STEREOCONTROLLED ADDITION OF ORGANOZINC REAGENTS DERIVED FROM 2-(BROMOMETHYL)ACRYLATES TO CHIRAL IMINES.

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Abstract : *Stereocontrolled addition of isolated organozinc reagents derived from 2-(bromomethyl)acrylates to imines can be achieved with ee ~ 100% using α-amino esters as chiral auxiliaries. High yields of pure RR or SS N-substituted α-methylene γ-lactams can be prepared by this method.*

We have previously shown[1] that the two step OHLER type reaction of organozinc reagents **1** derived from 2-(bromomethyl)acrylates with imines gives high yields of α-methylene γ-lactams **2**. Some of these products exhibit cytotoxic behaviour towards P 388 leukemia while their toxicity is ten times lower compared to the parent lactones.
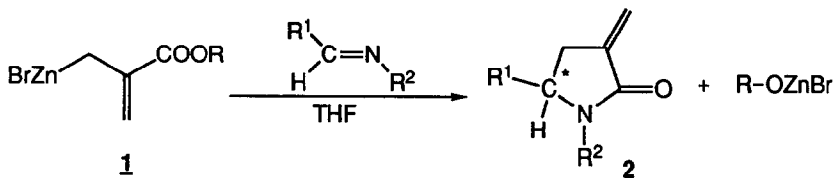

The organometallic method we have previously described gives rise to racemic lactams whilst the access to both enantiomers is now necessary for pharmaceutical purpose. Our challenge was to discover stereocontrolled conditions for the addition of α-functional allylic organozinc reagents to imines. It has been shown previously that chiral auxiliaries can undergo the stereocontrolled addition of allylic, vinylic or saturated organometallics (Li, Mg, Cu, Ti) to imines and derivatives and lead to the formation of chiral amines. In this way, the use of (S)-1-phenylethylamine[2,3,4,10] has been fully described. However, in our hands, it failed to induce asymmetric coupling giving both diastereoisomers. Further experiments showed that α-functional allylic organozinc reagents can undergo stereocontrolled addition to imines provided the chiral auxiliary can coordinate to the metal during the coupling. The use of an α-aminoester as a chiral auxiliary proved to be efficient.

Two recent publications by FUSIJAWA et al.[4] in the field of stereocontrolled addition of organometallics to chiral imines prompt us to disclose our results.

Chiral imines **3** have been obtained from aldehydes and α-amino esters in the presence of 4 Å

molecular sieves in methylene chloride. Addition of excess of the organozinc reagent **1** to racemic imines **3** gives rise to one diastereoisomer[5] (RR and SS) of the corresponding α-methylene γ-lactams **4** with a high yield. It can be transposed to homochiral analogues provided the excess of organometallic does not exceed 10%[6] (1.1 equivalent) and the temperature is controlled between 20° and 30°C. Under these conditions only one enantiomer (RR or SS) is formed and starting from each of the enantiomer of chiral α-aminoacid (alanine or phenylglycine), enables the preparation of only one product with ee>95%[7]. This result is then in agreement with the results published by Y. YAMAMOTO and W. ITO[3] who showed that allylic organozinc reagents add stereoselectively to chiral α-imines through a six membered ring transition state.
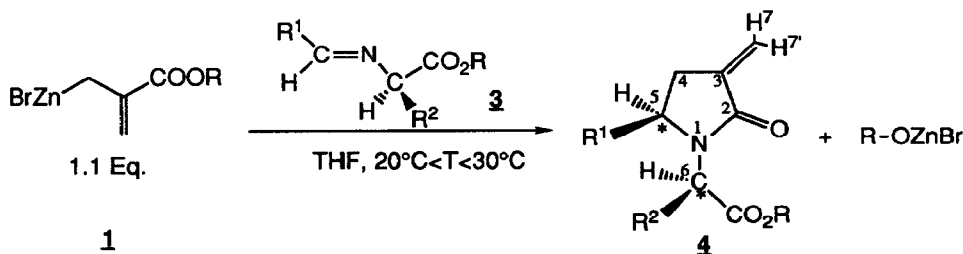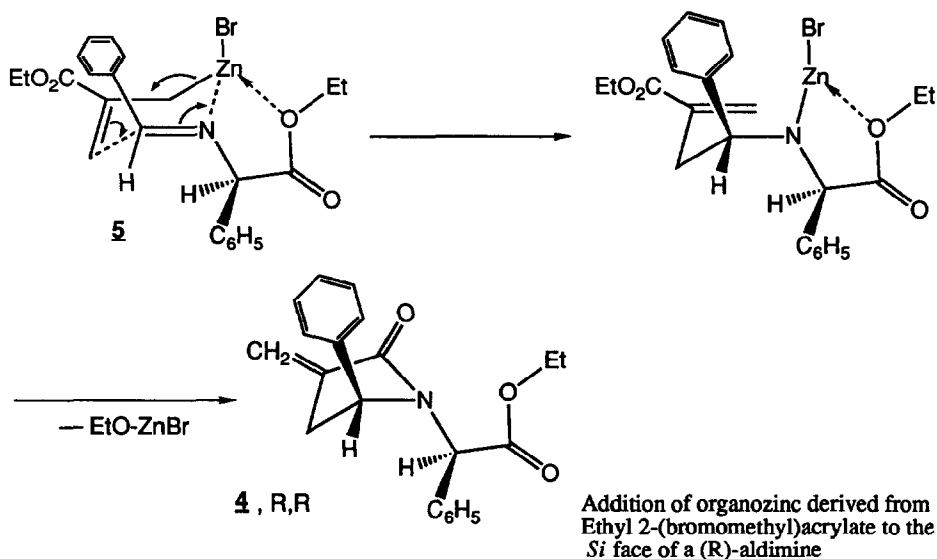

Some of our results are listed in the following table.

