Stereo Selective Synthesis of Substituted Dihydro- and Tetrahydropyrans

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Submitted by

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Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis enttled "*Stereo Selective Synthesis of Substituted Dihydro- and Tetrahydropyrans*" is the result of investigations carried out by me under the guidance of Dr. Anil K Saikia in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

September, 2010.
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CERTIFICATE

This is to certify that Chandramoulali Reddy, U. has been working under my supervision since July, 2006 as a regular registered Ph. D. student. I am forwarding his thesis entitled "***Stereo Selective Synthesis of Substituted Dihydro- and Tetrahydropyrans***" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

September 2010.
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Dr. Anil K Saikia
Supervisor

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Lastly, I wish to thank my brother-in-law Chandramohan Reddy. He has been my constant source of strength, and so I dedicate this thesis to him. He is the main soul and inspiration to achieve this goal.

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5.8 Selected Spectra of 4-Aryldihydropyrans

CHAPTER 1

Introduction to Multicomponent and Prins Cyclization Reactions

1.1 Multicomponent Reactions (MCRs)

1.1.1. Introduction

A multicomponent reaction (MCR) is a process in which three or more easily accessible components are combined together in a single reaction vessel to produce a final product. Generally, the MCR strategy affords savings in synthetic time and effort, and has significant advantages over conventional two-component reactions in several aspects, such as, (a) reduced reaction time and cost; (b) readily available starting materials; (c) operationally simple; (d) variable and high bond forming efficiency; (e) resource effective; (f) atom economical and (g) ecologically benign[1]. A MCR is a domino process, a sequence of elementary steps according to a program in which subsequent transformations are determined by the functionalities produced in the previous step. MCRs constitute an especially attractive synthetic strategy since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. As MCRs are one-pot reactions, they are easier to carry out than multistep syntheses. Coupled with high-through put library screening, this strategy is an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds. Libraries of small-molecule organic compounds are perhaps the most desired class of potential drug candidates. With a small set of starting materials, very large libraries can be built up within a short time, which can then be used for research on medicinal substances.

MCRs though fashionable these days, have in fact a long history. Indeed, many important reactions such as the Strecker amino acid synthesis (1850), the Hantsch synthesis (1882), the Biginelli dihydropyrimidine synthesis (1891), the Mannich reaction (1912), the isocyanide-based Passerini reactions (1921) and Ugi four-component reactions (Ugi-4CRs) (1959) are belongs to MCRs. In spite of the significant contribution of MCRs to the state of the art of modern organic chemistry and their potential use in complex organic synthesis, little attention was paid to the development of novel MCRs in the second half of the twentieth century. However, with the introduction of molecular biology and high-throughput biological screening, the demand on the number and the quality of compounds for drug discovery has increased enormously. By virtue of their inherent convergence and high productivity,

together with their exploratory and complexity-generating power, MCRs have naturally become a rapidly evolving field of research and have attracted the attention of both academic and industrial scientists.

The "ideal synthesis" should lead to the desired product in a few steps with good overall yield by using environmentally compatible reagents (*Figure 1.1.1*). The synthetic variables that have to be optimized are time, costs, overall yield, safety, simplicity of workup, and environmental acceptability. In multistep synthesis the preparative complexity increases in proportion to the number of steps in a first approximation. It is reflected in many isolation and purification operations, such as crystallization, extraction, distillation or chromatography. MCRs are more or less "Ideal" in nature.

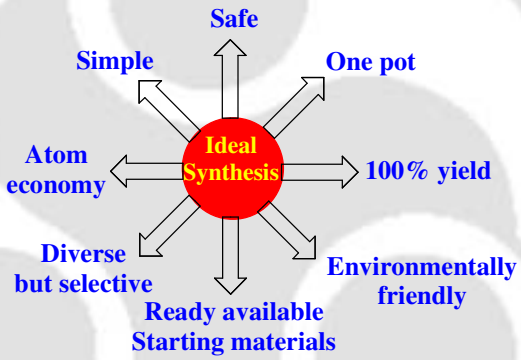
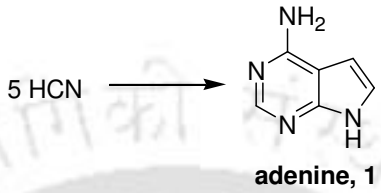


Figure 1.1.1. *The Ideal Chemical Synthesis*

It is nevertheless important to point out that MCRs have contributed to drug development, from lead discovery and lead optimization to production, long before the advent of combinatorial technologies. However, in the last decade, with the introduction of high-throughput biological screening, the importance of MCRs for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focused especially on the design and development of multi-component procedures for the generation of libraries of heterocyclic compounds. This growing interest is stimulated by the significant therapeutic potential that is associated with many heterocycles. The one-step synthesis of nifedipine, a highly active calcium antagonist, by a Hantzsch reaction is a classic demonstration. A more recent example is the synthesis of piperazine-2-carboxamide, the core structure of the HIV protease inhibitor Crixivan, by an Ugi-four component reaction.

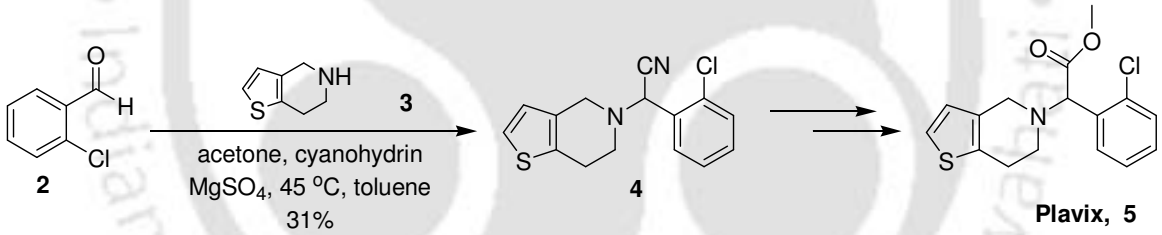
1.1.2. Synthetic Applications of MCRs

The concept of MCR has long been used in synthesis. As for example, adenine (**1**), one of the major constituents of DNA and RNA, was prebiotically formed by the condensation of five molecules of HCN, a plentiful component of prebiotic atmosphere, in a reaction catalyzed by NH_4OH (*Scheme 1.1.1*).[3]



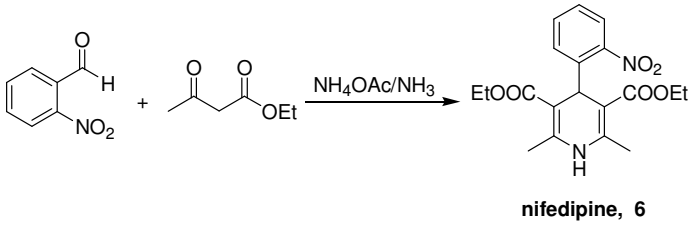
Scheme 1.1.1. *Prebiotic synthesis of adenine*

The first modern contribution to the development of multicomponent chemistry was made in 1850 by Strecker. This method was applied for the synthesis of α-amino nitrile (**4**), from the condensation of aldehyde **(2)** and amine **(3)** mediated by $MgSO_4$, an intermediate for the synthesis of Plavix **(5)** (*Scheme 1.1.2*).[4]



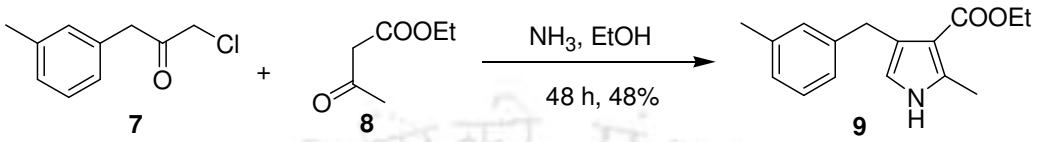
Scheme 1.1.2. *Strecker synthesis of Plavix*

Hantzsch in 1882[5a] developed a multi-component organic reaction between an aldehyde, two equivalents of a β-keto ester and ammonium acetate or ammonia to synthesize symmetrically substituted dihydropyridines (**6**) (*Scheme 1.1.3*).[5b]



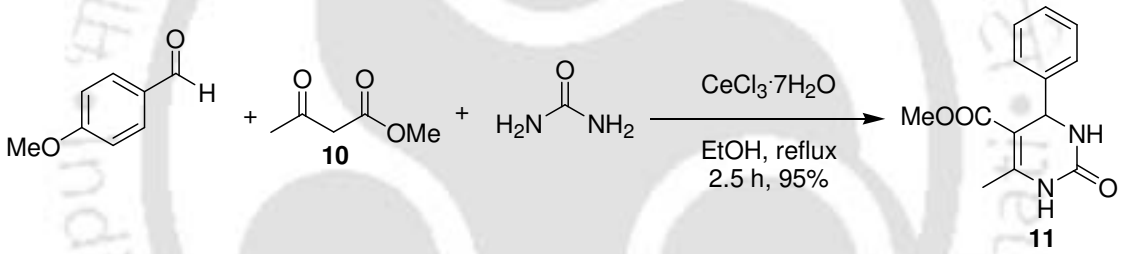
Scheme 1.1.3. *Hantzsch synthesis of dihydropyridines*

Another contribution made by Hantzsch to MCRs was the synthesis of pyrroles (**9**), by reacting β-ketoesters (**8**), and α-halogenated ketones (**7**) in presence of ammonia (*Scheme 1.1.4*).[6]



*Scheme **1.1.4.** Hantzsch multicomponent synthesis of pyrroles*

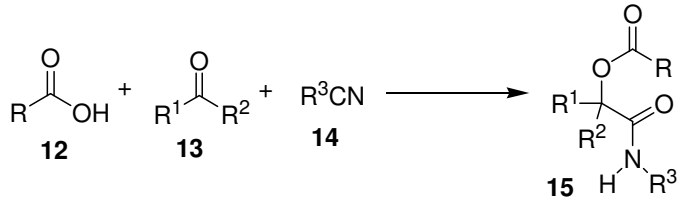
The Biginelli reaction first described in 1893[7a] represents a multiple-component chemical reaction that creates 3,4-dihydropyrimidin-2(1*H*)-ones (**11**) from methyl acetoacetate (**10**), an aryl aldehyde and urea (*Scheme 1.1.5).*[7b]



***Scheme 1.1.5.** Biginelli pyrimidone synthesis*

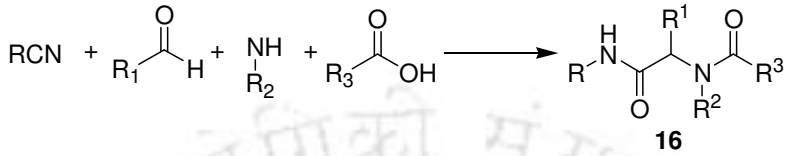
Isocyanides based reaction: The essentially nucleophilic isocyanides react with acid-activated aldehydes and ketones in combination with nucleophiles such as water, hydrazoic acid or carboxylic acids to yield α-hydroxycarboxamides or some of their derivatives.

