

Asymmetric Induction in the Base-catalysed Michael Addition of Nitromethane to Chalcone

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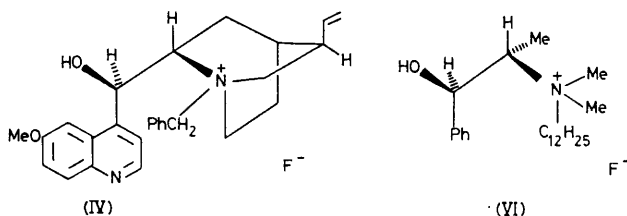
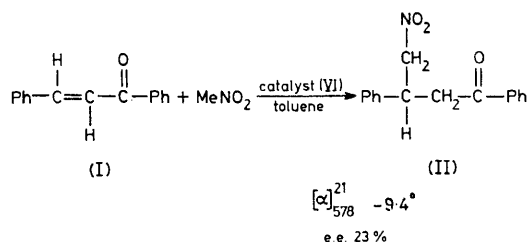
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Summary Asymmetric induction in the Michael addition of nitromethane to chalcone is greatly enhanced from 1% to *ca.* 20% by replacing as catalyst a chiral amine in methanol by its aminium fluoride salt in an aprotic solvent.

ASYMMETRIC induction in Michael-type addition reactions under the catalytic influence of chiral amines (especially cinchona alkaloids) has been described recently.¹ The relatively low basicity of amines precludes the successful application of this type of asymmetric synthesis to a larger range of Michael donors and acceptors.

It has recently been reported that unsolvated ('naked') fluoride anion, which can be generated in aprotic media by means of crown ethers or quaternary onium salts, can act as a strong base.² Its utility in Michael-type addition reactions has been confirmed,^{3,4} and it has been estimated to be slightly more basic than trialkylamines.⁴

We report here our investigations into the Michael addition of nitromethane to chalcone (I) in the presence of two types of chiral catalysts. First we studied the use of free chiral amines as the basic catalyst, and secondly chiral aminium fluoride salts in which the fluoride ion serves as the base and the aminium cation functions both as a solubilizing agent for the fluoride ion in the aprotic medium and as a supplier of chirality. The aminium fluorides were prepared *in situ* from a catalytic amount of a chiral aminium chloride or bromide and a large excess of potassium fluoride (which gives a heterogeneous reaction mixture). The catalysts we



used were quinine (III), its *N*-benzyl fluoride (IV, from its *N*-benzyl chloride⁵), *N*-methylephedrine (V),⁵ its *N*-dodecyl fluoride (VI, from its *N*-dodecyl bromide⁵) and *L*-(-)- α -phenylethylamine (VII). The enantiomeric purity of the product (II) could be determined by ¹H n.m.r. spectroscopy using Eu(dcm)₃ as shift reagent⁶ to an accuracy of $\pm 3\%$.

The results of the addition of nitromethane to chalcone to give the nitroketone (II), using the two catalyst types are given in the Table. With chiral amines as catalyst

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TABLE. Addition of MeNO₂^a to chalcone (I) at 20 °C

Solvent	Catalyst ^b	KF ^c present	Time/ days	Yield (%)	Enantiomeric excess (%)	$[\alpha]_{578}^{21}$ (CH ₂ Cl ₂)
MeCN	(III)	No	7	0		
CCl ₄	(III)	"	7	0		
Toluene	(III)	"	7	0		
MeOH	(VII)	"	7	60	1	+0.6°
"	(V)	"	7	80	0	0°
"	(III)	"	7	65	1	+0.5°
Toluene	(VI)	Yes	3	50	23	-9.4°
"	(IV)	"	4	100	10 ^d	-4.1°
MeCN	(IV)	"	3	96	3	-1.2°

^a 15 mol per mol of substrate. ^b 0.1 mol per mol of substrate. ^c 15 mol per mol of substrate. ^d The enantiomeric excess was determined on this sample and found to be 10% ± 3%. The e.e. of the other samples was then based on their optical rotations.

[(III), (V), or (VII)] no reaction occurs in aprotic solvents, whereas the reaction proceeds well in methanol. The amine probably is not basic enough to furnish the nitromethane anion in aprotic media. In methanol its formation is facilitated by hydrogen bond stabilization. Furthermore, hydrogen bonding with the carbonyl group of the chalcone catalyses the 1,4-addition. The asymmetric induction in the reaction is low.

When an aminium fluoride is employed as basic catalyst [(IV) and (VI)] reaction occurs readily in aprotic solvents. Apparently the fluoride ion is basic enough to produce the nitromethane anion. The asymmetric induction reaches a value of ca. 20%. The large increase, compared to the asymmetric induction of the free amine in methanol, points to a more structured transition state in the inert (non-hydroxylic) solvent. Probably the hydroxy-group in the

aminium ions plays an important role in the transition state and thus in the stereochemical course of the reaction. In methanol the function of the OH group is taken over by the solvent which might explain the low asymmetric induction.

Since nitro-ketones are useful starting materials for amino-ketones and amino-alcohols, the present technique is of value for the synthesis of chiral bifunctional compounds of this type. Michael donors with acidities comparable to nitromethane are currently being investigated, and our preliminary results indicate that chiral aminium fluorides as basic catalysts in the Michael reaction may lead to an important extension in the field of catalytic asymmetric synthesis.

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