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- Comparative ..... 0295
- Medieval ..... 0297
- Modern ..... 0298
- African ..... 0316
- American ..... 0591
- Asian ..... 0305
- Canadian (English) ..... 0352
- Canadian (French) ..... 0355
- English ..... 0593
- Germanic ..... 0311
- Latin American ..... 0312
- Middle Eastern ..... 0315
- Romance ..... 0313
- Slavic and East European ..... 0314

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- Biblical Studies ..... 0321
- Clergy ..... 0319
- History of ..... 0320
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- Archaeology ..... 0324
- Cultural ..... 0326
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- Banking ..... 0770
- Management ..... 0454
- Marketing ..... 0338

Canadian Studies ..... 0385
Economics
- General ..... 0501
- Agricultural ..... 0503
- Commerce-Business ..... 0505
- Finance ..... 0508
- History ..... 0509
- Labor ..... 0510
- Theory ..... 0511

Folklore ..... 0358
Geography ..... 0366
Gerontology ..... 0351
History
- General ..... 0578
- Ancient ..... 0579
- Medieval ..... 0581
- Modern ..... 0582
- Black ..... 0328
- African ..... 0331
- Asia, Australia and Oceania ..... 0332
- Canadian ..... 0334
- European ..... 0335
- Latin American ..... 0336
- Middle Eastern ..... 0333
- United States ..... 0337

History of Science ..... 0585
Law ..... 0398
Political Science
- General ..... 0615
- International Law and Relations ..... 0616
- Public Administration ..... 0617

Recreation ..... 0814
Social Work ..... 0452
Sociology
- General ..... 0626
- Criminology and Penology ..... 0627
- Demography ..... 0938
- Ethnic and Racial Studies ..... 0631
- Individual and Family Studies ..... 0628
- Industrial and Labor Relations ..... 0629
- Public and Social Welfare ..... 0630
- Social Structure and Development ..... 0700
- Theory and Methods ..... 0344

Transportation ..... 0709
Urban and Regional Planning ..... 0999
Women's Studies ..... 0453

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- General ..... 0473
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- Animal Culture and Nutrition ..... 0475
- Animal Pathology ..... 0476
- Food Science and Technology ..... 0359
- Forestry and Wildlife ..... 0478
- Plant Culture ..... 0479
- Plant Pathology ..... 0480
- Plant Physiology ..... 0817
- Range Management ..... 0777
- Wood Technology ..... 0746

Biology
- General ..... 0306
- Anatomy ..... 0287
- Biostatistics ..... 0308
- Botany ..... 0309
- Cell ..... 0379
- Ecology ..... 0329
- Entomology ..... 0353
- Genetics ..... 0369
- Limnology ..... 0793
- Microbiology ..... 0410
- Molecular ..... 0307
- Neuroscience ..... 0317
- Oceanography ..... 0416
- Physiology ..... 0433
- Radiation ..... 0821
- Veterinary Science ..... 0778
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- General ..... 0786
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Geology ..... 0372
Geophysics ..... 0373
Hydrology ..... 0388
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Paleobotany ..... 0345
Paleoecology ..... 0426
Paleontology ..... 0418
Paleozoology ..... 0985
Palynology ..... 0427
Physical Geography ..... 0368
Physical Oceanography ..... 0415

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Health Sciences
- General ..... 0566
- Audiology ..... 0300
- Chemotherapy ..... 0992
- Dentistry ..... 0567
- Education ..... 0350
- Hospital Management ..... 0769
- Human Development ..... 0758
- Immunology ..... 0982
- Medicine and Surgery ..... 0564
- Mental Health ..... 0347
- Nursing ..... 0569
- Nutrition ..... 0570
- Obstetrics and Gynecology ..... 0380
- Occupational Health and Therapy ..... 0354
- Ophthalmology ..... 0381
- Pathology ..... 0571
- Pharmacology ..... 0419
- Pharmacy ..... 0572
- Physical Therapy ..... 0382
- Public Health ..... 0573
- Radiology ..... 0574
- Recreation ..... 0575
- Speech Pathology ..... 0460
- Toxicology ..... 0383

Home Economics ..... 0386

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#### Pure Sciences
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- General ..... 0485
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Mathematics ..... 0405
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- General ..... 0605
- Acoustics ..... 0986
- Astronomy and Astrophysics ..... 0606
- Atmospheric Science ..... 0608
- Atomic ..... 0748
- Electronics and Electricity ..... 0607
- Elementary Particles and High Energy ..... 0798
- Fluid and Plasma ..... 0759
- Molecular ..... 0609
- Nuclear ..... 0610
- Optics ..... 0752
- Radiation ..... 0756
- Solid State ..... 0611

Statistics ..... 0463

#### Applied Sciences
Applied Mechanics ..... 0346
Computer Science ..... 0984
Engineering
- General ..... 0537
- Aerospace ..... 0538
- Agricultural ..... 0539
- Automotive ..... 0540
- Biomedical ..... 0541
- Chemical ..... 0542
- Civil ..... 0543
- Electronics and Electrical ..... 0544
- Heat and Thermodynamics ..... 0348
- Hydraulic ..... 0545
- Industrial ..... 0546
- Marine ..... 0547
- Materials Science ..... 0794
- Mechanical ..... 0548
- Metallurgy ..... 0743
- Mining ..... 0551
- Nuclear ..... 0552
- Packaging ..... 0549
- Petroleum ..... 0765
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Geotechnology ..... 0428
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General ..... 0621
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Personality ..... 0625
Physiological ..... 0989
Psychobiology ..... 0349
Psychometrics ..... 0632
Social ..... 0451

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# Table of Contents

# List of Schemes

# List of Tables

## List of Figures

# List of Abbreviations

| | |
|---|---|
| Ac | acetyl |
| AIBN | azobis(isobutyro)nitrile |
| APT | attached proton test |
| Ar | aryl |
| Bn | benzyl |
| Bu | butyl |
| BuLi | butyllithium |
| $Bu_3SnH$ | tributyltin hydride |
| Bz | benzoyl |
| CSA | (S)–(+)–10–camphorsulfonic acid |
| Cy | cyclohexyl |
| DEAD | diethyl azodicarboxylate |
| DIBAL | diisobutyl aluminum hydride |
| DMAP | *N*, *N*-dimethylaminopyridine |
| DMF | *N*, *N*-dimethyl formamide |
| DMSO | dimethylsulfoxide |
| E | carboethoxy |
| Et | ethyl |
| Ether | diethyl ether |
| GC | gas chromatography |
| HMPA | hexamethyl phosphorous triamide |
| HRMS | high resolution mass spectrum |
| Im | imidazole |
| iPr | isopropyl |
| IR | infra red |

| | |
|---|---|
| LDA | lithium diisopropyl amide |
| LRMS | low resolution mass spectrum |
| Me | methyl |
| NBS | N-bromosuccinimide |
| nmr | nuclear magnetic resonance |
| O/N | overnight |
| PCC | pyridiniumchlorochromate |
| Ph | phenyl |
| psi | pounds per square inch |
| psig | pounds per square inch (gauge) |
| ppm | parts per million |
| Pr | propyl |
| py | pyridine |
| rt | room temperature |
| $SmI_2$ | samarium iodide |
| TBDMS | *t*-butyl dimethylsilyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TMS | trimethylsilyl |
| TTMSS | tris(trimethylsilyl)silane |

# Acknowledgments

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I have been extremely fortunate in the amount of support I have received from my family and for this I will always be grateful.

# Abstract

The preparation of a variety of halo and keto C=N containing systems for use in free radical cyclization is described. The 6-exo radical cyclization of bromo oxazolines (**A**) was first examined under standard tin hydride conditions, but only reduction products were isolated. The use of syringe pump techniques also gave only the reduced product. The use of $Bu_3SnD$ demonstrated that a 1,5-hydrogen shift was responsible for the premature quenching of the alkyl radical. A related bromo-oxazoline was prepared which was not capable of undergoing a 1,5-hydrogen shift after generation of the radical was prepared, but it did not cyclize under any conditions employed.

Thus attention was directed towards hydrazones (**B**), whose reactivity in radical cyclizations has received little attention. This study has shown that simple bromo-hydrazones underwent an extremely efficient radical cyclization to give high yields of the cyclopentyl and cyclohexyl hydrazines (**C**). Decreasing the temperature of the alkyl radical reactions to -78 °C through the use of $SmI_2$ increased the diastereoselectivity of the 5-exo cyclization to >10:1. It was also noted that the steroselectivity of the 5-exo alkyl radical cyclization increased as the size of the substituent on the radical-bearing carbon increased. The corresponding 6-exo cyclizations gave modest cis/trans selectivities regardless of the size of the substituent or the temperature of the reaction.

Ketyl radicals were generated from the corresponding aldehydes and ketones (**D**) using $SmI_2$/HMPA and their intramolecular cyclizations onto hydrazones was shown to be a facile and high yielding process. Unlike the alkyl radical cyclizations, the ketyl radical reactions were more selective at higher temperatures. Thus at room temperature, the 5-exo ketyl radical cyclization gave >15:1 selectivity in favour of the isomer with the hydroxy and hydrazino groups trans (**E**). The difference between the ketyl and alkyl cyclizations is even more notable in the 6-exo cyclizations. These reactions gave generally modest selectivities

in the alkyl series but the 6-exo ketyl radical cyclizations were highly selective at all temperatures examined.

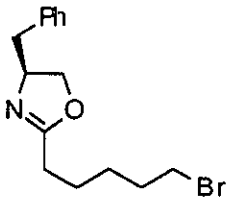
The products of these reactions, cyclic β-hydroxy hydrazines, are closely related to an important class of natural products, β-hydroxy amines. Thus methods for cleaving the N-N bond to yield the corresponding amines were examined. It was discovered that reduction of the N-N bond could be effected under mild conditions with the use of catalytic amounts of Pd/C and two equivalent of a protic acid (CSA). In the absence of this acid, the hydrazine was intact even after exposure to 500 psi of $H_2$ at 80 °C for extended periods of time. An alternative method for cleavage of the hydrazine N-N bond which involved preparation of the phenyl hydrazide and reduction with $SmI_2$. This procedure gave the corresponding amides in good yields and is a convenient alternative to the $Pd/H_2$ system. Functional group compatibility was demonstrated by reaction of a substrate containing a terminal olefin which survived the $SmI_2$ conditions.

Having developed conditions for cleavage of the N-N bond, the utility of the method was demonstrated in a brief synthesis of a penta-substituted β-hydrazino alcohol which is related to the allosimizoline class of antifungal and insecticidal agents. L-Xylose was used as the starting material for the preparation of the chiral hydrazone-aldehyde.

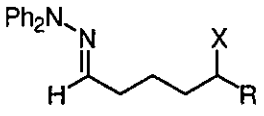
In the second portion of this thesis, we describe the determination of the rate constant for the 5 and 6 exo cyclizations of alkyl radicals using radical clock techniques. Thus a halo-hydrazone (**F**) was prepared that contained an alkene suitably positioned for a 5-exo hexenyl-type cyclization. This system was found to be effective for determination of the rate constant for the 6-exo cyclization at 80 °C ($k_{cis} = k_{trans} = 9.4 \times 10^5 s^{-1}$). The activation energies for the 6-exo reactions were also determined to be 5.6 and 6.2 kcal/mol for the *cis* and *trans* cyclizations respectively. The corresponding 5-exo hydrazone cyclization was surprisingly too fast to be measured with the 5-hexenyl clock. The rate constant for this fast reaction could be determined by running the cyclization in concentrated $Bu_3SnH$ and measuring the amounts of cyclized vs. reduced products. This

intermolecular clock gave a rate constant for the 5-exo cyclization of $k_{cis} = 1.1 \times 10^8 s^{-1}$ and $k_{trans} = 4.6 \times 10^7 s^{-1}$ at 80 °C, which is approximately 200 times faster than the corresponding alkene cyclization. From this data we calculated that a cyclization run in neat $Bu_3SnH$ at 80 °C would give a 12:1 ratio of products *in favour of the cyclized product.*

A related system (**G**) was prepared to test the 5 and 6 exo ketyl radical cyclizations. As in the simple alkyl radical systems, the hydrazone proved to be a more efficient radical acceptor than the corresponding alkene.

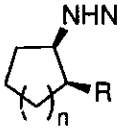



**A**



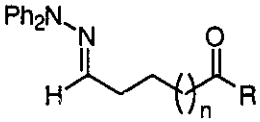

n=1, 2
R=Me, Cy, iPr
X=Br, I

**B**



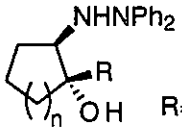

n=1, 2
R=Me, Cy, iPr

**C**



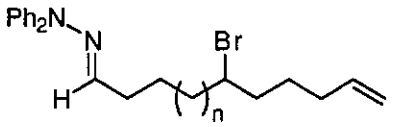

n=1, 2
R=H, Me

**D**

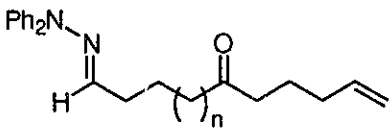



n=1, 2
R=H, Me

**E**




**F** n=1, 2




**G** n=1, 2

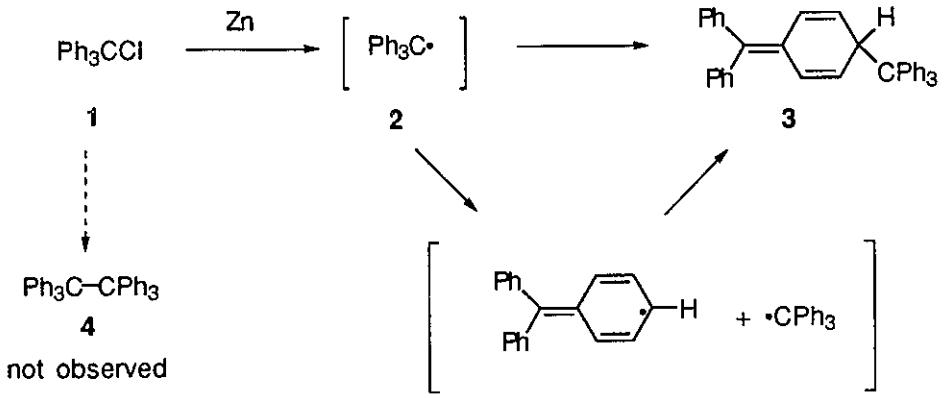
Dedicated to my parents Michele and Rosa and to my sister Silvana

# Chapter One: General Introduction

The use of free–radical based methods in synthetic organic chemistry has increased dramatically in the past decade.[1] During this time, impressive achievements have been realized in the areas of chemoselectivity and stereochemical control (both relative and absolute). Of equal importance, where once radical solutions to synthetic questions were seldom considered, today they find general acceptance and use.

Carbon radicals have been known since Gomberg's[2] original report in 1900 on the preparation of triphenylmethyl radical (**2**) in his attempted Wurtz coupling of triphenylmethyl chloride (**1**) to generate hexaphenylethane (Scheme 1). It was observed that on treatment with zinc, $Ph_3CCl$ generated the stable triphenylmethyl radical which slowly dimerized to **3**.

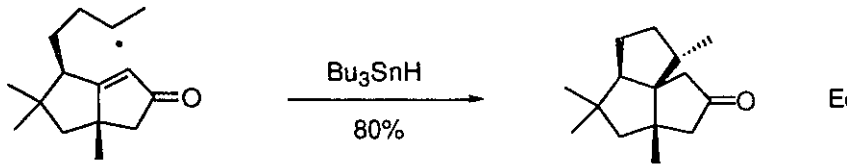
**Scheme 1: Gomberg's Preparation of Triphenylmethyl Radical**




There are several advantages of radical methods over the corresponding ionic reactions.[3] Radicals themselves are very reactive species while radical conditions are

generally neutral and mild, leaving many functional groups intact including OH or NH groups. Hence these functional groups need not be protected, and the removal of water is not necessary. As will be shown below, high levels of regio, chemo and even stereoselectivity can be achieved in radical reactions. The rates and stereoselectivities of these reactions often increase with increased molecular complexity. In contrast, ionic reactions tend to diminish in efficiency with increased substrate complexity.

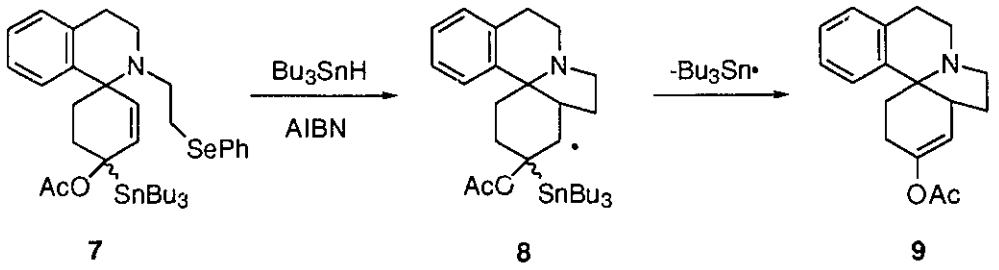
Radical additions to C=C bonds are strongly exothermic and irreversible, proceeding via an early transition state often leading to products of kinetic control.[4] Also, radicals are neutral species and hence are not burdened with bulky counterions or metal components and are effective at forming sterically crowded bonds as illustrated in Equation 1 below.[5] In this example, a 5–exo cyclization proceeded efficiently, creating a quartenary center in **6** in 80% yield.




**5** **6** Eq.1

In carbanionic reactions, generation of an anion β to a good leaving group tends to lead to elimination by-products. Reactions involving the formation of a carbocation suffer from capture by β OR or $NR_2$ functional groups. Neither of these unwanted side reactions is generally a concern in radical reactions. However, radicals can undergo β elimination of stable radicals such as SR, $SO_nR$, or $SnR_3$. The following example (Scheme 2) illustrates the chemoselective β–elimination of a stannyl radical regenerating an unsaturated functional group in **9**.[6]

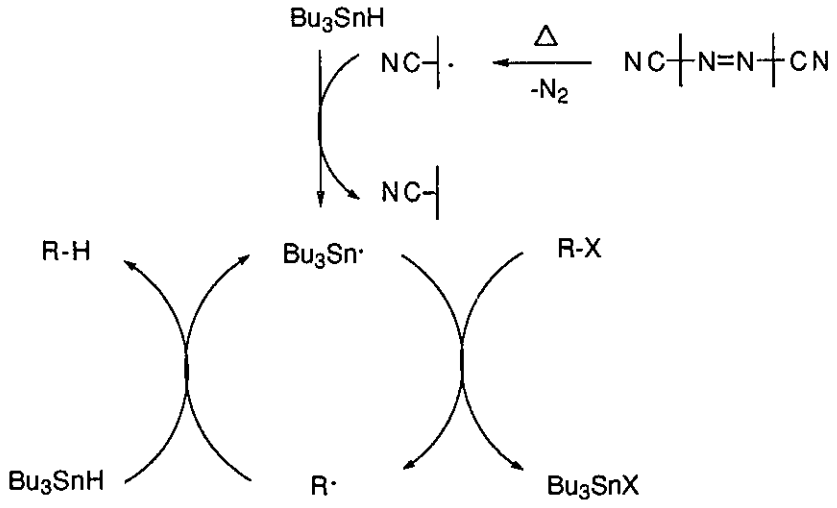
**Scheme 2: β–Elimination of a Stannyl Radical**



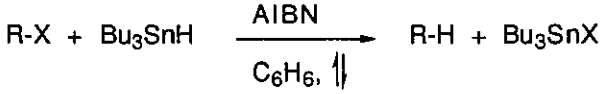

7 8 9

The most popular synthetic procedure for carrying out radical reactions is the "tin hydride method". This involves treating the starting substrate (R–X) with $Bu_3SnH$ and azobis(isobutyro)nitrile (AIBN) in benzene. The mechanism for the reaction involves a chain reaction as shown in Scheme 3.[7]

**Scheme 3: Mechanism of a Tin Hydride Mediated Reduction**




**Overall Reaction:**



This reaction is thermodynamically driven by the conversion of a C–X bond to a stronger C–H bond. X is usually a bromine or iodine but other radical groups have been used such as SePh, OC(S)SMe, and SPh. The rate of transfer of an X group from R–X to a tin radical follows the general order shown below.[8] The reactivity of primary, secondary or tertiary radicals with tin hydride is approximately the same.[9]

**Order of Reactivity Towards Tin Radicals:**

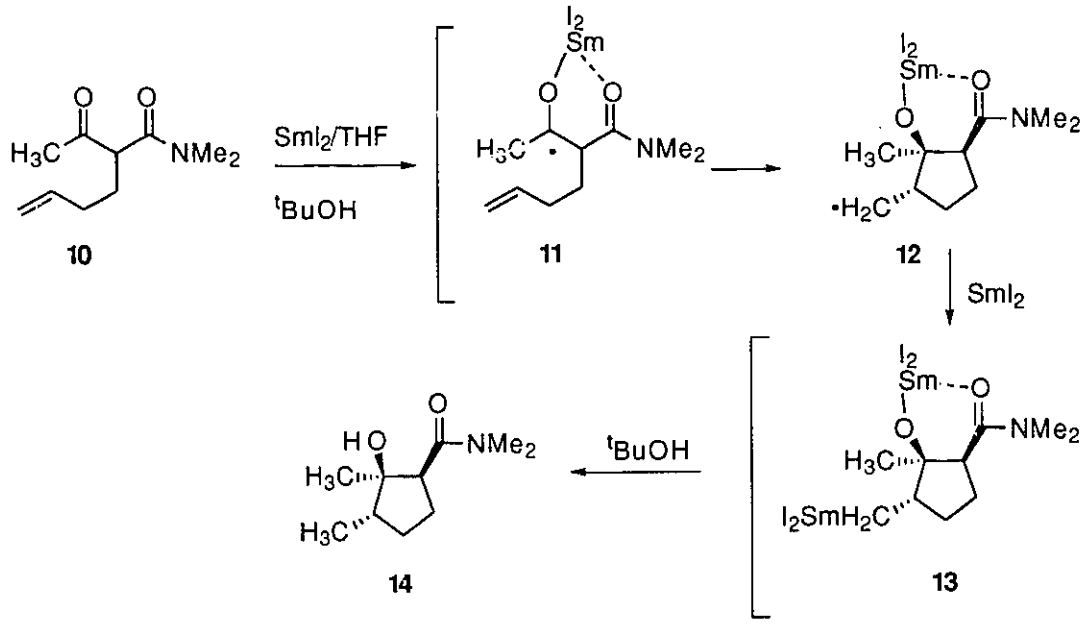
$$I > Br > SePh > \sim OC(S)SMe > Cl > SPh$$

Tributyltin hydride is a popular reagent for carrying out radical reactions because it is experimentally simple to use, it allows a long lifetime of the radical intermediate through the use of syringe pump techniques and its kinetic behavior has been extensively investigated.[9b] Drawbacks to its use include the toxicity of organostannanes and the difficulty sometimes encountered in removing the tin by–products from the reaction mixture. Many other methods for the generation of carbon radicals have recently been developed.[1a] Of these methods, samarium(II) iodide ($SmI_2$) has received considerable attention. $SmI_2$ is a powerful one electron reducing agent ($Sm^{2+}/Sm^{3+} = -1.55$ V[10]) that generates alkyl radicals from halides and ketyl radicals from carbonyl substrates. Two equivalents of $SmI_2$ are usually required, the first generates the radical and the second forms an organosamarium species that can either be hydrolyzed with water or further functionalized with an appropriate electrophile. The following scheme (4) illustrates the role of $SmI_2$ in a radical cyclization.

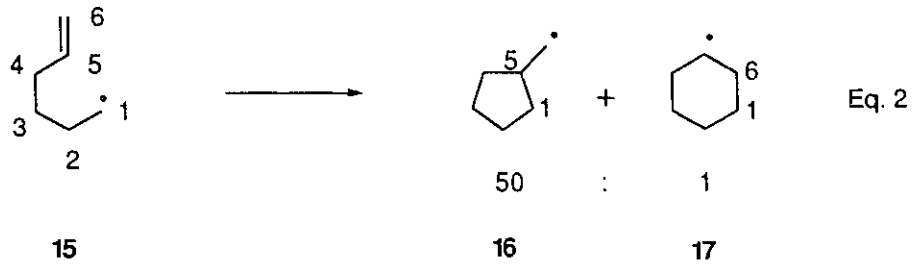
Electron transfer from $SmI_2$ to the ketone **10** generates the corresponding ketyl radical **11**. This radical then undergoes a highly stereoselective cyclization to generate the 1° radical **12**. This radical is then further reduced by $SmI_2$ to generate the

organosamarium intermediate **13** which, after protonation, generates the observed cyclic alcohol **14** in good yield (78%) with excellent diastereoselectivity (>200:1). This is a synthetically powerful method as three contiguous stereocenters are generated in one step with excellent control. Also note that $SmI_2$ behaves both as a reducing agent *and* a Lewis acid controlling the stereoselectivity of the ensuing radical cyclization.[11]

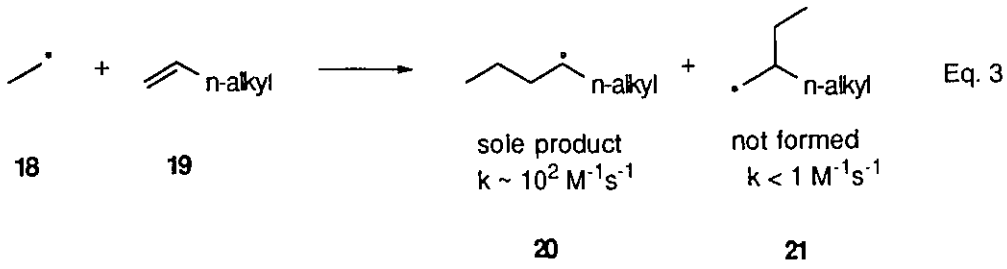
**Scheme 4: Samarium Iodide Induced Radical Cyclization**




As demonstrated by the above example, intramolecular radical cyclizations are very efficient for the preparation of cyclic compounds. There have also been extensive mechanistic studies into the 5–hexenyl radical cyclization which is a very well understood radical reaction. This reaction follows Baldwin's empirical rules of cyclization[12] with the 5–exo mode of ring closure favoured over the 6–endo closure by a factor of approximately 50 at 25 °C as shown in Equation 2 below.



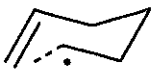

Consider also the addition of an ethyl radical to a terminal olefin as shown below in Equation 3.[13] As this example clearly demonstrates, there is a strong steric preference for a radical to add to the *less* substituted end of an alkene generating **20** as the sole product. In the 5–hexenyl system previously described, addition occurs to the *more* substituted end of the alkene. The reason for this regioselectivity lies in the transition states for the corresponding reactions.




Beckwith[14] proposed that the 5–hexenyl radical cyclization proceeds via a cyclohexane chair conformation (see Table 1 below). Subsequent calculations by Houk and Spellmeyer[15] have added to the understanding of the 5–hexenyl system. A summary of their findings is shown in Table 1. Their study suggests that at least three low energy transition states are accessible and should be considered: (i) 5–exo chair, (ii) 5–exo boat, and (iii) 6–endo chair. These calculations correctly predict that the radical cyclizations have an early transition state with an incipient bond length of approximately 2.4 Å. This distance is similar to the distance between C1 and C3 of a cyclohexane ring. There are several reasons the 5–exo cyclization is preferred. The predicted angle of attack for this

ring closure (106 °), is close to that of an unconstrained bimolecular addition (109 °). In contrast, for the 6–endo pathway, the predicted angle (94 °) would result in extra torsional and/or bending strain at the transition state compared to the 5–exo addition. Poor SOMO–LUMO interactions in the transition state also disfavour the 6–endo pathway. Furthermore, the 5–exo transition state is favoured over the 6–endo entropically as it retains a degree of freedom.

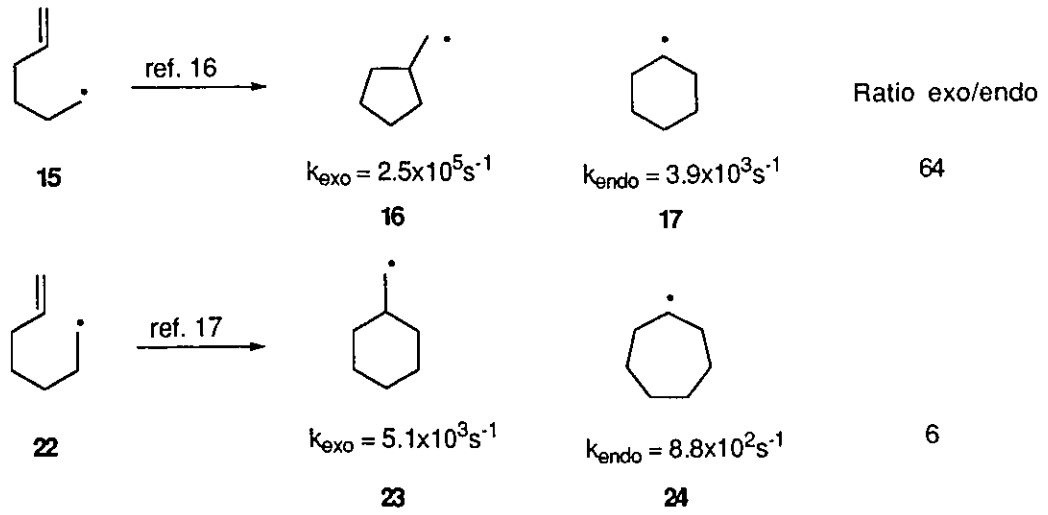
**Table 1: Transition States for the 5–hexenyl Radical Cyclization**

| | Relative energy | Angle of attack | Bond distance |
|---|---|---|---|
|  | | | |
| 5-exo chair | 0 Kcal/mole | 106 ° | 2.34 |
|  | | | |
| 5-exo boat | 1 Kcal/mole | 105 ° | 2.34 |
|  | | | |
| 6-endo chair | 3 Kcal/mole | 94 ° | 2.40 |

The exo–endo selectivities for the formation of 5, 6 and 7 membered rings are compared in Table 2. As can be seen from this table, while the 5–hexenyl cyclization displays a high level of exo/endo selectivity (~60) the corresponding 6–heptenyl

cyclization provides a lower level of selectivity (exo/endo ~ 6). Also, the rate of cyclization of the 6–exo cyclization is slower than the 5–hexenyl system.

**Table 2: Comparison of Exo and Endo Ring Closure at 25 °C**

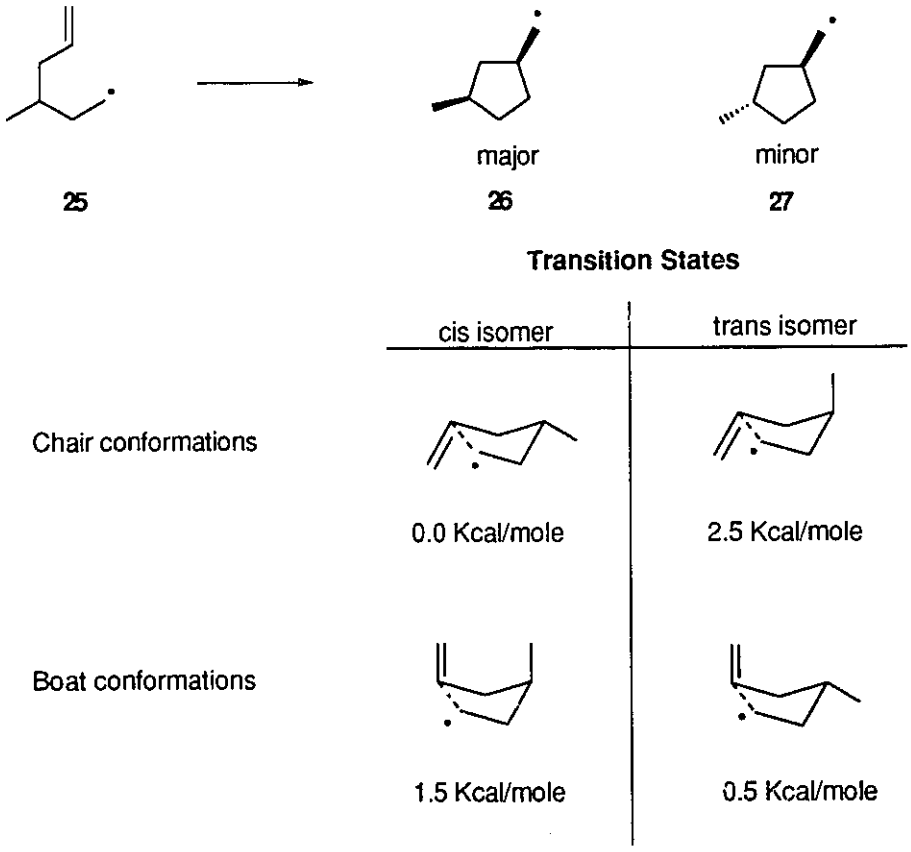



## Control of Relative Stereochemistry

There are currently many examples in the literature of highly stereoselective radical cyclizations. The Beckwith and Houk/Spellmeyer models that we encountered earlier to explain the regiochemical outcome of the 5–hexenyl cyclization can be adapted to explain and predict the stereochemical outcome of a radical cyclization. The major product can often be predicted by using the Beckwith chair conformation model and placing the larger substituents in pseudo–equatorial positions. As an illustrative example, consider the cyclization of a 3–substituted hexenyl system as shown in Scheme 5 below. The major product arises from a chair conformation by placing the methyl substituent in an equatorial position yielding the *cis* cyclopentane (**26**) as the major product.

Calculations by Houk and Spellmeyer[18] have revealed some interesting results and these are shown in Scheme 5. Their calculations show that the lowest energy transition state has a chair conformation with the methyl group in an equatorial position in accord with the Beckwith model. An intriguing finding in this study is that the minor *trans* product can arise from a boat conformation with the methyl in an equatorial position and that this transition state lies *only* 0.5 kcal/mol higher in energy than the chair conformation.

**Scheme 5: Radical Cyclizations of a 3-Substituted Hexenyl System**




In a given system, the major product will arise from cyclization through a cyclohexane chair conformation that places the larger substituent in an equatorial

position. A general rule for the relative stereochemical outcome at the two newly created stereogenic centers can be obtained from this as shown below:

C1 or C3 substitution $\Longrightarrow$ **cis**

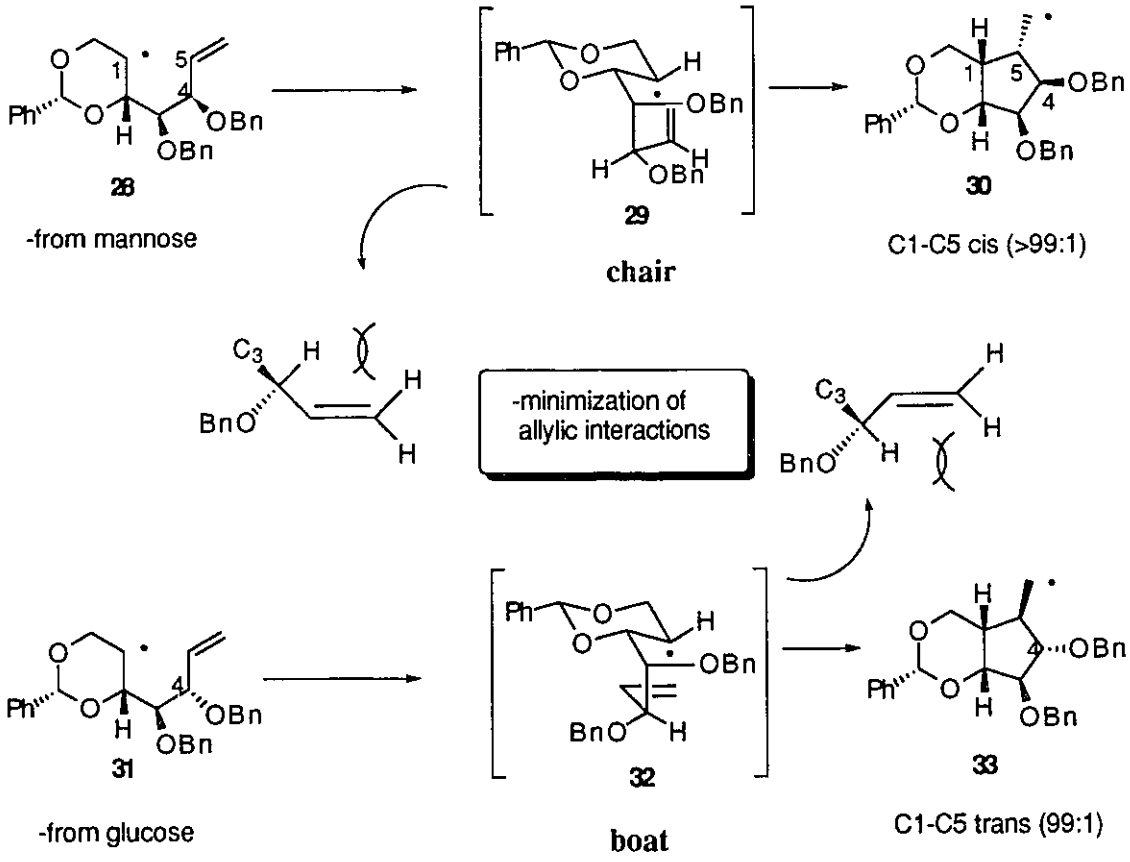
C2 or C4 substitution $\Longrightarrow$ **trans**

These guidelines predict the product of cyclization when one substituent is present, and the following section deals with more highly functionalized systems.

## Control of Absolute Stereochemistry

The elegant work of RajanBabu[19] has demonstrated that one can efficiently control the stereochemical outcome of radical cyclizations. Also, by using chiral non–racemic substrates, excellent control of the absolute stereochemistry at the two newly created stereogenic centers can be realized. Scheme 6 illustrates how a cyclization can be programmed to proceed via either a chair or boat conformation by controlling the substitution pattern.

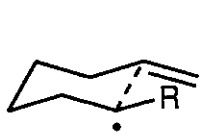
**Scheme 6: Substituent Control of the Chair vs. Boat Transition States**



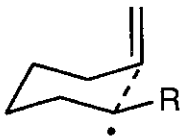

It was found that the absolute stereochemistry at the two newly formed stereogenic centers (C1 and C5) is controlled by the stereochemistry at C4.[20] For example cyclization of **28**, with a β benzyloxy substituent at C4, proceeded through the chair transition state **29** to yield the *cis* isomer **30** with excellent selectivity (>99:1). By simply inverting the stereochemistry at C4 from β to α the reaction now proceeds through the boat transition state **32** to furnish the *trans* isomer **33**, again with excellent control (99:1). *Thus one can efficiently control whether a cyclization occurs through a chair or boat transition state by the proper choice of starting material.* The controlling element in the above cyclization was reasoned to be the minimization of allylic strain experienced during the cyclization.

Unlike the high stereoselectivities available to the 5–exo hexenyl system, lower selectivities in general have been reported for the 6–exo heptenyl cyclization. The major product usually results from a chair conformation with any substituent present occupying an equatorial position[21] as shown below in Scheme 7.

**Scheme 7: Conformation of the 6–Heptenyl Cyclization**



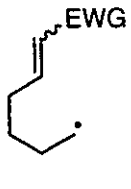

major



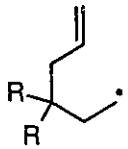

minor

As illustrated above, substituents play an important role in controlling the stereochemical outcome of a radical cyclization. Substituents can also have a pronounced influence on both the rate and regio–outcome of a radical cyclization. Scheme 8 briefly summaries the accelerating and decelerating[22] effects of certain substituents on the simple 5–hexenyl cyclization.

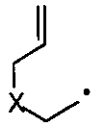
**Scheme 8a: Accelerating Substituents**



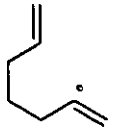

**34a**




**34b**




**34c**

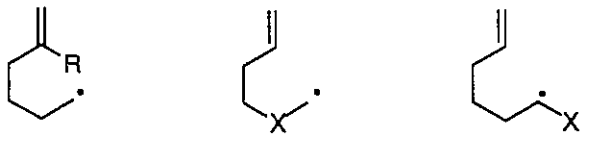


**34d**

EWG = electron withdrawing group

X = O, NR

**Scheme 8b: Decelerating Substituents**




**35a** $R \neq H$

**35b** X=O, NR

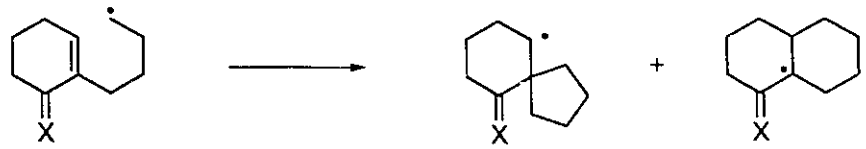
**35c**$^{\cdot}$ X=O, NR

Placement of an electron withdrawing group on the olefin as in **34a** accelerates the cyclization dramatically (ca. 100x). If geminal substitution is present at C3 as in **34b**, a rate enhancement of approximately 20 is observed. This geminal substitution brings the two reacting centers closer together and is referred to as the Thorpe–Ingold effect. The replacement of the C3 carbon for either oxygen or a nitrogen also results in a Thorpe–Ingold type effect with a rate acceleration of approximately 40 times. The last example in the accelerating section shows that vinyl radicals are considerably more reactive than alkyl radicals with a rate enhancement of approximately 200 times.

Radical cyclizations are generally sensitive to steric effects at the olefin acceptor center as illustrated by the first entry in the decelerating section. For example, by replacing a hydrogen for a methyl, the cyclization is slowed down by about 40 times and this cyclization is actually slightly endo selective (~1.5:1 endo/exo). Stabilization of the alkyl radical, as is the case with the remaining two entries, results in a slower cyclization.

Interesting observations have been made when activating groups are incorporated into the 5–hexenyl system to alter the normal 5–exo preference. For example, a carbonyl group suitably positioned as in **36b** in Scheme 9 dramatically alters the normal exo mode of cyclization observed with **36a** to provide the 6–endo product exclusively.[23]

**Scheme 9: Substituent Effects on Regiochemistry**

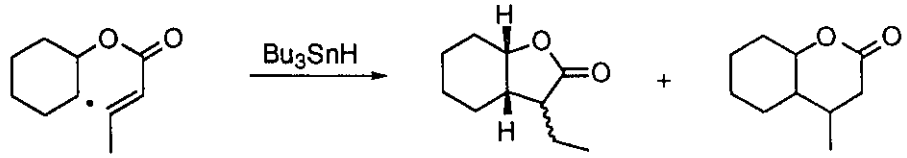


**36a** X=$CH_2$ **37a** major **38a** minor

**36b** X=O **37b** not observed **38b** only product

Recall that replacing the C3 of the hexenyl system with oxygen accelerates the 5–exo mode of cyclization as was shown in Scheme 8a. Substrate **39** in Scheme 10 represents an interesting case where two opposing activation elements are present; the carbonyl activates 6–endo cyclization and the ring oxygen favours 5–exo ring closure. Even in the presence of the activating carbonyl group, the ring oxygen restores the high 5–exo cyclization preference.[24]

**Scheme 10: Competitive 5–Exo or 6–Endo Cyclization in an Activated System**

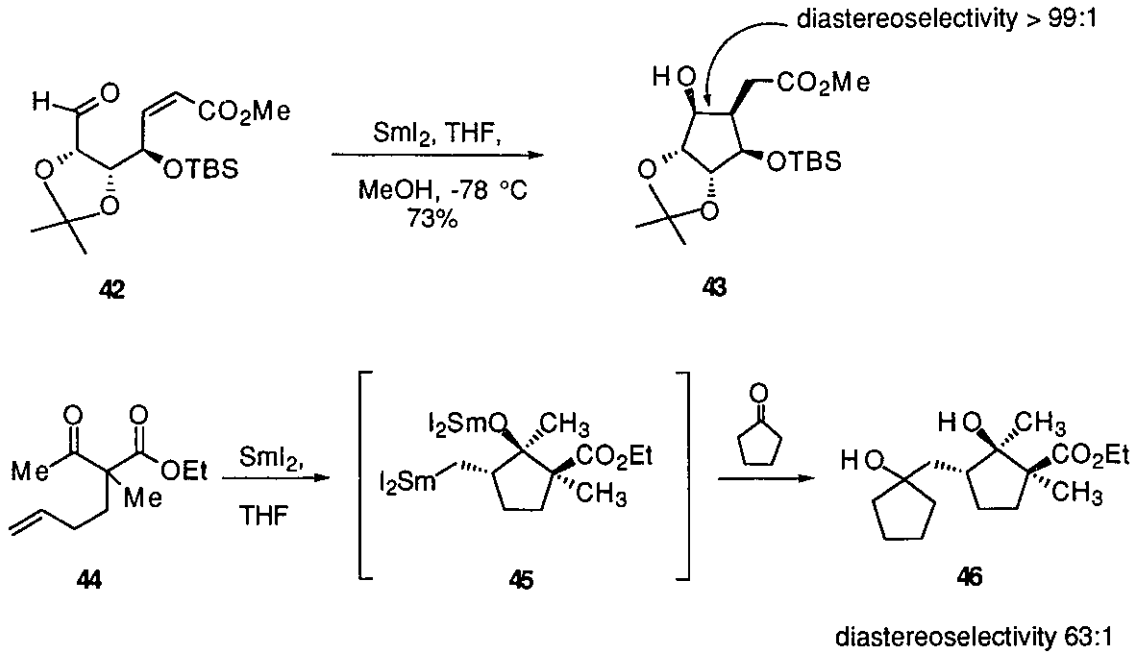


**39** only product **40** not observed **41**

Up to this point, a general discussion of the behavior of radical cyclizations has been presented. The following section highlights some examples from the current literature of the use of radical cyclizations, and radical reactions in general, with particular attention being paid to the issues of chemo and stereoselectivity. $SmI_2$

applications have dramatically increased in the past several years. The following two examples illustrate the use of $SmI_2$ in highly stereoselective cyclizations.

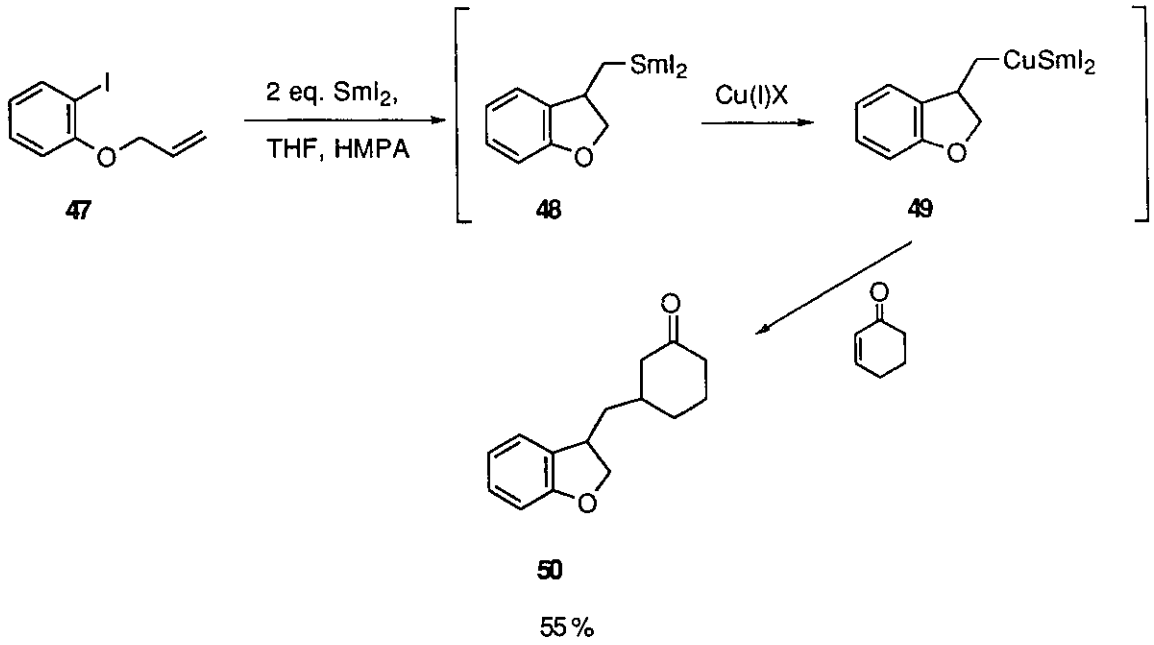
**Scheme 11: $SmI_2$ in Stereoselective Cyclizations**



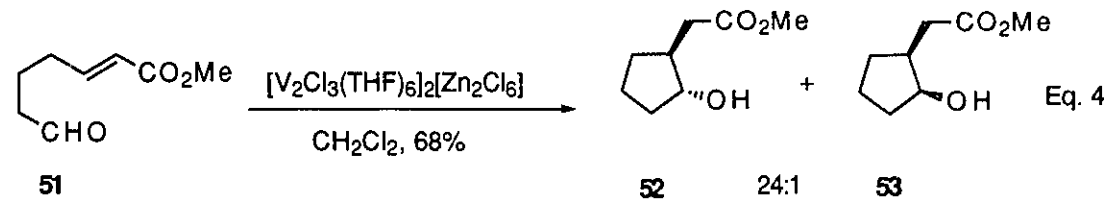

In the first example[25], the ketyl radical generated from aldehyde **42** undergoes a highly diastereoselective cyclization (>99:1) to afford the functionalized cyclopentane **43**. A drawback in traditional radical cyclizations is that the two participating functional groups are lost during the course of the reaction. A distinct advantage of using ketyl radical intermediates is that a synthetically useful hydroxyl group is recovered at the end of the reaction as found in the product **43**. This point is also demonstrated in the second example[26] in Scheme 11. In this case, the resulting organosamarium intermediate produced after cyclization is treated with cyclopentanone *introducing* functionality. An interesting report from Curran's lab[27] discloses the results of treating organosamarium intermediates with Cu(I) salts generating "organocuprates" that undergo Michael

additions to enones as highlighted in Scheme 12. In the absence of the Cu(I) salt, only 1, 2 addition to the enone was observed.

**Scheme 12: Cu(I) Mediated Michael Additions of Organosamarium Species**

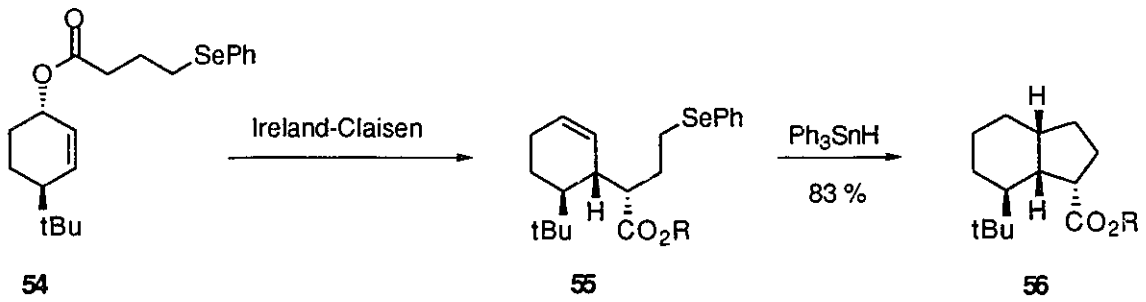



Pederson's group has recently reported a new bimetallic vanadium (II) species, $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$[28] generated from $VCl_3(THF)_3$ and zinc metal, which promises to be an important new reagent for pinacol and ketyl radical reactions. An example of its utility is provided in equation 4 below. Exposure of aldehyde **51** to the V(II) reagent generates a vanadium ketyl radical which undergoes a highly stereoselective cyclization.[29] The authors commented that the use of $SmI_2$/HMPA in this reaction gave only a modest level of diastereoselectivity (3:1).



Scheme 13 demonstrates an elegant example of planning a synthetic sequence around a 5–hexenyl radical cyclization.[30] The first step involves an Ireland–Claisen rearrangement of the readily available ester **54** to provide **55**. This reaction accomplishes two important tasks, (i) it creates a stereogenic center with excellent control and (ii) sets up a 5–hexenyl cyclization. Treatment of the phenyl selenide substrate with $Ph_3SnH$/AIBN resulted in a highly stereoselective radical cyclization to provide the *cis* fused 6, 5 system **56** in 83% yield.

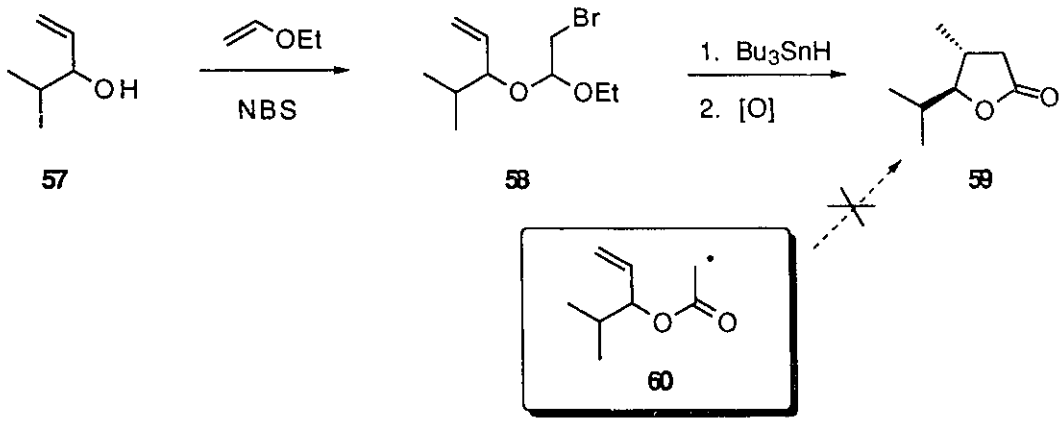
**Scheme 13: Ireland–Claisen–5–Hexenyl Cyclization Strategy**




**54** **55** **56**

A synthetically popular radical method involves the cyclization of halo acetals which was introduced by Stork and Ueno.[31] As shown in Scheme 14, treatment of an alcohol with a vinyl ether in the presence of NBS yields the key bromo acetal intermediate **58**. Further treatment with $Bu_3SnH$/AIBN effects radical cyclization to yield exclusively the *trans* product.[32] Oxidation of the acetal results in an efficient synthesis of lactone **59** with control of the two stereogenic centers.

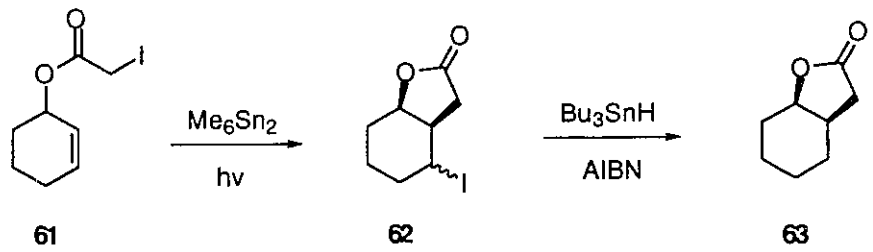
**Scheme 14: The Use of Halo Acetals in Radical Cyclizations**




Halo acetals, such as **58** were designed by Stork *et al.* to solve the problems encountered in the attempted cyclizations of α–ester radicals. Attempts at preparing lactone **59** from a cyclization of the α–ester radical **60** generated under tin hydride conditions, were completely unsuccessful.

Another elegant and effective solution to this problem is the atom–transfer method. Amazingly, when iodide **61** (Scheme 15) was treated with hexamethylditin ($Me_6Sn_2$) in benzene and irradiated, cyclization did occur to give the rearranged iodide **62**. Further treatment of this iodide with $Bu_3SnH$/AIBN provided the reduced lactone in 55% overall yield.[33] Attempts at cyclizing the α–iodo ester (**61**) with $Bu_3SnH$ under a variety of conditions only gave straight reduction.

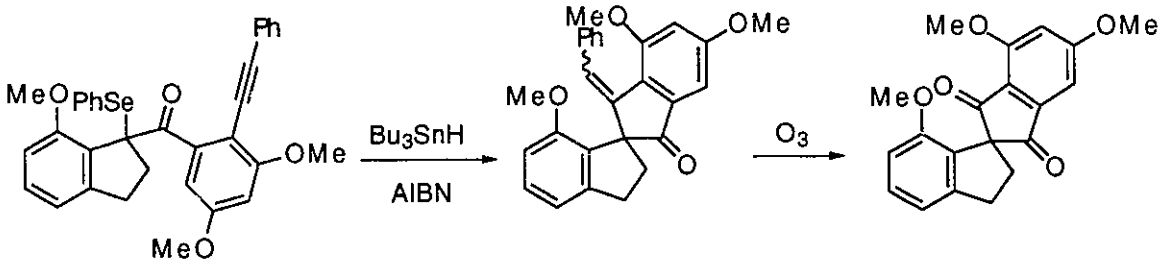
**Scheme 15: Atom Transfer Cyclization**




61 62 63

Even though α–ester radicals are reluctant to undergo cyclization, α–keto systems proved more fruitful as highlighted by the 5–exo cyclization of **64** to give the spiro compound **65** as shown in Scheme 16. The resulting alkene was then ozonolyzed to the corresponding ketone for further synthetic manipulation.[34]

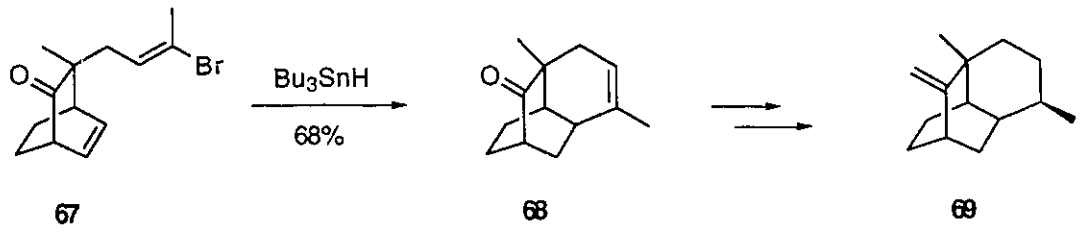
**Scheme 16: α–Keto Radical Cyclization**




64 65 66

Stork[35] has also pioneered the use of vinyl radicals in synthesis. An elegant example of this is shown in Scheme 17 below. Vinyl radicals are very reactive intermediates and often provide excellent yields of cyclized products. In the example provided, radical cyclization proceeded to give **68** in 70% yield.[36] A synthetic advantage offered by this approach is that the resulting olefin can undergo stereochemically controlled reductions *after* the key carbon–carbon bond forming reaction. Further elaboration of **68** provided the target Seychellene.

**Scheme 17: Vinyl Radical Cyclization**



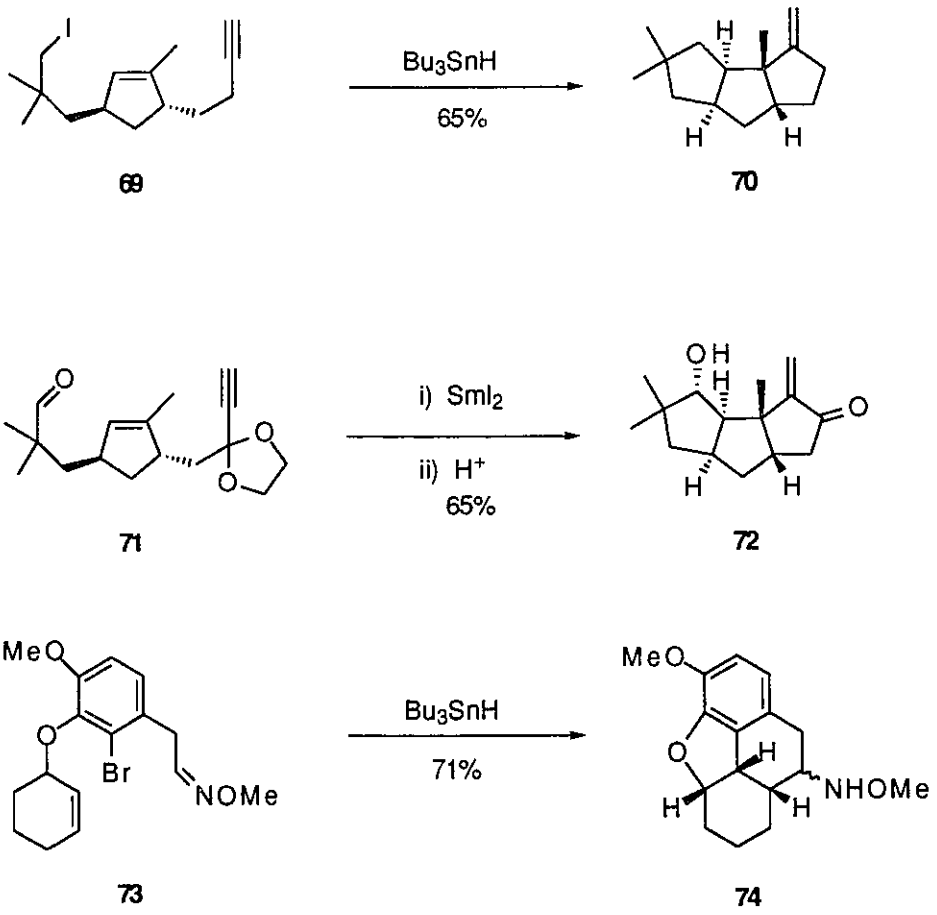

67 68 69

Seychellene

## Tandem Radical Cyclizations

In principal, the radical generated after one cyclization can participate in a second (or third, etc.) cyclization on a suitably positioned π system. This represents a very powerful synthetic method as several C–C bonds and/or rings are formed in a single experimental manipulation. Several representative examples from the current literature listed in Scheme 18 illustrate the power of this method. In the first example[37], generation of the initial radical is followed by cyclization to generate a 3° radical. This 3° radical undergoes a second cyclization to give the tricyclic compound **70** in 65 % yield. The second example is similar to the first but it involves a ketyl radical cyclization to provide the alcohol **72** in 65 % yield.[38] The third example illustrates how quickly molecular complexity can be achieved through the use of a tandem sequence.[39]

**Scheme 18: Tandem Radical Cyclizations**




## Nitrogen and Oxygen Centered Radicals

By far the most studied radical reactions involve carbon centered radicals. Cyclizations of heteroatom radicals, although useful, have received considerably less attention. It is important to note that the reactivities of oxygen and nitrogen centered radicals differ substantially from those of carbon. In general, oxygen radicals are more reactive and nitrogen less reactive than carbon radicals. This is an interesting trend since it does not correlate with the electronegativity differences. This difference can be seen in

Scheme 19 which compares the rates of the reactions of carbon, nitrogen[40] and oxygen[41] radicals with $Bu_3SnH$.

**Scheme 19: Reduction Rates of Heteroatom Radicals with $Bu_3SnH$**

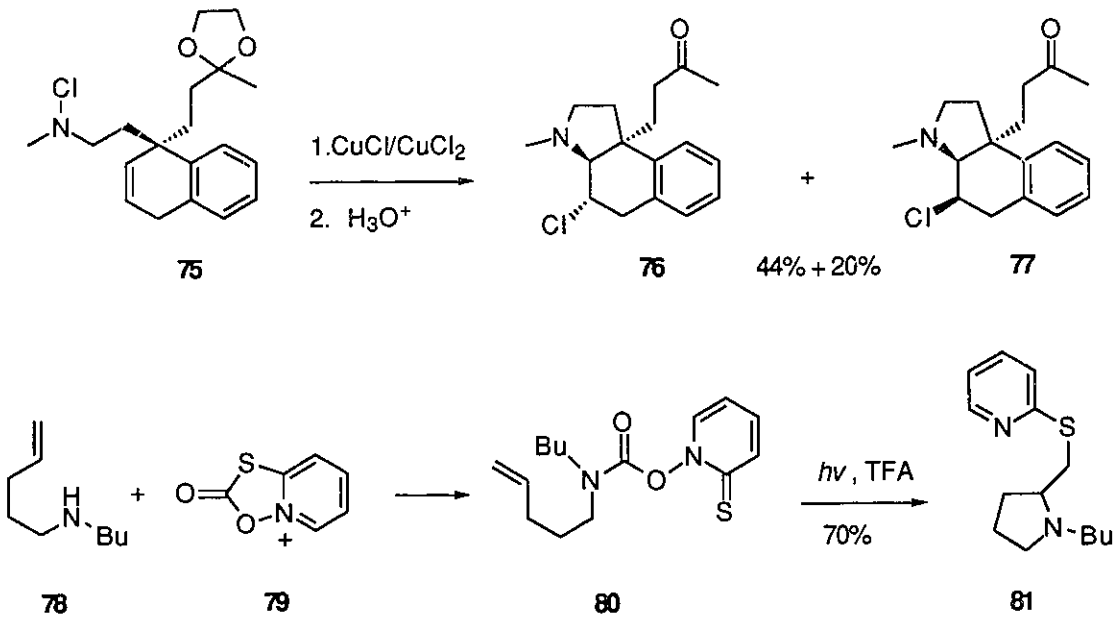
| radical | $R_3C\cdot$ | $R_2N\cdot$ | $RO\cdot$ |
|---|---|---|---|
| $k_H \approx$ | $3 \times 10^6\ M^{-1}s^{-1}$ | $8 \times 10^4\ M^{-1}s^{-1}$ | $2 \times 10^8\ M^{-1}s^{-1}$ |

## Nitrogen–Centered Radicals

The use of nitrogen centered radicals in organic synthesis has increased in recent years. The rate of cyclization of nitrogen radicals onto alkenes is slower than the cyclization of the corresponding carbon analog ($k_c \approx 3 \times 10^3$).[42]

Scheme 20 lists two recent examples of ammonium radical cyclizations. In the first[43], treatment of a chloro amine **75** with Cu(I) generates the nitrogen radical with undergoes cyclization to give chlorides **76** and **77** in 68 % yield. In the second example[44] the N–hydroxypyridine–2–thione carbamate **80** was prepared by treatment of amine **78** with the pyridine salt **79**. Photolysis of **80** in the presence of trifluoroacetic acid (TFA) generates the nitrogen radical which cyclizes onto the olefin to generate heterocycle **81** in 70 % yield.

