NOVEL SYNTHETIC TRANSFORMATIONS INVOLVING RADICAL CATIONS GENERATED BY CERIUM(IV) AMMONIUM NITRATE

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BY

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DECLARATION

I hereby declare that the matter embodied in the thesis entitled "**NOVEL SYNTHETIC TRANSFORMATIONS INVOLVING RADICAL CATIONS GENERATED BY CERIUM(IV) AMMONIUM NITRATE**" is the result of the investigations carried out by me in the Organic Chemistry Division of Regional Research Laboratory (CSIR), Trivandrum, under the supervision of Dr. Vijay Nair and the same has not been submitted elsewhere for a degree.

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CERTIFICATE

This is to certify that the work embodied in the thesis entitled "**NOVEL SYNTHETIC TRANSFORMATIONS INVOLVING RADICAL CATIONS GENERATED BY CERIUM(IV) AMMONIUM NITRATE**" has been carried out by Ms. Roshini Rajan under my supervision at the Organic Chemistry Division of the Regional Research Laboratory (CSIR), Trivandrum and the same has not been submitted elsewhere for any other degree.

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PREFACE

One of the fundamental tasks in the synthesis of complex organic molecules is the construction of carbon-carbon bonds. A wide spectrum of synthetic methods involving ionic, pericyclic and radical reactions are available for carbon-carbon bond formation. Of these, synthetic organic chemists have made only limited use of free radical reactions until recently. Today, however the use of radicals in organic synthesis has increased dramatically and has grown in importance to the point where they are routinely considered in strategy level planning of complex targets. Of the principal methods available for the generation of radicals *viz*., chemical, electrochemical, and photochemical, electron transfer processes based on chemical methods deserve special mention. Chemical electron transfer oxidation can be accomplished using a variety of metal salts, of which manganese(III) acetate and cerium(IV) ammonium nitrate (CAN) have attracted considerable attention. Although CAN has been shown to offer many advantages over Mn(III) acetate, its potential has remained largely untapped. Therefore, a detailed investigation aimed at exploring the synthetic potential of CAN was undertaken. The results obtained are presented in the thesis entitled **"Novel Synthetic Transformations Involving Radical Cations Generated by Cerium(IV) Ammonium Nitrate"**.

The thesis is divided into four chapters. Relevant references are given at the end of each chapter.

A general introduction to radical reactions and various synthetic transformations mediated by CAN is presented in chapter 1.

The second chapter describes a facile one-pot synthesis of 1-amino-4-aryltetralin derivatives by the CAN induced cyclodimerization of various styrenes. General information on the experimental procedures is given in this chapter.

The third chapter deals with the reactivity of four membered ring systems towards cerium(IV) ammonium nitrate. This chapter is divided into three sections. The first section is concerned with the reactivity of cyclobutanes with CAN. The second section deals with the reactivity of monoterpenes of the pinene family containing four membered rings as part of their structural framework towards

CAN. The CAN mediated regiospecific ring opening of oxetanes constitutes the final section.

Chapter 4 describes a mild and efficient method for the preparation of dimethyl, diethyl and diallyl acetals of aromatic aldehydes mediated by CAN.

It may be mentioned that each chapter of the thesis is presented as an independent unit and therefore the structures, schemes and figures are numbered chapter-wise.

A summary of the work is given towards the end of the thesis.

ABBREVIATIONS

AIBN	: azoisobisbutyronitrile
Boc	: *t*-butoxy carbonyl
br s	: broad singlet
CAN	: cerium(IV) ammonium nitrate
CCE	: constant current electrode
CNS	: central nervous system
d	: doublet
dd	: doublet of doublet
DCA	: dicyanoanthracene
DEPT	: distortionless enhancement by polarization transfer
DMAP	: *N,N*-dimethylaminopyridine
DME	: dimethoxyethane
DMP	: dimethoxypropane
DMSO	: dimethyl sulfoxide
EI	: electron impact
FAB	: fast atom bombardment
HPLC	: high pressure liquid chromatography
HRMS	: high resolution mass spectrum
IR	: infrared
J	: coupling constant
m	: multiplet
Me	: methyl
mg	: milligram
mL	: milliliter
mp	: melting point
NMR	: nuclear magnetic resonance
nOe	: nuclear Overhauser effect
NOESY	: nuclear Overhauser enhancement spectroscopy
p	: *para*
PMB	: *para*-methoxybenzyl
PPA	: polyphosphoric acid
PPTS	: pyridinium *p*-toluenesulfonate
s	: singlet
t	: triplet
TEMPO	: 2,2,6,6-tetramethyl-1-piperidinyloxy free radical
tert	: tertiary
tlc	: thin layer chromatography
TMS	: tetra methyl silane

Chapter 1

A Brief Survey of Synthetic Transformations Mediated by Cerium(IV) Ammonium Nitrate

1.1 Introduction

The thesis focuses on the chemistry of radicals and radical cations generated by Cerium(IV) Ammonium Nitrate (CAN) *via* oxidative electron transfer. In this chapter a brief review of various synthetic transformations induced by CAN is presented as a prologue to the present work. In order to put things in perspective, a brief retrospect into the genesis, evolution and merits of radical methodology with special emphasis on chemical electron transfer reactions is discussed first.

1.2 Radical Reactions in Organic Synthesis

The history of organic free radicals dates back to Moses Gomberg's monumental discovery of the triphenylmethyl radical in 1900.[1] Three decades later, elaborate mechanistic studies on radical reactions were carried out by Hey and Waters.[2] In spite of a clear understanding of the mechanistic background, radical reactions were misconstrued to be erratic, prone to give intractable mixtures and hence radicals were regarded as intermediates with limited synthetic potential. This view of radicals probably arose because of the erroneous notion that highly reactive intermediates cannot be selective. A dramatic change in this outlook which initiated an upsurge of interest in radical methodology, particularly over the last couple of decades can be attributed in large measure to the conceptualization and demonstration by Stork that the controlled generation and

addition of vinyl radicals to π- systems constitutes a powerful method for complex carbocyclic construction.[3] The insightful investigations of Julia, Beckwith, Ingold, and Giese have also contributed to a better appreciation of the structure and reactivity of radicals.[4-7] A number of others, most notably Curran and Pattenden, have made significant contributions to the general acceptance of radical methodology in the synthesis of biologically important molecules.[8,9] At present radical reactions occupy a pivotal place in organic synthesis comparable to those of ionic and pericyclic reactions. It is also worthy of note that a number of organic reactions previously believed to occur *via* ionic intermediates are now recognized to involve radical intermediates.

Radicals are now valued synthetic intermediates because they can be used for transformations that are often difficult to accomplish by other means and because transformations involving free radicals typically occur under very mild and neutral conditions where both selectivity and tolerance of functional groups are high. The kinds of protection schemes that are often essential for synthetic sequences of ionic reactions are rarely required for radical reactions as carbon centered radicals are inert towards common functional groups such as -NH and -OH groups. However, protecting groups may still be required for other steps in a synthetic sequence, and nearly all types of protecting groups are tolerated in radical reactions. The kinds of β-elimination reactions and 1,2 shifts that pervade anionic (organometallic) and cationic chemistry are rare in radical chemistry. Radical reactions usually proceed with a high degree of chemo-, regio-, and stereocontrol. Solvent effects are minimal in radical reactions. A unique property of radicals which differentiates them from carbocations and carbanions is the tendency of recombination which is unlikely with other species.

1.3 Electron Transfer Reactions

Of the various methods developed for the generation of radicals, redox processes based on electron transfer deserve special mention. Electron transfer is one of the most elementary processes in chemistry.[10] In a typical electron transfer

process the two species that are involved are the donor **D** and the acceptor **A**, and the electron transfer process can be represented by the following equilibrium.

$$D + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [D^{+\cdot}A^{-\cdot}] \underset{k_4}{\overset{k_3}{\rightleftharpoons}} D^{+\cdot} + A^{-\cdot}$$

The feasibility of the initial electron transfer to generate the ion pair $[D^{+\cdot}A^{-\cdot}]$ depends on the oxidation potential of the donor (E^0_{ox}) and the reduction potential of the acceptor (E^0_{red}). The fate of the ion pair decides the further course of the reaction. Eventhough the deciding factor in the formation of the ion pair is the oxidation/reduction potential of the donor/acceptor, knowledge of the potential is not sufficient to predict the feasibility of an electron transfer reaction. The most important factor, however, is the behavior of the contact ion pair and its further reaction, *viz.*, conversion to afford the products or back electron transfer to regenerate the reactants. The fate of the ion pair, and hence the outcome of the reaction is determined by the relative rates of these competing reactions. Although the reactivity cannot be predicted from the knowledge of redox potentials of the species involved, whether the ion pair is formed or not depends on the potential of the reacting species.[11]

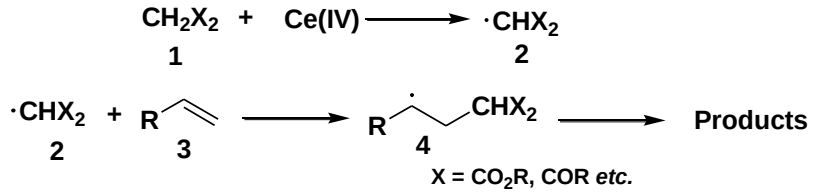
The term electron transfer refers to both oxidation as well as reduction. Oxidative electron transfer leads to the formation of radical cations. Radical cations as the term indicates are species having both a cationic and a radical center. The radical and cationic sites may be on the same atom or on distal atoms, species of the latter kind being called distonic species. Reactions involving radical cations usually have negligible activation barriers thereby allowing fast and selective reactions.

Electron transfer can be effected at an electrode, or by chemical or photochemical methods. Chemical methods for electron transfer oxidation are based on the use of salts of metal ions such as Mn(III), Ce(IV), Co(II), V(V), Cu(II), Fe(III), Ag(II) *etc*.[12] Of these, special mention may be made of Mn(III).[13] Its potential in generating electrophilic carbon centered radicals from enolic substrates has been tapped efficiently, particularly in intramolecular cyclizations.

However, the formation of side products and procedural problems associated with this reagent have encouraged the use of other one electron oxidants. Thus, today oxidizing agents based on cerium have emerged as suitable reagents for one electron oxidation.

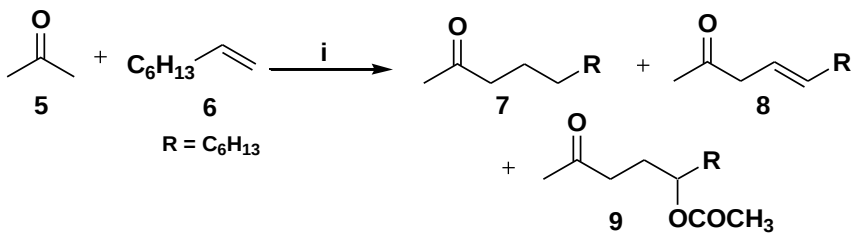
The ability of cerium to display stable adjacent oxidation states +3 and +4 renders it unique among the lanthanide elements. The most common oxidation state of the lanthanides is the +3 state. Cerium in its ground state has electronic configuration $[Xe]4f^2 6s^2$, where Xe represents Xenon configuration. The electronic configuration of the Ce^{+3} ion is $[Xe]4f^1$, while that of Ce^{+4} ion is $[Xe]4f^0$. The enhanced stability of the vacant *f* shell in Ce^{+4} accounts for the ability of Cerium to exist in the +4 oxidation state as well.

The generation of carbon centered radicals using Ce(IV) reagents dates back to the pioneering work of Heiba and Dessau in 1971. They have illustrated that electrophilic carbon centered radicals of the type $^{\cdot}CHX_2$ generated by the Cerium(IV) oxidation of compounds of the type CH_2X_2, where X is an electron withdrawing group, *viz.*, CO_2R, COR *etc.* can be trapped by various alkenes resulting in the formation of different products (Scheme 1).



Scheme 1

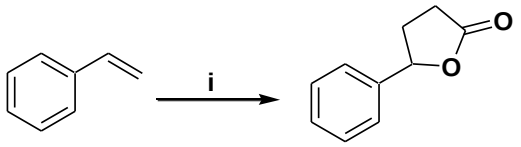
The addition of acetone **5** to 1-octene **6** provides an illustrative example (Scheme 2).[14]



i) Ce(IV) acetate, CH_3CO_2H, 10% CH_3COOK, 85 °C

Scheme 2

γ-Lactones were synthesized in good yields in a similar manner by the Ce(IV) acetate mediated oxidative addition of carboxylic acids to olefins (Scheme 3).[15]



10 **11**

i) Ce(IV) acetate, CH_3CO_2H, 120 °C, 75%

Scheme 3

It may be pointed out that most of the earlier experiments relied on the use of Ce(IV) acetate in acetic acid. However, procedural problems associated with the use of this reagent as well as its poor stability led to the use of Cerium(IV) Ammonium Nitrate (CAN) which has now emerged as the reagent of choice for various synthetic transformations. The non-toxicity, low cost, ease of handling, experimental simplicity and solubility in a number of organic solvents are some of the factors that have contributed to the general acceptance of CAN as an ideal one electron oxidant. CAN mediated reactions may be broadly classified into the following categories.

- ♦ Reactions Involving Carbon-Carbon Bond Formation.
- ♦ Reactions Involving Carbon-Heteroatom Bond Formation.
- ♦ Reactions Involving CAN as a Catalytic Oxidant.
- ♦ Deprotection-Protection Sequences Effected by CAN.
- ♦ Miscellaneous Transformations.

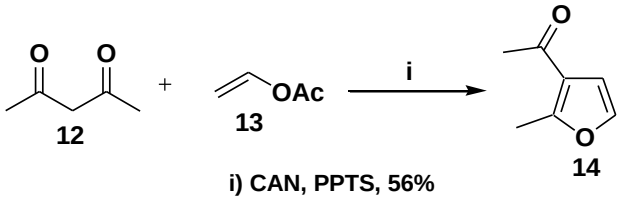
Selected examples from each of the above mentioned categories are discussed in the following sections.

1.4 Reactions Involving Carbon-Carbon Bond Formation

Carbon-carbon bond forming reactions mediated by Cerium(IV) Ammonium Nitrate can be broadly classified into two: i) Intermolecular Reactions and ii) Intramolecular Reactions. A few relevant examples of each type will be discussed in the following section.

1.4.1 Intermolecular Carbon-Carbon Bond Forming Reactions

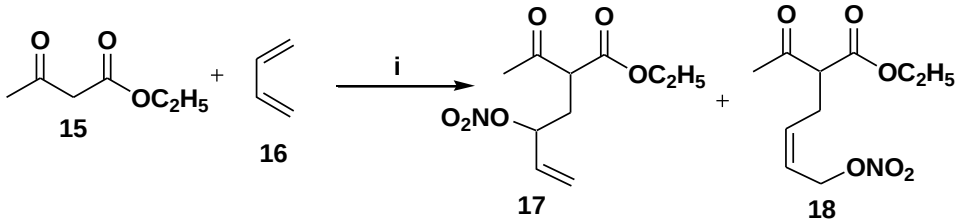
The oxidative addition of 1,3-dicarbonyl compounds such as acetylacetone **12** to activated alkenes like vinylacetate **13** prompted by CAN offers a facile route to the corresponding furan derivatives (Scheme 4).[16]



i) CAN, PPTS, 56%

Scheme 4

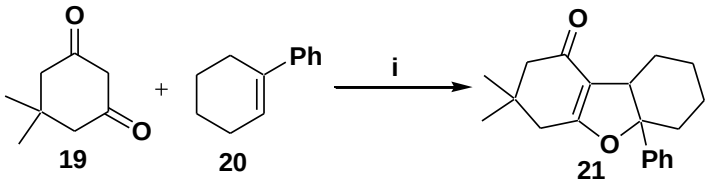
The reaction of ethylacetoacetate **15** with 1,3-butadiene **16** mediated by CAN has also been reported (Scheme 5).[17]



i) CAN, CH_3CN, 10 min

Scheme 5

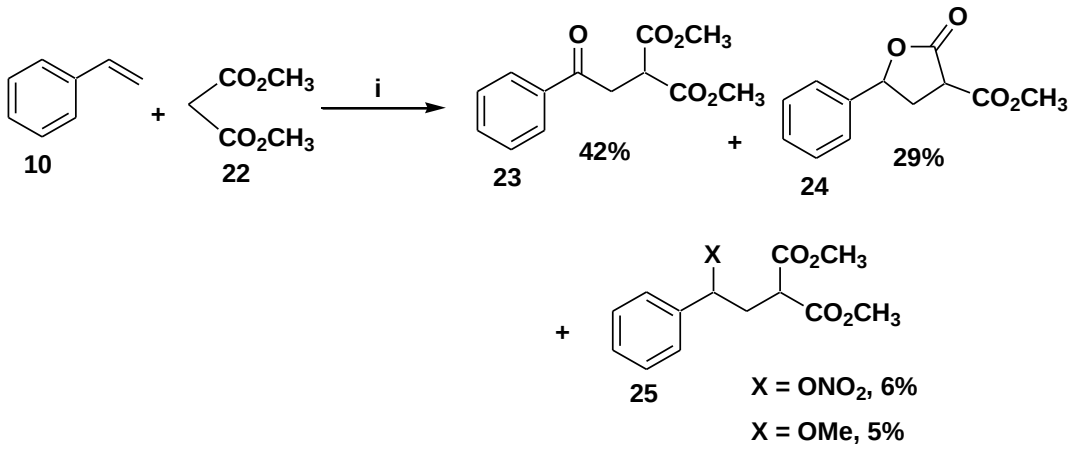
Extensive investigations on CAN mediated addition of active methylene compounds to olefins carried out in our laboratory have unravelled many interesting reactions. It has been shown that the reaction of 1,3-dicarbonyl compounds with unactivated alkenes in the presence of CAN constitutes a facile route to dihydrofuran derivatives. The addition of dimedone **19** to phenyl cyclohexene **20** is illustrative (Scheme 6).[18]



i) CAN, CH_3OH, 0 °C, 98%

Scheme 6

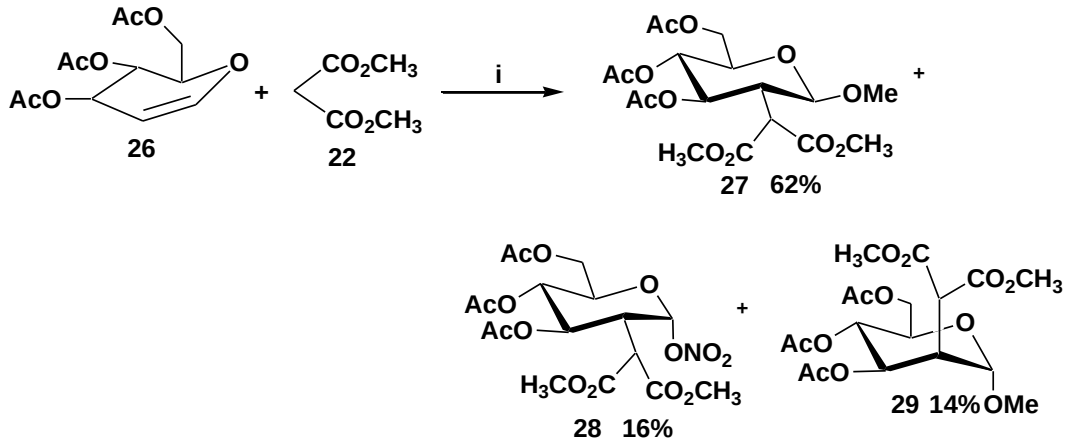
A mechanistically fascinating reaction was observed in the addition of dimethyl malonate **22** to styrene **10** (Scheme 7).[19]



i) CAN, CH_3OH, 20 °C

Scheme 7

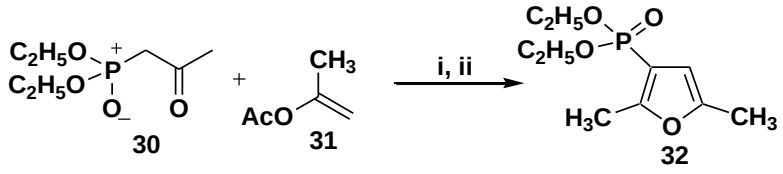
In a related reaction, Linker has developed an efficient synthesis of C-2 branched sugars by the CAN mediated addition of malonates to glycals (Scheme 8).[20]



i) CAN, CH_3OH, 0 °C

Scheme 8

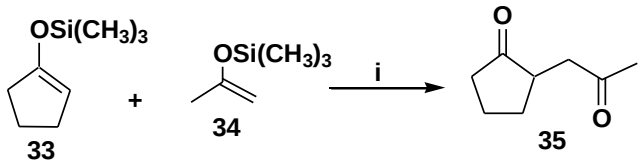
The oxidative addition of β-ketophosphonates to vinyl acetates followed by acid catalyzed cyclization affords substituted diethyl-3-furyl phosphonates (Scheme 9).[21]



i) CAN, CH_3OH, RT; ii) Amberlyst-15, toluene, reflux, 70%

Scheme 9

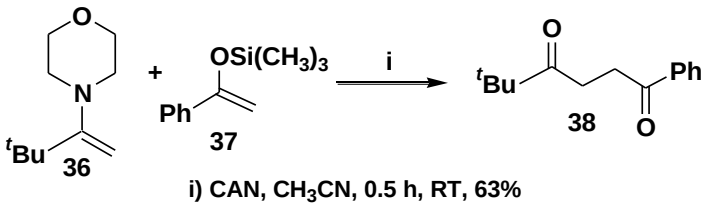
1-Substituted and 1,2-disubstituted silyl enol ethers on CAN mediated oxidative coupling afford 1,4-diketones in good yields (Scheme 10).[22]



i) CAN, $NaHCO_3$, CH_3CN, RT, 75%

Scheme 10

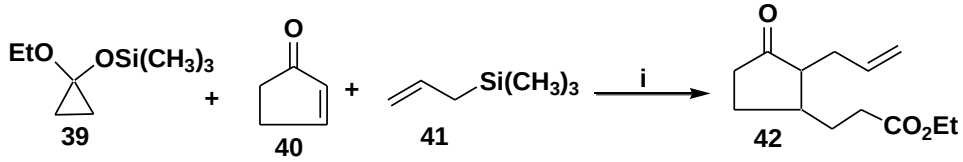
Similarly, CAN mediated oxidative addition of enamines to electron rich olefins such as silyl enol ethers constitutes a facile synthesis of 1,4-dicarbonyl compounds (Scheme 11).[23]



i) CAN, CH_3CN, 0.5 h, RT, 63%

Scheme 11

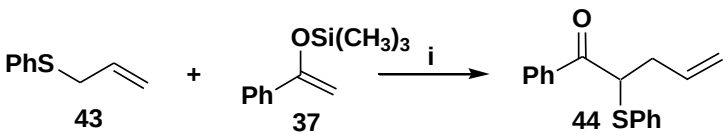
β-Carbonyl alkyl radicals generated by the CAN induced fragmentation of 1-ethoxy-1-trimethylsilyloxycyclopropane **39** add to *α,β*-unsaturated cycloalkenones in the presence of electron rich olefins, thus providing ready access to 2,3-disubstituted cycloalkanones (Scheme 12).[24]



i) CAN, CH_3CN, 48%, *trans:cis* = 6.3:1

Scheme 12

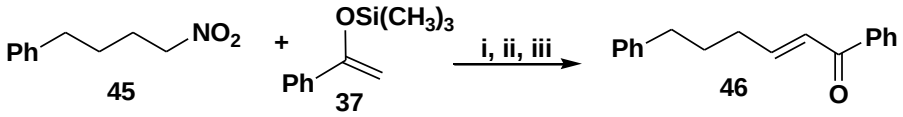
The oxidative addition of allylic sulfides to silyl enol ethers in the presence of CAN affords *α*-phenylthio-*γ*-*δ*-unsaturated ketones in good yields (Scheme 13).[25]



i) CAN, CH_3CN, RT, 75%

Scheme 13

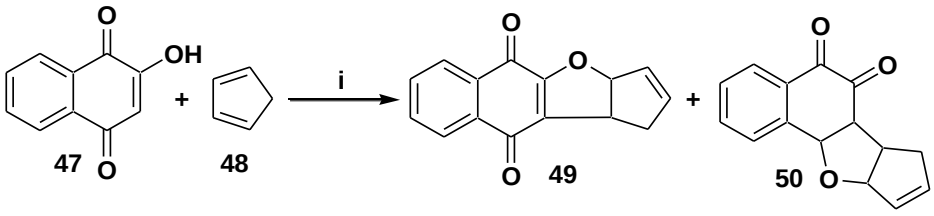
1-Nitroalkyl radicals generated by the CAN mediated oxidation of *aci*-nitroanions add to electron rich olefins to afford β-nitroketones. These β-nitroketones can be readily transformed to the corresponding α,β-unsaturated ketones. The following example is illustrative (Scheme 14).[26]



i) KOH, CH_3OH, RT; ii) CAN, CH_3OH, -78 °C, 15 min; iii) Et_3N, CH_3OH, RT, 99%

Scheme 14

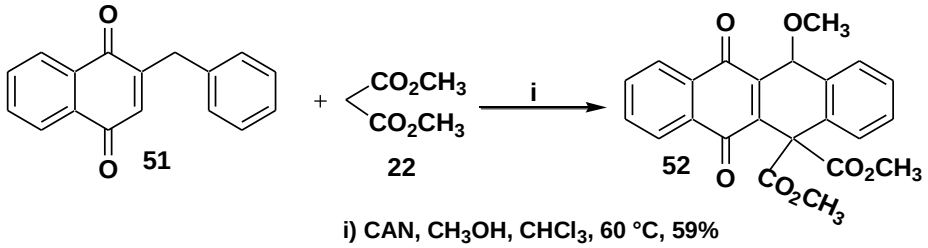
Studies in our laboratory have shown that CAN induced oxidative addition of 2-hydroxy-1,4-naphthoquinone **47** to dienes offers a simple and rapid one step procedure for the synthesis of naphthofurandiones (Scheme 15).[27]



i) CAN, CH_3CN, 0 °C, 80%, 1:3

Scheme 15

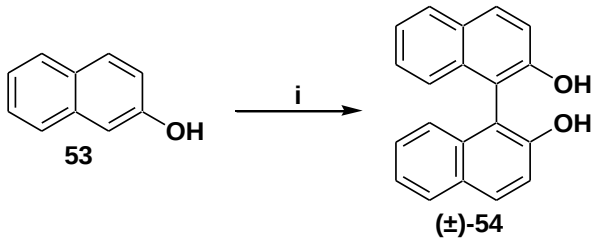
Electrophilic carbon centered radicals produced by the CAN mediated oxidation of β-dicarbonyl compounds undergo efficient addition to quinones, thus providing a facile route for the synthesis of naphthacene-1,2-diones (Scheme 16).[28]



i) CAN, CH_3OH, $CHCl_3$, 60 °C, 59%

Scheme 16

Oxidative coupling of naphthols **53** in the presence of Cerium(IV) Ammonium Nitrate affords (±)-binaphthols **54** in excellent yields (Scheme 17).[29]



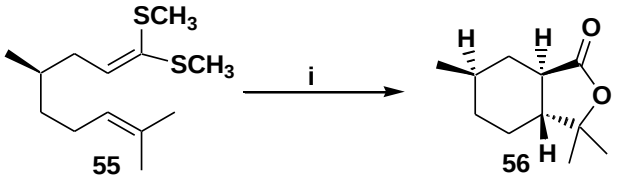
i) CAN, CH_3OH, RT, 10 min, 92%

Scheme 17

1.4.2 Intramolecular Carbon-Carbon Bond Forming Reactions

In contrast to the prevalent use of CAN in several intermolecular reactions, its potential in facilitating intramolecular reactions has remained largely unexplored. Hence, only a few reports are available in this area, a brief discussion of which is presented in the following section.

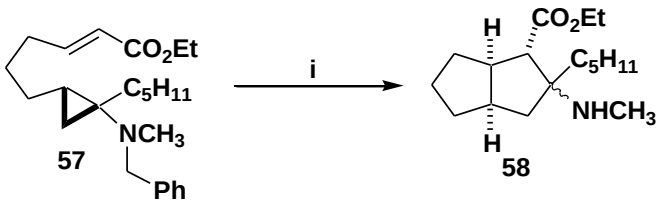
Unsaturated ketene dithioacetals undergo a facile conversion to the corresponding bicyclic lactones on treatment with CAN in wet acetonitrile (Scheme 18).[30]



i) CAN, CH_3CN:H_2O (20:1), 12 h, 25 °C

Scheme 18

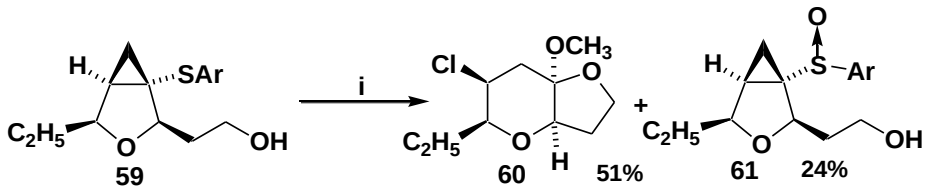
A novel CAN mediated tandem 5-*exo*-cyclization of tertiary aminocyclopropanes with suitably tethered olefins has been reported recently (Scheme 19).[31]



i) CAN, $NaHCO_3$, DMF, RT, 77% (6:1)

Scheme 19

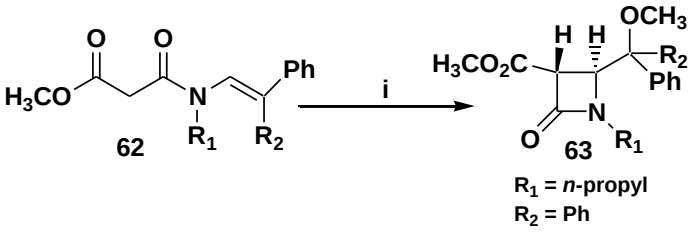
A facile stereoselective synthesis of *cis*-fused chlorinated bicyclic ethers has been achieved by the oxidative ring opening of cyclopropylsulfides of the type **59**. The example shown below is illustrative (Scheme 20).[32]



i) CAN, NH_4Cl, MS 3 Å, CH_3OH, RT

Scheme 20

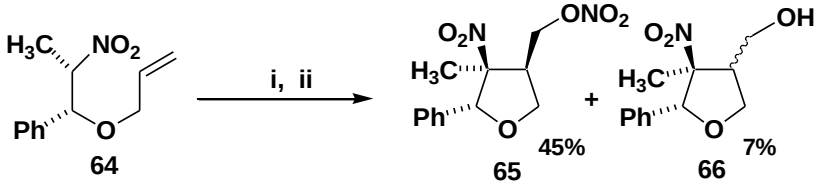
CAN mediated 4-*exo*-trig cyclization of α-carbonyl radicals generated from substituted enamides offers an expeditious route to functionalized β-lactams (Scheme 21).[33]



i) CAN, CH_3OH, RT, 0.5 h, 49%

Scheme 21

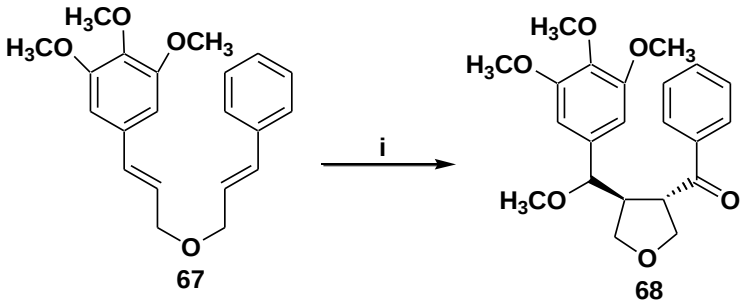
The intramolecular cyclization of 1-nitro-5-hexenyl radicals generated by the oxidation of *aci*-nitroanions with CAN results in the stereoselective formation of 3,4-functionalized tetrahydrofuran derivatives (Scheme 22).[34]



i) NaH, THF; ii) CAN, THF, -78 °C

Scheme 22

A novel CAN mediated oxidative intramolecular cyclization of cinnamyl ethers leading to a stereoselective synthesis of 3,4-*trans*-disubstituted tetrahydrofuran derivatives has been reported from our laboratory (Scheme 23).[35]

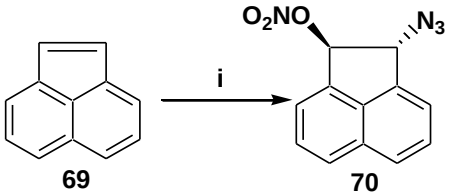


i) CAN, CH_3OH, 0 °C, Oxygen, 0.5 h, 56%

Scheme 23

1.5 Reactions Involving Carbon-Heteroatom Bond Formation

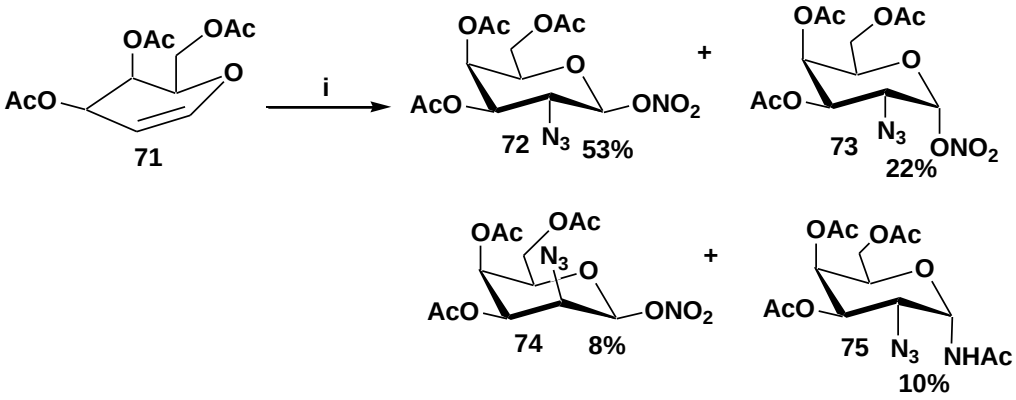
The first report of a carbon-heteroatom bond forming reaction mediated by CAN was by Trahanovsky and coworkers. The paper describes the azidation of alkenes to afford 1-azido-2-nitrato alkanes in excellent yields (Scheme 24).[36]



i) CAN, NaN_3, CH_3CN, RT, 100%

Scheme 24

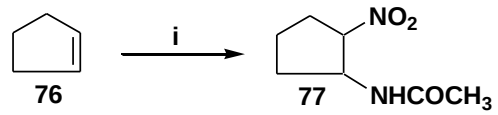
This protocol has been extended by Lemieux for the synthesis of azido sugars which serve as convenient precursors for the synthesis of aminosugars (Scheme 25).[37]



i) CAN, NaN_3, CH_3CN, 0 °C-RT

Scheme 25

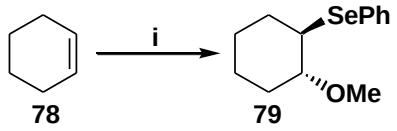
Nitroacetamidation of olefins using CAN and sodium nitrite in acetonitrile has been reported (Scheme 26).[38]



i) $NaNO_2$, CAN, CH_3CN, RT, 24 h, 64%

Scheme 26

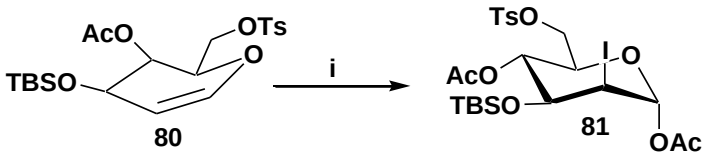
β-Methoxy alkyl selenides were obtained in good yields by the reaction of alkenes with diphenyldiselenide in the presence of CAN (Scheme 27).[39]



i) PhSeSePh, CAN, CH_3OH, RT, 0.5 h, 93%

Scheme 27

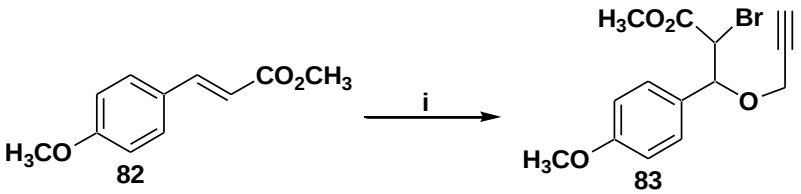
An expeditious and stereoselective synthesis of 2-deoxy-2-iodo-α-manno-pyranosyl acetates by the CAN mediated addition of iodide to glycals has been reported recently by Roush *et al.*(Scheme 28).[40]



i) NaI, CAN, CH_3COOH, CH_3CN, -25 °C-23 °C, 90%

Scheme 28

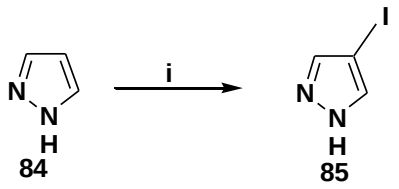
Selective bromoalkoxylation of activated cinnamyl systems has been achieved using lithium bromide and propargyl alcohol in the presence of CAN (Scheme 29).[41]



i) CAN, LiBr, propargyl alcohol, CH_3CN, RT, 3 h, 87%

Scheme 29

The regioselective iodination of pyrazoles **84** using elemental iodine in the presence of CAN constitutes a mild and efficient method for the preparation of 4-iodopyrazoles **85**. It is noteworthy that 4-iodopyrazoles are valuable intermediates for the synthesis of some biologically active compounds (Scheme 30).[42]

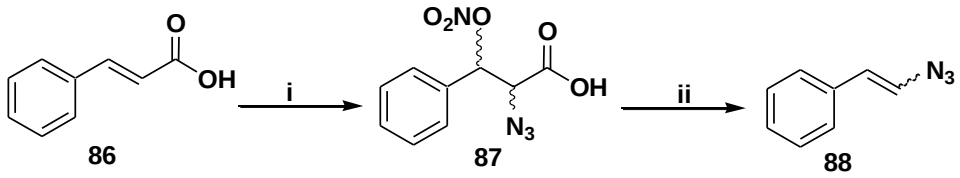


i) CAN, I_2, CH_3CN, RT, 3 h, 98%

Scheme 30

Recent investigations in our laboratory have uncovered several CAN mediated carbon-heteroatom bond forming reactions of synthetic importance. Representative examples are discussed below.

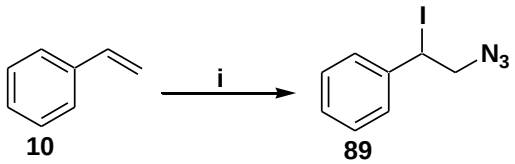
A facile CAN mediated addition of azides to α,β-unsaturated olefins like cinnamic acids, esters and amides afforded their corresponding α-azido-β-nitrato derivatives, which on treatment with sodium acetate afforded vinyl azides thus constituting a facile one-pot synthesis of the latter (Scheme 31).[43]



i) NaN_3, CAN, CH_3CN, 0 °C, Argon, 70%; ii) CH_3COONa, acetone, reflux, 66%

Scheme 31

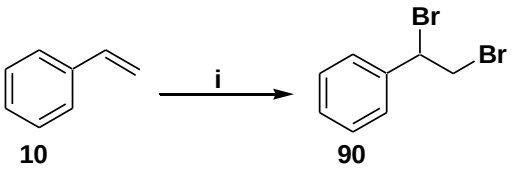
A one-pot double functionalization of alkenes to azidoiodides by the use of NaI, NaN_3 and CAN has also been achieved as illustrated below (Scheme 32).[44]



i) NaI, NaN_3, CAN, CH_3OH, 0 °C, 0.5 h, 71%

Scheme 32

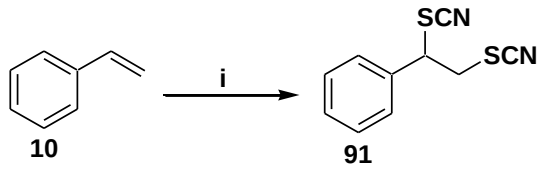
An efficient one-pot conversion of alkenes to dibromides by the use of KBr and CAN in a biphasic system of dichloromethane and water has been reported (Scheme 33).[45]



i) KBr, CAN, CH_2Cl_2-H_2O, RT, 0.5 h, 91%

Scheme 33

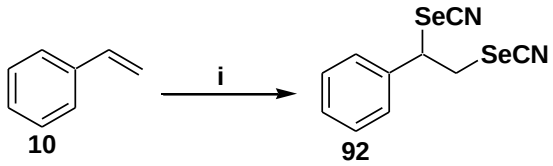
A facile dithiocyanation of alkenes using NH_4SCN and CAN has also been reported (Scheme 34).[46]



i) NH_4SCN, CAN, CH_3CN, RT, 95%

Scheme 34

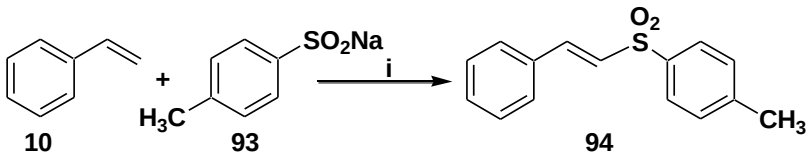
Similarly, diselenocyanation of alkenes using KSeCN and CAN has been achieved (Scheme 35).[47]



i) KSeCN, CAN, CH_3OH, Argon, 0 °C, 67 %

Scheme 35

Addition of arylsulfinates to alkenes in the presence of NaI and CAN led to a one-pot synthesis of vinyl sulfones (Scheme 36).[48]



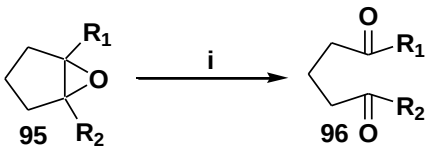
i) NaI, CAN, CH_3CN, RT, 45 min, 82%

Scheme 36

1.6 Reactions Involving CAN as a Catalytic Oxidant

Although CAN is far superior to many other one-electron oxidants, the vast majority of CAN mediated oxidations require stoichiometric quantities of the oxidant. This precludes its use in large scale transformations. However, there are a few reports available in the literature on CAN mediated reactions which are autocatalytic in nature. In particular, the study of CAN mediated oxidative transformations of epoxides has been pursued in detail. Some representative examples are given below.

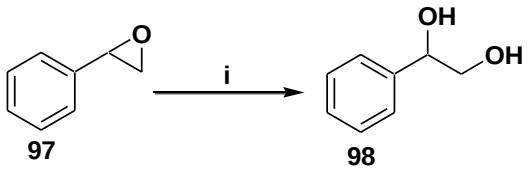
One of the early reports in this area involves the direct oxidative cleavage of epoxides to the corresponding dicarbonyl compounds by CAN in aqueous acetonitrile (Scheme 37).[49]



i) CAN (cat.), aq. CH_3CN, RT, 1 h

Scheme 37

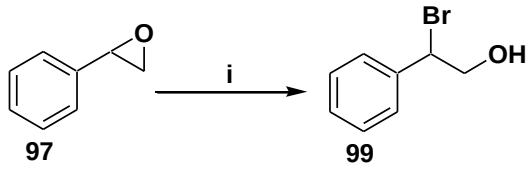
CAN has been employed as an efficient catalyst for the regioselective ring opening of epoxides in the presence of alcohols, water, thiols and acetic acid (Scheme 38).[50]



i) CAN (cat.), H_2O, RT, 10 min, 80%

Scheme 38

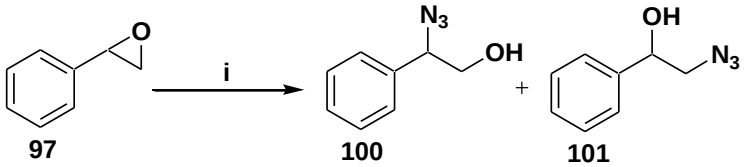
β-Halohydrins are synthesized in high yields by the CAN mediated regio- and stereoselective ring opening of epoxides in the presence of ammonium salts (Scheme 39).[51]



i) CAN (cat.), NH_4Br, ^tBuOH, RT, 2 h, 95%

Scheme 39

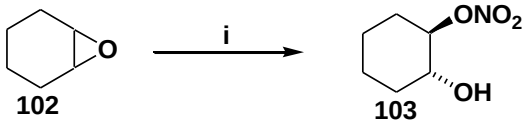
1,2-Azidoalcohols, important precursors of aminoalcohols, have been prepared in good yields by the regioselective ring opening of epoxides in the presence of sodium azide and catalytic amounts of CAN (Scheme 40).[52]



i) CAN (cat.), NaN_3, ^tBuOH, RT, 8 h, 96% (95:5)

Scheme 40

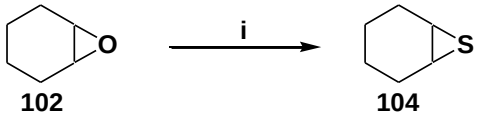
Epoxides are converted to the corresponding *β*-nitrato alcohols on treatment with catalytic amounts of CAN in the presence of excess nitrate ions present as the ammonium or tetra-*n*-butyl ammonium salts (Scheme 41).[53]



i) CAN (cat.), NH_4NO_3, aq. CH_3CN, RT, 15 min, 80%

Scheme 41

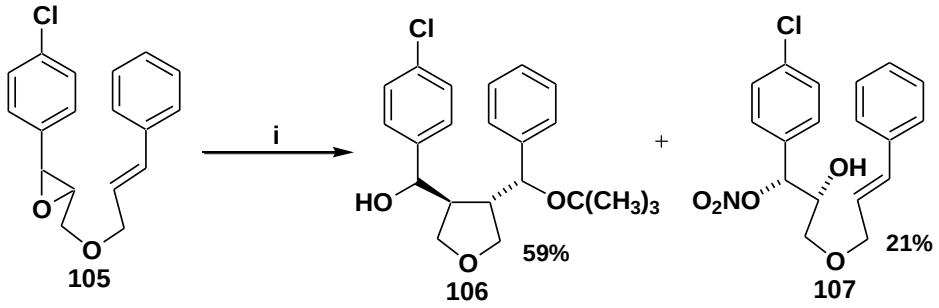
The efficient conversion of various epoxides to their corresponding thiiranes in the presence of ammonium thiocyanate and catalytic amounts of CAN has also been reported (Scheme 42).[54]



i) CAN (cat.), NH_4SCN, ^tBuOH, RT, 30 min, 92%

Scheme 42

Recent investigations in our laboratory have uncovered an intramolecular cyclization of epoxy ethers in the presence of catalytic quantities of CAN leading to 3,4-*trans*-disubstituted furan derivatives in good yields (Scheme 43).[55]

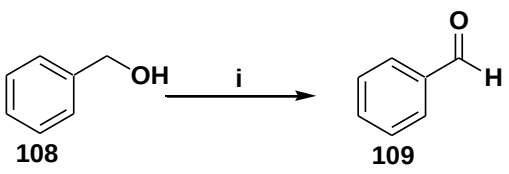


i) CAN (cat.), ^tBuOH, Argon, RT, 16 h

Scheme 43

Apart from the catalytic use of CAN in reactions involving epoxides, there are also a few reports on the catalytic use of CAN in oxidations with bromate ion serving as the co-oxidant. Examples are cited below.

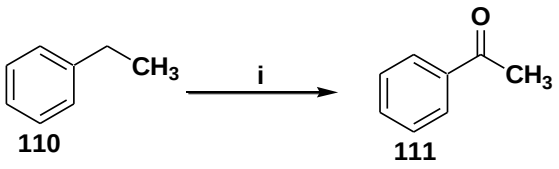
Oxidation of benzyl alcohols to the corresponding carbonyl compounds in the presence of CAN and sodium bromate as the co-oxidant has been reported (Scheme 44).[56]



i) CAN (cat.), $NaBrO_3$, aq. CH_3CN, 80 °C, 90%

Scheme 44

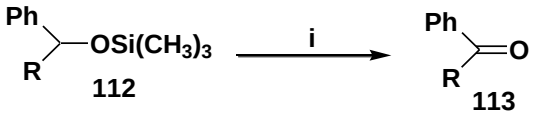
CAN catalyzed oxidation of alkyl aromatic compounds in the presence of potassium bromate as the dual oxidant furnishes aldehydes and ketones in excellent yields (Scheme 45).[57]



i) CAN (cat.), $KBrO_3$, aq. dioxan, 85 °C, 3.5 h, 90%

Scheme 45

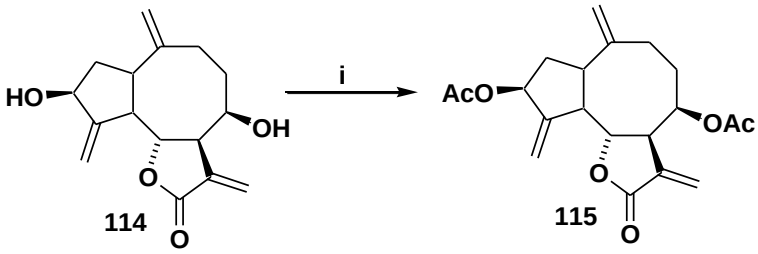
Alkyl ethers and trialkyl silyl ethers can be cleaved oxidatively with catalytic amounts of CAN and sodium bromate (Scheme 46).[58]



i) CAN (cat.), $NaBrO_3$, aq. CH_3CN, 80 °C, 84%

Scheme 46

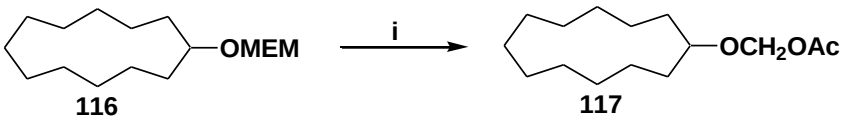
CAN acts as a versatile catalyst for the esterification of carboxylic acids and alcohols including steroids and other multifunctional compounds under mild reaction conditions (Scheme 47).[59]



i) CAN (cat.), CH_3CO_2H, 60 °C, 1 h, 98%

Scheme 47

2-Methoxyethoxymethyl ethers are readily cleaved by catalytic amounts of CAN in acetic anhydride to afford mixed acetal esters (Scheme 48).[60]



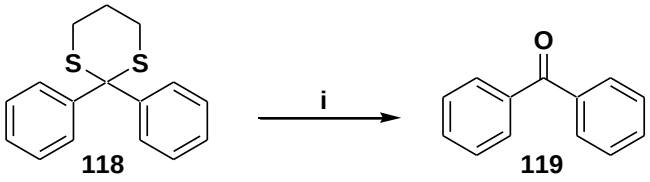
i) CAN (cat.), Ac_2O, 24 h, 82%

Scheme 48

1.7 Deprotection-Protection Sequences Mediated by CAN

The protection-deprotection sequence is probably the most frequently encountered functional group transformation in organic synthesis. This is testified by the plethora of reagents and methods of general and/or specific utility that have been devised to accomplish such transformations. In recent years, CAN has also proved to be an effective reagent in this regard. Illustrative examples from the recent literature are briefly discussed here.