The first MCR involving isocyanides was discovered in 1921 by Passerini.[8a] The reaction of carboxylic acids (**12**), carbonyl compounds (**13**) and isocyanides (**14**) afforded α-acyloxy carboxamides (**15**) in a one-pot procedure (*Scheme 1.1.6*).[8b]



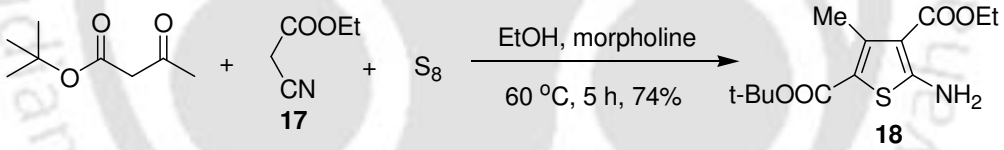
***Scheme 1.1.6.** Passerini 3-CR*

One of the most utilized multicomponent reactions was discovered in 1959 by Ugi *et al.*[9a] Synthesis of α-acylamino amides (**16**) was achieved by reacting aldehydes, primary amines, carboxylic acids and isocyanides (*Scheme 1.1.7*).[9b]



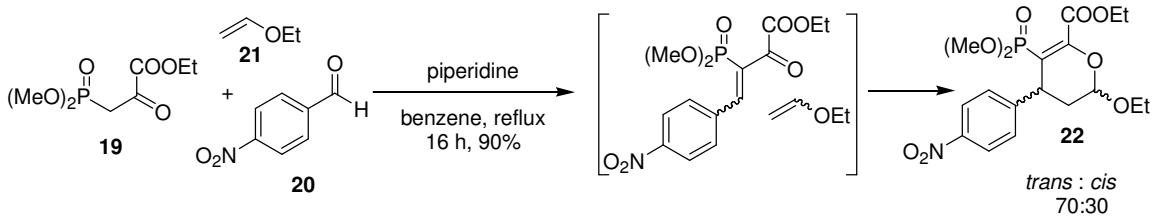
Scheme 1.1.7. *Ugi-4CR*

In 1961 Gewald and co-workers[10a] described the synthesis of polysubstituted thiophenes. Since 1970, 2-aminothiophenes have attracted tremendous interest because of their applications not only in drug discovery but also in agriculture, pesticides and dyes. The most elegant and simplest version consists of a one-pot procedure, facilitated by organic bases; a β-ketoester, cyanoacetate (**17**) and elemental sulfur condense to afford a thiophene (**18**) containing four positions of possible diversification (*Scheme 1.1.8*).[10b]



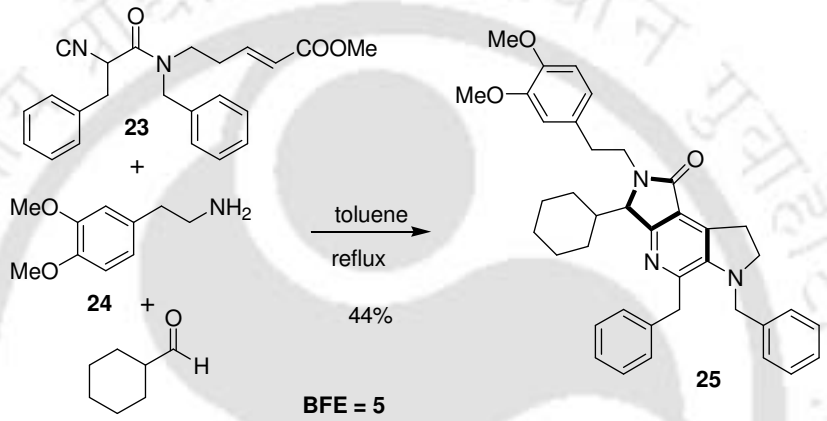
Scheme 1.1.8. *Gewald's aminothiophene synthesis*

A one-pot synthesis *via* a tandem-sequence Knoevenagel and hetero-Diels–Alder reactions was developed. Reaction of (**19**) with aromatic aldehydes (**20**) and ethyl vinyl ether (**21**) led to the expected 3,4-dihydro-*2H*-pyrans (**22**) via the intermediately formed 1-oxa-1,3-butadiene (*Scheme 1.1.*9).[11]



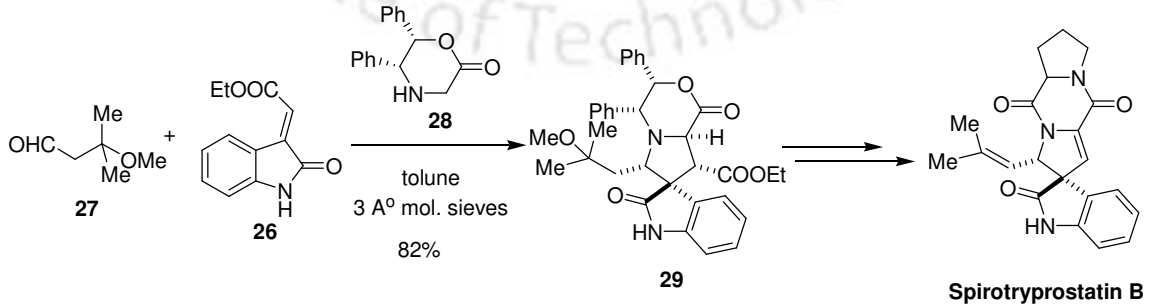
Scheme 1.1.9. *Tandem-sequence Knoevenagel–hetero-Diels–Alder reactions.*

The efficiency of multicomponent reactions can be exemplified by the following reaction. By simply heating a toluene solution of isocyanoacetamide (**23**), amine (**24**), and cyclohexane-carboxaldehyde, a clean three-component reaction occurred to provide the pyrrolidinone-fused azaindoline (**25**) (*Scheme 1.1.10*).[12a] In this multicomponent reaction, the isocyanoacetamide (**23**) reacted four times in a highly ordered manner creating three heterocyclic rings with the concurrent formation of five chemical bonds and a minimal loss of molecular weight. In this reaction, three C-C bonds and two C-N bonds were formed.



Scheme 1.1.10. *Synthesis of Polysubstituted 6-Azaindolines*

The reaction of oxazinone (**26**) with aldehyde (**27**) and oxindole (**28**) in toluene at room temperature in the presence of 3 Å mol sieves, afforded cycloadduct (**29**) in 82% yield (*Scheme 1.1.11*).[13] With this key intermediate synthesis of spirotryprostatin B was achieved in an efficient nine-step sequence.



Scheme 1.1.11. *Synthesis of spirotryprostatin*

1.2. Dihydro- and Tetrahydropyans

1.2.1. Introduction to Dihydro- and Tetrahydro-pyrans

Functionalized tetrahydropyran unit is present in many natural products and pharmaceuticals.[14] For example, over the last ten years thousands of tetrahydropyran containing compounds have been entered into preclinical and clinical trials. Consequently, a huge amount of effort has been directed towards developing ever more efficient methods to synthesize them. The most widely used methods to synthesize these natural products are the Prins and related cyclization reactions, hetero-Diels–Alder cyclization,[15] the intramolecular *oxo*-Michael additions[16] and ring-closing metathesis.[17] Other strategies include the *oxo*-palladation of allylic acetates[18] or terminal alkenes,[19] and also by alkene activation with selenonium[20] or iodonium ions.[21] Prins and related cyclization reactions made big impact on the synthesis of THP rings and related natural products.

