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Highly Stereoselective Aldol Reaction Based on Titanium Enolates from (*S*)-1-Benzyloxy-2-methyl-3-pentanone

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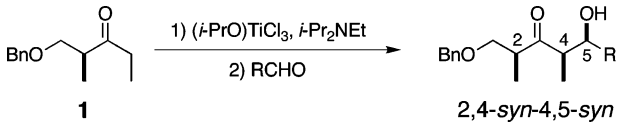


1 2,4-*syn*-4,5-*syn*

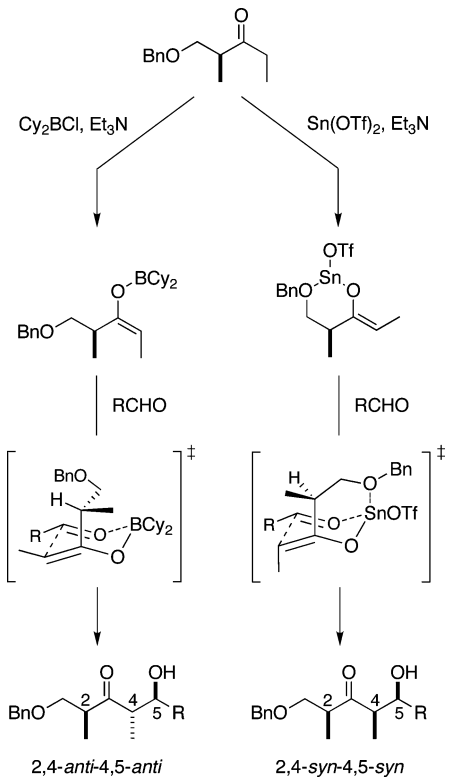
Alternative titanium-mediated aldol procedures based on several protected β-hydroxy ethyl ketones have been surveyed. Eventually, enolization of (*S*)-1-benzyloxy-2-methyl-3-pentanone (**1**) with (*i*-PrO)TiCl$_3$/*i*-Pr$_2$NEt provided a very reactive enolate that afforded the corresponding 2,4-*syn*-4,5-*syn* aldol adducts in high yields and diastereomeric ratios with a broad range of aldehydes

Despite the tremendous accomplishments achieved during the last two decades in the asymmetric aldol arena, there is still an ongoing pursuit of more efficient procedures to prepare optically active β-hydroxy carbonyl compounds.[1] Indeed, new catalytic methodologies are currently challenging classical approaches based on chiral auxiliaries.[1,2] However, traditional substrate-controlled aldol reactions, which rely upon the stereochemical bias imparted by chiral ketones or aldehydes, still hold a prominent position and are widely considered as one of the most powerful strategies to the stereoselective construction of polypropionate-like natural products.[3,4]

Particularly, much attention has been paid to chiral β-hydroxy ketones because the resulting aldol adducts can be easily incorporated into the molecular architecture.[4,5] In this context, enantiomerically pure 1-benzyloxy-2-methyl-3-pentanone, easily prepared from Roche ester, is arguably the most outstanding representative of such systems. This chiral ethyl ketone, introduced and mastered by Paterson,[4,6] gives access to several stereochemical arrays and has been successfully used in the synthesis of many natural products.[7] Thus, boron enolate shown in Scheme 1 provides 2,4-*anti*-4,5-*anti* aldols through a transition state that avoids lone pair repulsions between the enolate oxygen and that of the benzyl ether.[6b] Alternatively, tin(II) enolate takes advantage of the coordinating ability of benzyloxy group and affords stereoselectively the corresponding 2,4-*syn*-4,5-*syn* counterparts through a chelated transition state.[6c]

Regardless of the high levels of diastereocontrol achieved in the above-mentioned tin-based aldol reactions, the involvement of tin(II) triflate means a serious drawback

SCHEME 1



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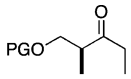
for this methodology because of the expense and operational complexity associated to this Lewis acid. Surprisingly, parallel titanium chemistry[5a,b] has been scarcely explored, and just a few examples, mainly concerned with matched cases in the double stereodifferentiating processes, have been reported.[8,9] Given our experience in titanium-mediated aldol reactions based on chiral α-hydroxy ketones,[10] we envisaged that the appropriate choice of titanium Lewis acid and hydroxyl-protecting group might trigger a stereoselective aldol process. Therefore, we surveyed alternative enolization conditions of β-hydroxy ketones **1**−**3** with different protecting groups such as Bn, PMB, or TBDPS.[11]



