SYNTHESIS OF CHIRAL DIAMINES AND DERIVATIVES AND THEIR APPLICATION IN STEREOSELECTIVE REACTIONS

A THESIS
SUBMITTED TO THE
UNIVERSITY OF PUNE
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

BY
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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthesis of Chiral Diamines and Derivatives and their Application in Stereoselective Reactions"** submitted by Mr. Mahesh G. Malusare was carried out by him under my supervision at the National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in the thesis.

S V Pansare

Dr. S. V. Pansare

Research Guide

Date: 15-3-99

DECLARATION

I hereby declare that the work incorporated in the thesis entitled **"Synthesis of Chiral Diamines and Derivatives and their Application in Stereoselective Reactions"**, submitted for the degree of Doctor of Philosophy to the University of Pune, has been carried out by me at the National Chemical Laboratory, Pune under the supervision of Dr. S. V. Pansare. The work is original and has not been submitted in part or full by me for any other degree or diploma to this or any other University.

M. G. Malusare

Date: 15-3-1999

Mahesh G. Malusare

TO

MY PARENTS

ACKNOWLEDGEMENTS

It is a great pleasure and privilege for me to be associated with Dr. S. V. Pansare, my research guide who taught me to be concise and correct in my approach from the formulation of ideas to the presentation of results. I thank him for his excellent guidance, teaching and help during my studies.

I thank Dr. R. G. Ravi and Dr. A. N. Dixit, my seniors, who helped me a lot during my research work. I also thank my labmates Sheetal, Rajendra, Anand, Annyt and Anbu for their extremely good cooperation while working in the lab.

I acknowledge the staff in the NMR facility for their help, especially Mr. A. G. Samuel, Mr. V. T. Sathe, Mrs. U. D. Phalgune and Mr. Rajendra P. Jain. I also thank Dr. S. S. Ramdasi from the Microanalysis Group for elemental analyses, Mrs. Santha Kumari from SIL for mass spectra, and Dr.(Mrs.) N. V. Bhalerao and Mrs. V. K. Kale of our division for infrared spectra.

I take this opportunity to thank my past and present teachers for their guidance. Special thanks go to all my friends in and around NCL with whom I shared many delightful moments.

I acknowledge CSIR for a research fellowship and thank the Director, NCL for providing the necessary research facilities.

Finally, I am grateful to my family members who gave me constant support and encouragement during my studies.

Mahesh G. Malusare

CONTENTS

List of Abbreviations:

Ac	acetyl
aq.	aqueous
Bu	butyl
d.e.	diastereomeric excess
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
e.e.	enantiomeric excess
equiv.	equivalent
Et	ethyl
FAB	fast-atom bombardment
g	gram
h	hour
HRMS	high resolution mass spectrum
IR	infrared
LAH	lithium aluminum hydride
M	molar
M^+	molecular ion
Me	methyl
min	minute
ml	millilitre
mmol	millimole
mp	melting point
MS	mass spectrum
NMR	nuclear magnetic resonance
Ph	phenyl
*p*Tol	*p*-tolyl
*p*TSA	*p*-toluene sulfonic acid
rt	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	chlorotrimethylsilane

ABSTRACT

The thesis entitled **"Synthesis of Chiral Diamines and Derivatives and their Application in Stereoselective Reactions"** is divided into three chapters.

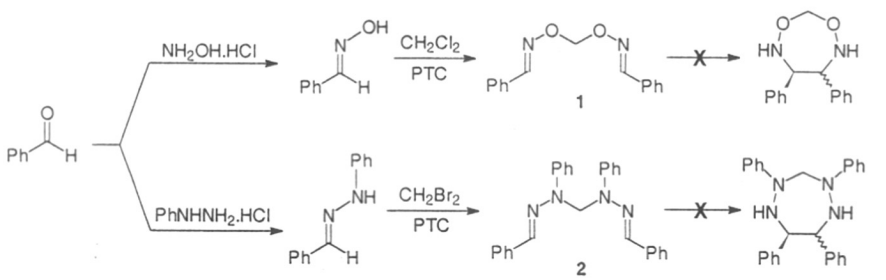
CHAPTER I

Synthesis of 1,2-diarylethanediamines:

The synthesis of chiral vicinal diamines has been intensely investigated in recent years due to their ability to function 1) as intermediates and auxiliaries in organic synthesis, and 2) as ligands in metal promoted asymmetric reactions. Most of the recent efforts have focused on preparation of C_2 symmetric diamines, although unsymmetrical vicinal diamines have also proved valuable in asymmetric synthesis. The objective of our study was to develop a stereoselective synthesis of vicinal diamines by intramolecular reductive coupling of pendant imines. The expected advantages of this approach are an easy access to symmetrical as well as unsymmetrical vicinal diamines and the generation of a cyclic intermediate in the intramolecular coupling reaction which should result in better stereoselectivity for the C_2 symmetric diamine (*trans* substitutents in the ring) compared to the intermolecular reductive coupling process.

For initial investigations benzaldehyde *O,O'*-methylene dioxime **1** and benzaldehyde methylenebis(phenylhydrazone) **2** were prepared. (Scheme 1). An important criterion in selecting these substrates was the possibility of removal of the linker between the two imines after the coupling to provide free diamines.

Scheme 1.

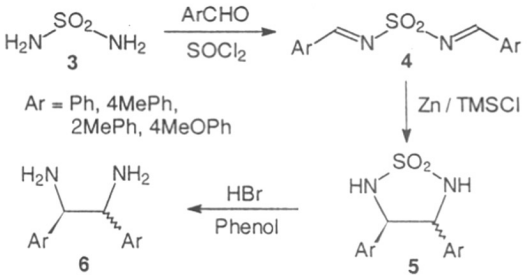


Reductive coupling of **1** and **2** could not be effected with a variety of reagents such as Zn(Hg)/EtOH, Al(Hg)/Ether, Zn/$MeSO_3H$, Mg/$TiCl_4$, and

Zn/TMSCl. Electrochemical methods for coupling of **1** and **2** were also investigated, but these caused extensive decomposition of starting materials.

As an alternative, sulfamide derived bismines **4** were chosen as substrates. These are readily available by reaction of sulfamide **3** with aryl aldehydes in the presence of thionyl chloride (Scheme 2).

Scheme 2.

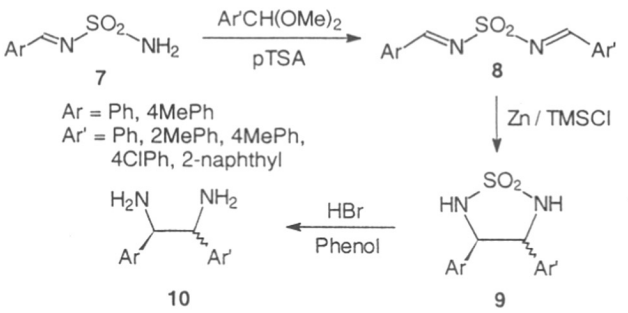


Most of the reagents that successfully couple *N*-substituted arylimines, either failed to induce any coupling in **4** or caused extensive decomposition. Although Zn metal in DMF or THF failed to yield coupled product, *in-situ* activation with TMSCl was beneficial and yielded coupled product **5** as a mixture of *cis/trans* isomers in 52-72% yield. Lowering the temperature improved diastereoselectivity in favour of the *cis* isomer.

Conversion of the 1,2,5-thiadiazolidine-1,1-dioxides **5** to 1,2-diarylethanediamines **6** proved challenging since **5** was inert to most reagents that reductively cleave sulfoxides or reduce sulfones to sulfides. Acid mediated cleavage studies of **5** indicated that it was inert to refluxing HBr or HCl. However, heating of **5** with HBr in the presence of phenol generated the free diamine **6**. The stereochemistry of the major isomer in symmetrical diamine **6** was determined to be *meso*.

The above methodology was applied to the synthesis of unsymmetrical 1,2-diarylethanediamines (Scheme 3). The unsymmetrical bisimines **8** were prepared by the reaction of monoarylidine sulfamide **7** with the dimethyl acetal of an aryl aldehyde. The procedure is quite general and is applicable to a variety of aromatic aldehydes either in the arylidene sulfamide or the acetal component.

Scheme 3.



Reductive coupling with Zn/TMSCl yielded unsymmetrical **9** as a mixture of *cis/trans* isomers. The *cis/trans* ratio was in the range of 1.5-3/1. The use of homogeneous reaction conditions (SmI_2 in THF) had no beneficial effect. Thus, unsymmetrical cyclic sulfamides **9** were readily available from **8** in 33-85% yield. These were treated with HBr/phenol to generate the free unsymmetrical diamines **10**. Various diamines with alkyl and halogen substitution in the aromatic ring were synthesized. An extension of this methodology for the synthesis of aryl-alkyl diamines was attempted.

The above route constitutes a novel approach to unsymmetrical 1,2-diamines involving an intramolecular cross-coupling of electronically similar imines.

CHAPTER II

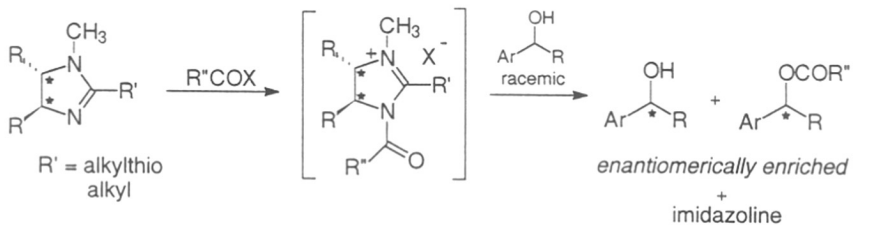
Synthesis of enantiomerically pure alkylthioimidazolines, amidines and guanidines and their application in stereoselective reactions:

Aminidines and guanidines are of considerable biological and chemical interest. Bicyclic amidines and guanidines have been examined in molecular recognition of oxoanions. The objective of our study was to synthesize enantiomerically pure 2-alkylthio-4,5-dihydroimdazoles, imdazolines (amidines) and guanidines derived from C_2 symmetric diamines and examine their utility in the kinetic resolution of secondary alcohols and in stereoselective carbon-carbon bond forming reactions. The chapter is divided into two sections.

(A) Synthesis and applications of chiral alkylthioimdazolines and amidines:

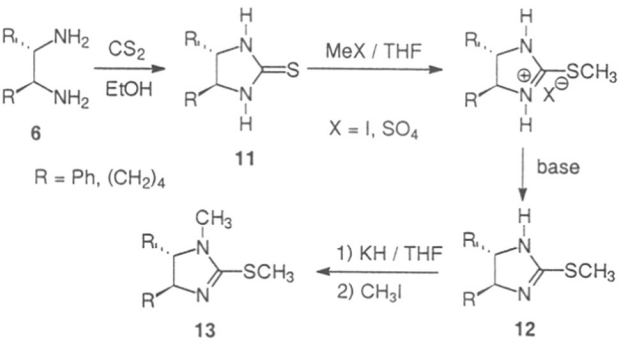
The initial objective was to investigate the possibilty of utilizing chiral 2-alkylthio-4,5-dihydroimidazoles as acyl transfer catalysts. It was envisaged that alkylthioimidazolines may be useful as acyl transfer agents as shown in Scheme 4. Thus, if a chiral alkylthioimdazoline is employed, it should be possible to carry out a kinetic resolution of racemic secondary alcohols. It was expected that the alkylthioimidazoline would first react with the acylating reagent to give an acyl imidazolinium ion which would then react preferentially with one of the enantiomers of the racemic secondary alcohol to give an enantiomerically enriched acetate, thereby effecting a kinetic resolution.

Scheme 4.



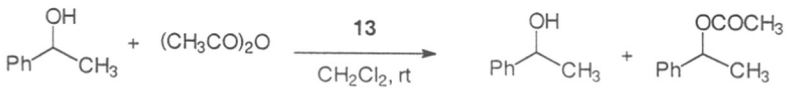
Enantiomerically pure 2-alkylthio-4,5-dihydroimdazoles were synthesized from readily available C_2 symmetric diamines **6**. Reaction of the diamines with carbon disulfide generated the thioureas **11** which were *S*-alkylated with methyl iodide or dimethyl sulfate and the resulting salts were treated with base to give the 2-methylthio-4,5-dihydroimidazoles **12.** These were *N*-methylated to give the target catalysts **13** (Scheme 5).

Scheme 5.



The alkylthioimidazolines were examined as catalysts for the kinetic resolution of 1-phenylethyl alcohol **14**. The acylation of **14** was carried out using acetic anhydride in the presence of **13** under a variety of conditions. The acetate **15** was obtained in 10-20% yield and with negligible enantiomeric excess (Scheme 6).

Scheme 6.

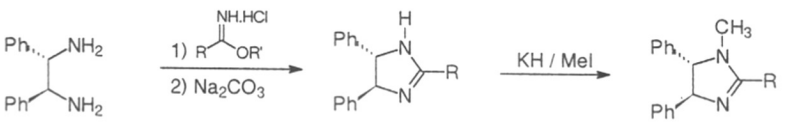


14 **15** (10 - 20%)

The addition of Lewis acidic metal salts did not have a beneficial effect on the rate of acylation. In addition, it was observed that the alkylthioimidazoline **13** is unstable under the acylation conditions. Hence, amidines were examined as alternative catalysts.

Amidines **17** were synthesised by reaction of enantiomerically pure C_2 symmetric diamines **6** with the imidate ester hydrochloride of an appropriate nitrile in 33-77% yield followed by *N*-methylation (Scheme 7).

Scheme 7.



6 R = Ph, CH_3 **16** **17**

Amidines **17** did catalyse the conversion of secondary alcohols to acetates more efficiently than alkylthioimidazolines **13** but only when a full equivalent of amidine was employed. This is probably because the acid generated from the acylating species deactivates the amidine by protonation. The enantiomeric excess of the acetate **15** obtained from these studies was 3-6% which suggests that the amidines may not be involved in the acyl transfer as expected but may be acting as conventional bases.

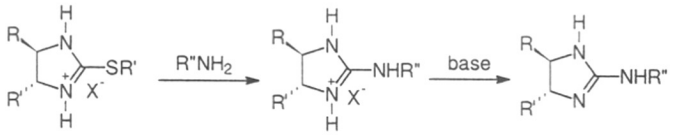
(B) Synthesis and application of chiral guanidines:

Guanidines are of interest in biological systems due to their hydrogen bond mediated interactions with other biomolecules. Although there are many

biological applications of guanidines, there are few reports on their use in organic synthesis.

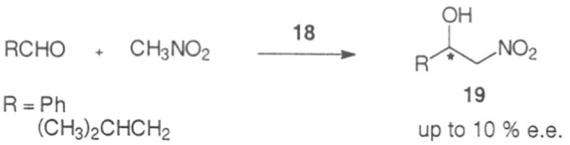
The objective of this study was to investigate the possibility of using chiral guanidines as chiral bases in a variety of carbon-carbon bond forming reactions. Several chiral guanidines **18** were synthesized from enantiomerically pure diamines **6**. The thioureas **11** were *S*-alkylated using either methyl iodide or dimethyl sulfate in quantitative yield. The resulting isothiouronium salts were reacted with primary amines to give the guanidines **18** in 72-92 % yield (Scheme 8).

Scheme 8.



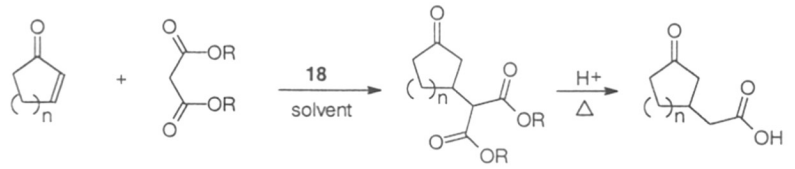
The enantiomerically pure guanidines were used as catalysts in the nitroaldol reaction. The reaction of an aldehyde with nitromethane in presence of a chiral guanidine gave the expected nitroaldol adduct **19** in 25-98 % yield with up to 10 % e.e. (Scheme 9).s

Scheme 9.



The application of chiral guanidines in the enantioselective Michael addition reaction was also investigated. The 1,4-addition of malonate esters to α,β-unsaturated ketones was examined (Scheme 10). Reaction of cyclopentenone or cyclohexenone with a variety of malonates in the presence of guanidines **18** (0.3 equiv.) generated the Michael adducts **20** which were converted to the corresponding cycloalkanone acetic acids **21**. The e.e. obtained in the reaction was in the range of 5-23%.

Scheme 10.



n = 1, 2 R = Et, CH_2Ph, $C(CH_3)_2$ **20** **21**

5 - 23% e.e.

The results indicate that enantiomerically pure guanidines can be used as enantioselective catalysts in carbon-carbon bond forming reactions such as the nitroaldol and the Michael addition reactions. The enantioselection in these reactions is not very high, but the present results serve as a foundation for the development of more efficient catalysts.

CHAPTER III

Synthesis of 1,2-diarylethanediketones:

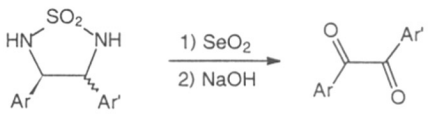
The 1,2-diketone functionality has found various applications in synthesis and biological systems. This chapter describes the results on a new approach to symmetrical and unsymmetrical 1,2-diaryl diketones that involves oxidation of 1,2,5-thiadiazolidine-1,1-dioxides **5** and **9** described in Chapter I.

During investigations on the cleavage of cyclic sulfamide **5** to vicinal diamines, we observed the formation of trace amounts of 1,2-diketones along with unreacted **5**. Considering that the acid mediated cleavage of sulfonamides involves a redox process, it seemed plausible that the diketones were obtained by oxidation of the thiadiazolidine-1,1-dioxide to a thiadiazole-1,1-dioxide which underwent hydrolysis during work-up. Attempts to optimize the reaction yield by treatment with HBr or HI were unsuccessful under a variety of conditions and so attention was focused on other oxidizing agents.

Initial experiments were performed with **5** (mixture of *cis* and *trans* isomers) and sodium hypochlorite as an oxidant. The yields of diketones **22** were higher than with HBr, but the products were always contaminated with aryl aldehydes. Although **5** could not be oxidized with lead tetraacetate or DDQ, oxidation with SeO_2 was successful. The reaction proceeded in DMF and the

crude oxidation product was hydrolyzed with aq. NaOH to furnish the α-diketones **22** in 17-66 % yields. (Scheme 11).

Scheme 11.



5, 9 **22**

17 - 66%

The conversion constitutes a new approach to 1,2-diaryldiketones involving a reductive coupling/oxidation sequence that is based on aryl aldehydes as starting materials. The reaction is applicable to a variety of substrates containing alkyl, alkyloxy substituents in the aromatic ring and provides an access to unsymmetrical diketones by a cross coupling of aryl aldehyde imines followed by oxidation.

CHAPTER I

SYNTHESIS OF 1,2-DIARYLETHANEDIAMINES

Part of work described in this chapter has been published in *Tetrahedron Lett.* **1996**, *37*, 2859.

1. INTRODUCTION

Vicinal diamines are of interest due to their numerous applications in asymmetric synthesis[1] and medicinal chemistry.[2] Enantiomerically enriched vicinal diamines are useful as chiral ligands in several reagents and catalysts which are employed in stereoselective Diels-Alder,[3] Michael,[4] aldol,[5] allylation,[6] osmylation[7] and epoxidation[8] reactions, for the asymmetric dihydroxylation of alkenes,[9] enantioselective reduction of ketones[10] and addition of organometallic reagents to aldehydes.[11] Enantiomerically pure diamine derivatives are also used as promoters in asymmetric hydrogenation reactions,[12] as Lewis acids for the generation of enolates,[13] in propargylation reactions,[14] and as ligands in salen[15] and other complexes.[16] In addition, derivatives of chiral diamines are also useful for the determination of enantiomeric excesses for chiral alcohols, thiols and amines.[17] They are effective reagents for the determination of the enantiomeric excess of carboxylic acids by NMR spectroscopy.[18] Vicinal diamines and their derivatives are also useful in molecular recognition[19] and in pharmacology.[20]

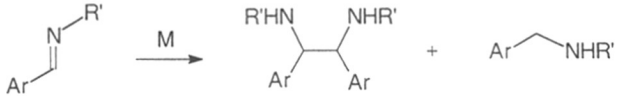
Due to the several applications of enantiomerically pure vicinal diamines in organic synthesis, their diastereoselective as well as enantioselective synthesis from readily available starting materials has been intensely investigated. Many methods for the synthesis of vicinal diamines have been described and a summary of these methods, based on key synthetic transformations, follows.

Syntheses of Vicinal Diamines:

A. Intermolecular Reductive Coupling of Imines:

The reductive coupling of imines is the simplest approach to vicinal diamines and the intermolecular version of this reaction has been studied extensively (Figure 1).

Figure 1. Intermolecular reductive coupling of imines

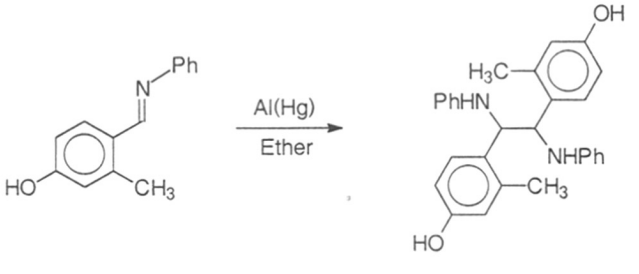


M = low valent metal

1) Reductive coupling with amalgams.

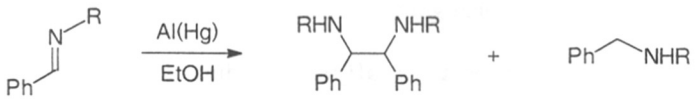
The use of a low valent metal for the reductive coupling reaction is known since 1908. Anselmino reported the reductive coupling of benzylidine anilines with aluminum amalgam to generate vicinal diamines (Scheme 1).[21]

Scheme 1.



A related study by Thies describes the reductive coupling of imines with aluminum amalgum in ethanol to give a diamine/monoamine mixture (2-5/1).[22] The monoamine arises from reduction of the imine which competes with the reductive coupling (Scheme 2).

Scheme 2.



R = Me, Et, *i*Pr dl / meso = 2-5 / 1

A reductive coupling of imines in the presence of zinc amalgam to give diamines and amines in the ratio of ~2/3 has also been reported.[23]

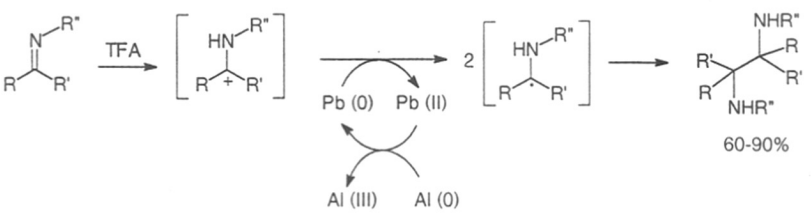
2) Reductive coupling with elements from Group 1, 2, 13, 14 and 15.

Reductive coupling can also be achieved by using alkali metals in a variety of solvents. Diamines are obtained by the coupling of imines in the presence of alkali metals such as Li or Na in solvents such as ether, THF, benzene or toluene.[24] The use of a Mg/MgI_2 system has also been reported.[25]

Sandhu has reported the coupling of imines with aluminum or bismuth in KOH/MeOH.[26] The ratio of reductive coupling to reduction was better with Al (4-9/1) than with Bi (1.5-3/1). Similarly, the dl/meso ratio for the diamine was better with Al (~ 3/1) than with Bi (~ 1/1).

The reductive dimerization of *N*-alkyl imines to vicinal diamines by the action of catalytic $PbBr_2$ in the presence of Al as a reducing agent has been studied by Tanaka.[27] The reaction proceeds in THF containing trifluoroacetic acid. Yields of the diamines are in the range of 60-90% (Scheme 3).

Scheme 3.

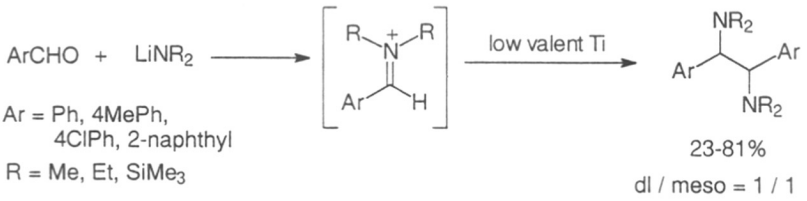


Newmann has demonstrated that a mechanism involving radicals as intermediates may be operating in these coupling reactions.[28] Schiff bases of the type ArRC=NR' react with $(Me_3Si)_2Hg$ to give carbon centered radicals $ArRC^{\bullet}(NR'SiMe_3)$ upon heating or irradiation. The latter are in equilibrium with the corresponding dimers, the 1,2-diaminoethanes. The equilibria strongly depend on steric strain in the dimers. With R=R'=Me, disproportionation products are isolated quantitatively.

3) Reductive coupling using transition metals.

Seebach has reported[29] a McMurray-type one pot reaction in which a lithium dialkylamide is added to aryl aldehydes to give an adduct, which is then treated with one equivalent of $TiCl_4$, to yield the iminium salt. After treatment with a low valent titanium reagent (generated by reduction of $TiCl_4$ with Mg or K), the coupling products are isolated as ca. 1/1 mixtures of dl/meso isomers (Scheme 4).

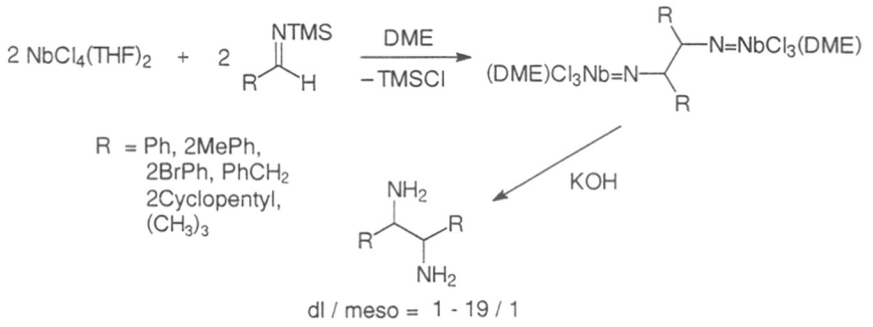
Scheme 4.



In a related study, Mangeney examined the use of a low valent titanium reagent (generated by reaction of magnesium amalgam with $TiCl_4$) to induce coupling.[30] Vicinal diamines and amines (ratio ca. 1-9/1) were obtained. The dl/meso ratio in the diamine varied from 2/1 to 9/1.

Other transition metals can also be employed to bring about the reductive coupling. Pederson has reported the preparation of free vicinal diamines with moderate to good anti selectivity by coupling *N*-(trimethylsilyl)imines with the d^1 niobium regent $NbCl_4(THF)_2$ (dl/meso ratio=1-19/1, Scheme 5).[31] Alternatively, the imine is generated in situ by reaction of a nitrile with tributyltin hydride. The resultant *N*-(tributyltin)imines react with $NbCl_4(THF)_2$ to generate vicinal diamines with a 1-8/1 dl/meso selectivity.

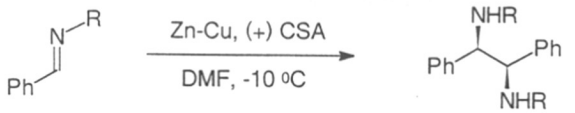
Scheme 5.



Kalyanam has employed indium for reductive coupling of aldimines under aqueous conditions to obtain *N*-substituted diamines in more than 90% yield.[32] Reductive coupling of imines with ytterbium to give diamines in 46-81% yields was reported by Takaki.[33] Imamato[34] and Enholm[35] have reported the reductive coupling of imines with samarium diiodide to give diamines in 60-90% yield. All of these methods employ *N*-alkyl imines as substrates.

Recently, Shimizu has described an enantioselective reductive coupling of benzaldimines with Zn-Cu couple in the presence of (+)-camphorsulphonic acid. Diamines are obtained with 34-97% e.e. and 60-80% yield (Scheme 6).[36]

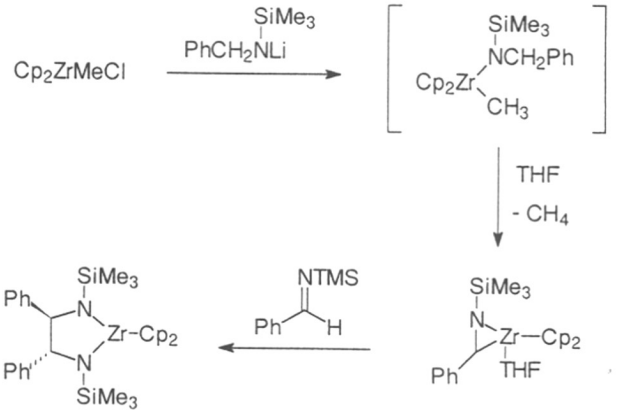
Scheme 6.



R = Ph, $PhCH_2$, 4MeOPh e.e. 34-97%

Organometallic reagents can also be used for imine coupling[37] (Scheme 7). Treatment of zirconocene (methyl) chloride with lithium dibenzylamide produces an adduct which loses methane upon heating at 110 °C. The resulting zirconium(trimethylsilyl)benzaldimine complex undergoes a diasteroeselective coupling reaction with *N*-(trimethylsilyl)benzaldimine to generate a zirconium chelate with good stereoselectivity (cis/trans = 8/92).

Scheme 7.



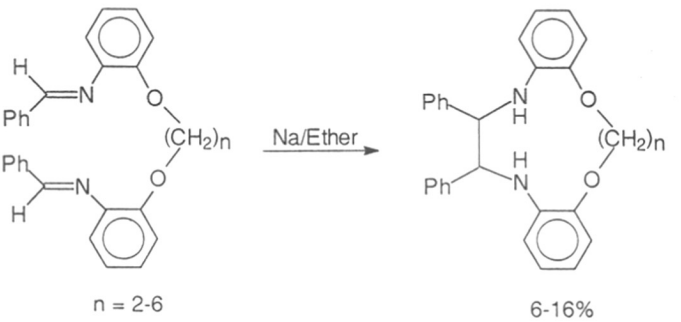
cis / trans = 8 / 92

B. Intramolecular Reductive Coupling of Imines:

The intramolecular reductive coupling of imines was first described by Jaunin.[38] Salicylaldehyde bisimines which are linked through the phenolic oxygen with a carbon tether were employed in this study. Reductive coupling with

sodium in ether led to the formation of macrocyclic ethers in modest yields (Scheme 8). The stereoselectivity of ring formation was not reported.

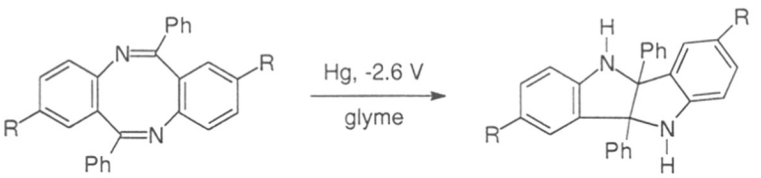
Scheme 8.



n = 2-6 6-16%

Electrochemical reduction of dimeric imines derived from *o*-amino benzophenones proceeds with concomitant transannular cyclization to generate dimeric indoloindoles incorporating the vicinal diamino functionality (Scheme 9).[39]

Scheme 9.

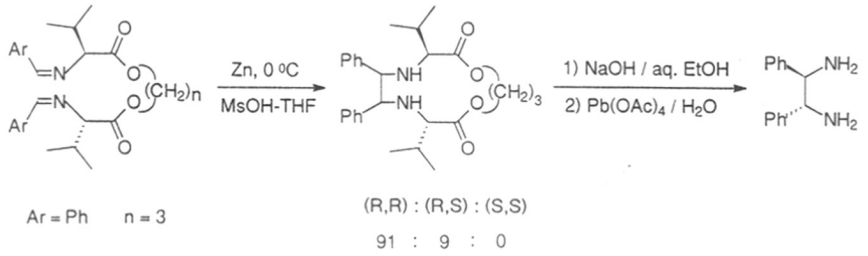


R = H, Cl

Recently, Shono and coworkers have described a stereoselective synthesis of (*R,R*)-1,2-diarylethanediamines by the reductive, intramolecular coupling of chiral aromatic bisimines, derived from (*S*)-valine.[40] A three carbon linkage between the two valine moieties afforded the best selectivity. The selectivity also improved for substrates having a *para*-electron donating substituent on the aryl group. Other macrocycles, staring from analogous bisimines (Ar = 4MeOPh,

4ClPh, 4CNPh, Scheme 10), have been prepared accordingly. The intramolecular coupling can be achieved by either electroreduction or with zinc (Scheme 10).

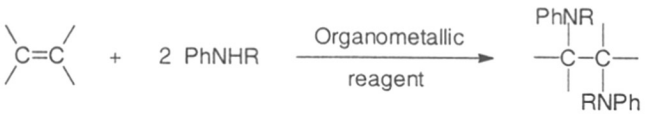
Scheme 10.



C. Synthesis of diamines by addition reactions of alkenes:

Amines can be made to undergo 1,2 addition type reactions with olefins to give vicinal diamines (Figure 2). In general, these reactions involve activation of the olefin by an electrophile and subsequent addition of the amine. Metal mediated reactions have also been investigated.

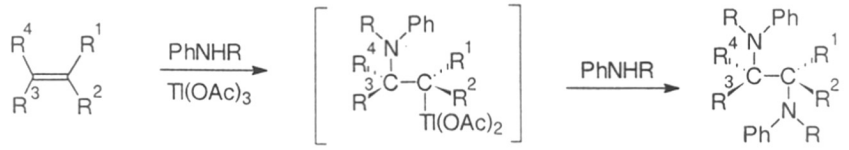
Figure 2. Addition of amines to olefins.



1) Metal mediated aminations.

Barluenga has reported a convenient preparation of aromatic vicinal diamines from olefins in the presence of thallium salts (Scheme 11).[41] Aromatic amines add to olefins giving vicinal diamines probably via the intermediacy of an unstable organothallium (III) derivative. Primary aliphatic amines do not add to alkenes under identical conditions. The procedure is thus limited to *N*-aryl amines.

Scheme 11.

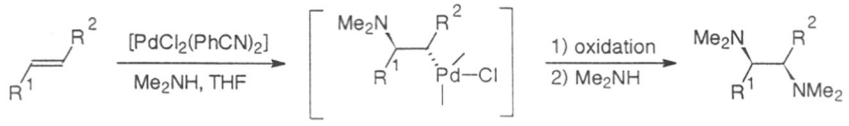


R^1, R^2 = H, alkyl, Ph
R^3, R^4 = H, alkyl
R = H, Me

50-93%

Bäckvall has demonstrated that the aminopalladation of *E*-alkenes, followed by oxidation with Br_2, *m*-chloroperbenzoic acid or *N*-bromosuccinimide and subsequent treatment with an excess of amine affords the corresponding vicinal diamines (Scheme 12).[42] The diamination proceeds with *syn* selectivity and terminal olefins were diaminated in good yields (35-87%). *Z*-alkenes were not examined as substrates and only dimethylamine was used for the amination.

Scheme 12.

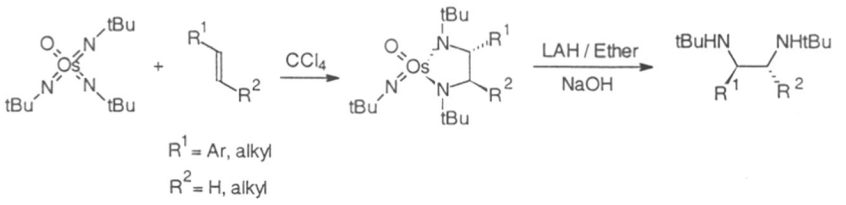


R^1, R^2 = H, alkyl

R^1 = R^2 = Me, 45%, de> 95%

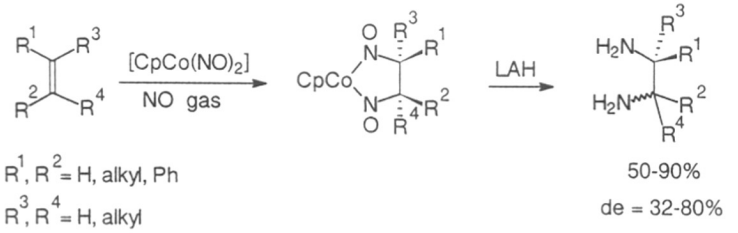
An elegant, osmium based amination protocol has been described by Sharpless.[43] A triimidoosmium complex, derived from osmium tetraoxide and *N*-*tert*-butyl tri-*n*-butylphosphinimine, reacts with mono- and disubstituted *E*-alkenes through a stereospecific *cis* addition to give vicinal diamines (Scheme 13). The complex is used in stoichiometric amounts and is unreactive towards disubstituted *Z*-olefins. Thus, the method only allows the preparation of secondary *N*-*tert*-butyl-substituted 1,2-diamines.

Scheme 13.



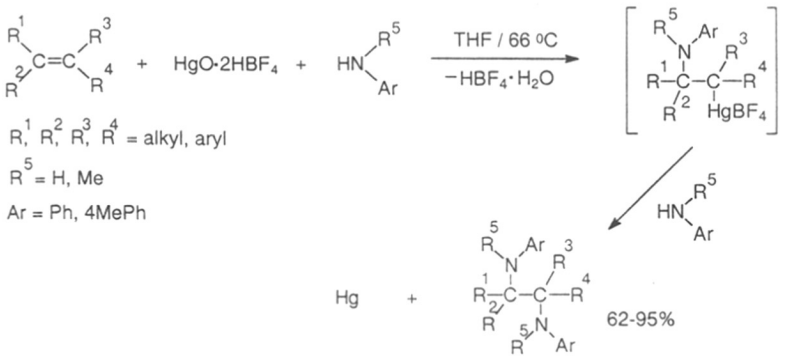
The 1,2-diamination of alkenes with nitric oxide and a cobalt complex has been described by Bergman.[44] Primary vicinal diamines are obtained in 50-90% yield with this procedure (Scheme 14). Despite the completely stereospecific *cis* addition in the first step, the diamines are obtained as a mixture of diastereomers due to epimerization during the $LiAlH_4$ reduction.

Scheme 14.



Barluenga has reported a one-pot procedure for the synthesis of aromatic vicinal diamines from olefins and aromatic amines in the presence of mercuric (II) oxide/tetrafluoboric acid (Scheme 15).[45] The reaction presumably proceeds *via* the formation of an intermediate β-aminomercury (II) tetrafluoborate.

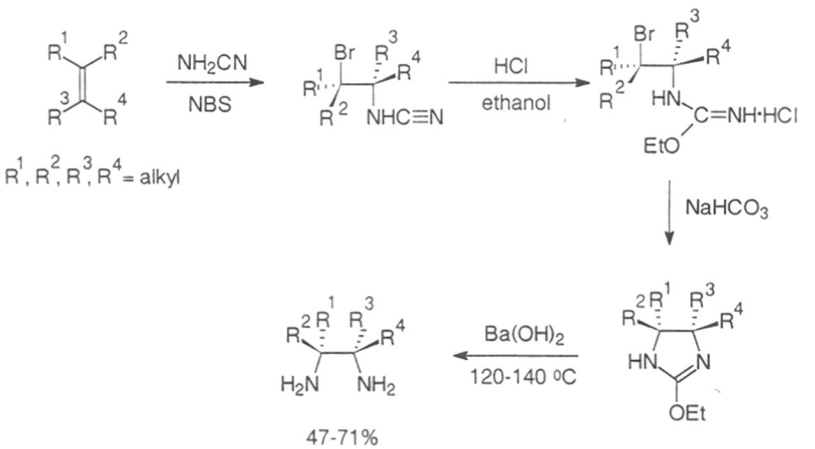
Scheme 15.



2) Aminations involving conventional electrophilic activation of the olefin.

A stereospecific synthesis of vicinal diamines from alkenes and cyanamide has been reported.[46] The treatment of an alkene with cyanamide and *N*-bromosuccinimide generates the bromoalkyl cyanamide. This adduct is converted into an isourea salt *in situ* with ethanolic HCl (Scheme 16). Treatment of the isourea salt with base gives an ethoxy imidazoline which upon basic hydrolysis yields the vicinal diamine in 47-71% overall yield.