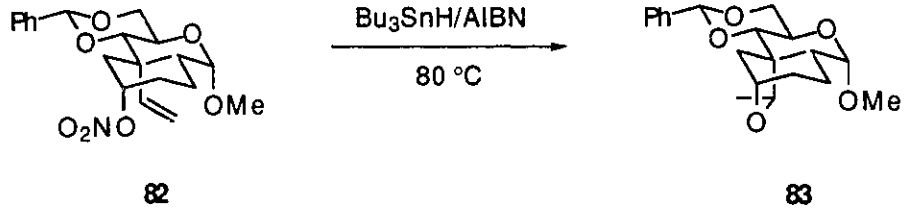
**Scheme 20: Cyclization of Nitrogen Centered Radicals**




## Oxygen–Centered Radicals

Oxygen centered radicals undergo very rapid and irreversible 5–exo cyclizations onto alkenes. The high reactivity of alkoxy radicals often present problems such as β–fragmentation and H–atom abstraction. There are nevertheless several examples[46] of alkoxy radical cyclizations, one of which is presented in Scheme 21 below. In this example from Fraser–Reid's lab[47], treatment of nitrate ester **82** under tin hydride conditions affords the oxygen cyclized product **83**.

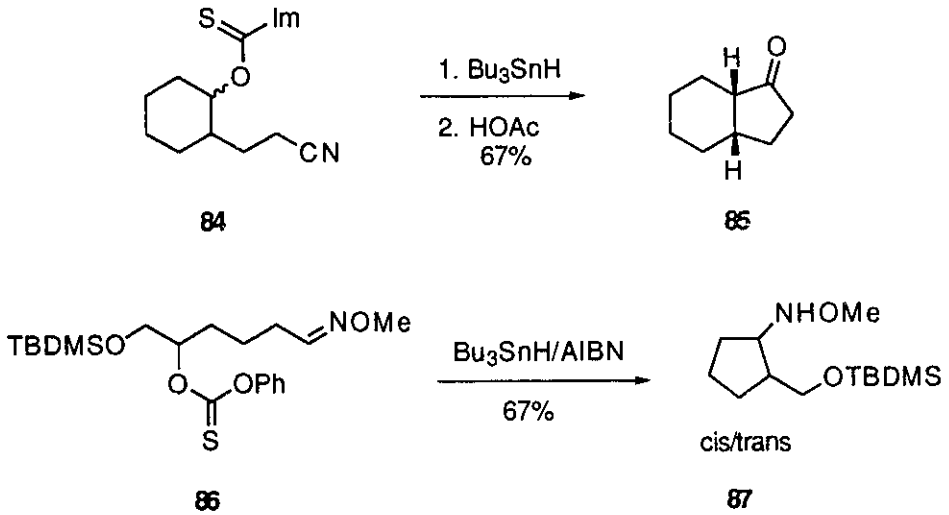
**Scheme 21: Alkoxy Radical Cyclization**



## Additions To C–O and C–N Multiple Bonds

The cyclization of a carbon radical onto C–N multiple bonds offers an attractive method for the preparation of nitrogen containing molecules. Nitriles[48] and oxime ethers[49] are the most used acceptors in this class. Scheme 22 provides an example of each of these reactions. In the first example, after generating the carbon radical from thiocarbamate **84**, a 5–exo cyclization onto the nitrile occurs to generate the intermediate imine which is hydrolyzed to ketone **85** in 67% yield. The rate constant for the 5–exo nitrile cyclization of a 1° radical has been measured[50] to be approximately 3.9 x $10^3$ $s^{-1}$ at 25 °C. For comparison, the rate constant of the corresponding 5–exo cyclization onto an alkyne[51] is approximately 2.6 x $10^4 s^{-1}$. It is usually preferable to follow a two step sequence of radical cyclization onto an alkyne followed by ozonolysis of the resulting double bond as was shown previously in the example from Clive's lab (see Scheme 16). In the second example, cyclization onto an oxime ether provides the cyclic amine **87** in 67 % yield.

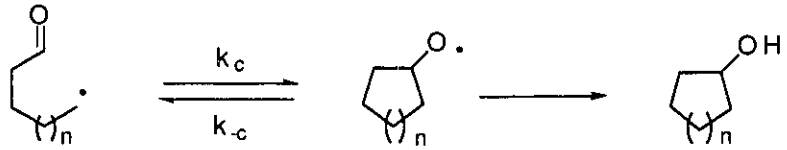
**Scheme 22: Radical Cyclization Onto C=N Systems**



## Additions onto Carbon–Oxygen Double Bonds

The pioneering work of Fraser–Reid and Tsang[52] has revealed the synthetic potential of aldehydes as radical acceptors. Radical cyclizations onto aldehydes are considerably different than cyclizations onto alkenes. Scheme 23 summarizes some of the kinetic data available for the 5 and 6–exo cyclizations onto aldehydes.[53]

**Scheme 23: Aldehyde Cyclization Kinetics**




n=1 **88**
n=2 **91**

n=1 **89**
n=2 **92**

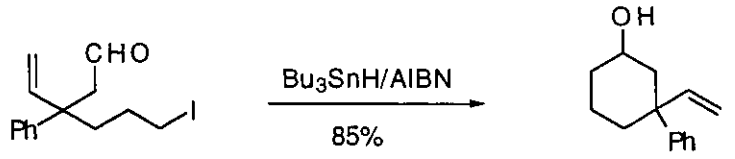
n=1 **90**
n=2 **93**

at 80 °C n=1, $k_c = 8.7 \times 10^5 s^{-1}$ $k_{-c} = 4.7 \times 10^8 s^{-1}$ $K_{eq} \sim 0.002$

n=2, $k_c = 1 \times 10^6 s^{-1}$ $k_{-c} = 1 \times 10^7 s^{-1}$ $K_{eq} \sim 0.1$

The key point to be noted in this system is that the cyclization is reversible and the equilibrium lies in favour of the ring opened form (**88** and **91**). Generally, better chemical yields are obtained for the 6–exo cyclization. One of the reasons for this is that the rate of ring opening ($k_{-c}$) is approximately fifty times faster for the cyclopentyl system than the cyclohexyl. The rate of cyclization is approximately equal for the 5 and 6 exo cyclizations, but the reverse 5–exo reaction is much faster than the corresponding reverse 6 exo reaction. Thus trapping of the open form (straight reduction) is more problematic in the attempted 5–exo cyclizations than in the related 6–exo systems. An

example of the utility of this 6-exo aldehyde cyclization in synthesis is shown below in Equation 5. Substrate **94** in Equation 5 has two potential reaction pathways, a 5–exo alkene and a 6–exo aldehyde cyclization. In the event[54], cyclohexanol **95** was isolated in 85% yield as the only cyclization product from the reaction.




**94** **95**

Eq. 5

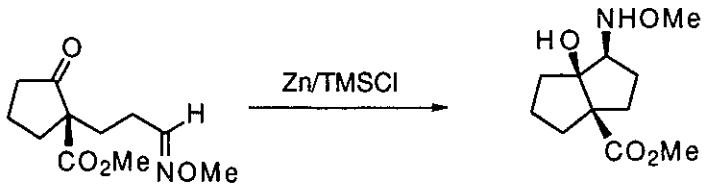
# Chapter Two: Samarium (II) Mediated Cyclization of Halo– and Carbonyl–Hydrazones

## Introduction

In contrast to the extensive literature on both the synthetic and kinetic aspects of radical additions to carbon–carbon π bonds, there has been considerably less work on carbon–nitrogen π systems. Interest in this area has increased as a means of either incorporating or manipulating nitrogen functionality in a molecule while taking advantage of the mild radical reaction conditions.

Of the reported C=N π bond radical acceptors, by far the most studied is the oxime ether ($R'_2C$=N–OR).[55] Historically, the first example of a radical cyclization onto an oxime ether was reported by Corey's group[56] and involves the addition of a zinc ketyl radical onto an oxime ether as shown in Scheme 24 below. This reaction proceeds to give the hydroxy amine (**97**) as a single diastereomer in 84% yield.

**Scheme 24: Ketyl Radical Additions onto Oxime Ethers**

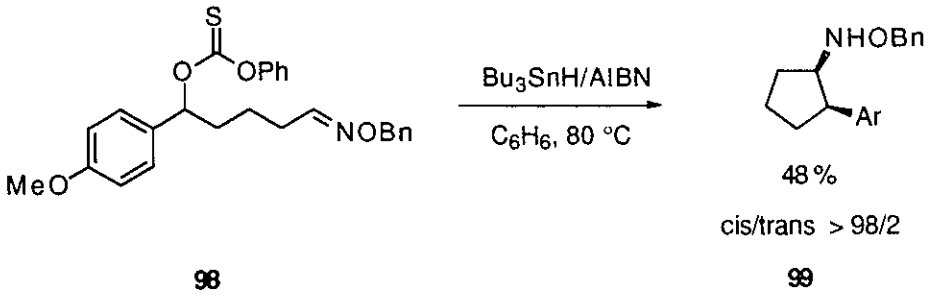



**96** **97**

The first example of an alkyl radical cyclization onto an oxime ether was reported by Bartlett's group[57] as shown in Scheme 25 below. In this example, generation of the alkyl radical from phenyl thiocarbonate **98** is followed by cyclization onto the oxime

ether to give the hydroxy amine **99** in 48% yield with excellent selectivity (*cis/trans*: > 98/2).

**Scheme 25: Intramolecular Alkyl Radical–Oxime Ether Cyclizations**

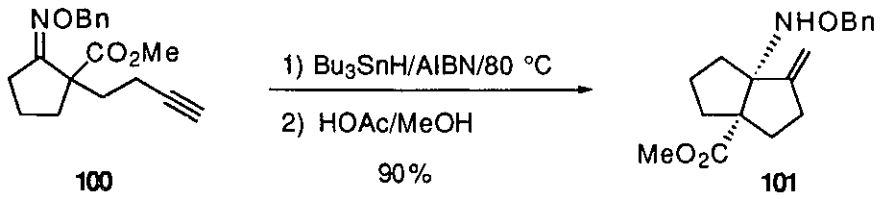



**98** **99**

Interestingly, in the article preceeding Bartlett's report on the intramolecular oxime ether radical cyclization, Hart et al.[58] described the intermolecular addition of alkyl radicals to oxime ethers. Newmann's tin pinoclate reagent ($Ph_2(OSnMe_3)C$–$C(OSnMe_3)Ph_2$)[59] was used in this study to avoid simple reduction of the initially formed radical. This system gave the corresponding hydroxyamines in good yields.

Another example of cyclization onto an oxime ether was reported by Enholm's group[60] and is shown in Scheme 26 below.

**Scheme 26: Vinyl Radical Addition to an Oxime Ether**



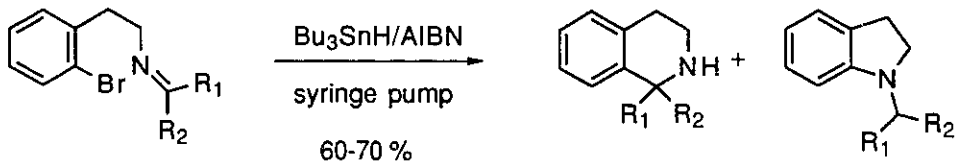

**100** **101**

Addition of the tributyltin radical ($Bu_3Sn\bullet$) to the terminal end of the alkyne in **100** generates the vinyl radical. Ring closure of this vinyl radical onto the oxime ether

generates the fused ring system with excellent stereocontrol. The resulting vinyl stannane is removed under acidic conditions to furnish the final product **101** in 90% isolated yield.

To the best of our knowledge, the only example of a radical cyclization onto an imine bond was just reported as we commenced this project. This work, which was reported by Tomaszewski and Warkentin[61], is briefly summarized in Scheme 27 below.

**Scheme 27: Aryl Radical Cyclization Onto Imines**




**102** **103** **104**

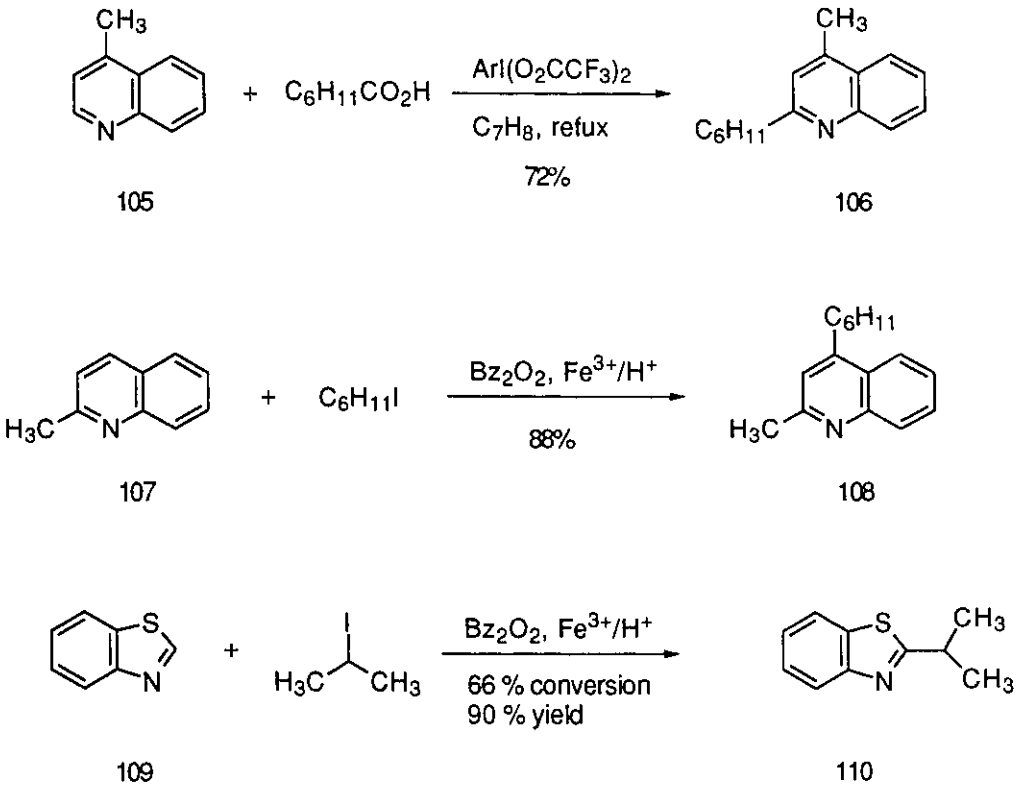
In this system, it was found that the cyclization of an aryl radical proceeded in a highly selective 6–endo fashion onto the carbon of the imine bond (up to 55:1, **103** : **104**). This reaction was found to be sensitive to steric congestion at the acceptor since the corresponding ketimines (**102**, $R_1$=$R_2$=$CH_2CH_3$) gave approximately 75% straight reduction (ratio 6–endo : 5–exo : straight reduction ≈ 1 : 2.5 : 8) when treated with tin hydride.

There are several reports in the literature on the intermolecular addition of radicals onto protonated aromatic C=N bonds (the Minisci reaction). Scheme 28 highlights some of these transformations.

In the first example[62], $ArI(O_2CCF_3)_2$ is used to generate a cyclohexyl radical from cyclohexylcarboxylic acid. The resulting cyclohexyl radical then adds to the C=N of the aromatic system in **105**. Of particular note in this reaction is that the C=N π bond is regenerated in the final product (**106**). The third[63] example in Scheme 28 is the addition of a propyl radical to the thiooxazoline **109** which proceeds to give compound

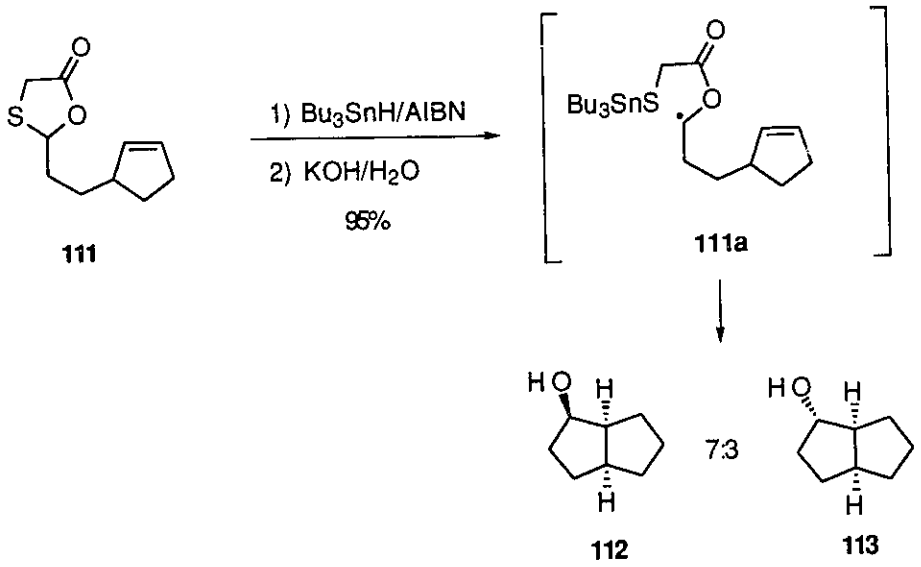
**110** in good chemical yield (60%). These results demonstrate that the intermolecular addition of radicals to C=N systems can proceed in good yields.

**Scheme 28: Intermolecular Addition of Nucleophilic Radicals to Aromatic C=N Bonds (Minisci Reaction)**




A synthetic liability in traditional radical cyclizations is the net loss of two functional groups. Several reports[64] have recently addressed this concern. Previous work in our lab[65] has demonstrated the utility of oxathiolones (**111**) as radical precursors as shown in Scheme 29. Homolytic cleavage of the C–S bond by $Bu_3Sn\cdot$ generates the corresponding alkyl radical (**111a**) which cyclizes onto the suitably positioned alkene present in **111**. After base hydrolysis, the alcohols **112** and **113** are obtained in excellent yields (95%).

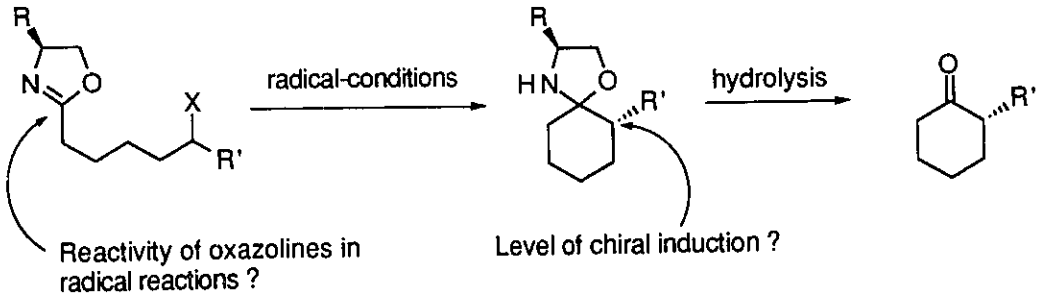
**Scheme 29: Use of Oxathiolones in Radical Cyclizations**




In this strategy, the radical center carries the functionality into the final product. An alternative approach for maintaining functionality in the radical cyclization is to use a functionalized radical acceptor. The following Scheme (30) outlines the proposed radical cyclization onto an oxazoline that was the focus of our initial studies.

Oxazolines were chosen because of the wide variety of methods reported for their preparation, and the availability of chiral non–racemic oxazolines to test the diastereoselectivity of the cyclization. Hydrolysis of the resulting N, O–ketal would generate useful α–substituted chiral cyclic ketones. The reactivity of oxazolines in intramolecular reactions is a key question to be addressed in this work.

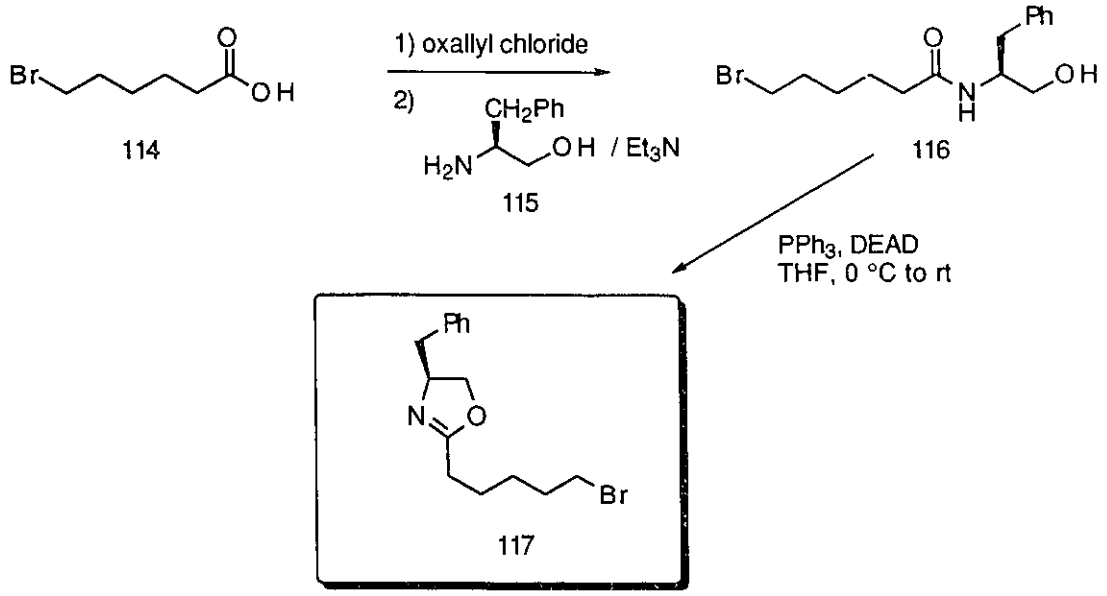
**Scheme 30: Proposed Radical Cyclization**



## Results and Discussion

The synthesis of the required oxazoline starting material is shown in Scheme 31 below.

**Scheme 31: Preparation of Oxazoline Starting Materials**



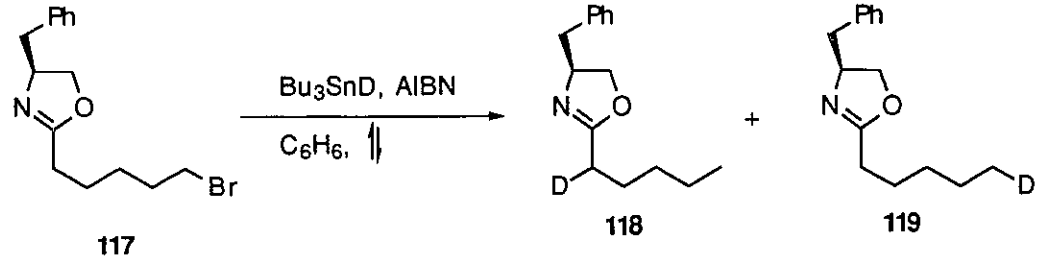

In initial experiments where the commercially available 6–bromohexanoic acid (**114**) was heated with amino alcohol **115** in benzene or toluene using a Dean–Stark apparatus for the removal of water, only an unextractable highly polar material was obtained. However, amide **116** could be prepared by treatment of the same carboxylic acid (**114**) with oxalyl chloride in benzene at room temperature. The resulting crude acid chloride was reacted with L–phenylalanol[66] (**115**) at 0 °C in dichloromethane to yield amide **116** in 73% yield. Compound **116** displayed a strong signal at 1674 $cm^{-1}$ in the IR spectrum indicative of an amide functional group. Treatment of amide **116** under dehydrating conditions, however, proved unsuccessful. Exposure to triphenylphosphine in $Et_2O$ at 0 °C followed by the dropwise addition of diethyl azodicarboxylate (DEAD), according to the procedure of Roush[67], was effective giving the desired oxazoline **117** in

59% yield. When THF was used as the reaction solvent, the yield of the oxazoline was increased to 73%. With the required oxazoline **117** in hand, we examined its reactivity under free-radical conditions.

Thus, a 0.004 M solution of oxazoline **117** in benzene was treated with tin hydride under standard conditions ($Bu_3SnH/AIBN/C_6H_6$/reflux).[1] Analysis of the crude product mixture revealed that only simple reduction had taken place. Presumably, the cyclization of the initially formed radical was too slow compared with hydrogen abstraction from $Bu_3SnH$. The experiment was repeated under the same conditions, except that a syringe pump was used to deliver the $Bu_3SnH$/AIBN. This should increase the lifetime of the radical and allow more time for the desired cyclization to occur. Analysis of the product mixture again revealed only the product of simple reduction. Other radical conditions such as $(TMS)_3SiH$/AIBN[68] and $SmI_2$/HMPA yielded the same reduction product. The addition of a protic acid ($MeSO_3H$) or MeI in an attempt to increase the electrophilicity of the imine led to very messy reactions from which we were unable to identify any cyclized material.

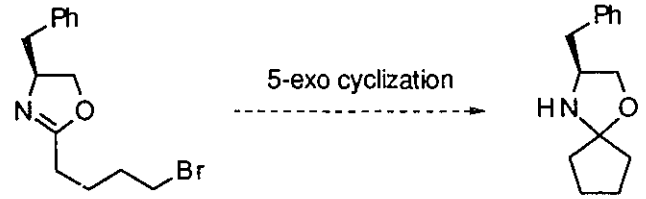
To explore if a 1, 5–hydrogen shift was interfering with the desired cyclization, we replaced $Bu_3SnH$ with $Bu_3SnD$ in these experiments which would give us information about the source of the premature quenching. The results of these experiments are outlined in Scheme 32.

**Scheme 32: Deuterium Labeling Experiment**



Analysis of the crude $^1H$ nmr spectrum of the reaction of oxazoline **117** with a 0.001 M solution of $Bu_3SnD$ in benzene revealed that a significant amount (≈20%) of the deuterium was incorporated α–to the oxazoline. This indicated that a 1, 5–hydrogen shift had indeed taken place. When $Bu_3SnD$ was delivered by syringe pump addition, the $^1H$ nmr spectrum of the crude reaction mixture indicated that essentially all of the initially formed radical suffered a 1,5–hydrogen shift and was then quenched with deuterium. To avoid this problem it was decided to examine the 5–exo cyclizations (shown in Scheme 33) since a 1, 5–hydrogen shift is unavailable to this molecule.

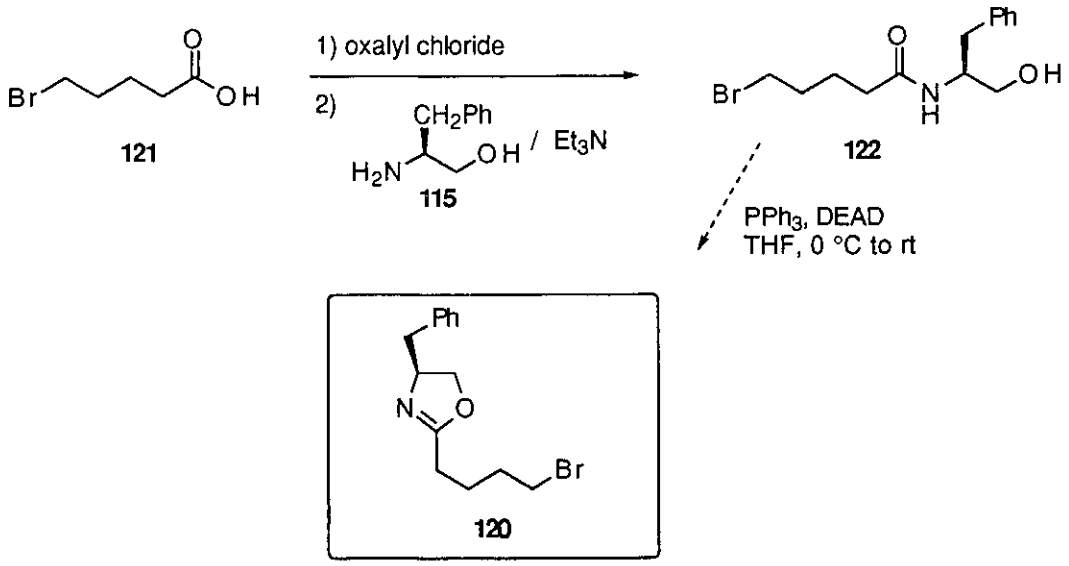
**Scheme 33: Proposed 5–Exo Oxazoline Cyclization**




**120**

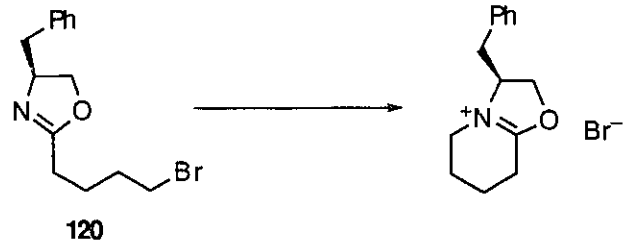
The preparation of the required oxazoline **120** was attempted following the route developed for the preparation of the higher homologue **117** which is shown in Scheme 34 below. Treatment of commercially available 5–bromovaleric acid **121** with oxalyl chloride followed by the addition of L–phenylalanol (**115**) provided, in 71% yield, amide **122**. Treatment of this amide with the triphenylphosphine/DEAD system yielded only a very polar unidentifiable material. When the reaction was repeated for a shorter time and quickly purified by flash chromatography, some of the desired oxazoline could be observed in the $^1H$ nmr spectrum. Unfortunately, this material proved unstable and decomposed overnight while stored in the freezer.

**Scheme 34: Preparation of the Oxazoline Substrate for Attempted 5-Exo Cyclization**



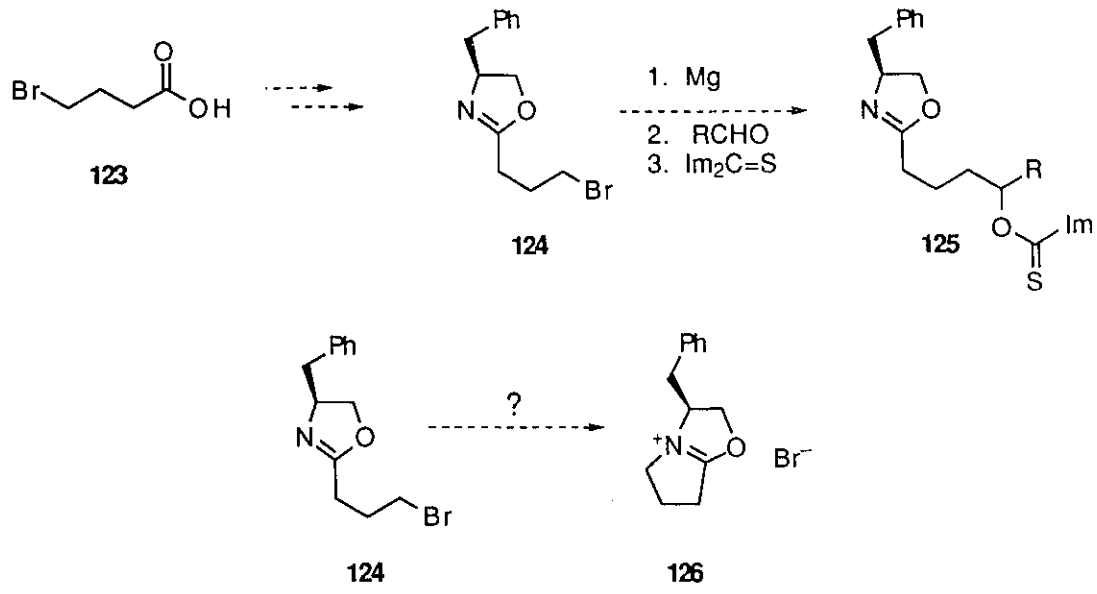

A possible reason for the instability of oxazoline **120** is the intramolecular displacement of bromide that could occur as shown in Scheme 35.

**Scheme 35: Proposed Decomposition of Oxazoline 120**



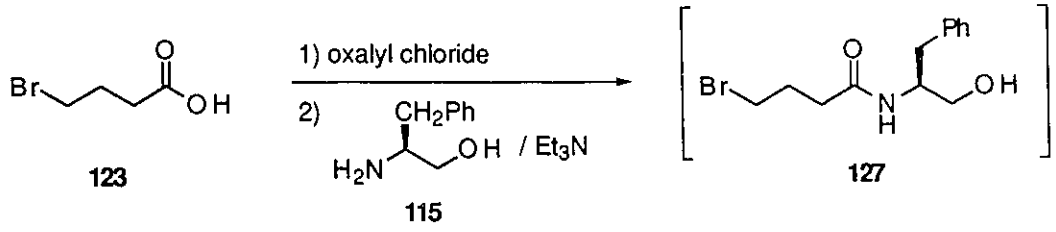

To avoid this displacement problem, an alternative route was devised which required the preparation of oxazoline **124** in Scheme 36 below. Iminium formation would not be expected to occur as readily in this system (**124** to **126**) because of ring strain. Standard transformations would allow preparation of radical precursor **125** as shown in Scheme 36.

**Scheme 36: Proposed Alternative Synthesis of Oxazoline System**



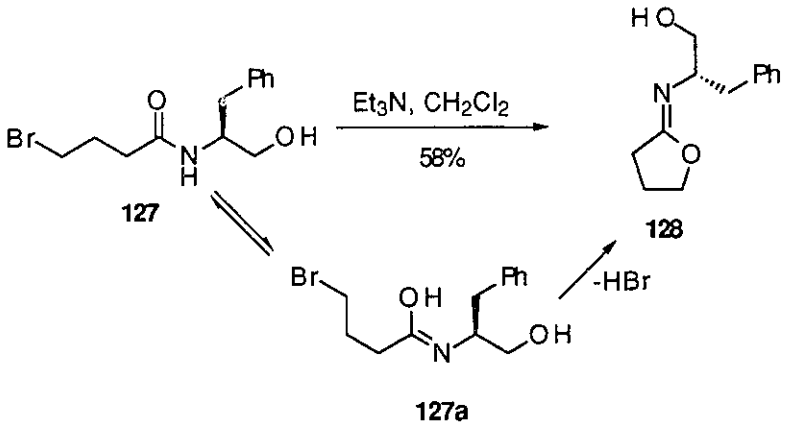

To test this idea, 4–bromobutyric acid **123** was treated with oxalyl chloride and then amino alcohol **115**. Initially, the structure of the product isolated from this apparently simple experiment was assigned as amide **127** shown in Scheme 37.

**Scheme 37: Preparation of Amide 127**



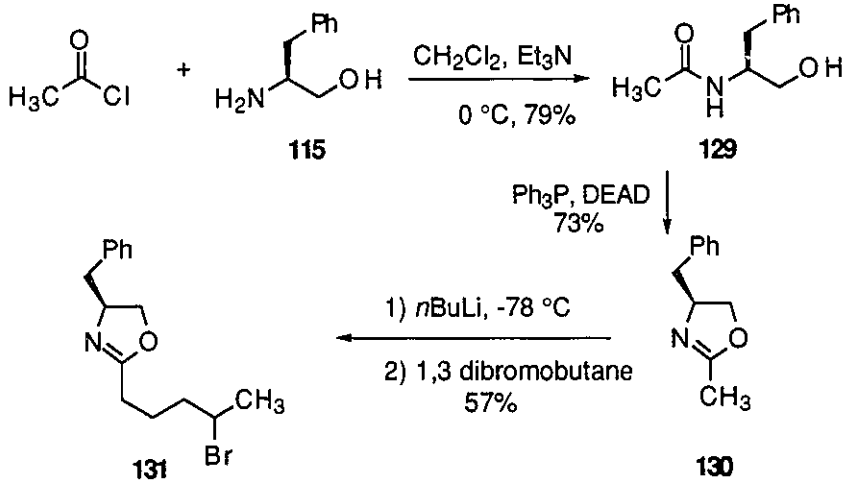

Analysis of the $^{13}C$ nmr spectrum of **127** revealed a signal at δ 168.9 ppm and the IR spectrum contained a peak at 1662 $cm^{-1}$, which are both consistent with an amide functional group.[69] However, the mass spectrum indicated the absence of bromine. Further analysis of the spectra of **127** indicated that the initially formed amide had eliminated HBr as shown in Scheme 38 below.

**Scheme 38: Dehydrobromination–Cyclization of Compound 127**




Under the reaction conditions, amide **127** enolizes to generate compound **127a** which eliminates HBr to generate **128**. To support the assignment of **128** as the product of the reaction, hydrolysis of the imine with *p*–toluenesulfonic acid in THF/$H_2O$ was carried out to give γ–butyrolactone in 76% yield. Compound **128** is produced as *only one geometric isomer* (>25:1) in which the nitrogen lone pair is syn to the methylene group. The high geometric purity of the imine bond in **128** is probably a result of the formation of the amide enol **127a**. Scheme 38 outlines the revised route undertaken for the preparation of the 5–exo substrate which did not require the preparation of a primary bromide.

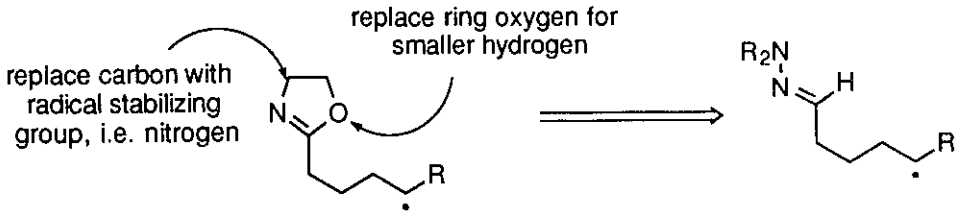
**Scheme 39: Revised Route to 5–Exo Oxazoline Substrate**



Thus the 5–oxazoline substrate was prepared by treatment of amino–alcohol **115** with acetyl chloride to give the expected methyl amide **129** in 79% yield. This amide was then subjected to the standard $Ph_3P$/DEAD dehydrating conditions which provided the methyl oxazoline **130** in 73% yield. Meyers et al.[70] have performed extensive studies on the deprotonation of oxazolines and according to their procedure, exposure of methyl oxazoline **130** to *n*BuLi at –78 °C generated the metallo–enamine which was subsequently quenched with 1, 3–dibromobutane to give the *stable* bromo–oxazoline in 57% yield. We were then in a position to try a 5–exo radical cyclization. Oxazoline **131** was subjected to standard tin hydride conditions but unfortunately, this reaction was very messy with no evidence of cyclization having occurred.

Given the lack of reactivity of the oxazolines under radical conditions and the difficulties we encountered during their preparation, we re–examined our original idea in an effort to increase the reactivity of the C=N bond. Scheme 40 illustrates the reasoning behind the structural modifications that were made.

**Scheme 40: Structural Modification of Oxazoline System**



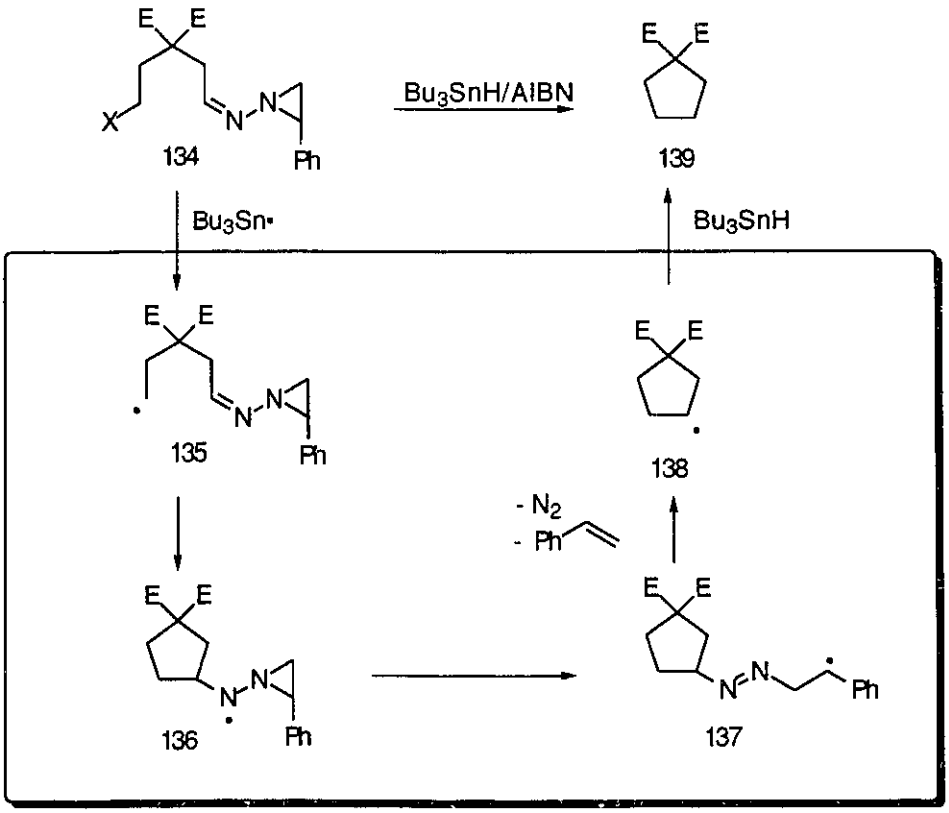

132 133

Replacing the ring oxygen with a smaller hydrogen atom should improve the cyclization reaction since steric interactions at the acceptor site will be less severe. Any angle strain involved in formation of the spiro center in the oxazoline cyclization should also be alleviated in the new system. Replacing the ring carbon α to nitrogen with a heteroatom (such as nitrogen) will help stabilize the developing radical on nitrogen

during cyclization.[71a] This system should parallel oxime ethers which are known to be good radical acceptors.

Redrawing structure **132** with the modifications indicated, leads to the hydrazone system **133** shown above. At the inception of this work, only one example of a radical hydrazone cyclization had been reported.[71b] The proposed mechanism for this specialized case is shown in Scheme 41 below.

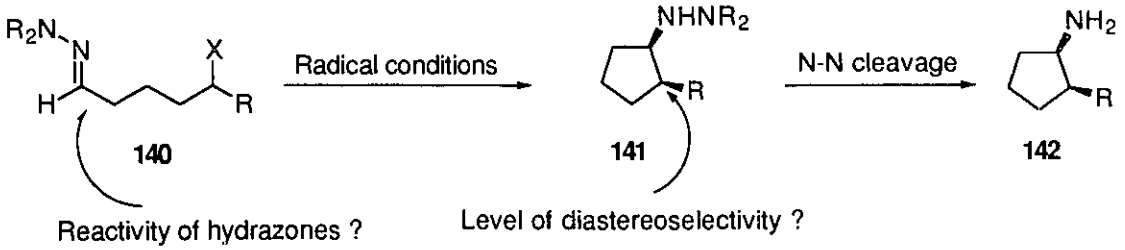
**Scheme 41: Proposed Mechanism for the N–Aziridinyl Imine Cyclization**




From substrate **134**, generation of radical **135** is followed by cyclization onto the hydrazone to give the nitrogen centered radical **136**. This radical then undergoes ring opening of the aziridine to form the benzylic radical **137** which extrudes styrene and $N_2$ to ultimately yield carbocycle **139** as the final product. The liberation of these neutral, stable molecules is clearly a driving force for this cyclization. Also, this system does not

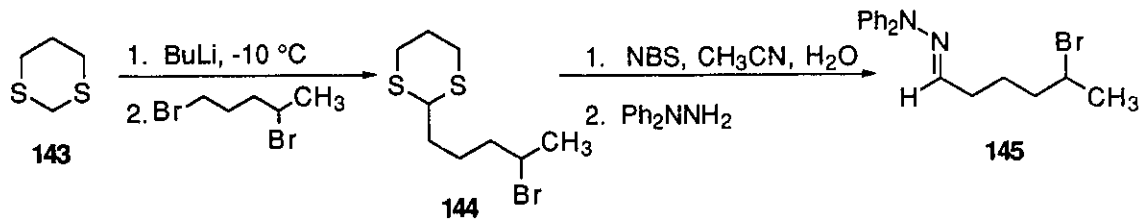
retain functionality in the product since the nitrogen group present in the starting hydrazone is lost as nitrogen gas. In fact, a highly functionalized bromo–aziridinyl imine is converted into a cyclopentane with the loss of three heteroatoms. Since this work from Kim's lab was the only reported example of a radical cyclization onto a hydrazone, it was not clear if *simple* hydrazones would be efficient radical acceptors. Scheme 42 below summarizes some of the questions concerning the proposed radical cyclization of simple hydrazones.

**Scheme 42: Proposed Hydrazone Radical Cyclization**




The reactivity of the C=N bond of the hydrazone in a radical cyclization was an initial question. Also, two stereogenic centers are created in the cyclization and the level of diastereoselectivity of this reaction is also of interest. The main synthetic advantage of using simple hydrazones in the radical reaction is that the cyclized product would retain the nitrogen functionality. If successful, reductive cleavage of the hydrazine N–N bond would provide nitrogen containing molecules such as **142** with the relative control of two stereogenic centers. The following Scheme (43) illustrates the preparation of a bromo–hydrazone used to test this proposal.

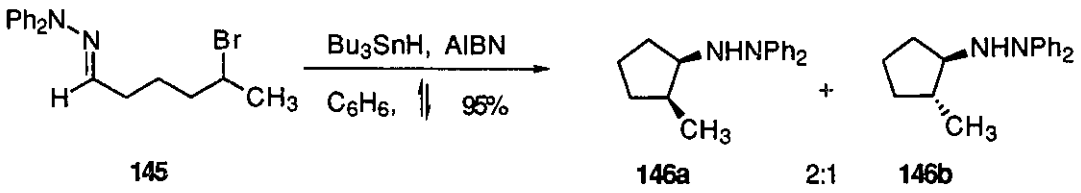
**Scheme 43: Preparation of Hydrazone Substrate**



Deprotonation of dithiane **143** with *n*–BuLi at –10 °C followed by the addition of 1,4–dibromopentane gave displacement of the primary bromide to provide compound **144** in 70% yield. Hydrolysis of dithiane **144** to the corresponding aldehyde was affected by treatment with $NBS/H_2O/CH_3CN$.[72] The resulting aldehyde was not purified but treated directly with $Ph_2NNH_2$ to yield bromo–hydrazone **145** in 35% yield. A key spectral feature of this hydrazone is that the vinylic hydrogen ($Ph_2N–N=C\underline{H}CH_2R$) appears as a clean triplet at δ 6.5 ppm in the $^1H$ nmr spectrum. It appears from the spectral data that condensation of the intermediate aldehyde with *N,N*–diphenylhydrazine provided a single geometric isomer. It is known from the literature that hydrazones are formed predominately as the E geometric isomer[73] and based on this precedence, compound **145** was assigned as the E hydrazone (with the $Ph_2N$ group syn to the hydrogen).

Having prepared the desired hydrazone, the time came to carry out a free–radical cyclization. Thus hydrazone **145** was treated with a 0.02M $Bu_3SnH$ solution in benzene with AIBN and heated to reflux. TLC analysis of the resulting mixture indicated the complete consumption of starting material with the formation of two new less polar compounds. Analysis of the $^1H$ nmr, $^{13}C$ nmr and mass spectra of the purified materials clearly demonstrated the success of the radical cyclization! The key $^1H$ nmr spectral features of the cyclopentylhydrazines was the appearance of two methyl doublets at δ 1.04 and δ 0.86 ppm with coupling constants of 7.0 and 6.8 Hz respectively. This result is summarized in Scheme 44 below.

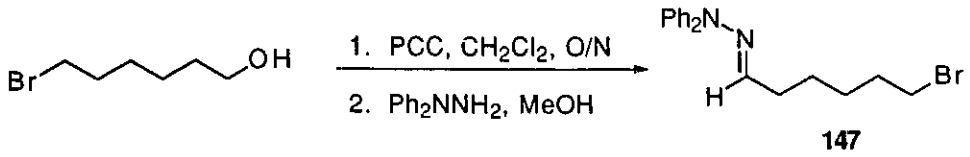
**Scheme 44: Radical Cyclization of a Simple Hydrazone**




**145** **146a** 2:1 **146b**

The high chemical yield (95%) of the cyclization was also very gratifying and it was the first indication that simple hydrazones are extremely efficient radical acceptors. Also, there was no evidence of simple reduction. The *cis/trans* selectivity, however, was a modest 2 to 1. We next turned our attention to the preparation of a related substrate to test a 6–exo cyclization. The following scheme (45) illustrates the straightforward preparation of the required hydrazone.

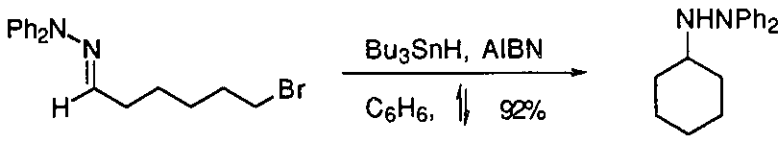
**Scheme 45: Preparation of 6–Exo Hydrazone Substrate**




**147**

Oxidation of commercially available 6–bromohexanol with pyridinium chlorochromate (PCC)[74] yielded the less polar (TLC) aldehyde which was then treated with $Ph_2NNH_2$ to give the corresponding hydrazone **147**, again as a single geometric isomer in 64% yield. This bromide was then reacted under the same $Bu_3SnH$/AIBN conditions as used with the 5–exo substrate. TLC analysis of the crude reaction mixture revealed the complete consumption of the starting materials with the formation of a single, less polar compound. The $^1H$ nmr and $^{13}C$ nmr spectra verified that the cyclohexylhydrazine **148** had been obtained. The isolated yield was again very high, 92%, and there was no evidence of the occurrence of simple reduction. This result is summarized in Scheme 46.

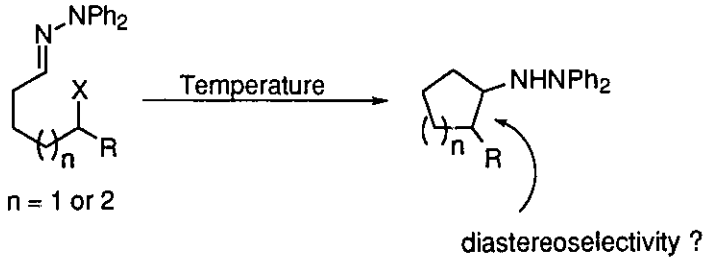
**Scheme 46: 6–Exo Hydrazone Radical Cyclization**




**147** **148**

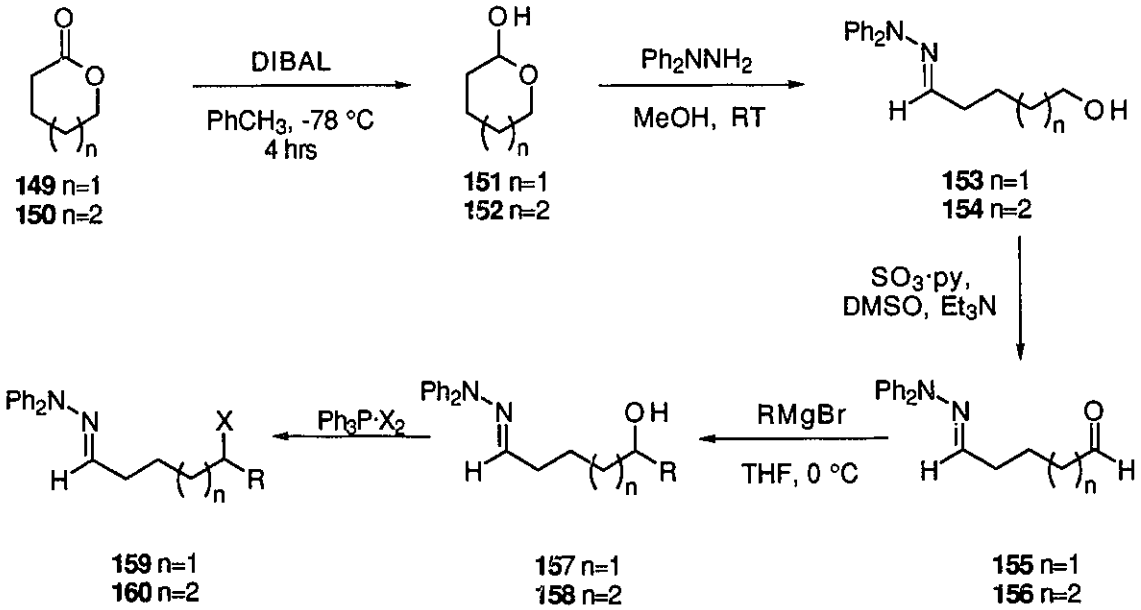
These two results establish the efficiency of both the 5 and 6–exo radical cyclizations of *N,N*–diphenylhydrazones **145** and **147**. We therefore decided to examine the effect of the substituent (R) and the temperature on the cyclization to give an indication of the scope and to optimize the diastereoselectivity of this reaction as outlined in Scheme 47 below.

**Scheme 47: General Substrates in the Radical Cyclization**




A general method for the synthesis of hydrazones with various R groups was required for this study. Several routes were examined, but the one that proved most successful is briefly outlined in Scheme 48 below.

**Scheme 48: General Route to Halo–Hydrazones**

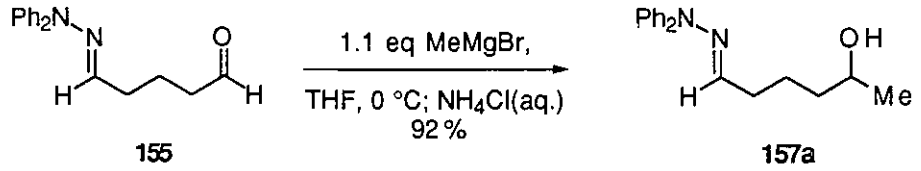


The syntheses of substituted hydrazones **159** and **160** commences with reduction of the commercially available lactones (valerolactone **149** or caprolactone **150**) with diisobutylaluminum hydride (DIBAL)[75] in toluene at –78 °C to give the corresponding lactols **151** and **152** in good yields (75–79%). Valerolactol[76] **151** exists predominately in the ring closed form as no aldehyde hydrogen could be observed in the $^1$H nmr spectrum. Conversely, caprolactol **152** exists primarily as the ring opened form. Treatment of these lactols with one equivalent of $Ph_2NNH_2$ in MeOH at room temperature provided the *N,N*–diphenylhydrazones **153** and **154** in 78–94% isolated yields. As with the two other hydrazones reported above, only a single geometric isomer (>25:1) was isolated from the reaction. The oxidation of the resulting primary alcohol **154** with PCC was found to be completely ineffective, giving only unidentifiable products. Swern oxidation[77] was initially more promising on a small scale (72 mg), giving the desired aldehyde in 60% isolated yield. Unfortunately, when this reaction was repeated on a larger scale (350 mg), extensive decomposition occurred. Finally, the use of $SO_3$·py/DMSO/$Et_3N$[78] as the oxidizing reagent provided the aldehydes **155** and **156** in good yields (71–78%) efficiently and reproducibly.

At this point, the chemoselective addition of various nucleophiles to the aldehydes without competitive addition to the hydrazone functionality was required. A recent report by Denmark[79] described the addition of various nucleophiles to hydrazones. It was hoped that in our system the aldehyde functional group would be more reactive than the diphenylhydrazone. When a THF solution of aldehyde **155** was cooled to 0 °C and treated with 1.1 equivalents of MeMgBr, TLC analysis of the reaction mixture revealed that the starting aldehyde had been completely consumed with the formation of only one more polar product. Isolation and spectral analysis of this new compound demonstrated that selective addition to the aldehyde had indeed occurred. The desired secondary alcohol **157a** was isolated in 92% yield. The chemospecificity can be easily discerned by analysis of the $^1$H nmr spectrum, since the vinyl hydrogen of the hydrazone remained in

the product, and the signal due to the aldehyde had disappeared. This result is summarized in the following Scheme (49).

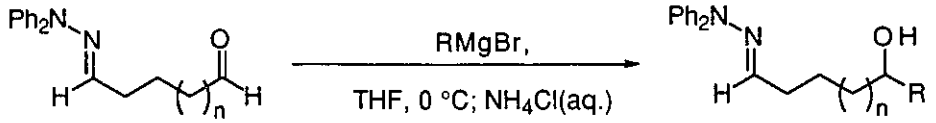
**Scheme 49: Chemoselective Addition of MeMgBr to Aldehyde 155**




**155** **157a**

The high selectivity of the reaction was reflected in the isolated yield (92%) of alcohol **157a**. This reaction was also successful for other Grignard reagents including isopropyl (*i*Pr) and cyclohexyl (Cy) which were added to aldehydes **155** and **156**. These results are summarized in Table 3.

**Table 3: Chemoselective Grignard Addition to Aldehydes**




155 n=1
156 n=2

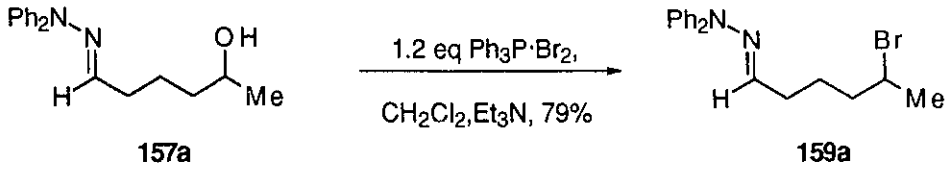
157 n=1
158 n=2

| Entry | n | Grignard | Alcohol | Yield (%) |
|---|---|---|---|---|
| a | 1 | MeMgBr | 157a | 92 |
| b | 1 | CyMgBr | 157b | 72 |
| c | 1 | *i*PrMgBr | 157c | 76 |
| d | 2 | MeMgBr | 158a | 90 |
| e | 2 | CyMgBr | 158b | 76 |

As is demonstrated by the results in Table 3, the chemoselective addition of Grignard reagents to aldehydes **155** and **156** is a general reaction that provides good yields of the corresponding secondary alcohols. In general there was no evidence for addition to the hydrazone under these conditions. The one exception to this is entry c of Table 3. Reaction of aldehyde **155** with *i*PrMgCl produced a single more polar compound (TLC) but after purification, the $^1$H nmr spectrum revealed *two* *i*Pr resonances in an approximate ratio of 10:1. By decreasing the reaction temperature to –78 °C and using exactly 1.0 equivalents of iPrMgBr the ratio increased to >25:1 in favour of the desired alcohol hydrazone, but the isolated yield decreased to 41%.

The last step required for the preparation of starting materials was conversion of the secondary alcohols to either bromides or iodides. The use of $PPh_3/CBr_4$[80] as the brominating agent gave poorer yields of the desired bromohydrazones, while $Ph_3P{\cdot}Br_2$[81] was found to be an effective reagent for the bromination of compound **157a** (see Scheme 50).

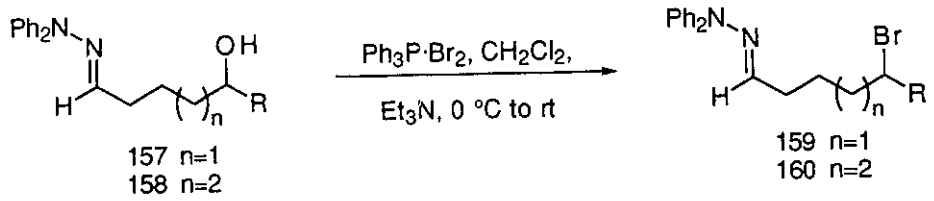
**Scheme 50: Bromination of the Hydroxy–Hydrazone Substrates**




**157a** **159a**

The use of $Et_3N$ in this reaction was found to be necessary to ensure high yields. This is presumably to protect the hydrazone functionality from the HBr released during the course of bromination. The following Table (4) summarizes the results for the conversion of the remaining alcohols into the corresponding bromides.

**Table 4: Bromination of Secondary Alcohols**



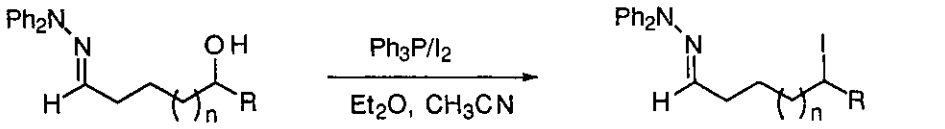

| Entry | n | R | Bromide | Yield (%) |
|---|---|---|---|---|
| a | 1 | Me | 159a | 79 |
| b | 1 | Cy | 159b | 63 |
| c | 1 | *i*Pr | 159c | 75 |
| d | 2 | Me | 160a | 85 |
| e | 2 | Cy | 160b | 44 |

The yields are generally good for the conversion of the alcohols to the bromides as shown in Table 4. It was observed, however, that as the steric bulk of the substituent increased, the yield decreased. TLC analysis of these reactions revealed the presence of a second compound which was isolated and determined to be the corresponding alkene. Another observation noted in these experiments is that the yields varied considerably from experiment to experiment. At the conclusion of this work, it was found that by quenching the reaction with saturated aqueous $NaHCO_3$ the yields improved and were more reproducible. Presumably, in the reactions where considerable alkene formation occurred, the HBr produced destroyed an equivalent amount of the hydrazone and this decomposition can be limited by using an aqueous $NaHCO_3$ workup.

The preparation of the iodides was found to be quite problematic. For iodination of the methyl alcohols **157a** and **158a**, treatment with $I_2/PPh_3$ following Smith's[82] procedure proved extremely efficient giving the corresponding iodides (**161a** and **162a**) in 86 and 82% yields respectively (see Scheme 51 below). Surprisingly, for the other

alcohols, only trace amounts of the iodides formed, if at all. The only other substrate that could be iodinated under these conditions was the cyclohexyl alcohol **158b**. In this case, the corresponding iodide **162b** was isolated in 34% yield. These results are summarized in Scheme 51 below.

**Scheme 51: Preparation of Iodides from the Secondary Alcohols**




**157a** n=1, R=$CH_3$
**158a** n=2, R=$CH_3$
**158b** n=2, R=Cy

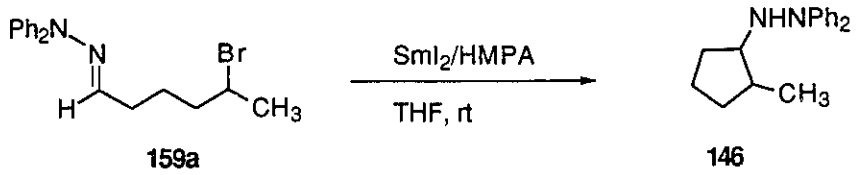
**161a** n=1, R=$CH_3$ (86%)
**162a** n=2, R=$CH_3$ (82%)
**162b** n=2, R=Cy (34%)

A possible explanation for the decomposition observed in the attempted iodination of the sterically hindered alcohols is related to the decreased rate of formation of the iodide products in these cases. If the iodination reaction is slow, free $I_2$ would have more time to react with the hydrazone group which would ultimately lead to decomposition.[83] Several other iodination procedures were attempted including preparation of the tosylate and reaction with NaI[84]; treatment of the alcohols with TMSI[85]; and $Ph_3P$/MeI[86], but all of these methods were ineffective. Faced with this problem, we turned our attention to examining the free–radical cyclization of the prepared halo–hydrazones.

