Tetrahedron Letters,Vol.22,No.47,pp 4691-4694,1981 0040-4039/81/474691-04$02.00/0
Printed in Great Britain

ERYTHRO SELECTIVE ALDOL CONDENSATION USING TITANIUM ENOLATES

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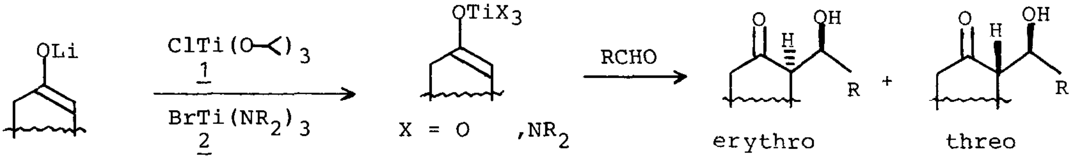
Abstract: Titanium enolates derived from ketones and esters react with aldehydes to afford erythro adducts with high diastereoselection.

The problem of diastereoselective aldol condensation has been largely solved by using prochirally pure or enriched metal enolates [1]. Under kinetic control Z-enolates generally favor erythro adducts and E-enolates the threo isomers. Thus, there is no simple way to prepare erythro aldols from cyclic ketones, since the enolates are geometrically fixed in the E-geometry. Notable exceptions pertain to bis(cyclopentadienyl)chloro-zirconium- [2a], triphenyltin- [2b] and tris(dialkylamino)-sulfonium- [2c] (TAS) enolates, which favor erythro product formation irrespective of the enolate geometry.

We wish to report the synthesis and properties of titanium enolates: They are easily accessible using cheap reagents, distillable and miscible in THF, ether, methylene chloride or pentane, and display pronounced erythro selectivity in reactions with aldehydes.



Solutions of Li-enolates [3] in THF were quantitatively quenched with 1 or 2 [4] at -78 °C, the solvent stripped off at room temperature and the Ti-enolate dissolved in pentane [5]. Aldol reactions were carried out by adding the aldehyde at -78 °C or -120 °C [6], stirring for 1 h and working up with saturated aqueous NH_4F. Conversion was nearly quantitative (>70 % isolated). Table 1 shows that erythro formation is consistently favored. Diastereoselection is better than with Zr- or Sn-enolates [2]. In case of TAS enolates [2c] only isobutyraldehyde has been added to cyclopentanone and cyclohexanone, erythro preference being complete at low temperatures and short reaction times. The $TiCl_4$ induced reaction of the silyl enol ether from cyclohexanone with benzaldehyde leads to a slight preference for the threo adduct [2a].

Table 1. Aldol Condensation Using Cyclic Ketones (10-20 mmol scale)

Enolate from	Ligand at Ti	Aldehyde	erythro:threo ratio [a)]
cyclopentanone	$N(C_2H_5)_2$	C_6H_5CHO	85:15
cyclohexanone	$N(C_2H_5)_2$	C_6H_5CHO	97:3
cyclohexanone	$N(CH_3)_2$	C_6H_5CHO	92:8
cyclohexanone	$OCH(CH_3)_2$	C_6H_5CHO	86:14
cyclohexanone	$OCH(CH_3)_2$	$(CH_3)_2CHCHO$	96:4
cycloheptanone	$N(C_2H_5)_2$	C_6H_5CHO	90:10
cycloheptanone	$OCH(CH_3)_2$	C_6H_5CHO	91:9

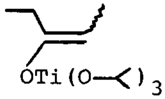
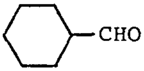
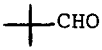
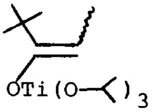
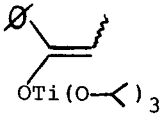
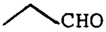
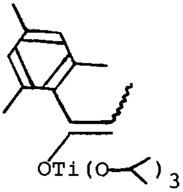
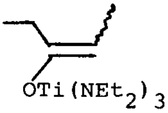
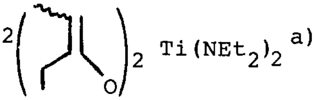
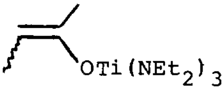
a) Determined by NMR and/or GC.

