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SYN SELECTIVE ALDOL REACTIONS OF TITANIUM AND ZIRCONIUM DIENOLATES.

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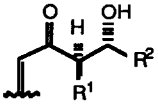
Abstract. The low temperature transmetallation of the lithium dienolate of 2-cyclohexene-1-one or 2-cyclopentene-1-one with chlorotitanium triisopropoxide or bis(η^5-cyclopentadienyl)dichlorozirconium gives the Z,E- titanium or zirconium dienolate. These transition metal dienolates participate in aldol reactions with achiral aldehydes resulting in the direct formation of a *syn* ß-hydroxy enone system.

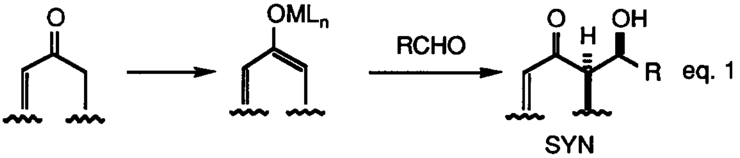
In the course of a program directed at the stereocontrolled synthesis of polyoxygenated natural products we have encountered the need for a simple and efficient method to selectively introduce a syn ß-hydroxy enone system having the general formulation 1. Our design for an entry into these systems postulated an aldol reaction between a dienolate and an aldehyde component, equation 1. An increase in the understanding of transition state structure in the aldol reaction has led to advances in the control of acyclic stereochemistry.[2] As a consequence, this process has become one of the most useful methods for controlling stereochemistry, and the use of sterically demanding transition-metal enolates has been found to display enhanced stereoselection in aldol reactions.[3] Conventional protocols for the preparation of the systems such as 1 and 2 must rely on the use of expensive reagents and multistep sequences. Thus, direct access to syn ß-hydroxy enone systems would represent an efficient alternative for the stereoselective synthesis of these potentially useful, highly functionalized intermediates.

1

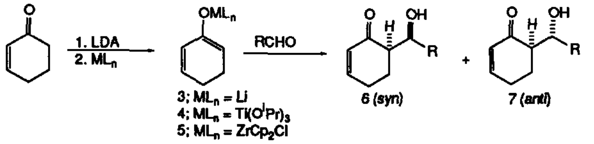


2

The ample precedent for *syn* selective aldol reactions of transition-metal enolates[4] together with the reports by Evans[5] and more recently Thornton[6] and Proctor[7] suggests that certain transition metals may be used as sterically demanding transition metal *dienolates* which could participate in stereoselective aldol reactions. In this Letter, we wish to disclose our observations on the aldol reactions of stereochemically fixed E,Z-titanium and zirconium dienolates of 2-cyclohexene-1-one and 2-cyclopenten-1-one with achiral aldehydes. The reaction results in the direct formation of *syn* ß-hydroxy enone systems (Equations 2 and 3).



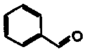
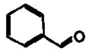
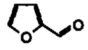
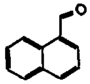
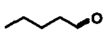
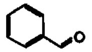
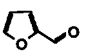
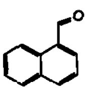
During this investigation, we encountered difficulty with the apparent thermal instability of the transmetallated dienolate. In contrast to observations reported by Reetz,[4a] Evans[5a] and Procter,[7] where their studies found titanium enolates, zirconium amide enolates, and titanium amide enolates to be thermally stable, at temperatures above -30 °C the *transition metal dienolates decompose, and the aldol reaction fails. After considerable experimental effort, specific* reaction conditions were defined for each lithium-transition metal exchange. However, our attempts to transmetalate the lithium dienolate of 2-cyclopenten-1-one with chlorotitanium triisopropoxide and perform the aldol reaction proved unsuccessful.[8] The titanium and zirconium dienolates were readily prepared and the syn selective aldol reactions were reproducible if the temperature of the transmetallation sequence was held below -30 °C for the formation of titanium dienolate 4 and -50 °C for zirconium dienolates 5 and 9. The results of our investigation are summarized in Tables 1 and 2. A comparison of the lithium, titanium and zirconium dienolates 3, 4, and 5 derived from 2-cyclohexen-1-one in *the aldol reaction with benzaldehyde reveals a complete reversal of selectivity* (Table 1, Entries 1,2 and 6). Entries 2 - 5 and 6 - 9 represent a comparison of the stereoselection of titanium and zirconium dienolates. The aldol reactions of lithium and zirconium dienolates 8 and 9 of 2-cyclopenten-1-one are summarized in Table 2. These experiments reveal that zirconium dienolate 9 gives a slightly higher stereoselection than either the titanium or zirconium dienolate of the cyclohexenone cases. The trend for zirconium dienolate 9 to exhibit higher stereoselection than the corresponding titanium dienolate 4 and zirconium dienolate 5 appears to be general for the range of aldehydes examined.



