ORGANIC LETTERS

2003
Vol. 5, No. 4
519−522

Highly Stereoselective Aldol Reactions of Titanium Enolates from Lactate-Derived Chiral Ketones

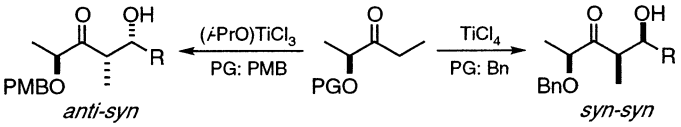
Joan G. Solsona, Pedro Romea,* Fèlix Urpí,* and Jaume Vilarrasa

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

furpi@qo.ub.es; promea@qo.ub.es

Received December 4, 2002

ABSTRACT



Highly stereoselective titanium-mediated aldol reactions based on lactate-derived ketones are reported. The stereochemical outcome of the process depends on the protecting group (PMB or Bn) and the Lewis acid (*i*-PrOTiCl$_3$ or TiCl$_4$) used in the enolization step, the corresponding anti–syn or syn–syn aldols being prepared in high yields and with diastereomeric ratios up to 99:1.

Metal enolates involved in stereoselective aldol reactions need to be easily obtained in quantitative yield with a well defined geometry. Furthermore, the metal still has to be amenable to coordination by the carbonyl group in such a way that the resulting ate complex can evolve through an ordered transition state leading to the desired aldol products with predictably high levels of stereoselection.[1]

Titanium enolates fulfill these requirements. Titanium(IV) is available from inexpensive sources and permits the incorporation of a large array of ligands to tune its acidity, and the resulting enolates are fairly reactive.[2] Despite these and other advantages,[1e,2] formation of titanium enolates from the corresponding carbonyl precursors using a titanium(IV) Lewis acid and a tertiary amine[3] has often been hampered by the need to strictly control the experimental conditions. However, over the past few years there has been an increasing number of cases showing their potential to the point that slight changes on the enolization conditions modify the stereochemical outcome of the process.[3j,l]

In this context, we have reported that putative *Z* titanium enolates of α-silyloxy ketones (PG = TBS, M = Ti, in Scheme 1) afford stereoselectively 2,4-*syn*-4,5-*syn*-aldols (syn−syn) through the transition state shown in eq 1 (see Scheme 1).[4] Therefore, we envisaged that the corresponding 2,4-*anti*-4,5-*syn*-aldols (anti−syn) might be obtained instead if the reaction could take place through a chelated transition

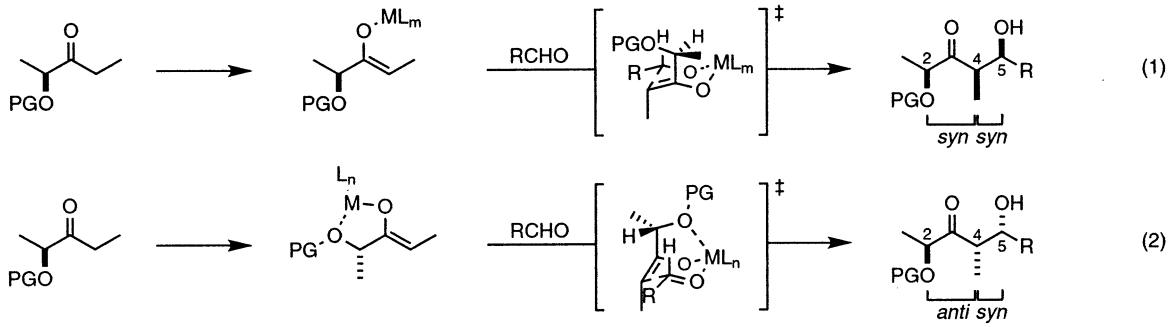
(1) See, for instance: (a) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 99. (b) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 133 and 181. (c) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 239. (d) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 277. (e) Paterson, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 301. (f) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 1. (g) Braun, M. *Houben-Weyl. Methods of Organic Chemistry. Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21b, p 1603.

(2) For reviews dealing with titanium complexes, see: (a) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807. (b) Cozzi, P. G.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Chem. Ber.* **1996**, *129*, 1361.