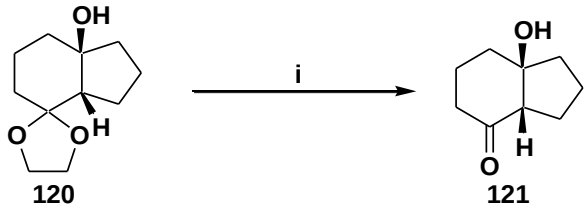
The deprotection of dithioacetals to the parent carbonyl compounds employing CAN was reported as early as 1972 by Ho *et al.* (Scheme 49).[61]



i) CAN, aq. CH_3CN, RT, 3 min, 86%

Scheme 49

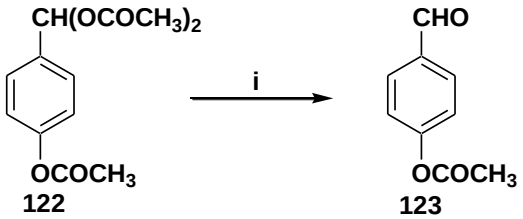
Recently Marko *et al.* have developed a highly efficient catalytic protocol for the deprotection of acetals under mildly basic conditions (Scheme 50).[62]



i) CAN (3 mol%), borate-HCl buffer (pH 8), aq. CH_3CN, 60 °C, 93%

Scheme 50

Benzaldehyde diacetates were selectively converted to the corresponding benzaldehydes by CAN coated on silica in dichloromethane (Scheme 51).[63]



i) CAN, SiO_2, CH_2Cl_2, 98%

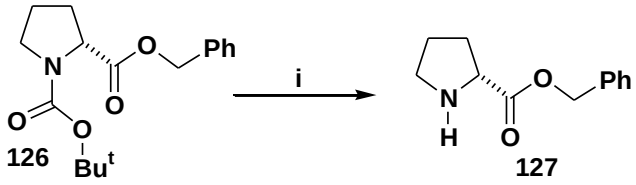
Scheme 51

An efficient method for the deprotection of *tert*-butyldimethylsilyl (TBDMS) and tetrahydropyranyl (THP) ethers using CAN has been reported (Scheme 52).[64]

i) CAN, CH_3OH, 0 °C, 2.5 h, 95%

Scheme 52

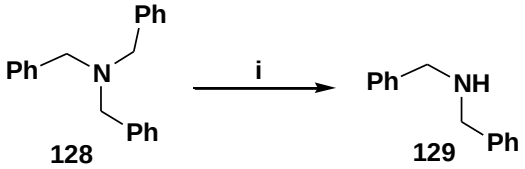
The deprotection of *tert*-butoxycarbonyl (Boc) group has been effected by the use of catalytic amounts of CAN (Scheme 53).[65]



i) CAN (cat.), CH_3CN, reflux, 2 h, 93%

Scheme 53

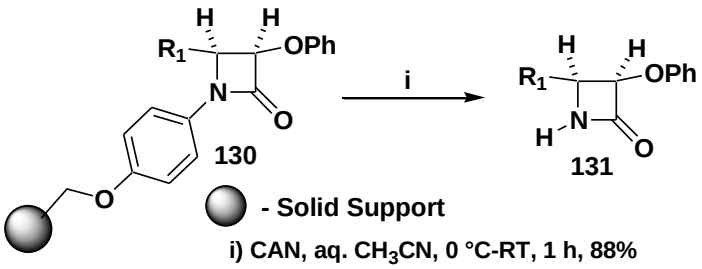
The reaction of tertiary amines having one or more *N*-benzyl protecting groups with CAN results in mono-debenzylation to afford the corresponding secondary amine (Scheme 54).[66]



i) CAN, aq. CH_3CN, 90%

Scheme 54

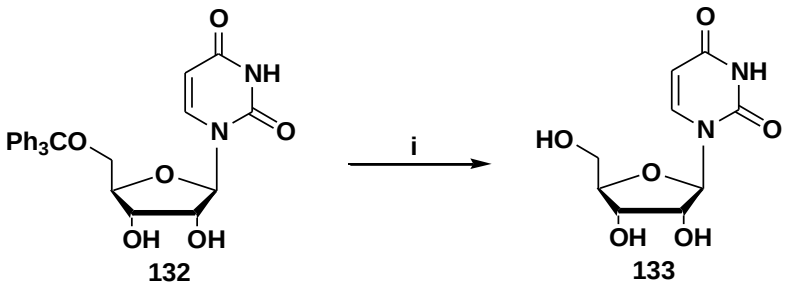
β-Lactams substituted at the amide nitrogen with a benzyloxy aniline linker when treated with CAN undergo facile oxidative cleavage of the benzyloxy group to afford the deprotected *N*-unsubstituted *β*-lactams in good yields (Scheme 55).[67]



i) CAN, aq. CH_3CN, 0 °C-RT, 1 h, 88%

Scheme 55

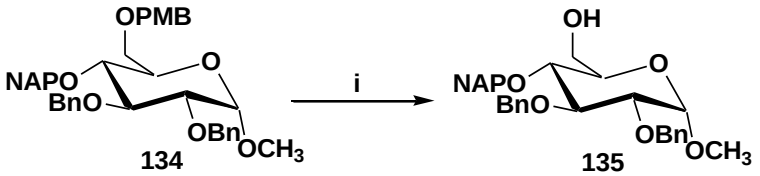
CAN supported on silica has been employed for the efficient and selective unmasking of trityl and silyl groups from protected nucleosides and nucleotides under mild conditions (Scheme 56).[68]



i) CAN-silica gel,CH_2Cl_2, 25 °C, 80%

Scheme 56

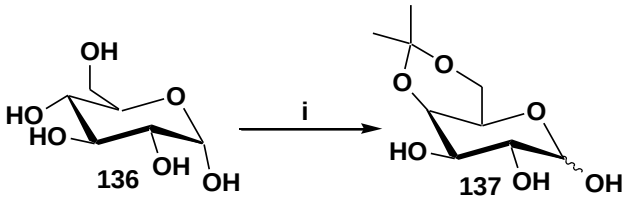
Selective cleavage of the PMB (*para*-methoxybenzyl) group in the presence of the NAP (2-naphthylmethyl) group was achieved using CAN with a range of monosaccharides. The following example is illustrative (Scheme 57).[69]



i) CAN, aq. acetone, 68%

Scheme 57

The wide spectrum of the reactivity of CAN is exemplified by its use in acetalization reactions as well. The acetonation of carbohydrates using 2,2-dimethoxy propane (DMP) in anhydrous DMF is illustrative (Scheme 58).[70]



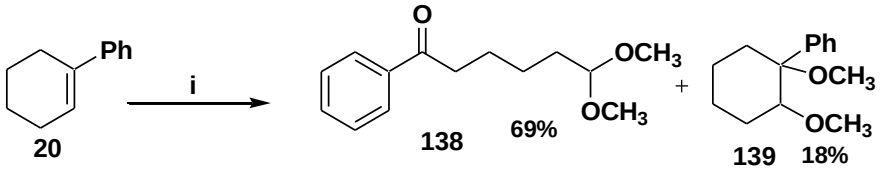
i) CAN, DMP, anhydrous DMF, RT, 1 h, 89%

Scheme 58

1.8 Miscellaneous Transformations

In addition to the reactions described above, CAN has also been effective in bringing about some novel and interesting processes. Such reactions also provide insight into the mechanistic details of several CAN mediated transformations. A few illustrative examples are cited below.

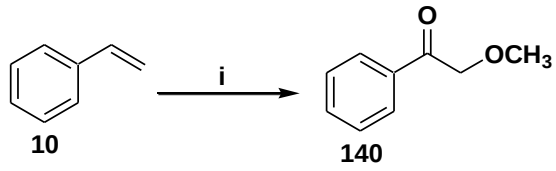
An interesting CAN mediated fragmentation of phenyl cycloalkenes leading to the direct synthesis of monoacetals of 1,n-dicarbonyl compounds has been reported by our group (Scheme 59).[71]



i) CAN, CH_3OH, 0 °C-RT, 30 min

Scheme 59

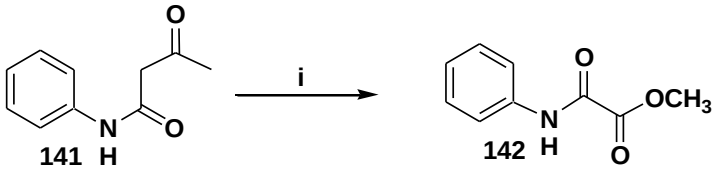
Styrenes are converted to the corresponding α-methoxy acetophenones on treatment with CAN in methanol (Scheme 60).[72]



i) CAN, CH_3OH, 0 °C, 55%

Scheme 60

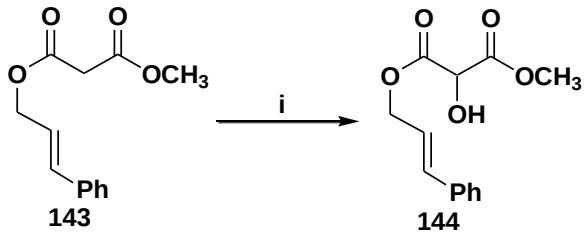
The reaction of acetoacetanilide with CAN in methanol, carried out with the objective of executing an intramolecular reaction to derive the oxindole, afforded the corresponding oxamate in good yields. Substantial enhancement of the overall yield was attained when the reaction was performed in an atmosphere of oxygen (Scheme 61).[73]



i) CAN, CH_3OH, Oxygen, RT, 15 min, 70%

Scheme 61

A similar effort towards effecting a CAN mediated intramolecular reaction of alkenylmalonates led to a novel synthesis of tatronic acid derivatives (Scheme 62).[74]



i) CAN, CH_3OH, 0 °C-RT, 6 h, 62%

Scheme 62

1.9 Conclusion and the Present Work

It is clear from the literature survey presented above that CAN is an excellent one electron oxidant for effecting a wide range of synthetic transformations. However, it is also evident that much of the potential of CAN still remains untapped. The present study is aimed at exploring the potential of CAN with a view to uncover novel reactions.

The first phase of the investigation deals with a CAN induced cyclodimerization of various styrenes to afford 1-amino-4-aryltetralin derivatives.

The reactivity of various four membered ring systems with CAN constitutes the second phase of the study.

The third and final phase of the work is concerned with an efficient method for the preparation of dimethyl, diethyl and diallyl acetals of aromatic aldehydes mediated by CAN.

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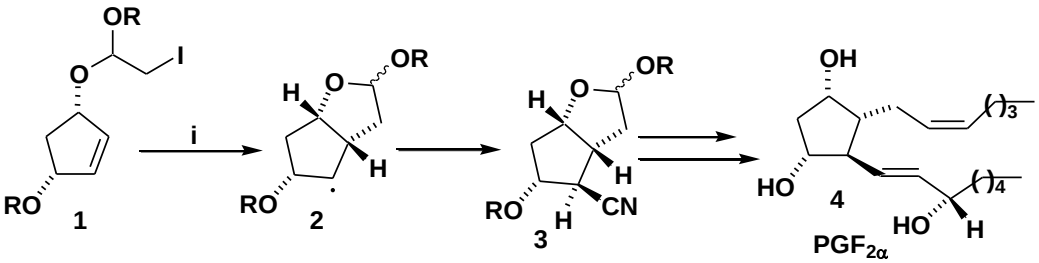
Chapter 2

Cerium(IV) Ammonium Nitrate Induced Cyclodimerization of Styrenes: A Novel and Expeditious Synthesis of 1-Amino-4-aryltetralin Derivatives

2.1 Introduction

One of the most important tasks in the synthesis of complex organic molecules is the construction of carbon-carbon bonds. All the known carbon-carbon bond forming reactions involve ionic, pericyclic or radical reactions. While ionic and pericyclic reactions have been well developed and are universally accepted as tools for the construction of complex organic molecules, free radical reactions did not find much application in organic synthesis for a long time. In recent times, however, the myth of free radicals as highly reactive intermediates giving rise to reactions that are uncontrollable and that lack selectivity has been dispelled. This is largely due to the advent of rationally designed, highly efficient free radical chain sequences permitting both high yielding interconversion of functional groups and formation of carbon-carbon bonds under mild and neutral conditions. This dramatic change in outlook, which has led to an upsurge of interest in radical methodology, can be attributed in large measure to the conceptualization and demonstration by Stork that the controlled generation and addition of vinyl radicals to alkenes offers a powerful method for complex carbocyclic construction. An elegant application of this protocol may be best exemplified by Stork's prostaglandin synthesis in six steps from the iodoacetal **1** (Scheme 1).[1]



i) Bu_3SnH, AIBN, ^tBuNC

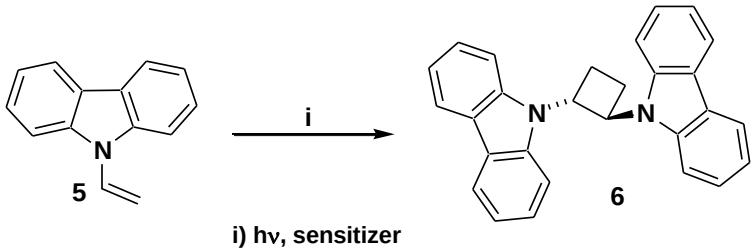
Scheme 1

2.2 Electron Transfer Reactions

Electron transfer is one of the most elementary processes in organic chemistry. Electron transfer can be effected by photochemical, electrochemical, or chemical methods. A brief account of carbon-carbon bond forming reactions involving radical cations generated by electron transfer by each of the above type processes is given in the following sections.

2.2.1 Carbon-Carbon Bond Formation by Photochemical Methods

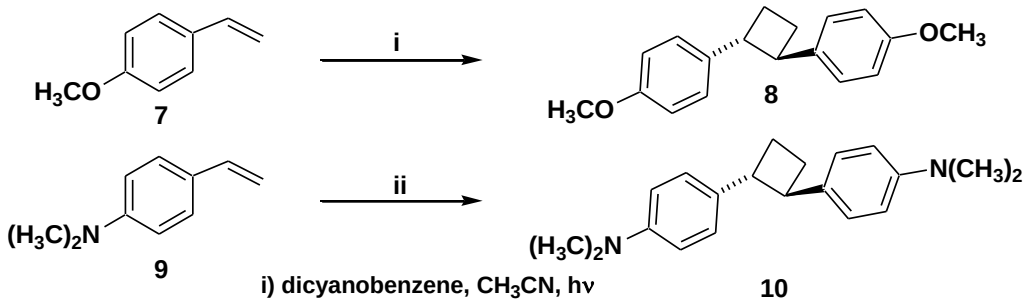
The first example of a reaction involving radical cations was the dimerization of *N*-vinylcarbazole **5** under photochemical conditions. This reaction could also be accomplished in good yields by Fe(III), Ce(IV) or Cu(II) salts (Scheme 2).[2]



i) hν, sensitizer

Scheme 2

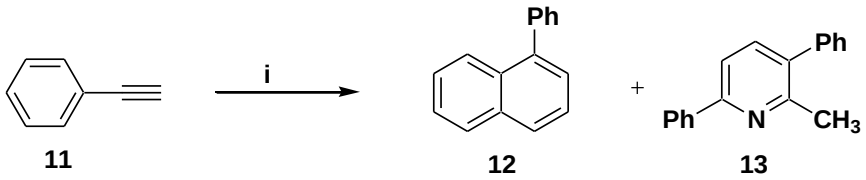
It was later shown that other electron rich systems like *p*-methoxy styrene **7** and *p*-(*N*,*N*-dimethylamino)styrene **9** also undergo photo-cyclodimerization to give the corresponding cyclobutanes (Scheme 3).[3]



i) dicyanobenzene, CH_3CN, hν
ii) CH_3CN, hν

Scheme 3

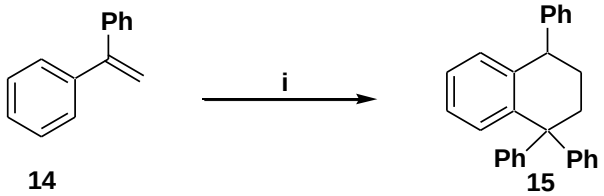
The photosensitized electron-transfer reaction of phenylacetylene **11** affords the dimer 1-phenylnaphthalene **12** and a solvent incorporated product 2-methyl-3,6-diphenyl pyridine **13** (Scheme 4).[4]



i) hν, tetracyanoanthracene, CH_3CN

Scheme 4

The photosensitized electron transfer dimerization of 1,1-diphenyl ethylene **14** in the presence of methyl-4-cyanobenzoate as the sensitizer gives the tetrahydronaphthalene derivative **15** (Scheme 5).[5]

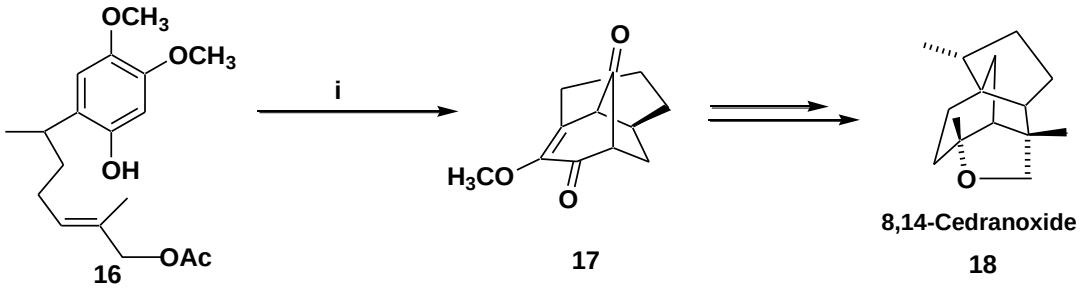


i) hν, methyl 4-cyanobenzoate, CH_3CN

Scheme 5

2.2.2 Carbon-Carbon Bond Formation by Electrochemical Methods

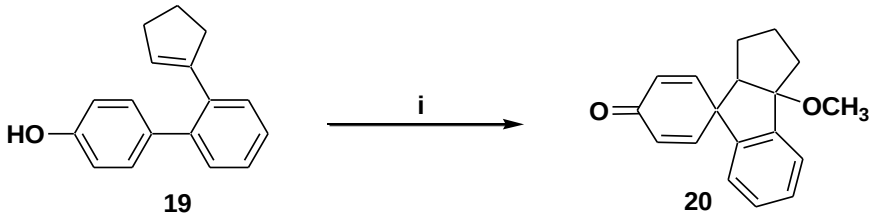
The total synthesis of the sesquiterpene 8,14-cedranoxide **18** has been accomplished by making use of the anodic oxidation of phenol **16** as the key step (Scheme 6).[6]



i) CCE at 2.5 mA (+900-1200 mV), *n*-Bu_4NBF_4, Ac_2O, 80% (4:1)

Scheme 6

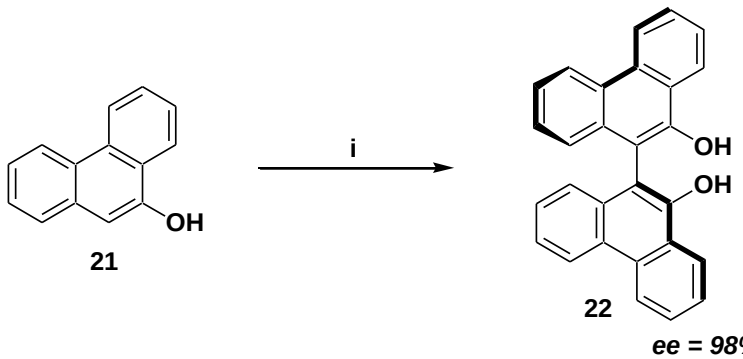
The anodic oxidation of 4-(2'-alkenylphenyl)-phenols in acetonitrile or methanol affords spirodienones arising from cyclization of the olefinic side chain to the 4-position of the phenol and reaction of the resulting benzylic cation with methanol (Scheme 7).[7]



i) 1 mA/cm^2, Pt anode, Cu cathode, CH_3OH/CH_3CN (4:1), 69%

Scheme 7

The enantioselective electrocatalytic oxidative coupling of phenanthrol **21** on a TEMPO-modified graphite felt electrode in the presence of (-)-sparteine has been reported (Scheme 8).[8]



***ee* = 98%**

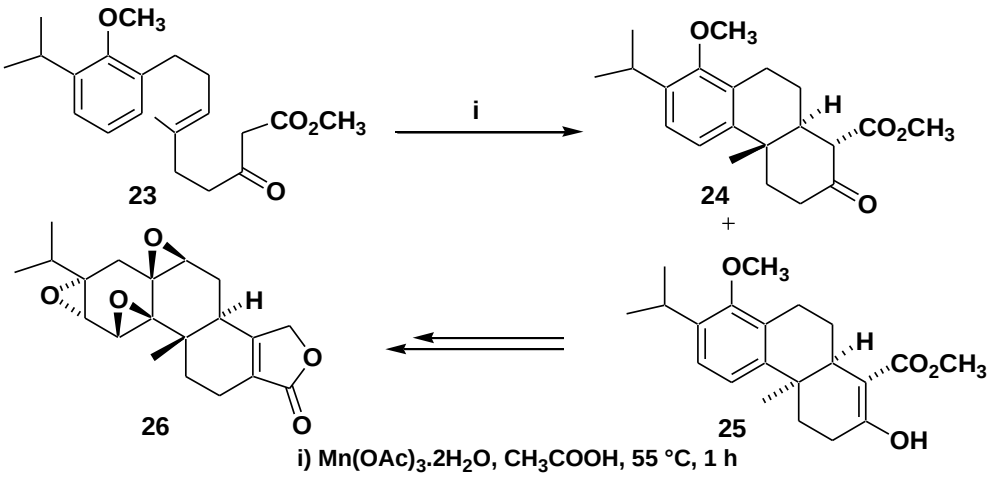
i) TEMPO-modified anode, (-) sparteine, $NaClO_4$-CH_3CN, 91%

Scheme 8

2.2.3 Carbon-Carbon Bond Formation by Chemical Methods

An efficient and stereoselective Mn(III) mediated oxidative radical cyclization of acyclic β-ketoesters has been used as the key step in the

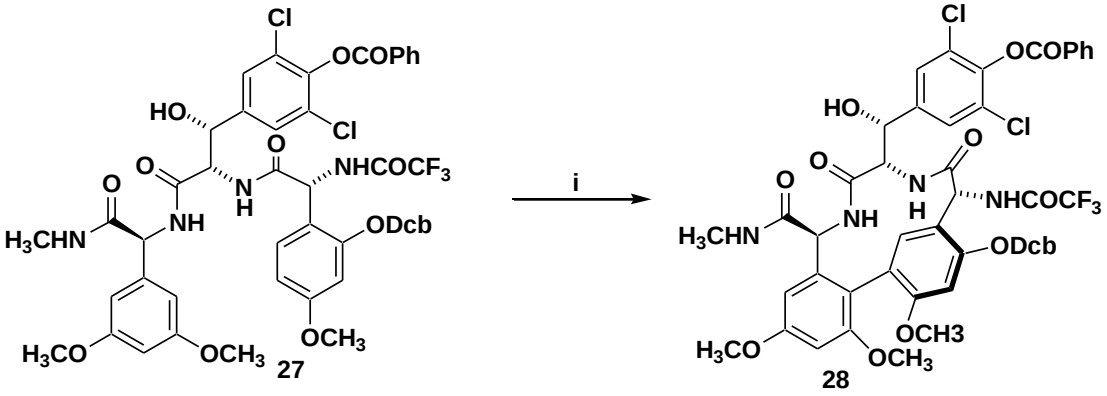
construction of tricyclic skeletons **24** and **25**, which are intermediates in the synthesis of the potent antitumor agent **26** and its various analogs (Scheme 9).[9]



i) $Mn(OAc)_3.2H_2O$, CH_3COOH, 55 °C, 1 h

Scheme 9

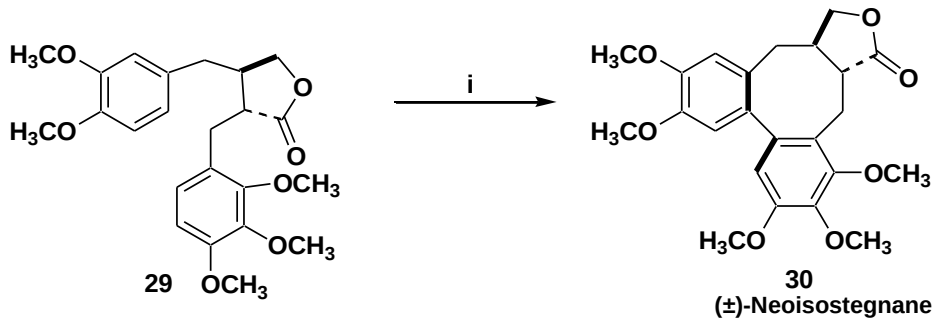
Pentavalent oxovanadium compounds have been shown to serve as Lewis acids with one electron oxidation capacity. Evans' elegant biomimetic oxidative coupling approach to the tripeptide macrocycle **27**, a structural subunit common to all members of the vancomycin family of antibiotics amply testifies the synthetic power of this reaction (Scheme 10).[10]



i) VOF_3, $BF_3.OEt_2$, TFA, TFAA, CH_2Cl_2, 0 °C, Zn, 58%

Scheme 10

Ruthenium(IV) dioxide dihydrate in fluoro acid medium was found to be a very efficient reagent for the oxidative coupling of non phenolic lignans as illustrated by the synthesis of (±)-neoisostegnane **30** (Scheme 11).[11]



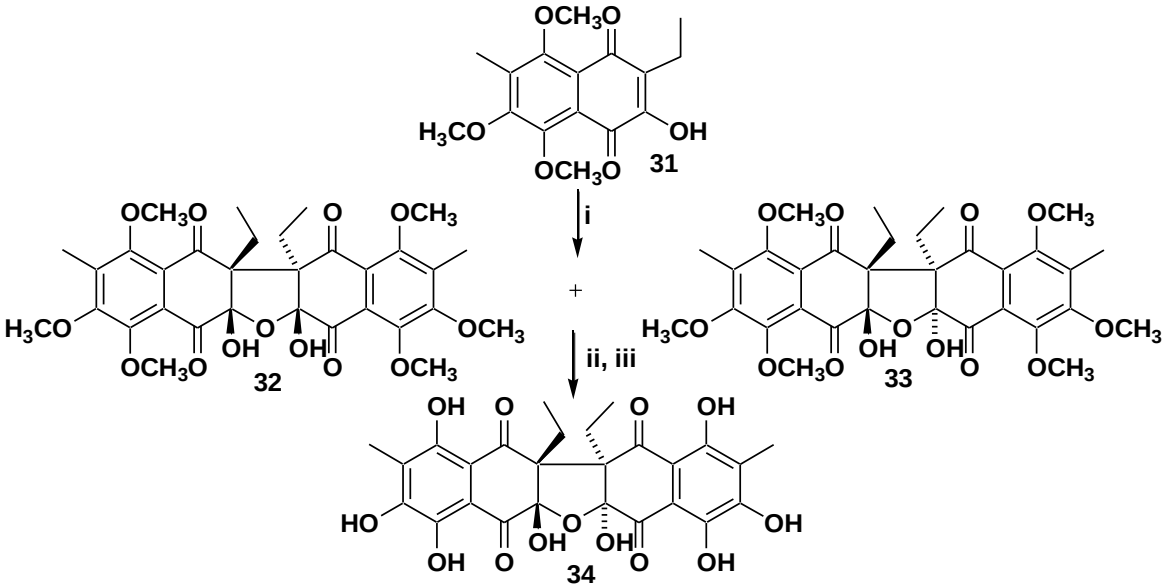
i) $RuO_2.2H_2O$ (2 eq.), TFA, TFAA, BF_3-Et_2O

Scheme 11

2.2.3.1 Carbon-Carbon Bond Forming Reactions Mediated by CAN

In recent years, Cerium(IV) ammonium nitrate (CAN) has emerged as a reagent of choice for single electron transfer reactions. Several examples of carbon-carbon bond forming reactions mediated by CAN have been discussed in **Chapter 1, p. 5, Section 1.4**. In the following section, only examples of CAN mediated dimerizations and cyclizations onto aromatic rings will be presented.

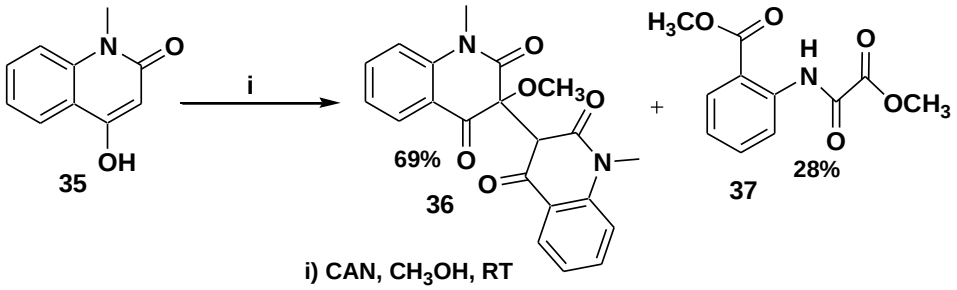
The synthesis of the racemic hybocarpone **34** based on CAN promoted oxidative dimerization of naphthazirin **31** has been reported recently by Nicolaou (Scheme 12).[12]



i) CAN, degassed CH_3CN, -35 °C-0 °C, 3 min, 36%; ii) CH_3COOH, 10 min, >95%; iii) $AlBr_3$, CH_3CH_2SH, CH_2Cl_2, 0 °C, 1h, 60%

Scheme 12

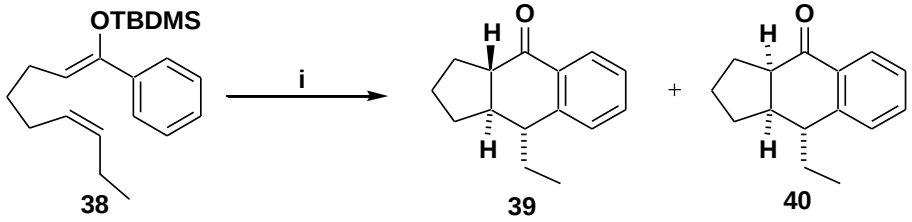
Novel CAN mediated dimerization of 4-hydroxyquinolin-2(1*H)*-ones has been reported (Scheme 13).[13]



i) CAN, CH_3OH, RT

Scheme 13

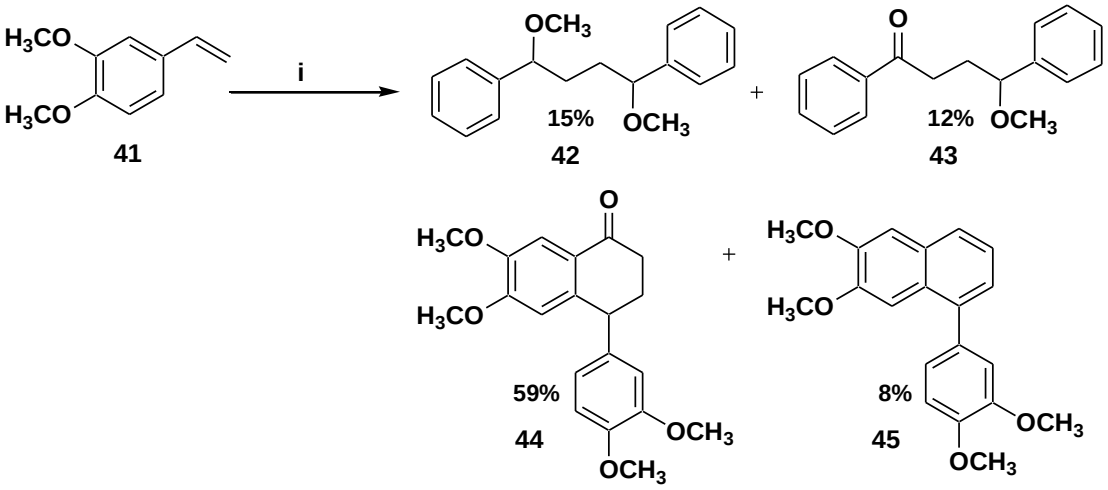
Oxidative cyclization of δ,ε- and ε,ϕ-unsaturated silyl enol ethers by CAN affording tricyclic ketones in high yield and excellent diastereoselectivity has been reported (Scheme 14).[14]



i) CAN, $NaHCO_3$, CH_3CN, 25 °C, 73%, (20:1)

Scheme 14

Investigations in our laboratory have uncovered a novel CAN mediated dimerization of alkoxy styrenes. The conditions employed were found to exert a profound influence on the nature of the products formed in these reactions. An illustrative example is given below (Scheme 15).[15]

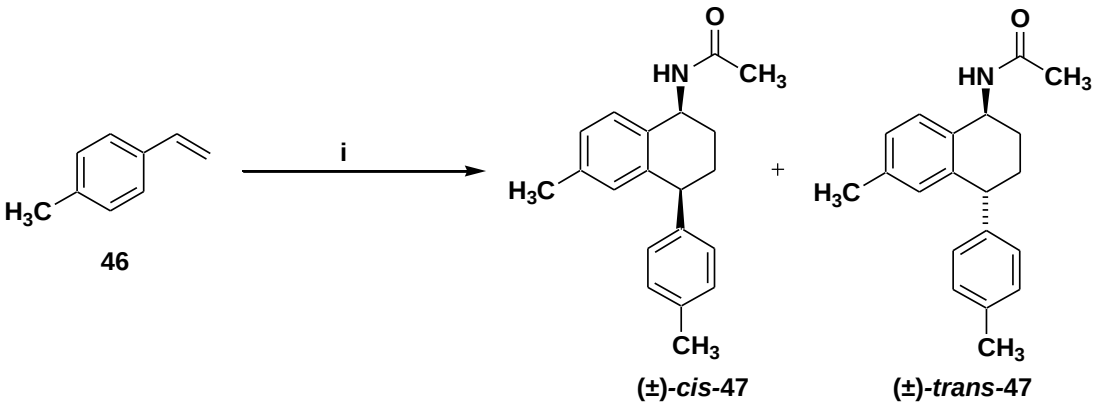


i) CAN, CH_3OH, 0 °C, 30 min

Scheme 15

Intrigued by the possibility that an α-aminotetralin derivative may be formed by the cyclodimerization of styrenes if the reaction takes place in an

environment conducive for the termination of the reaction by the Ritter trapping of the cationic intermediate, we exposed an acetonitrile solution of 4-methyl styrene **46** to cerium(IV) ammonium nitrate (CAN) in an argon atmosphere. In the event, a facile reaction occurred and the α-acetamido tetralins *cis*-**47** and *trans*-**47** were obtained (Scheme 16).



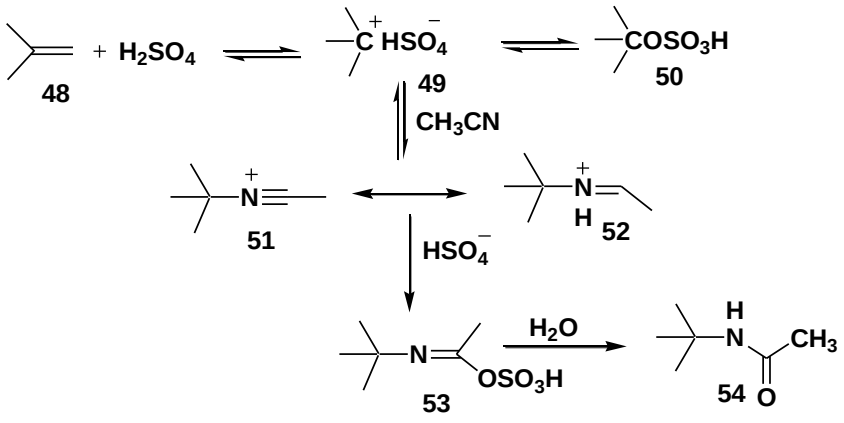
i) CAN (1.2 eq.), CH_3CN, Argon, RT, 2 h, 62%, 1.3:1

Scheme 16

Before discussing the reaction in detail, in order to put things in perspective, a brief report on the Ritter reaction and its importance, and the synthesis of α-aminotetralin derivatives will be presented in the following section.

2.3 The Ritter Reaction

The formation of *N*-substituted amides by the addition of nitriles to alkenes or tertiary alcohols in the presence of concentrated sulfuric acid was first described by Ritter in 1948.[16] Three intermediates are involved in this reaction (Scheme 17). Firstly, a carbenium ion **49** is produced under strongly acidic conditions. This reacts with the nitrile to produce a resonance stabilized nitrilium ion **51**, which in turn is converted to the corresponding imidate **53**. Finally, the latter is hydrolyzed to the amide **54**. Since all the three events occur in a one-pot process, frequently in high yield, the Ritter reaction is a simple, efficient and general synthetic procedure.



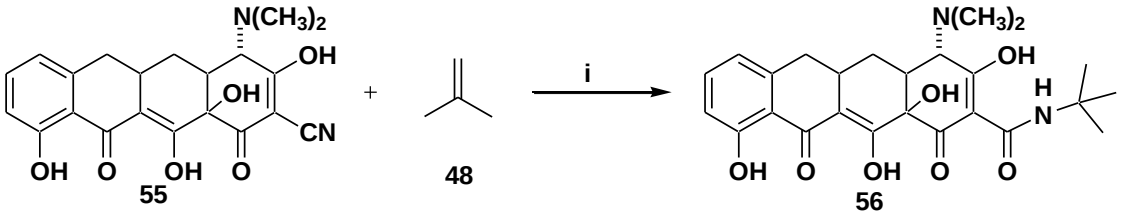
Scheme 17

2.3.1 Reaction Conditions

Optimum reaction times for the reaction are typically around 1-24 h and temperatures in the range 20-50 °C depending very much on the particular cases. Benzenesulfonic, fluoroboric, formic, hydrofluoric, methanesulfonic, perchloric, phosphoric, sulfuric, toluenesulfonic, and trifluoromethanesulfonic acids are amongst those used to generate the carbenium ion. The majority of workers, however, favor sufuric acid and, in cases where comparative studies have been carried out, this reagent gave the best yield.[17]

2.3.2 The Nitrile Component

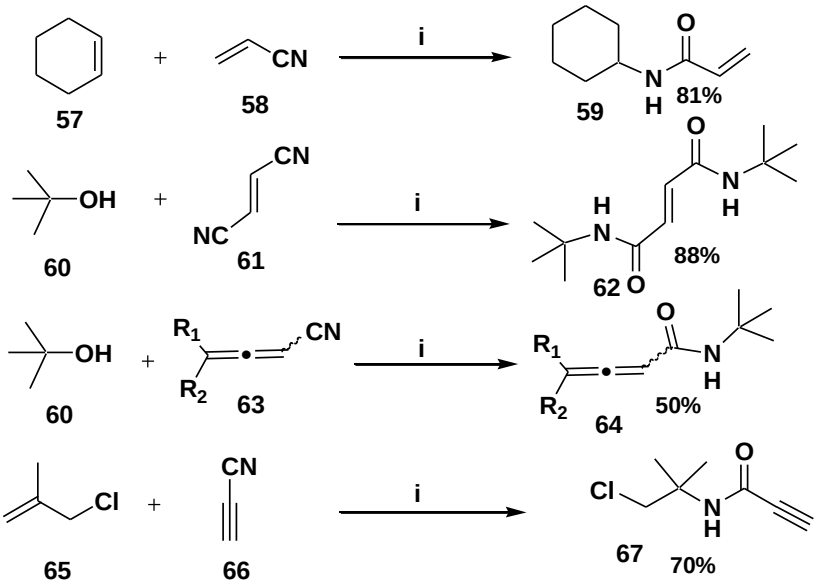
In general, most compounds containing a nitrile group undergo reaction with carbenium ions. Not only are hydrogen cyanide, aliphatic nitriles and aromatic nitriles all effective reagents, but the process also occurs with varying degrees of efficiency for nitrile derivatives such as cyanamide, cyanogen and dicyandiamide. Nitriles bearing other functional groups also undergo efficient Ritter reaction, a striking illustration being the tetracycline derivative **55** (Scheme 18).[18]



i) a. H_2SO_4, CH_3COOH; b. H_2O, 71%

Scheme 18

Conjugated nitriles such as acrylonitrile or fumaronitrile[19] are effective Ritter reagents. This is also true of conjugated allenic and alkynic nitriles as shown in the scheme below (Scheme 19).[20, 21]



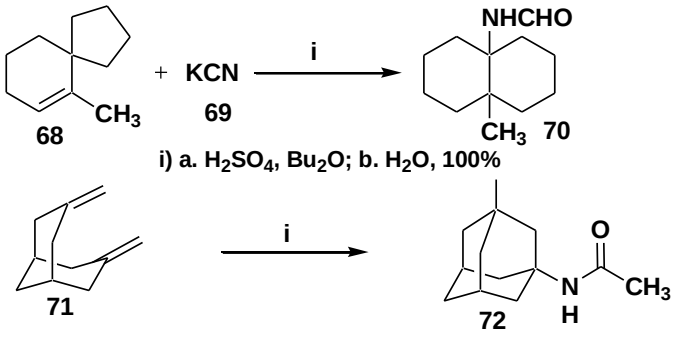
i) a. H_2SO_4, CH_3COOH, 45 °C ; b. H_2O

Scheme 19

2.3.3 The Carbenium Ion Source

Any functionality capable of producing a carbenium ion under strongly acidic conditions can participate in a Ritter type reaction. Such classes of compounds include alcohols, aldehydes, alkanes, alkenes, alkyl halides, carboxylic acids, dienes, epoxides, esters, ethers, glycols, ketones, *N*-methylol amides and oximes. The reaction has been reviewed by Krimen and Cota[22] and only representative examples are presented here.

When two reactive groups are in close proximity in the substrate, it is possible to combine transannular cyclization with the Ritter reaction (Scheme 20).[23, 24]

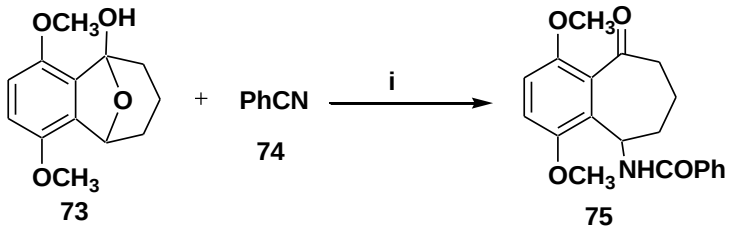


i) a. H_2SO_4, Bu_2O; b. H_2O, 100%

i) a. H_2SO_4, CH_3CN; b. H_2O, 74%

Scheme 20

Bridged hemiacetals react *via* their acyclic form in solution to afford amidoketones in good yield (Scheme 21).[25]

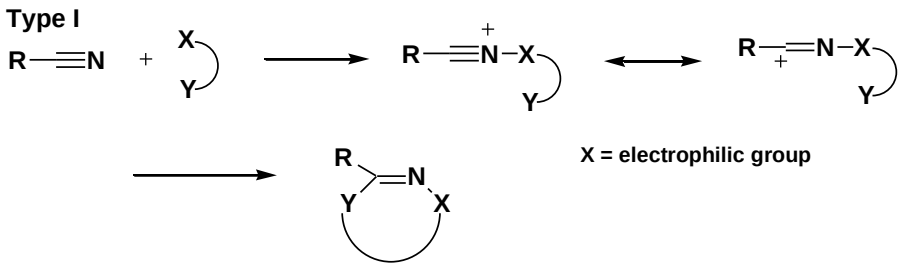


i) a. H_2SO_4,; b. H_2O

Scheme 21

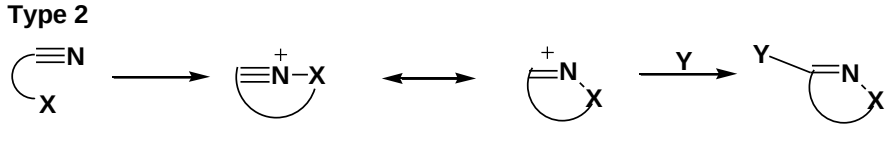
2.3.4 The Intramolecular Ritter Reaction

The intramolecular reaction takes place by either of the two processes described below. The more common Type I process commences in the normal way, with the addition of nitrile and carbenium ion generating a nitrilium species. The latter now undergoes intramolecular cyclization with a nucleophilic group in the same molecule to produce a heterocycle as depicted in the scheme below (Scheme 22).



Scheme 22

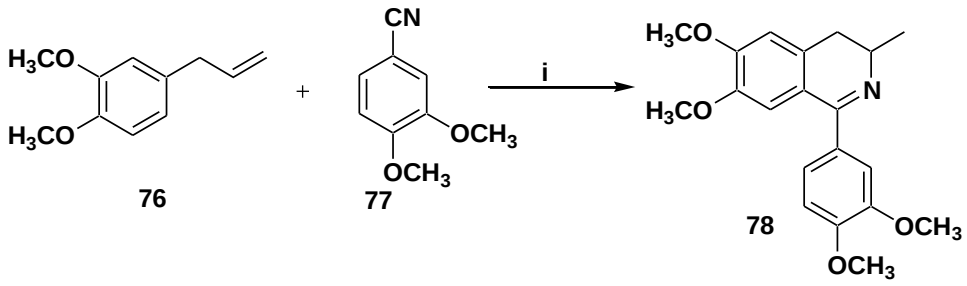
The less common reaction pathway Type II involves initial intramolecular formation of a cyclic nitrilium ion which is then quenched by an external nucleophile (Scheme 23).



Scheme 23

Formation of dihydroisoquinolines **78** from the reaction of methyl eugenol **76** with nitriles such as veratronitrile **77** is an example of the Type I process where an intramolecular cyclization of the nitrilium ion occurs. The reaction involves

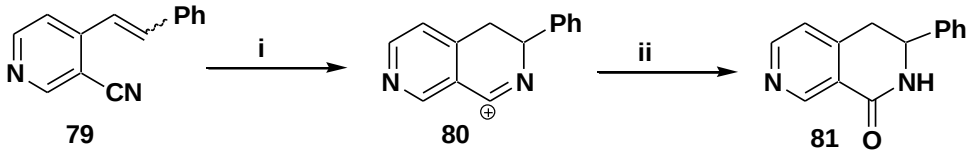
nucleophilic attack by the aromatic ring on the nitrilium ion, and is enhanced by the use of Lewis acids (Scheme 24).[26]



i) H_2SO_4, H_2O, 53%

Scheme 24

The conversion of 3-cyano-4-stilbazole **79** into a tetrahydrocopyrine derivative **81** illustrates the Type II process where an intramolecular formation of the nitrilium ion takes place first, and this is followed by attack of an external nucleophile (Scheme 25).[27]



i) PPA, 135 °C; ii) H_2O, 90%

Scheme 25

2.4 Aminotetralins - Importance and Synthesis

Aminotetralins form a class of biologically active compounds that are particularly important to the drug discovery process in the pharmaceutical industry and are also valuable intermediates in the synthesis of many natural products. They manifest a number of important therapeutically useful biological activities; some of them are potent CNS stimulants and others are antibiotics, immunomodulators and antitumor agents. A few examples of biologically active aminotetralins are depicted in Figure 1.

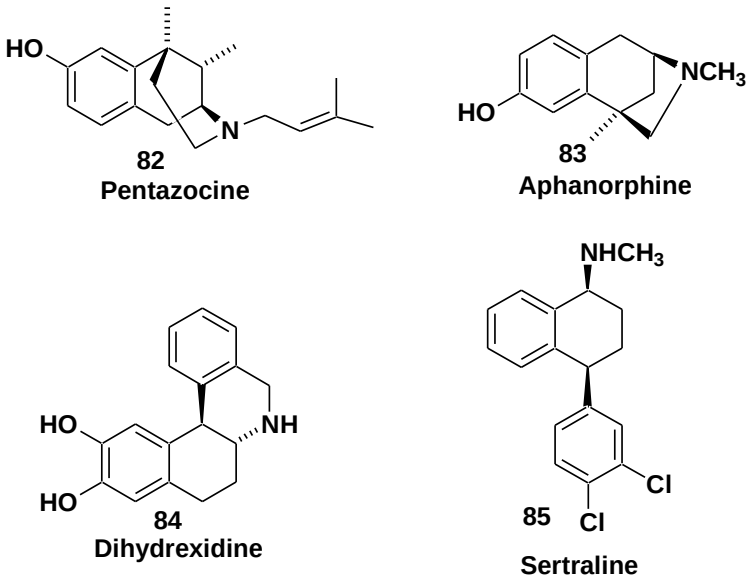
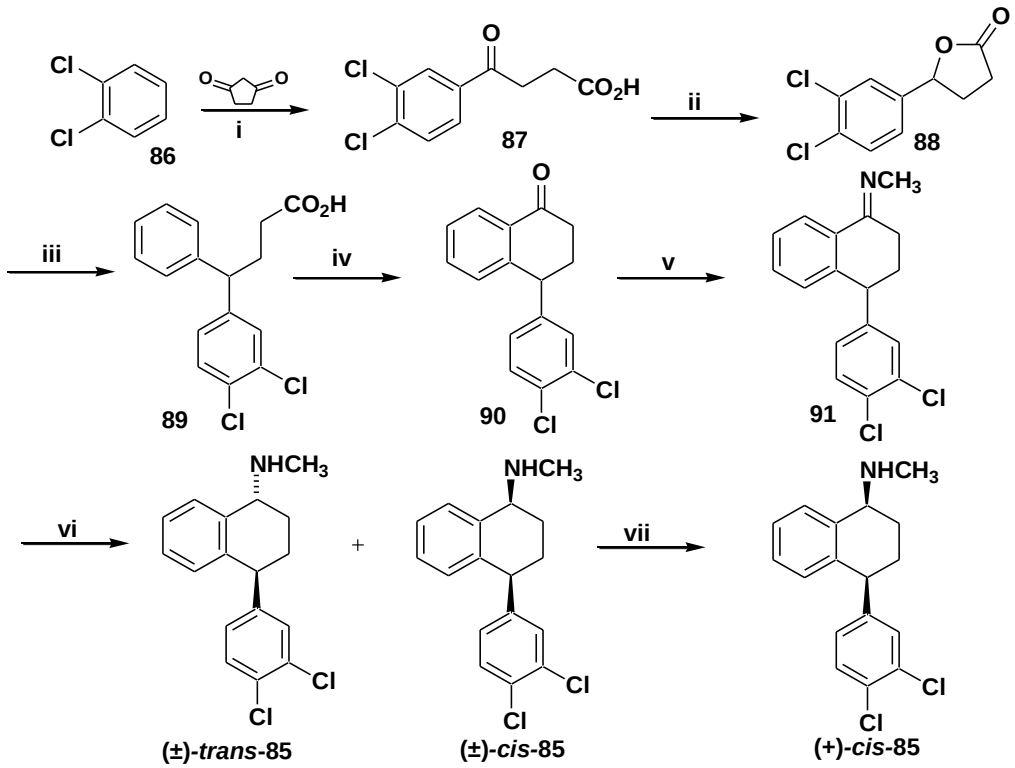


Figure 1

Of these, special mention may be made to the top selling antidepressant **Sertraline 85**, a selective competitive inhibitor of synaptosomal serotonin uptake. It is marketed as Zoloft® and is a very important pharmaceutical agent for the treatment of depression.[28]

The total synthesis of Sertraline has attracted the attention of a number of synthetic organic chemistry groups. Most efforts, however involve the synthesis of the racemic version followed by resolution of the racemate with *D*-mandelic acid.[29] A few asymmetric synthesis for Sertraline have also been reported recently.[30] Two selected synthesis representing each are discussed in the following section.