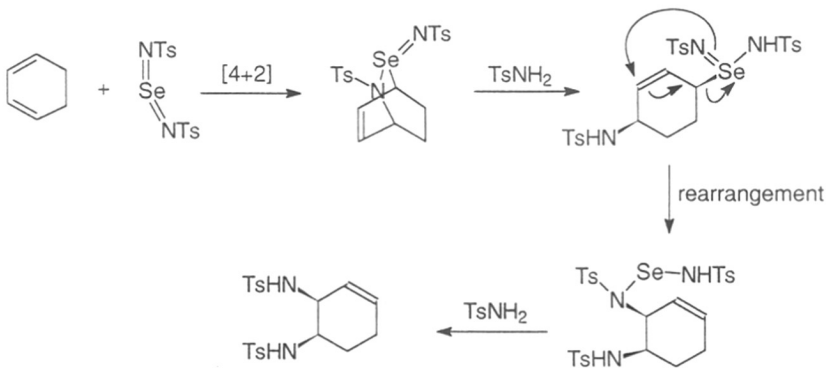
Scheme 16.



3) Cycloadditions with dienes.

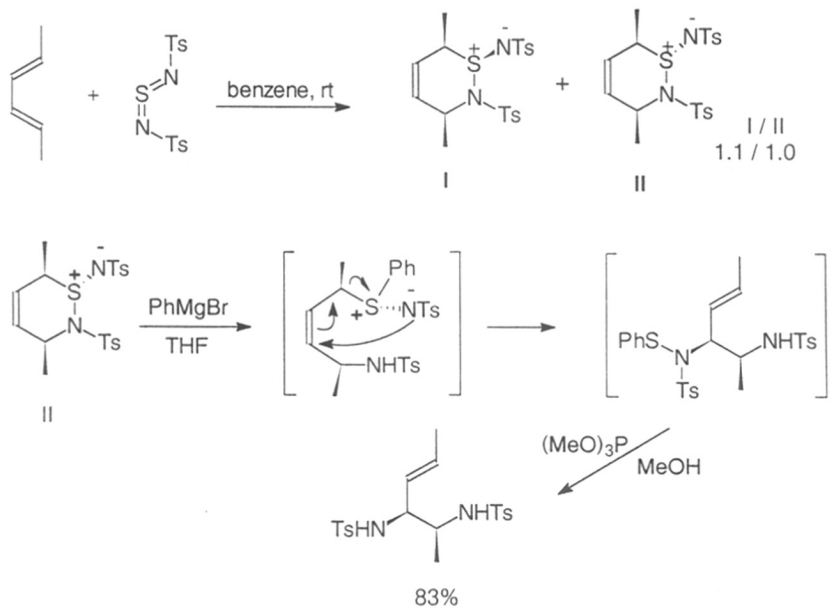
Sharpless[47] has demonstrated that the selenodiimide generated from selenium metal and *p*-toluenesulfonamide in the presence of Chloramine-T reacts with 1,3-dienes to produce 1,2-disulfonamidoalkenes to generate a cycloadduct which undergoes facile nucleophilic ring opening with tosylamide and subsequent [2,3]-sigmatropic rearrangement (Scheme 17). In the case of 1,3-cyclohexadiene the sulfonamide groups are introduced *cis* to each other (Scheme 17).

Scheme 17.



A related stereocontrolled synthesis of unsaturated vicinal diamines from the Diels-Alder adducts of sulfur dioxide diimides (generated from sulfur dioxide and *p*-toluenesulfonamide) and 1,3-dienes was reported by Weinreib.[48] When the 2,4-hexadiene derived adduct **II** was treated with phenylmagnesium bromide followed by trimethylphosphite, the *N,N*-ditosyl diamine derivative was obtained (Scheme 18). The reaction proceeds by initial ring opening by the Grignard reagent, which leads to an allylic sulfilimine that undergoes a [2,3]-sigmatropic rearrangement to a sulfenamide. Desulfurization of the sulfenamide with trimethylphosphite affords the diamine derivative.

Scheme 18.

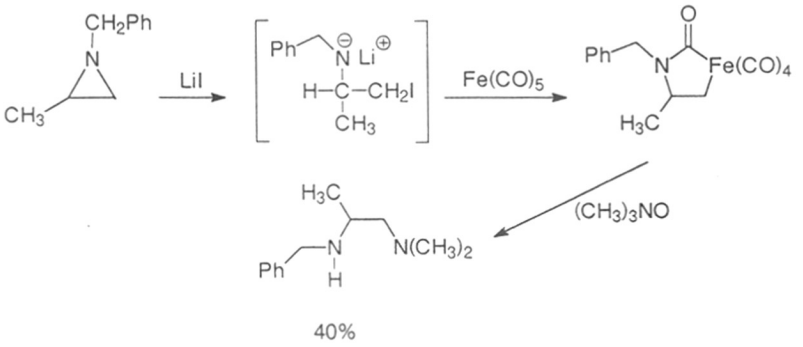


D. Other Methods for Preparation of 1,2-Diamines:

1) Synthesis of diamines from aziridines.

Unsymmetrical 1,2-diamines can be prepared from aziridines and amine oxides using lithium iodide and iron pentacarbonyl in THF. The yields for the process range from 40-60% (Scheme 19).[49] The first step of the transformation is ring opening of the aziridine by lithium iodide. The intermediate obtained then reacts with a carbonyl group in the $Fe(CO)_5$ with concomitant formation of a carbon-iron bond to generate a metallacycle, which is finally converted to the diamine by trimethylamine *N*-oxide. The mechanism of this conversion is not known.

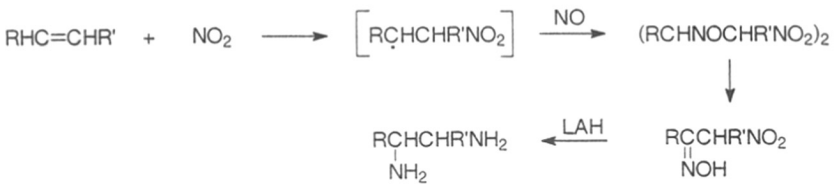
Scheme 19.



2) Synthesis of diamines by reduction of hydroxylamino oximes.

The reaction of olefins with dinitrogen trioxide or with a mixture of nitrogen oxides to form 1:1 adducts is a classical method of introducing two vicinal carbon-nitrogen bonds into an olefinic system. The dimeric adducts can be thermally rearranged to more stable α-nitrooximes which are subsequently reduced to vicinal diamines (Scheme 20).[50]

Scheme 20.

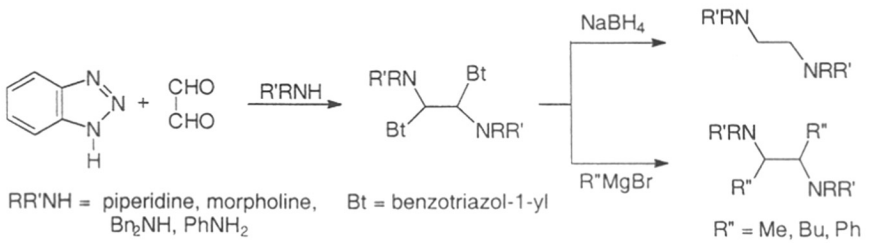


3) A benzotriazole based approach to vicinal diamines.

Katrizky has described the use of glyoxal as the starting material in a route to symmetrical secondary and tertiary vicinal diamines.[51] Condensation of glyoxal, benzotriazole and either aromatic or secodary aliphatic amines affords stable adducts. The benzotriazolyl group was removed reductively by treatment

with $NaBH_4$ or by nucleophilic displacement with Grignard reagents to give a variety of diamines as *syn/anti* mixtures (Scheme 21).

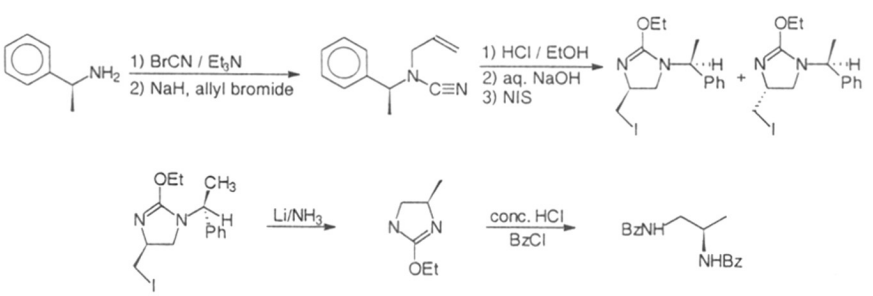
Scheme 21.



4) Vicinal diamines from allylic amines.

A synthesis of enantiomerically enriched 1,2-diamines starting from 3-(1-phenethyl)-5-iodomethyl-imidazolines is reported by Bruni.[52] The imidazolines are prepared from (*S*)-1-phenylethylamine. The amine is converted into the corresponding cyanamide, which is then allylated (NaH/allyl bromide) and converted to the isourea by treatment with HCl in dry EtOH. Subsequent cyclization is effected by treatment with *N*-iodosuccinimide. A 1/1 diastereomeric mixture of imdazolines is obtained which can be separated by chromatography. The imidazolines on hydrolysis gave 1,2-diamines in enantiomerically pure form (Scheme 22).

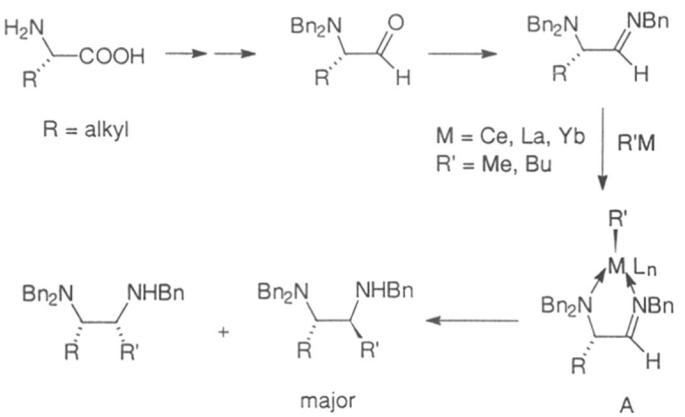
Scheme 22.



5) Stereoselective synthesis of 1,2 diamines from aminoaldehydes.

Reetz has described a synthesis of *N*-substituted diamines from *N,N*-dibenzyl aminoaldehydes which are readily prepared from amino acids.[53] The aminoaldehydes were converted into corresponding *N,N'*-dibenzyl aldimines and addition reactions with organometallic reagents were studied. The addition takes place through the intermediacy of chelates such as **A** (Scheme 23), which are attacked preferentially from the sterically less hindered side. Replacement of the *N*-benzyl group with the electron withdrawing tosyl group inhibits chelation and results in non-chelation controlled addition to the imine.

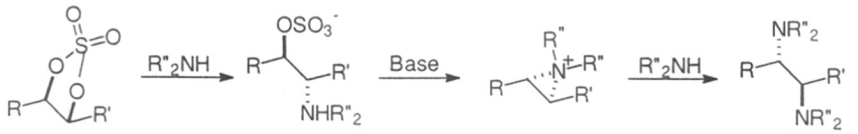
Scheme 23.



6) Synthesis of vicinal diamines from cyclic sulfates.

Sharpless has reported stereoselective synthesis of vicinal diamines using cyclic sulfates.[54] Nucleophilic opening of cyclic sulfates with secondary amines followed by treatment with base results in the formation of an aziridinium ion which undergoes ring opening by a second equivalent of the amine to give diamines in 41-82% yield.

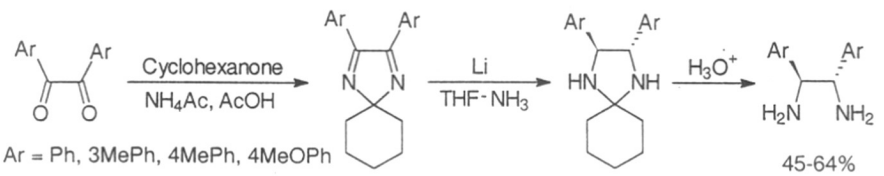
Scheme 24.



7) Synthesis of C_2 symmetric vicinal diamines from benzils.

Corey has described the synthesis of racemic C_2 symmetric vicinal diamines starting from substituted benzils.[55] The conversion of benzils to the corresponding 2,2-spirocyclohaxane-4,5-diphenyl-2H-imidazole was accomplished by heating in acetic acid with cyclohexanone and excess NH_4OAc. Dissolving metal reduction of the imidazole generates the *trans* imidazolidine which after acid hydrolysis gives C_2 symmetric diamines in 45-64% yield.

Scheme 25.



During the preparation of this thesis, an exhaustive review[56] on the synthesis and applications of vicinal diamines appeared in the literature.

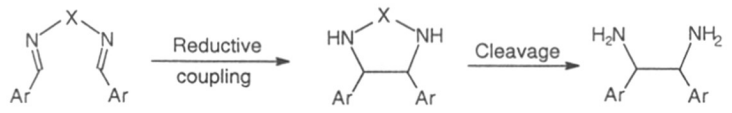
2. OBJECTIVE

The objective of our study was to develop a stereoselective synthesis of vicinal diamines by intramolecular reductive coupling of pendant imines.

Although reductive coupling of imines is the simplest approach to diaryl vicinal diamines and the intermolecular version of this reaction has been extensively studied, the reported methods suffer from the following drawbacks:

1) invariably, a mixture of *dl* and *meso* diamines is obtained, 2) with very few exceptions,[29,31] the coupling products are *N*-alkyl diamines which may not always be desirable, and 3) the separation of the diamines from the by product monoamine is tedious. We surmised that these problems may be minimized by conducting the reductive coupling in a intramolecular fashion. The main advantage expected from this modification is an improvement in the *dl/meso* ratio since the coupling proceeds with concomitant ring formation which is expected to proceed which some element of stereocontrol and may favor the product in which the aryl/alkyl moieties in the ring are placed *trans* to each other. Prior to this study, there were only two reports on the intramolecular coupling of pendant imines.[38,40] However, these methods have drawbacks in that one of them[38] is very ineffecient (coupling yield is 6-16%) and conversion of the resulting macrocycles to diamines has not been reported, and the second report[40] generates *N*-alkyl diamines which has already been identified as a limitation. Our approach therefore focused on a method that would yield free (no substituent on nitrogen) vicinal diamines. The intramolecular coupling is also expected to minimize unwanted reduction products. Finally, the major limitation of the known reductive coupling methods is their restriction to the homo-coupling mode. In contrast to the cross coupling of carbonyl compounds,[57] a similar reaction involving imines derived from two different carbonyl compounds has not been reported. Since unsymmetrical vicinal diamines are also important targets with several applications[1b,58], one of our objectives was the synthesis and reductive coupling of unsymmetrical bisimines. Our approach to vicinal diamines is summarized in Figure 3.

Figure 3. Intramolecular reductive coupling of imines.



X = removable functionality

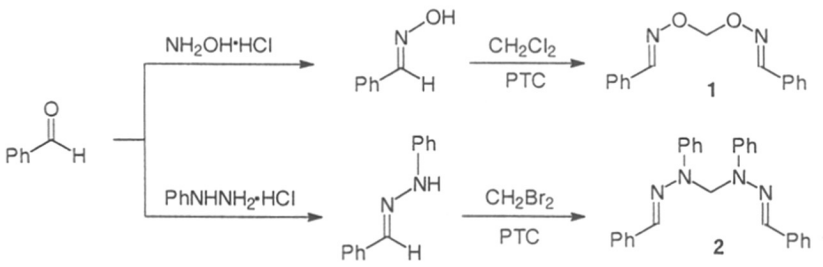
The choice of a linker depicted as 'X' is crucial since it must be readily removable to yield free diamines after the coupling step.

3. RESULTS AND DISCUSSION

For initial investigations, benzaldehyde *O,O'*-methylene dioxime **1** and benzaldehyde methylenebis(phenylhydrazone) **2** were chosen as substrates for reductive coupling.

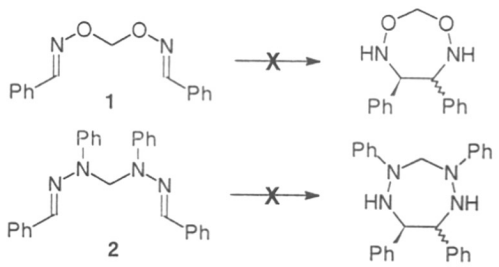
E-Benzaldoxime[59] and benzaldehyde phenylhydrazone[60] were prepared according to the literature procedures. Condensation of *E*-benzaldoxime with CH_2Cl_2 in the presence of tetrabutyl ammonium bromide generated the dioxime **1**.[61] Similarly, benzaldehyde phenylhydrazone was coupled with CH_2Br_2 to give bis(phenylhydrazone) **2** (Scheme 26).[62] As mentioned earlier, an important criterion in selecting these substrates was the possibility of removal of the linker between the two imines after the coupling, to provide free diamines.

Scheme 26.



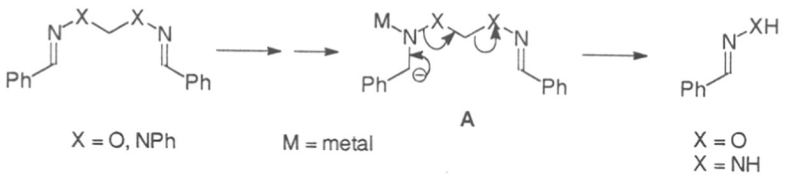
Various reagents such as Zn(Hg) in ethanol,[23] Al(Hg) in ether,[21] In/NH_4Cl in EtOH,[32] Na/naphthalene, $Zn/MeSO_3H$, Zn/TMSCl,[63] and $Mg/TiCl_4$[30] were examined for the coupling of **1** and **2**, but were unsuccessful under a variety of conditions (Scheme 27). In most cases the starting material was recovered or a large number of decomposition products were obtained which were difficult to purify and characterize. Electrochemical methods for coupling of **1** and **2** were also investigated, but these caused extensive decomposition of the starting materials.

Scheme 27.



It is possible that, in substrates **1** and **2**, cyclization of the initially formed radical anion to generate a seven membered ring is slow. Further reduction to the dianion stage would generate a species such as **A** (Figure 4) which is prone to undergo fragmentation at ambient temperatures.

Figure 4.

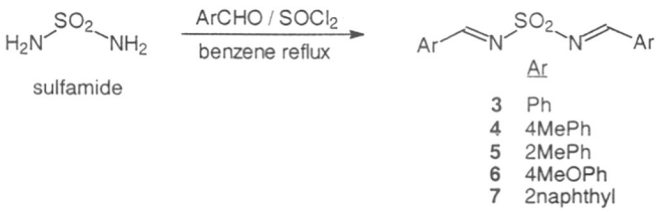


Examination of the ^1H NMR spectra of crude reaction products does indicate the presence of small amounts of *E*-benzaldoxime (~10%) and

benzaldehyde phenylhydrazone (~25%) which lends credence to the above postulate. These observations ruled out the possibility of using **1** and **2** as substrates for reductive coupling.

Our search for readily removable linkers between the two imines led us to examine sulfamide derived imines as substrates. These bisimines are readily available in quantitative yield by the reaction of sulfamide with aromatic aldehydes in the presence of thionyl chloride (Scheme 28).[64] Thus, bisimines **3-7** were obtained in excellent yields by adaptation of the literature procedure.[64]

Scheme 28.

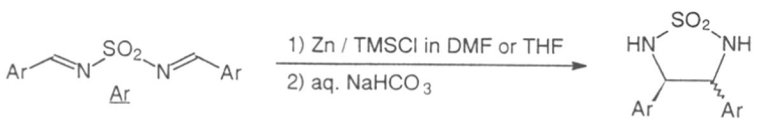


Intramolecular Reductive Coupling of Symmetrical Bisarylmethylene Sulfamides:

Initial studies were conducted with bisimine **3** as substrate. Most of the amalgams which are used for reductive coupling such as Al(Hg)/THF, Mg(Hg)/THF, In(Hg)/THF, other reagents that couple *N*-substituted arylimines, such as Zn(Hg) in ethanol,[23] In/NH_4Cl in EtOH,[32] Zn/$MeSO_3H$, and Mg/$TiCl_4$,[30] either failed to induce any coupling in bisimine **3** or caused extensive decomposition. Treatment of **3** with Al(Hg) in ether[21] did generate some of the coupling product **8** (Scheme 29) but the reaction was capricious, presumably due to hydrolysis of the bisimine by moisture in the amalgam. Although Zn metal in DMF or THF failed to yield any coupled product, *in-situ* activation of the zinc

with TMSCl[65] was beneficial and yielded the reductive coupling product 3,4-diphenyl thiadiazolidine-1,1-dioxide **8** as a mixture of *cis* **(8a)** and *trans* **(8b)** isomers respectively in a combined yield of 72%. The yields for the reductive coupling of 3 with Zn/TMSCl in solvents such as DMF or THF were comparable. A study of the temperature dependence of the process indicated that lowering the temperature improved the coupling diastereoselectivity. The Zn/TMSCl procedure was also applicable to other symmetrical bisimines **4-6** to give the cyclic sulfamides **9ab-11ab** in 52-58% yield (Scheme 29).

Scheme 29.



3 Ph
4 4MePh
5 2MePh
6 4MeOPh
7 2naphthyl

8ab-11ab
(52-85%)

Table 1 describes the results for the coupling of symmetrical imines **3-7** as well as effect of temperature on the *cis/trans* ratio of the coupled products **8-11**.

Table 1. Reductive coupling of symmetrical arylidinesulfamides.

Bisimine	Ar	Solvent	Temp ^{0}C	Product	Yield %	cis/trans (a/b)
3	Ph	DMF	25	**8ab**	72	2/1
3	Ph	DMF	0	**8ab**	85	3/1
3	Ph	DMF	-40	**8ab**	81	4/1
3	Ph	THF	-78	**8ab**	80	6/1
4	4MePh	DMF	25	**9ab**	58	1/1
5	2MePh	DMF	25	**10ab**	53	5/1
6	4MeOPh	DMF	25	**11ab**	52	3/1
7	2-naphthyl	DMF	25	**12**	a	-

a: not obtained.

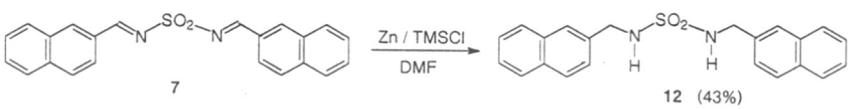
The stereochemical assignments for cyclic sulfamides **8-11** are based on their conversion to known diamines and is discussed in the following section. The

results indicate that lowering the temperature improves the diastereoselectivity in favor of the *cis* isomer. Surprisingly, bisimine **5**, which was employed with the intention of increasing steric requirements in the transition state leading to the *cis* product (due to the *ortho* substituents) also generates 5/1 *cis/trans* mixture of **10** at room temperature. Purification of the cyclic sulfamides **8ab-11ab** by column chromatography, results in an enrichment of the major diastereomer compared to the crude cyclic sulfamides. Thus, crude **10** yielded only *cis* diastereomer **10a** after purification by column chromatography and sufficient amounts of **10b** could not be isolated.

It is plausible that interactions involving the aromatic substituents, such as π stacking[66] and/or CH/π interactions,[67] favour the transition state assembly leading to the *cis* product. Alternatively, the zinc cation may be involved in organizing the transition state assembly by simultaneous coordination with one of the sulfamide oxygens and both the arene rings in the imine portion (metal-arene π coordination)[68] and may thus direct the coupling to proceed in a *cis* fashion. It should be emphasized, however, that the precise reasons for the preferential formation of the *cis* coupling product over the *trans* remain unclear at present.

It is noteworthy that treatment of bis(2-naphthylenylmethylene)sulfamide **7** with Zn/TMSCl does not result in reductive coupling but generates the reduced product **12** exclusively (Scheme 30).

Scheme 30.

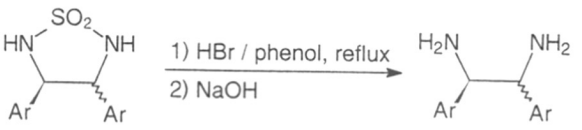


7 **12** (43%)

Conversion of cyclic sulfamides 8-11 to vicinal diamines:

The conversion of the cyclic sulfamides (1,2,5-thiadiazolidine-1,1-dioxides) **8-11** to vicinal diamines proved to be challenging. The cyclic sulfamides are inert towords most reagents that reductively cleave sulfoxides[69] or reduce sulfones to sulfides,[70] for example Ra-Ni/EtOH, Mg/EtOH, Mg(Hg), Na(Hg), Al(Hg), LAH/THF reflux and SmI_2 at ambient temperature. Treatment with excess SmI_2 at elevated temperature caused decomposition. Acid mediated cleavage[71] studies of **8a**, employing conditions known to cleave sulfonamides, indicated that it was inert to refluxing HBr or HCl, whereas heating in HBr/AcOH or AcOH/$HClO_4$ caused decomposition. However, heating in 48% aq. HBr in the presence of phenol generated the free diamine **13a** in 63% yield (Scheme 31). This procedure is an adaptation of a known method for cleavage of sulfonamides[72] and is a redox process, the mechanism of which is unclear at present. The procedure was applicable to cyclic sulfamides **9a** and **10a** which yielded diamines **14a** and **15a** in 51 and 58% yield respectively. The cleavage of **11** was not investigated due to potential demethylation of the methoxy groups in refluxing HBr.

Scheme 31.



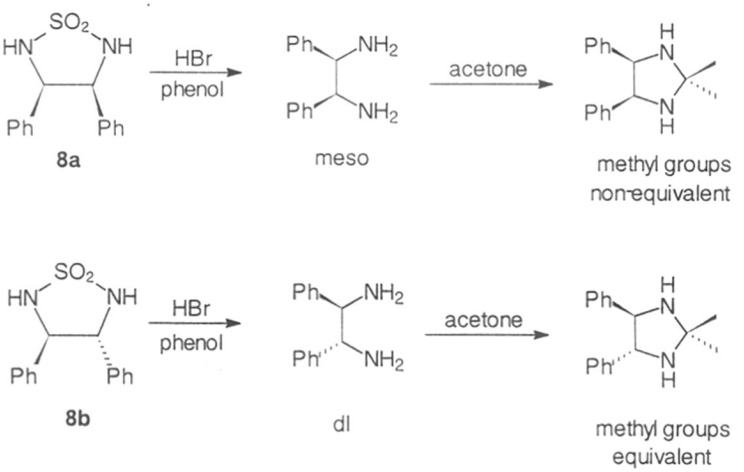
	Ar
8a	Ph
8b	Ph
9a	4MePh
10a	2MePh

13a	63%
13b	42%
14a	51%
15a	58%

Determination of the stereochemistry of cyclic sulfamides 8-10 and diamines 13-15:

The stereochemistry of the major isomer in **8** was confirmed to be *cis* since **8a** yielded the *meso* 1,2-diphenyl ethanediamine **13a**. Likewise, the minor isomer (*trans*, **8b**) yielded the C_2-symmetric 1,2-diphenyl ethanediamine **13b**. The stereochemistry of **13a** and **13b** was confirmed according to the literature procedure by preparation of the corresponding aminals derived from acetone[73] (Figure 5).

Figure 5. Determination of stereochemistry of 1,2-diamines:



It was observed that **13a** obtained from **8a** was the *meso* diamine, the aminal of which shows two non-equivalent methyl groups in the ^{1}H NMR spectrum. **13b** obtained from **8b** generates an aminal in which the two methyl groups are equivalent due to the C_2 symmetry in the molecule. Thus **8a** must be the *cis* cyclic sulfamide and **8b** must be the *trans* isomer. The stereochemistry of **9,10** and **11** is assigned by analogy in the ^{13}C NMR spectrum. In all cases, the benzylic methine carbon resonances in the major diastereomer (*cis*) are upfield

with respect to the minor diastereomer (*trans*). In addition the diamines **14a**[74] and **15a**[31,74] obtained from **9a** and **10a** respectively were observed to be *meso* by comparison of their ^{1}H NMR spectral data with that reported for the *meso* isomers.[73,74]

The results for the coupling of bisimines and conversion of the cyclic sulfamides to vicinal diamines are summarized in Table 2.

Table 2. Reductive coupling of **3-7** and cleavage of **8-11.**

Bisimine	Ar	Reagent	Solvent	Yield% 8-11	cis/trans	Yield% Diamine
3	Ph	Zn/TMSCl	DMF	72	2/1	62
4	4MePh	Zn/TMSCl	DMF	58	1/1	51
5	2MePh	Zn/TMSCl	DMF	53	5/1	58
6	4MeOPh	Zn/TMSCl	DMF	52	3/1	-
7	2naphthyl	Zn/TMSCl	DMF	a	-	-

a: not obtained.

The observation that bis(2-naphthalenylmethylene)sulfamide **7** does not undergo reductive coupling clearly indicates the preferential *syn* orientation of the two aryl groups in the bisimine in the transition state assembly. Thus for the bisimine **7**, the *cis* product is disfavored due to steric interactions between the large naphthyl moieties and the dominant reaction pathway is reduction, rather than coupling to generate a *trans* substituted five membered ring.

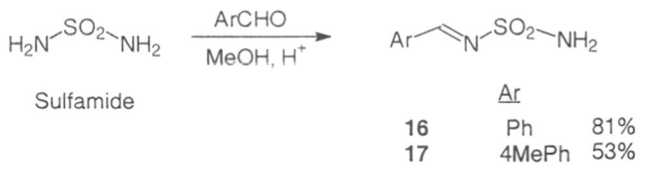
Synthesis of Unsymmetrical 1,2-Diaryl Ethanediamines:

During the studies on the intramolecular coupling reaction, we realized that the methodology would be particularly useful if one is able to prepare unsymmetrical bisimines leading to unsymmetrical 1,2-diaryl ethanediamines especially since there was no reported method for the cross-coupling of

electronically similar imines, a process which would be hampered by competing *homo*-coupling reactions. The solution would be to start with an unsymmetrical bisimine and carry out an intramolecular coupling reaction which would avoid the formation of *homo*-coupled products.

The sulfamide based approach is particularly useful for this purpose since monoarylmethylene sulfamides such as **16** and **17** are readily available by an acid catalyzed condensation of sulfamide with aromatic aldehydes[75] (Scheme 32). Thus benzaldehyde and *p*-tolualdehyde generate the monoarylmethylene sulfamides **16** and **17** respectively in good yields.

Scheme 32.



The synthesis of an unsymmetrical bisimine required the condensation of **16** or **17** with an aldehyde. This, however, proved to be unexpectedly difficult. For example, the reaction of **16** with *p*-tolualdehyde under different conditions such as $SOCl_2$/benzene reflux,[64] $TiCl_4/CH_2Cl_2$, rt.[76] or under acid catalysis (Amberlite-IR-120 resin/C_6H_6 reflux) led to complex mixtures in which only a small amount of the requisite unsymmetrical bisimine could be detected by ^1H NMR spectroscopy. The use of *p*-tolualdehydedimethylacetal[77] instead of the aldehyde was investigated next, and it's reaction with **16** under a variety of conditions such as Amberlite-IR-120 resin/C_6H_6, reflux; Al_2O_3/CH_2Cl_2, ambient temperature; *p*-toluenesulfonic acid/C_6H_6, reflux,[78] was studied. Of these, the procedure of choice was the reaction of **16** with the dimethylacetal of an aldehyde

in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene.

The reaction of monobenzylidine sulfamide **16** with *p*-tolualdehyde dimethylacetal **18** generated **24** in 95% yield. The procedure is quite general and is applicable to a variety of aromatic aldehydes either in the arylidine sulfamide (**16,17**) or the acetal component (**18-23**). The unsymmetrical bisimines are obtained in 86-98% yield (Scheme 33).

Scheme 33.

	Ar
16	Ph
17	4MePh

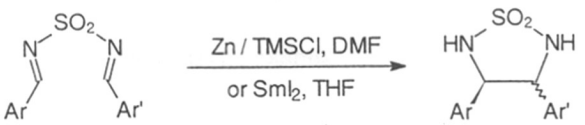
	Ar'
18	4MePh
19	2MePh
20	4ClPh
21	2naphthyl
22	4MeOPh
23	2,3-OCH_2O-Ph

86-98%

	Ar	Ar'
24	Ph	4MePh
25	Ph	2MePh
26	4MePh	2MePh
27	Ph	4ClPh
28	Ph	2naphthyl
29	Ph	4MeOPh
30	Ph	2,3-OCH_2O-Ph

Reductive coupling of the bisimines **24-30** with Zn/TMSCl yielded the cyclic sulfamides **31-37** consistently as a mixture of *cis/trans* isomers (Scheme 34). The use of SmI_2 in THF at ambient temperature also generates the requisite cyclic sulfamides, but there is no significant improvement in yield or stereoselectivity. Lowering the reaction temperature resulted in incomplete reaction with no change in stereoselectivity and the Zn mediated coupling is therefore advantageous from a practical viewpoint. Thus, cyclic sulfamides **31-37** were readily available from the bisimines in 54-85% yield (Table 3).

Scheme 34.



24-30 **31-37**

The results for the reductive coupling of unsymmetrical arylidinesulfamides **24-30** to cyclic sulfamides **31-37** are summarized in Table 3.

Table 3. Reductive coupling of unsymmetrical arylidinesulfamides.

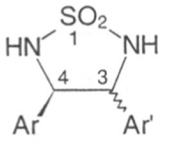
Bisimine	Ar	Ar'	Reagent	Solvent	Product	Yield%	cis/trans (a/b)
24	Ph	4MePh	Zn/TMSCl	DMF	**31ab**	85	2/1
			SmI_2	THF		95	3/1
25	Ph	2MePh	Zn/TMSCl	DMF	**32ab**	54	1/1
			SmI_2	THF		75	1/1
26	4MePh	2MePh	Zn/TMSCl	DMF	**33ab**	65	2.5/1
			SmI_2	THF		75	2/1
27	Ph	4ClPh	Zn/TMSCl	DMF	**34ab**	67	1.2/1
28	Ph	2-naphthyl	Zn/TMSCl	DMF	**35ab**	75	1.2/1
			SmI_2	THF		60	-
29	Ph	4MeOPh	Zn/TMSCl	DMF	**36ab**	69	2/1
30	Ph	2,3-OCH_2O-	Zn/TMSCl	DMF	**37ab**	33	2/1

Some of the substrates exhibit a preference for the *cis* coupling mode, and introduction of an *ortho* substituent into one of the aryl groups causes an increase in the amount of the *trans* product (*cis/trans* 2/1 for **24** and 1/1 for **25**). However a distinct trend in such steric effects and an explanation of the observed stereoselectivity is not obvious at present (eg. *cis/trans* = 2.5/1 for **26** and 1/1 for **4** (see Table 2)).

Determination of stereochemistry in cyclic sulfamides 31-37:

The stereochemistry of **31-37** was assigned by analogy to the symmetrical cyclic sulfamides **8-10**. The benzylic methine carbons for the major diastereomer in **31-37** appeared upfield in the ^{13}C spectra (Table 4) and these diastereomers were assigned the *cis* stereochemistry.

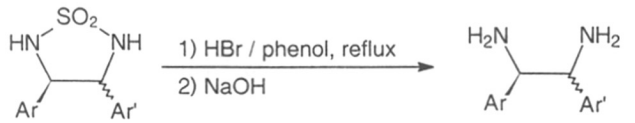
Table 4. Selected ^{13}C NMR chemical shifts for cyclic sulfamides **8-10, 31-37**.



Cyclic Sulfamide	Ar	Ar'	*C3, C4* for *cis* diastereomer	*C3, C4* for *trans* diastereomer
8	Ph	Ph	65.5	68.2
9	4MePh	4MePh	64.7	67.6
10	2MePh	2MePh	59.7	63.2
31	Ph	4MePh	63.5, 63.3	67.5, 67.3
32	Ph	2MePh	60.7, 59.7	64.5, 63.2
33	4MePh	2MePh	64.5, 59.7	63.1, 59.7
34	Ph	4ClPh	63.3, 62.7	63.6, 63.0
35	Ph	2-naphthyl	64.8, 64.6	64.8, 64.6
36	Ph	4MeOPh	64.5, 64.0	68.5, 64.2
37	Ph	2,3-OCH_2O-Ph	65.6, 65.4	68.2, 65.4

As for the symmetrical cyclic sulfamides, the unsymmetrical substrates **31-35** (mixture of diastereomers) were converted to the free diamines **38-42** by heating in 48% aq. HBr in the presence of phenol (Scheme 35). Thus, various unsymmetrical vicinal diamines with alkyl and halogen substituents in the aromatic ring were synthesized in 52-78% yield from the corresponding cyclic sulfamides (Table 5).

Scheme 35.



31-35 **38-42**

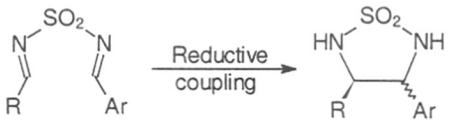
Table 5. Conversion of unsymmetrical cyclic sulfamides **31-35** to 1,2-diamines **38-42.**

Cyclic sulfamide	Ar	Ar'	Diamine	Yield %
31	Ph	4MePh	38	53
32	Ph	2MePh	39	69
33	4MePh	2MePh	40	52
34	Ph	4ClPh	41	78
35	Ph	2-naphthyl	42	75

Attempted Synthesis of aryl-alkyldiamines:

An extension of the above methodology for the synthesis of aryl-alkyldiamines was investigated. This would require an unsymmetrical bisimine derived from an aromatic and an aliphatic aldehyde. The target was a bisimine such as **B** (R = alkyl, Figure 6) which would undergo intramolecular cyclization to generate the cyclic sulfamides **C** which would be a precursor to the unsymmetrical diamine.

Figure 6. Reductive coupling of alkyl-aryl bisimines.

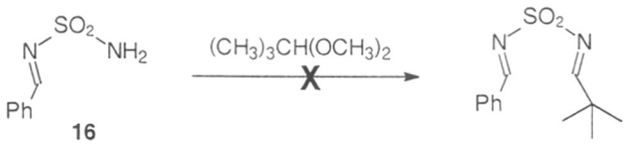


R = alkyl

B **C**

All attempts to prepare a bisimine from monobenzylidine sulfamide **16** and *n*-butyraldehyde dimethylacetal **43** were unsuccessful. This is not surprising, considering the known lability[79] of aliphatic imines. To circumvent problems arising from imine-enamine isomerization, reaction of phenylmethylene sulfamide **16** with pivalaldehyde dimethylacetal **44** was also examined, but bisimine formation could be effected (Scheme 36).

Scheme 36.



The possibility of preparing alkyl-aryl diamines using the intramolecular reductive coupling methodology therefore remains unexplored due to the unavailability of the required unsymmetrical bisimine.

4. CONCLUSION

A new synthesis of symmetrical as well as unsymmetrical 1,2 diaryl ethanediamines has been developed. The key step is an intramolecular reductive coupling in a bisarylmethylene sulfamide. The stereoselectivity of the coupling step is moderate, and favors the *cis* product over the *trans*. This methodology is the first example of a cross coupling between electronically similar imines and provides a novel approach to unsymmetrical 1,2 diaryl ethanediamines.

5. EXPERIMENTAL

General

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120 °C) which was cooled under argon. All organic layers obtained from extraction were dried over anhydrous Na_2SO_4. Solvents for anhydrous reactions were dried according to Perrin *et al.*[80] Benzene, THF and diethyl ether were distilled from sodium and benzophenone. Acetonitrile, DME, CH_2Cl_2 and triethylamine were distilled from CaH_2. DMF was dried over anhydrous barium oxide and distilled under reduced pressure. Solvents used for chromatography were distilled at the respective constant boiling point. Petroleum ether refers to the fraction boiling in the range 60-80 °C.

Commercial reagents were obtained from Aldrich Chemical Company, S. D. Fine Chemical Company or Loba Chemie Company. Progress of the reactions was monitored by TLC and was visualized by UV absorption by fluorescence quenching or I_2 staining or by both. Commercial precoated silica gel (Merck 60F-254) plates were used for TLC. Silica gel for column chromatography was 60-120 mesh obtained from S. D. Fine Chemical Company India or SRL India. Flash chromatography[81] was performed according to Still *et al.* using silica gel (230-400 mesh) from SRL India. A Büchi GKR-51 Kugelrohr distillation apparatus was used for distilling liquid samples.

