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Asymmetric Michael reaction under PTC conditions without solvent Importance of π interactions for the enantioselectivity

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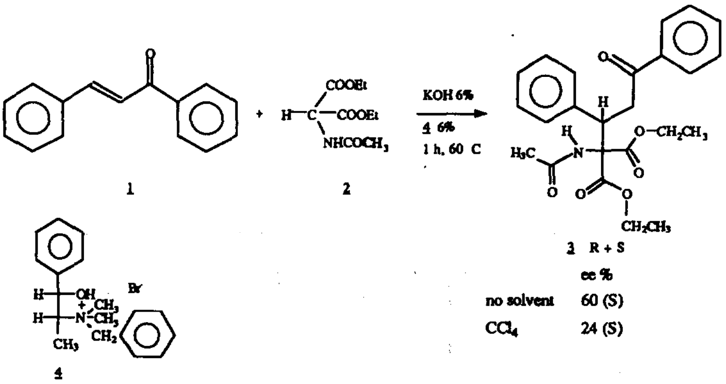
Abstract : Michael addition of diethyl acetylaminomalonate to chalcone under Asymmetric Phase Transfer Catalysis without solvent has been successfully carried out in the presence of ephedrinium salts. Substituent effects on the benzyl moiety of the ammonium part of the catalyst revealed the importance of π-π attractive interactions between the catalyst and the electrophile on enantioselectivity. The best result (82% ee) was obtained with easy accessible (S) binaphthyl compound.

In a previous paper, we have reported that omitting solvent during the reaction of chalcone 1 with diethyl acetylaminomalonate 2 under PTC conditions using (-) N-methyl N-benzyl ephedrinium bromide 4 as a chiral catalyst has led to an enhancement of the enantiomeric excess of the compound 3[1] (scheme 1). In this paper we wish to report our further investigations to maximize the enantioselectivity of this reaction.

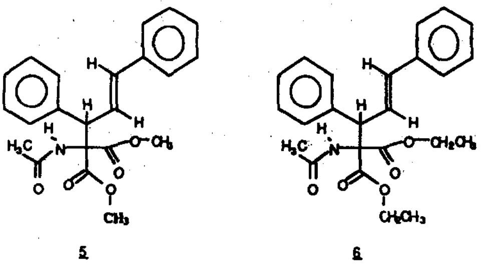
Reaction of chalcone 1 with diethyl acetamidomalonate 2 in the presence of potassium hydroxide (6% mol) and (-) N-methyl N-benzyl ephedrinium bromide (6% mol) leads to product 3 with 60% chemical yield and 60% enantiomeric excess, in favor of the S enantiomer (scheme 1).



	ee %
no solvent	60 (S)
CCl_4	24 (S)

scheme 1

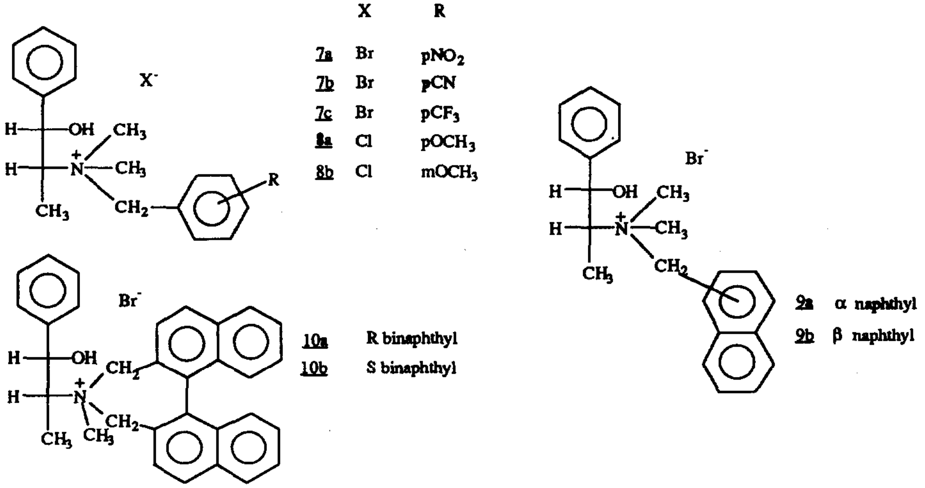
The attribution of the absolute configuration of the major enantiomer 3 has been carried out by chemical correlation with a known compound 1-acetamido-1-(1,3-diphenylprop-2-enyl)-1,1'methyl dicarboxylate 5[2] (scheme 2). Compound 6 obtained from 3 by subsequent reduction with $NaBH_4$ excess in methanol, followed by dehydration by heating with anhydrous oxalic acid (82% yield)[3]. Comparative NMR studies in the presence of $Eu(hfc)_3$ have shown that the major enantiomer 3 was S.