## Radical Cyclizations of Hydrazones

The first parameter examined was the effect of temperature on the *cis/trans* ratios of the cyclizations. There are several methods available that allow free–radical reactions to be performed at low temperatures.[1] Of these, the most attractive to us was the use of $SmI_2$ for several reasons: (i) experimental simplicity, (ii) facile control of reaction temperature, (iii) and the ability to use carbonyl substrates as well as halides. The following table (5) summarizes the initial experiments performed to determine the optimum experimental conditions.

**Table 5: Optimization of $SmI_2$ Cyclization Conditions**



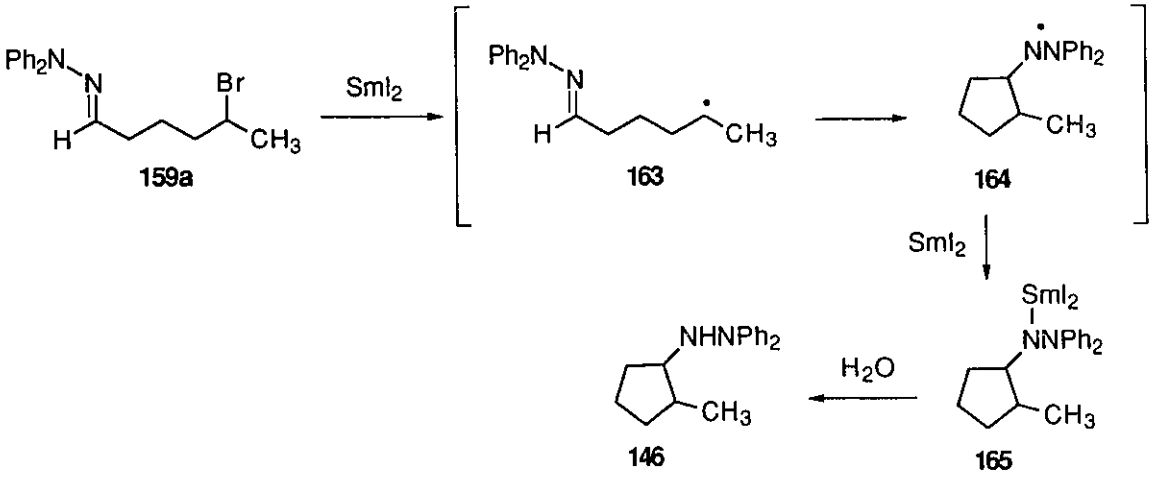

**159a** **146**

| Entry | Equivalents of $SmI_2$ | Yield of **146** (%) |
|---|---|---|
| a | 2.2 | 55 |
| b | 3.0 | 64 |
| c | 4.5 | 88 |

Initially, hydrazone **159a** was dissolved in THF containing HMPA and treated with $SmI_2$ (dropwise addition) at room temperature. TLC analysis of the crude reaction mixture revealed that the only UV active species present were the *cis* and *trans* hydrazines of **146** along with some starting material (**159a**). $^1H$ nmr analysis also demonstrated that cyclization had occurred (although some starting material remained) and there was no evidence of simple reduction. The number of equivalents of $SmI_2$ used

in the reaction was increased in order to convert the remaining starting material to the cyclic hydrazines. It was found that 4.5 equivalents of $SmI_2$ gave the best results as shown in entry c of Table 5. The influence of the amounts of THF and HMPA on the cyclization reactions was not examined but was based on literature examples. Thus we routinely employed 1.0–2.0 mL of HMPA and 40 mL of THF per mmol of substrate. The *standard $SmI_2$ conditions* used for the remainder of this chapter were thus 4.5 equivalents of $SmI_2$, 1.0–2.0 mL of HMPA per mmol of substrate and 40 mL of THF per mmol. It is not clear why more than four equivalents of $SmI_2$ were required to furnish good yields of the cyclized product since only two equivalents should, in theory, be sufficient. A likely mechanism for this reaction is shown in Scheme 52 below.

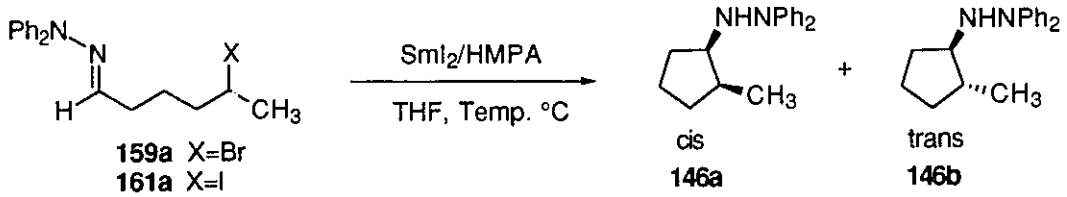
**Scheme 52: Mechanism for the $SmI_2$ Mediated Hydrazone Cyclization**




One equivalent of $SmI_2$ is consumed in generating the alkyl radical **163**. This radical subsequently cyclizes to generate the hydrazine radical **164**. A second electron transfer then occurs from Sm(II) to the nitrogen radical generating an N–$SmI_2$ species (**165**) and consuming the second equivalent of $SmI_2$. The N–$SmI_2$ bond is hydrolyzed on workup to give the observed hydrazine **146**.

Using the standard $SmI_2$ conditions described above, a temperature profile of the reaction was obtained and the results are listed in Table 6 below.

**Table 6: Temperature Profile of the $SmI_2$ Cyclization**



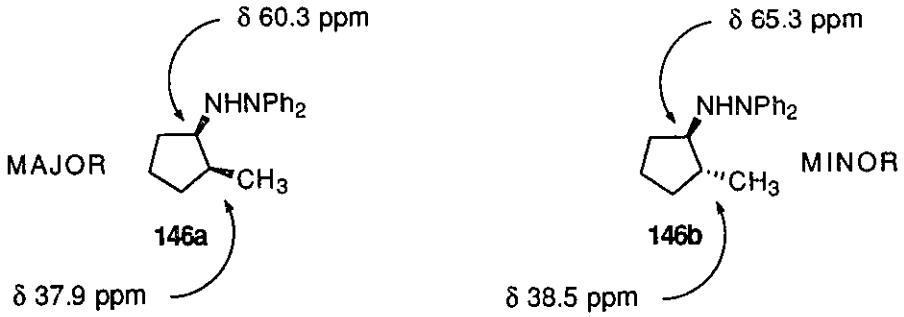

| Entry | X | Temp °C | *cis/trans* | yield |
|---|---|---|---|---|
| a | Br | 21 | 2:1 | 91 |
| b | Br | 0 | 3:1 | 85 |
| c | Br | –42 | 7:1 | 88 |
| d | Br | –78 | – | – |
| e | I | –78 | 11:1 | 62 |

The results described in Table 6 are worthy of comment. It was found that the *cis/trans* selectivity of the radical cyclization increased with decreasing temperature (compare entries a and e). At –78 °C (Table 6, entry e) the selectivity was as high as 11:1. The *cis/trans* isomers are readily separated by flash chromatography on silica gel which allows one to obtain good yields of a *single diastereomer*. Also notable is that bromide **159a** was found to be unreactive towards $SmI_2$/HMPA at –78 °C (entry d). The corresponding iodide **161a** (entry e) was more reactive and when treated with $SmI_2$/HMPA at –78 °C, homolytic cleavage of the C–I bond occurred in less than four hours giving the cyclopentylhydrazines in 62% yield.

Although the diastereoselectivity could be determined by examination of the $^1H$ nmr spectra, $^{13}C$ nmr was needed to determine the relative stereochemistry (i. e. *cis* or

*trans*) of the major isomer. Based on literature precedent[87], the isomer with the higher field methine signals in the $^{13}C$ spectrum can be assigned as having the two substituents *cis* to each other. In order to use this technique to assign the stereochemistry, it is essential to have both isomers in order to compare the chemical shifts. Since the room temperature cyclization gave a 2:1 mixture of readily separable diastereomers, we were able to measure the $^{13}C$ nmr spectra of both. Figure 1 lists the key $^{13}C$ nmr signals that were used to assign the relative stereochemistry.

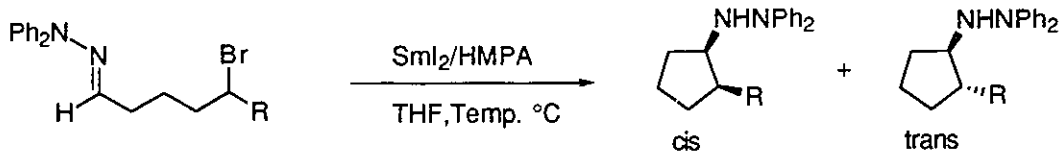
**Figure 1: Assignment of Stereochemistry**




Thus based on this nmr data, the major product from the cyclization can be assigned as the *cis* isomer **146a**.

The next variable that was examined in these cyclizations was the influence of the alkyl substituent (R) on the diastereoselectivity of the reaction. Table 7 summarizes the results that were obtained from these experiments.

**Table 7: $SmI_2$ Cyclizations of Substituted Hydrazone Systems**




**159a** R=Me
**159b** R=Cy
**159c** R=iPr

**146a** R=Me
**166a** R=Cy
**167a** R=iPr

**146b** R=Me
**166b** R=Cy
**167b** R=iPr

| Entry | R | Temp °C | *cis/trans* | Yield |
|---|---|---|---|---|
| a | Cy | 21 | 6:1 | 89 |
| b | Cy | –42 | – | – |
| c | Cy | –42 to –10 | 9.4:1 | 67 |
| d | *i*Pr | –42 to –10 | 10:1 | 70 |
| e | Me | 0 | 3:1 | 85 |
| f | Me | –42 | 7:1 | 88 |

The major product of the cyclization in each case was assigned as the *cis* isomer using the same technique described above for the methyl case. The effect of the size of the substituent (R) on the diastereoselectivity of the cyclization can be clearly seen in Table 7 by comparing entries c and d (R = Cy, *i*Pr) with the two methyl entries e and f. The trend noted from these reactions is that as the steric demand of the substituent increases, the *cis/trans* selectivity also increases.

It was surprising to note that the cyclohexyl substrate **159b** (Table 7, entry b) was completely unreactive when treated with $SmI_2$/HMPA at –42 °C. After 48 hours at this temperature the bromide was recovered unchanged. Increasing the amount of HMPA in the reaction did not induce cleavage of the C–Br bond. When the bath temperature was raised to –10 °C, the reaction proceeded in several hours to yield the cyclic hydrazines as

a 9.4:1 mixture of *cis* and *trans* isomers. The isopropyl substrate reacted similarly at –10 °C giving 70% yield of a 10:1 mixture of *cis* and *trans* isomers.

A cautionary note is warranted regarding these low temperature reactions. When examining these reactions by TLC, it is very important to remove the capillary containing the sample from the reaction pot and spot the TLC plate as quickly as possible. If the capillary is allowed to warm up even for several seconds before spotting the TLC plate, *cyclization will occur in the capillary tube* and the resulting TLC will be completely misleading. On several occasions the author quenched a low temperature reaction that appeared to be complete by TLC analysis only to find after workup that a considerable amount of starting material remained. Another observation noted in some of the halo–hydrazone cyclizations is that on occasion, the reaction mixture would turn a dark blue colour and repeated TLC analysis of these experiments indicated that the reaction had stopped. It was found that in these cases, the addition of several drops of HMPA restored the dark purple colour and the reactions would then go to completion.

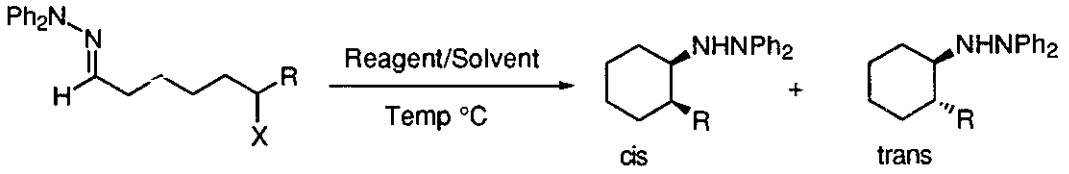
Thus the 5–exo hydrazone reaction described herein represents an efficient radical cyclization onto a C=N $\pi$ bond which provides good stereochemical control at the two newly created stereogenic centers. We propose that the role of $SmI_2$ in these reactions is simply to generate the radical and that it does not influence the stereochemistry. The increase in selectivity is ascribed to the decreased temperatures of some of the $SmI_2$ reactions. Evidence for this will be presented in the next chapter which deals with the kinetics of these cyclization reactions.

## 6–Exo Hydrazone Cyclizations

The 6–exo cyclization of a primary radical onto a hydrazone was previously shown to be efficient, with no evidence of straight reduction. As described for the 5–exo

system, we examined the influence of both substitution and temperature on the 6–exo cyclization. A summary of these studies is listed in Table 8 below.

**Table 8: 6–Exo Cyclization of Hydrazone System**




**148** R=H
**168a** R=Me
**169a** R=Cy

**168b** R=Me
**169b** R=Cy

| Entry | R | X | Reagent | Solvent | Temp (°C) | *cis/trans* | Yield (%) |
|---|---|---|---|---|---|---|---|
| a | H | Br | $Bu_3SnH$ | Benzene | 80 | – | 92 |
| b | H | Br | $SmI_2$/HMPA | THF | rt | – | 85 |
| c | Me | Br | $SmI_2$/HMPA | THF | –42 | 3:1 | 63 |
| d | Me | I | $SmI_2$/HMPA | THF | –78 | 5:1 | 75 |
| e | Cy | I | $SmI_2$/HMPA | THF | –78 | 1.3:1 | 75 |
| f | Cy | Br | $Bu_3SnH$ | Benzene | 80 | 1:1.5 | 69 |

As can be seen from the results compiled in Table 8, the 6–exo cyclization of an alkyl radical onto a hydrazone is a general reaction proceeding in good chemical yield. Entry a of Table 8 is the $Bu_3SnH$/AIBN result that was described at the beginning of this study. When the same substrate (Table 8, entry b) was subjected to the standard $SmI_2$/HMPA conditions at room temperature, the reaction again proceeded smoothly and all the starting bromide was consumed with the formation of only one new UV active compound as judged by TLC analysis. The cyclohexylhydrazine was isolated from this

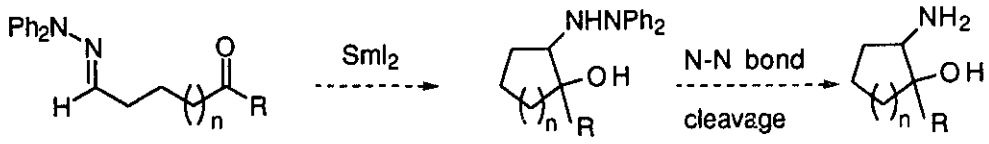
experiment in 85% yield. With the methyl substituted hydrazone, (Table 8, entry c), cyclization at –42 °C provided a good yield of the corresponding cyclohexylhydrazine (63%) but the *cis/trans* selectivity was a modest 3:1. When the reaction was repeated at –78 °C with the iodide substrate (Table 8, entry d), only a slight increase in diastereoselectivity was noted (from 3:1 to 5:1).

In the 5–exo cyclizations, better stereochemical control in the cyclization was obtained as the steric size of the alkyl substituent increased. However, treatment of the cyclohexylhydrazone (entry e) with $SmI_2$/HMPA at –78 °C gave very little stereochemical control (*cis/trans*=1.3:1). When this reaction was repeated at 80 °C using the tin hydride method efficient cyclization did occur but, interestingly, the reaction was actually slightly *trans* selective (*cis/trans*=1:1.5, 69% yield).[88] This is the first time the *trans* isomer was observed to be the major product. In general, then, the 6–exo alkyl radical cyclization onto hydrazones is an efficient reaction although it provides only modest *cis/trans* selectivity.

## Ketyl Radical Cyclizations onto Hydrazones

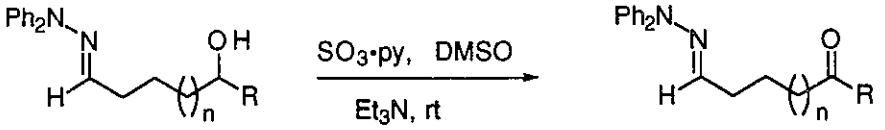
Samarium iodide has been used with considerable success in the formation of ketyl radicals from carbonyl substrates.[89] We therefore attempted the cyclization of ketyl radicals onto hydrazones to expand the scope of our method and provide a useful synthesis of the corresponding hydrazine–alcohols. This proposal is outlined in Scheme 53 below.

**Scheme 53: Proposed Ketyl Radical Cyclization**



This reaction, if successful, would yield a β–aminoalcohol (after reductive cleavage of the hydrazine N–N bond) which represents an important class of natural products.[90] The following table (9) summarizes the preparation of the carbonyl substrates used in this study. The first two entries are intermediates in the preparation of the halo–hydrazone substrates discussed earlier and are tabulated here for completeness.

**Table 9: Preparation of the Carbonyl Substrates**



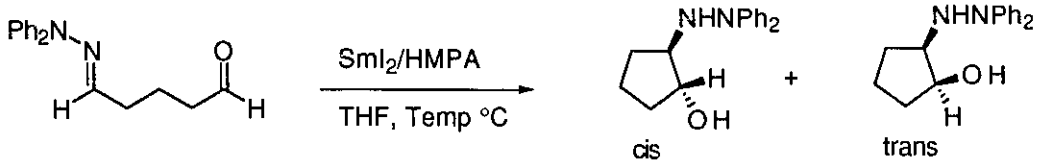

| Entry | R | n | Product | Yield (%) |
|---|---|---|---|---|
| a | H | 1 | 156 | 71 |
| b | H | 2 | 157 | 83 |
| c | Me | 1 | 170 | 58 |
| d | Me | 2 | 171 | 79 |

The preparation of the ketones follows from our earlier work on the oxidation of primary alcohols. Thus treatment of the secondary methyl alcohols **157a** and **158a** with $SO_3$·py/DMSO yielded the corresponding ketones **170** and **171** in good yields (Table 9, entries c and d). These substrates were then subjected to the standard $SmI_2$/HMPA conditions developed for the bromo–hydrazone cyclizations. It was found that 4.0 equivalents of $SmI_2$ were sufficient for the reaction to go to completion in these experiments.

In the first experiment (Table 10, entry a), a THF solution of aldehyde **156** was treated with 4.0 equivalents of $SmI_2$ in THF/HMPA at –78 °C (the experimental

conditions that gave the best stereoselection in the alkyl series). TLC analysis of this reaction revealed that the starting aldehyde had been completely consumed and two new, more polar, compounds were produced. $^1$H nmr analysis of the crude reaction mixture indicated that the cyclization had indeed occurred to give the *cis* and *trans* β–hydroxy hydrazines in a 6:1 ratio. After workup and purification, the two newly formed compounds were separated by silica gel chromatography in a combined yield of 53%.

**Table 10: 5–Exo $SmI_2$ Mediated Cyclization of Ketyl Radicals onto Hydrazones**




**156** **172a** **172b**

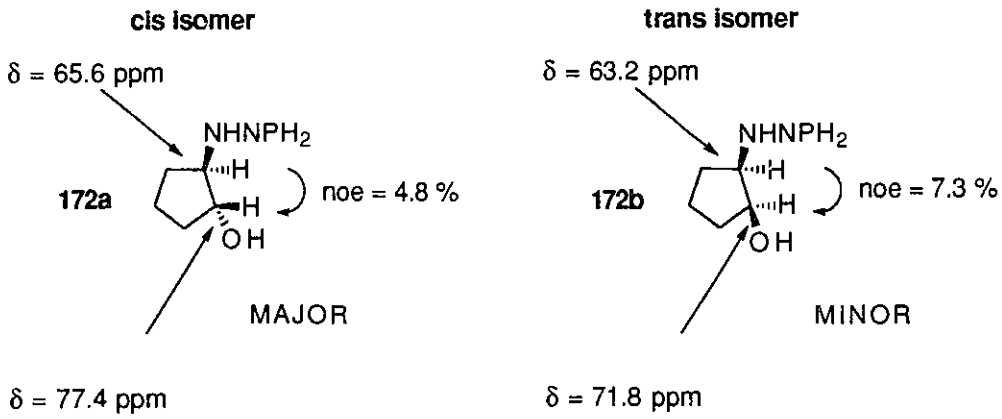
| Entry | Temp °C | *cis/trans* | Yield |
|---|---|---|---|
| a | –78 | 6:1 | 53 |
| b | –10 | 9:1 | 43 |
| c | 21 | >15:1 | 62 |

It should be noted that in compound **172a**, the hydroxy and hydrazine groups are *trans* to each other. In Table 10, this is referred to as the *cis* isomer in analogy with the halo–hydrazone series and with the keto–hydrazone cyclizations that will be described subsequently. In both of these systems, the designation *cis* refers to the hydrazine and alkyl groups. For the purposes of continuity, this nomenclature will be used throughout this thesis, even for the aldehyde substrates where R=H in the final product.

As in the alkyl series, the compound with the higher field methine carbon signals in the $^{13}$C nmr spectrum was assigned as the *cis* isomer (**172a**). The key spectral features

used to assign the stereochemistry in the hydroxy hydrazine series are shown below in Figure 2. Based on this nmr data, the major isomer from the cyclization is compound **172a** which has the hydroxy and hydrazine substituents in a *trans* relationship.

**Figure 2: Spectral Data for the Hydroxy–Hydrazines**



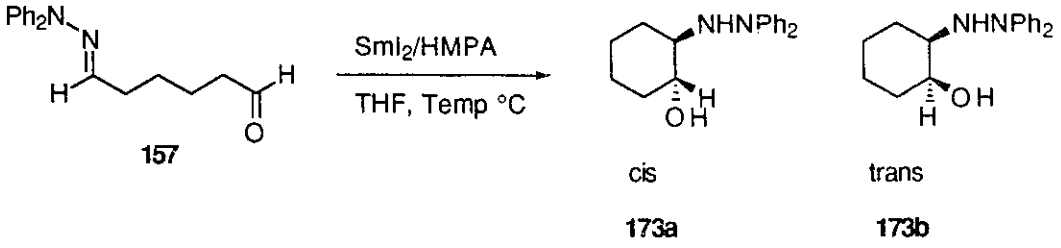

In the 5–exo alkyl radical cyclizations, the large alkyl substituent was *cis* to the hydrazine in the major product. In contrast, the 5–exo ketyl radical cyclizations place the large $OSmI_2$ substituent *trans* to the hydrazine in the major product. A rationale to account for these differences will be presented at the end of this section.

Interestingly, when the $SmI_2$/HMPA reaction was carried out at a *higher* temperatures (–10 °C and 21 °C, entries b and c in Table 10), the selectivity *increased* (9/1 and >15/1 respectively). This represents a marked departure from the trends observed in the alkyl radical cyclizations where, in general, the *cis/trans* selectivity increased with decreasing temperature. Thus the 5–exo ketyl radical cyclization proceeds efficiently and provides the β–hydroxy–hydrazines in good yields with excellent diastereoselectivities at ambient temperatures.

## 6–Exo Ketyl Radical Cyclizations onto Hydrazones

Having examined the 5–exo aldehyde–hydrazone reductive coupling, cyclization of the higher homologue was then attempted. Table 11 lists the results of the 6–ketyl radical cyclizations of aldehyde **157**.

**Table 11: 6–Exo $SmI_2$ Mediated Cyclizations of Ketyl Radicals onto Hydrazones**

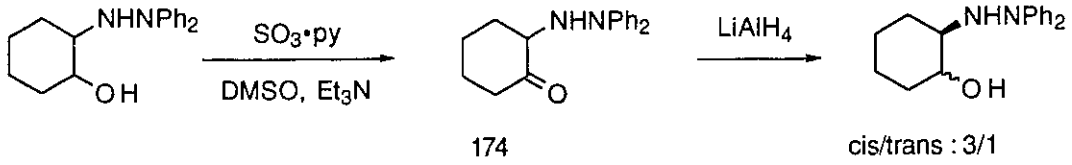



| Entry | Temp °C | *cis/trans* | Yield |
|---|---|---|---|
| a | 21 | >25:1 | 58 |
| b | –78 | >25:1 | 40 |

At 21 °C aldehyde **157** was treated with $SmI_2$/HMPA and TLC analysis of the resulting reaction mixture revealed the presence of only one new, more polar spot. $^1H$ nmr analysis of the crude reaction mixture also indicated the presence of only one diastereomer. Even by decreasing the temperature to –78 °C we were not able to observe any of the other diastereomer. These are very gratifying results since in the 6–exo alkyl series, the level of diastereoselection was modest at all temperatures examined. In contrast, the 6–exo ketyl radical cyclizations are highly stereoselective. We were unable to detect the minor isomer in *any* of our experiments with the 6–exo cyclization. As previously described, in order to determine the relative stereochemistry of the products using $^{13}C$ nmr, we needed the minor isomer for comparison. Thus we prepared an

authentic sample by the route shown in Scheme 54. We also wanted to confirm that the $^{1}H$ and $^{13}C$ signals of the minor isomer were not underneath those of the major product.

**Scheme 54: Preparation of a Cis and Trans Hydroxy–Hydrazine Mixture**



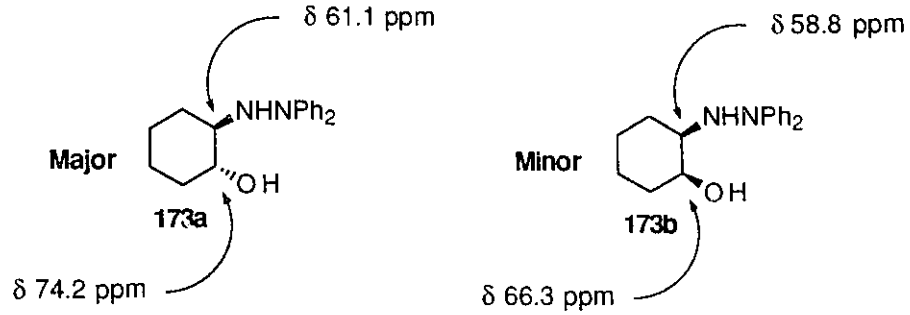

174

cis/trans : 3/1

Oxidation of the hydroxy–hydrazine with $SO_3$•py/DMSO/$Et_3N$ proceeded smoothly to furnish ketone **174** in 63% yield. Reduction of the ketone was carried out using lithium aluminum hydride (LAH) at room temperature. TLC analysis of the reaction mixture revealed the presence of 2 distinct spots. Workup of the reduction gave a combined yield of 93% of both diastereomeric alcohols which were readily separated by chromatography. It was thus established that the minor isomer did have a different $R_f$ value than the β–hydroxyhydrazine produced in the $SmI_2$/HMPA reaction. Analysis of the $^{1}H$ nmr spectra of the diastereomeric alcohols revealed that they also have distinctive spectral features. Re–examination of the $^{1}H$ nmr of the crude reaction mixture from the $SmI_2$/HMPA reaction verified that <3% of the other isomer could be detected.

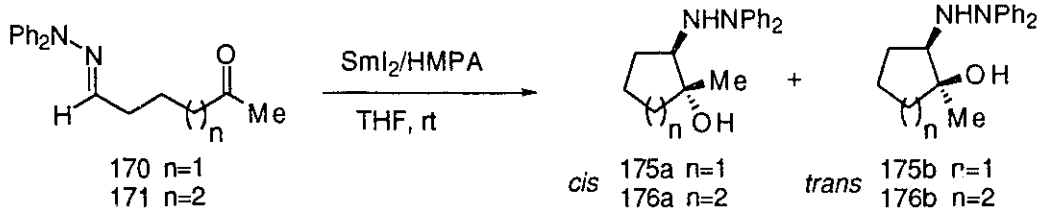
The relative stereochemistry could now be assigned based on $^{13}C$ nmr analysis of both isomers using the same technique used in the 5–exo cyclizations, and the key resonances are shown in Figure 3. These data confirm that the major product in the 6–exo ketyl radical cyclization is the *cis* isomer **173a**. (As in the 5–exo aldehyde–hydrazone cyclizations, the designation ***cis*** refers to the $HNNPh_2$ and H substituents.)

**Figure 3: Spectral Features of the Hydroxy–Hydrazines 173a and 173b**




Given the success of both the 5 and 6–exo ketyl radical cyclizations of aldehydes **155** and **156**, the next set of substrates examined were the ketones **170** and **171**. The results of the reductive couplings of the methyl ketones in 5–and 6–exo cyclizations with *N,N*–diphenylhydrazones are presented in Table 12. Treatment of methyl ketone **170** (Table 12, entry a) with $SmI_2$/HMPA resulted in the formation of a single, more polar (TLC) compound. Analysis of the crude $^1H$ nmr spectrum revealed the presence of only one methyl singlet with no evidence of a second diastereomer. After purification, 63% of the hydroxy hydrazine was isolated. The corresponding 6–exo reaction of ketone **171** (Table 12, entry b) also proceeded in good chemical yield (62%) and with excellent diastereoselectivity (>25:1). The level of stereochemical control in the 6–exo ketyl radical cyclization is again noteworthy when compared to the alkyl series.

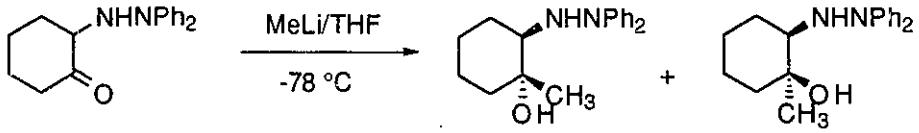
**Table 12: Ketone Substrates in the $SmI_2$/HMPA Cyclization**




| Entry | n | *cis/trans* | Yield |
|---|---|---|---|
| a | 1 | >15:1 | 63 |
| b | 2 | >25:1 | 62 |

Assignment of the relative stereochemistry of the major product in these reactions is not as straightforward as in the other hydroxy–hydrazines since only one methine carbon is present in this case. To assist in determining the relative stereochemistry of these products, ketone **174** was treated with MeLi at –78 °C. This gave a mixture of both diastereomers which were chromatographically separated. This result is summarized in Scheme 55.

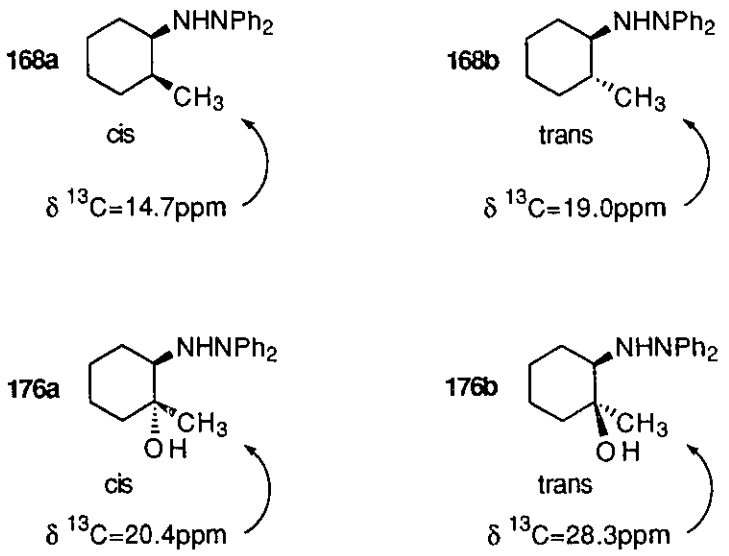
**Scheme 55: Preparation of Diastereomers 176a and 176b for Comparison of $^{13}C$ nmr Chemical Shifts**




176a 176b

The major isomer in the MeLi reaction was found to be the same as that obtained from the $SmI_2$/HMPA reaction. With both possible isomers in hand, we were able to compare the $^{13}C$ nmr chemical shifts of the methyl groups of **176a** and **176b** with the methyl signals in hydrazines **168a** and **168b** to assign the stereochemistry in this system. The following figure summarizes this nmr data.

**Figure 4: $^{13}C$ Chemical Shifts Data of Various Methyl Hydrazines**

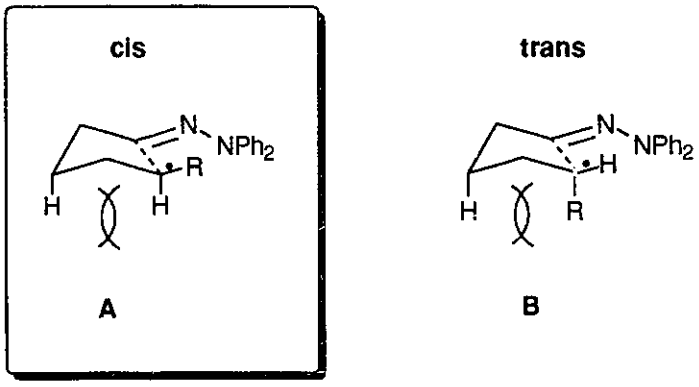



The methyl group in compound **168a** is syn to the diphenylhydrazine group and its carbon signal appears at a higher field than does the corresponding *trans* isomer **168b** (δ 14.7 ppm vs. 19.0 ppm, respectively). The methyl signals in the $^{13}C$ spectra of the isomers **176a** and **176b** were readily identified by an Attached Proton Test (APT) nmr spectrum and, in analogy with the other series, the isomer with the higher field methyl resonance is assigned as the *cis* isomer **176a**. This is also the isomer obtained from the $SmI_2$/HMPA cyclization and thus the ketyl radical cyclization is *cis* selective, giving only compound **176a**. It is interesting to note that the stereoselectivity of the ketone cyclization parallels the selectivity trends observed in both the alkyl and (aldehyde) ketyl radical cyclizations. In the alkyl radical series, the major isomer has the alkyl group *cis* to the hydrazine group, and in the aldehyde–ketyl radical series the hydroxy is *trans* to the hydrazine in the major product.

## Proposed Transition States

At this point, a rationale based on transition state models is proposed to account for both the stereochemical outcome of the radical cyclizations and the level of stereocontrol achieved. Consider first the alkyl radical cyclizations. We propose that these reactions proceed through chair conformations following Beckwith's[14] model as shown in Figure 5 below.

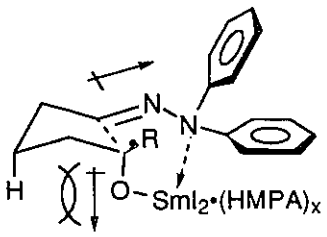
**Figure 5: Transition State Structures for the Alkyl Radical Cyclization**




Transition state A, which leads to the *cis* isomer, is preferred over structure B since it minimizes the 1,3 diaxial interactions. This model correctly predicts that as the size of the R group increases, the steric interactions in B increase which results in greater *cis/trans* selectivity, (see Table 7).

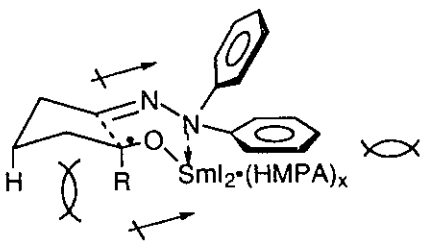
For the ketyl cyclizations, we propose that two factors (steric and electronic) are working in a co–operative sense to account for the stereoselection. The two possible transition states C and D are shown in Figure 6 below.

**Figure 6: Proposed Transition States for the Ketyl Radical Cyclizations**




C

cis isomer

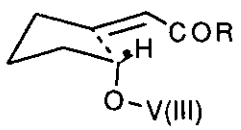



D

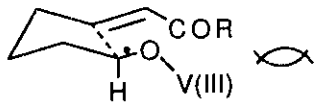
trans isomer

In terms of steric considerations, the 1,3 diaxial interaction in transition state structure C is probably not as severe as in transition state D. The 1,3 diaxial interaction in C may also be minimized by donation of the nitrogen lone pair to Sm(III) holding this substituent 'away' from the axial hydrogen. On the other hand, placing the oxygen substituent in a pseudo equatorial position would result in a serious gauche interaction of the very large $SmI_2$•HMPA complex and one of the phenyl substituents of the hydrazone (structure D). The stereoselection observed in our system is similar to the selectivity observed in the V(III) ketyl radical cyclizations shown in Figure 7 below. The authors[91] suggest that cyclization onto the enone occurs through transition state **177** to avoid the gauche interactions in **178**.

**Figure 7: V(III) Mediated Ketyl Radical Cyclizations**




177

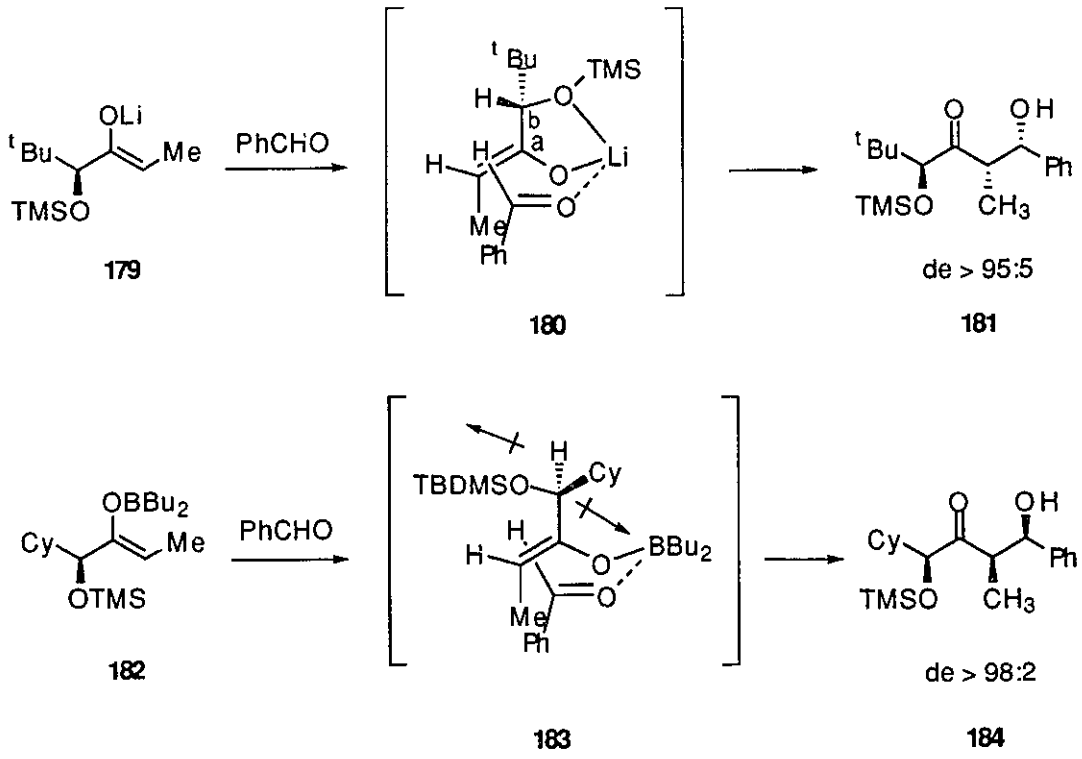



178

There is also an electronic component to this reaction that must be considered. It is generally true that in a molecule with several dipoles, the preferred transition state

geometry is the one that has the two dipoles aligned opposite to each other. An elegant example of this comes from the work of Heathcock[92] and Masamune[93] on the aldol reaction summarized in Scheme 56 shown below.

**Scheme 56: Control of Aldol Stereochemistry via Dipole Minimization**

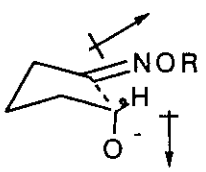



The first reaction involves the condensation of the lithium enolate **179** with benzaldehyde. In the proposed transition state **180**, the authors[92] suggest that oxygen of the siloxy group chelates to the lithium in effect locking the rotation around the stereogenic center (bond Ca–Cb in **180**). The incoming benzaldehyde then approaches opposite the large *t*Bu group to give the indicated product with the two newly created stereogenic centers anti to the silyloxy group. However, if a boron enolate is employed[93], as in compound **182**, the oxygen of the siloxy group is unable to chelate to the coordinatively saturated boron atom and it adopts a conformation which orients the

dipole of the silyloxy group *opposite* that of the C–O of the enolate (**183**). This locks the rotation around the stereogenic center and the incoming aldehyde approaches from behind the page opposite the large cyclohexyl group to give compound **184**. The diastereoselectivity in this system is excellent, (>98:2), with the syn product (**184**) being obtained as the major isomer which is opposite that obtained in the lithium reaction.

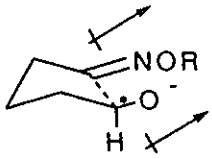
Returning to the hydrazone reaction, the dipoles in transition structure **D** are aligned with each other which disfavours this reaction pathway using the Heathcock/Masamune analogy. In proposed transition state **C**, the dipoles are more opposed favouring this structure. A similar dipole minimization argument has been invoked to account for the stereoselectivity of the electrochemical coupling of aldehydes and oxime ethers as shown in Figure 8. The authors[94] account for the high selectivity (>15:1) in this reaction by suggesting that transition state **185a** is favoured over **185b** due to dipole minimization at the transition state.

**Figure 8: Electrochemical Ketyl Radical Cyclization of Oxime Ethers**




**185a**

Favoured




**185b**

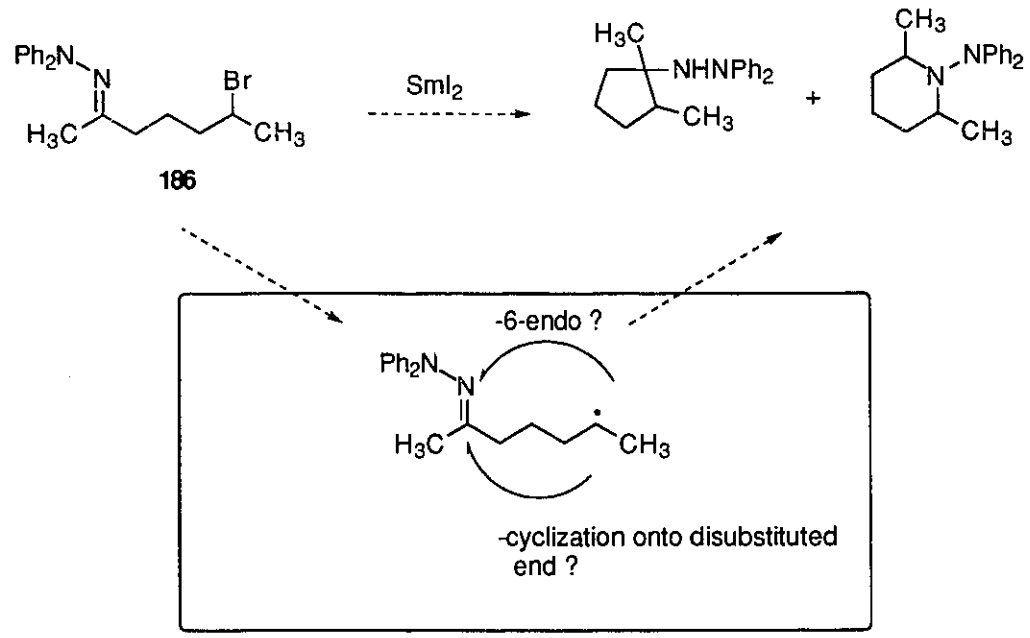
Disfavoured

The importance of the steric and/or the electronic (dipole-dipole) components in controlling the stereoselectivity of these radical reactions is not clear at the moment. Both of these components favour cyclization to provide the *cis* isomer.

## Cyclizations onto Hydrazones Derived from Ketones

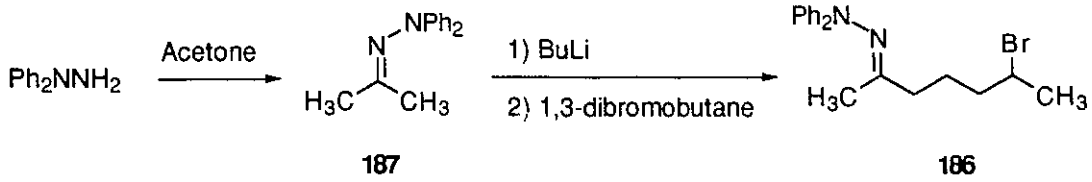
All of the experiments described above involve cyclization of alkyl and ketyl radicals onto monosubstituted hydrazones, which were derived from the corresponding aldehydes and diphenylhydrazine. We examined these systems initially to avoid potential steric interactions at the radical acceptor site as one of the modifications of the oxazoline system. Given the success of these cyclization reactions, we were interested in examining the radical cyclizations of disubstituted hydrazones derived from ketones as illustrated in Scheme 57 below.

**Scheme 57: Proposed Hydrazone Cyclization**




Considering the poorer reactivity of geminally disubstituted alkenes in radical reactions[1f], we were unsure initially whether or not the cyclization would take place, at all, and if it did, whether the 6–endo cyclization mode would occur. To answer some of these questions, the required starting material **186** was prepared as described in Scheme 58.

**Scheme 58: Preparation of a Ketone-Derived Hydrazone (186)**



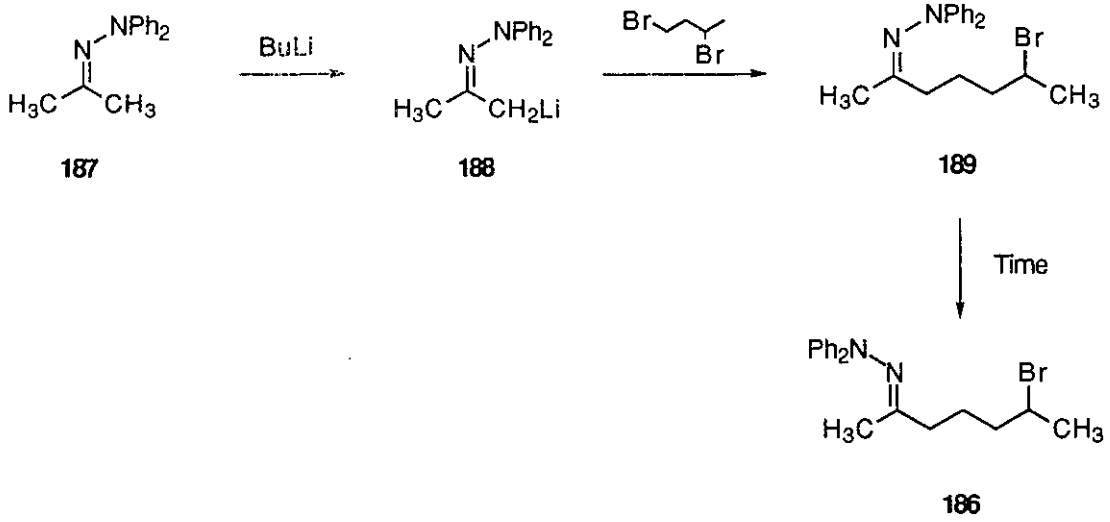

187 186

Condensation of *N,N*–diphenylhydrazine with acetone provided the expected dimethylhydrazone **187** in 56% yield. Deprotonation of the hydrazone was accomplished by treatment with *n*BuLi at –78 °C and the resulting anion was quenched with 1,3–dibromobutane to generate the desired bromide (**186**). TLC analysis of the alkylation reaction revealed that only one compound was produced in this experiment. After workup and attempted purification by flash chromatography on silica gel, a mixture of two compounds was isolated. One of these co–spotted with the original alkylation product and a new, less polar material was produced. $^1$H nmr analysis of this mixture revealed that the desired bromohydrazone **186** had in fact been produced, but as a mixture of syn and anti isomers about the C=N bond. This mixture was left in the nmr tube in $CDCl_3$ overnight, and analysis the next morning by TLC indicated that the initially observed more polar compound had been completely consumed and only the less polar compound remained. $^1$H nmr analysis also revealed that the previously described mixture had isomerized to give predominately one geometric isomer (>10:1).

It is likely that deprotonation of hydrazone **187** generates the metallo–enamine **188** which is known to exist as the more sterically hindered enolate[95] as shown in Scheme 59. Alkylation of this metallo–enamine results in the initially observed Z–hydrazone **189**, where the $NPh_2$ group is syn to the alkyl chain. Over time, slow isomerization around the C=N bond occurs to give the thermodynamically preferred E–hydrazone with the $NPh_2$ group syn to the less sterically demanding methyl group. The net result of this experiment is that the required hydrazone **186** had been prepared *and* we

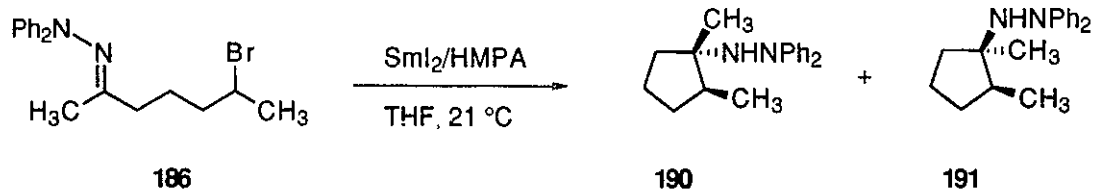
were now able to examine an additional parameter, namely the effect of hydrazone geometry on the cyclization reaction.

**Scheme 59: Alkylation of the Metallo–Enamine 188**




When the E–hydrazone was treated with $SmI_2$/HMPA at room temperature, the two possible 5–exo diastereomeric hydrazines were obtained in 44% combined yield of a 1:1 mixture as shown in Scheme 60.

**Scheme 60: $SmI_2$/HMPA Promoted Cyclization of an Alkyl Radical onto a Ketone–Derived Hydrazone**

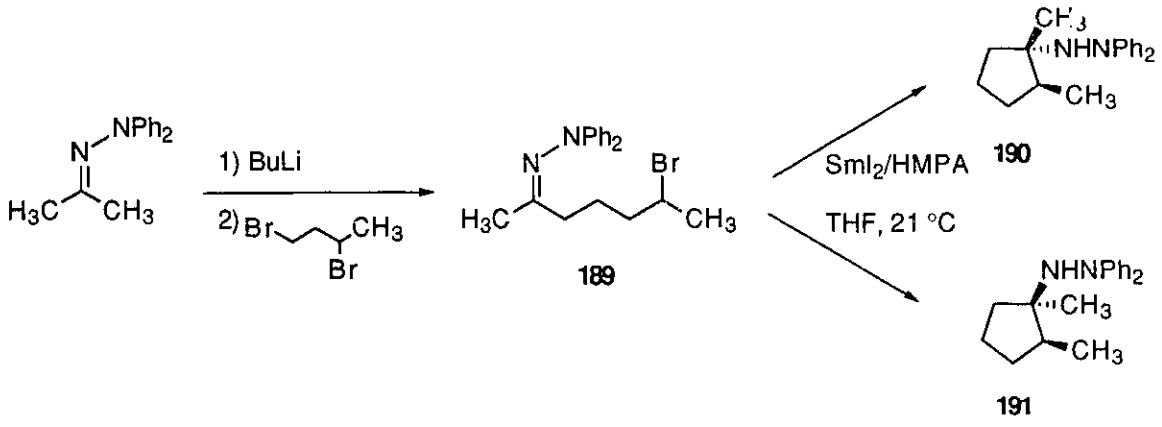



The cyclization had obviously occurred via the 5–exo pathway since each isomer possessed both a methyl singlet and a doublet in its $^1H$ nmr spectrum consistent with the

cyclopentyl structures **190** and **191**. Had cyclization occurred in a 6–endo fashion, both methyl signals would be doublets in the $^1$H nmr spectra. At this point we cannot completely rule out the formation of small amounts (<10%) of the 6–endo product since the $^1$H nmr spectrum of the crude reaction product was too congested in the diagnostic region (4–0.5 ppm) to make firm conclusions. However, the only isolable products from the reaction are those resulting from a 5–exo cyclization.

To examine the reactivity of the Z–hydrazone isomer in a radical cyclization, the bromo–hydrazone **189** was prepared as described above, but this time the alkylated product was not isolated but immediately treated with $SmI_2$ and HMPA. Analysis of the crude reaction mixture by TLC revealed the presence of two new compounds. However, it was not possible to determine the *cis/trans* ratio by examination of the crude $^1$H nmr, so the diastereoselectivity was assessed by isolation of the two separable compounds. Thus a 3:1 mixture of diastereomers was obtained with a combined isolated yield of 25%. This result is summarized in Scheme 61 below.

**Scheme 61: Radical Cyclization of a Z–Hydrazone**



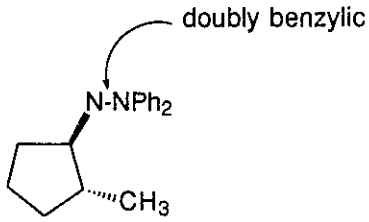

The $^1$H and $^{13}$C nmr spectra of the two isomers **190** and **191** were too similar to allow assignment of the relative stereochemistry. The general trend in these experiments

is that hydrazones derived from ketones give lower chemical yields and stereoselectivities in alkyl radical cyclizations than the corresponding monosubstituted hydrazones.

## Reductive Cleavage of the N–N Bond

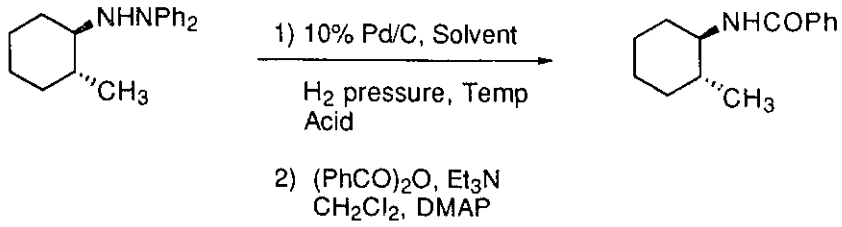
One of the original goals of this research was to use hydrazone–radical cyclizations as a method for the preparation of cyclic amines. To accomplish this, an efficient method for the cleavage of the hydrazine N–N bond was required. Since the N-N bond of the diphenylhydrazine product is doubly benzylic, it should be possible to cleave this bond by hydrogenolysis with standard metal supported catalysts.

**Figure 9: Cyclopentyl Hydrazine 146.**




To test the feasibility of hydrogenolyzing the N–N bond, hydrazine **186b** was treated under standard hydrogenation conditions[96] (10% Pd/C) with 500 psi of hydrogen in ethyl acetate and allowed to react overnight. TLC analysis of this reaction revealed only the presence of starting hydrazine. Hydrogenolysis did not occur, as there was no evidence for the formation of diphenylamine. Increasing the temperature to 80 °C for 12 hours was equally ineffective at reducing the N–N bond. This initial result is summarized in entry a of Table 13 below.

**Table 13: Hydrogenolysis of the Hydrazine N–N Bond**



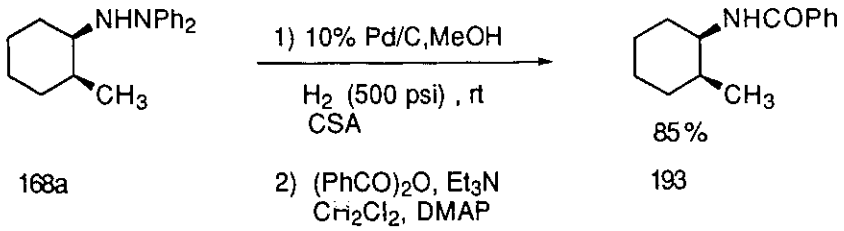

| Entry | Solvent | $H_2$ Pressure (psig) | CSA | Yield |
|---|---|---|---|---|
| a | EtOAc | 500 | – | – |
| b | MeOH | 500 | 2 equiv. | 87 |
| c | MeOH | 15 | 2 equiv. | 77 |
| d | MeOH | atm | 2 equiv. | 56 |

The reaction improved dramatically when 2 equivalents of (S)–(+)–10–camphorsulfonic acid[97] (CSA) was added to the reaction mixture. The experiment described in entry b of Table 13 was similar to the first experiment but 2 equivalents of CSA were added and the solvent changed from ethyl acetate to methanol to increase the solubility of the protonated hydrazine. After three hours at room temperature, TLC analysis of a neutralized aliquot revealed that the starting hydrazine had been completely consumed and this was accompanied by the formation of $Ph_2NH$. The resulting amine was benzoylated with $(PhCO)_2O$ in $CH_2Cl_2$ in the presence of triethylamine and after purification the corresponding benzoyl amide was isolated in 87% yield (two steps). The addition of a protic acid thus greatly improved the reactivity of the N–N bond and this is a very efficient and experimentally simple procedure to cleave the hydrazine. When the benzoylation was carried out in pyridine as the solvent, considerably lower yields of the amide were obtained (45%), which is partially due to difficulties in isolating the amide from the reaction mixture. The other results listed in Table 13 (entries c and d)

demonstrate that only moderate pressures of hydrogen are required for the hydrogenolysis in the presence of CSA.

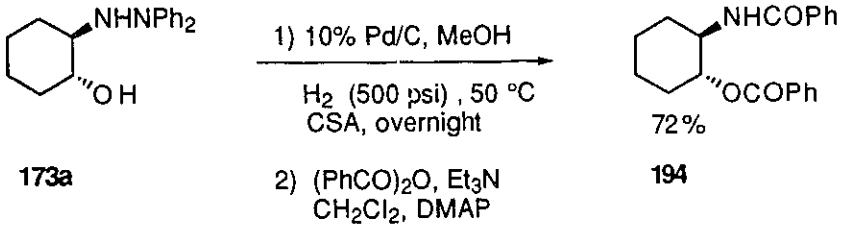
The isomeric *cis* methylhydrazine, **168a**, was also cleanly hydrogenolyzed as shown in Scheme 62, to give 85% isolated yield of the corresponding benzyl amide. In the hydrogenolysis experiments conducted for both isomers, there was no evidence of epimerization under the reaction conditions.

**Scheme 62: Hydrogenolysis of the N–N Bond of the *cis* Hydrazine 168a**




168a 193

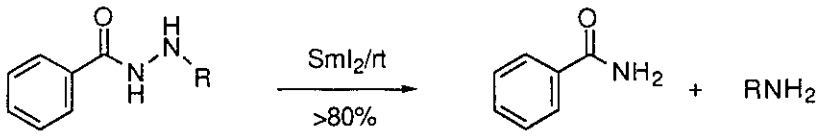
Cleavage of the N–N bond in the β–hydroxy hydrazine **173a** also proceeded cleanly affording the corresponding amide **194** in 72% yield. In this experiment, it was necessary to heat the reaction at 50 °C and a longer reaction time was also required.




**173a** **194**

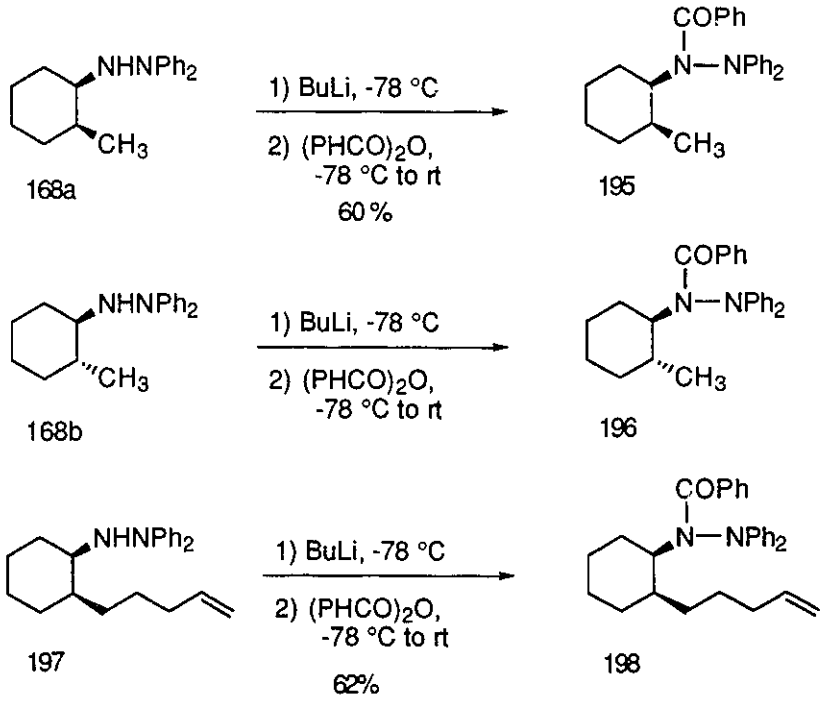
Thus the N–N bond of the hydrazines can be efficiently cleaved to give good yields of the corresponding amides. An interesting recent report from Burke and Feaster[98] described the cleavage of the N–N bond of hydrazides with $SmI_2$ as shown in Scheme 64.

**Scheme 64: Cleavage of the N–N Bond of Hydrazides Using $SmI_2$**




This is a nice method for cleaving hydrazides since it proceeds under mild reaction conditions and provides good yields of the reduced product. Furthermore, if this method worked in the diphenylhydrazine substrates, it would complement the hydrogenolysis conditions. For substrates with functional groups sensitive to hydrogen, such as alkenes, the $SmI_2$ reaction conditions would be more useful. Scheme 65 describes the preparation of several hydrazides to examine the use of $SmI_2$ in the N–N bond cleavage reaction.

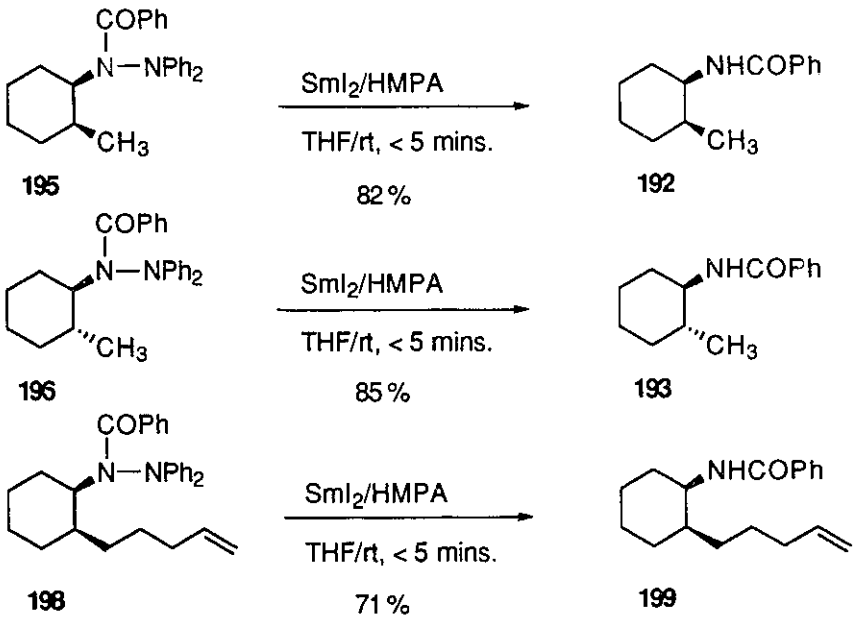
**Scheme 65: Preparation of Hydrazides 195–198**



Attempted deprotonation with *n*BuLi at room temperature gave a deep red solution along with extensive decomposition. Also, simply heating the hydrazine with benzoic anhydride in pyridine gave only trace amounts of the corresponding hydrazide. Deprotonation of hydrazine **168a** with *n*BuLi at –78 °C gave a faint orange solution which was subsequently treated with $(PhCO)_2O$ to provide hydrazide 195 in 60% yield. The other two hydrazides **196** and **198** were prepared with *n*–BuLi at -78 °C. To prepare the *trans* methyl hydrazide **196**, a mixture of *cis* and *trans* methylhydrazines **168a** and **168b** was treated first with *n*BuLi and then benzoic anhydride. The resulting mixture of hydrazides was separated chromatographically. Hydrazide **198** in the above Scheme was synthesized from the corresponding hydrazine (**197**) which was prepared for some competition studies which will be described in the next chapter.

To test the effectiveness of $SmI_2$ in the cleavage of the diphenylhydrazides, the hydrazide substrates were treated under the same $SmI_2$/HMPA conditions described for the cyclization experiments but in this case only 2.2 equivalents $SmI_2$ was employed. The results of these experiments are given in Scheme 66 below.