The most efficient synthesis of Sertraline **85** reported to date is the one developed at the Pfizer laboratories by Williams and Quallich.[29] In this synthesis the racemic tetralin is first prepared, followed by resolution of the racemate with *D*-mandelic acid. The strategy employed is outlined in the following scheme (Scheme 26).

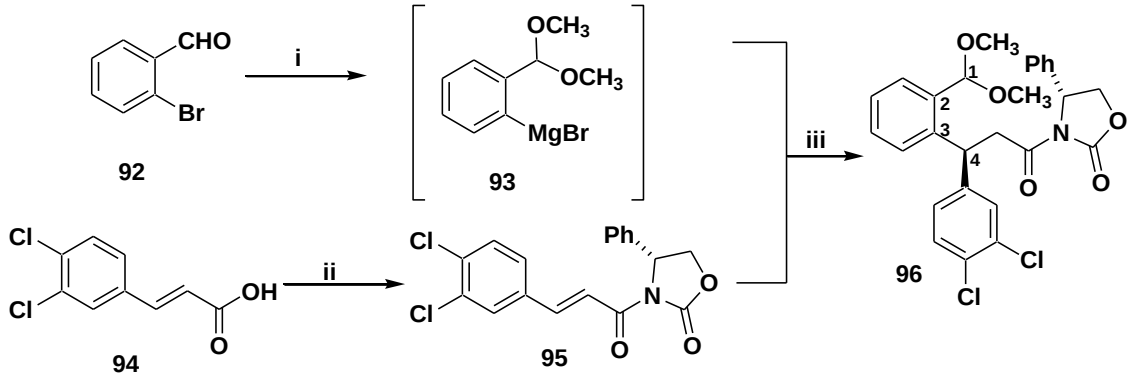


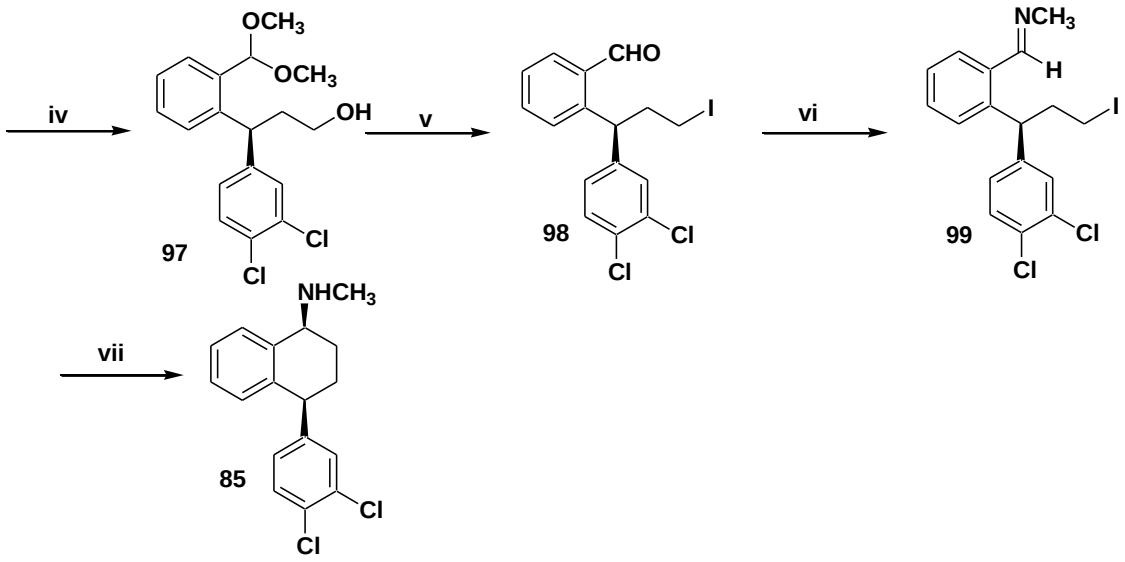
i) $AlCl_3$; ii) $NaBH_4$; iii) $AlCl_3$, benzene; iv) $SOCl_2$, $AlCl_3$; v) CH_3NH_2, $TiCl_4$; vi) $NaBH_4$; vii) chromatographic separation followed by resolution

Scheme 26

Reduction of the key intermediate with sodium borohydride gave a 1:1 mixture of racemic *cis* and *trans* amines. After chromatographic separation, each amine was resolved *via* its mandelate salt. After the resolution step (+)-*cis*-**85** was converted in high yield to the hydrochloride salt and the mandelic acid recovered.

An efficient enantioselective synthesis of Sertraline **85** *via* a novel intramolecular anionic ring closure to an imine in 45% overall yield in seven steps has been reported recently by Chen and Reamer (Scheme 27).[30c]





i) a.$(MeO)_3CH$, CH_3OH, cat. *p*-TsOH, b.Mg,THF; ii) $(CH_3)_3COCl$, Et_3N, LiCl, *(S)*-2-phenyl oxazolidinone; iii) 0.2eq $CuBrS(CH_3)_2$, THF, -30 °C to 0 °C; iv) $NaBH_4$ (3 eq.), THF-H_2O; v) a. PPh_3-I_2-imidazole, b. 2N HCl; or a. MsCl, Et_3N, b. excess NaI, acetone, reflux; vi) 2.0 M CH_3NH_2 in THF; vii) ^{t}BuLi (2.0 eq.) in THF-toluene, -78 °C.

Scheme 27

As illustrated in Scheme 27, the stereocenter at C-4 in **96** bearing the two aryl groups was established *via* conjugate addition of arylmagnesium bromide **93** to the imide conjugate derived from 3,4-dichlorocinnamic acid. Incorporation of a chiral auxilliary such as phenyloxazolidinone allowed the introduction of the stereocenter at C-4 in a reliable manner at an early stage in the synthesis. The final ring closure was facilitated with ^{t}BuLi in THF-toluene (1:1) to give Sertraline **85** as a single diastereomer.

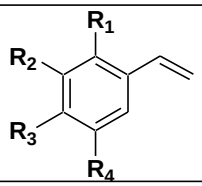
2.5 The Present Work

The above discussion reveals that the synthesis of biologically active α-aminotetralin derivatives, Sertraline in particular, usually involves multistep procedures. In this context, the CAN mediated one-pot procedure for the synthesis of α-aminotetralins seemed promising and a detailed study aimed at exploring the scope of this reaction was undertaken. The results of the investigation are presented in the following sections.

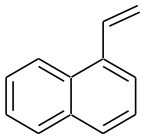
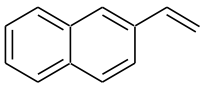
2.6 Results and Discussion

The styrenes selected for our studies are listed below (Figure 2).

Figure 2

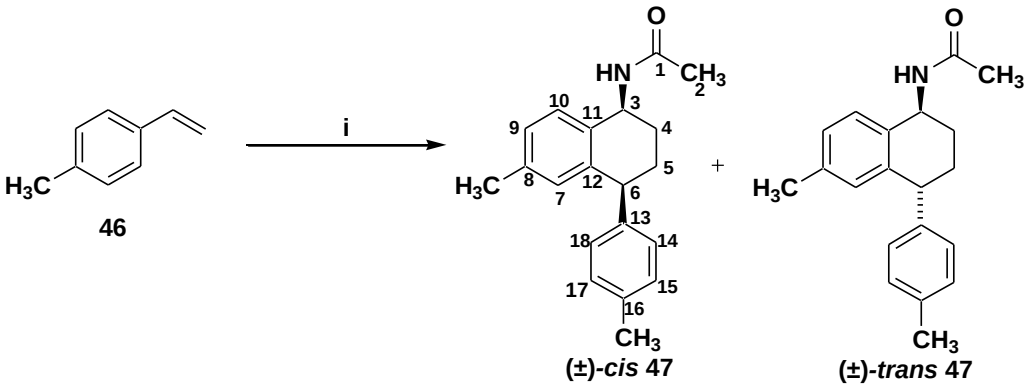


46	$R_1 = R_2 = R_4 = H, R_3 = CH_3$,
100	$R_1 = CH_3, R_2 = R_3 = R_4 = H$
101	$R_1 = R_3 = R_4 = H, R_2 = CH_3$,
102	$R_1 = R_3 = CH_3, R_2 = R_4 = H$
103	$R_1 = R_4 = CH_3, R_2 = R_3 = H$
104	$R_1 = R_2 = R_4 = H, R_3 = OAc$

105	$R_1 = H, R_2 = H, R_3 = H, R_4 = H$
106	$R_1 = H, R_2 = H, R_3 = Cl, R_4 = H$
107	
108	

2.6.1 Reactions in Acetonitrile

Our investigations were initiated with 4-methylstyrene **46**, an acetonitrile solution of which on treatment with a solution of CAN in acetonitrile at room temperature in a totally inert atmosphere of argon afforded the α-acetamido tetralins *cis*-**47** and *trans*-**47** in a total yield of 62%. The ratio of the *cis* to *trans* isomers was determined to be 1.3:1 by HPLC analysis (Scheme 28).



i) CAN (1.2 eq.), CH_3CN, Argon, RT, 2 h, 62%, 1.3:1

Scheme 28

The structures of *cis*-**47** and *trans*-**47** were elucidated by spectroscopic data. The IR spectrum of *cis*-**47** manifested a strong band at 3301 cm^{-1} characteristic of the -NH absorption. The sharp absorption at 1632 cm^{-1} was attributed to the amide carbonyl. In the ^1H NMR spectrum, the methyl protons of the amide moiety resonated as a singlet at δ 2.02, while the two methyl groups of the aromatic rings were observed as singlets at δ 2.19 and 2.34. The methylene protons on C-4 and

C-5 were discernible as multiplets centered at δ 1.85 and δ 2.08. The doubly benzylic proton resonated as a multiplet centered at δ 3.98. The benzylic proton geminal to the amide moiety displayed a multiplet centered at δ 5.14. The -NH proton manifested a doublet at δ 5.84 (J = 7.6) and was exchangeable by D_2O. In the ^{13}C NMR spectrum, the two methyl groups of the aromatic rings manifested a single resonance at δ 21.07 while the methyl carbon of the amide moiety resonated at δ 23.55. The signals resulting from C-4 and C-5 were seen at δ 27.58 and 29.71, while the signals due to C-3 and C-6 were observed at δ 44.91 and 47.54. The amide carbonyl resonated characteristically at δ 168.99. In the DEPT-135 NMR analysis of *cis*-**47**, peaks at δ 27.58 and 29.71 were negative indicating the presence of two methylene carbons. Finally, the configuration of the major diastereomer was ascertained to be *cis* by single crystal X-ray analysis (Figure 3).

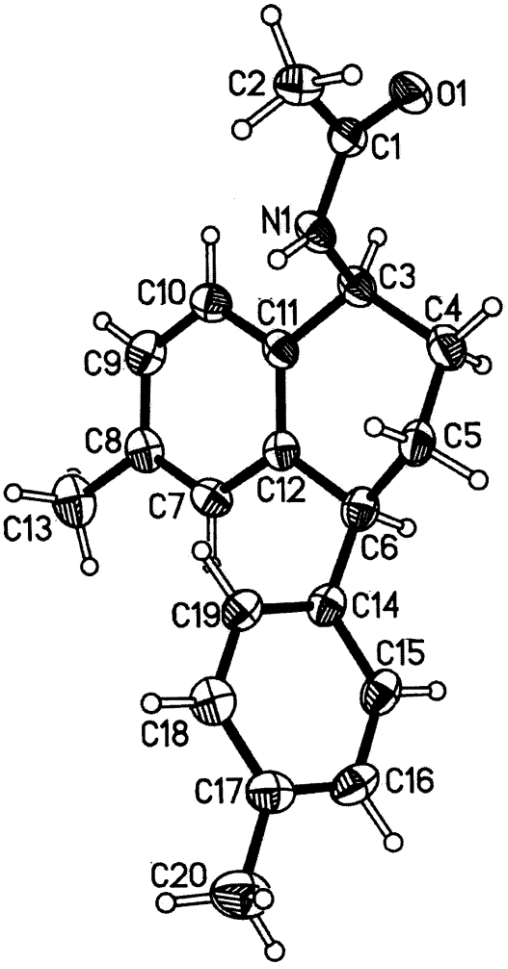


Figure 3 - X-Ray Crystal Structure of *cis*-47

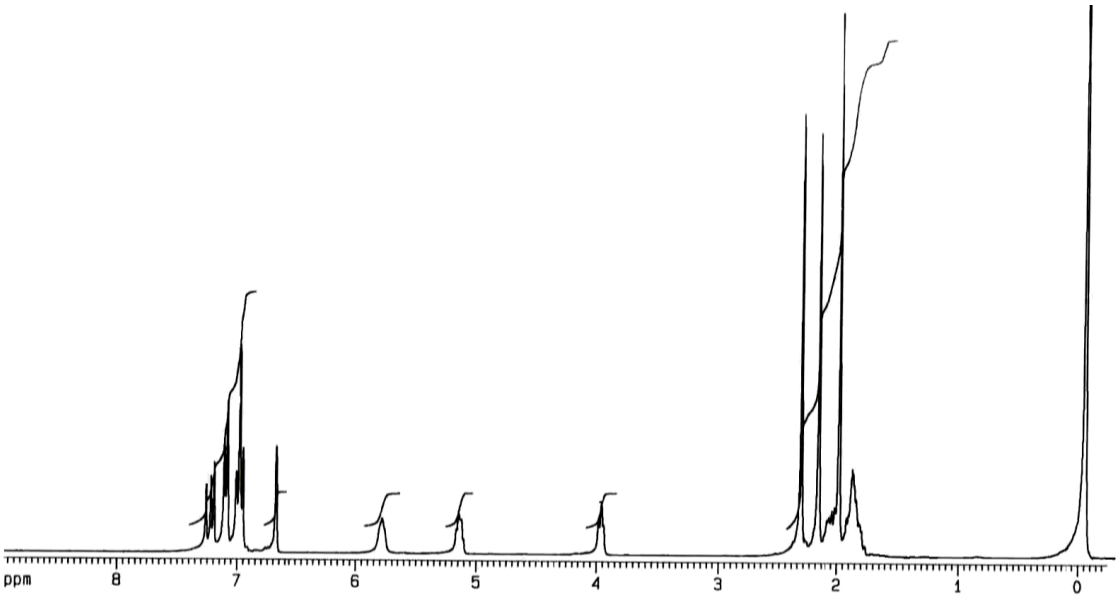


Figure 4 - ^{1}H NMR of *cis*-47

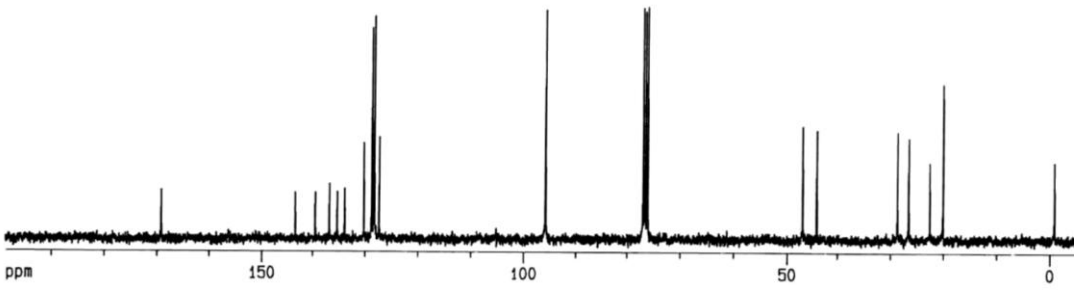


Figure 5 - ^{13}C NMR of *cis*-47

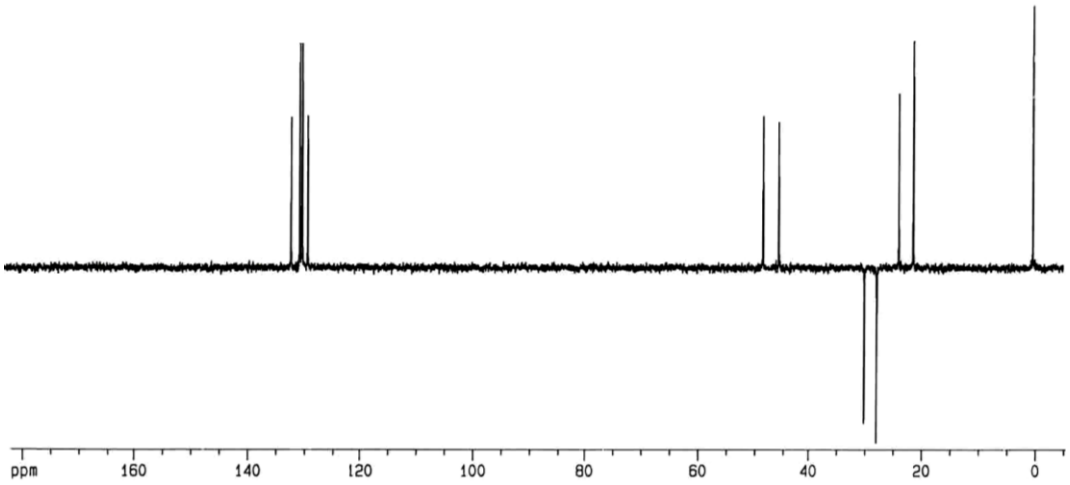
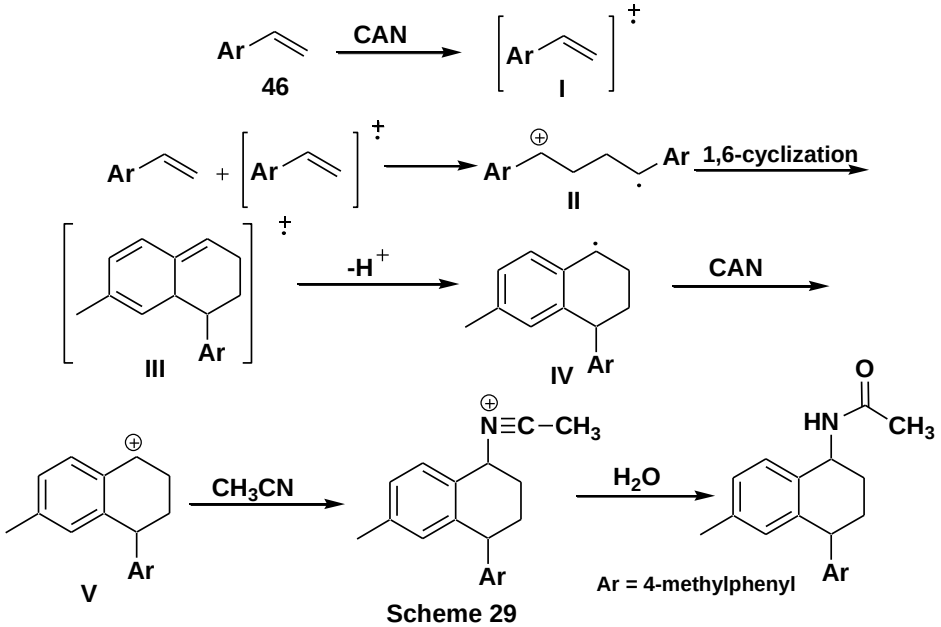


Figure 6 - DEPT-135 NMR of *cis*-47

The IR spectrum of *trans*-**47** displayed a strong absorption at 3288 cm^{-1} typical of an -NH functionality, while the amide carbonyl furnished a strong band at 1641 cm^{-1}. In the ^{1}H NMR spectrum, the doubly benzylic proton resonated as a multiplet centered at δ 4.04, while the benzylic methine proton geminal to the amide nitrogen furnished a multiplet centered at δ 5.26. The -NH proton resonated as a doublet at δ 5.69 (J = 8.5). In the ^{13}C NMR of *trans*-**47**, the amide carbonyl was seen at δ 169.07. All other signals also were in agreement with the assigned structure.

2.6.2 Mechanistic Considerations

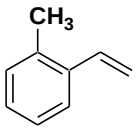
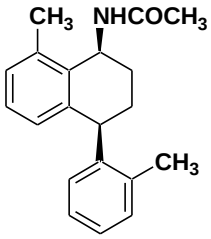
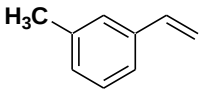
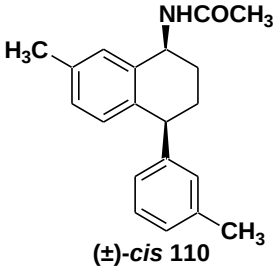
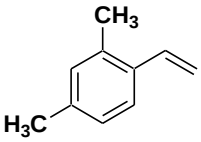
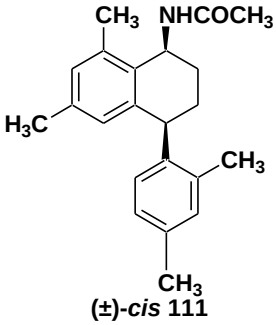
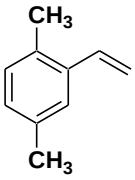
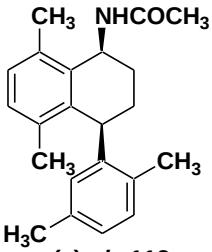
A mechanistic rationalization for the formation of the α-acetamido tetralins can be made along the following lines. The styrene **46** in the presence of Ce(IV) undergoes oxidative electron transfer to afford the radical cation **I**. This in turn would add to another styrene molecule to generate a distonic radical cation **II**. The latter undergoes 1,6-cyclization to give a substituted hexatriene radical cation **III** which on losing a proton yields the radical intermediate **IV**.[31] The radical intermediate **IV** undergoes oxidation to a cation **V** which subsequently gets trapped by the solvent acetonitrile in a manner analogous to the Ritter reaction (Scheme 29).[16]



Scheme 29

Similar reactivity was observed with other methylstyrenes **100-103**, which furnished the corresponding α-acetamido tetralins in moderate to good yields. The results obtained are presented in Table 1.

Table 1

Entry	Styrene	Time (h)	Product[a]	*cis/trans*[b] ratio	Yield (%)[*]
1.	 **100**	3	 **(±)-*cis* 109**	1.3:1	55
2.	 **101**	3	 **(±)-*cis* 110**	1.2:1	58
3.	 **102**	2	 **(±)-*cis* 111**	1.3:1	58
4.	 **103**	2	 **(±)-*cis* 112**	5:1	60

Reaction Conditions : CAN, dry CH_3CN, Argon, RT

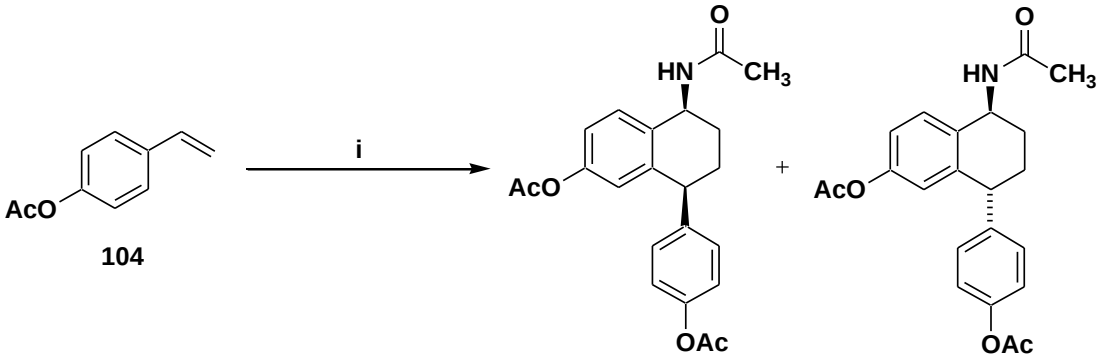
[a]Structure of the major isomer is shown

[b]Determined by HPLC analysis of the mixture of diasteriomers

[*]isolated yield

Analogous reactivity pattern was observed with 4-acetoxystyrene **104** which on treatment with CAN in acetonitrile under completely deoxygenated

conditions furnished the α-acetamido tetralins *cis*-**113** and *trans*-**113** in 58% yield (Scheme 30).

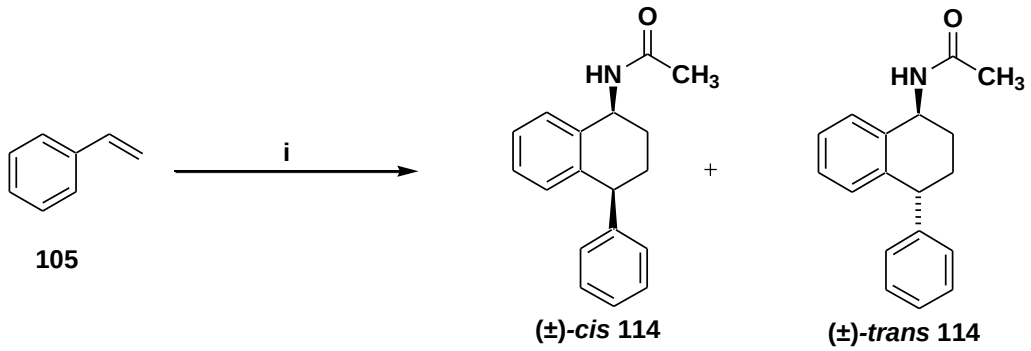


i) CAN (1.2 eq.), CH_3CN, Argon, RT, 3 h, 58%, 1.4:1

Scheme 30

In the IR spectrum of *cis*-**113**, the absorption corresponding to the -NH group was seen at 3278 cm^{-1}. The characteristic ester and amide group absorptions were seen at 1757 and 1643 cm^{-1} respectively. In the ^1H NMR spectrum, the methyl group of the amide functionality characteristically resonated at δ 2.04, while the methyl groups of the two acetate moieties were seen at δ 2.22 and 2.30. In the ^{13}C NMR spectrum, the carbonyl resonances were seen at δ 168.99, 169.11, and 169.18. All other signals were in accordance with the structure proposed. The *trans* isomer also furnished spectroscopic data consistent with the proposed structure.

Styrene **105** on reaction under similar conditions afforded the α-acetamido tetralins *trans*-**114** and *cis*-**114** in 40% yield. The ratio of the *cis* to *trans* isomer is 1.2:1 as determined by HPLC analysis (Scheme 31).

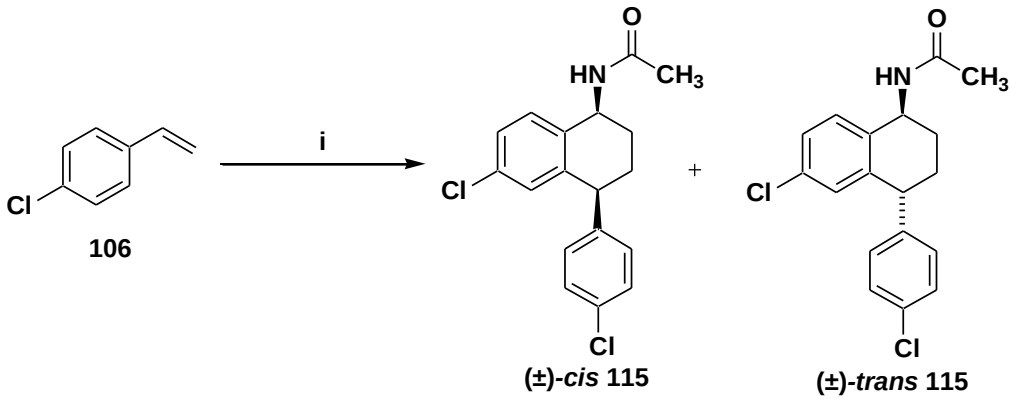


i) CAN (1.2 eq.), CH_3CN, Argon, RT, 12 h, 40%, 1.2:1

Scheme 31

In the IR spectrum of *cis*-**114**, the -NH absorption was seen at 3238 cm^{-1} while the amide carbonyl absorbed sharply at 1630 cm^{-1}. The ^{1}H NMR displayed a sharp singlet at δ 2.05 characteristic of the acetamido-methyl protons. The four methylene protons were discernible as multiplets in the region δ 1.89-2.01 and δ 2.12-2.17. The signals due to the nine aromatic protons were discernible in the region δ 6.87-7.33. In the ^{13}C NMR spectrum, the signal at δ 169.03 was typical of the amide carbonyl. All other peaks are in accordance with the structure assigned. *Trans*-**114** also furnished spectroscopic data consistent with the proposed structure.

Surprisingly, even styrenes with electron withdrawing substituents such as 4-chlorostyrene **106**, from which the formation of a radical cation is less favored, afforded the α-acetamido tetralins *cis*-**115** and *trans*-**115** in 42% yield (Scheme 32).



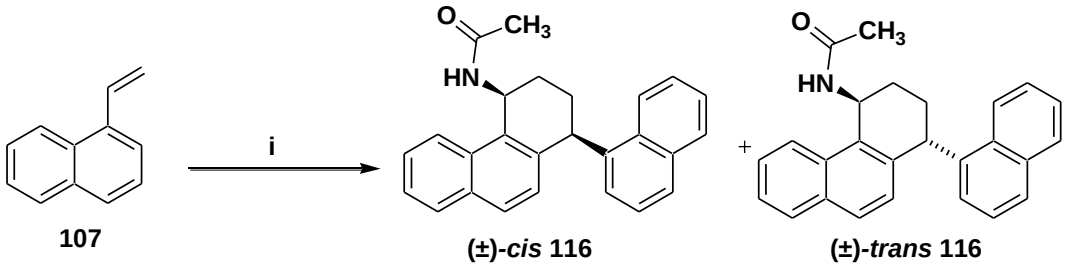
i) CAN (1.2 eq.), CH_3CN, Argon, RT, 12 h, 42%, 2.5:1

Scheme 32

Absorption due to the -NH stretching was present at 3293 cm^{-1} in the IR spectrum of *cis*-**115**. The absorption at 1632 cm^{-1} was typical of the amide carbonyl. In the ^{1}H NMR spectrum, the characteristic signal due to the acetamido-methyl protons was seen at δ 2.03. The doubly benzylic methine proton gave a signal at δ 3.99-4.03 as a multiplet, while the benzylic methine proton geminal to the amide moiety resonated as a multiplet centered at δ 5.14. In the ^{13}C NMR spectrum, the methyl carbon of the amide moiety resonated at δ 23.49 while the signal at δ 169.18 was attributed to the amide carbonyl. All other resonance

signals were compatible with the consigned structure. *Trans*-**115** also furnished spectroscopic data consistent with the proposed structure.

The best reactivity pattern was observed with vinyl naphthalenes **107** and **108**. When 1-vinyl naphthalene **107** was treated with a solution of CAN in acetonitrile under deoxygenated conditions, the α-acetamido-tetrahydro phenanthrene derivatives *cis*-**116** and *trans*-**116** were obtained in 82% yield (Scheme 33).



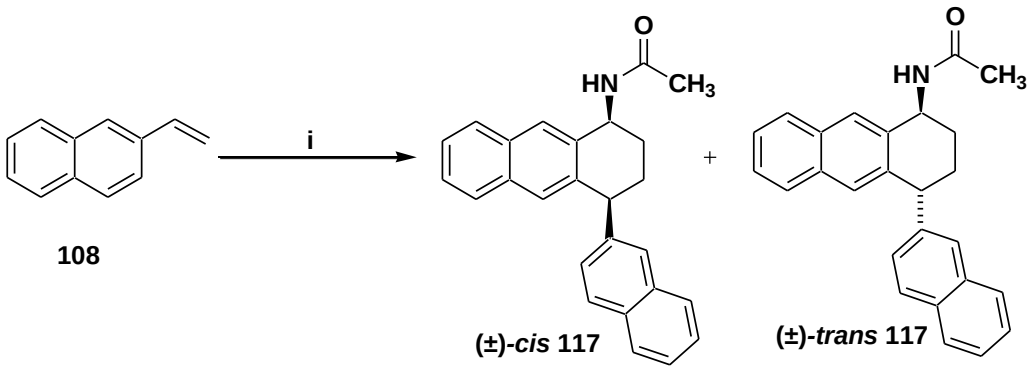
107 **(±)-*cis* 116** **(±)-*trans* 116**

i) CAN (1.2 eq.), CH_3CN, Argon, RT, 1h, 82%, 2.5 :1

Scheme 33

The IR spectrum of *cis*-**116** displayed a sharp vibration band at 3326 cm^{-1} due to the -NH absorption. A strong band at 1634 cm^{-1} indicated the presence of the amide carbonyl. In the ^1H NMR spectrum, a sharp singlet was seen at δ 2.03 characteristic of the acetamido-methyl protons. The doubly benzylic methine proton resonated as a multiplet centered at δ 5.04. The benzylic methine proton attached to the amide moiety furnished a multiplet centered at δ 5.87. In the ^{13}C NMR spectrum, the signal at δ 168.74 corresponds to the resonance of the amide carbonyl present in the molecule. All other resonances were in good agreement with the assigned structure. The *trans* isomer also furnished spectroscopic data consistent with the proposed structure.

Analogous reactivity profile was observed with 2-vinyl naphthalene **108** which under similar conditions afforded the α-acetamido-tetrahydroanthracene derivatives *cis*-**117** and *trans*-**117** in 80% yield (Scheme 34).



108 **(±)-*cis* 117** **(±)-*trans* 117**

i) CAN (1.2 eq.), CH_3CN, Argon, RT, 1h, 80%, 9:1

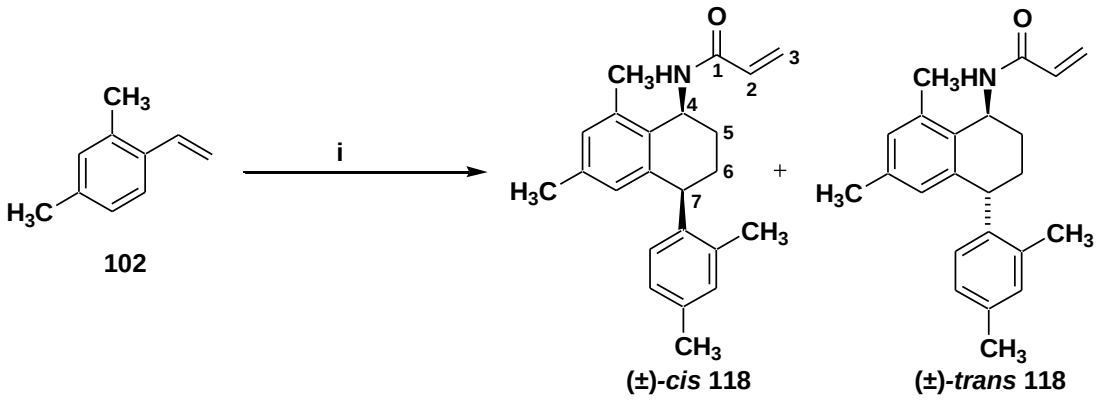
Scheme 34

As usual, the characterization of the products was carried out with the aid of spectroscopic data. In the vibrational spectrum of *cis*-**117**, the peak at 3179 cm^{-1} was attributed to the -NH absorption. The sharp vibration band at 1632 cm^{-1} was typical of the amide carbonyl. In the ^1H NMR spectrum, the sharp singlet at δ 1.99 was characteristic of the acetamido-methyl protons. The -NH proton resonated as a doublet at δ 5.96 (J = 7.2) and was exchangeable by D_2O. The thirteen aromatic protons resonated as a multiplet in the region δ 7.19-7.75. In the ^{13}C NMR spectrum, the peak at δ 168.64 was attributed to the amide carbonyl. All other resonances were in accordance with the assigned structure. The *trans* diastereomer also furnished spectroscopic data consistent with the assigned structure.

2.6.3 Reactions in Acrylonitrile

The reaction described above could be easily extended to employ acrylonitrile as the solvent system. The products were obtained in yields comparable to those obtained in acetonitrile.

Thus, when 2,4-dimethylstyrene **102** was treated with CAN in acrylonitrile, the α-acrylamido tetralins *cis*-**118** and *trans*-**118** were obtained in 72% yield (Scheme 35).



i) CAN (1.2 eq.), acrylonitrile, RT, 3 h, 72%, 1.2:1

Scheme 35

The structures of the products *cis*-**118** and *trans*-**118** were established by spectroscopic methods. In the IR spectrum of *cis*-**118**, the absorption due to the -NH stretching was observed at 3245 cm^{-1}. The sharp vibration band at 1654 cm^{-1} was typical of an α,β-unsaturated amide carbonyl, while the characteristic absorption of the alkene bond in conjugation with the carbonyl group was observed at 1613 cm^{-1}. In the ^{1}H NMR spectrum, the four methylene protons on C-5 and C-6 were discernible as multiplets in the region δ 1.77-2.02 and δ 2.07-2.17. The methyl groups of the aromatic rings resonated as sharp singlets at δ 2.13, 2.26, 2.31 and 2.33. The doubly benzylic methine proton on C-7 gave a multiplet centered at δ 4.16. The other benzylic proton also resonated as a multiplet centered at δ 5.26. The vinylic proton on C-3 *cis* to the proton on C-2 resonated as a doublet of doublet at δ 5.63 (J_1 = 10.2, J_2 = 1.3), while the other vinylic proton on C-3 *trans* to the proton on C-2 displayed another doublet of doublet at δ 6.29 (J_1 = 16.9, J_2 = 1.4). The -NH proton furnished a doublet at δ 5.77 (J = 7.4) which was exchangeable by D_2O. The proton on C-2 resonated as a doublet of doublet at δ 6.06 (J_1 = 16.9, J_2 = 10.2). The five aromatic protons were visible in the region δ 6.43-7.00. In the ^{13}C NMR spectrum, the carbons of the methyl groups gave signals at δ 18.78, 19.74, 20.99 and 21.03. The resonance signals due to C-5 and C-6 were observed at δ 27.33 and 29.31. Both the benzylic carbons resonated together at δ 44.83. The signal at δ 164.06 indicated the

presence of an α,β-unsaturated amide carbonyl in the molecule. All other signals were in accordance with the assigned structure.

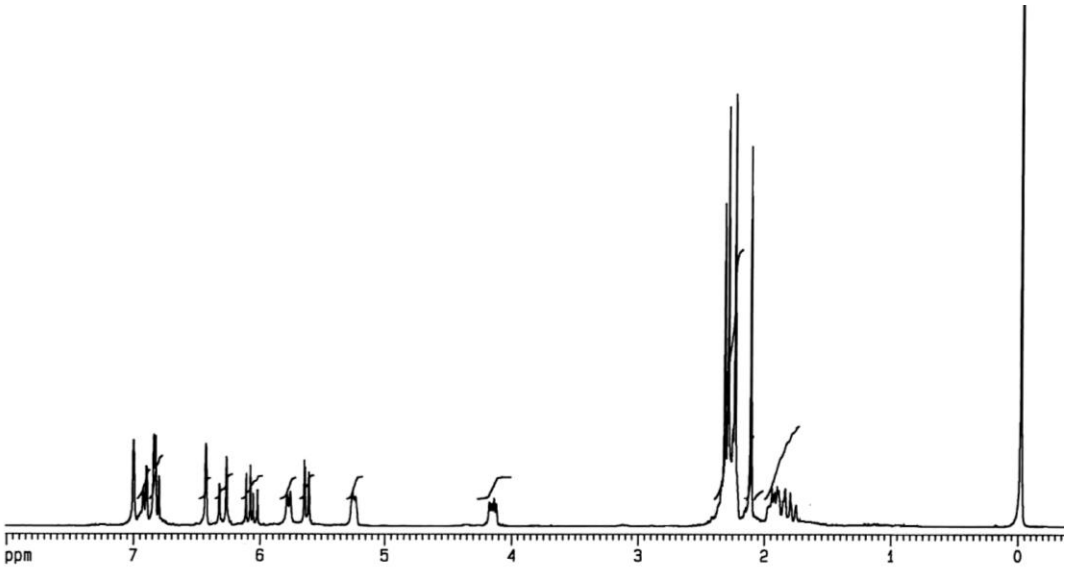


Figure 7 - ^{1}H NMR of *cis*-118

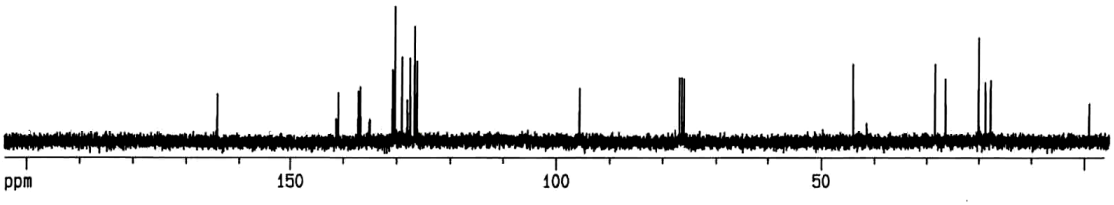
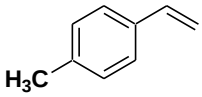
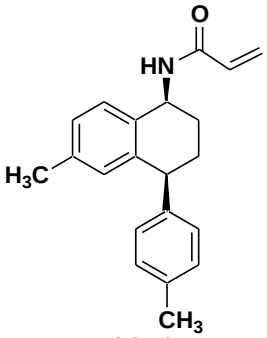
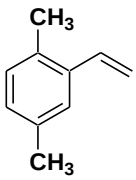
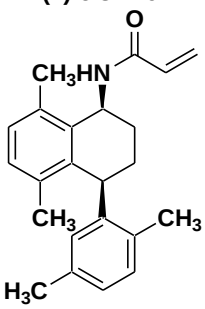
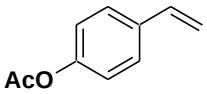
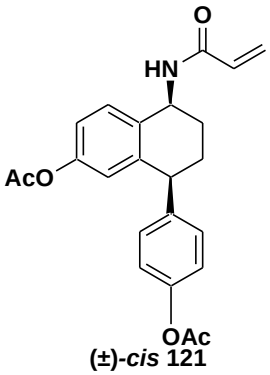


Figure 8 - ^{13}C NMR of *cis*-118

The *trans* diastereomer also furnished spectroscopic data consistent with the assigned structure.

Analogous reactivity profile was observed with 4-methylstyrene **46**, 2,5-dimethylstyrene **103** and 4-acetoxystyrene **104**. The results are summarized in Table 2.

Table 2

Entry	Styrene	Time (h)	Product[a]	*cis/trans*[b] ratio	Yield (%)*
1.	 **46**	3	 **(±)-*cis* 119**	1.3:1	52
2.	 **103**	3	 **(±)-*cis* 120**	7:1	64
3.	 **104**	3	 **(±)-*cis* 121**	1.3:1	54

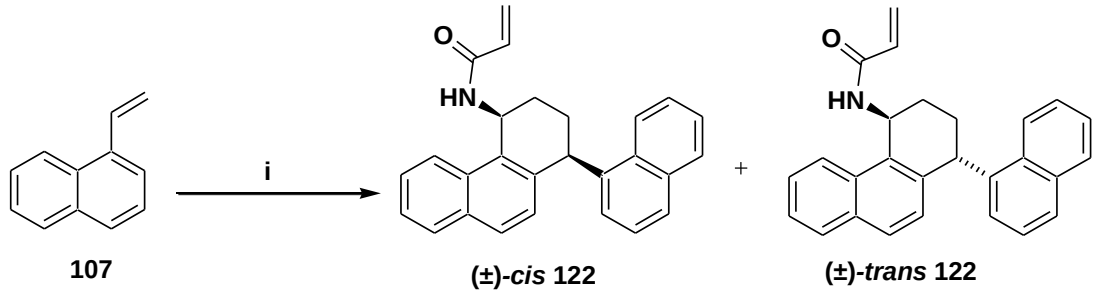
Reaction Conditions : CAN, acrylonitrile, Argon, RT

[a]Structure of the major isomer is shown

[b]Determined by HPLC analysis of the mixture of diasteriomers

***isolated yield**

1-Vinyl naphthalene **107** on treatment with a solution of CAN in acrylonitrile furnished the α-acrylamido-tetrahydrophenanthrenyl derivatives *cis*-**122** and *trans*-**122** in 71% yield (Scheme 36).



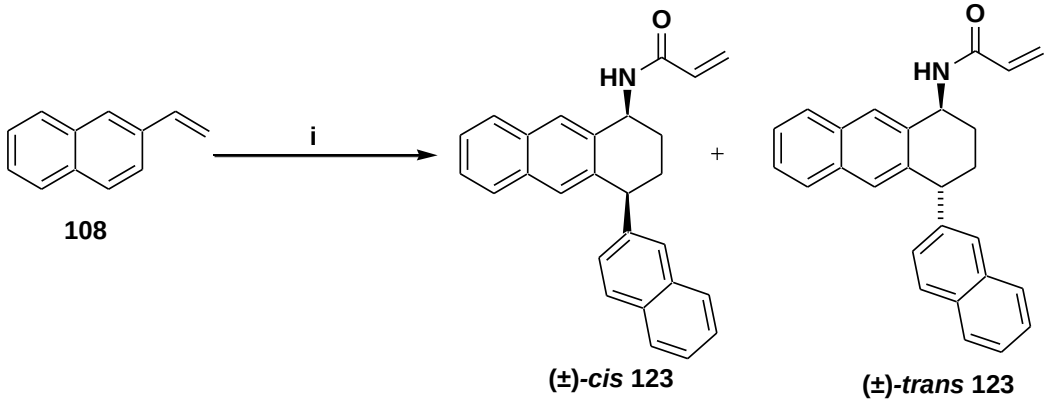
107 **(±)-*cis* 122** **(±)-*trans* 122**

i) CAN (1.2 eq.), acrylonitrile, RT, 2 h, 71%, 1.1:1

Scheme 36

As usual, the structure of the product was elucidated on the basis of spectroscopic data. The IR spectrum of *cis*-**122** exhibited characteristic vibration bands at 3252, 1654 and 1613 cm^{-1} diagnostic of the -NH stretching, amide carbonyl and alkene stretching frequencies respectively. In the ^{1}H NMR spectrum, the four methylene protons displayed multiplets at δ 2.04-2.27 and δ 2.28-2.50. The doubly benzylic methine proton resonated as a multiplet centered at δ 5.06. The benzylic methine proton geminal to the amide nitrogen together with the -NH proton resonated at δ 5.98 as a broad singlet. The resonance signal at δ 164.21 in the ^{13}C NMR spectrum was typical of an α,β-unsaturated amide carbonyl. All other signals were in good agreement with the assigned structure.

2-Vinyl naphthalene **108** under similar conditions afforded the α-acrylamido-tetrahydroanthracenyl derivative *cis*-**123** and *trans*-**123** in 57% yield (Scheme 37).



108 **(±)-*cis* 123** **(±)-*trans* 123**

i) CAN (1.2 eq.), acrylonitrile, RT, 2 h, 57%, 11:1

Scheme 37

In the vibrational spectrum of *cis*-**123**, the -NH absorption was seen at 3238 cm^{-1}, while the amide carbonyl absorbed sharply at 1654 cm^{-1}. The alkene

stretch was seen as a sharp vibration band at 1613 cm^{-1}. In the ^{1}H NMR spectrum, the four methylene protons resonated as multiplets centered at δ 2.00 and δ 2.33. One of the terminal vinylic protons resonated as a doublet at δ 5.64 (J = 10.2) while the other terminal vinylic proton resonated as a doublet at δ 6.32 (J = 16.8). The vinylic methine proton and the -NH proton resonated together as a multiplet centered at δ 6.04. In the ^{13}C NMR spectrum, the amide carbonyl gave a resonance signal at δ 164.15. All the other signals were also consistent with the proposed structure. The *trans* isomer also gave spectroscopic data completely consistent with the structure assigned.

2.7 Conclusion

In conclusion, we have uncovered a novel CAN induced cyclodimerization of styrenes, involving a Ritter trapping strategy for the one-pot synthesis of 1-amino-4-aryltetralins that bear close resemblance to potent therapeutic agents. This may be contrasted with the multistep synthesis of 1-amino-4-aryltetralins reported in the literature.

2.8 Experimental Details

General: Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz respectively on a Bruker Avance DPX-300 MHz NMR spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constant (J) is reported in Hertz (Hz). High resolution mass spectra were recorded under EI/FAB conditions using Auto Spec. M mass spectrometer. IR spectra were recorded on a Nicolet Impact 400D FT-IR spectrophotometer. Analytical HPLC was performed on a Shimadzu High Pressure Liquid Chromatograph (λ = 254 nm) using 80:20 methanol-water mixture as the eluent at a flow rate of 1 mL/minute. Cerium(IV) Ammonium Nitrate (CAN) was purchased from Aldrich Chemical Co. and was used without further purification. Commercial grade solvents were distilled prior to use. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate as the binder. Gravity column

chromatography was performed using 100-200 mesh silica gel and mixtures of hexane and ethyl acetate were used for elution.

Synthesis of α-Acetamido tetralin Derivatives by the CAN mediated Reaction of Styrenes in Acetonitrile

General Procedure: A solution of the styrene (2.0 mmol) in dry acetonitrile (5 mL) was taken in a two necked round bottom flask fitted with a pressure equalizing funnel containing a solution of CAN (2.4 mmol) in dry acetonitrile (15 mL). Both the solutions were simultaneously bubbled with argon (deoxygenated by passing through Fieser's solution) for 10 minutes. The CAN solution was then added dropwise and the reaction mixture was allowed to stir at room temperature. When the starting material was fully consumed as indicated by the tlc (usually 1 to 3 h) the acetonitrile was removed *in vacuo*. The crude residue was diluted with water (100 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The dichloromethane was removed on a rotary evaporator and the residue was subjected to column chromatography on silica gel. Elution with an appropriate mixture of hexane and ethyl acetate afforded the α-acetamido tetralin derivatives as white crystalline solids.

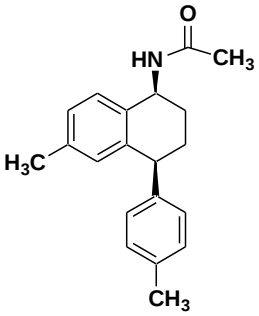
Synthesis of α-Acetamido tetralin Derivatives by the CAN mediated Reaction of Styrenes in Acrylonitrile

General Procedure: A solution of CAN (2.4 mmol) in acrylonitrile (30 mL) was added dropwise to a solution of styrene (2.0 mmol) also in the same solvent (5 mL). When the starting material was fully consumed as indicated by the tlc (usually 1 to 3 h) the acrylonitrile was removed *in vacuo*. The crude residue was diluted with water (100 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The dichloromethane was removed on a rotary evaporator and the residue was subjected to column chromatography on silica gel. Elution with appropriate mixtures of hexane and ethyl acetate afforded the α-acrylamido tetralin derivatives as white crystalline solids.

***N*-[6-methyl-4-(4-methylphenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]acetamide (*cis*-47 and *trans*-47)**

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of 4-methylstyrene (236 mg, 2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 2 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 80:20 hexane-ethyl acetate mixture gave the α-acetamido tetralins *cis*-**47** and *trans*-**47** as white crystalline solids (182 mg, 62%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 1.3 :1.

***cis*-47**



cis-47

mp : 207 °C.

