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Enolization of Chiral α-Silyloxy Ketones with Dicyclohexylchloroborane. Application to Stereoselective Aldol Reactions

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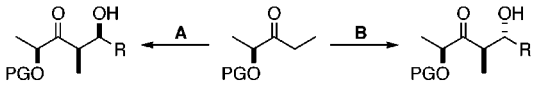
ABSTRACT



A. i. Chx_2BCl, Et_3N, Et_2O, –78 °C. ii. RCHO
B. i. Chx_2BCl, $EtMe_2N$, pentane, rt. ii. RCHO

Comprehensive analysis of the enolization of α-silyloxyketones by Chx_2BCl/R_3N has allowed us to design stereoselective Chx_2BCl-mediated aldol processes that afford *syn* or *anti* aldol products and to disclose a hypothesis that accounts for the subtle effects that determine their enolization.

Enolates constitute the main source of reagents to gain access to α-substituted carbonyl compounds and have therefore become useful intermediates for the synthesis of complex molecules. Provided that the geometry of an enolate determines the stereochemical outcome of the reactions it takes part in, the selective formation of enolates represents a key step in many bond-forming processes.[1] Despite the efforts focused on the development of versatile and highly stereoselective enolization methodologies, reliable procedures leading to ketone-derived *E*-enolates proved to be elusive until Brown et al. reported the use of dicyclohexylchloroborane, Chx_2BCl.[2,3] To the best of our knowledge, this bias has only been inverted when chelating groups (namely, OR ethers) are positioned α to the carbonyl.[4] The purpose of this letter is to report our findings on the enolization of α-silyloxy ketones and to disclose a hypothesis that accounts for the subtle influences that determine the stereoselective enolization of ketones by the aforementioned Lewis acid.

Our ongoing efforts directed toward the development of stereoselective processes based on α-chiral ketones[5] led us

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(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) Norin, T. *Houben-Weyl. Methods of Organic Chemistry. Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol E21a, p 697. (h) 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 603.

(2) (a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441. (b) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (c) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 2716. (d) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 7162.

(3) Cowden, C. J.; Paterson, I. In *Organic Reactions*; Paquette, L., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, p 1.

(4) (a) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (b) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677 and references therein.

(5) (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*, 5079 and 5083.

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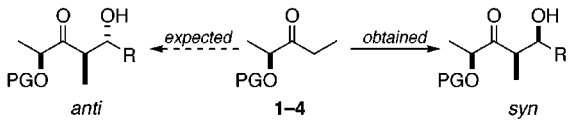
to study the Chx_2BCl-mediated aldol reactions of α-$OSiR_3$ ketones **1**−**4** (see Scheme 1).[6] Given the poor chelating

Scheme 1



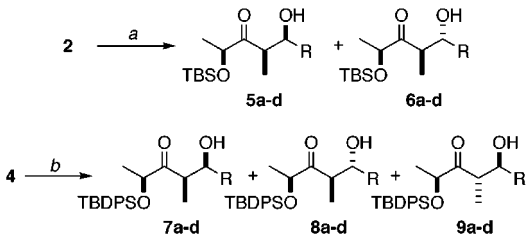
1. PG: TES; **2**. PG: TBS; **3**. PG: TIPS; **4**. PG: TBDPS

abilities of $OSiR_3$ groups,[7] the *anti* stereoisomer was expected to be the major aldol product. Unexpectedly, ketones **1**−**3** afforded essentially pure *syn*-aldol, whereas a mixture of *syn*/*anti* was obtained in the case of **4** in preliminary experiments, when enolization was carried out with Et_3N in Et_2O at −78 °C.[8]

As *syn* (*anti*) aldol products are supposed to evolve from *Z* (*E*) enolborinates through a cyclic chairlike transition state, it was decided to study the enolization step to gain insight into these puzzling results. Therefore, the effect of solvent, amine, temperature, and other variables on stereoselectivity of Chx_2BCl-mediated aldol reactions of **2** and **4** was evaluated.

