Tetrahedron Letters, Vol. 33, No. 12, pp. 1651-1654, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

Asymmetric Induction in Aza-Claisen Rearrangement of Carboxamide Enolates. Effect of Chiral Auxiliary on Nitrogen.

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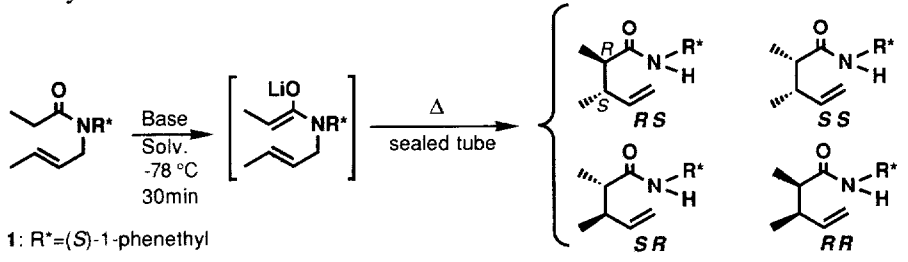
Key words amide enolate; aza-Claisen rearrangment; remote stereocontrol; asymmetric induction.

Abstract : *Aza-Claisen rearrangment of enolates of* N-*alkyl*-N-*(2E)-butenylpropanamides with chiral alkyl groups proceeded with high relative asymmetric induction as well as excellent internal asymmetric induction to give optically active* N-*alkyl*-syn-*2,3-dimethylpent-4-enamides.*

The Ireland-Claisen rearrangment of allyl ester enolates has frequently been applied to the stereocontrolled C-C bond formation because of its excellent diastereoselectivity.[1] However, being "self-immolative",[2] the reaction is not well suited for the asymmetric induction, and the most studies along this line utilized carboxamides or their equivalents.[3,4] As we have succeeded recently in achieving excellent internal asymmetric induction (syn:anti=199:1)[5] for the reaction of the enolate derived from *N*-(2*E*)-butenyl-*N*-butylpropanamide, we have extended the reaction to the amide enolates containing chiral alkyl groups (R*), and found high selectivitiy in relative asymmetric induction in addition to the syn selectivity described above.



1: R*=(*S*)-1-phenethyl

2: R*=(*S*)-1-phenethyl

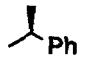
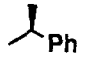
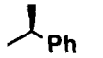
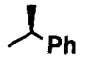
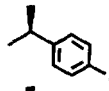
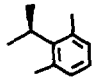
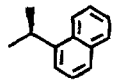
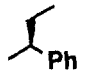
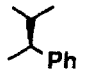
The typical reaction was carried out as follows. For example, (1'*S*)-*N*-(2*E*)-butenyl-*N*-1'-phenethylpropanamide (**1**) was treated with Li diisopropylamide (LDA) or Li hexamethyldisilazide (LHMDS) in THF or toluene at -78 °C under Ar atmosphere. After 30 min, the reaction mixture was allowed to warm up to room temperature, and sealed in a pressure

tube.[6] Heating of the sealed solution at 120~140 °C for 2~6 h gave a mixture of the rearranged products.[7]

While the absolute configuration of the major product ***2RS*** was established by its chemical transformation to (+)-2*R*,3*R*-dimethylsuccinic acid (**3**),[8] the diastereomeric ratio and the relative configuration of all products were confirmed by the comparison of their retention times (R_t) in LC or GLC with those obtained by the Claisen rearrangement of the enolate of (2*E*)-butenyl propanoate[9] and subsequent (*S*)-1-phenethyl amide formation (successive treatment with $(COCl)_2$ and (*S*)-1-phenethylamine). The *RS* product was always formed predominantly, and can easily be purified by SiO_2-column chromatography.

The effect of the bases and solvents was investigated using **1** and is shown in Table.