IR (KBr) ν_{max}: 3301, 3046, 2924, 1632, 1537, 1438, 1266, 1098 cm^{-1}.

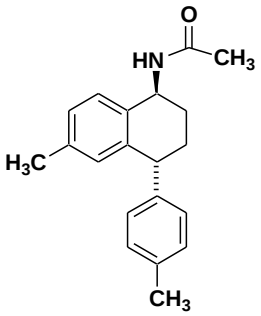
^{1}H NMR: δ 1.75-1.96 (m, 3H, C$\underline{H}_2$, C$\underline{H}$H), 2.02 (s, 3H, NHCOC$\underline{H}_3$), 2.06-2.11 (m, 1H, CH$\underline{H}$), 2.19 (s, 3H, C$\underline{H}_3$), 2.34 (s, 3H, C$\underline{H}_3$), 3.97-3.99 (m, 1H, C$\underline{H}CH_2$), 5.13-5.15 (m, 1H, C$\underline{H}$NH), 5.84 (d, 1H, *J* = 7.6, N$\underline{H}$), 6.67 (s, 1H, Ar$\underline{H}$), 6.96 (d, 2H, *J* = 7.8, Ar$\underline{H}$), 6.99 (d, 1H, *J* = 7.5, Ar$\underline{H}$), 7.10 (d, 2H, *J* = 7.7, Ar$\underline{H}$), 7.20 (d, 1H, *J* = 7.8, Ar$\underline{H}$).

^{13}C NMR: δ 21.07, 23.55, 27.58, 29.71, 44.91, 47.54, 127.68, 128.61, 128.72, 129.08, 130.56, 134.22, 135.63, 137.09, 139.77, 143.52, 168.99.

HRMS (FAB) Calcd for $C_{20}H_{23}NO + H^+$: 293.1858. Found: 294.1857.

Crystal data for *cis*-47: $C_{20}H_{23}NO$, FW = 293.39. The crystal used for the X-ray study has the dimensions of 0.36 x 0.16 x 0.08 mm^3. Tetragonal, space group $P4_3$. Unit cell dimensions: a = 9.4397(1) Å, α = 90°; b = 9.4397(1) Å, β = 90°; c = 18.55245(5), γ = 90°; Vol = 1653.17(5) $Å^3$. Density (calcd.) = 1.179 mg/m^3. Absorption coefficient = 0.072 mm^{-1}. R indices R1 = 0.0981, wR2 = 0.1133.

***trans*-47**



***trans*-47**

mp : 205 °C.

IR (KBr) ν_{max}: 3288, 3078, 2936, 2852, 1641, 1555, 1311 cm^{-1}.

^{1}H NMR: δ 1.66-1.69 (m, 1H, C<u>H</u>H), 1.82-1.90 (m, 1H, CH<u>H</u>), 2.03 (s, 3H, NHCOC<u>H</u>$_3$), 2.08-2.16 (m, 2H, C<u>H</u>$_2$), 2.19 (s, 3H, C<u>H</u>$_3$), 2.32 (s, 3H, C<u>H</u>$_3$), 4.03-4.06 (m, 1H, C<u>H</u>CH$_2$), 5.25-5.27 (m, 1H, C<u>H</u>NH), 5.69 (d, 1H, *J* = 8.5, N<u>H</u>), 6.67 (s, 1H, Ar<u>H</u>), 6.89 (d, 2H, *J* = 7.8, Ar<u>H</u>), 7.00 (d, 1H, *J* = 7.8, Ar<u>H</u>), 7.06 (d, 2H, *J* = 7.8, Ar<u>H</u>), 7.19 (d, 1H, *J* = 7.9, Ar<u>H</u>).

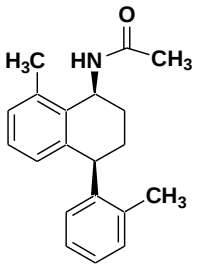
^{13}C NMR: δ 21.09, 23.60, 28.04, 30.23, 44.90, 47.58, 127.69, 128.05, 128.59, 129.10, 130.73, 134.49, 135.63, 136.99, 139.81, 143.47, 169.07.

HRMS (EI) Calcd for $C_{20}H_{23}NO$: 293.1779. Found: 293.1776.

***N*-[8-methyl-4-(2-methylphenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]acetamide (*cis*-109 and *trans*-109)**

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of 2-methylstyrene (236 mg, 2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 3 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 80:20 hexane-ethyl acetate mixture gave the α-acetamido tetralins *cis*-**109** and *trans*-**109** as white crystalline solids (161 mg, 55%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 1.3 :1.

***cis*-109**



mp : 235 °C.

IR (KBr) ν_{max}: 3240, 3050, 2851, 1630, 1538, 1371, 1278, 1111 cm^{-1}.

^{1}H NMR: δ 1.80-1.92 (m, 2H, C<u>H</u>$_2$), 2.01 (s, 4H, NHCOC<u>H</u>$_3$, C<u>H</u>H), 2.24-2.28 (m, 1H, CH<u>H</u>), 2.31 (s, 3H, C<u>H</u>$_3$), 2.38 (s, 3H, C<u>H</u>$_3$), 4.22-4.27 (m, 1H, C<u>H</u>CH$_2$), 5.21-5.23 (m, 1H, CHNH),

***cis*-109** 5.69 (d, 1H, *J* = 7.1, NH), 6.59-6.62 (m, 1H, ArH), 6.91-6.94 (m, 1H, ArH), 7.01 (d, 2H, *J* = 5.2, ArH), 7.07-7.18 (m, 3H, ArH).

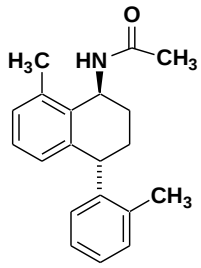
^{13}C NMR: δ 18.91, 19.85, 23.31, 27.10, 29.32, 42.64, 44.99, 126.26, 126.42, 127.73, 128.51, 130.52, 134.28, 135.92, 137.71, 141.38, 144.86, 168.51.

HRMS (FAB) Calcd for $C_{20}H_{23}NO + H^+$: 294.1858. Found: 294.1851.

***trans*-109**

mp : 194 °C.

IR (KBr) ν_{max}: 3299, 3063, 3016, 2935, 2861, 1640, 1539, 1458, 1371, 1276, 1094, 744 cm^{-1}.



***trans*-109**

^{1}H NMR: δ 1.73-1.77 (m, 1H, CHH), 1.86-1.92 (m, 2H, CH_2), 1.98 (s, 3H, $NHCOCH_3$), 2.12-2.23 (m, 1H, CHH), 2.34 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.44-4.46 (m, 1H, $CHCH_2$), 5.21-5.26 (m, 1H, CHNH), 5.61 (d, 1H, *J* = 7.2, NH), 6.33 (d, 1H, *J* = 7.6, ArH), 6.75-6.78 (m, 1H, ArH), 6.95 (t, 1H, *J* = 7.4, ArH), 7.03 (d, 1H, *J* = 7.4, ArH), 7.07-7.09 (m, 2H, ArH), 7.15 (d, 1H, *J* = 7.3, ArH).

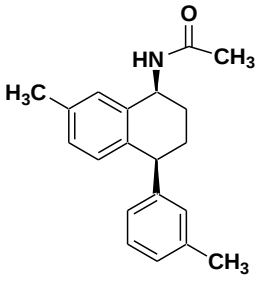
^{13}C NMR: δ 18.81, 19.43, 23.00, 23.91, 24.16, 40.09, 44.52, 125.48, 125.91, 127.61, 128.37, 128.79, 129.38, 130.27, 134.89, 135.00, 137.59, 139.91, 144.44, 168.51.

***N*-[7-methyl-4-(3-methylphenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]acetamide (*cis*-110 and *trans*-110)**

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of 3-methylstyrene (236 mg, 2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 3 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 80:20 hexane-ethyl acetate mixture gave the α-acetamido tetralins *cis*-**110** and *trans*-**110** as white

crystalline solids (170 mg, 58%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 1.3 :1.

***cis*-110**



***cis*-110**

mp :166 °C.

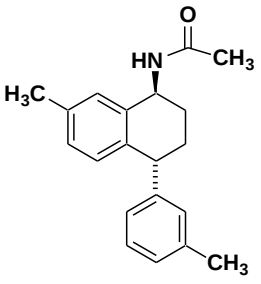
IR (KBr) ν_{max}: 3278, 3046, 2932, 2861, 1634, 1542, 1437, 1371, 1280, 1104, 880, 786 cm^{-1}.

^{1}H NMR: δ 1.82-1.96 (m, 3H, C$\underline{H}_2$, C$\underline{H}$H), 2.04 (s, 3H, NHCOC$\underline{H}_3$), 2.06-2.13 (m, 1H, CH$\underline{H}$), 2.30 (s, 3H, C$\underline{H}_3$), 2.32 (s, 3H, C$\underline{H}_3$), 3.93-3.98 (m, 1H, C$\underline{H}$CH_2), 5.12-5.18 (m, 1H, C$\underline{H}$NH), 5.83 (d, 1H, *J* = 8.0, N$\underline{H}$), 6.74 (d, 1H, *J* = 7.9, Ar$\underline{H}$), 6.85 (d, 1H, *J* = 7.6, Ar$\underline{H}$), 6.93 (d, 2H, *J* = 7.4, Ar$\underline{H}$), 7.01 (d, 1H, *J* = 7.5, Ar$\underline{H}$), 7.12 (d, 1H, *J* = 5.1, Ar$\underline{H}$), 7.17 (d, 1H, *J* = 7.5, Ar$\underline{H}$).

^{13}C NMR: δ 21.02, 21.51, 23.59, 27.86, 29.54, 45.13, 47.64, 125.85, 127.05, 128.26, 128.57, 129.34, 129.38, 130.14, 136.22, 136.78, 137.01, 137.86, 168.95.

HRMS (FAB) Calcd for $C_{20}H_{23}NO + H^+$: 294.1858. Found: 294.1862.

***trans*-110**



***trans*-110**

mp : 98 °C

IR (KBr) ν_{max}: 3272, 3063, 2935, 2867, 1647, 1546, 1452, 1371, 1276, 791 cm^{-1}.

^{1}H NMR: δ 1.63-1.78 (m, 2H, C$\underline{H}_2$), 1.94 (s, 3H, C$\underline{H}_3$), 1.96 (s, 3H, NHCOC$\underline{H}_3$), 2.12-2.29 (m, 2H, C$\underline{H}_2$), 2.29 (s, 3H, C$\underline{H}_3$), 4.18 (d, 1H, *J* = 4.3, C$\underline{H}$CH_2), 5.17-5.20 (m, 1H, C$\underline{H}$NH), 5.82 (d, 1H, *J* = 7.7, N$\underline{H}$), 6.61 (d, 1H, *J* = 7.6, Ar$\underline{H}$), 6.75 (d, 1H, *J* = 7.4, Ar$\underline{H}$), 6.83 (d, 2H, *J* = 7.6, Ar$\underline{H}$), 6.92 (d, 1H, *J* = 7.5, Ar$\underline{H}$), 7.01 (d, 1H, *J* = 5.4, Ar$\underline{H}$), 7.11 (d, 1H, *J* = 7.5, Ar$\underline{H}$).

^{13}C NMR: δ 19.68, 21.50, 23.43, 23.78, 27.62, 41.31, 47.11, 125.29, 126.82, 126.91, 127.86, 128.08, 128.92, 129.95, 137.10, 137.23, 137.42, 137.67, 144.60, 168.50.

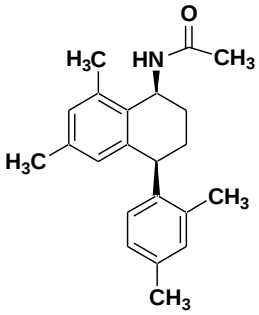
***N*-[4-(2,4-dimethylphenyl)-6,8-dimethyl-1,2,3,4-tetrahydro-1-naphthalenyl] acetamide (*cis*-111 and *trans*-111)**

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of 2,4-dimethylstyrene (264 mg, 2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 2 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate mixture gave the α-acetamido tetralins *cis*-**111** and *trans*-**111** as white crystalline solids (186 mg, 58%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 1.3 :1.

***cis*-111**

mp : 208 °C.

IR (KBr) ν_{max}: 3303, 3051, 2925, 2853, 1639, 1540, 1493, 1440, 1367, 1268, 1036, 903, 857 cm^{-1}.



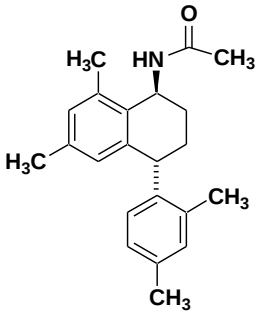
cis-111

^{1}H NMR: δ 1.71-1.95 (m, 3H, C$\underline{H}_2$, C$\underline{H}$H), 2.01 (s, 3H, NHCOC$\underline{H}_3$), 2.13 (s, 3H, C$\underline{H}_3$), 2.18-2.20 (m, 1H, CH$\underline{H}$), 2.27 (s, 3H, C$\underline{H}_3$), 2.32 (s, 3H, C$\underline{H}_3$), 2.34 (s, 3H, C$\underline{H}_3$), 4.13-4.17 (m, 1H, C$\underline{H}$CH$_2$), 5.14-5.23 (m, 1H, C$\underline{H}$NH), 5.59 (d, 1H, J = 6.9, N$\underline{H}$), 6.42 (s, 1H, Ar$\underline{H}$), 6.80 (d, 1H, J = 8.0, Ar$\underline{H}$), 6.84 (s, 1H, Ar$\underline{H}$), 6.92 (d, 1H, J = 8.3, Ar$\underline{H}$), 7.00 (s, 1H, Ar$\underline{H}$).

^{13}C NMR: δ 18.79, 19.76, 21.02, 21.05, 23.35, 27.34, 29.35, 44.83, 127.15, 127.99, 128.47, 129.50, 129.94, 131.26, 131.48, 135.48, 135.68, 137.23, 137.53, 141.41, 141.93, 168.45.

HRMS (FAB) Calcd for $C_{22}H_{27}NO + H^+$: 322.2171. Found: 322.2177.

***trans*-111**



***trans*-111**

mp : 262 °C.

IR (KBr) ν_{max}: 3299, 3009, 2935, 2854, 1640, 1539, 1499, 1445, 1371, 1270, 1101, 1027, 818 cm^{-1}.

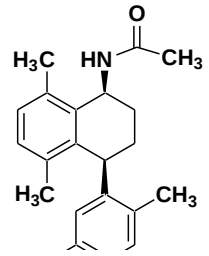
^{1}H NMR: δ 1.67-1.71 (m, 1H, C<u>H</u>H), 1.81-1.90 (m, 2H, C<u>H</u>$_2$), 1.96 (s, 3H, NHCOC<u>H</u>$_3$), 2.06-2.15 (m, 1H, CH<u>H</u>), 2.18 (s, 3H, C<u>H</u>$_3$), 2.26 (s, 3H, C<u>H</u>$_3$), 2.29 (s, 3H, C<u>H</u>$_3$), 2.43 (s, 3H, C<u>H</u>$_3$), 4.36 (d, 1H, *J* = 5.5, C<u>H</u>CH$_2$), 5.18-5.20 (m, 1H, C<u>H</u>NH), 5.57 (d, 1H, *J* = 7.5, N<u>H</u>), 6.23 (d, 1H, *J* = 7.8, Ar<u>H</u>), 6.58 (s, 1H, Ar<u>H</u>), 6.76 (d, 1H, *J* = 7.4, Ar<u>H</u>), 6.89 (s, 1H, Ar<u>H</u>), 6.98 (s, 1H, Ar<u>H</u>).

^{13}C NMR: δ 18.83, 19.40, 20.91, 23.23, 24.14, 24.22, 39.79, 44.46, 126.19, 129.38, 129.48, 129.94, 131.19, 132.09, 134.91, 135.29, 137.34, 137.49, 140.06, 141.64, 168.41.

***N*-[4-(2,5-dimethylphenyl)-5,8-dimethyl-1,2,3,4-tetrahydro-1-naphthalenyl] acetamide (*cis*-112 and *trans*-112)**

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of 2,5-dimethylstyrene (264 mg, 2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 2 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate mixture gave the α-acetamido tetralins *cis*-**112** and *trans*-**112** as white crystalline solids (193 mg, 60%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 5:1.

***cis*-112**



mp : 258 °C.

IR (KBr) ν_{max}: 3283, 3051, 2939, 2859, 1633, 1533, 1493, 1440, 1374, 1275, 1160, 811 cm^{-1}.

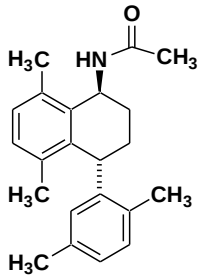
^{1}H NMR: δ 1.70-1.74 (m, 1H, C<u>H</u>H), 1.83 (s, 3H, C<u>H</u>$_3$), 1.87-

***cis*-112** 1.90 (m, 2H, C<u>H</u>$_2$), 1.96 (s, 3H, NHCOC<u>H</u>$_3$), 2.09 (s, 3H, C<u>H</u>$_3$), 2.12-2.16 (m, 1H, CH<u>H</u>), 2.33 (s, 3H, C<u>H</u>$_3$), 2.44 (s, 3H, C<u>H</u>$_3$), 4.31 (d, 1H, *J* = 5.8, C<u>H</u>CH$_2$), 5.24-5.26 (m, 1H, C<u>H</u>NH), 5.59 (d, 1H, *J* = 7.1, N<u>H</u>), 6.07 (s, 1H, Ar<u>H</u>), 6.85 (d, 1H, *J* = 6.9, Ar<u>H</u>), 6.87 (d, 1H, *J* = 7.8, Ar<u>H</u>), 7.04 (d, 2H, *J* = 9.7, Ar<u>H</u>).

^{13}C NMR: δ 18.89, 18.97, 19.15, 21.19, 23.22, 23.55, 23.93, 37.69, 45.05, 126.72, 128.62, 128.89, 130.08, 130.29, 132.03, 134.73, 134.86, 134.89, 135.19, 138.38, 142.59, 168.38.

HRMS (EI) Calcd for $C_{22}H_{27}NO$: 321.2092. Found: 321.2093.

***trans*-112**



***trans*-112**

mp : 249 °C.

IR (KBr) ν_{max}: 3287, 3049, 2934, 2861, 1633, 1537, 1441, 1369, 1275, 1165, 813 cm^{-1}.

^{1}H NMR: δ 1.69-1.73 (m, 1H, C<u>H</u>H), 1.82 (s, 3H, C<u>H</u>$_3$), 1.83-1.93 (m, 2H, C<u>H</u>$_2$), 1.94 (s, 3H, NHCOC<u>H</u>$_3$), 2.09 (s, 3H, C<u>H</u>$_3$), 2.07-2.20 (m, 1H, CH<u>H</u>), 2.32 (s, 3H, C<u>H</u>$_3$), 2.43 (s, 3H, C<u>H</u>$_3$), 4.28 (d, 1H, *J* = 5.6, C<u>H</u>CH$_2$), 5.21-5.23 (m, 1H, C<u>H</u>NH), 5.55 (br s, 1H, N<u>H</u>), 6.02 (s, 1H, Ar<u>H</u>), 6.81 (d, 1H, *J* = 7.5, Ar<u>H</u>), 6.93 (d, 1H, *J* = 7.6, Ar<u>H</u>), 7.00 (d, 2H, *J* = 8.4, Ar<u>H</u>).

^{13}C NMR: δ 18.88, 18.96, 19.13, 21.18, 23.16, 23.55, 23.91, 37.69, 45.02, 126.72, 128.60, 128.87, 130.06, 130.29, 132.00, 134.72, 134.85, 135.16, 138.36, 142.58, 168.37.

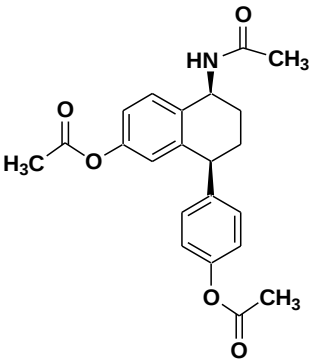
HRMS (FAB) Calcd for $C_{22}H_{27}NO + H^+$: 322.2171. Found: 322.2165.

5-(acetylamino)-8-[4-(acetyloxy)phenyl]-5,6,7,8-tetrahydro-2-naphthalenylacetate (*cis* 113 and *trans*-113)

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of 4-acetoxystyrene (324 mg,

2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 3 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 60:40 hexane-ethyl acetate mixture gave α-acetamido tetralins the *cis*-**113** and *trans*-**113** as white crystalline solids (221 mg, 58%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 1.4 :1.

***cis*-113**



cis-113

mp : 129 °C.

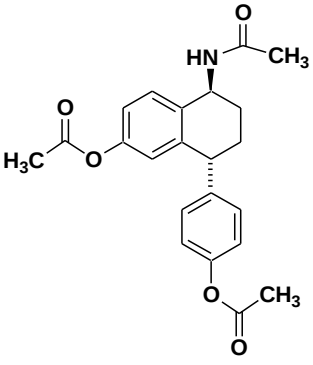
IR (KBr) ν_{max}: 3278, 3060, 2938, 2863, 1757, 1643, 1537, 1503, 1431, 1370, 1206, 1012, 905, 780 cm^{-1}.

^{1}H NMR: δ 1.88-1.94 (m, 3H, C$\underline{H}_2$, C$\underline{H}$H), 2.04 (s, 3H, NHCOC$\underline{H}_3$), 2.10-2.16 (m, 1H, CH$\underline{H}$), 2.22 (s, 3H, OCOC$\underline{H}_3$), 2.30 (s, 3H, OCOC$\underline{H}_3$), 4.03-4.07 (m, 1H, C$\underline{H}$CH$_2$), 5.19-5.23 (m, 1H, C$\underline{H}$NH), 5.76 (d, 1H, J = 7.6, N$\underline{H}$), 6.56 (s, 1H, Ar$\underline{H}$), 6.93 (d, 1H, J = 8.4, Ar$\underline{H}$), 7.01 (d, 2H, J = 8.6, Ar$\underline{H}$), 7.09 (d, 2H, J = 8.5, Ar$\underline{H}$), 7.36 (d, 1H, J = 8.5, Ar$\underline{H}$).

^{13}C NMR: δ 20.93, 21.05, 23.42, 27.47, 29.31, 44.87, 47.06, 120.54, 121.53, 122.57, 129.46, 130.20. 134.64, 141.05, 143.08, 149.14, 149.81, 168.99, 169.11, 169.18.

HRMS (EI) Calcd for $C_{22}H_{23}NO_5$: 381.1576. Found: 381.1560.

***trans*-113**



mp : 124 °C.

IR (KBr) ν_{max}: 3306, 3063, 2928, 2861, 1762, 1647, 1499, 1371, 1202, 1013, 912 cm^{-1}.

^{1}H NMR: δ 1.80-1.99 (m, 3H, C$\underline{H}_2$, C$\underline{H}$H), 2.03 (s, 3H, NHCOC$\underline{H}_3$), 2.08-2.19 (m, 1H, CH$\underline{H}$), 2.21 (s, 3H, OCOC$\underline{H}_3$), 2.29 (s, 3H, OCOC$\underline{H}_3$), 4.05-4.07 (m, 1H, C$\underline{H}$CH$_2$), 5.15-5.25 (m, 1H, C$\underline{H}$NH), 5.79 (d, 1H, J = 8.1,

***trans*-113** NH), 6.57 (s, 1H, ArH), 6.94 (d, 1H, *J* = 8.3, ArH), 7.01 (d, 2H, *J* = 8.4, ArH), 7.09 (d, 2H, *J* = 8.5, ArH), 7.35 (d, 1H, *J* = 8.5, ArH).

^{13}C NMR: δ 20.97, 21.08, 23.36, 28.42, 30.48, 45.05, 47.41, 120.41, 121.56, 122.77, 129.22, 129.49, 130.24, 135.14, 141.07, 143.21, 149.19, 149.84, 169.16, 169.23, 169.38.

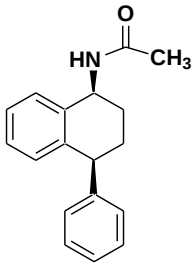
***N*-(4-phenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]acetamide (*cis* 114 and *trans*-114)**

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of styrene (208 mg, 2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 12 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 70:30 hexane-ethyl acetate mixture gave the α-acetamido tetralins *cis*-**114** and *trans*-**114** as white crystalline solids (119 mg, 45%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 1.2 :1.

***cis*-114**

mp : 190 °C.

IR (KBr) ν_{max}: 3238, 3059, 2932, 2856, 1630, 1543, 1489, 1446, 1384, 1105, 758 cm^{-1}.



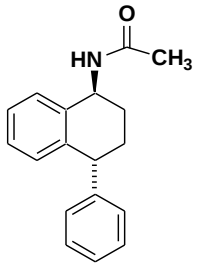
***cis*-114**

^{1}H NMR: δ 1.89-2.01 (m, 3H, CH$_2$, CHH), 2.05 (s, 3H, NHCOCH$_3$), 2.12-2.17 (m, 1H, CHH), 4.07-4.09 (m, 1H, CHCH$_2$), 5.19-5.21 (m, 1H, CHNH), 5.80 (d, 1H, *J* = 7.5, NH), 6.87 (d, 1H, *J* = 7.4, ArH), 7.06-7.33 (m, 8H, ArH).

^{13}C NMR: δ 23.58, 27.56, 29.58, 45.38, 47.74, 126.33, 126.83, 127.63, 128.43, 128.75, 128.87, 130.28, 137.17, 139.83, 146.41, 169.03.

HRMS (EI) Calcd for $C_{18}H_{19}NO$: 265.1467. Found: 265.1474.

***trans*-114**



***trans*-114**

mp : 147 °C.

IR (KBr) ν_{max}: 3306, 3070, 3022, 2935, 2854, 1640, 1553, 1492, 1445, 1371, 1276, 757 cm^{-1}.

^{1}H NMR: δ 1.66-1.77 (m, 1H, CHH), 1.82-1.96 (m, 1H, CHH), 2.04 (s, 3H, $NHCOCH_3$), 2.11-2.25 (m, 2H, CH_2), 4.06-4.13 (m, 1H, $CHCH_2$), 5.21-5.33 (m, 1H, CHNH), 5.83-5.88 (m, 1H, NH), 6.84 (d, 1H, J = 7.6, ArH), 7.02 (d, 2H, J = 6.9, ArH), 7.07-7.32 (m, 6H, ArH).

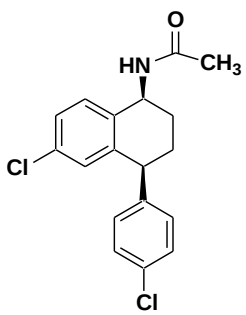
^{13}C NMR: δ 23.49, 28.34, 30.38, 45.48, 47.85, 126.29, 126.72, 127.41, 127.94, 128.40, 128.68, 130.31, 137.44, 139.86, 146.35, 169.28.

HRMS (FAB) Calcd for $C_{18}H_{19}NO + H^+$: 266.1545. Found: 266.1556.

***N*-[6-chloro-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]acetamide (*cis*-115 and *trans*-115)**

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of 4-chlorostyrene (280 mg, 2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 12 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 60:40 hexane-ethyl acetate mixture gave the α-acetamido tetralins *cis*-**115** and *trans*-**115** as white crystalline solids (140 mg, 42%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 2.5:1.

***cis*-115**



mp : 210 °C.

IR (KBr) ν_{max}: 3293, 3045, 2862, 1632, 1542, 1492, 1091, cm^{-1}.

^{1}H NMR: δ 1.80-1.99 (m, 3H, CH_2, CHH), 2.03 (s, 3H, $NHCOCH_3$), 2.07-2.16 (m, 1H, CHH), 3.99-4.03 (m, 1H, $CHCH_2$), 5.11-5.17 (m, 1H, CHNH), 5.96 (d, 1H, J = 8.2, NH),

***cis*-115** 6.81 (d, 1H, *J* = 1.4, ArH), 7.00 (d, 2H, *J* = 8.3, ArH), 7.15 (dd, 1H, *J* = 8.3, *J* = 1.9, ArH), 7.26 (s, 1H, ArH), 7.27 (d, 2H, *J* = 8.3, ArH).

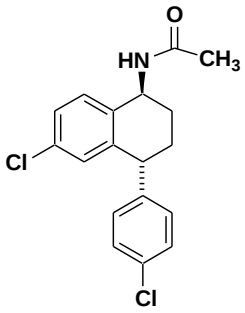
^{13}C NMR: δ 23.49, 27.23, 29.35, 44.66, 47.04, 127.39, 128.79, 129.71, 129.94, 130.39, 132.51, 133.51, 135.76, 141.07, 143.99, 169.18.

HRMS (EI) Calcd for $C_{18}H_{17}Cl_2NO$: 333.0687. Found: 333.0684.

***trans*-115**

mp : 205 °C.

IR (KBr) ν_{max}: 3291, 3059, 2927, 2865, 1639, 1537, 1479, 1373, 1149, 1087, 1011, 805 cm^{-1}.



***trans*-115**

^{1}H NMR: δ 1.63-1.75 (m, 1H, CHH), 1.81-1.91 (m, 1H, CHH), 2.05 (s, 3H, NHCOCH$_3$), 2.10-2.22 (m, 2H, CH$_2$), 4.02-4.07 (m, 1H, CHCH$_2$), 5.22-5.29 (m, 1H, CHNH), 5.77 (d, 1H, *J* = 8.6, NH), 6.78 (d, 1H, *J* = 1.4, ArH), 6.96 (d, 2H, *J* = 8.4, ArH), 7.16 (dd, 1H, *J* = 8.4, *J* = 1.9, ArH), 7.26 (s, 1H, ArH), 7.27 (d, 2H, *J* = 8.2, ArH).

^{13}C NMR: δ 23.51, 28.40, 30.46, 44.95, 47.31, 127.29, 128.85, 129.51, 129.75, 129.86, 132.55, 133.34, 136.05, 141.23, 143.92, 169.31.

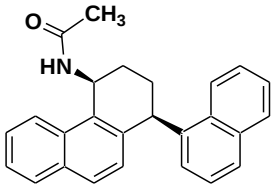
HRMS (EI) Calcd for $C_{18}H_{17}Cl_2NO$: 333.0687. Found: 333.0686.

***N*-[1-(1-naphthyl)-1,2,3,4-tetrahydro-4-phenanthrenyl]acetamide (*cis*-116 and *trans*-116)**

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of 1-vinylnaphthalene (308mg, 2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 1 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 80:20 hexane-ethyl acetate mixture gave the α-acetamido tetralins *cis*-**116** and *trans*-**116**

as white crystalline solids (299 mg, 82%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 5:2.

***cis*-116**



***cis*-116**

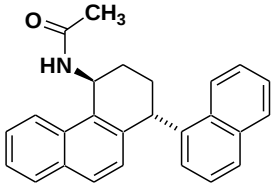
mp : 275 °C.

IR (KBr) ν_{max}: 3326, 3049, 2935, 2861, 1634, 1519, 1445, 1371, 1263, 1196, 1094, 778 cm^{-1}.

^{1}H NMR: δ 2.03 (s, 3H, NHCOC$\underline{H}_3$), 2.08-2.22 (m, 2H, C$\underline{H}_2$), 2.34-2.38 (m, 2H, C$\underline{H}_2$), 4.98-5.10 (m, 1H, C$\underline{H}$CH_2), 5.83-5.91 (m, 1H, C$\underline{H}$NH), 5.95 (d, 1H, *J* = 7.6, N$\underline{H}$), 6.94 (d, 1H, *J* = 8.6, Ar$\underline{H}$), 7.07-7.16 (m, 1H, Ar$\underline{H}$), 7.38 (t, 1H, *J* = 7.8, Ar$\underline{H}$), 7.45-7.57 (m, 5H, Ar$\underline{H}$), 7.76 (d, 2H, *J* = 7.9, Ar$\underline{H}$), 7.89-7.92 (m, 1H, Ar$\underline{H}$), 8.02 (d, 1H, *J* = 8.2, Ar$\underline{H}$), 8.05-8.16 (m, 1H, Ar$\underline{H}$).

^{13}C NMR: δ 23.48, 28.28, 29.35, 44.12, 123.48, 125.64, 125.72, 126.20, 127.13, 127.21, 128.00, 128.49, 128.56, 129.27, 131.91, 132.56, 134.21, 139.08, 168.74.

***trans*-116**



***trans*-116**

mp : 253 °C.

IR (KBr) ν_{max}: 3329, 3051, 2946, 2862, 1635, 1521, 1369, 1254, 824, 775 cm^{-1}.

^{1}H NMR: δ 1.99 (s, 3H, NHCOC$\underline{H}_3$), 2.04-2.12 (m, 3H, C$\underline{H}_2$, C$\underline{H}$H), 2.39-2.50 (m, 1H, CH$\underline{H}$), 5.19-5.21 (m, 1H, C$\underline{H}$CH_2), 5.85 (br s, 2H, C$\underline{H}$N$\underline{H}$), 6.49 (d, 1H, *J* = 6.5, Ar$\underline{H}$), 7.04 (d, 1H, *J* = 8.4, Ar$\underline{H}$), 7.19 (t, 1H, *J* = 7.6, Ar$\underline{H}$), 7.50-7.75 (m, 6H, Ar$\underline{H}$), 7.82 (d, 1H, *J* = 7.9, Ar$\underline{H}$), 7.89 (d, 1H, *J* = 7.7, Ar$\underline{H}$), 8.02 (d, 1H, *J* = 8.0, Ar$\underline{H}$), 8.28 (d, 1H, *J* = 8.4, Ar$\underline{H}$).

^{13}C NMR: δ 23.31, 24.41, 24.61, 39.95, 43.42, 122.99, 123.52, 124.99, 125.50, 125.78, 126.25, 127.02, 127.07, 127.65, 128.55, 128.64, 129.19, 131.28, 131.68, 131.84, 132.90, 134.06, 137.44, 140.96, 168.59.

HRMS (EI) Calcd for $C_{26}H_{23}NO$: 365.1779. Found: 365.1761.

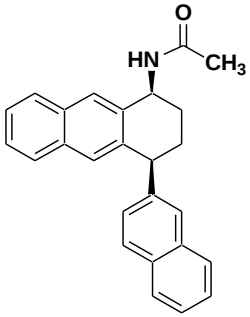
***N*-[4-(2-naphthyl)-1,2,3,4-tetrahydro-1-anthracenyl]acetamide (*cis*-117 and *trans*-117)**

A deoxygenated solution of CAN (1.31 g, 2.4 mmol) in dry acetonitrile (10 mL) was added dropwise to a deoxygenated solution of 2-vinylnaphthalene (308 mg, 2.0 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 1 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 80:20 hexane-ethyl acetate mixture gave the α-acetamido tetralins *cis*-**117** and *trans*-**117** as white crystalline solids (292 mg, 80%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 9:1.

***cis*-117**

mp : 246 °C.

IR (KBr) ν_{max}: 3179, 3037, 2926, 2874, 1632, 1553, 1372, 1300, 818, 727 cm^{-1}.



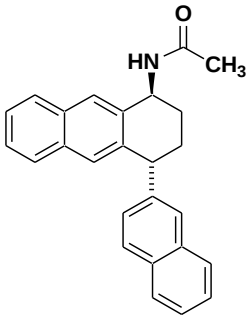
cis-117

^{1}H NMR: δ 1.81-1.85 (m, 1H, CHH), 1.99 (s, 3H, $NHCOCH_3$), 2.08-2.14 (m, 2H, CH_2), 2.29-2.32 (m, 1H, CHH), 4.92-5.00 (m, 1H, $CHCH_2$), 5.38 (br s, 1H, CHNH), 5.96 (d, 1H, J = 7.2, NH), 7.19-7.75 (m, 13H, ArH).

^{13}C NMR: δ 23.54, 23.83, 27.49, 40.73, 47.19, 124.81, 125.47, 125.78, 125.96, 126.46, 126.85, 126.95, 127.54, 127.69, 127.78, 128.20, 128.48, 131.86, 132.15, 133.36, 133.49, 133.93, 134.56, 142.64, 168.64.

HRMS (EI) Calcd for $C_{26}H_{23}NO$: 365.1779. Found: 365.1770.

***trans*-117**



***trans*-117**

mp : 225 °C.

IR (KBr) ν_{max}: 3272, 3056, 2935, 2854, 1634, 1539, 1438, 1371, 1276, 1209, 1081, 1007, 953, 818, 751 cm^{-1}.

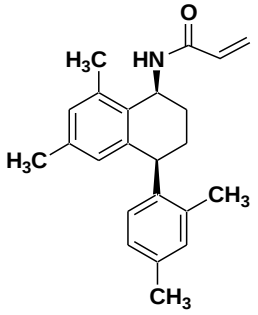
^{1}H NMR: δ 1.84-1.88 (m, 1H, CHH), 2.02 (s, 3H, $NHCOCH_3$), 2.05-2.20 (m, 2H, CH_2), 2.30-2.40 (m, 1H, CHH), 4.96 (d, 1H, J = 4.0, $CHCH_2$), 5.39-5.43 (m, 1H, CHNH), 5.86 (d, 1H, J = 8.1, NH), 7.24-7.81 (m, 13H, ArH).

^{13}C NMR: δ 23.61, 23.86, 27.54, 40.77, 47.23, 124.85, 125.50, 125.82, 125.99, 126.50, 126.87, 126.99, 127.57, 127.72, 127.81, 128.26, 128.52, 131.70, 132.19, 133.41, 133.53, 133.96, 134.60, 142.65, 168.59.

***N*-[4-(2,4-dimethylphenyl)-6,8-dimethyl-1,2,3,4-tetrahydro-1-naphthalenyl] acrylamide (*cis*-118 and *trans*-118)**

A solution of CAN (1.31 g, 2.4 mmol) in acrylonitrile (10 mL) was added dropwise to a solution of 2,4-dimethylstyrene (264 mg, 2.0 mmol) in acrylonitrile (5 mL). The reaction mixture was stirred at room temperature for 3 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 90:10 hexane-ethyl acetate mixture gave the α-acrylamido tetralins *cis* **118** and *trans*-**118** as white crystalline solids (239 mg, 72%). Ratio of the *cis*-and *trans* isomers was determined by HPLC analysis and was found to be 1.2:1.

***cis*-118**



mp : 186 °C.

IR (KBr) ν_{max}: 3245, 3036, 2935, 2861, 1654, 1613, 1539, 1445, 1411, 1236, 993, 865 cm^{-1}.

^{1}H NMR: δ 1.77-2.02 (m, 3H, CH_2, CHH), 2.07-2.17 (m, 1H, CHH), 2.13 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.13-4.19 (m, 1H, $CHCH_2$), 5.25-5.27 (m,

***cis*-118** 1H, CHNH), 5.63 (dd, 1H, *J* = 10.2, *J* = 1.3, =CHH), 5.77 (d, 1H, *J* = 7.4, NH), 6.06 (dd, 1H, *J* = 16.9, *J* = 10.2, CH=), 6.29 (dd, 1H, *J* = 16.9, *J* = 1.4, =CHH), 6.43 (s, 1H, ArH), 6.81 (d, 1H, *J* = 7.9, ArH), 6.84 (s, 1H, ArH), 6.91 (d, 1H, *J* = 8.0, ArH), 7.00 (s, 1H, ArH).

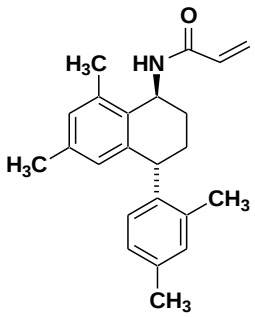
^{13}C NMR: δ 18.78, 19.74, 20.99, 21.03, 27.33, 29.31, 44.83, 126.67, 127.12, 127.97, 128.48, 129.50, 130.81, 131.23, 131.29, 135.46, 135.66, 137.28, 137.64, 141.44, 141.86. 164.06.

HRMS (EI) Calcd for $C_{23}H_{27}NO$: 333.2092. Found: 262.1725 (M^+- CH_2=$CHCONH_2$).

***trans*-118**

mp : 246 °C.

IR (KBr) ν_{max}: 3244, 3039, 2931, 2861, 1652, 1618, 1542, 1442, 1237, 1106, 1062, 949, 820 cm^{-1}.



***trans*-118**

^{1}H NMR: δ 1.67-1.72 (m, 1H, CHH), 1.87-1.93 (m, 2H, CH_2), 2.11-2.13 (m, 1H, CHH), 2.18 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.37 (d, 1H, *J* = 5.5, $CHCH_2$), 5.26-5.29 (m, 1H, CHNH), 5.63 (d, 1H, *J* = 10.2, =CHH), 5.71 (d, 1H, *J* = 7.6, NH), 6.01 (dd, 1H, *J* = 16.8, *J* = 10.2, CH=), 6.25 (d, 1H, *J* = 8.2, ArH), 6.29 (d, 1H, *J* = 17.2, =CHH), 6.59 (s, 1H, ArH), 6.77 (d, 1H, *J* = 5.6, ArH), 6.90 (s, 1H, ArH), 6.99 (s, 1H, ArH).

^{13}C NMR: δ 18.83, 19.40, 20.91, 24.16, 39.79, 44.34, 126.18, 126.58, 129.38, 129.48, 129.95, 130.79, 131.19, 131.90, 134.92, 135.30, 137.41, 137.62, 140.08, 141.61, 163.99.

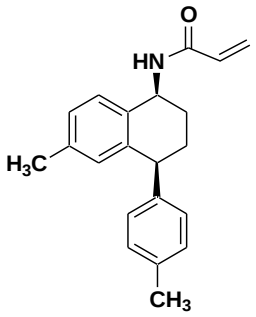
HRMS (EI) Calcd for $C_{23}H_{27}NO$: 333.2092. Found: 333.2091.

***N*-[6-methyl-4-(4-methylphenyl)-1,2,3,4-tetrahydro-1-naphthalenyl] acrylamide (*cis*-119 and *trans*-119)**

A solution of CAN (1.31 g, 2.4 mmol) in acrylonitrile (10 mL) was added

dropwise to a solution of 4-methylstyrene (236 mg, 2.0 mmol) in acrylonitrile (5 mL). The reaction mixture was stirred at room temperature for 3 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate mixture gave the α-acryl amido tetralins *cis*-**119** and *trans*-**119** as white crystalline solids (159 mg, 52%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 1.3 :1.

***cis*-119**



cis-119

mp : 195 °C.

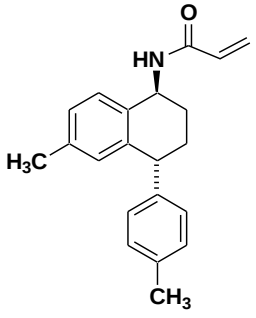
IR (KBr) ν_{max}: 3271, 3052, 2920, 2857, 1651, 1617, 1531, 1405, 1301, 1236, 1095, 989, 954, 810 cm^{-1}.

^{1}H NMR: δ 1.87-1.97 (m, 3H, C$\underline{H}_2$, C$\underline{H}$H), 2.06-2.13 (m, 1H, CH$\underline{H}$), 2.19 (s, 3H, C$\underline{H}_3$), 2.34 (s, 3H, C$\underline{H}_3$), 3.98-4.02 (m, 1H, C$\underline{H}$CH_2), 5.22-5.25 (m, 1H, C$\underline{H}$NH), 5.66 (d, 1H, J = 10.2, =C$\underline{H}$H), 5.91 (br s, 1H, N$\underline{H}$), 6.11 (dd, 1H, J = 16.8, J = 10.2, C$\underline{H}$=), 6.33 (d, 1H, J = 16.9, =CH$\underline{H}$), 6.68 (s, 1H, Ar$\underline{H}$), 6.96-6.99 (m, 3H, Ar$\underline{H}$), 7.09 (d, 2H, J = 7.7, Ar$\underline{H}$), 7.20 (d, 1H, J = 7.8, Ar$\underline{H}$).

^{13}C NMR: δ 21.09, 27.53, 29.72, 44.91, 47.56, 126.65, 127.73, 128.63, 128.80, 129.09, 129.47, 130.60, 131.02, 134.03, 135.65, 137.19, 139.82, 143.49, 164.55.

HRMS (EI) Calcd for $C_{21}H_{23}NO$: 305.1779. Found: 305.1781.

***trans*-119**



mp : 175 °C.

IR (KBr) ν_{max}: 3290, 3026, 2927, 2862, 1658, 1627, 1541, 1405, 1237, 984, 944, 805 cm^{-1}.

^{1}H NMR: δ 1.69-1.77 (m, 1H, C$\underline{H}$H), 1.83-1.93 (m, 1H, CH$\underline{H}$), 2.12-2.16 (m, 2H, C$\underline{H}_2$), 2.20 (s, 3H, C$\underline{H}_3$), 2.33 (s, 3H, C$\underline{H}_3$), 4.04-4.07 (m, 1H, C$\underline{H}$CH_2), 5.31-5.37 (m, 1H,

***trans*-119**

CHNH), 5.67 (dd, 1H, *J* = 10.2, *J* = 1.2, =CHH), 5.76 (d, 1H, *J* = 8.4, NH), 6.09 (dd, 1H, *J* = 16.9, *J* = 10.2, CH=), 6.34 (dd, 1H, *J* = 16.9, *J* = 1.2, =CHH), 6.69 (s, 1H, ArH), 6.91 (d, 2H, *J* = 7.9, ArH), 6.99 (d, 1H, *J* = 7.8, ArH), 7.07 (d, 2H, *J* = 7.7, ArH), 7.21 (d, 1H, *J* = 7.9, ArH).

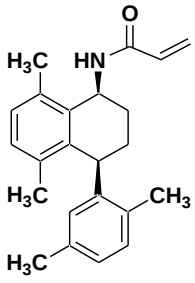
^{13}C NMR: δ 21.08, 27.93, 30.18, 44.88, 47.57, 126.61, 127.76, 128.16, 128.60, 129.10, 130.75, 131.07, 134.30, 137.10, 139.85, 143.44, 164.61.

HRMS (FAB) Calcd for $C_{21}H_{23}NO + H^+$: 306.1858. Found: 306.1866.

***N*-[4-(2,5-dimethylphenyl)-5,8-dimethyl-1,2,3,4-tetrahydro-1-naphthalenyl] acrylamide (*cis*-120 and *trans*-120)**

A solution of CAN (1.31 g, 2.4 mmol) in acrylonitrile (10 mL) was added dropwise to a solution of 2,5-dimethylstyrene (264 mg, 2.0 mmol) in acrylonitrile (5 mL). The reaction mixture was stirred at room temperature for 3 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 90:10 hexane-ethyl acetate mixture gave the α-acrylamido tetralins *cis*-**120** and *trans*-**120** as white crystalline solids (213 mg, 64%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 7:1.

***cis*-120**



***cis*-120**

mp : 222 °C.

IR (KBr) ν_{max}: 3272, 3016, 2942, 2867, 1661, 1620, 1526, 1452, 1222, 993, 960, 811cm^{-1}.

^{1}H NMR: δ 1.70-1.75 (m, 1H, CHH), 1.83 (s, 3H, CH_3), 1.89-1.98 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.11-2.15 (m, 1H, CHH), 2.31 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.32 (d, 1H, *J* = 5.7, $CHCH_2$), 5.31-5.33 (m, 1H, CHNH), 5.60 (d, 1H, *J* = 10.2, =CHH), 5.81 (br s, 1H, NH), 6.01 (dd, 1H, *J* = 16.9, *J* = 10.2, CH=), 6.08 (s, 1H, ArH), 6.27 (d, 1H, *J* = 16.9, =CHH),

6.84 (d, 1H, *J* = 7.6, ArH), 6.95-7.05 (m, 3H, ArH).

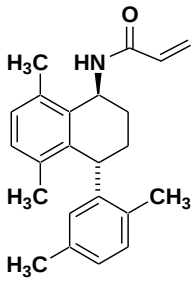
^{13}C NMR: δ 18.86, 18.94, 19.12, 21.17, 23.51, 23.94, 37.69, 44.99, 126.52, 126.70, 128.57, 128.86, 130.10, 130.28, 130.74, 131.99, 134.53, 134.83, 135.27, 138.36, 142.57, 163.96.

HRMS (FAB) Calcd for $C_{23}H_{27}NO + H^+$: 334.2171. Found: 334.2169.

***trans*-120**

mp : 232 °C.

IR (KBr) ν_{max}: 3282, 3022, 2938, 2863, 1652, 1621, 1540, 1448, 1231, 957, 810 cm^{-1}.



trans-120

^{1}H NMR: δ 1.71-1.75 (m, 1H, CHH), 1.84 (s, 3H, CH_3), 1.85-1.96 (m, 2H, CH_2), 2.11 (s, 3H, CH_3), 2.14-2.18 (m, 1H, CHH), 2.32 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.32 (d, 1H, *J* = 5.5, $CHCH_2$), 5.33-5.35 (m, 1H, CHNH), 5.63 (d, 1H, *J* = 10.2, =CHH), 5.69 (d, 1H, *J* = 9.9, NH), 6.01 (dd, 1H, *J* = 16.8, *J* = 10.2, CH=), 6.08 (s, 1H, ArH), 6.31 (d, 1H, *J* = 16.8, =CHH), 6.86 (d, 1H, *J* = 7.1, ArH), 6.97-7.05 (m, 3H, ArH).

^{13}C NMR: δ 18.91, 18.98, 19.16, 21.21, 23.52, 23.98, 37.71, 45.05, 126.63, 126.75, 128.61, 128.93, 130.17, 130.32, 130.76, 132.03, 134.58, 134.91, 135.33, 138.41, 142.58, 163.94.

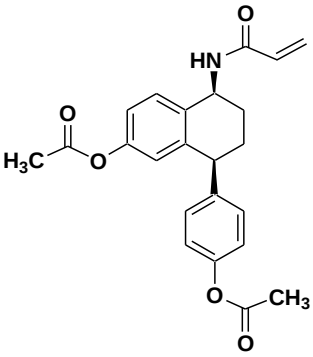
HRMS (EI) Calcd for $C_{23}H_{27}NO$: 333.2092. Found: 333.2084.

***trans*-5-(acrylamino)-8-[4-(acetyloxy)phenyl]-5,6,7,8-tetrahydro-2-naphthalenyl acetate (*cis*-121 and *trans*-121)**

A solution of CAN (1.31 g, 2.4 mmol) in acrylonitrile (10 mL) was added dropwise to a solution of 4-acetoxystyrene (324 mg, 2.0 mmol) in acrylonitrile (5 mL). The reaction mixture was stirred at room temperature for 3 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 70:30 hexane-ethyl acetate mixture gave the α-acryl

amido tetralins *cis*-**121** and *trans*-**121** as white crystalline solids (267 mg, 71%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 1.3 :1.

***cis*-121**



***cis*-121**

mp : 172 °C.

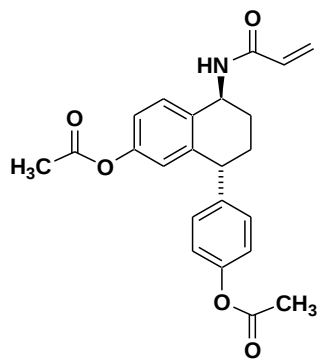
IR (KBr) ν_{max}: 3279, 3056, 2935, 2874, 1762, 1661, 1627, 1546, 1506, 1418, 1371, 1222, 1013, 912 cm^{-1}.