1.2.2. Importance of Dihydro- and Tetrahydro-pyrans

The tetrahydropyran ring is featured in a variety of biologically active natural products, marine toxins, and pheromones.[22] Phorboxazoles **30A** & **30B** (*Figure 1.2.1*) possess antifungal activity and are potent antineoplastic agents[23a-c] and also show high activity across the entire panel (mean GI_{50} 1.58 $\times 10^{-9}$M) with specific cell lines being inhibited at

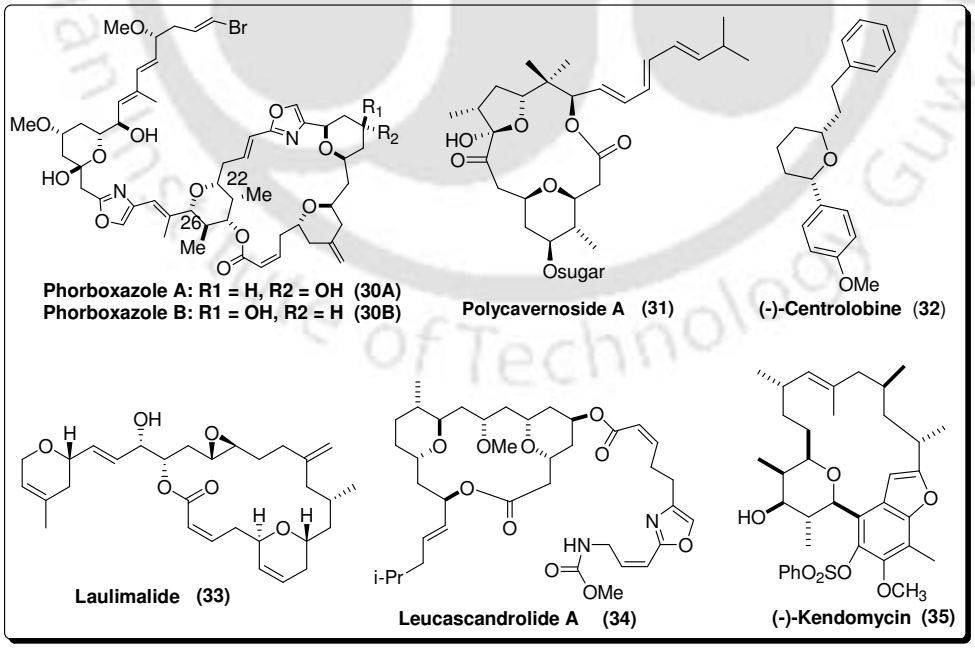


Figure 1.2.1. *Examples of biologically active tetrahydropyrans.*

subnanomolar concentrations. Polycavernoside A[24] **31** (*Figure 1.2.1*) was isolated from the edible red alga *Polyca*V*ernosa tsudai* as a causative toxin of sudden human intoxication in

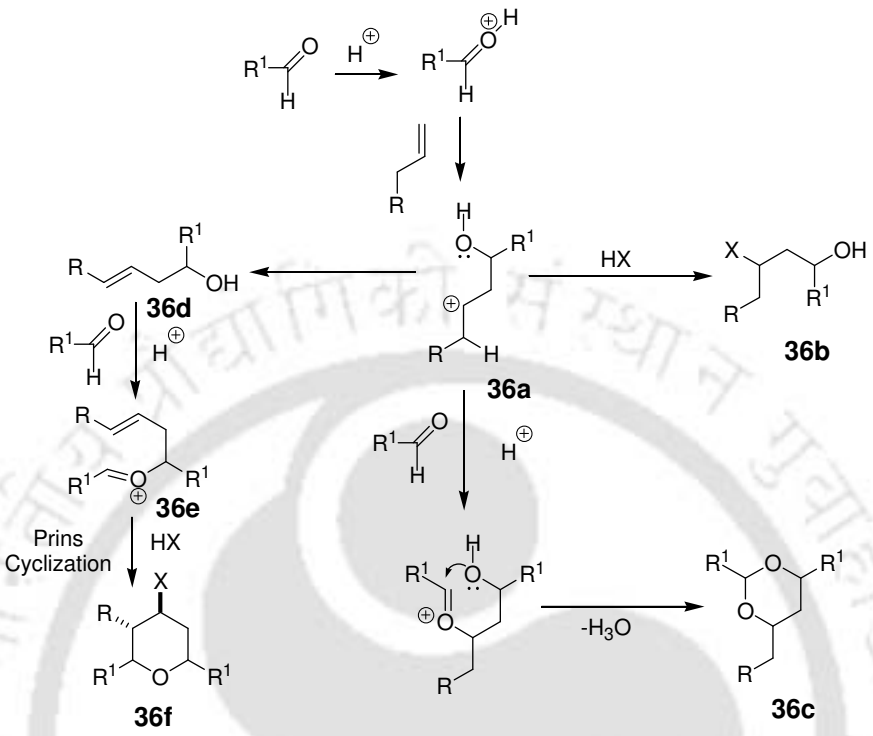
Guam in 1991. Centrolobine[25] **32** (*Figure 1.2.1*), an antibiotic, very effective against *T. cruzi* epimastigotes, with LDs = 0.33 mM, 0.22 mM and 0.35 mM, for the centrolobol. (-)-Laulimalide **33** (*Figure 1.2.1*) is a structurally novel cancer therapeutic lead, recently isolated in trace quantities from Pacific marine sponges.[26a-c] Laulimalide promotes abnormal tubulin polymerization and apoptosis in vitro, with a mode of action similar to that of Taxol® but with potentially less susceptibility to multidrug resistance.[26d] Leucascandrolide A[27] **34** (*Figure 1.2.1*) has shown high cytotoxicity in vitro against human KB tumor cell lines (IC_{50} = 50 ng/mL) and P388 leukemia cell lines (IC_{50} = 50 ng/mL) as well as potent antifungal inhibition against *Candida albicans*. (-)-Kendomycin[28] **35** (*Figure 1.2.1*) exhibits potent antagonism of the endothelia receptor, as well as anti osteoporotic properties from calcitonin receptor agonist.

1.3. Prins Cyclization

The Prins reaction is one of the fundamental methods for C–C bond formation. The addition of aldehydes or ketones to alkenes in the presence of acid is called the Prins reaction.[29] However, it is necessary to exert an accurate control of the experimental conditions, since several types of products can formally be formed, and mixtures are often isolated. We have attempted to highlight the Prins cyclization strategies by focusing on tetrahydropyran and related natural product synthesis.

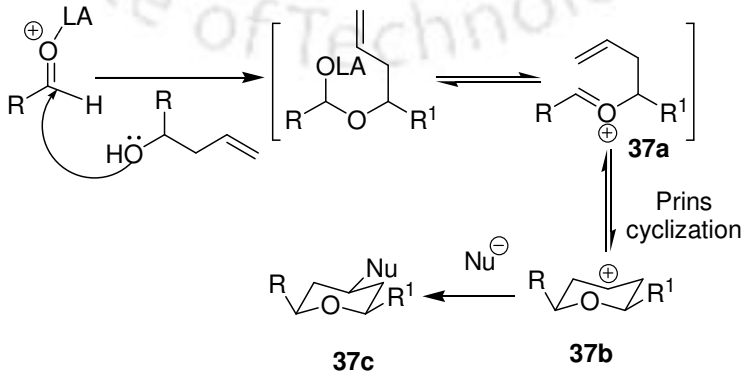
1.3.1. Prins Reaction Mechanism

The ene and Prins reactions are not mechanistically distinct, in case of Prins reaction intermediate carbocation trapped by nucleophiles, in ene reaction intermediate carbocation eliminates H^+ ion to generate olefin.[30] The general mechanism is shown in *Scheme 1.3.1*, the key intermediate β-hydroxy carbocation (**36a**) generates from the reaction of carbonyl compound and alkene in the presence of acid catalyst, which reacts with a nucleophile such as chloride, water or acetate to give **(36b),** or adds to a second molecule of aldehyde to give **(36c)** or loses a proton to give homoallylic alcohol (**36d**). In the presence of acid, homoallylic alcohol (**36d**) reacts with aldehyde to afford oxocarbenium ion (**36e**), which after Prins cyclization and subsequent addition of neucleophile gives the 2,4,6-trisubstituted-tetrahydropyran (**36f**).[31]



Scheme 1.3.1. *Prins reaction mechanism*

Many variations of the Prins reaction exist because it tends itself easily to cyclization reactions and it is possible to capture the oxo-carbenium ion with a large array of nucleophiles. In the simplest case, the reaction involves a homoallylic alcohol, an aldehyde and a Lewis acid. A general mechanism is shown in *Scheme 1.3.2*. The key intermediate, i.e., an oxocarbenium ion (**37a**), is generated from a carbonyl compound and homoallylic alcohol



Scheme 1.3.2. *Prins cyclization reaction mechanism*

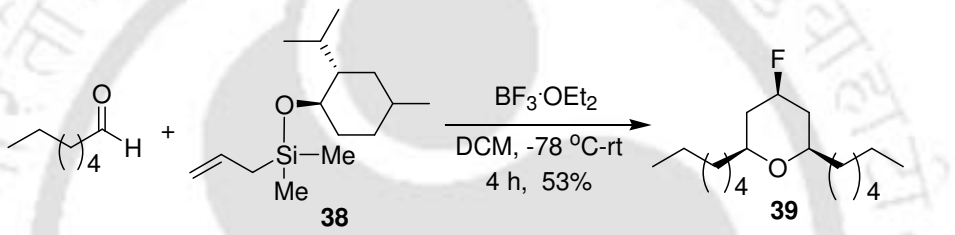
and undergoes cyclization to give tetrahydropyranyl carbocation (**37b**), it is trapped by various nucleophiles to give diastreoselective tetrahyhydropyran derivative.

1.3.2. Tandem Sakurai-Prins Cyclization

In these strategy homoallyl alcohol moiety generates *insitu* by using Hosomi-Sakurai reaction followed by Prins cyclization reaction takes place.

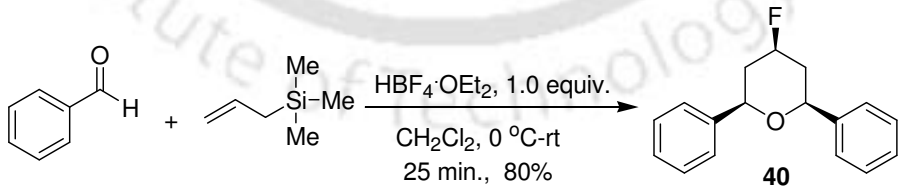
1.3.2.1. Synthesis of Symmetrical 4-Fluoro-tetrahydropyrans

The first example was described by Chan and co-workers. As illustrated in *Scheme 1.3.2*, the reaction of two equivalents of aldehyde, and alkoxyallylsilane (**38**) gave symmetrical *cis* 4-fluorotetrahydropyrans (**39**).[32]



Scheme 1.3.2.

