STEREOSELECTIVE SYNTHESIS OF THIADIAZOLIDINE- AND THIADIAZINE-1, 1-DIOXIDES AND THEIR CONVERSION TO DIAMINES AND STUDIES ON THE CATALYTIC *O*-ACYLATION AND NITRO-ALDOL REACTIONS

BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Stereoselective Synthesis of Thiadiazolidine- and Thiadiazine-1, 1-dioxides and their Conversion to diamines and studies on the catalytic *O*-Acylation and Nitro-Aldol 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.

Dr. S. V. Pansare

Date: Research Guide

DECLARATION

I hereby declare that the work incorporated in the thesis entitled **"Stereoselective Synthesis of Thiadiazolidine- and Thiadiazine-1, 1-dioxides and their Conversion to Diamines and Studies on the Catalytic *O*-Acylation and Nitro-Aldol 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.

Date: Anand Narain Rai

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Anand Narain Rai

List of Abbreviations:

Ac	acetyl
aq	aqueous
Bu	butyl
d.e.	diastereomeric excess
DME	1,2-dimethoxyethane
DMF	N, N-dimethylformamide
DMSO	dimethyl sulfoxide
e.e.	enantiomeric excess
equiv.	equivalent
Et	ethyl
g	gram
h	hour
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
pTol	p-tolyl
pTSA	p-toluene sulfonic acid
rt	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	Chlorotrimethylsilane

ABSTRACT

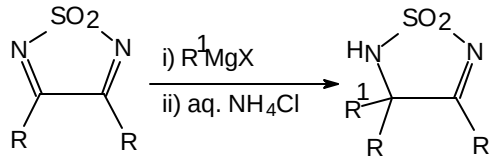
CHAPTER 1

(A) Stereoselective Synthesis of 1,2,5-Thiadiazolidine 1, 1-dioxides and their conversion to diamines:

Thiadiazolidine 1,1-dioxides are of interest due to their numerous applications in medicinal and synthetic organic chemistry. Despite their versatility, very few methods are available for their preparation from simple precursors. Practically all of the known methods employ condensation of a vicinal diamine or amino alcohol with sulfamide. This approach is limited by the availability of the precursor diamine or amino alcohol. The objective of our study was to develop a stereoselective synthesis of 1,2,5-thiadiazolidine 1,1-dioxides and examine the possibility of their conversion to vicinal diamines.

Initial investigations were conducted on 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide **1a** and 3,4-dimethyl thiadiazole 1,1 dioxide **1b**. Addition of Grignard reagents (one to two equivalents) to a solution of **1** in THF or benzene rapidly generated the thiadiazoline 1,1-dioxides **2** (85-99%) which were pure by ^{1}H NMR (Scheme 1).

Scheme 1.



1a, b

1a: R= Ph
1b: R= Me

2

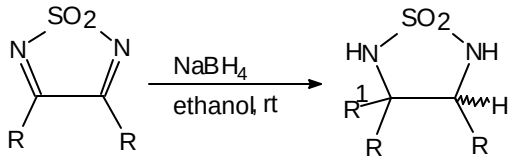
R^1= alkyl and aryl

An interesting feature of the above reaction is the relatively slow addition of the second equivalent of the nucleophile. Addition of excess MeMgBr (5

equivalents, 1.5 h, rt.) to **1a** generates a 2/1 mixture of *bis*- and *mono*-addition products whereas addition of excess *i*PrMgBr gives only the monoaddition product. This is presumably due to steric factors (quaternary center adjacent to the reaction site).

Reduction of **2** ($NaBH_4$/EtOH, rt. 2 h) produced the unsymmetrical 3,4-substituted thiadiazolidine 1,1-dioxide **3** (57-89%) as a mixture of *cis*/*trans* isomers. The addition of hydride is governed by the size of the substituent on the adjacent carbon. The ratio of *cis*/*trans* isomers was in the range of 1.2:1 to 19:1 (Scheme 2).

Scheme 2.



2

R= Ph, Me

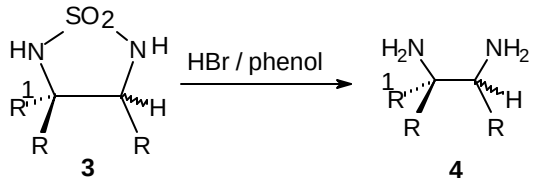
3

R^1 = alkyl and aryl

cis / trans = 1.2/1 to 19/1

Conversion of **3** to unsymmetrical vicinal diamines was studied next. Treatment of **3** with 2N HBr in the presence of phenol generated the diamines **4** in modest yield (33-52%) No cleavage of **3** or the *N*,*N*-dimethyl derivative of **3** is observed with excess Na/naphthalene or Na/liq. NH_3 (Scheme 3).

Scheme 3.



3 **4**

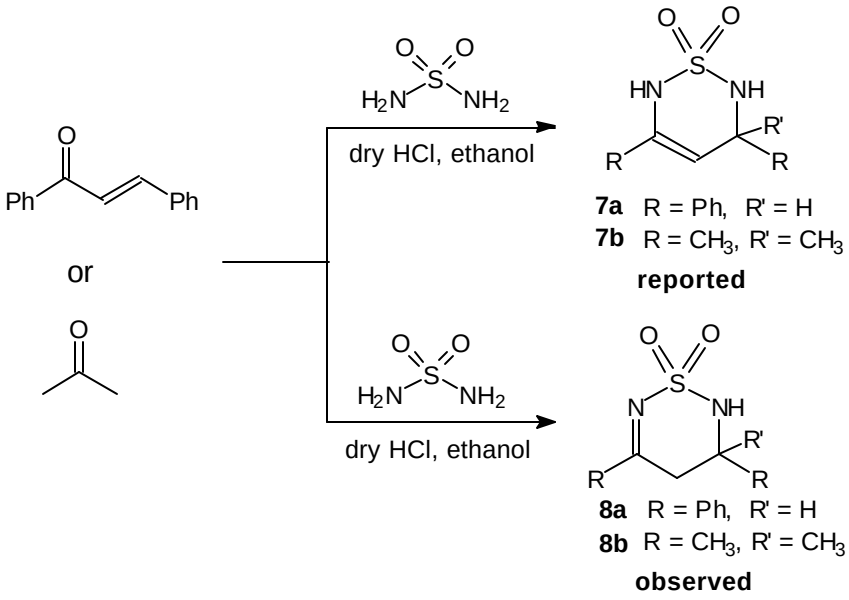
The above sequence provides easy access to a variety of unsymmetrical thiadiazolidine 1,1-dioxides as well as the corresponding vicinal diamines.

(B) Stereoselective synthesis of 1,2,6-Thiadiazine 1, 1-dioxides:

The 1,2.6-thiadiazine-1,1-dioxide moiety is an important pharmacophore and derivatives of the heterocycle are of interest in biology and medicine. Very few syntheses of 1,2,6-thiaidiazine-1,1-dioxides have been reported. Practically all the methods employ the condensation of a substituted 1,3-propanediamine unit with sulfamide as the key step. Our objective was to synthesize chiral thiadiazine 1,1-dioxides and also examine their conversion to chiral 1,3-diamines.

The condensation of sulfamide with an α,β unsaturated ketones has been reported to generate 3,6-dihydro-3,5-alkyl(aryl)-(2H)-1,2,6-thiadiazine 1,1-dioxides, 7. However, we have obtained the 3,4-dihydro-3,5-alkyl(aryl)-(2H)-1,2,6-thiadiazine 1,1-dioxides 8 as the major product from the condensation of sulfamide and 1,3-diphenyl-prop-2-ene-1-one or acetone (Scheme 4).

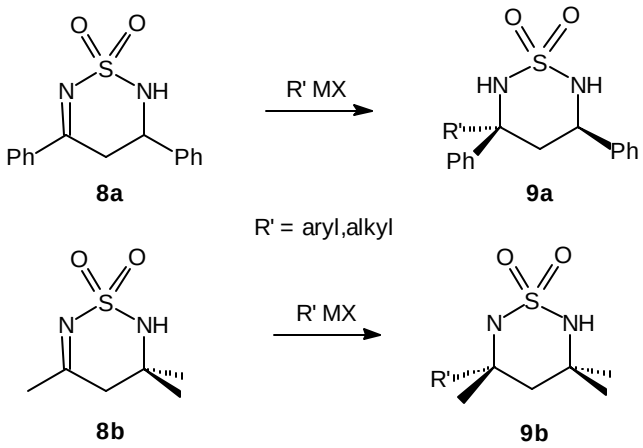
Scheme 4.



Stereoselective additions of organometallic reagents to 8a at 50 ^{o}C gives 3,4,5,6-tetrahydro-3-alkyl(aryl)-3,5-diphenyl-(2H)-1,2,6-thiadiazine 1,1-dioxides

9a in 43-83% yield. Similarly, addition of organometallic reagents to 8b at room temperature furnished 9b in modest yield (Scheme 5).

Scheme 5.



8a **9a** **8b** **9b**

Addition of Grignard reagents at room temperature generates thiadiazine 1,1-dioxides in poor yields whereas with more reactive alkyl lithium reagents and at elevated temperature, yield of the addition products were improved. The conversion of the thiadiazines to the corresponding diamines was examined under a variety of conditions. Only a small amount of some of the diamines is obtained (<5%) yield and the conversion is not synthetically useful.

Chapter 2

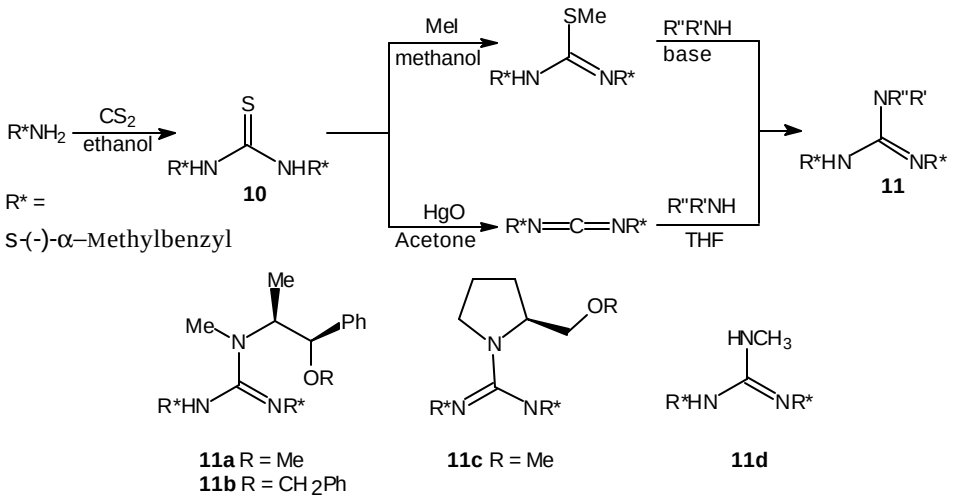
Section A: Synthesis of chiral guanidines and their application in stereoselective reactions:

Guanidines are of considerable interest in biology and synthetic organic chemistry. Although there are many biological applications of guanidines, relatively few studies have examined their use in organic synthesis. Guanidines can be used as catalysts in carbon-carbon bond forming reactions of malonates, 1,3-diketones and nitroalkanes. The objective of this study was to investigate the

possibility of using enantiomerically pure guanidines as bases in the nitroaldol (Henry) and Michael addition reaction. Chiral guanidines **11** were synthesized as shown in Scheme 6.

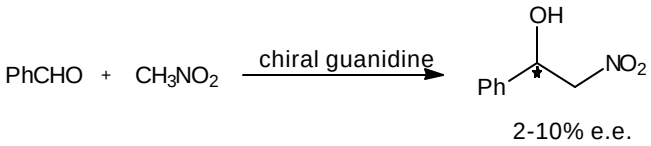
The reaction of carbon disulfide with an amine or a diamine in refluxing ethanol furnished thioureas **10** in 74-97% yield. Alkylation with methyl iodide in methanol at room temperature gave the *S*-methylisothiouronium iodide, which was reacted with amines to generate guanidines **11**. Alternatively, the guanidines could be prepared by conversion of the thiourea to the corresponding carbodiimide and subsequent reaction with amines (Scheme 6)

Scheme 6.



The enantiopure guanidines were used as catalysts in the nitroaldol reaction employing benzaldehyde and nitromethane as substrates (Scheme 7).

Scheme 7.



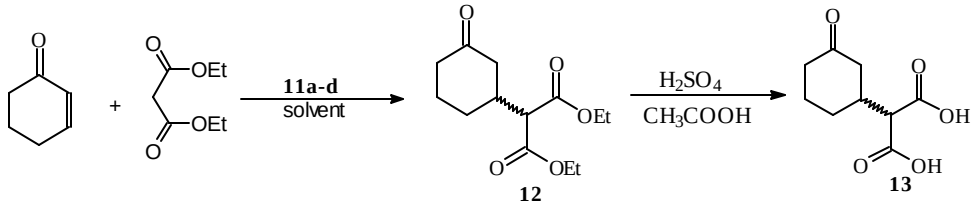
The reaction of an aldehyde with nitromethane in the presence of a chiral guanidine gave the expected nitroaldol product in 14-59% yield, albeit with low enantioselectivity (2-10% ee).

Section B. The catalytic asymmetric Michael addition reaction.

To the best of our knowledge, there is a sole study on a guanidine catalyzed asymmetric conjugate addition reaction. This study appeared in the literature during the course of our studies. The results suggested ample scope for improvement and 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-cyclohexene-1-one **44** with diethyl malonate **45** in the presence of a catalytic amount of guanidine **39-42** (0.3 eq.) in ethanol generated expected conjugate addition product **12** in moderate yield (scheme 15).

Scheme 15.



The effect of solvent and temperature on the enantioselectivity of the Michael addition reaction was also examined. The enantioselectivity of the Michael addition process is based on the optical rotation of the cyclohexanone acetic acids **13**. In most of the cases, the enantiomeric excess was quite low (1-10%) as judged by the specific rotation and an alternative determination of enantiomeric excess was not carried out.

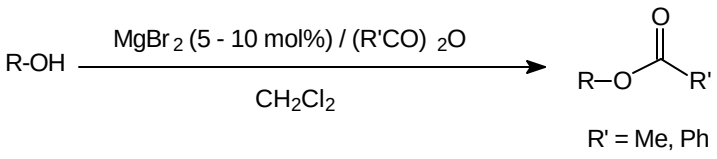
Chapter III

Magnesium bromide catalyzed acylation of alcohols

The acylation of an alcohol is usually achieved by reaction with an acid anhydride or acid chloride in the presence of a base and several acyl transfer reagents have been employed to facilitate the process. Recent investigations have focused on alternative reaction conditions and tributylphosphine, cobalt chloride and scandium triflate have been successfully employed as acylation catalysts in the absence of a base. The role of $MgBr_2$ as a Lewis acid is well known, especially in reactions of Grignard reagents, and other magnesium (II) salts have found application as Lewis acids in several synthetic transformations. We examined the possibility of employing $MgBr_2$ as an acylation catalyst under neutral conditions.

Initial investigations were conducted with menthol as the substrate. Treatment of a CH_2Cl_2 solution of menthol with acetic anhydride (6 equiv.) in the presence of $MgBr_2$ (5 mol%) for 3h at ambient temperature generated menthyl acetate in 72% isolated yield. Benzoic anhydride was also used as the acylating species to yield the corresponding benzoates. Several primary, secondary, tertiary, and β-substituted alcohols were acylated by using 5-10 mol% of magnesium bromide as the catalyst (Scheme 8).

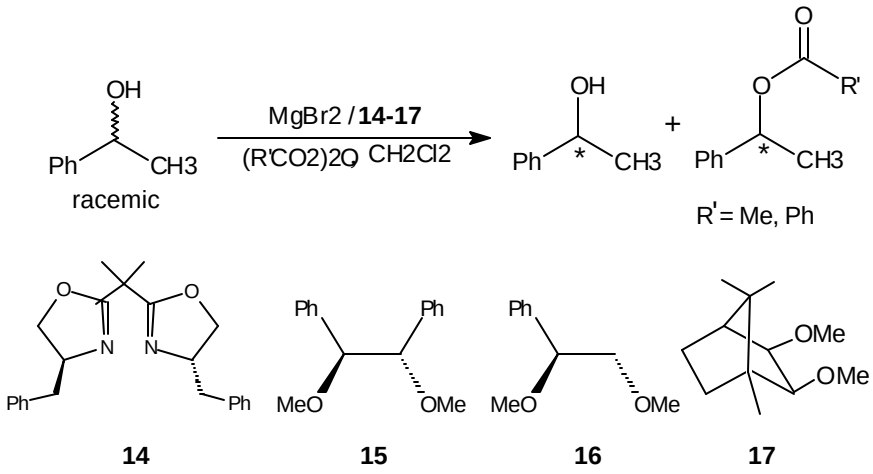
Scheme 8.



Acylation of 1-phenylethane-1,2-diol was unsuccessful, presumably due to irreversible complexation of $MgBr_2$ by the substrate, thereby reducing its Lewis acidity. This does not seem to be a difficulty with the other alcohol substrates although they are present in large excess during the initial stages of the reaction.

Magnesium bromide is known to complex with chiral, chelating ligands and chiral magnesium complexes have been used in catalytic asymmetric reactions such as conjugate additions and Diels-Alder reactions. We investigated the possibility of carrying out the kinetic resolution of racemic secondary alcohols using chiral Mg^{2+} complexes. In this connection, chiral ligands **14-17** were prepared and examined (Scheme 9).

Scheme 9.



The ligands **14-17** were used for complexation with $MgBr_2$ *in situ* and the complexes were examined as catalysts for the acylation of phenethylalcohol. Although the acylation proceed smoothly, the enantiomeric excess of the acylated product was low.

CHAPTER I

STEREOSELECTIVE SYNTHESIS OF 3,4-DISUBSTITUTED 1,2,5-THIADIAZOLIDINE 1,1-DIOXIDES AND THEIR CONVERSION TO UNSYMMETRICAL VICINAL DIAMINES.

Part of work described in this chapter has been published in *Synlett.* 1998, 623.

INTRODUCTION

SECTION 1: Stereoselective synthesis of 3,4-disubstituted 1,2,5-thiadiazolidine 1,1-dioxides and their conversion to vicinal diamines.

Thiadiazolidine 1,1-dioxides are of interest due to their numerous applications in organic synthesis and medicinal chemistry. Enantiomerically pure 1,2,5-thiadiazolidine 1,1-dioxides have been employed in asymmetric Diels-Alder[1] and aldol[2] reactions. Cephalosporins and penicillins having the 1,2,5-thiadiazolidine 1,1-dioxide ring are potent bactericides.[3] The 1,2,5-thiadiazolidine 1,1-dioxide moiety has also been utilized in various biologically active tryptamines.[4] 1,2,5-Thiadiazolidine 1,1-dioxides are also useful as modifying agents for textiles.[5]

Vicinal diamines are of interest due to their numerous applications in asymmetric synthesis[6] and medicinal chemistry.[7] Enantiomerically enriched vicinal diamines are useful as chiral ligands in several reagents and catalysts which are employed in stereoselective Diels-Alder,[8] Michael,[9] aldol,[10] allylation,[11] osmylation[12] and epoxidation[13] reactions, for the asymmetric dihydroxylation of alkenes,[14] enantioselective reduction of ketones[15] and addition of organometallic reagents to aldehydes.[16] Enantiomerically pure diamine derivatives are also used as promoters in asymmetric hydrogenation reactions,[17] as ligands in Lewis acids for the generation of enolates,[18] in propargylation reactions,[19] and as ligands in salen[20] and other complexes.[21] In addition, derivatives of chiral diamines are also useful for the determination of enantiomeric excess of chiral alcohols, thiols and amines.[22] They are effective reagents for the determination of the enantiomeric excess of carboxylic acids by

NMR spectroscopy.[23] Vicinal diamines and their derivatives are also useful in molecular recognition[24] and in pharmacology. [25]

Due to the several applications of 1,2,5-thiadiazolidine 1,1-dioxides and vicinal diamines in organic synthesis, their diastereoselective as well as enantioselective synthesis from readily available starting materials has been extensively investigated. Many methods for the synthesis of 1,2,5-thiadiazolidine 1,1-dioxides and vicinal diamines have been described and a summary of these methods, based on key synthetic transformations, follows.

Synthesis of 1,2,5-thiadiazolidine 1,1-dioxides:

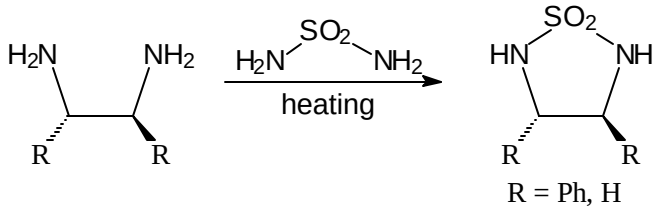
A. Condensation of diamines or amino alcohols with sulfamide:

The condensation of vicinal diamines or amino alcohols with sulfamide is the simplest approach to 1,2,5-thiadiazolidine 1,1-dioxides.

1. Condensation of diamines with sulfamide:

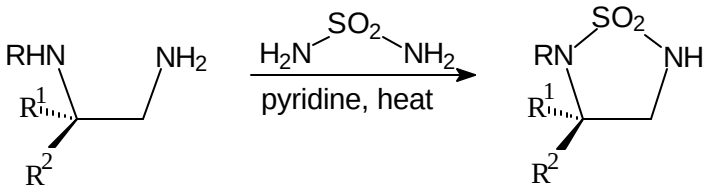
Nara *et. al.* reported the condensation of ethylenediamine with sulfamide to generate 1,2,5-thiadiazolidine 1,1–dioxides.[5] Similarly, Ahn and co-workers reported the synthesis of (3*S*,4*S*)-3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide by the condensation of 1,2-diphenyl-ethane-1,2-diamine with sulfamide in DMSO (Scheme 1).[2]

Scheme 1.



Recently, Castro *et. al.* have reported the synthesis of 3,3-dialkyl-1,2,5-thiadiazolidine 1,1-dioxides by the condensation of 1,1-dialkyl-ethane-1,2-diamines with sulfamide in pyridine (Scheme 2).[4]

Scheme 2.

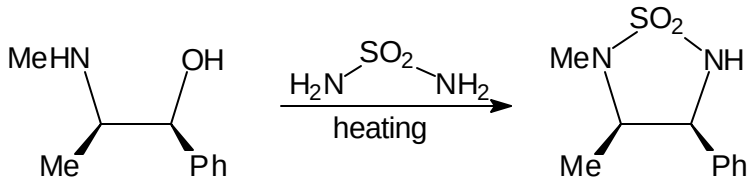


R = Me, Bu, *i*-Pr, H R^1, R^2 = H, Me

2. Condensation of Amino alcohols with sulfamide:

Kreiz has reported a convenient synthesis of a chiral thiadiazolidine by the condensation of sulfamide with ephedrine (Scheme 3).[26] The reaction involves heating ephedrine with sulfamide to generate the thiadiazolidine This thiadiazolidine has been employed as a chiral modifier in asymmetric Diels-Elder reactions.

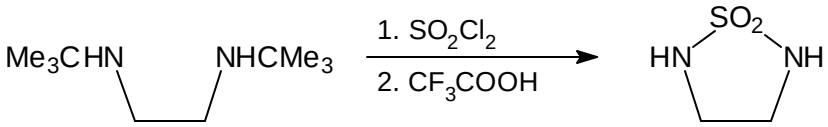
Scheme 3.