All melting points are uncorrected in degrees Celsius and were recorded on a Thermonik melting point apparatus or a Yanaco micro melting point apparatus. IR spectra were recorded on a Perkin-Elmer infrared spectrometer

model 599-B, model 1620 FT-IR and AIT Mattson, UK, model RS-1 FT-IR. IR bands are expressed in cm^{-1}. ^1H NMR spectra were recorded using TMS as internal reference on Bruker MSL-300, Bruker AC-200, Bruker WH-90 or Bruker FT-80A instruments using $CDCl_3$, $CDCl_3$/DMSO-d_6, or acetone-d_6 as solvent. Chemical shifts are reported in δ. Abbreviations used are as follows; s : singlet, d : doublet, t : triplet, dd : doublet of a doublet, br: broad, bs: broad singlet. ^{13}C NMR spectra were recorded on Bruker MSL-300 or Bruker AC-200 instruments operating at 75.5 MHz and 50.3 MHz respectively. Mass spectra were recorded on a Finnigan-Mat 1020C mass spectrometer and are obtained at an ionization potential of 70 eV. Optical rotations were measured at the sodium D line on a JASCO-181 digital polarimeter at ambient temperature. Elemental analyses were performed on Carlo Erba CHN-S EA 1108 or Elementar Vario EL Elemental Analysers or by conventional combustion techniques at the Microanalysis Facility at NCL, Pune.

Benzaldehyde *O,O'*-methylene dioxime (1):[82]

To a cooled solution of *E*-benzaldoxime (1.21 g, 10 mmol) and tetramethyl ammonium bromide (0.26 g, 0.8 mmol) in CH_2Cl_2 was added dropwise 10 ml of 10% NaOH. The reaction mixture was stirred at ambient temperature for 20h. and then diluted with water. The aqueous portion was extracted with CH_2Cl_2. The combined organic phases were washed with water, brine and concentrated to give 1.01 g (79%) of dioxime 1.

mp: 92-93 ^0C

^{1}H NMR (80 MHz, $CDCl_3$):

δ 8.1 (s, 2H, N=C*H*), 7.7-7.4 (m, 4H, Ar*H*), 7.4-7.1 (m, 6H, Ar*H*), 5.7 (s, 2H, OCH_2O).

IR ($CHCl_3$):

3040, 1620, 1510, 1470, 1230, 1090, 770, 710, 680 cm^{-1}.

Benzaldehyde methylenebis(phenylhydrazone) (2):[62]

To a solution of benzaldehyde phenylhydrazone (3.92 g, 20 mmol) in benzene (10 ml) was slowly added 20 ml of 50% (w/w) of NaOH solution. To this solution, tetrabutyl ammonium chloride (0.3 g, 1.1 mmol) was added followed by CH_2Br_2 (1.4 ml, 20 mmol). The reaction mixture was heated at 60 ^{0}C for 3h. Water was added and the mixture was extracted with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated. The residue obtained was recrystallized with acetone to give 2.63 g (65%) of bishydrazone **2**.

mp: 135-136 ^{0}C

^{1}H NMR (90 MHz, $CDCl_3$):

δ 7.6-7.0 (m, 22H, Ar*H*), 5.7 (s, 2H, CH_2)

IR ($CHCl_3$):

3040, 2420, 1610, 1585, 1510, 1415, 1350, 1300, 1230, 1180, 1130, 1090, 1040, 945, 890, 710, 685 cm^{-1}.

General procedure for preparation of bisaryl(methylene) sulfamides 3-7:[64]

To a suspension of sulfamide in anhydrous benzene was added the aldehyde, followed by thionyl chloride. The reaction mixture was heated to reflux for 12-18h in a well-ventilated fume-hood. After the reaction was complete, the mixture was poured into an Erlenmeyer flask and kept overnight at ambient temperature. Crystals obtained were filtered and washed with dry benzene. The crystalline bisimines were pure by ^{1}H NMR and attempted recrystallization resulted in partial decomposition due to their sensitivity to moisture. Hence, all bisimines were directly used further without purification.

Bis(phenylmethylene) sulfamide (3):[64]

The reaction of sulfamide (1.92 g, 20 mmol), benzaldehyde (6.9 ml, 68 mmol) and thionyl chloride (4.4 ml, 60 mmol) in benzene (100 ml) for 12h gave 3.27 gm (60%) of **3** as a colorless solid.

mp: 117-119 ^{0}C

^{1}H NMR (80 MHz, $CDCl_3$):

δ 9.1 (s, 2H, N=C*H*), 8.0-7.6 (m, 4H, Ar*H*), 7.6-7.2 (m, 6H, Ar*H*).

IR (Nujol):

1610, 1600, 1570, 1450, 1300, 1220, 1150, 930, 860, 830, 790, 760, 690, 660, 610 cm^{-1}.

Bis((4-methylphenyl)methylene) sulfamide (4):

The reaction of sulfamide (1.92 g, 20 mmol), 4-methyl benzaldehyde (7.1 ml, 60 mmol) and thionyl chloride (4.4 ml, 60 mmol) in benzene (100 ml) for 12h gave 5.16 gm (90%) of **4** as a colorless solid.

mp: 207-208 ^{0}C.

^{1}H NMR (90 MHz, $CDCl_3$):

δ 9.0 (s, 2H, N=C*H*), 7.9 (d, *J* = 8, 4H, Ar*H*), 7.2 (d, *J* = 8, 4H, Ar*H*), 2.4 (s, 6H, ArCH_3).

IR (Nujol):

1600, 1570, 1330, 1230, 1150, 880, 840, 820, 810, 630 cm^{-1}.

Bis((2-methylphenyl)methylene) sulfamide (5):

The reaction of sulfamide (0.96 g, 10 mmol), 2-methyl benzaldehyde (2.6 ml, 22 mmol) and thionyl chloride (2.2 ml, 30 mmol) in benzene (50 ml) for 15h gave 2.62 gm (91%) of **5** as a colorless solid.

mp: 135-137 ^{0}C

^{1}H NMR (90 MHz, $CDCl_3$):

δ 9.6 (s, 2H, N=C*H*), 8.2-8.0 (m, 2H, Ar*H*), 7.8- 7.2 (m, 6H, Ar*H*), 2.6 (s, 6H, ArCH_3).

IR (Nujol):

1580, 1560, 1450, 1360, 1315, 1220, 1140, 820, 760, 750, 640 cm^{-1}.

Bis((4-methoxyphenyl)methylene) sulfamide (6):[64]

The reaction of sulfamide (0.96 g, 10 mmol), 4-methoxy benzaldehyde (3.6 ml, 30 mmol) and thionyl chloride (2.2 ml, 30 mmol) in benzene (50 ml) for 15h gave 2.62 gm (87%) of **6** as a colorless solid.

mp: 180-181 ^{0}C

^{1}H NMR (80 MHz, $CDCl_3$):

δ 9.1 (s, 2H, N=C*H*), 8.0 (d, *J* = 8 , 4H, Ar*H*), 7.1 (d, *J* = 8 , 4H, Ar*H*), 3.9 (s, 6H, OCH_3)

IR (Nujol):

2860, 1590, 1570, 1510, 1460, 1420, 1330, 1320, 1270, 1230, 1170, 1150, 1030, 910, 880, 770 cm^{-1}.

Bis(2-naphthalenylmethylene) sulfamide (7):

The reaction of sulfamide (0.38 g, 4 mmol), 2-naphthaldehyde (1.37 g, 8.8 mmol) and thionyl chloride (0.88 ml, 12 mmol) in benzene (25 ml) for 15h gave 1.52 gm (quantitative yield) of **7** as a yellowish brown solid after concentration of the benzene solution.

mp: 158-160 ^{0}C

^{1}H NMR (90 MHz, $CDCl_3$+DMSO-d_6):

δ 9.0 (s, 2H, N=C*H*), 8.3 (s, 2H, Ar*H*), 8.1-7.8 (m, 6H, Ar*H*), 7.8-7.4 (m, 4H, Ar*H*), 7.2 (s, 2H, Ar*H*).

IR (Nujol):

2860, 1620, 1575, 1335, 1145, 930, 910, 870, 830, 750 cm^{-1}.

General procedure for the reductive coupling of bisimines 3-7:

To a solution of the bisimine in anhydrous DMF or THF was added activated zinc dust (325 mesh). The stirred mixture was cooled to 0 ^{0}C and TMSCl was added slowly (exotherm). The mixture was then stirred at ambient temperature for 12-14h and the reaction was monitored by TLC. Saturated

aqueous $NaHCO_3$ solution was added and the mixture was filtered. The filtrate was extracted with ethyl acetate. The combined ethyl acetate extracts were dried and concentrated to furnish the crude product which was purified by flash chromatography on silica gel.

3,4-Bisphenyl-1,2,5-thiadiazolidine-1,1-dioxide (8):[83]

The reaction of **3** (0.82 g, 3 mmol) with Zn (0.98 g, 15 mmol) and TMSCl (1.9 ml, 15 mmol) in DMF (60 ml) for 14h gave a 2/1 mixture of *cis/trans* **8** (^{1}H NMR of crude) which was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 3/1) to give 595 mg (72%, 410 mg *cis* isomer **8a**, 122 mg *trans* isomer **8b**, and 63 mg mixture of *cis* and *trans* isomers) of **8**.

Data for *cis* isomer (8a):

mp: 185-187 °C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.25-7.1 (m, 6H, Ar*H*), 7.05-6.9 (m, 4H, Ar*H*), 5.2 (m, 2H, NC*H*), 4.75 (bs, 2H, N*H*),

^{13}C NMR (50.3 MHz, acetone-d_6):

δ 137.4 (Ar*Cipso*), 128.5 (Ar*C*), 65.3 (N*C*H).

IR (Nujol):

3300, 2880, 1470, 1390, 1370, 1320, 1280, 1250, 1185, 1080, 1035, 780, 740, 720 cm^{-1}.

MS (EI, 70 eV):

m/z 57 (2), 69 (2), 77 (26), 91 (3), 106 (100), 165 (3), 210 (3).

Data for *trans* isomer (8b):

mp: 195-196 °C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4-7.2 (m, 10H, Ar*H*), 4.85 (bs, 2H, N*H*), 4.75 (bd, 2H, NC*H*).

^{13}C NMR (50.3 MHz, acetone-d_6):

δ 139.1 (Ar*Cipso*), 129.3, 129.1, 128.2 (Ar*C*), 68.1 (N*C*H).

IR (Nujol):

3300, 2880, 1420, 1330, 1240, 1170, 1050, 960, 920, 860, 820, 780, 720, 650 cm^{-1}.

MS (EI, 70 eV):

m/z 57 (2), 69 (2), 77 (26), 91 (3), 106 (100), 165 (3), 210 (3).

3,4-Bis(4-methylphenyl)-1,2,5-thiadiazolidine-1,1-dioxide (9):[83]

The reaction of **4** (0.6 g, 2 mmol) with Zn (0.79 g, 12 mmol) and TMSCl (1.5 ml, 12 mmol) in DMF (70 ml) for 14h gave a 1/1 mixture of *cis/trans* **9** (^{1}H NMR of crude) which was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 3/1) to give 351 mg (58%, 225 mg of the *cis* isomer **9a** and 126 mg of the *trans* isomer **9b**) of **9**.

Data for *cis* isomer 9a:

mp: 158-160 ^{0}C

^{1}H NMR(200 MHz, $CDCl_3$):

δ 6.95 (d, J = 8 , 4H, Ar*H*), 6.85 (d, J = 8, 4H, Ar*H*), 5.1 (bs, 2H, N*H*), 4.7 (brs, 2H, NC*H*), 2.25 (s, 6H, ArCH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 137.8 (Ar*Cipso*), 131.8 (Ar*Cipso*), 128.7, 121.1 (Ar*C*), 64.7 (N*C*H), 21.1 (CH_3).

IR (Nujol):

3210, 1260, 1150, 1050, 970, 810, 750, 630 cm^{-1}.

MS (EI, 70 eV):

m/z 55 (2), 65 (12), 77 (5), 91 (30), 120 (100), 238 (2), 303 (M+1, (<1)).

Data for *trans* isomer 9b:

mp: 148-150 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.15 (s, 8H, Ar*H*), 4.8-4.7 (bs, 4H, NC*H* and N*H*), 2.35 (s, 6H, CH_3)

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 138.7 (Ar*Cipso*), 132.9 (Ar*Cipso*), 129.5, 127.1 (Ar*C*), 67.6 (NCH), 21.0 (CH_3).

IR (Nujol):

3260, 1405, 1390, 1350, 1280, 1170, 1060, 1020, 830, 750 cm^{-1}.

MS (EI, 70 eV):

m/z 57 (5), 65 (6), 91 (28), 120 (100), 149 (5), 238 (1).

3,4-Bis(2-methylphenyl)-1,2,5-thiadiazolidine-1,1-dioxide (10):

The reaction of **5** (0.3 g, 1 mmol) with Zn (0.39 g, 6 mmol) and TMSCl (0.78 ml, 6 mmol) in THF (10 ml) for 20h gave after purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 3/1), 160 mg (53%, *cis* isomer **10a**) of **10**. In repeated experiments ca. 5/1 mixtures of cis/trans isomers were obtained as evidenced by ^{13}C NMR spectroscopy of the crude product. However, after chromatography, sufficient amounts of the *trans* isomer **10b** could not be isolated for characterization.

Data for *cis* isomer 10a:

mp: 167-169 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.2-6.9 (m, 8H, Ar*H*), 5.5 (s, 2H, ArC*H*), 4.85 (bs, 2H, N*H*), 2.05 (s, 6H, ArCH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 135.9 (Ar*Cipso*), 132.9 (Ar*Cipso*), 130.1, 128.2, 127.0, 125.9 (Ar*C*), 59.7 (N*C*H), 19.0 (CH_3).

IR (Nujol):

3290, 1320, 1290, 1170, 1060, 1050, 980, 950, 770, 760, 650 cm^{-1}.

MS (EI, 70 eV):

m/z 55 (5), 65 (16), 69 (4), 77 (8), 83 (3), 91 (38), 104 (4), 120 (100), 303 (M+1 (<1)).

Analysis for $C_{16}H_{18}N_2O_2S$:

Calcd: C, 63.53 H, 6.00 N, 9.27 S, 10.67.

Found: C, 63.23 H, 6.11 N, 9.24 S, 10.30.

3,4-Bis (4-methoxyphenyl)-1,2,5-thiadiazolidine-1,1-dioxide (11):

The reaction of **6** (166 mg, 0.5 mmol) with Zn (39 mg, 0.6 mmol) and TMSCl (120 μL, 1 mmol) in DMF (5 ml) for 5h gave after purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 7/3), 87 mg (52%, ca. 3/1 mixture of *cis* and *trans* isomers) of **11**. Separation of the two isomers was not possible.

Data for *cis* isomer 11a:

^{1}H NMR (80 MHz, $CDCl_3$):

δ 7.92 (d, *J* = 9.6, 4H, Ar*H*), 7.72 (d, *J* = 9.6, 4H, Ar*H*), 5.1 (brm, 2H, C*H*), 4.56 (bs, 2H, N*H*), 3.72 (s, 6H, ArOCH_3).

Visible peaks for minor (*trans*) diastereomer 11b:

δ 7.24 (d, *J* = 9.6, 4H, Ar*H*), 6.88 (d, *J* = 9.6, 4H, Ar*H*), 3.8 (s, 6H, ArOCH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 158.1 (Ar*Cipso*), 128.0, 127.3 (Ar*C*H), 112.4 (Ar*Cipso*), 63.5 (N*C*H), 54.3 (ArO*C*H_3).

IR (Nujol):

3277, 3235, 2854, 2361, 1612, 1515, 1304, 1268, 1249, 1154, 1023, 972, 837, 766, 668, 627, 524, 489 cm^{-1}.

MS (EI, 70 eV).

m/z 65 (8), 77 (10), 91 (8), 107 (4), 119 (6), 134 (100), 238 (4), 255 (5).

***N,N'*(2-naphthalenyl methyl) sulfamide (12):**

The reaction of **7** (335 mg, 0.9 mmol) with Zn (327 mg, 5 mmol) and TMSCl (640 μL, 5 mmol) in DMF (20 ml) for 15h gave after purification by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 7/3), 146 mg (43%) of **12**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.6-7.5 (m, 8H, Ar*H*), 7.4-7.2 (m, 6H, Ar*H*), 6.15-6.05 (brt, *J* = 9.8, 1H, N*H*), 5.15 (brs, 1H, N*H*), 4.15 (d, *J* = 9.8, 4H, NCH_2).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 134.6 (Ar*Cipso*), 132.1 (Ar*Cipso*), 131.5 (Ar*Cipso*), 126.9, 126.7, 126.5, 125.3, 125.2, 125.0, 124.7 (Ar*C*), 46.0 (NCH_2).

IR (Nujol):

3360, 3290, 2860, 1440, 1350, 1335, 1160, 1130, 1075, 1040, 960, 935, 900, 870, 820, 750 cm^{-1}.

MS (EI, 70 eV):

m/z 63 (6), 77 (8), 102 (5), 115 (15), 128 (34), 141 (27), 155 (100), 236 (38), 376 (M^+, <1).

General procedure for cleavage of cyclic sulfamides 8-10:

A mixture of cyclic sulfamide and phenol in HBr (aqueous, 48%) was heated at 130-140 ^{0}C for 20 min., cooled to room temperature and the solution was extracted with ethyl acetate to remove phenol. The aqueous phase was made basic with solid NaOH and the diamine was isolated by extraction with ethyl acetate. All diamines obtained by this procedure were pure by ^{1}H NMR.

R*,S* **1,2-Diphenyl-1,2-ethanediamine (13a):**[31]

Reaction of **8a** (270 mg, 1 mmol) in HBr (8 ml) and phenol (0.44 ml, 5 mmol) furnished 134 mg (63%) of **13a** (*meso* isomer).

^{1}H NMR (200MHz, $CDCl_3$):

δ 7.4-7.25 (m, 10H, Ar*H*), 4.05 (s, 2H, NC*H*), 1.55-1.4 (bs, 4H, NH_2).

IR (Nujol):

3300 (br), 3020, 2960, 1660, 1595, 1490, 1460, 1370, 1250, 1170, 1080, 1030, 770, 710 cm^{-1}.

***R*,R** 1,2-Diphenyl-1,2-ethanediamine (13b):**[31]

Reaction of **8b** (98 mg, 1 mmol) in HBr (4 ml) and phenol (0.15 ml, 5 mmol) furnished 32 mg (42%) of **13b** (*dl* isomer).

^{1}H NMR (200MHz, $CDCl_3$):

δ 7.25 (bs, 10H, Ar*H*), 4.1 (s, 2H, NC*H*), 1.9-1.75 (bs, 4H, NH_2).

IR (Nujol):

3377, 3354, 3260 (br), 2924, 2855, 1570, 1493, 1447, 1375, 941, 903, 876, 829, 773, 737, 700, 679 cm^{-1}.

***R*,S** 1,2-Bis (4-methylphenyl)-1,2-ethanediamine (14a):**[74]

Reaction of **9a** (60 mg, 0.2 mmol) in HBr (5 ml) and phenol (0.1 ml, 1 mmol) furnished 19 mg (51%) of **14a**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.35 (d, J = 8, 4H, Ar*H*), 7.1 (d, J = 8, 4H, Ar*H*), 4.1 (s, 2H, NC*H*,), 2.45 (s, 6H, CH_3), 2.0 (bs, 4H, NH_2).

IR ($CHCl_3$):

3020, 2922, 2858, 1580, 1514, 1452, 1383, 1117, 1013, 820, 762, 731, 559 cm^{-1}.

***R*,S** 1,2-Bis(2-methylphenyl)-1,2-ethanediamine (15a):**[74]

Reaction of **10a** (130 mg, 0.43 mmol) in HBr (5 ml) and phenol (0.2 ml, 2 mmol) furnished 60 mg (58%) of **15a**.

^{1}H NMR (90 MHz, $CDCl_3$):

δ 7.35-7.15 (m, 2H, Ar*H*), 7.15-6.95 (m, 6H, Ar*H*), 4.35 (s, 2H, NC*H*), 2.25 (s, 6H, ArCH_3), 1.65-1.4 (bs, 4H, NH_2).

IR ($CHCl_3$):

3400, 3040, 1620, 1600, 1500, 1480, 1220, 1050, 940, 780 cm^{-1}.

Phenylmethylene sulfamide (16):[75]

This was prepared by according to the literature procedure.[76] A solution of benzaldehyde (2.0 ml, 20.8 mmol) and sulfamide (1.0 gm, 10.4 mmol) in methanol (10 ml, made acidic with 20% HCl (10 μL)) was heated to reflux for 18h. The solution was concentrated, and the residue was extracted with boiling ether (150 ml). The ether solution was washed with water, brine, dried and concentrated to give 1.52 gm (81%) of **16** as a colorless, crystalline solid.

^{1}H NMR (90 MHz, $CDCl_3$+DMSO-d_6):

δ 9.2 (s, 1H, N=C*H*), 8.2-8.05 (m, 2H, Ar*H*), 7.9-7.6 (m, 3H, Ar*H*), 6.5 (brs, 2H, NH_2).

IR (Nujol):

3300, 3220, 1600, 1565, 1300, 1220, 1155, 910, 870, 800 cm^{-1}.

MS (EI, 70 eV):

m/z 64 (12), 77 (56), 96 (15), 104 (100), 184 (M^+, 26).

(4-Methylphenyl)methylene sulfamide (17):[75]

This was prepared according to the literature procedure.[76] A solution of 4-methylbenzaldehyde (4.8 ml, 40 mmol) and sulfamide (1.92 gm, 20 mmol) in

methanol (20 ml, made acidic with 20% HCl (20 μL)) was heated to reflux for 18h. The solution was concentrated, and the residue was extracted with boiling ether (150 ml). The ether solution was washed with water, brine, dried and concentrated to give 2.11 gm (53%) of **17** as a colorless solid.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.77 (s, 1H, N=C*H*), 7.75 (d, *J* = 6.6, 2H, Ar*H*), 7.2 (d, *J* = 6.6, 2H, Ar*H*), 6.36 (brs, 2H, NH_2), 2.32 (s, 3H, CH_3).

IR (Nujol):

3700-3000 (br), 1620, 1590, 1360, 1170, 930, 890, 830, 780 cm^{-1}.

MS (EI, 70 eV):

m/z 65 (25), 80 (23), 91 (43), 118 (100), 198 (M^+, 30).

General procedure for the synthesis of dialkylacetals of aromatic aldehydes:

The literature procedure was adapted.[77] To a solution of the aldehyde in anhydrous methanol was added Amberlite-IR-120 resin (activated by washing successively with 1N NaOH, water, 1N HCl, water, ethanol and ether) and trimethyl orthoformate. The reaction mixture was heated to reflux for 3-4h, cooled to ambient temperature and filtered from the resin. The filtrate was concentrated and the residue obtained was purified by Kugelrohr distillation.

1-(Dimethoxymethyl)-4-methyl-benzene (18):[84]

Prepared by the reaction of 4-methyl benzaldehyde (5.9 ml, 50 mmol), Amberlite-IR-120 resin (0.5 g) and trimethyl orthoformate (6.0 ml, 55 mmol) in anhydrous methanol (50 ml) for 3h to give after distillation 7.15 g (86%) of **18** as a colorless oil.

bp: 100 ^{0}C/10 mm Hg

^{1}H NMR (80 MHz, $CDCl_3$):

δ 7.5-7.3 (d, *J* = 6.4, 2H, Ar*H*), 7.3-7.1 (d, *J* = 6.4, 2H, Ar*H*), 5.3 (s, 1H, C*H*$(OCH_3)_2$), 3.2 (s, 6H, OC*H*$_3$), 2.2 (s, 3H, C*H*$_3$)

IR (Neat):

2980, 2955, 2900, 1685, 1600, 1570, 1500, 1440, 1360, 1310, 1280, 1210, 1100, 1050, 980, 910, 840, 810, 780, 760 cm^{-1}.

1-(Dimethoxymethyl)-2-methyl-benzene (19):[85]

Prepared by the reaction of 2-methyl benzaldehyde (4.2 ml, 36 mmol), Amberlite-IR-120 resin (0.4 g) and trimethyl orthoformate (4.4 ml, 40 mmol) in anhydrous methanol (40 ml) for 3h to give after distillation 4.78 g (80%) of **19** as a colorless oil.

bp: 115 ^{0}C/10 mm Hg

^{1}H NMR (90 MHz, $CDCl_3$):

δ 7.5-7.3 (m, 2H, Ar*H*), 7.3-7.0 (m, 2H, Ar*H*), 5.4 (s, 1H, C*H*$(OCH_3)_2$), 3.3 (s, 6H, OC*H*$_3$), 2.3 (s, 3H, C*H*$_3$)

IR (Neat):

2960, 2940, 2800, 1690, 1590, 1430, 1350, 1285, 1210, 1190, 1040, 980, 900, 750, 720 cm^{-1}.

1-chloro-4-(Dimethoxymethyl)-benzene (20):[86]

Prepared by the reaction of 4-chloro benzaldehyde (5.6 ml, 40 mmol), Amberlite-IR-120 resin (0.5 g) and trimethyl orthoformate (4.9 ml, 45 mmol) in

anhydrous methanol (50 ml) for 3.5h to give after distillation 6.61 g (89%) of **20** as a colorless oil.

bp: 130 ^{0}C/10 mm Hg

^{1}H NMR (90 MHz, $CDCl_3$):

δ 7.25 (s, 4H, Ar*H*), 5.3 (s, 1H, C*H*(OCH_3)), 3.2 (s, 6H, OC*H*$_3$)

IR (Neat):

2980, 2920, 2820, 1720, 1700, 1590, 1570, 1480, 1440, 1400, 1350, 1280, 1210, 1170, 1100, 1050, 1020, 980, 915, 890, 810 cm^{-1}.

2-(Dimethoxymethyl)-naphthalene (21):[87]

Prepared by the reaction of 2-naphthaldehyde (1.01 g, 6.5 mmol), Amberlite-IR-120 resin (0.2 g) and trimethyl orthoformate (0.9 ml, 8 mmol) in anhydrous methanol (20 ml) for 3h to give after distillation 1.19 g (91%) of **21** as a colorless oil.

bp: 185 ^{0}C/15 mm Hg

^{1}H NMR (90 MHz, $CDCl_3$):

δ 7.9-7.15 (m, 7H, Ar*H*), 5.5 (s, 1H, C*H*(OCH_3)$_2$), 3.3 (s, 6H, OC*H*$_3$)

IR (Neat):

3060, 2960, 2840, 1700, 1610, 1510, 1470, 1450, 1350, 1200, 1180, 1130, 1110, 1070, 1000, 940, 890, 810 cm^{-1}.

1-(Dimethoxymethyl)-4-methoxy benzene (22):[88]

Prepared by the reaction of 4-methoxy benzaldehyde (2.4 ml, 20 mmol), Amberlite-IR-120 resin (0.3 g) and trimethyl orthoformate (2.4 ml, 22 mmol) in

anhydrous methanol (20 ml) for 3h to give after distillation 2.56 g (70%) of **22** as a colorless oil.

bp: 105 ^{0}C/5 mm Hg

^{1}H NMR (90 MHz, $CDCl_3$):

δ 7.25 (d, *J* = 10, 2H, Ar*H*),6.8 (d, *J* = 10, 2H, Ar*H*), 5.3 (s, 1H, C*H*$(OCH_3)_2$), 3.82 (s, 3H, ArOC*H*$_3$), 3.25 (s, 6H, OC*H*$_3$).

IR (Neat):

2920, 2820, 1720, 1585, 1505, 1440, 1405, 1340, 1260, 1240, 1140, 1090, 1020, 980, 860, 800, 750, 730, 640 cm^{-1}.

5-(Dimethoxymethyl)-1,3-benzodioxole (23):[89]

Prepared by the reaction of 3,4-methylenedioxy benzaldehyde (3 g, 20 mmol), Amberlite-IR-120 resin (0.2 g) and trimethyl orthoformate (2.4 ml, 22 mmol) in anhydrous methanol (20 ml) for 3h. to give after distillation 3.27 g (83%) of **23** as a colorless oil.

bp: 125 ^{0}C/10 mm Hg

^{1}H NMR (200 MHz, $CDCl_3$):

δ 6.88 (d, *J* = 7.5, 2H, Ar*H*), 6.74 (d, *J* = 7.5, 1H, Ar*H*), 5.93 (s, 2H, OC*H*$_2$O), 5.3 (s, 1H, C*H*$(OCH_3)_2$), 3.3 (s, 6H, OC*H*$_3$).

IR (Neat):

2980, 2920, 2880, 1710, 1630, 1510, 1470, 1370, 1280, 1210, 1160, 1130, 1060, 1010, 960, 890, 820 cm^{-1}.

General procedure for the preparation of unsymmetrical bis(arylmethylene)sulfamides:

To a suspension of an (arylmethylene)sulfamide in anhydrous benzene was added the dimethylacetal of an aromatic aldehyde, followed by a catalytic amount of *p*-toluenesulfonic acid. The mixture was heated to reflux for 2-4h and benzene was distilled out. The residue was concentrated and the resultant solid bisimines were washed with dry benzene and dried thoroughly. These were pure by ^{1}H NMR and attempted purification resulted in partial decomposition due to hydrolysis. Hence, the crude product was used further without purification.

***N*-((4-Methylphenyl)methylene)-*N'*-(phenylmethylene) sulfamide (24):**

The reaction of (phenylmethylene)sulfamide **16** (0.7 g, 3.8 mmol) and 1-(dimethoxymethyl)-4-methyl-benzene **18** (0.6 ml, 4.1 mmol) in benzene (120 ml) for 3h furnished 1.03 g (95 %) of unsymmetrical bisimine **24**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 9.0 (s, 1H, N=C*H*), 8.9 (s, 1H, N=C*H*), 7.9-7.1 (m, 9H, Ar*H*), 2.27 (s, 3H, ArCH_3).

IR (Nujol):

1610, 1580, 1390, 1330, 1230, 1155, 870, 840, 760 cm^{-1}.

***N*-((2-Methylphenyl)methylene)-*N'*-(phenylmethylene)-sulfamide (25):**

The reaction of (phenylmethylene) sulfamide **16** (0.74 g, 4 mmol) and 1-(dimethoxymethyl)-2-methyl-benzene **19** (0.7 ml, 5 mmol) in benzene (120 ml) for 2.5h furnished 0.99 g (86 %) of unsymmetrical bisimine **25**.

^{1}H NMR (90 MHz, $CDCl_3$):

δ 9.35 (s, 1H, N=C*H*), 9.1 (s, 1H, N=C*H*), 8.0-7.9 (m, 3H, Ar*H*), 7.5-7.1 (m, 6H, Ar*H*), 2.57 (s, 3H, ArCH_3).

IR (Nujol):

2880, 1610, 1580, 1310, 1340, 1170, 950, 845, 820, 780 cm^{-1}.

***N*-((2-Methylphenyl)methylene)-*N'*-((4-methylphenyl)methylene) sulfamide(26):**

The reaction of ((4-methylphenyl)methylene) sulfamide **17** (0.59 g, 3 mmol) and 1-(dimethoxymethyl)-2-methyl-benzene **19** (0.5 ml, 3.6 mmol) in benzene (120 ml) for 3h furnished 0.88 g (97 %) of unsymmetrical bisimine **26**.

^{1}H NMR (80 Mz, $CDCl_3$):

δ 9.6 (s, 1H, N=C*H*), 9.1 (s, 1H, N=C*H*), 8.3-7.9 (m, 3H, Ar*H*), 7.7-7.1 (m, 5H, Ar*H*), 2.6 (s, 3H, ArCH_3), 2.4 (s, 3H, ArCH_3)

IR (Nujol):

1600, 1570, 1330, 1230, 1160, 780 cm^{-1}.

***N*-((4-Chlorophenyl)methylene)-*N'*-(phenylmethylene) sulfamide (27):**

The reaction of (phenylmethylene)-sulfamide **16** (0.74 g, 4 mmol) and 1-chloro-4-(dimethoxymethyl)-benzene **20** (0.6 ml, 4.4 mmol) in benzene (120 ml) for 3h furnished 0.99 g (81%) of unsymmetrical bisimine **27**.

^{1}H NMR (90 MHz, $CDCl_3$):

δ 9.1 (s, 1H, N=C*H*), 9.0 (s, 1H, N=C*H*), 8.0-7.7 (m, 4H, Ar*H*), 7.6-7.3 (m, 5H, Ar*H*).

IR (Nujol):

1600, 1570, 1460, 1330, 1220, 1150, 1090, 870, 800 cm^{-1}.

***N*-(2-naphthalenylmethylene)-*N'*-(phenylmethylene) sulfamide (28):**

The reaction of (phenylmethylene) sulfamide **16** (0.55 g, 3 mmol) and 2-(dimethoxymethyl)-naphthalene **21** (0.55 ml, 3.3 mmol) in benzene (120 ml) for 3h furnished 0.96 g (99 %) of unsymmetrical bisimine **28**.

^{1}H NMR (90 MHz, $CDCl_3$):

δ 9.3 (d, *J* = 2.5, 1H, N=C*H*), 9.1 (d, *J* = 2.5, 1H, N=C*H*), 8.4 (s, 1H, Ar*H*), 8.1-7.8 (m, 6H, Ar*H*), 7.8-7.3 (m, 5H, Ar*H*).

IR (Nujol):

1610, 1590, 1390, 1340, 1290, 1160, 940, 770 cm^{-1}.

***N*-((4-Methoxyphenyl)methylene)-*N'*-(phenylmethylene) sulfamide (29):**

The reaction of (phenylmethylene) sulfamide **16** (0.74 g, 4 mmol) and 1-(dimethoxymethyl)-4-methoxy-benzene **22** (0.8 ml, 4.5 mmol) in benzene (120 ml) for 3h furnished 1.03 g (90 %) of unsymmetrical bisimine **29**.

^{1}H NMR (90 MHz, $CDCl_3$):

δ 9.0 (s, 1H, N=C*H*), 8.85 (s, 1H, N=C*H*), 8.0-7.6 (m, 4H, Ar*H*), 7.6-7.1 (m, 3H, Ar*H*), 6.9 (d, *J* = 9, 2H, Ar*H*), 3.8 (s, 3H, ArOCH_3).

IR ($CHCl_3$):

2920, 2860, 1650, 1540, 1460, 1420, 1380, 1020 cm^{-1}.

***N*-((1,3-Benzodioxol-5-yl)methylene)-*N'*-(phenylmethylene) sulfamide (30):**

The reaction of (phenylmethylene) sulfamide **16** (0.37 g, 2 mmol) and 5-(dimethoxymethyl)-1,3-benzodioxole **23** (0.34 ml, 2.2 mmol) in benzene (120 ml) for 3h furnished 0.64 g (quantitative) of unsymmetrical bisimine **30**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 9.15 (s, 1H, N=C*H*), 9.05 (s, 1H, N=C*H*), 7.95 (d, *J* = 8, 2H, Ar*H*), 7.7-7.35 (m, 5H, Ar*H*), 6.95 (d, *J* = 8, 1H, Ar*H*), 6.1 (s, 2H, OCH_2O)

IR (Nujol):

1630, 1600, 1515, 1340, 1280, 1160, 1120, 1050, 950, 885, 860, 840, 820, 790 cm^{-1}.

General procedure for reductive coupling of unsymmetrical bis(arylmethylene)sulfamides 24-30:

To a solution of the unsymmetrical bisimine in anhydrous DMF was added activated zinc dust (325 mesh). The stirred mixture was cooled to 0 ^{0}C and TMSCl was added slowly (exotherm). The mixture was then stirred at ambient temperature for 12-14h and the reaction was monitored by TLC. Saturated aqueous $NaHCO_3$ solution was added and the mixture was filtered. The filtrate was extracted with ethyl acetate to furnish the crude product which was purified by flash chromatography on silica gel.

3-(4-methylphenyl)-4-phenyl-1,2,5-thiadiazolidine-1,1-dioxide (31):

The reaction of **24** (1.1 g, 3.9 mmol) with Zn (1.3 g, 20 mmol) and TMSCl (2.5 ml, 20 mmol) in DMF (60 ml) for 15h gave a ca. 2/1 mixture of *cis/trans* **31** (^{1}H NMR of crude) which was purified by flash chromatography

(SiO_2, petroleum ether/ethyl acetate, 4/1) to give 946 mg of pure **31** (85%, 640 mg *cis* isomer **31a**, 96 mg *trans* isomer **31b**, and 210 mg mixture of *cis* and *trans* isomers).

Data for *cis* isomer 31a:

mp: 117-120 ^{0}C

^{1}H NMR (300 MHz, $CDCl_3$):

δ 7.2-7.1 (m, 4H, Ar*H*), 7.0-6.8 (m, 5H, Ar*H*), 5.2-5.1 (m, 2H, NC*H*), 5.1-4.9 (m, 2H, N*H*), 2.25 (s, 3H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$ + DMSO-d_6):

δ 136.0 (Ar*Cipso*), 135.3 (Ar*Cipso*), 135.2 (Ar*Cipso*), 132.1, 132.0, 127.4, 126.7, 126.6, 126.5 (Ar*C*), 63.5 (N*C*H), 63.3 (N*C*H), 20.0 (CH_3).

IR (Nujol):

3250, 1460, 1380, 1300, 1270, 1240, 1170 cm^{-1}.

MS (EI, 70 eV):

m/z 65 (12), 77 (25), 91 (30), 106 (100), 118 (94), 120 (70), 289 (M+1, (<1)).

Analysis for $C_{15}H_{16}N_2O_2S$:

Calcd. C, 62.48 H, 5.59 N, 9.72.

Found C, 62.06 H, 5.72 N, 9.51.

Data for *trans* isomer 31b:

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4-7.25 (m, 4H, Ar*H*), 7.15 (s, 5H, Ar*H*), 5.1-4.95 (m, 2H, N*H*), 4.8-4.7 (m, 2H, NC*H*), 2.35 (s, 3H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 138.5 (Ar*Cipso*), 136.1 (Ar*Cipso*), 133.0 (Ar*Cipso*), 132.9, 129.4, 128.6, 127.1 (Ar*C*), 67.5 (N*C*H), 67.3 (N*C*H), 20.9 (*C*H_3).

IR ($CHCl_3$):

3260, 1510, 1400, 1320, 1170, 1050, 950 cm-1.

MS (EI, 70 eV):

m/z 65 (15), 77 (18), 91 (38), 106 (100), 118 (90), 120 (93), 289 (M+1, (<1)).

3-(2-Methylphenyl)-4-phenyl-1,2,5-thiadiazolidine-1,1-dioxide (32):

The reaction of **25** (0.29 g, 1 mmol) with Zn (0.39 g, 6 mmol) and TMSCl (0.8 ml, 6 mmol) in DMF (20 ml) for 16h gave a ca. 1/1 mixture of *cis/trans* **32** (^{1}H NMR of crude) which was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 4/1) to give 155 mg (54%, mixture of *cis* and *trans* isomers that was not separable by chromatography) of pure **32ab.**

mp: 128-130 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers):

δ 7.25-6.9 (m, 18H, Ar*H*), 5.6-5.5 (m, 2H, NC*H*), 5.25-5.15 (m, 2H, NC*H*), 4.9-4.8 (br, 4H, N*H*), 2.2 (s, 6H, ArCH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$) (mixture of diastereomers):

δ 135.9, 135.3, 135.2, 135.0, 133.1, 133.0 (Ar*Cipso*), 130.1, 128.7, 128.4, 128.2, 128.0, 127.9, 127.4, 127.2, 126.3, 125.9 (Ar*C*), 64.5, 63.2, 60.7, 59.7 (N*C*H), 19.1, 19.0 (ArCH_3).

IR (Nujol):

3260, 1470, 1290, 1160, 1050, 960 cm^{-1}.

MS (EI, 70 eV):

m/z 65 (10), 77 (21), 91 (26), 106 (100), 120 (38).

HRMS (FAB+) for $C_{15}H_{17}N_2O_2S$ (M+H):

Calcd. 289.10107

Found 289.10087

Analysis for $C_{15}H_{16}N_2O_2S$:

Calcd. C, 62.48 H, 5.59 N, 9.72

Found C, 62.14 H, 5.86 N, 9.74

3-(2-Methylphenyl)-4-(4-methylphenyl)-1,2,5-thiadiazolidine-1,1-dioxide (33)

The reaction of **26** (1.2 g, 4 mmol) with Zn (1.3 g, 20 mmol) and TMSCl (2.5 ml, 20 mmol) in DMF (60 ml) for 14h gave a ca. 2.5/1 mixture of *cis/trans* **33** (^{1}H NMR of crude) which was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 3/1) to give 787 mg (65%, mixture of *cis* and *trans* isomers that was not separable by chromatography) pure **33ab**.

mp: 66-68 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$):

Major diastereomer (*cis*) 33a:

δ 7.5-6.75 (m, 8H, Ar*H*), 5.5 (brd, *J* = 7.3, 1H, NC*H*), 5.15 (brd, *J* = 7.3, 1H, NC*H*), 4.8-4.65 (brm, 2H, N*H*), 2.25 (s, 3H, ArCH_3), 2.1 (s, 3H, ArCH_3).