First of all, the study of aldol reactions of **2** with benzaldehyde (**a**) was addressed. Nonpolar solvents (e.g., pentane), higher temperatures, and less bulky amines (e.g., $EtMe_2N$) eroded the stereoselectivity, but the 2,4-*syn*-4,5-*syn* stereoisomer, **5a**, was always the major component of the mixtures, contaminated by variable amounts of the 2,4-*syn*-4,5-*anti* one, **6a** (see Scheme 2). Optimization of this

Scheme 2



a. R: Ph; **b**. R: MeCH=CH; **c**. R: ^{i}Bu; **d**. R: ^{i}Pr

[a] See ref 9. [b] See ref 11.

reaction led to essentially pure **5a** (dr 99:1 by HPLC) in 90% yield when enolization (method A)[9] was carried out in Et_2O (0.2 M, −78 °C, 2 h) with Chx_2BCl/Et_3N (1.2/1.5 equiv). Highly stereoselective aldol reactions were also achieved with crotonaldehyde (**b**), isovaleraldehyde (**c**), and isobutyraldehyde (**d**) as shown in entries 1−4 of Table 1.

Table 1. Aldol Reactions of Ketones **2** and **4**

entry	ketone	method	aldehyde (R)	dr **5**:**6**	dr **7**:**8**:**9**	yield[a] (%)
1	**2**	A	**a** (Ph)	99:1[b]		90
2	**2**	A	**b** (MeCH=CH)	98:2[c]		82
3	**2**	A	**c** (iBu)	98:2[c]		92
4	**2**	A	**d** (iPr)	98:2[c]		76
5	**2**	B	**d** (iPr)	35:65[c]		61 (28)
6	**4**	B	**a** (Ph)		12:78:10[b]	78 (20)
7	**4**	B	**b** (MeCH=CH)		9:83:7[b]	87 (10)
8	**4**	B	**c** (iBu)		5:85:10[c]	83 (15)
9	**4**	B	**d** (iPr)		4:88:8[b]	78 (17)
10	**4**	A	**d** (iPr)		70:30:−[c]	36 (57)

[a] Isolated yield. In brackets, recovered ketone. [b] Diastereomeric ratio by HPLC. [c] Diastereomeric ratio by ^{1}H NMR.

Second, the study of aldol reactions of **4** was performed using isobutyraldehyde. In this case, optimum conditions previously achieved (method A) afforded a mixture (70:30) of 2,4-*syn*-4,5-*syn*, **7d**, and 2,4-*syn*-4,5-*anti*, **8d**, aldol stereosiomers (see entry 10 in Table 1). However, dramatic changes in the composition of the crude mixtures were observed when less polar solvents (e.g., pentane), a less bulky amine (e.g., $EtMe_2N$), higher temperatures, and lower concentration (e.g., 0.05 M) were employed. Then, the *anti*

(6) (a) Martín, R.; Pascual, O.; Romea, P.; Rovira, R.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1997**, *38*, 1633. (b) Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414.

(7) See, for instance: (a) Reetz, M. T.; Hüllmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600. (b) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. (c) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697.

(8) Brown et al. suggested (see ref 2d) that *E*-enolborinates are highly favored by the use of moderately sterically hindered amines, nonpolar solvents, and low temperatures.

(9) **Method A (*syn* aldol).** To a cooled (−78 °C) solution of Chx_2BCl (0.26 mL, 1.2 mmol) in Et_2O (3 mL) was added dropwise Et_3N (0.21 mL, 1.5 mmol) followed by **2** (216 mg, 1 mmol) in Et_2O (2 mL). The reaction mixture was stirred for 2 h at −78 °C, and the aldehyde (1.5 mmol) was added. The resulting solution was further stirred at −78 °C for 3 h and kept at −20 °C overnight. The mixture was partitioned between a pH 7 buffer (20 mL) and Et_2O (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was diluted in MeOH (5 mL), a pH 7 buffer (1 mL), and H_2O_2 30% (2 mL) at 0 °C; warmed to room temperature; and stirred for 2 h. It was partitioned between H_2O (20 mL) and CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with saturated $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. Isolation of the aldol product was achieved by column chromatography, and diastereomeric ratios were determined by ^{1}H NMR analysis and/or HPLC. The yields and diastereomeric ratios for **5** and **6** are given in Table 1.

(10) This isomer has not been isolated. Its stereochemistry has been assigned on the basis of NMR analysis.

