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ASYMMETRIC INDUCTION UNDER HIGH-PRESSURE. MICHAEL ADDITION OF NITROMETHANE TO CHALCONE CATALYZED BY CHIRAL ALKALOIDS1)

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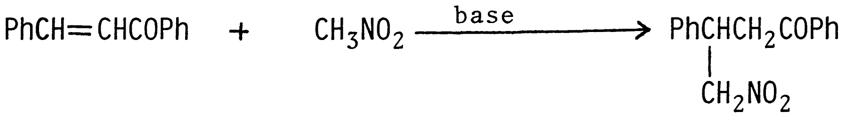
The Michael addition of nitromethane to chalcone was performed at 10 kbar in the presence of a catalytic amount of chiral alkaloids such as quinine, cinchonidine, quinidine, chinchonine, brucine, and strychinine. The extent of asymmetric induction reached up to 50 % e.e. with quinidine in toluene.

Asymmetric control in the C-C bond formation is one of the most challenging problems in organic synthesis.2) The use of high-pressure, which usually need to be greater than 5 kbar, to assist organic synthesis has proven valuable for the reactions in which bonds are formed, whether by ionic, radical, or concerted processes.3) However, examples of asymmetric induction under high-pressure are still rare, a little success having been obtained.4) At normal pressure, the title reaction did not take place with such a free chiral alkaloid as quinine in aprotic solvents, whereas the reaction proceeds well in methanol, though the asymmetric induction being below 1 % e.e.5) Only by replacement of a free chiral amine with its aminium fluoride the extent of asymmetric induction has reached up to 26.2 % e.e.6) We now briefly report on the aymmetric induction in the title reaction at 10 kbar catalyzed by chiral alkaloids.



$$\mathrm{PhCH{=}CHCOPh} \quad + \quad \mathrm{CH_3NO_2} \xrightarrow{\text{base}} \underset{\displaystyle \mathrm{CH_2NO_2}}{\mathrm{PhCHCH_2COPh}}$$

First, the catalyst effects on the chemical and optical yields were studied using dichloromethane as solvent. The chiral alkaloids used were quinine (**1**), cin-

Table 1. Michael Addition at 10 kbar; Effect of Catalyst[a]

catalyst	nitromethane (mmol)	total volume (ml)	reaction temp. (°C)	reaction time (h)	chemical yield (%)	$[\alpha]^{22}_{577}$ [b] (degree)	optical purity[c] (% e.e.)
1	30	10	13-14	20	100	-0.7	1.7
2	15	10	12-14	22	100	-1.1	2.7
3	30	10	9-10	24	100	+9.2	23
4	30	10	13-14	31	100	+11	27
5	30	5	14-16	38	86	0	0
6	30	5	24-25	12	37	0	0

a) Solvent: dichloromethane; catalyst: 0.3 mmol; chalcone: 3 mmol. b) Optical rotations were taken in dichloromethane (c 4.0-6.0). c) The enentiomeric excess of the adduct was calculated from the reported relationship between the optical rotation, $[\alpha]^{21}_{578}$ and the enantiomeric excess determined by ^{1}H n.m.r. spectroscopy with aid of $Eu(dcm)_3$.[5,6]

chonidine (2), quinidine (3), cinchonine (4), brucine (5), and strychinine (6). The results at 10 kbar are given in Table 1.[7] The (-) and the (+) enantiomer is the predominant one with the catalysts 1, 2, and 3, 4, respectively, but with brucine and strychinine[8] containing no β-hydroxy amine moiety the reaction proceeds slowly even at 10 kbar and gives no asymmetric induction. The quinidine type alkaloids are more effective in asymmetric induction than the quinine type alkaloids, being in contrast to the reactions at 1 bar; both types of the cinchona alkaloids usually gave comparable optical yields when similar conditions were used.[6,9]

Next, the solvent effects were investigated as the strong solvent effects on the extent of asymmetric induction have been reported in the related Michael additions.[6,9] The results at 10 kbar are summarized in Table 2, employing 1 and 3 as catalyst. The observed solvent effect on the extent of asymmetric induction is almost in the same tendency as that observed at normal pressure in the related Michael reactions. Of the aprotic solvents, the polar or hydrogen-bond accepting solvent gives a lower enantioselectivity, compared to the non-polar one which favors the formation of a tight ion pair of the carbanion and the base and consequently a tight transition state of the ion pair and chalcone. This would be more favored on application of pressure as observed in the present case. The change in enantioselectivity upon increasing the concentration of nitromethane is obviously associ-

Table 2. Michael Addition at 10 kbar; Effect of Solvent[a,b)]

catalyst	solvent	nitromethane (mmol)	reaction temp. (°C)	reaction time (h)	chemical yield (%)	$[\alpha]_{577}^{22}$ (degree)	optical purity (% e.e.)
1	dichloromethane	30	13-14	20	100	-0.7	1.7
1	toluene	30	13-14	28	100	-7.3	18
1	toluene	15	13-14	22	100	-9.9	24
1	carbon tetrachloride	15	14-16	24	87	-2.2	5.3
3	acetonitrile	15	13-14	23	100	+3.4	8.4
3	methanol	15	17-18	23	100	+0.7	1.7
3	dichloromethane	15	16-17	26	100	+6.0	15
3	tetrahydrofuran	15	14-16	23	100	+15	36
3	toluene	15	13-14	24	100	+21	51
3	carbon tetrachloride	15	17-18	23	88	+11	27

a) See footnotes in Table 1. b) Chalcone: 3 mmol; catalyst: 0.3 mmol; total volume: 10 ml.

ated with its participation in the solvent effect. The extents of asymmetric induction in quinidine are much higher than in quinine, thus again most significant is that the influence of the opposite orientation of the vinyl substituent with respect to C(8) C9) on enantioselectivity is observed in a more amplified fashion at high-pressure than at normal pressure;10) this may serve as a working guide for choosing or designing chiral amines that could be effective in asymmetric induction under high-pressure.

While much work remains to be done, for instance, on the effects of lower and higher pressures, reaction temperatures, as well as other catalysts and Michael donor-acceptor systems, we believe that the high-pressure technique potentially represents a powerful tactics for achieving asymmetric induction in Michael and related reactions such as annulation catalysed by chiral amines which are of moderate strength and therefore had been of limited use as bases in asymmetric synthesis.

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7) Chalcone (3mmol), nitromethane(15 or 30 mmol), and alkaloid(0.3 mmol) diluted with solvent are placed in a 10 ml(or 5 ml) Teflon capsule and kept under hydrostatic pressure at room temperature. The reaction mixture was worked up as described in the reference.[6)] A preliminary investigation of the reaction as a function of time has shown that the formation of the product is kinetically controlled and the product is optically stable under the reaction conditions.

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