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DIASTEREOSELECTIVITY IN THE ADDITION OF ENOLATE ANIONS TO N-METHOXYCARBONYLIMINES GENERATED IN SITU FROM α-METHOXY CARBAMATES[1]

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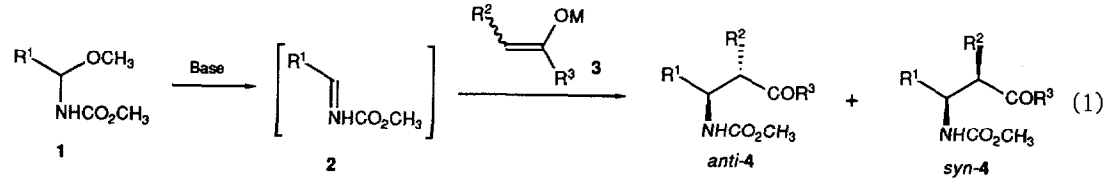
Summary: The diastereoselectivity of the addition of enolate anions of ketones or esters to N-Methoxycarbonylimines generated in situ from α-Methoxy carbamates was studied.

Recently we have reported that the nucleophilic addition of enolate anions of alkyl acetates or 2-methyloxazolines to N-methoxycarbonylimines 2 generated in situ from α-methoxycarbamates 1 gave β-amino acid derivatives.[2] We wish to report herein the diastereoselectivity in the addition of enolate anions 3 derived from ketones or esters to 2 (eq 1).



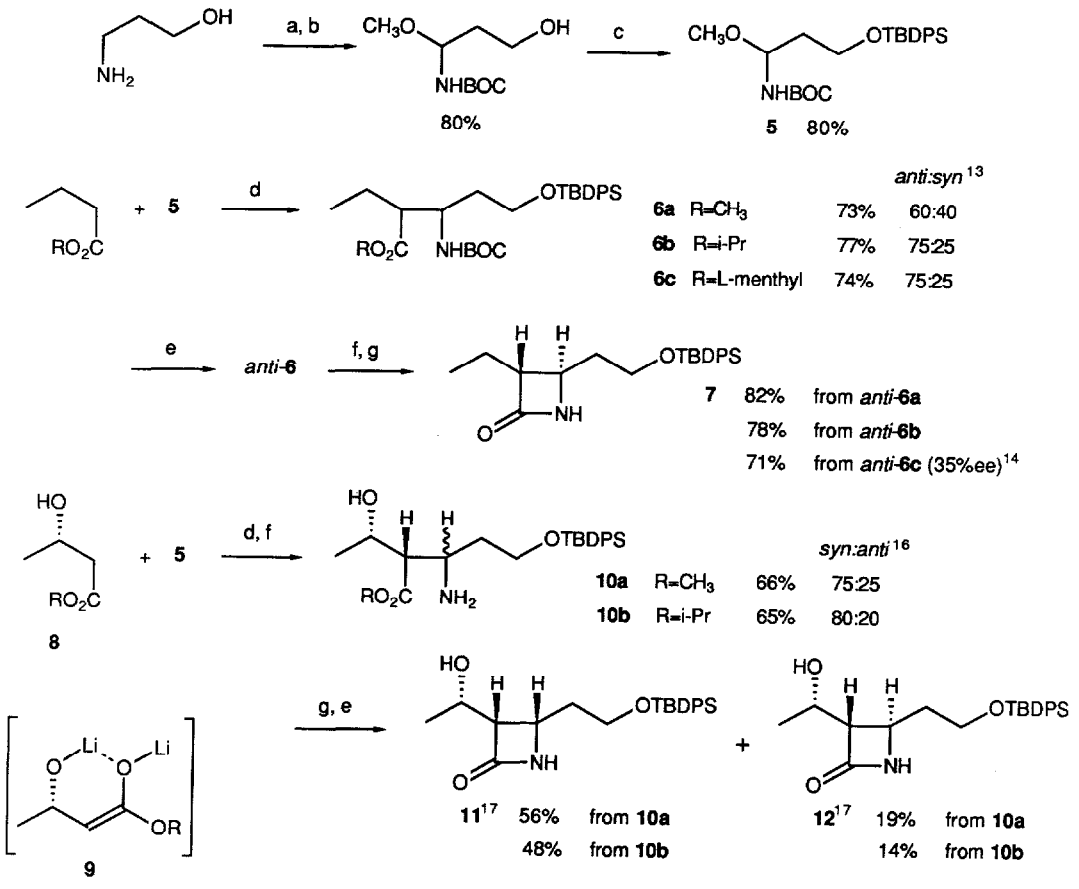
(1)