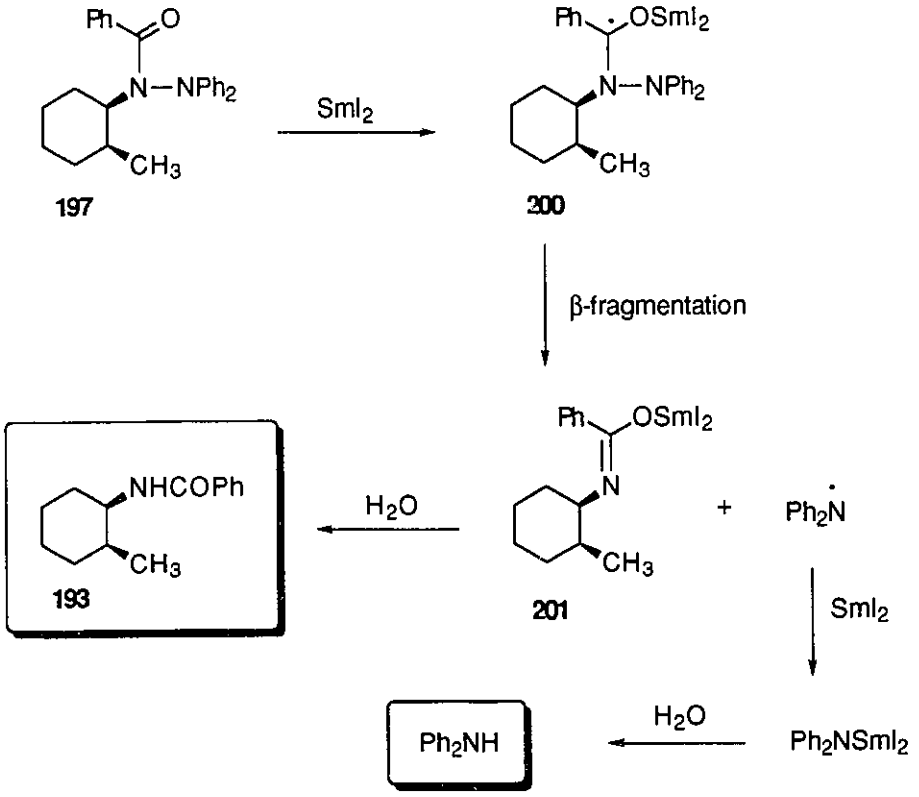
**Scheme 66: $SmI_2$ Mediated Cleavage of Hydrazides**



TLC analysis of the reaction mixture *immediately* after the delivery of the samarium iodide solution revealed the complete absence of the starting hydrazide with the formation of two new UV active compounds identified as $Ph_2NH$ and the expected amides. Of particular interest is the cleavage of the third hydrazide **198** since the alkene functionality was unaffected under the reaction conditions. Under the hydrogenolysis conditions previously described, the alkene in compound **199** would have been reduced to the alkane.

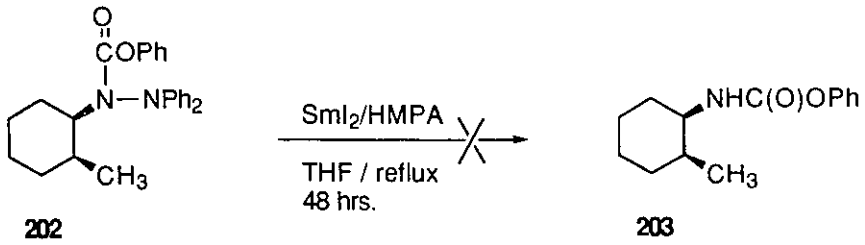
The β–cleavage of all the hydrazides examined was extremely efficient and the reaction was usually complete in several minutes at room temperature. A likely mechanism for this reaction is shown in Scheme 67. $SmI_2$ adds an electron to the carbonyl of hydrazide **197** to generate the corresponding ketyl radical **200**. This radical then suffers a β–cleavage of the N–N bond to form intermediate **201** which, upon workup, gives the observed amide **193**.

**Scheme 67: Proposed Mechanism for the $SmI_2$ Mediated Cleavage of Hydrazides**



Surprisingly, when the hydrazine–carbamate **202** shown in Scheme 68 was subjected to the same reaction conditions as used for the N–N bond cleavage in the hydrazide substrates, none of the cleaved material could be detected. Even heating a solution of this compound in THF at reflux for 48 hours did not give any of the expected carbamate **203**.[99]

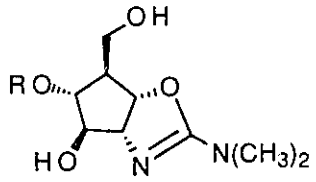
**Scheme 68: Attempted Cleavage of Hydrazine–Carbamate 202**




## Application of the $SmI_2$ Ketyl Radical Cyclization

In the recent literature there are many reports of the synthesis of cyclic β–amino alcohols.[100] Of these, allosamizoline (**204**, R=H) has attracted a considerable amount of attention. Allosamizoline is the central portion of the natural product allosamidin (**204**, R=disaccharide) which possesses potent chitinase activity. Chitin is a structural component found in fungal cell and insect exoskeletons.[101] Thus allosamizoline has fungicidal and insecticidal activity. This molecule is also of synthetic interest as it possesses a highly functionalized cyclopentane ring with *five* stereogenic centers.

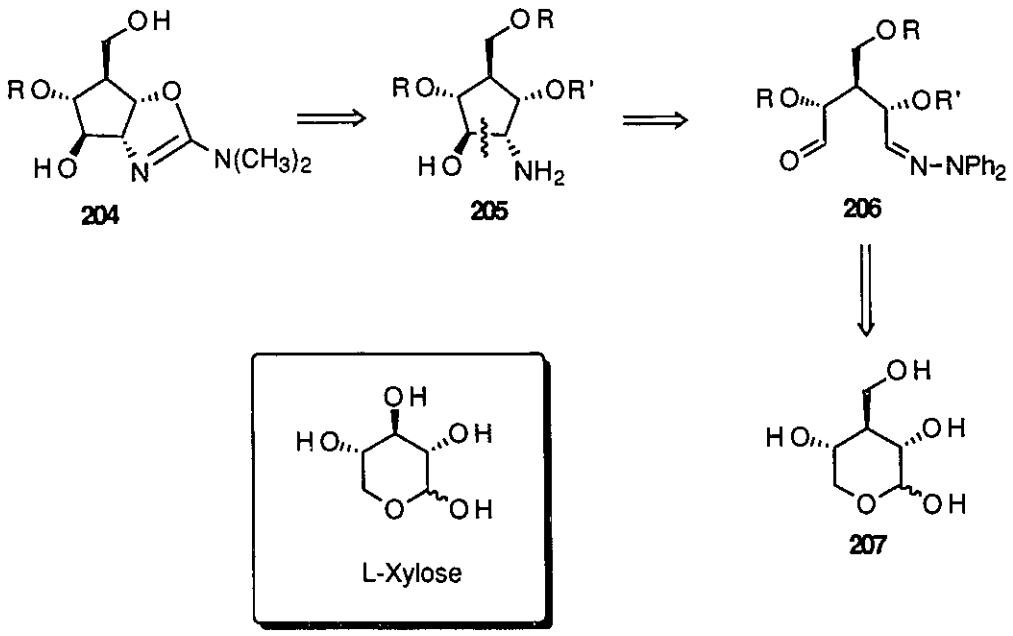
**Figure 10: Allosamizoline**



**204**

Inspection of this molecule reveals the presence of a β–hydroxy imine which could potentially be prepared via a $SmI_2$/HMPA reductive cyclization of an aldehyde and hydrazone. The following scheme outlines a retrosynthetic analysis of allosamizoline that employs a 5–exo hydrazone ketyl radical cyclization as the key step.

**Scheme 69: Retrosynthetic Analysis of Allosamizoline**

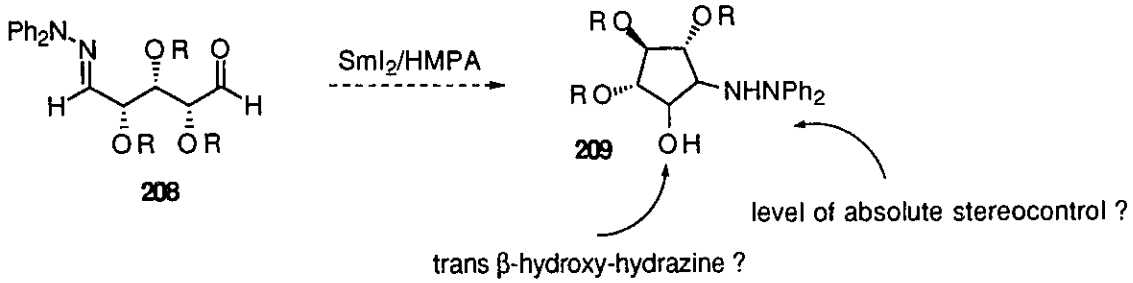



**204** **205** **206** **207**

As an initial model for the synthesis of allosamizoline, L–xylose was used as the carbohydrate starting material. Using this sugar, homologation of the C3 carbon of the carbohydrate by a $CH_2$ unit would be required after cyclization to obtain the exact structure present in allosamizonline.

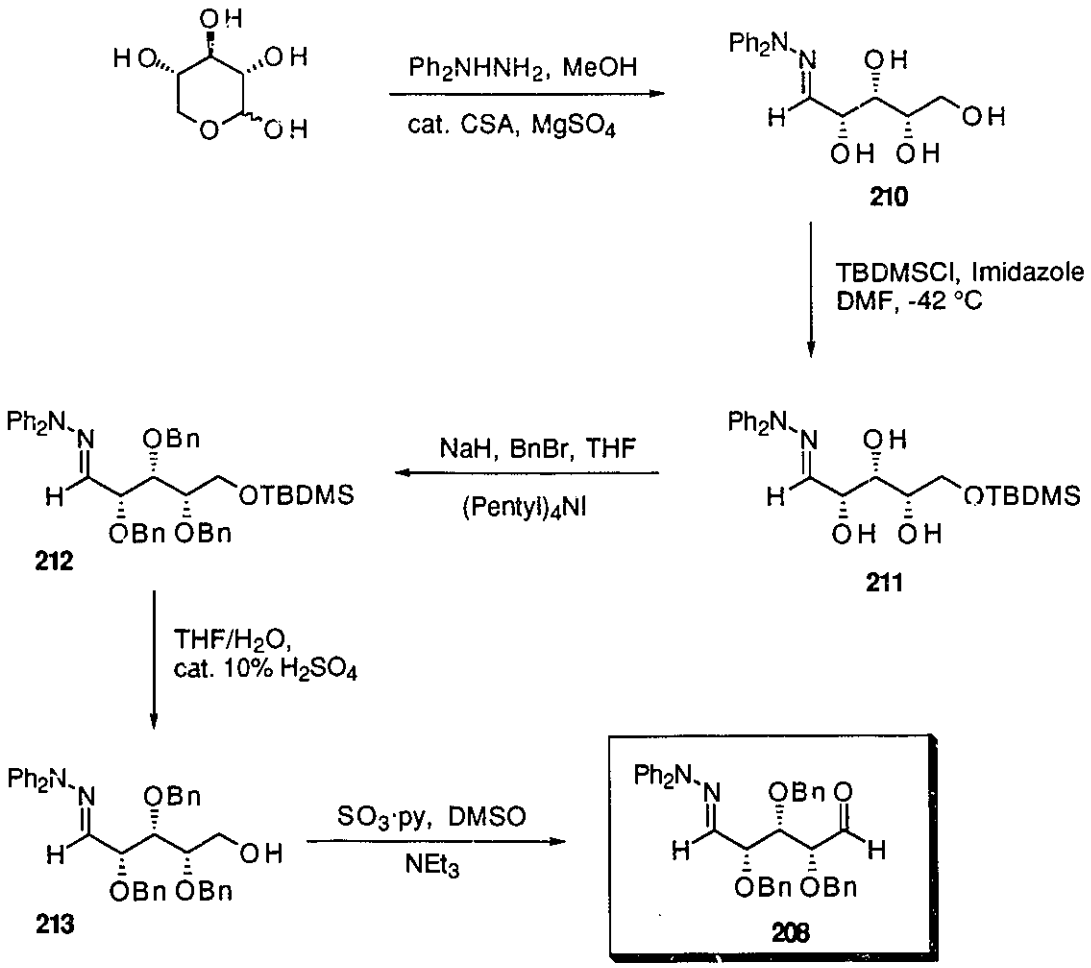
The key questions concerning this proposed entry into these cyclic hydroxy amines are whether the required chiral aldehyde (**208**) could be prepared without racemization of the carbon α to the hydrazone and whether the ketyl radical resulting from treatment of this aldehyde with $SmI_2$/HMPA would cyclize. Based on the trends observed in all the ketyl radical cyclizations performed in this study, the cyclization should occur to yield the hydroxy and hydrazine groups *trans* in the major product. However, hydrazone **208** is highly functionalized and the effect of the many oxygen substituents on the stereoselectivity of the radical cyclization in this system is not known.[102] Finally, there is still the question of absolute stereochemical control. Scheme 70 briefly summarizes the proposed cyclization.

**Scheme 70: Proposed Ketyl Radical Cyclization**




Scheme 71 summarizes the preparation of the required aldehyde substrate.

**Scheme 71: Preparation of Chiral Aldehyde 208**




Treatment of xylose in MeOH with *N,N*–diphenylhydrazine gave the corresponding hydrazone (**210**) in 44% yield. This reaction is significantly different from the condensation of the simple lactols with diphenylhydrazine described in the first part of this chapter. With simple lactols, the condensation was found to be complete in less than 30 minutes, and gave the hydrazone in good yields (78–94%). In contrast, the condensation of xylose with diphenylhydrazine was a slow reaction that gave only modest yields (ca. 40%). All attempts to optimize this result by the use of more polar solvents or heating failed, and we employed the conditions shown in Scheme 71 even though the yield was generally low.

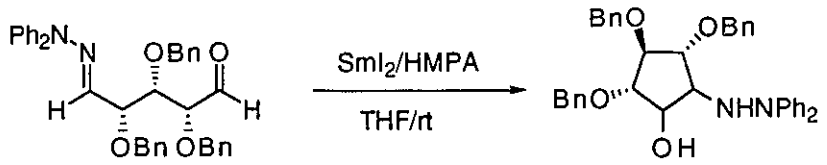
The tetrahydroxyhydrazone thus obtained was then treated with 1.1 equivalents of TBDMSCl ($t$Bu(Me$_2$)SiCl) at –42 °C in DMF[103] which permitted the selective silylation of the primary alcohol in 72% yield. The remaining secondary alcohols were then benzylated under standard conditions[104] (NaH, THF, BnBr, $R_4NI$) to yield the tribenzyl material in 67% yield. The next step in the sequence was the removal of the silicon protecting group. The first method evaluated was treatment of the hydrazone with tetrabutylammonium fluoride. TLC analysis of this reaction revealed that at least three compounds had been produced. Alternatively, when the siloxy–hydrazone was dissolved in a THF/$H_2O$ mixture and several drops of a 10% $H_2SO_4$[105] solution were added, TLC analysis of the crude reaction mixture revealed the presence of only one new, more polar compound. After neutralization of the reaction mixture and purification, the required alcohol was isolated in 68% yield. Both the $^1$H and $^{13}$C nmr spectra of this alcohol showed that racemization of the chiral center α to the hydrazone had not occurred.

The last step required to prepare the substrate for the $SmI_2$ cyclization was oxidation of the primary alcohol to an aldehyde. Initially, the $SO_3$•py/DMSO conditions that proved successful in the simple hydrazone–alcohol substrates were examined. Analysis of the reaction mixture by TLC was initially promising, since the alcohol was consumed and a single, less polar material was formed. It was found, however, that this material was difficult to isolate, and attempted purification by flash silica gel chromatography led to decomposition. The $^1$H nmr spectrum of the chromatographed material contained two aldehyde signals indicating that racemization of the stereogenic center α to the aldehyde had occurred. When the crude reaction mixture from the $SO_3$•py/DMSO oxidation was analyzed by $^1$H nmr before treatment with silica gel only one aldehyde signal was observed. This suggests that the chiral center does not racemize during the oxidation, but during exposure to silica gel.

The crude aldehyde was subjected to our standard $SmI_2$/HMPA reaction conditions at room temperature (this gave the best stereoselectivities in the simple

aldehyde systems). TLC analysis of the reaction mixture revealed the presence of two new spots of approximately equal intensity. Subsequent purification and separation showed that these were in fact the desired cyclized hydroxy–hydrazines. This result is summarized in Scheme 72 below.

**Scheme 72: $SmI_2$/HMPA Mediated Cyclization of Chiral Aldehyde 208**




**208** **209**

The combined yield of the cyclization was 57% and the less polar material was isolated in 36% yield. $^1H$ nmr analysis of this material suggested that it was a single diastereomer. The more polar material was isolated in 25% yield as a 2:1 mixture of stereoisomers (by $^1H$ nmr). Thus we have demonstrated that the cyclization of a carbohydrate derived hydrazone-aldehyde occurs in reasonably good yield to give three isolable diastereomers. The major product from this cyclization could be isolated in 36% yield, although the relative stereochemistry of this material has not been assigned.

For future work on this cyclization, it would be interesting to replace the benzyl substituents with silicon protecting groups. This would decrease any coordinating ability of the ether oxygens and would hopefully improve the stereoselectivity of the cyclization.

## Conclusions

In conclusion, we have shown that the 5- and 6-exo cyclizations of alkyl and ketyl radicals onto *N,N*-diphenylhydrazones proceed efficiently and in high chemical yield to provide the corresponding hydrazines. In all systems studied, with the exception of the 6-exo alkyl cyclizations, high levels (>15 or >25:1) of diastereoselectivities can be realized under appropriate conditions.

For the 5-exo alkyl cyclizations of 2° alkyl radicals, low reaction temperatures (–42 to –78 °C) gave the highest diastereoselectivities. For the 5-exo ketyl cyclizations, the reverse is true. The best results were obtained by performing the cyclizations at room temperature where the cis/trans ratios were too high to be detected by $^1$H nmr (>25:1).

The 6-exo alkyl cyclizations gave excellent yields of the cyclohexyl hydrazine products, but the stereoselectivity of the addition of the 2° radicals was poor at all temperatures studied. In contrast, the 6-exo ketyl radical cyclizations were highly diastereoselective at all temperatures examined. Even when the reaction was run at -78 °C, only one isomer could be detected in the crude reaction mixtures.

In all but one of the cyclizations, the major product had the hydrazine and the alkyl substituents in a *cis* relationship. The only exception to this is the 6-exo cyclization of the alkyl radical generated from compound **160b** which showed a slight preference for the *trans* isomer when the reaction was run at 80 °C. In the ketyl systems, the hydrazine and alkyl groups (R = H, Me or $CH_2CH_2CH_2CH{=}CH_2$) were also *cis* in the major product from every reaction. This means that the hydrazine and hydroxy groups are *trans*.

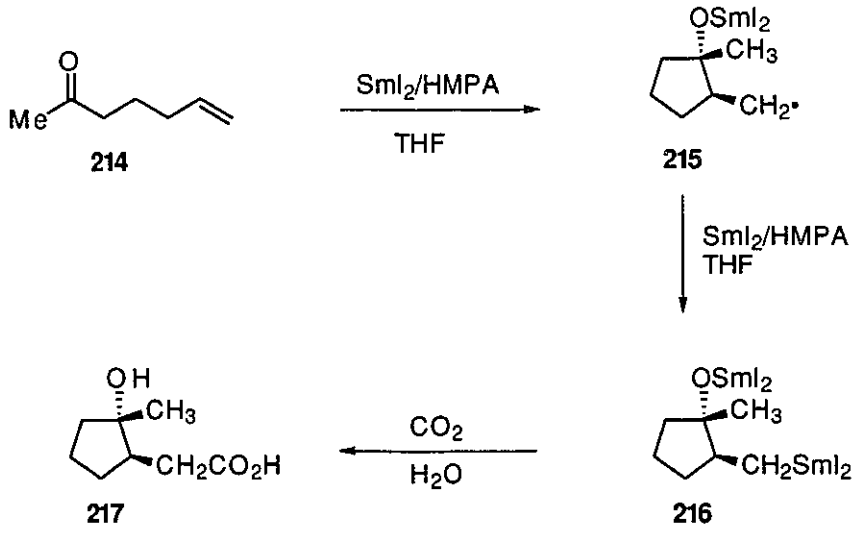
Since β-hydroxyamines are biologically important natural products, we developed complementary methods for cleavage of the N-N bond of the hydrazine to give the corresponding amine. Finally, a short synthesis of a pentasubstituted β-hydroxyhydrazine cyclopentane was performed using L-xylose as the starting materials.

# Chapter Three: Determination of Rate Constants for 5- and 6–exo 2° Alkyl Radical Cyclizations onto *N,N*-Diphenylhydrazones.

## Introduction

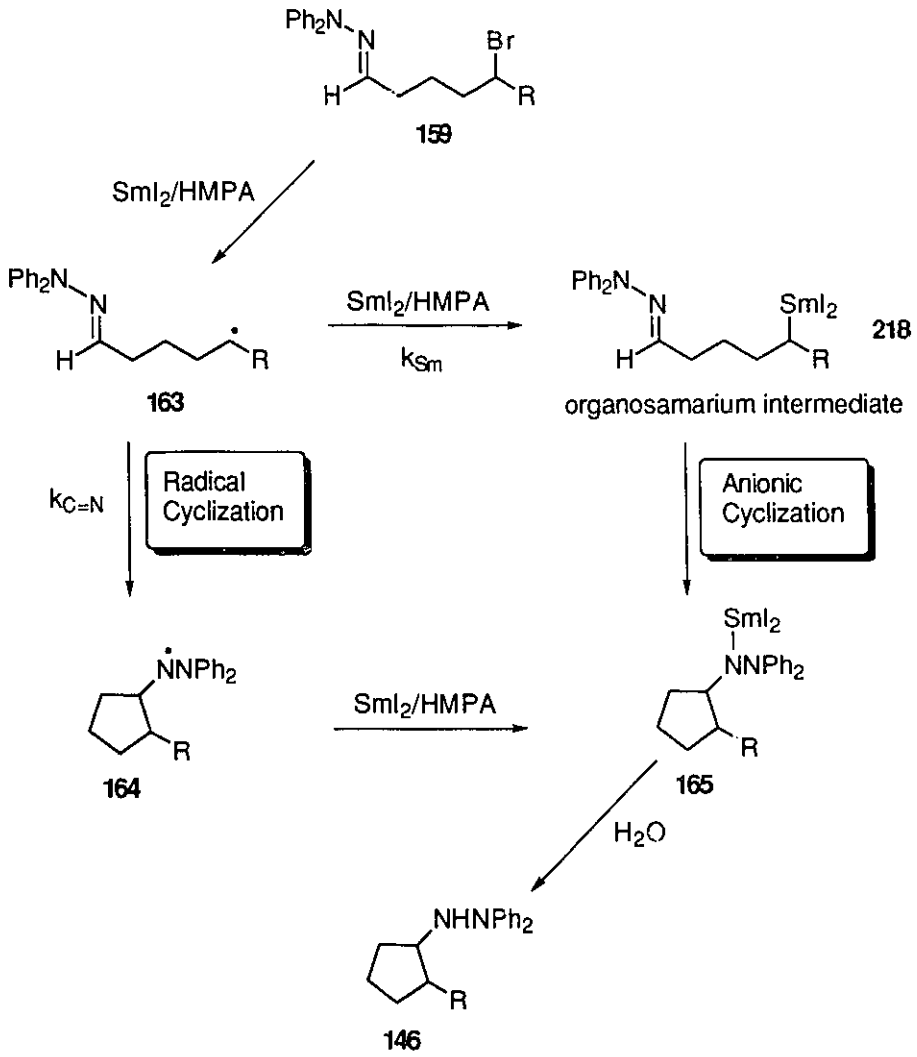
The previous chapter dealt with the synthetic utility of alkyl and ketyl radical cyclizations onto *N,N*–diphenylhydrazones. The mechanism we proposed invoked a radical ring closure onto the hydrazone functionality. The reaction clearly involves radical intermediates for the $Bu_3SnH$/AIBN experiments. The situation for the $SmI_2$/HMPA cyclizations though is not as straightforward. While $SmI_2$, like $Bu_3SnH$, generates radicals from halides it can also reduce the resulting radical generating anionic species. This has an important synthetic consequence since it allows functionalization of the resulting anion with an electrophile after cyclization, as illustrated by the following example.[106]

**Scheme 73: Radical Cyclizations–Nucleophilic Addition Reactions**



Under $SmI_2$/HMPA conditions, both radical and anionic reaction pathways are attainable. There are several reports in the literature on the addition of alkyl lithium, Grignard and organocerium reagents to hydrazones[107], thus demonstrating that the nucleophilic addition of carbanions to hydrazones is a viable reaction. There are thus two mechanistic possibilities for the $SmI_2$/HMPA mediated hydrazone cyclizations, a radical and anionic pathway, as illustrated in Scheme 74 below.

**Scheme 74: Possible Mechanism for the $SmI_2$/HMPA Mediated Cyclization of Hydrazones**



In the mechanism shown in Scheme 74, one equivalent of $SmI_2$ is consumed generating carbon radical **163** from the starting halide. At this point, radical cyclization can occur with a given rate constant $k_{C=N}$ to generate a cyclic nitrogen radical. This cyclization would then be followed by a second electron transfer from $SmI_2$ to the nitrogen radical generating the N–$SmI_2$ species which is hydrolyzed during the aqueous workup to give the observed cyclic hydrazine.

Alternatively, after generation of the carbon radical **163**, the second electron transfer could occur *on carbon* proceeding at a rate equal to $k_{Sm}$•[$SmI_2$] to generate an organosamarium species **218** (see Scheme 74). In this case, anionic ring closure would ultimately give the same hydrazine products. The key mechanistic question in this Scheme is the rate of radical cyclization onto the hydrazone functional group ($k_{C=N}$). If the hydrazone radical cyclization is fast relative to the bi molecular electron transfer from Sm(II) to intermediate **163**, the reaction will follow the radical route. On the other hand, if the hydrazone cyclization is slow then the reaction will most likely involve an organosamarium intermediate (**219**).

Recently, Hasegawa and Curran[108] have reported the rate constant for the electron transfer from $SmI_2$ to carbon radicals ($k_{Sm}$) to generate organosamarium species. This rate constant was determined by the system outlined in Scheme 75 below. In essence, this is a 'radical clock' system where the competing reactions are 5–hexenyl cyclization and the formation of organosamarium intermediate **222**. The resulting cyclized and uncyclized intermediates (**226** and **225**) were isolated as secondary alcohols after treatment with *p*–anisaldehyde. An interesting finding in this study is that the rate of reduction of carbon radicals by $SmI_2$ is proportional to the number of equivalents of HMPA used (relative to $SmI_2$).[109] The results of this study are outlined in Table 14 below. From this Table it can be seen that as the number of equivalents of HMPA are increased relative to $SmI_2$, the reduction potential of the $SmI_2$•HMPA complex

increases. A maximum was observed at approximately 5 equivalents of HMPA with a bimolecular rate constant of $6.8 \times 10^6$ $M^{-1}s^{-1}$ (Table 14, entry f).

**Scheme 75: Determination of the Sm(II) Electron Transfer Rate Constants to Carbon Radicals**

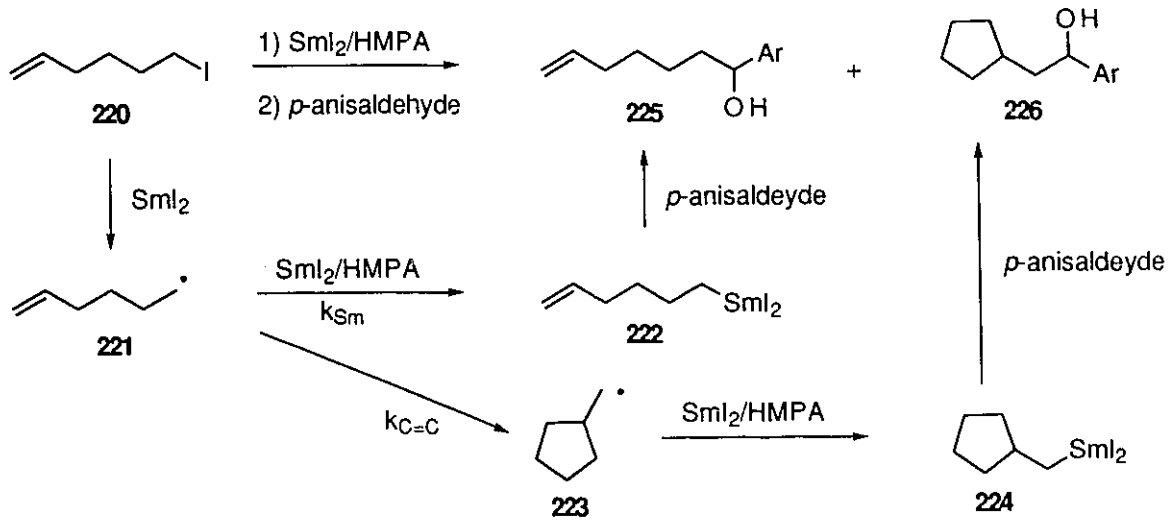



**Table 14: Dependence of the $SmI_2$ Reduction Rate Constant as a Function of HMPA Concentration**

| Entry | HMPA equiv. vs. $SmI_2$ | Ratio **225**:**226** | $k_{Sm}$ $M^{-1}s^{-1}$ ($x10^{-6}$) |
|---|---|---|---|
| a | 2.3 | 8:92 | 0.5 |
| b | 2.8 | 10:90 | 0.6 |
| c | 3.2 | 34:66 | 2.8 |
| d | 3.7 | 50:50 | 5.3 |
| e | 4.4 | 54:46 | 6.4 |
| f | 5.1 | 56:44 | 6.8 |
| g | 6.0 | 54:46 | 6.5 |
| h | 7.0 | 52:48 | 6.2 |
| i | 13.5 | 45:55 | 4.8 |

These results demonstrate that the formation of organosamarium intermediates from radicals can occur quickly. For example, in entry f, the ratio of 5–hexenyl cyclization to formation of the organosamarium intermediate is approximately 1:1.

As would be expected for a bimolecular reaction, the extent of reduction of radical **221** (vs. cyclization) decreases with lower concentrations of $SmI_2$. Table 15 summarizes the ratios of reduction to cyclization with decreasing concentrations of $SmI_2$. At lower samarium (II) concentrations, an increased proportion of cyclized material was isolated although the reduction potential of the Sm complex remained approximately the same as can be seen by the value of $k_{Sm}$ in the last column of Table 15.

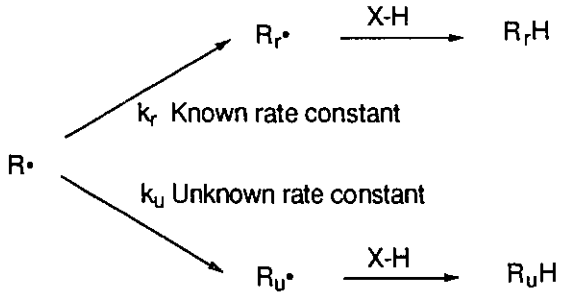
**Table 15: Effect of $SmI_2$ Concentration on Product Distribution**

| Entry | $[SmI_2]$ M | Ratio **225**:**226** | $k_{Sm}$ $M^{-1}s^{-1}$ ($x10^{-6}$) |
|---|---|---|---|
| a | 0.097 | 55:45 | 6.5 |
| b | 0.063 | 46:54 | 6.8 |
| c | 0.042 | 41:59 | 8.1 |
| d | 0.021 | 26:74 | 8.2 |

In our hydrazone system, knowledge of the rate constant for the radical cyclization ($k_{C=N}$) should shed considerable light on the extent of involvement, if any, of organosamarium intermediates in the ring closure reaction. There has been a considerable amount of work in the past several years on the direct measurements of radical reaction rates. Extensive studies using laser flash photolysis with time resolved UV–Visible spectroscopy has allowed the measurement of many radical reactions.[110] From a synthetic point of view, radical–clock systems[111] are convenient techniques for measuring rate constants. This idea involves designing a system where a radical

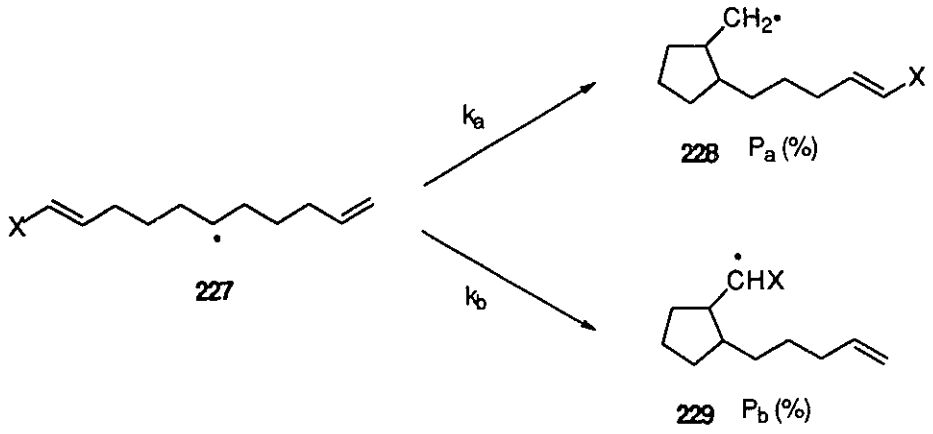
intermediate R• has the option of undergoing two competing reactions, one whose rate constant is to be measured and one whose rate constant is known (Scheme 76).

**Scheme 76: Principles of the Radical Clock System**




Thus intermediate R• can react to give Rr•, with some known rate constant $k_r$, or form $R_u$• with some unknown rate constant $k_u$. From the measurement of the product ratios ($R_rH/R_uH$) the unknown rate constant can be determined. As an example consider the following system in shown Scheme 77.

**Scheme 77: Intramolecular Radical Clocks for Determination of Rate Constants**



In this system, the competing reactions are a 5–exo cyclization onto the terminal alkene to generate $P_a$ (**228**) with a known rate constant $k_a$ and cyclization onto the substituted alkene to generate $P_b$ (**229**) with an undetermined rate constant. If the product ratio ($P_a/P_b$) can be measured analytically, then the unknown rate constant is given by the following equation.

$$k_b = k_a (P_b/P_a) \qquad \text{Eq. 6}$$

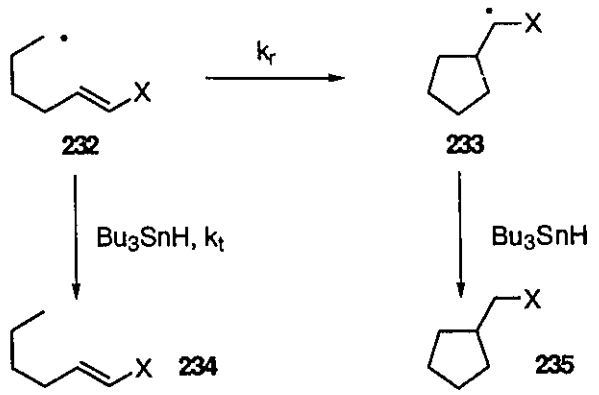
There are several implicit assumptions in the above analysis that should be pointed out. These radical reactions are generally considered to be irreversible and therefore the product ratios are assumed to result from the difference in reaction rates. Also, it is assumed that the rate constant for the structurally related 2° alkyl 5–hexenyl type cyclization (shown below) is a good approximation for the cyclization of the 2° radical (**230**) shown above. In general, these assumptions are valid.[110]


**230** **231**

Scheme 78 illustrates an intermolecular radical clock system. This system has been frequently employed and involves the competition between a radical cyclization with some unknown rate constant ($k_r$) and the intermolecular quenching of that radical with $Bu_3SnH$. Thus, the two competing reactions available to radical **232** are cyclization to generate compound **233** or quenching of the starting radical with $Bu_3SnH$.[112] If the ratio of the products from the reaction (**234**:**235**) can be measured (and knowing the concentration of $Bu_3SnH$ from the experimental data), it is possible to determine the unknown rate constant $k_r$. For this intermolecular clock system, the assumption is that the rate of quenching of radical **232** is closely related to the quenching of a simple

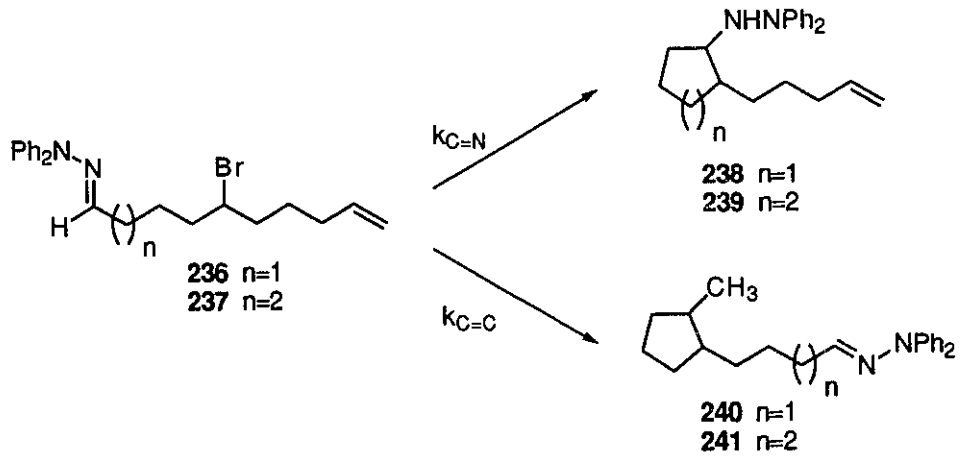
primary radical. In most cases, this assumption is valid, which makes this radical clock very useful.

**Scheme 78: Intermolecular Radical Clock System**




The following chapter will discuss the synthesis of the radical clock substrates **236** and **237**, as shown in Scheme 79 below, and the competitive radical cyclization experiments. The determination of the hydrazone rate constant is of interest for several reasons. It would represent the first report of a rate constant for a radical cyclization onto a hydrazone functional group *and* it will allow a mechanistic interpretation of the $SmI_2$/HMPA reactions described in the previous chapter.

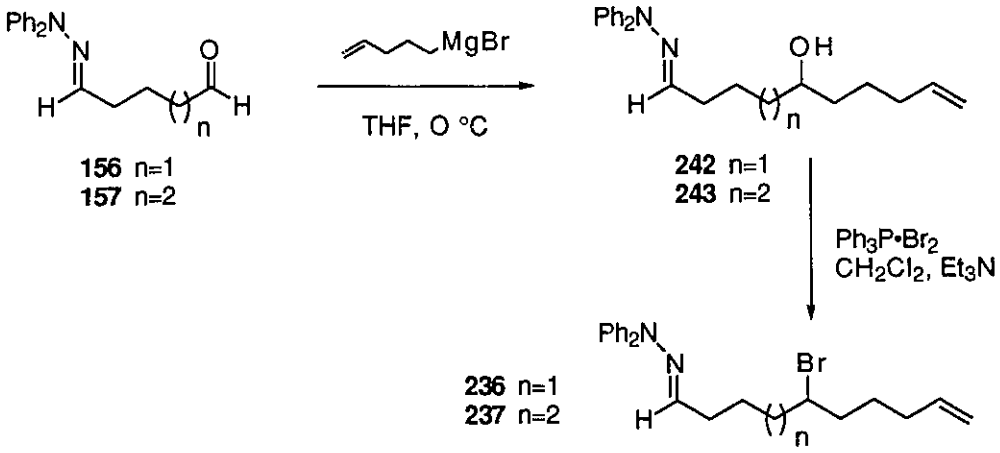
**Scheme 79: Proposed Radical Clock System**



## Results and Discussion

The following scheme briefly outlines the synthesis of the substrates that will be employed in the competition experiments.

**Scheme 80: Preparation of Hydrazone–Alkenes 236 and 237 for Radical Clock Experiments**



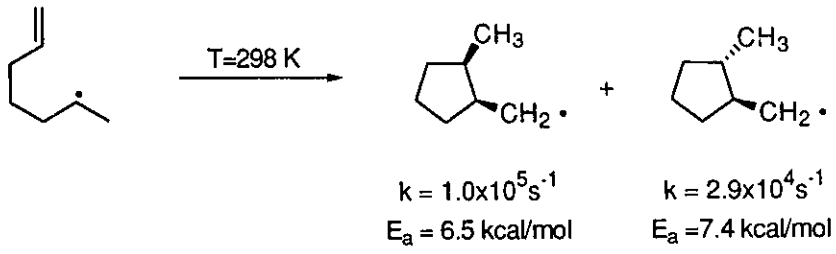

Aldehydes **156** and **157**, whose syntheses were presented in the previous chapter, were treated with the freshly prepared Grignard reagent from 5–bromopentene to yield the desired secondary alcohols in 57–61% yield. The alcohols thus obtained were then treated with $PPh_3 \cdot Br_2$ under the conditions described in Chapter Two to provide the secondary bromides **236** and **237** in 44–89 % yield.

There is a marked absence of kinetic data dealing with the cyclizations of alkyl radicals onto C=N π systems.[113] It was thus difficult for us to predict the outcome of the competitive cyclization experiment. Given the difficulties we experienced in attempting to cyclize an alkyl radical onto a variety of oxazoline systems, we initially speculated that the addition of a radical to a C=N π bond would be slower than the corresponding

addition to a C=C π system. This is also the general trend noted in certain ionic reactions where it has been proposed that imines are reluctant to undergo reactions in which the π bond is lost. Also, the C=N π bond is considered to be stronger than the corresponding C=C π bond[114] by about 10 kcal. In our hydrazone systems, the second nitrogen is anticipated to increase the rate of C=N radical cyclization. These radical clock experiments will be of considerable interest as they will give insight into the reactivity of the C=N π bond of *hydrazones* in radical reactions.

Before the competition experiments were carried out, the rate constants for the 2° radical 5–hexenyl *cis* and *trans* cyclizations at various temperatures were calculated from the literature value[115] reported at 25 °C and activation energies using the Arrhenius equation as shown in Scheme 81 below.

**Scheme 81: Literature Values for the 5–Hexenyl Cyclization**



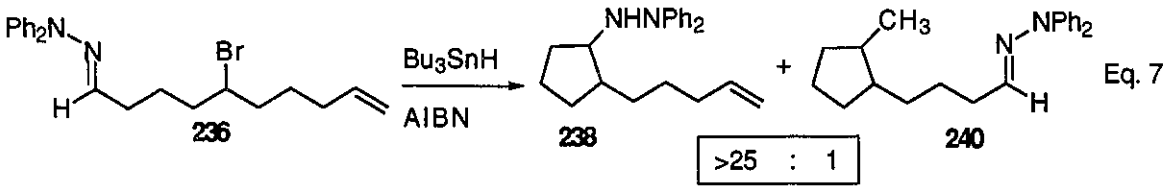

The following table summaries these calculated values. In the final column is the total rate constant of the cyclization (denoted $k_{total}$) which is simply the sum of the *cis* and *trans* components. This value represents the total global rate of the alkene cyclization at that temperature.

**Table 16: Calculated Rate Constants for the 5–Exo Alkene Cyclizations at Various Temperatures**

| Entry | Temperature ( °C) | $k_{cis}$ alkene ($s^{-1}$) | $k_{trans}$ alkene ($s^{-1}$) | $k_{total}$ ($s^{-1}$) |
|---|---|---|---|---|
| a | 80 | $5.5x10^5$ | $2.0x10^5$ | $7.5x10^5$ |
| b | 21 | $8.6x10^4$ | $2.5x10^4$ | $1.1x10^5$ |
| c | –10 | $2.3x10^4$ | $5.5x10^3$ | $2.9x10^4$ |
| d | –42 | $4.2x10^3$ | $7.8x10^2$ | $5.0x10^3$ |

The first kinetic experiments we performed involved treating substrate **236** under standard tin hydride conditions. Inspection of the resulting crude $^1H$ nmr spectrum surprisingly revealed that the hydrazone functional group had been completely consumed and that the alkene remained intact. The high chemoselectivity can be seen in the $^1H$ nmr spectra of the reaction provided in Figure 11 on the following page.

The first spectrum is of the starting hydrazone substrate and second is of the crude tin hydride reaction. As can be seen in the crude spectrum, there is no signal in the vinylic hydrazone region (δ 6.5 ppm). The absence of any measurable amounts of alkene cyclized material in the $^1H$ nmr spectrum meant that we could not assign an absolute rate constant for the hydrazone cyclization. We were, however, able to assign a lower limit since the hydrazone cyclization is at least 25 times faster than the 5–hexenyl radical cyclization. From this ratio (25:1), we calculated that the 5–exo *cis* and *trans* hydrazone cyclizations had a rate constant of at least $1.9x10^7 s^{-1}$ at 80 °C. This result is summarized in the following equation.



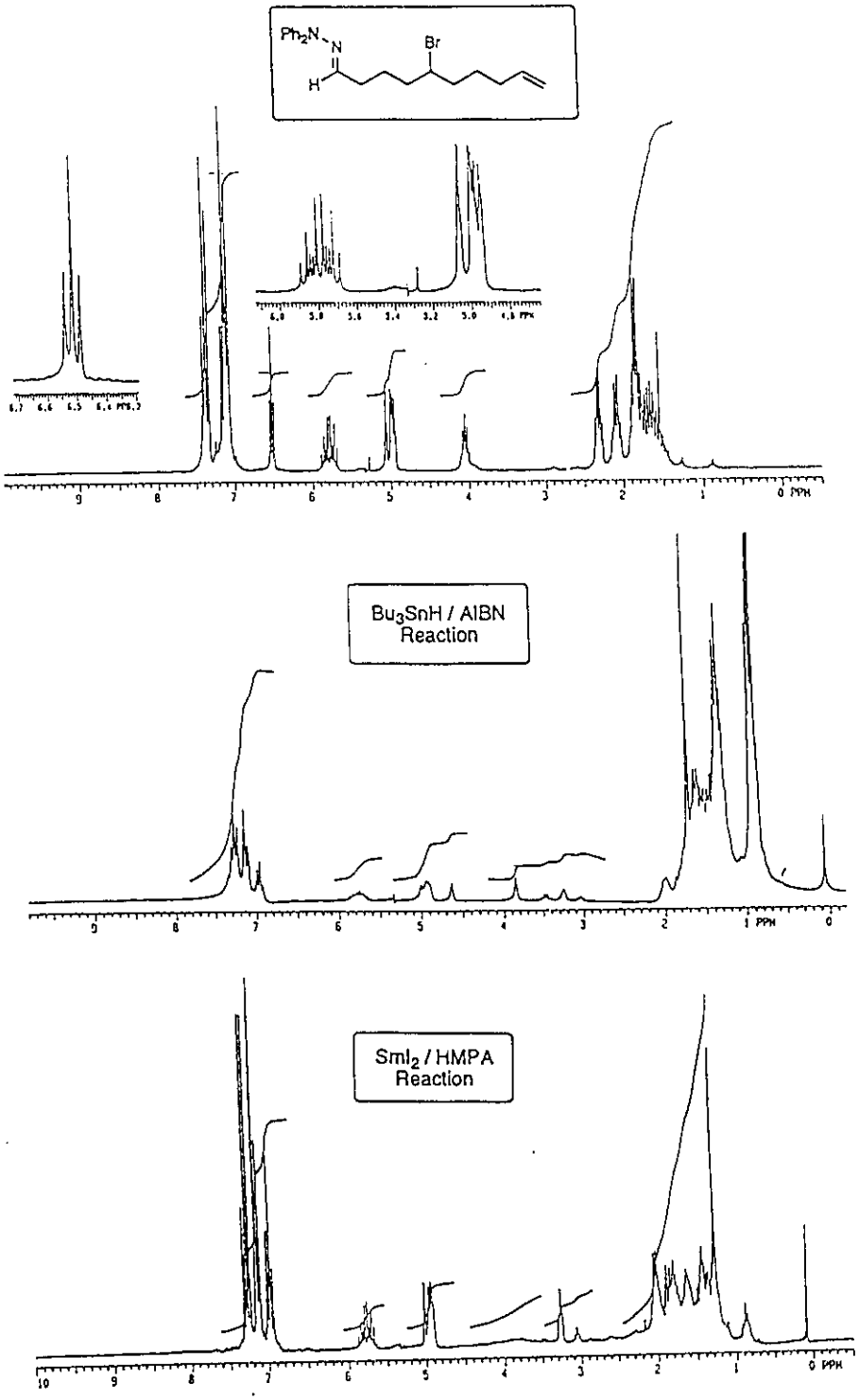
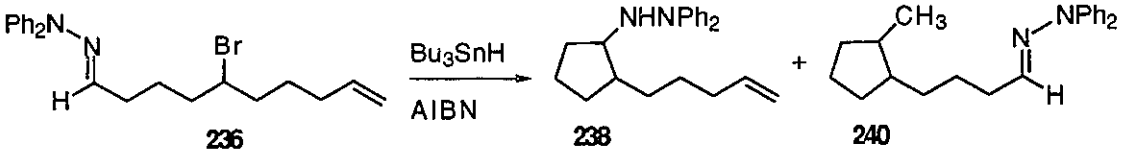



**Figure 11: Cyclization of Substrate 236 Under Free-Radical Conditions**

The cyclization was repeated at lower temperatures (21 °C and –42 °C) using $SmI_2$/HMPA and again there was no evidence for cyclization onto the alkene using nmr techniques. The third spectrum in Figure 11 is the crude $^1H$ nmr spectrum of the $SmI_2$/HMPA experiment performed at room temperature which is included for comparison. Again the absence of the hydrazone functionality is apparent. The results of these competitive cyclizations are summarized in the following Table along with lower limits for the hydrazone *cis* and *trans* cyclizations at different temperatures.

**Table 17: Lower Limits for the Rate Constants of the 5–Exo Hydrazone Cyclization**




236 238 240

| Entry | Reagent | Temp. ( °C) | ratio **238**:**240**[a] | $k_{cis}$ ($s^{-1}$) | $k_{trans}$ ($s^{-1}$) |
|---|---|---|---|---|---|
| a | $Bu_3SnH$ | 80 | >25:1 | $>1.9x10^7$ | $>1.9x10^7$ |
| b | $SmI_2$ | 21 | >25:1 | $>2.8x10^6$ | $>2.8x10^6$ |
| c | $SmI_2$ | –42 | >25:1 | $>1.3x10^5$ | $>1.3x10^5$ |

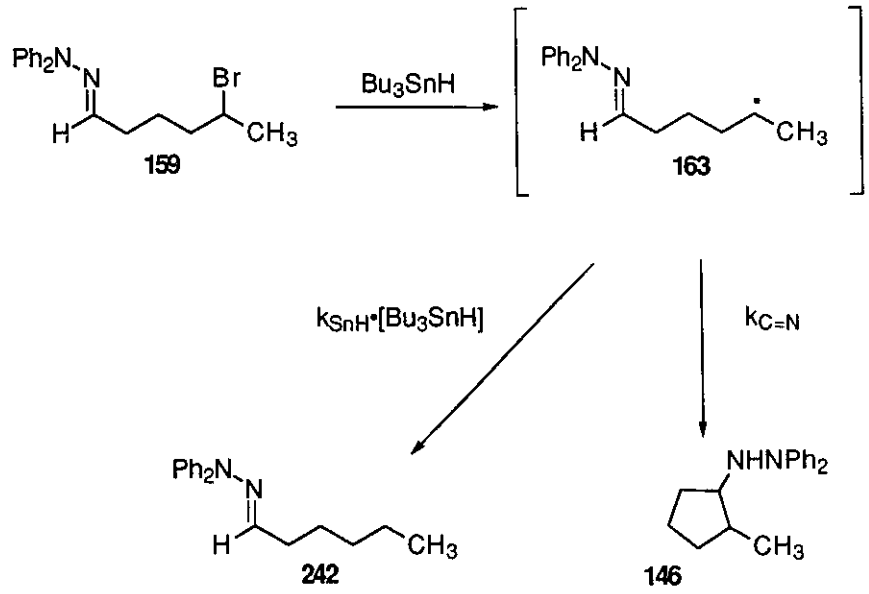
[a] ±5% by $^1H$ nmr spectroscopy

Surprisingly, therefore, the 5–hexenyl clock system is too slow to permit measurement of the 5–exo hydrazone rate constant even when the reaction was run at –42 °C. Attempts to examine the crude reaction mixture by GC were unsuccessful due to decomposition of the hydrazine and/or hydrazone to give diphenyl amine and other unidentifiable materials. Therefore, a faster radical clock system was required.

Scheme 82 illustrates the intermolecular clock system that was subsequently examined. In this system, after generation of the initial radical, the two competing

pathways are cyclization onto the hydrazone with a rate constant $k_{C=N}$ to generate the cyclic hydrazines (*cis* and *trans*) and quenching of the intermediate radical **163** with $Bu_3SnH$ to give the reduced product **242** proceeding with a rate of $k_{SnH}$•[$Bu_3SnH$]. The value of the quenching rate of a 2° alkyl radical ($Me_2CH$•) with $Bu_3SnH$ has been reported by Chatgilialoglu, Ingold and Scaiano to be $1.6x10^6$ $M^{-1}s^{-1}$ at 27 °C with an activation energy of 3.47 kcal/mol. Using the Arrhenius equation the reported rate constant at 27 °C was converted to a value of $3x10^6$ $M^{-1}s^{-1}$ at 80 °C for use in our radical clock system. The assumption that will have to be made in the following clock reaction is that the quenching rate of $Me_2CH$• can be used to approximate the quenching rate constant of the 2 ° radical **163** in Scheme 82 below. This seems to be a valid assumption given that the hydrazone functionality is remote from the radical center.

**Scheme 82: Intermolecular Radical Clock**

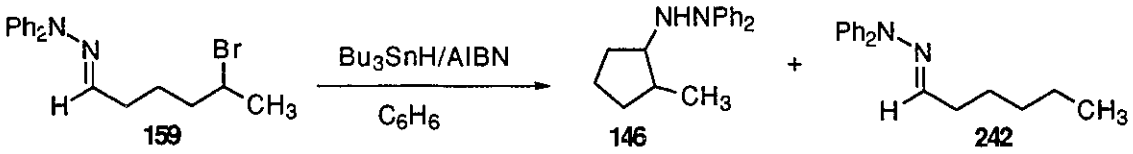



If the ratio of cyclized to reduced products from the competition experiment can be measured by $^1H$ nmr, then the rate constant for the 5–exo hydrazone cyclization can be obtained from the following equation.

$$\text{Ratio of cyclized to reduced} = \frac{\text{rate constant of cyclization}}{\text{rate constant of simple reduction x } [Bu_3SnH]} \qquad \text{Eq. 8}$$

Table 18 summaries the results of the competition study with varying concentrations of tin hydride. When the reaction was conducted with 0.9 M or 1.4 M $Bu_3SnH$ solutions in benzene (Table 18, entries a and b) analysis of the crude reaction mixture (see experimental section) revealed only the presence of cyclized material (>25:1 of **146**:**242**).

**Table 18: Intramolecular Radical Clock: Reduction versus Hydrazone Cyclization**



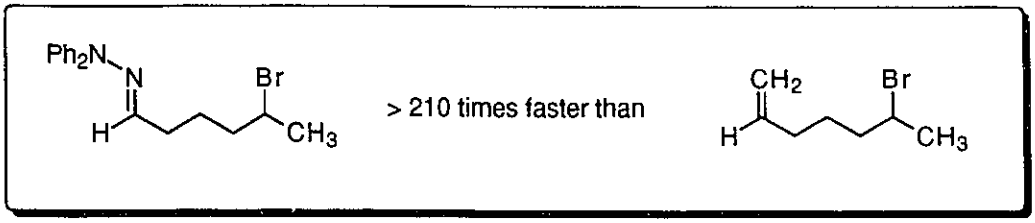

| Entry | [$Bu_3SnH$] (M) | Ratio **146:242**[a] | Yield % |
|---|---|---|---|
| a | 0.9 | > 25:1 | 83 |
| b | 1.4 | > 25:1 | 89 |
| c | 2.4 | 18.2:1 | 91 |

[a] ±5% by $^1H$ nmr spectroscopy

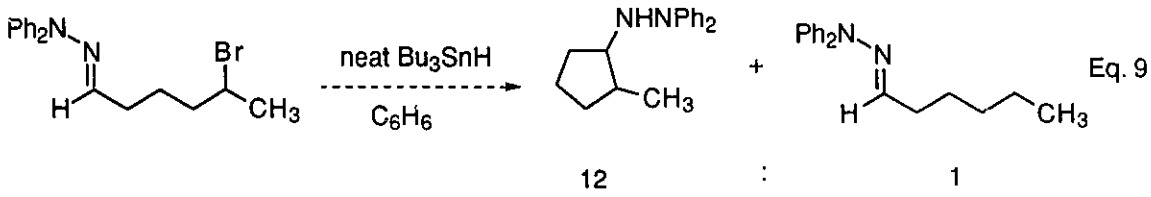
Using a 2.4 M $Bu_3SnH$ solution (2.0 mL of $Bu_3SnH$ in 1.0 mL $C_6H_6$, Table 18, entry c) we were finally able to observe some of the reduced hydrazone product. Thus a 18.2:1 mixture of cyclized to reduced compounds (**146:242**) was obtained in 91% isolated yield. The presence of the reduction product allowed us to calculate a rate constant for the hydrazone cyclization. Use of equation 8 gives a value of approximately $1.6 \times 10^8$ $s^{-1}$ at 80 °C as the total hydrazone cyclization rate constant. Also, analysis of the crude $^1H$ nmr spectrum of this experiment revealed that the *cis/trans* ratio was

approximately 2.5:1. This allowed us to partition the global rate constant into its *cis* and *trans* components. In doing so, we obtain rate constants of $k_{cis}=1.1x10^8$ $s^{-1}$ and $k_{trans}=4.6x10^7$ $s^{-1}$. Since the 5–hexenyl radical cyclization rate constant at 80 °C is $7.5x10^5$ $s^{-1}$, the 5–exo hydrazone cyclization is approximately *210 times faster* than the corresponding alkene reaction as shown in the following Scheme.

**Scheme 83: Comparison of the 5–Exo Hydrazone vs. Alkene Cyclization**




The 5–exo hydrazone radical cyclizations are therefore very fast reactions. In fact, if the competition experiment were to be performed in *neat* $Bu_3SnH$ (3.6 M), we can predict that greater than 90% of the product from this reaction would still be the cyclized hydrazine as shown in the following equation.




Although the 5–hexenyl system was too slow to measure the rate constant of the 5–exo hydrazone cyclization, it was able to measure the rate constant of the slower 6–exo hydrazone cyclization. As described above for the 5–exo hydrazone substrate, the required hydrazone (**237**) was reacted under standard tin hydride conditions. In this case the two competing reactions are a 5–hexenyl type cyclization and a 6–exo hydrazone

cyclization. In the event, analysis of the crude $^1$H nmr spectrum of the reaction showed that a 2.5:1 ratio of products was formed *in favour of the 6–exo hydrazone cyclization*.

The $^1$H nmr spectrum of the starting hydrazone substrate and the crude $^1$H nmr spectrum of the $Bu_3SnH$/AIBN experiment are shown in Figure 12. As can be seen in the crude spectrum, signals from both the alkene (δ 5.0 and 5.8 ppm) and hydrazone (δ 6.5 ppm) functional groups are present. The ratio of hydrazone and alkene cyclized products was determined by integrating the vinylic alkene signal vs. the vinylic hydrazone signal.

This tin hydride result is presented in Table 19. Also listed in this table are the results from the competition experiment using $SmI_2$/HMPA at various temperatures. For comparison, the crude $^1$H nmr spectrum from the $SmI_2$/HMPA experiment conducted at room temperature (Table 19, entry b) is also shown in Figure 12. This spectrum contains both hydrazone and cyclized material. As can be seen from the results in Table 19, the ratio of **239**:**241** is affected by the temperature. As the temperature is decreased (from 80 °C to –42 °C), the chemoselectivity of the reaction increased and at –42 °C (Table 19, entry d) the hydrazone cyclization was approximately 4.5 times faster than the 5–exo alkene cyclization. The stereoselectivity in the hydrazone cyclized material also increased from a 1:1 *cis*/*trans* mixture at 80 °C to 1.6:1 at –42 °C with the *cis* isomer being formed as the major product.

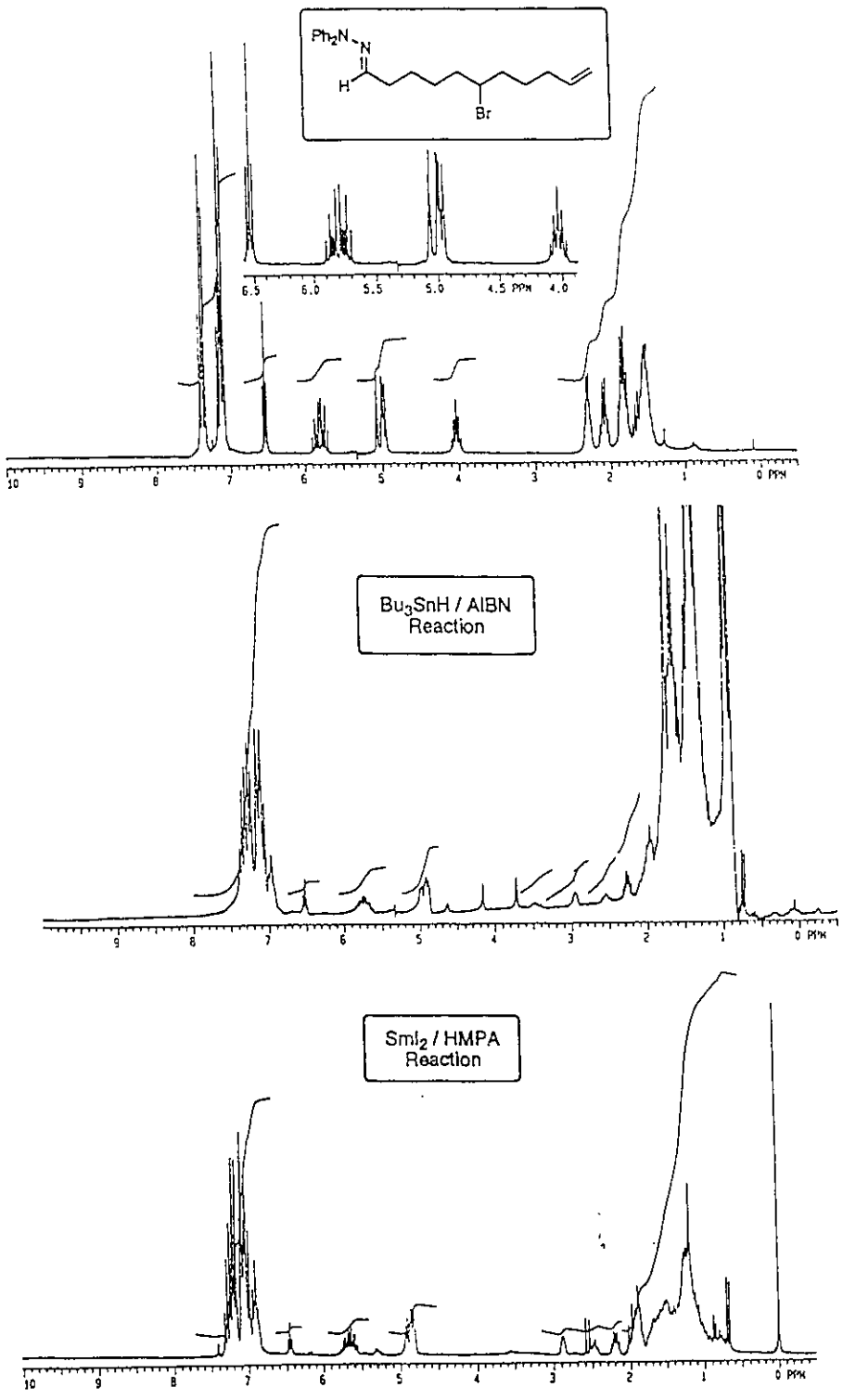
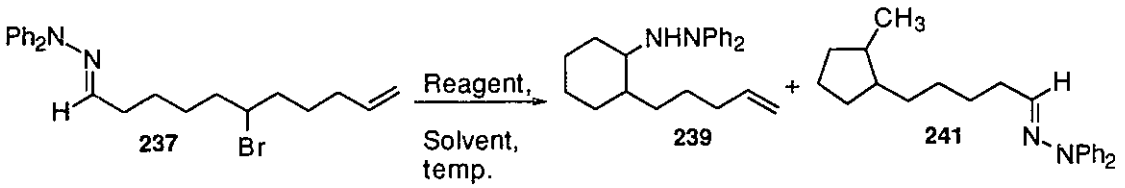



**Figure 12: Cyclization of Substrate 237 Under Free-Radical Conditions**

**Table 19: Measurement of the 6–Exo Hydrazone Cyclization**

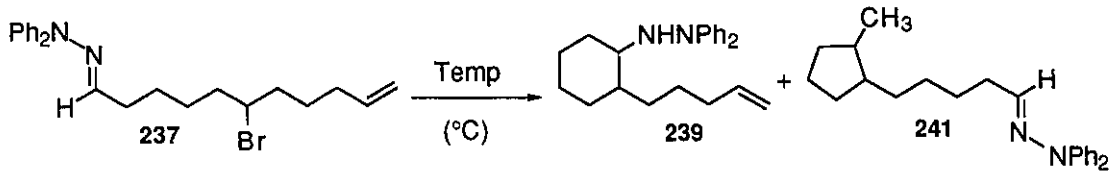



| Entry | Reagent | Temp (°C) | Solvent | Ratio **239**:**241**[a] | *Cis/Trans* | Yield % |
|---|---|---|---|---|---|---|
| a | $Bu_3SnH$/AIBN | 80 | Benzene | 2.5:1 | 1:1 | 93 |
| b | $SmI_2$/HMPA | 21 | THF | 2.9:1 | 1.3:1 | 75 |
| c | $SmI_2$/HMPA | –10 | THF | 3.5:1 | 1.4:1 | 80 |
| d | $SmI_2$/HMPA | –42 | THF | 4.5:1 | 1.6:1 | 88 |

[a] ±5% by $^1$H nmr spectroscopy

Since we were able to measure products from the hydrazone and alkene cyclizations as well as the *cis* and *trans* product ratios by examining the $^1$H nmr spectrum of the crude reaction mixtures, we could then calculate the *cis* and *trans* 6–exo hydrazone cyclization rate constants at various temperatures as shown in Table 20 below.