Enolates from acyclic ketones were also studied (Table 2). With the exception of entry 8 and 11 erythro adducts are favored irrespective of the geometry of the enolate. In order to check whether stereochemical integrity is maintained during the formation of the Ti-enolates, the enolate of entry 1 (obtained from a 36:64 Z/E mixture of Li-enolates) was quenched with trimethylchlorosilane. The resulting Z/E mixture of silyl enol ethers (34:66) shows that there is essentially no loss of stereochemistry. The same holds true for Z-enriched mixtures. The Ti-enolate in entry 6 was flash distilled (160-170 °C bath temp., 0.05 torr, 78 % yield). The NMR spectrum is identical to that of the non-distilled material [7]. Finally, kinetic control was demonstrated as follows: An independently synthesized erythro/threo mixture (34:66) of aldols from 3-pentanone and benzaldehyde was reacted with $CH_3Ti[OCH(CH_3)_2]_3$ liberating CH_4 and the Ti-enolate. The usual workup afforded an essentially unchanged erythro/threo mixture (36:64). The selectivities in tables 1 and 2 are presently difficult to rationalize. Either an acyclic transition state[2] is transversed, or a pericycle is involved, having a chair or boat conformation depending upon the substituents. A switch from chair to boat or vice versa could also be operating in irregularities reported for other enolates [1,2].

Reactions of titanium ate-complexes (Li-enolate + $Ti(OR)_4$) lead to lower selectivities. Initial experiments with trialkoxy-zirconium enolates also point to erythro diastereoselectivity. Finally, Ti- and Zr-enolates described here react with a variety of other electrophiles, e.g., acid chlorides (C-acylation-products).

The present study shows that the conversion of Li-reagents to Ti-analogs significantly alters selectivity, thereby extending the list of useful organotitanium reagents [8].

Table 2. Aldol Condensations Using Acyclic Ketones (10-20 mmol scale)

Entry	Enolate	(Z:E)	Aldehyde	erythro:threo ratio
1		(36:64)	C_6H_5CHO	89:11
2	"	"		77:23
3	"	"		81:19
4	"	(92:8)	C_6H_5CHO	88:12
5		(>98:2)	"	87:13
6		(>98:2)	"	87:13
7	"	"		89:11
8		(5:95)	C_6H_5CHO	20:80
9	"	(87:13)	"	90:10
10		(36:64)	"	76:24
11	"	(92:8)	"	41:59
12		(36:64)	"	84:16
13		(5:95)	"	74:26

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a) Prepared by the reaction of the Li-enolate with $Br_2Ti(NEt_2)_2$.

Acknowledgement: This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie

References and Notes:

1. Lithium: C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung and J. E. Sohn, J.Org.Chem. 45, 1066 (1980); S. Masamune, S. A. Ali, D. L. Snitman and D. S. Garvey, Angew.Chem. 92, 573 (1980); Angew.Chem., Int.Ed.Engl. 19, 557 (1980); J. F. Dubois and P. Fellmann, Tetrahedron Lett. 1975, 1225; H. O. House, D. S. Crumrine, A. Y. Teranishi and H. D. Olmstead, J.Am.Chem. Soc. 95, 3310 (1973); Boron: W. Fenzl and R. Köster, Liebigs Ann.Chem. 1975, 1322; D. A. Evans, E. Vogel and J. V. Nelson, J.Am.Chem.Soc. 101, 6120 (1979); M. Hirama, D. S. Garvey, L. D. L. Lu, S. Masamune, Tetrahedron Lett. 1979, 3937.
2. a) D. A. Evans and L. R. McGee, Tetrahedron Lett. 1980, 3975; Y. Yamamoto and K. Maruyama, ibid, 1980, 4607; b) Y. Yamamoto, H. Yatagai and K. Maruyama, J.Chem.Soc., Chem. Commun. 1981, 162; c) R. Noyori, I. Nishida and J. Sakata, J.Am.Chem.Soc. 103, 2106 (1981).
3. It makes no difference whether the Li-enolates are prepared by LDA deprotonation or by the reaction of silyl enol ethers with BuLi.
4. 1 is prepared by mixing $TiCl_4$ and $Ti[OCH(CH_3)_2]_4$; 2 is prepared similarly: $TiBr_4$ + $Ti(NR_2)_4$; see Gmelin Handbuch, Ti-Organische Verbindungen, 8. Auflage, Band 40, N.Y. 1977.
5. The effect of solvent on diastereoselectivity was found to be very small; chemical conversion is somewhat less than quantitative if THF is used.
6. Ti-enolates with amino groups as ligands were reacted at -78 °C, the alkoxy derivatives at -120 °C. Temperature effects were not substantial, however.
7. The H-NMR-spectrum is similar to that of the silyl enol ether.
8. For other cases see: M. T. Reetz, R. Steinbach, B. Wenderoth and J. Westermann, Chem. Industry, (London) 1981, 541; B. Weidmann, L. Widler, A. G. Olivero, C. D. Maycock and D. Seebach, Helv.Chim.Acta 64, 357 (1981).

(Received in Germany 1 September 1981)