General procedure is as follows: A mixture of 1 (5mmol) and a ketone or an ester (6mmol) in THF (5ml) was added to a solution of LDA (12mmol) in THF-hexane (15ml) at -70 °C. The temperature was gradually raised to 0°C and the mixture was stirred for additional 2 hrs. After usual work-up, the diastereomeric ratio was determined by GLC analysis. Each diastereomer could be separated by column chromatography on silica gel.

The results are summarized in Table 1. Cyclic ketones gave anti-adducts preferentially (Run 1-4), whereas acyclic ketones afforded syn-adducts mainly (Run 5-8). The reaction of ester enolates showed anti-diastereoselectivity (Run 9-16). These selectivities are consistent with those of the corresponding aldol reactions with aldehydes[3] and may be explained by Zimmerman-Traxlar transition states.[4]

Next, we have studied the reaction of ester enolate 3 (R^2=Et, R^3=OMe) with 1 in the presence of some Ti-complexes.[5] The diastereoselectivity was little influenced by the addition of $TiCl_4$, $TiCl_2(Oi\text{-}Pr)_2$, or $TiCl(Oi\text{-}Pr)_3$, while it was noteworthy that syn-selectivity was observed in the presence of $Ti(Oi\text{-}Pr)_4$ (R^1=Me: 89% yield, anti:syn=4:6; R^1=i-Pr: 90% yield, anti:syn=1:9). Although the role of $Ti(Oi\text{-}Pr)_4$ is not clear at present, such inversion of the selectivity brought by the addition of $Ti(Oi\text{-}Pr)_4$ has been hitherto unknown.[7]

The reaction of ester enolates with 1 is expected to be a useful method for the synthesis of 3,4-disubstituted β-lactams, which are precursors of carbapenem antibiotics. Some of our preliminary results are described in scheme 1.[10] Treatment of a mixture of an alkyl butyrate and 5 with LDA gave the anti-adduct preferentially. After separetion of the stereoisomers, anti-6 was transformed to trans-β-lactam 7. On the other hand, syn-adduct was obtained as the major isomer by the reaction of (S)-alkyl 3-hydroxybutyrate 8 with 5, since the generation of the intermediate Z-enolate 9 by the treatment of 8 with two equivalents of LDA made the formation of syn-adduct favorable. Treatment of the adducts 10 with LDA gave cis-β-lactam 11 (major) and trans-β-lactam 12 (minor). (R)-alkyl 3-hydroxybutyrate also gave the enantiomers of 11 and 12 by the same method.



(a) $(BOC)_2CO$, $CHCl_3$, reflux, 3h; (b) - e, 0.04M Et_4NOTs/MeOH, 8F/mol; (c) TBDPSCl, imidazole, DMF, 0°C, 2h; (d) LDA, THF, -70°C→0°C, 2h; (e) Seperation of isomers by column chromatography on silica gel; (f) TFA, 0°C, 30min; (g) LDA, THF, 0°C, 2h.

Scheme 1

Table 1

Run	1	R^1	3	R^2	R^3	Yield of 4 (%)[a]	anti-4/syn-4[b]
1	1a	Me	3a	$-(CH_2)_3-$		72	7/3
2	1b	i-Pr	3a	$-(CH_2)_3-$		52	9/1
3	1b	i-Pr	3b	$-(CH_2)_4-$		86	9/1
4	1c	Ph	3a	$-(CH_2)_3-$		57	7/3
5	1a	Me	3c	Me	Et	61	3/7
6	1b	i-Pr	3c	Me	Et	76	1/9
7	1b	i-Pr	3d	Me	Ph	88	2/8
8	1c	Ph	3c	Me	Et	61	3/7
9	1a	Me	3e	Et	OMe	78	7/3
10	1a	Me	3f	Et	Oi-Pr	83	8/2
11	1a	Me	3g	i-Pr	OMe	88	7/3
12	1b	i-Pr	3e	Et	OMe	86	7/3
13	1b	i-Pr	3f	Et	Oi-Pr	92	8/2
14	1b	i-Pr	3g	i-Pr	OMe	92	8/2
15	1b	i-Pr	3h	Ph	OMe	82	7/3
16	1d	t-Bu	3e	Et	OMe	93	9/1

a Isolated yields. Satisfactory spectroscopic and elemental analyses were obtained.
b Determined by GLC analysis. See ref. 8.