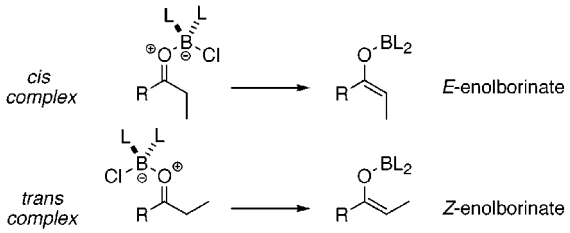
(11) **Method B (*anti* aldol).** To a cooled (0 °C) solution of **4** (340 mg, 1 mmol) in pentane (20 mL) was added dropwise Chx_2BCl (0.24 mL, 1.1 mmol) and $EtMe_2N$ (0.22 mL, 2 mmol). The resulting white suspension was stirred at 0 °C for 10 min and at room temperature overnight before cooling at −78 °C. The aldehyde (1.5 mmol) was added, and the mixture was stirred for 3 h and kept at −20 °C for 2 h. The mixture was partitioned between a pH 7 buffer (20 mL) and Et_2O (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was diluted in MeOH (2 mL), a pH 7 buffer (4 mL), and H_2O_2 30% (2 mL) at 0 °C; warmed to room temperature, and stirred for 1 h. It was partitioned between H_2O (20 mL) and CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with saturated $NaHCO_3$ (25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo. Isolation of the aldol products was achieved by column chromatography (pure samples of major diastereomers were obtained by MPLC), and diastereomeric ratios were determined by ^{1}H NMR analysis and/or HPLC. The yields and diastereomeric ratios for **7**−**9** are given in Table 1.

aldol, **8d**, became the major component of the mixtures, contaminated by the *syn*, **7d**, and a third one, **9d**, whose stereochemistry was assumed as 2,4-*anti*-4,5-*anti*[10] (dr **7d**:**8d**:**9d** 4:88:8 by HPLC in an overall 78% yield). The aforementioned enolization conditions (method B)[11] also gave similar diastereoselectivities with other aldehydes (see Scheme 2 and entries 6−9 in Table 1).

The broad spectrum of factors (temperature, base, concentration, and solvent) that determine the geometry of the enolborinates hints that the above enolization is a complex process that depends on subtle influences rooted on thermodynamic and kinetic grounds.

Goodman and Paterson[12] have pointed that the geometry of the initially formed C═O·BL_2Cl complexes (*cis* or *trans* in Scheme 3) conditions the subsequent deprotonation step.

Scheme 3



On the basis of electronic and steric preferences, *cis* coordination of Chx_2BCl to the carbonyl would enhance the acidity of the α-CH_2 and allow unhindered bases to kinetically deprotonate the corresponding complex leading to the *E*-enolborinate, whereas the *Z*-enolborinate would arise from the less favored *trans* complex (see Scheme 3).

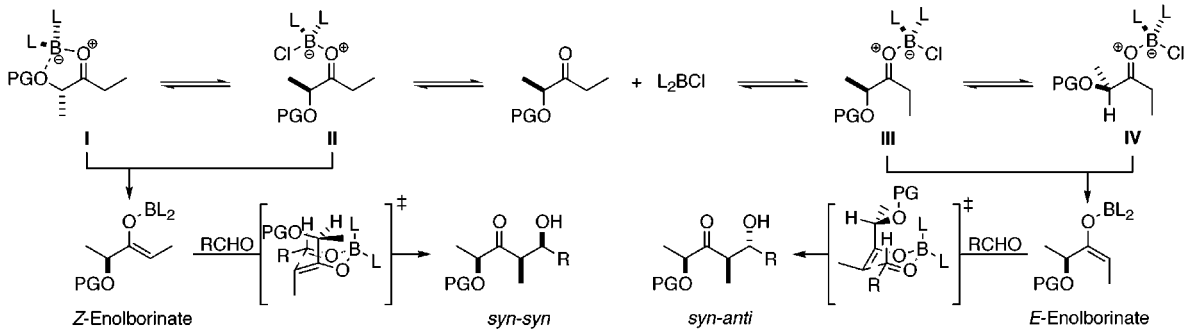
Exceptions previously reported, namely, α-OR ketones, might be accommodated to this model assuming that a chelated complex (see **I** in Scheme 4) plays a crucial role in the enolization step. Nevertheless, the intrinsic bias to afford the corresponding *Z*-enolborinates observed in the case of **1**−**4** and the low chelating ability of groups such as $OSiR_3$ suggest that mechanisms other than chelation must cooperate on their enolization.