^{1}H NMR: δ 1.88-1.98 (m, 3H, C$\underline{H}_2$, C$\underline{H}$H), 2.12-2.15 (m, 1H, CH$\underline{H}$), 2.20 (s, 3H, OCOC$\underline{H}_3$), 2.28 (s, 3H, OCOC$\underline{H}_3$), 4.04-4.08 (m, 1H, C$\underline{H}$CH$_2$), 5.22-5.30 (m, 1H, C$\underline{H}$NH), 5.67 (d, 1H, J = 10.2, =C$\underline{H}$H), 6.05-6.14 (m, 2H, C$\underline{H}$=, N$\underline{H}$), 6.32 (d, 1H, J = 16.9, =CH$\underline{H}$), 6.57 (s, 1H, Ar$\underline{H}$), 6.92 (dd, 1H, J = 8.4, J = 2.3, Ar$\underline{H}$), 7.00 (d, 2H, J = 8.5, Ar$\underline{H}$), 7.09 (d, 2H, J = 8.5, Ar$\underline{H}$), 7.34 (d, 1H, J = 8.4, Ar$\underline{H}$).

^{13}C NMR: δ 20.97, 21.09, 27.46, 29.38, 44.94, 47.07, 120.67, 121.58, 122.59, 126.91, 129.55, 130.36, 130.79, 134.59, 141.13, 143.18, 149.19, 149.90, 164.61, 169.16, 169.26.

HRMS (FAB) Calcd for $C_{23}H_{27}NO + H^+$: 394.1654. Found: 394.1651.

***trans*-121**



***trans*-121**

mp : 140 °C.

IR (KBr) ν_{max}: 3312, 3144, 2935, 2861, 1762, 1661, 1620, 1533, 1499, 1371, 1209, 1013, 912, 791 cm^{-1}.

^{1}H NMR: δ 1.69-1.78 (m, 1H, C$\underline{H}$H), 1.86-1.95 (m, 1H, CH$\underline{H}$), 2.12-2.19 (m, 2H, C$\underline{H}_2$), 2.21 (s, 3H, OCOC$\underline{H}_3$), 2.29 (s, 3H, OCOC$\underline{H}_3$), 4.11-4.14 (m, 1H, C$\underline{H}$CH$_2$), 5.34-5.39 (m, 1H, C$\underline{H}$NH), 5.68 (d, 1H, J = 10.2, =C$\underline{H}$H), 5.88 (d, 1H, J = 8.5, N$\underline{H}$), 6.09 (dd, 1H, J = 16.9, J = 10.2, C$\underline{H}$=), 6.34 (d, 1H, J = 16.9, =CH$\underline{H}$), 6.56 (s, 1H,

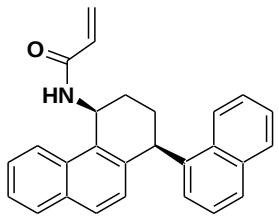
ArH), 6.91 (dd, 1H, *J* = 8.4, *J* = 2.3, ArH), 6.99 (d, 2H, *J* = 8.7, ArH), 7.04 (d, 2H, *J* = 8.7, ArH), 7.34 (d, 1H, *J* = 8.5, ArH).

^{13}C NMR: δ 20.99, 21.11, 28.34, 30.46, 45.06, 47.49, 120.49, 121.59, 122.82, 126.83, 129.36, 129.52, 130.85, 134.96, 141.19, 143.18, 149.22, 149.75, 164.84, 169.20, 169.30.

***N*-[1-(1-naphthyl)-1,2,3,4-tetrahydro-4-phenanthrenyl] acrylamide (*cis*-122 and *trans*-122)**

A solution of CAN (1.31 g, 2.4 mmol) in acrylonitrile (10 mL) was added dropwise to a solution of 1-vinylnaphthalene (308 mg, 2.0 mmol) in acrylonitrile (5 mL). The reaction mixture was stirred at room temperature for 2 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate mixture gave the α-acryl amido tetralins *cis*-**122** and *trans*-**122** as white crystalline solids (267 mg, 71%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 1.1 :1.

***cis*-122**



cis-122

mp : 265 °C.

IR (KBr) ν_{max}: 3252, 3049, 2928, 2861, 1654, 1613, 1533, 1404, 1236, 1094, 953, 778 cm^{-1}.

^{1}H NMR: δ 2.04-2.27 (m, 2H, CH$_2$), 2.28-2.50 (m, 2H, CH$_2$), 5.00-5.12 (m, 1H, CHCH$_2$), 5.68 (d, 1H, *J* = 10.2, =CHH), 5.98 (br s, 2H, CHNH), 6.08 (dd, 1H, *J* = 16.9, *J* = 10.2, CH=), 6.39 (d, 1H, *J* = 16.8, =CHH), 6.93 (d, 1H, *J* = 11.9, ArH), 7.11-7.13 (m, 1H, ArH), 7.38 (t, 1H, *J* = 7.5, ArH), 7.44-7.53 (m, 3H, ArH), 7.58 (d, 2H, *J* = 8.9, ArH), 7.77 (d, 2H, *J* = 8.0, ArH), 7.89-7.93 (m, 1H, ArH), 8.02 (d, 1H, *J* = 8.4, ArH), 8.09-8.19 (m, 1H, ArH).

^{13}C NMR: δ 28.28, 44.14, 123.47, 125.63, 125.69, 126.17,

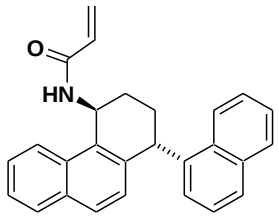
127.01, 127.14, 127.96, 128.48. 128.54, 129.24, 130.74, 131.89, 132.51, 134.17, 139.14, 164.21.

HRMS (FAB) Calcd for $C_{27}H_{23}NO + H^+$: 378.1858. Found: 378.1856.

***trans*-122**

mp : 255 °C.

IR (KBr) ν_{max}: 3319, 3049, 2948, 2921, 2861, 1647, 1613, 1512, 1398, 1330, 1229, 1088, 980, 831 cm^{-1}.



***trans*-122**

^{1}H NMR: δ 1.99-2.12 (m, 3H, C<u>H</u>$_2$, C<u>H</u>H), 2.42-2.47 (m, 1H, CH<u>H</u>), 5.22 (d, 1H, *J* = 5.9, C<u>H</u>CH$_2$), 5.64 (d, 1H, *J* = 10.3, =C<u>H</u>H), 5.97-6.06 (m, 3H, C<u>H</u>N<u>H</u>COC<u>H</u>=CH$_2$), 6.35 (d, 1H, *J* = 16.9, =CH<u>H</u>), 6.51 (d, 1H, *J* = 7.1, Ar<u>H</u>), 7.05 (d, 1H, *J* = 8.5, Ar<u>H</u>), 7.19 (t, 1H, *J* = 7.5, Ar<u>H</u>), 7.52-7.63 (m, 4H, Ar<u>H</u>), 7.69 (d, 2H, *J* = 8.4, Ar<u>H</u>), 7.81 (d, 1H, *J* = 7.8, Ar<u>H</u>), 7.89 (d, 1H, *J* = 8.0, Ar<u>H</u>), 8.01 (d, 1H, *J* = 8.4, Ar<u>H</u>), 8.27 (d, 1H, *J* =8.3, Ar<u>H</u>).

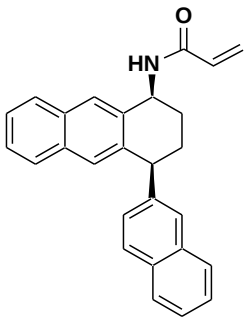
^{13}C NMR: δ 24.52, 40.04, 43.57, 123.06, 123.59, 125.06, 125.57, 125.88, 126.33, 126.90, 127.09, 127.20, 127.72, 128.59, 128.81, 129.26, 130.76, 131.34, 131.68, 132.97, 134.13, 137.61, 140.99, 164.16.

HRMS (FAB) Calcd for $C_{27}H_{23}NO + H^+$: 378.1858. Found: 378.1854.

N-[4-(2-naphthyl)-1,2,3,4-tetrahydro-1-anthracenyl] acrylamide (*cis*-123 and *trans*-123)

A solution of CAN (1.31 g, 2.4 mmol) in acrylonitrile (10 mL) was added dropwise to a solution of 2-vinylnaphthalene (236 mg, 2.0 mmol) in acrylonitrile (5 mL). The reaction mixture was stirred at room temperature for 2 h. It was then processed as described in the general procedure. The residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate mixture gave the α-acryl amido tetralins *cis*-**123** and *trans*-**123** as white crystalline solids (215 mg, 57%). Ratio of the *cis* and *trans* isomers was determined by HPLC analysis and was found to be 11:1.

***cis*-123**



***cis*-123**

mp : 247 °C.

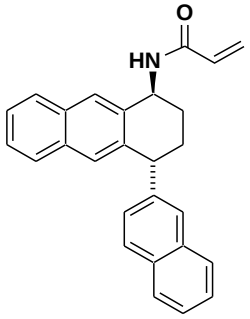
IR (KBr) ν_{max}: 3238, 3043, 2948, 2874, 1654, 1613, 1539, 1445, 1404, 1236, 987, 960, 818, 751 cm^{-1}.

^{1}H NMR: δ 1.87-2.14 (m, 3H, C$\underline{H}_2$, C$\underline{H}$H), 2.30-2.36 (m, 1H, CH$\underline{H}$) 4.95 (d, 1H, *J* = 4.0, C$\underline{H}CH_2$), 5.46-5.49 (m, 1H, C$\underline{H}$NH), 5.64 (d, 1H, *J* = 10.2, =C$\underline{H}$H), 6.00-6.09 (m, 2H, C$\underline{H}$=, N$\underline{H}$), 6.32 (d, 1H, *J* = 16.8, =CH$\underline{H}$), 7.20-7.37 (m, 6H, Ar$\underline{H}$), 7.47 (d, 1H, *J* = 8.5, Ar$\underline{H}$), 7.52-7.60 (m, 1H, Ar$\underline{H}$), 7.67 (d, 1H, *J* = 8.6, Ar$\underline{H}$), 7.72-7.78 (m, 4H, Ar$\underline{H}$).

^{13}C NMR: δ 23.76, 27.49, 40.73, 47.24, 124.83, 125.48, 125.82, 125.97, 126.39, 126.48, 126.85, 126.96, 127.54, 127.72, 127.78, 128.05, 128.25, 128.50, 130.93, 131.87, 132.15, 133.36, 133.53, 134.04, 134.35, 142.61, 164.15.

HRMS (FAB) Calcd for $C_{27}H_{23}NO + H^+$: 378.1858. Found: 378.1881.

***trans*-123**



***trans*-123**

mp : 237 °C.

IR (KBr) ν_{max}: 3252, 3049, 2948, 2874, 1654, 1620, 1539, 1404, 1236, 1074, 987, 953, 825 cm^{-1}.

^{1}H NMR: δ 1.89-1.94 (m, 1H, C$\underline{H}$H), 2.02-2.15 (m, 2H, C$\underline{H}_2$), 2.32-2.37 (m, 1H, CH$\underline{H}$), 4.97 (d, 1H, *J* = 4.5, C$\underline{H}CH_2$), 5.48-5.51 (m, 1H, C$\underline{H}$NH), 5.66 (d, 1H, *J* = 10.2, =C$\underline{H}$H), 5.97-6.10 (m, 2H, C$\underline{H}$=, N$\underline{H}$), 6.34 (d, 1H, *J* = 16.8, =CH$\underline{H}$), 7.21-7.38 (m, 6H, Ar$\underline{H}$), 7.48 (d, 1H, *J* = 8.5, Ar$\underline{H}$), 7.56-7.59 (m, 1H, Ar$\underline{H}$), 7.68 (d, 1H, *J* = 8.5, Ar$\underline{H}$), 7.73-7.81 (m, 4H, Ar$\underline{H}$).

^{13}C NMR: δ 23.74, 27.50, 40.72, 47.25, 124.84, 125.49, 125.84, 125.98, 126.50, 126.78, 126.88, 126.97, 127.55, 127.73, 127.79, 128.26, 128.51, 130.92, 131.86, 132.15,

133.15, 133.35, 134.06, 134.34, 142.61, 164.15.

HRMS (FAB) Calcd for $C_{27}H_{23}NO + H^+$: 378.1858. Found: 378.1855.

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Chapter 3

The Reactivity of Four Membered Ring Systems towards Cerium(IV) Ammonium Nitrate

3.1 Introduction

The matter presented in this chapter is divided into three sections. The first section gives an account of the CAN mediated transformations of cyclobutanes (Section 3.2). The second section deals with the CAN induced rearrangements of terpenes containing strained cyclobutane rings as part of their structural framework (Section 3.3). The regiospecific ring opening of oxetanes induced by CAN is dealt with in the final section (Section 3.4).

Investigations from our laboratory and elsewhere have unravelled several CAN mediated transformations of cyclopropanes.[1] However, the reactivity of four membered ring systems with CAN has not been pursued systematically and in detail. This, in addition to our general interest in extending the synthetic utility of CAN provided impetus to probe the chemistry of four membered ring systems towards CAN.

Four membered carbocycles or cyclobutanes, along with their three membered counterparts-cyclopropanes, form a class of compounds which inherently possess ring strain *viz.*, angle strain, torsional strain and steric strain. Angle strain refers to the strain due to the expansion or compression of bond angles. Torsional strain is the strain due to the eclipsing of bonds on neighboring atoms, while steric strain refers to the strain due to repulsive interactions when

atoms approach each other closely. A combination of all the above mentioned types of strains makes four and three membered cycloalkanes adopt their minimum energy conformations.

Cyclobutanes have less angle strain than cyclopropanes, but they have more torsional strain because of the larger number of ring hydrogens. As a result, the total strain for cyclobutanes and cyclopropanes is nearly the same. Studies show that the cyclobutane ring is not quite flat but is slightly bent so that one carbon atom lies about 25° above the plane of the other three. The effect of this slight puckering of the ring is to increase the angle strain but to decrease the torsional strain until a minimum-energy balance between the two opposing effects is achieved (Figure 1).

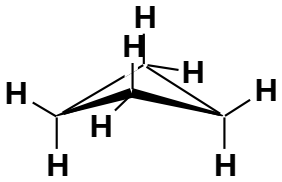
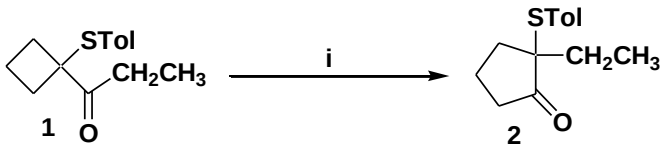


Figure 1

3.2 The Reactivity of Cyclobutanes

Cyclobutanes, by virtue of their inherent ring strain tend to undergo a variety of facile rearrangements leading to a number of interesting products. A few examples from the literature demonstrating the reactivity of cyclobutanes are discussed below.

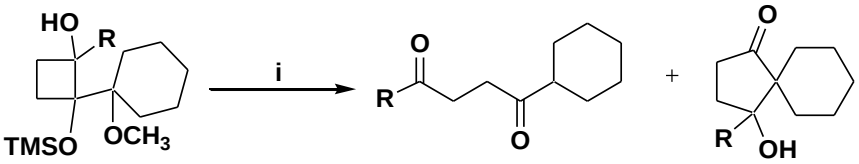
1-Acyl-1-(4-tolylthio)cyclobutanes **1** undergo ring expansion to cyclopentanones in the presence of Lewis acids such as $AlCl_3$ and $FeCl_3$ (Scheme 1).[2]



i) $AlCl_3$, CH_2Cl_2, 10 min, 93%

Scheme 1

In the presence of $SnCl_4$, silyl ethers of cyclobutane-1,2-diols having 1-alkoxy alkyl substituents at the 1-position undergo a facile ring opening reaction to afford the corresponding 1,4-diketones and β-hydroxy cyclopentanones (Scheme 2).[3]



3. R = CH_3
6. R = H

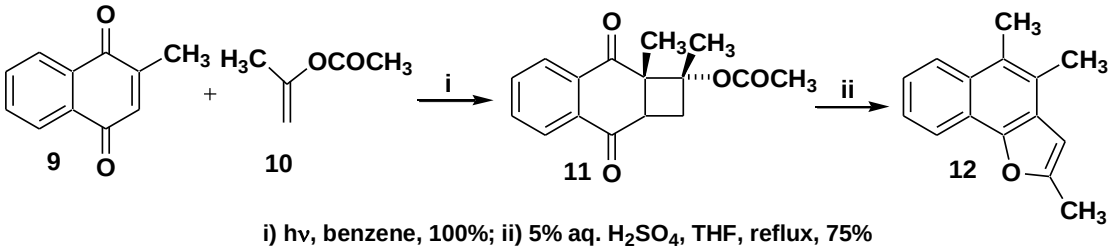
4. R = CH_3; 41%
7. R = H; 0%

5. R = CH_3; 22%
8. R = H; 81%

i) $SnCl_4$, -30 °C, 3 h

Scheme 2

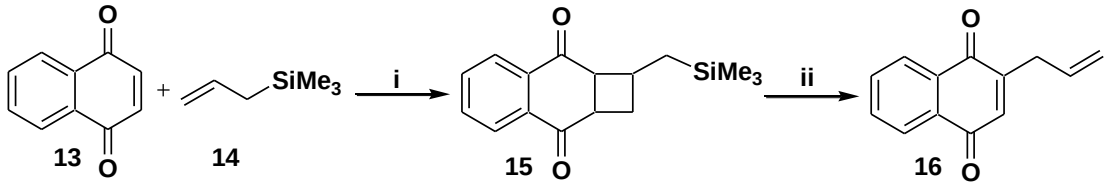
2-Methyl-1,4-naphthoquinone **9** undergoes facile photocycloaddition with isopropenyl acetate **10** to give a cyclobutane derivative in excellent yield. The photoadduct on treatment with dilute sulfuric acid undergoes skeletal rearrangement to give the naphthofuran **12** (Scheme 3).[4]



i) hν, benzene, 100%; ii) 5% aq. H_2SO_4, THF, reflux, 75%

Scheme 3

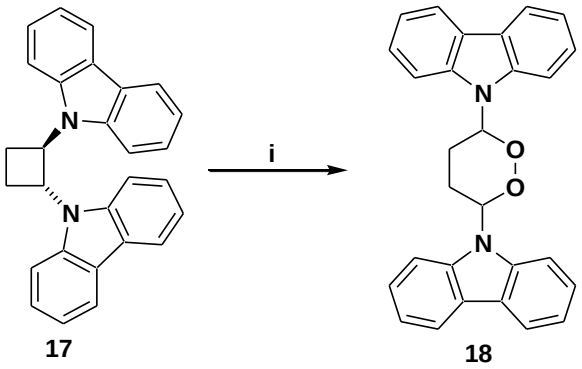
Trimethylsilyl group assisted opening of the cyclobutane ring of the product of the photochemical reaction of allyltrimethylsilane **14** with 1,4-naphthoquinone **13** followed by oxidation leads to the allyl naphthoquinone **16** (Scheme 4).[5]



i) hν, benzene, 69%; ii) a. $BF_3.OEt_2$, CH_2Cl_2, 0 °C; b. $FeCl_3$, 92%

Scheme 4

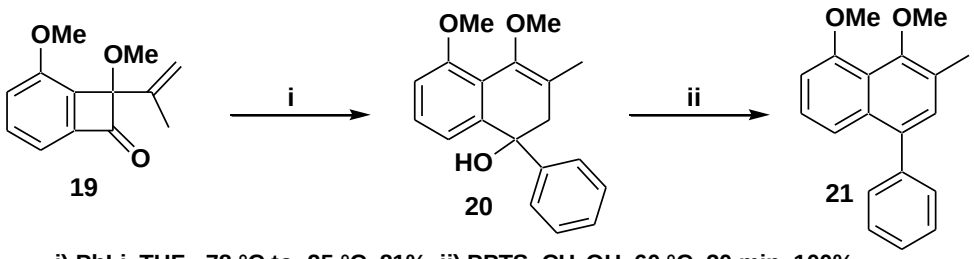
9,10-Dicyanoanthracene sensitized photo-oxygenation of *trans*-1,2-di-(carbazol-9-yl) cyclobutane **17** in acetonitrile efficiently affords 3,6-di(carbazol-9-yl)-1,2-dioxan **18** (Scheme 5).[6]



i) hν, DCA, Oxygen, CH_3CN, 60%

Scheme 5

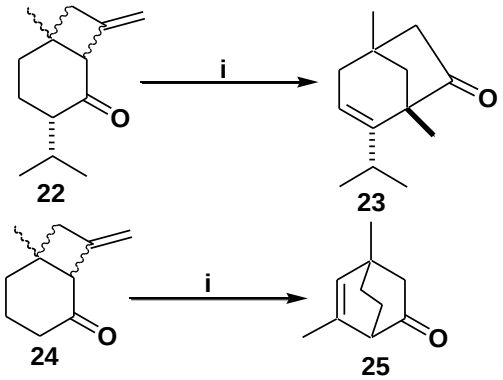
Various 1-arylnaphthalenes can be prepared by the treatment of alkenyl benzocyclobutenones with aryl lithium followed by dehydration of the resulting dihydronaphthalenes by PPTS in methanol (Scheme 6).[7]



i) PhLi, THF, -78 °C to -25 °C, 81%; ii) PPTS, CH_3OH, 60 °C, 30 min, 100%

Scheme 6

The reaction of 8-methylenebicyclo[4.2.0]-octan-2-ones **22** and **24** with *p*-toluene sulfonic acid in boiling benzene afforded the products **23** and **25** (Scheme 7).[8]



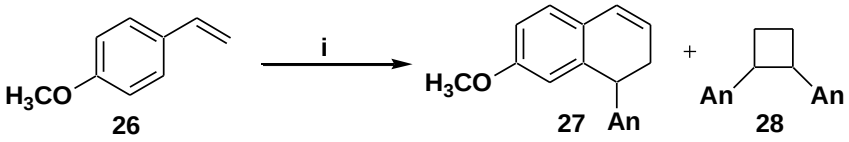
i) *p*-TSA, benzene, reflux, 2 h

Scheme 7

3.2.1 Background to the Present Work

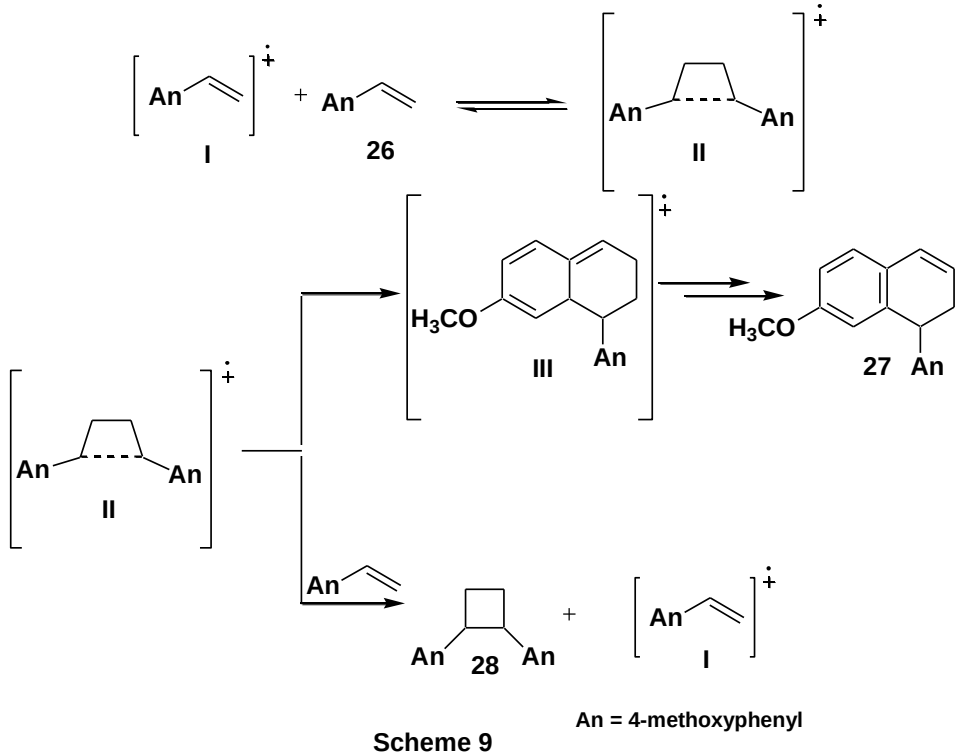
The dimerization of 4-methoxystyrene under photoinduced electron transfer conditions leading to the corresponding dihydronaphthalene **27** and cyclobutane **28**

is well documented (Scheme 8).[9]



Scheme 8

The mechanistic aspects of the PET induced dimerization of 4-methoxy styrene has been established by Bauld *et al.*[10] Mechanistically, it involves a concerted (but non-synchronous) [2+1] cycloaddition of the 4-methoxystyrene radical cation **I** to neutral 4-methoxystyrene **26** to give a long-bond cyclobutane radical cation **II** that can rearrange *via* a 1,3-sigmatropic shift to the substituted hexatriene radical cation **III**. Loss of a proton followed by electron transfer and loss of a second proton then gives the substituted dihydronaphthalene **27**. Alternatively, the long-bond cyclobutane radical cation **II** can also be reduced by electron transfer from neutral 4-methoxystyrene **26** in a chain propagation step to give the neutral cyclobutane **28** and the radical cation of 4-methoxystyrene **I** (Scheme 9).

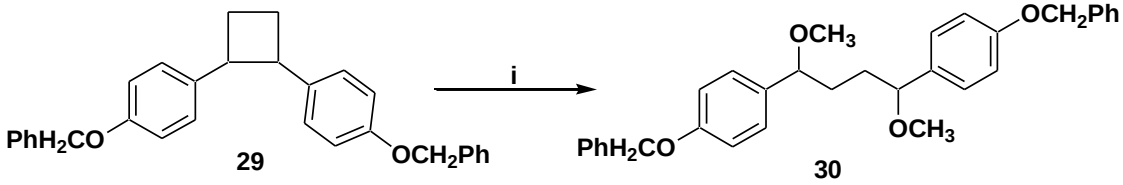


Scheme 9

Investigations in our laboratory have unravelled a novel CAN induced dimerization of alkoxystyrenes (for details see **Chapter 2, p. 34**).[11] The mechanism that we have proposed for this reaction was derived along the same lines as that proposed by Bauld *et al.* essentially involving the formation of a long-bond cyclobutane radical cation.[10] We reasoned that if the formation of the long-bond cyclobutane radical cation was involved, then the corresponding reaction of cyclobutanes with CAN should afford products similar to that obtained in the CAN mediated dimerization of alkoxystyrenes. Our results validating the above assumption are discussed in the following section.

3.2.2 Results and Discussion

Our studies were set in motion with the reaction of cyclobutane **29**, prepared by the photochemical [2+2] cylcloaddition of 4-benzyloxystyrene, with a methanolic solution of CAN, under completely oxygen free conditions. The reaction furnished the dimethoxy butane derivative **30** in 69% yield (Scheme 10).



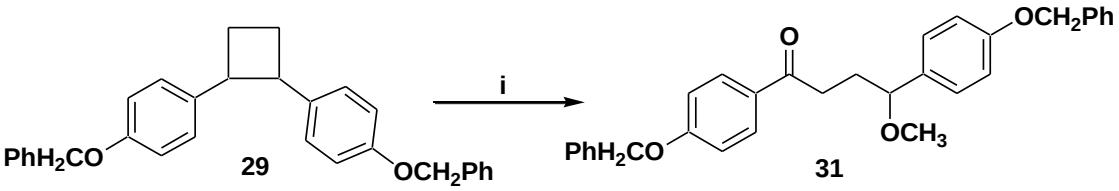
i) CAN (2.5 eq.), dry CH_3OH, Argon, RT, 2 h, 69 %

Scheme 10

The structure of the product **30** was ascertained by spectroscopic methods. In the ^{1}H NMR spectrum, the four methylene protons resonated to display a multiplet centered at δ 1.69. The six protons of the methoxy groups gave a sharp singlet at δ 3.13. The two methine protons geminal to the two methoxy groups resonated together as a multiplet centered at δ 3.96. The four methylene protons of the benzyloxy groups furnished a sharp singlet at δ 5.04. The eighteen aromatic protons resonated in the region δ 6.91-7.43. In the ^{13}C NMR spectrum, the methoxy carbons resonated together at δ 56.42 while the methylene carbons of the benzyloxy group resonated together at δ 70.05. The resonance signal due to the

benzylic carbons was seen at δ 83.65. All other signals were in accordance with the assigned structure.

When the cyclobutane **29** was treated with a solution of CAN in dry methanol under an atmosphere of oxygen, the keto-methoxy derivative **31** was obtained in 73 % yield (Scheme 11).



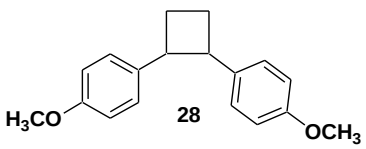
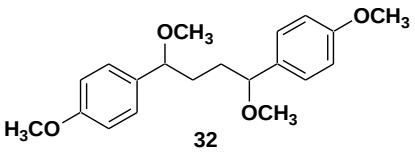
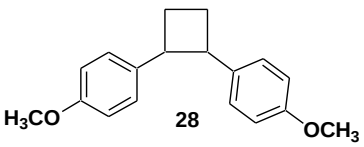
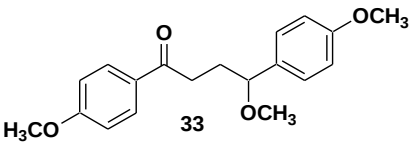
i) CAN (2.5 eq.), dry CH_3OH, Oxygen, RT, 2 h, 73 %

Scheme 11

The product **31** was purified by column chromatography and characterized on the basis of spectroscopic data. In the IR spectrum, the vibration band at 1681 cm^{-1} was attributed to the benzoyl group. In the ^1H NMR spectrum, the methylene protons adjacent to the keto group furnished a triplet at δ 2.96 (J = 7.1) while the methine proton attached to the carbon atom bearing the methoxy group furnished a multiplet centered at δ 4.15. In the ^{13}C NMR spectrum, the carbonyl was visible at δ 198.26. All other signals were in good agreement with the proposed structure.

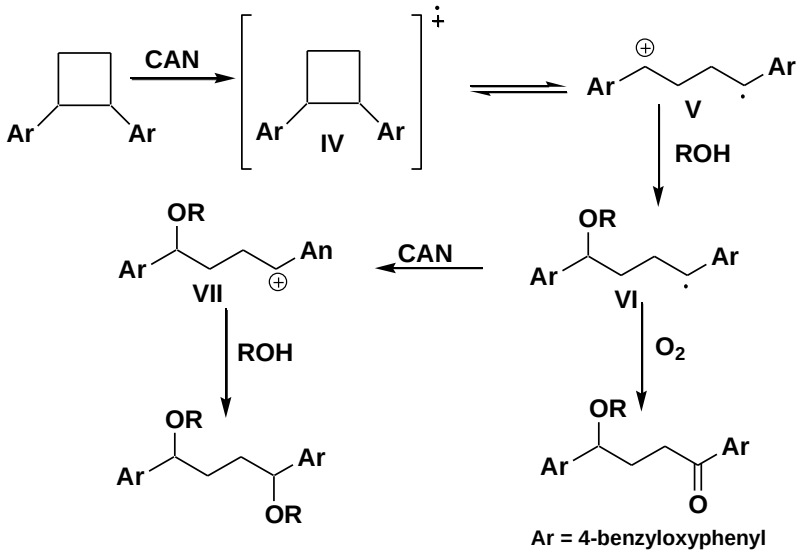
Similar results were obtained with the cyclobutane **28** obtained by the [2+2] photochemical reaction of 4-methoxy styrene and the results are tabulated in Table 1.

Table 1

Entry	Substrate	Reaction Conditions	Product	Yield (%)*
1		CAN, dry CH_3OH Argon, RT, 1 h		62
2		CAN, dry CH_3OH Oxygen, RT, 1 h		52

* isolated yield

A tentative mechanistic rationale for the formation of the above products is depicted in the following scheme (Scheme 12).

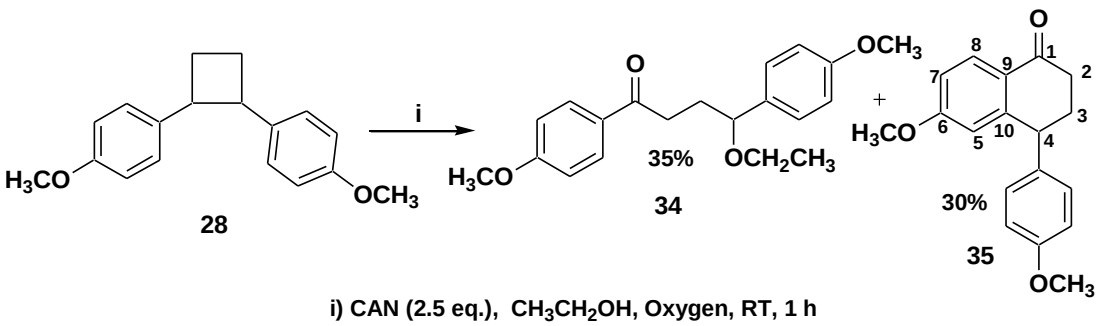


Ar = 4-benzyloxyphenyl
Ar = 4-methoxyphenyl

Scheme 12

The cyclobutanes undergo oxidative electron transfer in the presence of Ce(IV) to furnish the radical cation **IV** which presumably exists in equilibrium with **V**. Nucleophilic solvents like methanol can quench the cationic site of the radical cation **V** to generate the radical intermediate **VI**. The radical center in **VI** is intercepted by oxygen to afford the keto-methoxy products.[12] The radical intermediate **VI** on further oxidation by Ce(IV) generates the cationic intermediate **VII** which is eventually quenched by methanol to afford the dimethoxy products.

The reaction of cyclobutane **28** with a solution of CAN in ethanol under an atmosphere of oxygen afforded the products **34** and **35** in 35% and 30% yields respectively (Scheme 13).



i) CAN (2.5 eq.), CH_3CH_2OH, Oxygen, RT, 1 h

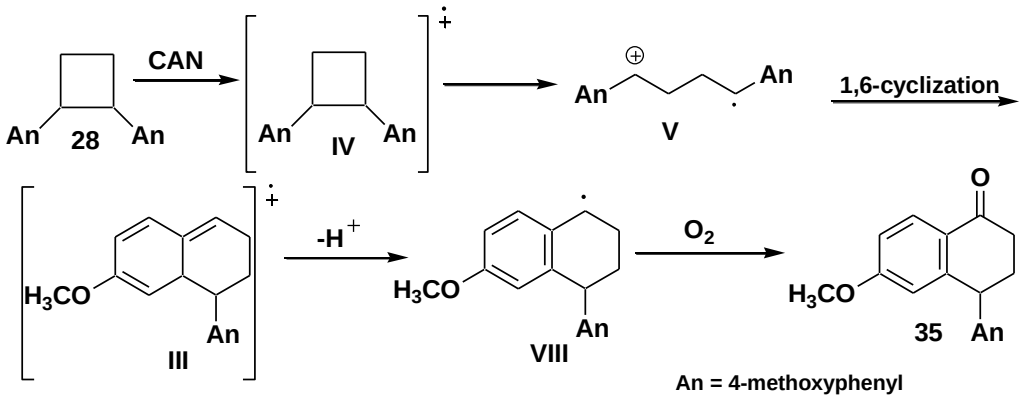
Scheme 13

The products **34** and **35** were purified by column chromatography and their structures ascertained on the basis of spectroscopic data. In the vibrational

spectrum of the keto-ethoxy derivative **34** the benzoyl carbonyl was visible at 1677 cm^{-1}. The ^{1}H NMR spectrum of **34** displayed a triplet at δ 1.14 (J = 6.9) corresponding to the methyl protons of the ethoxy group while the methylene protons of the ethoxy group resonated as a multiplet centered at δ 3.31. The methine proton geminal to the ethoxy group resonated as an uneven triplet at δ 4.26 (J_1 = 7.2, J_2 = 5.8). The signal at δ 198.22 in the ^{13}C NMR spectrum confirmed the presence of the benzoyl group.

The strong absorption at 1675 cm^{-1} in the IR spectrum of **35** was typical of the benzoyl group. In the ^{1}H NMR spectrum, the methine proton on C-4 furnished a multiplet centered at δ 4.17. The proton on C-5 *peri* to the proton on C-4 resonated characteristically as a singlet at δ 6.41. In the ^{13}C NMR spectrum, the carbonyl absorption was seen at δ 196.41. All other signals were in accordance with the assigned structure.

A probable mechanistic pathway for the formation of the tetralone is delineated in the following scheme (Scheme 14).



Scheme 14

The distonic radical cation **V** undergoes 1,6-cyclization to give a substituted hexatriene radical cation **III** which on losing a proton gives the radical intermediate **VIII** which is intercepted by oxygen to give the tetralone **35**, *via* the intermediacy of the peroxy radical.[12]

It is noteworthy that the reaction of cyclobutanes **28** and **29** with CAN affords products similar to those obtained by the CAN mediated dimerization of

alkoxystyrenes.[11] This observation validates our assumption of the formation of a long-bond cyclobutane radical cation in the CAN mediated dimerization of alkoxy styrenes. In view of the results obtained with the above cyclobutanes, we became interested in examining the reactivity of CAN towards cyclobutane rings present in some naturally occurring monoterpenes of the pinene family. The results of our studies are presented after a brief introduction to the latter and their reactivity profile.

3.3 Terpenes - Their Importance and Classification

Terpenes are amongst the most widespread and chemically interesting groups of natural products. All terpenoid structures are constituted of isoprene units. This immediately leads to a rational classification of terpenes depending upon the number of such isoprene units. Thus monoterpenes have ten carbon atoms, sesquiterpenes-C_{15}, diterpenes-C_{20}, sesterpenes-C_{25} and triterpenes-C_{30}. Some representative examples are shown in Figure 2.

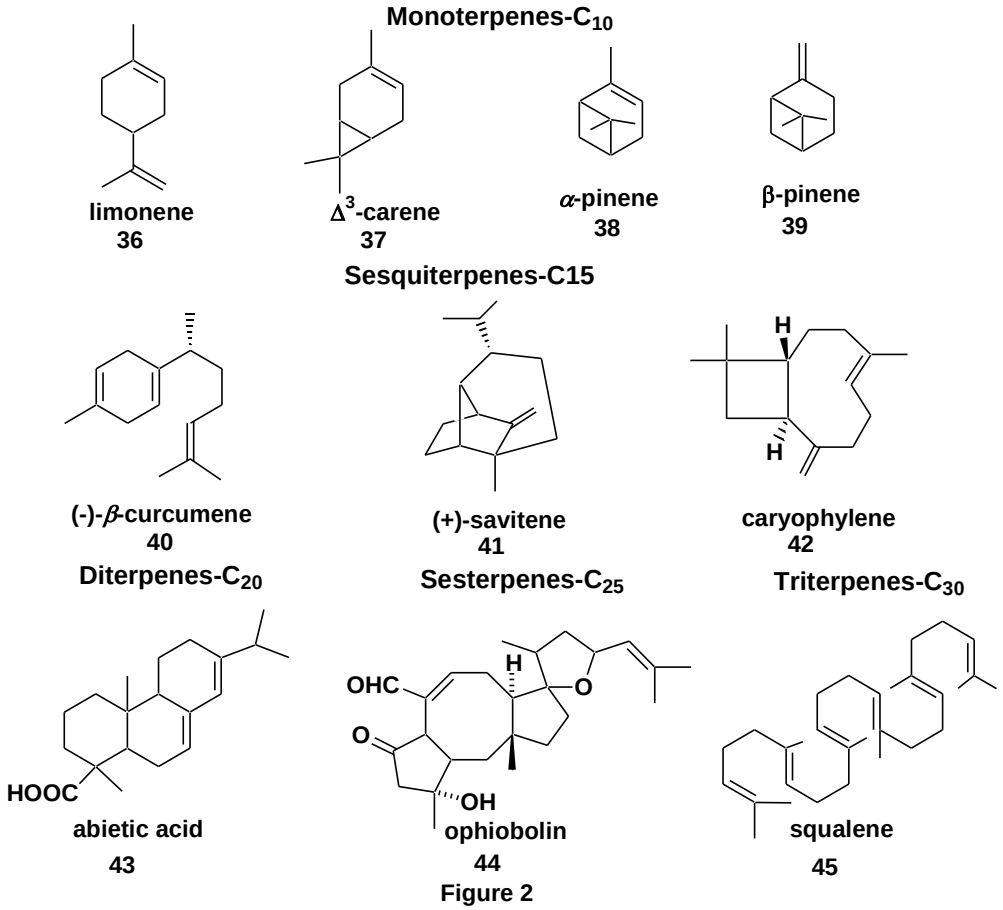


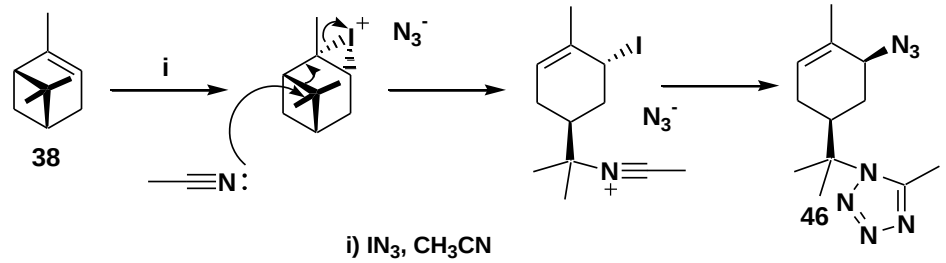
Figure 2

In addition to the formidable synthetic challenges posed by complex structures, the chemistry of terpenes has provided immense problems whose solutions have, in many instances, provided the stimulus for theories that are now fundamental to organic chemistry. The Wagner-Meerwein rearrangement of α-pinene, the various descriptions of the non-classical carbonium ions and the theories of conformational analysis have firm foundations in terpene chemistry. The same applies to the Woodward-Hoffman rules of cycloaddition reactions. The photochemistry of terpenoid substances such as santonin also has attracted considerable interest. The subtle variations in structure that are often available within a closely related group of terpenes provide the organic chemist an oppurtunity to gain insight into the interplay between electronic and stereochemical features that control the outcome of many organic reactions.

3.3.1 The Reactivity of Monoterpenes

The chemistry of terpenes dates back to about two centuries. Hence, an exhaustive discussion of the synthetic transformations of various terpenes is beyond the scope of this chapter. Only a few examples of special importance from the current literature, mostly involving the monoterpenes α- and β-pinene and their corresponding epoxides, are discussed here. Of these, α-pinene found abundantly in nature holds a place of special importance as it has been extensively used as a chiral bulding block in the synthesis of diverse natural products, most notably, in the total synthesis of Taxol.[13]

Iodine azide reacts with (+)-α-pinene **38** in acetonitrile to afford the tetrazole **46** in a one pot reaction in near quantitative yield (Scheme 15).[14]

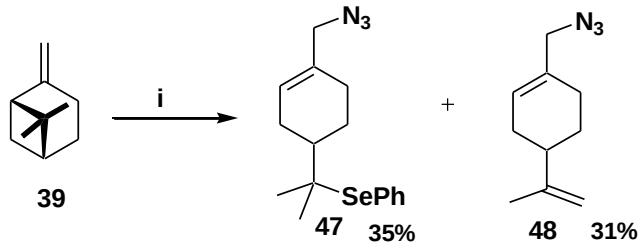


i) IN_3, CH_3CN

Scheme 15

A simple and mild azido-phenylselenenylation of β-pinene **39** by iodoso

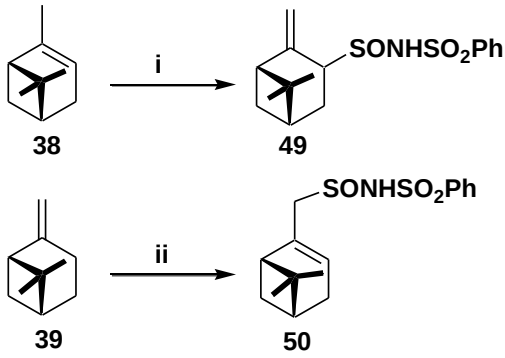
benzene diacetate and diphenyl diselenide has been reported by Tingoli *et al.* (Scheme 16).[15]



i) $PhI(OAc)_2$, $(PhSe)_2$, NaN_3, CH_2Cl_2, RT, 10-12 h

Scheme 16

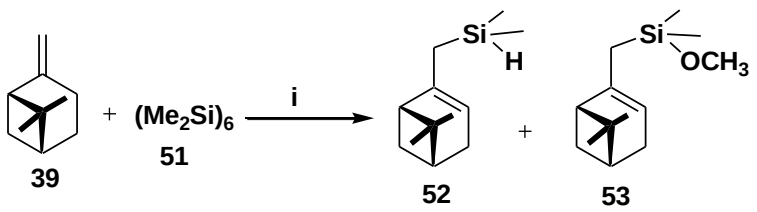
α- and β-pinenes undergo ene reactions with *N*-sulfinyl benzenesulfonamide to afford the products **49** and **50** respectively (Scheme 17).[16]



i) $PhSO_2NSO$, C_6H_6, 40 h, 43%
ii) $PhSO_2NSO$, C_6H_6, 2 h, 85%

Scheme 17

The photolysis of β-pinene **39** and dodecamethylhexasilane **51** followed by quenching with methanol afforded the allylsilane **52** and the methoxy silane **53** in a combined yield of 60-69% based on β-pinene. The reaction involves the attack of dimethylsilylene, generated by the photolysis of **51** (Scheme 18).[17]

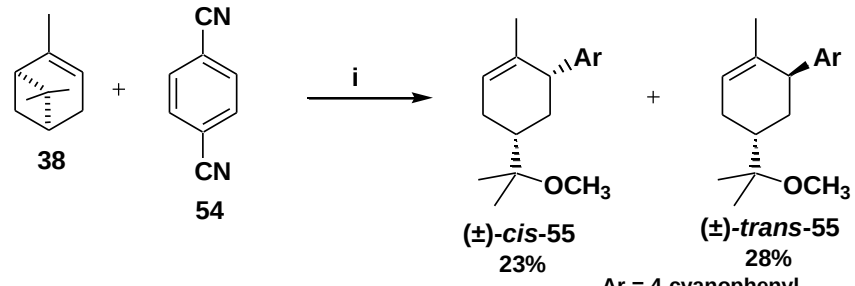


i) hν, cyclohexane, CH_3OH

Scheme 18

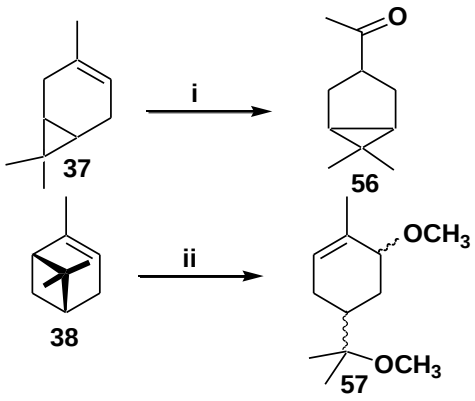
When a solution of (-)-α-pinene **38**, 1,4-dicyanobenzene **54** and biphenyl in methanol-acetonitrile (1:3) is irradiated, the cyclobutane ring in **38** cleaves to

afford the products *cis*-**55** and *trans*-**55** as racemic mixtures (Scheme 19).[18]



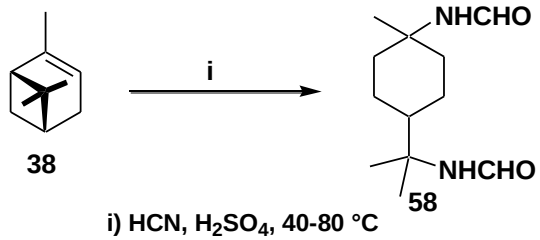
Scheme 19

The reaction of thallium(III) nitrate with Δ^3-carene **37** in methanol involves oxidative rearrangement giving exclusively 3-acetyl-6,6-dimethyl bicyclo[3.1.0] hexane **56**, while similar reaction with α-pinene results in a cleavage of the cyclobutane ring to furnish a mixture of *cis*-*trans* isomers of soberol dimethyl ether **57** (Scheme 20).[19]



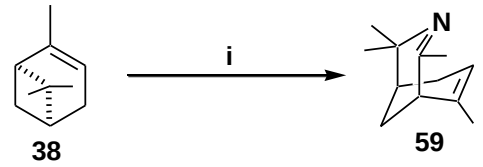
Scheme 20

Rearrangement of α-pinene **38** in the presence of hydrogen cyanide and sulfuric acid at slightly elevated temperatures affords 1,8-diformamido-*p*-menthane **58** (Scheme 21).[20]



Scheme 21

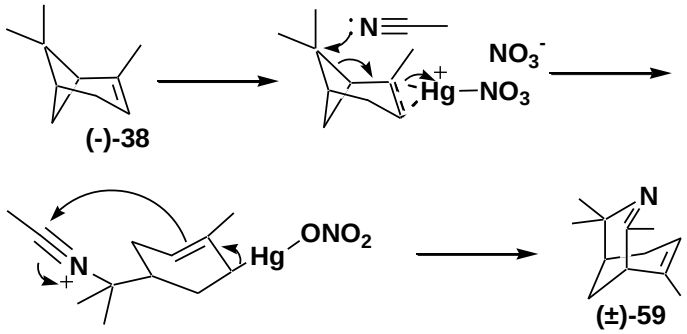
The reaction of (-)-α-pinene **38** with acetonitrile and mercury(II) nitrate afforded good yields of the racemic 3-azabicyclo[3.3.1]nonene derivative **59** (Scheme 22).[21]



i) $Hg(NO_3)_2$, CH_3CN

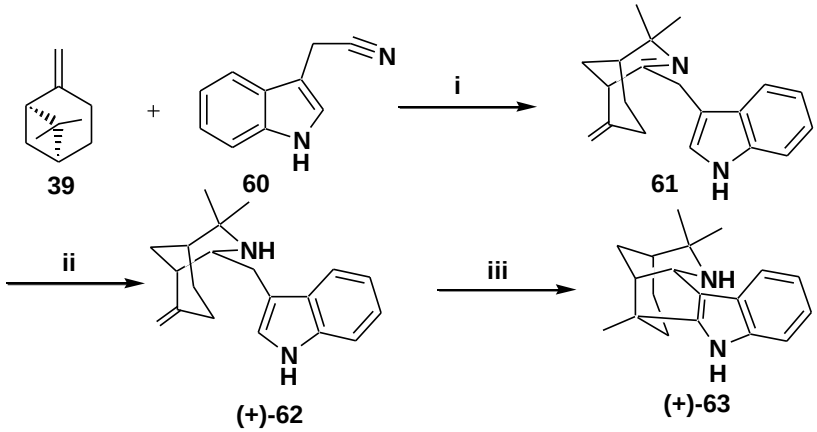
Scheme 22

The mechanism proposed for the reaction is shown below. The reaction essentially involves attack of acetonitrile in a manner analogous to the Ritter reaction followed by intramolecular nitrilium ion cyclization (Scheme 23).