**Table 20: Determination of 6–Exo Hydrazone Cyclization Rate Constant**



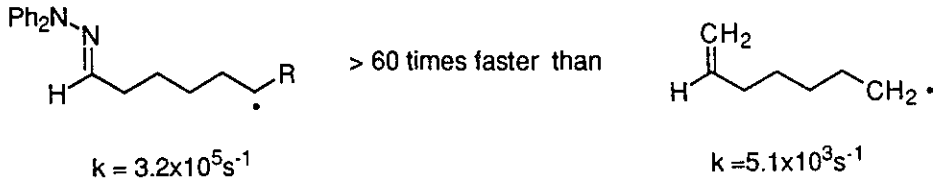

| Entry | Temp (°C) | *cis/trans*[a] | $k_{cis}$ ($s^{-1}$) | $k_{trans}$ ($s^{-1}$) |
|---|---|---|---|---|
| a | 80 | 1:1 | $9.4x10^5$ | $9.4x10^5$ |
| b | 21 | 1.3:1 | $1.8x10^5$ | $1.4x10^5$ |
| c | –10 | 1.4:1 | $5.9x10^4$ | $4.3x10^4$ |
| d | –42 | 1.6:1 | $1.4x10^4$ | $8.6x10^3$ |

[a] ±5% by $^1$H nmr spectroscopy

## Comparison of Rate Constants of 6–Exo Alkene and Hydrazone Cyclizations

The following figure compares the rate constant of the 6–exo cyclization onto the *N,N*–diphenylhydrazone with the 6–heptenyl rate constant available from the literature.

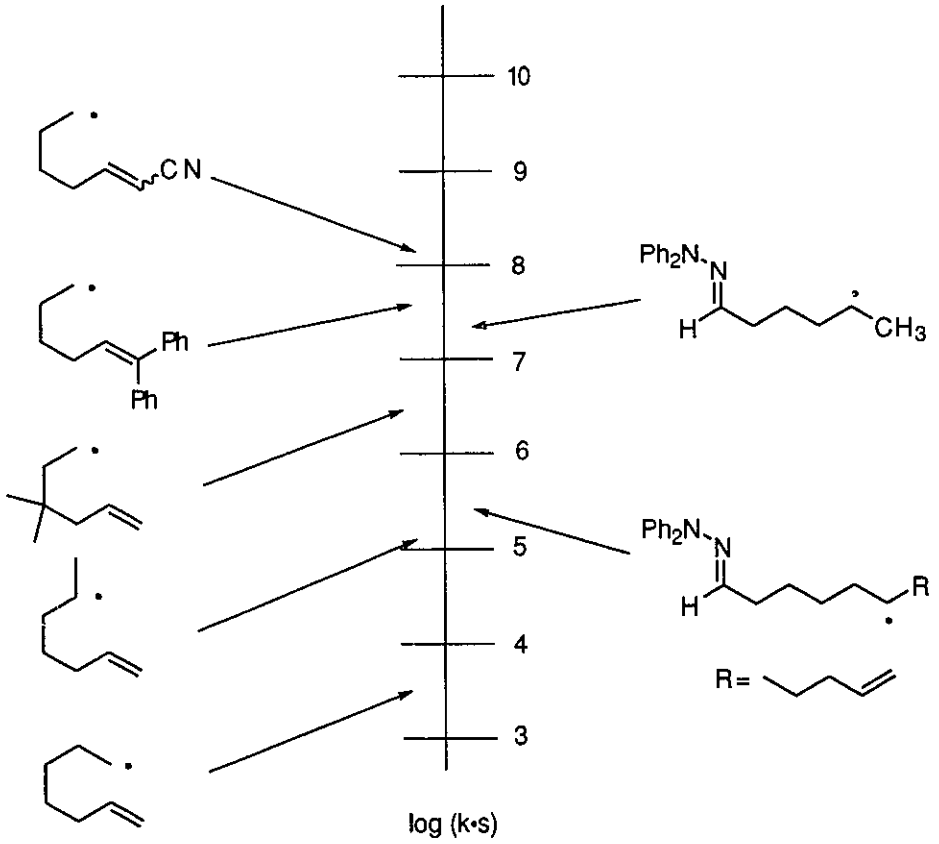
**Figure 13: Comparison of the 6–Exo Hydrazone and Alkene Cyclization Rate Constants at 25 °C**




As illustrated in Figure 13, the 6–exo cyclization of a 2° alkyl radical is approximately 60 times faster than the cyclization rate of a primary radical in a 6–heptenyl system.[116] However, in this case we are comparing our secondary radical with a primary radical (6–heptenyl) and these species have considerably different reactivities. Since the rate constant for a 6–exo cyclization of a secondary radical onto an alkene is not known, we are forced to make this comparison. However, if the rate constants for the cyclizations of a 1° and 2° radical in the 5–hexenyl system are examined, it can be seen that the 2° radical rate constant is slower than the 1° cyclization by a factor of approximately 2. So we can make a rough estimate that the 6–exo hydrazone 2° radical cyclization is approximately 100 times faster than the corresponding 2° radical 6–heptenyl system would be.

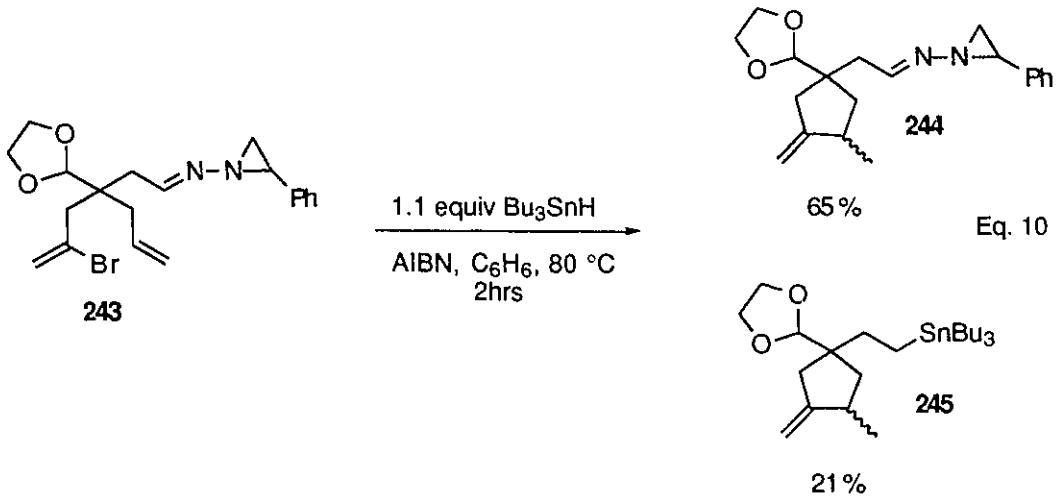
Up to this point we have only compared the hydrazone cyclizations to the 5–hexenyl and 6–heptenyl systems. The following Figure compares the 5 and 6–exo hydrazone rate constants determined in this study with those reported for other systems at 25 °C.[117]

**Figure 14: Comparison of Rate Constants of Various Functional Groups to Hydrazones**

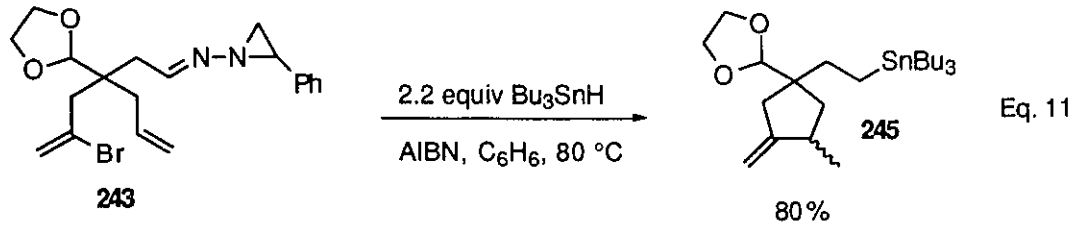



As can be seen in this Figure, the hydrazone cyclizations are very fast reactions. The 5–exo hydrazone cyclization is almost as fast as the cyclization of a radical onto the highly activated acrylonitrile system. Also, as described above, the 6–exo hydrazone cyclization is faster than the 5–hexenyl cyclization

Recently, Kim and Kee[118] have reported some competition studies with their N–aziridinyl imines and a 5–hexenyl system. Surprisingly, they obtain very different results from their kinetic experiments than we observed with the *N,N*–diphenylhydrazone. Their results are summarized in Equation 10.



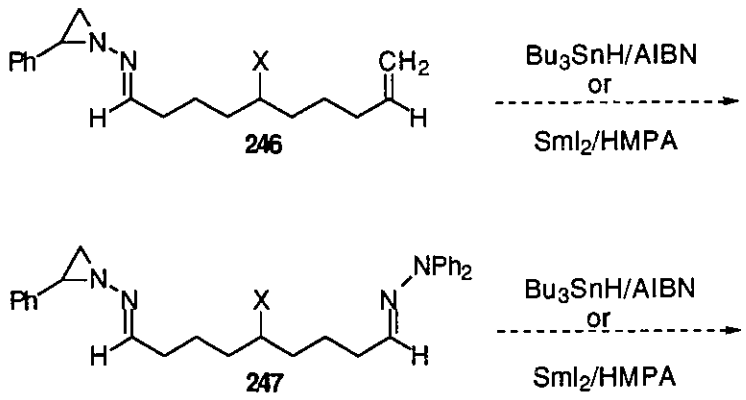

After generation of the vinyl radical from bromide **243**, a 5–exo cyclization onto the alkene occurred and there was *no evidence of cyclization onto the hydrazone.* This is in stark contrast to our findings where a 5–exo cyclization of an alkyl radical proceeded onto the hydrazone with *no evidence of cyclization onto the alkene.* The minor tin compound (**245**) in Equation 10 most likely results from the addition of $Bu_3Sn\bullet$ onto the C=N bond of hydrazone **244** which subsequently undergoes expulsion of styrene and $N_2$. In repeating the above reaction with 2.2 equivalents of $Bu_3SnH$ the organotin compound was the sole product of the reaction (80 % isolated yield), and again there was no evidence of hydrazone cyclization. This result is summarized in the following equation.




From these results, the authors conclude that their experiments "[demonstrate] the preference of the alkene group over the imino group as a radical acceptor". Given the amount of functionality present in compound **243**, conformational effects may play a

significant role in the chemoselectivity observed. Also, the nitrogen of the aziridine in **243** will be less effective in stabilizing the cyclized nitrogen radical. It would be of interest, for future studies, to use their N–aziridinyl imine in our kinetic system to allow for a more direct comparison of the two systems. Some potential radical–clocks to consider are shown in Scheme 84 below. The first system (**246**) compares, in a similar fashion to our studies, the 5–exo cyclization onto an aziridinyl imine vs. a 5–hexenyl cyclization. The second system is a competition between the two hydrazone units (**247**).

**Scheme 84: Proposed Comparison of *N,N*–Diphenylhydrazones vs. *N*–Aziridinyl Imines**




## Activation Energies for the *Cis* and *Trans* 6-Exo *N,N*-Diphenyl-Hydrazone Cyclizations

Since we were able to determine the 6–exo rate constant for the *cis* and *trans* cyclizations at various temperatures, (Table 20), we can also now calculate the activation energies for the cyclization reactions using the relationship $\ln k = -E_a/(RT)$, where $E_a$ is the activation energy for the reaction. A plot of ln k (for the *cis* and *trans* cyclization) versus 1/T should yield a straight line with slope equal to $-E_a/R$. Doing so will allow us

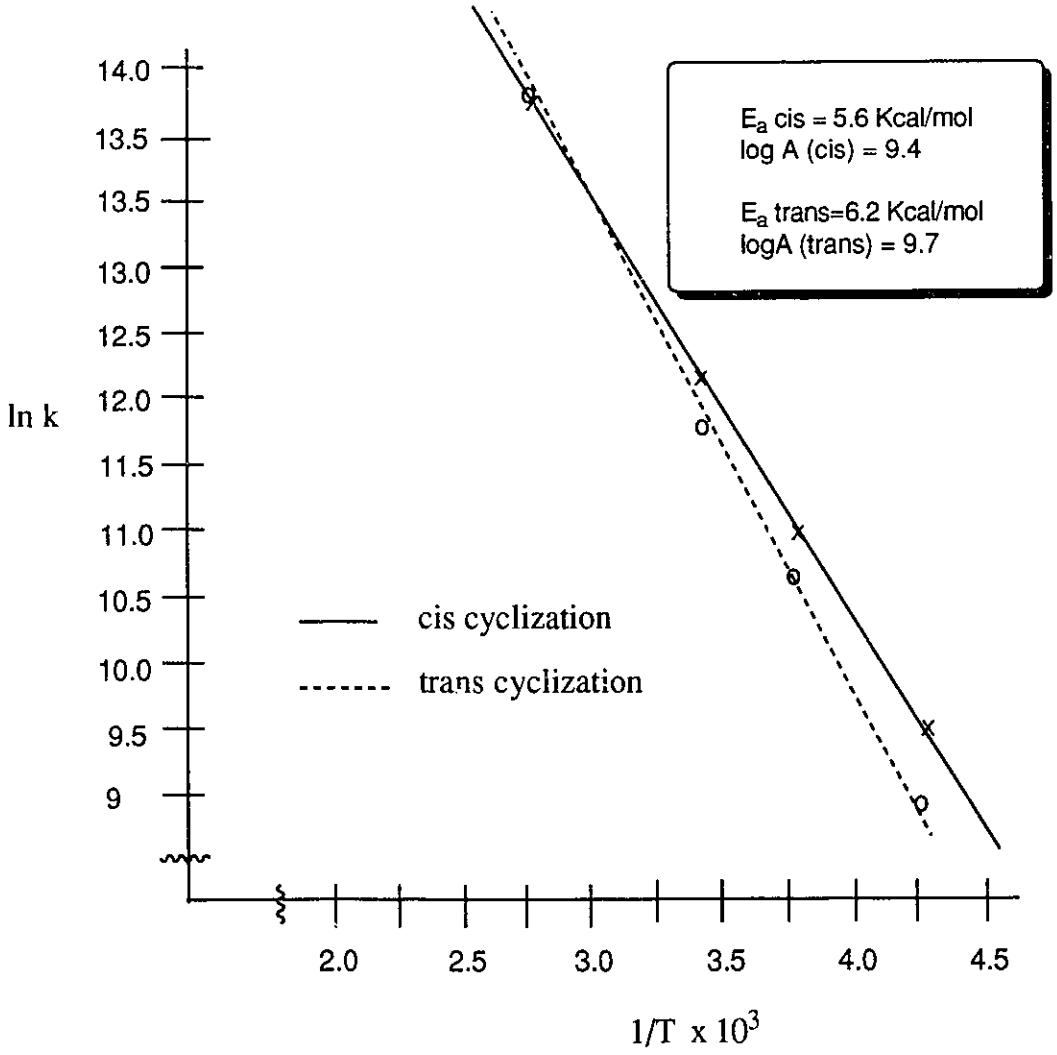
to calculate the activation energies for both the *cis* and *trans* cyclizations. The following Table enumerates the ln k and 1/T values obtained from Table 20 and following this is a plot of lnk vs. 1/T.

**Table 21: List of lnk and 1/T Values from the Competition Experiments**

| Entry | Temp °C | 1/T | ln $k_{cis}$ | ln $k_{trans}$ |
|---|---|---|---|---|
| 1 | 80 | $2.83 \times 10^{-3}$ | 13.75 | 13.75 |
| 2 | 21 | $3.40 \times 10^{-3}$ | 12.10 | 11.85 |
| 3 | –10 | $3.80 \times 10^{-3}$ | 10.99 | 10.67 |
| 4 | –42 | $4.33 \times 10^{-3}$ | 9.54 | 9.06 |

As can be seen from this graph, the points for the *cis* and *trans* cyclizations do indeed yield straight lines. Using linear regression, the equation for the best fit lines was obtained for both the *cis* and *trans* cyclizations. From the equations of these lines, the activation energies were determined to be $E_a^{cis} = 5.6$ kcal/mol and $E_a^{trans} = 6.2$ kcal/mol. For comparison, the activation barriers for the 2° radical *cis* and *trans* 5–hexenyl type cyclizations ($H_2C{=}CH(CH_2)_3CH{\bullet}CH_3$) are 6.5 and 7.4 kcal/mol respectively. Therefore, *hydrazone reactions have lower activation barriers than the corresponding alkene reactions*. This can also be seen qualitatively from the results of Table 19 where the chemoselectivity of the radical cyclization onto the *N,N*–diphenylhydrazone over the 5–exo alkene cyclization increased with decreasing temperature indicating a kinetic preference for the hydrazone cyclization. The log A values were also determined and found to be log A (*trans*) = 9.7 and log A (*cis*) = 9.4.

**Figure 15: Plot of lnk vs. 1/T for the 6-Exo Hydrazone Cyclizations**

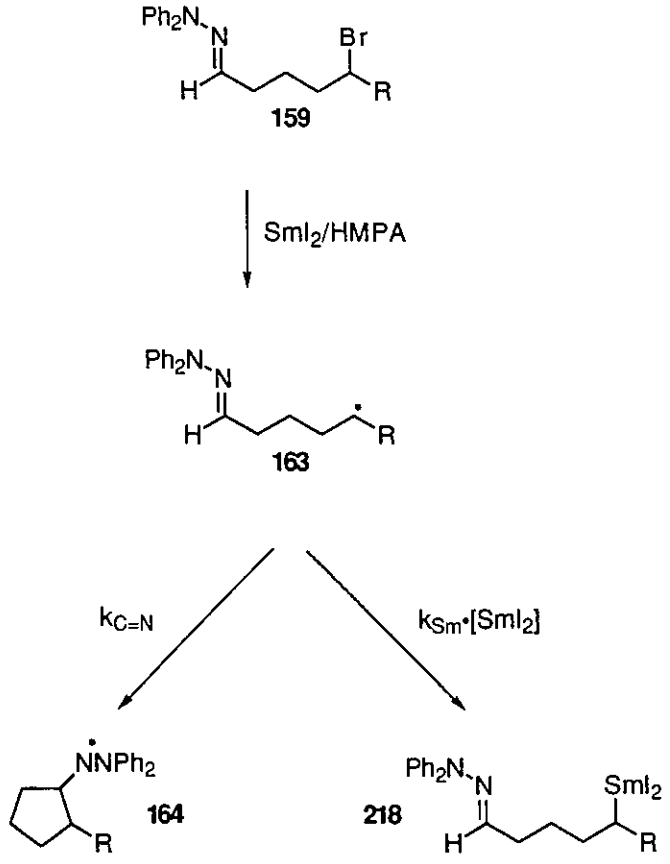



## Radical Versus Anionic $SmI_2$/HMPA Mediated Hydrazone Cyclizations

Having established approximate rate constants for the 5 and 6–exo radical cyclizations onto the *N,N*–diphenylhydrazones, we are now in a position to take a closer look at the mechanism of the $SmI_2$/HMPA reactions. The original mechanistic question

was whether organosamarium intermediates were involved in the cyclization onto the hydrazones as shown in Scheme 85 below.

**Scheme 85: Radical or Anionic Hydrazone Cyclization**




The competing pathways for the intermediate radical **163** are cyclization with a rate constant of $k_{C=N}$ or bimolecular reduction involving electron transfer from $SmI_2$ to generate the organosamarium species **218**. The rate of this reaction is $k_{Sm\bullet}[SmI_2]$. The value of $k_{Sm}$ is available from Curran's work. Before an analysis of the kinetics of this system can be given, an important experimental point must be considered. In our study, a THF solution of the $SmI_2$ reagent was *added* dropwise *to* a THF solution of the hydrazone and HMPA. In Curran's report, the substrate was added to a solution of

$SmI_2$/HMPA. Because of this difference, the kinetic analysis is not straightforward, especially given that the reduction potential of $SmI_2$ is a function of the number of equivalents of HMPA present. In our experiments, both the ratio of $SmI_2$/HMPA and the concentration of $SmI_2$ vary with time. A TLC experiment performed as the samarium iodide was being delivered dropwise to the halohydrazone solution indicated that some hydrazine product was generated. This suggests that the $SmI_2$ reagent was partially being consumed as its added to the reaction flask.

At the beginning of the 5–exo cyclization experiment, during the addition of $SmI_2$ the concentration of $SmI_2$ is low although the ratio of HMPA/$SmI_2$ is quite high. The value of $k_{Sm}$ at these ratios is not available so we will consider the largest value reported by Curran which yielded a 1:1 mixture of cyclization and reduction in the 5–hexenyl system. Given that the hydrazone radical cyclization is approximately 200 times faster than the 5–hexenyl cyclization and that the concentration of $SmI_2$ is low, the bimolecular formation of the organosamarium species is expected to be much slower than radical cyclization. Thus during the addition of the $SmI_2$ solution the reaction should proceed by a radical mechanism. After the addition of the $SmI_2$ solution is complete, the ratio of HMPA/$SmI_2$ is approximately 2.5:1 and the concentration of $SmI_2$ is about 0.05 M. Under these conditions Hasegawa and Curran report the ratio of 5–hexenyl radical cyclization to reduction by a second electron transfer from $SmI_2$ to be approximately 95:5 respectively. In our system then, the remaining substrate that did not react with $SmI_2$ during its addition should cyclize via a radical mechanism. Using a similar argument, given that the 6–exo hydrazone cyclization was found to be faster than the 5–hexenyl radical cyclization by a factor of 2.5, it is most likely that this reaction also proceeds via a radical mechanism.

The situation is actually easier to analyze for the low temperature experiments (–42 °C and –78 °C) since in these cases TLC analysis of the reaction mixture taken immediately *after* the addition of $SmI_2$ was complete (with care not to let the capillary

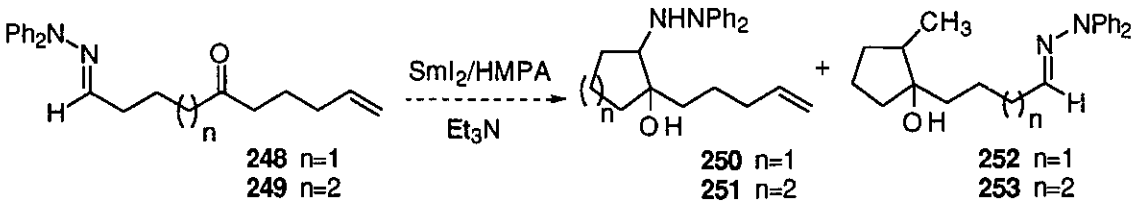
warm up) only showed trace amounts of the cyclized hydrazine. At this time the ratio of HMPA/$SmI_2$ is approximately 2.5 with a $SmI_2$ concentration of about 0.05 M. The value of $k_{Sm}$ at these temperatures has not been reported. However, the room temperature values (95:5; cyclized:reduced) serve as useful approximations. Under these conditions the 5 and 6–exo hydrazone cyclizations will most likely occur through a radical mechanism since they were both faster than the corresponding 5–hexenyl cyclizations.

It should also be noted that the value of $k_{sm}$ reported by Hasegawa and Curran is for the reduction of a primary radical with $SmI_2$. It is likely that the value of $k_{Sm}$ will be lower for the reduction of a secondary radical. For example, the reduction of a primary radical with $Bu_3SnH$ is faster than the reduction of a secondary radical. Also, as we have seen above, primary radicals cyclize faster than secondary radicals. If in fact the value of $k_{Sm}$ is found to be lower for the reduction of a 2° radical then this will strengthen our argument that the hydrazone cyclizations proceed by a radical mechanism since this will allow more time for the cyclization reaction to occur. Thus, the rate constant for the 5- and 6-exo alkyl radical cyclizations onto *N,N*-diphenylhydrazones has been shown to be fast radical reactions.

## Ketyl Radical Cyclizations

Having established approximate rate constants for the alkyl radical cyclizations and provided evidence that the $SmI_2$/HMPA reactions proceed by a radical mechanism we were interested in examining the ketyl radical[110] cyclizations to see if they showed a similar reactivity profile. The proposed systems are shown below in Scheme 86.

**Scheme 86: Proposed Competitive Ketyl–Hydrazone Cyclizations**



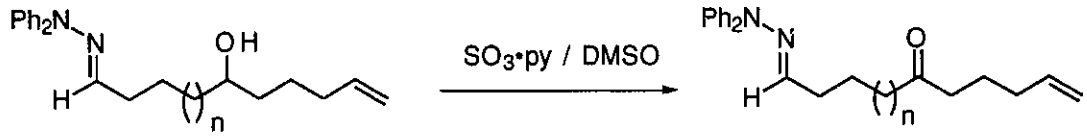

**248** n=1
**249** n=2

**250** n=1
**251** n=2

**252** n=1
**253** n=2

The required starting materials were readily prepared by $SO_3$•py/DMSO oxidation of the previously described secondary alcohols as shown in Scheme 87.

**Scheme 87: Preparation of Carbonyl Substrates for Competition Experiments**

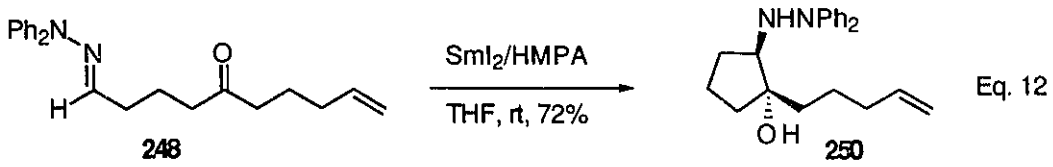



**254** n=1
**255** n=2

**248** n=1 72 %
**249** n=2 68 %

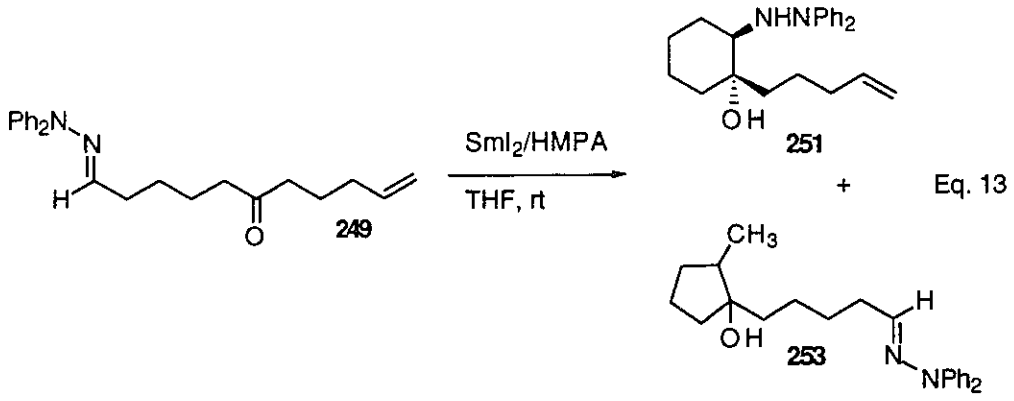
When ketone **248** was subjected to the standard $SmI_2$/HMPA reaction conditions, TLC analysis of the resulting crude reaction mixture revealed that the starting hydrazone had been completely consumed with the formation of a single new, more polar compound. Inspection of the $^1H$ nmr spectrum of the crude reaction mixture revealed

that the hydrazone functional group had been consumed and the alkene double bond remained unaffected. The resulting alcohol **250** was isolated in 72% yield as summarized in Equation 12 below. Interestingly, this reaction also displayed excellent diastereoselectivity as only one isomer could be detected in the $^{1}H$ nmr spectrum of the crude reaction mixture. The $^{13}C$ nmr spectrum of the purified alcohol did not show any evidence for the presence of the other diastereomer. The relative stereochemistry was assigned with the hydroxy group *trans* to the hydrazine based on the ketyl radical cyclization results presented in the previous chapter. This result demonstrates that both alkyl and ketyl radicals cyclize considerable faster onto *N,N*–diphenylhydrazones than onto alkenes.




Eq. 12

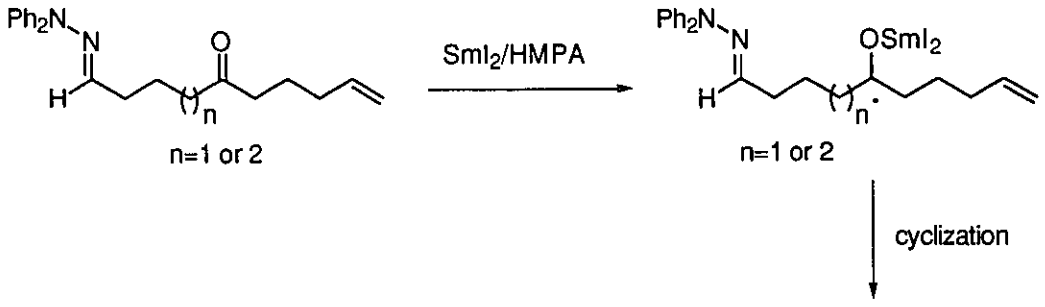
Turning to ketone **249**, generation of the ketyl radical can be followed by a 5–exo cyclization onto the alkene or a 6–exo cyclization onto the hydrazone functionality. When this ketone was subjected to the standard $SmI_2$/HMPA reaction conditions at room temperature, a mixture of alkene and hydrazone cyclized material was observed. As with the alkyl radical 6, 5 competition experiment, hydrazone cyclization dominated over the alkene by a ratio of approximately 4.5:1 as shown in Equation 13.




The major product **251** from the reaction was isolated and appears to be a single diastereomer according to the $^{13}C$ nmr spectrum. The relative stereochemistry was assigned with the hydroxy group *trans* to the hydrazine by analogy to our previous ketone cyclization reactions of Chapter Two. Thus both the 5 and 6–exo ketyl radical cyclizations parallel the alkyl radical systems and show high chemoselectivity towards cyclization onto the hydrazone over the alkene.

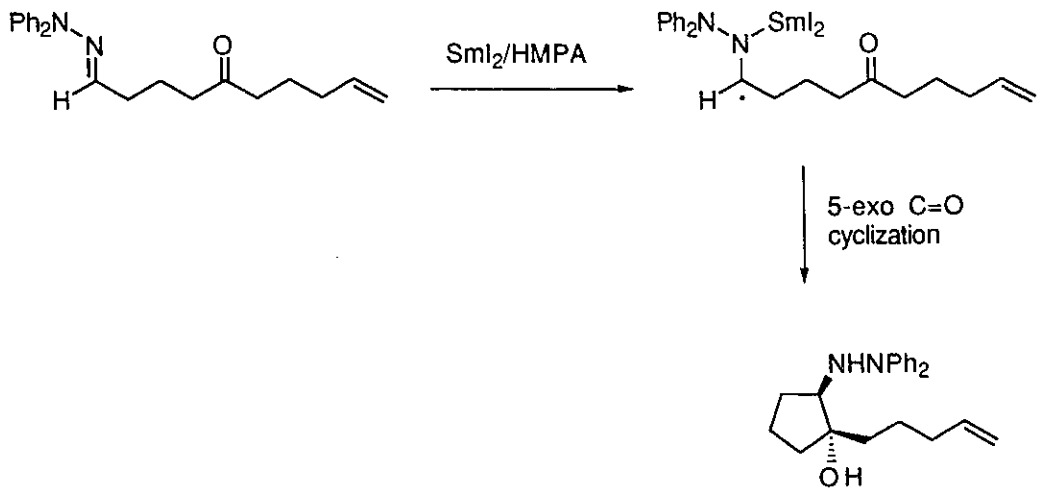
In the analysis presented above, it was assumed that the first step in the cyclization was the formation of the Sm(III) ketyl radical as shown in Scheme 88 below.

**Scheme 88: Proposed Mechanism of the Ketone–$SmI_2$ Ketone Reactions**

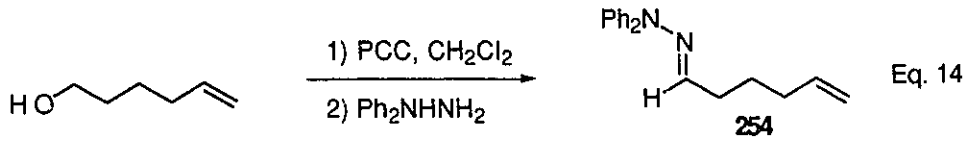



However, it is also possible that electron transfer occurs to the *imine* of the hydrazone followed by cyclization onto the ketone as shown in Scheme 89.

**Scheme 89: Alternative Mechanism for the Ketyl Cyclization Reactions**



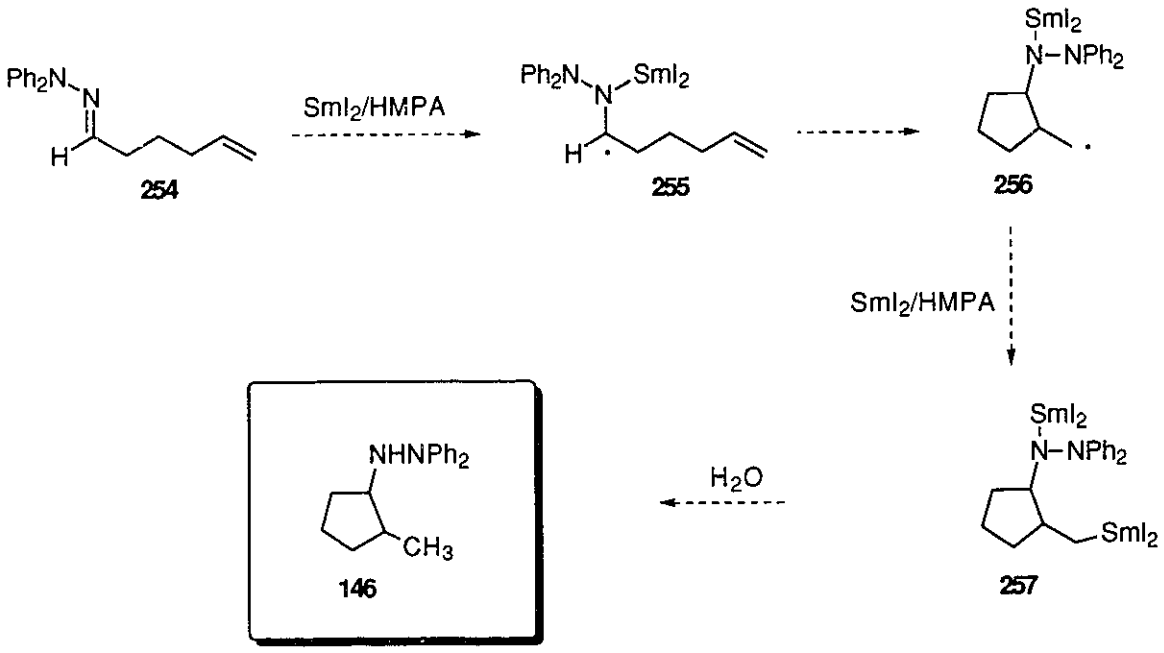

If the reaction proceeds by this mechanism, then the level of chemoselectivity observed in the 5–exo reaction (substrate **248**) is not surprising since only a 5–exo cyclization onto the ketone would be available to this system. To examine this possibility, and ensure that the imine bond was not participating in the $SmI_2$ reaction, hydrazone **254** was prepared as shown in equation 14 below.




Eq. 14

This alkene–hydrazone substrate was then subjected to our standard $SmI_2$/HMPA reaction conditions. If electron transfer to the hydrazone functionality does in fact occur, as shown below, then the resulting α–hydrazine radical would be expected to undergo a 5–exo cyclization onto the alkene to yield the cyclopentyl hydrazine, (**255** to **146** in scheme 90 below) a compound which we have prepared previously by cyclization of the corresponding alkyl radical onto the hydrazone (Scheme 44). Thus an authentic sample was available for comparison.

**Scheme 90: Alternative Mechanism for the Carbonyl–$SmI_2$ Cyclizations**



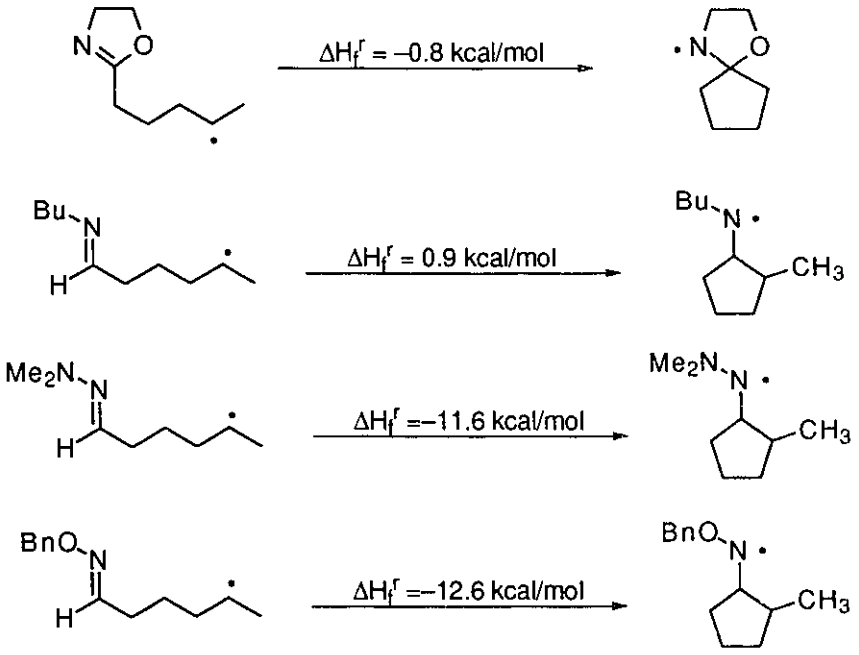

In the event, when the starting hydrazone **254** was subjected to the $SmI_2$/HMPA reaction conditions for 16 hours at room temperature, TLC analysis with an authentic sample of the cyclic hydrazine revealed that the starting hydrazone remained unchanged with no evidence of the cyclic hydrazine **146** being formed. Given the complete absence of cyclization from this control experiment, it is reasonable to conclude that the observed alcohols in the ketone–$SmI_2$ cyclizations involve ketyl radical intermediates which cyclize with high chemo and diastereoselectivity.

## Calculations of $\Delta H_f^r$ for Cyclizations onto C=N Systems

There is thus a dramatic difference in the reactivity of oxazolines and hydrazone functional groups in radical cyclizations. In our studies, we found that oxazolines were unreactive while hydrazones proved to be exceptional radical acceptors. To further

explore this reactivity difference, we performed calculations at the AM1-UHF level.[119] The results of these calculations on the heat of enthalpy for radical cyclizations onto various C=N containing systems are shown in Table 22.

**Table 22: Heat of Enthalpy Calculations for Radical Cyclizations onto C=N Containing Systems.**

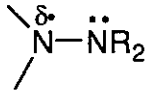



As shown in the first entry, radical cyclization in the oxazoline system was found to be approximately thermoneutral (–0.8 kcal/mol). This was somewhat surprising since the corresponding alkene cyclizations are approximately 10 kcal/mol exothermic.[120] The reason for this may be, as suggested earlier, that the C=N bond is believed to be ca. 10 kcal/mol stronger than the C=C bond.[121]

Radical cyclization onto a simple butyl imine was also calculated to be approximately thermoneutral (0.9 kcal/mole). Dimethyl hydrazones are completely different. (The dimethyl instead of diphenyl derivatives were examined for ease of calculations.) In this case, the reaction was found to be strongly exothermic (-11.6

kcal/mol). Similar exothermicity was noted for the oxime ether substrate shown in the last entry of Table 22. These calculations demonstrate the beneficial influence of $R_2N$ and RO substituents on reaction exothermicity for radical cyclizations. In fact, the calculations suggest that the hydrazone cyclizations are as exothermic as the corresponding alkene reactions.

The second nitrogen present in the hydrazone system is likely involved in a 2-center, 3-electron bond with the developing radical on the nitrogen of the imine, thus the nitrogen radical is likely shared between the two nitrogens.[122]



This three electron bond will help stabilize the developing nitrogen radical and this may be the reason for the increased exothermicity of hydrazones and oxime ethers compared to simple imines.

The high exothermicity of the hydrazone and oxime ether cyclizations implies that the reactions proceed via an early transition state. It is generally true that product stabilities are not as important at the transition states of exothermic reactions compared to endothermic reactions.[123] Nevertheless, there will be *some* radical character on nitrogen at the transition state of the hydrazone cyclization. The $R_2N$ substituent would then be expected to interact with this radical and help stabilize the system. This may explain why the 5- and 6-exo hydrazone cyclizations were found to have lower activation barriers than the corresponding alkene cyclizations.

## Conclusions

In conclusion, we have shown that the cyclization of alkyl and ketyl radicals onto *N,N*-diphenylhydrazones are extremely fast reactions. The intramolecular clock we designed to measure the rate constant for the 5- and 6- exo cyclizations of alkyl radicals onto hydrazones employed a competition between these reactions and a 5-hexenyl cyclization. In fact, the 5-hexenyl cyclization was too slow to measure the 5-exo hydrazone cyclization. It did, however, permit the determination of the 6-exo rate constant which we found to be $k_{cis} = 1.8 \times 10^5\ s^{-1}$ and $k_{trans} = 1.4 \times 10^5\ s^{-1}$ at room temperature. At 80 °C this rate was $k_{cis} = 9.4 \times 10^5\ s^{-1}$ and $k_{trans} = 9.4 \times 10^5\ s^{-1}$. Since we were able to measure the rate of cyclization at various temperatures, we could calculate the activation energy for the 6-exo cyclization, which was found to be: $E^a_{cis}$ = 5.6 kcal/mole and $E^a_{trans}$ = 6.2 kcal/mol. The corresponding activation energy for the 5-hexenyl cyclization is $E^a_{cis}$ = 6.5 kcal/mole and $E^a_{trans}$ = 7.5 kcal/mol, thus demonstrating a kinetic preference for cyclization onto the hydrazone functionality.

The intramolecular clock was too slow to measure the 5-exo hydrazone cyclization, although we were able to determine the rate constant using an intermolecular clock. The cyclization of a simple bromohydrazone was performed in a 2.4 M tin hydride solution at 80 °C and the ratio of cyclization versus quenching was found to be approximately 18.2:1. From this ratio we determined that the rate constant for the 5-exo cyclization of an alkyl radical onto a hydrazone was $k_{cis} = 1.1 \times 10^8\ s^{-1}$ and $k_{trans} = 4.6 \times 10^7\ s^{-1}$. This is 210 times faster than the 5-hexenyl cyclization.

Calculations done at the AM1-UHF level show that the cyclization onto a dimethylhydrazone is quite exothermic (-11.6 kcal/mol), and comparable to the corresponding oxime ether cyclizations. These calculations also demonstrated that the related oxazoline and imine cyclizations are thermoneutral.

# Chapter Four: Experimental

## General Considerations

Melting points were determined in capillary tubes with a Thomas-Hoover Unit-Melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bomem MB 100 FTIR spectrometer. Proton magnetic resonance spectra ($^1$H NMR) were measured at 200 MHz with a Varian Gemini spectrometer, at 300 MHz with a Varian XL-300 spectrometer or at 500 MHz with a Bruker AMX500 in deuterochloroform unless otherwise stated. Carbon magnetic resonance spectra ($^{13}$C NMR) were measured at 50 MHz (Varian Gemini), at 75 MHz (Varian XL-300) or at 125 MHz (Bruker). The residual signal was used as an internal lock; $CDCl_3$, $\delta$ 7.24 ppm; $^{13}$C: $\delta$ 77.0 ppm; Chemical shifts are reported in ppm downfield from tetramethylsilane ($\delta$ scale). The multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad), coupling constants and number of protons are indicated in parentheses. Mass spectra (MS) were determined on a V.G. micromass 7070 HS instrument using an ionization energy of 70 eV. Elemental analyses were conducted by M-H-W Laboratories, Phoenix, AZ, USA. Analytical thin layer chromatography (TLC) employed commercial aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 $F_{254}$ (E. Merck). Flash column chromatography using E. Merck silica gel 60 (70-230 or 230-400 mesh) was employed for all column chromatography. The purity of all title compounds was judged to be >95% as determined by $^1$H NMR and $^{13}$C NMR analyses.

Petroleum ether refers to the hydrocarbon fraction with boiling range 30-60 °C. Anhydrous hexamethylphosphoramide (HMPA) was obtained by distillation from calcium hydride and stored over 4A molecular sieves. Anhydrous THF was obtained from potassium/benzophenone, anhydrous diethyl ether was obtained from sodium/benzophenone. Solutions in organic solvents were dried over anhydrous sodium

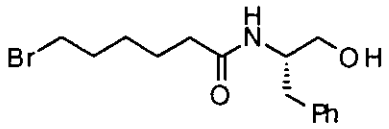
sulfate and stripped of the solvent with a Büchi rotatory evaporator connected to a water aspirator. Unless otherwise stated all reactions were conducted under an atmosphere of dry nitrogen in flame dried flasks equipped with a magnetic stirring bar and a rubber septum.

All commercial starting materials were purchased from Aldrich Chemical Company unless otherwise stated. L-phenylalaninol was prepared from L-phenylalanine by the literature procedure reported by Meyer's.[66] *N,N*-diphenylhydrazine was obtained by treating the commercially available $Ph_2NNH_2$·HCl with 1.0 equivalents of NaOMe in MeOH. The resulting solution was concentrated and then filtered through a sintered glass funnel with a pad of silica gel eluting with 100% EtOAc. The resulting *N,N*-diphenylhydrazine was used without further purification.

*General Procedure for $Bu_3SnH$/AIBN Reactions*

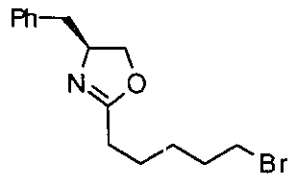
Into a dry round bottom flask equipped with a reflux condenser under argon was added the required substrate followed by freshly distilled benzene. To this solution was then added $Bu_3SnH$ (1.0-1.5 equiv.) and AIBN (0.1-0.3 equiv.). Argon was then bubbled through the solution for approximately 15 minutes. After this time the solution was heated at reflux for several hours. After cooling to room temperature, the solvent was removed and the resulting material was purified by flash chromatography on silica gel.

**Preparation of (*N*-(1-benzyl-2-hydroxyethyl))-6-bromohexamide (116)**



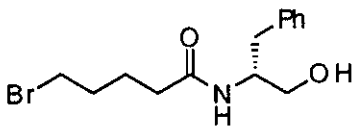

6-Bromohexanoic acid (1.67 g, 8.59 mmol) was placed in a dry round bottom flask (100 mL) and dissolved in benzene (50 mL). Oxalyl chloride (3.4 mL, 38.6 mmol) was added and the reaction mixture stirred at room temperature overnight. The solvent was removed and the resulting oil was dissolved in dichloromethane (30 mL) and cooled to -10 °C at which time L-phenylalaninol (1.31 g, 8.60 mmol) was added as a dichloromethane solution (20 mL) followed by $Et_3N$ (2.4 mL, 17.18 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the resulting material purified by flash chromatography on silica gel eluting with 100% ethyl acetate. Concentration of the appropriate fractions yielded 2.16 g (73%) of the title compound as a white solid; m.p. 58-59 °C; $[\alpha]_D^{21}$=-17.5 ° (c 3.20, $CHCl_3$); IR ($CHCl_3$, $cm^{-1}$) 3360 (br), 1674, 1387; $^1H$ NMR (200 MHz, $CDCl_3$) δ7.24-7.06 (m, 5H), 5.85 (br s, NH, 1H),4.11-4.03 (m, 1H), 3.60-3.51 (m, 2H), 3.25 (t, *J* = 6.7 Hz, 2H), 3.08 (br s, 1H), 2.79-2.72 (m, 2H), 2.04 (t, *J* = 7.9 Hz, 2H), 1.78-1.63 (m, 2H), 1.54-1.32 (m, 2H), 1.29-1.20 (m, 2H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 173.4, 137.6, 129.1, 128.6, 126.6, 64.0, 52.7, 36.9, 36.4, 33.6, 32.3, 27.5, 24.7 ppm; LRMS found 327.1 ($(M-H)^+$, 0.4%)

**Preparation of 4-Benzyl-2-(5-bromopentyl) Oxazoline (117)**



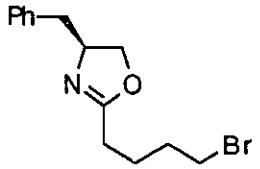

Amide **116** (363.9 mg, 1.05 mmol) was placed in a dry round bottom (100 mL) and treated with THF (2.1 mL), followed by $PPh_3$ (314.2 mg, 1.20 mmol) and cooled to 0 °C. DEAD was added dropwise to this mixture and the resulting faint yellow solution was allowed to stir at room temperature for overnight. At this time, the solvent was removed and the resulting material was purified by flash chromatography on silica gel eluting with 20% acetone in petroleum ether. Concentration of the appropriate fractions yielded 251.8 mg (73%) of the title compound as a clear colourless oil; $[\alpha]_D^{21}$=-39.6 ° (c 1.45, $CHCl_3$); IR (neat, $cm^{-1}$) 2912, 1665, 1456, 1375; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.31-7.08 (m, 5H), 4.42-4.27 (m 1H), 4.18-4.07 (m, 1H), 3.95-3.88 (m, 1H), 3.37 (t $J$ = 6.5 Hz, 2H), 3.06 (dd $J_1$ = 13.0 $J_2$ = 5.8 Hz, 1H), 2.61 (dd, $J_1$ = 13.0, $J_2$ = 9.1 Hz, 1H), 2.22 (t, $J$ = 7.0 Hz, 2H), 1.91-1.83 (m, 2H), 1.70-1.46 (m, 4H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 167.5, 137.6, 129.1, 128.3, 126.2, 71.2, 66.9, 41.5, 33.4, 32.2, 27.6, 27.5, 24.9 ppm;

**Preparation of (*N*-(1-Benzyl-2-hydroxyethyl))-5-bromopentamide (122)**



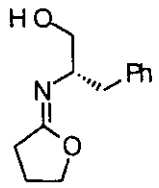
Following the general procedure for the preparation of amide **117**, 5-bromovaleric acid (5.02 g, 27.74 mmol) was treated with benzene (100 mL) and oxalyl chloride (9.7 mL, 110.9 mmol). The resulting acid chloride was then treated with dichloromethane (100 mL), the β-amino alcohol L-phenylalaninol (4.202 g, 27.4 mmol) and $Et_3N$ (8.0 mL, 57.03 mmol). Work up and purification yielded 6.16 g (71%) of the title compound as a viscous oil; IR ($CHCl_3$, $cm^{-1}$) 2942, 1654, 1513; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.31-7.16 (m, 5H), 5.94 (br d, $J$ = 7.7 Hz, 1H), 4.20-4.09 (m, 1H), 3.67-3.52 (m, 2H), 3.45 (t, $J$ = 6.1 Hz, 2H), 2.93-2.73 (m, 2H), 2.16-2.10 (m, 2H), 1.72-1.66 (m, 5H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 172.9, 137.6, 129.1, 128.5, 126.6, 63.9, 52.6, 36.9, 35.5, 33.2, 31.7, 24.1 ppm.

**Attempted Preparation of 4-Benzyl-2-(5-bromopentyl) Oxazoline (120)**



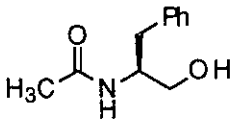

Following the procedure for the synthesis of oxazoline **117**, amide **122** (699.9 mg, 2.23 mmol) was treated with THF (4.5 mL), $PPh_3$ (640.1 mg, 2.41 mmol) followed lastly by DEAD (0.4 mL, 2.41 mmol). After stirring at room temperature for approximately for 3 hr the solvent was removed and the resulting oil was passed through a plug of silica gel eluting with 20% acetone in petroleum ether. The expected oxazoline was found to be unstable and decomposed several hours after isolation.

**Attempted Preparation of (*N*-(1-Benzyl-2-hydroxyethyl))-4-bromo-pentamide (127)**



Following the general procedure for the preparation of amide **117**, 4-bromobutyric acid (4.14 g, 24.8 mmol) was treated with benzene (20 mL) and oxalyl chloride (4.3 mL, 49.6 mmol). The resulting crude acid chloride was then treated with dichloromethane (50 mL), L-phenylalaninol (2.46 g, 16.32 mmol) and $Et_3N$ (6.5 mL, 48.96 mmol). Work up and purification yielded 2.07 g (58%) of a clear colourless oil; $[\alpha]_D^{21}$=-33.8 ° (c 1.71, $CHCl_3$); IR (neat, $cm^{-1}$) 3320, 2929, 1649, 1549, 1461; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.31-7.14 (m, 5H), 4.39-4.28 (m, 1H), 4.18 (m, 1H), 4.01 (br s, 1H), 3.99-3.91 (m, 1H), 3.68 (t, $J$ = 5.6 Hz, 2H), 3.03 (dd, $J_1$ = 13.7, $J_2$ = 5.0 Hz, 1H), 2.63 (dd, $J_1$ = 13.7, $J_2$ = 8.1 Hz, 1H), 2.41-2.33 (m, 2H), 1.93-1.81 (m, 2H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 168.6, 137.3, 128.9, 128.2, 126.2, 71.4, 66.4, 61.2, 41.3, 28.3, 25.0 ppm; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81. Found: C, 71.12; H, 7.53.

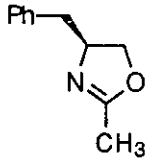
**Preparation of *N*-(1-Benzyl-2-hydroxyethyl) Acetamide 129**



Following the general procedure, β-amino alcohol **115** (1.46 g, 9.30 mmol) was treated with THF (10 mL), dichloromethane (10 mL), acetyl chloride (0.66 mL, 9.30 mmol) and $Et_3N$ (2.0 mL, 13.95 mmol). Work up and purification by flash

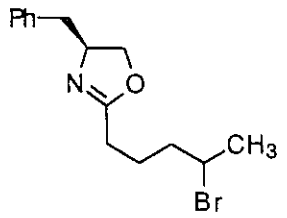
chromatography eluting with 15% isopropyl alcohol in ethyl acetate yielded 1.48 g (74%) of the title compound as a white solid; m.p. 100-102 °C; $[\alpha]_D^{21}$=-24.3 ° (c 0.74, $CHCl_3$); IR (Nujol, $cm^{-1}$) 1640, 1570, 1458; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.30-7.12 (m, 5H), 6.15 (br d, $J$ = 8.3 Hz, 1H), 4.18-4.05 (m, 1H), 3.65-3.42 (m, 3H), 2.84 (d, $J$ = 7.3 Hz, 2H), 1.90 (s, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 170.9, 137.6, 129.2, 128.6, 126.6, 63.8, 52.9, 36.9, 23.3 ppm.

**Preparation of 4-Benzyl-2-methyl Oxazoline (130)**



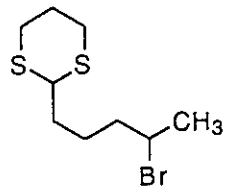

Following the general oxazoline procedure, amide **129** (312.2 mg, 1.39 mmol) was treated with THF (5 mL), $PPh_3$ (440.0 mg, 1.68 mmol) and DEAD (0.28 mL, 1.68 mmol). Work up and purification yielded 208.6 mg (73%) of the title compound as a clear colourless oil; $[\alpha]_D^{21}$=-19.9 ° (c 2.13, $CHCl_3$) IR (neat, $cm^{-1}$) 2942, 1654, 1513; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.23-7.12 (m, 5H), 4.32-4.22 (m, 1H), 4.09-4.05 (m, 1H), 3.90-3.82 (m, 1H), 3.02 (dd, $J_1$ = 13.9, $J_2$ =5.3 Hz, 1H), 2.58 (dd, $J_1$ = 13.9, $J_2$ = 8.4 Hz, 1H), 1.90 (s, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 164.7, 137.8, 128.9, 128.3, 126.2, 71.6, 67.2, 41.5, 13.7 ppm; HRMS calcd. for $C_{11}H_{13}NO$ ($M^+$): 175.0994. Found 175.1012.

**Preparation of 4-Benzyl-2-(4-bromopentyl) Oxazoline (131)**




Oxazoline **130** (172.7 mg, 0.99 mmol) was placed in a dry round bottom flask (25 mL) and treated with THF (3 mL) and cooled to -78 °C. *n*–BuLi (0.47 mL of a 2.5 M solution, 1.18 mmol) was added at -78 °C and the resulting solution was allowed to stir for 45 minutes. After this time 1,3-dibromobutane (0.14 mL, 1.18 mmol) was added and the resulting mixture was stirred at 0 °C for an additional 45 minutes. The reaction was quenched by the addition of brine and the resulting mixture poured into a separatory funnel containing brine and ether. The aqueous layer was extracted with ether (3 x 30 mL), dried and concentrated. Purification by flash chromatography eluting with 20% acetone in petroleum ether to yield 173. 4 mg (57%) of the title compound as a clear colourless oil; $^{1}$H NMR (200 MHz, $CDCl_3$) δ 7.30-7.15 (m, 5H), 4.39-4.26 (m, 1H), 4.17-4.01 (m, 2H), 3.95-3.88 (m, 1H), 3.05 (dd, $J_1$ = 13.8, $J_2$ = 5.6 Hz, 1H), 2.62 (dd, $J_1$ = 13.8, $J_2$ = 8.4 Hz, 1H), 2.29-2.22 (m, 2H), 1.81-1.74 (m, 4H), 1.67 (d, $J$ = 6.7 Hz, 3H) ppm; $^{13}$C NMR (50 MHz, $CDCl_3$) δ 167.5, 137.6, 129.2, 128.4, 126.4, 71.4, 66.9, 50.7, 41.6, 40.3, 27.2, 26.3, 24.1 ppm.

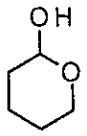
**Preparation of 2-(4-Bromopentyl)-1,3-dithiane (144)**




Dithiane (5.28 g, 43.97 mmol) was placed in a round bottom flask (250 mL) and dissolved in THF (50.0 mL). The resulting solution was cooled to –10 °C and treated with *n*–BuLi (21.1 mL of a 2.5 M solution, 53 mmol) and allowed to stirred at –10 °C for 45 minutes. To this solution at –10 °C was added 1, 4–dibromopentane (6.0 mL, 44.02 mmol) which was allowed to stir at –10 °C for an 2 additional hours. The reaction was quenched by the addition of brine (10 mL) and the resulting mixture was poured into separatory funnel containing ethyl acetate (100 mL) and brine (50 mL). The aqueous layer was extracted with ethyl acetate (3x150 mL), dried and concentrated. The resulting oil was purified by flash chromatography on silica gel eluting with 1.5% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 8.30 g (70%) of the title compound as a light yellow oil; IR (neat, $cm^{-1}$) 2914, 1435, 1378, 1275; $^1H$ NMR (200 MHz, $CDCl_3$) δ 4.10-3.96 (m, 2H), 2.83-2.75 (m, 4H), 2.10-2.04 (m, 1H), 1.91-1.63 (m, 7H), 1.71 (d, $J$ = 7.2 Hz, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 50.8, 47.0, 40.2, 34.4, 30.1, 26.1, 25.7, 24.7 ppm; HRMS calcd. for $C_9H_{17}S_2Br$ ($M^+$) : 267.9950. Found 267.9939.

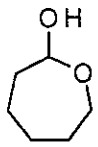
Hydrolysis of the dithiane was affected with $NBS/H_2O/H_3CCN$ as described in reference 71 which gave the corresponding aldehyde which was condensed *in situ* with *N,N*-diphenylhydrazine. The resulting hydrazone was obtained in 35% yield over these two steps, and its spectral data is presented in the next section.

**Preparation of δ-Valerolactol (151)**[124]



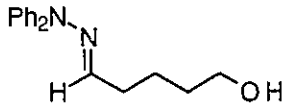

δ-Valerolactone (6.0 mL, 6.5 g, 64.6 mmol) was added to a flame dried flask (500 mL) containing freshly distilled toluene (100 mL) under argon. The solution was cooled to -78°C and DIBAL in toluene (44.5 mL, 1.5 M solution, 66.7 mmol, Aldrich) was added and the reaction mixture allowed to stir at this temperature for 4 hours. The reaction was quenched at -78 °C with methanol until gas evolution ceased. The solution was warmed to room temperature (21 °C) and saturated aqueous sodium potassium tartrate solution (100 mL) was added. This mixture was poured into a separatory funnel containing water and ethyl acetate. The aqueous layer was extracted 3 times with ethyl acetate, dried over anhydrous sodium sulfate and concentrated. The resulting oil was further purified by passage through a sintered glass funnel filled with silica gel and eluted with 50% ethyl acetate/petroleum ether under aspirator vacuum to afford 4.9 g (75%) of **151** as a faint yellow oil; IR (neat, $cm^{-1}$) 3375, 2912, 1449; $^1H$ NMR (200 MHz, $CDCl_3$) δ 4.80-4.90 (m, 1H), 4.70-4.50 (br s, 1H), 3.95-3.88 (m, 1H), 3.52-3.38 (m, 1H), 1.85-1.62 (m, 2H), 1.56.132 (m, 4H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 94.2, 63.6, 31.7, 25.0, 20.1 ppm;

**Preparation of ε-Caprolactol (152)**[125]



Following the procedure described above for the preparation of lactol **151**, ε-caprolactone (5.0 mL, 5.2 g, 45.3 mmol) in toluene (50 mL) was treated at -78 °C with DIBAL (36.5 mL, 1.5 M solution in toluene, 54.8 mmol). Workup and purification as described gave **152** (4.2 g, 79%); m.p. 82-84 °C; IR (Nujol, $cm^{-1}$) 3409, 2906, 1725, 1458; $^1H$ NMR (200 MHz, $CDCl_3$) δ 9.64 (t, $J$ = 1.6 Hz, 1H), 3.52 (t, $J$ = 6.2 Hz, 2H), 2.37-2.29 (m, 2H), 1.97-1.23 (m, 7H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 202.7, 62.4, 43.8, 32.3, 25.3, 21.7 ppm; HRMS calcd. for $C_6H_{12}O_2$ ($M^+$): 116.0834. Found: 116.0809: Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.20; H, 10.20.

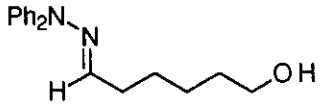
**Preparation of 5-Hydroxypentanal-*N,N*-diphenylhydrazone (153)**



Lactol **151** (2.59 g, 25.4 mmol) in methanol (30 mL) was added to a round bottom flask (100 mL) flame dried and cooled under Ar . To this solution was added dropwise a solution of $Ph_2NNH_2$ (4.65 g in 15 mL of methanol). The reaction mixture was allowed to stir at room temperature overnight. Concentration gave a purple oil which was purified by flash chromatography. The silica gel was deactivated by washing first with a 1% solution of $Et_3N$ added to the eluting solution 30% ethyl acetate/petroleum ether. After packing the column, fresh eluting solvent was used that did not contain $Et_3N$. *(N.B. all hydrazones and hydrazines were purified on silica gel deactivated in this manner.)*

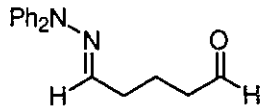
Concentration of the appropriate fractions yielded 5.28 g (78%) of the title alcohol as a faint yellow oil; IR (neat, $cm^{-1}$) 3380, 3044, 2917, 1592, 1492, 1303, 1090, 1066; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.46-7.30 (m, 4H), 7.21-6.99 (m, 6H), 6.52 (t, $J$ = 6.7 Hz, 1H), 3.72-3.58 (m, 2H), 2.42-2.35 (m, 2H), 1.70-1.52 (m, 4H), 1.40 (br s, 1H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.2, 139.6, 129.6, 123.8, 122.2, 62.3, 32.2, 32.0, 23.0 ppm; HRMS calcd. for $C_{17}H_{20}N_2O$ ($M^+$): 268.1571. Found: 268.1569.

