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Stereoselective titanium-mediated *syn*-aldol reaction from a lactate-derived chiral ethyl ketone

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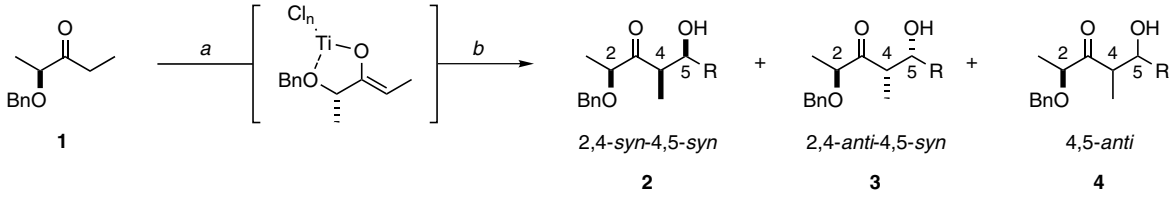
Abstract—Stereoselectivity of the titanium-mediated aldol process based on (*S*)-2-benzyloxy-3-pentanone, **1**, is dramatically modified by the presence of a Lewis acid. Among the Lewis acids surveyed, $TiCl_4$ has given access to the corresponding 2,4-*anti*-4,5-*syn* aldol adducts with the highest diastereomeric ratios. The excellent stereocontrol exerted by the aforementioned ketone has been demonstrated in double asymmetric reactions involving chiral α-methyl-β-OTBDPS aldehydes.

Although the Lewis acid-mediated aldol-type addition of a silyl enol ether to an aldehyde, the so-called Mukaiyama reaction,[1] has been thoroughly studied to the point that it constitutes nowadays one of the most powerful methodologies for the stereoselective construction of carbon–carbon bonds,[2] reactions of metal enolates with aldehydes in the presence of Lewis acids have received much less attention.[3] Regardless of their reaction mechanisms, which are not fully understood yet, highly ordered transition-state models are commonly invoked to rationalize the stereochemical outcome of such processes. Then, considering that we have recently disclosed that the titanium-mediated aldol reaction based on the lactate derived chiral ketone **1**[4] affords the corresponding 2,4-*syn*-4,5-*syn* adducts (**2** in Scheme 1), presumably through a chelated cyclic transition state,[5] we envisioned that the conformationally rigid titanium enolate shown in Scheme 1 might provide access to other adducts than those previously obtained if the reaction proceeded through a different transition state. We now report our studies on the Lewis acid-mediated aldol reaction involving the titanium enolate derived from **1**.[6–8]

As expected, preliminary experiments showed that the introduction of a Lewis acid produced dramatic changes on the stereochemical outcome of the above-mentioned process. In these early experiments, 1 equiv of several Lewis acids and 1.5 equiv of isobutyraldehyde, **a**, were subsequently added to a solution containing the titanium enolate from ketone **1** (method A). After 2 h, analysis of the reaction mixtures revealed the formation of up to three diastereomers, **2a**–**4a** (R = *i*-Pr in Scheme 1).[9] The results are summarized in Table 1.



Scheme 1. Reagents and conditions: (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 1.5 h; (b) Lewis acid, RCHO, −78 °C.

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Table 1. Stereoselectivity of the Lewis acid-mediated aldol reaction of **1**

Entry	Lewis acid	dr (**2a**:**3a**:**4a**)[a]
1	—	83:17:—
2	$BF_3{\cdot}OEt_2$	7:86:7
3	Et_2AlCl	30:69:1
4	$TiCl_4$	1:99:—
5	$TiCl_3(i\text{-PrO})$	5:95:—
6	$TiCl_2(i\text{-PrO})_2$	39:61:—
7	$Ti(i\text{-PrO})_4$	50:50:—
8	$SnCl_4$	1:74:25

[a] Diastereomeric ratios have been established by HPLC analysis of the crude reaction mixtures.

It was clear indeed that addition of any Lewis acid shifted the configuration of the major aldol adduct from 2,4-*syn*-4,5-*syn*, **2a**, to 2,4-*anti*-4,5-*syn*, **3a** (compare entries 1 and 2–8 in Table 1). Most importantly, $TiCl_4$ afforded **3a** in an excellent diastereomeric ratio (see entry 4 in Table 1).

Encouraged by these findings, we decided to study more deeply the influence of $TiCl_4$ on this transformation. Given that the stereoselectivity can also be dependent on the number of equivalents of Lewis acid and the order in which the reactants are combined, both issues were addressed.