scheme 2

As we previously showed[1], electronwithdrawing groups on the benzyl moiety of the catalyst lowers enantiomeric excess. It is well known in the literature that asymmetric induction is sensitive to electronic effects. Dolling et al. have thus shown that such effects occur between the catalyst and the nucleophile in an example of asymmetric alkylation via PTC with N-benzyl cinchoninium halides as chiral catalysts[4].

Consequently in order to optimize our previous results, we studied the behaviour of new ephedrinium catalysts bearing an electrondonating group (OCH_3) 8 and extended aryl groups to α-methylnaphthyl, β-methylnaphthyl 9 and methylbinaphthyl 10[5] (scheme 3). The main results are given in Table I.



scheme 3

Table 1 : $1 + 2 \xrightarrow[\text{catalyst 6\%}]{\text{KOH 6\%}} 3\ (R+S)$

entry	catalyst a)	yield % b)	ee % c)	σ_R
1	7a	56	20	0.81
2	7b	54	34	0.7
3	7c	42	46	0.53
4	8a	51	76	-0.28
5	8b	52	66	-0.1
6	9a	52	72	
7	9b	48	56	
8	10a	52	66	
9	10b	51	82	

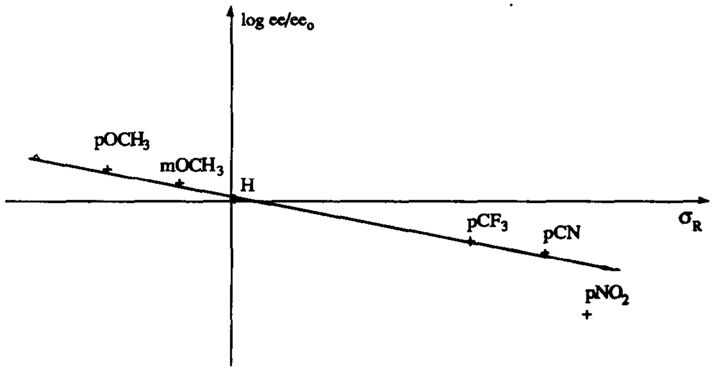
a) the counterion of the chiral catalyst has no significant effect on the enantioselectivity : N-methyl N-benzyl ephedrinium chloride, tosylate, mesylate and trifluoromethylsulfonate lead to enantiomeric excesses of 62%, 58%, 56% and 60% respectively.

b) isolated yield after flash chromatography on silica gel pentane/ethyl acetate 70/30.

c) the enantiomeric excess are evaluated by ^1H NMR with $Eu(hfc)_3$ and by chiral HPLC[6].

A Hammett plot of log ee/ee_0 vs the substituent constant σ of the N benzyl catalysts demonstrates clearly the linearity of the correlation except for the nitro group which lies apart from the line (scheme 4). The deviation to linearity with NO_2 could possibly be attributed to a contribution of mono-electronic transfer as this group is known to induce such process[7] and as this kind of intervention was proposed for Michael reaction[8].