**Preparation of 6-Hydroxyhexanal-*N,N*-diphenylhydrazone (154)**



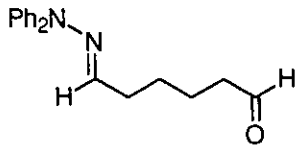

Following the above procedure, lactol **152** (1.0 g, 8.62 mmol) and $Ph_2NNH_2$ (1.40 g, 7.63 mmol) were mixed and yielded, after purification by chromatography, 2.03 g (94%) of the title compound was obtained as a faint grey oil; IR (Nujol, $cm^{-1}$) 3354, 3060, 2932, 2858, 1592, 1493, 1302, 1210, 749, 698; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.38-7.30 (m, 4H), 7.14-7.04 (m, 6H), 6.52 (t, $J$ = 5.3 Hz, 1H), 3.60 (t, $J$ = 6.4 Hz, 2H), 2.32-2.22 (m, 2H), 1.60-1.36 (m, 6H) ppm (O<u>H</u> proton not observed); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.1, 139.8, 129.5, 123.7, 122.2, 62.4, 32.5, 32.3, 26.6, 25.2 ppm; HRMS calcd. for $C_{18}H_{22}N_2O$ ($M^+$): 282.1727. Found: 282.1734; Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.33; H, 8.14; N, 10.01.

**Preparation of Butanal-(*N*,*N*-diphenylhydrazone)-4-carboxaldehyde (155)**



A round bottom flask (100 mL) flame dried under argon was charged with alcohol **153** (3.09 g, 11.5 mmol) along with DMSO (20 mL) and $Et_3N$ (12.9 mL, 92.8 mmol). A $SO_3$•pyridine/DMSO suspension (5.4 g of $SO_3$•pyridine, 34.5 mmol in 5 mL DMSO) was added dropwise to this mixture with stirring. After 30 min at room temperature, TLC analysis indicated the consumption of the alcohol. The resulting mixture was poured into a separatory funnel containing water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were washed with brine, dried and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on deactivated silica gel eluting with 10% ethyl acetate/petroleum ether. Concentration of the appropriate fractions yielded 2.17 g (71%) of the title compound as a faint yellow oil; IR (neat, $cm^{-1}$) 3045, 2896, 1723, 1595, 1491, 1303, 1209, 1069; $^1H$ NMR (200 MHz, $CDCl_3$) δ 9.77 (t, $J$ = 1.5 Hz, 1H), 7.40-7.32 (m, 4H), 7.16-7.04 (m, 6H), 6.49 (t, $J$ = 5.1 Hz, 1H), 2.51 (dt, $J_1$ = 7.3, $J_2$ = 1.5 Hz, 2H), 2.36-2.27 (m, 2H), 1.86 (m, 2H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 202.2, 144.0, 137.9, 129.6, 123.9, 122.2, 43.1, 31.8, 19.2 ppm; HRMS calcd. for $C_{17}H_{18}N_2O$ ($M^+$): 266.1415. Found: 266.1408.

**Preparation of Pentanal-(*N*,*N*-diphenylhydrazone)-5-carboxaldehyde (156)**



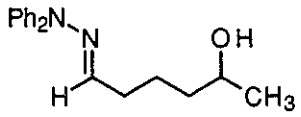
Following the procedure for the preparation of aldehyde **155**, alcohol **154** (67.8 mg, 0.24 mmol) was dissolved in DMSO (3 mL) and $Et_3N$ (0.27 mL). This mixture was then treated with $SO_3$•py (114.0 mg, 0.72 mmol) in DMSO (1 mL). After purification, 55.7 mg (83%) of the title compound was obtained as a light yellow oil. On a larger scale, a slightly lower yield was obtained (78% on a 1 g scale); IR (neat, $cm^{-1}$) 3426, 3046, 2901, 2720, 1725, 1593, 1491, 1302, 1210, 748, 698; $^1H$ NMR (200 MHz, $CDCl_3$) δ 9.74 (t, $J$ = 1.8 Hz, 1H), 7.38-7.30 (m, 4H), 7.14-7.03 (m, 6H), 6.49 (t, $J$ = 5.3 Hz, 1H), 2.44 (dt, $J_1$ = 7.0, $J_2$ = 1.5 Hz, 2H), 2.33-2.23 (m, 2H), 1.70-1.52 (m, 4H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 202.4, 144.2, 138.9, 129.6, 123.9, 122.3, 43.6, 32.3, 26.4, 21.6 ppm; HRMS calcd. for $C_{18}H_{20}N_2O$ ($M^+$): 280.1571. Found: 280.1562.

*General Procedure for Grignard Additions:*

Into a flame dried round bottom flask cooled under Ar was added the appropriate aldehyde along with THF (enough to make a 0.1–0.3M solution) and the resulting solution was cooled to 0 °C. The required Grignard reagent (1-1.1 equiv) was then added at 0 °C. The reaction was allowed to stir at 0 °C and monitored by TLC until starting material was consumed (typically 30 min). The reaction was quenched with saturated ammonium chloride and poured into a separatory funnel containing water and ethyl acetate. The aqueous layer was extracted three times with ethyl acetate and the combined

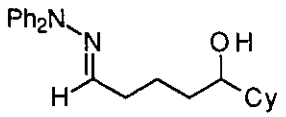
organic layers were washed with brine, dried and concentrated. Further purification of the resulting alcohol was effected with flash chromatography on deactivated silica gel.

**Preparation of 5-Hydroxyhexanal-*N,N*-diphenylhydrazone (157a)**



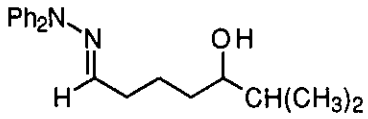

Following the general procedure, aldehyde **155** (239.9 mg, 0.86 mmol) was treated with MeMgBr (0.67 mL, 1.4 M solution in toluene/THF (3/1), 0.94 mmol). After purification, 234.5 mg (92%) of the title compound was isolated as a clear colorless oil; IR (neat, $cm^{-1}$) 3379, 3061, 2925, 1593, 1492, 1303, 1210, 911, 739, 698; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.40-7.24 (m, 4H), 7.15-7.07 (m, 6H), 6.55 (t, $J$ = 5.3 Hz, 1H), 3.81-3.78 (m, 1H), 2.35-2.26 (m, 2H), 1.93 (br s, 1H), 1.64-1.42 (m, 4H), 1.18 (d, $J$ = 6.2 Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.1, 139.6, 129.5, 123.7, 122.2, 67.5, 38.6, 32.4, 23.3, 23.0 ppm; HRMS calcd. for $C_{18}H_{22}N_2O$ ($M^+$): 282.1727. Found: 282.1710; Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.45; H, 7.72; N, 10.04.

**Preparation of 5-Cyclohexyl-5-Hydroxypentanal-*N,N*-diphenylhydrazone (157b)**



Following the general procedure, aldehyde **155** (1.09 g, 4.1 mmol) was treated with CyMgCl (2.2 mL as a 2.0 M solution in diethyl ether, 4.4 mmol) at 0 °C. After purification, 1.03 g (72%) of the title compound was obtained as a clear colorless oil ; IR (neat, $cm^{-1}$) 3997, 2925, 2852, 1593, 1494, 1450, 1302, 1210; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.38-7.29 (m, 4H), 7.20-7.02 (m, 6H), 6.52 (t, $J$ = 5.3 Hz, 1H), 3.35-3.32 (m, 1H), 2.33-2.24 (m, 2H), 1.80-0.93 (m, 16H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.9, 140.5, 130.2, 124.4, 122.9, 76.4, 44.1, 34.1, 33.2, 29.8, 28.3, 27.1, 26.9, 26.7, 23.9 ppm; HRMS calcd. for $C_{23}H_{30}N_2O$ ($M^+$): 350.2351. Found: 350.2375

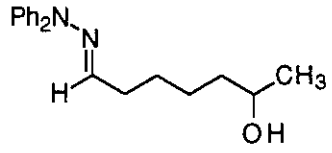
**Preparation of 5-Hydroxy-6-methylheptanal-*N,N*-diphenylhydrazone (157c)**



Following the general procedure, aldehyde **155** (1.79 g, 6.74 mmol) was treated with *i*-PrMgCl (3.7 mL as a 2.0 M solution in THF, 7.4 mmol). After purification, 1.58 g (76%) of the title compound was obtained as a faint yellow oil; IR (neat, $cm^{-1}$) 3401, 3060, 2924, 1592, 1486, 1302, 748, 697; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.39-7.30 (m, 4H), 7.23-7.04 (m, 6H), 6.53 (t, $J$ = 5.3 Hz, 1H), 3.36-3.33 (m, 1H), 2.29-2.25 (m, 2H), 1.68-1.40 (m, 6H), 0.894 (d, $J$ = 6.8 Hz, 3H), 0.886 (d, $J$ = 6.8 Hz, 3H) ppm; $^{13}C$ NMR

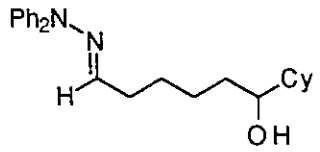
(50 MHz, $CDCl_3$) δ 144.3, 139.8, 129.6, 123.8, 122.3, 76.5, 33.5, 33.4, 32.6, 23.4, 18.8, 17.1 ppm; HRMS calcd. for $C_{20}H_{26}N_2O$ ($M^+$): 310.2039. Found: 310.2077.

**Preparation of 6-Hydroxyheptanal-*N,N*-diphenylhydrazone (158a)**




Following the general procedure, aldehyde **156** (0.78 g, 2.78 mmol) was treated with MeMgBr (2.2 mL as a 1.4 M solution in toluene/THF (3/1), 3.06 mmol). After purification, 0.74 g (90%) of the title compound was obtained as a faint red/orange oil; IR (neat, $cm^{-1}$) 3366, 2929, 2857, 1592, 1493, 1302, 1210, 749, 698; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.39-7.30 (m, 4H), 7.14-7.03 (m, 6H), 6.52 (t, $J$ = 5.3 Hz, 1H), 3.79-3.76 (m, 1H), 2.29-2.23 (m, 2H), 1.52-1.35 (m, 6H), 1.17 (d, $J$ = 6.2 Hz, 3H) ppm (OH proton not observed); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.1, 139.8, 129.5, 123.7, 122.1, 67.6, 38.8, 32.5, 26.8, 25.2, 23.3 ppm; HRMS calcd. for $C_{19}H_{24}N_2O$ ($M^+$): 296.1883. Found: 296.1889.

**Preparation of 6-Cyclohexyl-6-hydroxyhexanal-*N*, *N*-diphenylhydrazone (158b)**



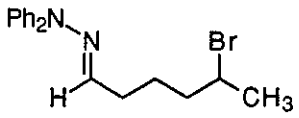

Following the general procedure, aldehyde **156** (250.6 mg, 0.89 mmol) was treated with CyMgCl (0.5 mL as a 2.0 M solution in diethyl ether, 1.0 mmol). After purification, 248.6 mg (76%) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 3405, 3061, 2925, 1593, 1493, 1450, 1302, 1210, 748, 733, 698; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.39-7.31 (m, 4H), 7.14-7.05 (m, 6H), 6.53 (t, $J$ = 5.3 Hz, 1H), 3.33-3.31 (br, 1H), 2.34-2.24 (m, 2H), 1.75-1.01 (m, 17H) ppm (OH not observed); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.3, 139.9, 129.6, 123.7, 122.3, 76.0, 43.5, 33.8, 32.6, 29.2, 27.6, 27.0, 26.5, 26.3, 26.1, 25.4 ppm; HRMS calcd. for $C_{24}H_{32}N_2O$ ($M^+$): 364.2507. Found: 364.2500.

*General Procedure for the Bromination of Alcohols:*

A round bottom flask flame dried under argon was charged with dichloromethane, (generally enough to prepare a 0.1–0.3M solution), triphenylphosphine (1.2 equiv), $Et_3N$ (1.2 equiv) and bromine (1.2 equiv, added dropwise as a 3M solution in dichloromethane until the reaction mixture turned a faint yellow). This mixture was cooled to 0 °C and the alcohol was added dropwise as a dichloromethane solution. The solution was allowed to stir at 0 °C for 30 min and at room temperature for 30 min. After this time, the reaction mixture was poured into a separatory funnel containing water and ethyl acetate. The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were washed with brine, dried and concentrated. The resulting oils were further purified by flash chromatography on deactivated silica gel. When R=*i*–Pr or Cy, the

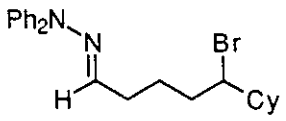
reactions were capricious producing significant amounts of the corresponding alkenes and HBr. For these cases, the reactions were quenched with saturated sodium bicarbonate and worked up as described above.

**Preparation of 5-Bromohexanal-*N*,*N*-diphenylhydrazone (159a)**



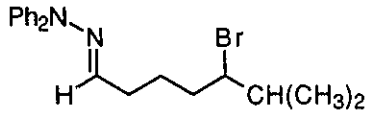

Following the general procedure, alcohol **157a** (183.9 mg, 0.65 mmol) was treated with triphenylphosphine (205.2 mg, 0.78 mmol), $Et_3N$ (0.11 mL, 0.78 mmol) and titrated with bromine solution as described above. After purification, 177.6 mg (79%) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 3060, 2936, 1592, 1493, 1031, 749, 698; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.45-7.34 (m, 4H), 7.20-7.06 (m, 6H), 6.42 (t, $J$ = 5.3 Hz, 1H), 4.35-4.08 (m, 1H), 2.40-2.21 (m, 2H), 1.95-1.55 (m, 4H), 1.75 (d, $J$ = 6.7 Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.1, 138.7, 129.6, 123.8, 122.2, 51.3, 40.4, 31.8, 26.4, 25.0 ppm; HRMS calcd. for $C_{18}H_{21}N_2Br$ ($M^+$): 344.0888. Found: 344.0880; Anal. Calcd for $C_{18}H_{21}N_2Br$: C, 62.62; H, 6.13; N, 8.11. Found: C, 62.64; H, 6.12; N, 8.12.

**Preparation of 5-Bromo-5-cyclohexylpentanal-*N*,*N*-diphenylhydrazone (159b)**




Following the general procedure, alcohol **157b** (627 mg, 1.79 mmol) was dissolved in dichloromethane (20 mL) and treated with triphenylphosphine (564 mg, 2.1 mmol), $Et_3N$ (0.3 mL, 2.14 mmol) and titrated with bromine solution as described above. After purification, 463 mg (63%) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 2931, 1593, 1494, 1302, 1211; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.40-7.31 (m, 4H), 7.15-7.04 (m, 6H), 6.51 (t, $J$ = 5.3 Hz, 1H), 4.00-3.96 (m, 1H), 2.34-2.25 (m, 2H), 1.92-1.51 (m, 10H), 1.49-1.19 (m, 5H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.2, 139.1, 129.7, 123.9, 122.3, 65.5, 44.4, 35.5, 32.0, 30.9, 29.3, 26.3, 26.1, 26.0, 25.3 ppm; HRMS calcd. for $C_{23}H_{29}N_2Br$ ($M^+$): 412.1513. Found: 412.1444.

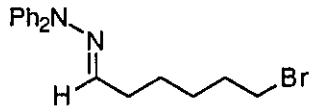
**Preparation of 5-Bromo-6-methylheptanal-*N*,*N*-diphenylhydrazone (159c)**




Following the general procedure, alcohol **157c** (431 mg, 1.39 mmol) was treated with triphenylphosphine (438 mg, 1.67 mmol), $Et_3N$ (0.25 mL, 1.73 mmol) and titrated with bromine solution as described above. After purification, 389 mg (76%) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 2924, 1592, 1492, 747, 696; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.41-7.34 (m, 4H), 7.16-7.07 (m, 6H), 6.52 (t, $J$ = 5.2 Hz, 1H), 4.08-4.01 (m, 1H), 2.36-2.27 (m, 2H), 1.93-1.27 (m, 5H), 1.03 (d, $J$ = 6.7

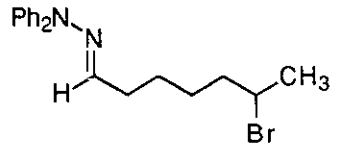
Hz, 3H), 0.98 (d, $J$ = 6.6 Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.2, 139.0, 129.6, 123.9, 122.3, 66.6, 35.9, 34.4, 31.9, 25.4, 20.9, 18.1 ppm; HRMS calcd. for $C_{20}H_{25}N_2O$ ($M^+$): 372.1196. Found: 372.1200.

**Preparation of 6-Bromohexanal-*N,N*-diphenylhydrazone 147 via an Alternative Route**



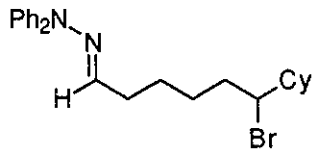

6-Bromohexanol (189.7 mg, 1.15 mmol) was placed in a dry round bottom flask (100 mL) and under argon $CH_2Cl_2$ (10.0 mL) was added. PCC (495.0 mg, 2.30 mmol) was then added and the resulting solution allowed to stir at room temperature for 3 hours. The resulting black mixture was diluted with ether (50.0 mL) and flushed through a sintered glass funnel containing a pad of silica gel eluting with 30% ethyl acetate in petroleum ether (200 mL). The resulting solution was concentrated and treated with MeOH (5.0 mL) and $Ph_2NNH_2$ (220.2 mg, 1.20 mmol) and allowed to stir at room temperature for 1 hour. The solution was concentrated and purified by flash chromatography on deactivated silica gel eluting with 2% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 231.3 mg (64%) of the title hydrazone as a clear colourless oil. This oil solidified after several weeks of storage in the freezer m.p. 92-94 °C; IR (neat, $cm^{-1}$) 3045, 2933, 1592, 1492, 1302, 1210; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H), 7.14-7.04 (m, 6H), 6.51 (t, $J$ = 5.3 Hz, 1H), 3.80 (t, $J$ = 6.8 Hz, 2H), 2.33-2.23 (m, 2H), 1.90-1.83 (m, 2H), 1.55-1.43 (m, 4H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.2, 139.3, 129.6, 123.8, 122.3, 33.7, 32.5, 32.4, 27.6, 26.0 ppm.

**Preparation of 6-Bromoheptanal-*N,N*-diphenylhydrazone (160a)**




Following the general procedure, alcohol **158a** (172 mg, 0.66 mmol) was dissolved in dichloromethane (5 mL) and treated with triphenylphosphine (190 mg, 0.72 mmol), $Et_3N$ (0.1 mL, 0.72 mmol) and titrated with bromine solution as described above. After purification, 178 mg (85%) of the title compound was obtained as a light yellow oil; IR (neat, $cm^{-1}$) 2931, 1592 ,1493, 1302; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.38-7.23 (m, 4H), 7.12-7.02 (m, 6H), 6.50 (t, $J$ = 5.2 Hz, 1H), 4.09 (m, 1H), 2.28-2.23 (m, 2H), 1.81-1.75 (m, 1H), 1.68 (d, $J$ = 6.6 Hz, 3H), 1.54-1.42 (m, 5H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 144.2, 139.4, 129.6, 123.8, 122.3, 51.7, 41.0, 32.6, 27.4, 26.6, 26.4 ppm; HRMS calcd. for $C_{19}H_{23}N_2Br$ ($M^+$): 358.1039. Found: 358.1048.

**Preparation of 6-Bromo-6-cyclohexylhexanal-*N,N*-diphenylhydrazone (160b)**



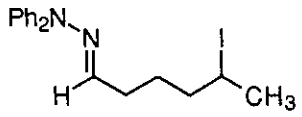

Following the general procedure, alcohol **158b** (215 mg, 0.59 mmol) was treated with triphenylphosphine (186 mg, 0.71 mmol), $Et_3N$ (0.10 mL, 0.71 mmol) and titrated with bromine solution as described above. After purification, 112 mg (44%) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 2923, 2854, 1593, 1494, 1450, 1302, 1210, 747, 698; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.40-7.32 (m, 4H), 7.15-7.07

(m, 6H), 6.53 (t, $J$ =.5.3 Hz, 1H), 3.98-3.94 (m, 1H), 2.31-2.28 (m, 2H), 1.84-1.18 (m, 17H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.2, 139.6, 129.6, 123.8, 122.3, 65.7, 44.4, 35.9, 32.4, 31.0, 29.2, 27.5, 26.4, 26.3, 26.2, 26.0 ppm; HRMS calcd. for $C_{24}H_{31}N_2Br$ ($M^+$): 426.1670. Found: 426.1693.

*General Procedure For the Iodination of Alcohols:*

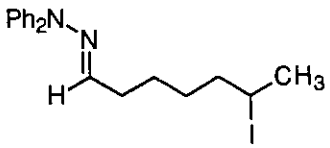
A round bottom flask flame dried under argon was charged with the starting alcohol, diethyl ether/acetonitrile (2/1) (generally enough to make a 0.1–0.3M solution), triphenylphosphine (1.2 equiv) and imidazole (1.2 equiv). This mixture was allowed to stir at room temperature for 5 min and then cooled to 0 °C. To this solution was added 1.2 equiv of iodine as a solution in diethyl ether, dropwise. Initially, the purple colour of each drop of the $I_2$ solution quickly discharged but at the end of the addition, the solution became a light yellow with the formation of a white precipitate. After TLC analysis indicated that the reaction was complete, the mixture was poured into a separatory funnel containing ether and saturated sodium sulfite. The aqueous layer was extracted twice with ether. The combined ether layers were washed with water, brine, dried and concentrated *in vacuo*. Further purification of the resulting oil by flash chromatography on deactivated silica gel was then performed.

**Preparation of 5-Iodohexanal-*N*,*N*-diphenylhydrazone (161a)**



Following the general procedure, alcohol **157a** (273 mg, 0.97 mmol) was treated with triphenylphosphine (304 mg, 1.16 mmol), ether (3 mL), acetonitrile (2 ml), imidazole (75 mg, 1.16 mmol) and iodine (294 mg, 1.16 mmol). After purification, 262 mg (86%) of the title compound was isolated as a clear colorless oil; IR (neat, $cm^{-1}$) 2939, 1593, 1494, 1303, 748, 698; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.40-7.24 (m, 4H), 7.15-7.04 (m, 6H), 6.51 (t, $J$ = 5.1 Hz, 1H), 4.22-4.18 (m, 1H), 2.34-2.25 (m, 2H), 1.92 (d, $J$ = 6.8 Hz, 3H), 1.84-1.53 (m, 4H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.1, 138.7, 129.6, 123.9, 122.2, 42.2, 31.7, 30.1, 28.9, 27.0 ppm; HRMS calcd. for $C_{18}H_{21}N_2I$ ($M^+$): 392.0747. Found: 392.0762.

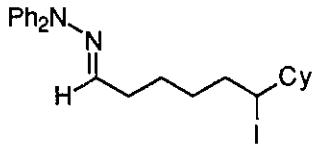
**Preparation of 6-Iodoheptanal-*N*, *N*-diphenylhydrazone 162a**



Following the general procedure, alcohol **158a** (105 mg, 0.35 mmol) was treated with triphenylphosphine (112 mg, 0.42 mmol), ether (0.75 mL), acetonitrile (0.35 mL), imidazole (27 mg, 0.42 mmol) and iodine (106 mg, 0.42 mmol). After purification, 119 mg (82%) of the title compound was isolated as a clear colorless oil; IR (neat, $cm^{-1}$) 2942, 1592, 1492, 1456; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.40-7.32 (m, 4H), 7.14-7.07 (m, 6H), 6.53 (t, $J$ = 5.3 Hz, 1H), 4.16 (m, 1H), 2.28 (br m, 2H), 1.91 (d, $J$ = 6.8 Hz,

3H), 1.82-1.61 (m, 1H), 1.55-1.44 (m, 5H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.1, 139.2, 129.5, 123.7, 122.2, 42.5, 32.3, 30.3, 29.1, 28.8, 26.0 ppm; HRMS calcd. for $C_{19}H_{23}N_2I$ ($M^+$): 406.0906. Found: 406.0891.

**Preparation of 6-Cyclohexyl-6-iodohexanal-*N*, *N*-diphenylhydrazone 162b**



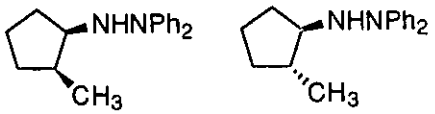

Following the general procedure, alcohol **158b** (789 mg, 2.16 mmol) was treated with triphenylphosphine (683 mg, 2.60 mmol), ether (4 mL), acetonitrile (2 mL), imidazole (164 mg, 2.60 mmol) and iodine (661 mg, 26 mmol). After purification, 345 mg of the title compound (34%) was isolated as a clear colorless oil; IR (neat, $cm^{-1}$) 3060, 2927, 2852, 1592, 1493, 1450, 1302, 1210. $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.41-7.33 (m, 4H), 7.16-7.04 (m, 6H), 6.54 (t, $J$ = 5.3 Hz, 1H), 4.13-4.09 (m, 1H), 2.32-2.26 (m, 2H), 1.92-1.01 (m, 17H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.2, 139.4, 129.6, 123.8, 122.3, 50.1, 44.8, 37.6, 32.7, 32.4, 31.1, 29.4, 26.3, 26.2, 26.03, 25.95 ppm; HRMS calcd. for $C_{24}H_{31}N_2I$ ($M^+$): 474.1526. Found: 474.1544.

*General Procedure for the $SmI_2$/HMPA Reactions:*

Into a dry Schlenk flask was added, under Ar, the starting hydrazone followed by THF (enough to make a 0.025M solution, with respect to the hydrazone) and HMPA (1.0–2.0 mL per mmol of substrate). The system was degassed using three freeze pump thaw cycles, introducing Ar after the last cycle. The solution was then cooled to the

required temperature, and a 0.1M solution of $SmI_2$ in THF was added (4.5 equiv for halide substrates and 4.0 equiv for carbonyl substrates) yielding a deep purple solution. In several experiments, the reaction would turn dark blue and repeated TLC analysis indicated that starting material was not consumed after several hours. The addition of several drops of HMPA to such solutions quickly restored the dark purple color and the reaction would then go to completion. Workup was affected by quenching with saturated sodium bicarbonate after TLC analysis indicated the consumption of starting material (typically < 2 h). The resulting mixture was poured into a separatory funnel containing water and ethyl acetate. The aqueous layer was extracted three times with ethyl acetate and the combined organic layers washed with brine, dried and concentrated. Residual HMPA had to be removed from the crude reaction mixture for the halo–hydrazone reactions since it interfered with the determination of the cis/trans ratios by $^1H$ nmr spectroscopy. This was affected by passing the crude oil through a short plug of deactivated silica gel and eluting with 20-30% dichloromethane/petroleum ether. After concentration, further purification was affected by flash chromatography on deactivated silica gel to separate the cis/trans isomers.

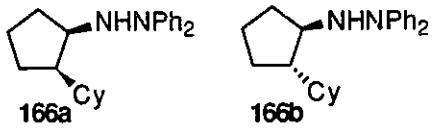
**Preparation of 1-Methyl-2-(*N*,*N*-diphenylhydrazino)-cyclopentanes 146a and b**




Following the general $SmI_2$/HMPA procedure, iodide **161a** (212 mg (0.54 mmol) was dissolved in THF (20 mL) and treated with HMPA (0.8 mL) and $SmI_2$ (20.2 mL as a 0.1M solution in THF, 2.02 mmol) at -78 °C. After workup and purification, 81.7 mg

(57%) of the cis isomer **146a** and 8.0 mg (5%) of the trans isomer **146b** were obtained. **Cis isomer**; IR (neat, $cm^{-1}$) 3060, 2953, 2869, 1591, 1494, 749, 696; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.35-7.15 (m, 8H), 7.03-6.96 (m, 2H), 3.92 (br s, 1H), 3.27-3.24 (m, 1H), 2.05-1.54 (m, 6H), 1.04 (d, $J$ = 7.0 Hz, 3H) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 148.2, 129.0, 122.0, 120.3, 60.3, 37.9, 32.2, 29.5, 22.3, 14.1 ppm; HRMS calcd. for $C_{18}H_{22}N_2$ ($M^+$): 266.1778. Found: 266.1765; Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found: C, 80.43; H, 8.27; N, 10.82. **Trans isomer**; IR (neat, $cm^{-1}$) 2946, 1589, 1495, 738; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.29-7.11 (m, 8H), 7.08-6.90 (m, 2H), 3.85 (br s, 1H), 2.95-2.90 (m, 1H), 2.05-1.46 (m, 6H), 1.24-1.16 (m, 1H), 0.86 (d, $J$ = 6.8 Hz, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 148.1, 129.0, 122.0, 120.3, 65.3, 38.5, 33.2, 30.5, 23.2, 19.4 ppm; HRMS calcd. for $C_{18}H_{22}N_2$ ($M^+$): 266.1778. Found: 266.1770.

**Preparation of 1-Cyclohexyl-2-(*N,N*-diphenylhydrazino)-cyclopentanes**

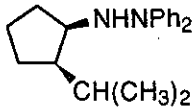



**166a** **166b**

Following the general $SmI_2$/HMPA procedure, bromide **159b** (92.2 mg, 0.22 mmol) was dissolved in THF (9.0 mL) and treated with HMPA (0.3 mL) and $SmI_2$ (10.0 mL as a 0.1M solution in THF, 1.0 mmol) at -42 °C and warmed to -10 °C. After workup and purification, 55.5 mg (74%) of the cis isomer as a white solid and 10.8 mg (15%) of the trans isomer as a clear colorless oil were obtained. **166a**; white solid m.p. 91-92 °C; IR (Nujol, $cm^{-1}$) 1591, 1496, 1450, 1028, 908; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.28-7.25 (m, 4H), 7.12-7.10 (m, 4H), 6.98-6.95 (m, 2H), 3.90 (br s, 1H),3.27 (apparent triplet, $J$ = 4.5 Hz, 1H), 1.95-1.92 (m, 2H), 1.82-1.78 (m, 2H), 1.70-1.51 (m, 4H), 1.48-1.12 (m, 8H), 0.86-0.82 (m, 2H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.2, 129.0, 122.0, 120.3, 57.0,

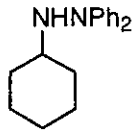
51.3, 37.4, 32.9, 32.4, 29.2, 28.0, 26.5, 26.3, 26.2, 22.1 ppm; HRMS calcd. for $C_{23}H_{30}N_2$ ($M^+$): 334.2408. Found: 334.2401; Anal. Calcd for: $C_{23}H_{30}N_2$: C, 82.59; H, 9.04; N, 8.37. Found: C, 82.54; H, 8.96; N, 8.36; **166b**: IR ($CHCl_3$, $cm^{-1}$) 3017, 2929, 1589, 1495; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.38-7.25 (m, 4H), 7.17-7.05 (m, 4H), 7.00-6.92 (m, 2H), 3.75 (br s, 1H),3.18-3.10 (m, 1H), 1.95-0.85 (m, 18H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.0, 129.0, 122.0, 120.4, 61.1, 50.5, 41.6, 32.1, 31.3, 31.0, 30.2, 26.6, 26.5, 26.4, 24.7 ppm; HRMS calcd. for $C_{23}H_{30}N_2$ ($M^+$): 334.2408. Found: 334.2414.

**Preparation of 1-Isopropyl-2-(*N,N*-diphenylhydrazino)-cyclopentane (167a)**



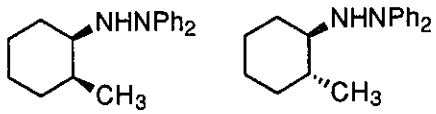

Following the general $SmI_2$/HMPA procedure, bromide **159c** (33.5 mg, 0.09 mmol) was dissolved in THF (4.0 mL) and treated with HMPA (0.14 mL) and $SmI_2$ (4.1 mL as a 0.1M solution in THF, 0.41 mmol) at -42 °C and warmed to -10 °C. After workup and purification, 16.5 mg (63%) of compound 167a and 1.8 mg (7%) of compound 167b were obtained. **167a**; white solid m.p. 97-98 °C; IR ($CHCl_3$, $cm^{-1}$) 2965, 1589, 1496, 1110; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.31-7.26 (m, 4H), 7.15-7.03 (m, 4H), 7.01-6.98 (m, 2H), 3.90 (br s, 1H), 3.29 (m, 1H), 2.00-1.82 (m, 3H), 1.75-1.61 (m, 5H), 0.93 (d, $J$ = 6.5 Hz, 3H), 0.81 (d, $J$ = 6.5 Hz, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 148.3, 129.0, 122.0, 120.3, 57.7, 53.0, 29.4, 28.6, 27.7, 22.5, 22.4, 21.7 ppm; HRMS calcd. for $C_{20}H_{26}N_2$ ($M^+$): 294.2089. Found: 294.2086

**Preparation of *N,N*-Diphenylhydrazinocyclohexane (148)**




Following the general $SmI_2$/HMPA procedure, the required bromide (**147**) (53.0 mg, 0.15 mmol) was dissolved in THF (20 mL) and treated with of HMPA (0.2 mL) and of $SmI_2$ (4.6 mL as a 0.1M solution in THF, 0.46 mmol). After purification, 34.8 mg (85%) of the title compound was obtained as a white solid; m.p. 92-94 °C; IR (neat, $cm^{-1}$) 3045, 2928, 2853, 1589, 1496, 748, 695; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.33-7.15 (m, 8H), 7.14-6.94 (m, 2H), 3.65 (br s, 1H), 2.81-2.79 (m, 1H), 1.86-1.61 (m, 5H), 1.32-1.21 (m, 5H). $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.1, 128.9, 121.8, 120.1, 55.5, 31.3, 26.2, 24.3 HRMS calcd. for $C_{18}H_{22}N_2$ ($M^+$): 266.1778. Found: 266.1776.

**Preparation of 1-Methyl-2-(*N*,*N*-diphenylhydrazino) cyclohexane**

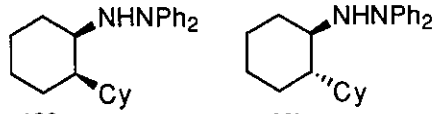



**168a** **168b**

Following the general $SmI_2$/HMPA procedure, bromide **160a** (88.1 mg, 0.24 mmol) was dissolved in THF (10.0 mL) and treated with HMPA (0.5 mL) and $SmI_2$ (9.4 mL as a 0.1M solution in THF, 0.94 mmol) at -42 °C. After workup and purification, 29.0 mg (42%) of the cis isomer and 14.1 mg (21%) of the trans isomer was obtained. When the reaction was performed at –78 °C, a 75% yield of a 5:1 cis/trans mixture was obtained; **168a**; IR (neat, $cm^{-1}$) 3044, 2927, 2857, 1591, 1482, 1287, 749, 696; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.30-7.24 (m, 4H), 7.16-7.12 (m, 4H), 7.00-6.95 (m, 2H), 3.77 (br s, 1H), 2.92-2.89 (m, 1H), 1.68-1.64 (m, 1H), 1.55-1.25 (m, 8H), 0.96 (d, $J$ = 7.1 Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.4, 129.0, 122.0, 120.4, 57.0, 32.7, 30.7,

26.6, 23.2, 22.8, 14.7 ppm; HRMS calcd. for $C_{19}H_{24}N_2$ ($M^+$): 280.1934. Found: 280.1944; Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.43; H, 8.64; N, 10.06. **168b**; IR (neat, $cm^{-1}$) 3044, 2927, 2855, 1590, 1497, 749, 695; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 4H), 7.18-7.12 (m, 4H), 6.99-6.92 (m, 2H), 4.27 (br s, 1H), 2.46-2.39 (m, 1H), 2.05-1.98 (m, 1H), 1.70-1.42 (m, 4H), 1.32-1.05 (m, 4H), 0.95 (d, $J$ = 7.2 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 148.1, 129.0, 121.8, 120.2, 61.3, 25.7, 34.0, 30.7, 25.7, 24.6, 19.0. HRMS calcd. for $C_{19}H_{24}N_2$ ($M^+$): 280.1934. Found: 280.1926; Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: 81.30; H, 8.45; N, 9.86.

**Preparation of 1-Cyclohexyl-2-(*N,N*-diphenylhydrazino) cyclohexane**

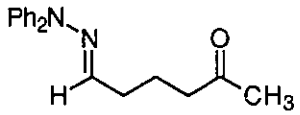



**169a** **169b**

Following the general $SmI_2$/HMPA procedure, iodide **162b** (261 mg, 0.56 mmol) was dissolved in THF (20.0 mL) and treated with HMPA (1.0 mL) and $SmI_2$ (25.0 mL as a 0.1M solution in THF, 2.5 mmol) at -78 °C. After workup and purification, 69.5 mg (36%) of the cis isomer and 75.0 mg (39%) of the trans isomer were isolated as clear colorless oils. **169a**; IR ($CHCl_3$, $cm^{-1}$) 3019, 2929, 2855, 1590, 1496; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.33-7.24 (m, 4H), 7.17-7.12 (m, 4H), 7.05-6.96 (m, 2H), 3.70 (br s, 1H), 3.11-3.09 (m, 1H), 2.17-2.07 (m, 1H), 1.86-0.79 (m, 19H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 149.1, 129.0, 122.4, 121.0, 51.2, 46.1, 38.4, 31.4, 30.2, 28.8, 27.0, 26.5 (2 carbons), 26.3, 24.3, 21.2 ppm; HRMS calcd. for $C_{24}H_{32}N_2$ ($M^+$): 348.2557. Found: 348.2575. **169b**; IR (neat, $cm^{-1}$) 2926, 2854, 1590, 1496, 908, 734; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.31-7.23 (m, 4H), 7.17-7.10 (m, 4H), 7.01-6.92 (m, 2H), 4.24 (br s, 1H), 2.71-2.62 (m, 1H), 2.05-2.04 (m, 1H), 1.69-0.76 (m, 19H) ppm; $^{13}C$ NMR (50 MHz,

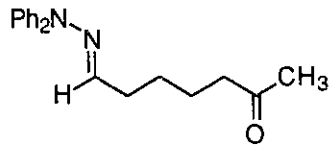
$CDCl_3$) δ 148.3, 128.9, 121.9, 120.3, 61.1, 55.7, 46.0, 37.4, 31.7, 31.0, 27.2, 27.0, 26.8, 25.9, 24.8, 24.4 ppm; HRMS calcd. for $C_{24}H_{32}N_2$ ($M^+$): 348.2557. Found: 348.2552; Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25; N, 8.04. Found: C, 82.76; H, 9.14; N, 7.89.

**Preparation of Hexanal-5-one-*N,N*-diphenylhydrazone (170)**



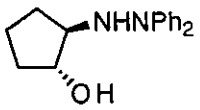

Following the procedure for the preparation of aldehyde **155**, alcohol **157** (532.2 mg, 1.89 mmol) was dissolved in DMSO (4 mL) and $Et_3N$ (2.0 mL, 14.2 mmol). This mixture was then treated with $SO_3$•pyridine (902.0 mg, 5.7 mmol). After purification, 306.8 mg (58%) of the title compound was obtained as a clear colorless oil; IR ($CDCl_3$, $cm^{-1}$) 2932, 1711, 1593, 1494, 1211, 1167, 1091, 1067; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.40-7.31 (m, 4H), 7.15-7.05 (m, 6H), 6.48 (t, $J$ = 5.1 Hz, 1H), 2.52-2.45 (t, $J$ = 7.3 Hz, 2H), 2.33-2.23 (m, 2H), 2.13 (s, 3H), 1.78 (q, $J$ = 7.2 Hz, 2H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 208.6, 144.0, 138.4, 129.6, 123.8, 122.2, 42.7, 31.9, 30.0, 20.8 ppm; HRMS calcd. for $C_{18}H_{20}N_2O$ ($M^+$): 280.1571. Found: 280.1591.

**Preparation of Heptanal-6-one-*N*,*N*-diphenylhydrazone (171)**

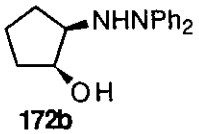


Following the procedure for the preparation of aldehyde **155**, alcohol **158** (408 mg, 1.38 mmol) was dissolved in DMSO (5 mL) and $Et_3N$ (1.5 mL, 11.0 mmol). This mixture was then treated with $SO_3$•pyridine (652 mg, 4.1 mmol) in DMSO (3.0 mL). After purification, 319 mg (79%) of the title compound as a clear colorless oil was obtained; IR (neat, $cm^{-1}$) 2932, 1714, 1593, 1494, 1494, 1453, 1302, 1210; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.39-7.30 (m, 4H), 7.14-7.03 (m, 6H), 6.50 (t, $J$ = 5.3 Hz, 1H), 2.43 (t, $J$ = 6.8 Hz, 2H), 2.32-2.22 (m, 2H), 2.11 (s, 3H), 1.60-1.47 (m, 4H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 208.7, 144.1, 139.1, 129.5, 123.7, 122.1, 43.3, 32.3, 29.7, 26.3, 23.1 ppm; HRMS calcd. for $C_{19}H_{22}N_2O$ ($M^+$): 294.1726. Found: 294.1717.

**Preparation of 1-Hydroxy-2-(*N*,*N*-diphenylhydrazino) cyclopentane (172)**



**172a**

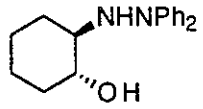


**172b**

Following the general $SmI_2$/HMPA procedure, aldehyde **156** (80.0 mg, 0.3 mmol) was dissolved in THF (10.0 mL) and treated with HMPA (0.27 mL) and $SmI_2$ (12.0 mL as a 0.1M solution in THF, 1.2 mmol) at 21 °C. After workup and purification, 50.2 mg (62%) of the cis hydrazine was obtained as a clear colorless oil. When the reaction was performed at –78 °C, a 53% yield of a 6:1 cis/trans mixture was obtained. **Isomer 172a**; IR (neat, $cm^{-1}$) 3395, 2930, 1591, 1489, 1373, 1057; $^1H$ NMR (200 MHz, $CDCl_3$) δ

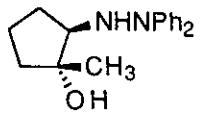
7.35-7.24 (m, 4H), 7.18-7.05 (m, 4H), 7.02-6.98 (m, 2H), 4.18-4.11 (m, 1H), 4.05-3.80 (br s, 1H), 3.35-3.22 (m, 1H), 2.17-2.04 (m, 1H), 1.97-1.43 (m, 5H) ppm (either OH or NH not observed); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.1, 129.2, 122.5, 120.5, 77.4, 65.6, 33.4, 28.6, 21.6 ppm; nOe of the two methine hydrogens = 4.8%; HRMS calcd. for $C_{17}H_{20}N_2O$ ($M^+$): 268.1571. Found: 268.1592; Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.09; H, 7.51; N, 10.38. **Isomer 172b**; IR (neat, $cm^{-1}$) 3472, 2936, 1590, 1494, 909; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.34-7.23 (m, 4H), 7.12-6.99 (m, 6H), 4.35-4.20 (m, 1H), 4.19-4.05 (m, 1H), 3.38-3.30 (m, 1H), 2.77-2.74 (m, 1H), 1.94-1.52 (m, 6H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.0, 129.3, 122.7, 120.2, 71.8, 63.2, 31.7, 26.4, 20.3 ppm; nOe of the two methine hydrogens = 7.3%. HRMS calculated for $C_{17}H_{20}N_2O$ ($M^+$): 268.1571. Found: 268.1600.

**Preparation of 1-Hydroxy-2-(*N*,*N*-diphenylhydrazino) cyclohexane (173a)**



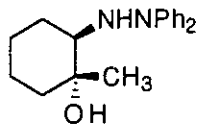

Following the general $SmI_2$/HMPA procedure, aldehyde **157** (90.3 mg, 0.32 mmol) was dissolved in THF (13.0 mL) and treated with HMPA (0.5 mL) and $SmI_2$ (12.9 mL as a 0.1M solution in THF, 1.29 mmol) at 21 °C. After workup and purification, 52 mg (58%) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 3372, 3047, 2932, 2859, 1590, 1496, 745, 696; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.33-7.16 (m, 8H), 7.04-6.96 (m, 2H), 4.60 (br, 1H), 3.61-3.54 (m, 1H), 2.79-2.67 (m, 1H), 2.42-2.39 (m, 1H), 1.95-1.87 (m, 1H), 1.72-1.87 (m, 2H), 1.32-1.13 (m, 4H) ppm (either OH or NH not observed); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 148.2, 129.0, 122.3, 120.5, 74.2, 61.1, 33.9, 29.4, 24.3, 23.9 ppm; HRMS calcd. for $C_{18}H_{22}N_2O$ ($M^+$): 282.1727. Found: 282.1719.

**Preparation of 1-Hydroxy-1-methyl-2-(*N,N*-diphenylhydrazino) cyclopentane (175a)**



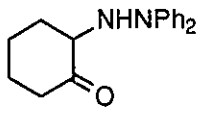

Following the general $SmI_2$/HMPA procedure, ketone **170** (211 mg, 0.75 mmol) was dissolved in THF (25.0 mL) and treated with HMPA (0.7 mL) and $SmI_2$ (30.0 mL as a 0.1M solution in THF, 3.0 mmol) at 21 °C. After workup and purification, 135 mg (63%) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 3432, 3063, 2962, 1595, 1486, 910, 740, 697; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 4H), 7.16-7.14 (m, 4H), 7.02-6.99 (m, 2H), 3.95 (br s, 1H), 3.17 (apparent triplet, 1H), 1.89-1.84 (m, 2H), 1.73-1.57 (m, 5H), 1.32 (s, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.1, 129.1, 122.4, 120.5, 80.9, 65.9, 39.0, 27.9, 22.5, 19.8 ppm; HRMS calcd. for $C_{18}H_{22}N_2O$ ($M^+$): 282.1726. Found: 282.1735; Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.42; H, 7.32; N, 9.72. Repeated analysis, Found: C, 76.10; H, 7.87; N, 9.85.

**Preparation of 1-Hydroxy-1-methyl-2-(N,N-diphenylhydrazino) cyclohexane (176a)**




Following the general $SmI_2$/HMPA procedure, ketone **171** (160 mg, 0.54 mmol) was dissolved in THF (21.0 mL) and treated with HMPA (0.8 mL) and $SmI_2$ (21.6 mL as a 0.1M solution in THF, 2.16 mmol) at 21 °C. After workup and purification, 97 mg (60%) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 3419, 3060, 2933, 2860, 1590, 1489, 912, 745, 696; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.31-7.15 (m, 8H), 7.03-6.94 (m, 2H), 4.35 (br s, 1H), 2.82-2.75 (m, 1H), 1.94-1.52 (m, 5H), 1.32 (s, 3H), 1.35-1.15 (m, 3H) ppm (either O<u>H</u> or N<u>H</u> not observed); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 148.3, 129.0, 122.3, 120.5, 73.7, 63.2, 40.7, 27.8, 24.2, 23.6, 20.4 ppm; HRMS calcd. for $C_{19}H_{24}N_2O$ ($M^+$): 296.1882. Found: 296.1896; Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.12; 7.98; N, 9.46.

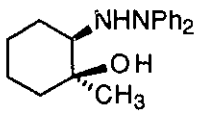
**Preparation of 2-(*N,N*-diphenylhydrazino) cyclohexan-2-one**




Hydrazine **173a** (153.2 mg, 0.54 mmol) was placed in a dry round bottom flask (50 mL) and treated with DMSO (2 mL) and $Et_3N$ (0.6 mL, 4.3 mmol). This mixture was then treated with $SO_3$·py (257.8 mg, 1.62 mmol) in DMSO (3.0 mL) and allowed to stir at room temperature for one hour. The resulting mixture was poured in a separatory funnel containing ethyl acetate (50 mL) and water (100 mL). The aqueous layer was

extracted with ethyl acetate (2 x 50 mL) and the combined organic layer were washed with brine (100 mL), dried and concentrated. The resulting oil was further purified by flash chromatography on silica gel eluting with 15% ethyl acetate in petroleum ether. Concentration of the appropriate fraction yielded 96.0 mg (63%) of the title compound as a clear colourless oil; IR (neat, $cm^{-1}$) 3045, 2939, 1708, 1591, 1494, 747, 696; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.30-7.23 (m, 4H),7.15-7.04 (m, 4H), 7.01-6.87 (m, 2H), 5.25 (br s, 1H), 3.55-3.46 (m, 1H), 2.53-2.47 (m, 2H), 2.32-2.15 (m, 1H), 2.09-1.54 (m, 5H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 209.3, 147.4, 129.0, 122.2, 120.1, 64.4, 40.7, 33.7, 26.9, 23.4 ppm; HRMS calcd. for $C_{18}H_{20}N_2O$ ($M^+$): 280.1570. Found: 280.1582.

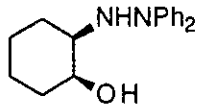
**Preparation of 1-Hydroxy-1-methyl-2-(*N,N*-diphenylhydrazino) cyclohexane (176b)**




Ketone **171** (34.8 mg, 0.12 mmol) was placed in a dry round bottom flask (50 mL), dissolved in THF (5.0 mL) and cooled to -78 °C. This cooled solution was treated with MeLi (90 μL of 1.3 M solution, 0.12 mmol) and allowed to stir at -78 °C for 0.5 hr and at room temperature for a further 0.5 hr. The reaction mixture was quenched by the addition of water (2.0 mL) and the resulting solution was poured into a separatory funnel containing ethyl acetate (20 mL) and water (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried and concentrated. The resulting oil was further purified by flash chromatography on deactivated silica gel eluting with 20% ethyl acetate in petroleum ether. Concentration of the appropriate fraction yielded 6.8 mg (15%, not optimized) of the title compound as

an oil. $^1$H NMR (200 MHz, $CDCl_3$) δ 1.38 ($CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 28.3 ($CH_3$) ppm; HRMS calcd. for $C_{19}H_{24}N_2O$ ($M^+$) : 296.1882. Found : 296.1870.

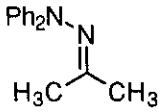
**Preparation of 1-Hydroxy-2-(N,N-diphenylhydrazino) cyclohexane (173b)**




Ketone **157** (51.6 mg, 0.18 mmol) was placed in a dry round bottom flask (50 mL) and, under argon at room temperature, treated with ether (5.0 mL) and lithium aluminium hydride (0.1 mL of a 1.0 M solution in ether, 0.1 mmol). The resulting suspension was allowed to stir at room temperature for approximately 3 hr. The reaction was quenched by the dropwise addition of a saturated aqueous potassium sodium tartrate solution (5.0 mL) and the mixture was diluted with ethyl acetate (20 mL) and allowed to stir at room temperature for 15 minutes. The resulting mixture was poured into a separatory funnel containing ethyl acetate (20 mL), water (10 mL) and brine (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were washed with brine and dried. The resulting oil was purified by flash chromatography on deactivated silica gel eluting with 20% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded the title compound (48.3 mg, 93%) as a 3:1 mixture of diastereomers. This mixture was subjected to medium pressure chromatography on deactivated silica gel eluting with 15% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 11.5 mg (22%) of the title alcohol as a clear colourless oil, and the yield of the other isomeric alcohol was not measured. IR (neat, $cm^{-1}$) 3418, 2933, 1589, 1494, 909; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.33-7.25 (m, 4H), 7.10-6.97 (m, 6H), 4.02-3.99 (m, 1H), 3.96 (br s, 1H), 2.99-2.90 (m,

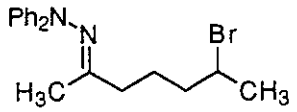
1H), 2.53 (br s, 1H), 1.97-1.89 (m, 1H), 1.72-1.24 (m, 7H) ppm; 13C NMR (50 MHz, $CDCl_3$) δ 148.4, 129.3, 122.7, 120.4, 66.3, 58.8, 29.9, 24.6, 24.0, 19.9 ppm; HRMS calcd. for $C_{18}H_{22}N_2O$ ($M^+$): 282.1727. Found: 282.1694.

**Preparation of 2-Propanone-N,N-diphenylhydrazone (187)**




To a solution of acetone (5.0 mL) was added *N, N*-diphenylhydrazine (1.69 g, 9.10 mmol), several crystals of (S)–(+)–(10)–camphor sulfonic acid and approximately 2 g of anhydrous $MgSO_4$. The resulting mixture was allowed to stir at room temperature overnight. The mixture was then filtered, concentrated and the resulting oil was purified by flash chromatography on deactivated silica gel eluting with 10% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 1.15 g (56%) of the title compound as a light grey oil; IR (neat, $cm^{-1}$) 3060, 2913, 1593 (broad), 1491. $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.36-7.28 (m, 4H), 7.13-7.06 (m, 6H), 2.18 (s, 3H), 1.84 (s, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 169.6, 148.0, 128.6, 122.3, 120.7, 24.7, 20.0 ppm; HRMS calcd. for $C_{15}H_{16}N_2$ ($M^+$) : 224.1310. Found : 224.1320.

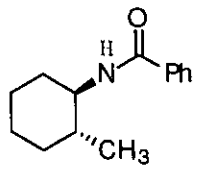
**Preparation of 6-Bromoheptan-2-one-(*N*,*N*-diphenylhydrazone) (186)**




Hydrazone **187** (356.9 mg, 1.6 mmol) was added to a dry round bottom flask (50 mL) under argon, dissolved in THF (15.0 mL) and cooled to -78 °C. This solution was treated with *n*--BuLi (6.7 mL of a 2.5 M solution, 1.75 mmol) and allowed to stir at -78 °C for 0.5 hr and at 0 °C for an additional 0.5 hr. To this solution was added 1,3-dibromobutane (210 μL, 1.75 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was poured into a separatory funnel containing ethyl acetate (20 mL) and water (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried and concentrated. The resulting oil was purified by flash chromatography on deactivated silica gel eluting with 5% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 179.9 mg (32%) of the title compound as a clear colourless oil; IR (neat, $cm^{-1}$) 3060, 1592, 1493, 1452. $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.32-7.24 (m, 4H), 7.03-6.98 (m, 6H), 4.19-4.16 (m, 1H), 2.44 (t, $J$ = 6.9 Hz, 2H), 1.91-1.78 (m, 4H), 1.77 (s, 3H), 1.72 (d, $J$ = 6.7 Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 171.7, 148.3, 128.9, 122.7, 121.1, 51.0, 40.5, 38.0, 26.4, 24.7, 19.1 ppm; HRMS calcd. for $C_{19}H_{23}N_2Br$ ($M^+$) : 358.1040. Found : 358.1067.

*Hydrogenolysis over Pd on Carbon:*

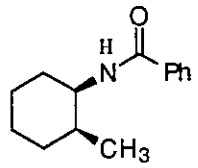
**Preparation of (*trans*)-*N*-(2-methylcyclohexyl) benzamide (193)**




Hydrazine **168b** (305 mg, 1.09 mmol), MeOH (10.0 mL), (S)–(+)–10–camphor sulfonic acid (506 mg, 2.18 mmol) ) and 10% Pd/C (31 mg) was placed into a glass liner of a stainless steel autoclave. The glass liner was then placed in the autoclave and the gauge and gauge block assembly attached. The hydrogen line and the system was flushed three times before pressurizing to 500 psi. The reaction mixture was stirred at 21 °C for 3 hours. After this time the excess gas was discharged and the reaction mixture filtered through a sintered glass funnel to remove the Pd/C The Pd/C was then rinsed with ethyl acetate and the volatiles removed in vacuo. To the resulting yellow foam was added dichloromethane (30 mL ), $Et_3N$ (0.75 mL , 5.5 mmol), benzoic anhydride (520 mg, 2.3 mmol) along with several crystal of DMAP and this mixture was allowed to stir overnight at room temperature. The resulting solution was concentrated and purified by flash chromatography on silica gel eluting with 5% ethyl acetate/dichloromethane. Concentration of the appropriate fractions yielded 205 mg (87%) of the title compound was obtained as a white solid; m.p. 149-151 $^oC$; IR (Nujol, $cm^{-1}$) 3231, 2906, 2855, 1628, 1566, 1457, 1376; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.78-7.72 (m, 2H), 7.51-7.24 (m, 3H), 5.92-5.87 (br m, 1H), 3.77-3.60 (dddd, $J_1 = 9.9$, $J_2 = 9.8$, $J_3 = 9.8$, $J_4 = 3.8$ Hz, 1H), 2.07-1.98 (m, 1H), 1.79-1.65 (m, 3H), 1.42-1.05 (m, 5H), 0.96 (d, $J = 6.4$ Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 166.9, 135.1, 131.0, 128.3, 126.8, 54.4, 38.4, 34.3, 33.6, 25.7, 25.4, 19.1 ppm; HRMS calcd. for $C_{14}H_{19}NO$ ($M^+$): 217.1461. Found:

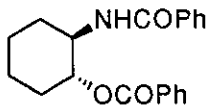
217.1451; Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.58; H, 8.87; N, 6.53.

**Preparation of (*cis*)-*N*-(2-methylcyclohexyl) benzamide (192)**



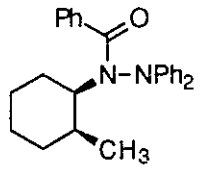

Following the procedure for the hydrogenolysis of hydrazine 168b, compound 168a (232.2 mg, 0.83 mmol) was placed in the glass liner of a steel autoclave along with methanol (10 mL), camphorsulphonic acid (385.2 mg, 1.67 mmol) and 10% Pd/C (25 mg) and pressurized to 500 psi of hydrogen. The crude reaction mixture was then treated with methylene chloride (20 mL), $Et_3N$ (0.58 mL), $(PhCO)_2O$ (393.1 mg, 1.74 mmol) and several crystals of DMAP and allowed to stir overnight. Workup and purification yielded 152.2 mg (85%) of the title compound as a white solid; m.p. 110–111 °C; IR (Nujol, $cm^{-1}$) 3326, 2927, 1629, 1528; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.76-7.72 (m, 2H), 7.50-7.37 (m, 3H), 6.10 (m, 1H), 4.29-4.21 (m, 1H), 1.94-1.22 (m, 9H), 0.92 (d, $J$ = 7.0 Hz, 3H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 166.9, 135.2, 131.1, 128.4, 126.7, 49.7, 33.5, 30.7, 29.5, 25.4, 22.3, 16.3 ppm; HRMS calcd. for $C_{14}H_{19}NO$ ($M^+$) : 217.1461. Found : 217.1460.

**Preparation of (2-Benzoyloxy)-*N*-cyclohexyl benzamide (194)**



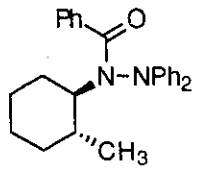

Following the procedure for the hydrogenolysis of hydrazine **168b**, compound **173a** (70.6 mg, 0.025 mmol), was placed in the glass liner of a steel autoclave along with MeOH (5.0 mL), (S)–(+)–10–camphor sulfonic acid (116.3 mg, 0.50 mmol) and 10% Pd/C (7.0 mg) was pressurized to 500 psi of hydrogen and heated to 50 °C overnight. The crude reaction mixture was then treated with dichloromethane (10.0 mL), $Et_3N$ (0.2 mL, 1.3 mmol) and $(PhCO)_2O$ (120.1 mg, 3.0 mmol) along with several crystals of DMAP and allowed to stir at room temperature for overnight. The resulting oil was purified by flash chromatography on silica gel eluting with 40% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 58.3 mg (72%) of the title compound as a white solid; m.p. 204-207 °C; IR (neat, $cm^{-1}$) 1702 (broad), 1636, 1544, 1456; $^1H$ NMR (200 MHz, $CDCl_3$) δ 8.01-7.97 (m, 2H), 7.67-7.62 (m, 2H), 7.51-7.27 (m, 6H), 6.60 (br d, $J$ = 8.2 Hz, 1H), 5.03 (ddd, $J$ = 10.5 Hz, $J$ = 10.5 Hz, $J$ = 4.7 Hz, 1H), 4.24-4.19 (m, 1H), 2.31-2.24 (m, 1H), 2.17-2.10 (m, 1H), 1.88-1.65 (m, 3H), 1.49-1.32 (m, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 167.7, 167.0, 134.5, 133.1, 131.2, 129.9, 129.7, 128.4, 128.3, 126.8, 75.4, 53.7, 32.2, 31.3, 24.3, 24.2 ppm; HRMS calcd. for $C_{20}H_{21}NO_3$ ($M^+$): 323.1516. Found: 323.1537

**Preparation of (*cis*)-1-methyl-2-(*N*,*N*-diphenyl-*N'*-benzoyl hydrazido) cylcohexane (195)**



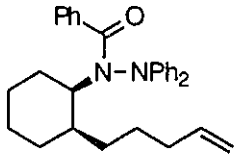

Hydrazine **168a** (153.5 mg, 0.55 mmol) was added to a dry round bottom flask (50 mL), dissolved in THF (10.0 mL) under argon and the resulting solution cooled to -78 °C. This solution was treated with *n*–BuLi (0.24 mL of a 2.5 M solution, 0.60 mmol) and allowed to stir at -78 °C for one hour. To the resulting light orange solution was added $(PhCO)_2O$ (135.6 mg, 0.60 mmol) and the reaction mixture was allowed to stir at room temperature for one hour. The reaction was quenched by the addition of water (5 mL) and the resulting mixture was poured into a separatory funnel containing ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3x50 mL) and the combined organic layers were washed with brine (50 mL), dried and concentrated. The oil thus obtained was further purified by flash chromatography on deactivated silica gel eluting with 20% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 125.3 mg (60%) of the title compound as a white foam; IR ($CHCl_3$, $cm^{-1}$) 2934, 1658, 159, 149; HRMS calcd. for $C_{26}H_{28}N_2O$ ($M^+$) : 384.2195. Found 384.2177. Both the $^1H$ nmr and $^{13}C$ nmr spectra were very broad probably resulting from restriced rotation.

**Preparation of (*trans*)-1-methyl-2-(*N*,*N*-diphenyl-*N'*-benzoyl hydrazido) cylcohexane (196)**




Following the procedure described above for compound **168a**, a mixture of cis and trans methyl cyclohexylhydrazine **168a** and **168b** were benzoylated. The resulting hydrazides were then separated by flash chromatography on deactivated silica gel eluting with 5% ethyl acetate in petroleun ether. The title compound was isolated as a white solid; m.p. 167–169 °C; IR (neat, $cm^{-1}$) 1648, 1591, 1492; $^1H$ NMR (500 MHz, $CDCl_3$) approximate 1:1 mixture of amide rotamers δ 7.68-7.67 (m, 1.5H), 7.46-7.42 (m, 3H), 7.41-7.31 (m, 3H), 7.30-7.18 (m, 1.5H), 7.17-7.00 (m, 2.5H), 6.88-6.87 (m, 3.5H), 4.40 (br s, 0.5H), 3.69-3.64 (m, 0.5H), 2.28-2.25 (m, 0.5 H), 2.19-2.16 (m, 0.5H), 1.99-1.91 (m, 0.5H), 1.78-1.71 (m, 1H), 1.63-1.45 (m, 2H), 1.37-1.31 (m, 1H), 1.30-1.24 (m, 1.5H), 1.18-1.09 (m, 1.5H), 1.01 (d, $J$ = 6.6 Hz, 1.5H), 0.66-0.58 (m, 0.5H), 0.45 (d, $J$ = 6.4 Hz, 1.5H). HRMS calcd. for $C_{26}H_{28}N_2O$ ($M^+$): 384.2195. Found: 384.2196. $^{13}C$ spectrum could not be recorded because the signals were very broad.

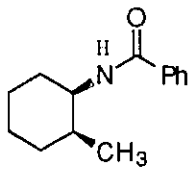
**Preparation of (*cis*)-1-Pent-4-enyl-2-(*N*,*N*-diphenyl-*N'*-benzoyl hydrazido) cylcohexane (198)**




Hydrazine **197** (53.3 mg, 0.16 mmol) was added to a dry 100 mL Schlenck flask and charged with THF (10.0 mL) and cooled to -78 °C. To this solution was added BuLi (80 μL, 2.5 M solution, 0.20 mmol) and allowed to stir at -78 °C for one hour. To the resulting light yellow solution was added benzoic anhydride (45 mg, 0.2 mmol) and the reaction was stirred at room temperature for one hour. The reaction was quenched by the addition of water (5 mL) and poured into a separatory funnel containing ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL), the combined organic layers were washed with brine, dried and concentrated. The resulting oil was further purified by flash chromatography eluting with 20% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 43.5 mg (62%) of the title compound as a light yellow oil; IR (neat, $cm^{-1}$) 2993, 1647, 1592, 1493, 1452; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.35-6.70 (br m, 15H), 5.60-5.81 (br m, 1H), 4.85-5.02 (br m, 2H), 4.36-4.40 (br m, 1H), 2.45 (br s, 1H), 2.02-1.00 (br m, 14H) ppm; HRMS calcd. for $C_{30}H_{34}N_2O$ ($M^+$) : 438.2663. Found : 438.2676. $^{13}C$ nmr spectra could not be recorded due to the broadness of the signals.