(3) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Borgia, A. L. *J. Org. Chem.* **1992**, *57*, 6339. (d) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H. C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613. (e) Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013. (f) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527. (g) Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809. (h) González, A.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949. (i) Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727. (j) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883. (k) Adrian, J. C., Jr.; Barkin, J. L.; Fox, R. J.; Chuck, J. L.; Hunter, A. D.; Nicklow, R. A. *J. Org. Chem.* **2000**, *65*, 6264. (l) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhury, K. *J. Org. Chem.* **2001**, *66*, 894. (m) Guz, N. R.; Phillips, A. J. *Org. Lett.* **2002**, *4*, 2253.

10.1021/ol0274054 CCC: $25.00
Published on Web 01/28/2003

Scheme 1. Mechanistic Models for Stereoselective *syn*-Aldol Reactions Based on Lactate-Derived Ketones



state as shown in eq 2 (see Scheme 1).[5] The purpose of this Letter is to report our findings on the titanium-mediated aldol reactions from lactate-derived ketones **1** and **2** (see Figure 1) in which the α-hydroxy group is protected as PMB and Bn ethers, respectively.[6]

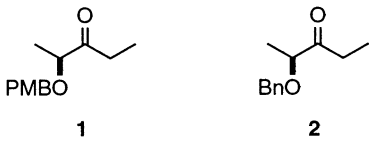
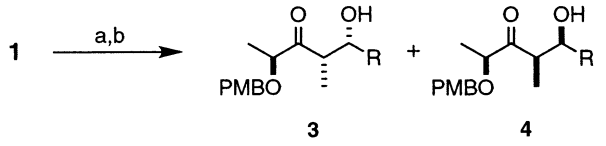


Figure 1.

Taking into account the sensitivity of the PMB group to acidic media,[7] we first evaluated $(i\text{-PrO})_2TiCl_2$- and $(i\text{-PrO})TiCl_3$-mediated aldol reactions of **1** with isobutyraldehyde (**a**). As expected, the poor Lewis acid character of $(i\text{-PrO})_2TiCl_2$ produced low conversions when the enolization was conducted under the standard conditions ($(i\text{-PrO})_2TiCl_2$, $i\text{-Pr}_2NEt$, CH_2Cl_2, −78 °C).[8] This drawback was overcome using the more powerful Lewis acid $(i\text{-PrO})TiCl_3$ and, although it was not possible to avoid a partial cleavage of the PMB group (<10%),[9] the anti−syn aldol **3a** (see Scheme 2) was obtained stereoselectively (dr 99:1) in 83% yield. This

Scheme 2 [a]



[a] Reaction conditions: (a) $(i\text{-PrO})TiCl_3$, $i\text{-Pr}_2NEt$, CH_2Cl_2, −78 °C. (b) RCHO, −78 °C.

experimental procedure[10] was subsequently generalized to other aldehydes, which allowed us to isolate the corresponding anti−syn aldols[11] (see Scheme 2) in high yields and with excellent diastereomeric ratios, even in the case of a sterically undemanding aldehyde such as propanal (98:2). The results are summarized in Table 1.

Table 1. $(i\text{-PrO})TiCl_3$-Mediated Aldol Reactions of **1**

entry	aldehyde	R	dr[a] **3:4**	yield (%)[b]
1	**a**	*i*-Pr	99:1	83
2	**b**	*i*-Bu	98:2	83
3	**c**	Et	98:2	82
4	**d**	H_2C=CH(Me)	94:6	83
5	**e**	Ph	97:3	85
6	**f**	4-ClC_6H_4	95:5	88

[a] Determined by HPLC. [b] Isolated yield of **3**.