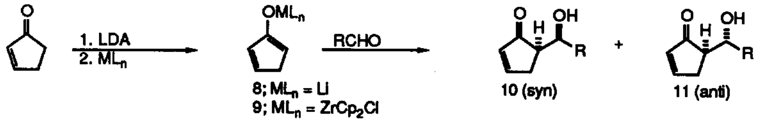
6 (*syn*) 7 (*anti*)

eq. 2

Table 1. SYN SELECTIVE ALDOL REACTIONS

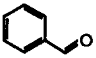
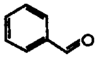
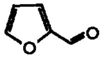
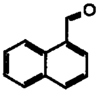
entry	dienolate	RCHO[a]	Ratio syn/anti[b]	yield %[c,d]
1.	3		19:81	83
2.	4		65:35	66
3.	4		70:30	73
4.	4		47:53	59
5.	4		50:50	54
6.	5		75:25	65
7.	5		70:30	52
8.	5		85:15	63
9.	5		52:48	55

a. The aldehydes were distilled prior to use. b. Ratios were determined by ^1H NMR (400 MHz) and HPLC analysis. c. Isolated yield after chromatography on SiO_2. d. All products gave ^1H NMR (400 MHz), IR, and Mass Spectra consistant with their assigned structure.



eq. 3

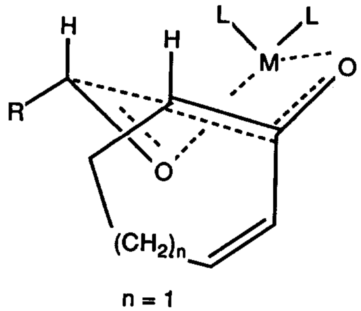
Table 2. SYN SELECTIVE ALDOL REACTIONS

entry	dienolate	RCHO[a]	Ratio syn/anti[b]	yield %[c,d]
1.	8		40:60	50
2.	9		85:15	65
3.	9		82:18	50
4.	9		89:11	55
5.	8		53:47	63
6.	9		57:43	47

a. The aldehydes were distilled prior to use. b. Ratios were determined by ^1H NMR (400 MHZ) and HPLC analysis. c. Isolated yield after chromatography on SiO_2. d. All products gave ^1H NMR (400 MHz), IR and Mass Spectra data consistant with their assigned structures.

The stereochemical outcome of the aldol reaction is generally rationalized through the use of a six-membered cyclic transition state. A dissection and analysis of these transition-states can be used to predict the stereochemical outcome of the aldol reaction, and a correlation between enolate geometry and stereoselection in many aldol reactions can be found. To account for the *syn* selectivity, we speculate that the sterically demanding Z,E-titanium and zirconium dienolates derived from cyclic a,ß-unsaturated ketones are reacting through a pseudo-boat transition state (Figure1).