Recently, a one-pot, three component synthesis of symmetrical 2,6-disubstituted 4-fluorotetrahydropyrans from the reaction of aldehydes and allyltrimethylsilane was achieved using an ethereal solution of tetrafluoroboric acid. Reaction of 2.2 equivalents benzaldehyde with allyltrimethylsilane using $HBF_4{\cdot}OEt_2$ gave symmetrical 4-flurotetrahydropyran (**40**) in 80% yield (*Scheme 1.3.3*).[33]



Scheme 1.3.3.

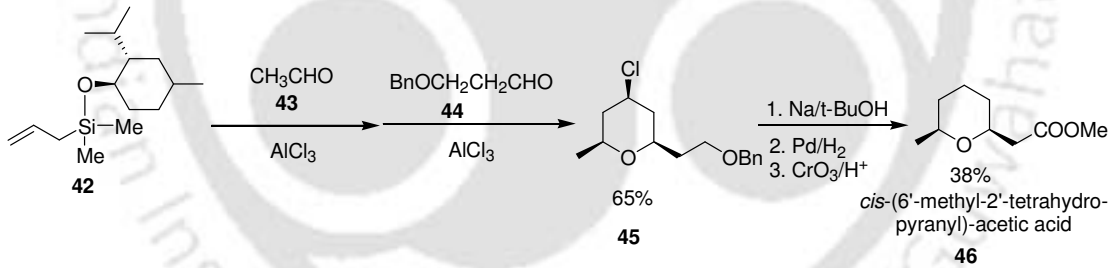
1.3.2.2. Synthesis of Symmetrical 4-Chloro-tetrahydropyrans

Chan *et al.* developed a method for the symmetrical *cis*-4-chlorotetrahydropyrans (**41**) from the reaction of the alkoxyallylsilane with two equivalents of aldehydes in the presence of $AlCl_3$ (*Scheme 1.3.4*).[34] Reaction worked well for aliphatic aldehyde and didn't work for

Scheme 1.3.4.

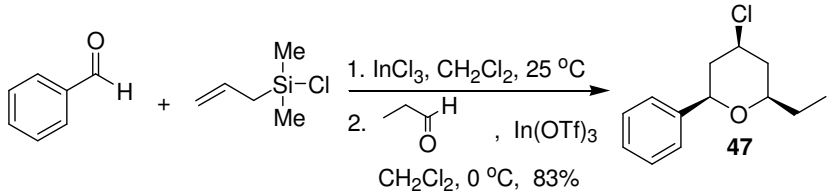
aromatic aldehydes and ketones. At lower reaction temperature gave better yield.

The above method was applied to enantioselective synthesis of *cis*-(6'-methyl-2'-tetrahydropyranyl) acetic acid (**46**),[35] a natural compound that was isolated from the glandular secretion of the civet cat (Veverra civetta). The tetrahydropyran (**45**) was prepared in a one-pot synthesis using optically active alkoxyallylsilane (**42**), acetaldehyde (**43**) and 3-(benzyloxy)propanal (**44**) as the aldehyde components and aluminum chloride as the Lewis acid in 65% yield (*Scheme 1.3.5*). The final compound (**46**) was achieved by sodium reduction followed by hydrogenolysis and subsequent oxidation with CrO_3 with 38% overall yield.



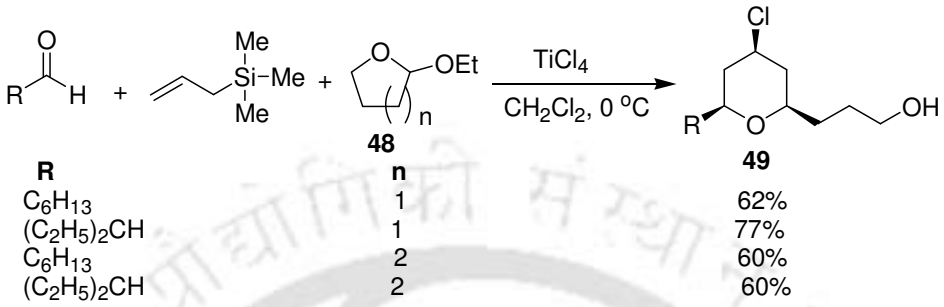
Scheme 1.3.5.

Loh *et al*. demonstrated the use of mild Lewis acid for the step-wise formation of homoallylic alcohol, which enable the coupling with another molecule of aldehyde in the presence of strong Lewis acid to form unsymmetrical 2,4,6-trisubstituted tetrahydropyran (**47**), with high yields and selectivity (*Scheme 1.3.6*).[36]



Scheme 1.3.6.

Cross reactions were applied for the synthesis of spirocyclic derivative from three component reaction (*Scheme 1.3.7*).[37] In this reaction homoallylalcohol was formed *insitu* from the



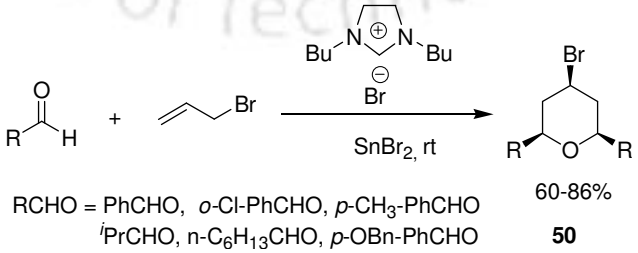
R	n	
C_6H_{13}	1	62%
$(C_2H_5)_2CH$	1	77%
C_6H_{13}	2	60%
$(C_2H_5)_2CH$	2	60%

Scheme 1.3.7.

allylsilane and aldehyde in the presence of $TiCl_4$, which after reaction with the compound (**48**) afford the tetrahydropyran (**49**). The same reaction was also catalyzed by $AlCl_3$ or $AlBr_3$.[38]

1.3.3. Tandem Barbier-Prins Cyclization

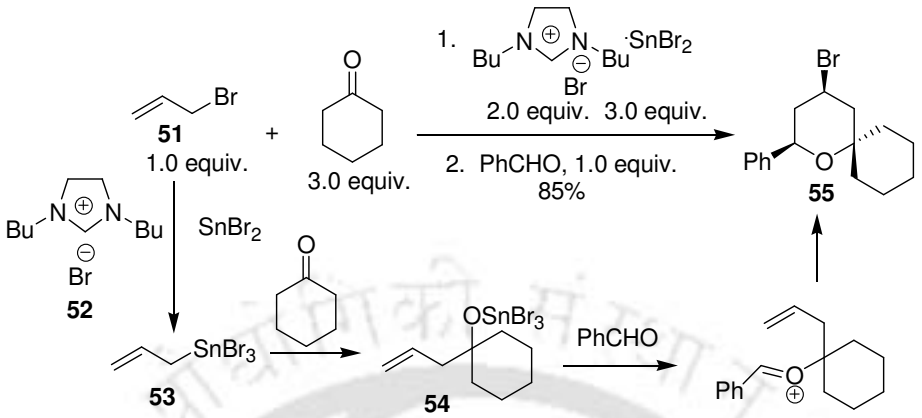
An interesting combination of Barbier reaction with Prins cyclization into a one-pot tandem reaction system for direct formation of tetrahydropyran was reported Tetrahydropyran compounds can be directly synthesized from ally bromide and carbonyl compounds by means of one-pot Barbier–Prins cyclization promoted by (N-benzyl pyridine halides) $BPyX/SnX_2$ or (Imidazole bromide salt) $BBIMBr/SnBr_2$ complex as ionic liquid under solvent-free conditions.[39] 2,6-Disubstituted-bromo-tetrahydropyrans (**50**) were prepared, with yields ranging from 60 to 86% *(Scheme 1.3.8).*



RCHO = PhCHO, *o*-Cl-PhCHO, *p*-CH_3-PhCHO
^{i}PrCHO, n-C_6H_{13}CHO, *p*-OBn-PhCHO

Scheme 1.3.8.

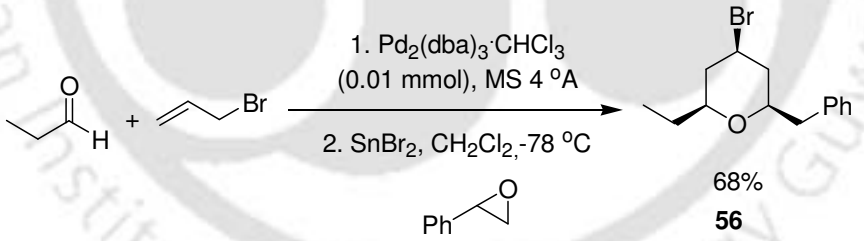
Cross reactions were applied for the synthesis of spirocyclic derivatives from the reaction of ketones, allybromide and aldehyde condensation (*Scheme 1.3.9*).[39] The first step is Barbier-



Scheme 1.3.9.

type reaction of allylbromide (**51**) with $SnBr_2$ in the presence of quaternary ammonium salt (**52**) to produce allyltin compound (**53**) which subsequently undergoes reaction with ketone to generate the reactive intermediate (**54**). The intermediate (**54**) is sufficiently active to react with another molecule of aldehyde to give Prins cyclization product (**55**).

Similarly, compound (**56**) was prepared from allyl bromide, propanaldehyde and styrene oxide in presence of palladium catalyst and $SnBr_2$ with 68% yield (*Scheme 1.3.10*).[40]



Scheme 1.3.10.