Scheme 23

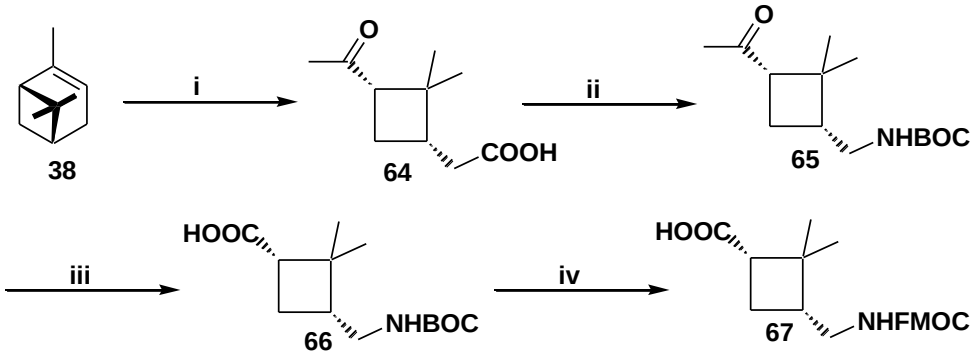
The above mercuration reaction has been adapted by Stevens and Kenney to perform an elegant stereospecific synthesis of *Aristotelia* indole alkaloids (+)-makomakine **62** and (+)-aristoteline **63** from (-)-β-pinene **39** and indol-3-ylacetonitrile **60** (Scheme 24).[22]



i) $Hg(NO_3)_2$, CH_2Cl_2, -30 °C; ii) $NaBH_4$, NaOH, 17%; iii) conc. HCl

Scheme 24

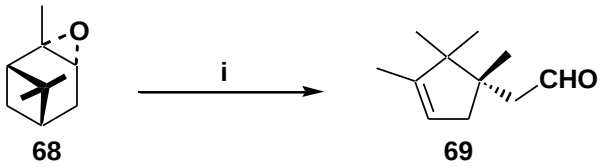
Optically active *N*-protected 1,3-cyclobutane amino acid **67** was prepared from (+)-α-pinene **38**. Such protein amino acid surrogates containing small rings can be used to mimic backbone and side chain conformations of peptides (Scheme 25).[23]



i) $KMnO_4$, $(NH_4)_2SO_4$, <16 °C, 5 h; ii) $(PhO)_2PON_3$, ^tBuOH, Et_3N, reflux, 79%; iii) NaBrO, dioxane, 0 °C, 3 h, 83%; iv) TFA, CH_2Cl_2, FMOC-OSu, DMF, Na_2CO_3(aq.), 8 h, 77%

Scheme 25

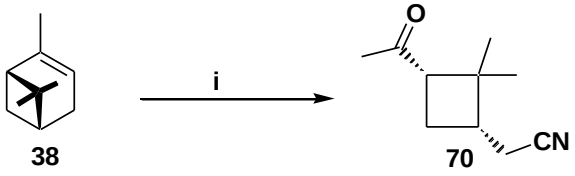
The isomerization of α-pinene oxide **68** to the industrially important 2,2,3-trimethyl-3-cyclopentene acetaldehyde **69** under the influence of catalytic amounts of aminium salts has been reported recently by Lopez *et al.* (Scheme 26).[24]



i) $(p\text{-}BrC_6H_4)_3N^{+}SbCl_6^{-}$, CH_2Cl_2, RT, 82%

Scheme 26

α-Pinene on reaction with iodosobenzenediacetate and trimethyl silyl azide afforded the cyclobutane derivative **70** in 65% yield (Scheme 27).[25]



i) $PhI(OAc)_2$, $(CH_3)_3SiN_3$, 65%

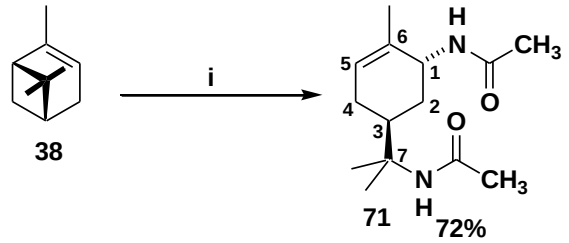
Scheme 27

It was evident from the literature survey that there are no reports on Ce(IV) mediated transformations of monoterpenes. In view of this and in the context of

our general interest of exploring the synthetic potential of CAN, we undertook an investigation of the reaction of monoterpenes like (+)-α-pinene **38**, (-)-nopol benzyl ether **76**, α-pinene oxide **68** and β-pinene oxide **80** with CAN. The results of our investigation are presented in the following section.

3.3.2 Results and Discussion

Our studies commenced by exposing (+)-α-pinene **38** to a solution of CAN in acetonitrile; a remarkable transformation culminating in the bisamide **71** in 72% yield occurred (Scheme 28).



i) CAN (2.3 eq.), CH_3CN, RT, 3h

Scheme 28

The product **71** was purified by column chromatography and its structure ascertained on the basis of spectroscopic data. In the vibrational spectrum of **71**, the strong band at 3285 cm^{-1} was attributed to the two -NH groups and the strong absorption at 1640 cm^{-1} indicated the presence of the amide carbonyls. In the ^1H NMR spectrum, the methyl groups furnished sharp singlets at δ 1.16, 1.29, 1.68, 1.90 and 1.97, the latter two being attributable to the acetyl groups. The olefinic proton was discernible as a broad singlet at δ 5.56. The -NH proton attached to the quaternary carbon C-7 resonated as a broad singlet at δ 5.35 while the -NH proton attached to C-1 resonated as a doublet at δ 5.77 (J = 7.5). Both the -NH protons were exchangeable by D_2O. In the ^{13}C NMR spectrum, the C-2 and C-4 carbons afforded signals at δ 27.02 and 30.58. C-1 and C-7 furnished signals at δ 48.39 and 56.11 while C-5 and C-6 resonated at δ 125.89 and 132.99 respectively. The amide carbonyls resonated characteristically at δ 169.29 and 169.71. In the DEPT-135 NMR spectrum, the peaks at δ 27.02 and 30.58 were negative indicating the presence of two methylene carbons.

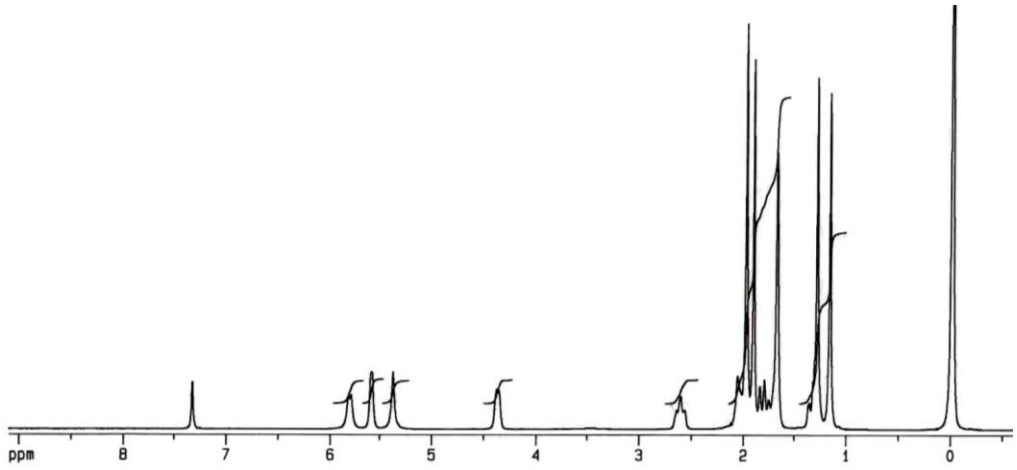


Figure 3: ^{1}H NMR of 71

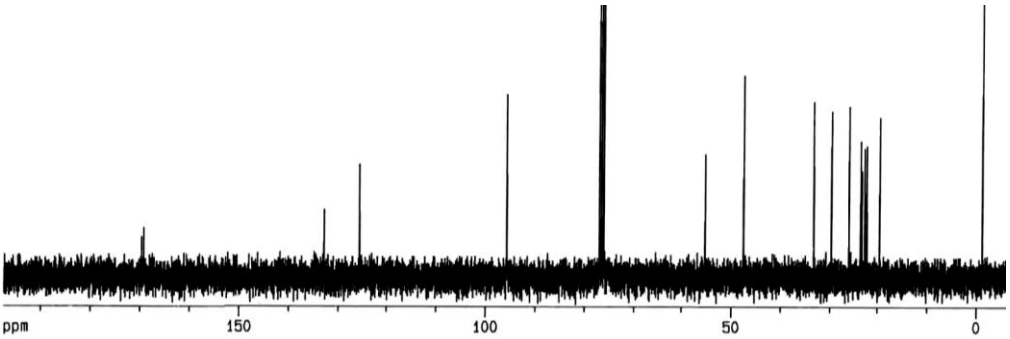


Figure 4: ^{13}C NMR of 71

The relative disposition of the sustituents at C-1 and C-3 was confirmed to be *trans* from the 2D-HOMOCOSY spectrum of **71** (Figure 5).

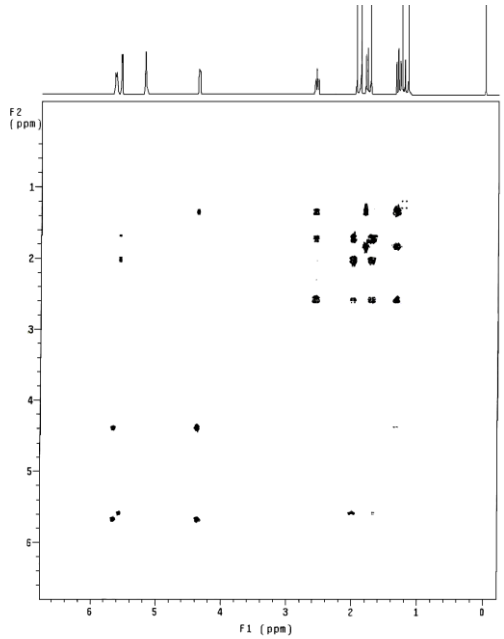


Figure 5: 2D-HOMOCOSY Spectrum of 71

The assignment of the H_3 proton on C-3 as axial was based on its large coupling constants with one of the protons on both C-2 and C-4 ($J_{H3\text{-}H2a}$ = 13.0 Hz, $J_{H3\text{-}H4a}$ = 11.7 Hz). The proton H_1 on C-1 was assigned as equatorial since it gave small coupling constants with both the protons on C-2 ($J_{H1\text{-}H2a}$ = 4.5 Hz and $J_{H1\text{-}H2e}$ = 2.0 Hz). Since H_1 on C-1 is equatorial and H_3 on C-3 is axial, H_1 and H_3 are *trans* with respect to each other and hence the substituents at C-1 and C-3 are *trans* to each other. Additional supporting information for the disposition of the various groups was obtained from the 2D-NOESY spectrum of **71**. Strong nOe cross peaks were observed between H_3-H_{2e} and H_3-H_{4e} while weak nOe cross peaks were observed between H_3-H_{2a} and H_3-H_{4a}, thus further indicating the axial disposition of H_3. H_{4a} gives nOe cross peaks with Me_8 and Me_9 and more importantly with H_{2a} showing its proximity to H_{2a} (Figure 6).

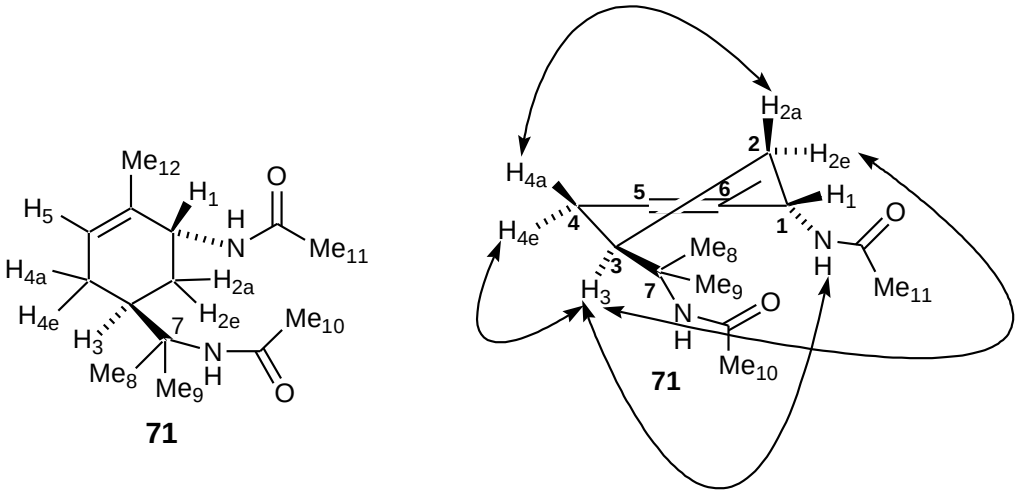
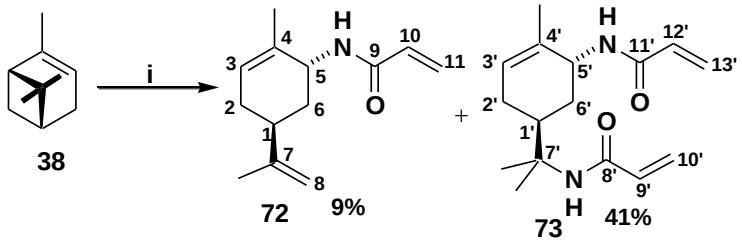


Figure 6: Selected NOESY data of 71

The reaction of (+)-α-pinene **38** with a solution of CAN in acrylonitrile furnished the products **72** and **73** in 9% and 41% yields respectively (Scheme 29).



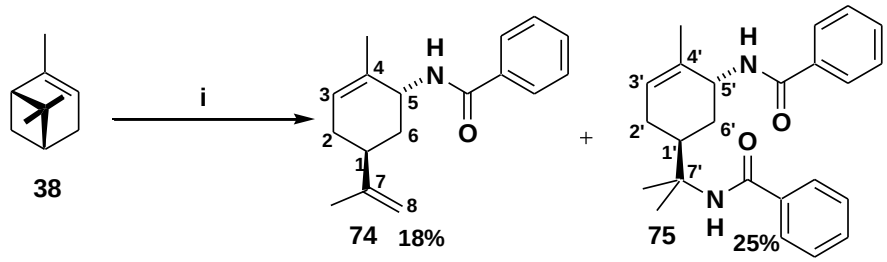
i) CAN (2.5 eq.), acrylonitrile, 3 h, RT

Scheme 29

The products were characterized on the basis of spectroscopic data. In the IR spectrum of **72** the absorption at 3285 cm^{-1} was attributed to the -NH functionality. The strong band at 1661 cm^{-1} was characteristic of an α,β-unsaturated amide carbonyl. In the ^{1}H NMR spectrum, the protons of the two methyl groups resonated together as a singlet at δ 1.71. The methine proton attached to the amide moiety furnished a multiplet centered at δ 4.50. The olefinic protons on C-8 resonated together as a doublet at δ 4.72 (J = 7.9). The vinylic proton on C-11 *cis* to the proton on C-10 furnished a doublet of doublet at δ 5.64 (J_1 = 10.2, J_2 = 1.5), while the other vinylic proton on C-11 *trans* to the proton on C-10 resonated as another doublet of doublet at δ 6.29 (J_1 = 16.9, J_2 = 1.5). The proton on C-11 displayed a doublet of doublet at δ 6.09 (J_1 = 16.9, J_2 = 10.2). In the ^{13}C NMR, the olefinic carbon atoms C-7 and C-8 resonated at δ 109.51 and 148.43, while the olefinic carbon atoms C-3 and C-4 resonated at δ 126.18 and 132.49 respectively. The carbon atoms of the acrylamido moiety C-10 and C-11 furnished signals at δ 126.47 and 131.02. The signal at δ 164.77 was characteristic of an α,β-unsaturated amide carbonyl. All other resonance signals were in good agreement with the assigned structure.

The bisamide **73** exhibited the -NH absorption band at 3326 cm^{-1} and the amide carbonyl absorption at 1654 cm^{-1}. The vibration band at 1627 cm^{-1} was typical of the alkene bond in conjugation with the carbonyl group. In the ^{1}H NMR spectrum, the protons of the three methyl groups resonated at δ 1.23, 1.33 and 1.68. The methine proton on C-5' resonated as a broad singlet at δ 4.48. One of the -NH protons, the endocyclic olefinic proton and the vinylic protons on C-10' and C-13' *cis* to the protons on C-9' and C-12' resonated together as a multiplet in the region δ 5.50-5.65. The other -NH proton, the vinylic protons on C-10' and C-13' *trans* to the protons on C-9' and C-12' along with the protons on C-9' and C-12' displayed a multiplet in the region δ 6.01-6.27. In the ^{13}C NMR, the amide bearing carbons gave resonance signals at δ 48.19 and 56.28. The signals at δ 164.78 and 165.19 were typical of the α,β-unsaturated amide carbonyls. All other signals were in agreement with the assigned structure.

Similarly, the reaction of (+)-α-pinene **38** with a solution of CAN in benzonitrile afforded the products **74** and **75** in 18% and 25 % yields respectively (Scheme 30).



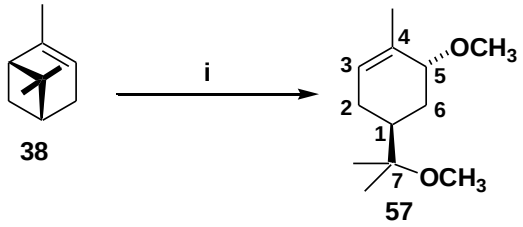
Scheme 30

The product **74** was characterized by routine spectroscopic analysis. The IR spectrum displayed typical vibration due to the -NH group at 3265 cm^{-1}. The amide carbonyl was discernible at 1626 cm^{-1}. In the ^1H NMR spectrum, the methine proton attached to the amide group furnished a multiplet centered at δ 4.61. The olefinic protons attached to C-8 resonated as a doublet at δ 4.73 (J = 4.6) while the olefinic proton on C-3 resonated as a broad singlet at δ 5.67. The five aromatic protons displayed two sets of multiplets in the region δ 7.40-7.51 and δ 7.75-7.77. The ^{13}C NMR spectrum diaplayed signals characteristic to **74**. The olefinic carbon atoms C-8 and C-7 resonated at δ 109.55 and 148.38. The amide carbonyl furnished a resonance signal at δ 166.68. All other signals were in good agreement with the assigned structure.

The structure of the bisamide **75** was assigned on the basis of spectroscopic data. In the vibrational spectrum, the -NH stretching band was seen at 3272 cm^{-1} and the absorption due to the amide carbonyl at 1627 cm^{-1}. In the ^1H NMR spectrum, the olefinic proton resonated at δ 5.62 as a broad singlet. The -NH proton attached to C-7' resonated as a singlet at δ 5.92 while the -NH proton attached to C-5' resonated as a doublet at δ 6.38 (J = 8.4). The ten aromatic protons resonated in the region δ 7.26-7.77. The ^{13}C NMR spectrum displayed a single resonance for the two amide carbonyls at δ 167.02.

The reaction of (+)-α-pinene **38** with a methanolic solution of CAN, afforded

the cyclohexenyl derivative **57** in 55% yield (Scheme 31).

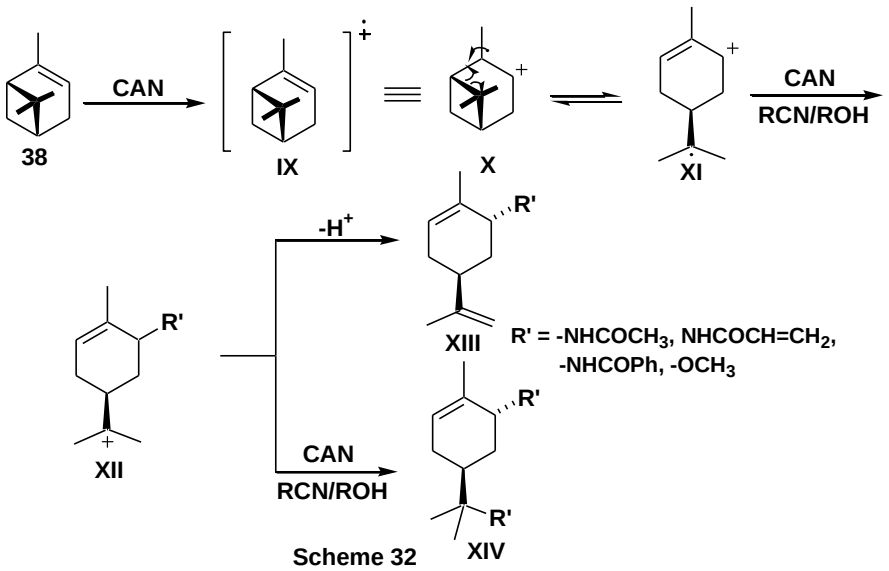


i) CAN (2.3 eq.), CH_3OH, 60 °C, 1h, 55%

Scheme 31

The structure of the product **57** was ascertained by spectroscopic methods. In the ^{1}H NMR spectrum, the three methyl groups resonated as singlets at δ 1.09, 1.12 and 1.75, while the protons of the methoxy groups furnished sharp singlets at δ 3.18 and 3.39. The methine proton attached to C-5 was discernible as a broad singlet at δ 3.48. The signal at δ 5.56 was characteristic of the olefinic proton. In the ^{13}C NMR spectrum, the signals at δ 48.49 and 56.94 were attributed to the methoxy carbons. The signals due to C-7 and C-5 were observed at δ 75.86 and 77.95 and those corresponding to the olefinic carbons C-3 and C-4 were discernible at δ 125.67 and 133.14 respectively. In the DEPT-135 NMR spectrum of compound **57**, peaks at δ 26.87 and 27.18 were negative indicating the presence of two methylene carbons while the peaks at δ 75.86 and 133.14 were absent indicating the presence of two quaternary carbons.

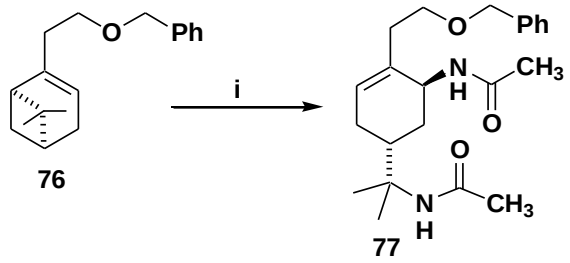
A probable mechanistic pathway for the formation of the various products in the above reactions is delineated in the following scheme (Scheme 32).



Scheme 32

It is conceivable that the initial event involves the single electron oxidation of (+)-α-pinene **38** to furnish a radical cation **IX** which presumably exists in equilibrium with its distonic version **XI**. The cationic center in **XI** is quenched by the solvent while the radical center is further oxidized by CAN to afford the cation **XII** which is readily neutralized by the solvent to afford the product **XIV**. Alternatively, the cationic intermediate **XII** loses a proton affording the product **XIII**.

The reaction of (-)-nopol benzyl ether **76** with CAN in acetonitrile also afforded the corresponding bisamide **77** in moderate yield (Scheme 33).

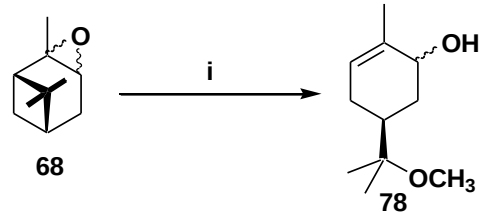


i) CAN, CH_3CN, RT, 5 h, 43%

Scheme 33

The bisamide **77** was chracterized with the aid of the usual spectroscopic tools. The methyl protons of the amide groups resonated at δ 1.83 and 1.90. The two benzylic protons gave a sharp singlet at δ 4.48. The olefinic proton resonated characteristically at δ 5.69. The aromatic protons resonated as a multiplet in the region δ 7.29-7.36. In the carbon spectrum, the amide carbonyls resonated characteristically at δ 169.31 and 169.71 respectively. All other resonance signals were in accordance with the assigned structure.

The reaction of α-pinene oxide **68** with catalytic amount of CAN in methanol afforded the product **78** in 50% yield (Scheme 34).

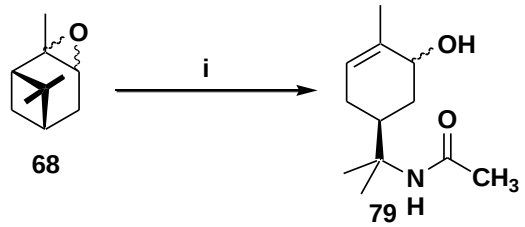


i) CAN (0.3 eq.), CH_3OH, 0 °C, 2 h, 50%

Scheme 34

Characterization of the product **78** was based on conventional spectroscopic data. In the IR spectrum, the absorption peak at 3424 cm^{-1} was assigned to the -OH group. In the ^1H NMR spectrum, the two *gem* methyl groups gave a single signal at δ 1.11 while the allylic methyl group resonated at δ 1.77. The -OH proton presented a broad singlet at δ 2.32 which was exchangeable with D_2O. The protons of the methoxy group afforded a sharp singlet at δ 3.18. The methine proton on the hydroxyl bearing carbon displayed a broad singlet at δ 3.99. In the ^{13}C NMR spectrum, the methoxy carbon resonated at δ 48.60. The signal at δ 68.44 was attributed to the quaternary carbon atom attached to the methoxy group. The carbon atom bearing the -OH group furnished a signal at δ 76.05. The olefinic carbons resonated at δ 125.24 and 134.43.

Similarly, the reaction of α-pinene oxide **68** with a solution of CAN in acetonitrile afforded the product **79** in 42% yield (Scheme 35).



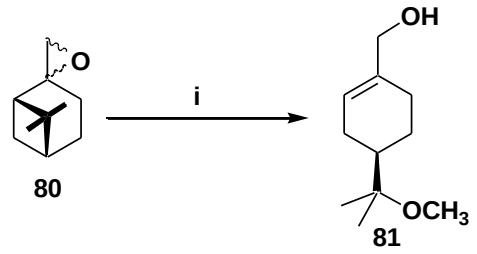
68 **79**

i) CAN (0.3 eq.), CH_3CN, 0 °C, 3 h, 42%

Scheme 35

The IR spectrum of **79** displayed the -OH absorption at 3393 cm^{-1} and the -NH absorption at 3292 cm^{-1}. The vibration band at 1634 cm^{-1} indicated the presence of an amide carbonyl. In the ^1H NMR spectrum, the methyl protons of the amide moiety resonated at δ 1.98. The olefinic proton resonated as a broad singlet at δ 5.59 while the -NH proton furnished a broad singlet at δ 5.65. In the ^{13}C NMR spectrum, the amide carbonyl was discernible at δ 169.42. All other signals were in accordance with the assigned structure.

The reaction of β-pinene oxide **80** with a methanolic solution of CAN afforded the product **81** in 60% yield (Scheme 36).

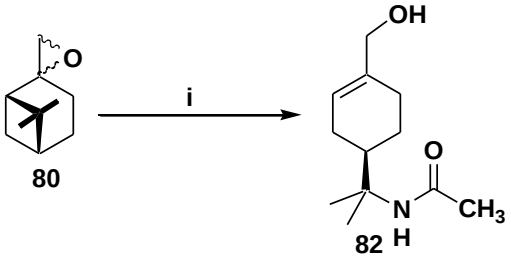


i) CAN (0.5 eq.), CH_3OH, RT, 5 h, 60%

Scheme 36

The product **81** was characterized on the basis of spectroscopic data. The IR spectrum showed a broad absorption band at 3387 cm^{-1} indicating the presence of an -OH group. In the ^1H NMR spectrum, the -OH proton gave a broad singlet at δ 2.36 which was exchangeable by D_2O. The protons of the methoxy group resonated as a sharp singlet at δ 3.17 while the olefinic proton resonated at δ 5.67. In the ^{13}C NMR, the signal at δ 66.78 was due to the carbon atom bearing the -OH group and the signal at δ 76.52 was attributed to the quaternary carbon bearing the methoxy group. The olefinic carbons resonated at δ 122.31 and 137.49.

Similarly, the reaction of β-pinene oxide **80** with a solution of CAN in acetonitrile furnished the product **82** in 35% yield (Scheme 37).



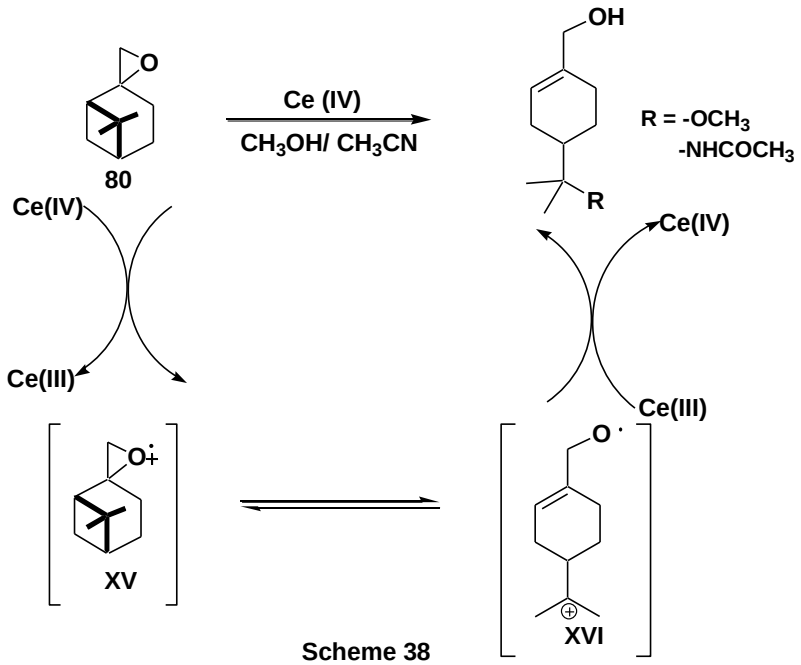
i) CAN (0.5 eq.), CH_3CN, RT, 5 h, 35%

Scheme 37

As usual the assignment of the structure is based on routine spectroscopic methods. The IR spectrum of **82** showed two absorption peaks at 3306 cm^{-1} and 3204 cm^{-1} indicating the presence of both the -OH and -NH groups. In the proton NMR, the -OH proton resonated at δ 1.66 and the methyl protons of the amide group furnished a sharp singlet at δ 1.92. The protons of the -OH bearing methylene carbon afforded a singlet at δ 3.98. The -NH proton resonated at δ 5.21 and the olefinic proton at δ 5.66. Both the -OH and -NH protons were

exchangeable by D_2O. In the ^{13}C NMR spectrum, the quaternary carbon attached to the amide group resonated at δ 55.76. The amide carbonyl furnished a characteristic resonance signal at δ 169.14.

A probable mechanistic pathway for the reaction of β-pinene oxide **80** to afford the above products is delineated in the following scheme (Scheme 38).



Scheme 38

In this conceptual framework, the epoxide moiety of β-pinene oxide **80** undergoes oxidation to the radical cation **XV** which exists in equilibrium with its distonic version **XVI**. The cationic center of the latter gets quenched by the solvent whereas the alkoxy radical will oxidize Ce(III) to Ce(IV), in the process undergoing reduction to the alkoxide, thus making the cycle catalytic.

As a logical follow-up of our studies concerned with the reactivity of cyclobutanes with CAN, we turned our attention to the reactivity of oxetanes towards CAN; the results of our investigations along with the relevant background material are discussed in the following sections.

3.4 The Reactivity of Oxetanes

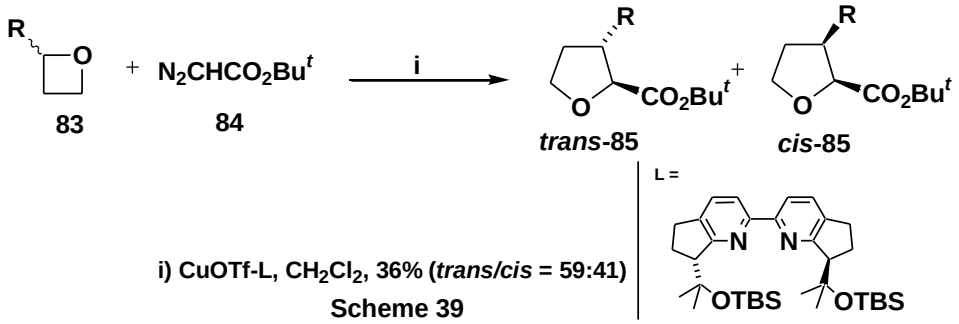
Four membered cyclic ethers, commonly referred to as oxetanes form a class of compounds that have stimulated considerable interest in the pharmaceutical community due to the potent biological activity exhibited by them,

especially taxol and its derivatives. The structure of oxetanes has been the subject of intensive research, and continues to be an active area of theoretical investigation. The chemistry of oxetanes is quite rich and varied and stems primarily from the relatively high degree of ring strain associated with the molecule. The basicity of the oxetane ring oxygen also plays a significant role in reactions with electrophilic reagents.

The X-ray crystal structure of oxetane was reported in 1984 and it revealed that the ring has exact C_s symmetry and is puckered with an angle of 10.7° at 90 K and 8.7° at 140 K.[26] The carbon-oxygen bond length was found to be unusually large. A comparision of X-ray data for tetrahydrofuran, dioxane, and oxetane reveals carbon-oxygen bond lengths of 1.429, 1.433 and 1.460 Å respectively.

The reactions of oxetanes range from thermal decomposition to cycloaddition reactions. Oxetanes readily undergo reactions with electrophiles due to the highly basic nature of the ring oxygen. Activation of the ring by Lewis acids can be followed by rearrangement or facile nucleophilic attack at carbon. Oxetanes are also susceptible to reductive ring cleavage and therefore serve as a source of carbanions for subsequent reactions with a variety of electrophiles. Substitution reactions of leaving groups attached to the oxetane ring are possible and comprise a large number of reactions of functionalized oxetanes. The synthesis of several natural products and biologically active oxetane derivatives have been accomplished by substitution reactions. Some important reactions illustrating the reactivity of oxetanes are described below.

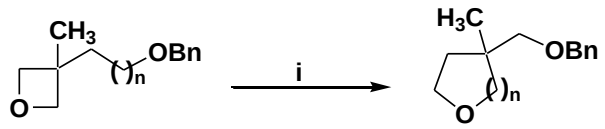
The enantiospecific ring expansion of oxetanes to tetrahydrofurans with diazoacetic acid ester was found to be catalyzed by the copper complex of (7*R*, 7'*R*)-7,7'-di(1-*tert*-butyldimethylsiloxy-1-methylethyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi-1,1'-pyridine **L**. For example, the reaction of *dl*-2-phenyloxetane **83** with *tert*-butyl diazoacetate **84** in presence of the copper complex **L** afforded both the *trans*- and *cis*-tetrahydrofurans **85** each with optical purity as high as 75% and 81% *ee* respectively (Scheme 39).[27]



i) CuOTf-L, CH_2Cl_2, 36% (*trans/cis* = 59:41)

Scheme 39

Oxetanes possessing ethereal groups on the side chain were found to rearrange in the presence of $BF_3.OEt_2$ to afford tetrahydrofuran and pyran ring systems in good yields (Scheme 40).[28]



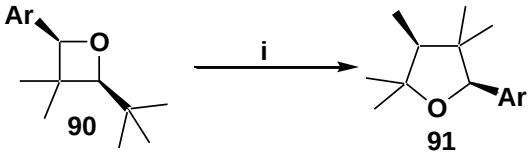
86. n = 1
88. n = 2

87. n = 1 ; 66%
89. n = 2 ; 77%

i) $BF_3.OEt_2$ (0.2 eq.); CH_2Cl_2; 0 °C, 20 min

Scheme 40

The ring expansion of aryl-*t*-butyloxetanes in the presence of Lewis acids leading to substituted tetrahydrofurans has also been reported (Scheme 41).[29]

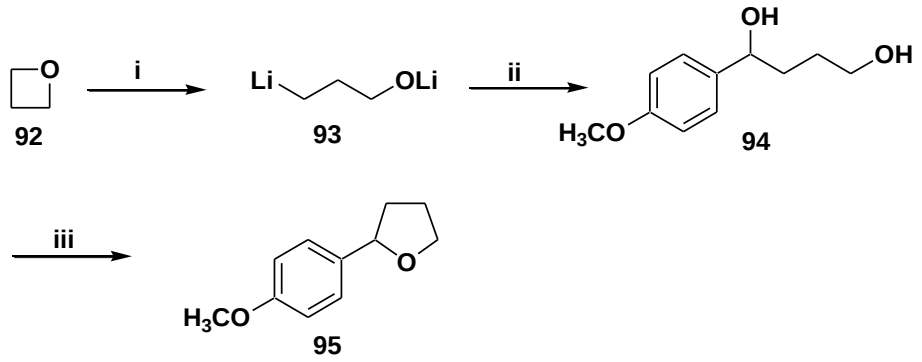


Ar = 2-FC_6H_4

i) $BF_3.OEt_2$, 30 h, 79%

Scheme 41

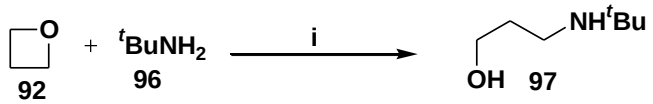
Oxetanes are cleaved at 0 °C in THF by lithium 4,4'-di-*tert*-butylbiphenylide giving γ-lithioalkoxides of the type **93**. These can be trapped with aldehydes and ketones to give 1,4-diols which on acid catalyzed cyclization afford 2-substituted tetrahydrofurans (Scheme 42).[30]



i) LDBB, 0 °C, THF; ii) a. *p*-MeOC$_6$H$_4$CHO b. H$_2$O, 71%; iii) TsOH (cat.), CH$_2$Cl$_2$, 93%

Scheme 42

$LiBF_4$ in acetonitrile efficiently catalyzes the aminolysis of **92** and 2-octyl oxetane **98** under mild conditions to give the corresponding γ-aminoalcohols in very good yields (Scheme 43).[31]

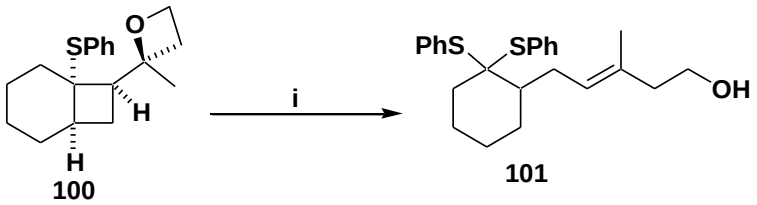


i) LiBF$_4$, CH$_3$CN, RT, 95%

ii) LiBF$_4$, CH$_3$CN, 80 °C, 95%

Scheme 43

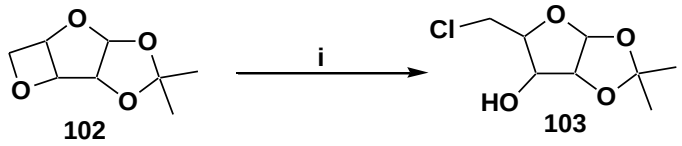
Titanium(IV) promoted ring opening reactions of 2-(2-phenylthio cyclobutyl)oxetane **100** proceed with high stereospecificity to give allyl and homoallyl alcohols in good yields (Scheme 44).[32]



ii) TiCl$_3$(OPr^i), Me$_3$SiSPh, CH$_2$Cl$_2$, 15 min, 70%, (*E*/*Z* = 99:1)

Scheme 44

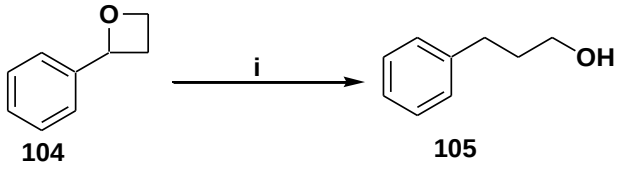
Efficient synthesis of chlorohydrins by the cleavage of oxetanes using $POCl_3$ or PCl_3 in the presence of DMAP has been recently reported (Scheme 45).[33]



i) $POCl_3$, DMAP, CH_2Cl_2, RT, 77%

Scheme 45

Substituted oxetanes give exclusively terminal alcohols by regiospecific ring opening with lithium and catalytic biphenyl (Scheme 46).[34]



i) Li (2.2 eq.), cat. biphenyl, THF, reflux

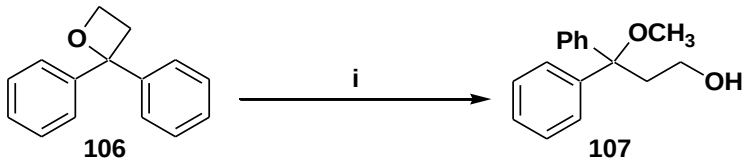
Scheme 46

3.4.1 Background to the Present Work

The oxidative protocol for the ring opening of epoxides has received considerable attention. In particular, the study of cerium(IV) ammonium nitrate mediated oxidative transformations of epoxides in the presence of different nucleophiles has been pursued in detail (for details, see **Chapter 1, p. 16**). An intriguing aspect of mechanistic importance evolves from the fact that all these reactions are autocatalytic in nature whereas the vast majority of CAN mediated oxidations require stoichiometric or super stoichiometric quantities of the oxidant. A brief survey of the literature reveals that the reactions of oxetanes with CAN remains hitherto unexplored. This, in addition to our general interest in the reactivity of four membered ring systems, prompted us to explore the reactivity of oxetanes with CAN.

3.4.2 Results and Discussion

In a pilot experiment, when the oxetane **106** (for the synthesis of oxetanes see **p. 126**) was treated with a catalytic amount of CAN in methanol at room temperature it underwent facile ring opening to afford the product **107** in 90% yield (Scheme 47).

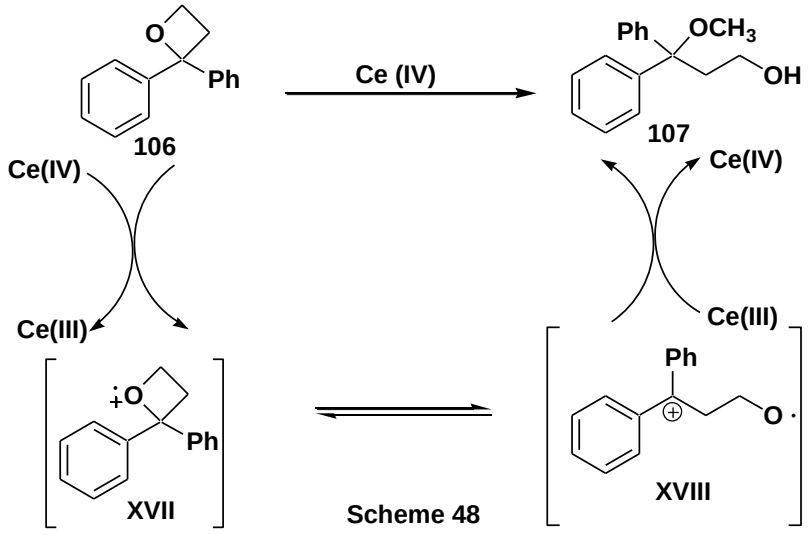


i) CAN (0.5 eq.), CH_3OH, RT, 30 min, 90%

Scheme 47

The product **107** was characterized with the aid of conventional spectroscopic tools. In the IR spectrum, the absorption at 3341 cm^{-1} was typical of the hydroxyl group. In the ^1H NMR spectrum, the -OH proton resonated as a broad singlet at δ 2.50 and was exchangeable by D_2O. The protons of the methoxy group were discernible as a sharp singlet at δ 3.08. The protons of the -OH bearing methylene resonated as a triplet at δ 3.52 (J = 6.1). In the ^{13}C NMR spectrum, the methoxy carbon afforded a peak at δ 50.78. The signal due to the -OH bearing carbon was seen at δ 59.28. The benzylic carbon furnished a signal at δ 83.24. All other signals were in agreement with the assigned structure.

A tentative mechanistic rationale for the formation of the product **107** is depicted in the following scheme (Scheme 48).

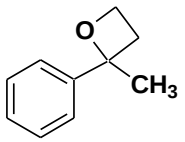
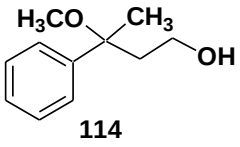
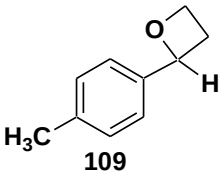
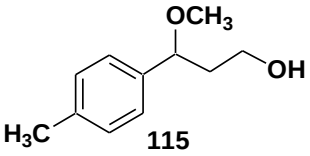
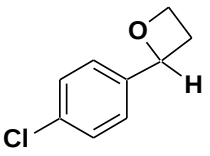
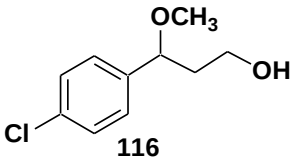
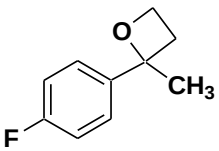
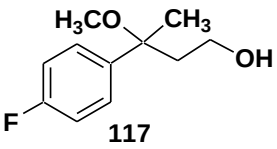
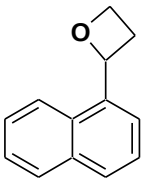
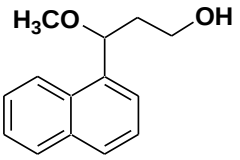


Scheme 48

The oxetane **106** is initially oxidized by Ce(IV) to the radical cation **XVII** which presumably exists in equilibrium with its distonic version **XVIII**. The alkoxy radical in **XVIII** gets reduced to the anion with the concomitant re-oxidation of Ce(III) to Ce(IV), making the cycle catalytic. The cationic center in **XVIII** gets quenched by methanol affording the final product.

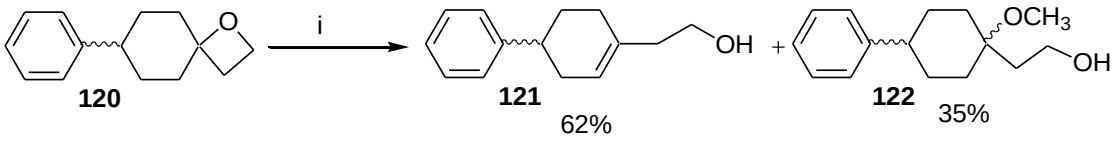
Similar results were obtained with a number of other oxetanes and the results are shown in Table 2.

Table 2

Entry	Oxetane	Product	Yield (%)
1	 **108**	 **114**	70
2	 **109**	 **115**	82
3	 **110**	 **116**	91
4	 **111**	 **117**	91
5	 **112**	 **118**	87

Reaction Conditions: cat. CAN, CH_3OH, RT

Interestingly, the reaction of the oxetane **120** with a catalytic amount of CAN in methanol at room temperature afforded two products, the cyclohexenyl derivative **121** in 62% yield and the usual product **122** as a 3:1 mixture of diastereoisomers in 35% yield (Scheme 49).



120 **121** 62% **122** 35%

i) CAN (0.5 eq.), CH_3OH, RT

Scheme 49

The products **121** and **122** were purified by column chromatography and characterized on the basis of spectroscopic data. In the IR spectrum of **121**, the strong absorption at 3339 cm^{-1} was indicative of the -OH group. In the ^{1}H NMR spectrum, the olefinic proton resonated as a singlet at δ 5.59. The olefinic carbons resonated at δ 123.60 and 134.09 in the ^{13}C NMR spectrum.

In the IR spectrum of product **122**, the -OH group gave a sharp absorption band at 3400 cm^{-1}. In the ^{1}H NMR spectrum, the methoxy protons of the two diastereoisomers gave separate peaks at δ 3.23 and 3.27. In the ^{13}C NMR spectrum, the quaternary carbon bearing the methoxy group in the two diastereoisomers resonated at δ 74.49 and 77.51. All other signals were in accordance with the assigned structure.

3.5 Conclusion

In conclusion, our studies have uncovered novel reactivity of cyclobutanes towards CAN leading to a variety of interesting products. These studies have also validated our hypothesis of the involvement of a long-bond cyclobutane radical cation in the CAN mediated dimerization of alkoxy styrenes. Remarkable CAN mediated transformations of monoterpenes of the pinene family culminating in potentially useful amides and ether derivatives has been uncovered. It is noteworthy that the bisamides on base catalyzed hydrolysis can afford the corresponding amines which are useful in the preparation of linear polymers, and also unusually stable Schiff bases which are of use as chiral ligands.[20] The regiospecific ring opening of oxetanes with catalytic amounts of CAN leading to functionalized alcohols has also been achieved.

3.6 Experimental Details

General information about the experiments is given in Section **2.8** of Chapter **2**. The cyclobutanes were prepared according to a literature procedure.[35] 1*R*-(+)-α-pinene **38**, 1*R*-(-)-nopol benzyl ether **76**, (-)-α-pinene oxide **68** and (+)-β-pinene oxide **80** were purchased from Aldrich Co. and were used without further purification. The oxetanes were prepared by a known literature procedure.[36]

General Procedure for the Synthesis of Cyclobutanes 28 and 29

A solution of 4-methoxystyrene or 4-benzyloxystyrene in acetonitrile (250 mL) was irradiated with a 500 W high pressure mercury lamp through a pyrex filter under argon for 10 h. After evaporation of the solvent from the reaction mixture, the cyclobutanes were isolated by column chromatography on silca gel.

General Procedure for the CAN Mediated Reactions of Cyclobutanes

A solution of CAN in the specified solvent (methanol or ethanol, 10 mL) was added dropwise to a solution of the cyclobutane in the same solvent. When the addition was complete, the reaction mixture was stirred at room temperature. The progress of the reaction was monitored at intervals of 10 minutes by thin layer chromatography. On complete consumption of the starting material, the reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with water, brine and then dried over anhydrous sodium sulfate. After the removal of the solvent on a rotary evaporator, the residue was subjected to column chromatography on silica gel. Elution with the appropriate mixture of hexane-ethylacetate furnished the pure products.

General Procedure for the CAN Mediated Reactions of Cyclobutanes under Argon Atmosphere

A deoxygenated solution of CAN in methanol (10 mL) was added dropwise to a deoxygenated solution of the cyclobutane in methanol (5 mL) stirred at ambient temperature. Argon, thoroughly deoxygenated by passing through Fieser's solution, was continuously bubbled through the reaction mixture. On completion of the reaction, the mixture was worked up as described in the general procedure. The crude residue was purified by chromatography on silica gel using the appropriate mixtures of hexane-ethylacetate to afford the pure products.

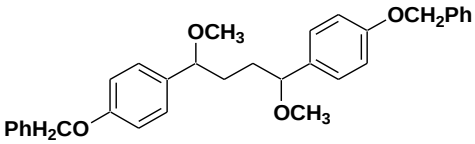
General Procedure for the CAN Mediated Reactions of Cyclobutanes under Oxygen Atmosphere

A solution of CAN in methanol, saturated with oxygen, was added dropwise to an oxygenated solution of the cyclobutane in methanol at ambient

temperature. Oxygen was continuously passed through the reaction mixture. On completion of the reaction, the mixture was worked up as described in the general procedure. The crude residue was purified by silica gel chromatography using the appropriate mixtures of hexane-ethylacetate to afford the pure products.