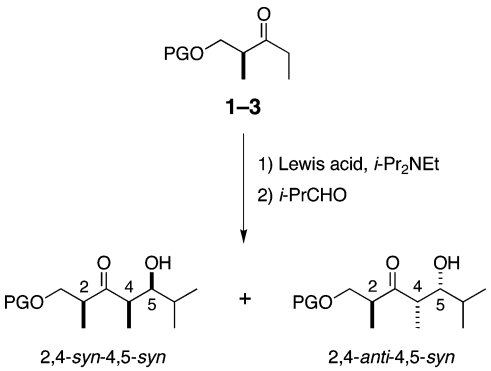
1 PG = Bn **2** PG = PMB **3** PG = TBDPS

Preliminary experiments with isobutyraldehyde showed that the $TiCl_4$-mediated aldol reaction based on ketone **1** afforded the corresponding 2,4-*syn*-4,5-*syn* adduct (***SS***) in good yield but nonsynthetic useful diastereomeric ratio (see entry 1 in Table 1). Otherwise, we were pleased to observe that diastereoselectivity is dramatically improved by addition of a second equivalent of $TiCl_4$ to the reacting mixture, or even better, when a softer Lewis acid as (*i*-PrO)$TiCl_3$ is employed (see entries 2 and 3 in Table 1). Most importantly, the yield and the diastereomeric ratio are both remarkably high and match those obtained with tin chemistry. In the case of β-OPMB ketone **2**, the less robust protecting group precluded the use of a powerful titanium Lewis acid as $TiCl_4$,[12] but it was possible to carry out the enolization with (*i*-PrO)$TiCl_3$, which provided similar yield and stereocontrol than ketone **1** (compare entries 3 and 4 in Table 1). Eventually, the less satisfactory results obtained in the case of β-OTBDPS ketone **3** (see entries 5−7 in Table 1) clearly prove that a β-chelating protecting group is required to control the stereochemical outcome of the process.

Following a short evaluation of the reaction times, the (*i*-PrO)$TiCl_3$ procedure based on ketone **1** was applied to a representative range of aldehydes. In all cases, high 4,5-*syn* aldol selectivity was observed (4,5-*anti* aldol adducts accounted for ≤2% of the product). Moreover, the 2,4-*syn*-4,5-*syn* diastereomer **4** was formed preferentially irrespective of the aldehyde with a *dr* higher than 93:7. Finally, purification of the reaction mixture through column chromatography permitted us to isolate *syn* aldols in 87−95% yields. The results are summarized in Table 2.

At this point, the stereochemistry of aldols **4c**, **4e**, and **4f** was secured by comparison with the physical and

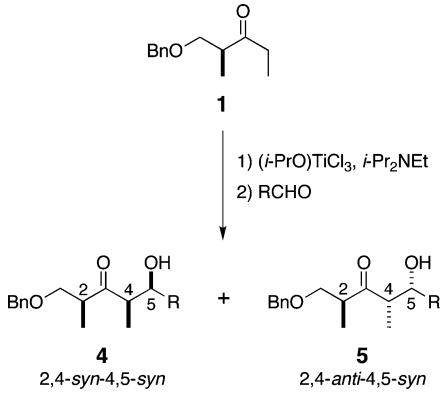
TABLE 1. Titanium-Mediated Aldol Reactions Based on Ketones 1−3 with Isobutyraldehyde



entry	ketone (PG)	Lewis acid	dr (***SS***:***AS***)	yield[a] (%)
1	**1** (Bn)	$TiCl_4$	77:23[b]	95
2	**1** (Bn)	$TiCl_4$ (2 eq)	95:5[b]	88
3	**1** (Bn)	(*i*-PrO)$TiCl_3$	97:3[b]	93
4	**2** (PMB)	(*i*-PrO)$TiCl_3$	95:5[b]	88
5	**3** (TBDPS)	$TiCl_4$	70:30[c]	95
6	**3** (TBDPS)	$TiCl_4$ (2 eq)	80:20[c]	90
7	**3** (TBDPS)	(*i*-PrO)$TiCl_3$	80:20[c]	65[d]

[a] Overall isolated yield. [b] Determined by HPLC. [c] Determined by ^{1}H NMR (400 MHz). [d] 30% of ketone **3** was recovered.