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References and Notes

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2. T. Shono, N. Kise, F. Sanda, S. Ohi, and K. Tsubata, Tetrahedron Lett., 29, 231 (1988).
3. C. H. Heathcock, In "Asymmetric Synthesis"; J. D. Morrison, Ed.; Academic Press: London, 1984; Vol III, pp 111-212.
4. H. E. Zimmerman and M. P. Traxlar, J. Am. Chem. Soc., 79, 1920 (1957).
5. Reetz and Peter have reported that the reactions of Ti-enolate (Li-enolate + $TiClX_3$) and Ti ate-complex (Li-enolate + $Ti(Oi\text{-}Pr)_4$) derived from ketones generally showed syn-selectivity irrespective of enolate geometry.[6]
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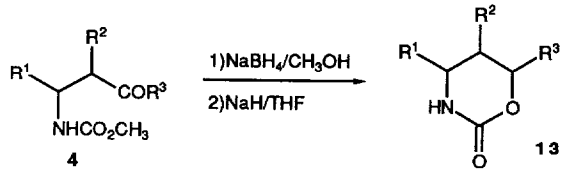
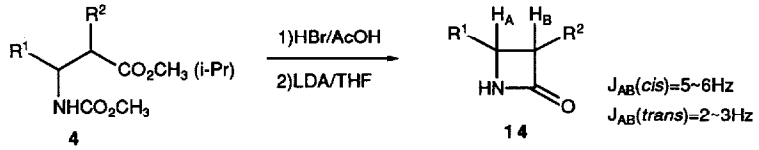
8. Stereoconfiguration of the adducts 4 obtained from ketones (Run 1-8) were determined by their transformation to cyclic carbamates 13 and their ^{1}H-NMR analysis according to the reported method.[9]



Stereochemistry of 4 derived from esters (Run 9-16) was confirmed by their conversion to β-lactams 14 and their ^{1}H-NMR spectra.



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10. PS-5[11] and 8-Epithienamycin[12] were synthesized from 7 and 12, respectively.

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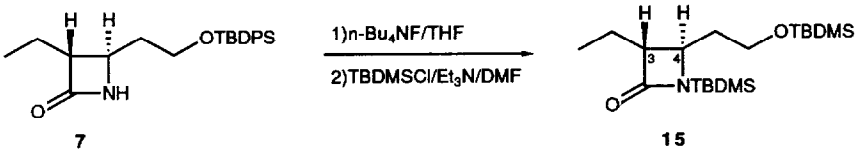
13. The diastereomeric ratio was determined by 400MHz ^{1}H-NMR spectrum.

14. The absolute configuration was determined to be 3R4R by its conversion to 15: $[\alpha]_D^{20}$=-13.7 (c1.5, $CHCl_3$)(Lit.[15] -39.6).



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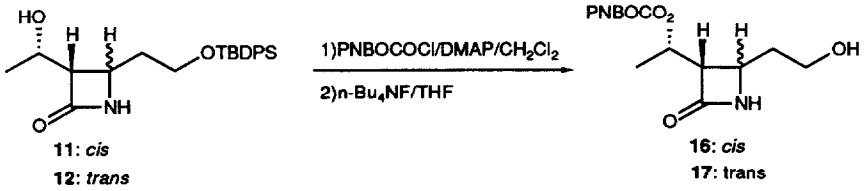
16. The adduct 10 was found to be a mixture of two stereoisomers on the basis of 400MHz ^{1}H-NMR analysis, though these could not be separated.

17. 11: $[\alpha]_D^{20}$=-7.5 (c1.0, $CHCl_3$). 12: $[\alpha]_D^{20}$=+18.0 (c1.0, $CHCl_3$). Stereostructures of 11 and 12 were assinged by their transformation to the known compounds 16 and 17.[18]



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