1,4-Bis(4'-benzyloxyphenyl)-1,4-dimethoxybutane 30

A deoxygenated solution of CAN (329 mg, 0.60 mmol) in dry methanol (10 mL) was added dropwise to a deoxygenated solution of the cyclobutane **29** (100 mg, 0.24 mmol) in dry methanol (5 mL) at ambient temperature. After stirring for 2 h, the reaction mixture was processed as described in the general procedure. The residue obtained was subjected to silica gel column chromatography using 90:10 hexane-ethylacetate mixture to afford **30** as a white crystalline solid (80 mg, 69%).



30

mp: 177 °C.

IR (KBr) ν_{max}: 3022, 2962, 2921, 2840, 2813, 1607, 1512, 1452, 1384, 1243, 1101, 933 cm^{-1}.

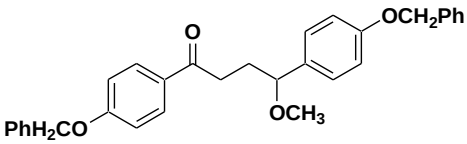
^{1}H NMR: δ 1.59-1.79 (m, 4H, C$\underline{H}_2$), 3.13 (s, 6H, OC$\underline{H}_3$), 3.90-4.02 (m, 2H, C$\underline{H}$), 5.04 (s, 4H, OC$\underline{H}_2$Ph), 6.91 (d, 4H, J = 8.5, Ar$\underline{H}$), 7.15 (d, 4H, J = 8.5, Ar$\underline{H}$), 7.30-7.43 (m, 10H, Ar$\underline{H}$).

^{13}C NMR: δ 34.73, 56.42, 70.05, 83.65, 114.74, 127.48, 127.87, 127.96, 128.61, 134.65, 137.17, 158.34.

1,4-Bis(4'-benzyloxyphenyl)-4-methoxybutan-1-one 31

A solution of CAN (329 mg, 0.60 mmol) in dry methanol (10 mL), saturated with oxygen was added dropwise to an oxygenated solution of the cyclobutane **29** (100 mg, 0.24 mmol) in dry methanol (5 mL). The reaction mixture was stirred at ambient temperature for 2 h. It was then processed as described in the general procedure. The residue obtained was subjected to silica

gel column chromatography using 90:10 hexane-ethylacetate mixture to afford **31** as a white crystalline solid (82 mg, 73%).



31

mp: 161 °C.

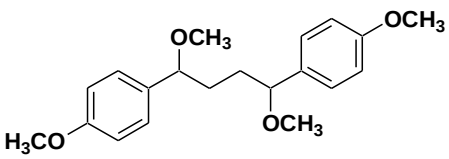
IR (KBr) ν_{max}: 2928, 2881, 2827, 1681, 1593, 1512, 1458, 1249, 1169, 1013 cm^{-1}.

^{1}H NMR: δ 2.04-2.15 (m, 2H, C$\underline{H}_2$), 2.96 (t, 2H, J = 7.1, C$\underline{H}_2$), 3.17 (s, 3H, OC$\underline{H}_3$), 4.13-4.17 (m, 1H, C$\underline{H}$), 5.05 (s, 2H, OC$\underline{H}_2$Ph), 5.11 (s, 2H, OC$\underline{H}_2$Ph), 6.95 (t, 4H, J = 8.8, Ar$\underline{H}$), 7.19-7.40 (m, 12H, Ar$\underline{H}$), 7.90 (d, 2H, J = 8.7, Ar$\underline{H}$).

^{13}C NMR: δ 32.66, 34.28, 70.00, 70.07, 82.47, 114.50, 114.77, 127.42, 127.45, 127.82, 127.95, 128.22, 128.58, 128.69, 130.33, 130.40, 134.21, 136.23, 154.77, 158.38, 162.45, 198.26.

1,4-Bis(4'-methoxyphenyl)-1,4-dimethoxybutane 32

A deoxygenated solution of CAN (614 mg, 1.12 mmol) in dry methanol (10 mL), was added dropwise to a deoxygenated solution of the cyclobutane **28** (121 mg, 0.45 mmol) in dry methanol (5 mL) at room temperature. After stirring for 1 h, the reaction mixture was processed as described in the general procedure. The residue obtained was subjected to silica gel column chromatography using 98:2 hexane-ethylacetate mixture to afford **32** as a white crystalline solid (92 mg, 62%).



32

mp: 99 °C.

IR (KBr) ν_{max}: 2957, 2918, 2848, 1611, 1510, 1464, 1173, 1029 cm^{-1}.

^{1}H NMR: δ 1.49-1.92 (m, 4H, C$\underline{H}_2$), 3.13 (s, 6H, OC$\underline{H}_3$), 3.79 (s, 6H, ArOC$\underline{H}_3$), 3.96-4.05 (m, 2H, C$\underline{H}$), 6.82 (d, 2H, J = 8.4, Ar$\underline{H}$), 6.84 (d, 2H, J = 8.5, Ar$\underline{H}$), 7.13 (uneven t, 4H, J_1 = 7.4, J_2 = 8.4, ArH).

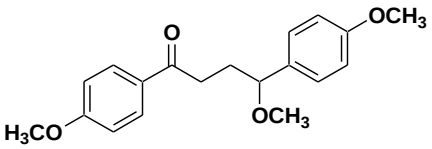
^{13}C NMR: δ 34.21, 34.74, 55.15, 56.37, 83.43, 83.62, 113.76, 127.80, 127.87, 134.19, 134.29, 159.03.

1,4-Bis(4'-methoxyphenyl)-4-methoxybutan-1-one 33

A solution of CAN (685 mg, 1.25 mmol) in dry methanol (10 mL), saturated with oxygen was added dropwise to an oxygenated solution of the cyclobutane **28** (134 mg, 0.50 mmol) in dry methanol (5 mL). The reaction mixture was stirred at ambient temperature for 1 h. It was then processed as described in the general procedure. The residue obtained was subjected to silica gel column chromatography using 95:5 hexane-ethylacetate mixture to afford **33** as a white crystalline solid (82 mg, 52%).

mp: 108 °C.

IR (KBr) ν_{max} : 2962, 2928, 2847, 1667, 1593, 1512, 1465, 1310, 1263, 1169, 1094, 987 cm^{-1}.



33

^{1}H NMR: δ 2.02-2.18 (m, 2H, C$\underline{H}_2$), 2.94-2.99 (m, 2H, C$\underline{H}_2$), 3.18 (s, 3H, OC$\underline{H}_3$), 3.80 (s, 3H, ArOC$\underline{H}$3), 3.85 (s, 3H, ArOC$\underline{H}_3$), 4.16 (dd, 1H, J_1 = 7.5, J_2 = 5.6, C$\underline{H}$), 6.85-6.91 (m, 4H, Ar$\underline{H}$), 7.21 (d, 2H, J = 8.5, Ar$\underline{H}$), 7.91 (d, 2H, J = 8.8, Ar$\underline{H}$).

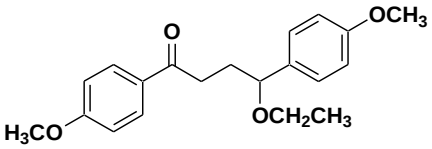
^{13}C NMR: δ 32.71, 34.31, 55.17, 55.35, 56.46, 82.52, 113.66, 113.88, 127.82, 130.32, 133.95, 159.18, 163.35, 198.31.

1,4-Bis(4'-methoxyphenyl)-4-ethoxybutan-1-one 34 and 4-(4'-methoxyphenyl)-6-methoxy-1-tetralone 35

A solution of CAN (685 mg, 1.25 mmol) in dry ethanol (10 mL), saturated with oxygen was added dropwise to an oxygenated solution of the cyclobutane **28** (134 mg, 0.50 mmol) in dry ethanol (5 mL). The reaction mixture was stirred at ambient temperature for 1 h. It was then processed as described in the general procedure. The residue obtained was subjected to silica gel column

chromatography using 98:2 hexane-ethylacetate mixture to afford **34** (57 mg, 35%) as a colorless oil. Further elution with the same solvent afforded **35** (42 mg, 30%) as a white solid.

1,4-Bis(4'-methoxyphenyl)-4-ethoxybutan-1-one 34



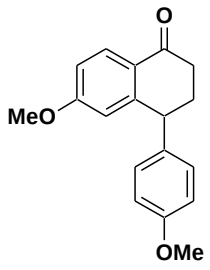
34

IR (film) ν_{max} : 2970, 2933, 2838, 1677, 1601, 1511, 1249, 1171, 1091, 1033 cm^{-1}.

^{1}H NMR: δ 1.14 (t, 3H, J = 6.9, $OCH_2C\underline{H}_3$), 2.02-2.16 (m, 2H, $C\underline{H}_2$), 2.95-3.00 (m, 2H, $C\underline{H}_2$), 3.24-3.39 (m, 2H, $OC\underline{H}_2CH_3$), 3.80 (s, 3H, $ArOC\underline{H}_3$), 3.86 (s, 3H, $ArOC\underline{H}_3$), 4.26 (uneven t, 1H, J_1 = 7.2, J_2 = 5.8, C<u>H</u>), 6.84-6.91 (m, 4H, Ar<u>H</u>), 7.23 (t, 2H, J = 8.2, Ar<u>H</u>), 7.91 (d, 2H, J = 8.6, Ar<u>H</u>).

^{13}C NMR: δ 15.28, 32.83, 34.19, 55.02, 55.20, 63.79, 80.41, 113.51, 113.69, 127.54, 130.19, 134.62, 158.92, 163.18, 198.22.

4-(4'-methoxyphenyl)-6-methoxy-1-tetralone 35



35

mp: 117 °C.

IR (KBr) ν_{max}: 3002, 2941, 2837, 1675, 1598, 1511, 1462, 1333, 1264, 1180, 1033 cm^{-1}.

^{1}H NMR: δ 2.21-2.29 (m, 1H, C<u>H</u>H), 2.38-2.44 (m, 1H, CH<u>H</u>), 2.49-2.66 (m, 2H, $C\underline{H}_2$), 3.73 (s, 3H, $ArOC\underline{H}_3$), 3.79 (s, 3H, $ArOC\underline{H}_3$), 4.15-4.19 (m, 1H, C<u>H</u>), 6.41 (s, 1H, Ar<u>H</u>), 6.83 (d, 3H, J = 8.4, Ar<u>H</u>), 7.01 (d, 2H, J = 8.4, Ar<u>H</u>), 8.06 (d, 1H, J = 8.7, Ar<u>H</u>).

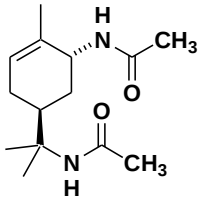
^{13}C NMR: δ 32.02, 36.40, 44.89, 55.10, 55.18, 113.25, 113.56, 114.04, 126.57, 129.43, 129.63, 135.46, 148.99, 158.44, 163.65, 196.41.

General Procedure for the CAN Mediated Reactions of Monoterpenes

A solution of CAN in the specified solvent (methanol, acetonitrile, acrylonitrile or benzonitrile) was added dropwise to a solution of the monoterpene in the same solvent. The progress of the reaction was monitored by tlc. On complete consumption of the starting material, the solvent was removed *in vacuo*. The crude residue was diluted with water (20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with water, brine and then dried over anhydrous sodium sulfate. After the removal of the solvent on a rotary evaporator, the residue was subjected to column chromatography on silica gel. Elution with the appropriate mixture of hexane-ethylacetate furnished the pure products.

N^1-{1-[5-(acetylamino)-4'-methyl-cyclohex-3-enyl]-1-methyl ethyl} acetamide 71

A solution of CAN (1.26 g, 2.30 mmol) in acetonitrile (10 mL) was added dropwise to a solution of (+)-α-pinene **38** (136 mg, 1.00 mmol) in acetonitrile (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h. It was then processed as described in the general procedure (extracted with chloroform). The residue was subjected to silica gel column chromatography. Elution using chloroform-methanol mixture (95:5) afforded **71** as a white crystalline solid (181 mg, 72%).



71

mp: 203 °C.

IR (KBr) ν_{max}: 3285, 3076, 2975, 2935, 2840, 1640, 1546, 1438, 1371, 1297, 1196, 1094, 1040, 933, 811, 730 cm^{-1}.

^{1}H NMR: δ 1.16 (s, 3H, C$\underline{H}_3$), 1.29 (s, 3H, C$\underline{H}_3$), 1.33-1.37 (m, 1H, C$\underline{H}$H), 1.68 (s, 3H, C$\underline{H}_3$), 1.69-1.83 (m, 2H, C$\underline{H}_2$), 1.90 (s, 3H, NHCOC$\underline{H}_3$), 1.97 (s, 3H, NHCOC$\underline{H}_3$), 1.99-2.05 (m, 1H, CH$\underline{H}$), 2.56-2.63 (m, 1H, C$\underline{H}$), 4.35 (br s, 1H, C$\underline{H}$NH), 5.35 (br s, 1H, N$\underline{H}$COCH$_3$), 5.56 (br s, 1H, olefinic), 5.77 (d, 1H, J = 7.5, N$\underline{H}$COCH$_3$).

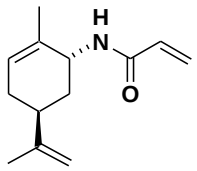
^{13}C NMR: δ 20.85, 23.39, 23.84, 24.43, 24.66, 27.02, 30.58, 34.17, 48.39, 56.11, 125.89, 132.99, 169.29, 169.71.

HRMS (EI) Calcd for $C_{14}H_{24}N_2O_2$: 252.1838. Found: 252.1849.

N-(5-Isopropenyl-2-methyl-cyclohex-2-enyl)-acrylamide 72 and N¹-{1-[5'-(acrylamino)-4'-methyl-cyclohex-3'-enyl]-1-methylethyl}acrylamide 73

A solution of CAN (1.37 g, 2.50 mmol) in acrylonitrile (20 mL) was added dropwise to a solution of (+)-α-pinene **38** (136 mg, 1.00 mmol) in acrylonitrile (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using hexane-ethylacetate mixture (80:20) to afford **72** as a colorless viscous liquid (18 mg, 9%). Further elution using hexane-ethylacetate mixture (50:50) afforded **73** as a white crystalline solid (113 mg, 41%).

N-(5-Isopropenyl-2-methyl-cyclohex-2-enyl)-acrylamide 72



72

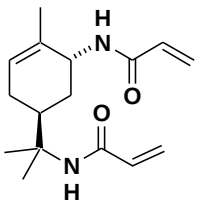
IR (KBr) ν_{max}: 3285, 2928, 1661, 1620, 1546, 1445, 1243, 1067, 993 cm^{-1}.

^{1}H NMR: δ 1.60-1.65 (m, 1H, C<u>H</u>H), 1.71 (s, 6H, C<u>H</u>$_3$), 1.83-1.96 (m, 2H, C<u>H</u>$_2$), 2.04-2.18 (m, 2H, CH<u>H</u>+C<u>H</u>), 4.46-4.54 (m, 1H, C<u>H</u>NH), 4.72 (d, 2H, J = 7.9, olefinic), 5.62-5.68 (m, 2H, N<u>H</u>COCH=CH$_2$+olefinic), 5.64 (dd, 1H, J_1 = 10.2, J_2 = 1.5, NHCOCH=C<u>H</u>$_2$), 6.09 (dd, 1H, J_1 = 16.9, J_2 = 10.2, NHCOC<u>H</u>=CH$_2$), 6.29 (dd, 1H, J_1 = 16.9, J_2 = 1.5, NHCOCH=C<u>H</u>$_2$).

^{13}C NMR: δ 20.83, 20.96, 30.80, 34.10, 36.30, 40.25, 47.86, 109.51, 126.18, 126.47, 131.02, 132.49, 148.43, 164.77.

N¹-{1-[5'-(acrylamino)-4'-methyl-cyclohex-3'-enyl]-1-methylethyl}acrylamide 73

mp: 168 °C.



73

IR (KBr) ν_{max}: 3326, 2969, 2935, 2915, 2881, 1654, 1627, 1539, 1411, 1371, 1249, 1067, 960 cm^{-1}.

^{1}H NMR: δ 1.23 (s, 3H, C<u>H</u>$_3$), 1.33 (s, 3H, C<u>H</u>$_3$), 1.36-1.45 (m, 1H, C<u>H</u>H), 1.68 (s, 3H, C<u>H</u>$_3$), 1.74-1.82 (m, 2H, C<u>H</u>$_2$),

1.99-2.05 (m, 1H, CHH), 2.64-2.72 (m, 1H, CH), 4.48 (br s, 1H, CHNH), 5.50-5.65 (m, 4H, NHCOCH=CH_2+olefinic), 6.01-6.27 (m, 5H, NHCO CH=CH_2).

^{13}C NMR: δ 20.86, 23.82, 24.62, 27.02, 30.87, 34.58, 48.19, 56.28, 125.74, 125.88, 125.93, 131.30, 131.79, 133.03, 164.78, 165.19.

HRMS (FAB) Calcd for $C_{16}H_{24}N_2O_2 + H^+$: 277.1916. Found: 277.1902.

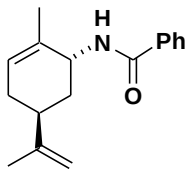
N-(5-Isopropenyl-2-methyl-cyclohex-2-enyl)-benzamide 74 and N^1-{1-[5'-(acryl amino)-4'-methyl-cyclohex-3'-enyl]-1-methylethyl}benzamide 75

A solution of CAN (1.26 g, 2.30 mmol) in benzonitrile (10 mL) was added dropwise to a solution of (+)-α-pinene **38** (136 mg, 1.00 mmol) in benzonitrile (2 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 h. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using hexane-ethylacetate mixture (95:5) to afford **74** as a white solid (46 mg, 18%). Further elution using hexane-ethylacetate mixture (80:20) afforded **75** as a white crystalline solid (94 mg, 25%).

N-(5-Isopropenyl-2-methyl-cyclohex-2-enyl)-benzamide 74

mp: 134 °C.

IR (KBr) ν_{max}: 3265, 2914, 1626, 1532, 1492, 1444, 1350,1269, 1080, 905, 696 cm^{-1}.



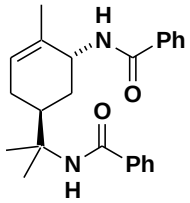
74

^{1}H NMR: δ 1.65-1.69 (m, 1H, CHH), 1.92-2.06 (m, 2H, CH_2), 1.73 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.16-2.19 (m, 2H, CHH+CH), 4.59-4.64 (m, 1H, CHNH), 4.73 (d, 2H, J = 4.6, olefinic), 5.67 (br s, 1H, olefinic), 6.12 (d, 1H, J = 7.7, NHCOPh), 7.40-7.51 (m, 3H, ArH), 7.75-7.77 (m, 2H, ArH).

^{13}C NMR: δ 20.89, 21.08, 30.85, 34.17, 36.39, 48.28, 109.55, 126.32, 126.96, 128.54, 131.36, 132.65, 134.84, 148.38, 166.68.

HRMS (FAB) Calcd for $C_{17}H_{21}NO + H^+$: 256.1701. Found: 256.1700.

N[1]-{1-[5'-(acrylamino)-4'-methyl-cyclohex-3'-enyl]-1-methylethyl}benzamide 75



75

mp: 175 °C.

IR (KBr) ν_{max}: 3272, 3063, 2928, 2854, 1661, 1627, 1546, 1512, 1485, 1371, 1081, 790 cm^{-1}.

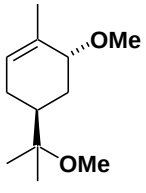
^{1}H NMR: δ 1.29 (s, 3H, C$\underline{H}_3$), 1.45 (s, 3H, C$\underline{H}_3$), 1.49-1.55 (m, 1H, C$\underline{H}$H), 1.73 (s, 3H, C$\underline{H}_3$), 1.82-1.86 (m, 1H, CH$\underline{H}$), 1.93-1.97 (m, 1H, C$\underline{H}$H), 2.09-2.15 (m, 1H, CH$\underline{H}$), 2.87-2.95 (m, 1H, C$\underline{H}$), 4.61 (br s, 1H, C$\underline{H}$NH), 5.62 (br s, 1H, olefinic), 5.92 (s, 1H, N$\underline{H}$COPh), 6.38 (d, 1H, J = 8.4, N$\underline{H}$COPh), 7.26-7.30 (m, 2H, Ar$\underline{H}$), 7.36-7.48 (m, 4H, Ar$\underline{H}$), 7.54 (d, 2H, J = 7.1, Ar$\underline{H}$), 7.77 (d, 2H, J = 6.8, Ar$\underline{H}$).

^{13}C NMR: δ 20.95, 23.83, 24.82, 27.21, 31.10, 34.85, 48.59, 56.55, 125.99, 126.58, 127.10, 128.41, 131.11, 131.19, 133.29, 134.77, 135.59, 167.02.

HRMS (FAB) Calcd for $C_{24}H_{28}N_2O_2 + H^+$: 377.2229. Found: 377.2228.

1-(4'-Methyl-5'-methoxy-cyclohex-3'-enyl)-1-methylethylmethylether 57

A solution of CAN (1.26 g, 2.30 mmol) in methanol (10 mL) was added dropwise to a solution of (+)-α-pinene **38** (136 mg, 1.00 mmol) in methanol (5 mL) at room temperature. The reaction mixture was stirred at 60 °C for 1 h. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using hexane-ethylacetate mixture (99:1) to afford **57** as a colorless fragrant liquid (109 mg, 55%).



57

IR (film) ν_{max}: 2975, 2928, 2827, 1458, 1371, 1249, 1189, 1088, 946, 804 cm^{-1}.

^{1}H NMR: δ 1.09 (s, 3H, C$\underline{H}_3$), 1.12 (s, 3H, C$\underline{H}_3$), 1.14-1.18 (m, 1H, C$\underline{H}$H), 1.69-1.76 (m, 1H, CH$\underline{H}$), 1.75 (s, 3H, C$\underline{H}_3$), 1.92-2.02 (m, 2H, C$\underline{H}_2$), 2.10-2.15 (m, 1H, C$\underline{H}$), 3.18 (s,

3H, OC$\underline{H}_3$), 3.39 (s, 3H, OC$\underline{H}_3$), 3.48 (br s, 1H, C$\underline{H}$OCH$_3$), 5.56 (d, 1H, J = 4.5, olefinic).

^{13}C NMR: δ 21.02, 22.34, 22.66, 26.87, 27.18, 34.93, 48.49, 56.94, 75.86, 77.95, 125.67, 133.14.

HRMS (FAB) Calcd for $C_{12}H_{22}O_2$+H^+: 199.1698. Found 199.1699.

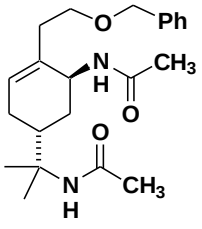
N-{1-[5-Acetylamino-4-(2-benzyloxy-ethyl)-cyclohex-3-enyl]-1-methyl-ethyl}-acetamide 77

A solution of CAN (1.26 g, 2.30 mmol) in acetonitrile (10 mL) was added dropwise to a solution of (-)-nopol benzyl ether **76** (256 mg, 1.00 mmol) in acetonitrile (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 h. It was then processed as described in the general procedure (extracted with chloroform). The residue was subjected to silica gel column chromatography using chloroform-methanol mixture (98:2) to afford **77** as a white crystalline solid (160 mg, 43%).

mp: 130 °C.

IR (KBr) ν_{max}: 3298, 3265, 3069, 2975, 2934, 2853, 1640, 1559, 1458, 1377, 1121, 737 cm^{-1}.

^{1}H NMR: δ 1.17 (s, 3H, C$\underline{H}_3$), 1.29 (s, 3H, C$\underline{H}_3$), 1.30-1.34 (m, 1H, C$\underline{H}$H), 1.75-1.79 (m, 1H, CH$\underline{H}$), 1.83 (s, 3H, NHCOC$\underline{H}_3$), 1.90 (s, 3H, NHCOC$\underline{H}_3$), 1.92-2.07 (m, 2H, C$\underline{H}_2$), 2.19-2.29 (m, 2H, C$\underline{H}_2$), 2.54-2.60 (m, 1H, C$\underline{H}$), 3.47-3.61 (m, 2H, -CH$_2$C$\underline{H}_2$OCH$_2$Ph), 4.37 (br s, 1H, C$\underline{H}$NH), 4.48 (s, 2H, -OC$\underline{H}_2$Ph), 5.19 (s, 1H, N$\underline{H}$COCH$_3$), 5.69 (br s, 1H, olefinic), 5.95 (d, 1H, J = 7.7, N$\underline{H}$COCH$_3$), 7.29-7.36 (m, 5H, Ar$\underline{H}$).

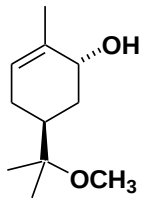


77

^{13}C NMR: δ 23.10, 23.61, 24.25, 24.56, 27.04, 30.35, 34.20, 34.52, 47.45, 55.85, 69.21, 72.90, 127.48, 127.58, 127.71, 127.83, 128.33, 128.40, 133.96, 138.14, 169.31, 169.71.

1-(5'-Hydroxy-4'-methyl-cyclohex-3'-enyl)-1-methylethylmethylether 78

A solution of CAN (164 mg, 0.30 mmol) in methanol (10 mL) was added dropwise to a solution of α-pinene oxide **68** (152 mg, 1.00 mmol) in methanol (5 mL). The reaction mixture was stirred at ice temperature for 2 h. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 80:20 hexane-ethylacetate to afford **78** (92 mg, 50%) as a fragrant liquid.



78

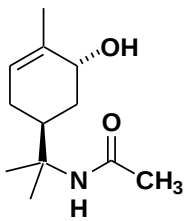
IR (film) ν_{max}: 3424, 2978, 2918, 2843, 1457, 1382, 1158, 1064, 958 cm^{-1}.

^{1}H NMR: δ 1.11 (s, 6H, C$\underline{H}_3$), 1.32-1.41 (m, 1H, C$\underline{H}$H), 1.77 (s, 4H, C$\underline{H}_3$+CH$\underline{H}$), 1.88-2.04 (m, 3H, C$\underline{H}_2$+C$\underline{H}$), 2.32 (br s, 1H, O$\underline{H}$), 3.18 (s, 3H, OC$\underline{H}_3$), 3.99 (br s, 1H, C$\underline{H}$OH), 5.55 (br s, 1H, olefinic).

^{13}C NMR: δ 20.86, 22.09, 22.39, 27.02, 32.73, 35.46, 48.60, 68.44, 76.05, 125.24, 134.43.

N^1-{1-methyl-1-[5'-(hydroxy)-4'-methyl-cyclohex-3-enyl]ethyl}acetamide 79

A solution of CAN (164 mg, 0.30 mmol) in acetonitrile (10 mL) was added dropwise to a solution of α-pinene oxide **68** (152 mg, 1.00 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at ice temperature for 3 h. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 20:80 hexane-ethylacetate to afford **79** (89 mg, 42%) as a colorless viscous liquid.



IR (film) ν_{max}: 3393, 3292, 2975, 2928, 1634, 1539, 1445, 1378, 1283, 1175, 926 cm^{-1}.

^{1}H NMR: δ 1.16 (s, 3H, C$\underline{H}_3$), 1.18 (s, 3H, C$\underline{H}_3$), 1.24-1.55 (m, 3H, C$\underline{H}_2$+O$\underline{H}$), 1.69 (s, 3H, C$\underline{H}_3$), 1.73-1.83 (m, 2H, C$\underline{H}_2$), 1.98 (s, 3H, NHCOC$\underline{H}_3$), 2.08-2.13 (m, 1H, C$\underline{H}$), 4.38-4.40 (m, 1H, C$\underline{H}$OH), 5.59 (s, 1H, olefinic), 5.65 (s,

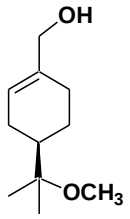
79 1H, N<u>H</u>COCH$_3$).

^{13}C NMR: δ 20.91, 23.42, 26.51, 26.87, 27.41, 30.33, 39.89, 47.98, 72.12, 125.95, 132.66, 169.42.

1-(4'-Hydroxymethyl-cyclohex-3-enyl)-1-methylethylmethylether <u>81</u>

A solution of CAN (274 mg, 0.50 mmol) in methanol (10 mL) was added dropwise to a solution of β-pinene oxide **80** (152 mg, 1.00 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 5 h. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 80:20 hexane-ethylacetate to afford **81** (110 mg, 60%) as a fragrant liquid.

IR (film) ν_{max}: 3387, 2975, 2935, 2834, 1587, 1465, 1378, 1148, 1074, 1007 cm^{-1}.



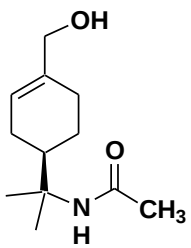
<u>81</u>

^{1}H NMR: δ 1.11 (s, 6H, C<u>H</u>$_3$), 1.16-1.32 (m, 1H, C<u>H</u>H), 1.65-1.89 (m, 3H, CH<u>H</u>), 1.90-2.14 (m, 3H, C<u>H</u>$_2$+C<u>H</u>), 2.36 (br s, 1H, O<u>H</u>), 3.17 (s, 3H, OC<u>H</u>$_3$), 3.96 (s, 2H, C<u>H</u>$_2$OH), 5.67 (br s, 1H, olefinic).

^{13}C NMR: δ 21.79, 22.14, 23.49, 26.41, 26.56, 41.81, 48.56, 66.78, 76.52, 122.31, 137.49.

N^{1}-[1-Methyl-1-(4'-hydroxymethyl-cyclohex-3-enyl)ethyl]acetamide <u>82</u>

A solution of CAN (274 mg, 0.50 mmol) in acetonitrile (10 mL) was added dropwise to a solution of β-pinene oxide **80** (152 mg, 1.00 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 5 h. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 80:20 hexane-ethylacetate to afford **82** (74 mg, 35%) as a white crystalline solid.



mp: 152 °C.

IR (KBr) ν_{max}: 3306, 3204, 2955, 2867, 1647, 1573, 1452, 1378, 1303, 1236, 1061, 980 cm^{-1}.

^{1}H NMR: δ 1.28 (s, 4H, C<u>H</u>$_3$+C<u>H</u>H), 1.31 (s, 3H, C<u>H</u>$_3$), 1.66

82 (br s, 1H, O<u>H</u>), 1.80-1.85 (m, 2H, C<u>H</u>$_2$), 1.92 (s, 3H, NHCOC<u>H</u>$_3$), 2.03-2.11 (m, 3H, CH<u>H</u>+C<u>H</u>$_2$), 2.20-2.28 (m, 1H, C<u>H</u>), 3.98 (s, 2H, C<u>H</u>$_2$OH), 5.21 (s, 1H, N<u>H</u>COCH$_3$), 5.66 (s, 1H, olefinic).

^{13}C NMR: δ 23.59, 23.65, 23.92, 24.08, 26.07, 26.54, 40.58, 55.76, 66.01, 121.14, 137.77, 169.14.

HRMS (FAB) Calcd for $C_{12}H_{21}NO_2 + H^+$: 212.1650. Found: 212.1643.

General Procedure for the Preparation of Oxetanes

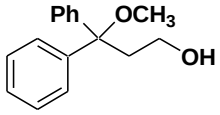
To a soution of 4 equivalents of trimethylsulfoxonium iodide in ^{t}BuOH (20 mL) was added a solution of 4 equivalents of pottasium-*tert*-butoxide in ^{t}BuOH (60 mL) at 50 °C under argon. After 30 minutes of stirring, 1equivalent of the aldehyde or ketone in ^{t}BuOH (20 mL) was added dropwise. After three days of stirring at 50 °C, the resulting solution was evaporated to remove the ^{t}BuOH. The resulting residue was washed with water (50 mL) and extracted with hexane (3 x 40 mL). The combined organic extracts were washed with brine and then dried over anhydrous sodium sulfate. After the removal of the solvent *in vacuo* on a rotary evaporator, the crude product was subjected to column chromatography on basic alumina. Elution with 99:1 hexane-ethylacetate afforded the pure oxetanes.

General Procedure for the CAN Mediated Reactions of Oxetanes

A solution of CAN (0.50 equivalents) in methanol (10 mL) was added dropwise to a solution of the oxetane in methanol (5 mL). When the addition was complete, the reaction mixture was stirred at room temperature. On complete consumption of the starting material as indicated by thin layer chromatography, the reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with water and brine and then dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo* on a rotary evaporator, the residue was subjected to column chromatography on silica gel. Elution with an appropriate mixture of hexane-ethylacetate furnished the pure products.

3,3-Diphenyl-3-methoxy-1-propanol 107

A solution of CAN (274 mg, 0.50 mmol) in methanol (10 mL) was added dropwise to a solution of the oxetane **106** (230 mg, 1.10 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 30 min. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 80:20 hexane-ethylacetate solvent mixture to afford pure **107** as a colorless viscous liquid (240 mg, 90%).



107

IR (film) ν_{max}: 3341, 3059, 2946, 2893, 2827, 1598, 1490, 1446, 1190, 1100, 1059, 1036 cm^{-1}.

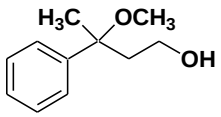
^{1}H NMR: δ 2.50 (br s, 1H, OH), 2.58 (t, 2H, J = 6.2, CH_2), 3.08 (s, 3H, OCH_3), 3.52 (t, 2H, J = 6.1, CH_2OH), 7.18-7.33 (m, 10H, ArH).

^{13}C NMR: δ 37.24, 50.78, 59.28, 83.24, 126.96, 127.06, 128.13, 144.46.

EIMS m/z (%): 242 (M^+, 0.8), 210 (9), 197 (100), 165 (83), 139 (8), 115 (21), 105 (98), 77 (98), 51 (63).

3-Methoxy-3-phenyl-1-butanol 114

A solution of CAN (274 mg, 0.50 mmol) in methanol (10 mL) was added dropwise to a solution of the oxetane **108** (148 mg, 1.00 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 30 min. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 80:20 hexane-ethylacetate solvent mixture to afford pure **114** as a colorless viscous liquid (126 mg, 70%).



114

IR (film) ν_{max}: 3434, 2975, 2942, 2827, 1499, 1445, 1371, 1169, 1074, 1047, 764 cm^{-1}

^{1}H NMR: δ 1.65 (s, 3H, CH_3), 1.88-2.04 (m, 2H, CH_2), 3.12 (s, 3H, OCH_3), 3.20 (br s, 1H, OH), 3.55-3.67 (m, 1H, CHHOH), 3.69-3.74 (m, 1H, CHHOH), 7.23-7.35 (m, 5H, ArH).

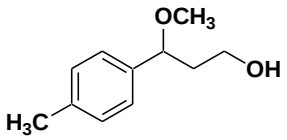
^{13}C NMR: δ 22.56, 45.30, 50.37, 59.42, 80.49, 125.80, 126.99, 128.28, 144.29.

EIMS m/z (%): 180 (M^+, 0.8), 165 (11), 147 (5), 135 (100), 115 (23), 103 (83), 91 (60), 77 (83), 65 (17), 51 (44).

3-(4-Methylphenyl)-3-methoxy-1-propanol 115

A solution of CAN (274 mg, 0.50 mmol) in methanol (10 mL) was added dropwise to a solution of the oxetane **109** (60 mg, 0.40 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 30 min. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 80:20 hexane-ethylacetate solvent mixture to afford pure **115** as a colorless viscous liquid (60 mg, 82%).

IR (film) ν_{max}: 3400, 2931, 2882, 2822, 1512, 1451, 1350, 1107, 1053, 810 cm^{-1}.



115

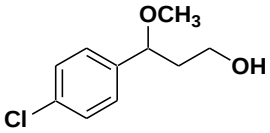
^{1}H NMR: δ 1.79-1.87 (m, 1H, C<u>H</u>H), 1.96-2.06 (m, 1H, CH<u>H</u>), 2.34 (s, 3H, ArC<u>H</u>$_3$), 3.03 (br s, 1H, O<u>H</u>), 3.20 (s, 3H, OC<u>H</u>$_3$), 3.72-3.74 (m, 2H, C<u>H</u>$_2$OH), 4.31-4.35 (m, 1H, C<u>H</u>), 7.13-7.19 (m, 4H, Ar<u>H</u>).

^{13}C NMR: δ 21.04, 40.42, 56.34, 60.60, 83.12, 126.39, 129.10, 137.18, 138.41.

EIMS m/z (%): 180 (M^+, 18), 165 (2), 135 (100), 119 (72), 105 (55), 91 (95), 77 (34), 65 (49), 51 (21).

3-(4-Chlorophenyl)-3-methoxy-1-propanol 116

A solution of CAN (274 mg, 0.50 mmol) in methanol (10 mL) was added dropwise to a solution of the oxetane **110** (50 mg, 0.29 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 30 min. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 80:20 hexane-ethylacetate solvent mixture to afford pure **116** as a colorless viscous liquid (54 mg, 91%).



116

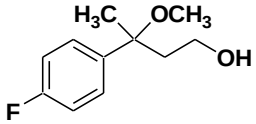
IR (film) ν_{max}: 3418, 2937, 2886, 1488, 1409, 1091, 1014, 823 cm^{-1}.

^{1}H NMR: δ 1.77-1.84 (m, 1H, C<u>H</u>H), 1.95-2.03 (m, 1H, CH<u>H</u>), 2.87 (br s, 1H, O<u>H</u>), 3.21 (s, 3H, OC<u>H</u>$_3$), 3.69-3.79 (m, 2H, C<u>H</u>$_2$OH), 4.34-4.38 (m, 1H, C<u>H</u>), 7.24 (d, 2H, *J* = 8.3, Ar<u>H</u>), 7.32 (d, 2H, *J* = 8.4, Ar<u>H</u>).

^{13}C NMR: δ 40.42, 56.62, 60.37, 82.46, 127.80, 128.69, 133.40, 140.08.

3-(4-Fluorophenyl)-3-methoxy-1-butanol <u>117</u>

A solution of CAN (274 mg, 0.50 mmol) in methanol (10 mL) was added dropwise to a solution of the oxetane **111** (166 mg, 1.00 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 30 min. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 80:20 hexane-ethylacetate solvent mixture to afford pure **117** as a colorless viscous liquid (180 mg, 91%).



117

IR (film) ν_{max}: 3387, 2940, 2827, 1607, 1513, 1229, 1162, 1081, 838 cm^{-1}.

^{1}H NMR: δ 1.64 (s, 3H, C<u>H</u>$_3$), 1.88-2.03 (m, 2H, C<u>H</u>$_2$), 3.11 (s, 4H, OC<u>H</u>$_3$+O<u>H</u>), 3.58-3.69 (m, 2H, C<u>H</u>$_2$OH), 6.99-7.06 (m, 2H, Ar<u>H</u>), 7.31-7.32 (m, 2H, Ar<u>H</u>).

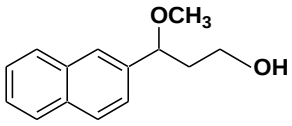
^{13}C NMR: δ 22.63, 45.32, 50.29, 59.36, 80.08, 115.22, 127.60, 140.16, 163.44.

EIMS m/z (%): 198 (M+, 0.8), 183 (15), 165 (6), 153 (100), 135 (40), 121 (95), 95 (69), 75 (48), 57 (32).

3-Methoxy-3-naphthyl-1-propanol <u>118</u>

A solution of CAN (274 mg, 0.50 mmol) in methanol (10 mL) was added dropwise to a solution of the oxetane **112** (184 mg, 1.00 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 30 min. It was then processed as described in the general procedure. The residue was subjected to

silica gel column chromatography using 80:20 hexane-ethylacetate solvent mixture to afford pure **118** as a colorless viscous liquid (188 mg, 87%).



118

IR (film) ν_{max}: 3400, 3049, 2935, 2881, 2820, 1512, 1445, 1390, 1115, 1061, 784 cm^{-1}.

^{1}H NMR: δ 2.02-2.17 (m, 2H, C$\underline{H}_2$), 2.78 (br s, 1H, O$\underline{H}$), 3.29 (s, 3H, OC$\underline{H}_3$), 3.79-3.83 (m, 2H, C$\underline{H}_2$OH), 5.12-5.16 (m, 1H, C$\underline{H}$), 7.42-7.47 (m, 3H, Ar$\underline{H}$), 7.53 (d, 1H, J = 6.8, Ar$\underline{H}$), 7.75 (d, 1H, J = 8.0, Ar$\underline{H}$), 7.82-7.85 (m, 1H, Ar$\underline{H}$), 8.13-8.16 (m, 1H, Ar$\underline{H}$).

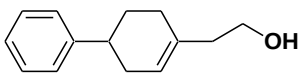
^{13}C NMR: δ 39.70, 56.81, 60.91, 81.11, 123.09, 123.76, 125.35, 125.48, 125.95, 128.04, 128.90, 130.84, 133.98, 136.94.

EIMS m/z (%) : 216 (M^+, 40), 171 (100), 155 (55), 128 (89), 115 (23), 77 (14), 63 (11), 51 (9).

4'-Phenylcyclohex-1'-enyl-1-ethanol 121 and 2-(1'-methoxy-4'-phenylcyclohexyl)-1-ethanol 122

A solution of CAN (274 mg, 0.50 mmol) in methanol (10 mL) was added dropwise to a solution of the oxetane **120** (100 mg, 0.49 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 30 min. It was then processed as described in the general procedure. The residue was subjected to silica gel column chromatography using 85:15 hexane-ethylacetate solvent mixture to afford the products **121** (62 mg, 62%) and **122** as pale yellow viscous liquids (41 mg, 35%).

4'-Phenylcyclohex-1'-enyl-1-ethanol 121



121

IR (film) ν_{max}: 3339, 2921, 2840, 1492, 1458, 764 cm^{-1}.

^{1}H NMR: δ 1.74-2.32 (m, 9H, C$\underline{H}_2$ + O$\underline{H}$), 2.71-2.74 (m, 1H, C$\underline{H}$Ph), 3.68 (t, 2H, J = 6.2, C$\underline{H}_2$OH), 5.59 (s, 1H, olefinic), 7.18-7.29 (m, 5H, Ar$\underline{H}$).

^{13}C NMR: δ 28.78, 29.95, 33.48, 39.99, 40.72, 60.29,

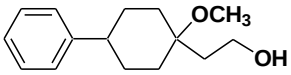
123.60, 125.98, 126.76, 128.33, 134.09, 146.78.

EIMS m/z (%): 202 (M^+-H_2O, 92), 184 (21), 169 (9), 156 (58), 128 (31), 115 (53), 104 (100), 91 (95), 65 (40), 51 (38).

2-(1'-Methoxy-4'-phenylcyclohexyl)-1-ethanol <u>122</u>

IR (film) ν_{max}: 3400, 3022, 2935, 2867, 1458, 757 cm^{-1}.

^{1}H NMR: δ 1.35-2.07 (m, 11H, C<u>H</u>$_2$+O<u>H</u>), 2.47-2.58 (m, 1H, C<u>H</u>Ph), 3.23 (s, 0.75H, OC<u>H</u>$_3$), 3.27 (s, 2.25H, OC<u>H</u>$_3$), 3.79 (t, 2H, J = 6.0, C<u>H</u>$_2$OH), 7.16-7.29 (m, 5H, Ar<u>H</u>).



<u>122</u>

^{13}C NMR: δ 28.85, 30.78, 33.50, 33.57, 34.30, 37.97, 43.64, 43.93, 48.11, 48.38, 58.73, 58.99, 74.49, 77.51, 125.96, 126.15, 126.69, 126.79, 128.28, 128.37, 145.97, 147.03.

EIMS m/z (%): 234 (M^+, 0.2), 202 (100), 184 (28), 169 (9), 156 (70), 129 (35), 115 (65), 104 (92).

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Chapter 4

An Efficient Method for the Preparation of Dimethyl, Diethyl and Diallyl Acetals of Aromatic Aldehydes Mediated by Cerium(IV) Ammonium Nitrate

4.1 Introduction

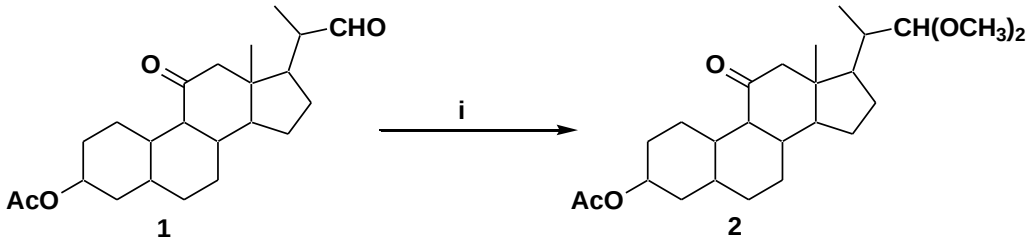
When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites have to be temporarily blocked. For this, the organic chemist invariably resorts to the use of suitable protective groups.[1] A protective group must fulfill a number of requirements. It must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available and preferably non-toxic reagents that do not attack the regenerated functional group. The protective group should have a minimum of additional functionality to avoid further sites of reaction. All things considered, there is not one protective group that is perfect. Protective groups play a crucial role in the total synthesis of almost all natural and unnatural products. Thus, the development of new methods for functional group protection and deprotection continues.

The five major functional groups that require protective groups during organic transformations include the following groups: -OH, -NH, -SH, -COOH and the >C=O group. As the present chapter deals with the protection of the >C=O group, a brief insight into some of the important methods available in the literature for the protection of the carbonyl group is presented in the following section.

4.2 Protection for the Carbonyl Group

During a synthetic sequence, a carbonyl group may have to be protected against attack by various reagents such as strong or moderately strong nucleophiles including organometallic reagents; acidic, basic, catalytic or hydride reducing agents and some oxidants. The most useful protective groups are the acyclic and cyclic acetals, and acyclic or cyclic thioacetals. The protective group is introduced by treating the carbonyl compound with an alcohol, diol, thiol or dithiol in the presence of either a protic acid or a Lewis acid.

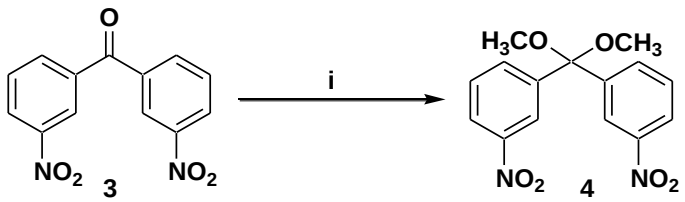
Dimethyl acetals of aldehydes are most commonly prepared by the reaction of the aldehyde with dry HCl in methanol under reflux conditions (Scheme 1).[2]



i) CH_3OH, dry HCl, reflux, 2 min

Scheme 1

While dialkyl and arylalkyl ketones can be easily converted to their acetals, diaryl ketones yield acetals often with much difficulty. However, acetals of diaryl ketones have been prepared in high yield by treatment with an alcohol and the corresponding trialkyl orthoformate in the presence of catalytic amount of trifluoromethane sulfonic acid with nitromethane as the solvent (Scheme 2).[3]

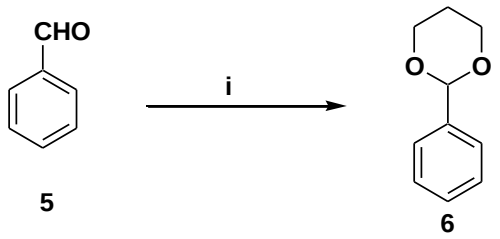


i) CH_3OH, $(CH_3O)_3CH$, CH_3NO_2, CF_3SO_3H, 95%

Scheme 2

Various types of carbonyl compounds can be converted to the corresponding 1,3-dioxolanes in the presence of ethyl orthoformate, 1,3-propanediol and a catalytic amount of NBS *via* an *in situ* acetal exchange process.

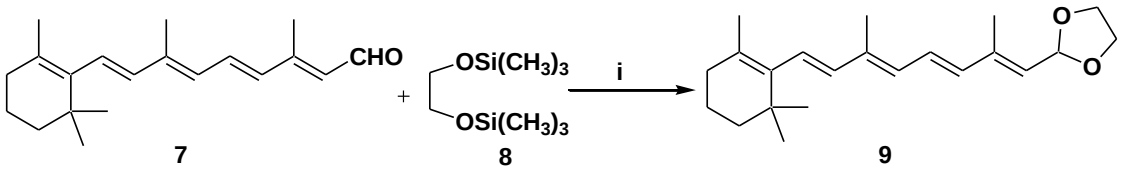
Acid sensitive substrates such as THP ethers remain intact under these conditions (Scheme 3).[4]



i) $HO(CH)_3OH$ (3 eq.), $(CH_3CH_2O)_3CH$ (1 eq.), NBS (1 mol%), CH_3OH (2 eq.), CH_2Cl_2, RT, 6 h, 95%

Scheme 3

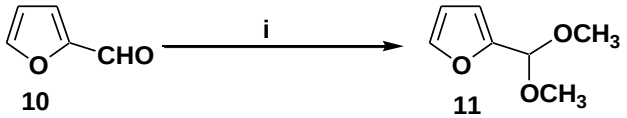
The 1,3-dioxolanation of α,β-unsaturated aldehydes with 1,2-bis((trimethyl silyl)oxy)ethane in the presence of trimethylsilyl trifluoro methanesulfonate as catalyst has been reported by Hwu *et al*. These silylated reagents readily acetalize aliphatic, highly conjugated aliphatic and aromatic α,β-unsaturated aldehydes (Scheme 4).[5]



i) $(CH_3)_3SiOTf$, CH_2Cl_2, -78 °C, 74 %

Scheme 4

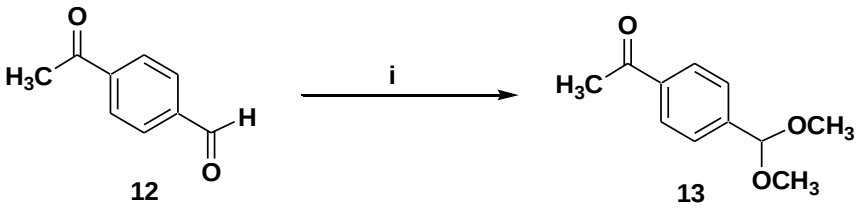
The acetalization of carbonyl compounds with methanol in the presence of cation-exchanged montmorillonite (Ce^{3+}-Mont) was found to be an effective catalyst for substrate-selective acetalization. Cyclohexanones, benzaldehydes and acid sensitive 2-furancarboxaldehyde were converted in good yields to the corresponding acetals in methanol in the presence of Ce^{3+}-mont (Scheme 5).[6]



i) Ce^{3+}-mont, CH_3OH, 25 °C, 30 min, 76%

Scheme 5

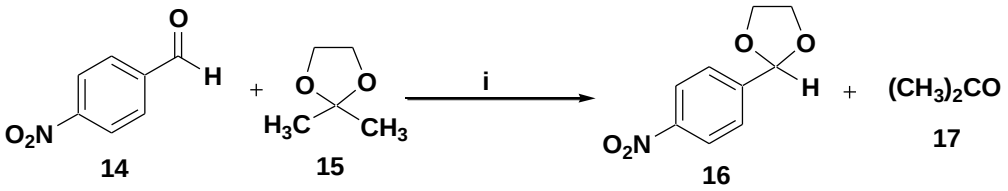
In substrates containing both aldehyde and ketone functionalities, the aldehyde can be chemoselectively converted to its dimethyl acetal under the above conditions (Scheme 6).[6]



i) Ce^{3+}-mont, CH_3OH, 25 °C, 30 min, 76%

Scheme 6

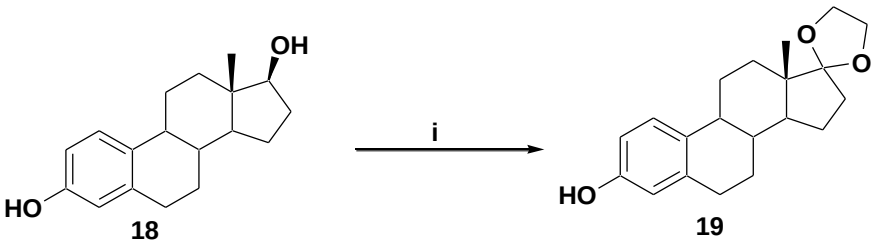
The protection of aldehydes and ketones as acetals or dioxolanes catalyzed by KSF clay or PTSA has been achieved in the presence of trialkyl orthoformates, 1,2-ethanediol or 2,2-dimethyl-1,3-dioxolane without solvent under microwave irradiation (Scheme 7).[7]



i) KSF clay, MW, 98%

Scheme 7

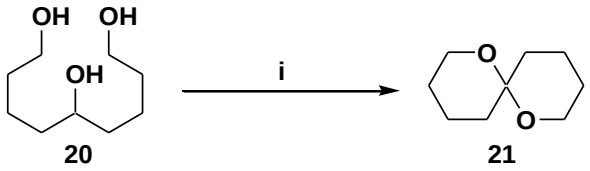
Secondary alcohols are oxidized preferentially by DMSO and the catalyst $ReOCl_3(PPh_3)_2$ in the presence of ethylene glycol and refluxing toluene, producing the corresponding acetals. The reactions are rapid and proceed in good to excellent yields (Scheme 8).[8]



i) 5% $ReOCl_3(PPh_3)_2$, DMSO (1.2 eq.), $HO(CH_2)_2OH$ (8 eq.)

