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Asymmetric Induction in the Baylis-Hillman Reaction

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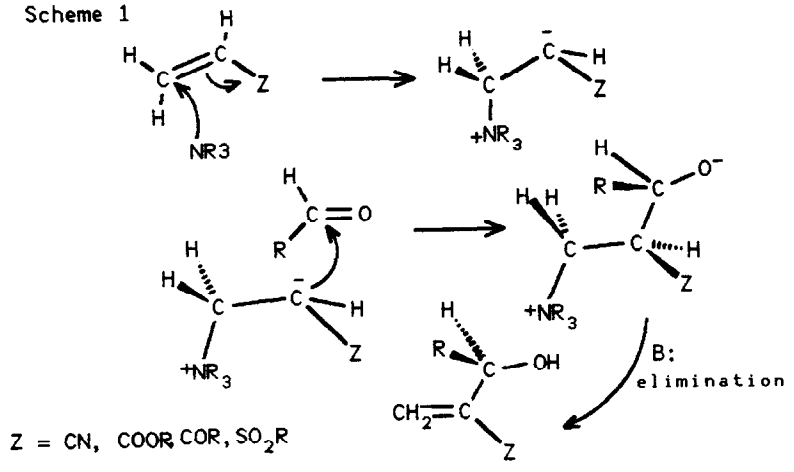
Abstract; Asymmetric induction in the product of the Baylis-Hillman reaction between an aldehyde and an acrylic compound in the presence of a tertiary amine base, may be controlled by chirality in the aldehyde, acrylic ester, base or solvent;
R-CHO + CH_2=CH-COOR' (B:, solvent) --> CH_2=C(C*HROH)-COOR'
Examples of each are described but the best stereochemical result, 100% ee, is obtained from the high pressure reaction of benzaldehyde with (-)-menthyl acrylate .

The Baylis-Hillman Reaction is the name given to the addition of an acrylic derivative to an aldehyde or ketone in the presence of a tertiary amine to form an α-(hydroxyalkyl) acrylic product by the sequence, depicted in Scheme 1 (1-4):

Scheme 1



The product contains a new chiral centre and there exist in this reaction rich possibilities for induction of enantiomeric excess at the new centre. Four possible origins of a chiral environment for the transition state may be considered by the use of a chiral acrylate ester, a chiral aldehyde or ketone, a chiral base or a chiral solvent. This communication reports the application of chiral directors in each of these categories. However, only by the use of chiral acrylic esters has high enantiomeric excess in some products been found, this amounting to ca.100% in one case. Rates of these reactions are known to be highly susceptible to pressure (4). Indeed, in many cases no product may be formed at all at atmospheric pressure even after several weeks while good yields may be obtained overnight at 7-8 kbar, conditions which were used in the main in the present work. In order to minimise polymerisation of the acrylate esters which can also be induced by high pressure, an excess of the aldehyde (4:1)was used. Previous studies have also shown that the nature of the base has a profound effect on rates of the reaction. Diazabicyclo[2,2,2]octane (DABCO) is among the most active catalysts and was used for most experiments. When this was replaced by other bases, as of necessity when examining chiral catalysts, yields were usually poor or the reaction even failed altogether. Analysis of the products was carried out by hplc using an ionic Pirkle column based on leucine (DNBPL), by which means complete resolution of some of the diastereomeric products was achieved, while others failed to be resolved and therefore their enantiomeric purity has not yet been determined. Tables 1-3 summarise the results.

The rate-determining step is the attack of the aldehyde on the stabilised carbanion. Evidently the base attached to the β-carbon is too remote from the reaction centre to influence the stereochemistry to any extent. These reactions suffer from the added disadvantage that the chiral bases are all poor catalysts for the reactions and yields were low, even zero. Similarly the solvent has little effect. Although it has been shown that hydroxylic solvents are able to increase rates of reaction, 1,2-diols are more efficient, possibly by a chelation effect. It would be of interest to compare enantiomeric induction in the presence of a chiral diol as solvent. Of the other modes for introduction of a chiral environment to the transition state of Baylis-Hillman reaction, only small degrees of enantiomeric discrimination occur in reactions of acrylonitrile with the chiral aldehydes at 4-5 kbar. Furthermore, at atmospheric pressure no enantiomeric excess at all was observed. Molecular models suggest preferred attack by the carbanion would occur at the *si*-face both of (1R)-myrtenal and of isopropylidene-(R)-glyceraldehyde . It appears that the examples used may have structures in which the discriminatory part of the molecule is again too remote from the reaction site to be very effective. The remaining location for a

