TRANSFORMATION OF *N*-ARYLSULFONYLAZIRIDINES TO ACHIRAL AND CHIRAL DIAMINES AND DIAMINO ACIDS

by

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in fulfilment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

to the

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June, 2005

DEDICATED

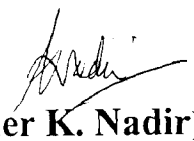
TO

MY PARENTS

CERTIFICATE

This is to certify that the thesis entitled, "**Transformation of *N*-arylsulfonylaziridines to achiral and chiral diamines and diamino acids**", being submitted by Ms. Anamika Singh to the Indian Institute of Technology, Delhi, for the award of the degree of Doctor of Philosophy in Chemistry, is a record of bonafide research work carried out by her. Ms. Anamika Singh has worked under my supervision and guidance and has fulfilled all the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results embodied in this thesis have not been submitted, in part or in full to any other University or Institute for the award of any degree or diploma.



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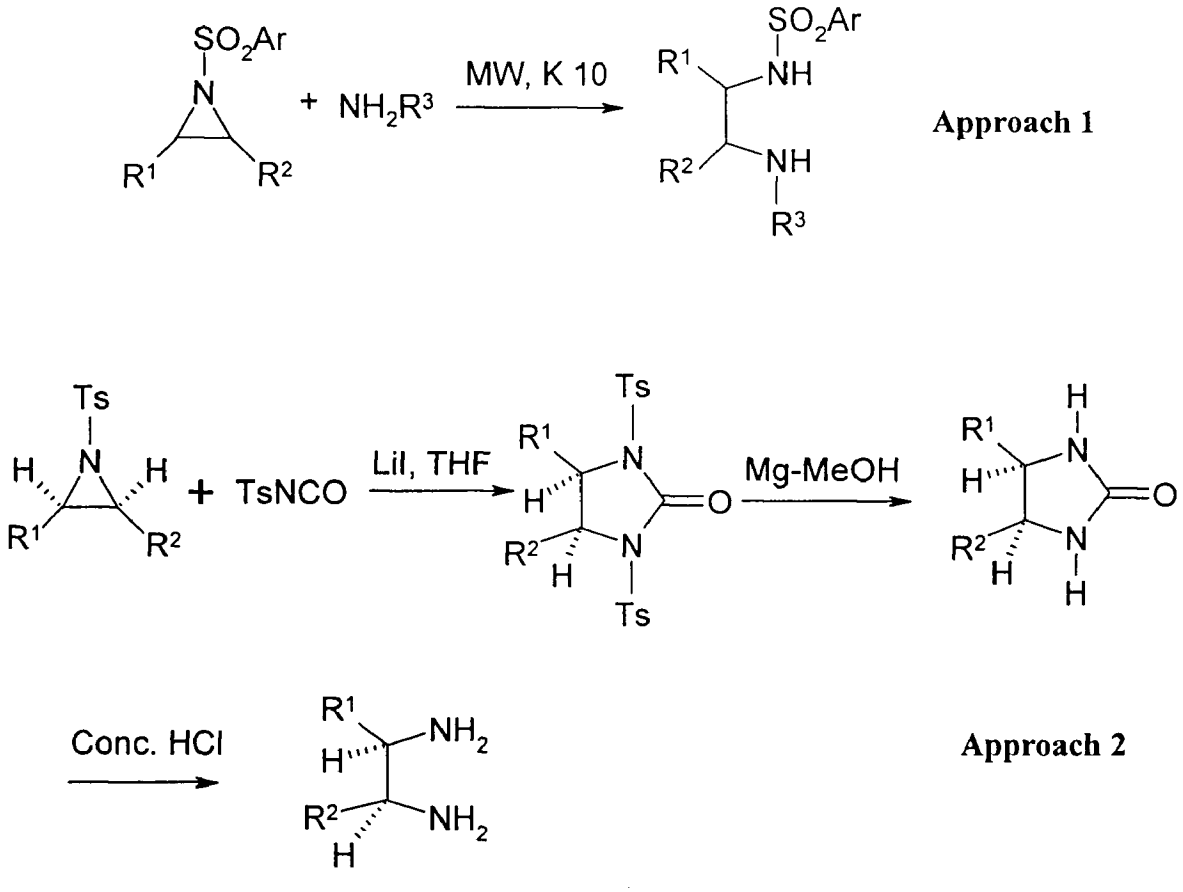
Anamika Singh