Initially, we evaluated the influence of the supplementary equivalents of $TiCl_4$ added to the reaction mixture on the diastereoselectivity. The results are summarized in Table 2. The stereochemical dependence of the Lewis acid stoichiometry can be related to the existence of two parallel mechanistic pathways. When no supplementary $TiCl_4$ is added to the reaction mixture, the process probably goes through the chelated cyclic transition state previously reported[5] and the 2,4-*syn*-4,5-*syn* diastereomer is mainly obtained (see Scheme 1). Then, as the amount of extra Lewis acid increases a new pathway, leading to the 2,4-*anti*-4,5-*syn* diastereomer, becomes more important and finally overrides the former.

Next, two new experimental protocols were examined. Simultaneous addition of 2 equiv of $TiCl_4$ in the enolization step (method B), keeping constant all the other reaction parameters, also gave access to **3a** in good yield (77% yield) and very good diastereomeric ratio (dr **2a**:**3a** 3:97). Alternatively, the isobutyraldehyde was added precomplexed with 1 equiv of $TiCl_4$ (method C); once again, 2,4-*anti*-4,5-*syn* aldol **3a** was isolated in good yield (76% yield) and excellent diastereomeric ratio (dr **2a**:**3a** 1:99). In spite of these encouraging results, some aspects deserve to be commented. Method B afforded **3a** but in a somewhat slightly diminished diastereomeric ratio, which was dramatically eroded when other aldehydes were used.[10] Otherwise, method C was more suitable, but $TiCl_4$-aldehyde precomplexation produced a yellow suspension, which made its transfer more difficult and prevented its use on large scale preparations. Therefore, the original experimental procedure (method A) turned out to be the most suitable one and was used henceforth.[11]

Despite leading to the same diastereomer, the three reported processes A–C do not necessarily follow identical mechanistic pathways. The stereochemical outcome of the reaction in the case of method C might be ruled by an open transition state involving the antiperiplanar approach of a $TiCl_4$–aldehyde complex to the less hindered *Re* face of the chelated enolate shown in Scheme 1.[12a] Alternatively, we speculate that the addition of a second equivalent of $TiCl_4$ (methods A and B) might produce a new enolate-like species that could evolve through a cyclic transition state.[12b] Mechanistic details of these reactions are the subject of ongoing investigations.

Further studies revealed that the addition of the titanium enolate derived from **1** to isobutyraldehyde was very fast, and the starting material was almost consumed in 5 min. Eventually, we were able to isolate pure 2,4-*anti*-4,5-*syn* aldol **3a** in 85% yield after 30 min. Moreover, no changes on the diastereomeric ratio were observed from 5 min to 2 h, which suggests that the process takes place under kinetic control and no equilibration occurs over the reaction time.

Once the reaction had been optimized, representative aldehydes were surveyed in order to gain insight into the synthetic potentiality of the process. The results are summarized in Table 3. As shown, aliphatic aldehydes **a**–**c** reacted with uniformly excellent diastereoselectivities and a single diastereomeric aldol adduct **3** (see Scheme 1) was observed (dr **2**:**3** 1:99), even in the case of propanal. In the case of aromatic and α,β-unsaturated aldehydes, **d**–**g**, the corresponding aldol adducts **3** were isolated in equally good yields but with a slightly lower diastereoselectivity (dr **2**:**3** 6:94).[9]

Table 2. Influence of the additional $TiCl_4$ on the stereoselectivity of the titanium-mediated aldol reaction of **1**

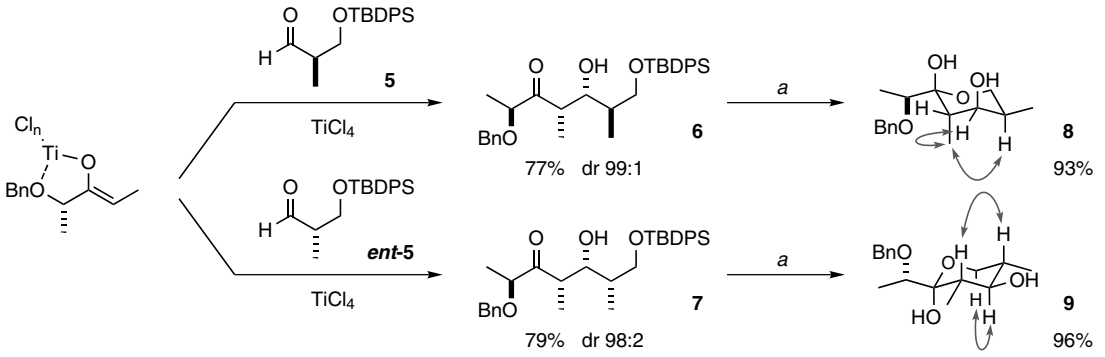
Entry	Supplementary $TiCl_4$ equivalents	dr (**2a**:**3a**)[a]
1	—	83:17
2	0.25	62:38
3	0.50	38:62
4	0.75	12:88
5	1.0	1:99
6	2.0	1:99

[a] Diastereomeric ratios have been established by HPLC analysis of the crude reaction mixtures.