Visible peaks for the minor (*trans*) diastereomer 33b:

δ 7.5-6.75 (m, 8H, Ar*H*), 5.45 (brd, *J* = 7.3, 1H, NC*H*), 5.2 (brd, *J* = 7.3, 1H, NC*H*), 4.8-4.65 (brm, 2H, N*H*), 2.3 (s, 3H, ArCH_3), 2.05 (s, 3H, ArCH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$):

Major diastereomer (*cis*) 33a:

δ 137.6, 135.9, 133.0, 132.0 (Ar*Cipso*), 130.0, 128.7, 128.0, 127.1, 127.0, 125.8 (Ar*C*), 64.5, 59.7 (N*C*H), 20.9, 18.9 (*C*H_3).

Visible peaks for the minor diastereomer (*trans*) 33b:

δ 137.9, 135.9, 135.3, 132.0 (Ar*Cipso*), 129.3, 128.5, 127.8, 127.3, 126.4, 125.8 (Ar*C*), 63.1, 60.8 (N*C*H), 20.9, 19.1 (*C*H_3).

IR ($CHCl_3$):

3300, 1320, 1230, 1170, 1050, 1030, 760 cm^{-1}.

MS (EI, 70 eV):

65 (10), 77 (5), 91 (25), 120 (100), 238 (1), 303 (M+1, (<1)).

3-(4-Chlorophenyl)-4-phenyl-1,2,5-thiadiazolidine-1,1-dioxide (34):

The reaction of **27** (0.92 g, 3 mmol) with Zn (1.18 g, 18 mmol) and TMSCl (2.3 ml, 18 mmol) in DMF (60 ml) for 12h gave a ca. 1.2/1 mixture of *cis/trans* **34** (^{13}C NMR of crude) which was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 3/1) to give 624 mg (67%, mixture of *cis* and *trans* isomers that was not separable by chromatography) of pure **34ab**.

mp: 158-160 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers):

δ 7.2-7.1 (m, 10H, Ar*H*), 7.0-6.9 (m, 8H, Ar*H*), 5.25-5.15 (m, 4H, NC*H*), 4.9-4.8 (m, 4H, N*H*).

^{13}C NMR (75.5 MHz, $CDCl_3$):

Major diastereomer (*cis*) 34a:

δ 134.3 (Ar*Cipso*), 134.0 (Ar*Cipso*), 132.5 (Ar*Cipso*), 128.3, 127.1, 126.9, 126.8, 126.7, 126.6 (Ar*C*), 63.3 (NCH), 62.7 (NCH).

Visible peaks for the minor (*trans*) diastereomer 34b:

δ 135.5 (Ar*Cipso*), 135.0 (Ar*Cipso*), 132.3 (Ar*Cipso*), 63.6 (NCH), 63.0 (NCH).

IR (Nujol):

3240, 1500, 1260, 1170, 1100, 1070, 980 cm^{-1}.

MS (EI, 70 eV):

m/z 51 (29), 77 (45), 89 (5), 106 (100), 140 (53), 165 (2), 309 (M+1, (<1)).

HRMS (FAB+) for $C_{14}H_{14}N_2O_2S^{35}Cl$ (M+H):

Calcd. 309.04645

Found 309.04590

3-(2-Naphthalenyl)-4-(phenyl)-1,2,5-thiadiazolidine-1,1-dioxide (35):

The reaction of **28** (0.96 g, 3 mmol) with Zn (1.18 g, 18 mmol) and TMSCl (2.3 ml, 18 mmol) in DMF (40 ml) for 15h gave a ca. 1.2/1 mixture of *cis/trans* **35** (^{13}C NMR of crude) which was purified by flash chromatography

(SiO_2, petroleum ether/ethyl acetate, 4/1) to give 720 mg (75%, mixture of *cis* and *trans* isomers that was not separable by chromatography) of pure **35ab**.

mp: 66-68 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers):

δ 7.9-7.3 (m, 14H, Ar*H*), 7.25-6.6 (m, 10H, Ar*H*), 5.45-5.2 (m, 4H, NC*H*), 5.0-4.8 (m, 4H, N*H*).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 134.9, 132.8, 132.7, 132.5 (Ar*Cipso*), 128.8, 128.1, 127.9, 127.7, 127.4, 127.2, 126.8, 126.7, 126.2, 124.7 (Ar*C*), 64.8, 64.6 (N*C*H).

IR (Nujol):

3280, 1480, 1390, 1330, 1280, 1170, 1050 (br) cm^{-1}

MS (EI, 70 eV):

64 (5), 77 (16), 91 (6), 106 (100), 115 (5), 127 (30), 141 (5), 155 (75), 229 (2), 244 (2), 325 ((M+1),<1).

HRMS (FAB+) for $C_{18}H_{17}N_2O_2S$ (M+H):

Calcd. 325.10107

Found 325.09941

3-(4-Methoxyphenyl)-4-phenyl-1,2,5-thiadiazolidine-1,1-dioxide (36):

The reaction of **29** (1.13 g, 3.7 mmol) with Zn (1.3 g, 20 mmol) and TMSCl (2.5 ml, 20 mmol) in DMF (60 ml) for 14h gave a ca. 2/1 mixture of *cis/trans* **36** (^{1}H NMR of crude) which was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 3/1) to give 780 mg (69%, mixture of *cis* and *trans* isomers that was not separable by chromatography) of pure **36ab**.

mp: 112-115 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers):

δ 7.35-7.15 (m, 4H, Ar*H*), 7.05-7.0 (m, 2H, Ar*H*), 6.95-6.8 (m, 6H, Ar*H*), 6.75-6.65 (m, 6H, Ar*H*), 5.2-5.1 (m, 4H, NC*H*), 4.8-4.7 (m, 4H, N*H*), 3.75 (s, 3H, OCH_3).

Visible peaks for the minor (*trans*) diastereomer:

δ 3.8 (s, 3H, OCH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 159.0 (Ar*Cipso*), 135.2 (Ar*Cipso*), 128.4, 127.9, 127.8, 127.3 (Ar*C*), 126.9 (Ar*Cipso*), 113.3 (Ar*C*, ortho *C* to $ArOCH_3$), 64.5, 64.0 (N*C*H), 54.9 (Ar*C*H_3).

Visible peaks for the minor (*trans*) diastereomer:

δ 160.0 (Ar*Cipso*), 114.0 (ArC, ortho *C* to $ArOCH_3$), 68.5, 64.2 (N*C*H).

IR (Nujol):

3240, 2880, 1620, 1530, 1390, 1320, 1280, 1260, 1170, 1070, 1040, 990, 970, 850, 780 cm^{-1}.

MS (EI, 70 eV):

m/z 65 (16), 77 (26), 91 (8), 106 (100), 119 (6), 134 (82), 210 (1), 305 (M+1, (<1)).

3-((1,3-Benzodioxol-5-yl)methyl)-4-phenyl-1,2,5-thiadiazolidine-1,1-dioxide (37):

The reaction of **30** (0.62 g, 2 mmol) with Zn (0.65 g, 10 mmol) and TMSCl (1.2 ml, 10 mmol) in DMF (15 ml) for 14h gave a ca. 2/1 mixture of

cis/trans **37** (^{1}H NMR of crude) which was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 3/1) to give 211 mg (33%, mixture of *cis* and *trans* isomers that was not separable by chromatography) of pure **37ab.**

mp: 112-115 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers):

δ 7.25-7.1 (m, 6H, Ar*H*), 7.1-6.95 (m, 4H, Ar*H*), 6.75-6.65 (m, 2H, Ar*H*), 6.65-6.5 (m, 2H, Ar*H*), 6.5-6.4 (m, 2H, Ar*H*), 5.85 (s, 2H, OCH_2O), 5.2-5.05 (m, 4H, NC*H*), 4.9-4.7 (bs, 4H, N*H*).

Visible peaks for the minor (*trans*) diastereomer:

δ 5.95 (s, 2H, OCH_2O).

^{13}C NMR (75.5 MHz, acetone-d_6):

δ 148.4 (Ar*Cipso*), 137.5 (Ar*Cipso*), 131.4 (Ar*Cipso*), 128.7, 128.6, 122.3, 109.0, 108.3 (Ar*C*), 102.0 (O*C*H_2O), 65.6, 65.4 (N*C*H).

Visible peaks for the minor (*trans*) diastereomer:

δ 149.0 (Ar*Cipso*), 148.1 (Ar*Cipso*), 132.9 (Ar*Cipso*), 129.2, 129.0 (Ar*C*), 102.4 (O*C*H_2O), 68.2 (N*C*H).

IR (Nujol):

3380, 2920, 2880, 1390, 1320, 1270, 1240, 1180, 1050, 950, 830 cm^{-1}.

MS (EI, 70 eV):

m/z 63 (8), 77 (9), 91 (5), 106 (7), 121 (14), 148 (100), 194 (3), 254 (2), 318 (M^+, (<1).

General procedure for cleavage of unsymmetrical cyclic sulfamides 31-35:

A mixture of the unsymmetrical cyclic sulfamide and phenol in HBr (aqueous, 48%) was heated at 130-140 ^{0}C for 20 min., cooled to ambient

temperature and the resulting suspension was extracted with ethyl acetate to remove phenol. The aqueous phase was made basic with solid NaOH and the diamine was isolated by extraction with ethyl acetate. All diamines obtained by this procedure were pure by ^{1}H NMR.

R*,S* **1-(4-Methylphenyl)-2-phenyl-1,2-ethanediamine (38):**

Reaction of *cis* **31a** (0.23 g, 0.8 mmol) in HBr (5 ml) and phenol (0.35 ml, 4 mmol) furnished 96 mg (53%) of **38a** as a solid.

mp: 80-82 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4-7.25 (m, 7H, Ar*H*), 7.2-7.05 (m, 2H, Ar*H*), 4.0-3.85 (m, 2H, NC*H*), 2.35 (s, 3H, CH_3), 1.8-1.6 (brs, 4H, NH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 142.5 (Ar*Cipso*), 139.2 (Ar*Cipso*), 137.1 (Ar*Cipso*), 129.1, 128.3, 127.4, 126.9 (Ar*C*), 62.4, 62.1 (N*C*H), 21.0 (CH_3).

IR ($CHCl_3$):

3300, 1600 (br), 1520, 1500, 1460, 1220 cm^{-1}.

MS (EI, 70 eV):

77 (15), 93 (17), 106 (75), 120 (100), 166 (2), 227 (M+1, <1)

R*,S* **1-(2-Methylphenyl)-2-phenyl-1,2-ethanediamine (39):**

Reaction of **32** (0.58 g, 2 mmol) in HBr (5 ml) and phenol (0.6 g, 6.5 mmol) furnished 310 mg (69%) of analytically pure **39** as a ca. 1.1/1 mixture of diastereomers.

^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers):

δ 7.5-7.1 (m, 18H, Ar*H*), 4.42 (s, 1H, NC*H*), 4.33 (d, *J* = 7.8, 1H, NC*H*), 4.09 (d, *J* = 7.8, 1H, NC*H*), 4.02 (s, 1H, NC*H*), 2.38 (s, 3H, ArCH_3), 2.30 (s, 3H, ArCH_3), 1.41 (bs, 8H, NH_2),.

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 142.2 (Ar*Cipso*), 140.1 (Ar*Cipso*), 136.3 (Ar*Cipso*), 130.1, 128.1, 127.5, 127.4, 126.8, 126.0, 125.9 (Ar*C*), 61.9 (N*C*H), 56.7 (N*C*H), 19.5 (Ar*C*H_3).

Visible peaks for the minor isomer:

142.0 (Ar*Cipso*), 140.0 (Ar*Cipso*), 136.3 (Ar*Cipso*), 130.0 (Ar*C*), 62.1 (N*C*H), 56.0 (N*C*H), 19.3 (Ar*C*H_3).

IR ($CHCl_3$):

3400 (br), 3040, 1600, 1510, 1470, 1060, 890, 770, 710, 680 cm^{-1}.

MS (CI, NH_3):

106 (48), 120 (100), 210 (70), 227 (MH^+, (65)).

Analysis for $C_{15}H_{18}N_2$:

Calcd: C, 79.60 H, 8.02 N, 12.38.

Found: C, 79.83 H, 8.06 N, 12.12.

***R*,S** 1-(2-Methylphenyl)-2-(4-methylphenyl)-1,2-ethanediamine (40):**

Reaction of **33** (0.15 g, 0.5 mmol) in HBr (4 ml) and phenol (0.2 ml, 2.5 mmol) furnished 63 mg (52%) of **40** as a ca. 5/1 mixture of diastereomers.

^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers):

δ 7.5-7.2 (m, 16H,Ar*H*), 4.45 (s, 2H, NC*H*), 4.35 (d, *J* = 8, 1H, NC*H*), 4.1 (d, *J* = 8, NC*H*), 2.4 (s, 3H, ArCH_3), 2.35 (s, 3H, ArCH_3), 2.3 (s, 3H, ArCH_3), 1.7 (bs, 8H, NH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 140.0, 139.7,137.5, 136.6 (Ar*Cipso*) 130.3, 129.1, 127.5, 127.4, 127.1, 126.1 (Ar*C*), 62.4, 56.0 (Ar*C*H), 21.0, 19.4 (ArCH_3)

IR ($CHCl_3$):

3309, 3022, 2922, 2868, 1670, 1603, 1514, 1489, 1462, 1381, 1043, 822, 758, 731cm^{-1}.

MS (CI, NH_3):

106 (18), 120 (100), 224 (50), 241 (MH^+, (26))

R*,S* **1-(4-Chlorophenyl)-2-phenyl-1,2-ethanediamine (41)**

Reaction of **34** (0.31 g, 1 mmol) in HBr (6 ml) and phenol (0.4 ml, 5 mmol) furnished 194 mg (78%) of **41** as a ca. 1/1 mixture of diastereomers.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4-7.2 (m, 9H, Ar*H*), 4.1-4.0 (m, 4H, NC*H*), 2.1 (bs, 8H, NH_2).

Visible peaks for the minor isomer:

δ 6.9-6.7 (m, 9H, Ar*H*).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 141.6, 140.3, 132.9 (Ar*Cipso*), 128.6, 128.5, 128.1, 127.1, 115.6 (Ar*C*), 61.4, 61.3 (N*C*H)

Visible peaks for the minor isomer:

δ 140.6, 140.4, 132.8 (Ar*Cipso*), 129.1, 128.6, 128.5, 127.4, 119.1 (Ar*C*), 62.0, 61.3 (N*C*H).

IR ($CHCl_3$):

3200 (br), 2860, 1610, 1505, 1390, 1230, 1110, 1030, 850, 780, 710 cm^{-1}.

MS (CI, NH_3):

106 (25), 140 (100), 230 (18), 247 (MH^+, (35)).

***R*,S** 1-(2-Naphthalenyl)-2-phenyl-1,2-ethanediamine (42):**

Reaction of **35** (0.2 g, 0.6 mmol) in HBr (5 ml) and phenol (0.3 ml, 3 mmol) furnished **42** (92 mg, 58%) as a ca. 1/1 mixture of diastereomers.

^{1}H NMR (200 MHz, $CDCl_3$): (mixture of diastereomers)

δ 7.9-7.8 (m, 8H, Ar*H*), 7.8-7.2 (m, 16H, Ar*H*), 4.35-4.05 (m, 4H, NC*H*), 1.8 (brs, 4H, NH_2).

^{13}C NMR (200 MHz, $CDCl_3$):

δ 142.1, 139.6, 133.2, 132.7 (Ar*Cipso*), 129.3, 128.4, 128.2, 127.8, 127.5, 126.7, 126.0, 125.8, 125.3, 115.7 (Ar*C*), 62.5, 61.2 (Ar*C*H).

IR ($CHCl_3$):

3327, 3159, 2916, 2849, 1668, 1599, 1495, 1454, 1367, 1267, 1124, 974, 947, 895, 854, 826, 700, 658 cm^{-1}.

MS (CI, NH_3):

106 (52), 122 (19), 144 (20), 156 (100), 215 (58), 263, (MH^+, (18)).

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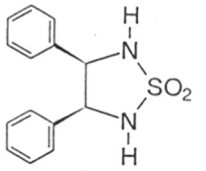

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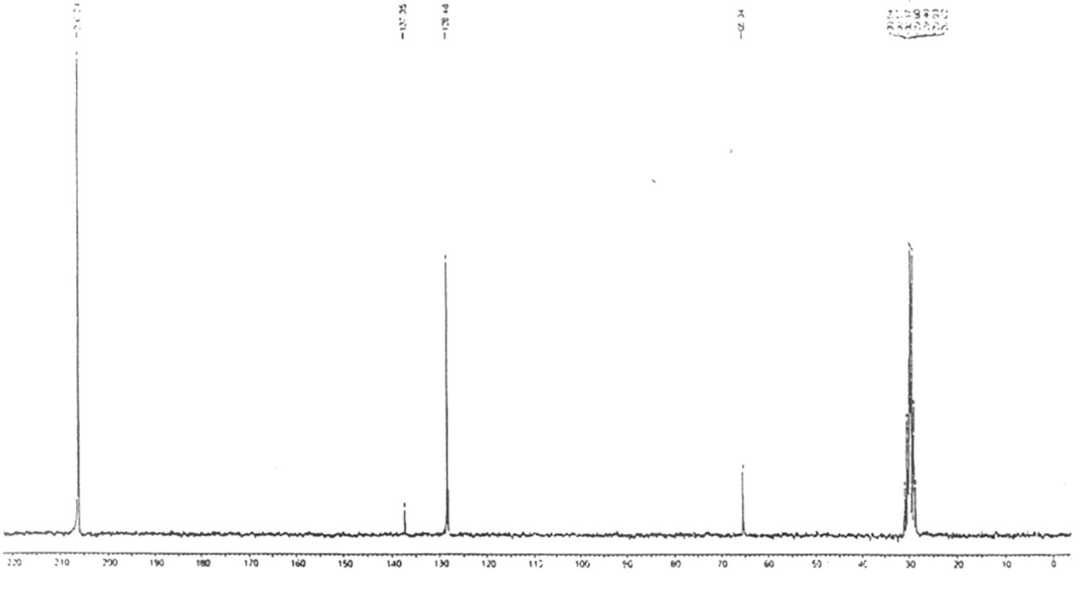

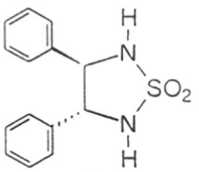

8b
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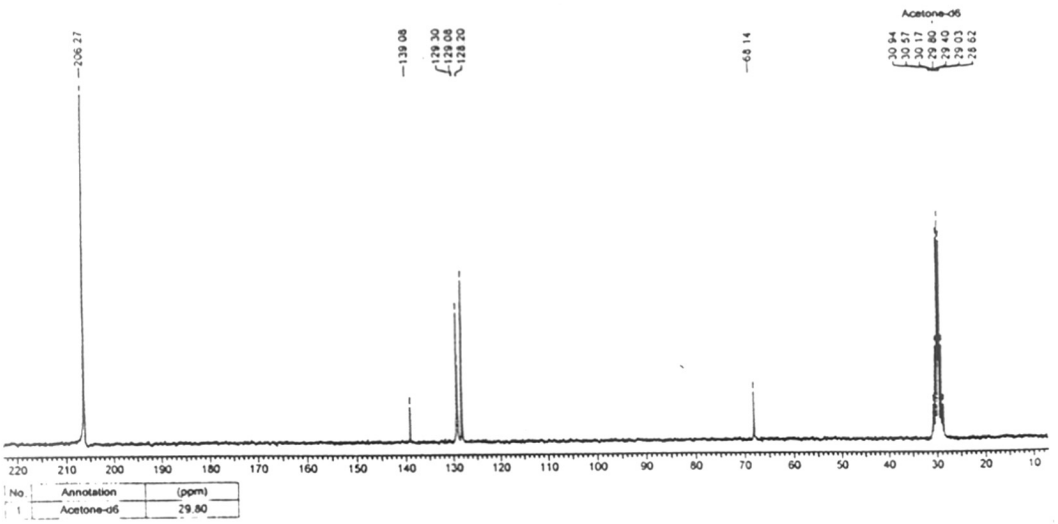

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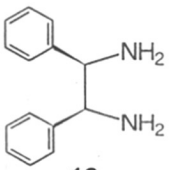

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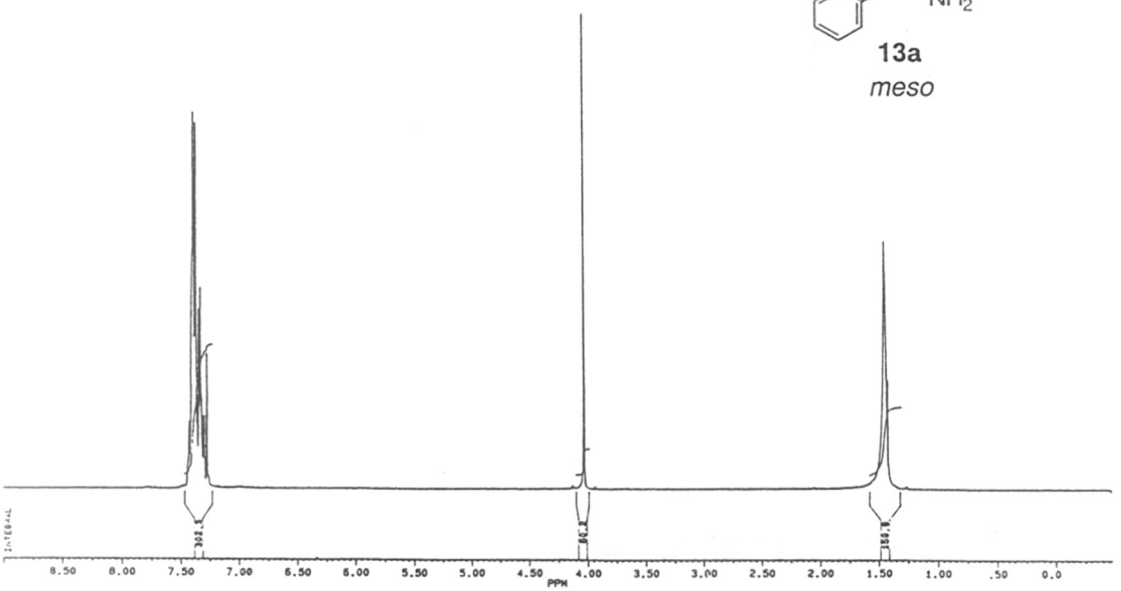

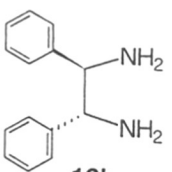

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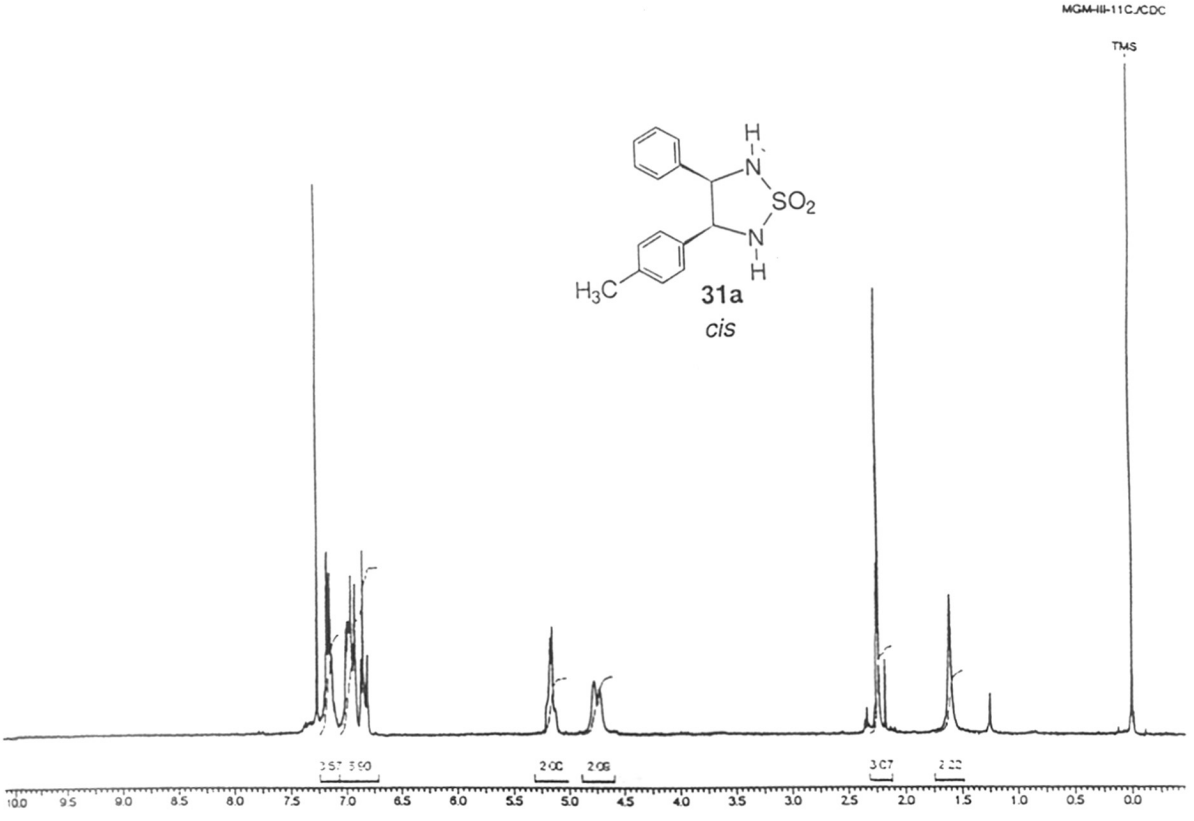
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H
H3C
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9.0
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8.0
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6.5
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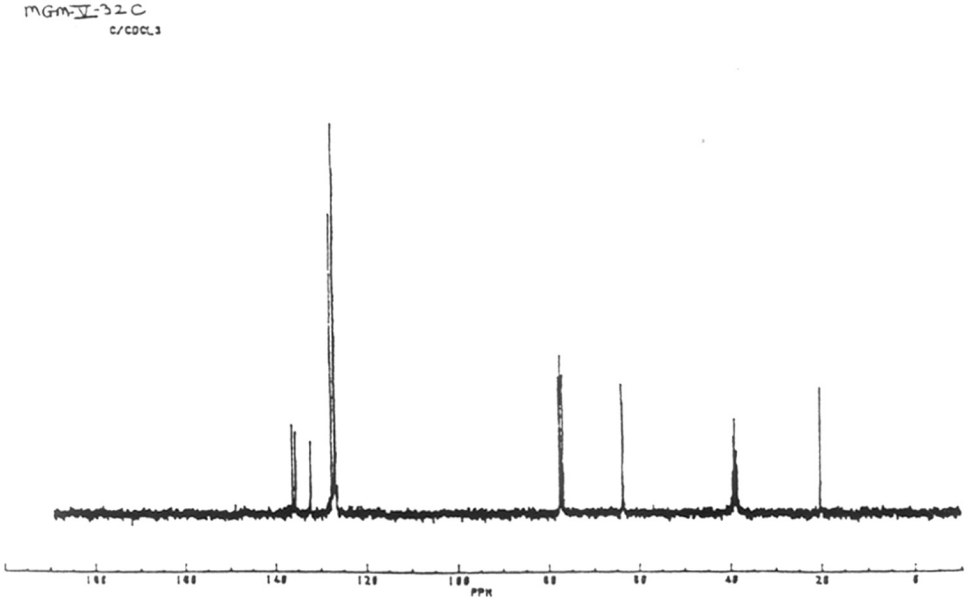
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C/CDCL3
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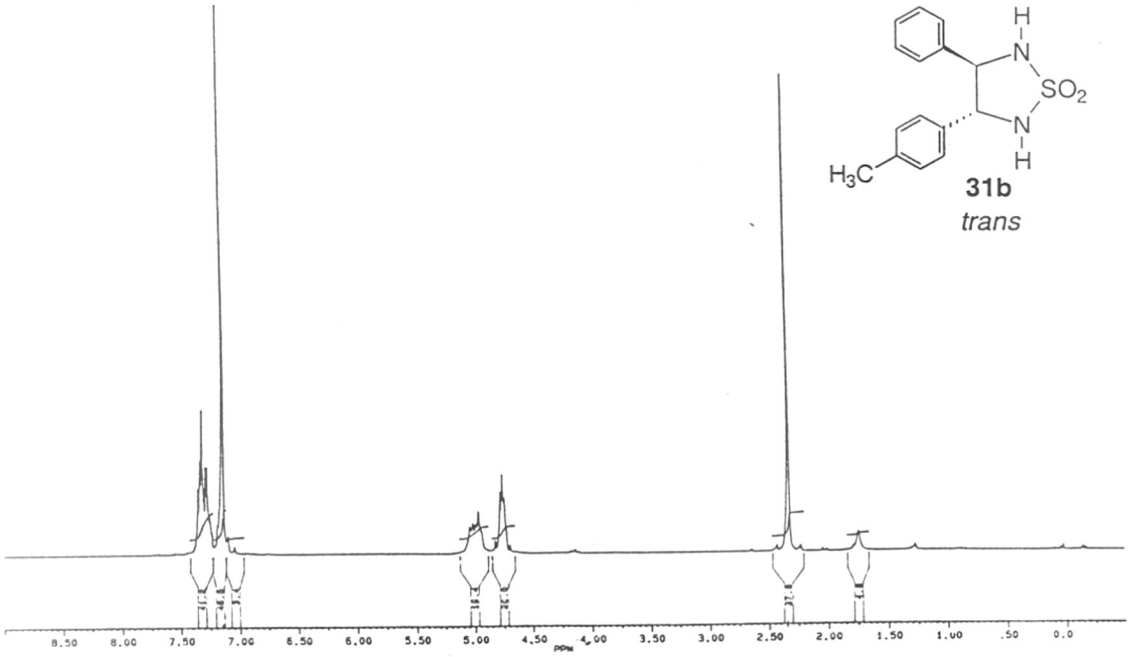

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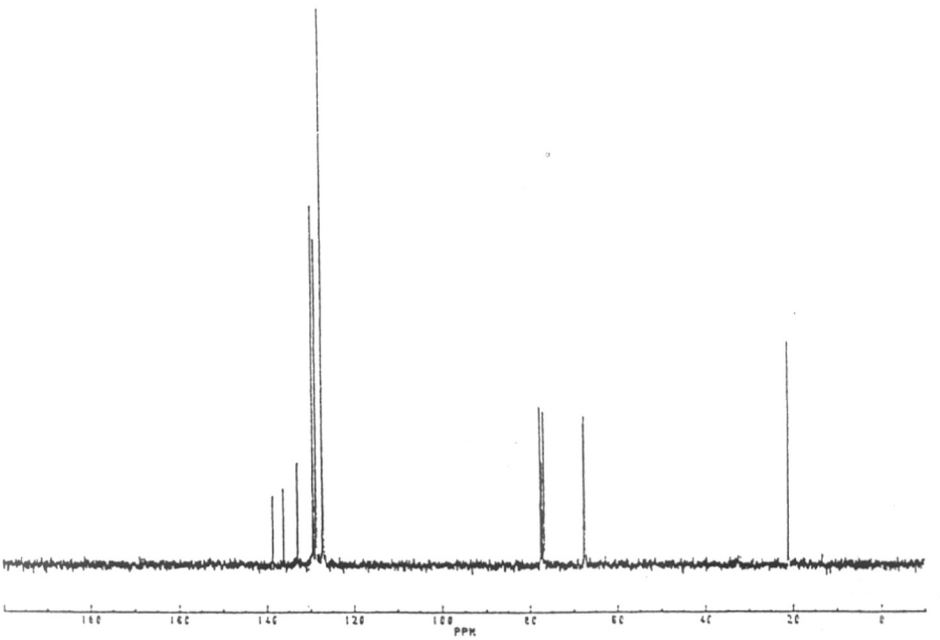

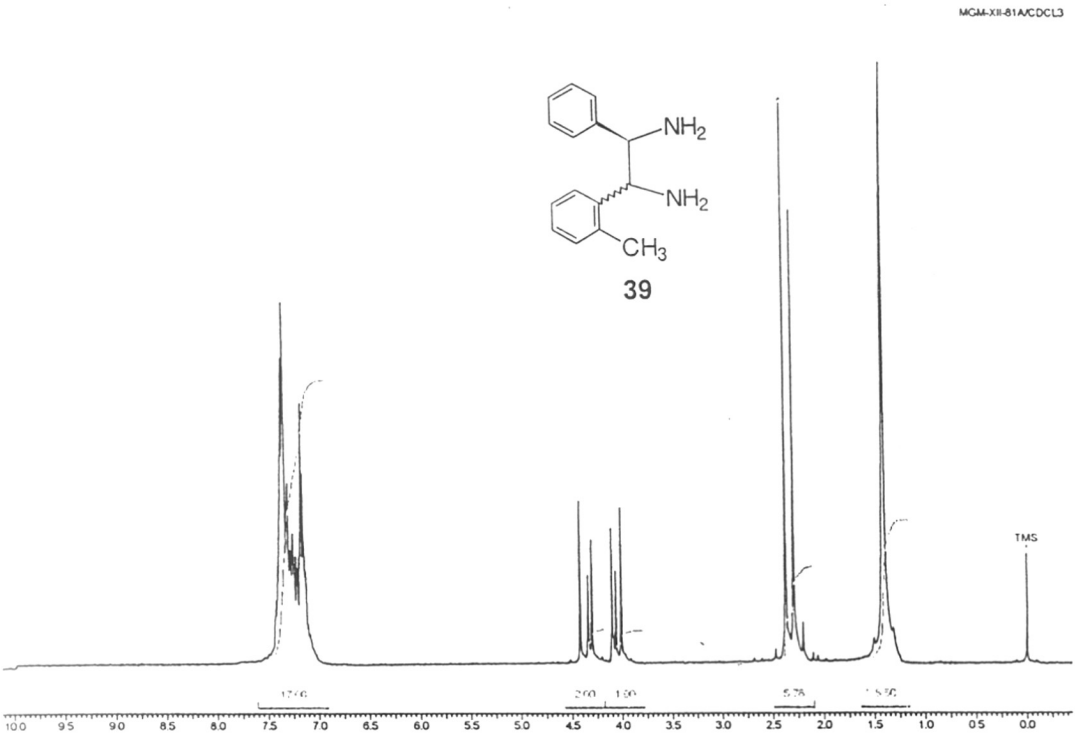
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TMS
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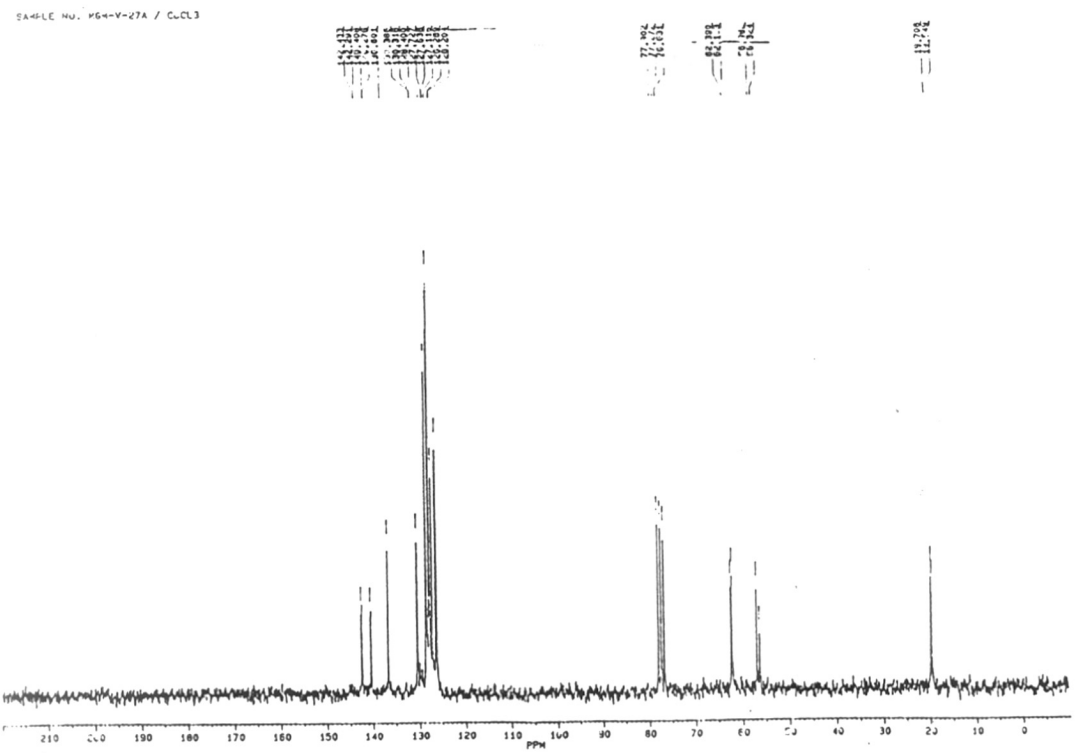
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CHAPTER II

SYNTHESIS OF ENANTIOMERICALLY PURE ALKYLTHIOIMIDAZOLINES, AMIDINES AND GUANIDINES AND THEIR APPLICATION IN STEREOSELECTIVE REACTIONS

1. INTRODUCTION

Amidines and guanidines are of considerable chemical and biological interest. Hydrogen-bond mediated interactions between guanidinium ions and phosphate-containing biomolecules[1] have lead to molecular recognition studies in chemical systems involving oxoanions capable of forming similar hydrogen bonded complexes with guanidines.[2] Several naturally occuring guanidines are of interest as neuroactive agents.[3] Amidines have been employed in organic synthesis as strong bases, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[4] being the most familiar of this class of molecules. However, synthetic applications of enantiomerically pure amidines and guanidines have been relatively less explored.

2. OBJECTIVE

The objective of this study was to synthesize enantiomerically pure 4,5-dihydroimidazoles (amidines), 2-alkylthio-4,5-dihydroimidazoles (amidine analogues) and guanidines derived from C_2 symmetric 1,2-diamines and to investigate their utility in a variety of stereoselective reactions.

3. RESULTS AND DISCUSSION

The following sections describe the synthesis of chiral 2-alkylthio-4,5-dihydroimidazoles, amidines and guanidines and their application in stereoselective reactions.

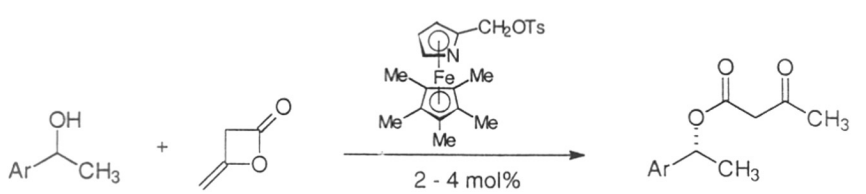
Section 1. Application of chiral amidines in the kinetic resolution of secondary alcohols.

Introduction:

The enzymatic resolution of chiral alcohols has been extensively investigated and the topic has been reviewed recently.[5] Among the non-enzymatic methods, the use of stoichiometric amounts of chiral acylating agents has been examined and highly enantioselective procedures have been developed.[6] In contrast, very few studies[7-9] have addressed the catalytic enantioselective acylation of racemic alcohols with synthetic organic or organometallic catalysts as an alternative to enzymatic resolution.

Recently, Fu has examined the use of chiral heterocycle/transition metal π-complexes as nucleophilic acylation catalysts. (π-Heterocycle)FeCp* complexes[7] (2-4 mol%) catalyze the acylation of secondary alcohols with moderate to good (53-87%) enantioselectivity (Scheme 1).

Scheme 1.



53-87% e.e.

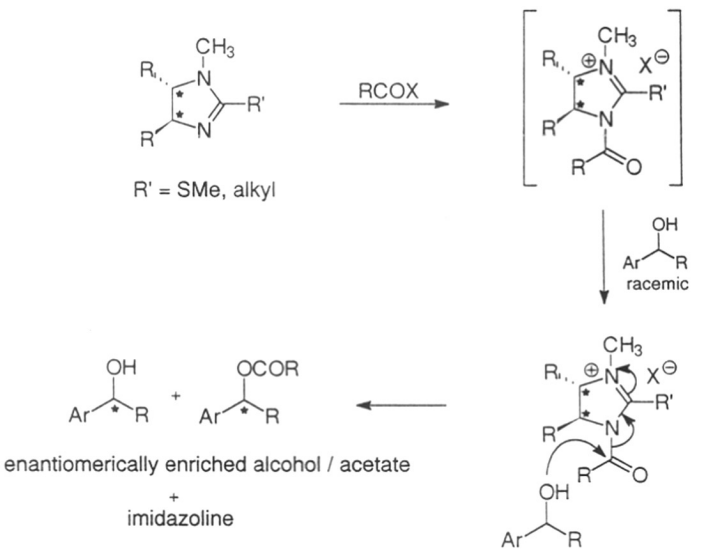
Other catalysts incorporating a pyridinyl ring/η^5-C_5Me_5 or a η^5-C_5Ph_5 group were also examined with the objective of creating a more asymmetric environment in the vicinity of the nucleophilic nitrogen atom. These catalysts exhibited better enantioselectivity for the acylation of several unsaturated

secondary alcohols.[8] The effect of solvent on the rate of acylation was also examined.[9]

Objective:

The objective of this study was to investigate the possibility of utilizing enantiomerically pure 2-alkylthio-4,5-dihydroimidazoles and amidines as acyl transfer catalysts in the acylation of secondary alcohols. It was envisaged that the imidazoline ring may act as an acyl transfer agent as shown in Figure 1.