TABLE 2. (*i*-PrO)$TiCl_3$-Mediated Aldol Reactions of Ketone 1 with Achiral Aldehydes



entry	R	aldehyde	dr[a] (**4**:**5**)	yield (%)
1	*i*-Pr	**a**	97:3	95[b]
2	*i*-Bu	**b**	94:6	95[b]
3	Et	**c**	93:7	88[b]
4	Ph	**d**	94:6	87[c]
5	$H_2C{=}C(CH_3)$	**e**	97:3	91[b]
6	(*E*) $CH_3CH{=}CH$	**f**	96:4	93[b]

[a] Determined by HPLC. [b] Overall isolated yield. [c] Isolated yield of **4**.

(8) To the best of our knowledge, there is just a single mention of a $TiCl_4$-mediated aldol reaction of ketone **1** with an achiral aldehyde. In the case of methacrolein, Paterson reported a 62:38 mixture of the corresponding 2,4-*syn*-4,5-*syn* and 2,4-*anti*-4,5-*syn* aldols (see footnote 11 in ref 6c). Similarly, Morris described that $TiCl_4$-mediated aldol reaction of (*S*)-1-hydroxy-2-methyl-3-pentanone with isobutyraldehyde produces 2,4-*syn*-4,5-*syn* aldol in 92% yield and 88:12 diastereoselectivity. See: Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013−3019.

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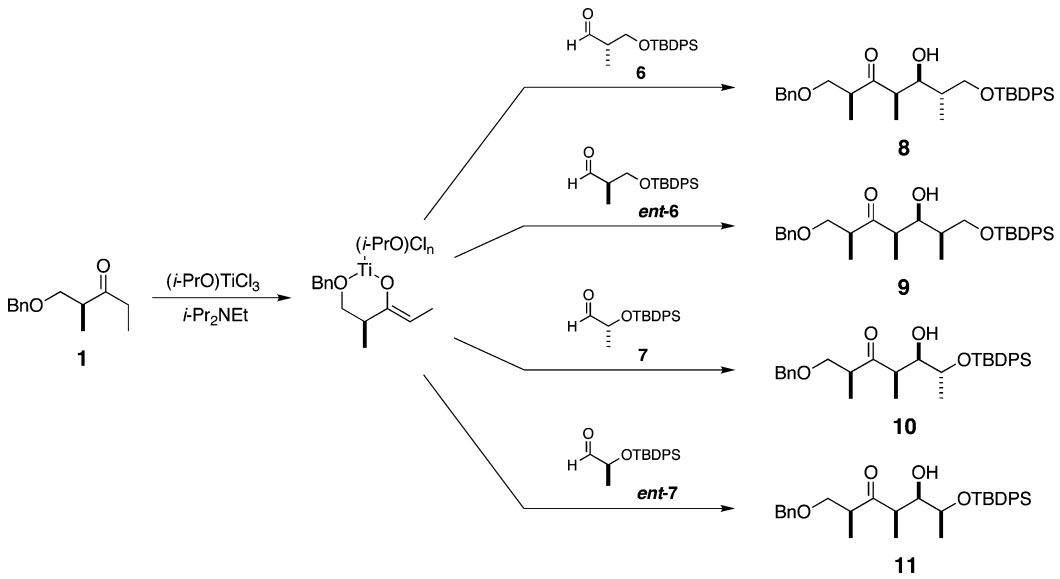
TABLE 3. (*i*-PrO)TiCl$_3$-Mediated Aldol Reactions of Ketone 1 with Chiral Aldehydes



entry	aldehyde	dr[a]	major diastereomer	yield (%)[b]
1	**6**	>97:3	**8**	88
2	*ent*-**6**	94:6	**9**	92
3	**7**	72:28	**10**	90
4	*ent*-**7**	>97:3	**11**	95
5[c]	*ent*-**7**	>97:3	**11**	87

[a] Determined by HPLC. [b] Overall isolated yield. [c] 1.1 equiv of aldehyde was used; reaction time was 1 h.

spectroscopic data already reported in the literature. Furthermore, catalytic hydrogenation of aldols **4a** and **4e** yielded quantitatively the same ketodiol, which guarantees the 2,4-*syn*-4,5-*syn* configuration of aldol **4a** (see Supporting Information).

