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Diastereofacial Selection in Titanium Tetrachloride-Promoted Aldol Reactions with the Silyl Ketene Acetal of Methyl (R)-3-Hydroxybutanoate

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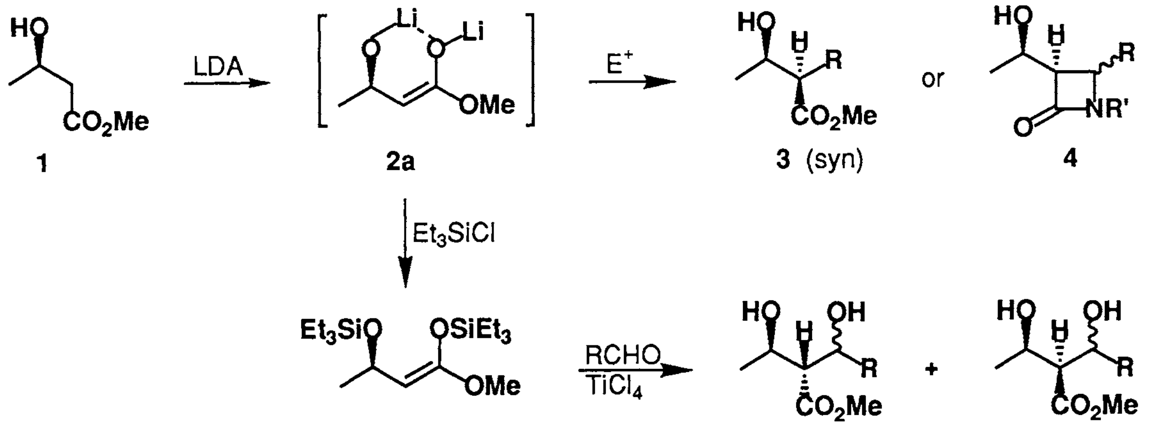
The title reaction is shown to exhibit a high level of "anti" diastereofacial selection, in contrast to the "syn" selection observed for the reaction with the dilithium enolate of the chiral ester. Mechanistic grounds for the "anti" stereoselection are discussed.

Recently much effort has been directed to the utilization of optically active 3-hydroxybutanoates such as **1**, now commercially available, as chiral building blocks,[1] especially for the carbapenem synthesis.[2] The previous studies have shown that the reactions of the dilithium enolate (**2a**) derived from **1** with carbon electrophiles (E^+) such as alkyl halides[3] and aldimines[2,4] show a high level of "syn" diastereofacial selection to afford selectively the products of type **3** and **4**, respectively (Scheme 1). However, we have recently found that the $TiCl_4$-promoted double-asymmetric aldol reaction of the silyl ketene acetal (**2b**) with (S)-2-methyl-3-benzyloxypropanal affords the "anti"-aldol of type **5** in an extremely high stereoselectivity.[5,6] This rather surprising observation prompted us to investigate the diastereofacial selection in the aldol reaction of **2b** with aldehydes in details. Herein we wish to disclose that the $TiCl_4$-promoted aldol reactions with the silyl ketene acetal **2b** provide a high level of "anti" diastereofacial selection in general, while the reactions with the dilithium enolate **2a** exhibit the "syn" selection as expected.



Scheme 1.

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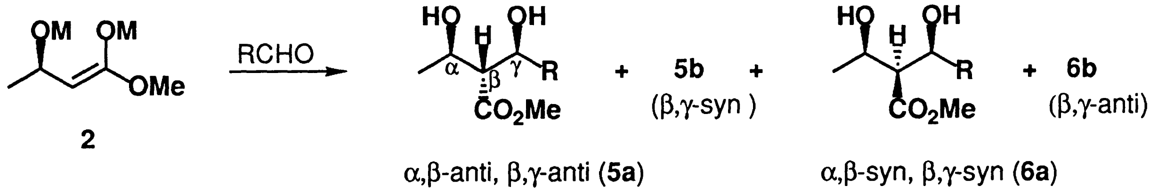
The reactions of **2b**[5)] with aldehydes were carried out in the presence of $TiCl_4$ (1 equiv.) under the standard conditions (CH_2Cl_2, -78 °C). Table 1 summarizes the stereochemical outcomes thus obtained, along with the results of similar reactions of the dilithium enolate **2a** which were run in THF at -78 °C. The stereochemical assignments of the products were made on the basis of ^1H NMR analysis of their acetonide derivatives[7)] and the stereoisomer distributions were determined by capillary GLC analysis.