Figure 1. Catalytic action of alkylthioimidazolines and amidines in the acylation of secondary alcohols.



Treatment of a chiral 4,5-dihydroimidazole (imidazoline) with an acylating agent should generate an *N*-acyl imidazolinium intermediate which should act as an acyl transfer agent. It seemed plausible that the reaction of the acyl imidazolinium species with a racemic secondary alcohol would be subject to chiral discrimination between the two enantiomers of the alcohol and result in preferential acylation of one enantiomer over the other. The net result would be a

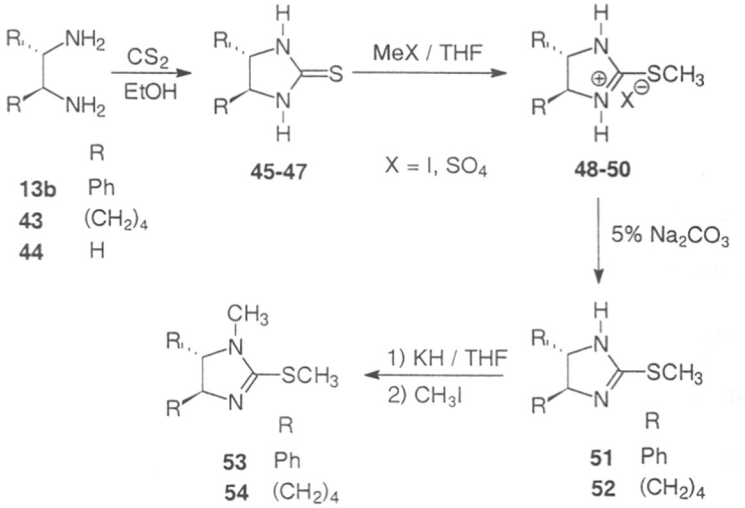
kinetic resolution of the alcohol. The proposed acyl transfer from the alkylthioimidazoline is similar to one of the proposed models[10] for biotin mediated carboxylation in biological systems.

Results and discussion:

For initial studies, we chose to investigate the utility of chiral 2-alkylthio 4,5-dihydroimidazoles as acyl transfer catalysts since they may be readily prepared from diamine derived thioureas and introduction of chirality at sites other than the diamine portion would be possible by using chiral *S*-alkylating agents during the synthesis.

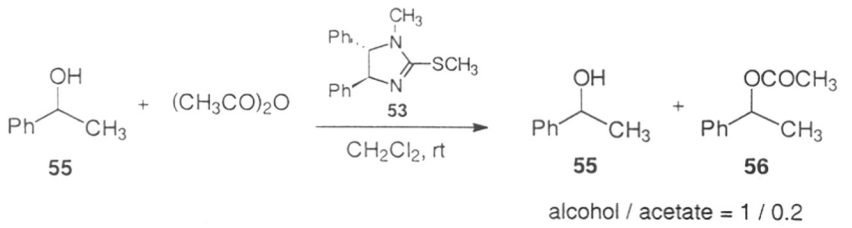
1-Methyl-2-methylthio-4,5-dihydro-4,5-diphenylimidazole **53** and 1-methyl-2-methylthio-4,5-dihydro-4,5-tetramethyleneimdazole **54** were chosen as candidates for this study. **53** and **54** were prepared starting from the corresponding thioureas[11] **45** and **46** generated by the reaction of carbon disulfide with (1*S*, 2*S*)-(-)-1,2-diphenylethanediamine **13b** and (1*R*, 2*R*)-(+)-1,2-cyclohexyldiamine **43** respectively. The reaction of thioureas **45** and **46** with the methyl iodide or dimethyl sulfate gave the 2-methylthioimidazoline salts[12] **48** and **49**. These were treated with 5% Na_2CO_3 and the resultant free imidazolines[12] **51** and **52** were *N*-methylated with potassium hydride/methyl iodide to give 1-methyl-2-methylthio-4,5-dihydroimidazoles **53** and **54** in 74 and 86% yields respectively (Scheme 2). Thiourea **47**, derived from ethylenediamine, and the corresponding 2-methylthioimidazoline salt **50** were also prepared for elaboration into other chiral imidazolines.

Scheme 2.



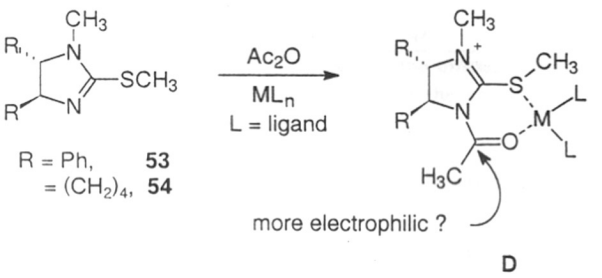
Orienting experiments were conducted with the imidazoline **53** and 1-phenylethyl alcohol **55**. Control experiments indicated that the unscatalyzed acylation of 1-phenylethyl alcohol with acetyl chloride was extremely rapid and acetic anhydride was therefore used as the acylating agent in this study. Treatment of racemic 1-phenylethyl alcohol with half an equivalent of acetic anhydride in the presence of 0.1 equivalent of **53** did not generate any of the requisite acetate at an appreciable rate. Use of an excess of acetic anhydride generated a small amount of 1-phenylethyl acetate **56** (alcohol/acetate = 1/0.1 after 48h). When stoichiometric amount of **53** was used, the rate of the acylation reaction increased marginally (alcohol/acetate = 1/0.2 after 48h, Scheme 3). Throughout this study, an excess of acetic anhydride was employed so that the acylation proceeded at a reasonable rate. Since the yield of the acetate did not exceed 50%, the excess acetic anhydride is not detrimental to the kinetic resolution if any.

Scheme 3.



The very slow rate of acylation prompted us to explore the use of a metal salt in conjunction with the imidazoline. It was expected that the metal ion would form a chelate such as **D** (Figure 2) and increase the electrophilicity of the acyl carbonyl group in the intermediate. This would increase the rate of the acyl transfer step.

Figure 2. Formation of a metal chelate from a *N*-acetyl-2-methylthio-4,5-dihydroimidazole.



The effect of the metal salt was examined in the presence as well as absence of alkylthioimidazoline to determine the extent, if any, of the background (not catalyzed by imidazoline) acylation reaction. Somewhat unexpectedly, the presence of the imidazoline actually decreased the rate of the acylation reaction. Thus, acylation is faster with $Hg(OAc)_2$ and $MgBr_2$ in the absence of alkylthioimidazoline. A possible explanation would be the complexation of the metal salt by the unacylated imidazoline thereby decreasing it's Lewis acidity.

LiCl, $Ti(OiPr)_4$ and $Sc(OTf)_3$ do catalyze the acylation but there is no rate enhancement in the presence of the alkylthioimidazoline (Table 1).

Table 1. Acylation of 1-phenylethyl alcohol catalyzed by 2-methylthio imidazolines **53, 54**.

No.	Imidazoline	equiv. used	Salt/amine [a]	Time h	Alcohol 55/Acetate 56 [b]
1.	-	-	-	48	1 / 0.05
2.	53	0.1	-	48	1 / 0.1
3.	53	1	-	48	1 / 0.2
4.	-	-	LiCl	48	1 / 0.7
5.	53	1	LiCl	48	1 / 0.9
6.	-	-	$Sc(OTf)_3$	3	1 / 10
7.	53	1	$Sc(OTf)_3$	3	1 / 10
8.	-	-	$HgCl_2$	48	1 / 0.05
9.	53	1	$HgCl_2$	48	1 / 0.2
10.	-	-	$MgBr_2$	24	1 / 10
11.	53	1	$MgBr_2$	48	1 / 3.3
12.	-	-	$Hg(OAc)_2$	48	1 / 1.3
13.	53	1	$Hg(OAc)_2$	48	1 / 0.6
14.	-	-	$Ti(OiPr)_4$	48	1 / 0.1
15.	53	1	$Ti(OiPr)_4$	48	1 / 0.1
16.	-	-	Et_3N	48	1 / 0.4
17.	53	1	Et_3N	48	1 / 0.2
18.	-	-	$Ti(OiPr)_4$	48	1 / 0.2
19.	54	1	$Ti(OiPr)_4$	48	1 / 0.3

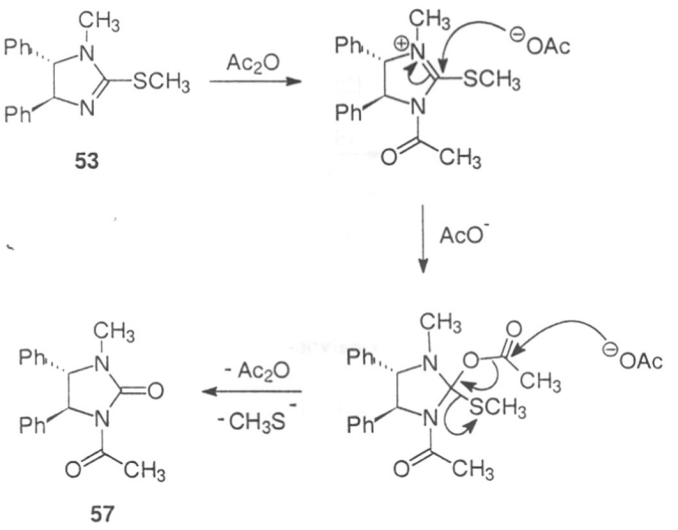
a: an equivalent of metal salt or amine (with respect to the imidazoline) was used. b: the alcohol/acetate ratios are based on ^1H NMR spectra of the crude product and are an average of a minimum of two measurements.

The only exception is the **53**/$HgCl_2$ catalyzed acylation (alcohol/acetate = 1/0.2, entry 9, Table 1) which is faster than the background $HgCl_2$ catalyzed acylation (alcohol/acetate = 1/0.05, entry 8). However, the alcohol/acetate ratio for the reaction catalyzed only by **53** is also 1/0.2 (entry 3) which indicates that there is practically no synergistic effect of the alkylthioimidazoline/$HgCl_2$ combination. The lack of any rate enhancement by $HgCl_2$ is also indicated by the identical alcohol/acetate ratio obtained in entry 8 (1/0.05) with that for the control reaction (entry 1, no additive). The 1-phenylethyl acetate as well as the unreacted alcohol obtained by this protocol had negligible optical activity and thus, chiral

alkylthioimidazolines are not useful as enantiodifferentiating acyl transfer catalysts.

The lack of effective catalysis by the alkylthioimidazoline may be due to several reasons. One possibility is protonation of the alkylthioimidazoline by acetic acid generated during the acylation with acetic anhydride. However, examination of an equimolar mixture of 53 and acetic acid by ^{1}H NMR spectroscopy reveals no change in the chemical shifts of the benzylic methine protons as well as the *N*-methyl group in 53. This indicates that the ring nitrogens in 53 are not protonated by acetic acid. However, prolonged exposure of 53 to excess acetic anhydride leads to the formation of the *N*-acyl imidazolidinone[13] 57 which indicates that the alkylthioimidazoline itself is not stable under the reaction conditions-a situation which precludes effective catalysis. A possible mechanism for the formation of 57 from 53 is shown in Scheme 4.

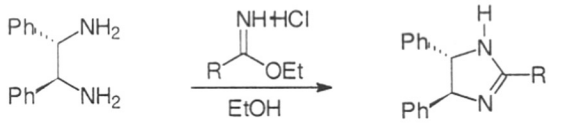
Scheme 4.



The formation of **57** suggested a change in the structural requirements of the catalyst and hence amidines **62** and **63** were investigated next. It was expected that amidines would be more stable than alkylthioimidazolines under the reaction conditions since nucleophilic addition at C2 would be reversible in the absence of the alkylthio leaving group.

Amidines[14] can be synthesized either by the reaction of nitriles with amines or by reaction of activated amides or their derivatives with amines. The chiral amidines **60** and **61** were prepared by adaptation of the literature procedures for amidine synthesis (Pinner synthesis).[15] The imidoester hydrochlorides of benzonitrile **(58)** and acetonitrile **(59)** were prepared by the usual procedure.[16] Reaction of **58** with (1*S*, 2*S*)-(-)-1,2-diphenyl ethanediamine **(13b)** gave the required 4,5-dihydro-2,4,5-triphenylimidazole **60** in 72% yield.[17] Similarly, reaction of **59** with **(13b)** gave the 2-methyl-4,5-dihydro-4,5-diphenylimidazole **61** in 98% yield. (Scheme 5).

Scheme 5.



(1*S*, 2*S*)

13b

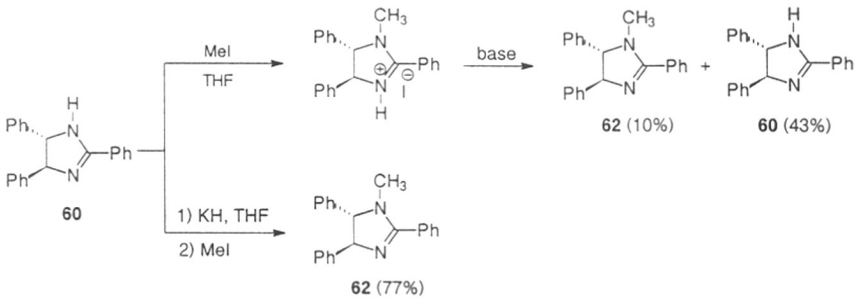
R = Ph, **60**

CH_3 **61**

To prevent irreversible *N*-acylation and to enable acyl transfer, preparation of the corresponding *N*-alkyl derivatives was necessary. This, however, proved to be unexpectedly difficult. Amidine **60** was first treated with methyl iodide to give the corresponding *N*-alkyl amidinium hydroiodide which was then treated with various bases such as aqueous ammonia, methanolic KOH

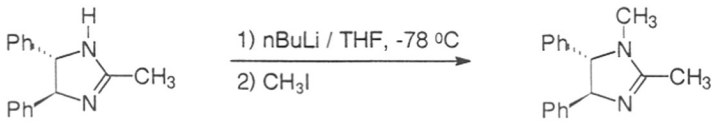
and NaOMe/MeOH (Scheme 6). However, these procedures invariably generated a mixture of the *N*-methyl amidine **62** and the precursor amidine **60**. Separation of **62** from **60** was extremely difficult. Finally, amidine **60** was converted to 1-methyl-4,5-dihydro-2,4,5-triphenylimidazole **62** in 77% yield by deprotonation with KH in THF followed by *N*-alkylation with methyl iodide (Scheme 6).

Scheme 6.



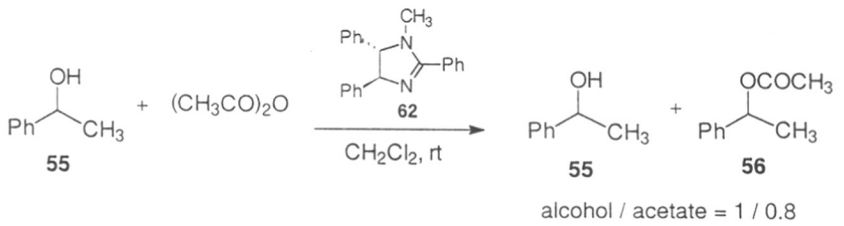
The attempted *N*-alkylation of amidine **61** by deprotonation with potassium hydride followed by treatment with methyl iodide generated a mixture of *N*-methylated as well as *C*-methylated products (^{1}H NMR spectra of the crude product) which were difficult to separate by conventional purification methods. *C*-alkylation could be suppressed by conducting the reaction at lower temperature. Thus, deprotonation of **61** with BuLi at -78 °C followed by alkylation with methyl iodide generated the 1,2-dimethyl-4,5-dihydro-4,5-diphenylimidazole **63** in 38% yield (Scheme 7).

Scheme 7.



Amidines **62** and **63** were used for the acylation of 1-phenylethyl alcohol (**55**). Reaction of 1-phenylethyl alcohol with acetic anhydride was catalyzed by amidine **62** to generate the acylated product **56** (Scheme 8).

Scheme 8.



alcohol / acetate = 1 / 0.8

While there was practically no reaction when alcohol and anhydride were alone mixed together (alcohol/acetate = 1/0.05 after 48 h), the reaction proceeded smoothly in the presence of one equivalent of amidine **62** and gave acetate in 43% yield (alcohol/acetate = 1/0.8). The acylation is proceeded faster than the one mediated by the alkylthioimidazoline **53** (alcohol/acetate = 1/0.8 for **62** and 1/0.1 for **53**). When a catalytic amount (0.2 eq.) of **62** was used in the reaction very little conversion alcohol to acetate was observed (alcohol/acetate = 1/0.05) which may be due to protonation of the amidine **62** by acetic acid.

Amidine **63** was also used for the acylation of 1-phenylethylalcohol. The acylation reaction proceeded with one equivalent of **63** to give alcohol/acetate in 1/0.4 ratio. The yield of the isolated acetate was 14% and the e.e. obtained was 6%. ($[\alpha]_D$ = -6.0 ^{0} (*c* 0.7, $CHCl_3$), Lit.[18] $[\alpha]_D$ = + 105.0 ^{0} (*c* 1.3, $CHCl_3$) for the *'R'* isomer of **56** with 97% e.e.). There was no rate enhancement when a combination of **63** and $HgCl_2$ was employed. The results of the acylation study are summarized in Table 2.

Table 2. Acylation of 1-phenylethyl alcohol catalyzed by amidines **62** and **63**.

Amidine	equiv. used	Salt/amine [a]	Time h	Alcohol 55/Acetate 56 [b]	% e.e. 63 [c]
-	-	-	48	1 / 0.05	-
62	1	-	48	1 / 0.8	-
62	0.2	-	48	1 / 0.05	-
63	1	-	48	1 / 0.4	6
63	1	$HgCl_2$	48	1 / 0.3	5
63	1	Et_3N	48	1 / 0.9	3

a: an equivalent amount of metal salt or amine (with respect to amidine) was used. b: the ratios alcohol/acetate are based on ^1H NMR spectra of the crude product. c: based on specific rotation.

The enantiomeric excess of the acetate isolated was quite low and the overall effeciency of the system was not much different from the alkylthioimidazoline study. Although the amidines are better catalysts than the related alkylthioimidazolines (**55/56** = 1/0.8 after 48 h as compared to 1/0.2) there is no significant improvement in the enantioselectivity of the acylation. Since a stoichiometric amount of **62** or **63** is necessary for a reasonable conversion rate, it is possible that the amidines function as conventional bases and their involvement in the acyl transfer step may not be as expected. The enantioselectivity for acylation is therefore low.

Conclusion:

The acylation of 1-phenylethyl alcohol is subject to catalysis by enantiomerically pure 2-alkylthio-4,5-dihydroimidazoles as well as 4,5-dihydroimidazoles (amidines). However, the acylation rate enhancement in the presence of these heterocycles is only marginal. The enantioselectivity of the acylation process is low.

Section 2. Application of chiral guanidines in stereoselective carbon-carbon bond forming reactions.

The following sections describe the synthesis of chiral guanidines and their applications in asymmetric nitroaldol and asymmetric Michael addition reactions.

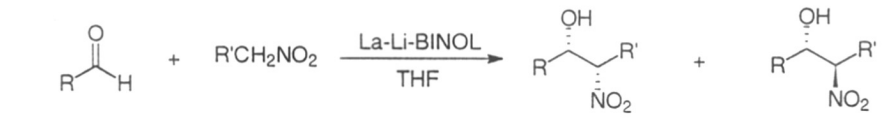
Introduction:

The catalytic asymmetric nitroaldol (Henry) reaction.

The nitroaldol reaction, one of the oldest carbon-carbon bond forming reactions, has found extensive use in organic synthesis.[19] The catalytic asymmetric version of the nitroaldol reaction has also been the focus of several recent investigations.

Shibasaki has developed a number of complexes derived from a rare earth metal chloride and (*R*)-binaphthol[20, 21] as catalysts for the asymmetric nitroaldol reaction. The nitroaldol adducts were obtained with 79-91% e.e. Bimetallic complexes such as the La-Li-(*R*)-BINOL complex[21] were examined for their effect on diastereoselectivity as well as enantioselectivity (Scheme 9). The reactions proceeded with good diastereoselectivity (3-9/1) as well as enantioselectivity (65-97% e.e. of the *syn* adduct).

Scheme 9.



R = 2-phenylethyl
Bu

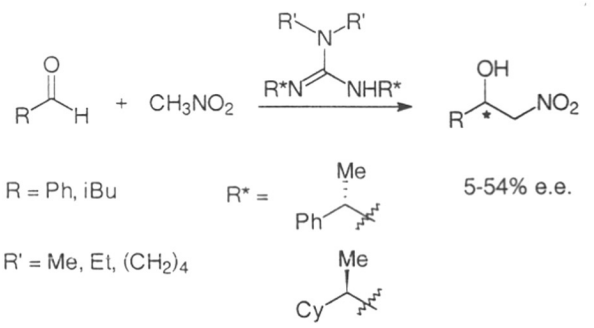
R' = Et, Pr

syn major

50 - 84% d.e., 65 - 97% e.e.

During the course of our investigations on the guanidine catalyzed asymmetric nitroaldol reaction, the use of enantiomerically pure guanidines as catalysts in the condensation of nitromethane with aldehydes was reported by Najera.[22] The nitroaldol adducts were obtained in 31-85% yield but the enantioselectivity was low (5-34%) and in one case 54% e.e was obtained at -78 °C (Scheme 10).

Scheme 10.

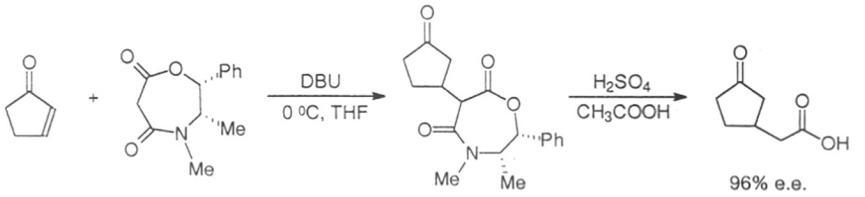


The catalytic asymmetric Michael addition reaction.

The asymmetric Michael addition reaction has also been the subject of several recent investigations and the topic has been reviewed recently.[23] Mukaiyama and co-workers have described the asymmetric synthesis of δ-oxocarboxylic acids by the Michael addition reaction involving a chiral malonic acid derivative.[24] The reaction of (2*R*, 3*S*)-dimethyl-5,7-dioxo-2-phenylperhydro-1,4-oxazepine (synthesized from methyl hydrogen malonate and (1*R*, 2*S*)-ephedrine hydrochloride) and 2-cyclopenten-1-one in the presence of DBU, followed by hydrolysis and decarboxylation of the resulting adduct generates 3-

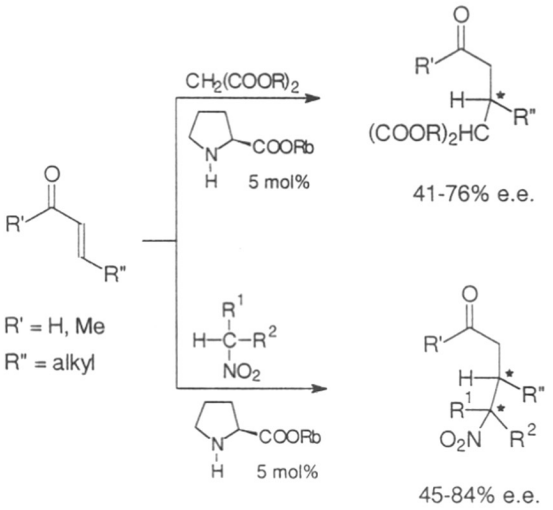
oxocyclopentane acetic acid with 96% e.e. (Scheme 11). Lower enantioselectivity (55%) was observed with 1-phenyl-2-buten-1-one as the Michael acceptor.

Scheme 11.



A catalytic enantioselective Michael addition reaction of a malonate ester to α, β unsaturated ketones and aldehydes has been reported (Scheme 12).[25]

Scheme 12.

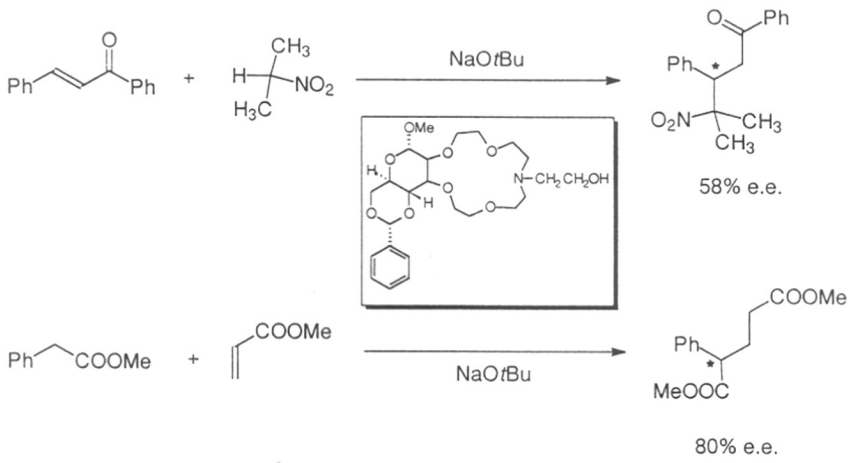


The catalyst in these reactions is the rubidium salt of L-proline. Adducts were obtained in 62-98% yield and 41-76% e.e.. L-proline salts have also been employed as catalysts for the addition of nitroalkanes to enones and enals.[26] In these studies, Michael adducts were obtained in 40-84% yield and with 45-84% e.e.

Taguchi and co-workers studied the enantioselective Michael addition reaction of malonates to enones.[27] A proline derived catalyst ((2-pyrrolidyl)alkyl ammonium hydroxide) was employed. The Michael adducts were obtained in 52-96% yield and with 21-69% e.e.

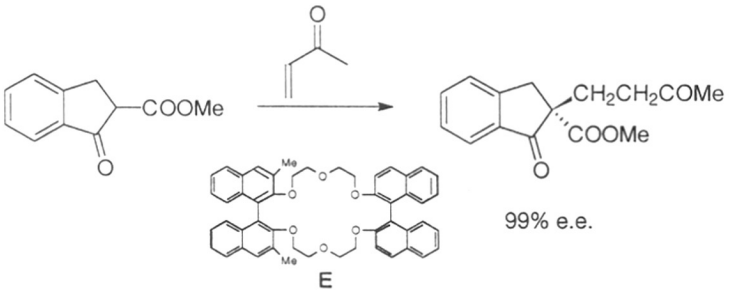
Crown ethers anellated to sugar units (Scheme 14) have been used as chiral complexing agents in the NaO*t*Bu catalyzed enantioselective Michael addition reactions of methyl phenylacetate to methyl acrylate[28] (up to 80% e.e.). Moderate asymmetric induction is observed in the Michael addition reaction of 2-nitropropane to chalcone (Scheme 13).[29]

Scheme 13.



Excellent asymmetric induction (99% e.e.) has been achieved in the Michael addition of the 2-methoxycarbonyl-1-indanone to methyl vinyl ketone in the presence of the BINOL derived crown ether **B** and KO*t*Bu at -78 ^{0}C (Scheme 14).[30]

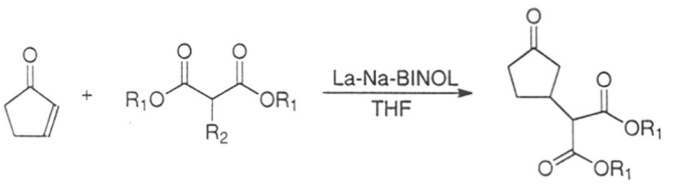
Scheme 14.



Rhodium (I)[31] and copper (II)[32] catalysts containing chiral ligands have also been employed as catalysts in Michael addition reactions with moderate to good enantioselectivity.

Shibasaki has examined the rare earth metal-BINOL complex catalyzed asymmetric Michael addition reaction. The La-BINOL complex catalyzes the addition of malonates to enones (62-92% e.e.).[33] A heterobimetallic catalyst (La-Na-BINOL complex) is more effecient and provides adducts with up to 92% e.e. (Scheme 15).[34]

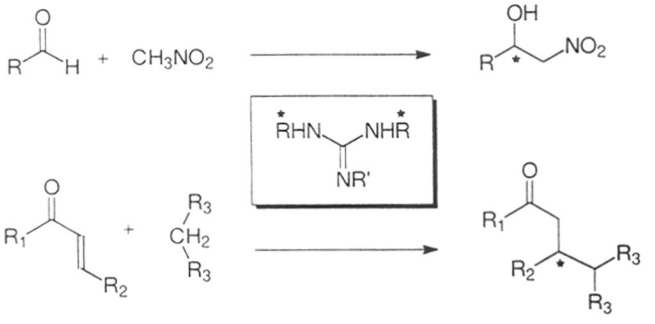
Scheme 15.



Objective:

The objective of our work was to study the utility of enantiomerically pure guanidines in stereoselective carbon-carbon bond forming reactions such as the asymmetric nitroaldol and Michael addition reactions (Figure 3).

Figure 3. Guanidine catalyzed carbon-carbon bond forming reactions.



Results and discussion:

Various methods are available for the synthesis of guanidines through intermediates such as thioureas,[35] aminoiminomethanesulfonic acids,[36] chloroformamidines,[37] dichloroisocyanides,[38] carbodiimides[39] or cyanamides.[40]

In the present study, several enantiomerically pure guanidines were synthesized from chiral 1,2-diamines. Reaction of (1*S*, 2*S*)-(-)-1,2-diphenylethanediamine **(13b)** with carbon disulfide in refluxing ethanol furnished the required thiourea **45** in 77% yield.[11] Similarly, thioureas **46** and **47** were prepared in 77 and 81% yield respectively. The thioureas were *S*-alkylated by using either methyl iodide to give the corresponding hydroiodide salts **48a-50a**, or with dimethyl sulfate to give the methylsulfate salts **48b** and **49b** respectively. The 2-methylthio-4,5-dihydroimidazole salts **48-50** were converted to the corresponding guanidines by reaction with methyl amine or an aromatic amine (Scheme 16). Table 3 summarizes the results for the synthesis of guanidines used in this study.

Scheme 16.

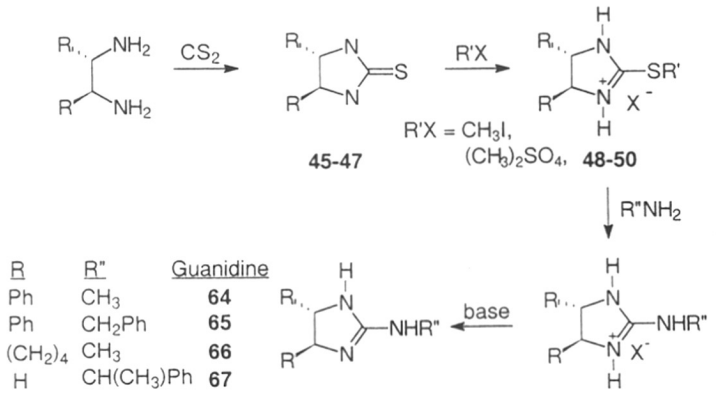


Table 3. Synthesis of chiral guanidines **64-67**.

Thiourea	Yield %	Salt	Yield %	Amine	Guanidine	Yield %
45	77	48	98	CH_3NH_2	64	90
45	77	48	98	$PhCH_2NH_2$	65	75
46	77	49	98	CH_3NH_2	66	72
47	81	50	83	$Ph(CH_3)CHNH_2$	67	92

Guanidines as catalysts in the enantioselective Nitroaldol reaction.

Initial investigations were conducted with guanidine **64** and it's effect on the condensation of benzaldehyde with nitromethane was studied as a function of solvent and temperature. The results are summarized in Table 4. The yield of the nitroalcohol **68** obtained varied from 19-94% (Scheme 17).

Scheme 17.

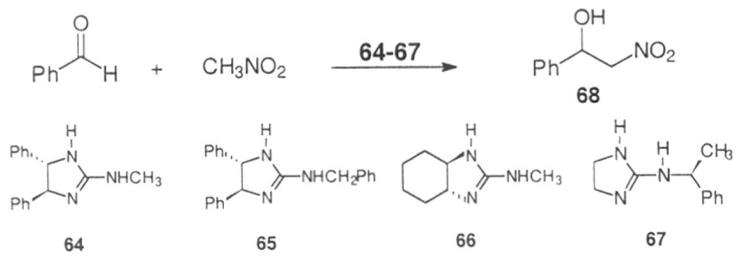


Table 4. Guanidine catalyzed enantioselective nitroaldol reaction.

No.	guanidine	equiv. of guanidine	Solvent	Time h	Temp. ^0C	Adduct % yield	Adduct [22] % e.e. [a] (config.)
1.	**64**	0.1	ether	24	25	71	3 *(S)*
2.	**64**	0.1	hexane	24	25	67	5 *(R)*
3.	**64**	1.0	hexane	8	25	34	3 *(R)*
4.	**64**	1.0	hexane	8	-40	19	5 *(R)*
5.	**64**	1.0	hexane	8	-78	16	6 *(R)*
6.	**64**	0.1	toluene	24	25	74	10 *(R)*
7.	**64**	0.1	nitromethane	24	25	79	4 *(R)*
8.	**64**	0.1	DMSO	24	25	94	1
9.	**64**	0.1	THF	4	25	62	5 *(R)*
10.	**64**	0.1	THF	24	25	80	7 *(R)*
11.	**64**	0.1	DME	24	25	72	1
12.	**64**	0.1	CH_2Cl_2	24	25	42	4 *(S)*
13.	**65**	0.1	hexane	24	25	50	3 *(R)*
14.	**66**	0.1	ether	24	25	53	9*(R)*
15.	**66**	0.1	hexane	24	25	25	3 *(S)*
16.	**66**	0.1	toluene	24	25	47	3 *(S)*
17.	**66**	0.1	nitromethane	24	25	70	2 *(S)*
18.	**66**	0.1	DMSO	24	25	98	7 *(R)*
19.	**66**	0.1	THF	24	25	82	3 *(R)*
20.	**66**	0.1	DME	24	25	50	9 *(R)*
21.	**66**	0.1	CH_2Cl_2	24	25	25	9 *(R)*
22.	**67**	0.1	hexane	24	25	38	4 *(S)*

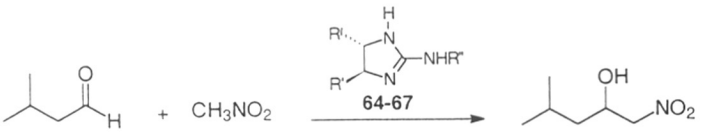
a: based on optical rotation.

The results indicate that the guanidines **64-67** are not effective asymmetric catalysts as evidenced by the low enantioselectivity of the process. Lowering the reaction temperature improves the selectivity marginally but slows down the reaction considerably (entries 3, 4, 5). The best result (10% e.e.) was obtained at ambient temperature with toluene as the solvent (entry 6).

Similar results were obtained with guanidines **65-67**. The effect of solvent was marginal in this case and the product e.e. ranges from 2-9%.

The guanidine catalyzed nitroaldol reaction of nitromethane and isovaleraldehyde was also examined (Scheme 18).

Scheme 18.



69

The enantiomeric excess in this case was also quite low thereby indicating that the nature of the aldehyde does not affect the stereoselectivity of the process. The results are summarized in Table 5.

Table 5. Enantioselective nitroaldol reaction catalyzed by guanidines.

No.	guanidine (equiv.)	Solvent	Time h	Temp. 0 °C	Adduct % yield	Adduct % e.e.[a]
1.	**64** (0.1)	toluene	24	25	47	6
2.	**65** (0.1)	toluene	24	25	62	6
3.	**67** (0.1)	toluene	24	25	24	9

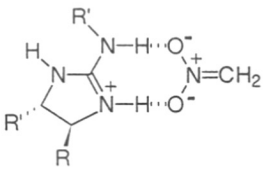
a: based on optical rotation.

In all of the nitroaldol reactions studied, the enantiomeric excess was very low (1-10%) as determined by the specific rotation of the product and hence an alternative verification of enantiomeric excess was not carried out.

One reason for the low selectivity may be an erosion of enantiomeric excess during the reaction due to the retro-nitroaldol process. However, this is probably not the case, since the observed enantiomeric excess is not dependent on the reaction time and yield as can be seen from entries 2-5, 9 and 10 in Table 4. This suggests that the lack of enantioselectivity is probably due to the absence of any direct influence of the stereogenic centers in the guanidine, which in turn is an outcome of the distance between these centers and the reaction site. If the reactive species is the nitronate ion which is hydrogen bonded to the guanidine,[41]

the chiral center in the guanidine is separated from the nitronate carbon by four atoms and may be too distant for effective asymmetric induction.

Figure 4. Hydrogen bonding of the nitronate ion with a C_2 symmetric guanidine.

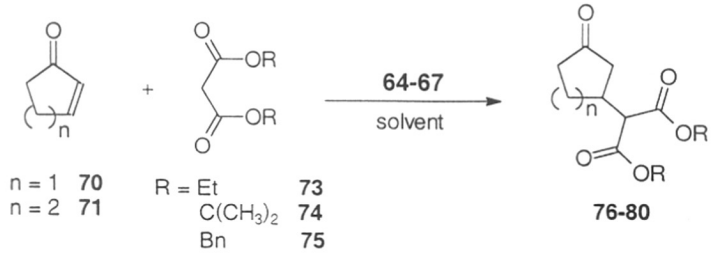


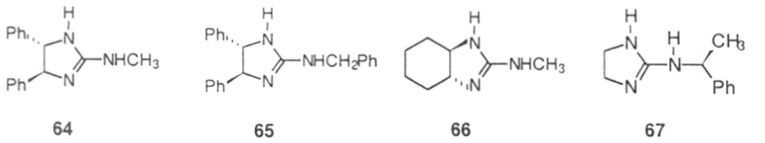
Guanidines as enantioselective catalysts in Michael addition reaction.

To the best of our knowledge, the guanidine catalyzed conjugate addition reaction, asymmetric or otherwise, is not reported. We chose to investigate this possibility with malonate esters as the nucleophilic component since their deprotonation with guanidines was expected to be quite facile.

Reaction of 2-cyclopenten-1-one **70** with diethyl malonate **73** in the presence of a catalytic amount of guanidine **64** (0.3 eq.) in THF did not generate any of the expected conjugate addition product. However, a change of solvent was beneficial and the reaction proceeded smoothly in solvents such as ethanol, benzene or 1,2-dichloroethane. Better yields were obtained in ethanol and hence it was the solvent of choice. A variety of substrates such as 2-cyclopenten-1-one **70**, 2-cyclohexen-1-one **71** and chalcone **72** were used in combination with nucleophiles such as diethyl malonate **73**, Meldrum's acid **74**, dibenzyl malonate **75** or nitromethane in presence of guanidines **64-67** (Scheme 19). The effect of temperature on the enantioselectivity of the Michael addition reaction was also examined. Table 6 summarizes the results for the enantioselective Michael addition reaction.

Scheme 19.





64 65 66 67

Table 6. Michael addition reaction catalyzed by guanidines **64-67**

No	enone	malonate	guanidine[a]	solvent	temp. °C	time h	Adduct (%yield)
1.	**70**	**73**	**64**	ethanol	0	72	**76** (63)
2.	**70**	**73**	**64**[b]	ethanol	0	15	**76** (58)
3.	**70**	**73**	**64**	ethanol	-24	144	**76** (50)
4.	**70**	**73**	**64**[b]	ethanol	-24	72	**76** (62)
5.	**70**	**74**	**64**	benzene	10	72	**77** (61)
6.	**70**	**73**	**67**	ethanol	0	72	**76** (84)
7.	**70**	**73**	**65**	ethanol	0	72	**76** (79)
8.	**70**	**75**	**64**	benzene	10	72	**78** (50)
9.	**71**	**73**	**64**	ethanol	0	96	**79** (50)
10.	**71**	**73**	**67**	ethanol	0	72	**79** (65)
11.	**71**	**73**	**65**	ethanol	0	72	**79** (50)
12.	**71**	**74**	**65**	ethanol	0	72	**80** (35)

a: 0.3 equivalents of guanidine were employed. b : pyrrolidine was used as an additive.