B. Condensation of sulfuryl chloride with diamine:

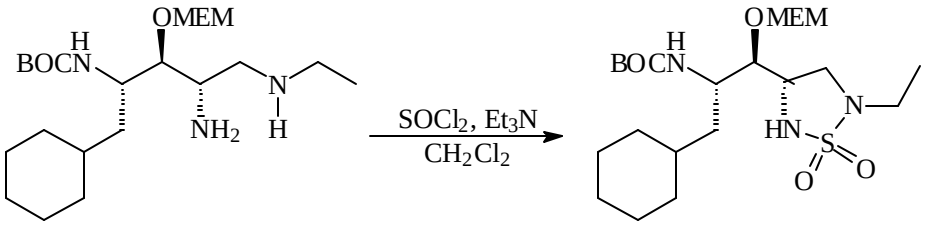
Priess *et. al* reported the synthesis of 2,5-di-*tert*-butyl-1,2,5-thiadiazolidine dioxide by the reaction of sulfuryl chloride with *N,N'*-di-*tert*-butyl-ethane-1,2-diamine, which after cleavage with triflic acid gave 1,2,5-thiadiazolidine (Scheme 4).[27]

Scheme 4.



Rosenberg *et. al.*[28] have reported the synthesis of potent renin inhibitors (effective at nanomolar concentrations) containing the substituted 1,2,5-thiadiazolidine 1,1-dioxide moiety. The key step involves the condensation of an appropriately substituted diamine with sulfuryl chloride (Scheme 5).

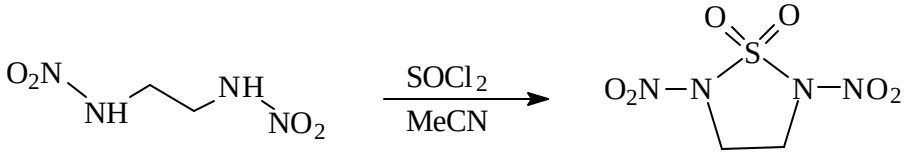
Scheme 5.



MEM = 2-methoxyethoxymethyl

Anikin *et. al*[29] have reported the synthesis of *N*-nitro 1,2,5-thiadiazolidine 1,1-dioxide by condensation of *N*,*N*'-dinitrosulfamide and sulfuryl chloride (Scheme 6).

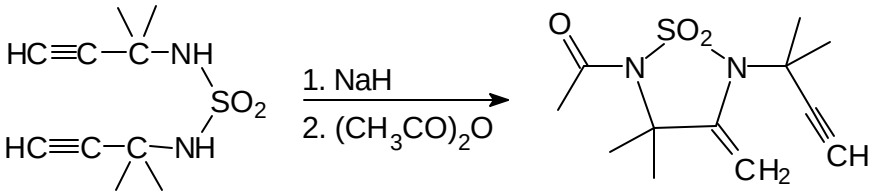
Scheme 6.



C. Reductive cyclization of alkenyl sulfamides:

Baker *et. al.* reported the synthesis of substituted thiadiazolidine 1,1-dioxide by reductive cyclization of *N*,*N*'-bis (1,1-dimethyl-2-propynyl)sulfamide (Scheme 7).[30]

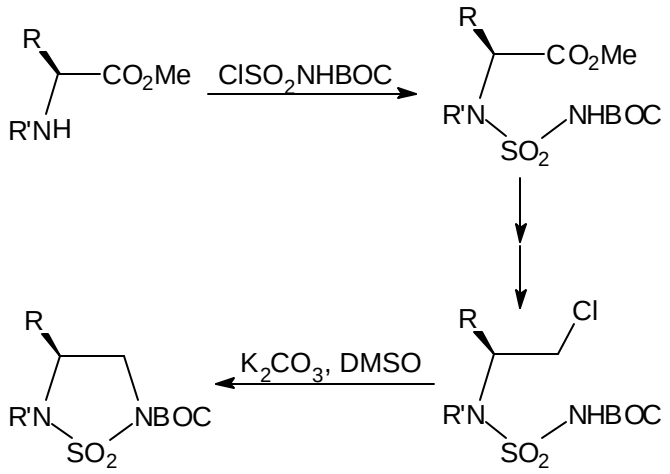
Scheme 7.



D. Reaction of chlorosulfonylisocyanate with amino acids:

In a recent study, Rega?nia *et. al.*[31] reported that the reaction of chlorosulfonylisocyanate and amino acid esters generates an *N*-sulfonamido amino acid. Ring closure in this intermediate is achieved by conversion of the ester to an alcohol followed by activation and subsequent treatment with a base. Variously substituted 1,2,5-thiadiazolidine 1,1-dioxides were prepared by this method (Scheme 8).

Scheme 8.

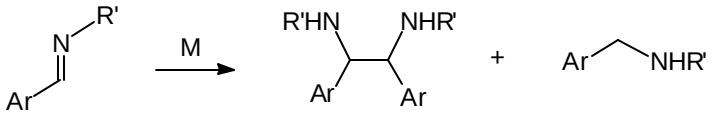


Syntheses of Vicinal Diamines:

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

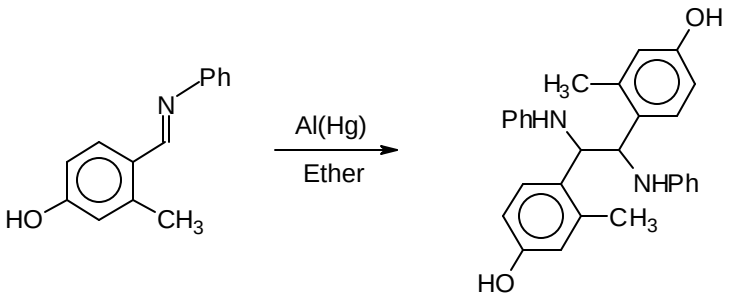


M = low valent metal

1) Reductive coupling with amalgams.

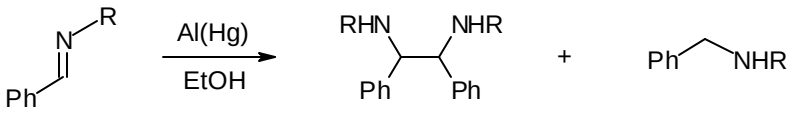
The use of a low valent metal for the reductive coupling reaction is known since 1908. Anselmino reported the reductive coupling of benzylidine anilines with aluminum amalgam to generate vicinal diamines (Scheme 9).[32]

Scheme 9.



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).[33] The monoamine arises from reduction of the imine which competes with the reductive coupling (Scheme 10).

Scheme 10.



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.[34]

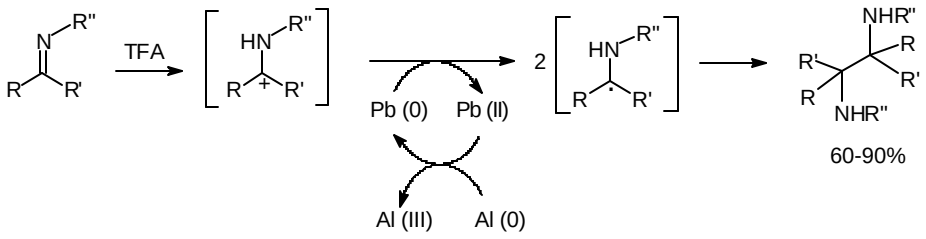
2) Reductive coupling with elements from Group 1, 2, 13, 14 and 15.

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.[35] The use of a Mg/MgI_2 system has also been reported.[36]

Sandhu has reported the coupling of imines with aluminum or bismuth in KOH/MeOH.[37] 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.[38] The reaction proceeds in THF containing trifluoroacetic acid. Yields of the diamines are in the range of 60-90% (Scheme 11).

Scheme 11.

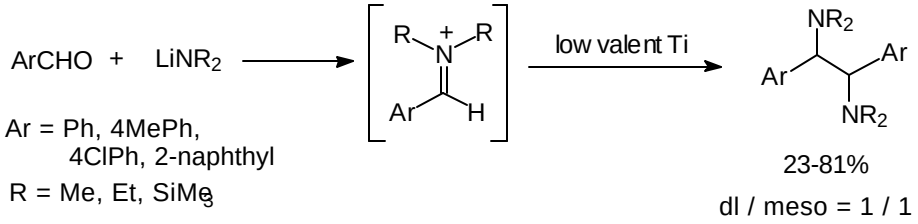


Newmann has demonstrated that a mechanism involving radicals as intermediates may be operating in these coupling reactions.[39] Schiff bases of the type ArRC=NR' react with $(Me_3Si)_2Hg$ to give carbon centered radicals $ArRC^{\cdot}(NR'SiMe_3)$ upon heating or irradiation. The later are in equilibrium 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[40] 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 12).

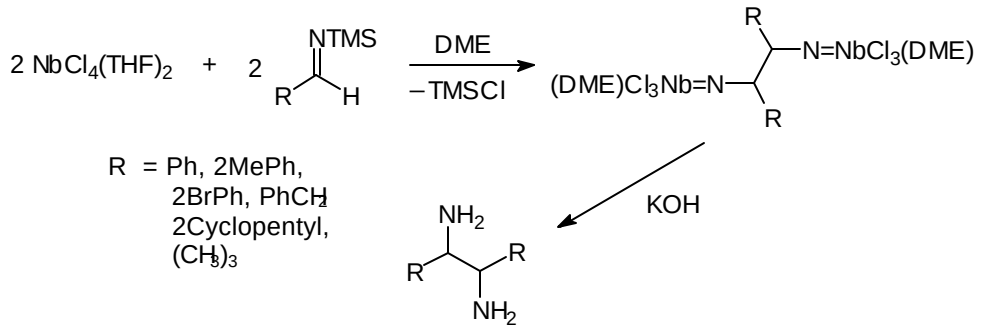
Scheme 12.



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.[41] 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 13).[42] 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.

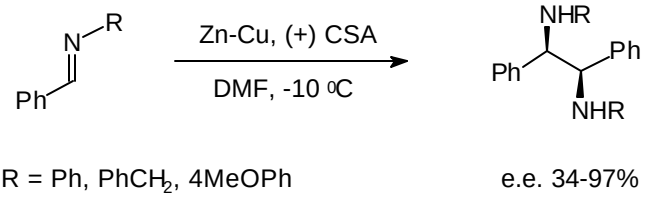
Scheme 13.



Kalyanam has employed indium for reductive coupling of aldimines under aqueous conditions to obtain *N*-substituted diamines in more than 90% yield.[43] Reductive coupling of imines with ytterbium to give diamines in 46-81% yields was reported by Takaki.[44] Imamato[45] and Enholm[46] 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.

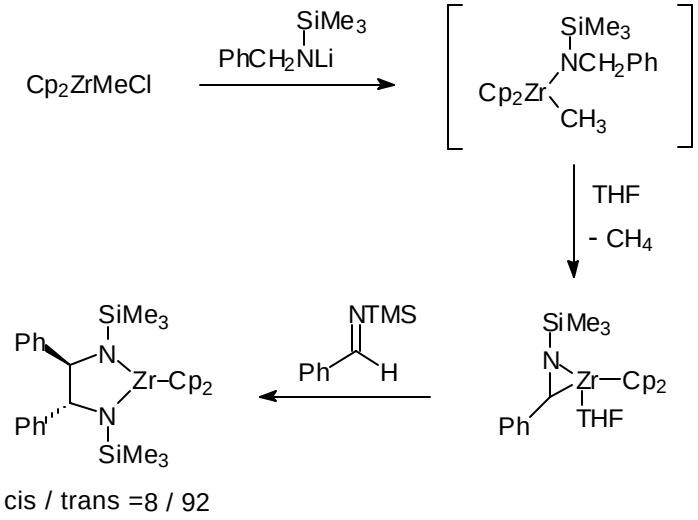
Recently, Shimizu has described an enantioselective reductive coupling of benzaldimines with Zn-Cu couple in the presence of (+)-camphorsulphonic acid. Diamines are obtained with 34-97% e.e. and 60-80% yield (Scheme 14).[47]

Scheme 14.



Organometallic reagents can also be used for imine coupling[48] (Scheme 15). Treatment of zirconocene (methyl) chloride with lithium dibenzylamide produces an adduct which loses methane upon heating at 110 ^{0}C.

Scheme 15.

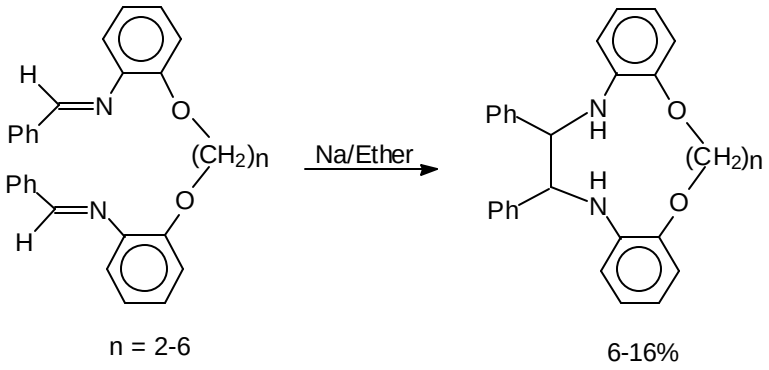


The resulting zirconium(trimethylsilyl)benzaldimine complex undergoes a diasteroeselective coupling reaction with *N*-(trimethylsilyl)benzaldimine to generate a zirconium chelate with good stereoselectivity (*cis/trans* = 8/92).

B. Intramolecular Reductive Coupling of Imines:

The intramolecular reductive coupling of imines was first described by Jaunin.[49] Salicylaldehyde bisimines which are linked through the phenolic oxygen with a carbon tether were employed in this study.

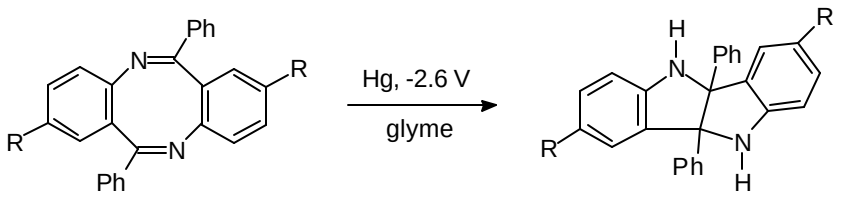
Scheme 16.



Reductive coupling with sodium in ether led to the formation of macrocyclic ethers in modest yields (Scheme 16). The stereoselectivity of ring formation was not reported.

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 17).[50]

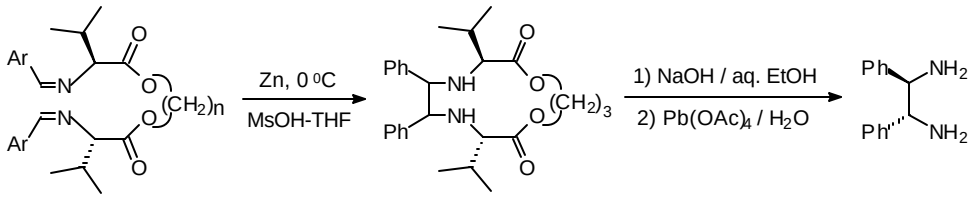
Scheme 17.



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.[51] 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, starting 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 18).

Scheme 18.



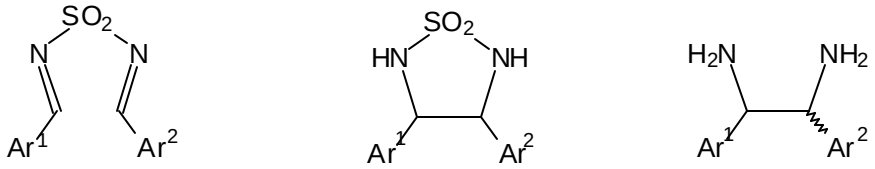
Ar = Ph n = 3

(R,R) : (R,S) : (S,S)

91 : 9 : 0

Studies in our research group have examined the synthesis of unsymmetrical 1,2-diarylethanediamines by the reductive, intramolecular cross-coupling of aromatic bisimines that are prepared from sulfamide (Scheme 19).[52]

Scheme 19.



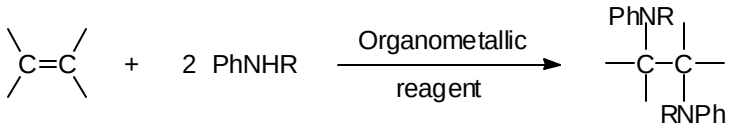
cis/trans 51-67%

Most of the substrates exhibit preference for the cis coupling mode and an introduction of *ortho* substituents into one of the aryl groups causes an increases in the amount of trans product. Substrate having bulky substituent (Ar^1=Ar^2 = 2-naphthyl) could not give the coupling product, presumably due to steric crowding in the transition state.

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.

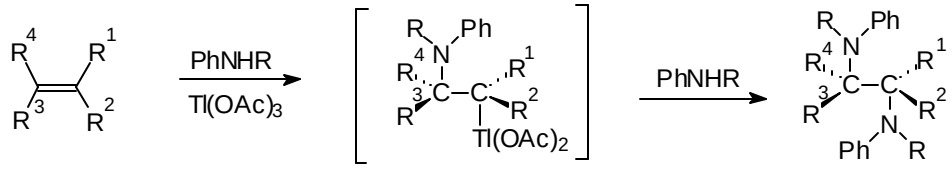


Metal mediated aminations.

Barluenga has reported a convenient preparation of aromatic vicinal diamines from olefins in the presence of thallium salts (Scheme 20).[53] 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 20.

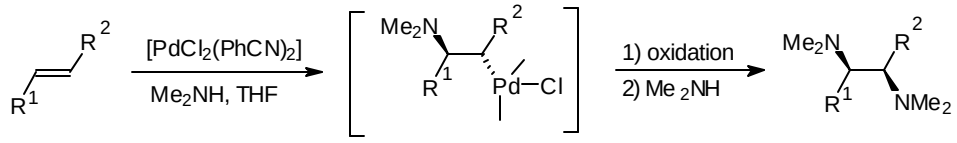


R^1, R^2 = H, alkyl, Ph
R^3 R^4 = H, alkyl
R = H, Me

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 21).[54] 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 21.



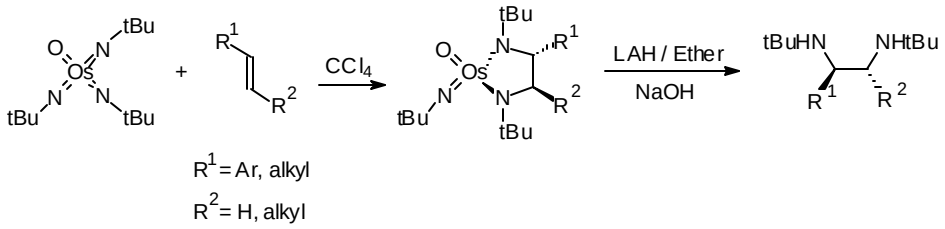
R^1, R^2 = H, alkyl

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

An elegant, osmium based amination protocol has been described by Sharpless.[55] 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 22). 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 22.

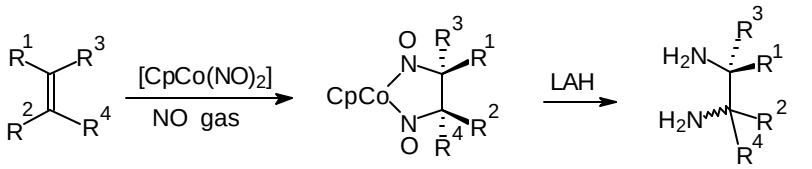


R^1 = Ar, alkyl

R^2 = H, alkyl

The 1,2-diamination of alkenes with nitric oxide and a cobalt complex has been described by Bergman.[56] Primary vicinal diamines are obtained in 50-90% yield with this procedure (Scheme 23). 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 23.



R^1, R^2 = H, alkyl, Ph

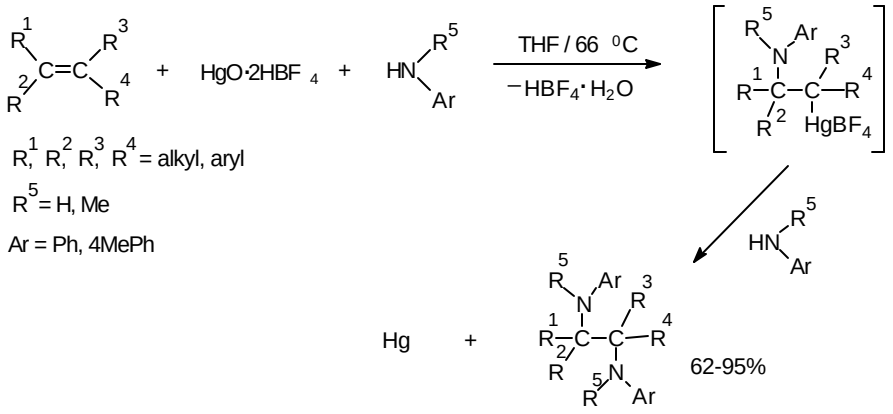
R^3, R^4 = H, alkyl

50-90%

de = 32-80%

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 24).[57] The reaction presumably proceeds *via* the formation of an intermediate β-aminomercury (II) tetrafluoborate.

Scheme 24.

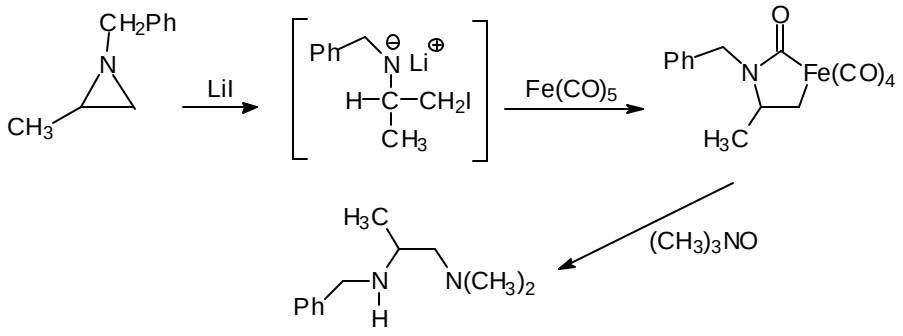


D. Other Methods for Preparation of 1,2-Diamines:

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 25).[58] 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 metallocle, which is finally converted to the diamine by trimethylamine *N*-oxide. The mechanism of this conversion is not known.

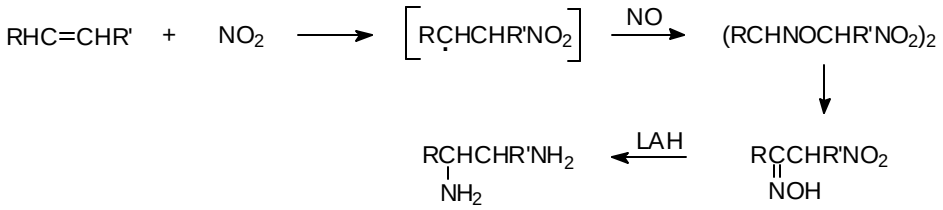
Scheme 25.



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 26).[59]

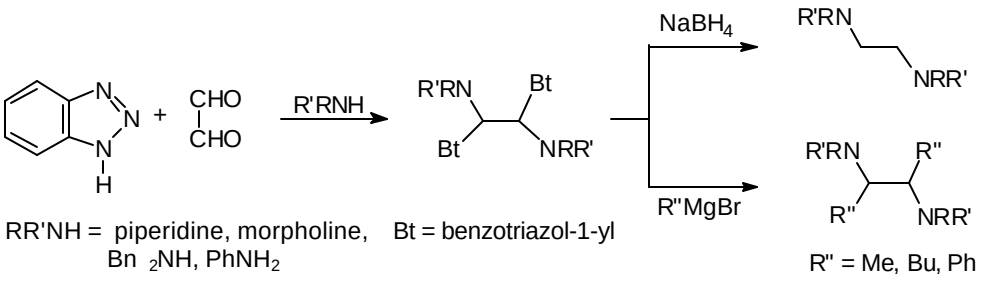
Scheme 26.



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.[60] 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 27).

