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SOLID-LIQUID PHASE TRANSFER CATALYSIS WITHOUT SOLVENT : AN IMPROVEMENT FOR CHIRAL MICHAEL ADDITION OF N-ACETYLAMINOMALONATE TO CHALCONE

André LOUPY[a)*], **Jean SANSOULET**[a)], **Anne ZAPARUCHA**[a)] and **Claude MERIENNE**[b)]

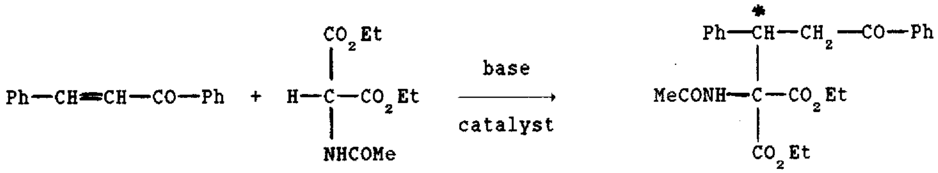
I.C.M.O. , Bâtiment 410, Université Paris-Sud, 91405 ORSAY (France)
a) Laboratoire des Réactions Sélectives sur Supports, UA CNRS 478
b) Laboratoire de Chimie de Coordination Bio-organique, UA CNRS 255

Summary: *Solid-liquid phase transfer catalysis (PTC) without added solvent efficiently promotes chiral Michael addition when the reaction is achieved in presence of quaternary salts derived from (+) or (-) N-methyl ephedrine. Enantiomeric excesses are significantly increased by "omitting" the organic solvent during the reaction.*

We have recently emphasized that solid-liquid PTC in the absence of any organic solvent (1,2) leads to noticeable improvements in organic synthesis as far as anionic activation is concerned. This technique was successfully applied in performing Michael additions of hindered carbanions to alpha enones under very simple and mild conditions (3-5) .

For the last decade, attention has been paid to the possibility of asymmetric Michael additions under phase transfer catalysis conditions using chiral amines or optically active tetraalkylammonium salts as catalysts (6-10). However, the results obtained in classical PTC conditions(either in liquid-liquid or solid-liquid systems) seem to be rather limited. Further improvements in enantiomeric excesses (ee) are desirable. It can be assumed, when the reaction will be performed in the absence of added organic solvent, that the system can be more rigidified and consequently can lead to a decrease in molecular motions. The result could be therefore an enhancement in chiral recognition.

To this purpose, we choosed to study the behaviour of some chiral ammonium salts in the absence of solvent on the course of the reaction of chalcone 1 with acetylaminomalonate 2 as these species are useful synthons for the preparation of natural and unnatural aminoacids (11,12).



$$\mathrm{Ph{-}CH{=}CH{-}CO{-}Ph} + \mathrm{H{-}C(CO_2Et)_2{-}NHCOMe} \xrightarrow[\text{catalyst}]{\text{base}} \mathrm{Ph{-}\overset{*}{C}H(C(CO_2Et)_2NHCOMe){-}CH_2{-}CO{-}Ph}$$

1 2 3 (+) and (-)

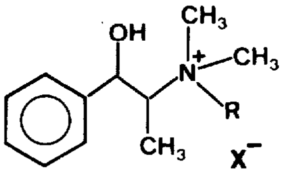
Therefore, the aim of this preliminary study consists in investigations of the influences of the chiral catalyst nature and of solvent effects.

PROTOCOL

Chalcone 1 and malonate 2 in stoechiometric amounts (5 mmoles) were vigorously shaken with a mechanical stirrer during 1 hour at the required temperature (generally 60°C) in the presence of catalytic quantities (6% mol) of base (KOH or K_2CO_3) and chiral ammonium salt. Then, the reaction mixture was cooled to room temperature and extracted with methylene chloride (50 ml). Products 3 were purified by chromatography on silicagel (isolated chemical yields). Enantiomers (+) and (-) of 3 were determined by chiral HPLC and NMR chiral shift using Europium salts (13).- Values of yields and enantiomeric excesses indicated in the tables are results from at least 3 identical experiments which don't differ each other more than 2%.

INFLUENCE OF THE NATURE OF THE CHIRAL CATALYST (Table I)

The following catalysts derived from (+) and (-) N-methyl ephedrine **4**, quinine **5a** (-), cinchonine **5b** (+) and cinchonidine **5b** (-) were tested. For sake of comparison and control, a non chiral salt was also used (benzyltriethylammonium chloride: TEBA,Cl).