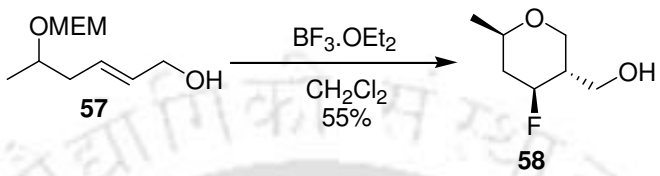
1.3.4. Prins Cyclization Involving Homoallylic alcohol Derivatives

Prins cyclization involving homoallylic alcohol and carbonyl is the method of choice for the synthesis of 4-substituted tetrahydropyran such as as C-4 oxygenated, C-4 halogenated, C-4 amido and C-4 azido tetrahydropyran.

1.3.4.1. Halo-Prins Cyclization

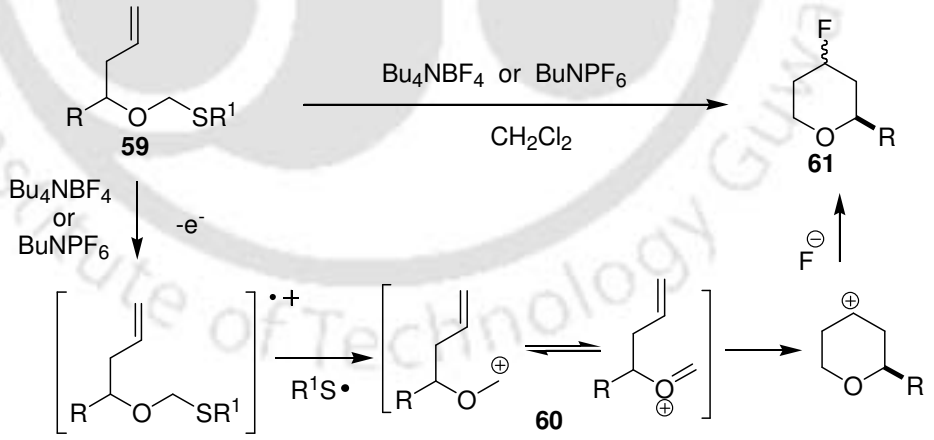
1.3.4.1.1. Synthesis of 4-Fluoro-tetrahydropyrans

There have been only a few reports on the synthesis of fluorinated tetrahydropyrans.[41a,b] Willis and co-workers have prepared 2,6-substituted 4-fluorotetrahydropyrans (**58**) by reacting acetal (**57**) with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 with 55% yield and excellent control of the diastereoselectivity (*Scheme 1.3.11*)[42].



Scheme 1.3.11.

Anodic oxidation of α-organothio ethers results in the cleavage of the carbon-sulfur bond and the introduction of carbon nucleophiles onto the carbon, suggesting the effectiveness of organothio groups as electro auxiliaries (*Scheme 1.3.12*).[43a] This intramolecular cyclization was achieved by the anodic oxidation of α-phenylthio- or α-methylthioethers (**59**) having a carbon-carbon double bond. The anodic oxidation in Bu_4NBF_4 or Bu_4NPF_6 in CH_2Cl_2 gave rise to the cleavage of the C-S bond (**60**) and the C-C bond formation with one of the olefinic carbon and the introduction of fluoride onto the other olefinic carbon led to 4-fluro-

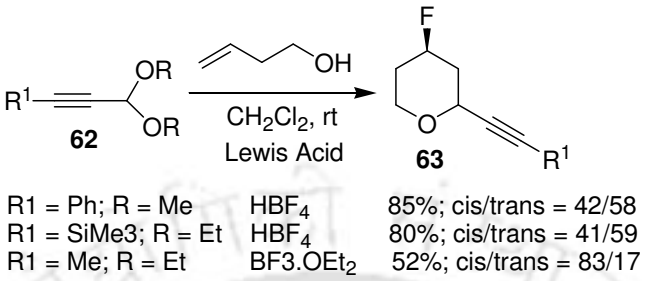


R = C_7H_{15}, R^1 = Me	Bu_4NBF_4	64%	cis/trans = 3.3/1
R = C_9H_{19}, R^1 = Ph	Bu_4NBF_4	61%	cis/trans = 4.8/1
	Bu_4NPF_6	87%	cis/trans = 1.4/1

Scheme 1.3.12.

tetrahydropyran (**61**). The similar transformation has been achieved by using triorganotin as an electroauxilary.[43b]

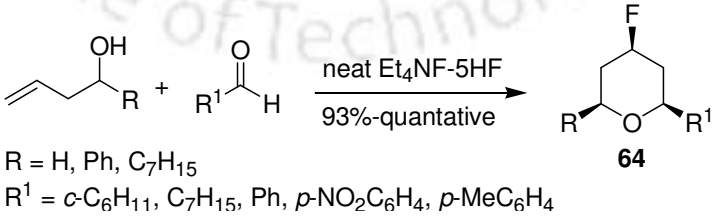
In Prins cyclization reaction conjugated alkynyl aldehyde are inactive or gives poor yield. Dicobalt hexacarbonyl complexes derived from propargylic acetals undergo Lewis acid-



Scheme 1.3.13.

mediated Nicholas–Prins cyclization in the presence of homoallylic alcohols. The complexation of the triple bond contributes to the suppression of the side reactions and very significantly increases both the yield and the diastereoselectivity of the reaction. The Nicholas–Prins procedure enables the synthesis of 2-alkynyl-4-fluoro-tetrahydropyrans (**63**) from dicobalt hexacarbonyl complexes of propargylic acetals (**62**) and homoallylic alcohol. Yields ranging from 52-85% were obtained using either HBF_4 or $BF_3{\cdot}OEt_2$ as mediator (*Scheme 1.3.13*).[44]

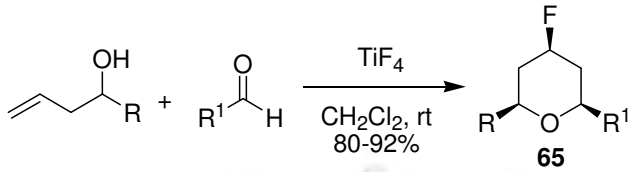
Recently, Fuchigami *et al*. developed a methodology for the synthesis of developed 4-fluoro-tetrahydropyrans (**64**) using ionic liquid HF salts without use of any organic solvents. Quantitative yields have been reported while using $Et_4NF.5HF$ (*Scheme 1.3.14*).[45] The method was extended to ketones, but it showed quite low or no reactivity. Similarly, aza-Prins cyclization proceeded smoothly to provide 4-fluoropiperidines and thia-Prins cyclization proceeded to provide 4- fluorothiacyclohexanes.



Scheme 1.3.14.

Very recently Saikia and coworkers[46] developed titanium tetrafluoride catalyzed Prins cyclization reaction for the effective synthesis of 4-fluorotetrahydropyrans (**65**). As illustrated

in *Scheme 1.3.15,* the titanium tetrafluoride acted as a Lewis acid and fluorinating agent. The method is general and can be used for aldehydes as well as ketones. The method can be



65

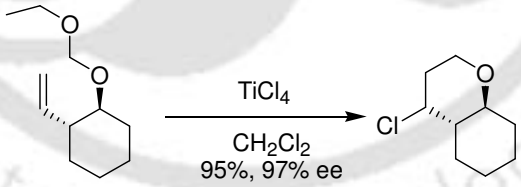
R = Ph, 4-NO_2Ph, 3-NO_2Ph, 4-ClPh, 2-ClPh, 3-BrPh,4-CF_3Ph, 4-MeOPh, 4-CO_2MePh, 4-MePh, 4-$MeSO_3$Ph, 4-MeSPh, 4-FPh, C_3H_7, $PhCH_2CH_2$, Cy, $C_{10}H_{21}$, n-Hex.
R^1 = H, 4-NO_2Ph, 4-CO_2MePh

Scheme 1.3.15.

initiated with readily available starting materials and proceeds with high yield and excellent streoselectivity.

1.3.4.1.2. Synthesis of 4-Chloro-tetrahydropyrans

Thomson *et al.*[47a-d] developed a methodology for cyclization of the unsaturated acetals in a straight forward fashion by titanium tetrachloride (*Scheme 1.3.16*).[47e] 1-Ethoxymethoxy-2-vinyl-cyclohexane (**66**) is cyclized by titanium tetrachloride to afford 4-chlorotetrahydropyran (**67**) at -45 ^oC in 95% yield with high stereoselctivity (97%).

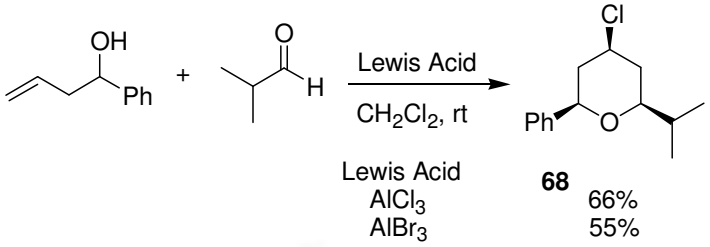


66 **67**

Scheme 1.3.16.

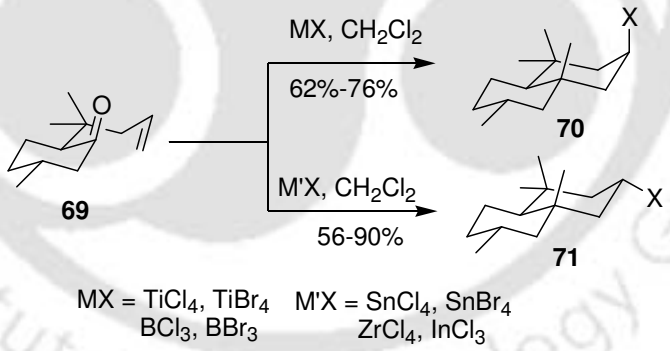
Similarly, aldehydes undergo a rapid coupling with 3-buten-1-ol utilizing 20 mol% of niobium (V) chloride to afford 4-chlorotetrahydropyran derivatives under extremely mild conditions within short reaction times in excellent yields with high selectivity.[48]

A stereoselective synthesis of 4-halotetrahydropyran (**68**) is reported starting from aldehydes and homoallylic alcohols in the presence of $AlC1_3$ or $AlBr_3$ (*Scheme 1.3.17*).[49]



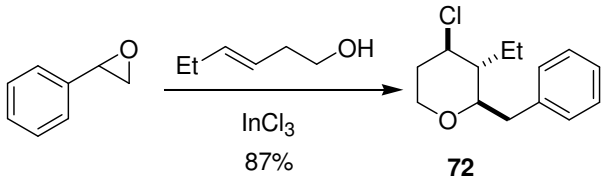
Scheme 1.3.17.