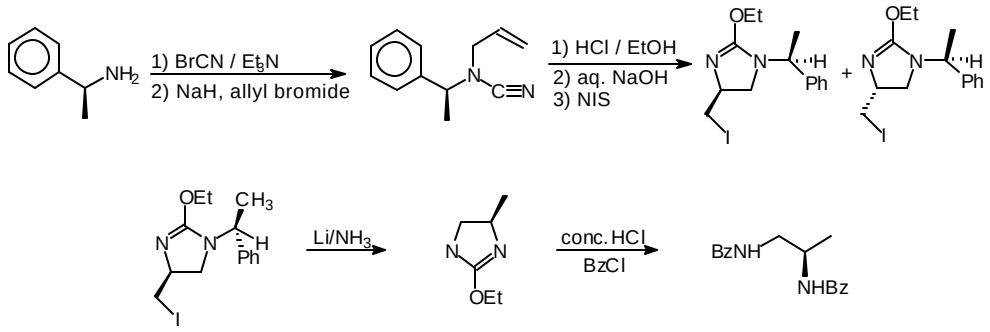
Scheme 27.



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.[61] 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 imiazolines is obtained which can be separated by chromatography. The imidazolines on hydrolysis gave 1,2-diamines in enantiomerically pure form (Scheme 28).

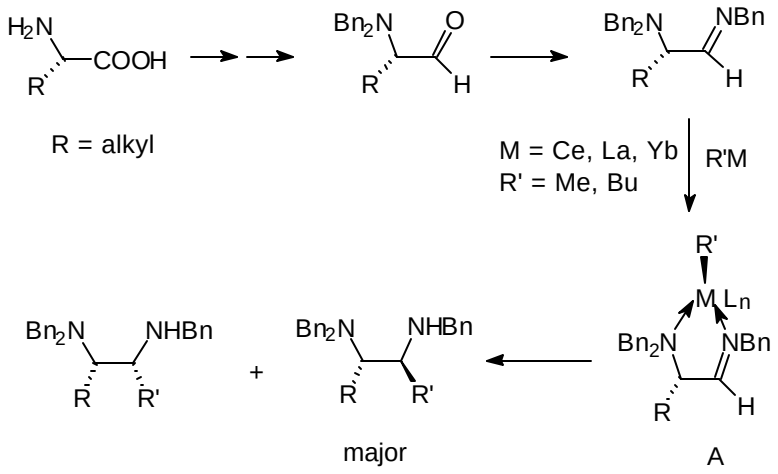
Scheme 28.



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.[62] 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 29), 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.

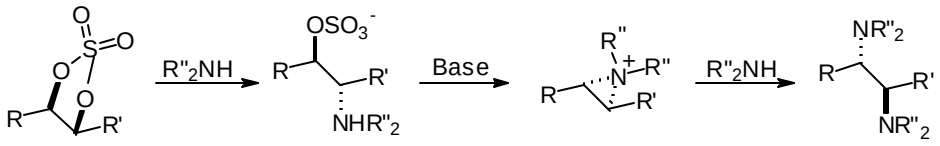
Scheme 29.



6) Synthesis of vicinal diamines from cyclic sulfates.

Sharpless has reported stereoselective synthesis of vicinal diamines using cyclic sulfates.[63] 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 30).

Scheme 30.

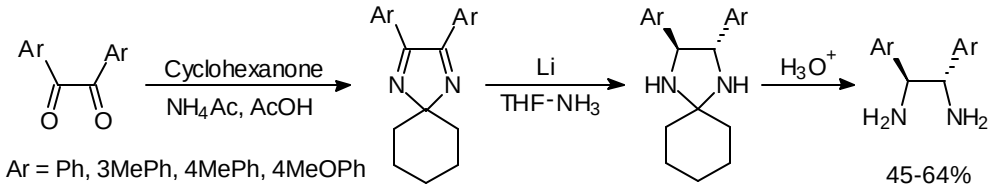


7) Synthesis of C_2 symmetric vicinal diamines from benzils.

Corey has described the synthesis of racemic C_2 symmetric vicinal diamines starting from substituted benzils (Scheme 31).[64] 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 31.



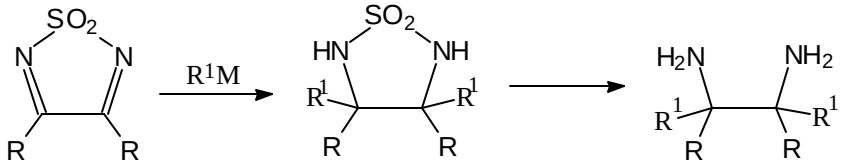
During the course of our studies, an exhaustive review[65] on the synthesis and applications of vicinal diamines appeared in the literature.

2. OBJECTIVE

The objective of our study was to develop a stereoselective synthesis of 3,4-disubstituted 1,2,5-thiadiazolidine 1,1-dioxides and their conversion to unsymmetrical vicinal diamines.

Although the condensation of a diamine or an amino alcohol with sulfamide is the simplest approach to thiadiazolidines, the approach is limited by the availability of the precursor diamine or amino alcohol. An alternative approach involving reductive cyclization of alkenyl sulfamides also has similar restriction.[30] Our approach to the substituted thiadiazolidine nucleus is based on α-diketone precursors that are readily converted to thiadiazole 1,1-dioxides by reaction with sulfamide. We hypothesized that it should be possible to add nucleophiles to the thiadiazoles by utilizing the electrophilicity of the *C-N* double bonds in the ring. If successful, the approach should generate thiadiazolidines which would then be converted to vicinal diamines (Fig 3).

Figure 3. Addition of organometalic reagents followed by conversion to diamines

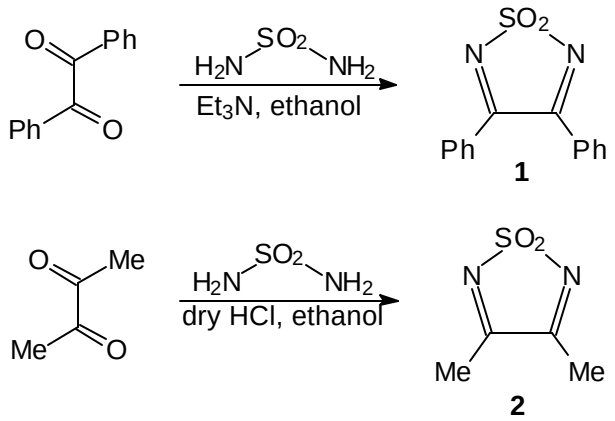


3. RESULTS AND DISCUSSION

For initial investigation 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide **1** and 3,4-dimethyl 1,2,5-thiadiazole 1,1-dioxide **2** were chosen as substrates for the addition of carbon nucleophiles since a) to the best of our knowledge, nucleophilic addition to the *C-N* double bond in these substrate has not been studied[66] and b) the addition of second nucleophile should be subject to some stereocontrol due to the adjacent stereogenic center formed in the first step.

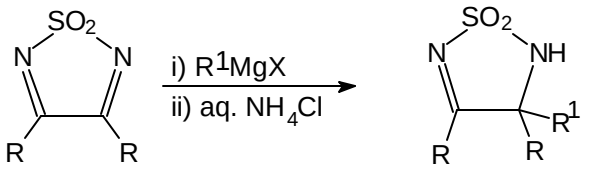
Thiadiazole 1,1dioxides **1** and **2** were prepared according to the literature procedures. Condensation of benzil with sulfamide in the presence triethylamine generated **1** (36%).[67] Diacetyl was condensed with sulfamide under acidic conditions to give **2** (48%, Scheme 32) [68].

Scheme 32.



Addition of alkyl Grignard reagents (one to two equivalents) to a solution of **1** in THF/benzene generates the thiadiazoline 1,1-dioxides **3-6** in good yield (85-99%) These are pure by ^{1}H NMR and can be used further as such. Similarly, addition of addition of aryl and alkyl Grignard reagents to **2** cleanly generates **7** and **8** (quantitative yield of crude product, Scheme 33, Table 1).

Scheme 33.



	R
1	Ph
2	Me

	3	**4**	**5**	**6**	**7**	**8**
R	Ph	Ph	Ph	Ph	Me	Me
R^1	Me	Et	Bu	*i*Pr	Ph	Et

Table 1. Addition of Grignard reagent to thaidiadiazole 1,1-dioxides.

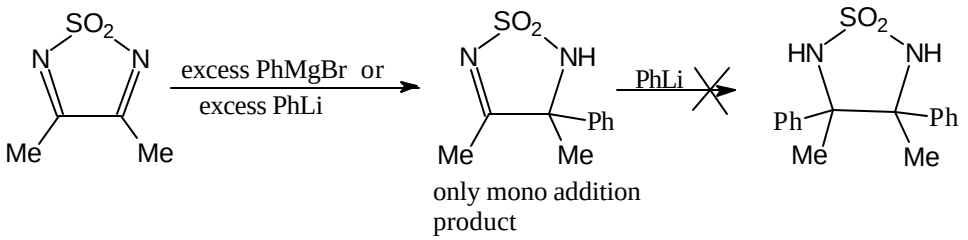
Compound	**R**	**R^1**	**% Yield**
3	Ph	Me	95[c]
4	Ph	Et	99[c]
5	Ph	Bu	98[c]
6	Ph	*i*-Pr	85[c]
7	Me	Ph	83
8	Me	Et	74

c: yield of crude product

An interesting feature of the Grignard addition is the relatively slow addition of second equivalent of the reagent. Thus, reaction of **1** with excess MeMgBr (5 equivalents, 1.5 h, rt.) generates a 2/1 mixture of *bis*- and *mono*-addition products, whereas with excess *i*-PrMgBr (3 equivalents) **6** is the only product isolated. This is presumably due to the steric hindrance by the isopropyl group. In general, it was observed that the addition of a second carbon nucleophile (other than methyl) was difficult in these substrates. For example,

treatment of **2** with a large excess of PhMgBr or PhLi in a variety of solvents at different temperatures resulted either in mono-addition or decomposition of the *mono*-adduct under the reaction conditions. Conducting the addition on pure *mono*-adduct derived from **2** had no beneficial effect (Scheme 34)

Scheme 34.



We therefore investigated the possibility of reducing the thiadiazolines **3-8** to the corresponding thiadiazolidines.

Reduction of thiadiazoline 1,1-dioxides to thiadiazolidine 1,1-dioxides.

Initial studies were conducted on **3**. Surprisingly, **3** was resistant to hydrogenation (H_2 (60 psi), Pd/C, EtoAc, 3h.). However, reduction with $NaBH_4$ could be effected in several solvents of which the $NaBH_4$/EtOH system was optimal. Thus, reduction of **3** ($NaBH_4$/EtOH, rt. 2 h) produced the unsymmetrical 3,4-substituted thiadiazolidine 1,1-dioxide **9** (89%) as a 6/1 mixture of *cis*/*trans* isomers (Scheme 35, Table 2). This reduction protocol was also applicable to the thiadiazolines **4-8** (57-89% yield of thiadiazolidine **10-13**, reaction time 2-5 h), the only exception being **6** which could not be reduced with $NaBH_4$, presumably due to the increased steric demands in the system arising from the isopropyl group. The use of THF as solvent in the borohydride reduction has no beneficial effect on the stereoselectivity. All crude reduction products were examined for isomer composition by 200 MHz ^{1}H NMR. Although, in some cases, separation of the *cis* and *trans* isomers in **9-13** was possible, no attempt was made to

optimize the separation and in most cases the diastereomeric mixture was used further.

Scheme 35.

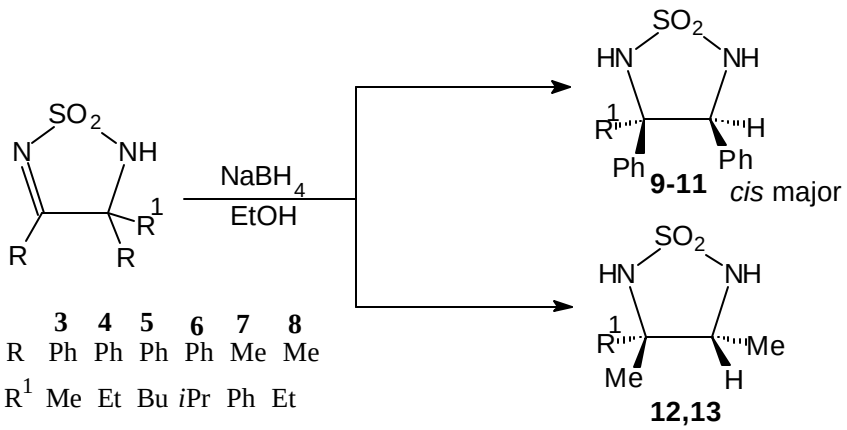


Table 2. Reduction of thiadiazolidine 1,1-dioxides to thiadiazolidine 1,1-dioxide.

Compound	R	R^1	% Yield	Diastereomer ratio[b]
9	Ph	Me	89	6/1
10	Ph	Et	84	7/1
11	Ph	Bu	77	6/1
12	Me	Ph	69	1.5/1 (6.5/1[d])
13	Me	Et	57	1.4/1 (3.7/1[d])

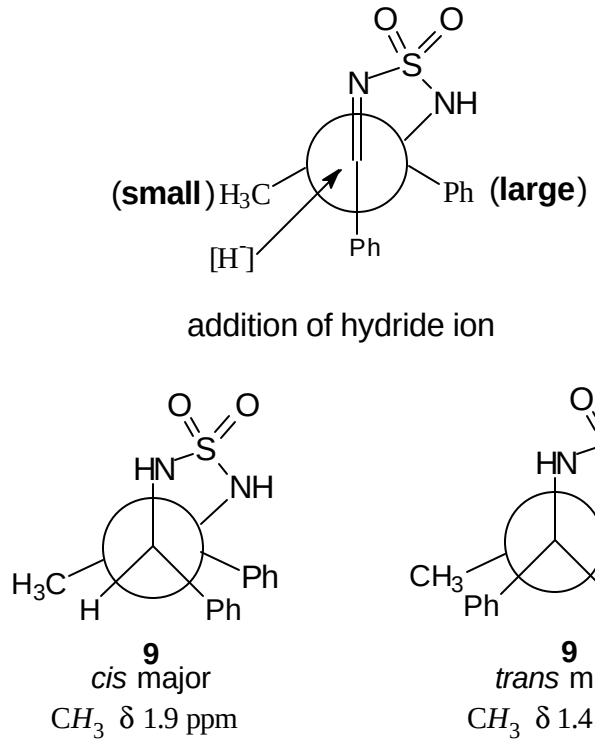
b: ratio based on the ^{1}H NMR of the crude reaction mixture, d: reduction with LAH

The formation of the *cis* (3*R**,4*S** for **9-11** and 3*S**,4*R** for **12** and **13**) isomer as the major product may be explained by a sterically controlled reduction of the thiadiazoline 1,1-dioxide in which the phenyl group dictates the diastereofacial selectivity in most cases. Figure 4 summarizes the reduction stereocontrol in the conversion of **3-8**.

The stereochemical assignments are based on the upfield shift of the methyl hydrogens in *trans* **9** (1.4 ppm), as compared to *cis* **9** (1.9 ppm) and an

upfield shift of the *ortho* hydrogens in one of the phenyl rings in *cis* **9-11** (shielding by the adjacent phenyl ring; reduction from the face opposite to the phenyl group (Fig 4).

Figure 4. Stereocontrolled reduction of 1,2,5-thiadiazolidine 1,1-dioxides.

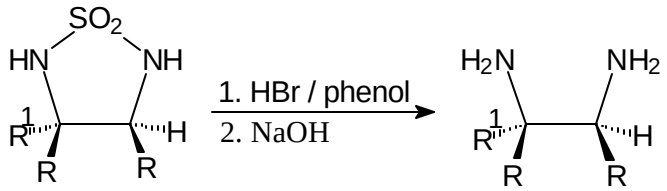


Although the low selectivity for **13** (*cis*/*trans* = 1.4/1) may be attributed to marginal steric differentiation between the ethyl and methyl groups, it is unclear why the reduction of **3** is more selective than that of **7** (*cis*/*trans* = 6/1 for **9** and 1.5/1 for **12**). Use of $LiAlH_4$ in THF increases the stereoselectivity of reduction in **7** and **8** and generates **12** (33%) and **13** (52%) as a 6.5/1 and 3.7/1 *cis*/*trans* mixture respectively. The above procedure involving sequential functionalization at C3 and C4 of thiadiazole 1,1-dioxides constitutes a new, stereoselective approach to unsymmetrical thiadiazolidine 1,1-dioxides.

Conversion of thiadiazolidine 1,1-dioxides to diamines

The conversion of the cyclic sulfamides (1,2,5-thiadiazolidine-1,1-dioxides) **9-13** to vicinal diamines proved to be challenging. The cyclic sulfamides are inert towords most reagents that reductively cleave sulfoxides[69] for example Mg(Hg), Na/C_2H_5OH and SmI_2 at ambient temperature. Pyridine-H_2O, Na/Naphthalene[70] were used to cleave sulfoxide but could not cleave the cyclic sulfamides. However, heating 3-methyl-3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide **9** 1,1-dioxide in 2N HBr in the presence of phenol (a modification of our previously described procedure)[52] generated the free diamine **14** in 37% yield. The procedure was applicable to cyclic sulfamides **10-13** which yielded diamines **15-18** in 33-52% yield (Scheme 36).

Scheme 36



9-13 **14-18**

Table 3. Conversion of thiadiazolidine 1,1-dioxides **9-13** to 1,2-vicinal diamine.

Compound	R	R^1	% Yield	diastereomer ratio
14	Ph	Me	37	6.5/1
15	Ph	Et	33	19/1
16	Ph	Bu	44	19/1
17	Me	Ph	52	1.2/1
18	Me	Et	48	1.8/1

The yields in the HBr/Phenol cleavage of thiadiazolidine 1,1-dioxides **9-13** to diamine **14-18** may be low due to competing side reactions such as

oxidation[71]. This method is an adaptation of a known method for the cleavage of sulfonamides[72]and is a redox process, the mechanism of which is unclear at present.

4. CONCLUSION

A new stereoselective synthesis of unsymmetrical thaidiazolidine 1,1-dioxides has been developed from readily available thiadiazoles. The stereoselctivity in the reduction of thiadiazolines to thiadiazolidines is moderate and favors the *cis* product over the *trans*. Conversion of the thiadiazolidine 1,1-dioxide to unsymmetrical vicinal diamines is an added advantage. The overall sequence represents a novel funtio nalization of α-diketones.

1. INTRODUCTION

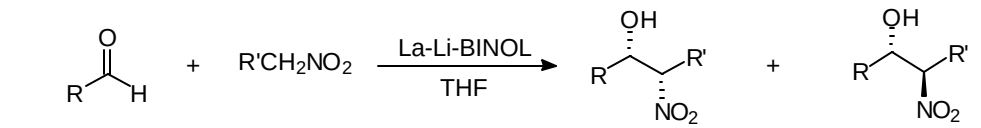
Guanidines are of considerable chemical and biological interest. Hydrogen-bond mediated interactions between guanidinium ions and phosphate-containing biomolecules[1] have lead to molecular recognition studies in chemical systems involving oxoanions capable of forming similar hydrogen bonded complexes with guanidines.[2] Several naturally occuring guanidines are of interest as neuroactive agents.[3] However, synthetic applications of enantiomerically pure guanidines have been relatively less explored.

A. 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.[4] 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[5,6] 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[6] were examined for their effect on diastereoselectivity as well as enantioselectivity (Scheme 1).

Scheme 1.



R = 2-phenylethyl, Bu R' = Et, Pr

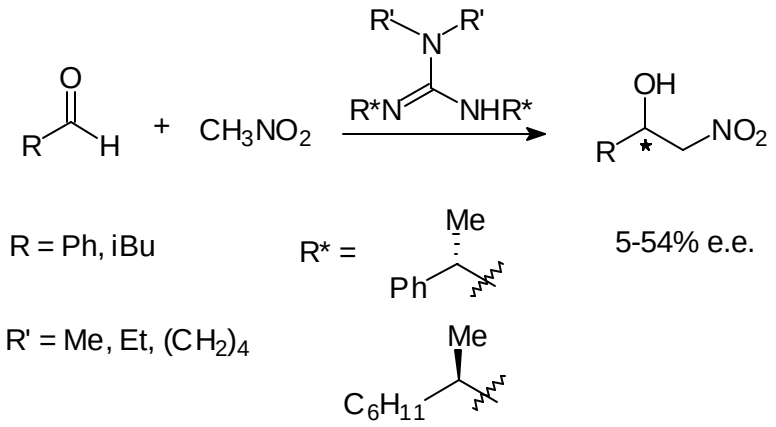
syn major

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

The reactions proceeded with good diastereoselectivity (3-9/1) as well as enantioselectivity (65-97% e.e. of the *syn* adduct).

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.[7] 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 ^{o}C (Scheme 2).

Scheme 2.

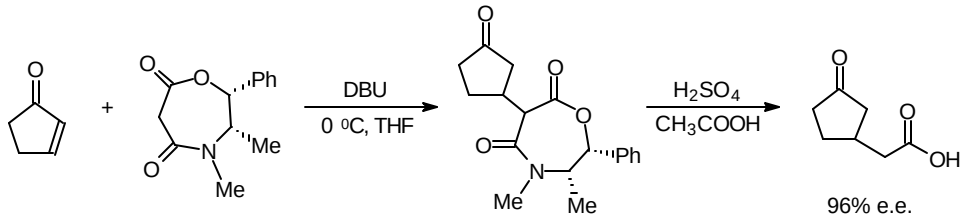


B. The catalytic asymmetric Michael addition reaction.

The asymmetric Michael addition reaction has also been the subject of several recent investigations and the topic has been reviewed recently.[8] Mukaiyama and co-workers have described the asymmetric synthesis of *d*-oxocarboxylic acids by the Michael addition reaction involving a chiral malonic acid derivative.[9] 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-

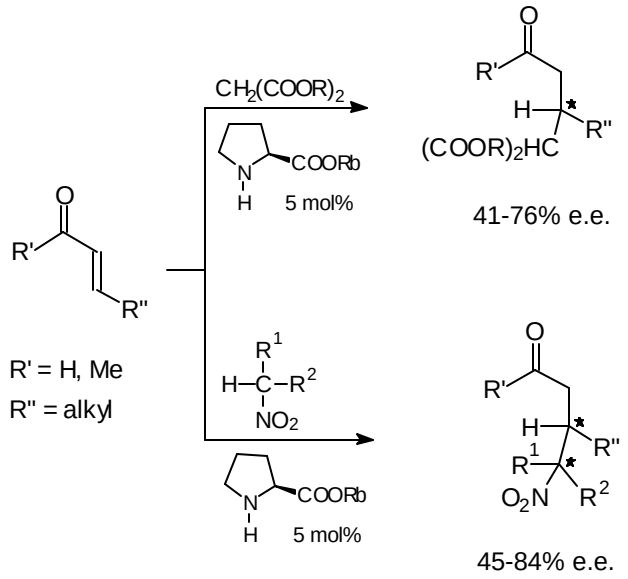
oxocyclopentane acetic acid with 96% e.e. (Scheme 3). Lower enantioselectivity (55%) was observed with 1-phenyl-2-buten-1-one as the Michael acceptor.

Scheme 3.



A catalytic enantioselective Michael addition reaction of a malonate ester to α, β unsaturated ketones and aldehydes has also been reported (Scheme 4).[10]

Scheme 4.