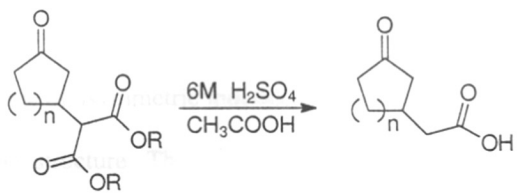
The yield of the conjugate addition reaction varied from 30 to 84% and lowering the reaction temperature slowed down the reaction considerably. Thus,

while a 66% yield of adduct **76** was obtained after 24h at ambient temperature, the reaction at -24 °C had to be conducted for 6 days to obtain a yield of 50%.

The use of pyrrolidine as an additive was also examined since previous studies[25] have suggested that conversion of the enone to an iminium species enhances it's electrophilicity. We reasoned that a catalytic amount of pyrrolidine would generate the requisite iminium species in a reversible fashion and enhance the rate of the reaction. This was indeed the case (entries 1/2 and 3/4 in Table 6) and reaction times were reduced at lower temperature. However there was a negligible effect on the enantioselectivity which may indicate that the pyrrolidine is functioning as a base rather than forming an iminium species from the enone.

The Michael adducts were hydrolyzed with concomitant decarboxylation to furnish the cycloalkanone 3-acetic acids **81** and **82** by heating in 6M H_2SO_4/CH_3COOH.[24] The acids were obtained in 15-60% yield.

Scheme 20.



76-79

n = 1 **81**
= 2 **82**

The enantioselectivity of the Michael addition process is based on the optical rotation of the cycloalkanone acetic acids. In most of the cases, the enantiomeric excess was quite low (3-23%) as judged by the specific rotation and an alternative determination of enantiomeric excess was not carried out. The results are summarized in Table 7.

Table 7. Hydrolysis of Michael adducts **76-79**.

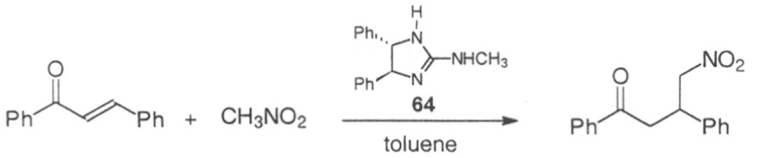
No.	guanidine	Adduct (% yield)	Acid	Acid % yield	Acid $[\alpha]_D^0$	Acid[42] % e.e. [b]
1.	**64**	**76** (63)	**81**	58	-6.6	12 (*S*)
2.	**64**[a]	**76** (58)	**81**	20	-1.6	3 (*S*)
3.	**64**	**76** (50)	**81**	40	-2.6	5 (*S*)
4.	**64**[a]	**76** (62)	**81**	60	-3.5	7 (*S*)
5.	**64**	**77** (61)	**81**	15	-6.7	13 (*S*)
6.	**67**	**76** (84)	**81**	54	-2.4	5 (*S*)
7.	**65**	**76** (79)	**81**	46	-6.0	11 (*S*)
8.	**64**	**78** (50)	**81**	22	-3.3	6 (*S*)
9.	**64**	**79** (50)	**82**	40	+0.9	8 (*R*)
10.	**67**	**79** (65)	**82**	55	+2.7	23 (*R*)
11.	**65**	**79** (50)	**82**	33	-2.5	19 (*S*)

a: In addition to guanidine, pyrrolidine was used as an additive in the conjugate addition reaction. b: based on specific rotation.

Reactions with cyclohexenone proceeded with slightly better stereoselection than those with cyclopentenone. The low enantioselectivity may be due to a retro-Michael reaction. However, even if operative, this process must be quite slow since the Michael adducts are obtained in good yield. It should be noted that the sense of asymmetric induction in the Michael addition is dependent on the guanidine structure. Thus, the enantioselectivity is reversed when the stereogenic center in the guanidine is shifted from the diamine portion (guanidine **65**, entry 11, Table 7) to the primary amine portion (guanidine **67**, entry 10, Table 7).

The reaction of chalcone **72** and nitromethane in the presence of **64** (0.3 equiv.) gave the Michael adduct **83** in 38% yield and 5% e.e. in the '*S*' enantiomer[43] (Scheme 21).

Scheme 21.



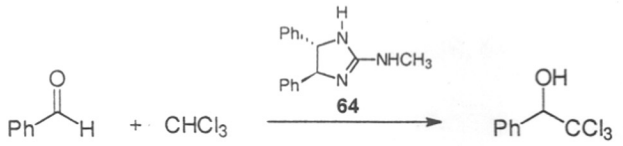
72 **83**

Deprotonation of chloroform by guanidines 64-67:

During the characterization of guanidines **64-67** by NMR spectroscopy we observed fairly intense signals due to $CHCl_3$ in both the ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum in CD_2Cl_2 clearly shows the signals due to the exchangeable N-H protons which are completely absent in the ^1H NMR spectrum in $CDCl_3$ (see pages 140 and 141). A plausible explanation is H/D exchange between the highly basic guanidines and $CDCl_3$. This suggested the interesting possibility of using the guanidines as chiral bases for the asymmetric synthesis of chiral trichloromethyl carbinols[44] which are useful synthetic intermediates.

As expected, guanidine **64** did catalyze the reaction of chloroform with benzaldehyde to give the adduct **84**. However, the reaction was very slow (<5% yield of **84**) and was therefore not investigated in detail (Scheme 22). The possibility of improving the process remains unexplored at present.

Scheme 22.



84

4. CONCLUSION

Enantiomerically pure C_2 symmetric 2-alkylthio-4,5-dihydroimidazoles, amidines and guanidines were synthesized from the corresponding vicinal diamines. The alkylthioimidazolines and amidines were examined as acyl transfer agents in the kinetic resolution of secondary alcohols. Acylation of 1-phenylethylalcohol in the presence of alkylthioimidazolines and amidines was slow and proceeded with low enantioselectivity. The guanidines were used as catalysts in the asymmetric nitroaldol and Michael addition reactions. Enantioselection was low for both these reactions which suggests that the stereogenic centers in the guanidine are far away from the reaction site. To the best of our knowledge, the guanidine catalyzed Michael addition reaction is not reported and the above study provides useful information regarding the structural features that will have to be incorporated into enantiomerically pure guanidines to achieve good levels of asymmetric induction.

5. EXPERIMENTAL

General experimental techniques have been described in the experimental section of Chapter 1.

General procedure for the synthesis of thioureas 45-47:[11]

To a cooled (5-10 ^{0}C) solution of the diamine in ethanol was added carbon disulfide. Initial addition was done slowly to avoid a vigorous initiation of the reaction. As the reaction initiated, the cooling bath was removed and the mixture was heated at 60 ^{0}C. The remaining carbon disulfide was added over a period of 30-40 min. After the addition was complete, the reaction mixture was heated to reflux for 18-48h and the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was concentrated and the residue was purified by either crystallization or by flash chromatography on silica gel.

(4*S*, 5*S*)-(-)-*trans*-4,5-Dihydro-4,5-diphenylimidazole-2-thione (45):[11]

The reaction of (1*S*, 2*S*)-(-)-1,2-diphenyl ethanediamine **(13b)** (0.64 g, 3 mmol), carbon disulfide (0.2 ml, 3.3 mmol) in anhydrous ethanol (20 ml) for 19h gave, after purification (SiO_2, petroleum ether/ethyl acetate, 3/1), 0.59 g (77%) of **45**.

mp: 198-199 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.3 (m, 6H, Ar*H*), 7.3-7.2 (m, 4H, Ar*H*), 6.7 (bs, 2H, N*H*), 4.8 (s, 2H, NC*H*).

IR (Nujol):

3166, 2854, 1524, 1277, 1200, 765, 701 cm^{-1}.

MS (EI, 70 eV):

m/z 57 (38), 69 (19), 79 (28), 89 (19), 97 (6), 106 (100), 121 (12), 148 (14), 165 (8), 183 (5), 254 (M^+, 33).

Analysis for $C_{15}H_{14}N_2S$:

Calcd. C, 70.83 H, 5.55 N, 11.01 S, 12.61

Found C, 70.74 H, 5.86 N, 11.16 S, 12.84

$[\alpha]_D$ = -58.7 ^{0} (*c* 0.2, $CHCl_3$).

(4*R*, 5*R*)-(+)-*trans*-4,5-Dihydro-4,5-tetramethyleneimidazole-2-thione (46):[11]

Reaction of (1*R*, 2*R*)-(+)-1,2-cyclohexyl diamine **(43)** (0.23 g, 2 mmol) (generated from (1*R*, 2*R*)-(+)-1,2-cyclohexyl diamine L-tartarate and potassium carbonate) and carbon disulfide (0.24 ml, 4 mmol) in ethanol (2 ml) for 46h gave after purification (SiO_2, petroleum ether/ethyl acetate, 3/1), 0.24 g (77%) of **46**.

mp: 146-147 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 6.5 (s, 2H, N*H*), 3.4-3.2 (m, 2H, NC*H*), 2.1-1.9 (m, 2H, Cy-C_αH), 1.9-1.6 (m, 2H, Cy-C_α*H*), 1.6-1.2 (m, 4H, Cy-C_β*H*).

IR (Nujol):

3260, 2880, 1400, 1320, 1230, 1190, 1155, 1120 cm^{-1}.

Analysis for $C_7H_{12}N_2S$:

Calcd. C, 53.81 H, 7.74 N, 17.93

Found C, 53.97 H, 7.28 N, 18.00

$[\alpha]_D$ = +52.4 ^{0} (*c* 1.0, $CHCl_3$).

4,5-Dihydroimidazole-2-thione (47):[45]

The reaction of ethylenediamine **(44)** (13 ml, 0.18 mol), carbon disulfide (12 ml, 0.2 mol) in ethanol-water (25+25 ml) for 14h gave, after work up 15.2 g (81%) of crystalline **47**.

mp: 198-199 ^{0}C. [Lit.[45] mp: 197-199 ^{0}C]

IR (Nujol):

3280, 2890, 1520, 1325, 1290, 1220, 1020, 935 cm^{-1}.

MS (EI, 70 eV):

m/z 59 (2), 73 (7), 102 (100).

Analysis for $C_3H_6N_2S$:

Calcd. C, 35.27 H, 5.92 N, 27.42

Found C, 35.45 H, 5.68 N, 27.60

General procedure for the synthesis of 2-methylthio-4,5-dihydroimidazole salts:[12]

To a solution of thiourea in anhydrous methanol, benzene or THF, was added methyl iodide or dimethyl sulfate. The reaction mixture was heated to reflux for 1-3h, concentrated and dried thoroughly to give the requisite salts which were pure by ^{1}H NMR spectroscopy.

(4*S*, 5*S*)-(-)-*trans*-2-Methylthio-4,5-dihydro-4,5-diphenylimidazole hydroiodide (48a):[12]

The reaction of (4*S*, 5*S*)-(-)-*trans*-4,5-dihydro-4,5-diphenylimidazole-2-thione **(45)** (0.25 g, 1 mmol) with methyl iodide (0.15 ml, 2 mmol) in THF (5 ml) for 2.5h at 70-75 ^{0}C gave 0.4 g (quantitative) of **48a.**

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.3 (m, 4H, Ar*H*), 7.3-7.15 (m, 6H, Ar*H*), 5.1 (s, 2H, NC*H*), 2.85 (s, 3H, SCH_3)

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 170.3 (N-*C*=N), 136.7 (Ar*Cipso*), 128.7, 126.0 (Ar*C*), 68.9 (N*C*H), 15.6 (S*C*H_3).

IR ($CHCl_3$):

3030, 2880, 1532, 1164, 760, 698 cm^{-1}.

MS (EI, 70 eV):

m/z 55 (28), 69 (18), 79 (22), 89 (22), 106 (100), 121 (21), 127 (34), 142 (42), 148 (56), 163 (15), 254 (45), 396 (M^+, <1).

(4*S*, 5*S*)-(-)-*trans*--2-Methylthio-4, 5-dihydro-4,5-diphenylimidazole methyl sulfate (48b):

The reaction of (4*S*, 5*S*)-(-)-*trans*-4,5-dihydro-4,5-diphenylimidazole-2-thione **(45)** (0.89 g, 3.5 mmol) with dimethyl sulfate (0.17 ml, 1.8 mmol) in benzene (10 ml) for 2h at 85-90 ^{0}C gave 1.18 g (89%) of **48b**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 9.95 (bs, 1H, N*H*), 7.4-7.25 (m, 5H, Ar*H*), 7.25-7.0 (m, 5H, Ar*H*), 5.0 (s, 2H, NC*H*), 3.25 (s, 3H, $CH_3SO_4^-$), 2.6 (s, 3H, SCH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 170.6 (N=*C*-S), 137.4 (Ar*Cipso*), 128.6, 125.9 (Ar*C*), 69.6 (N*C*H), 53.9 ($CH_3SO_4^-$), 13.3 (S*C*H_3).

IR ($CHCl_3$):

2900, 1544, 1496, 1456, 1256, 1196, 1058, 1008, 840 cm^{-1}.

MS (EI, 70 eV):

m/z 77 (4), 89 (6), 104 (8), 117 (6), 121 (22), 148 (100), 163 (45), 219 (3), 268 (24).

(4*R*, 5*R*)-(+)-*trans*-2-Methylthio-4,5-dihydro-4,5-tetramethyleneimidazole hydroiodide (49a):

The reaction of **46** (0.56 g, 3.6 mmol) with methyl iodide (0.25 ml, 4 mmol) in methanol (2 ml) for 3h at 80-90 ^{0}C gave 1.05 g (98%) of **49a.**

^{1}H NMR (200 MHz, $CDCl_3$):

δ 3.7-3.4 (m, 2H, NC*H*), 2.9 (s, 3H, SCH_3), 2.6-2.4 (m, 2H, Cy-C$_\alpha$*H*), 2.0-1.75 (m, 2H, Cy-C$_\alpha$*H*), 1.75-1.25 (m, 4H, Cy-C$_\beta$*H*).

IR ($CHCl_3$):

3020, 2956, 1512, 1358, 1144, 1096, 1066, 668 cm^{-1}.

(4*R*, 5*R*)-(+)-*trans*-2-Methylthio-4,5-dihydro-4,5-tetramethyleneimidazole methyl sulfate (49b):

The reaction of **46** (0.15 g, 1 mmol) with dimethyl sulfate (0.05 ml, 0.5 mmol) in benzene (5 ml) for 2h at 85-90 ^{0}C gave 0.28 g (quantitative) of **49b**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 9.75 (s, 1H, N*H*), 3.75 (s, 3H, C$H_3SO_4^-$), 3.5-3.4 (m, 2H, NC*H*), 2.75 (s, 3H, SCH_3), 2.5-2.35 (m, 2H, Cy-C$_\alpha$*H*), 1.95-1.85 (m, 2H, Cy-C$_\alpha$*H*), 1.65-1.4 (m, 2H, Cy-C$_\beta$*H*), 1.4-1.2 (m, 2H, Cy-C$_\beta$*H*).

IR ($CHCl_3$):

3028, 2840, 1598, 1580, 1494, 1452, 1346, 1278, 1242, 1184, 1156, 1078, 1006, 874 cm^{-1}.

2-Methylthio-4,5-dihydroimidazole hydroiodide (50a):[45]

The reaction of 4,5-dihydroimidazole-2-thione **(47)** (10.2 g, 0.1 mole) with methyl iodide (6.9 ml, 0.11 mole) in methanol (10 ml) for 3h at 75-80 ^0C gave 20.3 g (83%) of **50a.**

mp: 140-141 ^0C.

^1H NMR (90 MHz, D_2O):

δ 3.9 (s, 4H, CH_2), 2.6 (s, 3H, SCH_3).

^{13}C NMR (50.3 MHz, D_2O):

δ 172.0 (N-*C*=N), 46.5 (CH_2), 15.5 (SCH_3).

IR (Nujol+$CHCl_3$):

2880, 1635, 1560, 1530, 1515, 1420, 1310, 1200, 1160, 1010, 920 cm^{-1}.

MS (EI, 70 eV):

m/z 72 (5), 87 (4), 102 (36), 116 (11), 127 (66), 142 (100).

Analysis for $C_4H_9IN_2S$:

Calcd. C, 19.68 H, 3.72 N, 11.48

Found C, 19.79 H, 3.49 N, 11.67

General procedure for the synthesis of 2-methylthioimidazolines 51, 52:

The 2-methylthioimidazoline hydroiodide or methylsulfate salt was dissolved in dichloromethane and the resultant organic phase was washed 2-3 times with 5% aqueous sodium carbonate solution followed by water and brine.

The solution was dried over anhydrous sodium sulfate and concentrated to give the free imidazoline that was pure by ^{1}H NMR spectroscopy.

(4*S*, 5*S*)-(-)-*trans*-2-Methylthio-4,5-dihydro-4,5-diphenylimidazole (51):[12]

(4*S*,5*S*)-(-)-*trans*-2-Methylthio-4,5-dihydro-4,5-diphenylimidazole hydroiodide **(48a)** (0.98 g, 2.5 mmol) in dichloromethane (10 ml) was washed with 5% aqueous sodium carbonate solution (3 x 5 ml) to give 0.61 g (91%) of **51**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.1 (m, 10H, Ar*H*), 4.75 (bs, 2H, NC*H*), 2.65 (s, 3H, SCH_3), 1.75 (bs, 1H, N*H*).

IR ($CHCl_3$):

2934, 2895, 1572, 1493, 1454, 1412, 1173, 1030, 995, 970, 926 cm^{-1}.

MS (EI, 70 eV):

m/z 63 (9), 77 (21), 89 (18), 104 (12), 121 (18), 148 (100), 163 (44), 268 (M^+, 26).

(4*R*,5*R*)-(+)-*trans*-2-methylthio-4,5-dihydro-4,5-tetramethyleneimidazole (52):

(4*R*,5*R*)-(+)-*trans*-2-Methylthio-4,5-dihydro-4,5-tetramethyleneimidazole hydroiodide **(49a)** (0.45 g, 1.5 mmol) in dichloromethane (5 ml) was washed with 5% aqueous sodium carbonate solution (2 x 5 ml) to give 0.19 g (56%) of **52**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 3.1-3.0 (m, 2H, NC*H*), 2.5 (s, 3H, SCH_3), 2.3-2.1 (m, 2H, Cy-C$_\alpha$*H*), 1.9-1.7 (m, 2H, Cy-C$_\alpha$*H*), 1.6-1.2 (m, 4H, Cy-C$_\beta$*H*).

IR (Nujol):

3140, 2880, 1545, 1480, 1400, 1390, 1350, 1330, 1280, 1250, 1230, 1200, 1160, 1120, 1100, 1060, 1000, 950, 840, 710, 700 cm^{-1}.

General procedure for the preparation of 1-methyl-2-methylthio imidazolines 53, 54:

To a cooled (0 ^{0}C) suspension of potassium hydride in anhydrous THF (5 ml) was added a solution of 2-methylthioimidazoline in THF (5 ml) dropwise The mixture was stirred at 0 ^{0}C for 20-30 min. Methyl iodide was added and stirring was continued for 3-5h. Cold water was added to the reaction mixture which was then concentrated followed by partitioning of the residue in water and dichloromethane. The organic phase was dried, concentrated and the residue was purified by flash chromatography on silica gel to give 1-methyl-2-methylthioimidazoline.

(4*S*,5*S*)-(-)-1-Methyl-2-methylthio-4,5-dihydro-4,5-diphenylimidazole (53):

The deprotonation of imidazoline **51** (0.61 g, 2.5 mmol) in anhydrous THF (4 ml) with potassium hydride (0.3 g, 2.5 mmol) in anhydrous THF (2 ml) followed by reaction with methyl iodide (0.15 ml, 2.5 ml) for 4.5h, gave after purification (SiO_2, petroleum ether/ethyl acetate, 7/3), 0.52 g (74%) of **53**.

mp: 98-100 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4- 7.1 (m, 10H, Ar*H*), 4.8 (d, J = 12.5, 1H, NC*H*), 4.2 (d, J = 12.5, 1H, NC*H*), 2.7 (s, 3H, NCH_3), 2.65 (s, 3H, SCH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 165.9 (N-*C*=N), 143.0 (Ar*Cipso*), 140.0 (Ar*Cipso*), 128.7, 128.3, 127.8, 127.1, 126.9 (Ar*C*), 79.1, 77.9 (N*C*H), 32.9 (N*C*H_3), 14.0 (S*C*H_3).

IR (Nujol):

2880, 1580, 1395, 1350, 1290, 1270, 1215, 1125, 1090, 1020, 980, 800, 770 cm^{-1}.

MS (EI, 70 eV):

m/z 89 (4), 121 (7), 148 (100), 163 (55), 178 (7), 282 (M^+, 20).

Analysis for $C_{17}H_{18}N_2S$:

Calcd. C, 72.30 H, 6.42 N, 9.92 S, 11.35

Found C, 72.21 H, 6.39 N, 9.84 S, 11.37

$[\alpha]_D$ = -54.9 ^{0} (*c* 1.0, $CHCl_3$).

(4*R*, 5*R*)-(+)-1-Methyl-2-methylthio-4,5-dihydro-4,5-tetramethyleneimidazole (54):

The deprotonation of imidazoline **52** (0.2 g, 1.2 mmol) in anhydrous THF (3 ml) with potassium hydride (0.18 g, 1.5 mmol) in anhydrous THF (2 ml) followed by reaction with methyl iodide (0.12 ml, 2 ml) for 2.5h, gave after purification by Kugelrohr distillation (bp: 125 ^{0}C / 5 mm Hg), 0.19 g (86%) of **54**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 3.0-2.9 (m, 1H, NC*H*), 2.65 (s, 3H, NCH_3), 2.45 (s, 3H, SCH_3), 2.45-2.4 (m, 1H, NC*H*) 2.4-2.25 (m, 1H, Cy-C$_\alpha$*H*), 2.1-2.0 (m, 1H, Cy-C$_\alpha$*H*), 1.9-1.8 (m, 2H, Cy-C$_\alpha$*H*), 1.45-1.15 (m, 4H, Cy-C$_\beta$*H*)

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 168.9 (N-*C*=N), 73.1, 70.7 (N*C*H), 32.6 (N*C*H_3), 30.9, 28.5, 25.2, 24.2 (*C*H_2), 13.5 (S*C*H_3)

IR (Neat):

3400, 2950, 2880, 1720, 1545, 1460, 1390, 1310, 1270, 1230, 1210, 1160, 1130, 1095, 1070, 780, 680 cm^{-1}.

MS (FAB+, NBA):

m/z 55 (5), 81 (6), 88 (6), 110 (5), 155 (8),185 (MH^+).

HRMS (FAB+) for $C_9H_{17}N_2S$ (M+H):

Calcd. 185.11125

Found 185.11126

$[\alpha]_D$ = +27.4 ^{0} (*c* 1.23, $CHCl_3$).

General procedure for the acylation of 1-phenylethyl alcohol (55):

To a solution of the alcohol and amidine or 2-alkylthioimidazoline in dichloromethane was added acetic anhydride. The mixture was stirred at ambient temperature for 24-48h and diluted with dichloromethane. The solution was washed successively with 0.5 N HCl, water, brine, dried over anhydrous sodium sulfate and concentrated to give a mixture of alcohol and acetate, which was analyzed for acetate/alcohol ratio by ^{1}H NMR spectroscopy. Pure acetate was isolated by flash chromatography on silica gel.

1-Phenylethyl acetate (56):[18]

The reaction of 1-phenethyl alcohol **(55)** (36 mg, 0.3 mmol) and acetic anhydride (30 mg, 0.3 mmol) in the presence of amidine **63** (75 mg, 0.3 mmol) in

dichloromethane gave after purification (SiO_2, petroleum ether/ethyl acetate, 95/5), 7 mg (15%) of **56**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.45-7.25 (m, 5H, Ar*H*), 5.9 (q, *J* = 8, 1H, C*H*), 2.1 (s, 3H, COCH_3), 1.55 (d, *J* = 8, 3H, CH_3).

IR (Neat):

3020, 1850, 1750, 1510, 1470, 1390, 1250, 1220, 1140, 1070, 1040, 960, 910, 880 cm^{-1}.

MS (EI, 70 eV):

m/z 77 (35), 104 (100), 122 (60), 164 (M^+, 28).

$[\alpha]_D$ = - 6.1 ^{0} (*c* 0.7, $CHCl_3$), e.e. = 6% (Lit.[18] $[\alpha]_D$ = + 105.1 ^{0} (c = 1.3, $CHCl_3$) for *'R'* isomer with 97% e.e.).

Benzenecarboximidic acid, ethyl ester hydrochloride (58):[16]

Through a solution of anhydrous benzonitrile (20 ml, 0.2 mole) and anhydrous ethanol (12 ml, 0.21 mole) was passed dry HCl gas for 3h. The crystalline product appeared in 2 days which was filtered and dried to give 36.6 g (98%) of **58**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ12.6 (bs, 1H, N*H*), 11.9 (bs, 1H, N*H*), 8.4-8.3 (d, *J* = 7, 2H, Ar*H*), 7.7-7.6 (m, 1H, Ar*H*), 7.6-7.45 (m, 2H, Ar*H*), 4.9 (q, *J* = 8.7, 2H, OCH_2), 1.65 (t, *J* = 8.7, 3H, CH_3).

IR ($CHCl_3$):

3020, 2880, 1635, 1440, 1390, 1360, 1080, 1010, 870 cm^{-1}.

Methanecarboximidic acid, ethyl ester hydrochloride (59):[16]

Through a solution of anhydrous acetonitrile (52 ml, 0.99 mole) and anhydrous ethanol (59 ml, 1.05 mole) was passed dry HCl gas for 4.5 h. The crystalline product appeared in 2 days which was filtered and dried to give 41.5 g (34%) of **59**.

^{1}H NMR (90 MHz, $CDCl_3$):

δ 12.1 (bs, 1H, N*H*), 11.3 (bs, 1H, N*H*), 4.55 (q, J = 8, 2H, OCH_2), 2.46 (s, 3H, CH_3), 1.46 (t, J = 8, 3H, CH_3).

IR (Nujol):

2880, 1660, 1620, 1580, 1500, 1440, 1400, 1170, 1130, 1030, 960, 880, 860, 820 cm^{-1}.

General procedure for the preparation of amidines 60, 61:

To a mixture of (*S*,*S*)-(-)-1,2-diphenylethanediamine and the appropriate imidate hydrochloride was added dry ethanol. After stirring for 1h, a homogeneous solution was obtained which was heated to reflux for 4-6h. The reaction mixture was concentrated and the residue was dissolved in dichloromethane. The organic phase was successively washed with 5% aqueous sodium carbonate solution (2-3 times), water and brine. Concentration of the organic phase gave a solid which was recrystallized from toluene.

(4*S*, 5*S*)-(-)-4,5-Dihydro-2,4,5-triphenylimidazole (60):[17]

The reaction of (*S*,*S*)-(-)-1,2-diphenylethanediamine **(13b)** (0.53 g, 2.5 mmol) and benzenecarboximidic acid ethyl ester hydrochloride **(58)** (0.46g, 2.5 mmol) in dry ethanol (10 ml) gave after 5h, 0.53 g (72%) of **60**.

mp: 181-182 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.0-7.9 (m, 2H, Ar*H*), 7.55-7.4 (m, 3H, Ar*H*), 7.4-7.25 (m, 10H, Ar*H*), 4.9 (bs, 2H, NC*H*), 2.0-1.8 (broad, 1H, N*H*).

IR (Nujol):

2880, 1610, 1580, 1520, 1350, 1290, 1210, 1030, 770, 710 cm^{-1}.

MS (EI, 70 eV):

m/z 63 (5), 77 (8), 89 (32), 104 (8), 166 (16), 194 (100), 298 (M^+, 18).

$[\alpha]_D$ = -54.3 ^{0} (*c* 1.1, EtOH).

(4*S*, 5*S*)-(-)-2-Methyl-4,5-dihydro-4,5-diphenylimidazole (61):[17]

The reaction of (*S*,*S*)-(-)-1,2-diphenylethanediamine **(13b)** (0.8 g, 3.8 mmol) and methanecarboximidic acid ethyl ester hydrochloride **(59)** (0.5 g, 4 mmol) in dry ethanol (5 ml) gave after 48h, 0.91 g (quantitative) of **61**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4-7.1 (m, 10H, Ar*H*), 4.7 (s, 2H, NC*H*), 3.6-3.4 (broad, 1H, N*H*), 2.1 (s, 3H, CH_3).

IR (Nujol):

2860, 1630, 1505, 1465, 1440, 1390, 1360, 1315, 1290, 1210, 1040, 990, 770, 710 cm^{-1}.

MS (EI, 70 eV):

m/z 63 (4), 77 (6), 90 (34), 104 (12), 131 (100), 165 (5), 236 (M^+, 36).

$[\alpha]_D$ = -180.9 ^{0} (*c* 1.1, EtOH).

1-Methyl-4,5-dihydro-2,4,5-triphenylimidazole (62):

To a cooled (0 ^{0}C) suspension of potassium hydride (0.23 g, 2 mmol) in anhydrous THF (5 ml) was added solution of amidine **60**(0.6 g, 2 mmol) in THF (5 ml) dropwise. A yellow solution was obtained. The reaction mixture was stirred at 0 ^{0}C for 20 min, methyl iodide (0.6 ml, 10 mmol) was added and stirring was continued at 0 ^{0}C for 2h., cold water was added and the mixture was concentrated The residue obtained was partitioned in water and ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, concentrated and the residue (0.61 g) was purified (SiO_2, petroleum ether/ethyl acetate, 7/3) to give 0.48 g (77%) of **62** as an oil.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.8-7.75 (m, 2H, Ar*H*), 7.55-7.45 (m, 3H, Ar*H*), 7.45-7.25 (m, 10H, Ar*H*), 5.0 (d, *J* = 10.8, 1H, NC*H*), 4.3 (d, *J* = 10.8, 1H, NC*H*), 2.75 (s, 3H, CH_3).

IR ($CHCl_3$):

3040, 1620, 1600, 1510, 1420, 1350, 1300, 1230, 1080, 1040, 950, 830, 780, 710, 680 cm^{-1}.

(4*S*, 5*S*)-(-)-1,2-Dimethyl-4,5-dihydro-4,5-diphenylimidazole (63):

To a solution of amidine **61** (0.46 g, 2 mmol) in dry THF (5 ml) at -78 ^{0}C (dry ice/acetone bath), was added n-butyllithium (1.5 ml, 1.5M solution in hexane, 2.25 mmol) and the mixture was stirred for 20 min. Methyl iodide (0.12 ml, 2 mmol) was added and the reaction mixture was stirred for 2.5h at -78 ^{0}C. The reaction was worked up by concentration followed by partitioning in water and dichloromethane. The organic phase was concentrated and the residual solid

obtained (0.45 g) was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate/aqueous ammonia, 95/5/5) to furnish 0.18 g (38%) of **63**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4-7.2 (m, 10H, Ar*H*), 4.8 (d, J = 10.4, 1H, NC*H*), 4.15 (d, J = 10.4, 1H, NC*H*), 2.7 (s, 3H, NCH_3), 2.15 (s, 3H, CCH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 164.0 (N-*C*=N), 143.5 (Ar*Cipso*), 141.0 (Ar*Cipso*), 128.7, 128.3, 127.8, 127.1, 126.9, 126.8 (Ar*C*), 77.6, 77.3 (N*C*H), 32.2 (NCH_3), 14.4 (CCH_3).

IR ($CHCl_3$):

2940, 1620, 1420, 1000, 710 cm^{-1}.

MS (FAB+, NBA):

m/z 56 (16), 91 (7), 131 (12), !73 (7), 251 (MH^+).

HRMS (FAB+) for $C_{17}H_{19}N_2$ (M+H):

Calcd. 251.15482

Found 251.15476

$[\alpha]_D$ = -73.2 ^{0} (*c* 1.1, EtOH).

General procedure for the synthesis of guanidines 64, 66:

To a solution of the 2-methylthio-4,5-dihydro-iimdazole hydroiodide or methyl sulfate salt in ethanol was added 40% aqueous solution of methylamine in excess. The reaction mixture was heated at 50 ^{0}C. The reaction was monitored by TLC, aqueous methylamine was added to the reaction mixture periodically and heating was continued for 48-72h. After completion of the reaction, the mixture was concentrated and dried thoroughly. The residue was suspended in water and

the mixture was cooled to 0 ^{0}C and excess 4N NaOH solution was added. The resulting mixture was extracted with ethyl acetate or dichloromethane. The combined organic extracts were washed with water, brine, dried and concentrated to give the required guanidine which was pure by ^{1}H NMR spectroscopy.

(4*S*,5*S*)-(-)- 2-Methylamino-4,5-dihydro-4,5-diphenylimidazole (64):[12]

The reaction of (4*S*, 5*S*)-(-)-2-methylthio-4,5-dihydro-4,5-diphenylimidazole hydroiodide **(48a)** (0.58 g, 1.5 mmol) and 40% aqueous methyl amine solution (1 ml, added in three portions) in ethanol (5 ml) at 50 ^{0}C for 24h, gave 0.34 g (90%) of **64**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.35-7.15 (m, 10 H, Ar*H*), 4.5 (s, 2H, NC*H*), 2.75 (s, 3H, NCH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 162.2 (N-*C*=N), 143.4 (Ar*Cipso*), 128.1, 126.9, 126.2 (Ar*C*), 72.6 (N*C*H), 28.6 (CH_3).

IR (Nujol):

3385, 2853, 2731, 1614, 1556, 1416, 1273, 1157, 1018, 764, 698 cm^{-1}.

MS (EI, 70 eV):

m/z 77 (20), 91 (8), 106 (100), 117 (23), 131 (82), 145 (52), 152 (5), 165 (8), 178 (8), 251 (M^+, 37).

HRMS (FAB+) for $C_{16}H_{18}N_3$ (M+H):

Calcd. 252.15007

Found 252.15010

$[\alpha]_D$ = -44.8 ^{0} (*c* 1.2, EtOH).

(4*R*, 5*R*)-(+)-2-Methylamino-4,5-dihydro-4,5-tetramethyleneimidazole (66):

The reaction of (4*R*, 5*R*)-(+)-2-methylthio-4,5-dihydro-4,5-tetramethyleneimidazole methyl sulfate **(49b)** (0.28 g, 1 mmol) and 40% aqueous methyl amine solution (0.3 ml, added in portions periodically) in ethanol (3 ml) at 50 ^{0}C for 48h, gave 0.11 g (72%) of **66**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 3.15-3.05 (m, 2H, NC*H*), 2.85 (s, 3H, NCH_3), 2.2-2.1 (m, 2H, Cy-C$_\alpha$*H*), 1.85-1.75 (m, 2H, Cy-C$_\alpha$*H*), 1.5-1.2 (m, 4H, Cy-C$_\beta$*H*)

IR (Nujol):

3320, 1690, 1600, 1580, 1430, 1230, 1170 cm^{-1}.

MS (FAB+, NBA):

m/z 57 (5), 81 (5), 98 (5), 110 (4), 154 (MH^+)

HRMS (FAB+) for $C_8H_{16}N_3$ (M+H):

Calcd. 154.13442

Found 154.13440

$[\alpha]_D$ = +40.0 ^{0} (*c* 0.9, EtOH).

General procedure for the synthesis of guanidines 65, 67:

To a solution of 2-methylthio-4,5-dihydroimidazole hydroiodide or methyl sulfate salt in anhydrous acetonitrile was added trimethyl amine followed by the appropriate amine and the reaction mixture was heated to reflux for 12-14h. During this period, argon was continuously bubbled through the reaction mixture to remove the methanethiol generated in the reaction. After the reaction was complete, the mixture was cooled and dry ether was added. The guanidinium salt separated out as an oil. The salt was dissolved in dichloromethane and

washed successively with 4N NaOH, water and brine. The organic phase was concentrated to give the requisite guanidine.

(4*S*, 5*S*)-(-)- 2-Benzylamino-4,5-dihydro-4,5-diphenylimidazole (65):

The reaction of (4*S*, 5*S*)-(-)-2-methylthio-4,5-dihydro-4,5-diphenyl imidazole hydroiodide **(48a)** (0.99 g, 2.5 mmol), benzylamine (0.27 ml, 2.5 mmol), and triethylamine (0.35 ml, 2.5 mmol) in acetonitrile (5 ml) at 90 ^{0}C for 14h, gave after purification by conventional chromatography (basic alumina, ethyl acetate/methanol, 4/1) 0.61 g (75%) of **65**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4-7.15 (m, 8H, Ar*H*), 7.1-7.0 (m, 2H, Ar*H*), 4.45 (s, 2H, NC*H*), 4.3-4.2 (AB system, J = 12, 2H, PhCH_2).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 164.9 (N-*C*=N), 141.4 (Ar*Cipso*), 137.9 (Ar*Cipso*), 128.6, 127.8, 127.5, 127.2, 126.2 (Ar*C*), 70.5 (N*C*H), 46.7 (Ph*C*H$_2$).

IR ($CHCl_3$):

3050, 2860, 1690, 1620, 1510, 1470, 1370, 1300, 1230, 1040, 930 cm^{-1}.

MS (FAB+, NBA):

m/z 55 (8), 77 (7), 91 (46), 106 (13), 131 (7), 165 (5), 196 (7), 250 (5), 328 (MH^+).

HRMS (FAB+) for $C_{22}H_{22}N_3$ (M+H):

Calcd. 328.18137

Found 328.18133

$[\alpha]_D$ = - 43.1 ^{0} (*c* 1.04, EtOH).

(2'*S*)-(-)-2-(2'-Methyl)-benzylamino-4,5-dihydroimidazole (67):

The reaction of 2-methylthio-4,5-dihydroimidazole hydroiodide **(50a)** (1.22 g, 5 mmol), (*S*)-(-)-1-methyl benzylamine (0.65 ml, 5 mmol), and triethylamine (0.7 ml, 5 mmol) in acetonitrile (10 ml) at 90 ^{0}C for 14h, gave 0.87 g (92%) of **67**. An analytical sample was obtained by recrystallization of the picrate salt. When required, the guanidine was obtained by neutralization of an appropriate amount of the picrate salt with NaOH and used as such.

^{1}H NMR (200 MHz, $CDCl_3$):

Mixture of tautomers:

δ 7.3-7.1 (m, 5H, Ar*H*), 4.8-4.6 (m,1H, PhC*H*), 3.8-3.3 (m, 4H, CH_2CH_2), 1.45 (d, 3H, CH_3)

^{13}C NMR (50.3 MHz, $CDCl_3$):

Mixture of tautomers:

δ 159.9, 158.4 (N-C=N), 145.2, 143.3 (Ar*Cipso*), 128.8, 128.4, 128.3, 127.1, 126.5, 125.7, 125.4 (Ar*C*), 53.4, 52.7 (*C*H), 46.3, 45.8, 43.8 (CH_2), 24.6, 23.8 (CH_3).

IR (Nujol):

3400, 1670, 1580, 1290, 1090, 770, 710 cm^{-1}.

MS (EI, 70 eV):

m/z 72 (8), 79 (18), 87 (10), 100 (8), 106 (100), 116 (31), 120 (48), 134 (7), 188 (M-1, 3)

Analysis for $C_{17}H_{18}N_6O_7$: (Guanidium picrate derivative)

Calcd. C, 48.80 H, 4.34 N, 20.09

Found C, 48.40 H, 4.45 N, 19.79

$[\alpha]_D$ = - 40.0 ^{0} (*c* 1.1, EtOH).

General procedure for the nitroaldol reaction:[22]

The aldehyde was dissolved in an organic solvent and guanidine was added to the solution followed by slow addition of nitromethane. The reaction mixture was stirred at ambient temperature for 24h, concentrated, and the residue was dissolved in dichloromethane. The dichloromethane solution was washed successively with 0.5N HCl, water, brine, dried and concentrated to give the crude product which was purified by flash chromatography on silica gel.

2-Nitro-1-phenylethan-1-ol (68):[22]

The reaction of benzaldehyde (0.1 ml, 1 mmol) and nitromethane (0.1 ml, 1.5 mmol) in the presence of guanidine **64** (26 mg, 0.1 mmol) in toluene for 24h gave after purification (SiO2, petroleum ether/ethyl acetate, 9/1), 0.12 g (74%) of 68.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4 (bs, 5H, Ar*H*), 5.55-5.4 (m, 1H, C*H*OH), 4.7-4.5 (m, 2H, CH_2NO_2), 3.0 (bd, 1H, O*H*).