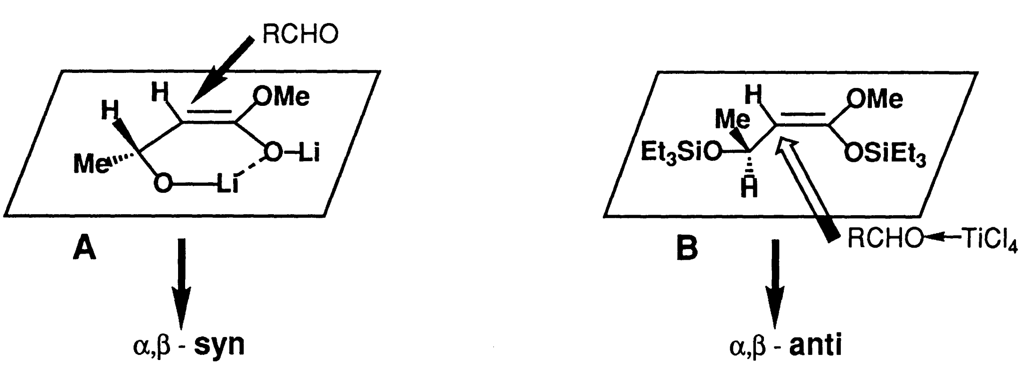
Table 1. Aldol Reactions of **2** with Aldehydes



RCHO	M in **2**	Diastereofacial selection α,β-anti (**5**) : syn (**6**) [a)]	Diastereoselection β,γ-anti : syn [b)]	Yield/%
$Me_3SiC{\equiv}CCHO$	$SiEt_3$	70 : 30	69 : 1	77
	Li	30 : 70	35 : 35	85
C_6H_5CHO	$SiEt_3$	93 : 7	85 : 8	75
	Li	22 : 78	34 : 44	86
$BnO(CH_2)_2CHO$	$SiEt_3$	85 : 15	69 : 16	47
	Li	18 : 82	30 : 52	64

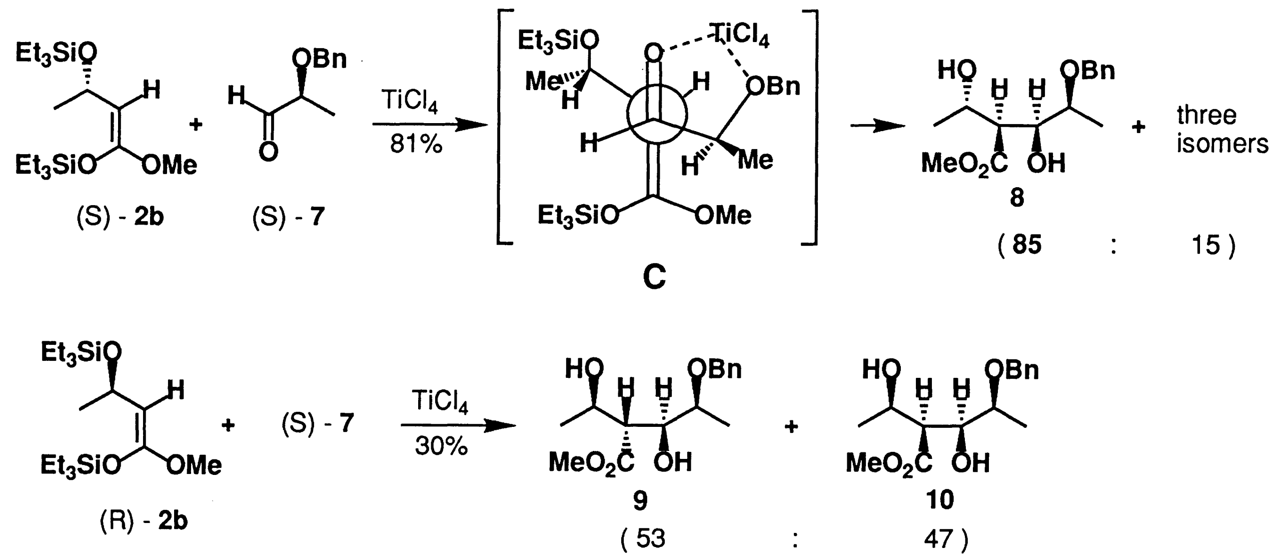
a) Calculated from the isomer distributions. b) Refers to the ratio only for the major diastereomer (**5** or **6**) determined by capillary GLC (URBON HR20M, 50 m).

Inspection of the data in Table 1 reveals that the aldol reactions with the silyl ketene acetal **2b** exhibit a relatively high "anti" diastereofacial selection in general, which contrasts with the "syn" selection generally observed with the dilithium enolate **2a**. The "syn" selectivity observed with **2a** is easily explained in terms of the chelated conformation **A** where the reaction occurs preferentially from the less congested top-side.[1)] On the other hand, the "anti" selection observed with **2b** requires a different preferred conformation for **2b**. Among possible candidates,[8)] we suggest the conformation **B** as the best one which should undergo the reaction preferentially from the less hindered bottom-side to provide the "anti" selection as we actually observed (Scheme 2).



Scheme 2.

To test this transition state model, we further carried out the double-asymmetric aldol reactions of (S)- and (R)-**2b** with (S)-2-benzyloxypropanal (**7**) with the prediction that the (S)-**2b**/(S)-**7** pair provides a higher stereoselectivity than the (R)-**2b**/(S)-**7** pair. Indeed, we found that the reaction of (S)-**2b** with (S)-**7** afforded the aldol product **8** with the α,β-anti configuration in a remarkably high stereoselectivity, whereas the (R)-**2b**/(S)-**7** pair provided a much lower degree of the α,β-anti selectivity to produce an almost 1:1 mixture of the aldols **9** and **10** (Scheme 3).9,10) The predominate formation of the isomer **8** is understandable as a result of the favorable double stereodifferentiation in which the inherent diastereofacial preferences of the two reactants may reinforce each other. In other words, it is likely that the reaction of the (S)-**2b**/(S)-**7** pair proceeds preferentially through the chelated antiperiplanar transition state (**C**) in which the silyl ketene acetal component **2b** possesses the conformation **B** described above.