Encouraged by these findings we addressed our attention to the ketone **2** containing the more stable benzyl group. In this case, the aforementioned reaction conditions did not produce any cleavage of the protecting group and the yields were again high, the diastereoselectivity being slightly eroded (compare entries 1−6 in Tables 1 and 2). However, when $(i\text{-PrO})TiCl_3$ was replaced by $TiCl_4$, the stereochemical course of the reaction was surprisingly reversed, since the

Table 2. Titanium-Mediated Aldol Reactions of **2**

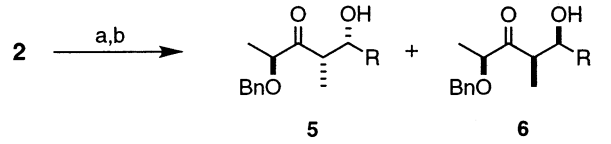
entry	aldehyde	R	Lewis acid	dr[a] **5:6**	yield (%)[b]
1	**a**	*i*-Pr	$(i\text{-PrO})TiCl_3$	97:3	86
2	**b**	*i*-Bu	$(i\text{-PrO})TiCl_3$	94:6	91
3	**c**	Et	$(i\text{-PrO})TiCl_3$	98:2	90
4	**d**	H_2C=CH(Me)	$(i\text{-PrO})TiCl_3$	92:8	81
5	**e**	Ph	$(i\text{-PrO})TiCl_3$	92:8	96
6	**f**	4-ClC_6H_4	$(i\text{-PrO})TiCl_3$	91:9	97
7	**a**	*i*-Pr	$TiCl_4$	17:83	74
8	**b**	*i*-Bu	$TiCl_4$	18:82	95
9	**c**	Et	$TiCl_4$	31:69	92
10	**d**	H_2C=CH(Me)	$TiCl_4$	4:96	77
11	**e**	Ph	$TiCl_4$	7:93	91
12	**f**	4-ClC_6H_4	$TiCl_4$	9:91	96

[a] Determined by HPLC. [b] Overall isolated yield.

(4) (a) Figueras, S.; Martín, R.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1997**, *38*, 1637. (b) Esteve, C.; Ferreró, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 5083.

syn−syn aldols **6** were obtained as the major diastereomers (see Scheme 3 and Table 2).[12,13] In this case, it is worth noting the different diastereoselectivities displayed by aliphatic (**a**−**c**) and conjugated (**d**,**f**) aldehydes (compare entries 7−12 in Table 2), which suggests that this variability is mainly rooted in stereoelectronic grounds.

Scheme 3 [a]



5 6

[a] Reaction conditions: (a) (*i*-PrO)$TiCl_3$ or $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C. (b) RCHO, −78 °C.

Due to the coordinating capability of (*i*-PrO)$TiCl_3$ and $TiCl_4$, it is expected that both Lewis acids produce chelated enolates such as that shown in eq 2 (see Scheme 1). Then, it might be argued that the slight differences existing among the diastereomeric ratios of the (*i*-PrO)$TiCl_3$-mediated aldol reactions of **1** and **2** are due to the unequal chelating abilities of PMB and Bn protecting groups. However, the reversal of the stereochemistry observed in these ketones (compare entries 1−6 and 7−12 in Table 2 and see ref 13), depending on the Lewis acid used in the enolization step, requires further analysis because the strong chelating ability of $TiCl_4$ does not agree with the process evolving through an open transition state as shown in eq 1 (see Scheme 1).[14] As a consequence, these results are not easily rationalized using the pathways depicted in Scheme 1, which suggests that this mechanistic model has to be reevaluated.

Keeping in mind that the structure of titanium enolates has not been unambiguously established, any attempt to rationalize their behavior is rather speculative. However, evidence arising from structural studies gives support to a chelated and octahedral geometry for the titanium(IV)-ate complexes (**I** and **II** in Scheme 4) involved in those reactions. Given that ligands on such titanium complexes are placed around the metal center according to a sequence based on stereoelectronic considerations,[15] it can be anticipated that thermodynamic and kinetic properties of ate complexes **I** and **II** derived from (*i*-PrO)$TiCl_3$ or $TiCl_4$ may be highly influenced by the replacement of *i*-PrO^- by Cl^-.

Therefore, assuming that each ate complex goes through a different cyclic transition state to the corresponding syn aldol product (see Scheme 4), if both diastereomeric complexes, **I** and **II**, do not rapidly establish equilibrium and do not interconvert directly by any octahedral isomerization, the stereochemical outcome of the process could be dependent on the ate complex formation step.[16] Thus, ligands not only tune the titanium acidity but may also have a dramatic influence on the stereochemistry of the ate complex and, as a consequence, of the syn aldol product (see Scheme 4).[17,18] Further investigations into the mechanism of this process are currently underway.

