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On the Reversal of the Stereoselectivity in the Evans Aldol Reaction of α-Amino Aldehydes

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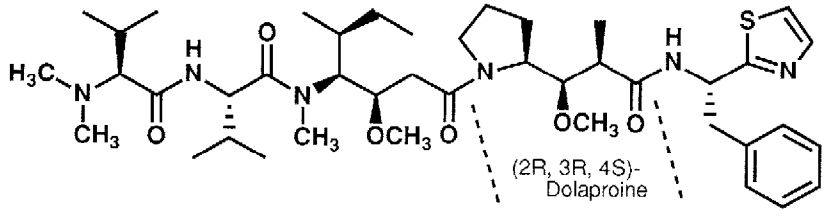
Key Words: Evans aldol reaction; stereoselectivity; α-amino aldehyde; dolastatin 10; syn and anti isomers

Abstract : Reversal of the stereoselectivity in the Evans aldol reaction of Boc-(S)-prolinal (**3**), observed during the total synthesis of dolastatin 10 (**1**), was proved to be due to the amounts of dibutylboron triflate and triethylamine. (R)-Alaninal derivatives (**14**) also showed the analogous reversal of the stereoselectivity.

We have already accomplished[1] the stereoselective total synthesis of dolastatin 10 (**1**), a potent antineoplastic pentapeptide isolated from an Indian Ocean sea hare *Dolabella auricularia*.[2-4] In our preparation of (2R,3R,4S)-dolaproine,[1] one of the constituents of dolastatin 10, the unexpected reversal of the stereoselectivity was observed in the Evans aldol reaction of *tert*-butyloxycarbonyl (Boc)-(S)-prolinal (**3**) with the oxazolidinone **2**. We now wish to report the detailed investigation of this reaction and the extension of the reaction to the other α-amino aldehydes and benzaldehyde.



Dolastatin 10 (**1**)

Our initial interest was turned toward the effects of the amounts of the reagents, dibutylboron triflate and triethylamine, as well as the order of the addition of these reagents. The results of the aldol reaction of Boc-(S)-prolinal (**3**) with the oxazolidinone **2** are summarized in Table 1.[5]

Only the expected syn adduct **4** was produced in excellent yield when triethylamine was used in excess over dibutylboron triflate (entries 1-4). The anti adduct **5** could not be found in the product at all. In contrast to this, the anti adduct **5** was produced as the major product when an excess of dibutylboron triflate existed (entries 5 and 6).[6,7] However, the order of the addition of the reagents did not affect the product ratio

(compare entries 1, 3, and 5 with entries 2, 4, and 6, respectively). Thus, it was clearly proved that an excess of dibutylboron triflate over triethylamine caused the reversal of the stereoselectivity in the Evans aldol reaction while the order of the addition of the reagents was indifferent in the stereochemical course.[8]

Scheme 1

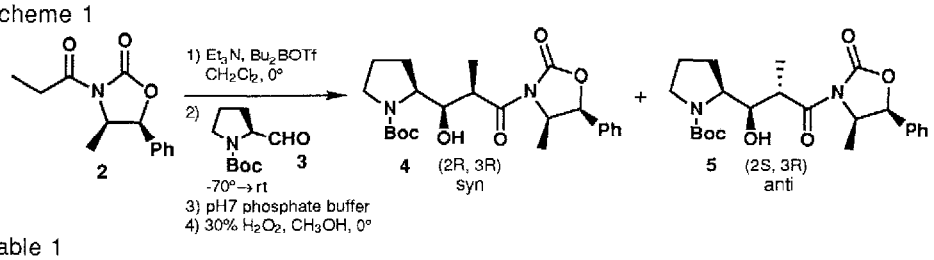


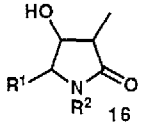
Table 1

entry	addition order[a]	2 (eq)	Et_3N (eq)	Bu_2BOTf (eq)	3 (eq)	product ratio[b] 4 : 5	combined[c] yield (%)
1	A	0.9	1.2	1.0	1.0	100:0	82
2	B	0.9	1.2	1.0	1.0	100:0	92
3	A	1.8	2.0	1.8	1.0	100:0	99
4	B	1.8	2.0	1.8	1.0	100:0	92
5	A	0.77	1.08	1.15	1.0	0:100[d]	53(85)
6	B	0.77	1.08	1.15	1.0	5:95	83

a) A: Et_3N then Bu_2BOTf; B: Bu_2BOTf then Et_3N. *b*) Determined from isolated yields. *c*) The value in parentheses is conversion yield. *d*) The other diastereomer with unknown stereochemistry was obtained in 5% yield.

We subsequently expected this phenomenon to be extended to the other aldehydes. The α-amino aldehydes **11**-**14**[9] and benzaldehyde (**15**) similarly reacted with either the oxazolidinone **2** or **6** under the reaction conditions by use of an excess of either triethylamine (condition A) or dibutylboron triflate (condition B).[5] As shown in Table 2, (S)-prolinal protected with the benzyloxycarbonyl (Z) group (**11**) gave the similar result as in the case of the Boc derivative **3**. (R)-Alaninal protected with the Boc or Z group (**14a** or **14b**) also reacted with the oxazolidinone **6** to give the corresponding anti aldol adducts **10** as the major products when an excess of dibutylboron triflate over triethylamine was used. Both the chemical yield and the stereoselectivity, however, were moderate in this case. In contrast to these, Boc-(S)-valinal (**12a**), Boc-(S)-N-methylvalinal (**12b**), Boc-(S)-isoleucinal (**13**), and benzaldehyde (**15**) always afforded the syn isomers even when an excess of dibutylboron triflate was used. In general, use of an excess of dibutylboron triflate caused the decrease of the combined yields of the syn and anti isomers.