The halo Prins cyclization have been developed for the formation of five, six- and larger member rings in the presence of $TiCl_4$.[50a] As shown in (*Scheme 1.3.18*), ten acyclic and monocyclic *δ*,ε-unsaturated ketones (**69**) underwent halide-terminated Prins cyclization under anhydrous conditions in the presence of Lewis acids.[50b] $TiCl_4$, $TiBr_4$, BCl_3, and BBr_3 promoted *syn*-selective cyclization to sterically congested *trans*-halo-tetrahydropyran (**70**), while $SnCl_4$, $SnBr_4$, $InCl_3$, $ZrCl_4$, and several other Lewis acids effected highly *anti*-selective reactions to furnish the corresponding *cis*-halotetrahydropyrans (**71**). The stronger Lewis acids (TiX_4 and BX_3) favor the *syn* process that involves axial delivery of a halide ion.



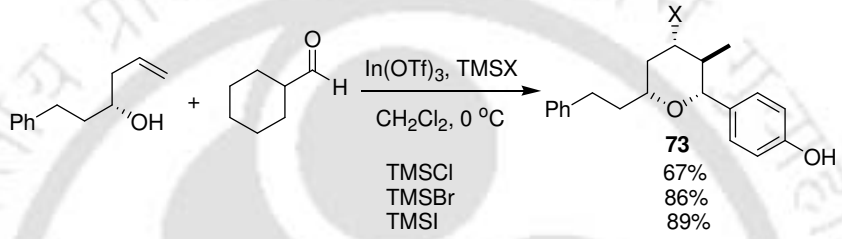
Scheme 1.3.18.

A cross-cyclization between epoxides and homoallylic alcohols catalyzed by indium chloride generates tetrahydropyran derivatives in high yields. Styrene epoxide was reacted with homoallylic alcohol in dry chloroform. The mixture was stirred with indium chloride at room temperature to give 4-chorotetrahydropyran (**72**) (*Scheme 1.3.19*).[51a] Thus, the *Z*-Alkenes led to *cis* isomers, whereas *E*-alkenes led to *trans* isomers.



Scheme 1.3.19.

Under similar conditions epoxides undergo cross-cyclization with homoallylic alcohols in the presence of zirconium tetrachloride to afford the corresponding tetrahydropyran derivatives in excellentyields.[51b]

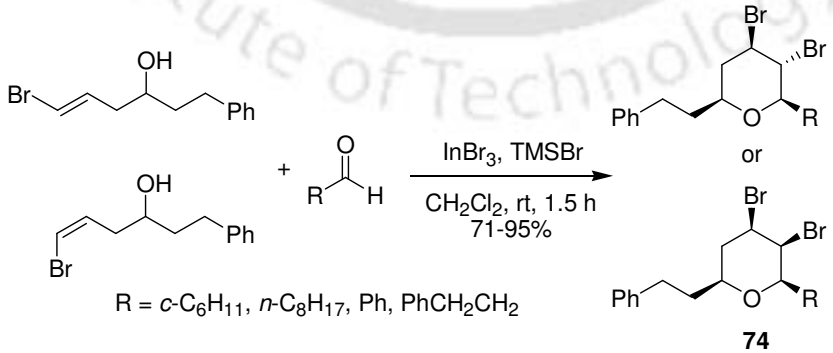


Scheme 1.3.20.

A catalytic Prins cyclization reaction has also been developed. The involvement of trimethylsilyl halides with Indium triflate offers a versatile route to the formation of *cis*-4-halo-2,6- disubstituted tetrahydropyran rings (**73**) (*Scheme 1.3.20*).[52]

1.3.4.1.3. Synthesis of 4-Bromo-tetrahydropyrans

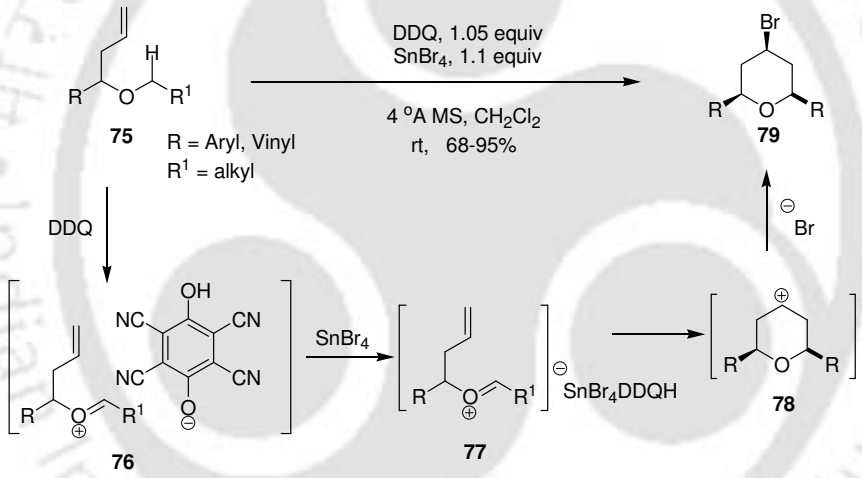
There have been numerous reports in the literature for the synthesis of 4-bromotetrahydropyrans. Loh *et al*. developed an efficient method to construct 2,6-*cis*-4,5-



Scheme 1.3.21.

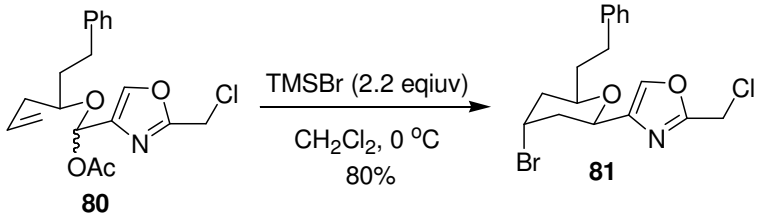
dibromo-tetrasubstituted tetrahydropyran rings (**74**) using $InBr_3$ and TMSBr with well-controlled stereochemistry in moderate to high yields (*Scheme 1.3.21*).[53]

A step-economic method had been developed to construct the tetrahydropyran ring by She and co-workers.[54] As shown in *Scheme 1.3.22,* it involved a sequential benzylic/allylic (**75**) C-H bond activation via DDQ oxidation and followed by nucleophilic attack of an unactivated olefin. In the first step involves a single electron transfer from the arene or alkene by DDQ to generate a radical cation and DDQ radical anion, followed by hydride abstraction from the benzylic or allylic position of the substrate, to afford a charge-transfer complex (**76**). The oxonium ion is weak in electrophilicity to capture the terminal olefin. Upon treatment with strong Lewis acid $SnBr_4$, the resulting tin-"ate" oxonium ion (**77**), with better activity than the charge-transfer complex (**76**), undergoes rapid C-C bond formation and generates cyclic intermediate (**78**) through a chair like transition state. Subsequently, the carbocation was trapped by bromide ion, to give desired 4-bromotetrahydropyran (**79**).



Scheme 1.3.22.

Rychnovsky *et al.* found a Prins cyclization under specific conditions to produce tetrahydropyrans with almost exclusive formation of the axial 4-bromo-substituent.[55] TMSBr

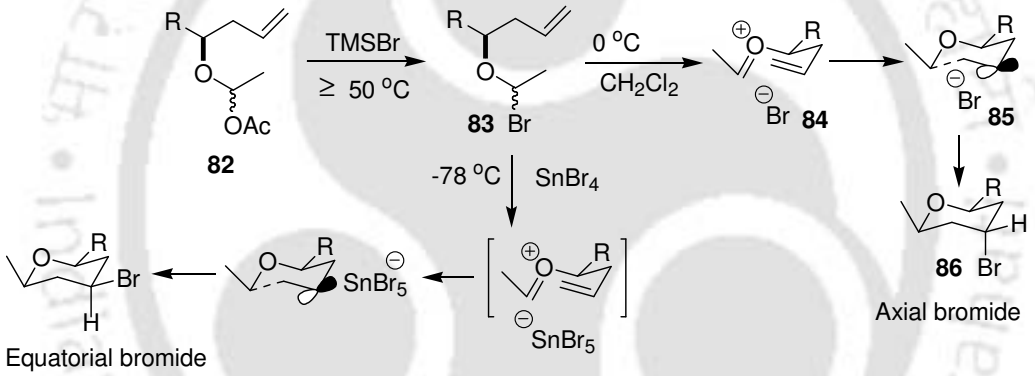


Scheme 1.3.23.

and AcBr both lead to axial-selective Prins cyclization with α-acetoxy ether substrates in the presence of lutidine. The treatment of the α-acetoxy ether (**80**) with TMSBr in CH_2Cl_2 at 0 °C

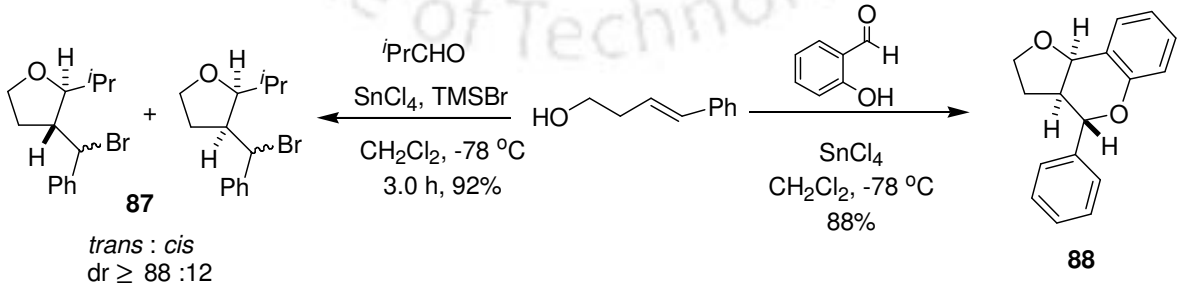
gave the tetrahydropyran (**81**) as a single axial-bromide isomer in excellent yield. Similarly TMSI also catalyzed the reaction to form 4-iodotetrahydropyrans with axial selectivity.