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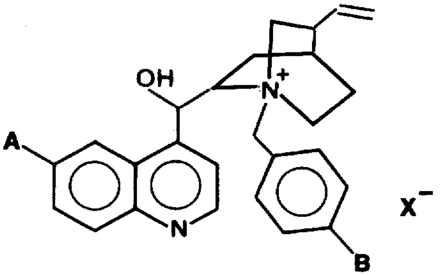

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4a R = CH_3
4b R = $C_{12}H_{25}$
4c R = $CH_2-C_6H_5$
4d R = $CH_2-C_6H_4-_pNO_2$
4e R = $CH_2-C_6H_4-_pCN$
4f R = $CH_2-C_6H_4-_pCF_3$

5a A = OCH_3 B = H
5b A = H B = H
5c A = H B = NO_2

TABLE I - Reaction of 1 and 2 (5 mmoles) in presence of 6% mol. KOH and catalyst for 1 hour at 60°C.

Catalyst , X		Chemical Yield (%)	Enantiomeric Excess (ee)
TEBA	Cl	71	0
(-) 4a	Br	68	32 (-)
(-) 4b	Br	41	48 (-)
(-) 4c	**Br**	**56**	**60 (-)**
(+) 4c	**Br**	**48**	**62 (+)**
(-) 4c	**Cl**	**57**	**68 (-)**
(-) 4d	Br	58	20 (-)
(-) 4e	Br	54	34 (-)
(-) 4f	Br	42	46 (-)
(-) 5a	Cl	47	38 (-)
(-) 5b	Cl	51	32 (-)
(+) 5b	Cl	57	36 (+)
(-) 5c	Br	62	34 (-)

First, we have to point out that chemical yields are relatively moderate (≤68% in isolated pure products). This fact is probably due to the reversibility of this Michael addition in these conditions.

From a selectivity point of view, among all the chiral catalysts tested, the most efficient appears to be N-benzyl N-methyl ephedrinium chloride (4c,Cl) which is itself slightly better than the bromide salt 4c,Br.

It is particularly obvious to observe complementary results as far as selectivity is concerned when two enantiomeric chiral tetraalkylammonium salts are used. Enantiomeric excesses are very close but with opposite selectivity with (+) and (-) 4c,Br as catalysts: the ratio of the enantiomers 3 (+) / 3 (-) is respectively 80/20 and 19/81.

Electron-withdrawing groups in the benzyl moiety of the catalyst lead to decreases in ee. This behaviour is different from the observations of Hughes and al. (14) in catalytic asymmetric methylation of phenyl indanone. Here, as in few other cases yet described (15,16), stabilizing interactions between aromatic groups (from catalyst and electrophile in the present case) can be evoked. However, a precise and reliable interpretation of these observations needs more experiments.

EFFECT OF SOLVENT (Table II)

In order to test our hypothesis concerning the influence of the absence of solvent, we performed some experiments in presence of some additional organic solvents (i.e. under classical solid-liquid PTC conditions).

As generally non polar solvents are the most suitable in asymmetric synthesis (7,14,17), toluene and carbon tetrachloride were investigated as additional solvents. We also tested mesitylene (1,3,5 trimethylbenzene) and n-hexylbenzene as recently they were claimed to be the most efficient during the course of a Diels-Alder asymmetric reaction (18).

TABLE II - Reaction of 1 and 2 (5 mmoles) in presence of 6% mol. KOH and catalyst for 1 hour at 60°C. Catalyst = (-) 4c , Br.

Solvent	Volume (ml)	Chemical Yield (%)	Enantiomeric Excess (ee)
---	0	56	60 (-)
Toluene	1 or 5	51	28 (-)
"	20	17	28 (-)
CCl_4	1 or 5	55	16 (-)
"	20	12	12 (-)
Mesitylene	1 or 5	28	24 (-)
n-Hexylbenzene	1 or 5	31	8 (-)

It appears clearly that ***the best enantiomeric excess is observed when the reaction is performed in the absence of any added organic solvent***. As we previously assumed, the increase in asymmetric induction under solid-liquid PTC conditions without solvent can be understood if one consider a greater rigidification of the systems due to the absence of diluent. In these conditions, reactive species are probably highly aggregated and consequently need a greater organization of the system leading thus to an increase in selectivity.

However, the only precedent in this field, which consists in chiral amine catalyzed addition of aromatic thiols to cyclohexenones under homogeneous conditions (6), lead to opposite result (decreases in ee in the absence of solvent). These opposite behaviours can result from very different reaction media (homogeneous or heterogeneous, variations in reactions and catalysts...) and consequently large differences in aggregation degrees of reactive species.

In conclusion, heterogeneous solid-liquid PTC conditions without added solvent are favourable for observation of asymmetric induction during the reaction of chalcone 1 with malonate 2 as enantiomeric excess is increased when the solvent is "omitted". Generalization of this preliminary study, and consequently interpretation of the involved phenomena, are at the present time in progress.

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