that take into account the known, distinct chelating abilities of the two series. Further studies are in progress.

Acknowledgments

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7. Selected data for **3az**, R' = isopropyl: $[\alpha]_D$ +24.7 (*c* 0.89, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.19 (q, *J* 7.0, 1 H), 3.42 (dd, *J* 8.8, *J* 2.4, 1 H), 3.32 (qd, *J* 7.2, *J* 2.4, 1 H), 1.67 (m, 1 H), 1.32 (d, *J* 7.0, 3 H), 1.11 (d, *J* 7.2, 3 H), 1.00 (d, *J* 6.6, 3 H), 0.90 (s, 9 H), 0.82 (d, *J* 6.8, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 219.7, 76.0, 74.6, 41.3, 30.4, 25.7, 21.4, 19.4, 18.8, 18.0, 9.4, –4.7, –5.0. For **3az**, R' = propyl: $[\alpha]_D$ +9.1 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.19 (q, *J* 6.9, 1 H), 3.82 (m, 1 H), 3.10 (qd, *J* 7.2, *J* 2.8, 1 H), 1.55–1.40 (m, 2 H), 1.35–1.22 (m, 2 H), 1.31 (d, *J* 6.9, 3 H), 1.11 (d, *J* 7.2, 3 H), 0.91 (t, *J* 7.2, 3 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 219.1, 74.5, 70.6, 44.1, 36.1, 25.7, 21.3, 19.2, 18.0, 14.0, 9.9, –4.7, –5.0. For **3az**, R' = propen-2-yl: $[\alpha]_D$ +12.4 (*c* 0.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.10 (m, 1 H), 4.94 (m, 1 H), 4.21 (q, *J* 6.9, 1 H), 3.30 (qd, *J* 7.2, *J* 2.8, 1 H), 1.67 (m, 3 H), 1.28 (d, *J* 6.9, 3 H), 1.06 (d, *J* 7.2, 3 H), 0.91 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 219.2, 143.2, 111.8, 74.6, 73.2, 41.8, 25.7, 21.3, 19.6, 18.0, 9.6, –4.6, –5.0. For **3az**, R' = phenyl: $[\alpha]_D$ +4.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 4 H), 7.23 (m, 1 H), 5.03 (d, *J* 3.7, 1 H), 4.14 (q, *J* 6.9, 1 H), 3.37 (qd, *J* 7.2, *J* 3.7, 1 H), 1.27 (d, *J* 6.9, 3 H), 1.05 (d, *J* 7.2, 3 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 218.7, 141.7, 128.2, 127.2, 125.9, 74.6, 72.8, 46.9, 25.7, 21.0, 18.0, 10.4, –4.7, –5.0.
8. Stereochemical assignments for cases **3az**, **3bz**, and **3cz** (all, R' = isopropyl) as well as for **3az**, R' = Ph, according to the procedure of Heathcock et al. (ref. 2a): deprotection of the benzyl group (H_2, Pd/C, EtOH, overnight, rt) or TBS group (48% HF, CH_3CN, rt) yield dihydroxy ketones which were oxidized ($NaIO_4$) to known β-hidroxy acids. After hydrogenation, compound **3az**, R' = propen-2-yl, gave the same stereoisomer as **3az**, R' = isopropyl.
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