IR (Neat):

3754, 3446, 2921, 1553, 1454, 1418, 1380, 1066, 896, 763, 700 cm^{-1}.

$[\alpha]_D$ = - 3.6 ^{0} (*c* 1.0, EtOH), e.e. = 10% (Lit.[22] $[\alpha]_D$ = - 34.0 ^{0} (EtOH) for '*S*' enantiomer).

4-Methyl-1-nitropentan-2-ol (69):[22]

The reaction of isovaleraldehyde (0.1 ml, 1 mmol) and nitromethane (0.1 ml, 1.5 mmol) in the presence of guanidine **64** (26 mg, 0.1 mmol) in toluene for 24h gave after purification (SiO_2, petroleum ether/ethyl acetate, 92/8), 0.07 g (74%) of **69**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.4-4.2 (m, 3H, C*H*OH and CH_2NO_2), 3.0-2.7 (bs, 1H, O*H*), 1.9-1.7 (m, 1H, CH_2CH), 1.6-1.4 (m, 1H, CH_2CH), 1.3-1.1 (m, 1H, $CH_2CH(CH_3)_2$), 0.96 (d, J = 8, 3H, CH_3), 0.93 (d, J = 8, 3H, CH_3).

IR (Neat):

3440 (br), 3000, 1570, 1485, 1440, 1410, 1290, 1240, 1180, 1110, 1070, 925, 770 cm^{-1}.

$[\alpha]_D$ = + 1.2 ^{0} (*c* 3.0, EtOH), e.e. = 5% (Lit.[22] $[\alpha]_D$ = + 22.0 ^{0} (EtOH)).

General procedure for the guanidine catalyzed Michael addition reaction:

To a cooled (0 ^{0}C) solution of the enone in ethanol or benzene was added the guanidine followed by diethyl malonate or Meldrum's acid. The homogeneous reaction mixture was kept at 0 ^{0}C for 24-72h, after which the solution was concentrated. The residue obtained was dissolved in dichloromethane and the solution was successively washed with 0.5 N HCl, water, brine, dried and concentrated to give the crude product which was purified by flash chromatography on silica gel.

(3-Oxocyclopentyl)propanedioic acid, diethyl ester (76):[46]

The reaction of cyclopentenone **(70)** (0.26 ml, 3 mmol) and diethyl malonate **(73)** (0.3 ml, 2 mmol) in the presence of guanidine **64** (0.15 g, 0.6 mmol) in ethanol (2 ml) at 0 ^{0}C for 72h gave after purification (SiO_2, petroleum ether/ethyl acetate, 9/1), 0.31 g (64%) of **76**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.2-4.1 (2 x q, *J* = 9, 4H, OCH_2), 3.25 (d, J = 11, 1H, $CH(COOEt)_2$), 2.95-2.75 (m, 1H, H_2CCHCH_2), 2.5-2.35 (dd, *J* = 5.5, 11, 1H, $COCH_2CH$), 2.35-2.1 (m, 3H, CH_2CH_2), 2.0-1.9 (dd, *J* = 8, 11, 1H, $COCH_2CH$), 1.7-1.55 (m, 1H, CH_2CH_2), 1.25-1.15 (2 x t, *J* = 9, 6H, CH_2CH_3).

IR (Neat):

3000, 1740, 1480, 1460, 1420, 1390, 1340, 1320, 1290, 1260, 1220, 1180, 1110, 1040, 870 cm^{-1}.

MS (EI, 70 eV):

m/z 69 (3), 83 (16), 95 (20), 105 (18), 113 (100), 123 (42), 133 (79), 141 (28), 160 (80), 168 (4), 185 (5), 197 (7), 243 (M+1, <1).

$[\alpha]_D$ = - 5.0 ^{0} (*c* 2.0, $CHCl_3$).

2,2-Dimethyl-5-(3-oxocyclopentyl)-1,3-dioxane-4,6-dione (77):

The reaction of cyclopentenone **(70)** (0.26 ml, 3 mmol) and Meldrum's acid **(74)** (0.29 g, 2 mmol) in the presence of guanidine **64** (0.15 g, 0.6 mmol) in ethanol (3 ml) at 0 ^{0}C for 72h gave after purification (SiO_2, petroleum ether/ethyl acetate, 7/3), 0.28 g (57%) of **77**.

mp: 146-149 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 3.75 (d, *J* = 5.4, 1H, C*H*$(CO)_2$), 3.25-3.05 (m, 1H, CH_2CHCH_2), 2.55-2.4 (m, 3H, $COCH_2CH$, $COCH_2$), 2.35-2.0 (m, 3H, CH_2CH_2CH, $COCH_2CH_2$), 1.85 (s, 3H, CCH_3), 1.8 (s, 3H, CCH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$):

δ 216.6 (CH_2COCH_2), 164.2 ($CH(CO)_2$), 105.2 ($C(CH_3)_2$), 48.5 (COCHCO), 41.1 ($COCH_2$), 38.3 ($COCH_2$), 34.5 (CH_2CHCH_2), 28.4 (CCH_3), 26.6 (CH_2CH_2CH), 25.7 (CH_3).

IR (Nujol):

2880, 1800, 1750, 1395, 1350, 1320, 1310, 1280, 1270, 1220, 1190, 1080, 1020, 895 cm^{-1}.

MS (EI, 70 eV):

m/z 68 (27), 82 (100), 91 (5), 96 (68), 113 (15), 123 (36), 140 (40), 169 (52).

Analysis for $C_{11}H_{14}O_5$:

Calcd. C, 58.39 H, 6.24

Found C, 58.28 H, 6.47

$[\alpha]_D$ = - 3.2 ^{0} (*c* 2.0, $CHCl_3$).

(3-Oxocyclopentyl)-propanedioic acid, bis(phenylmethyl) ester (78):[34]

The reaction of cyclopentenone **(70)** (0.13 ml, 1.5 mmol) and dibenzyl malonate **(75)** (0.25 ml, 1 mmol) in the presence of guanidine **64** (0.08 g, 0.3

mmol) in benzene (2 ml) at 0 ^{0}C for 72h gave after purification (SiO_2, petroleum ether/ethyl acetate, 9/1), 0.18 g (50%) of **78**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.4-7.2 (m, 10H, Ar*H*), 5.2-5.1 (AB system, *J* = 8, 2H, OC*H*$_2$Ph), 3.45 (d, *J* = 11, 1H, C*H*(COOPh)$_2$), 2.95-2.75 (m, 1H, H_2CC*H*CH_2), 2.5-2.35 (dd, *J* = 5.5, 16.5, 1H, COC*H*$_2$CH), 2.35-2.15 (m, 3H, COC*H*$_2$CH, COC*H*$_2$CH$_2$), 2.1-1.9 (dd, *J* = 11, 16.5, 1H, CH_2C*H*$_2$CH), 1.7-1.55 (m, 1H, CH_2C*H*$_2$CH).

IR ($CHCl_3$):

1750, 1170, 1030, 780 cm^{-1}.

$[\alpha]_D$ = - 2.0 ^{0} (*c* 2.0, $CHCl_3$).

(3-Oxocyclopentyl)-propanedioic acid, diethyl ester (79):[34]

The reaction of cyclohexenone **(71)** (0.29 ml, 3 mmol) and diethyl malonate **(73)** (0.3 ml, 2 mmol) in the presence of guanidine **64** (0.15 g, 0.6 mmol) in ethanol (3 ml) at 0 ^{0}C for 96h gave after purification (SiO_2, petroleum ether/ethyl acetate, 7/3), 0.26 g (51%) of **79**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 4.2-4.1 (2 x q, *J* = 6, 4H, OC*H*$_2$), 3.25 (d, *J* = 11, 1H, COC*H*$_2$CO), 2.55-2.4 (m, 1H, CH_2C*H*CH_2), 2.4-2.25 (m, 1H, COC*H*$_2$CH), 2.25-2.15 (m, 3H, COC*H*$_2$CH, COC*H*$_2$), 2.05-1.95 (m, 1H, CH_2C*H*$_2$CH), 1.95-1.85 (m, 1H, CH_2C*H*$_2$CH), 1.7-1.55 (m, 1H, CH_2C*H*$_2$CH$_2$), 1.55-1.45 (m, 1H, CH_2C*H*$_2$CH$_2$), 1.25-1.15 (2 x t, *J* = 6, 6H, CH_2C*H*$_3$).

IR (Neat):

3000, 1760, 1460, 1420, 1390, 1340, 1320, 1260, 1220, 1180, 1110, 1040, 870 cm^{-1}.

$[\alpha]_D$ = - 0.7 ^{0} (*c* 2.6, $CHCl_3$).

2,2-Dimethyl-5-(3-oxocyclohexyl)-1,3-dioxane-4,6-dione (80):[47]

The reaction of cyclohexenone **(71)** (0.15 ml, 1.5 mmol) and Meldrum's acid **(74)** (0.14 g, 1 mmol) in the presence of guanidine **67** (0.1 g, 0.3 mmol) in ethanol (3 ml) at 0 ^{0}C for 72h gave after purification (SiO_2, petroleum ether/ethyl acetate, 7/3), 86 mg (36%) of **80**.

mp: 152-155 ^{0}C.

^{1}**H NMR** (200 MHz, $CDCl_3$):

δ 3.45 (d, *J* = 3.7, 1H, COC*H*CO), 3.0-2.75 (m, 2H, CH_2CHCH_2, $COCH_2$), 2.45-2.25 (m, 3H, $COCH_2CH$, $COCH_2CH_2$), 2.2-1.9 (m, 2H, CH_2CH_2CH), 1.8 (s, 3H, CCH_3), 1.75 (s, 3H, CCH_3), 1.75-1.6 (m, 2H, $CH_2CH_2CH_2$).

^{13}**C NMR** (50.3 MHz, $CDCl_3$):

δ 209.2 (CH_2COCH_2), 164.2 ($CH(CO)_2$), 164.0 ($CH(CO)_2$), 105.0 ($C(CH_3)_2$), 49.5 (COCHCO), 43.2 ($COCH_2CH$), 40.6 ($COCH_2CH_2$), 36.3 (CH_2CHCH_2), 28.1 (CCH_3), 26.8 (CCH_3), 26.7 ($CHCH_2CH_2$), 24.6 ($CH_2CH_2CH_2$).

IR ($CHCl_3$):

1800, 1765, 1725, 1400, 1320, 1070, 1010, 680 cm^{-1}.

MS (EI, 70 eV):

m/z 55 (52), 59 (22), 68 (88), 81 (38), 96 (50), 110 (20), 126 (18), 136 (25), 147 (12), 154 (100), 164 (8), 183 (18), 212 (5), 225 (2), 240 (M^+, 1).

Analysis for $C_{12}H_{16}O_5$:

Calcd. C, 59.98 H, 6.72

Found C, 59.63 H, 6.54

General procedure for hydrolysis of the Michael adducts:

To a suspension of the Michael adduct in acetic acid was added 6M H_2SO_4 (exotherm). The reaction mixture was heated at 130-140 ^{0}C for 2-6h. It was then concentrated and thoroughly dried. The residue was purified by flash chromatography on silica gel.

3-Oxocyclopentaneacetic acid (81):[42]

The reaction of **76** (0.29 g, 1.2 mmol) in acetic acid (5 ml) and 6M H_2SO_4 (9 ml) at 130 ^{0}C for 6h gave, after purification (SiO_2, dichloromethane/methanol, 95/5), 84 mg (49%) of **81**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.5-8.2 (bs, 1H, COOH), 2.7-2.4 (m, 4H, CH_2COOH, $COCH_2CH$, $COCH_2$), 2.4-2.1 (m, 3H, $COCH_2CH$, $COCH_2CH_2$) 1.95-1.8 (m, 1H, CH_2CH_2CH), 1.7-1.5 (m, 1H, CH_2CH_2CH).

IR (Neat):

2966, 2612, 1734, 1404, 1273, 1246, 1165, 1134, 872, 619 cm^{-1}.

MS (EI, 70 eV):

m/z 55 (10), 60 (5), 69 (6), 83 (100), 96 (9), 99 (4), 113 (18), 125 (4), 142 (M^+, 18).

$[\alpha]_D$ = - 6.6 ^{0} (*c* 0.7, $CHCl_3$), e.e. = 12% (Lit.[42] $[\alpha]_D$ = - 53.1 ^{0} (c = 1.75, $CHCl_3$) for 'S' enantiomer with 97% e.e.).

3-Oxocyclohexaneacetic acid (82):[42]

The reaction of **79** (0.12 g, 0.4 mmol) in acetic acid (2 ml) and 6M H_2SO_4 (3 ml) at 130 ^{0}C for 4h gave, after purification (SiO_2, dichloromethane/methanol, 95/5), 40 mg (57%) of **82.**

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.4-7.9 (bs, 1H, COOH), 2.6-2.2 (m, 6H, CH_2COOH, COCH_2CH, COCH_2CH_2), 2.2-1.9 (m, 3H, $COCH_2CH$, $COCH_2CH_2$), 1.8-1.55 (m, 1H, $CH_2CH_2CH_2$), 1.55-1.2 (m, 1H, $CH_2CH_2CH_2$).

IR (Neat):

2936, 1713, 1448, 1418, 1346, 1312, 1271, 1227, 1159, 1097, 868 cm^{-1}.

$[\alpha]_D$ = - 2.5 ^{0} (*c* 1.0, $CHCl_3$), e.e. = 18% (Lit.[42] $[\alpha]_D$ = - 13.2 ^{0} (c = 1.0, $CHCl_3$) for *'S'* enantiomer with 98% e.e.).

1,3-Diphenyl-4-nitro-1-butanone (83):[43]

The reaction of chalcone **(72)** (0.42 g, 2 mmol) and nitromethane (0.16 ml, 3 mmol) in the presence of guanidine **64** (51 mg, 0.2 mmol) in toluene (4 ml) at ambient temperature for 80h gave after purification (SiO_2, petroleum ether/ethyl acetate, 85/15), 0.2 g (38%) of **83.**

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.9 (d, *J* = 7.1, 2H, Ar*H*), 7.6-7.5 (m, 1H, Ar*H*), 7.35-7.15 (m, 2H, Ar*H*), 7.35-7.15 (m, 5H, Ar*H*), 4.85-4.7 (d of AB system, *J* = 6.6, 12.3, 2H, CH_2NO_2), 4.2 (quint, *J* = 7.3 1H, PhC*H*), 3.5 (dd, *J* = 7, 17.7, 1H, PhCOCH_2), 3.4 (dd, *J* = 7, 17.7, 1H, PhCOCH_2).

IR (Nujol):

2855, 1688, 1541, 1597, 1541, 1497, 1435, 1410, 1333, 1240, 1180, 1003, 770, 745, 702 cm^{-1}.

$[\alpha]_D$ = - 2.2 ^{0} (*c* 1.0, $CHCl_3$), e.e. = 5% (Lit.[43] $[\alpha]_D$ = - 41.0 ^{0} (CH_2Cl_2) for '*S*' enantiomer).

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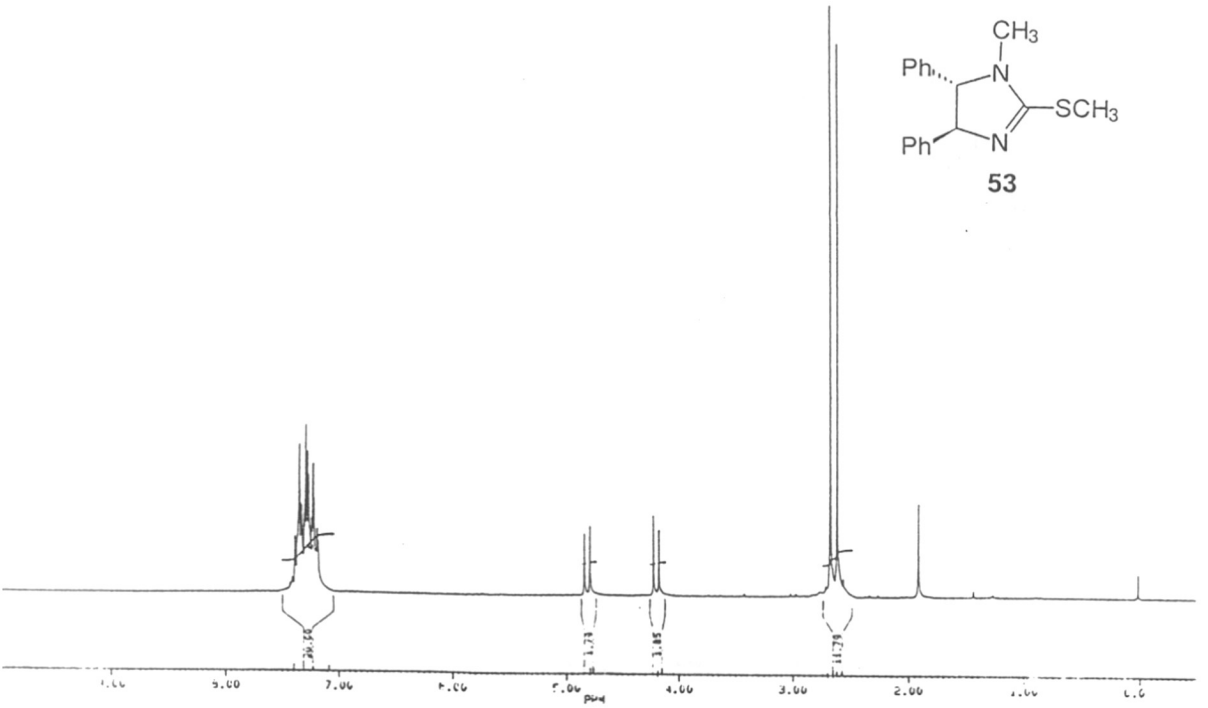

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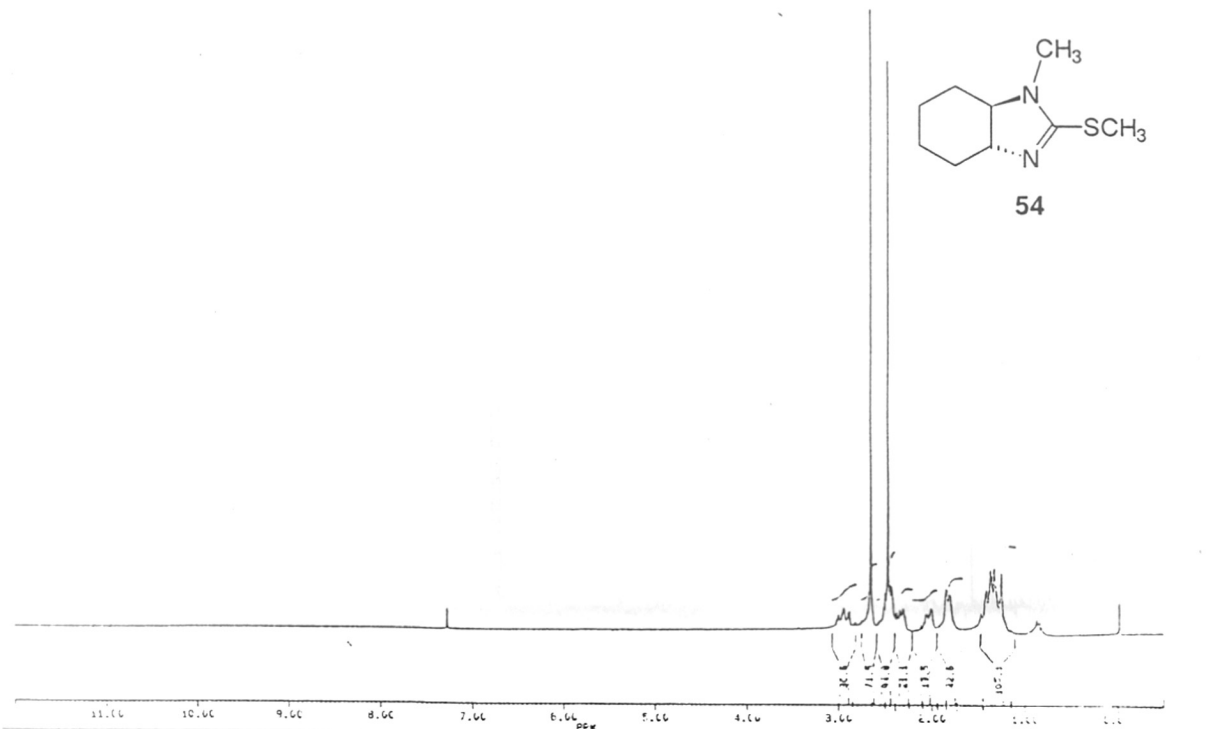

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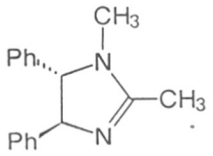

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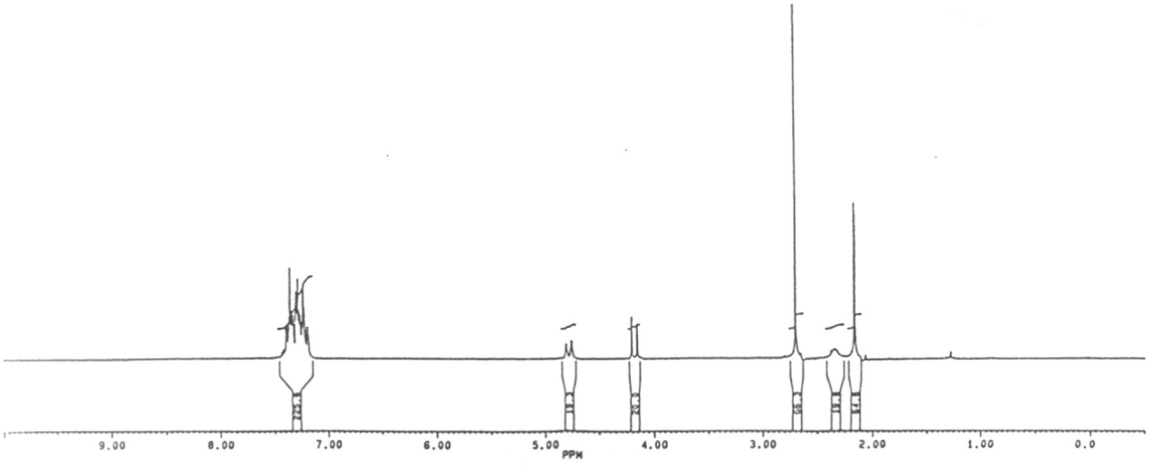

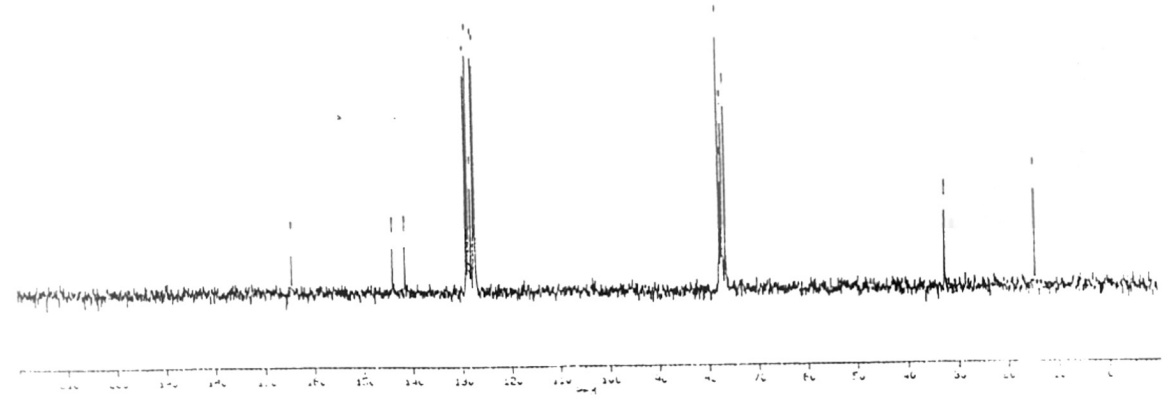

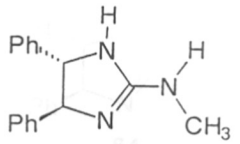

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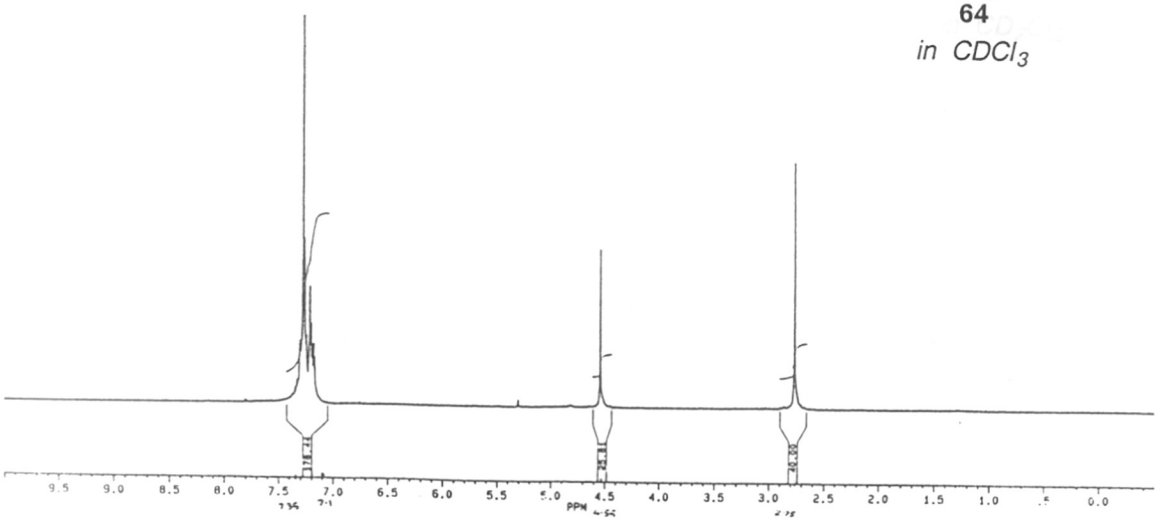

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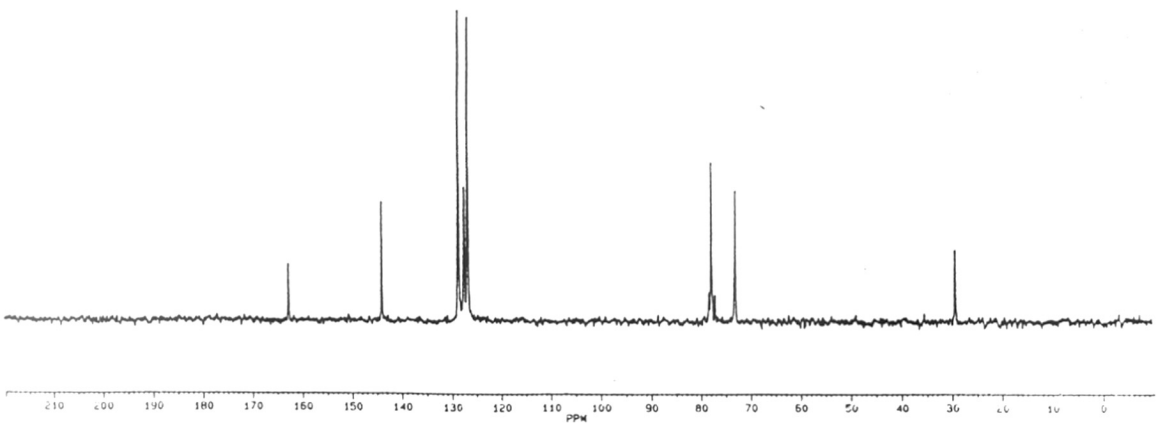

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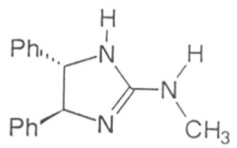

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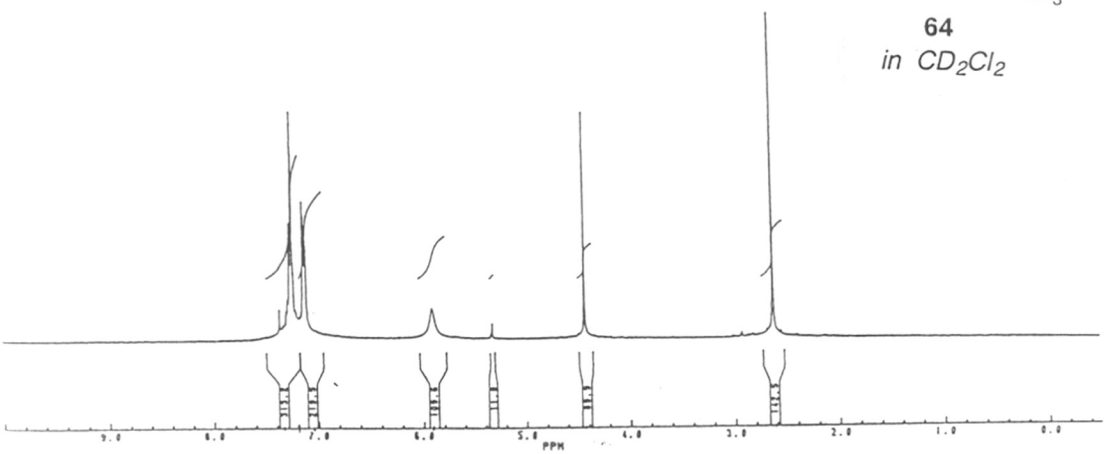
in CD_2Cl_2



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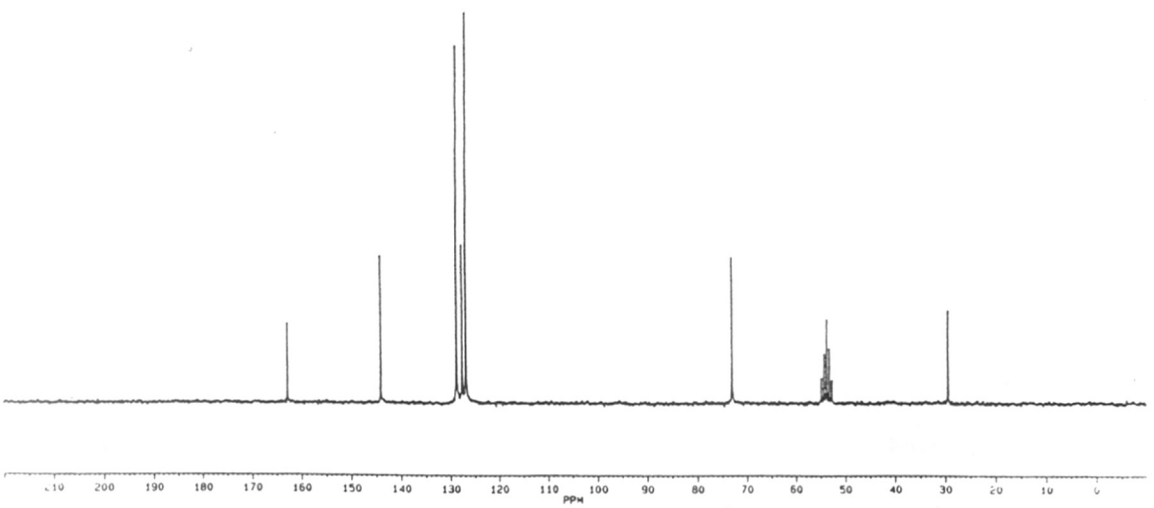

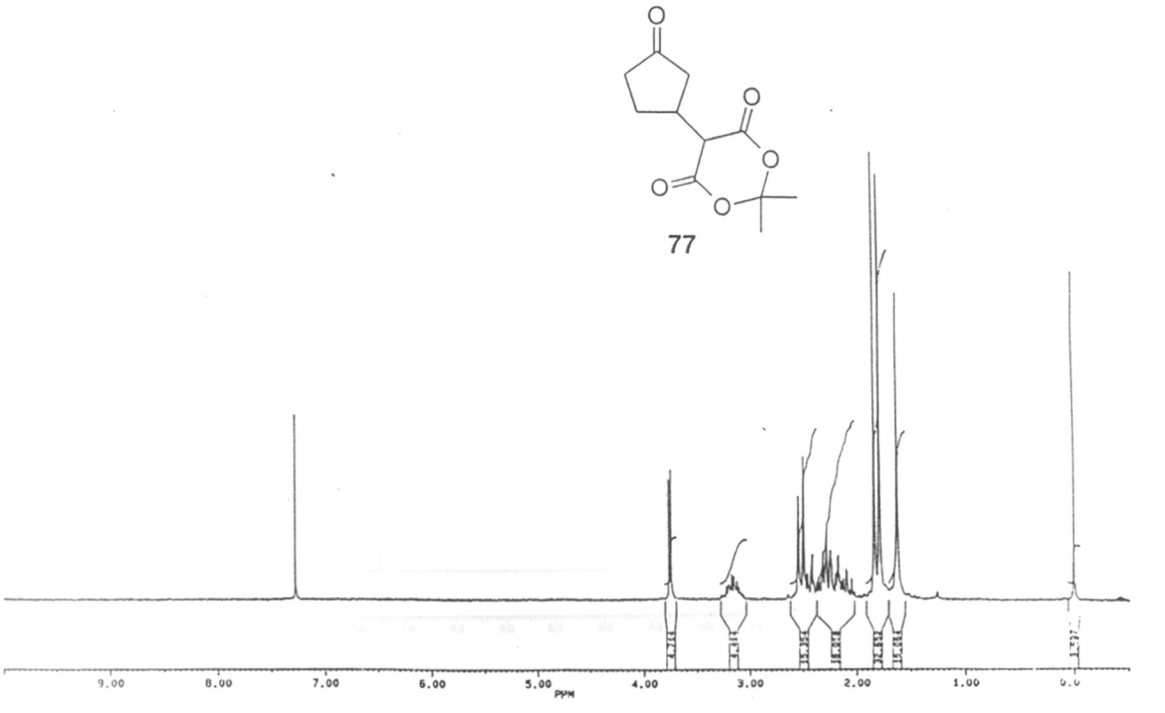
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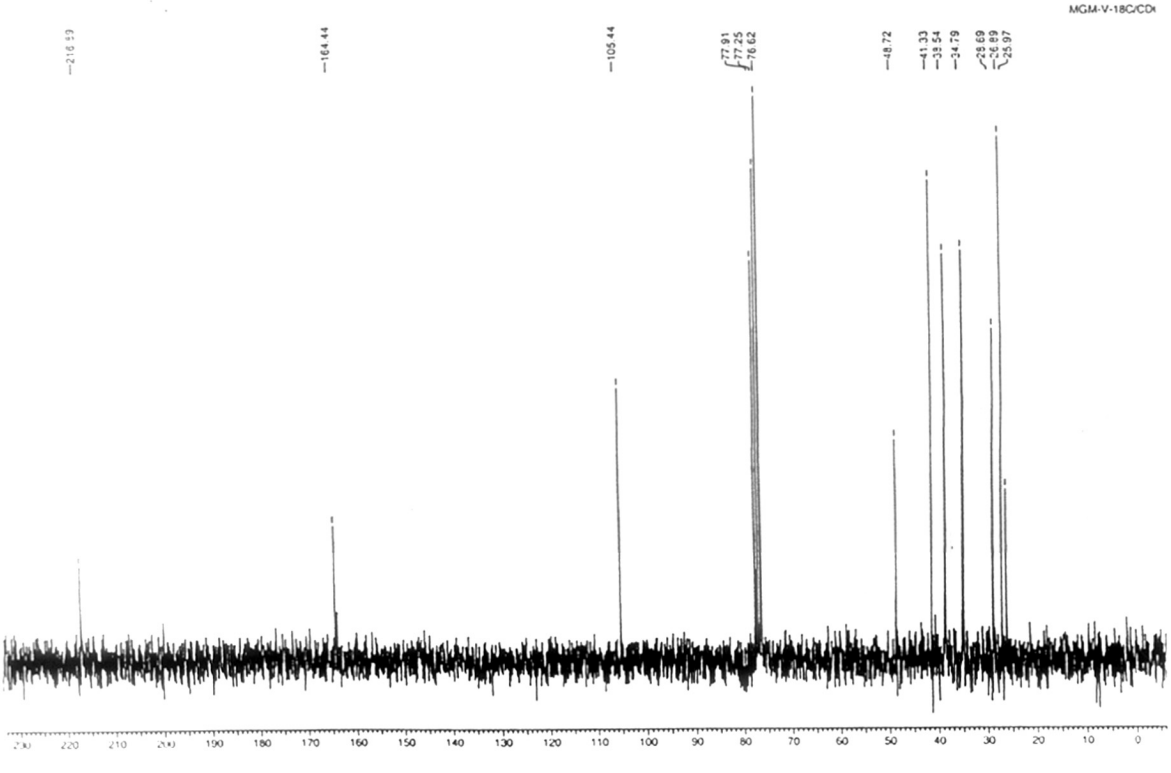
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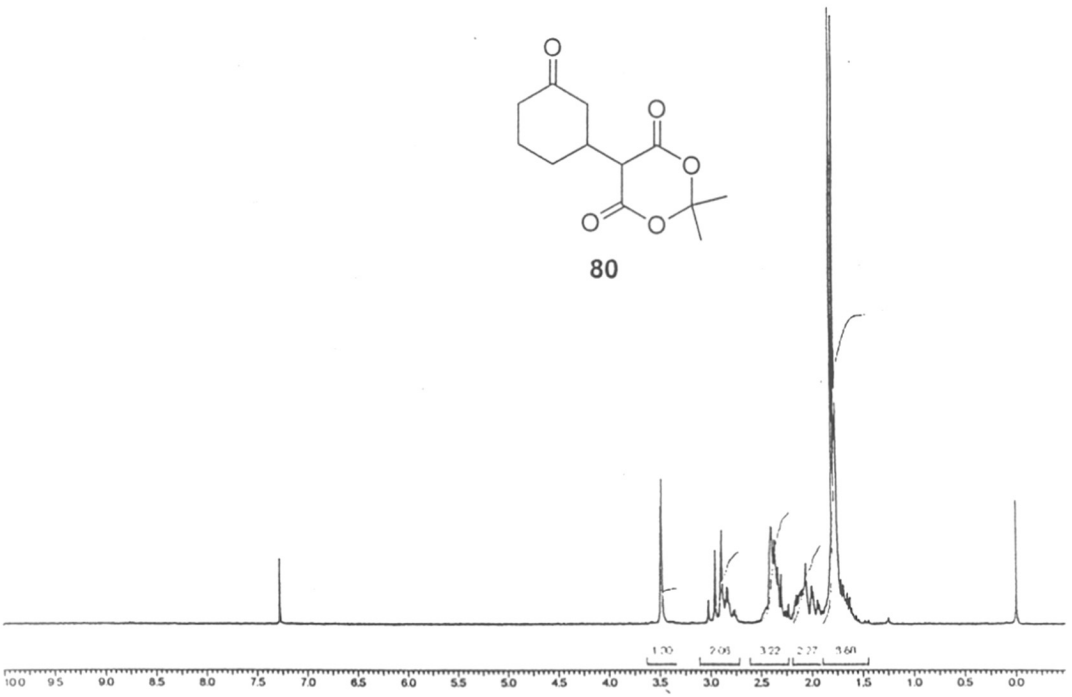

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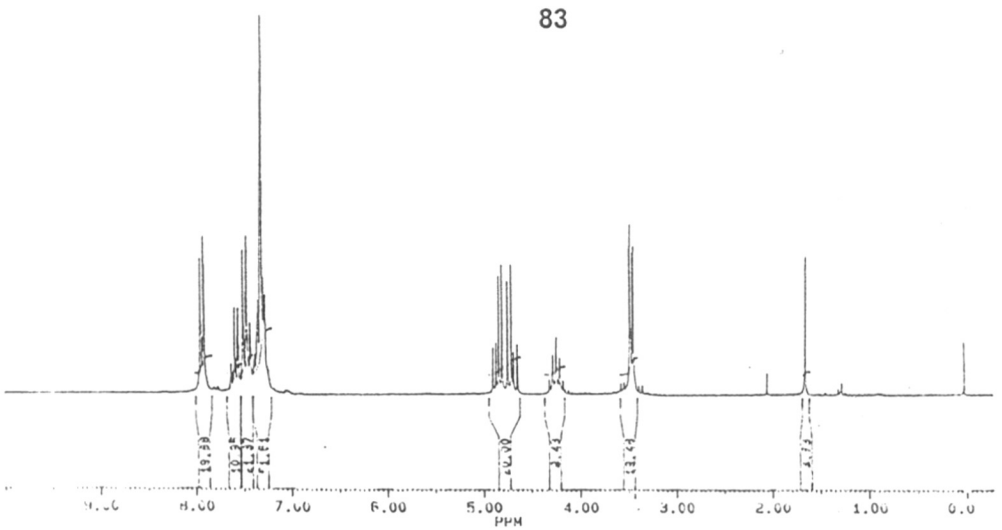

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CHAPTER III

SYNTHESIS OF 1,2-DIARYLDIKETONES

Part of work described in this chapter has been published in *Synlett* **1997**, 671.

