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ENANTIOSELECTIVE SYNTHESIS OF α-FUNCTIONALLY-SUBSTITUTED CYCLOHEXANONES

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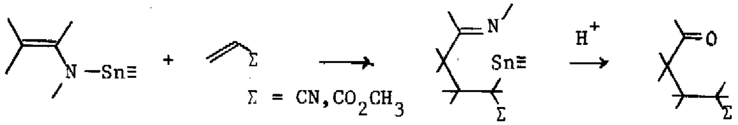
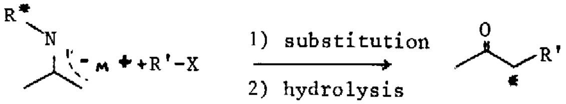
We have already reported the synthesis of δ-imino-esters and -nitriles by addition of organotin enamines to electrophilic alkenes (1) :



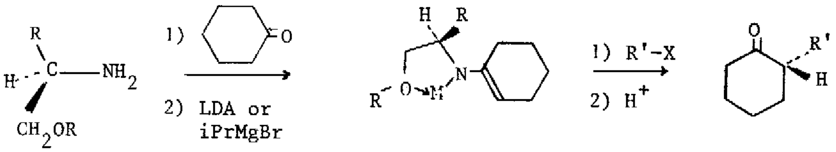
We wish to report here the application of this reaction to the enantioselective preparation of chiral methyl-3-(2-oxocyclohexyl)propionate, choosen to illustrate the usefulness of this reaction in asymmetric synthesis.

The substitution reaction involving alkyl halides and various metal salts of chiral imines, has been commonly used for the enantioselective preparation of substituted carbonyl derivatives :



The firts results in this area were reported by HOREAU (2) who, starting with the metal salts of the imine derivated from isobornylamine and cyclohexanones, obtained chiral 2-substituted cyclohexanones.

A major improvement in this field was effected by MEYERS (5,6) and WITHESELL (7) who obtained an enantioselectivity better than 90%, using intramolecularly coordinated magnesium or lithium salts which react with alkyl halides leading to a very large enantiomeric excess of 2-alkyl cyclohexanones :

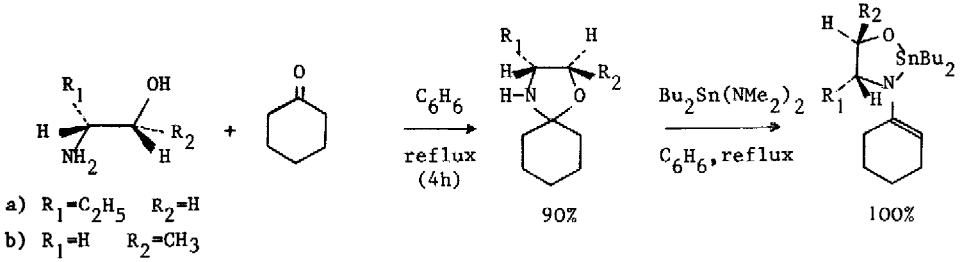


To our knowledge, only one application of enamines, via their addition to electrophilic alkenes, to the preparation of chiral functionaly substituted cyclohexanone has been published : YAMADA (3,4) reported in 1969 the preparation of methyl 3-(2-oxocyclohexyl)propionate and propionitrile, by addition of enamines derived from proline esters to methyl acrylate and acrylonitrile. The best enantiomeric excess obtained was 59% for a chemical yield of 17%.

The use of the imino salts mentioned above was prohibited since the lithium derivatives induce the polymerisation of the alkene (8) and we verified that the magnesium salts behave similarly.

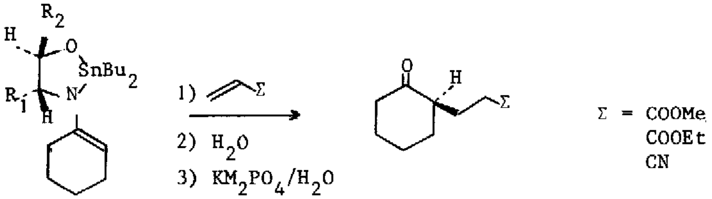
Since no such polymerisation was observed in the case of the addition of organotin enamines, their application in enantioselective addition was investigated, following the principles concerning the steric requirements determined in our preliminary study (1).

In view of the better results obtained in substitution by the use of a rigid conformation, we prefered to start with a five-membered heterocyclic tin enamine instead of an open chain organotin enamine ; this new compound is easily obtained in the following way :



The preparation of the organotin compound can be monitored by the disappearance of the NMR signal of the NMe_2 group, and the crude product is used without further purification (its structure was however proved by NMR and mass spectrometry).

Various conditions for the addition reaction (solvent, temperature, nature of R_1 and R_2, method of hydrolysis of the resulting imine) were tried to optimise the optical and chemical yield :



Our best results are summarized in the table. The high enantioselectivity obtained in case d) is remarkable in view of the slight steric difference between the two faces (Me versus H) at the reactive sites, and it should be noted that, in this case, the starting optically active alcohol is a commercially available -and inexpensive- compound .

The absolute configuration of the ketone obtained suggests, as did MEYERS's results for the alkylation (5), that the mechanism involves a six membered transition state in which the trans conformation of R_1 and of the cyclohexenyl group is prefered :

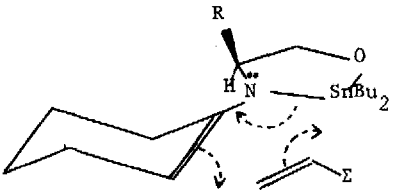
	R_1	R_2	Σ	T°C	Time (h)	Amino-alcohol R(-) %	Chemical[a] yield %	α_{365}^{20} [b]	Enantiomeric[c] excess %	Optical[d] yield %	Configuration
a)	H	H	CN	20	2	-	33	-	-	-	-
b)	H	H	CO_2CH_3	60	1	-	50	-	-	-	-
c)	H	H	$CO_2C_2H_5$	60	1	-	46	-	-	-	-
d)	C_2H_5	H	CO_2CH_3	60	1	67	63	-52,98	58	86	S
e)	H	CH_3	CO_2CH_3	60	1	30	50	+7,05	8	26	R

(*a*) from the chiral oxazolidine

(*b*) calculated from YAMADA's results (3,4)

(*c*) experimental results

(*d*) corrected from the purity of the starting alcohol



This enantioselective addition was also found to apply with other alkenes (ethyl acrylate, acrylonitrile) but the observed optical rotations are less significant, as the maximum optical rotation and absolute configuration of the resulting functionally-substituted ketones are as yet unknown, and we cannot at the present time deduce the extent of enantioselectivity of the reactions. Our next work will be aimed at such determinations, but the results reported here for the only familiar optically active compound, indicate the usefulness of organotin enamines in the asymmetric synthesis of such compounds, which constitute in many cases key intermediates in the synthesis of natural products.

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