(ANAMIKA SINGH)

ABSTRACT

This dissertation is based on investigations undertaken to transform *N*-arylsulfonylaziridines to achiral and chiral diamines and diamino acids, which are of current interest.

The achiral diamines and diamino acids were synthesized through two approaches (**Scheme 1**). In the first one, *N*-*p*-toluenesulfonylaziridines were reacted with amines under microwave irradiation and on a solid support like Montmorillonite K-10 or silica gel to get *N*-tosyl-*N'*-alkyl or aryl substituted diamine derivatives (**Approach 1**; **Scheme 1**).



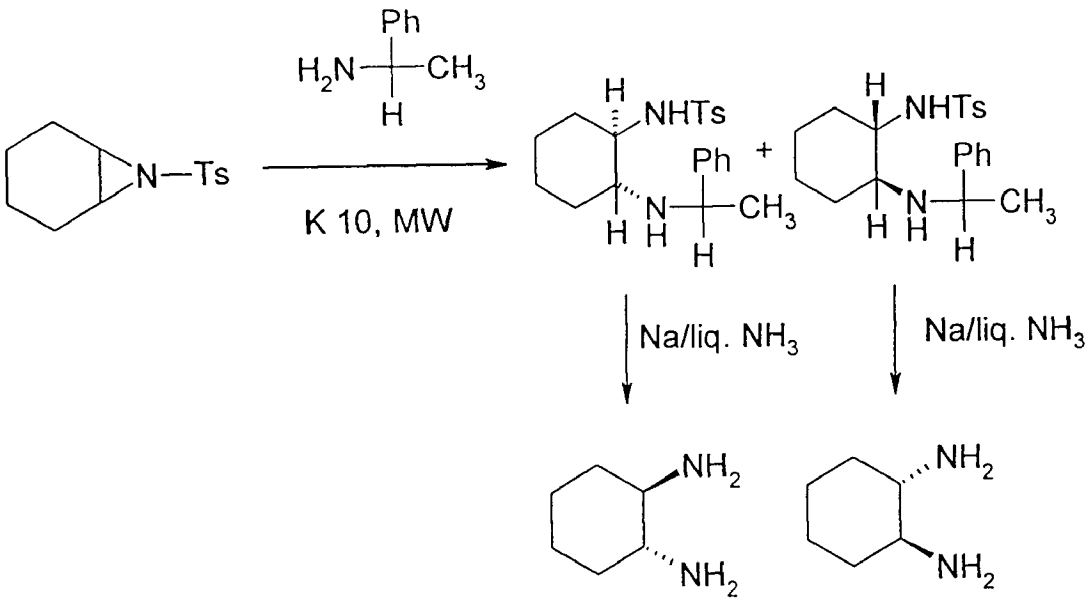
Scheme 1

Using an ester aziridine, diamino esters were obtained which could be hydrolysed to the appropriate diamino acid. The aziridine ring opening was found to be completely stereo-selective with inversion at the attacked carbon. The regioselectivity was, however, dependant

Although the above approach was successful, it failed in two cases: *Cis*-2,3-diphenyl-*N*-*p*-toluenesulfonylaziridine did not react with amines so that the *threo*-diamines could not be prepared and 2,3-cyclohexyl-*N*-*p*-toluenesulfonylaziridine could only be *cis*-fused so that the corresponding *cis*-diamine could not be synthesized. For these and others, a complementary approach was studied. The aziridines were converted to 2-imidazolidinones by treatment with *p*-toluenesulfonyl isocyanate and LiI and the products detosylated with Mg-MeOH. Hydrolysis with conc. HCl furnished the diamines (**Approach 2**; **Scheme 1**). The first reaction in this sequence is stereo-selective with the imidazolidinone retaining the aziridine geometry, so that the diamine finally has the corresponding stereo-structure. Thus *trans*-2,3-diphenyl-*N*-*p*-toluenesulfonylaziridine under these conditions afforded the *threo*-diamine and in the case of 2,3-cyclohexyl-*N*-*p*-toluenesulfonylaziridine, the corresponding *cis*-diamine was obtained.