Table 1; Diasteroisomeric Excess in Reactions Between Chiral Acrylic Esters and Aldehydes; (base catalyst, DABCO);

acrylic ester	aldehyde	r*	p/kbar	T/°C	t/h	Yield/%	de/%
(-)-menthyl	acetaldehyde	1:11	7	30	113	36	16
(-)-menthyl	acetaldehyde	1:1	0.001	16	430	95	14
(-)-bornyl	acetaldehyde	1:5	5.5	26	21	48	-
(-)-nopyl	acetaldehyde	1:4	5.5	26	21	30	36
(-)-menthyl	thiophene-2-aldehyde	1:4	6	27	144	52	-
(-)-menthyl	furfural	1:4	0.001	17	1150	15	17
(-)-menthyl	naphth-aldehyde	1:4	6	27	140	57	23
(-)-menthyl	benzaldehyde	1:4	0.001	17	1150	93	22
(-)-menthyl	benzaldehyde	1:4	7.5	30	21	42	100
(-)-menthyl	p-tolualdehyde	1:4	0.001	17	1150	30	100
(-)-menthyl	p-tolualdehyde	1:4	8.5	31	46	31	87
(-)-menthyl	p-ethylbenz-aldehyde	1:4	8.5	31	46	32	94
8-phenyl menthyl	benzaldehyde	1:4	8	35	70	31	86

* (r = molar ratio of acrylate to aldehyde)

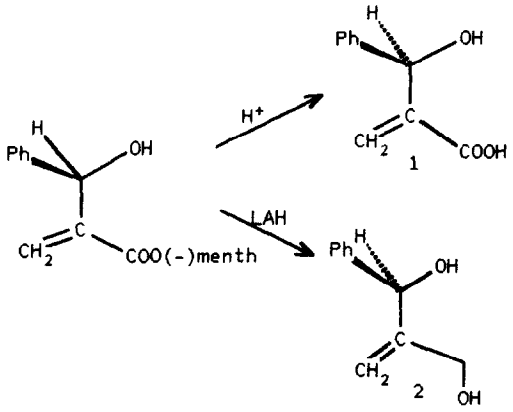
Table 2: Diastereoisomeric Excess in Reactions Between Acrylic Compounds and Chiral Aldehydes

acrylic cmpd.	aldehyde	r*	p/kbar	T/°C	t/h	Yield/%	de/%
acrylonitrile	(R)-myrtenal	1:4	5.5	23	42	42	16
acrylonitrile	isopropylidene (R)-glyceraldehyde		4	25	21	47	23
ethyl acrylate	isopropylidene (R)-glyceraldehyde		4	25	21	39	-

Table 3; Enantiomeric Excess in Reactions Between Acrylonitrile and Acetaldehyde in the Presence of Chiral Bases or Solvent.

Base / Solvent	p/kbar	T/°C	t/h	Yield	ee/%
(-)-quinine	9	60	48	0	-
1R-2S-N-methylephedrine	9	36	100	18	10
S(-)-nicotine	9	35	45	15	11
S(-)-1-methylpyrrolidenyl-methanol	9	40	74	28	17
+/- 3-hydroxyquinuclidine in ethyl-L-(+)-lactate	5	25	24	81	3

chiral director shows more promise of being of use synthetically. However, only modest degrees of chiral discrimination were found in reactions between acetaldehyde and the chiral acrylate esters. Acetaldehyde is the most reactive carbonyl component in these reactions but evidently the small size of the side chain precludes much stereochemical differentiation. The really significant observation of 95-100% discrimination occurred when aromatic aldehydes reacted with chiral acrylate esters. In the best example studied, the reaction between benzaldehyde and (-)-menthyl acrylate under high pressure conditions, only one diastereoisomeric product could be discerned by hplc so the de is close to 100%. Molecular models suggest the most favourable attack occurs at the si-face of the carbanion leading to S-configuration at the new centre. Again, when the reaction was conducted at atmospheric pressure both diastereomers were formed and the de was only 22%. Similar high de values were obtained for the p-methyl and p-ethyl benzaldehydes reacting at 7 kbar though neither naphthaldehyde nor the furan or thiophene aldehydes performed as well.
Since the products may be hydrolysed or cleaved reductively, the Baylis-Hillman reaction may be considered as a source of pure enantiomeric compounds of structures 1 and 2.



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References;

1 A.B.Baylis and M.E.D.Hillman, German Patent 2155113 (1972); Chem.Abs.,77 34174, (1972).

2 S.E.Drewes and H.P.Roos, Tetrahedron, **44**, 4653 ,(1988).

3 H.M.R.Hoffmann and J.Rabe, Angew.Chem. Int.Ed. 22, 795, (1982);
A.Weichert and H.M.R.Hoffmann , J.Org.Chem., 56, 4098, (1991).

4 J.S.Hill and N.S.Isaacs, Tetrahedron, 27, 5007 (1986).