

ASYMMETRIC SYNTHESIS WITH AMINO ACID II
 ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE
 4,4-DISUBSTITUTED-2-CYCLOHEXENONE

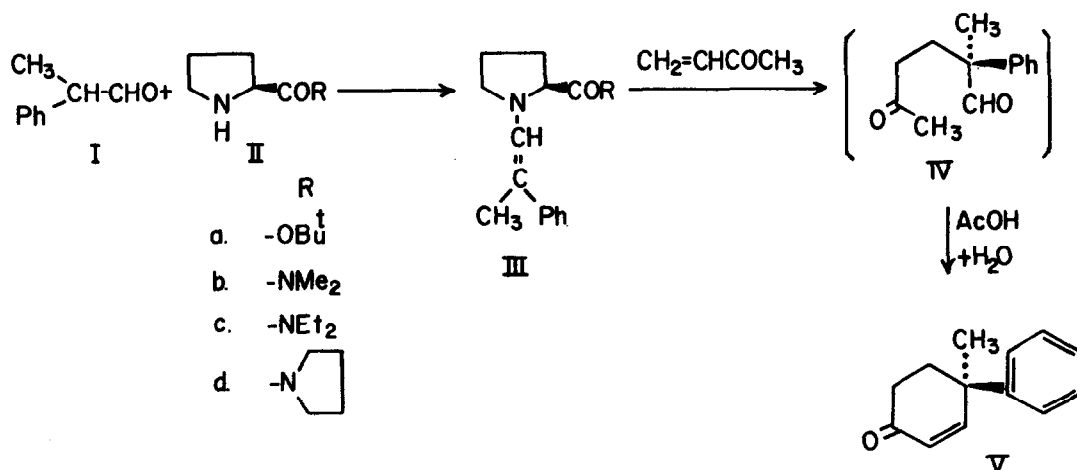
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In an earlier communication¹⁾, asymmetric alkylation of cyclohexanone enamine was described. This paper deals with an extension of this reaction to the aldehyde enamine. Enamine alkylation was devised by Stork and his co-workers²⁾ for the alkylation of carbonyl compounds. In this method, pyrrolidine is generally used as an amino component. Using asymmetric induction, alkylation of several enamines from aldehydes and L-proline derivatives, pyrrolidines with an asymmetric center, were examined. We successfully obtained optically active 4,4-disubstituted 2-cyclohexenones which are ring-closed compounds of α -alkylated aldehyde.



As a model experiment, 2-phenylpropanal I was selected as an aldehyde component and several L-proline derivatives (IIa-d), as amines for enamine formation. Proline t-butyl ester gave the highest optical yield on alkylation of cyclohexanone enamine¹⁾. The enamines (IIIa-d), prepared from I and IIa-d were alkylated with methyl vinyl ketone in methanol at 0°C for 4 hrs. Aqueous acetic acid was added to this reaction mixture which was refluxed for another 2 hrs. In each experiment, R(+)-4-Methyl-4-phenyl-2-cyclohexenone V was obtained in 40-50% yields without isolation of ketoaldehyde IV. The optical yield of V was highest when IIc was employed as an amine component (Table 1).

Table 1 Asymmetric Synthesis of V with Various L-Proline Derivatives (II).
(0°C, 4 hrs., in MeOH)

R	ya)		
	Yield (%) ^{b)}	$[\alpha]_D$ (EtOH)	Optical Yield (%) ^{c)}
-OBut	43	+7.6°	6.0
-N $\begin{array}{l} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{array}$	42	+40.3°	31.0
-N $\begin{array}{l} \diagup \text{C}_2\text{H}_5 \\ \diagdown \text{C}_2\text{H}_5 \end{array}$	53	+34.9°	26.8
-N $\begin{array}{l} \diagup \text{C}_6\text{H}_5 \\ \diagdown \text{C}_6\text{H}_5 \end{array}$	48	+47.4°	36.5

a) b.p. 120-22°C/3 mmHg. Semicarbazone m.p. 193-95°C.

b) Based on I.

c) Based on S(-)-3-methyl-3-phenylglutaric acid anhydride ($[\alpha]_D^{19}$ -144° (THF)) to which V was led.