R^1	R^2	R	Yield (%) *	Physical state	$[\alpha]_D^{26}$ CHCl₃ **	Configuration
C_6H_5	C_6H_5	CH_3	70	*amorphous*	+ 25 c = 2	5-(S) 6-(S)
"	" racemic	CH_2CH_3	85	*white crystals*	—	5-(S)-6-(S) and 5-(R)-6-(R)***
"	"	"	80	*amorphous*	+ 27 c = 1.8	5-(S) 6-(S)
"	"	"	82	*amorphous*	- 29 c = 2.1	5-(R) 6-(R)
"	CH_3	"	78	*amorphous*	+ 24 c = 1.9	5-(S) 6-(S)
"	"	"	77	*amorphous*	- 25 c = 2.1	5-(R) 6-(R)
$(CH_3)_3C$	C_6H_5	"	75	*white crystals* M.P. (EtOH) : 135°C	+ 24 c = 1.5	5-(S) 6-(S)
"	"	"	82	*white crystals* M.P. (EtOH) : 135°C	- 25 c = 1.9	5-(R) 6-(R)

*Based on the imine, as a pure isolated product.
** Optical rotatory powers were measured using a AA. 10 OPTICAL ACTIVITY polarimeter.
***Relative configuration was determined from the X-ray structure of the crystallized racemic diastereoisomer

The mechanism of the reaction must include a chelation between the metal of the functional allylic organozinc reagent and the ester[8] moiety of the chiral anti aldimine, together with allylic transposition[9] during the coupling. The model proposed by Y. YAMAMOTO et al[3,10] showed that the inductive effect of α-phenylethylimine towards the bulky allyl-9-BBN must be associated with the chelating effect of the ester function involving the formation of a bicyclic rigid reaction intermediate **5**. Molecular modelling including chelation of zinc by the ester function, shows that the preferential addition of the organozinc reagent to the *anti aldimine moiety* must occur at the face opposed to the bulky phenyl group of the chiral auxiliary leading to RR or SS α-methylene γ-lactam **4** following the scheme :

Addition of organozinc derived from
Ethyl 2-(bromomethyl)acrylate to the
*Si* face of a (R)-aldimine

It seems also that there may be important steric interactions between the carbalkoxy group of the organozinc reagent and the phenyl group of the initial α-aminoester. However more experiments have to be performed to confirm this hypothesis. We are working now on the cleavage of the carbon-nitrogen bond to obtain the corresponding chiral secondary α-methylene γ-lactams. The catalytic hydrogenolysis of nitrogen-benzylic carbon bonds, generally used for this purpose, has failed. The presence of a strongly electrophilic α-methylene γ-lactam function combined with a second benzylic carbon when R^1 is an aromatic substituent is certainly responsible for the difficulties encountered. We are studying other methods including cleavage with non nucleophilic reagents.

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5-The stereochemistry has been deter- mined by a single crystal X-ray analysis. Crystal data : $C_{21}H_{21}NO_3$, M = 335.4, monoclinic, group space $P2_1/n$, a = 8.772(2), b = 19.435 (3), c = 10.966 (2) Å, β =103.71 (1)°, u = 1816.2Å^3. Z = 4, D calc = 1.23g/cm^{-3}, F(OOO) = 712. Monochromated Mo-Kα radiation λ = 0.71069 Å, μ = 0.8 cm^{-1}. R = 0.042 for 1796 unique reflexions with I>3σ(I).
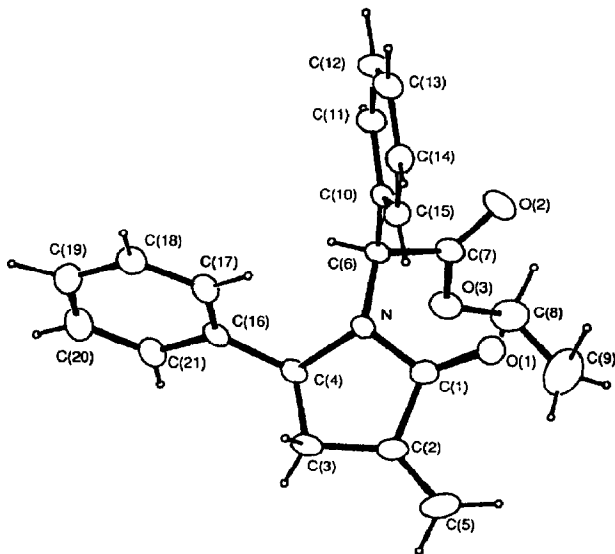
ORTEP Diagram of $C_{21}H_{21}NO_3$

6-Organozinc or zinc bromide in excess seems to undergo total racemization of the chiral auxiliary before addition to the imine function.

7 -The enantiomeric excess has been evaluated on the basis of NMR data after complexation with the chiral complexing agent Eu(hfc)$_3$ the methylenic proton H$^{7'}$ exhibiting 2 signals for the racemic compound.

8-This sort of chelation of the zinc atom has been found to take place in the organometallic itself : F. Lambert, B. Kirschleger, J. Villiéras. *J. Organometal. Chem.* 1991, **405**, 273.

9 -Allylic transposition minimizes the steric interactions during the coupling of carbonyl compounds with **1**. F. Lambert, B. Kirschleger, J. Villiéras. *J. Organometal. Chem.*, 1991, **406**, 71.

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