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HIGH ASYMMETRIC INDUCTION IN THE BASE CATALYZED REACTIONS OF ETHYL PHENYL KETENE WITH 1-PHENYLETHANOL AND 2,2-DIMETHYL-1-PHENYLPROPANOL

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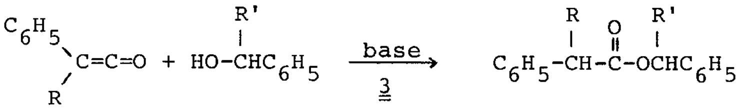
Abstract Diastereomer ratios in 4 as high as 99:1 are reached in the title reaction.

We have recently shown$^{1)}$ that the degree of asymmetric induction in the reaction of methylphenylketene 1 ($R=CH_3$) with 1-phenylethanol 2 ($R'=CH_3$) is considerably increased by the addition of tertiary amines. Diastereomer ratios d in the resulting hydratropic acid 1-phenylethylester 4 ($R=CH_3$, $R'=CH_3$) as high as 90:10 were reported$^{1)}$, when the reactions were conducted below $-40^{\circ}C$ and e.g. when pyridine was the catalysing base in toluene solution.



$$C_6H_5(R)C=C=O + HO-CH(R')C_6H_5 \xrightarrow[3]{\text{base}} C_6H_5-CH(R)-C(=O)-OCH(R')C_6H_5$$

1 2 4

When ethylphenylketene 1 ($R=C_2H_5$)$^{2)}$ is allowed to react with optically pure (-)S-1-phenylethanol 2 ($R'=CH_3$) under similar conditions at $0^{\circ}C$, the corresponding ester 4 ($R=C_2H_5$,$R'=CH_3$) is obtained with a diastereomer ratio d= [S,S]:[R,S]= 89:11. This ratio was deduced from GC analysis$^{3)}$ and from the optical rotation $[\alpha]_D^{25}=+72.99$ (benzene,c=2.43) of the 2-phenylbutyric acid$^{4)}$, isolated after saponification of the ester with aqueous hydrochloric acid. The same diastereomer ratio d was found when racemic 2 ($R'=CH_3$) was used (see Lit.$^{1)}$). For synthetic purposes ketene 1 ($R=C_2H_5$) was generated in situ from 2-phenylbutyroyl chloride and an equivalent amount Et_3N in diethylether, held at $25^{\circ}C$ for 3h. Then equimolar amounts of 2 ($R'=CH_3$) and pyridine were added at $0^{\circ}C$. Ester 4 ($R=C_2H_5$,$R'=CH_3$) was isolated in 91%

yield (d=[R,R + S,S]:[R,S + S,R]= 83:17[3]). When ketene 1 (R=C_2H_5) was allowed to react with 2 (R'=t-C_4H_9), ester 4 (R=C_2H_5,R'=t-C_4H_9) was obtained with a diastereomer ratio[5] d=[R,R + S,S]:[R,S + S,R] as high as 99:1 under suitable conditions (see table). The influence on the selectivity of the base 3, the solvent, the temperature and the modification of R and R' in 1 and 2, respectively, is shown by the data in the table and by fig.1.

Figure 1 Temperature dependance of the selectivities of the reactions of 1 (R=C_2H_5,CH_3) and 2 (R'=CH_3,t-C_4H_9) catalyzed by base 3 (the numbers refer to the entries in the table).

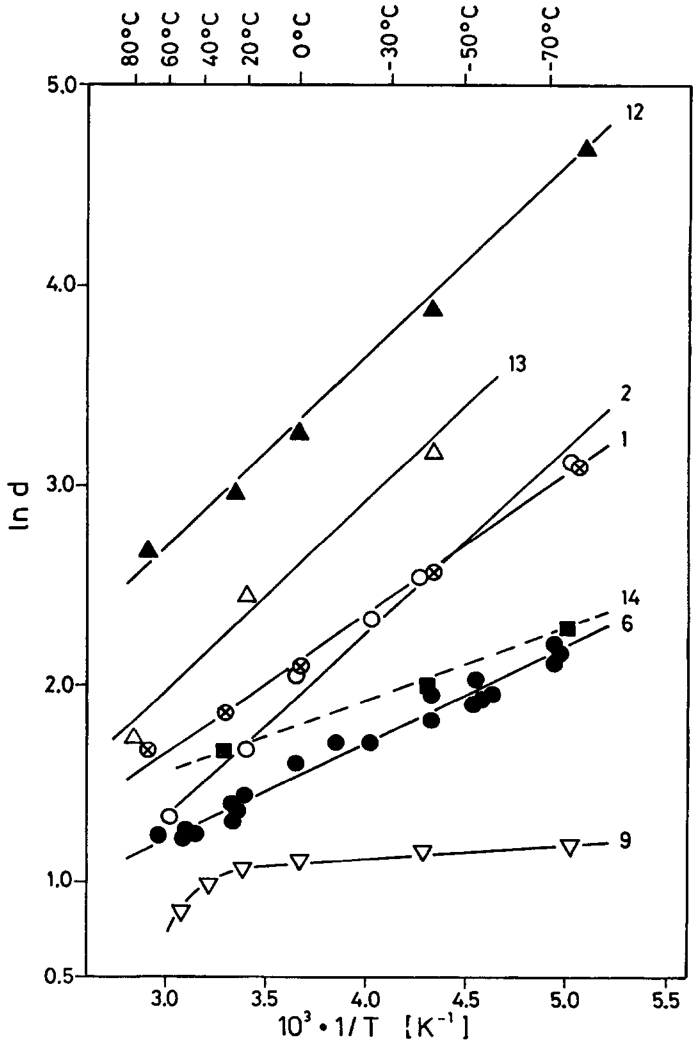


Table Stereoselectivities for the reactions of ethylphenylketene and alcohols 2 ($R'=CH_3$, $t\text{-}C_4H_9$) catalyzed by base 3