A mechanistic proposal for the axial-selective Prins cyclization is outlined in *Scheme 1.3.24*. Treatment of α-acetoxy ether (**82**) with TMSBr in CH_2Cl_2 at low temperature produced an intermediate that have been identified as the α-bromo ether (**83**). Solvolysis of (**83**) provides the intimate ion pair (**84**). Cyclizations to Alder's chair intermediate (**85**), still as an intimate ion pair, and proximal addition of the bromide produces the observed axial adduct (**86**). According to the principle of the least motion pathway, axial bromide attack would occur. The role of the lutidine is to shut down the less selective HBr-catalyzed cyclization. Further support for a mechanism involving solvolysis of α-bromo ether comes from the cyclization of (**83**) with AcBr, a reagent commonly used to produce α-bromo ethers.



Scheme 1.3.24.

White *et al*. developed a $SnBr_4$ promoted oxonium-Prins cyclization to form 2,3-disubstituted tetrahydrofurans (**87**).[56] For this transformation, a stepwise oxonium-

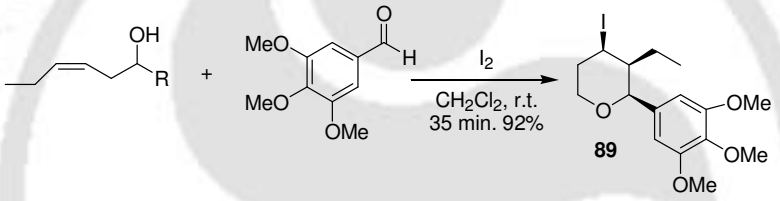


Scheme 1.3.25.

Prins/cation trapping pathway rather than orthoquinonemethide formation/hetero-Diels-Alder cycloaddition is supported computationally (*Scheme 1.3.25*).

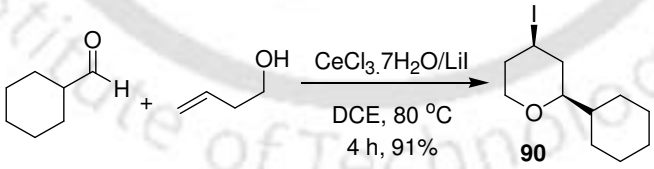
1.3.4.1.4. Synthesis of 4-Iodo-tetrahydropyrans

The reaction of aldehydes with homoallylic alcohols in the presence of TMSI generated in situ from TMSCl and NaI produced 4-iodo-tetrahydropyrans in good yields as a mixture of diastereoisomers. These iodo pyrans were reported for the first time. This methodology was extended to the synthesis of (±)-centrolobine.[57] Yadav *et al*. found that, iodine is an efficient reagent for the coupling of homoallylic alcohols with aldehydes under mild conditions to produce 4-iodotetrahydropyran derivatives in excellent yields in a short reaction time with high selectivity.[58] Reaction of 3,4,5-trimethoxybenzaldehyde with homoallylalcohol in the presence of molecular iodine at ambient temperature gave the corresponding 4-iodotetrahydropyran (**89**) in 92% yield with all *cis*-selectivity (*Scheme 1.3.26*).



Scheme 1.3.26.

Homoallylic alcohols undergo smooth coupling with a variety of aldehydes in the presence of $CeCl_3.7H_2O$–LiI reagent system in refluxing dichloroethane under neutral conditions to produce the corresponding 4-iodotetrahydropyran derivatives (**90**) in high yields (*Scheme 1.3.27*). The spirocyclic-4-iodotetrahydropyrans were obtained in case of cyclic ketones.[59]



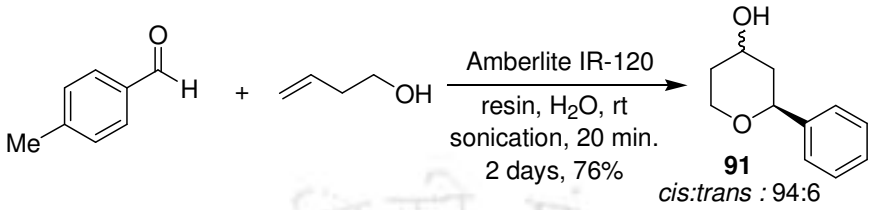
Scheme 1.3.27.

1.3.4.2. Trapping of 4th Position by Oxygenated Nucleophiles

Many examples of Prins cyclization are concerned with the trapping of the tetrahydropyranyl cation by oxygen-centered nucleophiles. Methodologies leading to 4-hydroxy are most often observed and others 4-alkoxy, and 4-alkoxycarbonyl derivatives are also developed.

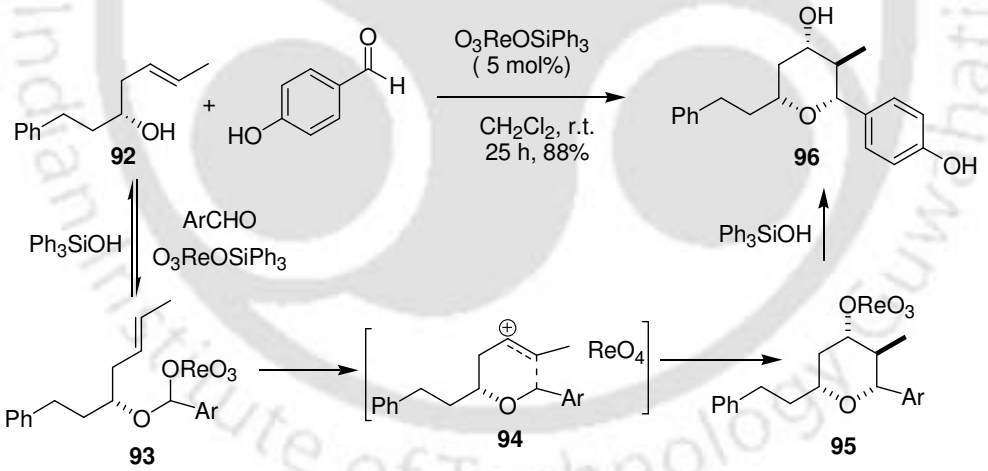
Amberlite® IR-120 Plus resin, a readily regenerated acidic solid resin, mediates the formation of tetrahydropyranol derivatives in water.[60] A mixture of a resin, tolualdehyde in

water after sonication and subsequent addition of homoallylic alcohol affords 4-bromotetrahydropyran (**91**) in two days (*Scheme 1.3.28*).



Scheme 1.3.28.

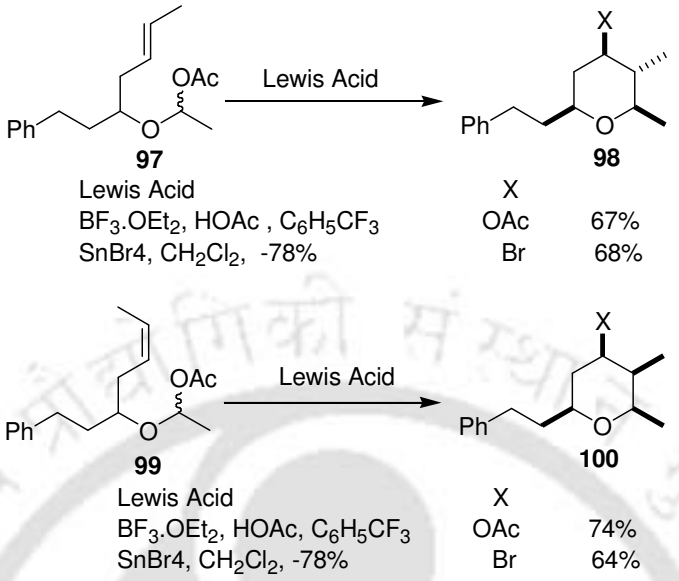
The Rhenium(VII) complex ($O_3ReOSiPh_3$) is particularly effective catalyst for Prins cyclization using aromatic and α, β-unsaturated aldehydes. The reaction proceeds with good selectivity in favor of the formation of equatorial 4-hydroxy-tetrahydropyrans (**96**) in low polarity solvents (*Scheme 1.3.29*).[61] Activation is achieved by forming perrhenate ester (**93**) from homoallylalcohol (**92**). Solvolysis of ester (**93**) generates the intermediate (**94**) as a contact ion



Scheme 1.3.29.