Furthermore, when Boc-(S)-valinal (**12a**) and benzaldehyde (**15**) were used under the reaction condition B, the third aldol products (syn) were produced in ca. 25% yield. The stereochemistry of the aldol products were determined after conversion to the pyrrolidone derivatives **16** by their ^{1}H-NMR spectra.[10]



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Scheme 2

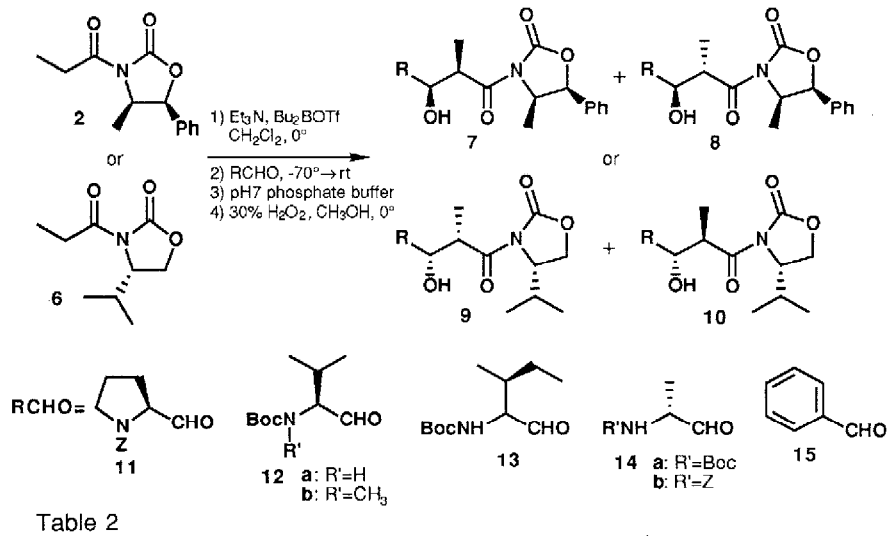
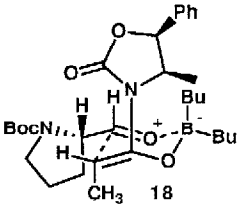


Table 2

entry	RCHO	oxazolidinone	reaction condition[a]	product ratio[b] syn : anti	combined yield (%)[c]
1	**11**[d]	**2**	A	**7**:**8**, 100:0	82
2	**11**[d]	**2**	B	**7**:**8**, 2:98	74 (99)
3	**12a**	**2**	A	**7**:**8**, 100:0	100
4	**12a**	**2**	B	**7**:**8**, 63:14[e]	18 (53)
5	**12b**	**2**	A	**7**:**8**, 100:0	96
6	**12b**	**2**	B	**7**:**8**, 100:0	8 (41)
7	**13**	**2**	A	**7**:**8**, 100:0	100
8	**13**	**2**	B	**7**:**8**, 100:0	15 (55)
9	**14a**	**6**	A	**9**:**10**, 100:0	100
10	**14a**	**6**	B	**9**:**10**, 38:62	25 (44)
11	**14b**[d]	**6**	A	**9**:**10**, 100:0	53
12	**14b**[d]	**6**	B	**9**:**10**, 18:82	36 (100)
13	**15**	**2**	A	**7**:**8**, 100:0	91
14	**15**	**2**	B	**7**:**8**, 66:8[e]	87

a) A: aldehyde (1eq), imide (1.8eq), Et_3N (2eq), Bu_2BOTf (1.8eq); B: aldehyde (1eq), imide (0.77eq), Et_3N (1.08eq), Bu_2BOTf (1.15eq). *b*) Determined from isolated yield. *c*) Isolated yield. The values in parentheses are conversion yields. *d*) Used without purification. *e*) Corresponding another aldol adducts were respectively produced in the ratio of 23% for entry 4 and 26% for entry 14.

Although the stereochemical outcome in the Evans aldol reaction lacks the generality, the reaction of both prolinal and alaninal derivatives may be explained by the transition states **18** and **19**.[6] When triethylamine is used in excess, the closed transition state **18** will be dominant. On the contrary, the reaction will proceed mainly via the open transition state **19** when an excess of dibutylboron triflate is present.



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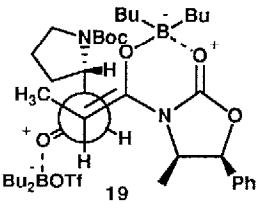

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In conclusion, the cause of the reversal of the stereoselectivity in the Evans aldol reaction is the presence of an excess of dibutylboron triflate but not the addition order initially suggested.[1]

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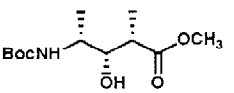
5. Each reaction was carried out analogously to the procedure by Gage, J.R.; Evans, D.A. *Org. Synth.* **1989**, *68*, 83.
6. (a) Danda, H.; Hansen, M.M.; Heathcock, C.H. *J. Org. Chem.* **1990**, *55*, 173. (b) Heathcock, C.H. *Aldrichimica Acta* **1990**, *23*, 99.
7. See the reference 1 for the assignment of the stereochemistry of the aldol adducts **4** and **5**.
8. Our initial suggestion that the change of the stereochemical course is due to the addition order[1] should be corrected.
9. Prepared according to our method. (a) Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921. (b) Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252.
10. The syn adduct **9** from **14a** was led to the known compound **17**, the spectral data of which was identical with that of the literature: DiPardo, R.M.; Bock, M.G. *Tetrahedron Lett.* **1983**, *24*, 4805.



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