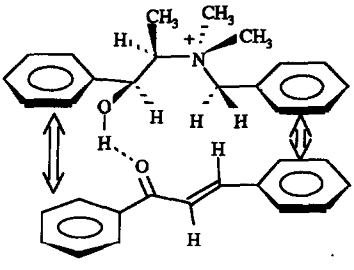
Consequently, it seems well established that increasing electron donating power improves the catalyst selectivity (entry 4). Unfortunately all our attempts to synthetize ephedrinium catalysts bearing a stronger electrondonating group on the benzyl moiety such p-amino (σ -0.57) and p-dimethylamino(σ -0.63) have failed.



scheme 4

This correlation suggests that a π interaction occurs between the benzyl moiety group of the catalyst and at least one of the two phenyl groups of the electrophile 1. The π interaction should be such that an α methylnaphthyl group increases the interaction (entry 6) whereas a β methylnaphthyl group has no significant effect (entry 7). *In our hands the best result is obtained with a catalyst bearing a S binaphthyl group (entry 9).*

We concluded thus that π-π attractive interactions between aryl groups of catalyst and electrophile 1 are responsible for the enantioselectivity of the reaction. They can be enhanced when reactions are performed in the absence of solvent[1]. This conclusion is in agreement with recent observations showing that the origin of high enantioselectivities in Diels Alder reaction[9], nucleophilic additions[10] or enolates alkylations[11] probably lies in attractive π-π interactions between aromatic groups of the two reactants.



scheme 5

We believe that π-π attractive interactions between the aryl group of the benzyl moiety of the catalyst and one of the two phenyls of the electrophile 1 are responsible for the enantioselectivity of the reaction (scheme 5).

Further works and molecular mechanics calculations are under investigations to determinate the nature of the interaction, including reactions with non-aryl substituted electrophiles and bulky nucleophiles.

References and notes

(1) A. Loupy, J. Sansoulet, A. Zaparucha, C. Merienne, *Tetrahedron Lett.*, 1989, 30, 333-336.

(2) M. Yamaguchi, T. Shina, T. Yamagishi, M. Hida, *Tetrahedron Lett.*, 1990, 31, 5049-5052; *Tetrahedron: Asymmetry*, 1991, 2, 663-666.
T. Hayashi, A. Yamamoto, T. Hagihara, Y. Ito, *Tetrahedron Lett.*, 1986, 27, 191-194.
H. Wren, H. Williams, *J. Chem. Soc.*, 1916, 109, 572.

(3) G. W. Perold, A. P. Steyn, F. V. K. Von Reiche, *J. Am. Chem. Soc.*, 1957, 79, 462-465.

(4) U. H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, 106, 446-447.
D. L. Hughes, U. H. Dolling, K. M. Ryan, E. F. Schoenewaldt, E. J. J. Grabowski, *J. Org. Chem.*, 1987, 52, 4745-4752.
U. H. Dolling, D. L. Hughes, A. Bhattacharya, K. M. Ryan, S. Karady, L. M. Weinstock, E. J. J. Grabowski, *Phase Transfer Catalysis, ACS Symposium Series 326*, Washington 1987, ch. 7.

(5) Catalysts are synthesized by reaction of (-) N-methyl ephedrine with the correspondent halide in refluxing of toluene. Reaction times vary according to the halide reactivity. The salt was filtered, washed with ethyl acetate and dried under vacuum. Chemical yields vary from 49 to 88.5%. Salts 10a and 10b have been synthesized by Dr. J. P. Mazaleyrat. J. P. Mazaleyrat, *Tetrahedron Lett.*, 1983, 45, 1243-1246. N. Maigrot, J. P. Mazaleyrat, *Synthesis*, 1985, 317-320.

(6) E. Delée, I. Jullien, L. Le Garrec, A. Loupy, J. Sansoulet, A. Zaparucha, *J. Chromatogr.*, 1988, 450, 183-189.

(7) M. Chanon, M. Rajzmann, F. Chanon, *Tetrahedron*, 1990, 46, 6193-6299.

(8) T. Cohen, W. D. Abraham, M. Myers, *J. Am. Chem. Soc.*, 1987, 109, 7923-7924.

(9) E. J. Corey, Y. Matsumura, *Tetrahedron Lett.*, 1991, 32, 6289-6292.

(10) H. Sakuraba, S. Ushiki, *Tetrahedron Lett.*, 1990, 31, 5349-5352.

(11) J. M. Mc Intosh, R. K. Leavitt, P. Mishra, K. C. Cassidy, J. E. Drake, R. Chadha, *J. Org. Chem.*, 1988, 53, 1947-1952

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