In summary, we have described highly stereoselective aldol reactions based on the titanium enolates of lactate-derived

(5) For stereoselective aldol reactions based on chiral hydroxy ketones involving chelated transition states, see: (a) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499. (b) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233. (c) Choudhury, A.; Thornton, E. R. *Tetrahedron Lett.* **1993**, *34*, 2221. (d) Palomo, C.; González, A.; García, J. M.; Landa, C.; Oiarbide, M.; Rodríguez, S.; Linden, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 180. (e) Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2001**, *3* 123. (f) Paterson, I.; Temal-Laïb, T. *Org. Lett.* **2002**, *4*, 2473.

(6) Ferreró, M.; Galobardes, M.; Martín, R.; Montes, T.; Romea, P.; Rovira, R. Urpí, F.; Vilarrasa, J. *Synthesis* **2000**, 1608.

(7) Greene, T. W.; Wuts, R. G. M. In *Protective Groups in Organic Synthesis*; Wiley & Sons: New York, 1999.

(8) Isolated yield of **3a** and **4a** (see Scheme 2) = 55%. Diastereomeric ratio (**3a**:**4a**) = 84:16.

(9) When (*i*-PrO)$TiCl_3$ and *i*-Pr_2NEt were added to ketone **1** at −90 °C, and the enolization and the further aldol reaction with isobutyraldehyde were carried out at −78 °C, the cleavage of the PMB was reduced to less than 5%.

(10) **Typical Experimental Procedure.** Freshly distilled Ti(*i*-PrO)$_4$ (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 yellow mixture was stirred for 10 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) for 10−15 min to a solution of **1** (195 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 1.5 h at −78 °C. After the dropwise addition of 1.5 equiv of aldehyde, 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 room temperature. The mixture was diluted with Et_2O (200 mL) and washed with H_2O (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The aqueous phases were extracted with Et_2O (75 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oil was analyzed by HPLC and purified by flash chromatography (hexanes/EtOAc).

(11) Stereochemistry of **3f** was established by X-ray diffraction analysis; see Supporting Information. The stereochemistry of **3a** was confirmed by chemical correlation.

(12) Stereochemistry of **5f** was established by X-ray diffraction analysis; see Supporting Information. The stereochemistry of **5a** and **6a** was confirmed by chemical correlation.

(13) Same reversal of the stereochemistry was observed in the case of ketone **1** when enolization was carried out with $TiCl_4$/*i*-Pr_2NEt. For instance, $TiCl_4$−mediated aldol reaction of **1** with benzaldehyde (**e**) afforded a mixture of **3e** and **4e** (see Scheme 2) in low yield (58%) and with a poor diastereomeric ratio (**3e**:**4e** = 25:75), the syn−syn aldol being the major diastereomer. This result is opposite to that obtained with (*i*-OPr)$TiCl_3$ (compare with entry 5 in Table 1), which proves the crucial role played by the Lewis acid on the stereochemical outcome of these reactions.

(14) Aforementioned reversal of stereoselectivity is not observed when the equivalent TBS-protected ketone is submitted to the same reaction conditions. As expected, the titanium-mediated aldol reaction of this ketone with aliphatic or aromatic aldehydes affords the corresponding syn−syn aldols (see eq 1 in Scheme 1) in high yields with dr > 96:4 irrespective of the Lewis acid ($TiCl_4$ or (*i*-PrO)$TiCl_3$) used in the enolization. These results suggest that the fickle behavior observed in the titanium−mediated aldol reactions of **1** and **2** is related to the formation of a chelated enolate, whose more rigid architecture has a crucial influence on the stereodetermining step of the process.