Solvents used in alkylation significantly effected the optical yield. Among alcohols such as CH₃OH, C₂H₅OH and t-BuOH, the less bulkier alcohols increased optical yields. In the case of CH₃OH diluted with non-hydroxylic solvents optical yield increased as the added solvent became less polar. When alkylation reaction was performed in MeOH-benzene (1:9), optical yield went up to approximately 50%. (Table 2)

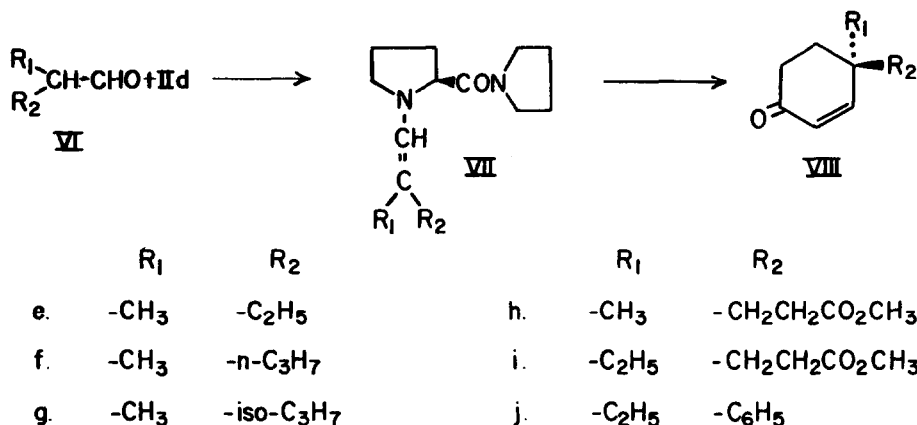
This enamine was alkylated only in the presence of alcohols not in non-hydroxylic solvents which have previously been reported to be used in enamine alkylation.

Table 2 Solvent Effect on Alkylation of III to Optical Yield of V. (0°C, 24 hrs.)

Solvents	V	
	α_D (EtOH)	Optical Yield (%)
MeOH-THF (10:3) ^{a)}	+47.2°	37
EtOH-THF (10:3) ^{a)}	+35.7°	28
t-BuOH-THF (10:3) ^{a)}	+28.0°	22
MeOH-DMSO (1:9)	+18.7°	14.4
MeOH-CHCl ₃ (1:9)	+53.0°	40.8
MeOH-CCl ₄ (1:9)	+61.6°	47.3
MeOH-C ₆ H ₆ (1:9)	+63.8°	49.1

a) THF was added in t-BuOH to inhibit freezing at lower temperatures and for comparison of t-BuOH with MeOH and EtOH, the same ratio of THF was added to both.

Fig 1



The asymmetric synthesis mentioned above was confirmed to be generalized in combination with other α -disubstituted aldehydes (VIe-j) and IIId which gave the highest optical yield. (Fig 1) Enamines from disubstituted acetaldehydes (VIe-j) and IIId were alkylated with methyl vinyl ketone in methanol at 0°C and all 4,4-disubstituted 2-cyclohexenones (VIII) obtained were optically active. (Table 3)

Table 3 Asymmetric Synthesis of 4,4-Disubstituted 2-Cyclohexenones VIII

VIII	R ₁	R ₂	B.P. °C (m.m.)	Yield (%)	α_D (MeOH)
e	CH ₃	C ₆ H ₅	92-94 (15)	15	+1.11 (2.16)
f	CH ₃	n-C ₈ H ₇	101-103 (14)	13	+4.96 (2.26)
g	CH ₃	iso-C ₈ H ₇	96-98 (10)	10	-5.96 (1.11)
h	CH ₃	CH ₃ -CH ₂ -COOCH ₃	124-126 (3)	46	+12.4 (1.35)
i	C ₆ H ₅	CH ₃ -CH ₂ -COOCH ₃	139-140 (3) ^{a)}	11.4	+7.55 (1.06)
j	C ₆ H ₅	C ₆ H ₅	126-129 (5)	35	+42.8 (1.13)

a) The optically inactive compound has been synthesized by Stork et al.¹⁾

All these cyclohexenones obtained showed a positive Cotton effect at the 350 m μ region, hence these have the same absolute configuration. Absolute configurations of the two compounds, (+)V (EtOH)³⁾, and (-)VIIIg (MeOH)⁴⁾, were established by chemical correlation and were proven to be the structures V and VIII. Accordingly, when conformation energy of the substituent R₁ is smaller than that of R₂, the absolute configuration of cyclohexenones obtained in this asymmetric synthesis is expressed by the structure VIII.

This is the first work ever reported for efficient asymmetric synthesis by alkylation of aldehyde enamines. This method may be useful in the synthesis of optically active compounds. An extension of this work to the synthesis of natural products such as alkaloids, terpenes and others is now in progress.

References

- 1) S. Yamada, K. Hiroi, and K. Achiwa, Tetrahedron Letters.
- 2) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, J. Am. Chem. Soc., **85**, 207 (1963).
- 3) The compound, (+)V(EtOH) was chemically correlated to 2-methyl-2-phenylbutanoic acid whose absolute configuration had been known. (D.J. Gram, and J. Allinger, J. Am. Chem. Soc., **76**, 4516 (1954).
- 4) The compound (-)VIIIg(MeOH) was also chemically correlated to 2-methyl-2-isopropylsuccinic acid which had been known of absolute configuration. (M.V. Kulkarni, and E.J. Eisenbraun, J. Org. Chem., **33**, 1661 (1968)).