The high diastereoselectivity achieved with achiral aldehydes prompted us to challenge the synthetic potentiality of the above-mentioned methodology in double stereodifferentiating processes[13] involving chiral aldehydes **6** (and ***ent-6***)[14] and **7** (and ***ent-7***)[15] represented below. The results summarized in Table 3 show that most reactions are highly stereoselective, which confirms the remarkable stereocontrol exerted by (*i*-PrO)TiCl$_3$ enolate from ketone **1**. As expected, the less selective pair concerns the more demanding (*R*) lactate-derived aldehyde **7**, which gives the mismatched anti*Felkin* adduct **10** in a rather disappointing diastereomeric ratio (72:28).[16,17] With the exception of this case, these double stereodifferentiating aldol reactions give access to a wide array of enantiopure intermediates useful for stereoselective syntheses.[18] Finally, it is worth mentioning that this aldol reaction can be carried out using 1.1 equiv of aldehyde with similar results (compare entries 4 and 5 in Table 3).

Although the mechanistic details of this reaction are still poorly understood, the reported results closely resemble those arising from α-hydroxy ketones.[10] The stereochemical outcome of the process is consistent with a selective formation of a *Z*-enolate and addition to the aldehyde through a chelating chair transition state. Furthermore, the impact of the titanium Lewis acid used in the enolization step on the stereochemical outcome of the aldol reaction is once more noteworthy, which clearly proves that choice of ligands must be carefully evaluated. As a matter of fact, the incorporation of different ligands in the titanium(IV) not only tunes its acidity but also affects the structure of the enolate complex and has a dramatic influence on the aldol transition state (Scheme 2).

In summary, we have demonstrated that enolization of (*S*)-1-benzyloxy-2-methyl-3-pentanone, the Paterson well-known dipropionate equivalent, with (*i*-PrO)TiCl$_3$/*i*-Pr$_2$NEt permits highly stereoselective aldol reactions in excellent yields with a broad range of achiral and chiral aldehydes. The reported methodology is simple and practical and might be applied to other *β*-chelating O-protecting groups. Investigations along this line are currently underway in our laboratory.

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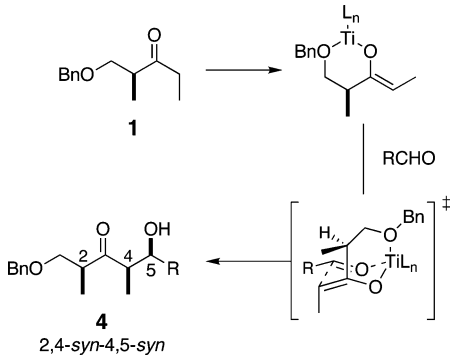
SCHEME 2



Experimental Section

General (*i*-PrO)$TiCl_3$-Mediated Aldol Procedure. Freshly distilled (*i*-PrO)$_4$Ti (83 μL, 0.28 mmol) was added dropwise to a solution of $TiCl_4$ (92 μL, 0.84 mmol) in CH_2Cl_2 (1 mL) at 0 °C under N_2. The mixture was stirred for 10 min at 0 °C and 10 min at room temperature and diluted with CH_2Cl_2 (1 mL), and the resulting colorless solution was added via cannula or syringe (2 × 0.5 mL) to a solution of **1** (206 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) at −78 °C under N_2 (alternatively, a stock solution of 0.55 M (*i*-PrO)$TiCl_3$ in CH_2Cl_2 (2 mL, 1.1 mmol) was added dropwise to a solution of **1** (206 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) at −78 °C under N_2). The pale yellow solution was stirred for 2 min, and *i*-Pr_2NEt (190 μL, 1.1 mmol) was added dropwise. The resulting orange-red solution was stirred for 30 min at −78 °C, and 1.5 equiv of aldehyde were added. After 30−40 min at −78 °C the reaction was quenched by addition of saturated NH_4Cl (5 mL) and vigorously stirred at room temperature. The mixture was diluted with Et_2O and washed with H_2O, saturated $NaHCO_3$, and brine. The aqueous layers were extracted with Et_2O, and the combined extracts were dried ($MgSO_4$) and concentrated. The resulting oil was analyzed by HPLC and purified by flash chromatography on silica gel (hexanes/EtOAc or CH_2Cl_2).