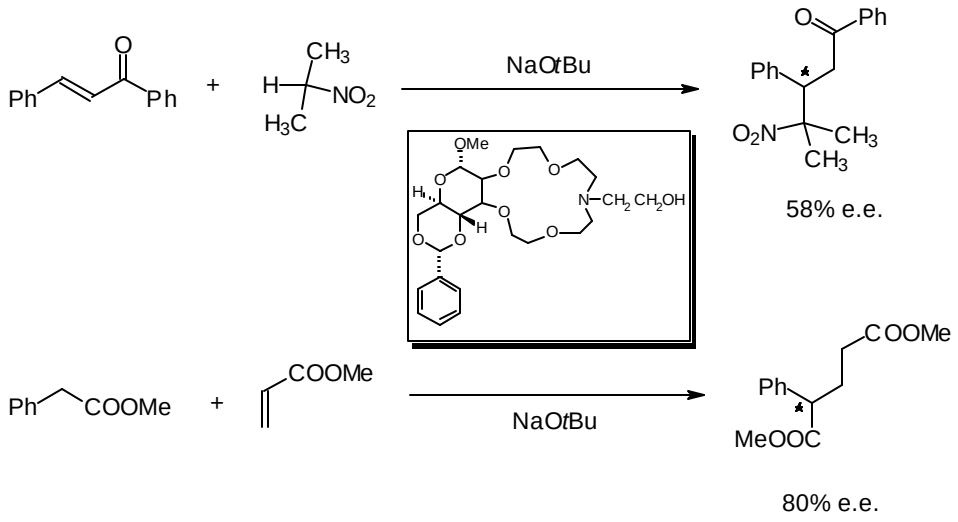


The catalyst in these reactions is the rubidium salt of L-proline. Adducts were obtained in 62-98% yield and 41-76% e.e.. L-proline salts have also been employed as catalysts for the addition of nitroalkanes to enones and enals.[11] In these studies, Michael adducts were obtained in 40-84% yield and with 45-84% e.e.

Taguchi and co-workers studied the enantioselective Michael addition reaction of malonates to enones.[12] 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.

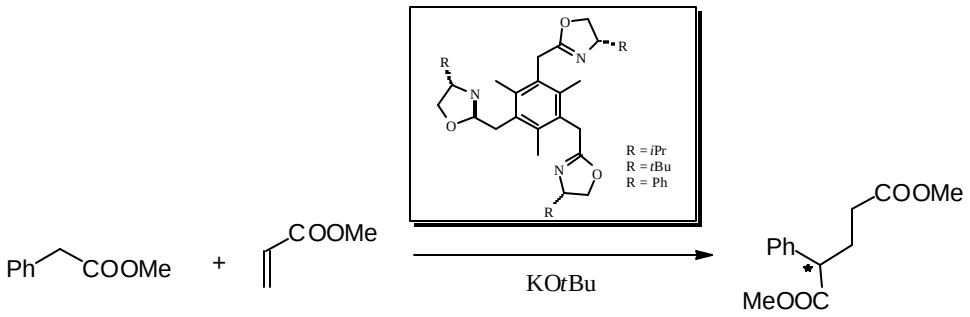
Crown ethers anellated to sugar units (Scheme 5) have been used as chiral complexing agents in the NaO*t*Bu catalyzed enantioselective Michael addition reactions of methyl phenylacetate to methyl acrylate[13] (up to 80% e.e.). Moderate asymmetric induction is observed in the Michael addition reaction of 2-nitropropane to chalcone (Scheme 5).[14]

Scheme 5.



Recently, Ahn and coworkers studied the enantioselective Michael addition reaction catalyzed by chiral tripodal oxazoline-*t*BuOK complexes. The benzene-based tripodal oxazoline system has significant affinity for the potassium cation. This property was used in asymmetric reactions involving potassium enolates. Michael adducts were obtained in 17-86% e.e. (Scheme 6)[15].

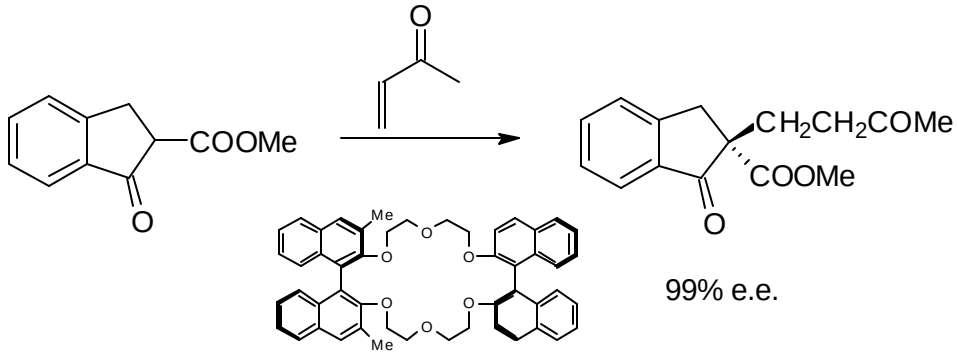
Scheme 6.



17-86 % e.e.

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 **A** and KO*t*Bu at -78 ^{0}C (Scheme 7).[16]

Scheme 7.



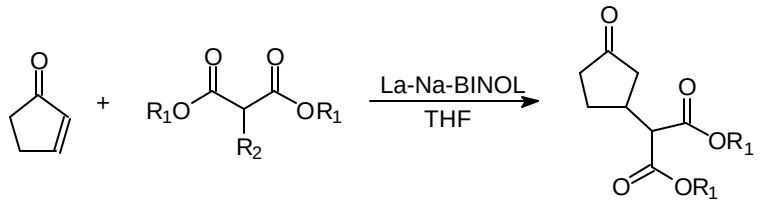
A

Rhodium (I)[17] and copper (II)[18] 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.).[19] A heterobimetallic catalyst (La-

Na-BINOL complex) is more effecient and provides adducts with up to 92% e.e. (Scheme 8).[20]

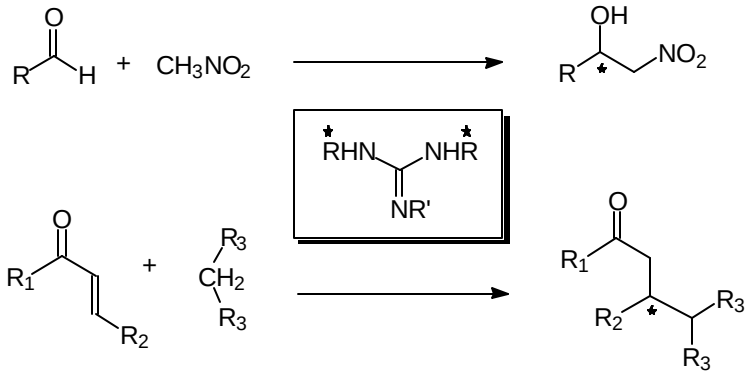
Scheme 8.



2. OBJECTIVE

The objective of our work was to synthesize and study the utility of enantiomerically pure guanidines as chiral bases in stereoselective carbon-carbon bond forming reactions such as the asymmetric nitroaldol and Michael addition reactions (Figure 1).

Figure 1. Guanidine catalyzed carbon-carbon bond forming reactions.

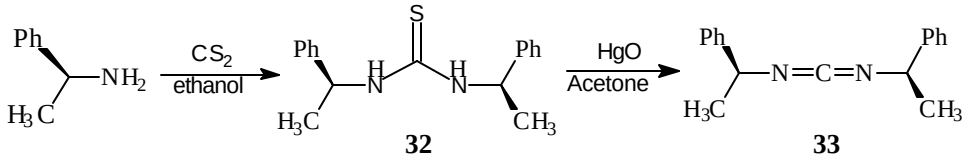


3. RESULTS AND DISCUSSION

Various methods are available for the synthesis of guanidines through intermediates such as thioureas,[21] aminoiminomethanesulfonic acids,[22] chloroformamidines,[23] dichloroisocyanides,[24] carbodiimides[25] or cyanamides.[26]

In the present study, several enantiomerically pure guanidines were synthesized from a (*S*)-(-)-α- methylbenzylamine derived carbodiimide and various amine. Reaction of (*S*)-α-methylbenzylamine with carbon disulfide in refluxing ethanol furnished the required thiourea **32** in 77% yield.[7] Thiourea **32** was converted to carbodiimde **33** using mercury oxide.[27] (Scheme 9).

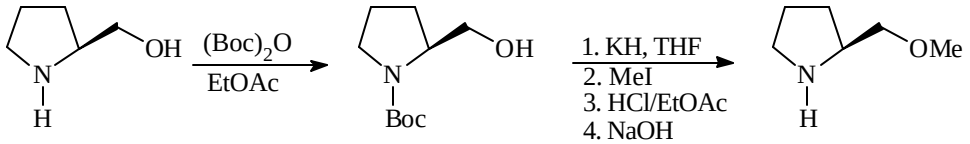
Scheme 9.



32 **33**

The prolinol-derived amine[28] **33** was synthesized from (*S*)-(-)-prolinol. Protection of prolinol with *tert*-dibutyldicarbonate generated Boc-prolinol **32** in 90% yield.[29] *O*-methylation of **32** by deprotonation with potassium hydride followed by treatment with methyl iodide generated (*S*)-*N*-Boc-2-methoxymethyl pyrrolidine in 80% yield which on treatment with Conc. HCl in EtOAc followed by basification with NaOH generated **33** in 71% yield (Scheme 10).

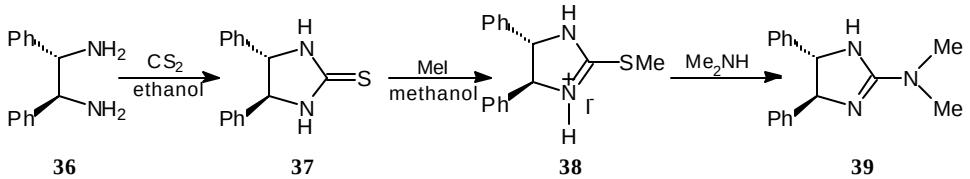
Scheme 10.



34 **35**

Thiourea[30] **37** was prepared in 81% yield from the reaction of (1*S*, 2*S*)-(-)-1,2-diphenyl ethanediamine[31] **36** and carbon disulfide (Scheme 11).

Scheme 11.

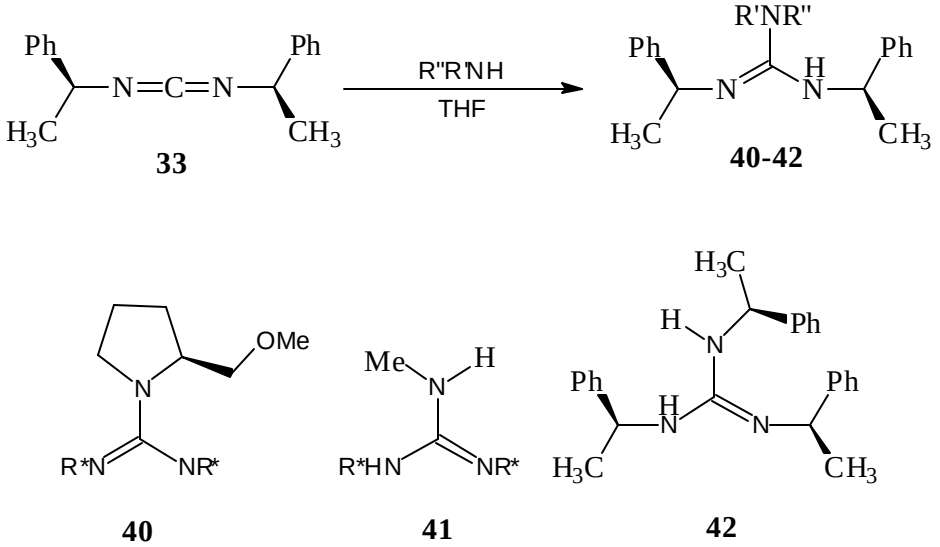


36 **37** **38** **39**

The thiourea **37** was *S*-methylated by with methyl iodide to give 2-methylthio-4,5-dihydro-iimdazole hydroiodide **(38)** which was converted to the corresponding guanidine **39** by reaction with dimethylamine.

Carbodiimde **33** on treatment with different various amines generated guanidines (scheme 12).

Scheme 12.



33 **40-42**

40 **41** **42**

Table 1 summarizes the results for the synthesis of guanidines used in this study.

Table 1. Synthesis of chiral guanidines **39-42**.

Thiourea	**Yield %**	**Salt/ carbodiimide**	**Yield %**	**Guanidine**	**Yield %**
37	69	**38**	95	**39**	22
32	70	**33**	76	**40**	50
32	70	**33**	76	**41**	93
32	70	**33**	76	**42**	70

Guanidines as catalysts in the enantioselective Nitroaldol reaction.

Initial investigations were conducted with benzaldehyde and nitromethane. The guanidines **39-42** were employed as bases in substoichiometric

amounts (typically 0.1 molar equivalents) and the nitroaldol reaction was studied as a function of solvent and temperature. The results are summarized in Table 2. The yield of the nitroalcohol **43** obtained varied from 22-70% (Scheme 13).

Scheme 13.

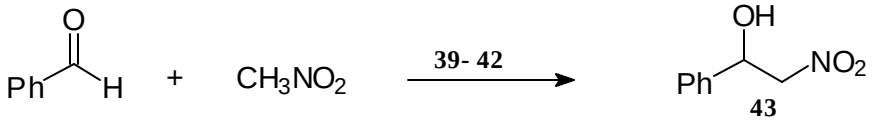


Table 2. Guanidine catalyzed enantioselective nitroaldol reaction.

No.	guanidine	equiv. of guanidine	Solvent	Time h	Temp. ^{0}C	Adduct % yield	Adduct % e.e. [a] (config.)
1.	**39**	0.1	THF	40	25	50	3 (*R*)
2.	**39**	0.1	hexane	42	25	37	5 (*R*)
3.	**40**	0.1	DME	48	25	56	-
4.	**40**	0.1	Hexane	48	25	49	-
5.	**40**	0.1	neat	48	25	56	-
6.	**41**	0.1	ether	40	25	37	5 (*R*)
7.	**41**	0.1	hexane	12	25	35	1
8.	**41**	0.1	THF	40	25	32	6 (*R*)
9.	**41**	0.1	chloroform	8	-40	19	1
10.	**41**	0.1	ethanol	8	-78	16	1
11.	**41**	0.1	ethanol	40	25	59	1
12.	**41**	0.1	toluene	24	25	74	1
13.	**42**	0.1	DME	48	25	67	3 (*R*)
14.	**42**	0.1	DME	48	25	43	-
15	**42**	0.1	neat	48	25	58	-
16	**42**	0.1	THF	48	25	43	-
17	**42**	0.1	DCM	48	25	72	-

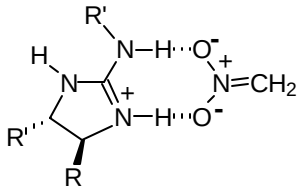
a: based on optical rotation.

The results indicate that the guanidines **39-42** are not effective asymmetric catalysts as evidenced by the low enantioselectivity of the process. Lowering the reaction temperature also does not affect the selectivity. The best result (6% e.e.) was obtained with guanidine **41** at ambient temperature with THF as the solvent.

In all of the nitroaldol reactions studied, the enantiomeric excess was very low (1-6%) 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 10 and 11 in Table 2. 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,[32] the chiral center in the guanidine is separated from the nitronate carbon by four atoms and may be too distant for effective asymmetric induction.

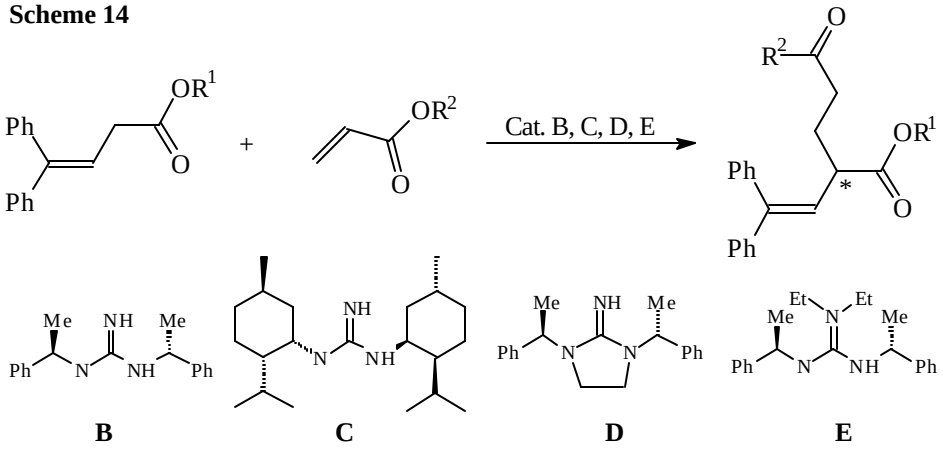
Figure 2. Hydrogen bonding of the nitronate ion with a C_2 symmetric guanidine.



Guanidines as enantioselective catalysts in Michael addition reaction.

To the best of our knowledge, there is a sole study on a guanidine catalyzed asymmetric conjugate addition reaction (Scheme 14).[33]

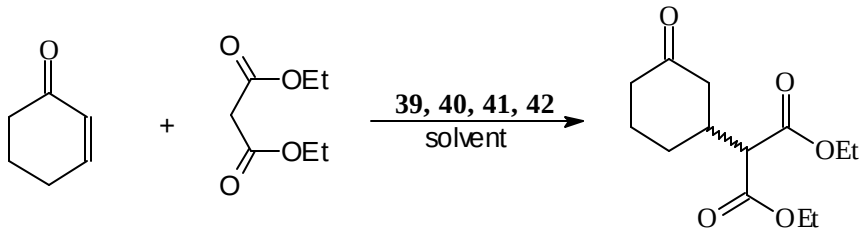
Scheme 14



This study appeared in the literature during the course of our studies. The results suggested ample scope for improvement and 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-cyclohexene-1-one **44** with diethyl malonate **45** in the presence of a catalytic amount of guanidine **39-42** (0.3 eq.) in ethanol generated expected conjugate addition product in moderate yield (scheme 15).

Scheme 15.



44 **45** **46**

The effect of solvent and temperature on the enantioselectivity of the Michael addition reaction was also examined. Table 3 summarizes the results for the enantioselective Michael addition reaction.

Table 3. Michael addition reaction catalyzed by guanidines **39-42.**

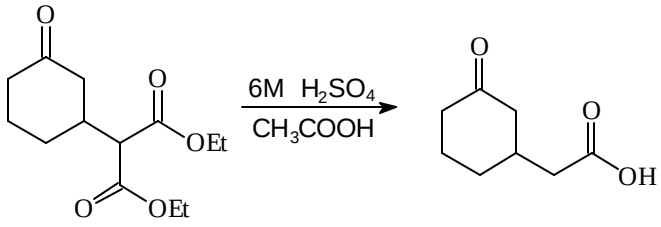
No	enone	malonate	guanidine[a]	solvent	temp. ^{0}C	time h	Adduct (%yield)
1.	**44**	**45**	**39**	ethanol	-20	60	**46** (40)
2.	**44**	**45**	**39**	ethanol	0	60	**46** (46)
3.	**44**	**45**	**39**	ethanol	10	28	**46** (55)
4.	**44**	**45**	**40**	ethanol	10	32	**46** (65)
5.	**44**	**45**	**40**	ethanol	0	48	**46** (52)
6.	**44**	**45**	**41**	benzene	10	48	**46** (48)
7.	**44**	**45**	**41**	ethanol	-20	72	**46** (31)
8.	**44**	**45**	**41**	ethanol	0	72	**46** (39)

a: 0.3 equivalents of guanidine were employed.

The yield of the conjugate addition reaction varied from 31 to 65% and lowering the reaction temperature slowed down the reaction considerably. Thus, while a 65% yield of adduct **46** was obtained after 32h at ambient temperature, the reaction at 10 ^{o}C had to be conducted for 48h to obtain a yield of 48%.

The Michael adducts were hydrolyzed with concomitant decarboxylation to furnish the cyclohexanone 3-acetic acids **47** by heating in 6M H_2SO_4/CH_3COOH.[9] The acids were obtained in 11-60% yield.

Scheme 16.



46 **47**

The enantioselectivity of the Michael addition process is based on the optical rotation of the cyclohexanone acetic acids. In most of the cases, the enantiomeric excess was quite low (1-10%) as judged by the specific rotation and an alternative determination of enantiomeric excess was not carried out. The results are summarized in Table 4.

Table 4. Hydrolysis of Michael adducts.

No.	**guanidine**	**Adduct** (% yield)	**Acid**	**Acid** % yield	**Acid** $[\alpha]_D^0$	**Acid**[34] % e.e. [a]
1.	**42**	**46** (40)	**47**	38	-1.37	10
2.	**42**	**46** (46)	**47**	19	-0.94	7
3.	**42**	**46** (55)	**47**	11	-0.28	2
4.	**42**	**46** (65)	**47**	22	-0.06	1
5.	**42**	**46** (52)	**47**	46	-0.10	1
6.	**42**	**46** (48)	**47**	60	-0.24	2
7.	**42**	**46** (31)	**47**	41	-0.71	5
8.	**38**	**46** (39)	**47**	39	-0.08	1

a: based on specific rotation.

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.

4. CONCLUSION

Enantiomerically pure guanidines were synthesized and 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. The 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.

(*S*,*S*)-N,N'-Bis(1-phenylethyl)thiourea (32):[7]

A solution of carbon disulfide (1.2 ml, 20 mmol) and the (*S*)-(-)-1-phenylethylamine (5.14 ml, 40 mmol) in ethanol (35 ml) was heated to reflux for 20 h. The solution was cooled to ambient temperature and the crystals obtained were filtered off, washed with hexane and ether, and air-dried to give 4.20 g (74%) of **32**.

mp: 200-202 ^{0}C.

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

δ 7.02-7.21 (m, 10H, Ar*H*), 6.24 (bs, 2H, 2 x N*H*), 5.04 (bs, 2H, 2 x C*H*), 1.45 (d, *J* = 6.8, 6H, 2xCH_3).

IR ($CHCl_3$):

3200, 1525, 1320, 1065, 740, 680 cm^{-1}.

[a]$_D^{25}$ = + 102.2 (c 1.3, $CHCl_3$)

(*S*,*S*)-bis(1-Phenylethyl)carbodiimde (33):[7]

A mixture of thiourea **32** (5 g, 17.6 mmol) and HgO (7.62 g, 35.2 mmol) in acetone was heated to reflux for 1 h. Reaction mixture was filtered through celite and the filtrate was concentrated. The residue was redissolved in pentane and cooled to –30 ^{0}C to precipitate the urea by-product which was then filtered off. The filtrate was concentrated to give 3.34 g (76%) of **33**.

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

δ 7.35-7.19 (m, 10H, Ar*H*), 4.59-4.49 (q, *J* = 6.8, 2H, 2 x C*H*), 1.47-1.43 (d, 6H, 2 x CH_3).

IR (neat):

3083, 3062, 3028, 2974, 2953, 2925, 2869, 2119, 1492, 1452, 1373, 1299, 1276, 1203, 1070, 1027, 757, 698 cm^{-1}.

(*S*)-(-)-1-(*tert*-Butoxycarbonyl)-2-pyrrolidinemethanol (34):[29]

To a cooled solution of prolinol (202 mg, 2 mmol) in ethyl acetate (5 ml) was added $(BoC)_2O$ (457 mg, 2.1 mmol). The reaction mixture was stirred for 2h. After the reaction was complete ethyl acetate (5 ml) was added and the solution was washed with 1N HCl, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure gave 365 mg (90%) of **34** as oil that solidified on cooling.

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

δ 3.65 (bs, 1H, CH_2OH), 3.61-3.25 (m, 5H, CH_2OH, CH_2N, CHN), 2.06-1.70 (m, 4H, CH_2CH_2), 1.47 (s, 9H, 3xCH_3).

(*S*)-(+)-2-Methoxymethylpyrrolidine (35):[28]

To a cooled suspension of sodium hydride (25 mg, 1.05 mmol) and MeI (0.3 ml, 4.75 mmol) in THF (2 ml) was added **34** (192 mg, 0.96 mmol, in 2ml THF) dropwise. And the mixture was stirred for 2 h at 10 °C. After the reaction was complete sat. aqueous NH_4Cl was added and the mixture was extracted with EtOAc (3 x 5 ml). Evaporation of solvent under reduced pressure gave 165 mg

(77%) of the *O*-methylated product. Deprotection (165 mg, 0.76 mmol) with conc. HCl in EtOAc gave 57 mg (65%) of **35.**

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

δ 3.92 (m, 1H, NC*H*), 3.6-3.28 (m, 4H, CH_2N, CH_2OCH_3), 3.37 (s, 3H, OCH_3), 1.95-1.77 (m, 4H, 2 x CH_2).