Table 3. $TiCl_4$ Mediated aldol reaction of **1**

Entry	Aldehyde	R	dr (**2**:**3**)[a]	Yield[b] (%)
1	**a**	*i*-Pr	1:99	85
2	**b**	*i*-Bu	1:99	82
3	**c**	Et	1:99	81
4	**d**	Ph	6:94	88
5	**e**	4-ClPh	6:94	87
6	**f**	$(E)CH_3CH{=}CH$	6:94	65
7	**g**	$H_2C{=}C(CH_3)$	6:94	70

[a] Diastereomeric ratios have been established by HPLC analysis of the crude reaction mixtures.
[b] Overall isolated yield.



Scheme 2. Reagents and conditions: (a) TBAF·3H_2O, AcOH, THF, rt, 2 h.

Finally, the stereocontrol exerted by **1** under the aforementioned experimental procedure was challenged in double stereodifferentiating reactions[13] involving chiral aldehydes **5** and ***ent*-5**.[14] As represented in Scheme 2, both processes were highly stereoselective and virtually one diastereomer was obtained irrespective of the configuration of the aldehyde. The configuration of adducts **6** (*anti* Felkin) and **7** (Felkin) was established by ^{1}H NMR through analysis of coupling constants $^3J(H_4–H_5)$ and NOE studies on hemiacetals derivatives **8** and **9** generated by deprotection of the silyl ether (diagnostic NOE interactions are indicated in Scheme 2).[15,16]

In summary, it has been documented the dramatic influence of Lewis acids on the titanium-mediated aldol reaction based on ketone **1**, which gives access to enantiomerically pure *syn*-aldol adducts in high yields. Furthermore, considering how easily the aldols generated from lactate-derived ketones can be manipulated,[6b,c,17] the ready availability of **1** from lactate esters and the use of inexpensive $TiCl_4$, the reported methodology represents an appealing and practical entry to the synthesis of polypropionate-like natural products.

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8. For a catalytic aldol process based on the trichlorosilyl enolates from a lactate-derived ketone, see Denmark, S. E.; Pham, S. M. *Org. Lett.* **2001**, *3*, 2201–2204.
9. The relative and absolute configuration of *syn*-aldols **2** and **3** have been established by comparison of ^{1}H and ^{13}C NMR spectra as well as specific rotations with those previously reported by us. See Ref. 5. The absolute configuration of *anti*-aldols **4** has not been established.
10. Method B afforded a 15:85 mixture of **2d**:**3d** in the case of benzaldehyde.
11. Typical experimental procedure: $TiCl_4$ (0.12 mL, 1.1 mmol) was added dropwise to a solution of **1** (198 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at −78 °C under N_2, and, 2 min later, *i*-Pr_2NEt (0.19 mL, 1.1 mmol). The resulting dark red enolate solution was stirred for 1.5 h at −78 °C. Then, $TiCl_4$ (0.11 mL, 1.0 mmol) was added dropwise, the solution was allowed to stir for 10 min, and 1.5 equiv of aldehyde was added. Stirring was continued for 30 min at −78 °C. The reaction was quenched by the addition of saturated NH_4Cl (5 mL) and vigorously stirred at rt. The mixture was diluted with Et_2O, washed with saturated $NaHCO_3$, and brine. The aqueous phases were extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oil was analyzed by HPLC and purified by flash chromatography on silica gel (hexanes/EtOAc).
12. (a) The stereochemical outcome of the aldol reaction of boron enolates derived from oxazolidinones in the presence of Lewis acids has been rationalized using this model.

See Ref. 3a; (b) It has been suggested that additional $TiCl_4$ equivalents can produce the abstraction of a chloride anion or the formation of chloro bridged species. See Ref. 3e.