For accessing chiral diamines and diamino acids, three approaches were explored (**Scheme 4**). Two of these were extensions of the methods described above.

Thus reaction of a racemic *N*-arylsulfonylaziridine with the chiral α-phenylethylamine gave a mixture of two diastereomeric diamines in almost 1:1 ratio which, however, could be separated by column chromatography. These on treatment with excess Na in liq. NH_3 led to cleavage of both the *N*-tosyl and *N*-α-phenylethyl groups to yield non-racemic diamines (**Approach 1; Scheme 4**). In the other approach, the aziridines were reacted with the chiral α-phenylethyl isocyanate in the presence of LiI to give a diastereomeric mixture of chiral imidazolidinones (**Approach 2**; **Scheme 4**).


Ph
H2N
CH3
H
N—Ts
K 10, MW
H
NHTs
Ph
+
N
CH3
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H
Na/liq. NH3
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NH2
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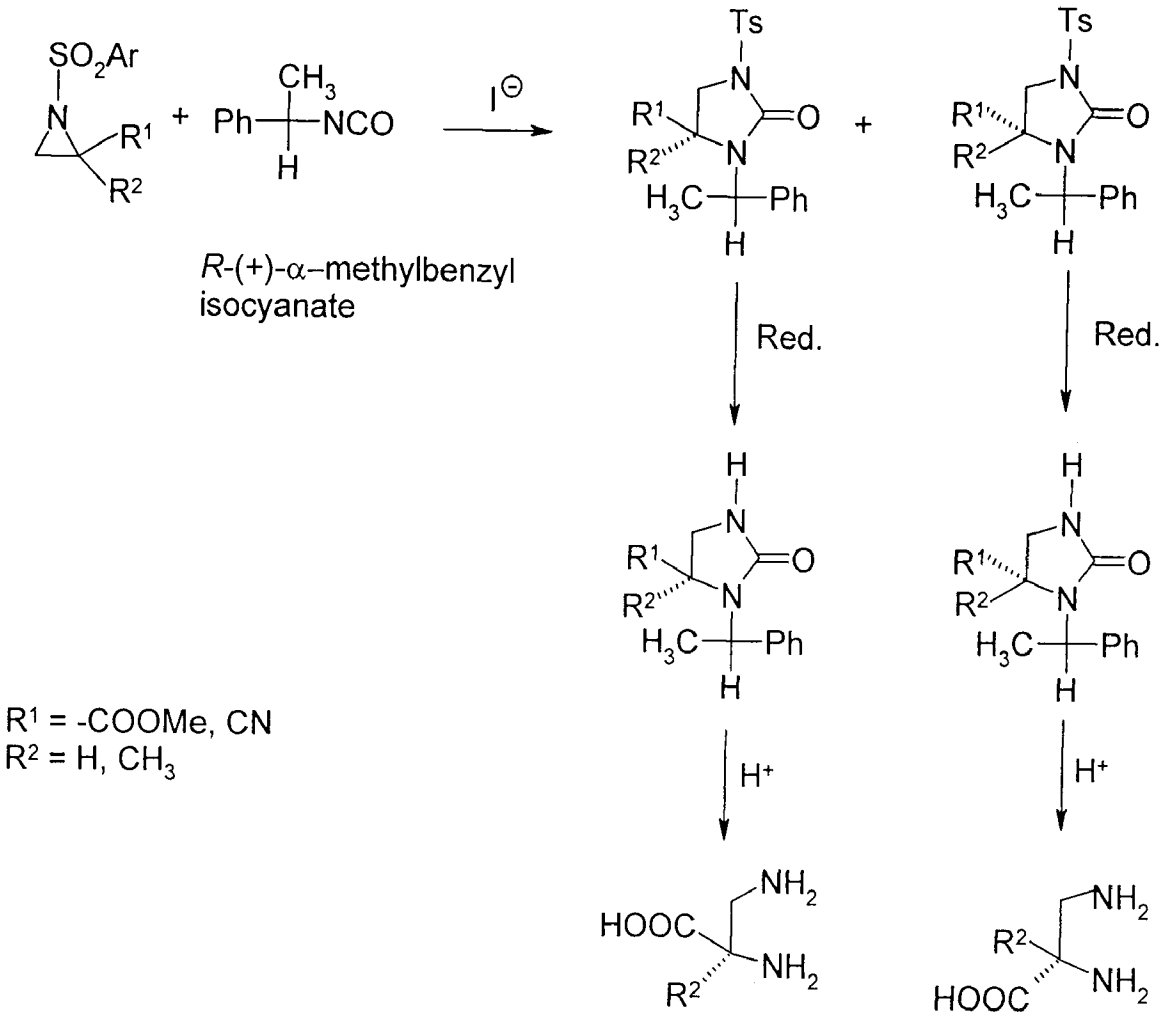
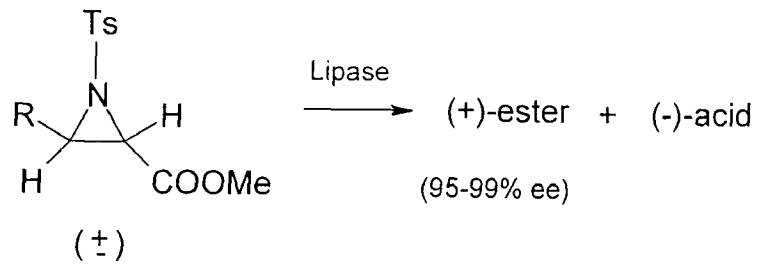
NH2