[a]$_D^{25}$ = + 2.78 (c 5.8, ethanol) (Lit.[28] $[\alpha]_D$ = + 2.81 (c 5.8, ethanol)

(4*S*, 5*S*)-(-)-*trans*-4,5-Dihydro-4,5-diphenylimidazole-2-thione (37):[30]

To a cooled (5-10 ^{0}C) solution of the (1*S*, 2*S*)-(-)-1,2-diphenyl ethanediamine **36** (0.64 g, 3 mmol) in ethanol (20 ml) 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 19h (monitored by TLC). After the reaction was complete, the mixture was concentrated and the residue was purified by crystallization with ethyl acetate/ pet. ether to give 739 mg (97%) of **37.**

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*S*, 5*S*)-(-)-*trans*-2-Methylthio-4,5-dihydro-4,5-diphenylimidazole hydroiodide (38):

To a solution of (4*S*, 5*S*)-(-)-*trans*-4,5-dihydro-4,5-diphenylimidazole-2-thione **37** (0.25 g, 1 mmol) in THF (5 ml) was added methyl iodide (0.15 ml, 2 mmol). The reaction mixture was heated to reflux for 1h, concentrated and dried thoroughly to give 0.4 g (quantitative) of **38,** which was pure by NMR.

^{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*)-(-)- 2,2 -Dimethylamino -4,5-dihydro -4,5 -diphenylimidazole (39):

To a solution of the 2-methylthio-4,5-dihydro-iimdazole hydroiodide **38** in ethanol was added 40% aqueous solution of dimethylamine in excess. The reaction mixture was heated at 50 ^{0}C. The reaction was monitored by TLC, aqueous dimethylamine was added to the reaction mixture periodically and heating was continued for 48h. 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 **39** which was pure by ^{1}H NMR spectroscopy.

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

δ 7.30 (brs, 10H, Ar*H*), 4.70 (s, 2H, C*H*), 3.05 (s, 6H, 2 x NCH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

162.2 (*C*=N), 144.2 (Ar*Cipso*), 128.3, 127.1, 126.4 (Ar*C*), 74.2 (*C*-H), 38.1 (2 x *C*H_3).

IR (Neat):

2923, 2854, 1610, 1463, 1377, 1348, 1263, 1191, 1035, 771, 700 cm^{-1}.

Anal. for $C_{17}H_{19}N_3$:

Calcd. C, 76.94 H, 7.22 N, 15.84.

Found C, 76.74, H, 7.43 N, 15.45.

[a **]$_D$ =** + 40 (*c* 0.5, $CHCl_3$).

General procedure for the prepartion of Guanidines 40-42 from the carbodiimide 33:

A mixture of the carbodiimde (1 eq.) and amine (1 eq.) was stirred at room temperature for 8 h. 2N HCl (3ml) was added, the mixture was stirred for 5 minutes and then washed with ethyl acetate (3 x 5ml). The aqueous layer was cooled and was basified with 12 N NaOH. The resulting mixture was extracted with dichloromethane (4 x 5ml). Drying and concentration of the combined dichloromethane extracts gave the guanidine that was pure by ^{1}H NMR spectroscopy.

(2*S*)-2-Methoxymethyl)-N,N'-bis[(1*S*)-1-phenylethyl]pyrrolidine-1-carboximidamide (40):

Reaction of *S*-(+)-2-methoxymethylpyrrolidine **35** (115 mg, 1 mmol) and the carbodiimide **33** (250 mg, 1 mmol) for 8h gave 182 mg 49%) of **40**.

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

δ 7.17 (m, 10H, Ar*H*), 4.34-4.18 (m, 3H, C*H*$_2$OMe, C*H*N (ring), 3.37-3.31 (m, 2H, C*H*$_2$N), 3.14 (s, 3H, C*H*$_3$), 2.01-1.29 (m and d, *J* = 6.8, 10H, 2 x C*H*$_2$, C*H*$_3$).

^{13}C NMR (50 MHz, $CDCl_3$):

152.3 (*C*=N), 128.3, 128.0, 126.3, 126.0, (Ar*C*), 74.8 (CH_2OMe), 58.5 (H*C*-N) 56.3 (O*C*H$_3$), 49.8 (*C*H$_2$N), 29.1 (*C*H$_2$), 24.6 (*C*H$_2$).

IR (Neat):

3334, 3082, 3060, 3026, 2968, 2925, 2869, 1612, 1581, 1492, 1450, 1390, 1384, 1352, 1301, 1278, 1217, 1203, 1107, 910, 756, 732, 700 cm^{1}.

MS (EI, 70 eV):

m/z 84 (100), 105 (16), 120 (7), 141 (1), 190 (1), 216 (1), 245 (1), 334 (1), 365 (M^+, 1).

[a]$_D$ = + 72 (*c* 0.6, ethanol).

(*S, S*)-*N*-Methyl-*N',N''*-bis(1-phenylethyl)guanidine (41):

Reaction of methylamine (2M soln. in THF, 7.5 ml, 15 mmol) and carbodiimde **33** (250 mg, 1mmol) for 12h gave 790 mg (93%) of **41**.

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

δ 7.25-7.05 (m, 10H, Ar*H*), 4.85-4.70 (q, *J* = 6.7, 2H, C*H*), 2.85 (s, 3H, NCH_3), 1.50-1.45 (d, *J* = 6.7, 6H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

δ 153.8 (*C*=N), 143.8 (Ar*Cipso*), 129.1, 127.7, 126.1 (Ar*C*), 77.8 (C*H*), 52.8 (N*C*H_3), 24.7 (*C*H_3).

IR (Neat):

2972, 3279, 3440, 1631, 1529, 1452, 1210, 1086, 1023, 912, 759 cm^{-1}.

MS (EI, 70 eV):

m/z 57 (8), 77 (50), 91 (12), 105 (100), 176 (8), 266 (5.1), 281 (M^+, 24).

[a]$_D$ = 61 (*c* 1.1, ethanol).

***N, N', N''-tris*(1-Phenylethyl)guanidine (42):**

Reaction of 1-phenethylamine (363 mg, 3mmol) and cabodiimde (250 mg, 1mmol) for 8h gave 790 mg (71%) of **42**.

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

δ 7.16-7.11 (m, 10H, 2xAr*H*), 6.75-6.74 (m, 5H, Ar*H*), 4.51 (brs, 3H, 3xC*H*), 1.32-1.29 (d, *J* = 6.8, 9H, 3xCH_3).

^{13}C NMR (50 MHz, $CDCl_3$):

148.9 (*C*=N), 128.5, 127.8, 127.4, 126.8, 126.0, 125.6 (Ar*C*), 52.0 (*C*-H), 24.7 (CH_3).

IR (Neat):

3429, 3058, 3026, 2996, 2923, 2867, 1637, 1492, 1450, 1365, 1269,1143, 1085, 1068, 1026, 761, 700 cm^{-1}.

MS (EI, 70 eV):

m/z 65 (32), 77 (48), 91 (65), 105 (100), 120 (51), 155 (32), 184 (23), 371 (M^+, 14).

$[\alpha]_D$ = + 265 (*c* 1.2, ethanol).

2-Nitro-1-phenylethan-1-ol (43):[7]

The reaction of benzaldehyde (0.1 ml, 1 mmol) and nitromethane (0.1 ml, 1.5 mmol) in the presence of guanidine **41** (31mg, 0.1 mmol) in toluene for 40h gave after purification (SiO_2, petroleum ether/ethyl acetate, 9/1), 53 mg (32%) of **43**.

^{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}.

[a]$_D$ = 2.0 ^{0} (*c* 1.0, EtOH), e.e. = 6 % (Lit.[7] $[\alpha]_D$ = - 34.0 ^{0} (EtOH) for *'S'* enantiomer).

(3-Oxocyclohexyl)-propanedioic acid, diethyl ester (46):

To a cooled (-20 ^{0}C) solution of the cyclohexenone **(44)** (0.29 ml, 3 mmol) in ethanol was added the guanidine followed by diethyl malonate **(45)** (0.3 ml, 2 mmol). The homogeneous reaction mixture was kept at -20 ^{0}C for 60 h, 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, after purification (SiO_2, petroleum ether/ethyl acetate, 7/3), 0.26 g (50%) of **46**.

^{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_2CHCH_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_2CH_2CH), 1.95-1.85 (m, 1H, CH_2CH_2CH), 1.7-1.55 (m, 1H, $CH_2CH_2CH_2$), 1.55-1.45 (m, 1H, $CH_2CH_2CH_2$), 1.25-1.15 (2 x t, *J* = 6, 6H, CH_2CH_3).

IR (Neat):

3000, 1760, 1460, 1420, 1390, 1340, 1320, 1260, 1220, 1180, 1110, 1040, 870 cm^{-1}.

3-Oxocyclohexaneacetic acid (47):[34]

To a suspension of the **46** (0.12 g, 0.47 mmol) in acetic acid was added 6M H_2SO_4 (exotherm). The reaction mixture was heated at 130-140 ^{0}C for for 4h.

It was then concentrated and thoroughly dried. The residue was purified by flash chromatography (SiO_2, dichloromethane/methanol, 95/5) to yield 40 mg (55%) of **47**.

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

δ 8.4-7.9 (bs, 1H, COOH), 2.6-2.2 (m, 6H, C*H*$_2$COOH, COC*H*$_2$CH, COC*H*$_2$CH$_2$), 2.2-1.9 (m, 3H, COCH$_2$C*H*, COCH$_2$C*H*$_2$), 1.8-1.55 (m, 1H, CH$_2$CH$_2$C*H*$_2$), 1.55-1.2 (m, 1H, CH$_2$CH$_2$CH$_2$C*H*$_2$).

IR (Neat):

2936, 1713, 1448, 1418, 1346, 1312, 1271, 1227, 1159, 1097, 868 cm^{-1}.

[a]$_D$ = - 1.37 (*c* 1.0, $CHCl_3$), e.e. = 10 % (Lit.[32] $[\alpha]_D$ = - 13.2 ^{0} (*c* = 1.0, $CHCl_3$) for '*S*' enantiomer with 98% e.e.).

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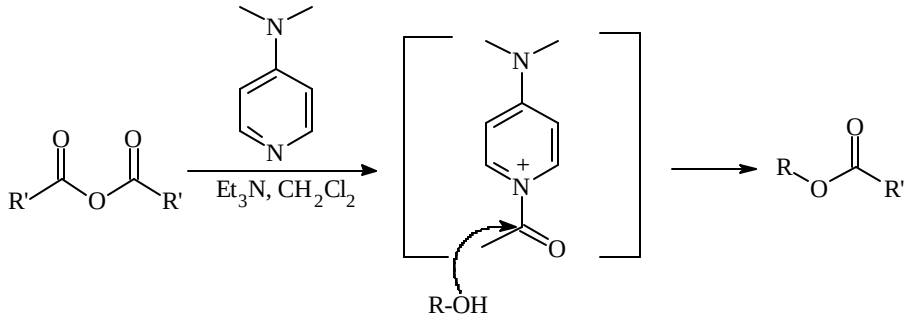
SECTION 1: Magnesium bromide catalyzed acylation of alcohols.

1. INTRODUCTION

The acylation of an alcohol is usually achieved by the reaction of an acid anhydride or acid chloride in the presence of amine bases such as triethylamine, pyridine or 4-(N,N'-dimethylamino)pyridine (DMAP)[1]. In these reactions, the base is considered to provide activation to acylating reagent (as nucleophilic catalyst, e.g DMAP) whereas in some cases the base is used to trap the generated acid (Scheme 1).

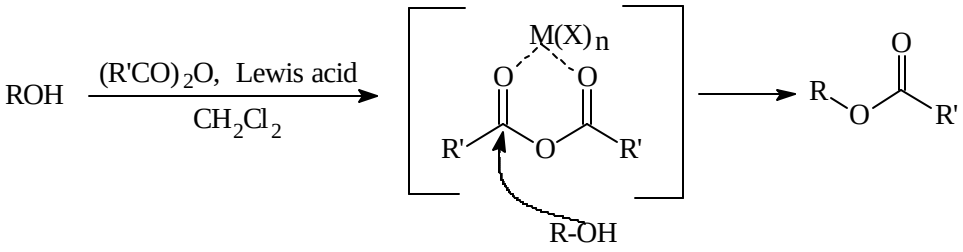
Scheme1.



Recently Vedejs *et al.* reported tributyl phosphine as a similar catalyst for acylation of alcohols. [2] Although the mechanism of tributyl phosphine catalysis is not yet clear.

Besides the above catalysts, various lewis acids such as InI_3,[3] $Bi(OTf)_3$,[4] $FeCl_3$,[5] $In(OTf)_3$,[6] $Sc(OTf)_3$/DMAP,[7] $TaCl_5$,[8] Sc(perfluoroalkanesulfonyl)imide,[9] $Sc(OTf)_3$,[10] $Sc(OAc)_3$,[11] and $COCl_2$[12] are known to catalyze the acylation of alcohols (Scheme 2).

Scheme 2.



M(X)n = Lewis acid

Lewis acids:

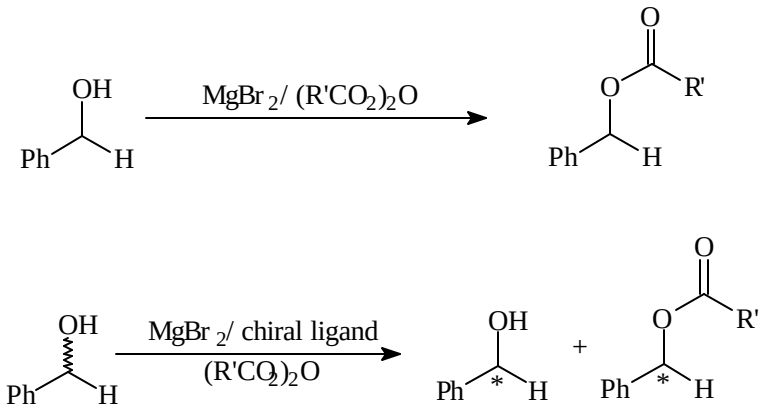
InI_3, $Bi(OTf)_3$, $FeCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, $TaCl_5$, Sc(perfluorosulfonyl)imide, $Sc(OTf)_3$, $Sc(OAc)_3$, $CoCl_2$.

The role of magnesium bromide as a lewis acid is well known, especially in the reactions of Grignard reagents, and other magnesium (II) salts have found application as lewis acids in several synthetic transformations.[13] To the best of our knowledge, $MgBr_2$ has not been used as a catalyst for the acylation of alcohols.[14]

2. OBJECTIVE:

The objective of our work was to study the utility of magnesium bromide as a catalyst for acylation of alcohol and possibility of carrying out kinetic resolution of secondary alcohols using chiral Mg^{2+} complexes (Scheme 3).

Scheme 3.



3. RESULTS AND DISCUSSION:

For initial investigation, menthol **48** was chosen as the substrate. Treatment of a CH_2Cl_2 solution of menthol with acetic anhydride in the presence of $MgBr_2$ for 3h at ambient temperature generated menthyl acetate **60** in 72% isolated yield. Acylation was very slow in the absence of $MgBr_2$ (ca. 10% conversion after 3h at ambient temperature).

Various solvents were examined for the solvent study using menthol **48** as a substrate (Table 1). Rate of acylation is comparable in benzene and toluene but is considerably reduced in ether (60% isolated yield after 16h at ambient temperature) and acetonitrile (60%, 48h).

Table 1: Effect of solvents.

Compound	Solvent	Time (h)	Yield (%)
48	Benzene	2.45	69
48	Ether	16	60
48	Acetonitrile	48	60
48	dichloromethane	3	71
48	Toluene	5	65

Use of dichloromethane as solvent generated acylated product in optimum yield.

The acylation (acetylation and benzoylation) is applicable to variety of substrate (Table 2, Scheme 4).

Scheme 4.

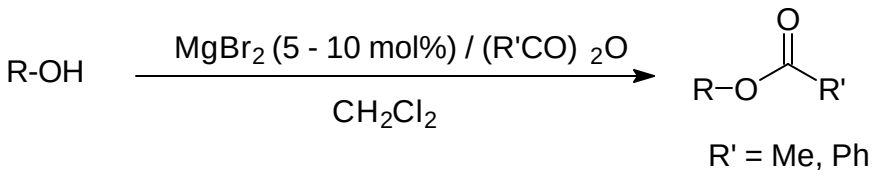
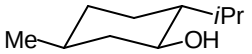
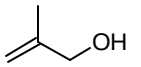
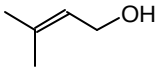
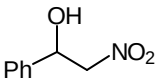
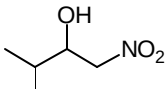
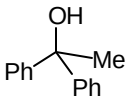
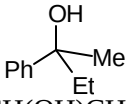


Table 2. $MgBr_2$ catalysed acylation of alcohols

Substrate	No.	Anhydride	mol% $MgBr_2$	Reacn. Time	ester	Yield % ester
	**48**	Ac_2O	5	3 h	**60**	72
$PhCH(OH)CH_3$	**49**	Ac_2O	5	5 h	**61**	83
	**50**	Ac_2O Bz_2O	5 5	3 h 5 h	**62** **63**	65 67
	**51**	Bz_2O Bz_2O	5 25	16 h 45 min	 **64**	62 80
	**52**	Bz_2O	10	30 min	**65**	63
2,6-di*tert*butyl-4-methylphenol	**53**	Ac_2O	5	12 h	**66**	65
	**54**	Ac_2O	10	48 h	**67**	95[a]
	**55**	Ac_2O	5	45 min	**68**	93[a]
	**56**	Ac_2O	5	24 h[b] 12 h	**69** **70**	- -	(30[d]) (90[d])
	**57**	Ac_2O	5	24 h[b] 5 h	**71** **72**	60[c] -	 (83[d])
$PhCH(OH)CH_2OH$	**58**	Ac_2O	5	24 h		-	
Benzoin	**59**	Ac_2O	5	72 h	**73**	30	

a: yield of crude product (pure by ^1H NMR). b: reaction at 0 ^oC. c: GC yield.
d: yield of olefin.

The rate of acylation increases with increase in amount of the $MgBr_2$ employed (Entry 4, Table 2). Nitroalcohol **54** undergoes dehydration during acetylation in basic condition.[15] Treatment of **54** with $MgBr_2/Ac_2O$ affords the acylated product in excellent yield (95%, pure by ^1H NMR) thereby emphasizing the advantage of nonbasic reaction conditions. Attempted acylation of the tertiary alcohols **56** and **57** with the $MgBr_2/Ac_2O$ system resulted in elimination at

ambient temperature. Conducting the acylation of **56** at O °C reduced the rate of elimination process, but no acetate was obtained (30% olefin plus unreacted **56** after 24 h by 1H NMR analysis of the crude product). However acetylation of **57** was success at lower temperature (<5% olefin from 10 at 0 °C and 60% conversion to the acetate).

Acylation of 1-phenylethane-1,2-diol **(58)** was unsuccessful, presumably due to irreversible complexation of $MgBr_2$ by the substrate, thereby reducing its Lewis acidity. Interestingly, this does not seem to be a difficulty with the other alcohol substrates although they are present in large excess during the initial stages of the reaction. Similarly, nitroalcohols **54** and **55** are acetylated quite efficiently, although they are potential chelators of $MgBr_2$. In comparison, the acetylation of benzoin **(59)** proceeds at a much slower rate, presumably due to steric reasons and/or complexation with $MgBr_2$.

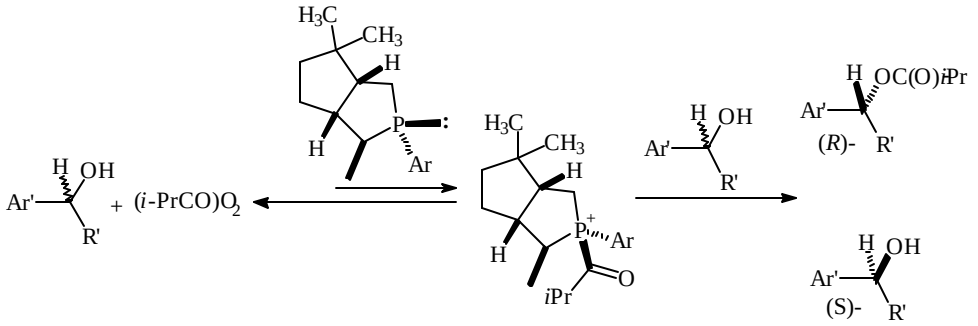
Section 2. Application of $MgBr_2$ in the kinetic resolution of secondary alcohols.

1. Introduction:

The enzymatic resolution of chiral alcohols has been extensively investigated and the topic has been reviewed recently.[16] Among the non-enzymatic methods, the use of stoichiometric amounts of chiral acylating agents has been examined and highly enantioselective procedures have been developed.[17] In contrast, very few studies[18-20] have addressed the catalytic enantioselective acylation of racemic alcohols with synthetic organic or organometallic catalysts as an alternative to enzymatic resolution.

Recently, Vedejs has examined the use of chiral phosphine catalyst to catalyze the acylation of secondary alcohols with moderate to good (29-98%) enantioselectivity (Scheme 5).[21]

Scheme 5.



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.[19] The effect of solvent on the rate of acylation was also examined.[20] Chandrasekhar *et. al.* reported $TaCl_5$-chiral ligands for the kinetic resolution of secondary alcohols albeit in low e.e.[8]

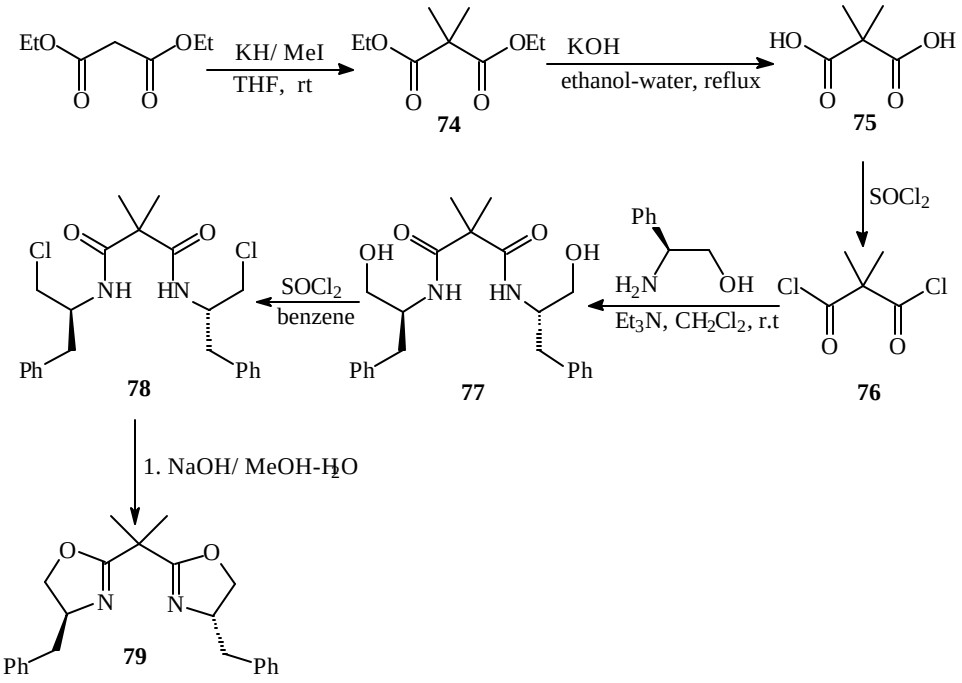
2. OBJECTIVE:

Magnesium bromide is known to complex with chiral ligands and chiral magnesium complexes have been employed in catalytic assymetric reactions such as conjugate additions[22], Diels-Alder reactions.[23] Our objective was to explore the possibility of carrying out kinetic resolution of secondary alcohols using chiral $MgBr_2$-ligands.