Scheme 3.

In summary, we have demonstrated that the $TiCl_4$-promoted aldol reactions of the silyl ketene acetal **2b** of **1** provide a high level of "anti" diastereofacial selection in general, in contrast to the "syn" selection generally observed with the dilithium enolate **2a**. The present aldol methodology is potentially useful for the synthesis of carbapenem antibiotics. Further work along this line is in progress.

References

1) D. Seebach, R. Imwinkelried, and T. Weber, "Modern Synthetic Method 1986," ed by R. Scheffold, Springer-Verlag, Berlin (1986), Vol. 4, p. 204.

2) Review: T. Nakai and T. Chiba, *Farumashia*, **22**, 611 (1986).

3) G. Frater, *Helv. Chem. Acta.*, **62**, 2825 (1979).

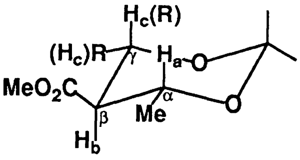
4) T. Chiba, M. Nagatsuma, and T. Nakai, *Chem. Lett.*, **1984**, 1927; T. Chiba, M. Nagatsuma, and T. Nakai, *ibid.*, **1985**, 651; T. Chiba and T. Nakai, *Tetrahedron Lett.*, **26**, 4647 (1985); D.-C. Ha, D. J. Hart, and T.-K. Yang, *J. Am. Chem. Soc.*, **106**, 4819 (1984); G. I. Georg, *Tetrahedron Lett.*, **25**, 3779 (1984); G. Cainelli, M. Contento, D. Giacomini, and M. Panunzio, *ibid.*, **26**, 937 (1985); In contrast,

however, the boron enolate derived from the phenylthio ester of **1** has been reported to exhibit "anti" diastereofacial selection in the reaction with an imine: T. Iimori and M. Shibasaki, *ibid.*, **26**, 1523 (1985).

5) F. Shirai and T. Nakai, *Tetrahedron Lett.*, **29**, 6461 (1988).

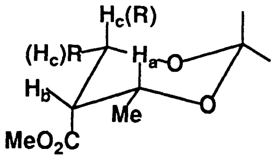
6) More recently it has also been reported that the reactions of the trimethylsilyl analog (**2b'**) of **2b** with benzylideneaniline and benzenediazonium tetrafluoroborate afford the "anti" products selectively: G. Guanti, E. Narisano, and L. Banfi, *Tetrahedron Lett.*, **28**, 4335 (1987); G. Guanti, L. Banfi, and E. Narisano, *Tetrahedron,* **44**, 5553 (1988). However, the sulfenylation of **2b'** has been reported to exhibit the "syn" diastereofacial selection: G. Guanti, L. Banfi, E. Narisano, and S. Thea, *Chem. Lett.*, **1988**, 1683.

7) For similar stereochemical assignment of structurally related acetonides, see: S.Thaisrivongs and D. Seebach, *J. Am. Chem. Soc.*, **105**, 7407 (1983). The most informative are the coupling constants for the diastereomeric acetonides derived from the aldols **5** and **6** as exemplified below. In a similar way, the β,γ-configurations of **5** and **6** were also assigned on the basis of the observed J_{bc}-values.



(acetonide of **5**)

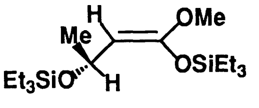
J_{ab} = 8.4 - 10.5 Hz



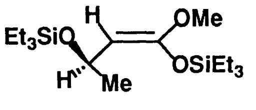
(acetonide of **6**)

J_{ab} = 2.7 - 7.2 Hz

8) Our experimental results could not be rationalized in terms of the conformation **B'**, similar to the preferred conformation of α-substituted allylic ethers proposed by Kishi for the osmylation: J. K. Cha, W. J. Chirst, and Y. Kishi, *Tetrahedron,* **40**, 2247 (1984). Another conformation **B"** is also unfavorable in terms of the great allylic strain, although we have previously proposed **B"** as the favorable conformation for **2b** (Ref. 5).



B'



B"

9) The stereochemistry of the aldols **8-10** was assigned by the ^{1}H NMR analysis of their acetonides as described in Ref. 7. The J_{ab}- and J_{bc}-values thus observed are as follows, respectively: 10.5 and 10.5 Hz for **8**; 8.8 and 5.9 Hz for **9**; 6.6 and 9.0 Hz for **10**.

10) In contrast, the reaction of the dilithium enolate (S)-**2a** with (S)-**7** was found to provide the α,β-syn diastereomers as the major products (α,β-syn / anti = 72:28) with the ratio of β,γ-syn / anti = 25:47.

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