It might be argued that the *E*/*Z* ratio stems from the balance of two independent but related steps: formation of the carbonyl−Lewis acid complex and its subsequent deprotonation. Provided that several complexes (see **I**−**IV** in Scheme 4) are accessible, some issues should be addressed: (i) Which one is more stable? (ii) Which one is more reactive? (iii) Which step determines the geometry of the enolborinate? Assuming that *E* (*Z*) enolborinates arise from *cis* (*trans*) complexes, it may be envisioned that stereoelectronic effects in the initially formed complexes **I**−**IV** influence the subsequent deprotonation step: *E*-enolborinates would only arise from *cis* complexes if a C−H bond may be positioned antiperiplanar to the C═OB bond (see **IV** in Scheme 4) to minimize allylic (1,3) strain[13] in a putative late transition state. If this condition is not easily reached, *Z*-enolborinates would be obtained instead, through a chelated or acyclic complex (see **I** and **II** in Scheme 4) irrespective of their relative stability.

Conformational analysis of α-substituted carbonyls suggests that electrostatic interactions between the C−OB and the C_α−O dipoles make antiperiplanar arrangements **II** and **III** the most stable ones.[14,15] Low temperatures must then stress this trend with *syn*-*syn* aldols mainly obtained through complex **II** because A(1,3) in the corresponding transition state is minimized compared to those from **III** (compare entries 4−5 and 9−10 in Table 1). Therefore, conformational issues would play a crucial role in rationalizing the observed behavior under enolization conditions A. Alternatively, collusion of high temperatures, an extremely unhindered amine ($EtMe_2N$), and low concentrations[16] may overcome this bias and produce *E*-enolborinates from **IV**; thus, the major *anti* aldol stereoisomer might arise from *cis* complex **IV** through a cyclic chairlike transition state[17] shown in Scheme 4. Relative stability of complexes **I**−**IV** would then justify the trend observed under enolization conditions B.

Although the proposed model allows accommodation of the results obtained in the case of α-OSi ketones, it is evident that it does not account for the quantitative differences observed for TBS (ketone **2**) and TBDPS (ketone **4**) protecting groups (compare entries 4−10 and 5−9). At this point, it is still unclear the role of the steric size and the electronic properties of the silicon protecting groups on the reaction pathway.

Scheme 4



Further studies addressed to analyze the effect of the solvent, the concentration, and the differences observed for TBS and TBDPS groups are in progress and will be reported in due course.

Acknowledgment. We thank Dr. Ian Paterson for kind and fruitful discussions. Financial support from the DGICYT, Ministerio de Educacion y Cultura (PM95-0061 and PB98-1272), from the Direcció General de Recerca, Generalitat de Catalunya (1996SGR00102 and 1998SGR00040), and from the Universitat de Barcelona for a doctorate studentship to M. Galobardes is gratefully acknowledged.

Supporting Information Available: Spectroscopic data for compounds **5** and **8**. Stereochemical proof of aldol diastereomers **5a** and **8d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Goodman, J. M. *Tetrahedron Lett.* **1992**, *33*, 7219. (b) Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1992**, *33*, 7223.

(13) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(14) Frenking and Reetz have postulated that conformational effects are responsible for a significant portion of the energy difference between competing transition states involved in 1,2-stereoinduction: Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 8991; *Tetrahedron* **1993**, *49*, 3971. See also: Lecea, B.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1997**, *62*, 6485.

(15) Dipolar interactions have also been invoked to rationalize the 1,3-asymmetric induction observed in the Mukaiyama aldol addition of enol silyl ethers to β-substituted aldehydes. See, for instance: (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322. (b) Bonini, C.; Esposito, V.; D'Auria, M.; Righi, G. *Tetrahedron* **1997**, *53*, 13419.

(16) Brown et al. pointed out (see ref 2d) that formation of Chx-derived *E*-enolborinates is favored in dilute medium. In preliminary experiments, we have found that the enolization of **4** in pentane at 0 °C affords a mixture of *syn/anti* aldols whose composition depends on the concentration (19:81 at 0.25 M; 8:92 at 0.05 M). This trend suggests that acid−base ($Chx_2BCl-EtMe_2N$) coordination might play a secondary role in the mechanism shown in Scheme 4 in the sense of producing new reacting species, as $[Chx_2B-NEtMe_2]^+$, whose behavior would be closer to R_2BOTf. Therefore, polar solvents and higher concentrations might favor the formation of *Z*-enolborinates through an alternative pathway.

(17) Theoretical calculations of transition states associated to *E*-enolborinates support the preference of the $C_{\alpha-H}$ bond to eclipse the enolborinate double bond to minimize the allylic strain. See: (a) Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685. (b) Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron: Asymmetry* **1995**, *6*, 2613.