3. RESULTS AND DISCUSSION

For initial investigation bisoxazolidine **79** was chosen. Bisoxazolidine **79** was prepared from condensation of dimethylmalonylchloride **76** and phenylalaninol followed by cyclization.[24]

Scheme 6.

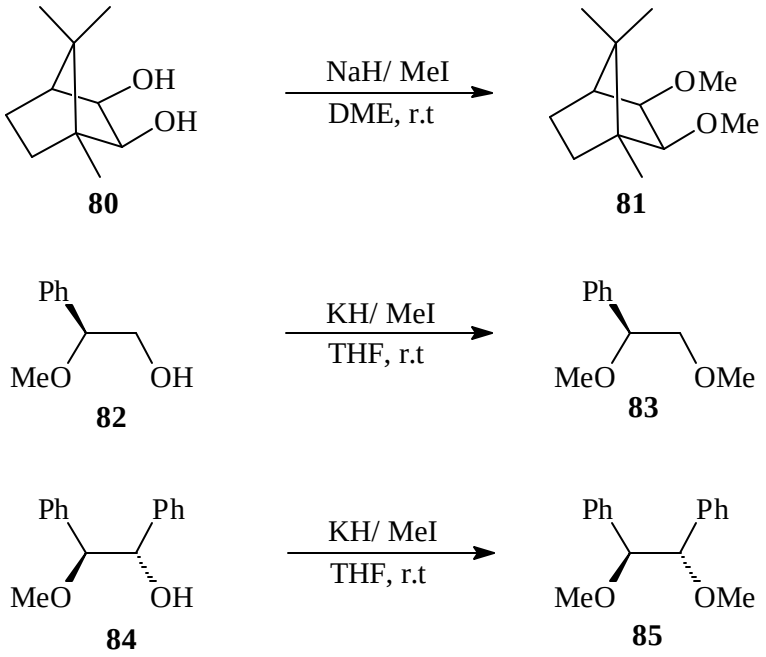


Deprotonation of diethylmalonate with KH (2.5 equiv.) in THF followed by treatment with MeI (2 eq.) generate **74** in 89% yield. Hydrolysis of **74** with KOH in alcohol-water mixture gave **75** in 64% yield. Reaction of **75** with $SOCl_2$ generated dimethylmalonylchloride **78** in quantitative yield. Condensation of **76** and phenylalalinol at 0 ^{o}C generated **77** in 61% yield. Chlorination of **77** generated **78** which after treatment with NaOH in 1:1 mixture of MeOH-water generated bisoxazolidine **79** in 61% yield (Scheme 6).

O-methylation of camphordiol **80** with KH/MeI gave **81** in 41% yield.[25] Simmilarly (*R*)-1,2-dimethoxy-1-phenylethane[25] **83** and (*R, R*) 1,2-dimethoxy-1,2-diphenylethane[25] **85** was prepared by the *O*-methylation of 1,2-dihydroxy-1-

phenylethane **82** and 1,2-dimethoxy-1,2-diphenylethane **84** respectively (Scheme 7).

Scheme 7.



The ligands **79**, **81**, **83**, **85** were used for complexation with $MgBr_2$ *in situ* and the complexes were examined as catalysts for the acylation of phenethylalcohol (Scheme 8).

Scheme 8.

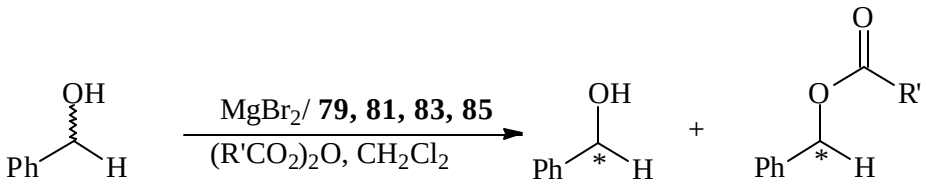


Table 3 summarizes the result of acylation of secondary alcohol using chiral complexes.

Table 3. Acylation of 1-phenylethyl alcohol using chiral complexes **79**, **81**, **83**, **85**.

Ligands	Anhydride	Time (h)	Temp (^oC)	Yield (%)	% e.e. [c]
79	Ac_2O	3	r.t.	34	-
79	Ac_2O	4	10	28	-
79	Ac_2O	48	-18	10	1
81	Bz_2O	5	r.t	24	-
83	Bz_2O	8	r.t	33	3
83	Ac_2O	8	-16	11	-
85	Ac_2O	12	r.t	38	-
85	Ac_2O	12	10	12	-

c: based on specific rotation.

The selectivity is very low which reveals that the complexes are ineffective for the kinetic resolution of secondary alcohol.

4. CONCLUSION:

Magnesium bromide has been demonstrated to be a useful catalyst for the acylation of a variety of alcohols. The mildness of the procedure is exemplified by the successful acetylation of nitroalcohol substrates which are prone to dehydration.

Selectivity in kinetic resolution was quite low may be because $MgBr_2$ was unable to complex with the ligands or the complexation was very weak.

5. EXPERIMENTAL

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

General procedure for the acylation of alcohols:

To a solution of acetic anhydride and magnesium bromide in dichloromethane at ambient temperature was added alcohol. The mixture was stirred at ambient temperature. After the reaction was complete, the reaction mixture was diluted with dichloromethane. The solution was washed with water, dried over Na_2SO_4 and concentrated to give the acetate.

Menthyl acetate (60):

The reaction of menthol **48** (156 mg, 1mmol) with acetic anhydride (0.57 ml, 6 mmol) in the presence of magnesium bromide (10 mg, 0.05 mmol) in dichloromethane gave 140 mg (70 %) of **60**, which was pure by ^{1}H NMR.

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

δ 4.74-4.61 (dt, *J* = 4.4, 10.7, 1H, $CH_2CHOCOCH_3$), 2.04 (s, 3H, $COOCH_3$) 1.94-0.75 (m, 19H, $3CH_3$, $3CH_2$, 4C*H*).

IR (Neat):

2955, 2896, 1736, 1455, 1370, 1244, 1182, 1155, 1096, 1024, 982, 904, 841, 651, 609, 503, 476 cm^{-1}.

MS (EI, 70 eV):

m/z 55 (17), 67 (27), 81 (94), 95 (100), 109 (17), 123 (36), 138 (44).

1-Phenylethyl acetate (61):

The reaction of phenethylalcohol **49** (1.012 ml, 1 mmol) with acetic anhydride (0.48 ml, 25 mmol) in the presence of magnesium bromide (46 mg, 0.25 mmol) in dichloromethane (3ml) for 5hr. gave after purification (SiO_2, petroleum ether/ethyl acetate, 85/15), 680 mg (83 %) of **61**.

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

δ 7.34 (m, 5H, Ar*H*), 5.88 (q, *J* = 7, 1H, C*H*OAc), 2.07 (s, 3H, COOCH_3), 1.53 (d, *J* = 7, 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).

Cyclohexyl Acetate (62):

The reaction of cyclohexanol **50** (0.53 ml, 5 mmol) with acetic anhydride (0.71 ml, 7.5 mmol) in the presence of magnesium bromide (46 mg, 0.25 mmol) in dichloromethane (5ml) for 3hr. gave 0.46 mg (65 %) of **62**, which was pure by ^{1}H NMR.

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

δ 4.79-4.67 (m, 1H, C*H*), 2.03 (s, 3H, COOCH_3), 1.92-1.20 (m, 10H, 5xCH_2).

IR (neat):

2937, 2860, 1827, 1763, 1451, 1378, 1364, 1240, 1124, 1045, 1022, 967, 904, 840, 824, 653, 607 cm^{-1}.

Cyclohexyl benzoate (63):

The reaction of cyclohexanol **50** (0.106 ml, 1 mmol) with benzoic anhydride (1.130g, 5 mmol) in dichloromethane (3 ml) in the presence of magnesium bromide (9.2 mg, 0.05 mmol) for 5h gave after flash column chromatography 132 mg (65%) of **63**.

^{1}H NMR (200 MHz, CDCl3**)**:

δ 8.07-8.04 (m, 2H, Ar*H*), 7.59-7.40 (m, 3H, Ar*H*), 5.09-4.99 (m, 1H, C*H*), 1.98-1.42 (m, 11H, CH_2),

IR (neat**)**:

2937, 2860, 1716, 1450, 1338, 1315, 1278, 1176, 1112, 1070, 1037, 1026, 1016, 943, 711 cm^{-1}.

MS (EI, 70 eV):

m/z 55 (25), 77 (71), 67 (42), 82 (33), 105 (100), 123 (94), 204 (M^+, 1).

Phenyl 2-methyl-2-propen-1-oate (64):

The reaction of 2-methyl-2-propen-1-ol **51** (0.084 ml, 1 mmol) with benzoic anhydride (1.130g, 5 mmol) in the presence of magnesium bromide (46 mg, 0.25 mmol) in dichloromethane (5 ml) for 5hr. gave after purification (SiO_2, petroleum ether/ethyl acetate, 85/15), 140 mg (80 %) of **64**.

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

δ 8.10-8.06 (m, 2H, Ar*H*), 7.61-7.44 (m, 3H, Ar*H*), 5.09 (s, 1H, C*H*), 4.99 (s, 1H, C*H*), 4.75 (s, 2H, CH_2), 1.84 (s, 3H, COOCH_3).

IR (neat):

1722, 1658, 1601, 1451, 1363, 1314, 1270, 1176, 1113, 1069, 1026, 986,

949, 905, 710 cm^{-1}.

MS (EI, 70 eV):

m/z 55 (14), 77 (51), 105 (100), 176 (M^+, 1).

Phenyl 3-methyl-2-butene-1-oate (65):

The reaction of **52** (0.2 ml 2 mmol) with benzoic anhydride (1.130, 10 mmol) in the presence of magnesium bromide (36.8 mg, 0.20 mmol) in dichloromethane (4 ml) for 30 min. gave after purification (SiO_2, petroleum ether/ethyl acetate, 85/15), 240 mg (63 %) of **65**.

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

δ 8.07-8.03 (m, 2H, Ar*H*), 7.58-7.24 (m, 3H, Ar*H*), 5.51-5.48 (m, 1H, C*H*), 4.84-4.80 (d, *J* = 19 2H, C*H*), 1.78 (s, 3H, CH_3).

IR ($CHCl_3$):

3062, 2927, 1718, 1601, 1584, 1450, 1378, 1332, 1314, 1270, 1175, 1105, 1069, 1025, 936, 822, 772, 711, 687cm^{-1}.

MS (EI, 70 eV):

m/z 55 (19), 68 (55), 77 (32), 105 (100), 125 (30), 190 (M^+, 1).

2,6-di-*tert*-butyl-4-methyl phenyl acetate (66):

The reaction of di-*tert*-butyl-4-methyl phenol **53** (220 mg, 1 mmol) with acetic anhydride (0.56 ml, 6 mmol) in the presence of magnesium bromide (19.2 mg, 0.05 mmol) in dichloromethane (2 ml) for 12h gave 171 mg (65 %) of **66**, which was pure by ^{1}H NMR.

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

δ 6.98 (s, 2H, Ar*H*), 2.27 (s, 3H, COOCH_3), 1.43 (s, 21H, CH_3).

IR ($CHCl_3$):

3463, 2956, 2871, 1750, 1602, 1431, 1394, 1362, 1312, 1230, 1154, 1119, 1025, 886, 863, 762, 667, 618, 577 cm^{-1}.

MS (EI, 70 eV):

m/z 57 (79), 77 (14), 91 (16), 105 (16), 145 (13),

2-phenyl-1-nitro ethyl acetate (67):

The reaction of 2-phenyl-1-nitroethanol **54** (84 mg 0.5 mmol) with acetic anhydride (0.05 ml, 0.5 mmol) in the presence of magnesium bromide (9 mg, 0.05 mmol) in dichloromethane (1 ml) for 48h gave 99 mg (95 %) of **67**, which was pure by ^{1}H NMR.

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

δ 7.38 (s, 5H, Ar*H*), 6.47-6.40 (dd, 1H, *J* = 3.4, 10, PhC*H*), 4.87-4.75 (dd, 1H, *J* = 10, 13, CH_2) 4.60-4.51 (1H, dd, 3.4, 13, CH_2), 2.08 (s, 3H, COOCH_3).

IR ($CHCl_3$):

3034, 2924, 2853, 1750, 1634, 1557, 1520, 1495, 1453, 1420, 1377, 1344, 1226, 1078, 1946, 948, 839, 765, 699, 660, 620, 593, 524, 482 cm^{-1}.

MS (EI, 70 eV):

m/z 66 (26), 77 (100), 91 (49), 102 (49), 120 (9), 133 (7), 149 (36), 209 (M^+, 1).

3-Methyl-1-nitro butyl acetate (68):

The reaction of nitroalcohol **55** (660 mg, 4.96 mmol) and acetic anhydride

(2.35 ml, 6 mmol) in the presence of magnesium bromide (46 mg, 0.25 mmol) in dichloromethane (5ml) for 5h gave 810 mg (93 %) of **68**, which was pure by ^{1}H NMR.

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

δ 5.41-5.32 (q, *J* = 5.8, 1H, C*H*), 4.55-4.52 (d, *J* = 5.8, 2H, CH_2), 2.19-1.93 (s, m, 4H, COOCH_3, C*H*), 1.07-1.00 (d, *J* = 6.8, 6H, CH).

IR (neat):

2970, 1748, 1559, 1469, 1425, 1376, 1232, 1116, 1046, 938, 838,723, 662, 606 cm^{-1}.

MS (EI, 70 eV):

m/z 55 (29), 69 (100), 86 (77), 100 (8), 115 (11), 132 (36), 176 (M+1, 1).

Benzoin acetate (73):

The reaction of benzoin **59** (1.06 g, 5 mmol) with acetic anhydride (0.95 ml, 0.5 mmol) in the presence of magnesium bromide (46 mg, 0.25 mmol) in dichloromethane (5 ml) for 72h gave after purification (SiO_2, petroleum ether/ethyl acetate, 85/15), 381 mg (30 %) of **73**.

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

δ 7.95- 7.92 (m, 2H, Ar*H*), 7.48-7.34 (m, 8H, Ar*H*), 2.21 (s, 3H, COOCH_3).

IR ($CHCl_3$):

2954, 2923, 2854, 1741, 1728, 1693, 1595, 1456, 1448, 1373, 1267, 1242, 1228, 1180, 1054, 702, 584, 520, 459, 441, 426 cm^{-1}.

MS (EI, 70 eV):

m/z 77 (64), 105 (100), 149 (15), 165 (7), 254 (M^+, 1).

2-phenylbutene -2 (72):

The reaction of 2-phenyl-2-butanol-1 **57** (0.30 ml, 2 mmol) with acetic anhydride (2 ml, mmol) in the presence of magnesium bromide (18.4 mg, 0.1 mmol) in dichloromethane (3ml) for 5hr. gave 264 mg (83 %) of **70** as a mixture of isomer.

For major isomer:

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

δ 7.39-7.18 (m, 5H, Ar*H*), 5.91-5.81 (q, *J* = 6.35, 1H, =C*H*(CH_3), 2.03 (s, 3H, =C(Ph)C*H*$_3$), 1.81-1.78 (d, *J* = 6.35, 3H, CHC*H*$_3$).

visible minor isomer peak:

δ 5.28 (s, 1H, =C*H*), 2.57 (q, *J* = 7.32, 2H, C*H*$_2$CH$_3$), 1.14-1.07 (t, *J* = 7.32, 3H, CH_2C*H*$_3$).

IR ($CHCl_3$):

2954, 2923, 2854, 1741, 1728, 1693, 1595, 1456, 1448, 1373, 1267, 1242, 1228, 1180, 1054, 702, 584, 520, 459, 441, 426 cm^{-1}.

MS (EI, 70 eV):

m/z 77 (64), 105 (100), 149 (15), 165 (7), 132 (M^+, 1).

Diethyldimethylmalonate (74):[24]

To a suspension of KH (2g, 50 mmol) in THF (40ml) was added diethyl malonate (3.03 ml, 20mmol) dropwise. The reaction mixture was stirred for 2h. To this reaction mixture was added MeI (3.12 ml, 50 mmol) with stirring. Reaction mixture was further stirred for 8h. Reaction mixture was quenched with MeOH (5 ml) and to that sat. NH_4Cl was added. Reaction mixture was extracted

with ether (3 x 20 ml). Ether layer was washed with brine, dried over Na_2SO_4 and concentrated to give 3.36g (89%) of **74.**

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

δ 4.24-4.13 (q, *J* = 7.3, 2H, OCH_2CH_3), 1.43 (s, 3H, 2 x CH_3), 1.24-1.21 (t, *J* = 7.3, 3H, OCH_2CH_3).

Dimethylmalonic acid (75):[24]

To a solution of **74** (3.361 g, 17.88 mmol) in ethanol (15 ml) was added aqueous solution of KOH (2.50 g in 3ml water). Reaction mixture was refluxed for 3h. Ethanol was completely removed on rotavapor and small amount of water (5 ml) was added. To this reaction mixture conc. H_2SO_4 was added till the solution become slightly acidic (pH ~ 3). Reaction mixture was extracted with ether (3 x 15 ml) to yield crude product which after crystallizatrion gave 1.520 g (64%) of **75**.

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

δ 1.1 (s, 3H, 2 x CH_3).

Dimethylmalonylchloride (76):[24]

Dimethylmalonic acid (1.4g, 10.6 mmol) **75** was refluxed with $SOCl_2$ (3.7 ml, 53 mmol) 24 h. Excess $SOCl_2$ was removed on vaccuo to give 1.35g (98%) of **76** which was used for futher reaction without any further purification.

(R,R)-N,N'-bis(1-benzyl-2-hydroxyethyl)-2,2-dimethylpropane-1,3-diamide (77): [24]

To a cold (0 °C) solution of phenyl alaninol (8.30 g, 55 mml) and Et_3N

(19.1 ml, 137.5 mmol) in dichloromethane (40 ml) was added dimethylmalonyldichloride **76** (4.6 g, 27.2 mmol) dropwise. Reaction mixture was stirred for 12 h at 25 ^{o}C. Reaction mixture was diluted with dichloromethane and washed with water, $NaHCO_3$, 0.1 N HCl and brine. Dichloromethane layer was concentrated and crude compound was purified by flash column chromatography (SiO_2, MeOH/ EtOAc 1/99) to generate 5.6 g (51%) of **77**.

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

δ 7.32-7.14 (m, 10H, Ar*H*), 6.50-6.46 (bd, 2H, N*H*), 4.21 (m, 2H, C*H*), 3.74-3.67 (dd, *J* = 3.4, 11.2, 1H, CH_2OH), 3.48-3.39 (dd, *J* = 6.3, 11.2, 1H, CH_2OH), 2.88-2.65 (m, 2H, CH_2Ph), 1.21 (s, 6H, CH_3).

(R,R)-N,N'-bis(1-benzyl-2-chloroethyl)-2,2-dimethylpropane-1,3-diamide (78) :[24]

A mixture of **77** (398 mg, 1 mmol) and $SOCl_2$ (0.19 ml, 5 mmol) in benzene (4 ml) was refluxed for 7 h. Reaction was quenched by adding saturated aq. NH_4Cl and extracted with EtOAc (3 x 5 ml). Ethyl acetate layer was concentrated to give crude compound, which after purification by flash chromatography (SiO_2, pet.ether/ EtOAc, 4/1) gave 300 mg (68%) of **78.**

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

δ 7.35-7.20 (m, 10H, Ar*H*), 6.25-6.20 (bd, 2H, N*H*), 4.45-4.35 (m, 2H, C*H*), 3.70-3.60 (dd, *J* = 4.4, 11.2, 1H, CH_2Cl), 3.55-3.45 (dd, *J* = 3.4, 11.2, 1H, CH_2Cl), 2.9-2.85 (d, *J* = 7.3, 2H, CH_2Ph), 1.35 (s, 6H, CH_3).

(R,R)-2,2'-(methylethylidene)bis(5-benzyl-4,5-dihydrooxazole) (79) : [24]

A mixture of **78** (4.35 g, 10 mmol) and NaOH (1 g, 25 mmol) in EtOH-

THF (1:10) refluxed for 3h. Solvents were evaporated and the residue was taken in water. Resulting mixture was extracted with dichloromethane (3 x 15 ml) to give crude product, which was recrystallized (pet. ether-ethyl acetate, 0 ^{o}C) to give 1.5 g (41%) of **79** as a crystalline solid.

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

δ 7.34-7.18 (m, 10H, Ar*H*), 4.46-4.36 (m, 2H, C*H*), 4.22-3.97 (dd, *J* = 8.3, 9.0, 1H, CH_2O), 3.55-3.45 (dd, *J* =7.3, 9.0, 1H, CH_2O), 3.14-3.04 (dd, *J* = 4.8, 13.6, 1H, CH_2Ph), 2.72-2.61 (dd, *J* = 8.3, 13.6, 1H, CH_2Ph), 1.46 (s, 6H, CH_3).

[a]$_D^{25}$: +42.8 (c = 0.83, ethanol).

General procdure for the *O*-methylation of diols 81, 83, 85.

To a cooled (0 ^{0}C) suspension of KH in anhydrous THF/DME was added a solution of diol in THF/DME drop wise. The mixture was stirred at 25 ^{o}C for 1h. Methyl iodide was added and stirring was continued for 12 h. 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 *O*-methylated. diol .

(*R*)- (1*l*, 2*l*, 3*u*,4*u*)-2,3-dimethoxy-4,7,7 -trimethylbicyclo[2.2.1]heptane (81):[25]

The deprotonation of **78** (40 mg, 0.23 mmol) in anhydrous DME (1 ml) with potassium hydride (27 mg, 0.69 mmol) in anhydrous THF (2 ml) followed by reaction with methyl iodide (0.04 ml, 0.69 mmol) for 10 h, gave after purification (SiO_2, petroleum ether/ethyl acetate, 20/1), 19 mg (41%) of **81**.

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

δ 3.42 (s, 3H, C*H*$_3$), 3.39-3.33 (d, 1H, *J* = 6.97, C*H*), 3.37 (s, 3H, C*H*$_3$), 3.15-3.13 (d, 1H, *J* = 6.97, C*H*), 1.84-1.82 (d, *J* = 4.76, 1H, C*H*), 1.71-1.60 (m, 2H, C*H*$_2$), 1.50-1.41 (dt, *J* = 3.67, 11.73, 1H, C*H*), 1.08 (s, 3H, C*H*$_3$), 1.03-0.91 (m, 1H, C*H*), 0.89 (s, 3H, C*H*$_3$), 0.76 (s, 3H, C*H*$_3$).

[a **]$_D^{25}$:** -95^0 (c = 2.87, ethanol).

(*R*)-1,2-dimethoxy-1-phenylethane (83):[25]

The deprotonation of styrene diol **82** (550 mg, 3.98 mmol) in anhydrous THF (15 ml) with potassium hydride (398 mg, 9.95 mmol) followed by reaction with methyl iodide (0.62 ml, 9.95 mmol) for 12 h, gave after purification (SiO_2, petroleum ether/ethyl acetate, 9/1) 660 mg (64%) of **83**.

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

δ 7.38-7.29 (m, 5H, Ar*H*), 4.31(dd, *J* = 8, 4.2, 1H, C*H*$_2$OCH$_3$), 3.31 (s, 6H, 2xC*H*$_3$), 2.33 (dd, 1, *J* = 8.7, 4.1).

[a **]$_D^{25}$:** -163.5 (c = 2.2, ethanol).

(*R*,*R*)-1,2-dimethoxy-1,2-diphenylethane (85):[25]

The deprotonation of 1,2-dihydroxy-1,2-diphenyl **84** (100 mg, 0.46 mmol) in anhydrous THF (3 ml) with potassium hydride (28 mg, 0.7 mmol) in anhydrous THF (3 ml) followed by reaction with methyl iodide (0.04 ml, 0.7 mmol) for 2 h gave 105 mg (94%) of **85** which was pure by ^{1}H NMR.

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

δ 7.15-6.95 (m, 10H, Ar*H*), 4.30 (s, 2H, C*H*OMe), 3.25 (s, 6H, OC*H*$_3$).