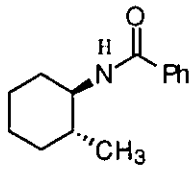
*$SmI_2$ Mediated Cleavage Reactions*

**Preparation of (*cis*)-*N*-(2-methylcyclohexyl) benzamide (192)**



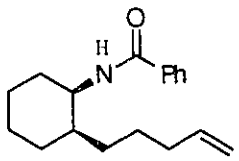

Following the general $SmI_2$/HMPA procedure, hydrazide **195** (166.5 mg, 0.43 mmol) was dissolved in THF (16 mL) and treated with HMPA (0.65 mL) and $SmI_2$ (9.1 mL of a 0.1 M solution in THF, 0.91 mmol) at room temperature and allowed to stir for 15 minutes. The reaction was quenched with the addition of saturated aqueous sodium bicarbonate (10 mL) and the resulting mixture was poured into a separatory funnel containing ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were washed with brine (30 mL), dried and concentrated. The resulting oil was further purified by flash chromatography on deactivated silica gel eluting with 20% ethyl acetate in petroleum ether. Concentration of the appropriate fraction yieldeds 77.3 mg (82%) of the title compound as a white solid. This compound was found to be identical to the one prepared by the hydrogenolysis method.

**Preparation of (*trans*)-*N*-(2-methylcyclohexyl) benzamide (193)**



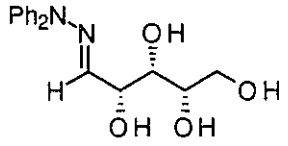

Into a dry Schlenk flask was placed of hydrazide **196** (110 mg, 0.29 mmol) along with THF (12.0 mL) and HMPA (0.43 mL). The system was degassed using three freeze pump thaw cycles, introducing Ar after the last cycle. At room temperature, $SmI_2$ in THF (6.0 mL, 0.60 mmol, of a 0.1M solution) was added. Each drop of $SmI_2$ initially turned purple but the colour quickly discharged and became yellow. After the addition of $SmI_2$ was complete, TLC analysis of the resulting yellow solution indicated the complete absence of starting material. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (10 mL). The resulting mixture was poured into a separatory funnel containing 50 mL of water and 50 mL of ethyl acetate. The aqueous layer was extracted three times with ethyl acetate and the combined organic layers washed with brine, dried and concentrated. Further purification was affected by flash chromatography on silica gel eluting with 15% ethyl acetate/petroleum ether. Concentration of the appropriate fractions yielded 53 mg (85%) of the title compound as a white solid. This compound was found to be identical to the one prepared by the hydrogenolysis method.

**Preparation of (*cis*)-*N*-((2-pent-4-enyl)cyclohexyl) benzamide (199)**



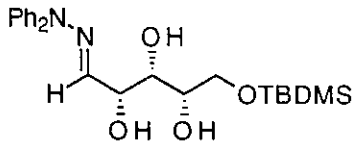

Following the general procedure, hydrazide **198** (38.1 mg, 0.09 mmol) was dissolved in THF (3.5 mL) and treated with HMPA (0.17 mL) and $SmI_2$ (1.9 mL as a 0.1 M solution in THF, 0.19 mmol) at room temperature and allowed to stir for 15 minutes. The reaction was quenched with an aqueous saturated $NaHCO_3$ solution (10 mL) and this mixture was poured into a separatory funnel containing ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL), dried and concentrated. The resulting oil was further purified by flash chromatography eluting with 30% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 16.7 mg (71%) of the title compound as a white solid; m. p. 60-62 °C; IR ($CHCl_3$, $cm^{-1}$) 3017, 2931, 1655 (broad), 1515, 1485; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.73-7.71 (m, 2H), 7.53-7.37 (m, 3H), 6.12 (d, $J$ = 8.3 Hz, 1H), 5.85-5.65 (m, 1H), 5.00-4.85 (m, 2H), 4.38-4.30 (m, 1H), 2.05-1.92 (m, 2H), 1.89-1.82 (m, 1H), 1.77-1.13 (m, 12H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 166.8, 138.7, 135.3, 131.2, 128.5, 126.7, 114.4, 48.1, 39.2, 33.7, 31.1, 30.4, 27.9, 26.1, 24.5, 21.7 ppm; HRMS calcd. for $C_{18}H_{25}NO$ ($M^+$) : 271.1930. Found : 271.1921.

**Preparation of (2R*, 3S*, 4S*, 5)-tetrahydroxypentanol-*N,N*-diphenylhydrazone (210)**



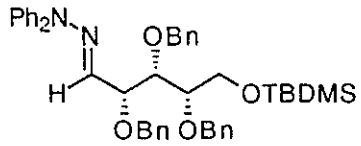
*N,N*-Diphenylhydrazine hydrochloride salt (2.42 g, 11.95 mmol) was placed in a dry round bottom flask along with MeOH (150 mL) and sodium methoxide (644.0 mg, 11.95 mmol) and this mixture was allowed to stir at room temperature for 0.5 hr. After this time, L-xylose (1.80 g, 12.04 mmol) was added along with approximately 2 g of anhydrous $MgSO_4$ and several crystals of (S)–(+)–(10)–camphor sulfonic acid. This mixture was allowed to stir at room temperature overnight. The resulting solution was filtered through a sintered glass funnel containing a pad of silica gel eluting with a 2% MeOH/ethyl acetate solution and the filtrate was concentrated. Purification by flash chromatography on deactivated silica gel and eluted with 2% MeOH in ethyl acetate gave 1.63 g (44%) of the title compound as a light grey solid; $[\alpha]_D^{21}$=+1.2 ° (c 1.95, MeOH); IR (Nujol, $cm^{-1}$) 3416 (broad), 1599, 1494, 1376; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.45-7.02 (m, 10H), 6.52 (d, *J* = 3Hz, 1H), 4.45-4.40 (m, 1H), 3.81-3.75 (m, 4H), 3.10 (br s, 4H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 143.2, 135.3, 129.8, 124.7, 122.2, 72.7, 72.5, 72.0, 64.1 ppm; HRMS calcd. for $C_{17}H_{20}N_2O_4$ ($M^+$) : 316.1418. Found : 316.1440; Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.62; H, 6.48; N, 8.77.

**Preparation of (2R*, 3S*, 4S*)-trihydroxy-5-(*t*-butydimethyl) siloxypentanal-*N*,*N*-diphenylhydrazone (211)**



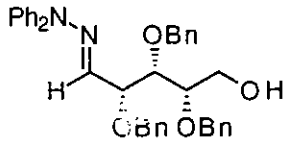

Hydrazone **210** (3.84 g, 12.17 mmol) was placed in a dry round bottom flask (250 mL) under argon and disolved in dry DMF (150 mL) and cooled to -42 °C. To the resulting cooled solution was added imidazole (911.6 mg, 13.39 mmol) and TBDMSCl (1.85 g, 12.20 mmol) and the mixture stirred at -42 °C for 4 hr. The solution was then warmed to room temperature and poured into separatory funnel containing ethyl acetate (150 mL) and water (150 mL). The aqueous layer was extracted with ethyl acetate (3 x 150 mL) and the combined organic layers were washed first with water (2 x 30 mL) and then brine (100 mL). The solution was then dried and concentrated. Purification of the resulting oil by flash chromatography eluting with 50% ethyl acetate in petroleum ether yielded 3.75 g (72%) of the title compound as a light grey oil; $[\alpha]_D^{21}$=+10.8 ° (c 1.93, $CHCl_3$); IR (neat, $cm^{-1}$); 3404 (broad), 2910, 1593, 1483; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.39-7.31 (m, 4H), 7.17-7.04 (m, 6H), 6.56 (d, *J* = 3.5 Hz, 1H), 4.44 (m, 1H), 3.76-3.68 (m, 4H), 3.00 (br s, 3H), 0.86 (s, 9H), 0.05 (s, 6H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 143.4, 135.9, 129.8, 124.6, 122.3, 73.1, 72.2, 71.8, 64.6, 25.8, 18.3, -5.4 ppm; LRMS found : 430.0 ($M^+$).

**Preparation of (2R*, 3S*, 4S*)-tribenzyloxy-5-(*t*-butydimethyl) siloxypentanal-*N*,*N*-diphenylhydrazone (212)**



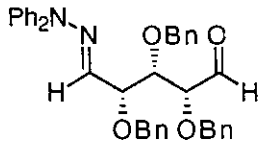

Hydrazone **211** (1.42 g, 3.31 mmol) was placed in a dry round bottom flask (250 mL) along with THF (150 mL) and cooled to 0 °C. To this solution was added NaH (350.6 mg of an 80% suspension in mineral oil, 11.6 mmol) and then stirred at room temperature for one hour. At this time the solution was re-cooled to 0 °C and benzyl bromide (1.4 mL, 11.6 mmol) was added along with $(C_5H_{11})_4NI$ (approx. 20 mg). The resulting mixture was allowed to stir at room temperature overnight. The resulting solution was poured into a separatory funnel containing ethyl acetate (100 mL) and water (100 mL). The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were washed with brine (50 mL), dried and concentrated. Purification of the resulting oil by flash chromatography yielded 1.57 g (67%) of the title compound as a faint yellow oil; $[\alpha]_D^{21}$=-27.9 ° (c 4.14, $CHCl_3$); IR (neat, $cm^{-1}$) 3063, 2938, 1591, 1494, 1301; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.33-7.01 (m, 25H), 6.46 (d, *J* = 7.0 Hz, 1H), 4.50-4.39 (m, 7H), 3.69-3.54 (m, 4H), 0.81 (s, 9H), -0.07 (s, 3H), -0.08 (s, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 143.5, 138.7, 138.5, 138.3, 136.0, 129.7, 129.3, 128.3, 128.1, 127.9, 127.5, 127.3, 124.3, 122.2, 120.9, 117.7 (one aromatic carbon is coincident with a signal listed), 80.1 (2), 80.0, 74.9, 73.1, 70.9, 62.4, 25.9, 18.1, -5.4 ppm.

**Preparation of 5-Hydroxy-(2R*, 3S*, 4S*)-tribenzyloxypentanal-*N,N*-diphenylhydrazone (213)**



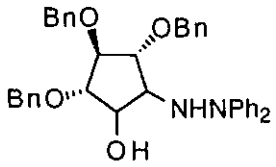

Hydrazone **212** (923.3 mg, 1.32 mmol) was placed in a dry round bottom flask (250 mL) along with THF (50 mL), water (10 mL) and an aqueous 10% $H_2SO_4$ solution (3 mL) and allowed to stir at room temperature overnight. The resulting solution was poured into a separatory funnel containing ethyl acetate and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was extracted with the saturated aqueous $NaHCO_3$ solution (4 x 50 mL). The combined aqueous layers were extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried and concentrated. Purification of the resulting oil by flash chromatography eluting with 20% ethyl acetate in petroleum ether yielded 522.6 mg (68%) of the title compound as a clear colourless oil; $[\alpha]_D^{21}$=-30.9 ° (c 0.98, $CHCl_3$); IR (neat, $cm^{-1}$) 3431 (broad), 3030, 1591, 1494, 1454; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.30-7.02 (m, 25H), 6.45 (d, $J$ = 7.3 Hz, 1H), 4.59-4.51 (m, 6H), 4.43-4.32 (m, 1H), 3.66-3.57 (m, 3H), 3.49-3.38 (m, 1H), 1.99 (br s, 1H, OH) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 143.4, 138.2, 137.9, 135.4, 129.8, 128.3, 128.2, 127.9, 127.2, 124.4, 122.2 (remaining 6 aromatic carbon signals are coincident with the signals listed), 80.8, 79.5, 79.3, 74.6, 72.8, 70.8, 61.5 ppm.

**Preparation of (2R*, 3S*, 4R*)-tribenzyloxybutanal-*N*,*N*-diphenyl-hydrazone-4-carboxaldehyde (208)**



Following the general $SO_3$·py/DMSO oxidation procedure, hydrazone **213** (246.1 mg, 0.42 mmol) was treated with DMSO (6 mL), $Et_3N$ (0.5 mL, 3.6 mmol) and $SO_3$·py (202.1 mg, 1.27 mmol, in 2 mL DMSO). The resulting slurry was stirred at room temperature for 1 hour. TLC analysis at this time revealed that the oxidation was incomplete, and another aliquot of $SO_3$·py (ca. 50 mg) was added to the reaction mixture. Usual work up yielded 164.4 mg (67%) of the title compound as a yellow oil. Due to its instability to silica gel, this compound was used without further purification.

**$SmI_2$ mediated cyclization of chiral aldehyde 208**

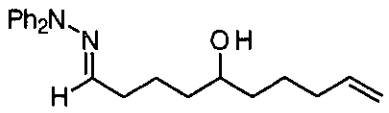


Following the general $SmI_2$/HMPA procedure, crude aldehyde **208** (111.1 mg, 0.19 mmol) was treated with THF (8 mL), HMPA (0.4 mL) and $SmI_2$ (8.0 mL of 0.1 M solution in THF, 0.8 mmol) at room temperature. Purification by flash chromatography on silica gel eluting with 15% ethyl acetate in petroleum ether yielded two fractions: the first fraction ($F_1$) contained 35.2 mg (32% as a single diastereomer) and the second fraction ($F_2$) contained 28.4 mg (25% as a mixture of diastereomers) of the title

compound; (less polar isomer, $\mathbf{F_1}$): IR (neat, $cm^{-1}$) 3414 (br), 3031, 1590, 1494, 1454; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.26-7.06 (m, 23H), 6.97-6.89 (m, 2H), 4.58-4.41 (m, 6H), 4.01-3.88 (m, 4H), 3.54-3.51 (m, 1H), 2.62 (br s, 1H, either OH or NH, the other proton does not appear) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 147.6, 137.9, 137.4, 129.0 (2), 128.1 (2), 128.0, 127.7, 127.6, 127.5 (2), 127.4, 122.5, 121.0 (2), 88.1, 86.6, 82.5, 71.9, 71.7, 71.6, 71.4, 61.9 ppm; HRMS calcd. for $C_{38}H_{38}N_2O_4$ ($M^+$): 586.2822. Found: 586.2812.

*Chapter 3*

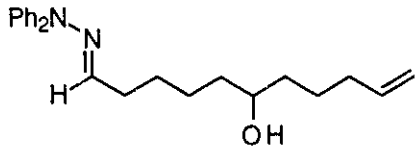
**Preparation of 5-hydroxydec-9-en-1-al-*N,N*-diphenylhydrazone (242)**




Into a dry 100 mL round bottom flask was added 5-bromopentene (1.0 mL, 8.45 mmol) along with freshly ground Mg turnings (225 mg, 9.30 mmol) and THF (15 mL) along with several crystals of iodine. The mixture was allowed to stir at room temperature for 1 hour. A separate dry 100 mL round bottom flask was charged, under Ar, with the corresponding aldehyde **156** (590.8 mg, 2.2 mmol) and THF (15 mL) and cooled to 0 °C. To this cooled solution was added the Grignard solution dropwise in portions. The reaction was monitored by TLC and the Grignard reagent was added until the starting aldehyde was consumed (approximately 4.5 mL of the solution was required). The reaction was quenched by the addition of 0.2 mL of water and the resulting mixture poured into a separatory funnel containing 100 mL of water and 100 mL of ethyl acetate. After separation of the layers, the aqueous layer was extracted with ethyl acetate (3x75 mL). The combined organic layers were washed with brine, dried, filtered and

concentrated. The resulting yellow oil was further purified by flash chromatography on deactivated silica gel eluting with 15% ethyl acetate in petroleun ether. The product was isolated from the appropriate fractions as a faint yellow oil (425.2 mg, 57%); IR (neat, $cm^{-1}$) 3386, 3066, 2929, 1593, 1493, 1210, 911; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.41-7.24 (m, 4H), 7.16-7.08 (m, 6H), 6.56 (t, $J$ = 5.2 Hz, 1H), 5.92-5.72 (m, 1H), 5.07-4.95 (m, 2H), 3.60 (br s, 1H), 2.36-2.26 (m, 2H), 2.07-2.03 (m, 2H), 1.81-1.23 (m, 8H) (O<u>H</u> proton not observed) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.1, 139.6, 138.6, 129.5, 123.7, 122.2, 114.5, 71.2, 36.7 (2), 33.6, 32.5, 24.8, 22.9 ppm; HRMS calcd. for $C_{22}H_{28}N_2O$ ($M^+$): 336.2193. Found: 336.2190.

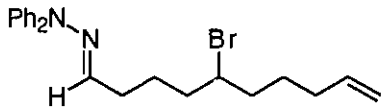
**Preparation of 6-hydroxyundec-10-en-1-al-*N,N*-diphenyl hydrazone (243)**




Following the procedure outlined for the preparation of alcohol **242** described above, the required Grignard reagent was prepared by treating 5-bromopentene (0.65 mL, 5.5 mmol) with freshly ground Mg turnings (130 mg, 5.3 mmol) in THF (15 mL). Treatment of aldehyde **156** (247.2 mg, 0.9 mmol) at 0 °C with an aliquot of the prepared Grignard solution yielded, after purification, 187.4 mg (61 %) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 3380, 3065, 2914, 1640, 1593, 1493, 1210, 1091; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.40-7.31 (m, 4H), 7.15-7.06 (m, 6H), 6.54 (t, $J$ = 5.3 Hz, 1H), 5.88-5.71 (m, 1H), 5.07-4.92 (m, 2H), 3.58 (br s, 1H), 2.28-2.45 (m, 2H), 2.06-2.02 (m, 2H), 1.63-1.27 (m, 10H) (O<u>H</u> proton not observed) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.2, 139.8, 138.6, 129.6, 123.8, 122.3, 114.5, 71.5, 37.1, 36.8, 33.7, 32.6, 26.9, 25.1, 24.8 ppm; HRMS calcd. for $C_{23}H_{30}N_2O$ ($M^+$): 350.2351. Found:

350.2360; Anal. Calcd for $C_{23}H_{30}N_2O$: C, 78.82; H, 8.63; N, 7.99. Found: C, 78.72; H, 8.49; N, 8.13.

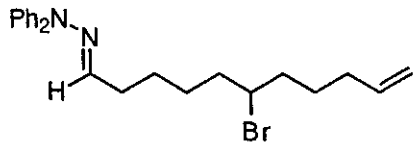
**Preparation of 5-bromodec-9-en-1-al-*N,N*-diphenylhydrazone (236)**




A round bottom flask (100 mL) flame dried under argon was charged with freshly distilled dichloromethane (10 mL), triphenylphosphine (81.6 mg, 0.3 mmol) and titrated with an approximate 3 M solution of bromine in dichloromethane until the solution remained a faint yellow. Triethylamine (45 mL, 0.3 mmol) was added to this solution and the mixture was cooled to 0 °C. The alcohol **242** was then added as a dichloromethane solution dropwise (95.5 mg, 0.28 mmol in 3 mL dichloromethane). The resulting solution was allowed to react at 0 °C for approximately 10 minutes and at room temperature for 30 minutes. The reaction as quenched by the addition of saturated aqueous sodium bicarbonate (10 mL) and poured into a separatory funnel containing water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography on deactivated silica gel eluting with 15% dichloromethane in petroleum ether. Concentration of the appropriate fractions yielded 49.3 mg (44%) of the title compound was obtained as a light yellow oil; IR (neat, $cm^{-1}$) 2941, 2864, 1640, 1593, 1494, 1211; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.41-7.32 (m, 4H), 7.24-7.02 (m, 6H), 6.51 (t, $J$ = 5.3 Hz, 1H), 5.86-5.69 (m, 1H), 5.07-4.94 (m, 2H), 4.08-3.99 (m, 1H), 2.39-2.25 (m, 2H), 2.13-2.02 (m, 2H), 1.92-1.43 (m, 8H) ppm; $^{13}C$ NMR

(50 MHz, $CDCl_3$) δ 144.2, 138.9, 138.2, 129.7, 123.9, 122.3, 114.9, 58.0, 38.5 (2), 33.0, 32.0, 26.7, 24.9 ppm; Anal. Calcd for $C_{22}H_{27}N_2Br$: C, 66.16; H, 6.81; N, 7.01. Found: C, 66.37; H, 6.71; N, 7.08.

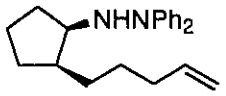
**Preparation of 6-bromoundec-10-en-1-al-*N*,*N*-diphenylhydrazone (237)**

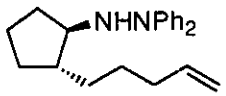



A round bottom flask (100 mL) flame dried under argon was charged with freshly distilled dichloromethane (20 mL), triphenylphosphine (335.8 mg, 1.28 mmol) and titrated with an approximate 3 M solution of bromine in dichloromethane until the solution remained a faint yellow. Triethylamine (180 mL, 1.28 mmol) was added to this solution and the mixture was cooled to 0 °C. The alcohol (**243**) was then added dropwise as a dichloromethane solution (375.2 mg, 1.07 mmol in 5 mL dichloromethane). The resulting solution was allowed to react at 0 °C for approximately 10 minutes and at room temperature for 30 minutes. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (10 mL) and poured into a separatory funnel containing water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). Over the course of the extraction, brine (20 mL) was added to break up an emulsion that formed. The combined organic layers were washed with brine, dried, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography on deactivated silica gel eluting with 15% dichloromethane in petroleum ether. Concentration of the appropriate fractions yielded 392.9 mg (89%) of the title compound was obtained as a light yellow oil; IR (neat, $cm^{-1}$) 3065, 2933, 2858, 1640, 1593, 1493, 1455, 1303, 1210; $^1H$ NMR (200 MHz, $CDCl_3$) δ

7.41-7.32 (m, 4H), 7.16-7.05 (m, 6H), 6.54 (t, $J$ = 5.3 Hz, 1H), 5.90-5.70 (m, 1H), 5.08-4.94 (m, 2H), 4.00-3.97 (m, 1H), 2.35-2.26 (m, 2H), 2.14-2.03 (m, 2H), 1.89-1.74 (m, 4H), 1.71-1.51 (m, 6H) ppm; $^{13}$C NMR (50 MHz, $CDCl_3$) δ 144.2, 139.4, 138.2, 129.6, 123.8, 122.3, 114.9, 58.2, 38.8, 38.4, 33.0, 32.4, 27.0, 26.7, 26.3 ppm; HRMS calcd. for $C_{23}H_{29}N_2Br$ ($M^+$): 412.1508. Found: 412.1526; Anal. Calcd for $C_{23}H_{29}N_2Br$: C, 66.82; H, 7.07; N, 6.78. Found: C, 66.86; H, 6.88; N, 6.73.

**Preparation of (cis)- and (trans)-1-(Pent-4-enyl)-2-(*N,N*-diphenylhydrazino) cyclopentane (238)**

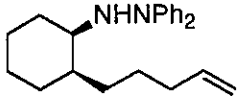


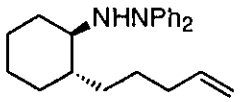

Following the general $SmI_2$/HMPA procedure, bromide **236** (23.5 mg, 0.078 mmol) in THF (3.0 mL) was treated with HMPA (0.15 mL) and $SmI_2$ (3.5 mL as a 0.1 M solution in THF). After workup and purification the title compound was isolated (21.3 mg, 85%) as a clear colorless oil; **Cis isomer**; IR (neat, $cm^{-1}$) 3066, 2933, 1640, 1590, 1495; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.31-7.20 (m, 4H), 7.14-7.10 (m, 4H), 7.04-6.93 (m, 2H), 5.83-5.70 (m, 1H), 5.00-4.90 (m, 2H), 3.86 (br s, 1H), 3.26-3.23 (m, 1H), 2.03-1.91 (m, 2H), 1.87-1.24 (m, 10H) ppm; $^{13}$C NMR (50 MHz, $CDCl_3$) δ 148.1, 138.8, 129.0, 121.9, 120.3, 114.5, 59.0, 44.3, 34.0, 29.9, 29.6, 28.5, 28.1, 22.3 ppm; HRMS calcd. for $C_{22}H_{28}N_2$ ($M^+$): 320.2246. Found: 320.2277; Anal. calcd for $C_{22}H_{28}N_2$: C, 82.45; H, 8.81; N, 8.74. Found: C, 82.45; H, 8.75; N, 8.63. **Trans isomer**: IR (neat, $cm^{-1}$) 3012, 1640, 1590, 1495, 1459, 1172; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.35-7.26 (m, 4H), 7.18-7.10 (m, 4H), 7.00-6.92 (m, 2H), 5.84-5.62 (m, 1H), 5.00-4.85 (m, 2H), 3.85 (br s, 1H), 3.10-3.00 (m, 1H), 2.08-1.95 (m, 2H), 1.81-1.20 (m, 10H) ppm; $^{13}$C NMR (50

MHz, $CDCl_3$) δ 148.1, 138.9, 129.0, 122.0, 120.3, 114.3, 63.8, 43.9, 34.1, 33.9, 31.5, 30.7, 27.5, 23.6 ppm; HRMS calcd. for $C_{22}H_{28}N_2$ ($M^+$): 320.2246. Found: 320.2272.

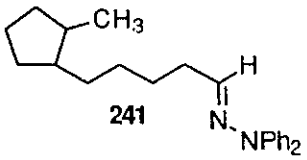
**Preparation of (cis)- and (trans)-1-(Pent-4-enyl)-2-(*N*,*N*-diphenylhydrazino) cyclohexane 239a, 239b and 5-(2-methylcyclopentyl)-pentanal-*N*,*N*-diphenylhydrazone 241**




**239a**




**239b**

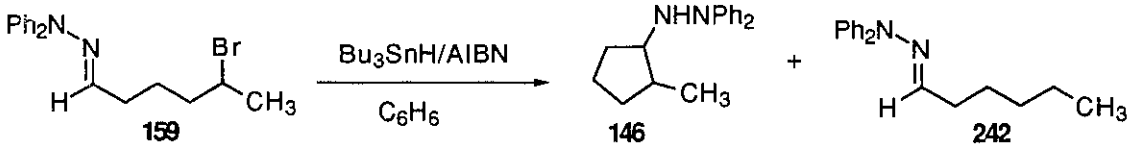



**241**

Following the general $SmI_2$/HMPA procedure, bromide **237** (110.5 mg, 0.27 mmol) in THF (10.7 mL) was treated with HMPA (0.5 mL) and $SmI_2$ (10.8 mL as a 0.1 M solution in THF, 0.11 mmol). After workup and purification, the title compound was isolated (66.7 mg, 75%) as a clear colourless oil. **Cyclohexane 239a;** IR (neat, $cm^{-1}$) 3067, 2928, 2857, 1640 ,1590, 1496, 909; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.23-7.13 (m, 4H), 7.05-6.98 (m, 4H), 6.94-6.86 (m, 2H), 5.75-5.61 (m, 1H), 4.94-4.86 (m, 2H), 3.80 (br s, 1H), 3.05-3.02 (m, 1H), 2.00-1.93 (m, 2H), 1.90-1.31 (m, 13H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.6, 139.0, 129.0, 122.1, 120.6, 114.3, 55.8, 39.1, 34.0, 29.1, 27.7, 27.5, 26.9, 24.1, 22.7 ppm; HRMS calcd. for $C_{23}H_{30}N_2$ ($M^+$): 334.2402. Found: 334.2399; Anal. Calcd for $C_{23}H_{30}N_2$: C, 82.59; H, 9.04; N, 8.37. Found: C, 82.75; H, 8.93; N, 8.43. **Cyclohexane 239b and cyclopentanes 241** (inseparable mixture): IR (neat, $cm^{-1}$) 3064, 2928, 2858, 1640, 1592, 1480, 910, 748, 696; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.5, 148.2, 140.4, 138.9, 138.8, 129.6, 129.0, 128.9, 123.8, 122.1, 121.9, 120.5, 120.3, 114.5, 114.3, 58.7, 55.8, 43.2, 39.9, 39.0, 35.9, 34.5, 34.0, 33.5, 32.7, 31.5, 30.3, 30.2, 29.7, 28.3, 28.1, 27.6, 27.5, 27.4, 26.8, 25.6, 25.2, 24.1, 22.7, 22.4, 14.8 ppm;

Anal. calcd for $C_{23}H_{30}N_2$: C, 82.59; H, 9.04; N, 8.37. Found: C, 82.75; H, 8.93; N, 8.43.

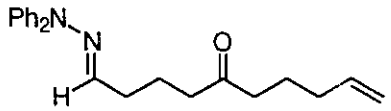
**Intramolecular Quenching Experiment: Preparation of 1-Methyl-2-(*N,N*-diphenylhydrazino) cylopentane (146) and hexanal *N,N*-diphenyl hydrazone (242)**




A dry round bottom flask (10 mL) equipped with a reflux condenser was charged with the starting bromide **159** (67.2 mg, 0.2 mmol) along with $C_6H_6$ (1.0mL), $Bu_3SnH$ (2.0 mL, 7.2 mmol) and AIBN (8.1 mg, 0.05 mmol). Argon was gently bubbled through the solution for 15 minutes. The solution was then heated at reflux for one hour. The resulting solution was concentrated and purified by flash chromatography on deactivated silica gel eluting with petroleum ether (to remove $Bu_3SnH$ and $Bu_3SnBr$). After the tin compounds were eluted from the column the column was flushed with 50% $CH_2Cl_2$/petroleum ether. All the fractions not containg tin including approximately 100 mL after the last fraction containg UV active material were collected and concentrated. $^1H$ nmr analysis of this 'semi-crude' mixture indicated a ratio of 18.2:1 of cyclized (**146**) to reduced (**242**) material. Further purification resulted in the isolation of 51.6 mg (91%) of a clear colorless oil containing **146** and **242** as an inseparable mixture. Authentic **242** was prepared (for comparison) by adding to a dry 50 mL round bottom flask *n*–hexanal (82 mL, 0.67 mmol) along with methanol (2.0 mL) and $Ph_2NNH_2$ (126.3 mg, 0.67 mmol). The mixture was allowed to stir at room temperature for 2 hours, concentrated and purified by flash chromatography on deactivated silica gel eluting with 15%

$CH_2Cl_2$/petroleum ether. The title compound was isolated 97.1 mg (53%) as a clear colourless oil. This material was found to co-spot (TLC) with the products isolated from the $Bu_3SnH$ reaction and exhibited the following spectral data; IR (neat, $cm^{-1}$) 3061, 2937, 2859, 1593, 1493, 747, 697; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.39-7.30 (m, 4H), 7.14-7.05 (m, 6H), 6.53 (t, $J$ = 5.3 Hz, 1H), 2.31-2.21 (m, 2H), 1.49-1.43 (m, 2H), 1.32-1.25 (m, 4H), 0.87 (m, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 144.4, 140.3, 129.6, 123.7, 122.3, 32.7, 31.4, 26.7, 22.4, 14.0 ppm; HRMS calcd. for $C_{18}H_{22}N_2$ ($M^+$): 266.1778. Found: 266.1778; Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 81.72; H, 7.49; N, 10.63.

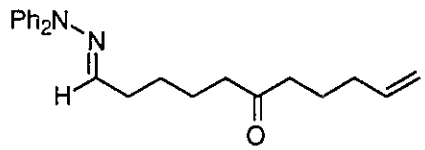
**Preparation of Dec-6-one-9-en-1-al-(N,N)-diphenylhydrazone (248)**




A flame dried round bottom flask (50 mL) cooled under argon was charged with alcohol **242** (178.0 mg, 0.53 mmol) along with DMSO (3.0 mL) and $Et_3N$ (0.5 mL, 3.6 mmol). To this stirred mixture was added dropwise $SO_3$•py (253 mg, 1.6 mmol in 2 mL DMSO). This slurry was allowed to stir at room temperature for 90 minutes at which time it was poured into a separatory funnel containing ethyl acetate (100 mL) and water (100 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried, filtered and concentrated in vacuo. The resulting oil was further purified by flash chromatography on deactivated silica gel eluting with 10% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 126.6 mg (72%) of the title compound was obtained as a clear colorless oil; IR (neat, $cm^{-1}$) 2931, 1709, 1593, 1493, 1202, 910; $^1H$ NMR (200

MHz, $CDCl_3$) δ 7.41-7.26 (m, 4H), 7.16-7.05 (m, 6H), 6.48 (t, *J* = 5.3 Hz, 1H), 5.85-5.65 (m, 1H), 5.05-4.93 (m, 2H), 2.49-2.37 (m, 4H), 2.30-2.22 (m, 2H), 2.06-1.92 (m, 2H), 1.82-1.61 (m, 4H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 210.6, 144.1, 138.5, 137.9, 129.6, 123.9, 122.2, 115.1, 42.0, 41.9, 33.0, 32.0, 22.8, 20.9 ppm; HRMS calcd. for $C_{22}H_{26}N_2O$ ($M^+$): 334.2039. Found: 334.2052; Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.01; H, 7.83; N, 8.38. Found: C, 78.97; H, 7.72; N, 8.30.

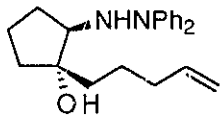
**Preparation of Undec-6-one-10-en-1-al-(N,N)-diphenylhydrazone (249)**




A flame dried round bottom flask (100 mL) was charged with alcohol **243** (187.4 mg, 0.54 mmol) and treated with DMSO (5 mL), $Et_3N$ (0.6 mL, 4.3 mmol) followed by the dropwise addition of $SO_3$•py (254 mg, 1.6 mmol in 3.0 mL DMSO). The resulting slurry was allowed to stir at room temperature for 2 hours at which time TLC analysis showed the consumption of the starting alcohol. The reaction was poured into a separatory funnel containing ethyl acetate (75 mL) and water (75 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with brine, dried , filtered and concentrated in vacuo. The resulting oil was further purified by flash chromatography on deactivated silica gel eluting with 10% ethyl acetate in petroleum ether. Concentration of the appropriate fractions yielded 125.8 mg (68%) of the title compound as a clear colorless oil; IR (neat, $cm^{-1}$) 1710, 1640, 1593, 1301, 1092; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.39-7.14 (m, 4H), 7.10-6.99 (m, 6H), 6.50 (t, *J* = 5.4 Hz, 1H), 5.82-5.64 (m, 1H), 5.03-4.93 (m, 2H), 2.50-2.42 (m, 4H), 2.40-2.35 (m, 2H), 2.22-1.98 (m, 2H), 1.75-1.43 (m, 6H) ppm; $^{13}C$ NMR

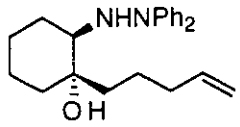
(50 MHz, $CDCl_3$) δ 210.9, 144.2, 139.3, 138.0, 129.6, 123.8, 122.3, 115.2, 42.5, 41.9, 33.1, 32.4, 26.5, 23.3, 22.8 ppm; HRMS calcd. for $C_{23}H_{28}N_2O$ ($M^+$): 348.2195. Found: 348.2198; Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.18; H, 8.24; N, 7.88.

**Preparation of 1-hydroxyl-1-(4-pentenyl)-2-(*N,N*-diphenylhydrazino) cyclopentane (250)**



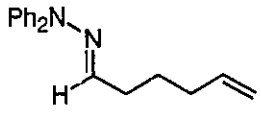

Following the general procedure ketone **248** (90.9 mg, 0.27 mmol) in THF (10.9 mL) was treated with HMPA (0.54 mL) and $SmI_2$ (10.9 mL of a 0.1 M solution in THF, 0.11M). After workup and purification isolated 65.6 mg (72%) of the title compound as a clear colourless oil; IR (neat, $cm^{-1}$) 3407, 2929, 1639, 1590, 1495, 1291; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.24-7.15 (m, 4H), 7.06-7.00 (m, 4H), 6.95-6.88 (m, 2H), 5.76-5.62 (m, 1H), 4.95-4.83 (m, 2H), 3.80 (br s, 1H), 3.05-3.02 (m, 1H), 2.00-1.93 (m, 2H), 1.89-1.31 (m, 10H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 148.1, 138.6, 129.1, 122.4, 120.5, 114.8, 83.6, 65.6, 36.9, 34.5, 34.2, 27.6, 23.2, 20.5 ppm; HRMS calcd. for $C_{22}H_{28}N_2O$ ($M^+$): 336.2195. Found: 336.2195; Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.66; H, 8.38; N, 8.24.

**Preparation of 1-hydroxyl-1-(4-pentenyl)-2-(*N,N*-diphenylhydrazino) cyclohexane (251)**




Following the general procedure ketone **249** (84.1 mg, 0.24 mmol) was dissolved in THF (10 mL) and treated with HMPA (0.5 mL) and $SmI_2$ (9.7 mL as a 0.1 M solution in THF, 0.97 mmol). After workup and purification, the major isomer of the title compound (**251**) was isolated (39.6 mg, 47%) as a clear colourless oil; IR (neat, $cm^{-1}$) 3440, 2917, 1632, 1591, 1496, 1460, 910; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.24-7.16 (m, 4H), 7.12-7.08 (m, 4H), 7.00-6.89 (m, 2H), 5.81-5.67 (m, 1H), 5.00-4.84 (m, 2H), 4.14 (br s, 1H), 2.78-2.70 (m, 1H), 2.06-1.95 (m, 2H), 1.84-1.02 (m, 13H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 148.4, 138.9, 129.0, 122.4, 120.7, 114.5, 75.0, 63.8, 36.0, 34.3, 30.8, 27.3, 24.0, 22.9, 21.7 ppm; HRMS calcd. for $C_{23}H_{30}N_2O$ ($M^+$): 350.2351. Found: 350.2343; Anal. Calcd for $C_{23}H_{30}N_2O$: C, 78.82; H, 8.63; N, 7.99. Found: C, 78.81; H, 8.56; N, 7.93.

**Preparation of hex-5-en-1-al-*N,N*-diphenylhydrazone (254)**




A round bottom flask (100 mL) cooled under argon was charged with 5-hexene-1-ol (1.50 mL, 12.5 mmol) along with dichloromethane (20 mL) and PCC (5.37g, 25.0 mmol). The resulting mixture was allowed to stir at room temperature for 2 hours. TLC

at this time indicated the presence of starting material and additional PCC was added (250 mg, 1.1 mmol) and allowed to stir at room temperature. To the resulting mixture was added ether (50 mL), shaken vigorously and decanted the organic layer from the black tar. This was repeated twice (2 x 50 mL). The combined organic layers were concentrated and passed through a sintered glass with a pad of silica gel eluting with 50% ether–petroleum ether and the resulting solution concentrated. In a separate round bottom flask (50 mL), was added $Ph_2NNH_2 \cdot HCl$ (2.75g, 12.5 mmol), MeOH (10 mL) and sodium methoxide (743 mg, 13.7 mmol) were mixed and allowed to stir at room temperature for approximately one hour. To this solution was added the unsaturated aldehyde as a methanol solution (10 mL) and stirred for an additional 0.5 hour. The mixture was filtered, concentrated and further purified by flash chromatography on deactivated silica gel eluting with 20% $CH_2Cl_2$–petroleum ether. The title compound was isolated (1.86 g, 57%) as a light grey oil; IR (neat, $cm^{-1}$) 3066, 2927, 1640, 1593, 1493, 1302, 1091; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.31-7.23 (m, 4H), 7.16-6.99 (m, 6H), 6.47 (t, $J$ = 5.3 Hz, 1H), 5.81-5.62 (m, 1H), 4.98-4.84 (m, 2H), 2.26-2.15 (m, 2H), 2.05-1.93 (m, 2H), 1.58-1.42 (m, 2H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 144.2, 139.5, 138.3, 129.6, 123.8, 122.2, 114.8, 33.2, 32.0, 26.2 ppm; HRMS calcd. for $C_{18}H_{20}N_2$ ($M^+$): 264.1622. Found: 264.1609; Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 81.72; H, 7.49; N, 10.63.

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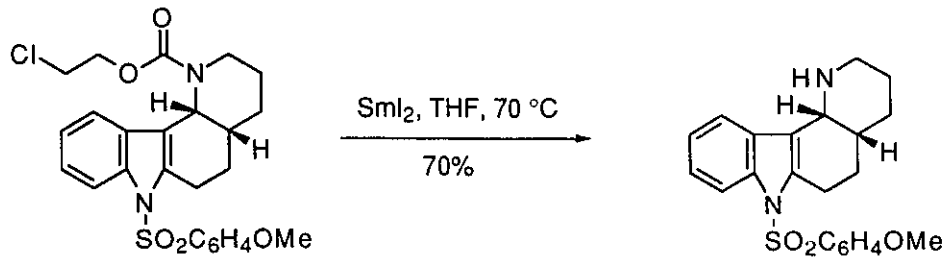


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# Claims to Original Research

1. We have reported the first example of the cyclization of alkyl and ketyl radicals onto simple hydrazones.[1] We have shown that this reaction is general and gives the hydrazine products in high chemical yields. Under appropriate conditions, high diastereoselectivites are also observed.

2. We have demonstrated that the N-N bond of hydrazines can be cleaved under complementary conditions ($H_2$, Pd/C or $SmI_2$/HMPA) which allows for a wide range of functional group compatibilities.

3. The $SmI_2$/HMPA hydrazone cyclization was used in the sysnthesis of a pentasubstituted cyclic β-hydroxyhydrazine which is related to the Allosamizoline class of antifungal and insecticidal hydroxy-amines.

4. We have utilized an intra- and intermolecular radical clock system to determine the rate constants for the cyclization of 2° alkyl radicals onto hydrazones.[2] these reactions were found to be extremely fast with rate constant for the 6-exo hydrazone cyclization: $k_{cis} = k_{trans} = 9.4 \times 10^5\ s^{-1}$ at 80 °C and for the 5-exo hydrazone cyclization: $k_{cis} = 1.1 \times 10^8\ s^{-1}$ and $k_{trans} = 4.6 \times 10^7\ s^{-1}$.

5. We have shown through calculations at the AM1 level that the hydrazone cyclizations are highly exothermic reactions (≈-12 kcal/mol), as are the related oxime ether cyclizations.

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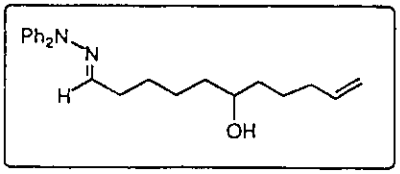
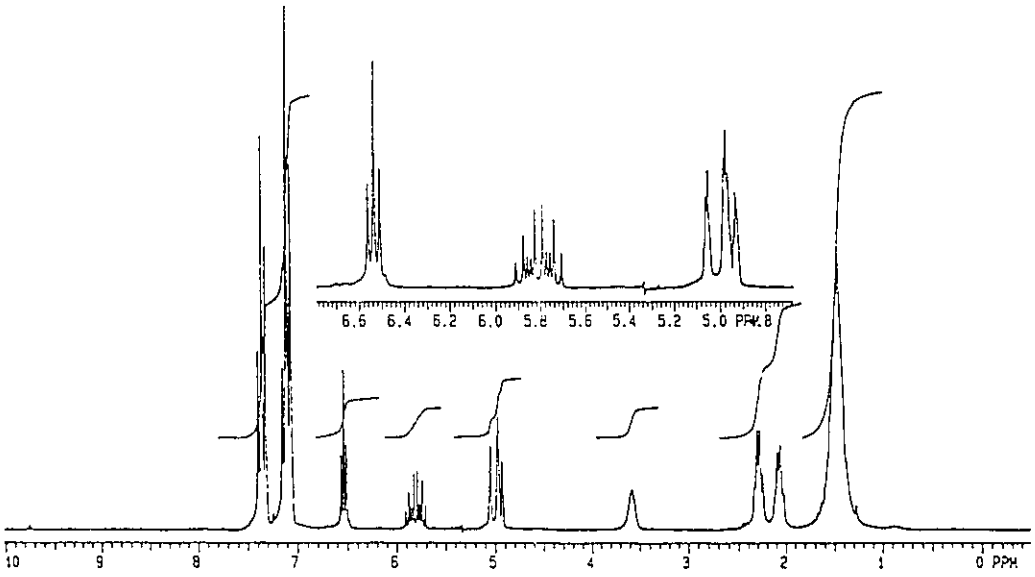
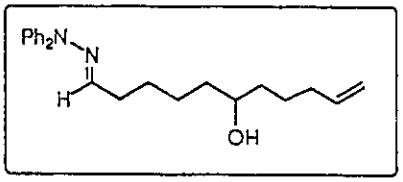
# Appendix One: Selected Spectra

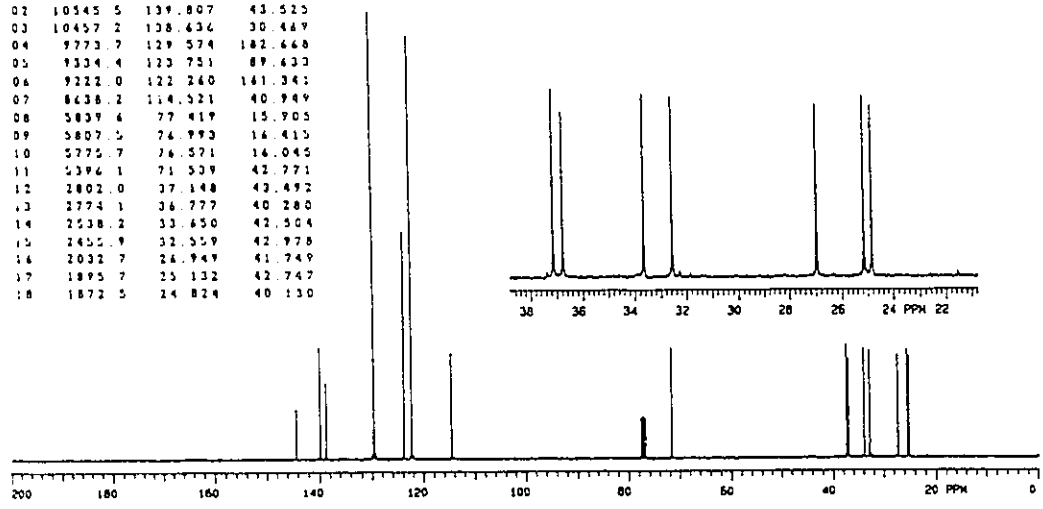


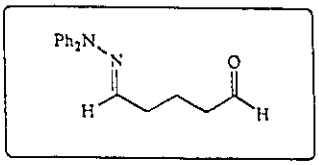



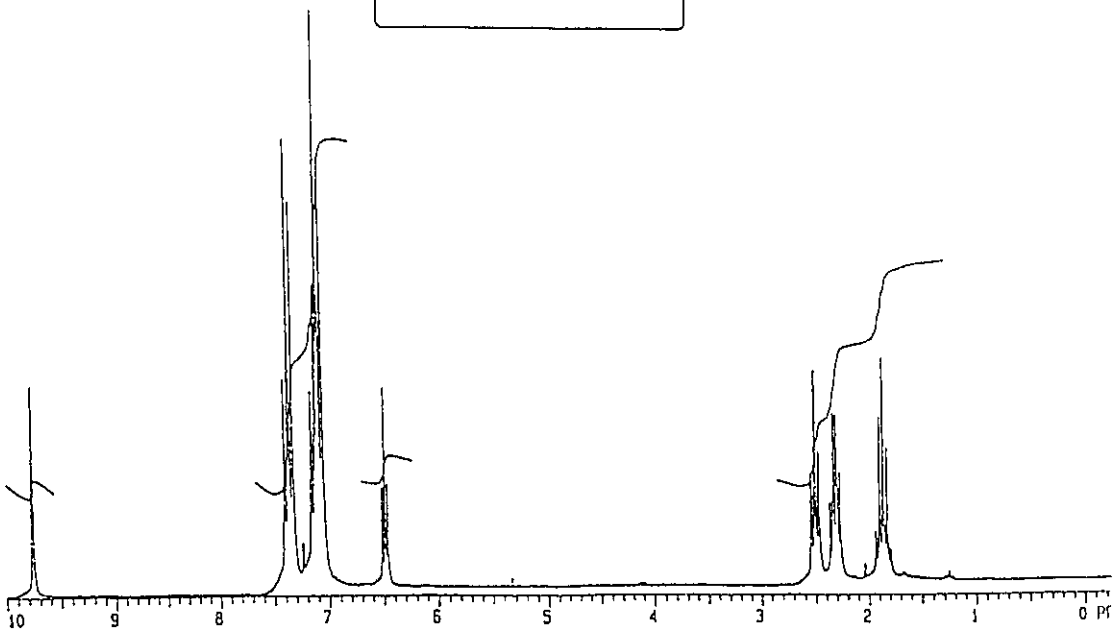



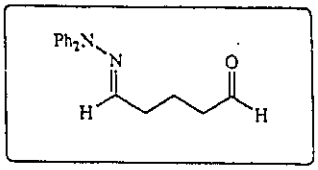

VARIAN XL-300
SPECTRAL LINES FOR TH= 11.9:
SFL= 6137.9 RFP= 5808.0

| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 10880.4 | 144.246 | 19.452 |
| 02 | 10545.5 | 139.807 | 43.525 |
| 03 | 10457.2 | 138.634 | 30.669 |
| 04 | 9773.7 | 129.574 | 182.668 |
| 05 | 9334.4 | 123.751 | 89.633 |
| 06 | 9222.0 | 122.260 | 161.345 |
| 07 | 8638.2 | 114.521 | 40.949 |
| 08 | 5839.6 | 77.419 | 15.905 |
| 09 | 5807.5 | 76.993 | 16.415 |
| 10 | 5775.7 | 76.571 | 16.045 |
| 11 | 5396.1 | 71.539 | 42.771 |
| 12 | 2802.0 | 37.148 | 43.492 |
| 13 | 2774.1 | 36.777 | 40.280 |
| 14 | 2538.2 | 33.650 | 42.504 |
| 15 | 2455.9 | 32.559 | 42.978 |
| 16 | 2032.7 | 26.949 | 41.749 |
| 17 | 1895.7 | 25.132 | 42.747 |
| 18 | 1872.5 | 24.824 | 40.130 |



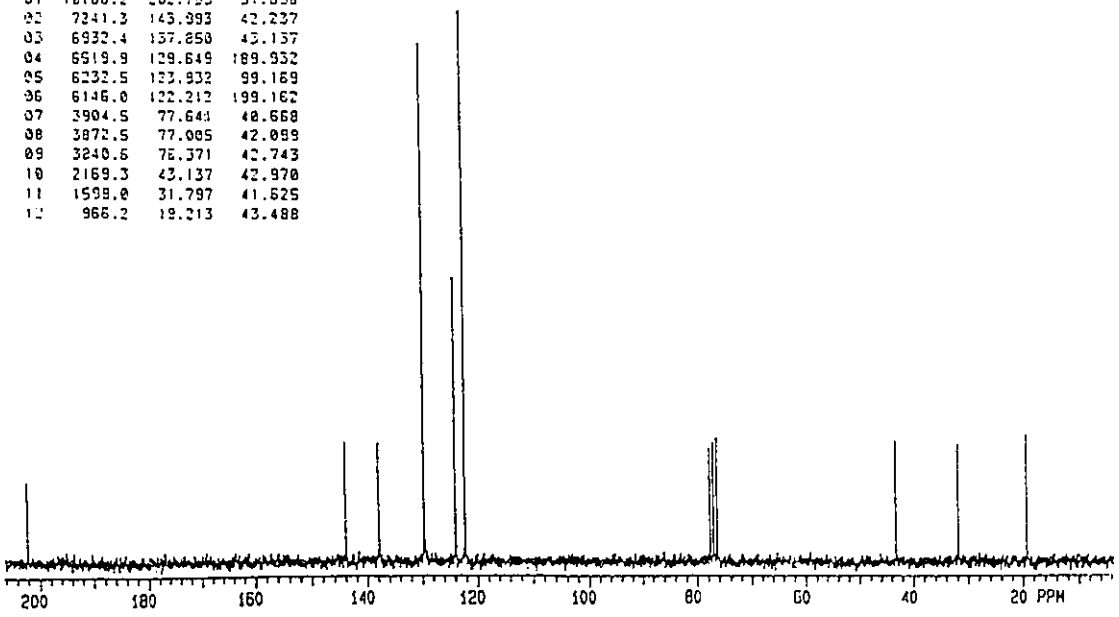


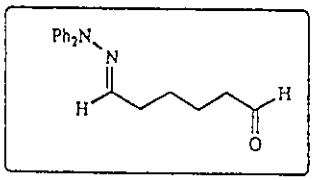



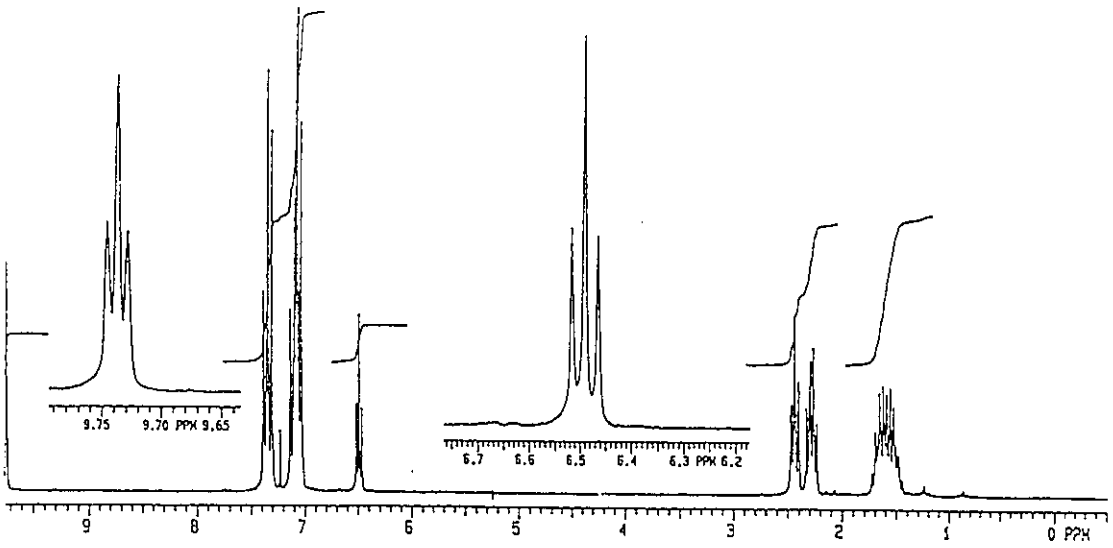



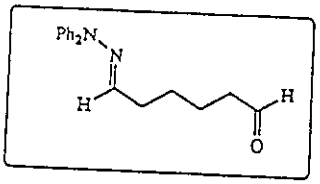

SPECTRAL LINES FOR TH= 19.69
RFL= 4519.4 RFP= 3872.3

| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 18166.2 | 202.153 | 31.656 |
| 02 | 7241.3 | 143.393 | 42.237 |
| 03 | 6932.4 | 137.250 | 43.157 |
| 04 | 6619.9 | 129.649 | 189.932 |
| 05 | 6232.5 | 123.932 | 99.169 |
| 06 | 6146.0 | 122.212 | 199.162 |
| 07 | 3904.5 | 77.644 | 48.668 |
| 08 | 3872.5 | 77.005 | 42.099 |
| 09 | 3840.6 | 76.371 | 42.743 |
| 10 | 2169.3 | 43.137 | 42.970 |
| 11 | 1598.0 | 31.797 | 41.625 |
| 12 | 966.2 | 19.213 | 43.488 |



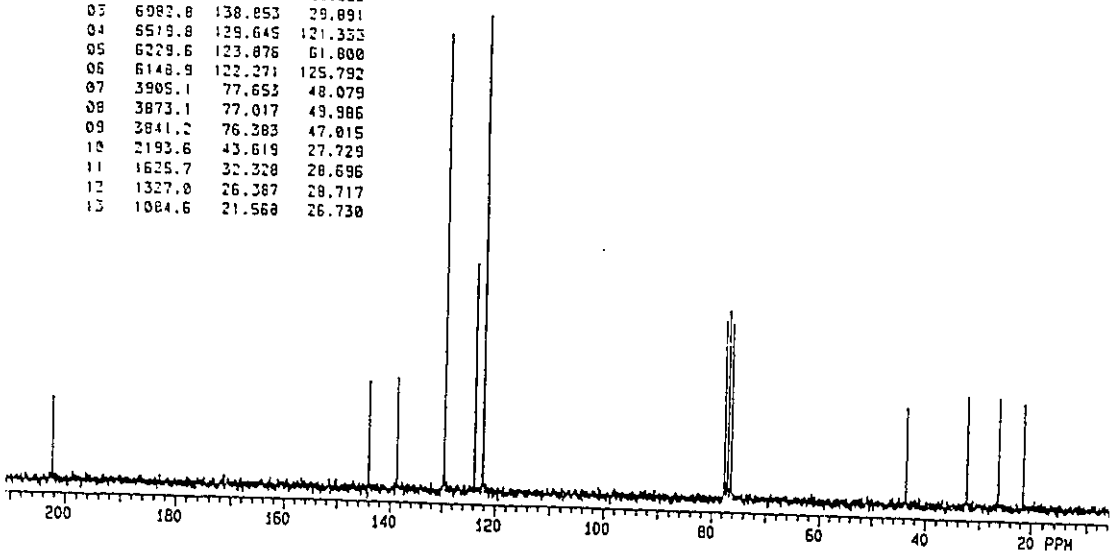


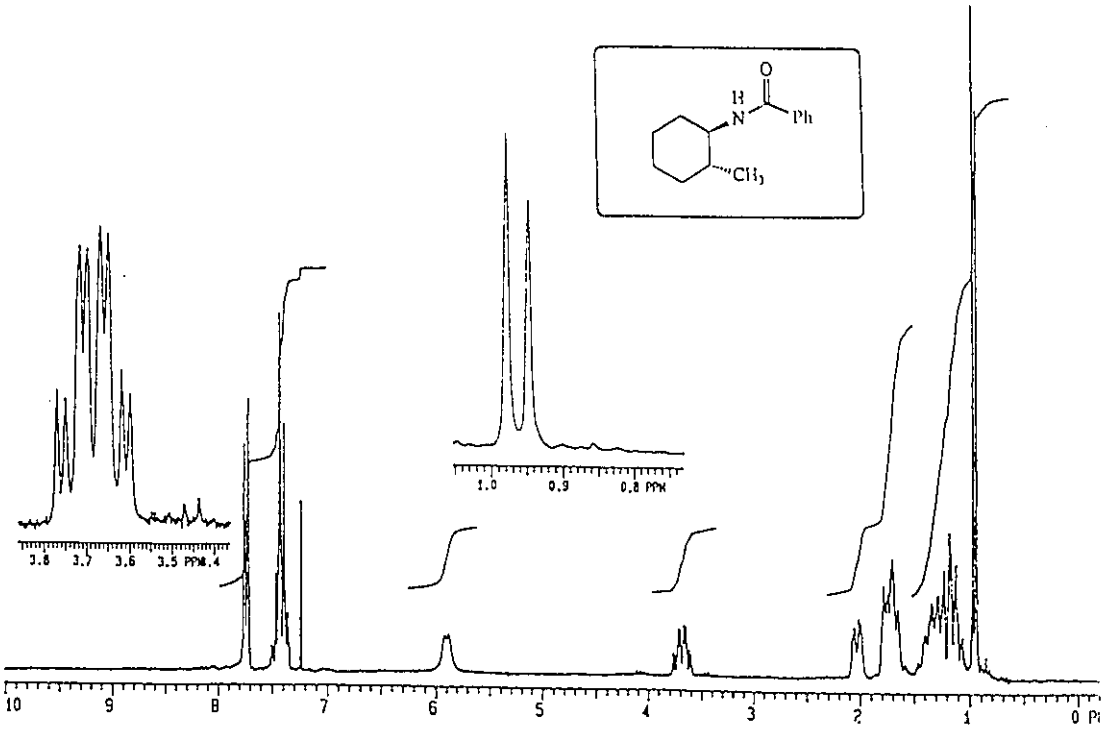



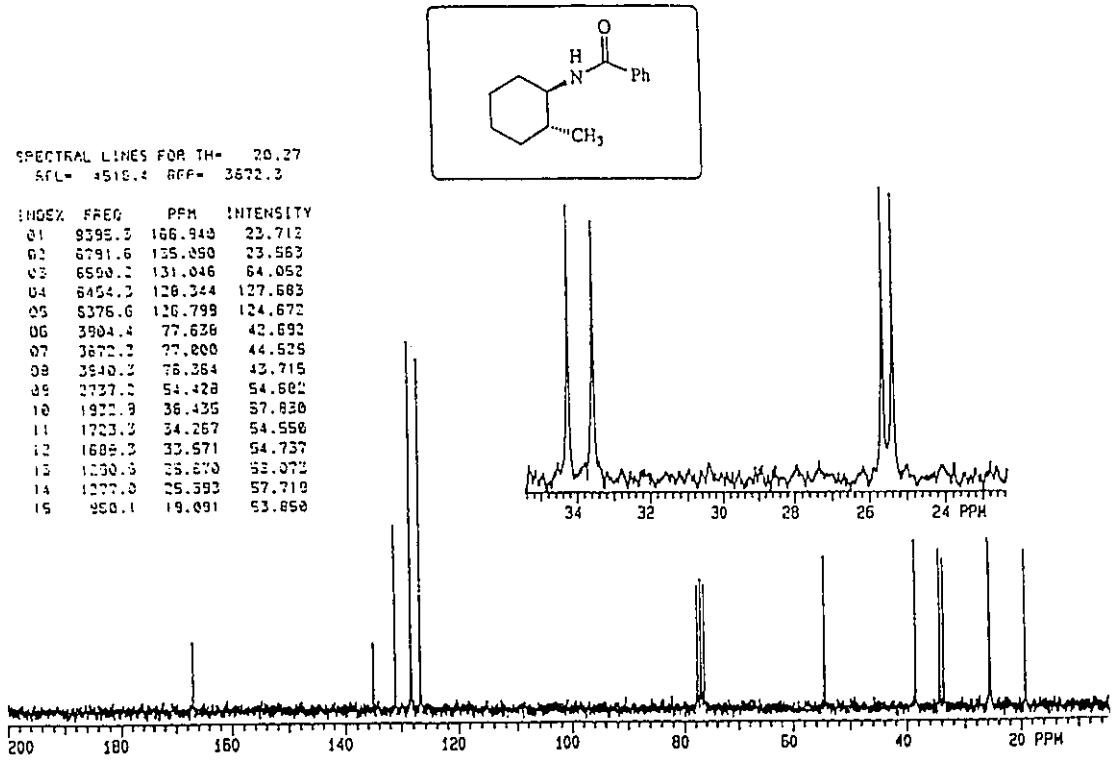



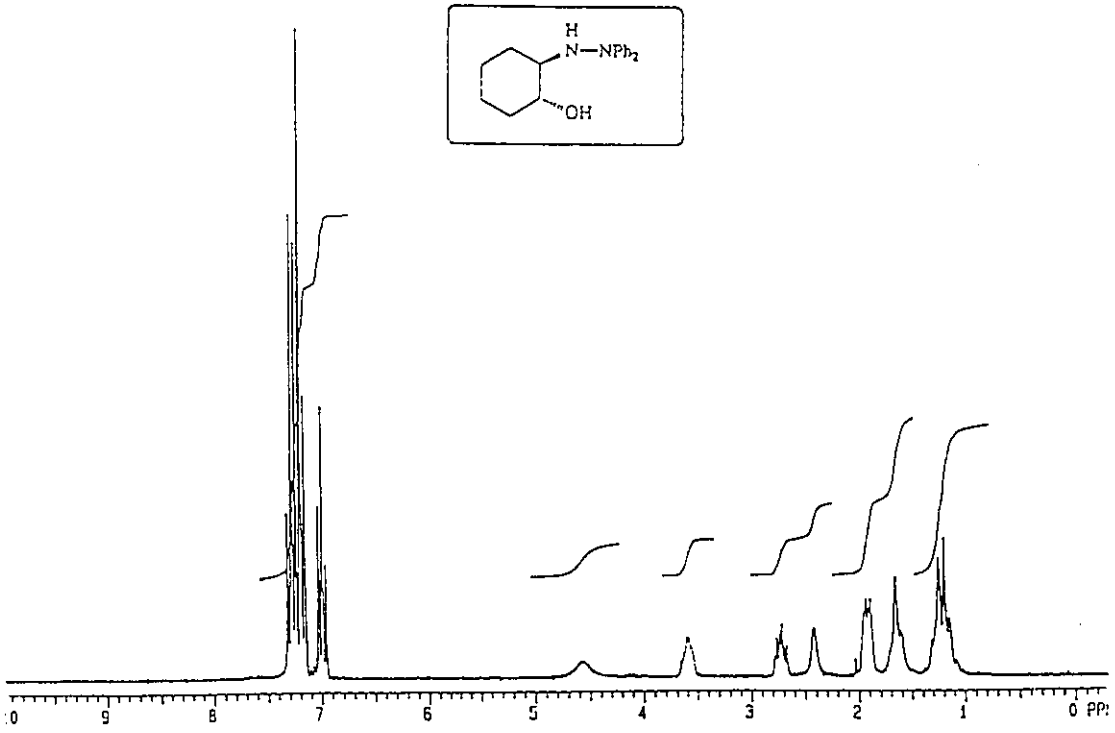

SPECTRAL LINES FOR TH= 17.23
RFL= 4484.6 RFP= 3872.3

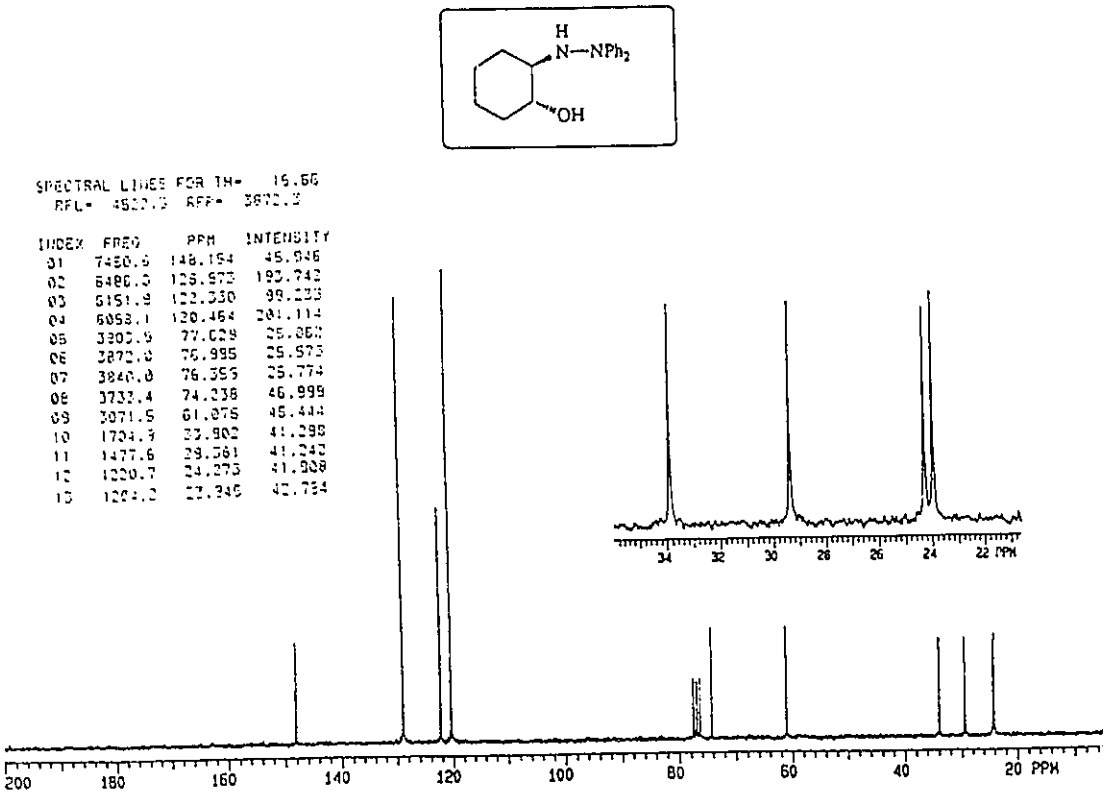
| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 10179.6 | 202.421 | 22.129 |
| 02 | 7249.7 | 144.159 | 29.525 |
| 03 | 6982.8 | 138.853 | 29.891 |
| 04 | 6519.8 | 129.645 | 121.353 |
| 05 | 6229.6 | 123.876 | 61.800 |
| 06 | 6148.9 | 122.271 | 125.792 |
| 07 | 3905.1 | 77.653 | 48.079 |
| 08 | 3873.1 | 77.017 | 49.986 |
| 09 | 3841.2 | 76.383 | 47.015 |
| 10 | 2193.6 | 43.619 | 27.729 |
| 11 | 1625.7 | 32.328 | 28.696 |
| 12 | 1327.0 | 26.387 | 28.717 |
| 13 | 1084.6 | 21.568 | 26.730 |