Approach 1



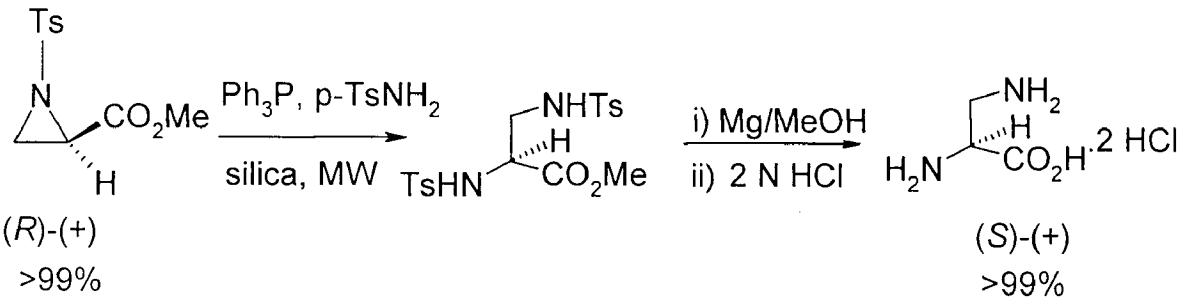


Scheme 4

In the case of reaction of 2-methoxycarbonyl-*N*-*p*-toluenesulfonylaziridine, the diastereomers could be separated by column chromatography and these on successive treatment with Mg-MeOH and Conc. HCl furnished both enantiomers of 2,3-diaminopropanoic acid. The diastereomeric imidazolidinones from 2-methoxycarbonyl-2-methyl-*N*-*p*-

toluenesulfonylaziridine could not be separated and so the mixture was detosylated with Mg-MeOH and the components separated by column chromatography. These on hydrolysis gave both enantiomers of 2-methyl-2,3-diamino propanoic acid.