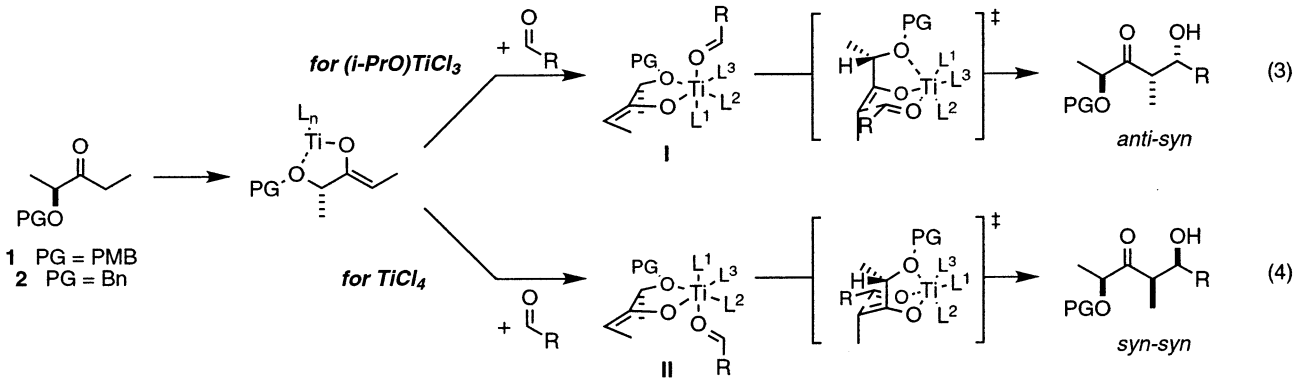
(15) Gau, H.-M.; Lee, C.-S.; Lin, C.-C.; Jiang, M.-K.; Ho, Y.-C.; Kuo, C.-N. *J. Am. Chem. Soc.* **1996**, *118*, 2936.

(16) This hypothesis is supported by the lithium-mediated aldol reaction of **2**, which affords the corresponding anti−syn aldol (i.e., **5a**:**6a** = 72:28, 46% yield). Given that the stererochemical outcome of this reaction is rationalized using the model shown in eq 2 (Scheme 1), it is clear that the stereodetermining step of the $TiCl_4$-mediated aldol reactions of **2** cannot be linked to the carbon−carbon bond formation step.

(17) For related discussions on the structure of titanium complexes involved in stereoselective Diels−Alder reactions, see: (a) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788. (b) Haase, C.; Sarko, C. R.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 1777. (c) Gothelf, K. V.; Jorgensen, K. A. *J. Org. Chem.* **1995**, *60*, 6847. (d) García, J. I.; Martínez-Merino, V.; Mayoral, J. A. *J. Org. Chem.* **1998**, *63*, 2321.

(18) For related examples on the impact of additives on titanium-mediated aldol reactions, see for instance, refs 3k−m and: Nakamura, S.; Hayakawa, T.; Nishi, T.; Watanabe, Y.; Toru, T. *Tetrahedron* **2001**, *57*, 6703.

Scheme 4. Proposed Mechanistic Model for Titanium-Mediated Aldol Reactions of Ketones **1** and **2**



ketones **1** and **2**. The protecting groups (PMB or Bn) and the titanium Lewis acid (*i*-PrOTiCl$_3$ or TiCl$_4$) employed in the enolization determine the stereochemical outcome of the process, affording the corresponding anti−syn or syn−syn aldols in high yields and with diastereomeric ratios up to 99:1. A working hypothesis based on the crucial role played by the stereochemistry of the ate complexes has been proposed to account for the aforementioned results.

Acknowledgment. We thank Dr. Xavier Solans and Dr. Mercè Font-Bardia (Universitat de Barcelona) for X-ray analyses. Financial support from the Ministerio de Educación y Cultura (DGESIC, Grant PM98-1272), the Ministerio de Ciencia y Tecnología and Fondos FEDER (Grant BQU2002-01514), and the Generalitat de Catalunya (2001SGR00051), as well as a doctorate studentship (Universitat de Barcelona) to J.G.S. are acknowledged.

Supporting Information Available: Spectroscopic data for aldols **3**, **5**, and **6**, copies of ^{1}H NMR spectra of **3a**,**d**−**e** and **5a**,**d**−**e**, and X-ray crystal data for **3f** and **5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0274054