Table. Asymmetric Aza-Claisen Rearrangement of Chiral Propanamides

		Conditions				Isolated	Ratio (syn / anti)
Entry	R*	Base [a]	Solv.	Temp. (°C)	Period (h)	Yield (%)	***RS*** / ***SR*** / ***SS*** / ***RR***
1		LDA	THF	120	6	66	77 / 21 / <1 / 1
2		LDA	THF	140	2	79	77 / 22 / - / -
3		LDA	Toluene	120	6	68	89 / 11 / - / -
4		LHMDS	Toluene	120	6	85	89 / 11 / - / -
5		LHMDS	Toluene	120	6	76	88 / 12 / - / - [b]
6		LHMDS	Toluene	120	6	90	87 / 12 / 1.6 / - [b, c]
7		LHMDS	Toluene	120	6	83	82 / 16 / - / 1.6
8		LHMDS	Toluene	120	6	80	92 / 8 / - / - [b]
9		LHMDS	Toluene	120	6	76	85 / 15 / - / - [b]
10		t-BuLi	Toluene	150	4	38	10 / 90 / - / -

a. 1.2 equiv. of LDA and 1.5 equiv. of LHMDS were employed.

b. The absolute configuration was assigned in analogy with the case of **1** (entry 1) using the R_t values of diastereomers in LC.

c. Absolute configuration of anti isomers was assigned by the retention times in LC in analogy with syn isomers, and is therefore ambiguous.

LDA in THF gave the syn products **2*RS*** and **2*SR*** in the ratio of about 3.7:1 (entry 1), but higher temperature in shorter period gave the products in better yield (entry 2). In toluene, the ratio increased to 8.1:1 but the yield lowered probably due to the solubility of LDA in toluene (entry 3). The use of LHMDS in toluene at 120 °C for 6 h afforded only syn products (**2*RS*** and **2*SR***) in 85% yield with the same ratio (entry 4).

Having attained satisfactory result, the effect of other chiral auxiliaries was examined under the best conditions (entry 4). The results are also shown in Table. The electronic factor has little effect (entry 5); the increase in the bulkiness of the aromatic part of the phenethyl group resulted in the similar yields but lower ratios (entries 6 and 7); the increase of bulkiness in methyl part increased the ratio to some extent (entries 8 and 9). Thus, neither electronic nor steric effect was not dramatic. The reaction of 1,2,2-trimethylpropyl amide proceeded very slowly, and, surprisingly enough, reversed the ratio (9:1) in favor of the *SR* product to *RS* (entry 10).

Although a rationale for the *S*, *R* selectivity, especially the reversal of the selectivity, observed here have to wait further elaboration, the high selectivity in the relative asymmetric induction as well as the excellent syn selectivity in the internal asymmetric induction disclosed in the present study would make aza-Claisen rearrangement useful methodology in asymmetric synthesis.

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4. Quite recently, excellent enantioselective Ireland-Claisen rearrangement using a chiral boron reagent has been reported. Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026-4028.
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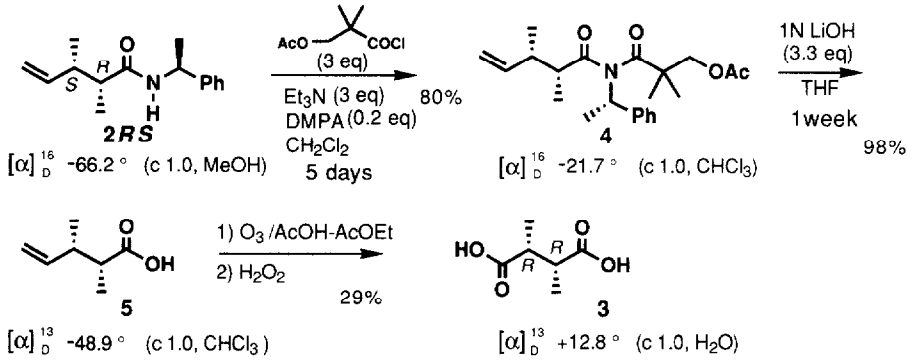
6. An air-tight cylinder for high pressure experiments available at Alltech Associates, Inc..
7. The solvent exchange procedure practiced in the previous paper [5a)] was modified as described here. The present method is simpler and more reliable, and gives better diastereomeric ratio in general.

8. For example, two isomers obtained in entry 2, Table, were separated by SiO_2-column chromatography, and the major product **2*RS*** was hydrolyzed[10] to the corresponding carboxylic acid **5**, via the imide **4**. Ozonolysis of **5** afforded (+)-2*R*,3*R*-dimethylsuccinic acid **3**.[11]



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(Received in UK 4 November 1991)