[a **]$_D^{25}$:** -14.1 (c = 1.39, $CHCl_3$).

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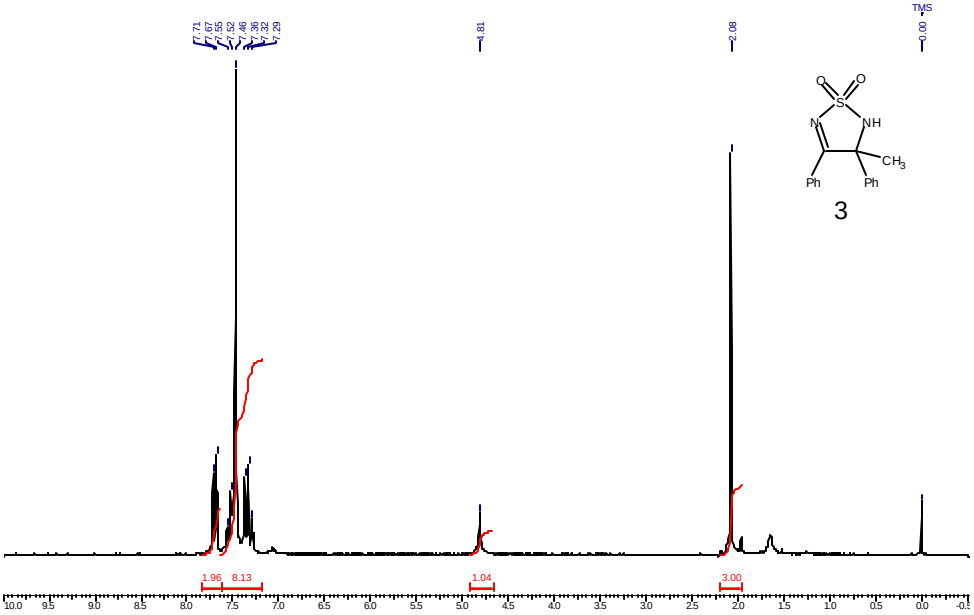
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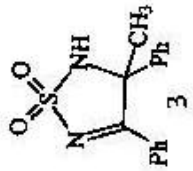

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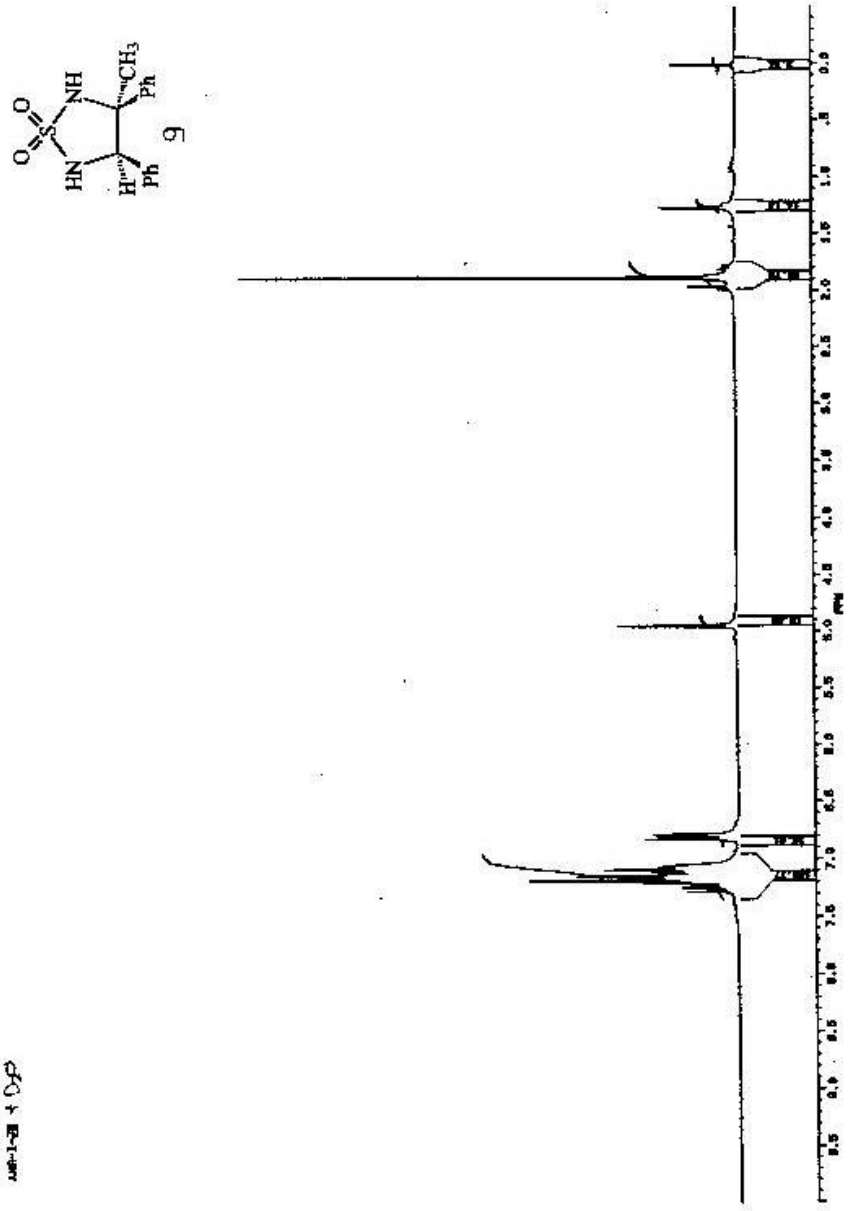
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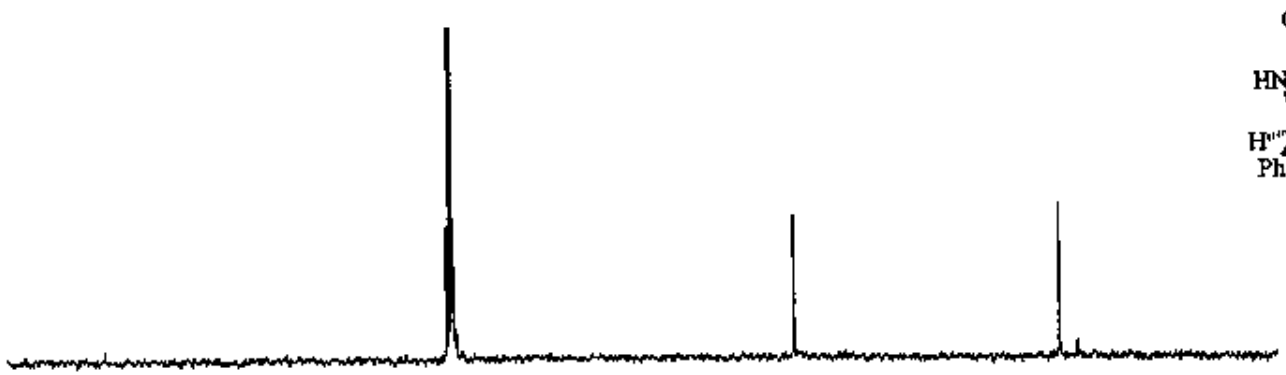

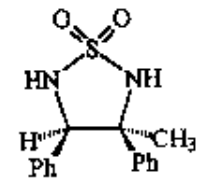

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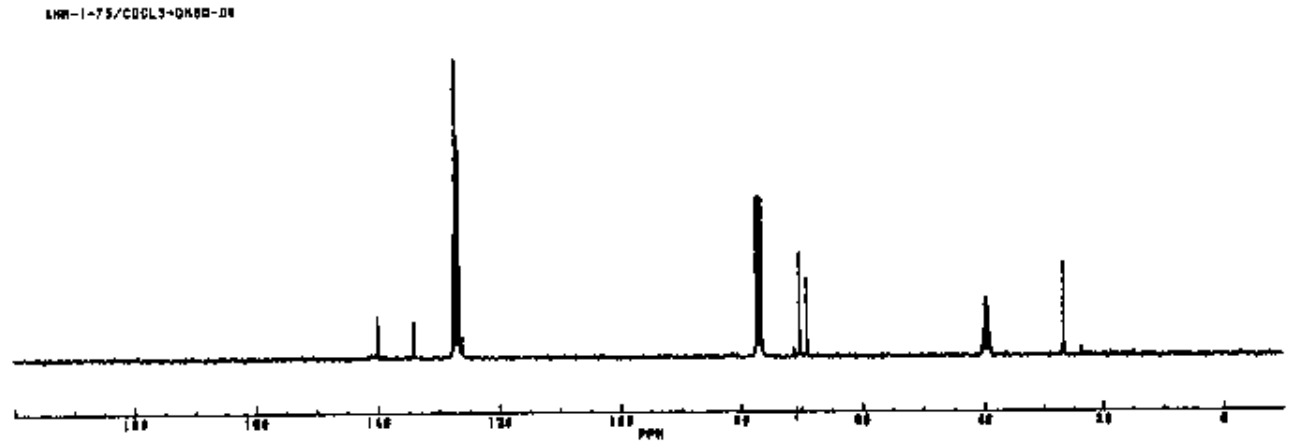

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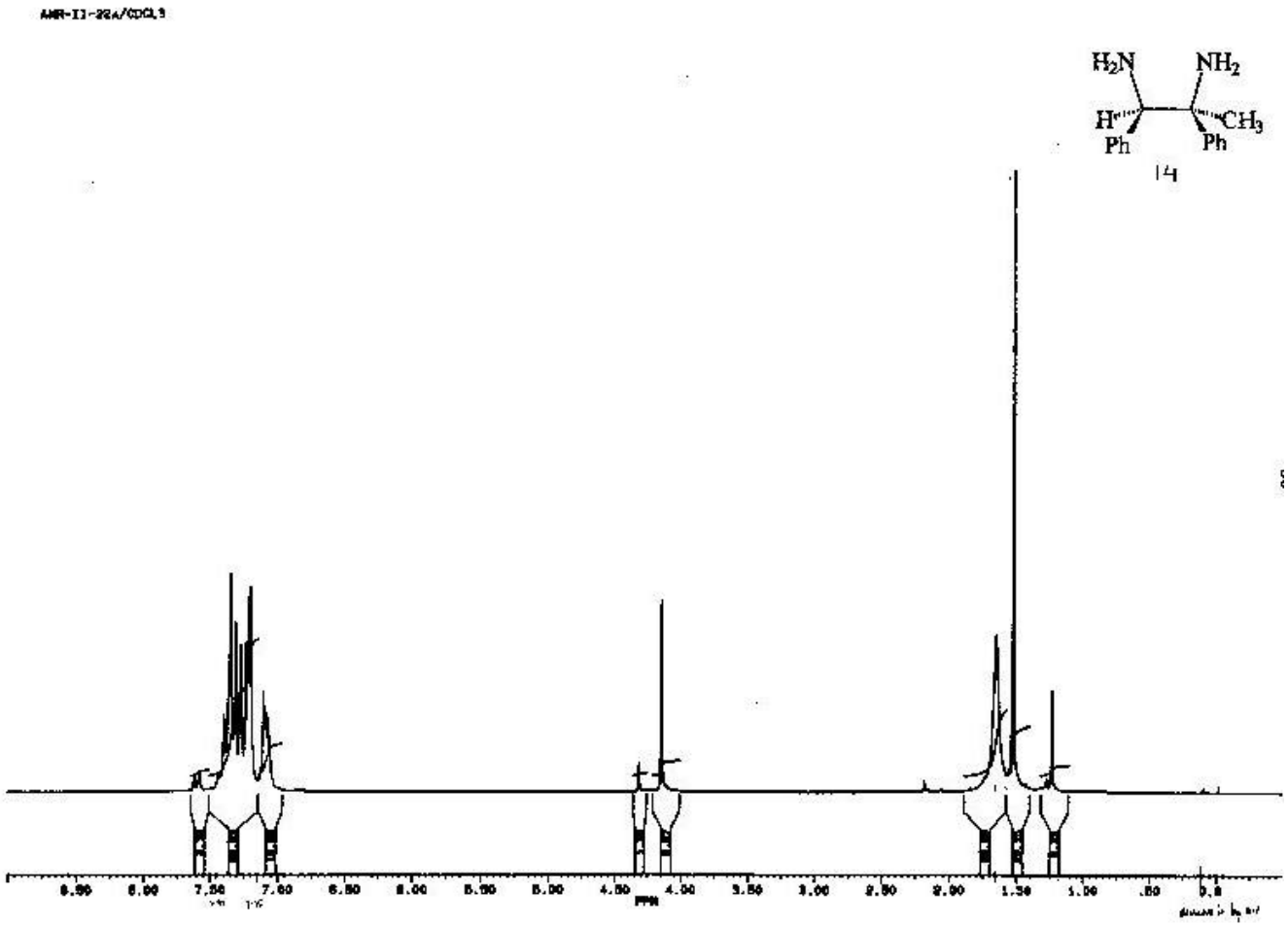
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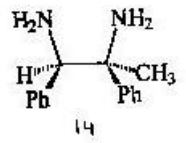

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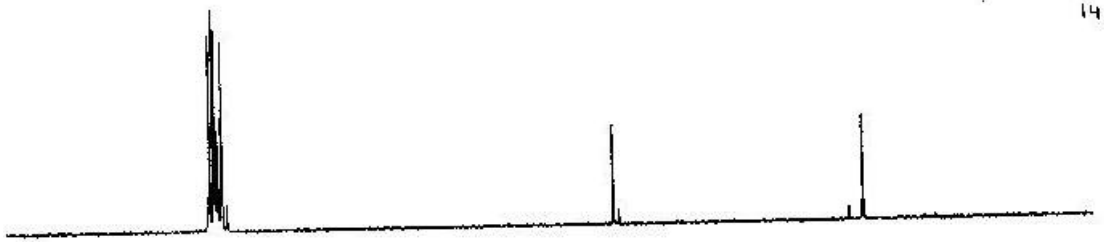

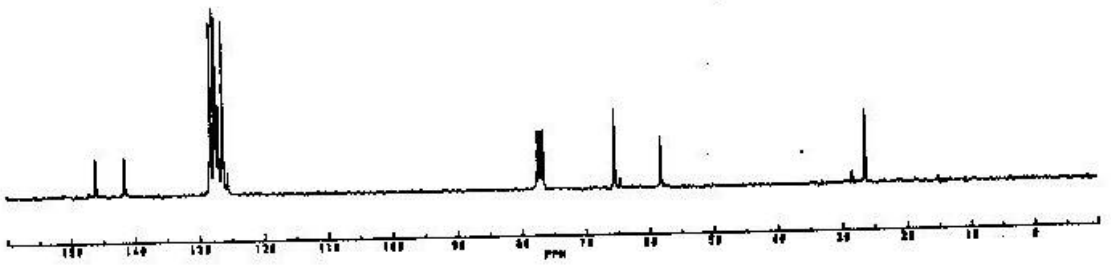

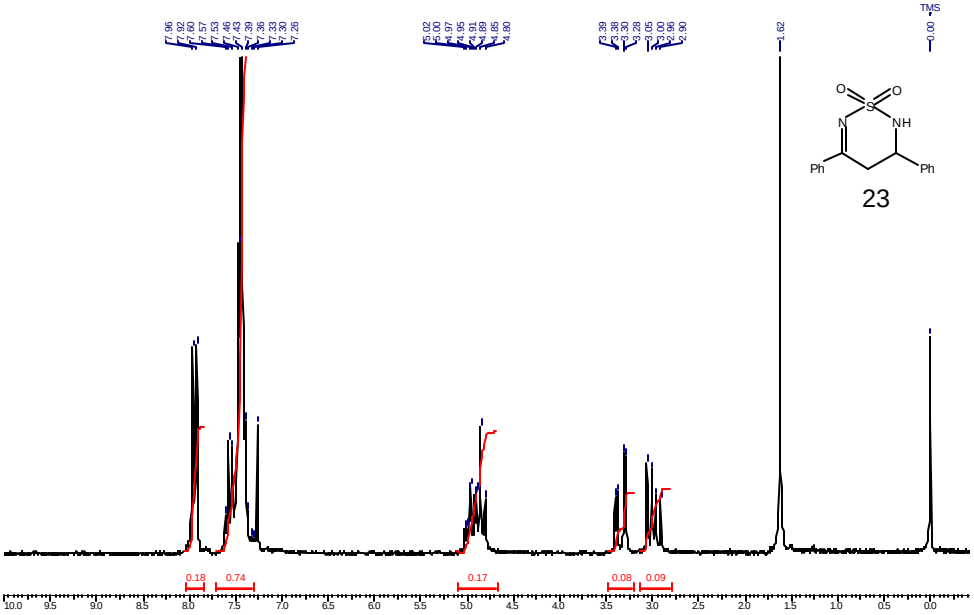
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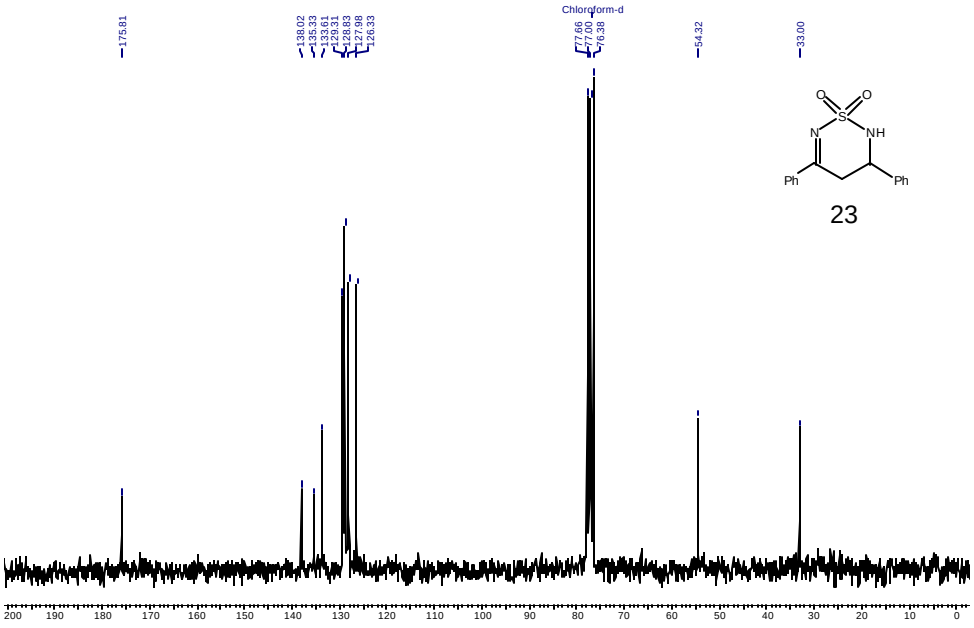
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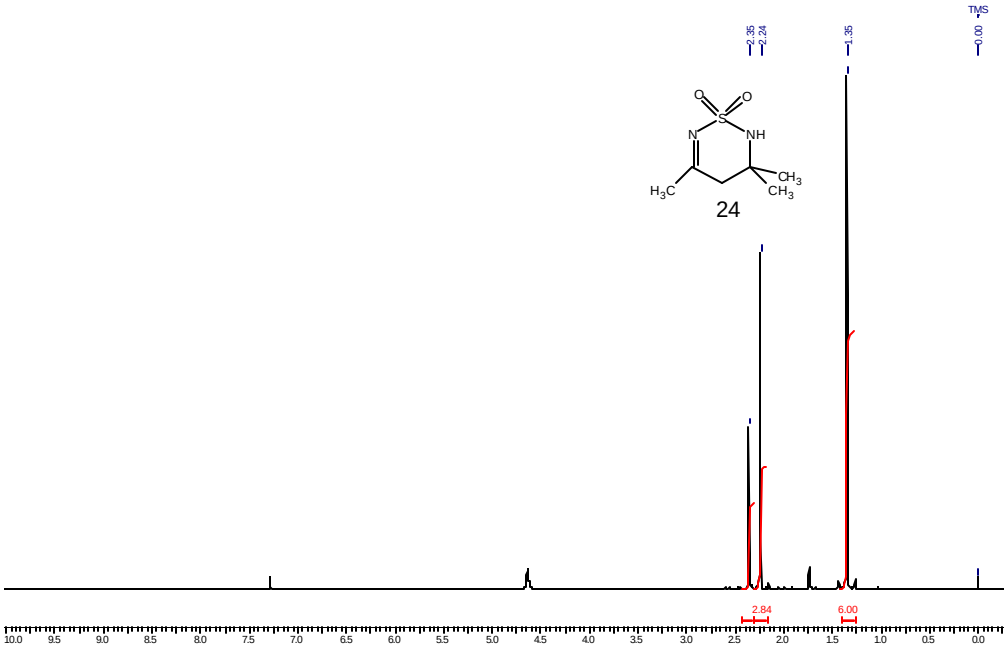
23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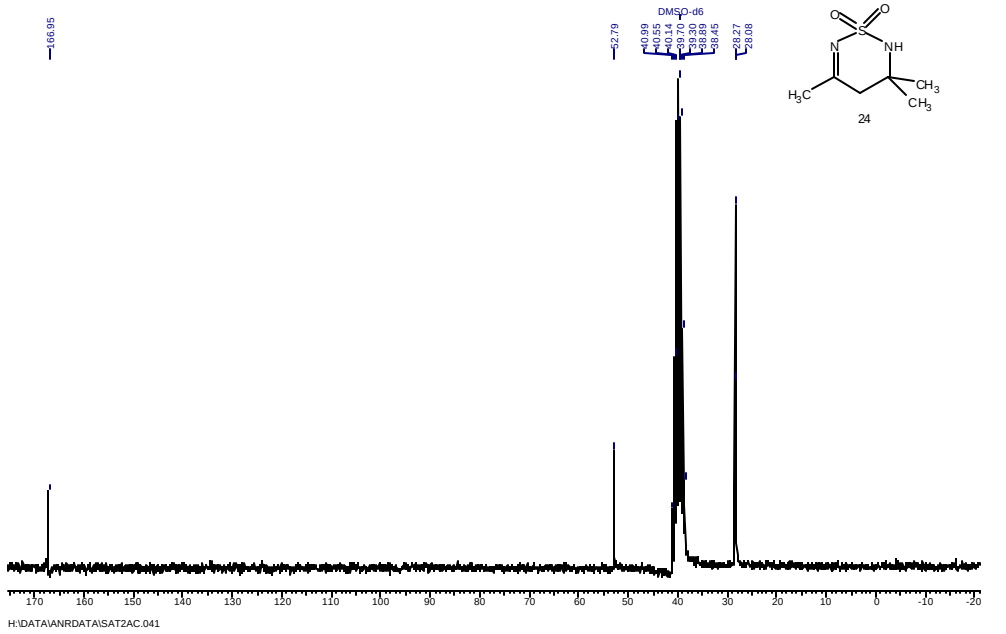
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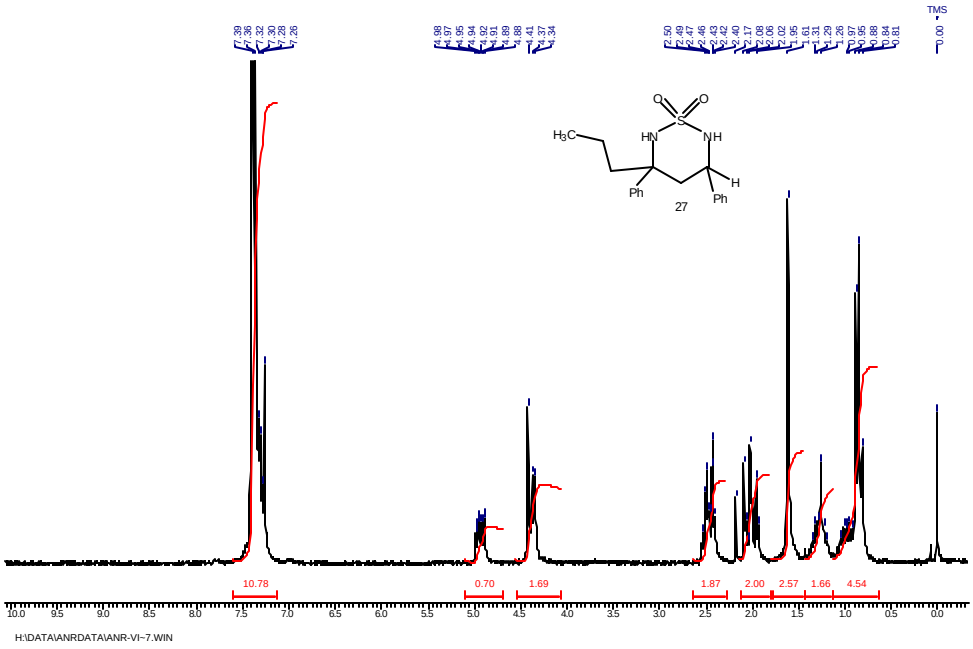
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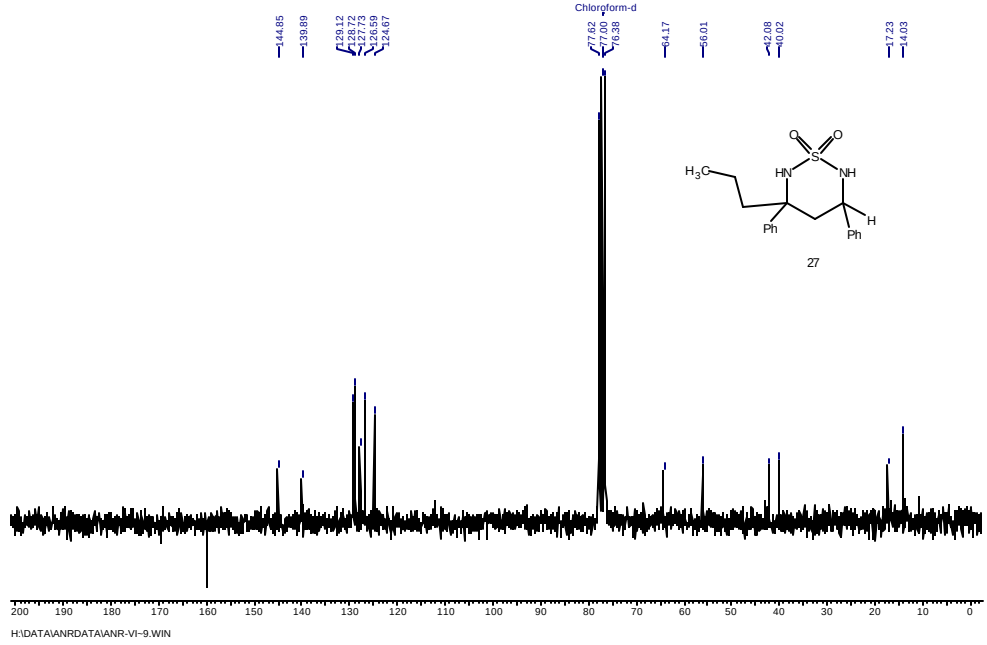
22 Apr 2002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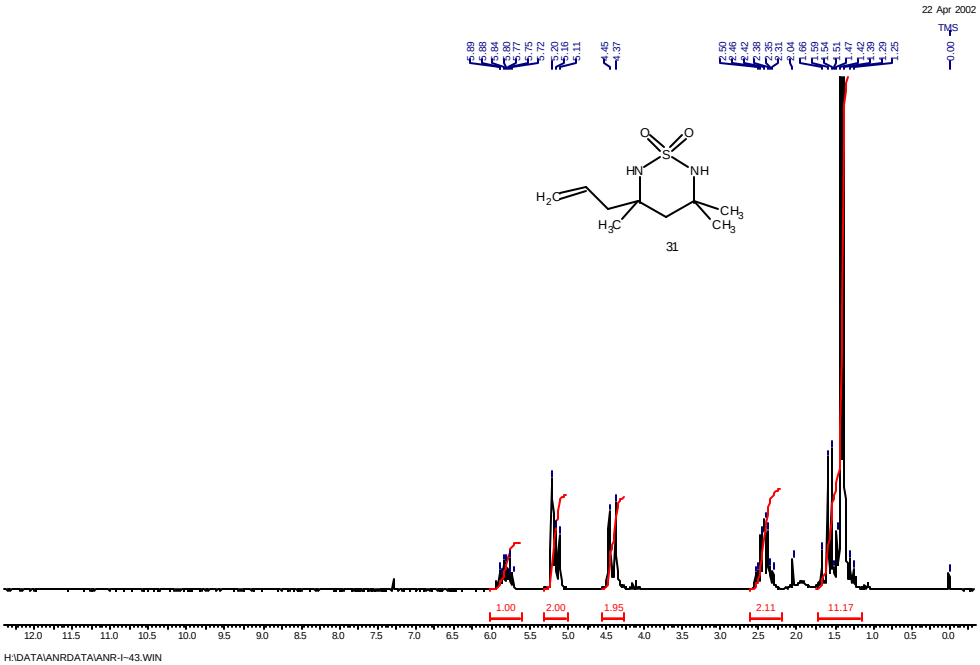