In the third route, racemic aziridine esters were subjected to enzymatic kinetic resolution to get aziridine esters with high enantiomeric excess (**Approach 3**; **Scheme 4**). For the two aziridine esters, 2-methoxycarbonyl-*N*-*p*-toluenesulfonylaziridine and 2-methoxycarbonyl-3-phenyl-*N*-*p*-toluenesulfonylaziridine, optimum conditions in terms of the kind of lipase, temp., reaction time etc. were defined to get the aziridines in >99% and >95% ee respectively.

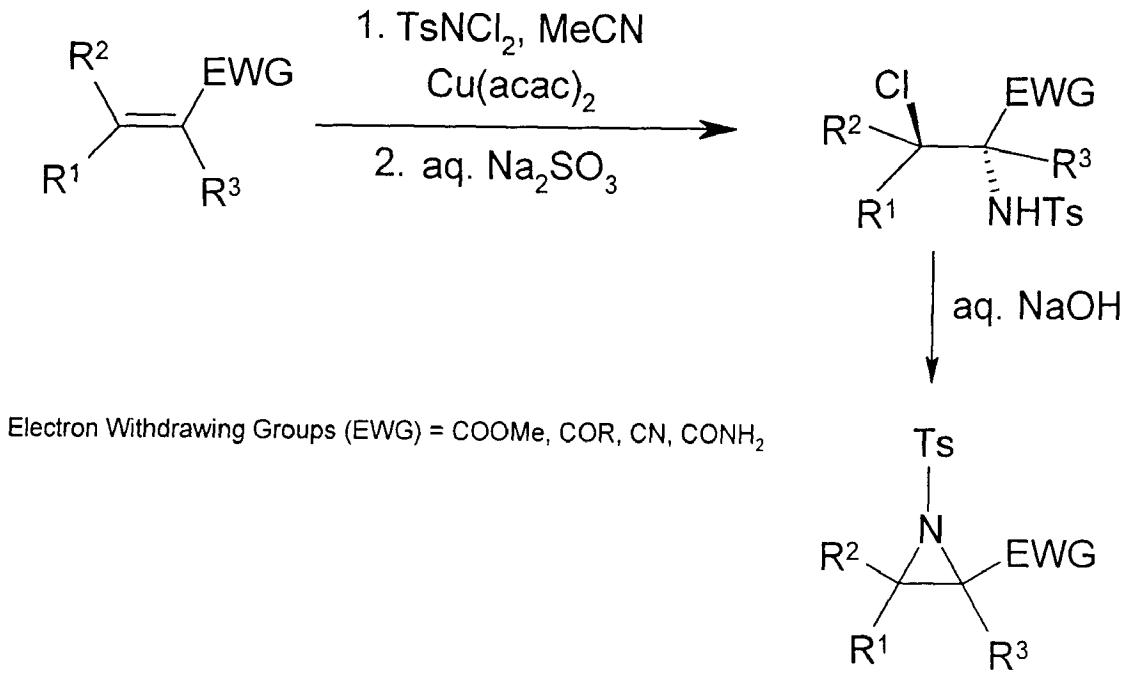


Scheme 5

These were then treated with *p*-toluenesulfonamide under microwave irradiation on silica gel support to get the ditosyl derivatives, which on detosylation and hydrolysis gave the corresponding diamino acids with high ee (**Scheme 5**).

The *N*-arylsulfonylaziridines used in these studies were prepared by known methods. Most, however, were found inadequate for aziridines derived from olefins bearing electron-withdrawing groups like ester, cyano or carboxamido etc. For these a new procedure involving addition of *N*,*N*-dichloro-*N*-arylsulfonamides to the appropriate olefin in the

presence of $Cu(acac)_2$ followed by successive treatment with Na_2SO_3 and NaOH, was developed (**Scheme 6**).



Scheme 6

The procedure was found to be general and stereo-selective and *trans*-olefins afforded *trans*-aziridines exclusively.

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