Scheme 8

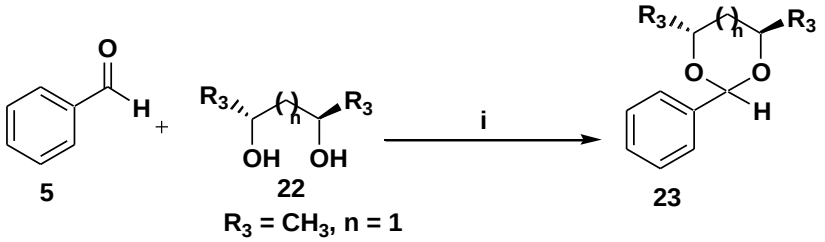
Further evidence of the synthetic utility of this method was illustrated by the one-step synthesis of the olive fly pheromone **21** by directly oxidizing 1,5,9-nonane triol **20** (Scheme 9).[8]



i) 5% $ReOCl_3(PPh_3)_2$, 5% 2,4,6-collidine, DMSO (1.2 eq.), HO-$(CH_2)_2$-OH

Scheme 9

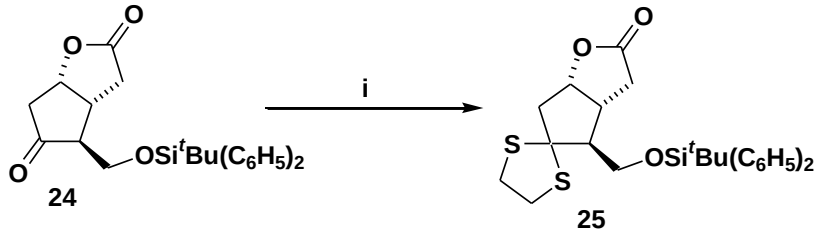
The direct synthesis of chiral acetals from carbonyl compounds and chiral diols has been accomplished by the use of catalytic amount of $Sc(OTf)_3$ (Scheme 10).[9]



i) $Sc(OTf)_3$ (cat.), benzene, RT, 2 days, 93%

Scheme 10

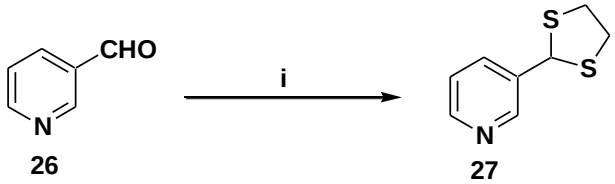
The reaction of a variety of ketones with ethane-1,2-dithiol to form thioacetals proceeds very efficiently and under mild conditions using magnesium or zinc triflate as catalyst (Scheme 11).[10]



i) $HS(CH_2)_2SH$, $Zn(OTf)_2$, CH_2Cl_2, 23 °C, 3.5 h, then reflux for 2 h, 85%

Scheme 11

Silica gel treated with thionyl chloride was found to be an effective as well as highly selective catalyst for thioacetalization of aldehydes (Scheme 12).[11]

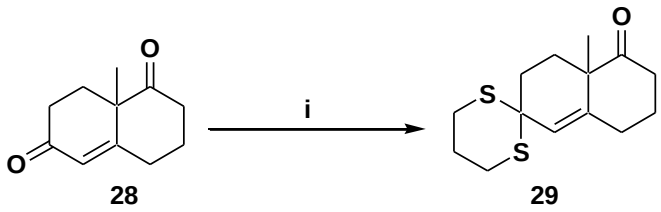


i) $HS(CH_2)_2SH$, $SOCl_2$-SiO_2, dry benzene, 20 °C, 5 h, 72%

Scheme 12

Under the same conditions, ketones were more slowly acetalized. This difference in reactivity between aldehydes and ketones was successfully utilized for thioacetalization of aldehydes in the presence of ketones.

When aldehydes were allowed to react with alkane thiols or alkane dithiols in 1,2-dichloroethane for 2-3 h at room temperature in the presence of tellurium chloride, thioacetalization proceeded smoothly giving the corresponding dithioacetals in good yields. Under these conditions, aliphatic ketones were dithioacetalized readily, but aromatic ketones were recovered almost intact. When the Wieland-Miescher ketone **28** was reacted with 1,3-propanedithiol under the above conditions, the α,β-unsaturated carbonyl in **28** was selectively dithio acetalized to give the product **29** in 68% yield (Scheme 13).[12]



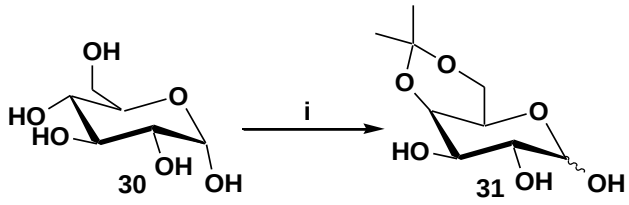
28 **29**

i) $HS(CH_2)_3SH$, $TeCl_4$, $Cl(CH_2)_2Cl$, RT, 68%

Scheme 13

4.3 The Present Work

In addition to the extensive use of Cerium(IV) ammonium Nitrate (CAN) in a variety of oxidative transformations, of late, it has also been used as a highly efficient reagent in deprotection sequences (for details, see **Chapter 1**, **p. 19**, **Section 1.7**). To date, however there is only one report available in the literature involving its use in the formation of acetals. This involves the acetonation of carbohydrates in the presence of dimethoxy propane and CAN in anhydrous DMF (Scheme 13).[13]



30 **31**

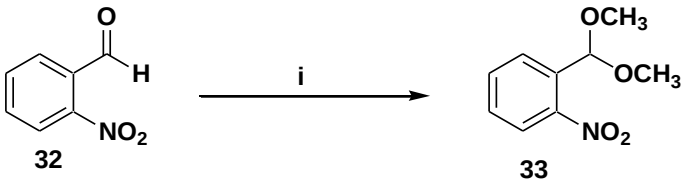
i) CAN, DMP, anhydrous DMF, RT, 1 h, 89%

Scheme 14

In the context of our sustained interest in the area of CAN mediated carbon-carbon bond forming reactions, we were intrigued by the possibility of CAN mediated oxidative addition of aldehydes to alkenes. However, preliminary experiments showed that no addition occurred and instead the aldehyde was transformed to the dimethylacetal. Impressed by the efficiency of the acetalization, we decided to pursue this reaction in some detail. The results of our investigations are discussed below.

4.4 Results and Discussion

In a pilot experiment, when 2-nitrobenzaldehyde **32** was refluxed with CAN, in the presence of Na_2CO_3, in dry methanol it afforded the dimethylacetal **33** in 97% yield (Scheme 15).



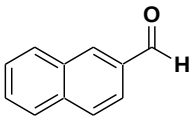
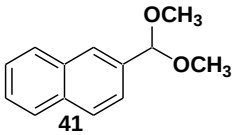
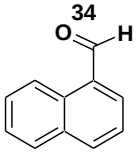
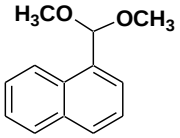
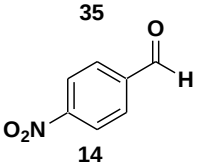
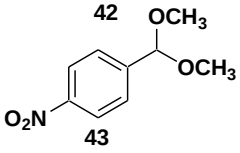
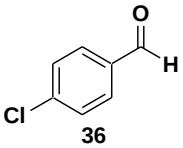
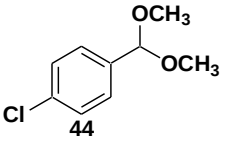
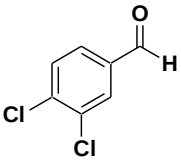
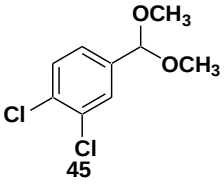
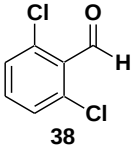
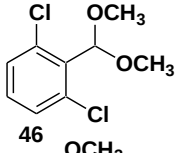
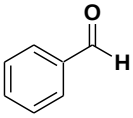
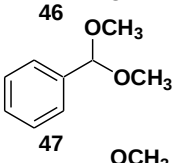
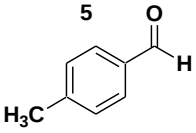
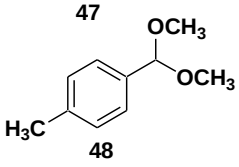
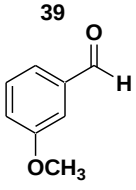
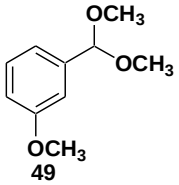
i) CAN (1.2 eq.), Na_2CO_3 (2.0 eq.), dry CH_3OH, Reflux, 45 min, 97%

Scheme 15

The acetal **33** was characterized on the basis of spectroscopic data. In the ^{1}H NMR spectrum, the six protons of the two methoxy groups resonated together at δ 3.39. The acetal methine proton flanked by the two methoxy groups resonated characteristically at δ 5.91. In the ^{13}C NMR spectrum, the resonance signal at δ 54.32 was attributed to the methoxy carbon. The acetal carbon resonated characteristically at δ 99.69. All other signals were in accordance with the assigned structure.

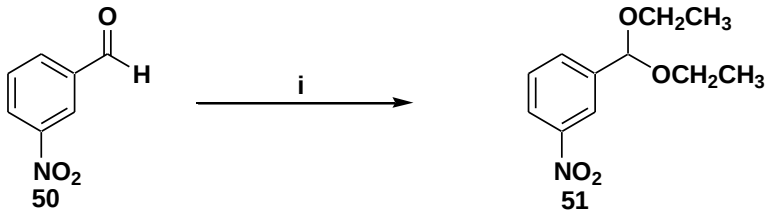
Subsequently it was found that a number of aromatic aldehydes can be converted to their corresponding dimethyl acetals in good to excellent yields and these results are given in Table 1.

Table 1: Acetalization of aromatic aldehydes in the presence of CAN

Entry	Aldehyde	Acetal	Yield (%)
1	 **34**	 **41**	94
2	 **35**	 **42**	90
3	 **14**	 **43**	94
4	 **36**	 **44**	83
5	 **37**	 **45**	64
6	 **38**	 **46**	63
7	 **5**	 **47**	72
8	 **39**	 **48**	68
9	 **40**	 **49**	61

Reaction Conditions: CAN, dry MeOH, Reflux, 45 min.

Similarly, when an ethanolic solution of CAN was treated with a solution of 3-nitrobenzaldehyde **50** and Na_2CO_3 in ethanol under reflux conditions, it afforded the diethyl acetal **51** in 68% yield (Scheme 16).

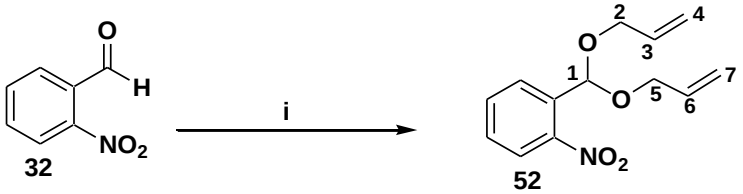


i) CAN (1.2 eq.), Na_2CO_3, dry CH_3CH_2OH, 70 °C, 45 min, 68%

Scheme 16

The diethyl acetal **51** was characterized with the aid of spectroscopic data. In the ^{1}H NMR spectrum, the six methyl protons resonated as a triplet at δ 1.26 (J = 7.0) while the four methylene protons resonated as a multiplet centered at δ 3.59. The acetal proton resonated characteristically at δ 5.58. In the ^{13}C NMR, the signals at δ 14.97 and 60.93 were attributed to the methyl and methylene carbons of the ethoxy groups. The acetal carbon resonated characteristically at δ 99.71.

Interestingly it was found that diallyl acetals could be synthesized by employing allyl alcohol as the reaction medium. Thus, when 2-nitrobenzaldehyde **32** and Na_2CO_3 in allyl alcohol were treated with a solution of CAN in allylalcohol under reflux conditions, the corresponding diallyl acetal **52** was obtained in 76% yield (Scheme 17).



i) CAN (1.2 eq.), Na_2CO_3, allylalcohol, 70 °C, 45 min, 76%

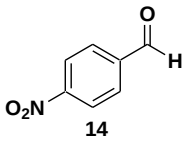
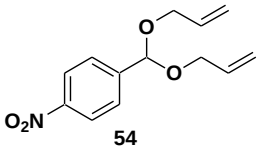
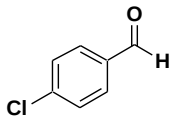
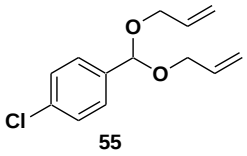
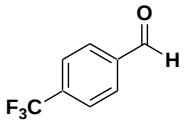
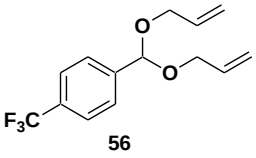
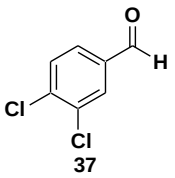
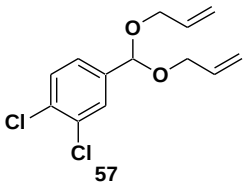
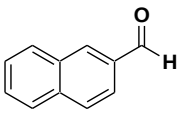
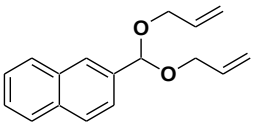
Scheme 17

The diallyl acetal **52** was characterized with the aid of conventional spectroscopic tools. In the ^{1}H NMR spectrum, the four methylene protons adjacent to the oxygen atoms resonated as a multiplet between δ 4.06-4.17. The olefinic protons on C-4 and C-7 *cis* to the olefinic methine protons on C-3 and C-6 resonated as a doublet of doublet at δ 5.19 (J_1 = 10.4, J_2 = 1.2), while the other two olefinic protons on C-4 an C-7 *trans* to the protons on C-3 and C-6 resonated as a doublet of doublet at δ 5.30 (J_1 = 17.2, J_2 = 1.5). The olefinic protons on C-3 and C-6 furnished a multiplet centered at δ 5.91. The acetal proton resonated as a

singlet at δ 6.16. In the ^{13}C NMR spectrum, the acetal carbon resonated at δ 97.23. All other signals were in agreement with the proposed structure.

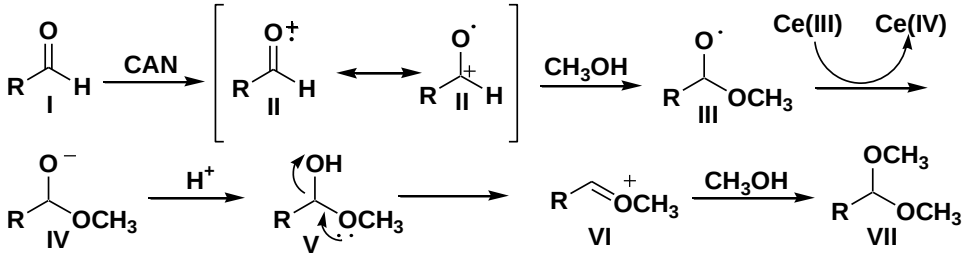
The reaction was found to be general for aromatic aldehydes and the results are given in Table 2.

Table 2: Diallyl acetals of aromatic aldehydes in the presence of CAN

Entry	Aldehyde	Acetal	Yield (%)
1	 14	 54	61
2	 36	 55	63
3	 53	 56	64
4	 37	 57	81
5	 35	 58	40

Reaction Conditions: CAN, Allyl alcohol, Reflux, 45 min.

Subsequently, it was found that the acetalization works with catalytic amounts of CAN. A mechanistic rationalization for the formation of the acetals is shown below. (Scheme 18).



Scheme 18

The aldehyde **I** is initially oxidized by Ce(IV) to the radical cation **II**. The cationic center in **II** is quenched by methanol to afford the radical intermediate **III**. The alkoxy radical **III** gets reduced to the anion **IV** with concomitant re-oxidation of Ce(III) to Ce(IV) making the cycle catalytic. The anion **IV** picks up a proton, resulting in the formation of the hemiacetal **V** which is then converted to the acetal **VII**.

4.4 Conclusion

In conclusion, we have developed a novel and efficient procedure for the preparation of dimethyl, diethyl and diallyl acetals of aromatic aldehydes under mild conditions.

4.5 Experimental

General information about the experiments is given in **Chapter 2, p. 56, Section 2.8**.

Preparation of Dimethyl and Diethyl Acetals of Aromatic Aldehydes in the Presence of CAN

General Procedure: A solution of the aldehyde (1.00 mmol) and Na_2CO_3 (2.00 mmol) in 10 mL of the appropriate solvent (dry methanol, dry ethanol) was taken in a two necked round bottom flask equipped with a reflux condenser and a pressure equalizing funnel containing a solution of CAN (1.10 mmol) in the same solvent (10 mL). To the refluxing solution of the aldehyde and Na_2CO_3, the CAN solution was added dropwise and the refluxing continued for 45 minutes during which time the reaction mixture becomes pale yellow. The solvent was then removed *in vacuo.* The crude residue was diluted with water (100 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The residue obtained after removal of the solvent by distillation was purified by silica gel column chromatography to afford the acetals as viscous liquids.

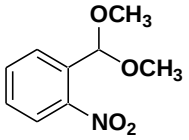
Preparation of Diallyl Acetals of Aromatic Aldehydes in the Presence of CAN

General Procedure: A solution of the aldehyde (1.00 mmol) and Na_2CO_3 (2.00 mmol) in allyl alcohol (5 mL) was taken in a two necked round bottom flask

equipped with a reflux condenser and a pressure equalizing funnel containing a solution of CAN (2.00 mmol) in the same solvent (10 mL). To the refluxing solution of the aldehyde and Na_2CO_3, the CAN solution was added dropwise and the refluxing continued for 45 minutes during which time the reaction mixture becomes pale yellow. The allyl alcohol was then removed *in vacuo*. The crude residue was diluted with water (100 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The residue obtained after removal of the solvent by distillation was purified by silica gel column chromatography to afford the diallyl acetals as viscous liquids.

2-Nitrobenzaldehyde dimethylacetal 33

To a mixture of 2-nitrobenzaldehyde **32** (151 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of CAN (603 mg, 1.10 mmol) in dry methanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:2 hexane-ethylacetate mixture to afford **33** as a pale yellow viscous liquid (191 mg, 97%).



33

IR (film) ν_{max}: 2995, 2938, 2834, 1533, 1361, 1200, 1107, 1074, 985, 786, 740 cm^{-1}.

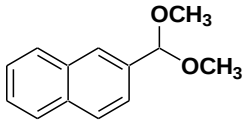
^{1}H NMR: δ 3.39 (s, 3H, OC<u>H</u>$_3$), 5.91 (s, 1H, C<u>H</u>), 7.47 (t, 1H, *J* = 7.6, Ar<u>H</u>), 7.59 (t, 1H, *J* = 7.4, ArH), 7.79 (t, 2H, *J* = 7.6, Ar<u>H</u>).

^{13}C NMR: δ 54.32, 99.69, 124.09, 128.14, 129.29, 132.27, 132.65, 149.04.

2-Naphthaldehyde dimethylacetal 41

To a mixture of 2-naphthaldehyde **34** (156 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of CAN (603 mg, 1.10 mmol) in dry methanol (10 mL). The reaction mixture was

refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:2 hexane-ethylacetate mixture to afford **41** as a pale yellow viscous liquid (190 mg, 94%).



41

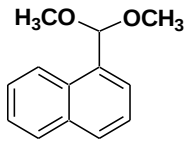
IR (film) ν_{max}: 3062, 2937, 2831, 1513, 1345, 1176, 1095, 1052, 989 cm^{-1}.

^{1}H NMR: δ 3.32 (s, 6H, OC$\underline{H}_3$), 5.51 (s, 1H, C$\underline{H}$), 7.40-7.43 (m, 2H, Ar$\underline{H}$), 7.51 (d, 1H, *J* = 8.4, Ar$\underline{H}$), 7.52-7.86 (m, 3H, Ar$\underline{H}$).

^{13}C NMR: δ 52.40, 102.91, 124.37, 125.97, 126.08, 127.59, 127.91, 128.23, 132.98, 133.37, 135.45.

1-Naphthaldehye dimethylacetal 42

To a mixture of 1-naphthaldehyde **35** (151 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of CAN (603 mg, 1.10 mmol) in dry methanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:2 hexane ethylacetate-mixture to afford **42** as a pale yellow viscous liquid (181 mg, 90%).



42

IR (film) ν_{max}: 3062, 2937, 2831, 1513, 1345, 1176, 1095, 1052, 989 cm^{-1}.

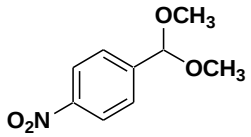
^{1}H NMR: δ 3.32 (s, 6H, OC$\underline{H}_3$), 5.51 (s, 1H, C$\underline{H}$), 7.40-7.43 (m, 2H, Ar$\underline{H}$), 7.51(d,1H, *J* = 8.4, Ar$\underline{H}$), 7.52-7.86 (m, 3H, Ar$\underline{H}$), 8.25 (d, 1H, *J* = 8.0, Ar$\underline{H}$)

^{13}C NMR: δ 52.40, 102.91, 124.37, 125.97, 126.08, 127.59, 127.91, 128.23, 132.98, 133.37, 135.45.

4-Nitrobenzaldehyde dimethylacetal 43

To a mixture of 4-nitrobenzaldehyde **14** (151 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of

CAN (603 mg, 1.10 mmol) in dry methanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:2 hexane-ethylacetate mixture to afford **43** as a pale yellow viscous liquid (185 mg, 94%).



43

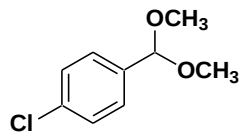
IR (film) ν_{max}: 3079, 2938, 1606, 1524, 1346, 1204, 1101, 985 cm^{-1}.

^{1}H NMR: δ 3.33 (s, 6H, OC<u>H</u>$_3$), 5.48 (s, 1H, C<u>H</u>), 7.64 (d, 2H, J = 8.4, Ar<u>H</u>), 8.21 (d, 2H, J = 8.7, Ar<u>H</u>).

^{13}C NMR: δ 52.43, 101.20, 123.29, 127.75, 144.98, 147.92.

4-Chlorobenzaldehyde dimethylacetal <u>44</u>

To a mixture of 4-chlorobenzaldehyde **36** (140 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of CAN (603 mg, 1.1 mmol) in dry methanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:1 hexane-ethylacetate mixture to afford **44** as a colorless viscous liquid (154 mg, 83%).



44

IR (film) ν_{max}: 2943, 2831, 1595, 1489, 1351, 1201, 1095, 1058, 977 cm^{-1}.

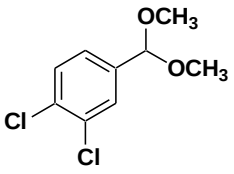
^{1}H NMR: δ 3.27 (s, 6H, OC<u>H</u>$_3$), 5.35 (s, 1H, C<u>H</u>), 7.29-7.37 (m, 4H, Ar<u>H</u>).

^{13}C NMR: δ 52.23, 102.01, 128.18, 128.29, 134.20.

3,4-Dichlorobenzaldehyde dimethylacetal <u>45</u>

To a mixture of 3,4-dichlorobenzaldehyde **37** (151 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of CAN (603 mg, 1.10 mmol) in dry methanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described

in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:1 hexane-ethylacetate mixture to afford **45** as a colorless viscous liquid (141 mg, 64 %).



45

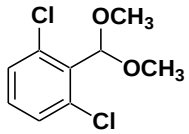
IR (film) ν_{max}: 3002, 2942, 2840, 1472, 1351, 1202, 1108, 1061, 987, 825 cm^{-1}.

^{1}H NMR: δ 3.29 (s, 6H, OC<u>H</u>$_3$), 5.34 (s, 1H, C<u>H</u>), 7.26 (dd, 1H, *J* = 8.2, *J* = 1.7, Ar<u>H</u>), 7.42 (d, 1H, *J* = 8.3, Ar<u>H</u>), 7.54 (s, 1H, Ar<u>H</u>).

^{13}C NMR: δ 52.34, 101.23, 126.12, 128.97, 130.17, 132.49, 138.41.

2,6-Dichlorobenzaldehyde dimethylacetal <u>46</u>

To a mixture of 2,6-dichlorobenzaldehyde **38** (175 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of CAN (603 mg, 1.10 mmol) in dry methanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:1 hexane-ethylacetate mixture to afford **46** as a colorless viscous liquid (139 mg, 63%).



46

IR (film) ν_{max}: 2993, 2931, 2831, 1576, 1432, 1114 cm^{-1}.

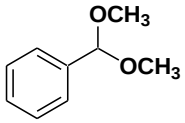
^{1}H NMR: δ 3.44 (s, 6H, OC<u>H</u>$_3$), 5.82 (s, 1H, C<u>H</u>), 7.11-7.27 (m, 3H, Ar<u>H</u>).

^{13}C NMR: δ 55.35, 103.55, 128.95, 129.56, 132.57, 134.72.

Benzaldehyde dimethylacetal <u>47</u>

To a mixture of benzaldehyde **5** (106 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of CAN (603 mg, 1.10 mmol) in dry methanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column

chromatography using 98:1 hexane-ethylacetate mixture to afford **47** as a colorless liquid (109 mg, 72%).



47

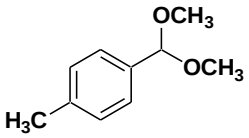
IR (film) ν_{max}: 2993, 2943, 2837, 1457, 1357, 1201, 1168, 1058, 977 cm^{-1}.

^{1}H NMR: δ 3.30 (s, 6H, OC<u>H</u>$_3$), 5.38 (s, 1H, C<u>H</u>), 7.26-7.36 (m, 3H, Ar<u>H</u>), 7.41-7.43 (m, 2H, Ar<u>H</u>).

^{13}C NMR: δ 52.36, 102.84, 126.68, 128.08, 128.32, 137.99.

4-Methylbenzaldehyde dimethylacetal <u>48</u>

To a mixture of 4-methylbenzaldehyde **39** (120 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of CAN (603 mg, 1.10 mmol) in dry methanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:1 hexane-ethylacetate mixture to afford **48** as a colorless viscous liquid (113 mg, 68%).



<u>48</u>

IR (film) ν_{max}: 2984, 2932, 2827, 1459, 1362, 1212, 1110, 939 cm^{-1}.

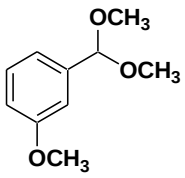
^{1}H NMR: δ 2.35 (s, 3H, ArC<u>H</u>$_3$), 3.30 (s, 6H, OC<u>H</u>$_3$), 5.35 (s, 1H, C<u>H</u>), 7.15 (d, 2H, J = 7.7, Ar<u>H</u>), 7.31 (d, 2H, J = 7.8, Ar<u>H</u>).

^{13}C NMR: δ 21.22, 52.38, 102.97, 126.64, 128.81, 135.10, 137.95.

3-Methoxybenzaldehyde dimethylacetal <u>49</u>

To a mixture of 3-methoxybenzaldehyde **40** (136 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry methanol, was added dropwise a solution of CAN (603 mg, 1.10 mmol) in dry methanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel

column chromatography using 98:2 hexane-ethylacetate mixture to afford **49** as a colorless viscous liquid (111 mg, 61%).



49

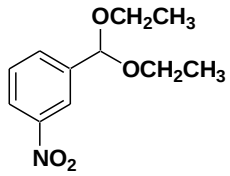
IR (film) ν_{max}: 2993, 2937, 2831, 1601, 1489, 1445, 1357, 1264, 1189, 1059, 983 cm^{-1}.

^{1}H NMR: δ 3.31 (s, 6H, OC<u>H</u>$_3$), 3.80 (s, 3H, ArOC<u>H</u>$_3$), 5.35 (s, 1H, CH), 6.87 (d, 1H, ArH), 6.99 (s, 1H, ArH), 7.02 (d, 1H, ArH), 7.25 (t, 1H, *J* = 7.6, ArH).

^{13}C NMR: δ 52.46, 55.29, 102.81, 111.94, 114.26, 119.06, 129.09, 139.62, 159.60.

3-Nitrobenzaldehyde diethylacetal <u>51</u>

To a mixture of 3-nitrobenzaldehyde **50** (151 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL dry ethanol, was added dropwise a solution of CAN (603 mg, 1.10 mmol) in dry ethanol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:2 hexane-ethylacetate mixture to afford **51** as a pale yellow viscous liquid (144 mg, 68%).



<u>51</u>

IR (film) ν_{max}: 2980, 2881, 1526, 1339, 1208, 1120, 1064, 815, 727 cm^{-1}.

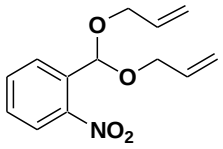
^{1}H NMR: δ 1.26 (t, 6H, *J* = 7.0, C<u>H</u>$_3$), 3.59 (m, 4H, C<u>H</u>$_2$), 5.58 (s, 1H, C<u>H</u>), 7.55 (t, 1H, *J* = 7.9, Ar<u>H</u>), 7.82 (d, 1H, *J* = 7.5, Ar<u>H</u>), 8.16 (d, 1H, *J* = 7.9, Ar<u>H</u>), 8.33 (s, 1H, Ar<u>H</u>).

^{13}C NMR: δ 14.97, 60.93, 95.96, 99.71, 121.70, 122.96, 128.92, 132.63, 141.33, 148.13.

2-Nitrobenzaldehyde diallylacetal <u>52</u>

To a mixture of 2-nitrobenzaldehyde **32** (151 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL allyl alcohol, was added dropwise a solution of CAN (603 mg, 2.00 mmol) in allyl alcohol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general

experimental procedure. The residue was then subjected to silica gel column chromatography using 98:2 hexane-ethylacetate mixture to afford **52** as a pale yellow viscous liquid (189 mg, 76%).



52

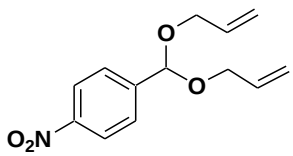
IR (film) ν_{max}: 3083, 2921, 2874, 1526, 1431, 1357, 1115, 1054, 993, 791 cm^{-1}.

^{1}H NMR: δ 4.06-4.17 (m, 4H, OC<u>H</u>$_2$), 5.19 (dd, 2H, J_1 = 10.4, J_2 = 1.2, =C<u>H</u>$_2$), 5.30 (dd, 2H, J_1 = 17.2, J_2 = 1.5, =C<u>H</u>$_2$), 5.85-5.98 (m, 2H, =C<u>H</u>), 6.16 (s, 1H, C<u>H</u>), 7.48 (t, 1H, J = 7.7, ArH), 7.61 (t, 1H, J = 7.5, ArH), 7.81 (d, 1H, J = 7.9, ArH), 7.86 (d, 1H, J = 7.3, ArH).

^{13}C NMR: δ 68.17, 97.23, 117.35, 124.11, 128.24, 129.25, 132.33, 133.14, 133.76.

4-Nitrobenzaldehyde diallylacetal <u>54</u>

To a mixture of 4-nitrobenzaldehyde **14** (151 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL allyl alcohol, was added dropwise a solution of CAN (603 mg, 2.00 mmol) in allyl alcohol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:2 hexane-ethylacetate mixture to afford **54** as a pale yellow viscous liquid (143 mg, 61%).



54

IR (film) ν_{max}: 3083, 2921, 2867, 1600, 1533, 1344, 1202, 1047, 933, 852, 724 cm^{-1}.

^{1}H NMR: δ 4.02-4.07 (m, 4H, OC<u>H</u>$_2$), 5.20 (dd, 2H, J = 10.3, J = 1.2, =C<u>H</u>$_2$), 5.32 (dd, 2H, J = 17.1, J = 1.5, =C<u>H</u>$_2$), 5.70 (s, 1H, C<u>H</u>), 5.85-5.96 (m, 2H, =C<u>H</u>), 7.68 (d, 2H, J = 8.6, Ar<u>H</u>), 8.22 (d, 2H, J = 8.8, Ar<u>H</u>).

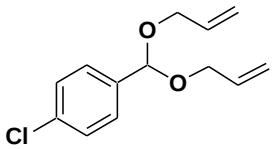
^{13}C NMR: δ 66.20, 98.96, 117.24, 123.42, 127.81, 133.88, 145.38, 148.05.

EIMS m/z (%) : 250 (M^++1-C_3H_6, 15), 192 (100), 150 (100), 134 (6), 115 (17), 105 (55), 77 (95), 51 (97).

HRMS (FAB) Calcd for $C_{13}H_{15}NO_4$+H^+: 250.1079. Found: 250.1077.

4-Chlorobenzaldehyde diallylacetal 55

To a mixture of 4-chlorobenzaldehyde **36** (140 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL allyl alcohol, was added dropwise a solution of CAN (603 mg, 2.00 mmol) in allyl alcohol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:1 hexane-ethylacetate mixture to afford **55** as a colorless viscous liquid (149 mg, 63%).



55

IR (film) ν_{max}: 3083, 2921, 2861, 1647, 1600, 1492, 1404, 1337, 1216, 1094, 1047, 933 cm^{-1}.

^{1}H NMR: δ 4.01-4.03 (m, 4H, OC$\underline{H}_2$), 5.17 (dd, 2H, J = 10.3, J = 1.2, =C$\underline{H}_2$), 5.29 (dd, 2H, J = 17.2, J = 1.5, =C$\underline{H}_2$), 5.60 (s, 1H, C$\underline{H}$), 5.84-5.97 (m, 2H, =C$\underline{H}$), 7.32 (d, 2H, J = 8.5, Ar$\underline{H}$), 7.43 (d, 2H, J = 8.3, Ar$\underline{H}$).

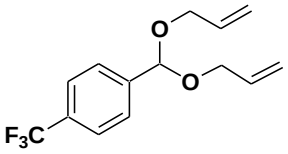
^{13}C NMR: δ 65.95, 99.58, 116.88, 128.23, 128.42, 134. 33, 136.99.

EIMS m/z (%) : 237 (M+-1, 0.2), 197 (8), 181 (100), 153 (9), 139 (100), 125 (77), 111 (81), 89 (28), 77 (97), 51 (81).

4-Trifluromethylbenzaldehyde diallylacetal 56

To a mixture of 4-trifluoromethylbenzaldehyde **53** (174 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL allyl alcohol, was added dropwise a solution of CAN (603 mg, 2.100 mmol) in allyl alcohol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel

column chromatography using 98:1 hexane-ethylacetate mixture to afford **56** as a colorless viscous liquid (175 mg, 64%).



56

IR (film) ν_{max}: 3083, 2915, 2867, 1654, 1620, 1418, 1330, 1169, 1135, 1067, 1020, 933 cm^{-1}.

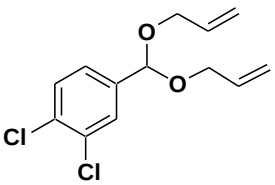
^{1}H NMR: δ 4.04-4.05 (m, 4H, OC$\underline{H}_2$), 5.19 (dd, 2H, J = 10.3, J = 1.2, =C$\underline{H}_2$), 5.31 (dd, 2H, J = 17.2, J = 1.5, =C$\underline{H}_2$), 5.67 (s, 1H, C$\underline{H}$), 5.85-5.98 (m, 2H, =C$\underline{H}$), 7.62 (s, 4H, Ar$\underline{H}$).

^{13}C NMR: δ 66.10, 99.44, 117.04, 125.19, 127.25, 134. 18, 142.38.

EIMS m/z (%) : 271 (M+-1, 0.2), 231 (12), 215 (100), 173 (100), 155 (12), 145 (95), 127 (84), 107 (8), 95 (25), 77 (31), 69 (18), 57 (40).

3,4-Dichlorobenzaldehyde diallylacetal 57

To a mixture of 3,4-dichlorobenzaldehyde **37** (174 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL allyl alcohol, was added dropwise a solution of CAN (603 mg, 2.00 mmol) in allyl alcohol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:2 hexane-ethylacetate mixture to afford **57** as a colorless viscous liquid (222 mg, 81%).



57

IR (film) ν_{max}: 3083, 2935, 2861, 1479, 1330, 1202, 1094, 1040, 926 cm^{-1}.

^{1}H NMR: δ 4.01-4.03 (m, 4H, OC$\underline{H}_2$), 5.18 (dd, 2H, J = 10.3, J = 1.2, =C$\underline{H}_2$), 5.30 (dd, 2H, J = 17.2, J = 1.5, =C$\underline{H}_2$), 5.57 (s, 1H, C$\underline{H}$), 5.84-5.96 (m, 2H, =C$\underline{H}$), 7.31 (d, 1H, J = 8.1, Ar$\underline{H}$), 7.42 (d, 1H, J = 8.2, Ar$\underline{H}$), 7.58 (s, 1H, ArH).

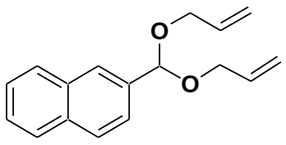
^{13}C NMR: δ 65.99, 98.77, 117.03, 126.11, 128.92, 130.20, 134.04, 138.76.

EIMS m/z (%) : 237 (M^+-C_2H_4, 0.2), 173 (100), 147 (50), 145 (76), 111 (46), 86 (24), 75 (96), 61 (17), 51 (15).

2-Naphthaldehyde diallylacetal 58

To a mixture of 2-naphthaldehyde **38** (156 mg, 1.00 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 5 mL allyl alcohol, was added dropwise a solution of CAN (603 mg, 2.00 mmol) in allyl alcohol (10 mL). The reaction mixture was refluxed at 70 °C for 45 minutes. It was then processed as described in the general experimental procedure. The residue was then subjected to silica gel column chromatography using 98:2 hexane-ethylacetate mixture to afford **58** as a colorless viscous liquid (101 mg, 40%).

IR (film) ν_{max}: 3063, 2928, 2867, 1694, 1654, 1330, 1175, 128, 1047, 926 cm^{-1}.



58

^{1}H NMR: δ 4.07-4.09 (m, 4H, OC<u>H</u>$_2$), 5.16 (dd, 2H, J = 10.4, J = 0.9, =C<u>H</u>$_2$), 5.32 (dd, 2H, J = 17.2, J = 1.3, =C<u>H</u>$_2$), 5.77 (s, 1H, C<u>H</u>), 5.88-6.00 (m, 2H, =C<u>H</u>), 7.43-7.46 (m, 2H, Ar<u>H</u>), 7.58 (d, 1H, J = 8.5, Ar<u>H</u>), 7.78-7.84 (m, 3H, Ar<u>H</u>), 7.96 (s, 1H, Ar<u>H</u>).

^{13}C NMR: δ 66.03, 100.35, 116.77, 124.50, 126.06, 126.19, 127.66, 128.05, 128.33, 133.03, 133.44, 134.55, 135.79.

4.6 References

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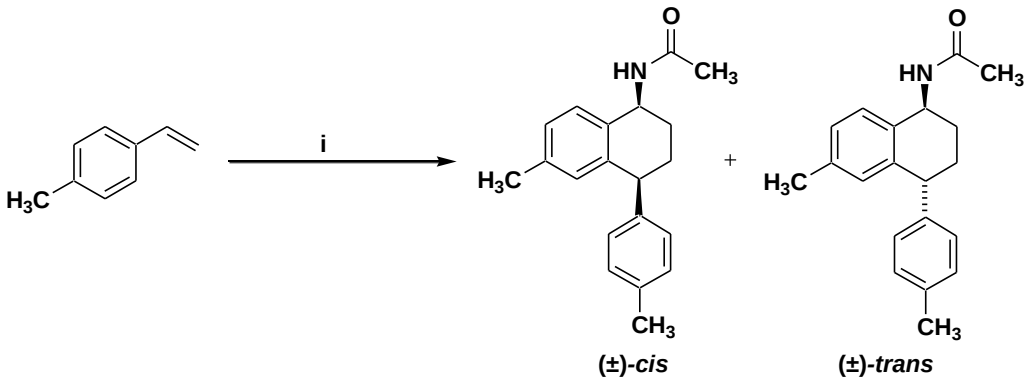
SUMMARY

The thesis entitled **"Novel Synthetic Transformations Involving Radical Cations Generated by Cerium(IV) Ammonium Nitrate"** embodies the results of the investigations carried out to explore the synthetic potential of CAN.

A general introduction to radical reactions followed by a brief survey of the various synthetic transformations mediated by CAN is presented in Chapter 1.

The second chapter of the thesis deals with a CAN induced cyclodimerzation of styrenes leading to a novel and expeditious synthesis of 1-amino-4-aryltetralin derivatives. The reaction of various styrenes with a solution of CAN in acetonitrile under deoxygenated conditions resulted in the formation of α-acetamido tetralin derivatives. Typical examples are given in Scheme 1.



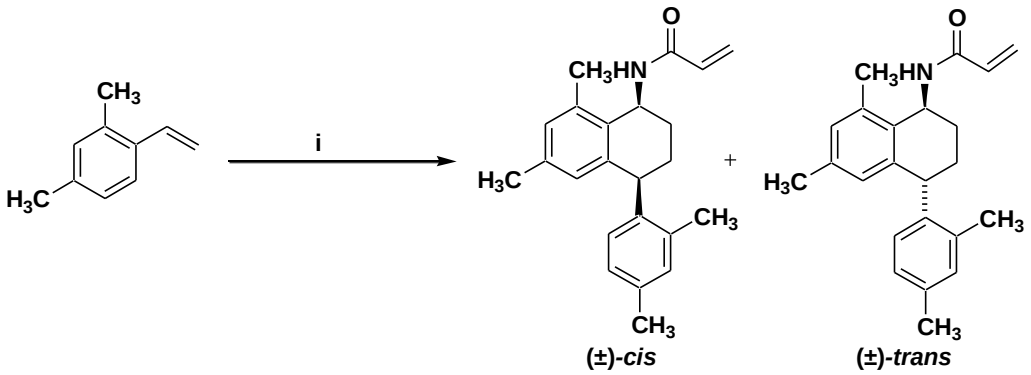
(±)-*cis* **(±)-*trans***

i) CAN (1.2 eq.), CH_3CN, Argon, RT, 2 h, 62%, 1.3:1

Scheme 1

It is noteworthy that α-aminotetralin derivatives manifest a number of important and therapeutically useful biological activities; some of them are potent CNS stimulants and others are antibiotics, immunomodulators and antitumor agents. Special mention may be made of the top selling antidepressant **Sertraline**.

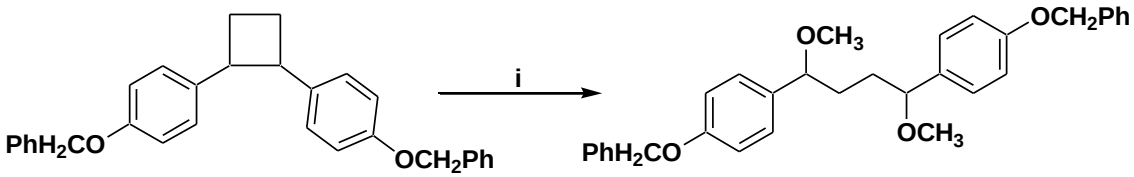
The reaction described above could be easily extended to employ acrylonitrile as the solvent system, to afford the corresponding α-acrylamido tetralins (Scheme 2).



i) CAN, acrylonitrile, RT, 3 h, 72%, 1.2:1

Scheme 2

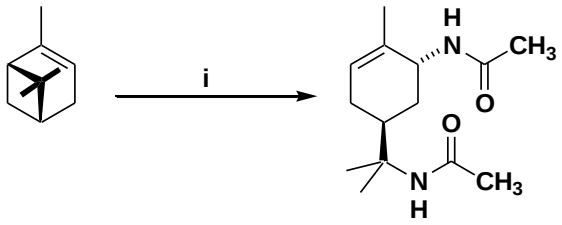
The third chapter deals with the reactivity of four membered ring systems towards CAN. The matter presented in this chapter is divided into three sections. The first section gives an account of the CAN mediated transformations of cyclobutanes. An illustrative example is the reaction of cyclobutane with CAN (Scheme 3).



i) CAN (2.3 eq.), dry CH_3OH, Argon, RT, 2 h, 69 %

Scheme 3

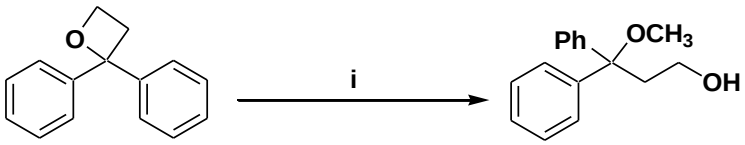
The second section deals with the CAN induced rearrangement of monoterpenes containing four membered rings as a part of their structural framework. When α-pinene was exposed to a solution of CAN in acetonitrile, a remarkable transformation culminating in the bisamide in 72% yield occurred (Scheme 4). The reactivity of a few other monoterpenes of the pinene family towards CAN is also described in this chapter.



i) CAN (2.3 eq.), CH_3CN, RT, 3h, 72%

Scheme 4

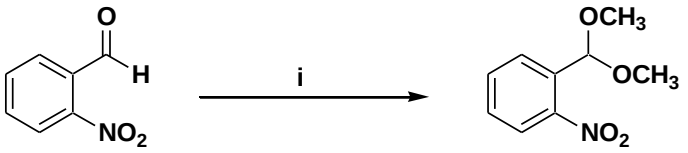
The regiospecific ring opening of oxetanes induced by CAN as illustrated below is dealt with in the final section (Scheme 5).



i) CAN (0.5 eq.), CH_3OH, RT, 30 min, 90%

Scheme 5

An efficient method for the preparation of dimethyl, diethyl and diallyl acetals of aromatic aldehydes mediated by CAN forms the subject matter of the fourth chapter. The following examples are illustrative (Scheme 6).



i) CAN (1.2 eq.), Na_2CO_3 (2.0 eq.), dry CH_3OH, 70 °C, 45 min, 97%

ii) CAN (1.2 eq.), Na_2CO_3, allyl alcohol, 70 °C, 45 min, 76%

Scheme 6

In conclusion, we have uncovered a novel strategy for the one-pot synthesis of α-aminotetralin derivatives related to Sertraline. The reactivity of monoterpenes of the pinene family towards CAN has been investigated and a novel process for the synthesis of potentially useful amides and ethers was uncovered. The reactivity of the radical cations generated from strained ring systems such as oxetanes and cyclobutanes has been studied. A simple strategy for the protection of aldehydes as dimethyl, diethyl and diallyl acetals by the use of Cerium(IV) Ammonium Nitrate has also been developed.

List of Publications

1. A CAN Induced Cyclodimerization-Ritter Trapping Strategy for the One-Pot Synthesis of 1-Amino-4-aryltetralin Derivatives from Styrenes. Nair, V.; **Rajan, R**.; Rath, N. P. *Org. Lett*. **2002**, *4*, 1575.
2. Cerium(IV) Ammonium Nitrate Induced Dimerization of Methoxy Styrenes. Nair, V.; Sheeba, V.; Panicker, S. B.; George, T. G.; **Rajan R**.; Balagopal, L.; Vairamani, M.; Prabhakar, S. *Tetrahedron* **2000**, *56*, 2461.
3. An Exceedingly Mild and Efficient CAN Mediated Method for the Deprotection of Acetals. Nair, V.; Balagopal, L.; **Rajan, R**. *Ind. J. Chem.* **1999**, *38B,* 1234.
4. A Novel CAN Mediated Oxidative Rearrangement of Monoterpenes. Nair, V.; **Rajan, R.**; Balagopal, L.; Thomas, S.; Narasimlu, K. *Tet. Lett*. **2002**, *43*, 8971.
5. CAN Mediated Intramolecular Cyclization of Epoxypropyl Cinnamyl Ethers: A Facile Synthesis of 3,4-*trans*-disubstituted Tetrahydrofuran Derivatives. Nair, V.; Balagopal, L.; **Rajan, R.**; Varma, L. R. (*Tetrahedron Letters* **2002**, *accepted subject to revision*).
6. Novel Oxidative Rearrangements of Four Membered Ring Systems Mediated by Cerium(IV) Ammonium Nitrate. Nair, V.; **Rajan, R**. (*to be communicated to Synthesis*)
7. A Mild and Efficient Procedure for the Preparation of Dimethyl Acetals of Aromatic Aldehydes mediated by CAN. Nair, V.; Nair, L. G.; **Rajan, R**.; Balagopal, L. (*to be communicated to Synthesis*).

Posters Presented at Symposia

1. Nair, V.; Balagopal, L.; **Rajan, R.** "Oxidative Cyclization of Cinnamyl Ethers Mediated by CAN: A Stereoselective Synthesis of 3,4-*trans*-disubstituted Tetrahydrofuran Derivatives" presented at the Fourth National Symposium in Chemistry held at Pune, February 1-3, **2002**.