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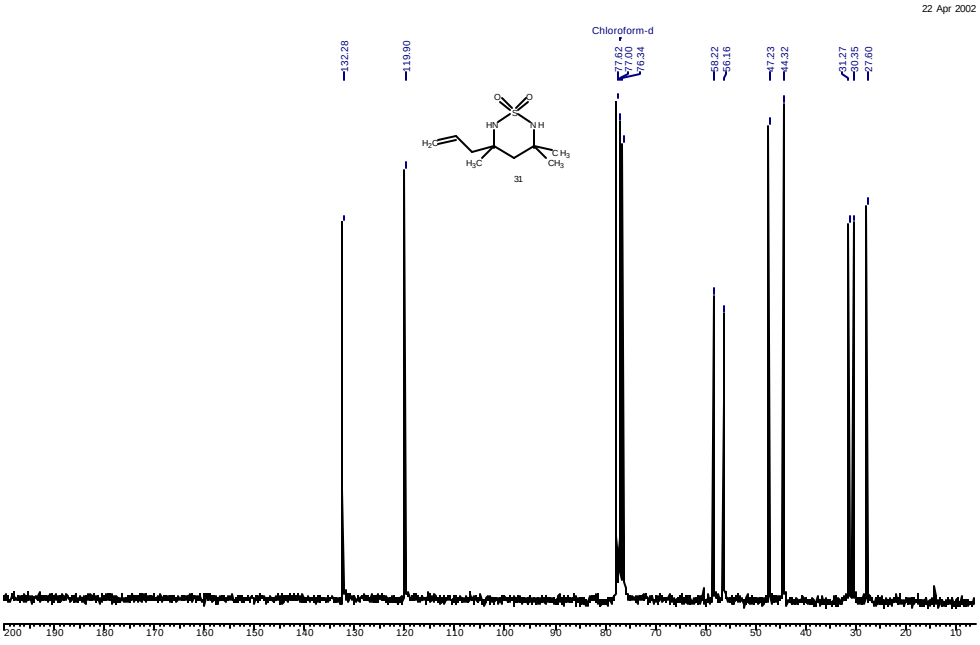

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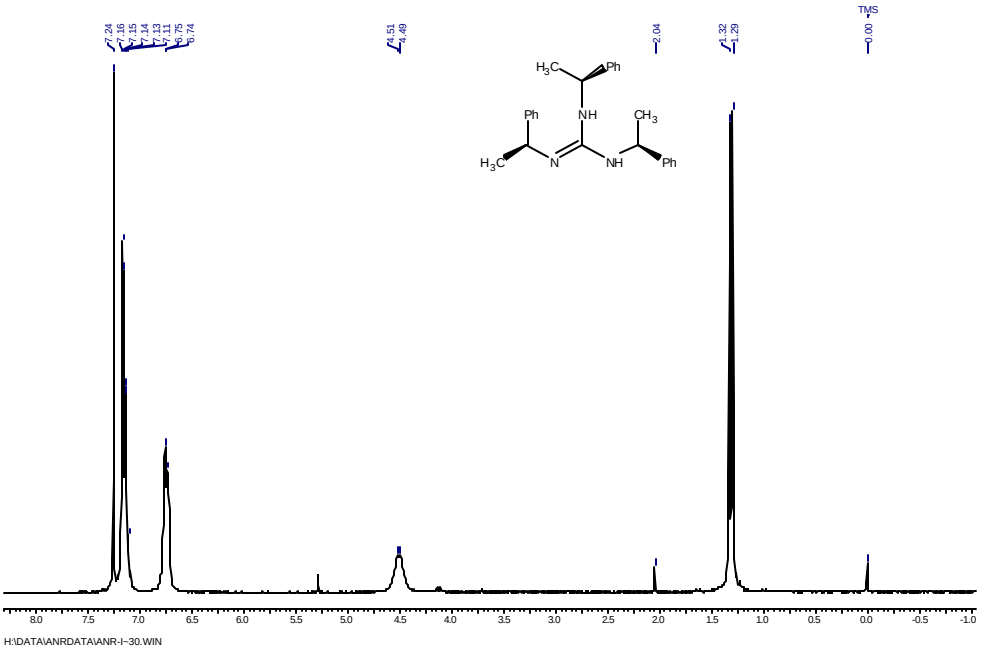
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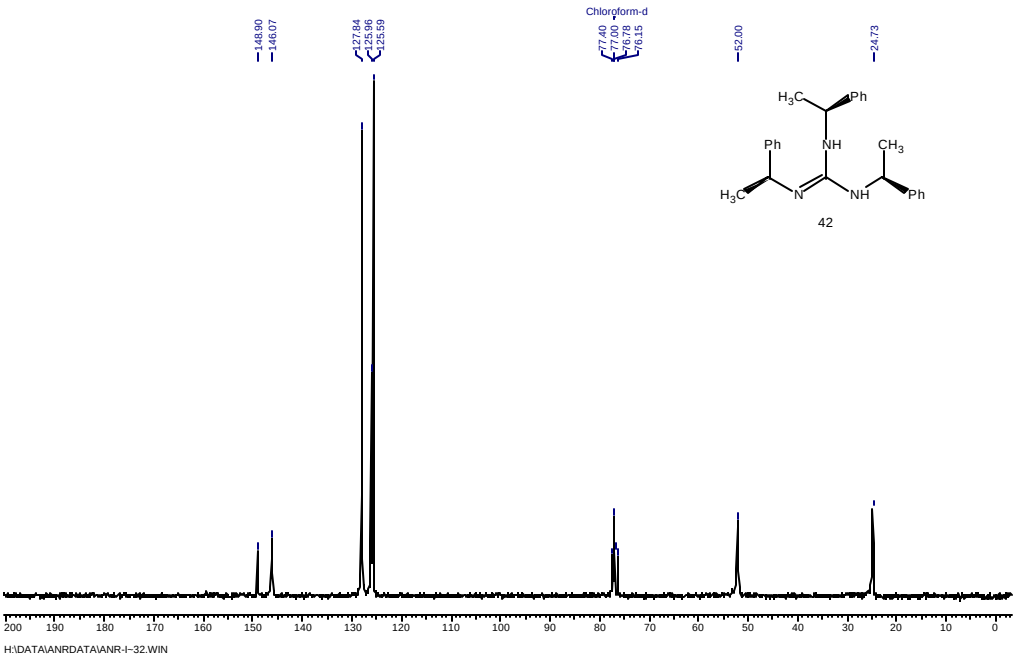
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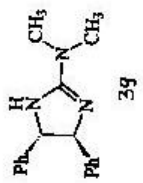

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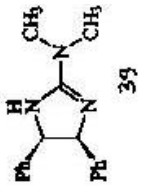

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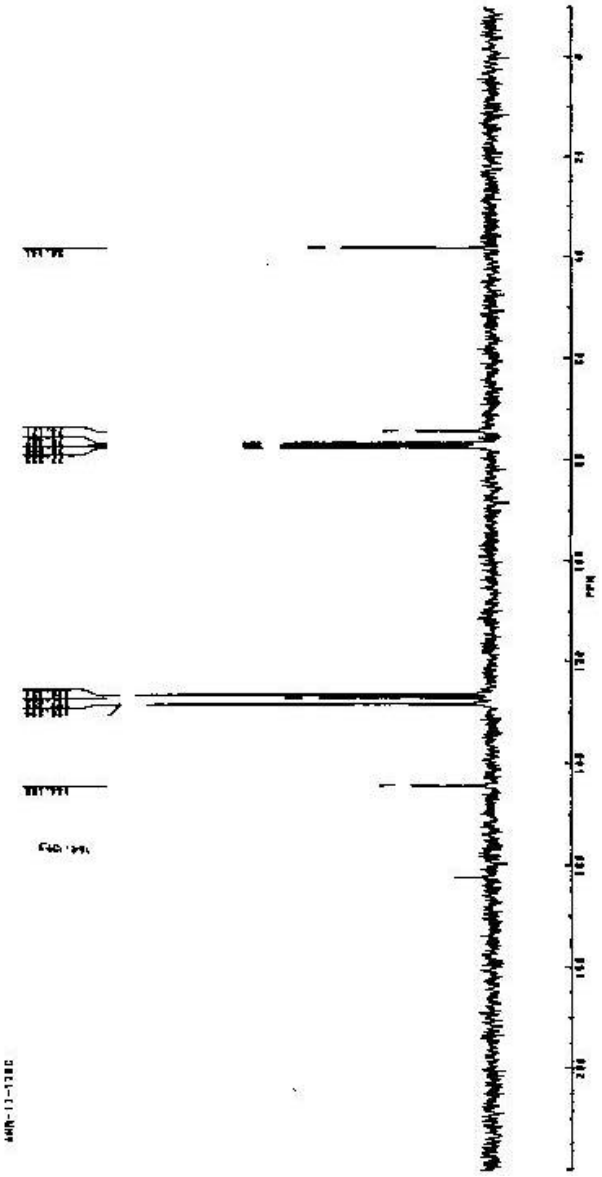

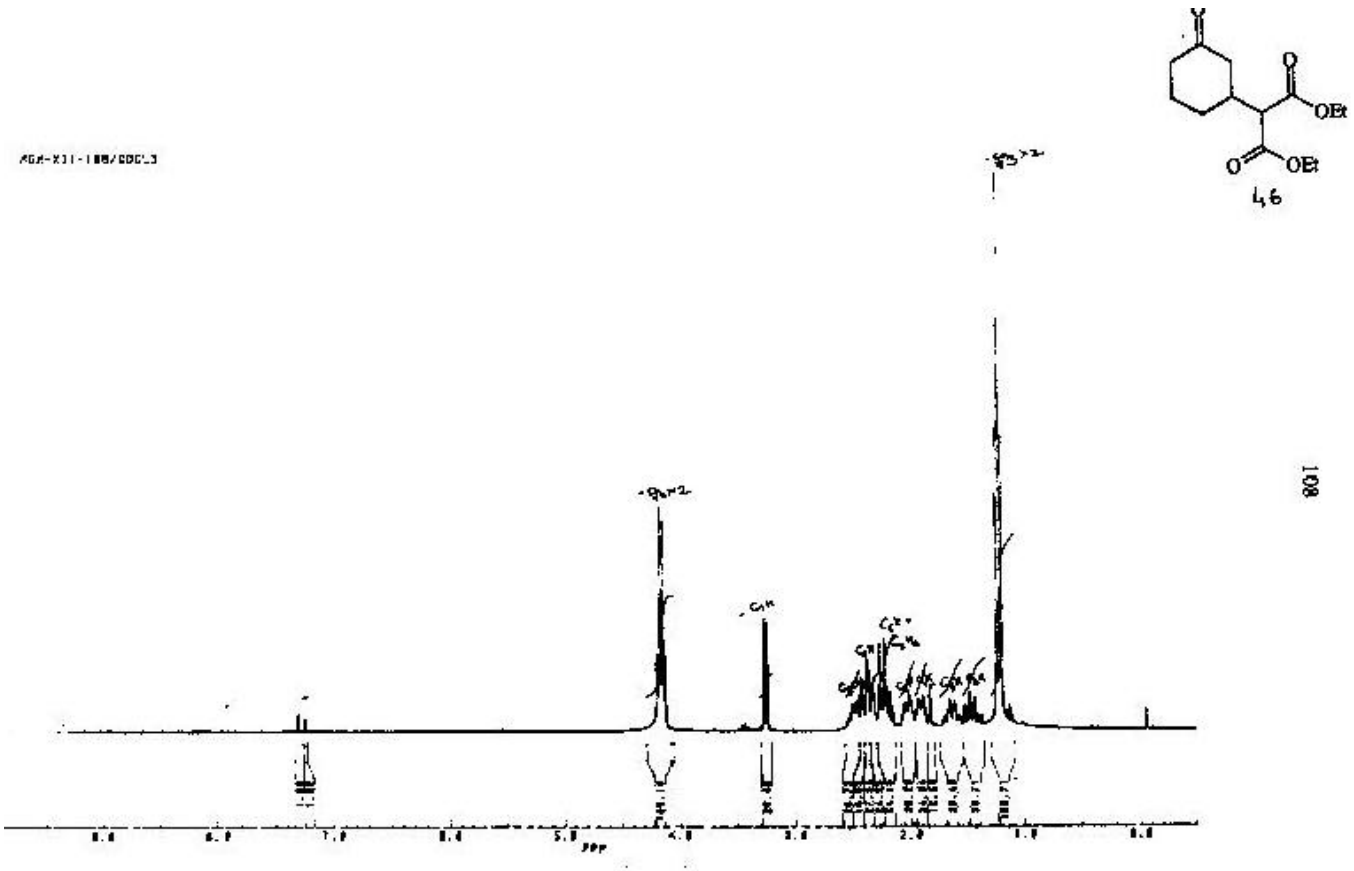
OEt
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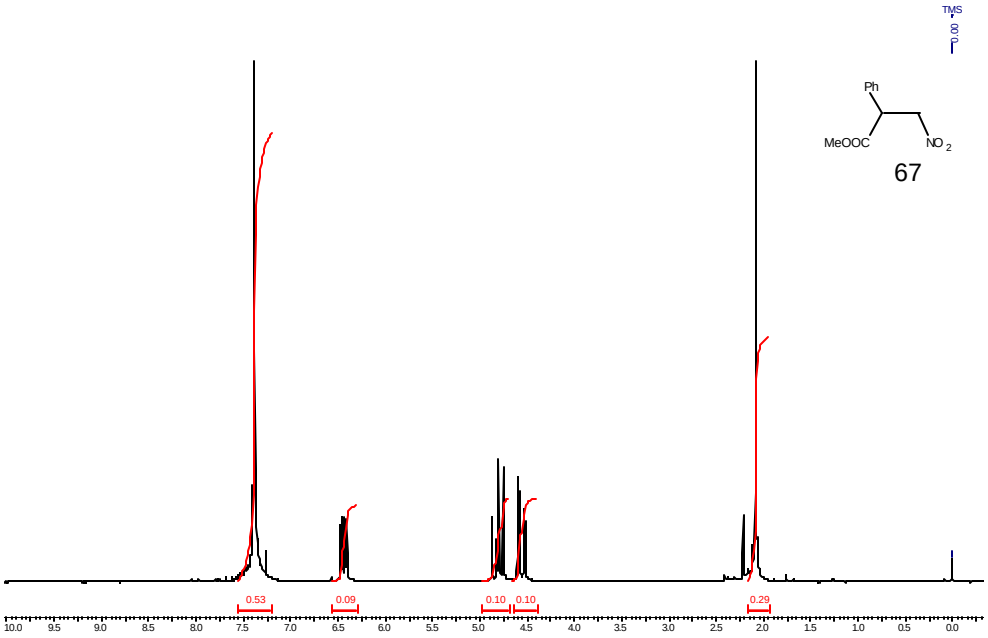
46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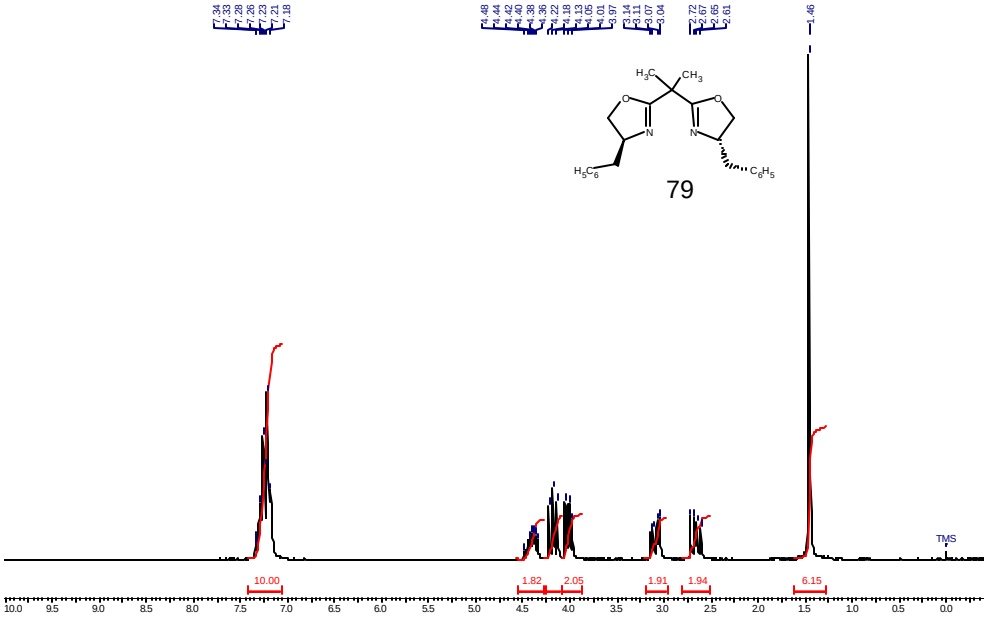
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3.04
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CH3
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C6H5
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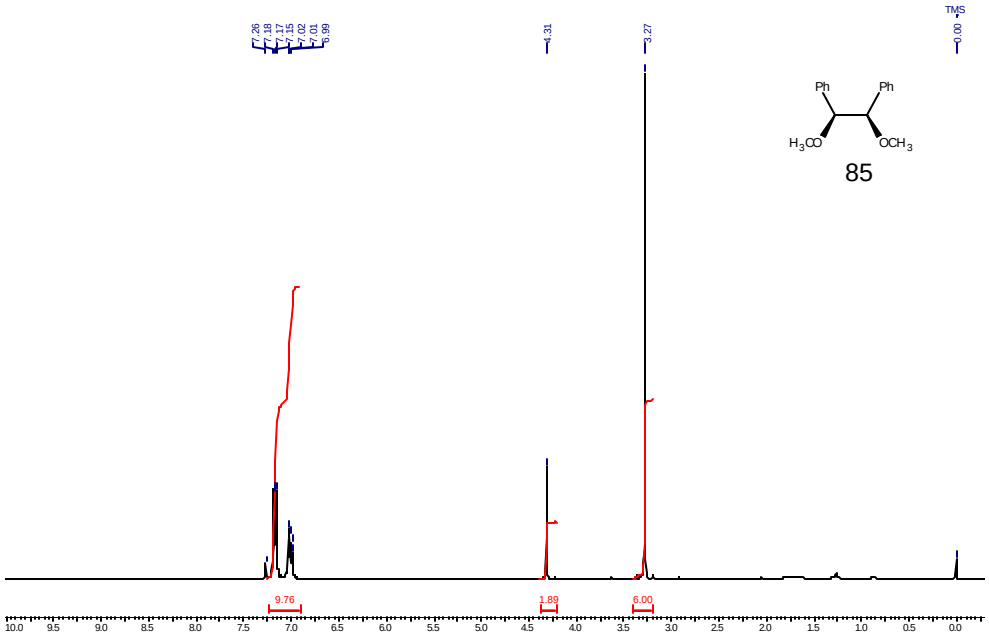
79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85