O
H
N
Ph
CH3
3.8 3.7 3.6 3.5 PPM
1.0 0.9 0.8 PPM
10 9 8 7 6 5 4 3 2 1 0

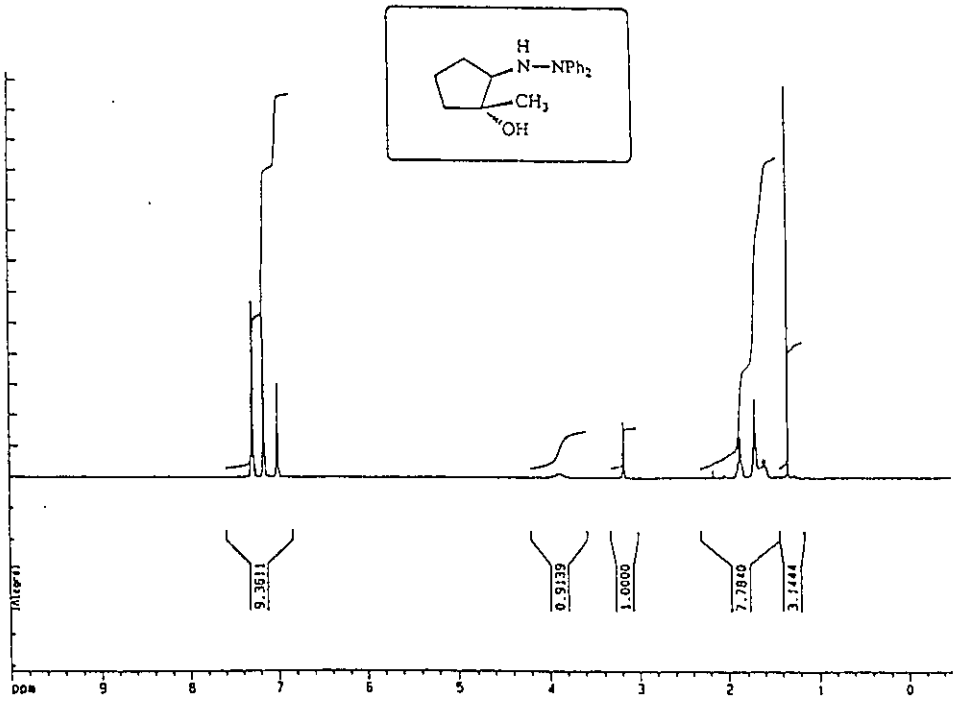

O
H
N
Ph
CH3
SPECTRAL LINES FOR TH= 20.27
SFL= 4518.4 BFF= 3672.3
INDEX FREQ PPM INTENSITY
01 9398.3 166.948 22.712
02 6791.6 135.050 23.563
03 6590.2 131.046 64.052
04 6454.2 128.344 127.683
05 6376.6 126.799 124.672
06 3904.4 77.636 42.692
07 3872.2 77.000 44.525
08 3840.2 76.364 43.715
09 2737.2 54.428 54.602
10 1932.9 38.435 57.830
11 1723.3 34.267 54.550
12 1688.3 33.571 54.737
13 1630.6 32.870 53.072
14 1277.8 25.593 57.710
15 950.1 19.091 53.850
34 32 30 28 26 24 PPM
200 180 160 140 120 100 80 60 40 20 PPM

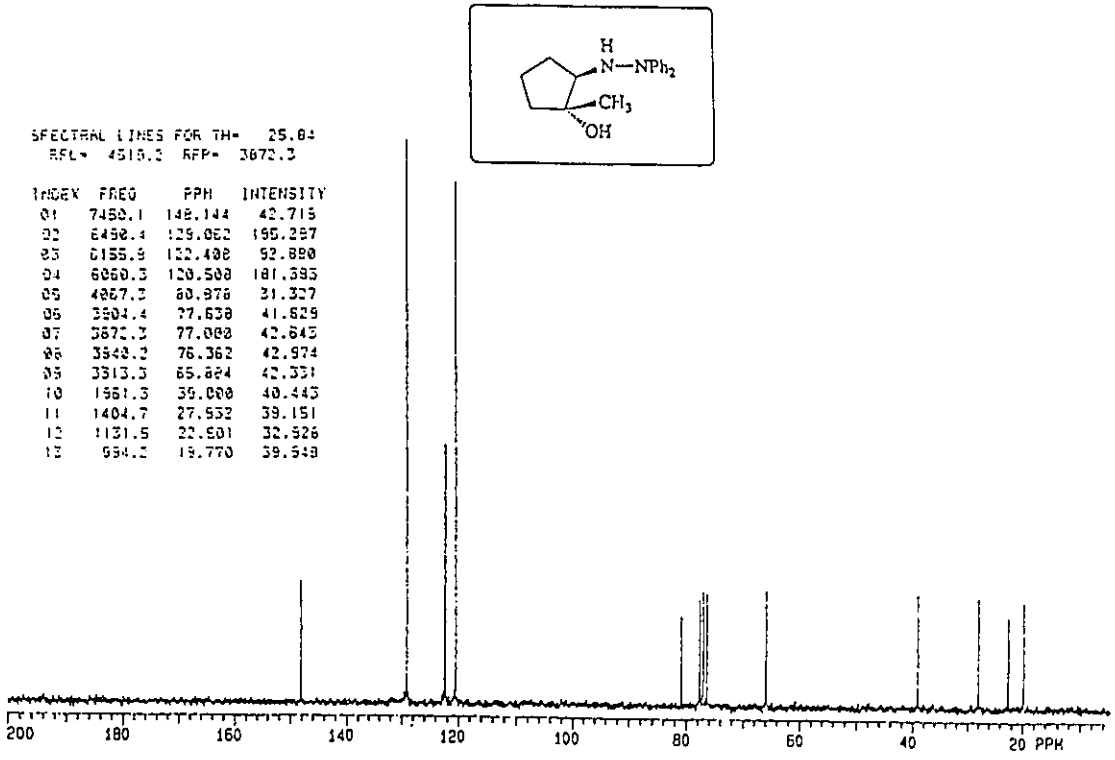


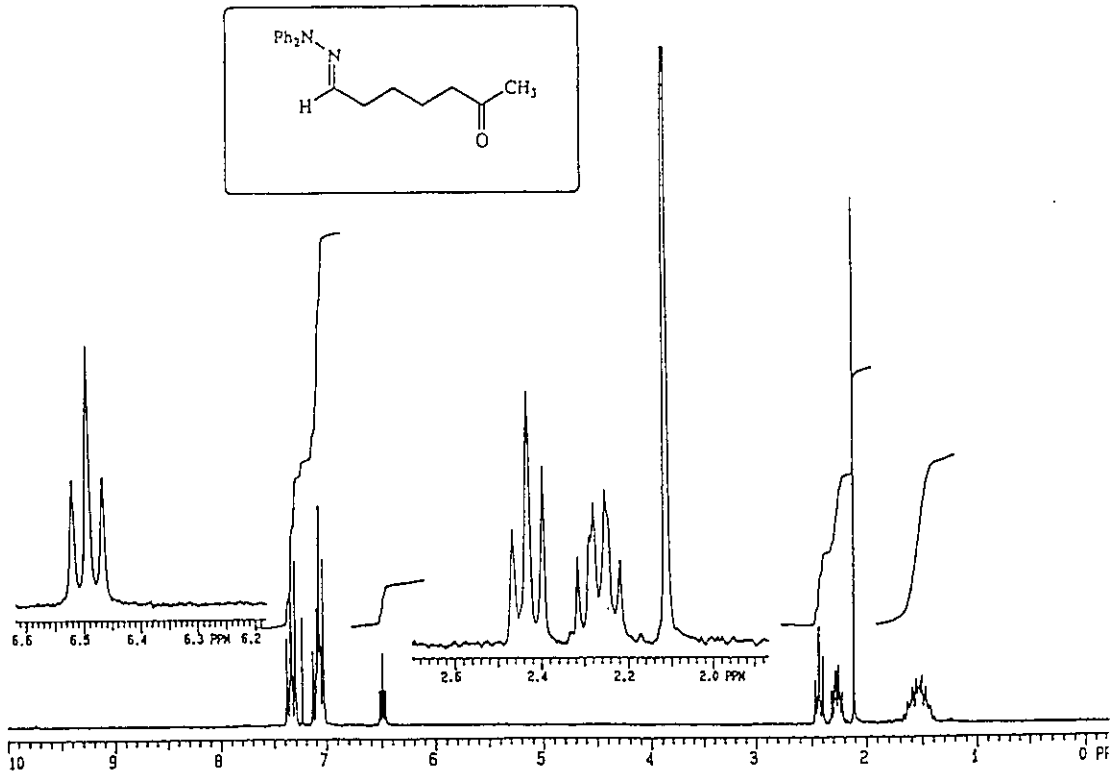



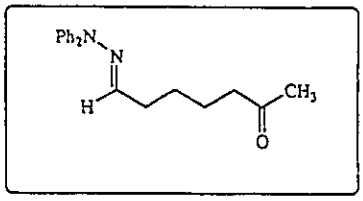

SPECTRAL LINES FOR TH= 16.66
REL= 4522.0 REF= 3872.0

| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 7450.6 | 148.154 | 45.946 |
| 02 | 6480.0 | 128.973 | 193.742 |
| 03 | 6151.9 | 122.330 | 99.233 |
| 04 | 6058.1 | 120.464 | 201.114 |
| 05 | 3903.9 | 77.629 | 25.861 |
| 06 | 3872.0 | 76.995 | 25.573 |
| 07 | 3840.0 | 76.359 | 25.774 |
| 08 | 3732.4 | 74.238 | 46.999 |
| 09 | 3071.5 | 61.076 | 45.444 |
| 10 | 1704.9 | 33.902 | 41.298 |
| 11 | 1477.6 | 29.381 | 41.243 |
| 12 | 1220.7 | 24.275 | 41.908 |
| 13 | 1204.2 | 23.946 | 42.784 |


H
N—NPh2
CH3
OH
9.3611
0.9139
1.0000
7.7840
3.7444
ppm
9
8
7
6
5
4
3
2
1
0

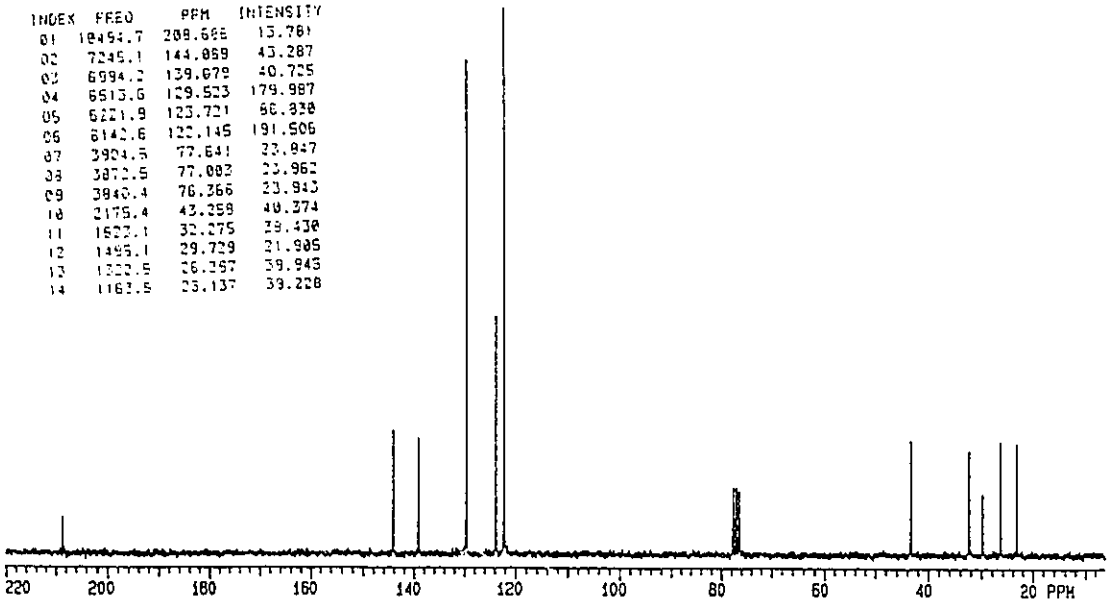

H
N—NPh2
CH3
OH
SPECTRAL LINES FOR TH= 25.84
RFL= 4515.2 RFP= 3672.2
INDEX FREQ PPM INTENSITY
01 7450.1 148.144 42.716
02 6458.4 129.062 196.287
03 6155.9 122.408 92.880
04 6060.3 120.508 181.395
05 4067.2 80.878 31.327
06 3904.4 77.638 41.629
07 3872.3 77.000 42.643
08 3843.2 76.362 42.974
09 3313.3 65.824 42.331
10 1961.3 39.000 40.445
11 1404.7 27.932 39.151
12 1131.5 22.501 32.526
13 994.2 19.770 39.948
200
180
160
140
120
100
80
60
40
20 PPM

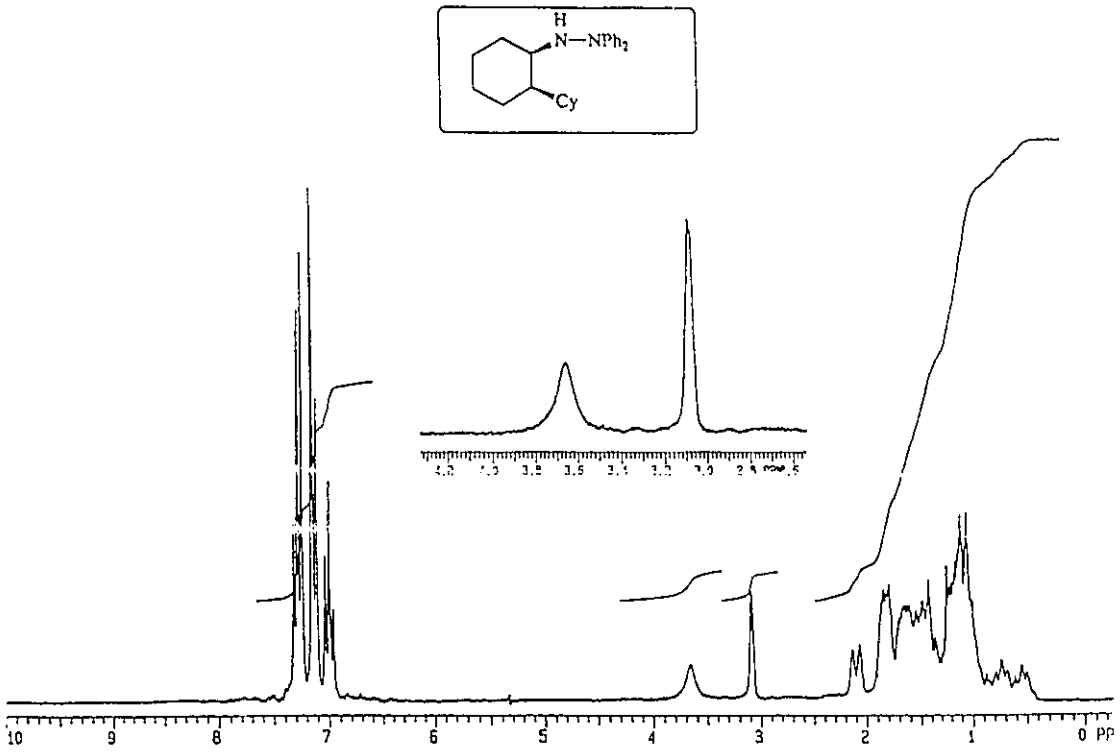


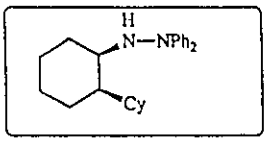




SPECTRAL LINES FOR TH= 10.86
REL= 4923.0 REF= 3872.3

| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 10454.7 | 208.666 | 13.781 |
| 02 | 7245.1 | 144.659 | 43.287 |
| 03 | 6994.2 | 139.679 | 40.725 |
| 04 | 6513.6 | 129.523 | 179.987 |
| 05 | 6221.9 | 123.721 | 66.838 |
| 06 | 6142.6 | 122.145 | 191.506 |
| 07 | 3904.5 | 77.641 | 23.847 |
| 08 | 3872.5 | 77.003 | 23.962 |
| 09 | 3840.4 | 76.366 | 23.943 |
| 10 | 2175.4 | 43.259 | 40.374 |
| 11 | 1622.1 | 32.275 | 39.430 |
| 12 | 1495.1 | 29.729 | 21.905 |
| 13 | 1322.5 | 26.297 | 39.943 |
| 14 | 1163.5 | 23.137 | 39.228 |

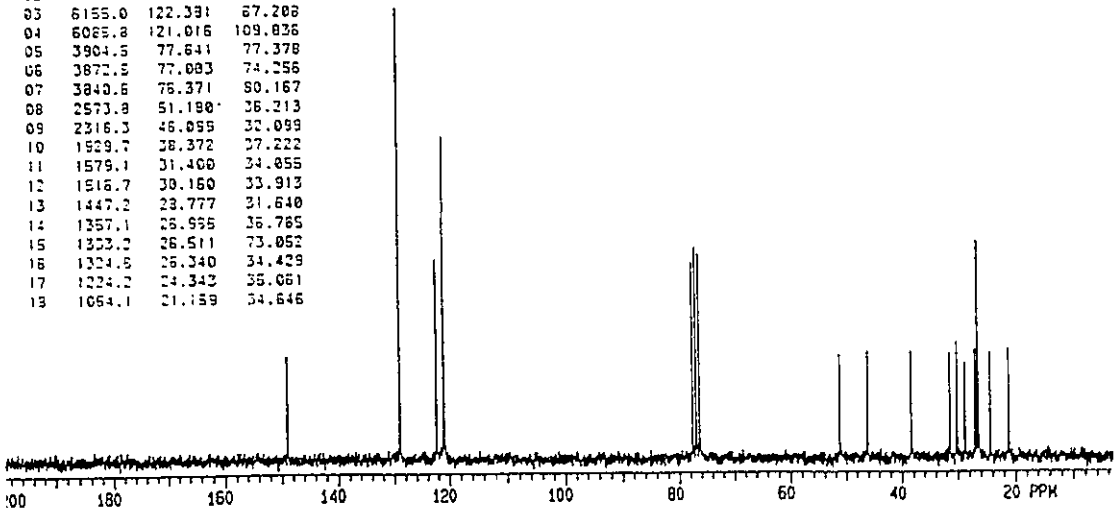


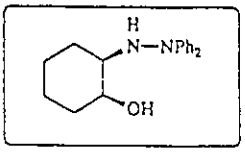


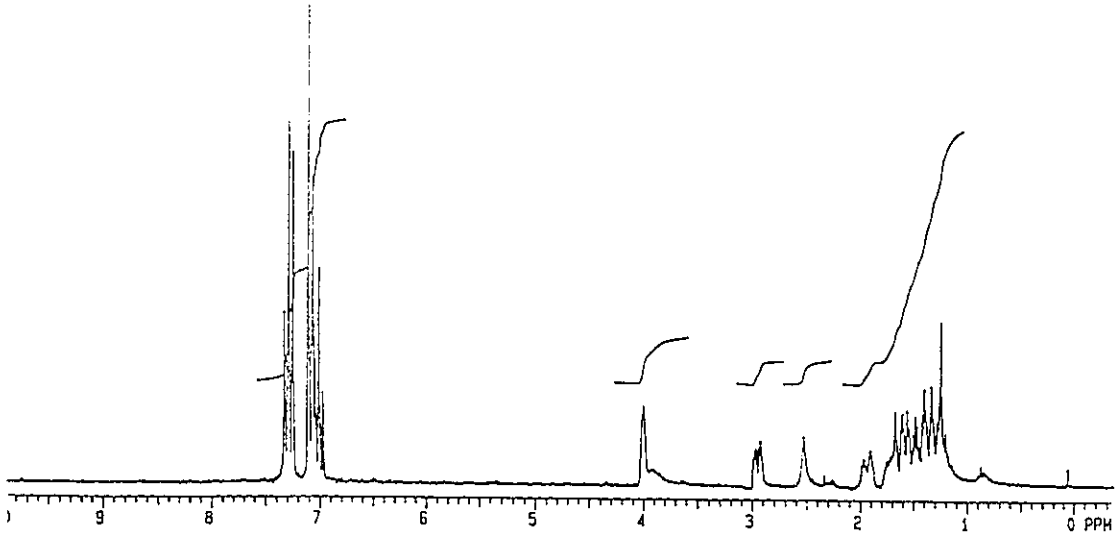



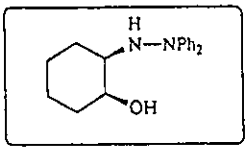

SPECTRAL LINES FOR TH= 18.08
RFL= 4515.3 RFP= 3672.3

| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 7455.1 | 148.058 | 30.315 |
| 02 | 6468.4 | 128.021 | 155.952 |
| 03 | 6155.0 | 122.391 | 87.208 |
| 04 | 6085.8 | 121.016 | 109.836 |
| 05 | 3904.5 | 77.641 | 77.378 |
| 06 | 3872.5 | 77.003 | 74.256 |
| 07 | 3840.6 | 76.371 | 80.167 |
| 08 | 2573.8 | 51.190 | 36.213 |
| 09 | 2316.3 | 46.065 | 32.099 |
| 10 | 1929.7 | 38.372 | 27.222 |
| 11 | 1579.1 | 31.400 | 34.055 |
| 12 | 1516.7 | 30.160 | 33.913 |
| 13 | 1447.2 | 28.777 | 31.640 |
| 14 | 1357.1 | 26.985 | 36.765 |
| 15 | 1333.2 | 26.511 | 73.052 |
| 16 | 1324.6 | 26.340 | 34.429 |
| 17 | 1224.2 | 24.343 | 35.061 |
| 18 | 1064.1 | 21.159 | 34.646 |



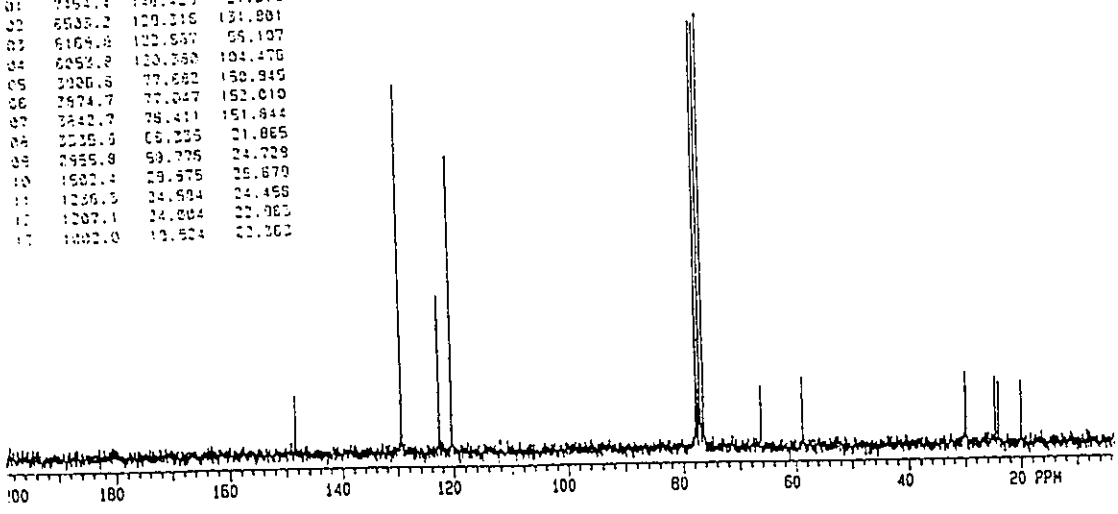


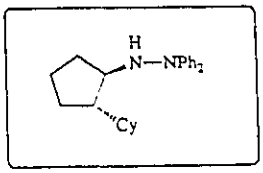



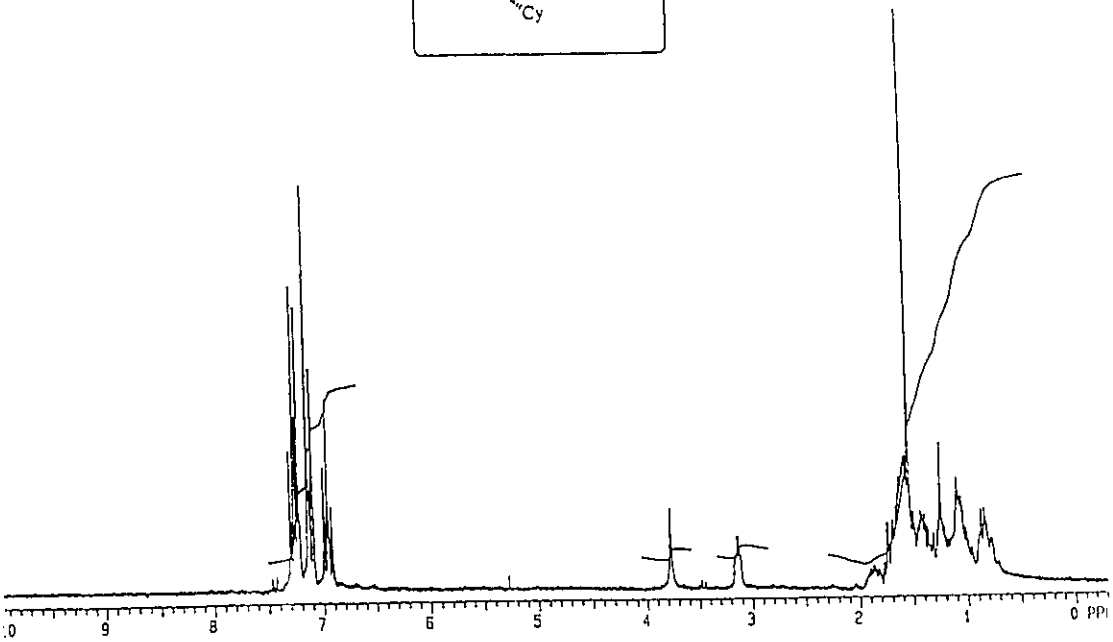



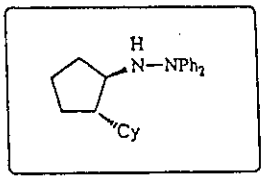

SPECTRAL LINES FOR IN= 10.11
REF= 4511.9 SFR= 3973.0

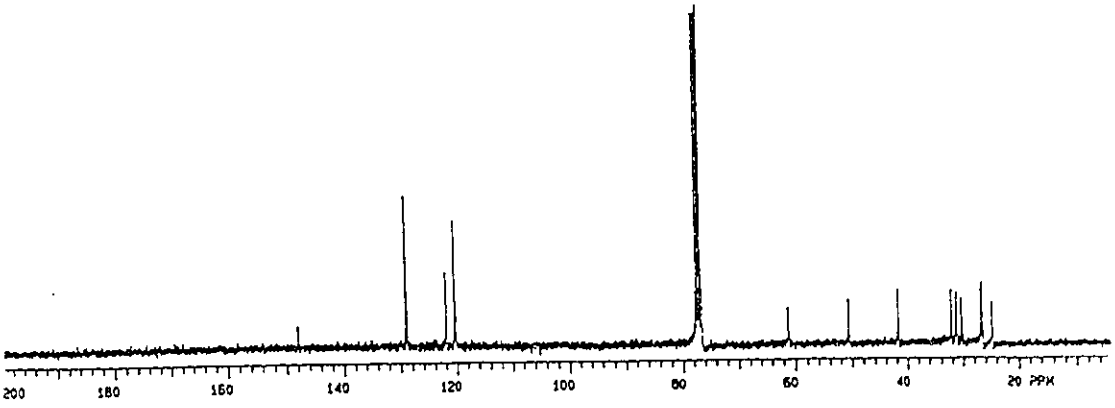
| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 7254.4 | 136.429 | 21.319 |
| 02 | 6538.2 | 122.915 | 131.881 |
| 03 | 6169.8 | 115.967 | 56.197 |
| 04 | 6052.8 | 113.765 | 104.476 |
| 05 | 3930.6 | 73.892 | 150.945 |
| 06 | 3874.7 | 72.842 | 152.010 |
| 07 | 3842.7 | 72.241 | 151.844 |
| 08 | 3535.0 | 66.455 | 21.865 |
| 09 | 3495.8 | 65.719 | 24.729 |
| 10 | 1502.4 | 28.239 | 25.879 |
| 11 | 1296.5 | 24.364 | 24.456 |
| 12 | 1287.1 | 24.187 | 22.983 |
| 13 | 1282.0 | 24.091 | 23.362 |

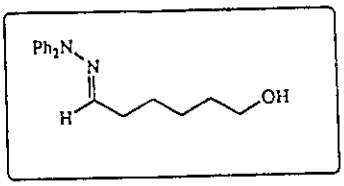


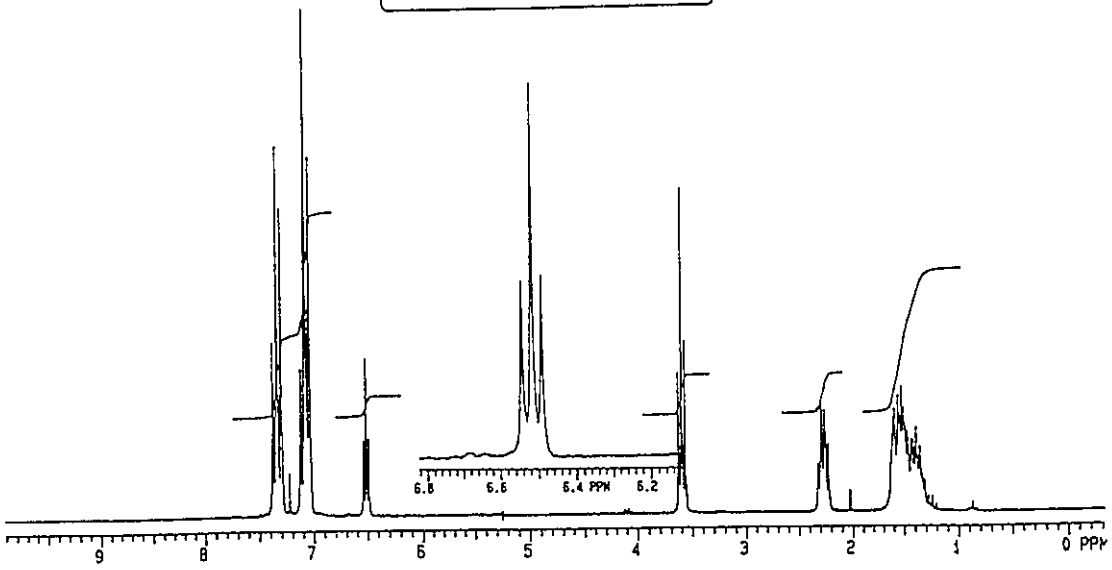

H
N—NPh2
Cy

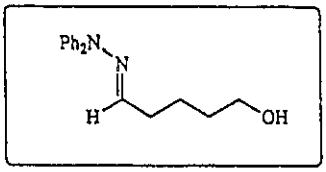

9
8
7
6
5
4
3
2
1
0 PPM


H
N—NPh2
Cy


200
180
160
140
120
100
80
60
40
20 PPM

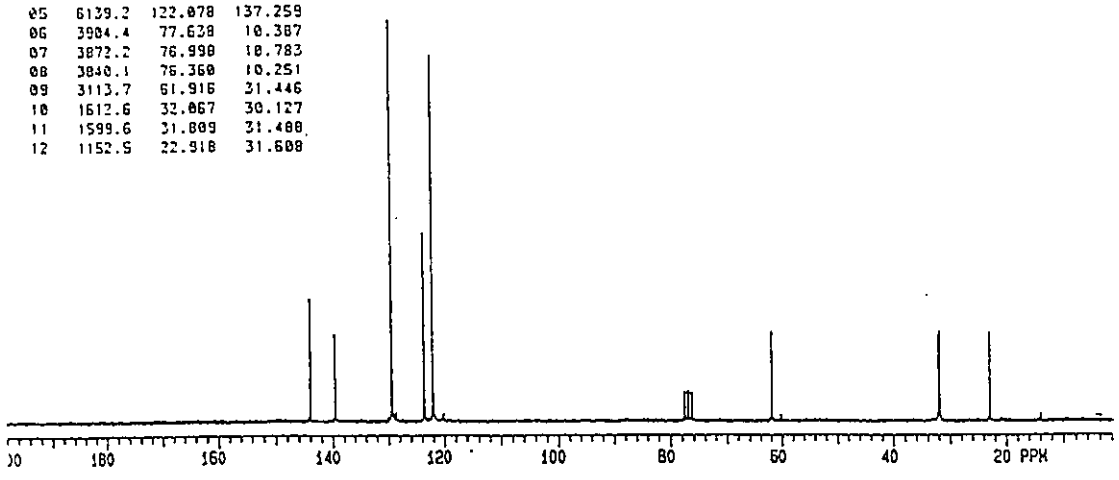


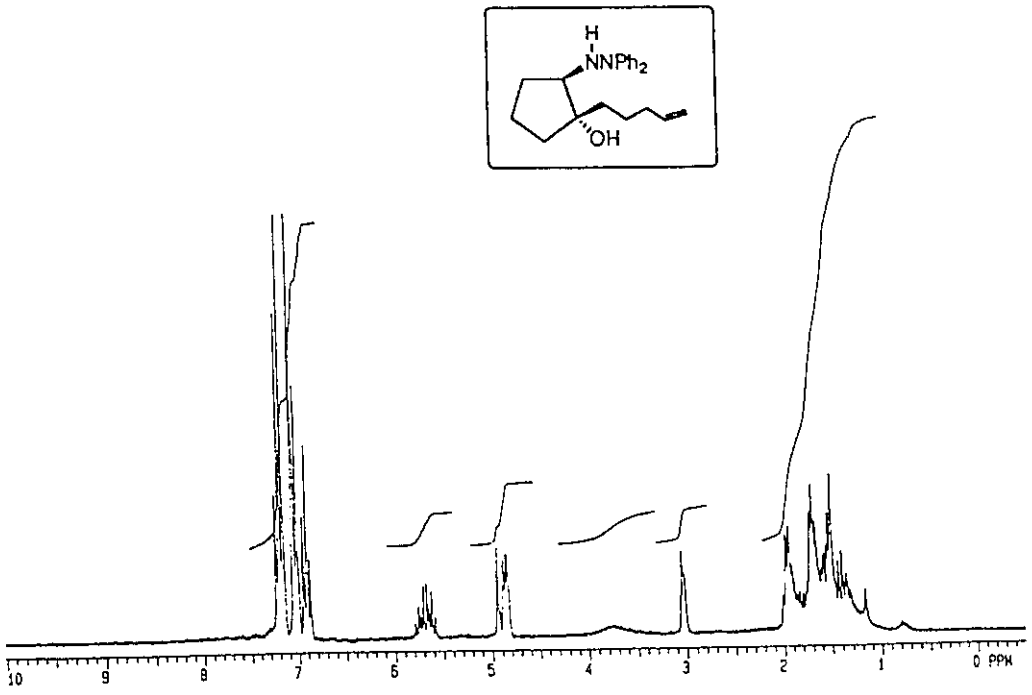



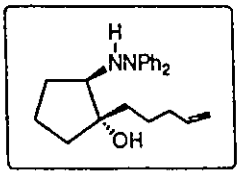




SPECTRAL LINES FOR TH= 8.73
RFL= 4531.5 RFP= 3872.3

| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 7241.4 | 143.995 | 42.980 |
| 02 | 7021.1 | 139.613 | 30.569 |
| 03 | 6508.6 | 129.423 | 145.525 |
| 04 | 6217.7 | 123.638 | 67.194 |
| 05 | 6139.2 | 122.078 | 137.259 |
| 06 | 3904.4 | 77.638 | 10.387 |
| 07 | 3872.2 | 76.998 | 10.783 |
| 08 | 3848.1 | 76.360 | 10.251 |
| 09 | 3113.7 | 61.916 | 31.446 |
| 10 | 1612.6 | 32.067 | 30.127 |
| 11 | 1599.6 | 31.809 | 31.488 |
| 12 | 1152.5 | 22.918 | 31.608 |

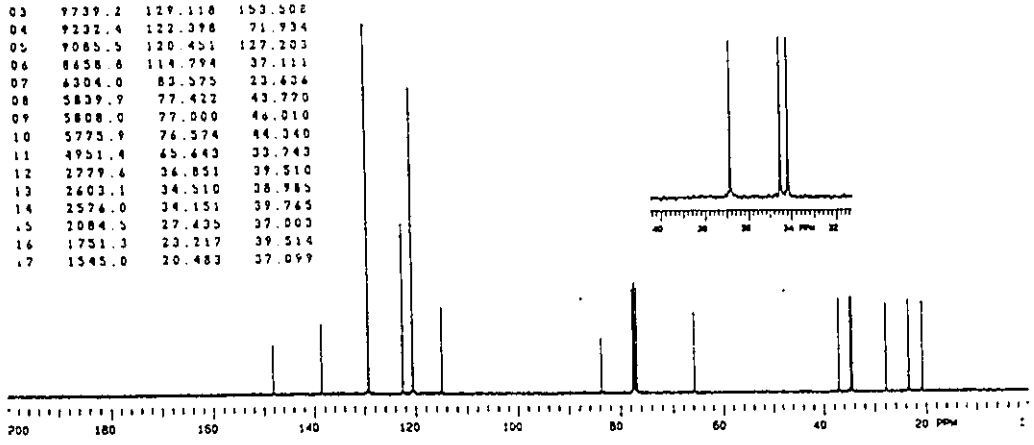


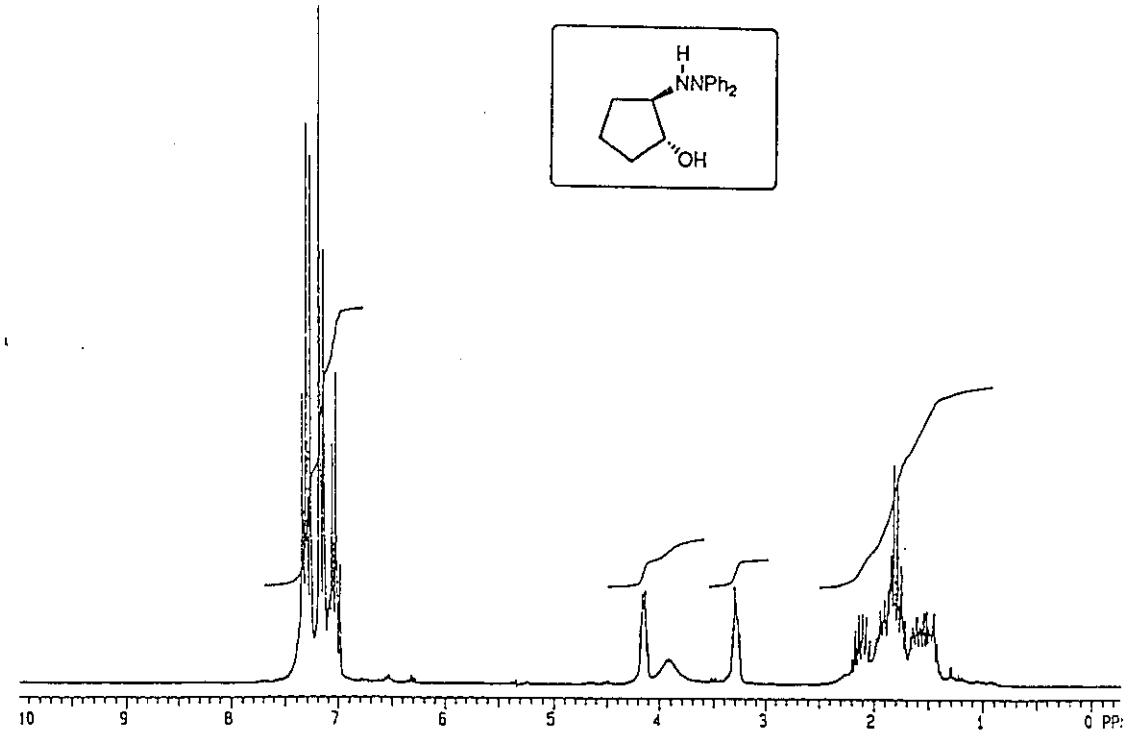


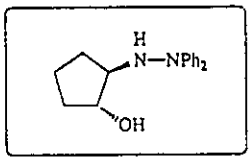




VARIAN XL-300
SPECTRAL LINES FOR TH= 13.11
RFL= 6131.9 RFP= 5808.0

| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 11149.4 | 148.078 | 21.117 |
| 02 | 10449.8 | 138.538 | 28.723 |
| 03 | 9739.2 | 129.118 | 153.508 |
| 04 | 9232.4 | 122.398 | 71.934 |
| 05 | 9085.5 | 120.451 | 127.203 |
| 06 | 8658.8 | 114.794 | 37.111 |
| 07 | 6304.0 | 83.575 | 23.636 |
| 08 | 5839.9 | 77.422 | 43.770 |
| 09 | 5808.0 | 77.000 | 46.010 |
| 10 | 5775.9 | 76.574 | 44.340 |
| 11 | 4951.4 | 65.643 | 33.743 |
| 12 | 2779.6 | 36.851 | 39.510 |
| 13 | 2603.1 | 34.510 | 38.985 |
| 14 | 2576.0 | 34.151 | 39.765 |
| 15 | 2084.5 | 27.635 | 37.003 |
| 16 | 1751.3 | 23.217 | 39.514 |
| 17 | 1545.0 | 20.483 | 37.099 |

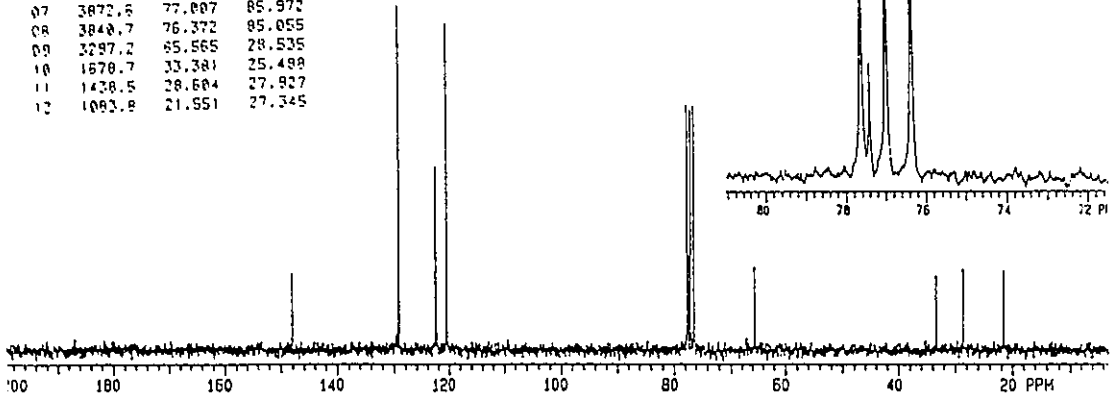


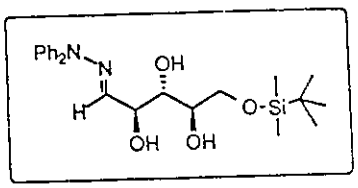



SPECTRAL LINES FOR TH= 18.85
REL= 4515.2 REF= 3872.3

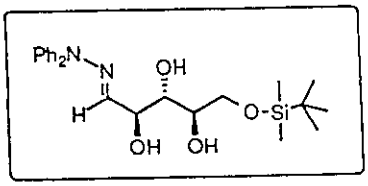
| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 7446.2 | 148.068 | 26.377 |
| 02 | 6496.1 | 129.175 | 127.408 |
| 03 | 6161.1 | 122.512 | 63.268 |
| 04 | 6057.8 | 120.459 | 122.399 |
| 05 | 3904.5 | 77.641 | 85.376 |
| 06 | 3893.6 | 77.424 | 33.064 |
| 07 | 3872.6 | 77.007 | 85.972 |
| 08 | 3848.7 | 76.372 | 85.055 |
| 09 | 3297.2 | 65.565 | 28.535 |
| 10 | 1670.7 | 33.381 | 25.488 |
| 11 | 1438.5 | 28.604 | 27.927 |
| 12 | 1083.8 | 21.551 | 27.345 |





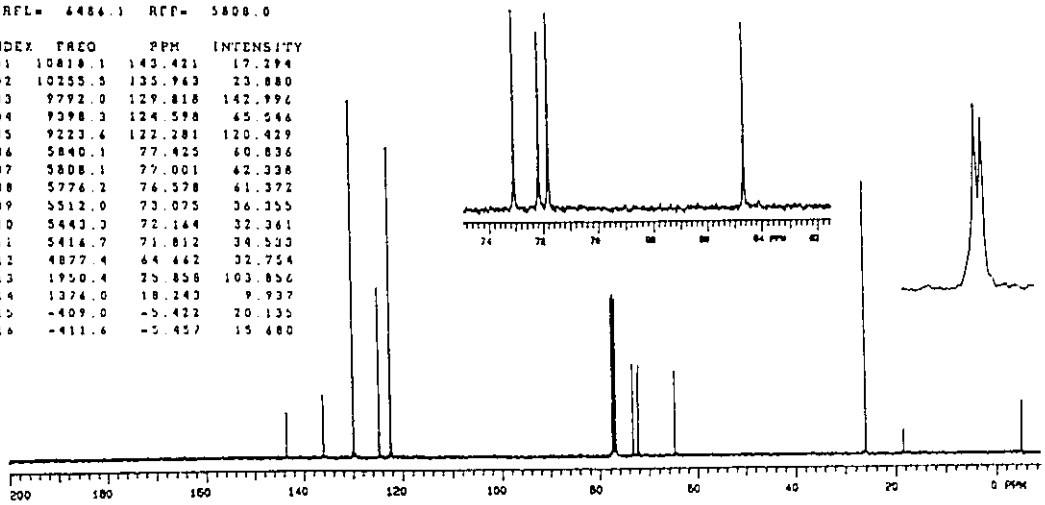


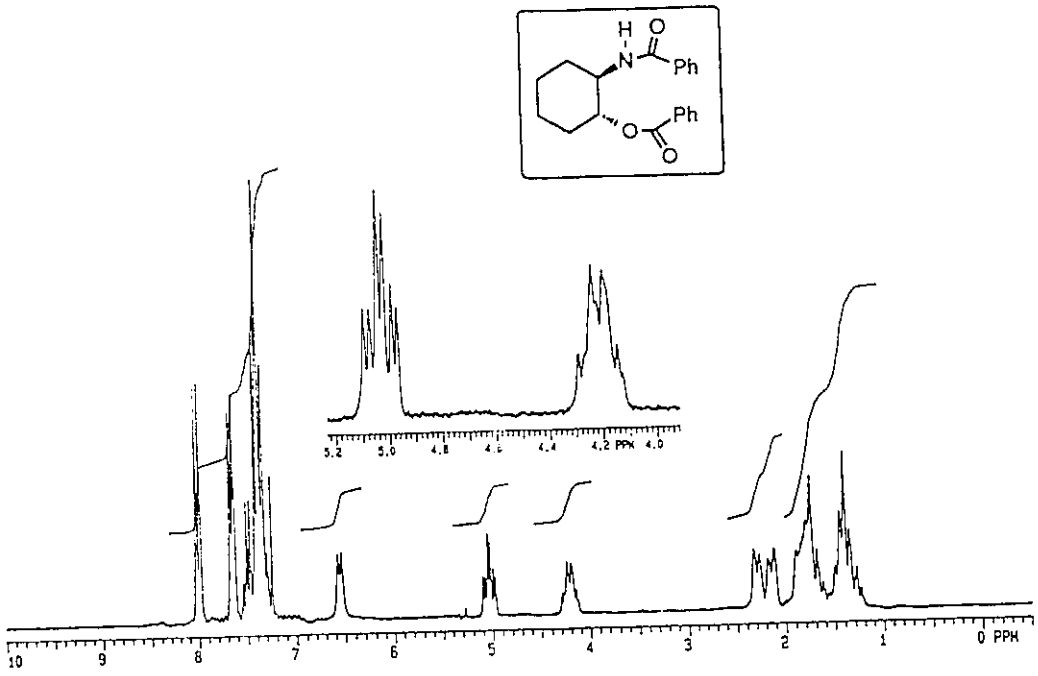


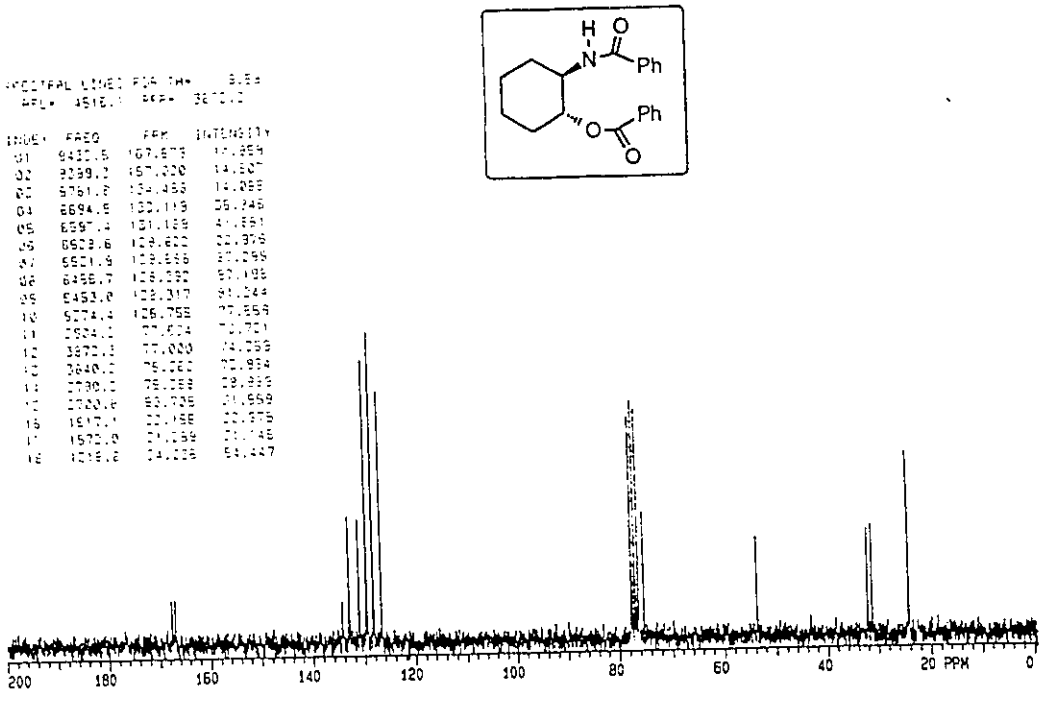


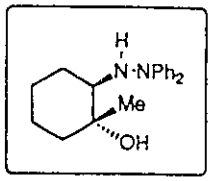

VARIAN XL-300
SPECTRAL LINES FOR TM= 7.66
RFL= 6484.1 RFP= 5808.0

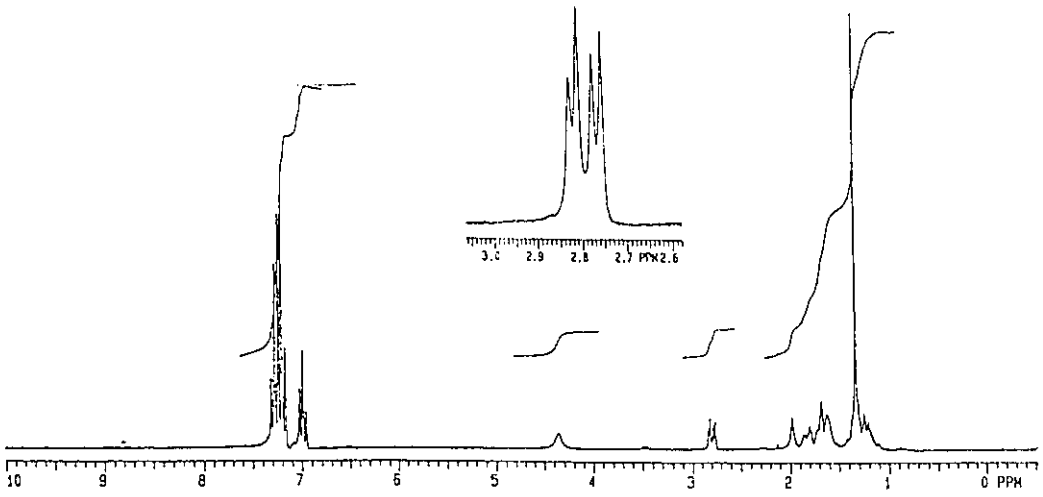
| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 10818.1 | 143.421 | 17.294 |
| 02 | 10255.5 | 135.963 | 23.880 |
| 03 | 9792.0 | 129.818 | 142.996 |
| 04 | 9398.3 | 124.598 | 65.546 |
| 05 | 9223.6 | 122.281 | 120.429 |
| 06 | 5840.1 | 77.425 | 60.836 |
| 07 | 5808.1 | 77.001 | 62.338 |
| 08 | 5776.2 | 76.578 | 61.372 |
| 09 | 5512.0 | 73.075 | 36.355 |
| 10 | 5443.3 | 72.164 | 32.361 |
| 11 | 5416.7 | 71.812 | 34.533 |
| 12 | 4877.4 | 64.662 | 32.754 |
| 13 | 1950.4 | 25.858 | 103.856 |
| 14 | 1374.0 | 18.243 | 9.937 |
| 15 | -409.0 | -5.422 | 20.135 |
| 16 | -411.6 | -5.457 | 15.680 |

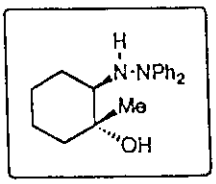



H
O
N
Ph
Ph
O
O
5.2
5.0
4.8
4.6
4.4
4.2 PPM
4.0
10
9
8
7
6
5
4
3
2
1
0 PPM


H
O
N
Ph
Ph
O
O
200
180
160
140
120
100
80
60
40
20 PPM
0

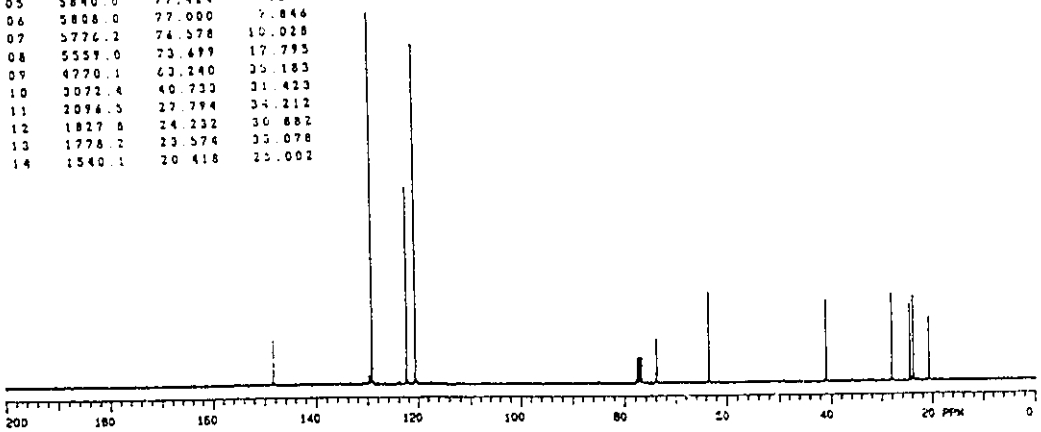


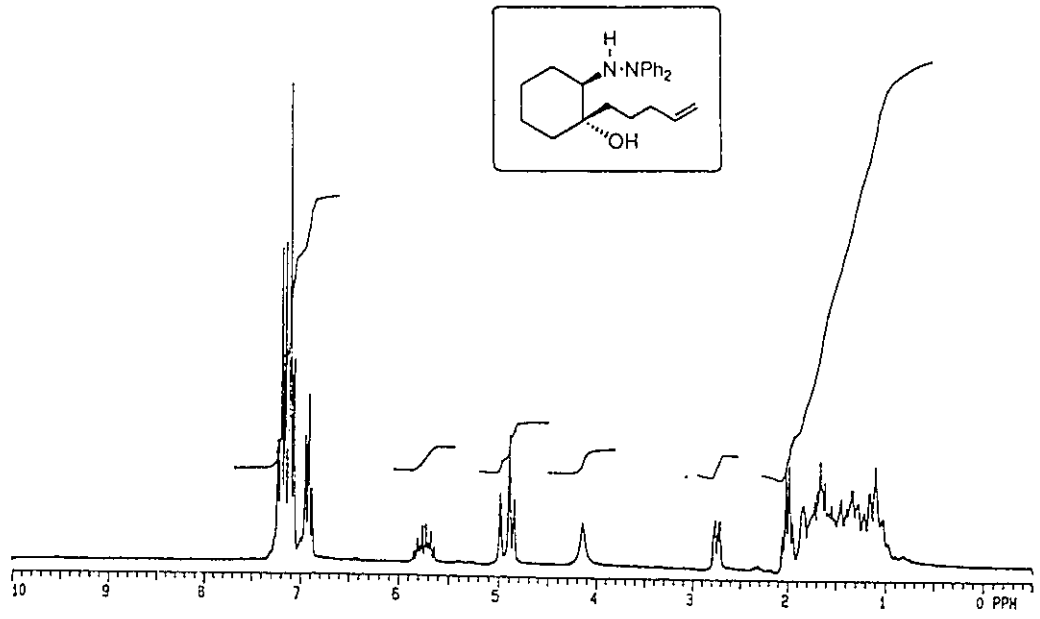



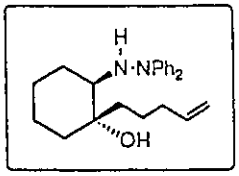




VARIAN XL-300
SPECTRAL LINES FOR TIL= 7.44
RFL= 6126.5 RFP= 5808.0

| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 11184.5 | 148.279 | 17.124 |
| 02 | 9728.1 | 128.971 | 141.735 |
| 03 | 9232.0 | 122.260 | 74.016 |
| 04 | 9086.3 | 120.468 | 130.015 |
| 05 | 5840.0 | 77.424 | 7.593 |
| 06 | 5808.0 | 77.000 | 7.846 |
| 07 | 5776.2 | 76.578 | 10.028 |
| 08 | 5559.0 | 73.699 | 17.795 |
| 09 | 4770.1 | 63.240 | 35.183 |
| 10 | 3072.4 | 40.733 | 31.423 |
| 11 | 2096.5 | 27.794 | 34.212 |
| 12 | 1827.8 | 24.232 | 30.882 |
| 13 | 1778.2 | 23.574 | 33.078 |
| 14 | 1540.1 | 20.418 | 25.002 |






VARIAN XL-300
SPECTRAL LINES FOR TH= 33 39
RFL= 6132.9 RFP= 5808.0

| INDEX | FREQ | PPM | INTENSITY |
|---|---|---|---|
| 01 | 11193.7 | 148.401 | 21.840 |
| 02 | 10476.6 | 138.893 | 31.308 |
| 03 | 9732.4 | 129.027 | 182.079 |
| 04 | 9235.1 | 122.434 | 86.325 |
| 05 | 9100.8 | 120.654 | 164.793 |
| 06 | 8637.4 | 114.510 | 42.602 |
| 07 | 5809.8 | 77.021 | 36.807 |
| 08 | 5807.9 | 76.999 | 37.660 |
| 09 | 5775.1 | 76.573 | 37.292 |
| 10 | 5654.4 | 74.970 | 21.231 |
| 11 | 4814.5 | 63.829 | 24.397 |
| 12 | 2718.9 | 36.044 | 36.044 |
| 13 | 2590.2 | 34.339 | 44.537 |
| 14 | 2322.5 | 30.790 | 15.914 |
| 15 | 2058.1 | 27.286 | 34.621 |
| 16 | 1813.8 | 24.046 | 32.024 |
| 17 | 1730.7 | 22.945 | 38.503 |
| 18 | 1638.6 | 21.724 | 41.60- |