(2*S*,4*R*,5*S*)-1-Benzyloxy-5-hydroxy-2,4,6-trimethyl-3-heptanone (4a): colorless oil. R_f (hexanes/EtOAc 85:15) = 0.2; HPLC (hexanes/*i*-PrOH 99.5:0.5) t_R = 18.1 min; $[\alpha]_D$ +25.4 (*c* 2.22, $CHCl_3$) [lit.[6c] ***ent*-4a** $[\alpha]_D$ −26.1 (*c* 3.2, $CHCl_3$)]; IR (film): υ 3511, 3032, 2964, 2936, 1706, 1456, 1373, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.26 (5H, m), 4.47 (1H, AB system, J = 11.9), 4.44 (1H, AB system, J = 11.9), 3.64 (1H, t, J = 8.8), 3.61 (1H, dd, J = 9.0, J = 2.3), 3.46 (1H, dd, J = 8.8, J = 4.9), 3.21−3.12 (1H, m), 2.85 (1H, qd, J = 7.0, J = 2.3), 1.70−1.61 (1H, m), 1.07 (3H, d, J = 7.0), 1.02 (3H, d, J = 7.0), 0.99 (3H, d, J = 6.4), 0.81 (3H, d, J = 6.4); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 218.2 (C), 137.5 (C), 128.4 (CH), 127.8 (CH), 127.7 (CH), 75.4 (CH), 73.5 (CH_2), 73.3 (CH_2), 48.4 (CH), 44.4 (CH), 30.3 (CH), 19.6 (CH_3), 18.8 (CH_3), 13.7 (CH_3), 7.9 (CH_3); HRMS (+FAB): *m/z* calcd for $C_{17}H_{27}O_3$ $[M + H]^+$: 279.1960. Found: 279.1960.

(2*S*,4*R*,5*R*,6*S*)-1-Benzyloxy-6-(*tert*-butyldiphenylsilyloxy)-5-hydroxy-2,4-dimethyl-3-heptanone (11): Colorless oil. R_f (CH_2Cl_2) = 0.2; HPLC (hexanes/*i*-PrOH 99.5:0.5) t_R = 8.5 min; $[\alpha]_D$ +5.3 (*c* 1.04, $CHCl_3$); IR (film): υ 3525, 3070, 2934, 2858, 1710, 1456, 1428, 1108 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72−7.64 (4H, m), 7.46−7.22 (11H, m), 4.40 (2H, s), 3.91 (1H, dd, J = 7.2, J = 3.5), 3.75 (1H, dq, J = 7.2, J = 6.1), 3.59 (1H, t, J = 8.7), 3.43 (1H, dd, J = 8.7, J = 5.0), 3.18−3.06 (2H, m), 1.05 (3H, d, J = 6.1), 1.05 (9H, s), 1.02 (3H, d, J = 6.9), 0.96 (3H, d, J = 7.0); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 217.7 (C), 137.7 (C), 135.9 (CH), 135.8 (CH), 134.4 (C), 133.4 (C), 129.8 (CH), 129.6 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 74.7 (CH), 73.4 (CH_2), 73.0 (CH_2), 69.7 (CH), 47.3 (CH), 44.8 (CH), 27.0 (CH_3), 19.8 (CH_3), 19.3 (C), 13.8 (CH_3), 9.3 (CH_3); HRMS (+FAB): *m/z* calcd for $C_{32}H_{43}O_4Si$ $[M + H]^+$: 519.2931. Found: 519.2918.

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Supporting Information Available: Experimental procedures reported in Table 1, characterization data of aldols **4** and **8**−**10**, stereochemical proof for aldols **4a** and **11**, and ^{1}H and ^{13}C spectra of aldols **4** and **8**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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