Figure 1



n = 1
=2

In conclusion, the aldol reactions of titanium and zirconium dienolates derived from 2-cyclohexen-1-one and 2-cyclopentene-1-one result in the selective formation of *syn* ß-hydroxy enone systems. The high *syn* selection for these stereochemically rigid transition metal dienolates appear to be general for the range of aldehydes examined with the exception of 1-napthaldehyde (Table 1, entry 5) and pentanal (Tables 1 and 2). Direct access to these systems has potentially broad ramifications and indicates that these transition metal dienolates may be useful in organic synthesis. Efforts to further improve the stereoselection and applications in total synthesis are currently under investigation.[10]

References and Footnotes

1. NSF-REU undergraduate research participant, **1987.**
2. For a review see: Heathcock, C.H. in "*Asymmetric Synthesis* ", Academic Press, **1984**, Morrision, J.D. Ed. Vol. #3, Chapter 2.
3. (a) Evans, D.A., Vogel, E., Nelson, J.V. *J. Am. Chem. Soc.* **1979**, 101, 6120; (b) Inoue, T., Mukyaiyama, T., *Bull. Chem. Soc., Jpn.* **1980**, 53, 174; (c) Hirama, H., Garvey, D.S., Lu, L.D.L., Masamune, S. *Tetrahedron Lett.* **1979**, 3937.
4. (a) Reetz, M.T., Peter, R. *Tetrahedron Lett.* **1981**, 22, 4691; (b) Yamamoto, Y., Maruyama, K. *Tetrahedron Lett.* **1980**, 21, 4607.
5. (a) Evans, D.A., McGee, L.R. *J. Am. Chem. Soc.* **1981**, 103, 2876; (b) Evans, D.A., McGee, L.R., *Tetrahedron Lett.* **1980**, 21, 3975.
6. Siegel, C., Thornton, E.R. *Tetrahedron Lett.* **1986**, 27, 457;
7. Murphy, P.J., Procter, G., Russell, A.T. *Terahedron Lett.* **1987**, 28, 2040.
8. We surmise that the competitive formation of a (hydroxycyclopentadienyl)titanium species is preventing the expected aldol product formation.
9. Representative procedures for the synthesis of syn ß-hydroxy enones follow. For the reaction of titanium dienolate **4** to give the aldol product **6**, 2-cyclohexen-1-one (96.13 mg, 1.0 mmole) was added to a solution of LDA (1.2 equiv.) in THF (4.0 mL) at -78 °C under N_2. The reaction was immediately warmed to 0 °C (15 min) to accelerate deprotonation and then cooled to -78° C. A solution of chlorotitanium triisopropoxide (2.5 equiv.) in THF (0.5 mL) was added and the reaction warmed to -30 °C (1 h). The solution containing the titanium dienolate was cooled to -78 °C and treated with the aldehyde (1.2 equiv.). After 30 minutes (-78 °C) the reaction was diluted with saturated NH_4F (ca. 25 mL). Extractive isolation (EtOAc) followed by chromatography on SiO_2 gave adducts **6** and **7**, equation 2 and Table 1.

   Illustrated with the zirconium dienolate **9** to give aldol product **10**; 2-cyclopenten-1-one (82.10 mg, 1 mmole) was added to a solution of LDA (1.2 equiv) in THF (4.0 mL) at -78 °C under N_2. After 15 minutes (-78 °C, 0 °C for dienolate **5**), a solution of bis(η^5-cyclopentadienyl)dichlorozirconium (1.1 equiv.) in THF (4.0 mL) was added. The lithium-zirconium exchange proceeded at -50 °C for one hour. The reaction solution was cooled to -78 °C and treated with the aldehyde (1.2 equiv.). After 30 minutes at -78 °C, the reaction was diluted with saturated NH_4F (ca. 25 mL) followed by extractive isolation and chromatography on SiO_2 to give the adducts **10** and **11**, equation 3 and Table 2.
10. This work was supported by the National Science Foundation (grant No. CHE - 8712942) and Boston University. We thank Professors Ronald Halterman and John Snyder for helpful discussions.

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