1. INTRODUCTION

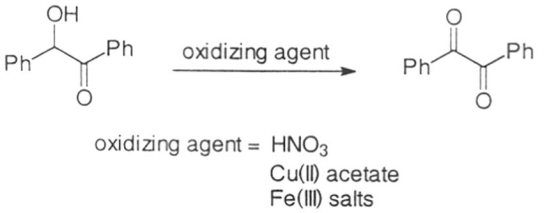
The 1,2-diketone functionality has found several applications in organic synthesis and in biological systems. α-Diketones are important precursors for a variety of aliphatic, aromatic and heterocyclic products possessing several valuable properties.[1] Recently amino acids and dipeptides incorporating the 1,2-diketone moiety have shown to be a novel class of electron deficient carbonyl inhibitors for serine and cysteine proteinases.[2] They are also used as intermediates in preparation of antiarrythmic agents,[3] and are constituents of some antiinflammatory agents.[4] α-Dicarbonyl compounds are of interest in the study of molecular configuration by conformational analysis,[5] electron spectroscopy,[6] and photochemical methods.[7] They are also used in the synthesis of thermostable polymers.[8] The synthesis of symmetrical and unsymmetrical 1,2-diketones has therefore been actively investigated in recent years. A brief summary of the existing methods for the synthesis of 1,2-diketones follows. It should be emphasized that the list is not exhaustive and is intended to provide the reader with a general perspective of the major synthetic methods available for the preparation of 1,2-diketones.

Synthesis of 1,2-diketones:

Oxidation of Acyloins:

The first observations indicating that benzoin could be oxidized by nitric acid to benzil were made more than 150 years ago by Zinin.[9] Since then the reaction conditions and the oxidizing agents have been varied (Scheme 1).

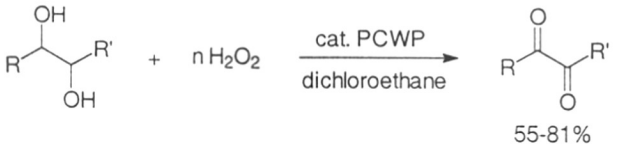
Scheme 1.



The most widely used oxidants have been copper (II) salts employed in the presence of regenerating agents such as air or ammonium nitrate.[10] Salts of trivalent iron can also be used for this purpose.[11]

More recently, α-hydroxyketones and vicinal diols were successfully oxidized to the corresponding diketones with aqueous H_2O_2 in the presence of a catalytic amount of peroxotungstophosphate (PCWP).[12] This method provides a straightforword route to 1,2-diketones which are difficult to prepare by conventional oxidation of vicinal diols (Scheme 2).

Scheme 2.



Aliphatic α-hydroxyketones and vicinal diols are converted into the corresponding diketones in 71-81% yield, whereas aromatic diols are oxidized to diketones in 55-58% yield.

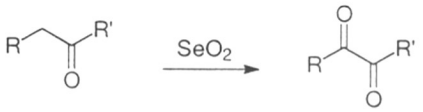
Oxidation of α-methylene-carbonyl compounds:

Riley first demonstrated that selenium dioxide is a specific reagent for oxidizing a methylene group α to a carbonyl group to generate 1,2-diketones.[13]

Since then selenium dioxide has been widely used for obtaining α-dicrbonyl compounds from aliphatic or aliphatic-aromatic aldehydes and ketones under mild conditions.

In contrast to other reagents such as $KMnO_4$ or CrO_3 that primarily oxidize the carbonyl group, SeO_2 acts on a methyl or methylene group attached to various activating groups such as an aldehyde, ketone, carboxylic acid, ester, amide, anhydride or an aromatic ring to give diketones in moderate to good yield[14] (Scheme 3).

Scheme 3.



R, R' = activating group

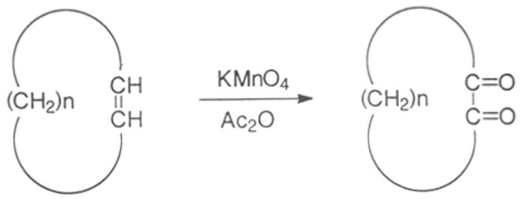
Oxidation of compounds containing carbon-carbon multiple bonds:

The oxidation of acetylenes by $KMnO_4$ has been successfully applied for the preparation of bis α-diketones[15] (Scheme 4).

Scheme 4.

Potassium permanganate in acetic anhydride has also been used to obtain 1,2-diketones in 50-69% yield from higher cycloalkanes (Scheme 5). Trace amounts of diacids are obtained as by products from these reactions.[15]

Scheme 5.

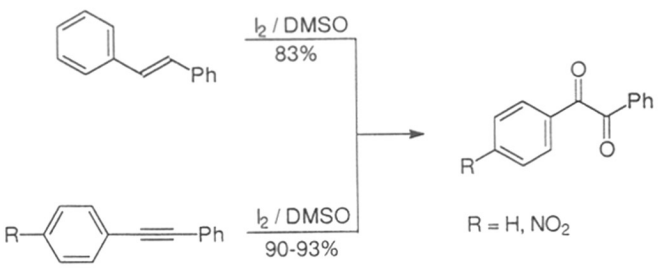


n = >10 50-69%

The oxidation of carbon-carbon triple bonds has also been accomplished by selenium dioxide in the presence of catalytic H_2SO_4[16], $Tl(NO_3)_3$[17] or ozone.[18]

Yusybov has demonstrated that the oxidation of 1,2-diaryl ethenes with HBr in DMSO[19] yields diaryl α-diketones. However, alkynes are not oxidized efficiently with this reagent. A recent modification[20] employs iodine in dimethyl sulfoxide for the oxidation. A variety of alkenes and alkynes can be efficiently oxidized to α-diketones in good (83-93%) yield with the modified reagent (Scheme 6).

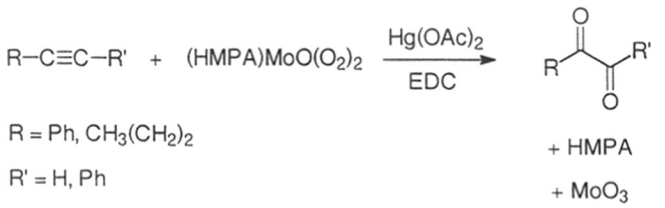
Scheme 6.



Ballistreri[21] and coworkers showed that mercuric acetate promoted oxidation of diaryl, dialkyl, and aryl-alkyl alkynes with $(HMPA)MoO(O_2)_2$ in 1,2-dichloroethane affords the corresponding α-diketones in good yields.

Terminal alkynes can also be converted into α-ketoaldehydes with this oxidizing system (Scheme 7).

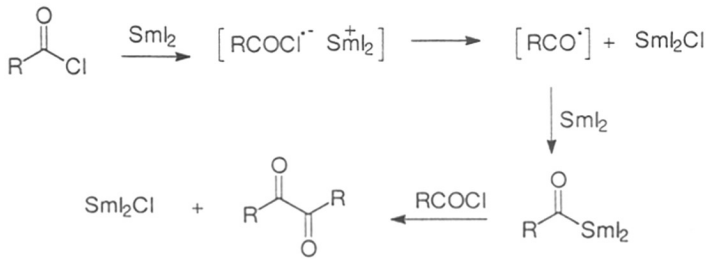
Scheme 7.



Preparation of α-diketones from acid chlorides:

Kagan has demonstrated that acid chlorides can be coupled by reaction with SmI_2 to yield the corresponding diketones in 40-80% yield.[22] The reaction is initiated by an electron transfer from SmI_2 to RCOCl. The radical anion $(RCOCl)^{\cdot -}$ thus formed fragments into an acyl radical, $(RCO^{\cdot})$ and chloride ion. The acyl radical is rapidly reduced to an acyl anion,[23] which reacts with unreacted acid chloride *in-situ* to give the α-diketone (Scheme 8).

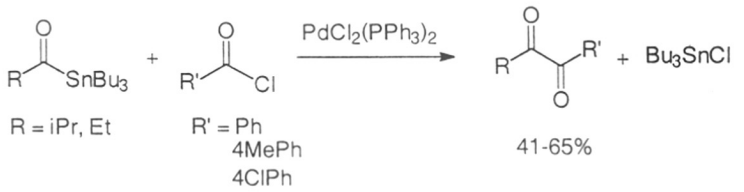
Scheme 8.



Unsymmetrical α-diketones have been obtained via cross-coupling of acyltin compounds with acid chlorides under $PdCl_2(PPh_3)_2$ catalysis, while symmetrical α-diketones have been readily obtained via *in-situ* formation of

acyltins using hexabutyltin and acyl chlorides under similar conditions (Scheme 9).[24]

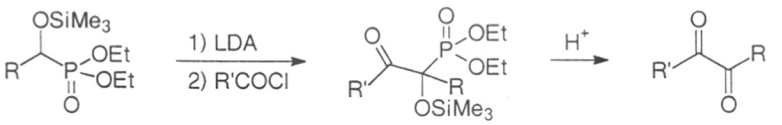
Scheme 9.



These diketones are generally accompanied by two side products, namely, the ketones RCOR' and RCOnBu.

Olah has reported the use of masked acyl anions for the synthesis of 1,2-diketones.[25] Acylation of the anion derived from diethyl 1-phenyl(or alkyl)-1-(trimethylsiloxy)methanephosphonates with readily available acyl chlorides followed by hydrolysis generates the α-diketones under mild conditions in moderate to good yields (Scheme 10).

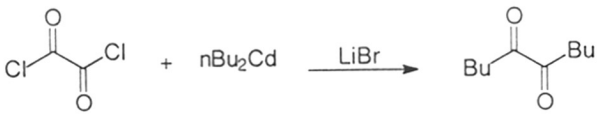
Scheme 10.



Synthesis of 1,2-diketones from oxalic acid derivatives.

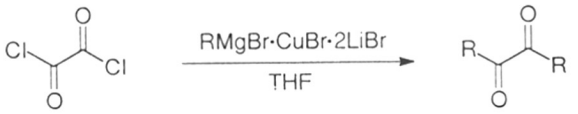
Several reports describe the use of the oxalic acid derivatives for the synthesis of α-diketones. The use of oxalyl chloride for α-diketone synthesis was first reported[26] by Kollonitsch. The reaction of dibutylcadmium with oxalyl chloride generates 5,6-decadione albeit in low yield (37%). Only one example was reported (Scheme 11).

Scheme 11.



Recently, Marchese and coworkers reported the reaction of oxalyl chloride with organocopper reagents to give symmetrical α-diketones in good yields (75-98%).[27] Various aliphatic, aromatic, alicyclic and heterocyclic organocopper reagents can be efficiently used leading to essentially pure 1,2-diketones (Scheme 12). LiBr is essential for the reaction.

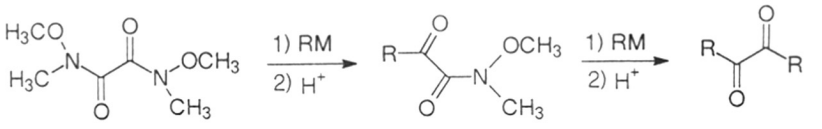
Scheme 12.



R = Ph, 4MePh, 2-Thienyl, Octyl, Cyclohexyl

Sibi and coworkers have examined reactions of the methoxy methyl amine derived *bis*-amide of oxalyl chloride with alkyl lithium and Grignard reagents(Scheme 13).[28] If so required, the reaction can be used to generate α-keto amides by utilizing one equivalent of the organometallic reagent. Use of excess organometallic reagent generates α-diketones in good yield.

Scheme 13.

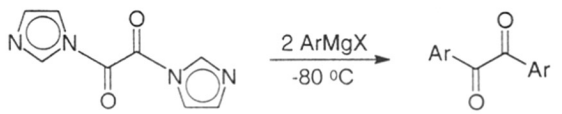


R = Ph, 4MePh, 4ClPh
M = Li, MgBr

70 - 90%

Mitchell has reported the reaction of 1,1'-oxalylimidazole (made from oxalyl chloride and imidazole) with Grignard reagents at low temperature to give diaryl 1,2-diketones (Scheme 14).[29]

Scheme 14.

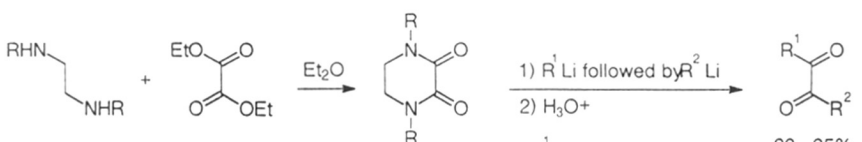


Ar = Ph, 4MePh, 4ClPh

55 - 80%

Symmetrical and unsymmetrical α-diones can be conveniently synthesized from 1,4-dialkylpiperazine-2,3-dione (made from *N,N'*-dimethyl ethylenediamine and diethyl oxalate) and RLi or RMgBr.[30] The piperazinediones react with two equivalents of organolithium or Grignard reagents to form, after hydrolysis, symmetrically substituted α-diones in excellent yields. The sequential addition of one equivalent each of two different organolithium compounds affords unsymmetrical α-diones when more soluble longer chain dialkyl derivatives of piperazine-2,3-dione are employed. The dialkylethylenediamines can be conveniently recovered and recycled to the 1,4-dialkylpiperazine-2,3-dione (Scheme 15).

Scheme 15.



R = CH_3, $C_{10}H_{21}$

R^1 = Ph, Bu

R^2 = 2-naphthyl, 4-anisyl

20 - 95%

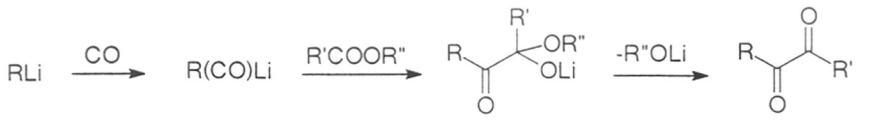
Insertion reactions of carbon monoxide:

Nudelman examined the insertion reaction of carbon monoxide into a metal-carbon bond.[31] It was observed that aryllithums in presence of carbon monoxide generate mixtures of the ketone and diketone (Scheme 16). The ratio of ketone to diketone is temperature dependent, with more ketone being formed at higher temperature.

Scheme 16.

Seyferth has demonstrated that the addition of a variety of alkyllithiums to an ethereal solution of an ester saturated with carbon monoxide at low temperature (< -110 ^{0}C) followed by hydrolysis results in the formation of 1,2-diketones in 65-80% yield (Scheme 17).[32]

Scheme 17.



Oxidation of phoshorus ylides:

A convenient preparation of unsymmetrically substituted benzils by permanganate oxidation of β-oxo phosphorus ylides[33] was reported by Aitken. Oxidative cleavage of a range of ylides using $KMnO_4$ in a two phase system gave unsymmetrical benzils and 1-aryl-1,2-propanediones in moderate to good yield

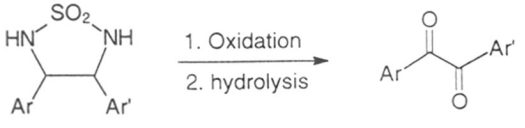
The ylid formation and oxidation can be combined in a convenient one-pot method (Scheme 18).

Scheme 18.

2. OBJECTIVE

The objective of this study was to examine the oxidative conversion of 3,4-diaryl-1,2,5-thiadiazolidine 1,1-dioxides to α-diketones (Figure 1).

Figure 1. Oxidative conversion of 3,4-diaryl-1,2,5-thiadiazolidine 1,1-dioxides to 1,2-diketones



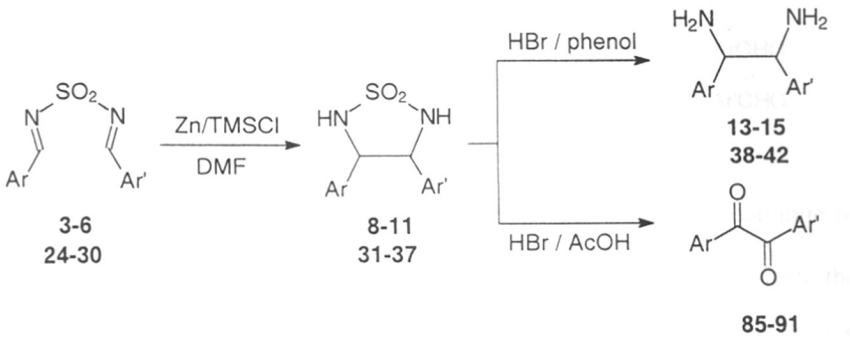
3. RESULTS AND DISCUSSION

Acid mediated cleavage of thiadiazolidines:

During our studies on the conversion of 3,4-diaryl-1,2,5-thiadiazolidine-1,1-dioxides to vicinal diamines (Chapter 1)[34], we observed that the reaction of these cyclic sulfamides in refluxing HBr/AcOH generates trace amounts of 1,2-diketones (Scheme 19). Conversion to diamines was not observed under these conditions. Considering that acid mediated cleavage of sulfonamides involves a redox process,[35] it seemed plausible that the diketones were obtained by oxidation

of the thiadiazolidine to a thiadiazole which underwent hydrolysis[36] during workup.

Scheme 19.

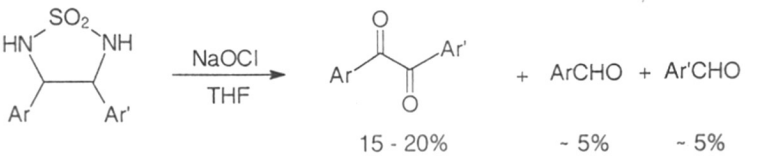


Attempts to optimize the oxidation of the thiadiazolidine by treatment with HBr, HI or bromine under a variety of conditions were unsuccessful and we therefore focused on other oxidizing agents.

Oxidative cleavage of thiadiazolidine 1,1-dioxides:

Initial experiments on the oxidation of thiadiazolidine 1,1-dioxides were performed with sodium hypochlorite[37] as the oxidant (Scheme 20).

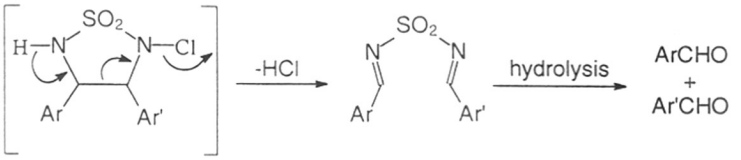
Scheme 20.



Although the yield of the diketones (15-20%) was higher than with HBr/AcOH, the product was always contaminated with the aldehydes used for preparing the starting thiadiazolidine 1,1-dioxide and purification of the diketone was difficult. The aldehydes are probably obtained from the precursor bisimine

which may be formed *in-situ* by mono *N*-chlorination of the thiadiazolidine 1,1-dioxides followed by a fragmentative elimination of HCl (Figure 2).

Figure 2. Oxidation of thiadiazolidine 1,1-dioxide with sodium hypochlorite.

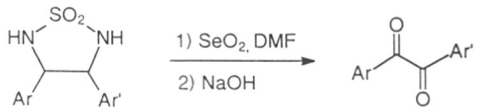


Modification of the procedure by treatment with sodium hypobromite or *tert*-butyl hypochlorite[38] did not suppress aldehyde formation. Although the thiadiazolidines could not be oxidized with lead tetraacetate[39] or with DDQ,[40] oxidation with selenium dioxide[41] was successful. It should be noted that the oxidation of primary and secondary amines with SeO_2 has been reported to produce compounds having N-Se bonds, with aliphatic vicinal diamines yielding selenodiazoles.[41b-d] However, oxidation of the amine to a carbonyl compound was not reported.

Oxidation of thiadiazolidines with selenium dioxide:

The selenium dioxide oxidation of the thiadiazolidine-1,1-dioxides proceeded in solvents such as acetic acid, dioxane or benzene but the solvent of choice was DMF. The crude oxidation product obtained by treatment of **31** with SeO_2 was hydrolysed with aq. NaOH to furnish the diketone **88** in 66% yield (Scheme 21).

Scheme 21.

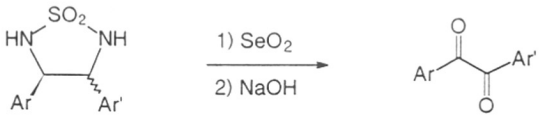


8 - 11
31, 32
34 - 37

Ar	Ar'	
Ph	Ph	**85**
4MePh	4MePh	**86**
4MeOPh	4MeOPh	**87**
Ph	4MePh	**88**
Ph	2-naphthyl	**89**
Ph	4MeOPh	**90**
Ph	2,3-OCH_2OPh	**91**

The reaction is applicable to a variety of substrates with alkyl and alkoxy substitution in the aromatic ring and more importantly, provides an access to the unsymmetrical diketones by a cross-coupling of aryl aldehyde imines followed by oxidation. The results are summarized in Table 1. The conversion of **31** to **88** also emphasizes the utility of 1,2,5-thiadiazolidine 1,1-dioxides as synthetic intermediates for vicinally functionalized molecules.

Table 1. Conversion of 3,4-diaryl 1,2,5-thiadiazolidine 1,1-dioxides to diaryl 1,2-diketones.

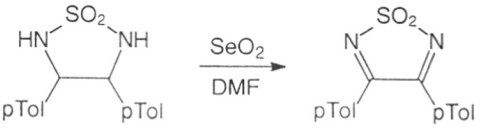


8 - 11, 31, 32, 34 - 37 **85 - 91**

Cyclic sulfamide	Ar	Ar'	1,2-diketone	Yield %, 1,2-diketone
8	Ph	Ph	85	58
9	4MePh	4MePh	86	17
11	4MeOPh	4MeOPh	87	48
31	Ph	4MePh	88	66
32	Ph	2MePh	-	-
34	Ph	4ClPh	-	-
35	Ph	2-naphthyl	89	52
36	Ph	4MeOPh	90	52
37	Ph	2,3-OCH_2OPh	91	46

The SeO_2 oxidation of the thiadiazolidine 1,1-dioxide probably generates the corresponding thiadiazole 1,1-dioxide which was isolated (**92**, 21% yield) in the oxidation of **9** (Scheme 22).

Scheme 22.



9 **92**

It is reasonable to assume therefore, that in all cases, the SeO_2 oxidation generates a 3,4-diaryl thiadiazole 1,1-dioxide. However, due to the instability of the thiadiazole 1,1-dioxides on silica gel and the presence of other products which render crystallization impractical, the crude oxidation product was used further without purification.

The reasons for the lack of diketone formation from **32** and **34** are not apparent at present.

4. CONCLUSION

A new approach to diaryl α-diketones from the readily available aryl aldehydes has been developed. The method is applicable to the synthesis of unsymmetrical 1,2-diaryl 1,2-ethanediones containing alkyl and alkoxy substituents in the aromatic ring. The conversion constitutes a new approach to aryl α-diketones involving a reductive coupling/oxidation sequence that is based on the aryl aldehydes as starting materials.

5. EXPERIMENTAL

General experimental techniques have been described in the experimental section of Chapter 1.

General procedure for the preparation of 1,2-diketones:

To a solution of 3,4-diaryl-1,2,5-thiadiazolidine-1,1-dioxide in anhydrous DMF was added SeO_2. The mixture was heated at 78-80 ^{0}C under argon for 10-12h or at 160-165 ^{0}C for 2-3h. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate, filtered through celite and the filtrate was washed with saturated aqueous $NaHCO_3$, aqueous thiourea and water. The residue obtained after concentration was used further without purification. The crude oxidation product was dissolved in THF and 2N NaOH was added. The mixture was stirred at ambient temperature for 4-6h after which it was extracted with ethyl acetate. Concentration of the combined ethyl acetate extracts gave the crude diketone which was purified by conventional chromatography on basic alumina.

1,2-Diphenyl 1,2-ethanedione (85): [42]

Reaction of **8** (137 mg, 0.5 mmol) with SeO_2 (222 mg, 2.0 mmol) in anhydrous DMF (6 ml) at 78-80 °C for 12h furnished 128 mg of a red gum which was dissolved in THF (3 ml), 2N NaOH (2 ml) added and the mixture was stirred at ambient temperature for 6h. The residue obtained after workup (79 mg) was purified (basic alumina, petroleum ether/ethyl acetate, 95/5) to give 61 mg, (58%) of **85**.

mp: 91-92 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.1-7.9 (m, 4H, Ar*H*), 7.7-7.6 (m, 2H, Ar*H*), 7.6-7.45 (m, 4H, Ar*H*).

IR ($CHCl_3$):

1680, 1605, 1590, 1455, 1220, 1180, 875, 760 cm^{-1}.

MS (EI, 70 eV):

m/z 77 (58), 105 (100), 178 (4), 210 (M^+, 18).

1,2-Bis(4-methylphenyl) 1,2-ethanedione (86):[43]

Reaction of **9** (101 mg, 0.33 mmol) with SeO_2 (222 mg, 2.0 mmol) in anhydrous DMF (5 ml) at 165-170 °C for 3h furnished 109 mg of a red gum which was dissolved in THF (2 ml), 2N NaOH (2 ml) added and the mixture was stirred at ambient temperature for 4h. The residue obtained after work up (71 mg) was purified (SiO_2, pet ether/ethyl acetate, 97/3) to give 13 mg (17%) of **86.**

mp: 102-103 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.87 (d, *J* = 9.6, 4H, Ar*H*), 7.3 (d, *J* = 9.6, 4H, Ar*H*), 2.45 (s, 6H, 2ArCH_3).

IR ($CHCl_3$):

1660,1600, 1210, 760 cm^{-1}.

MS (EI, 70 eV):

m/z 65 (15), 91 (38), 119 (100), 238 (M^+, 14).

1,2-Bis(4-methoxyphenyl) 1,2-ethanedione (87):[44]

Reaction of **11** (166 mg, 0.5 mmol) with SeO_2 (222 mg, 2.0 mmol) in anhydrous DMF (5 ml) at 78-80 °C for 12h furnished 172 mg of a red gum which was dissolved in THF (5 ml), 2N NaOH (3 ml) added and the mixture was stirred at ambient temperature for 4h. The residue obtained after workup (139 mg) was purified (basic alumina, petroleum ether/ethyl acetate, 85/15) to give 65 mg (48%) of **87**.

mp: 130-131 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.95 (d, J = 9.8, 4H, Ar*H*), 7.0 (d, J = 9.8, 4H, Ar*H*), 3.9 (s, 6H, 2ArOCH_3).

IR ($CHCl_3$):

1670, 1610, 1585, 1520, 1470, 1430, 1320, 1280, 1230, 1170, 1030, 890, 850, 770 cm^{-1}.

MS (EI, 70 eV):

m/z 63 (6), 77 (13), 92 (12), 107 (10), 135 (100), 270 (M^+, 10).

1-(4-Methylphenyl)-2-phenyl 1,2-ethanedione (88):[43]

Reaction of **31** (430 mg, 1.5 mmol) with SeO_2 (390 mg, 3.5 mmol) in anhydrous DMF (12 ml) at 78-80 °C for 16h furnished 373 mg of a red gum which was dissolved in THF (4 ml), 2N NaOH (2 ml) added and the mixture was stirred at ambient temperature for 4h. The residue obtained after workup was purified (basic alumina, petroleum ether/ethyl acetate, 95/5) to give 221 mg (66%) of **88**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.05-7.9 (m, 2H, Ar*H*), 7.85 (d, *J* = 9.5, 2H, Ar*H*), 7.75-7.6 (m, 1H, Ar*H*), 7.6-7.45 (m, 2H, Ar*H*), 7.3 (d, *J* = 9.5, 2H, Ar*H*), 2.45 (s, 3H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 194.6, 194.1 (Ar*C*O), 146.0 (Ar*Cipso*), 134.6 (Ar*C*), 132.8 (Ar*Cipso*), 130.3 (Ar*Cipso*), 129.7, 129.6, 128.8 (Ar*C*), 21.6 (CH_3).

IR (CCl_4):

2921, 1668, 1604, 1517, 1450, 1097, 1071, 975, 934, 800, 769, 627 cm^{-1}.

MS (EI, 70 eV):

m/z 65 (28),77 (42), 91 (45), 105 (48), 119 (100), 210 (2), 224 (M^+, 2).

1-(2-Naphthalenyl)-2-phenyl 1,2-ethanedione (89):[45]

Reaction of **35** (390 mg, 1.2 mmol) with SeO_2 (330 mg, 3.0 mmol) in anhydrous DMF (10 ml) at 160-165 °C for 3h furnished 396 mg of a red gum which was dissolved in THF (2 ml), 2N NaOH (2 ml) added and the mixture was stirred at ambient temperature for 5 min. The residue obtained after workup (291 mg) was purified (basic alumina, petroleum ether/ethyl acetate, 95/5) to give 162 mg (52%) of **89**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.4 (brs, 1H, Ar*H*), 8.2-7.85 (m. 6H, Ar*H*), 7.75-7.4 (m, 5H, Ar*H*).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 194.6 (Ar*C*O), 136.4 (Ar*Cipso*), 134.8, 133.4 (Ar*C*), 133.2 (Ar*Cipso*), 132.3 (Ar*Cipso*), 130.4 (Ar*Cipso*), 129.9, 129.5, 129.1, 129.0, 127.9, 127.2, 123.7 (Ar*C*).

IR (CCl_4):

3061, 1668, 1595, 1450, 1125, 1097, 1073, 1021, 1000; 955, 933, 920, 904, 891, 868, 838, 821, 733, 716, 685, 644 cm^{-1}.

MS (EI, 70 eV):

m/z 77 (83), 105 (95), 127 (81), 155 (100), 210 (5), 260 (M^+, 14).

1-(4-Methoxyphenyl)-2-phenyl 1,2-ethanedione (90):[46]

Reaction of **36** (152 mg, 0.5 mmol) with SeO_2 (222 mg, 2.0 mmol) in anhydrous DMF (5 ml) at 160-165 °C for 3h furnished 160 mg of a red gum which was dissolved in THF (1 ml), 2N NaOH (2 ml) added and the mixture was stirred at ambient temperature for 4h. The residue obtained after work-up was purified (basic alumina, petroleum ether/ethyl acetate, 95/5) to give 62 mg (52%) of **90**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.05-7.9 (m,4H, Ar*H*), 7.6-7.5 (m, 1H, Ar*H*), 7.6-7.45 (m, 2H, Ar*H*), 7.0 (d, J = 9.8, 2H, Ar*H*), 3.9 (s, 3H, OCH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 194.9, 193.1 (Ar*C*O), 165.0 (Ar*Cipso*), 134.7 (Ar*C*), 133.3 (Ar*Cipso*), 132.4, 129.9, 129.0 (Ar*C*), 126.2 (Ar*Cipso*), 114.4 (Ar*C*), 55.6 (OCH_3).

IR (CCl_4):

2937, 2842, 1676, 1597, 1511, 1424, 1317, 1296, 1184, 1120, 1111, 1074, 1049, 999, 936, 787, 700, 676, 640 cm^{-1}.

MS (EI, 70 eV):

m/z 63 (9), 77 (42), 92 (15), 105 (14), 135 (100), 240 (M^+, 2).

1-(2-(1,3-Benzodioxol-5-yl))-2-phenyl 1,2-ethanedione (91):

Reaction of **37** (160 mg, 0.5 mmol) with SeO_2 (222 mg, 2.0 mmol) in anhydrous DMF (5 ml) at 78-80 ^{0}C for 14h furnished 151 mg of a red gum which was dissolved in THF (4 ml), 2N NaOH (3 ml) added and the reaction mixture was stirred at ambient temperature for 14h. The residue obtained after workup (80 mg) was purifed (basic alumina, petroleum ether/ethyl acetate, 95/5) to give 58 mg (46%) of **91**.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 8.0-7.95 (m, 2H, Ar*H*), 7.7-7.6 (m, 1H, Ar*H*), 7.6-7.45 (m, 4H, Ar*H*), 6.9 (d, J = 8.5, 1H, Ar*H*), 6.1 (s, 2H, OCH_2O).

^{13}C NMR (75.5 MHz, $CDCl_3$):

δ 194.4, 192.7 (Ar*C*O), 153.4 (Ar*Cipso*), 148.6 (Ar*Cipso*), 134.7 (Ar*C*), 133.2 (Ar*Cipso*), 129.8, 128.9, 127.8, 108.4 (Ar*C*), 102.2 (OCH_2O).

IR (CCl_4):

3066, 1663, 1599, 1503, 1488, 1446, 1364, 1179, 1145, 1112, 1102, 1074, 1036, 999, 935, 924, 882, 850, 821, 810, 788 cm^{-1}.

MS (EI, 70 eV):

m/z 65 (50), 77 (60), 91 (9), 105 (30), 121 (26), 149 (100), 254 (M^+, 2).

Analysis for $C_{15}H_{10}O_4$:

Calcd. C, 70.86 H, 3.96.

Found C, 70.67 H, 4.00.

3,4-Bis(4-methylphenyl)-1,2,5-thiadiazole-1,1-dioxide (92):[47]

To a solution of cyclic sulfamide **9** (101 mg, 0.33 mmol) in acetic acid (3 ml) was added SeO_2 (111 mg, 1 mmol). The resulting mixture was heated to reflux for 6h and the reaction was monitored by TLC. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate, filtered through celite and the filtrate was washed with saturated aqueous $NaHCO_3$ and water. The residue obtained after concentration (160 mg) was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 4/1) to furnish 20 mg (21%) of **92**.

mp: 204-205 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.5 (d, J = 9.8, 4H, Ar*H*), 7.25 (d, J = 9.8, 4H, Ar*H*), 2.45 (s, 6H, 2CH_3).

IR ($CHCl_3$):

1620, 1545, 1515, 1380, 1220, 1190, 980, 775 cm^{-1}.

MS (EI, 70 eV):

m/z 90 (17), 117 (100), 149 (8), 266 (7), 298 (M^+, 3).

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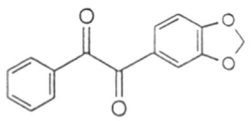

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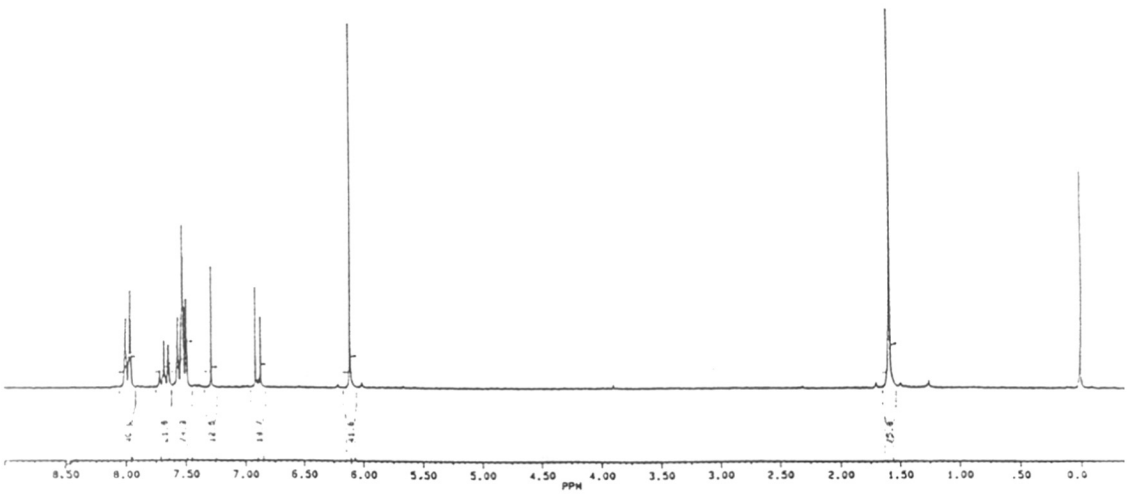

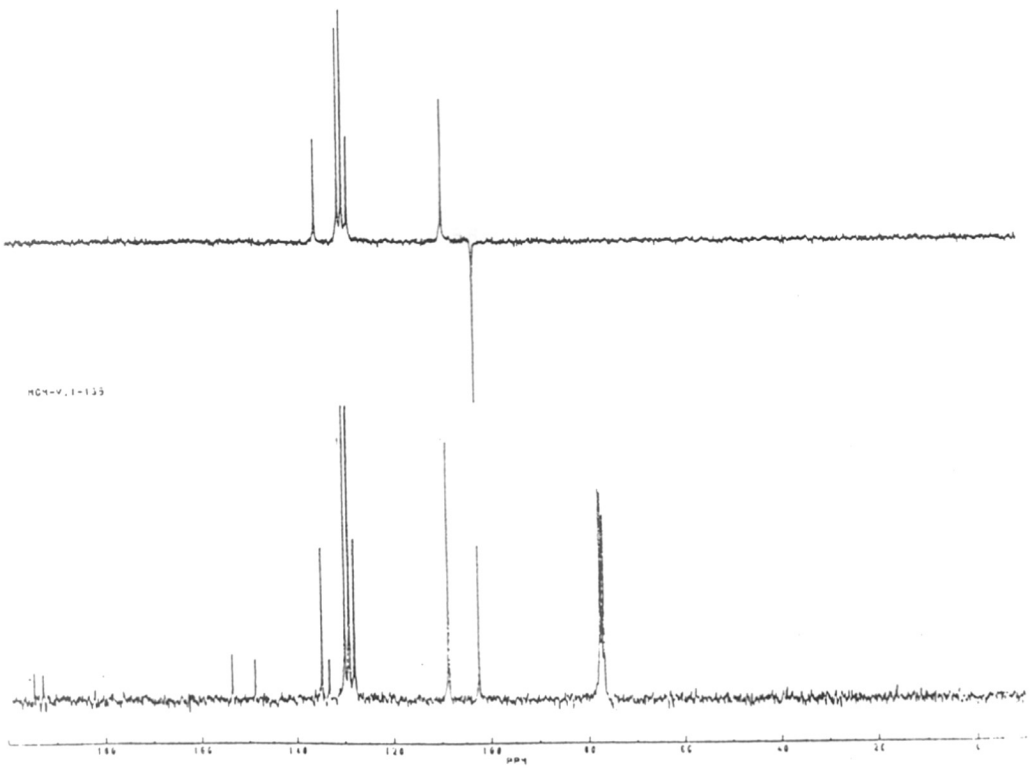

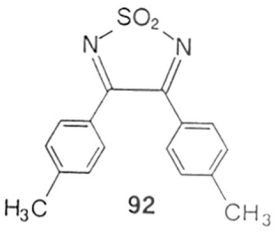

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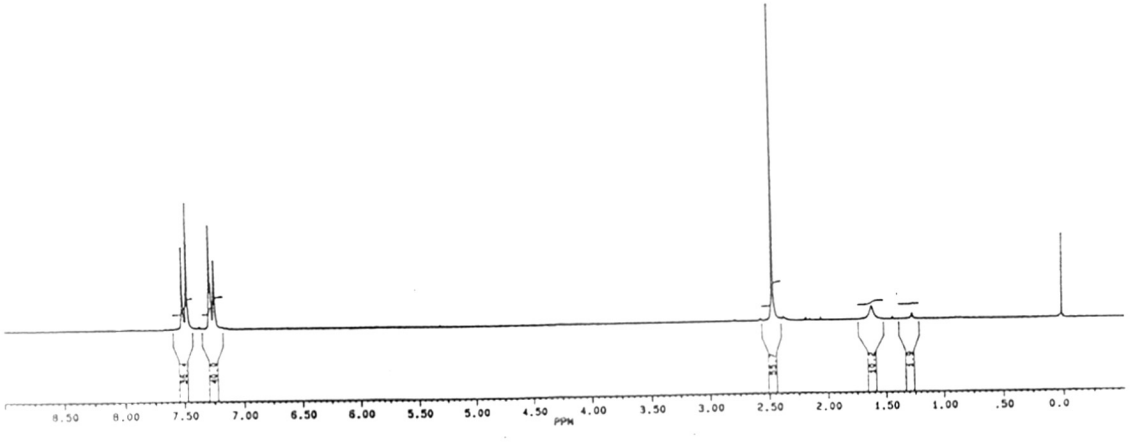

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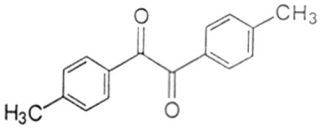

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