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15. Selected physical and spectroscopic data.
6: colourless oil; R_f (hexanes/EtOAc 90:10) = 0.1; $[\alpha]_D$ −7.7 (*c* 1.42, $CHCl_3$); IR (film): 3496, 3072, 2933, 2860, 1711, 1455, 1428, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.67 (4H, m, ArH), 7.46–7.28 (11H, m, ArH), 4.58 (1H, d, $J = 11.7$ Hz, $PhCH_xH_yO$), 4.52 (1H, d, $J = 11.7$ Hz, $PhCH_xH_yO$), 4.11 (1H, q, $J = 6.9$ Hz, CHOBn), 3.99 (1H, dt, $J = 8.7$ Hz, $J = 2.9$ Hz, CHOH), 3.78 (1H, dd, $J = 10.1$ Hz, $J = 4.4$ Hz, CH_xH_yOSi), 3.67 (1H, dd, $J = 10.1$ Hz, $J = 6.1$ Hz, CH_xH_yOSi), 3.53 (1H, d, $J = 2.9$ Hz, OH), 3.12 (1H, qd, $J = 7.0$ Hz, $J = 2.9$ Hz, $COCHCH_3$), 1.84–1.71 (1H, m, $CHCH_2$), 1.38 (3H, d, $J = 6.9$ Hz, CH_3CHOBn), 1.10 (3H, d, $J = 7.0$ Hz, $COCHCH_3$), 1.04 (9H, s, $C(CH_3)_3$), 0.85 (3H, d, $J = 7.0$ Hz, CH_2CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.2, 137.7, 135.6, 133.0, 132.9, 129.8, 128.4, 127.8, 127.7, 79.3, 74.4, 71.7, 68.0, 44.2, 37.6, 26.8, 19.2, 17.4, 13.6, 8.7.
7: colourless oil; R_f (hexanes/EtOAc 90:10) = 0.1; $[\alpha]_D$ −9.7 (*c* 1.18, $CHCl_3$); IR (film): 3505, 3072, 2933, 2860, 1711, 1457, 1428, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (4H, m, ArH), 7.47–7.29 (11H, m, ArH), 4.57 (1H, d, $J = 11.7$ Hz, $PhCH_xH_yO$), 4.54 (1H, d, $J = 11.7$ Hz, $PhCH_xH_yO$), 4.20–4.00 (2H, m, CHOBn and CHOH), 3.73 (1H, dd, $J = 10.2$ Hz, $J = 3.9$ Hz, CH_xH_yOSi), 3.60 (1H, dd, $J = 10.2$ Hz, $J = 4.7$ Hz, CH_xH_yOSi), 3.27 (1H, quintet, $J = 6.8$ Hz, $COCHCH_3$), 3.07 (1H, br s, OH), 1.69–1.61 (1H, m, $CHCH_2$), 1.35 (3H, d, $J = 6.8$ Hz, CH_3 CHOBn), 1.18 (3H, d, $J = 6.8$ Hz, $COCHCH_3$), 1.08 (9H, s, $C(CH_3)_3$), 1.00 (3H, d, $J = 7.0$ Hz, CH_3CHCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5, 137.5, 135.6, 135.5, 133.0, 132.9, 129.8, 129.7, 128.4, 127.8, 127.7 (×3), 79.3, 74.4, 71.6, 68.2, 44.0, 37.4, 26.8, 19.1, 16.5, 12.6, 11.3.
16. The deprotection of the aldol adduct **6** affords a thermodynamical mixture of two hemiacetals, the major component being **8** both in $CDCl_3$ (dr 80:20) and C_6D_6 (dr 65:35). In the case of adduct **7**, a single hemiacetal **9** was observed. Selected NMR data:
8: ^1H NMR (400 MHz, C_6D_6) δ 7.30–7.00 (5H, m, ArH), 4.44 (1H, d, $J = 11.3$ Hz, OCH_xH_yPh), 4.06 (1H, d, $J = 11.3$ Hz, OCH_xH_yPh), 3.88 (1H, t, $J = 11.8$ Hz, CH_xH_yO), 3.46 (1H, q, $J = 6.2$ Hz, CHOBn), 3.34 (1H, dd, $J = 11.8$ Hz, $J = 5.3$ Hz, CH_xH_yO), 3.05 (1H, br s, CHOH), 2.23 (1H, qd, $J = 7.1$ Hz, $J = 2.8$ Hz, $CH_3CHC(OH)O$), 1.75–1.65 (1H, m, CH_3CHCH_2O), 1.38 (3H, d, $J = 6.2$ Hz, CH_3CHOBn), 0.78 (3H, d, $J = 7.1$ Hz, $CH_3CHC(OH)O$), 0.64 (3H, d, $J = 6.9$ Hz, CH_3CHCH_2O).
9: ^1H NMR (500 MHz, C_6D_6) δ 7.30–7.00 (5H, m, ArH), 4.42 (1H, d, $J = 11.7$ Hz, OCH_xH_yPh), 4.16 (1H, d, $J = 11.7$ Hz, OCH_xH_yPh), 3.58 (1H, t, $J = 11.2$ Hz, CH_xH_yO), 3.53 (1H, dd, $J = 11.2$ Hz, $J = 5.2$ Hz, CH_xH_yO), 3.46 (1H, q, $J = 6.3$ Hz, CHOBn), 3.17 (1H, t, $J = 10.0$ Hz, CHOH), 1.92 (1H, dq, $J = 10.0$ Hz, $J = 6.6$ Hz, $CH_3CHC(OH)O$), 1.56–1.46 (1H, m, CH_3CHCH_2O), 1.18 (3H, d, $J = 6.6$ Hz, $CH_3CHC(OH)O$), 1.14 (3H, d, $J = 6.3$ Hz, CH_3CHOBn), 0.74 (3H, d, $J = 6.5$ Hz, CH_3CHCH_2O).
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