No	R'	Base	Solvent	T_{max}/d [a]	T_{min}/d [a]	n [b]	$\Delta\Delta H^{\ddagger} \pm \sigma$ [c] kcal mol^{-1}	$\Delta\Delta S^{\ddagger} \pm \sigma$ [c] e u
Ethyl phenyl ketene $R=C_2H_5$ [d]								
1	CH_3	quinuclidine	toluene	+69/84 16	-76/96 4	5	-1 36 ± 0 06	-0 75 ± 0 22
2	CH_3	pyridine	toluene	+58/79 21	-74/96 4	6	-1 81 ± 0 10	-2 71 ± 0 40
3	CH_3	γ-picoline	toluene	0/88 12	-	-	-	-
4	CH_3	DABCO[e]	toluene	+21/88 12	-25/92 8	-	-	-
5	CH_3	quinoline	toluene	+21/77 23	0/80 20	-	-	-
6	CH_3	triethylamine[f]	toluene	+47/77 23	-71/90 10	6	-1 00 ± 0 03	-0 66 ± 0 12
7	CH_3	4-acetyl-pyridine	toluene	0/76 24	-	-	-	-
8	CH_3	pyridine	hexane	+38/78 22	-58/90 10	4	-1 24 ± 0 12	-1 39 ± 0 48
9	CH_3	pyridine[g]	THF	+22/74 26	-74/76 24	4	-0 10 ± 0 03	+1 85 ± 0 12
10	CH_3	pyridine[h]	ether	+22/82 18	-58/91 9	-	-	-
11	CH_3	-	toluene[i]	0/75 25	-	-	-	-
12	$t\text{-}C_4H_9$	quinuclidine	toluene	+71/94 6	-77/99 1	5	-1 85 ± 0 08	-0 22 ± 0 30
13	$t\text{-}C_4H_9$	pyridine	toluene	+80/85 15	-42/96 4	3	-1 89 ± 0 03	-1 79 ± 1 01
Methyl phenyl ketene $R=CH_3$ [k]								
14	CH_3	pyridine	toluene	+50/85 15	-80/89 11		-0 34 ± 0 04	+2 4 ± 0 2

a) Highest and lowest temperature in °C for linear function of ln d vs 1/T [K^{-1}] (cf fig 1), d= ratio of diastereomers 4 (R,R + S,S) (R,S + S,R)

b) Number of temperatures at which selectivity was measured for determination of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$

c) σ= standard deviation

d) C_o(1)= 0 25 mol l^{-1}, 1 2 3 = 1 1 1

e) 1 4-Diazabicyclo[2 2 2]octane, C_o(1)=0 17 mol l^{-1}

f) The variation of the ratio 1 2 3 has no significant influence on $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$; see fig 1, in which 1 2 3 = 1 1 0 8 or 1 1 5 or 1 3 5 for curve 6

g) Above +22°C the function ln d vs 1/T is no longer linear (see fig 1)

h) In diethylether σ was too large to allow estimation of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$

i) Ratio ketene alcohol = 3

k) C_o(1)= 0 1 mol l^{-1}, 1 2 3 = 1 1 1

All bases used as catalysts increase the stereoselectivity in a remarkable way (see no. 11 in the table). For the pyridine catalyzed reaction smaller selectivities are obtained in THF, ether and hexane than in toluene. Ethylphenylketene 1 ($R=C_2H_5$) reacts, under comparable conditions at low temperature, more selectively than does methylphenylketene 1 ($R=CH_3$)[1]) (see nos. 2 and 14 in the table), but at +20°C an isoselective temperature is reached[7]. Because changes in temperature strongly influence the relative selectivities within the various reaction series (e.g. solvent effects or base effects), $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ must be used instead of the selectivities (ln d) in any attempt to interpret these results[7,8].

$$\ln d = -\frac{\Delta H^{\ddagger}_{S,S}-\Delta H^{\ddagger}_{R,S}}{RT} + \frac{\Delta S^{\ddagger}_{S,S}-\Delta S^{\ddagger}_{R,S}}{R} = -\frac{\Delta\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R}$$

The selectivity is increased by negative values of $\Delta\Delta H^{\ddagger}$ and by positive ones of $\Delta\Delta S^{\ddagger}$. Accordingly, in most examples of the table, enthalpy and entropy effects on the stereoselectivity oppose each other and both change within a reaction series. An interpretation of these data might be attempted in terms of a molecular model for the transition state of the proton transfer to the prochiral center of the ketenes, or of the intermediate complexes of ketene and base[1], but the compensatory behaviour and small numerical values of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ force us to exercise restraint in this matter. We recommend in general the use of transition state models for the interpretation of asymmetric synthesis with such restraint, as long as it is not known whether enthalpy or entropy effects are responsible for the observed selectivities[9].

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3) GC-conditions for separation of diastereomers of 4: 25 m glass capillary column, Carbowax 20 M, 176-180°C.

4) see R.Weidmann and A.Horeau, Bull.Soc.Chim.Fr. 1967, 117 for absolute configuration.

5) The direction of the stereoselectivity was determined with optically active (+)R-2 (R'=t-C_4H_9)[6] which gave [R,R]-ester 4 (R=C_2H_5,R'=t-C_4H_9)[4].

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9) This has been pointed out before very clearly, in the early pioneer work of H.Pracejus[8].

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