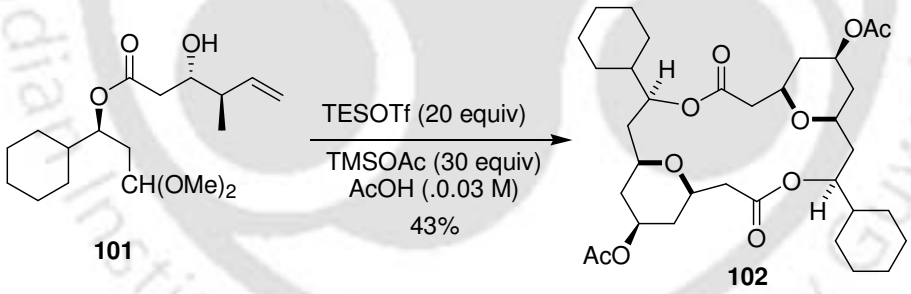
pair. Cyclization and followed by trapping of nucleophile lead to perrhenate ester (**95**). Ester exchange with Ph_3SiOH would regenerate the catalyst. Re_2O_7 and perrhenic acid are equally effective in catalyzing these cyclizations.

Rychonovsky and coworkers synthesized the highly substituted tetrahydropyran by treatment of α-acetoxy ether, with Lewis acid. Alkene geometries dictate the product configurations, with *E*-alkenes (**97**) leading to equatorial substituents (**99**) and *Z*-alkenes (**98**) leading to axial substituents (**100**) (*Scheme 1.3.20*).[62]



Scheme 1.3.20.

Prins-macro cyclization: A tandem dimerization/macrocyclization reaction utilizing the Prins cyclization has been developed. As illustrated in *Scheme 1.3.21*, triethylsilyl



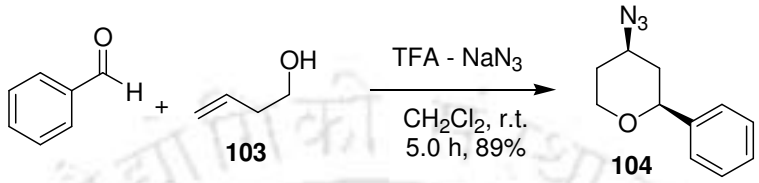
Scheme 1.3.21.

trifluoromethane-sulfonate catalyzed the cyclization of dimethyl acetal (**101**) with trimethylsilyl acetate in acetic acid to give dimeric macrolide (**102**) in 43% yield.[63]

1.3.4.3. Trapping of 4th Position by Nitrogen-centered Nucleophiles

There are rather a few examples of 4-tetrahydropyranyl carbocation trapping by nitrogen-centered nucleophiles in the literature. Methods developed to synthesize 4-Azido- and 4-amido-tetrahydropyrans, are summarized below and in Chapter 2.

A three component coupling of aldehydes, homoallylic alcohols (**103**) and sodium azide in the presence of trifluoroacetic acid in dichloromethane had been developed to produce 4-azidotetrahydropyran (**104**) derivatives in high yields with all *cis*-selectivity (*Scheme 1.3.22*).[64]

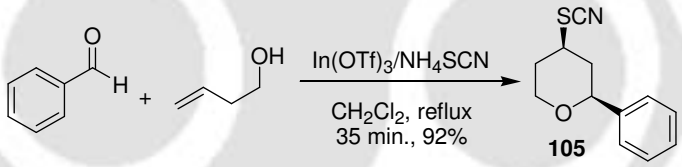


Scheme 1.3.22.

This methodology was improved by replacing strongly acidic conditions and explosive sodium azide with trimethylsilyl azide and 10 mol % phosphomolybdic acid in dichloromethane.[65]

1.3.4.4. Trapping of 4th Position by Sulfur-centered Nucleophiles

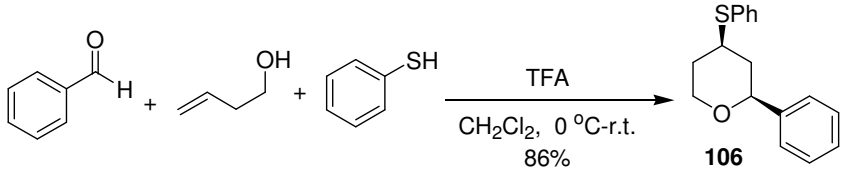
A three-component coupling of aldehydes, homoallylic alcohols and ammonium thiocyanate is achieved in the presence of 10 mol % of $In(OTf)_3$ in refluxing dichloromethane



Scheme 1.3.23.

to produce 4- thiocyanotetrahydropyrans (**105**) in excellent yields with all *cis*-selectivity (*Scheme 1.3.23*).[66]

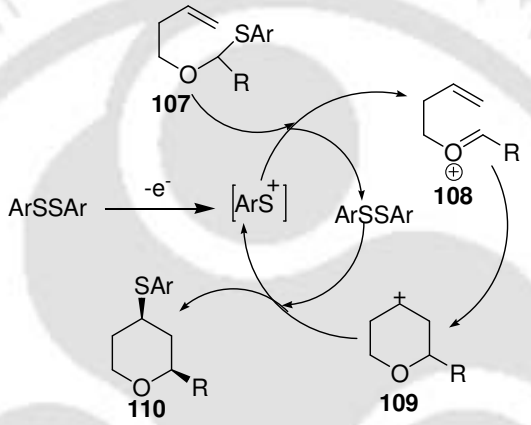
Similarly, a three-component coupling of aldehyde, homoallylic alcohol and aryl thiol has been achieved in the presence of trifluoroacetic acid in dichloromethane at room temperature



Scheme 1.3.24.

to produce 4-arylthiotetrahydropyrans (**106**) in good yields with all *cis*-selectivity (*Scheme 1.3.24*).[67]

The treatment of an olefinic thioacetal (**107**) with a catalytic amount of $ArS(ArSSAr)^+B(C_6F_5)_4^-$, or the electrolysis of a mixture of an olefinic thioacetal and ArSSAr gives rise to effective intramolecular carbon-carbon bond formation. As shown in *Scheme 1.3.25*, the initial electrolysis generates "ArS^+", which reacts with (**107**) to give alkoxycarbenium ion (**108**) and ArSSAr. The cyclization gives (**109**), which reacts with ArSSAr to give product (**110**).

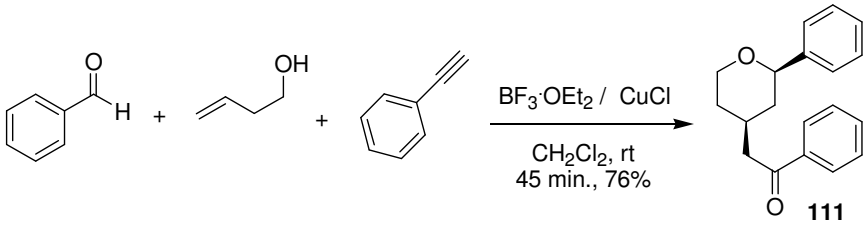


Scheme 1.3.25.

1.3.4.5. Trapping of 4th Position by Carbon-centered Nucleophiles

There are rather a few examples of 4-tetrahydropyranyl carbocation trapping by carbon-centered nucleophiles in the literature. The most frequently encountered examples of C–C bond formation from Prins cyclization involve the Friedel-Crafts reaction. These are summarized below and subsequent Chapters.

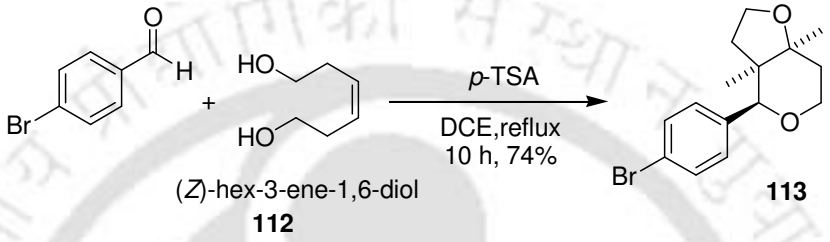
Aldehyde, homoallylic alcohol, and alkyne undergo smooth Prins-type cyclization in the presence of $BF_3.OEt_2$/CuCl (10 mol % each) in dichloromethane under mild reaction conditions to afford 4-phenacyl tetrahydropyran derivatives (**111**) in good yields with short reaction time (*Scheme 1.3.26*).[68]



Scheme 1.3.26.

1.3.4.6. Intramolecular Prins Cyclization

p-Toluenesulfonic acid is found to catalyze the coupling of (*Z*)-hex-3-ene-1,6-diol (**112**) with a series of aldehydes by means of intramolecular-Prins-cyclization to provide the corresponding hexahydro-2*H*-furo[3,2-c]pyran derivatives (**113**) in good yields with complete *cis*-selectivity, whereas the coupling of (*E*)-hex-3-ene-1,6-diol with aliphatic aldehydes give *trans*-fused bicyclic furopyrans (*Scheme 1.3.27*).[69]

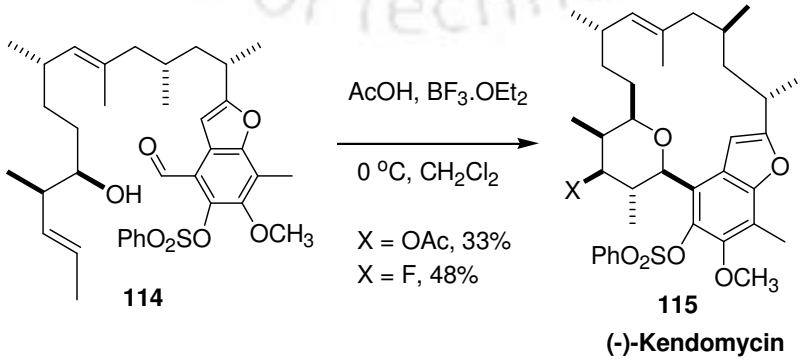


Scheme 1.3.27.

1.3.4.7. Application in Natural Product Synthesis

The Prins cyclization is a potentially powerful method for preparing tetrahydropyran rings. A number of research groups have been investigating Prins cyclization reactions towards the synthesis of natural products.

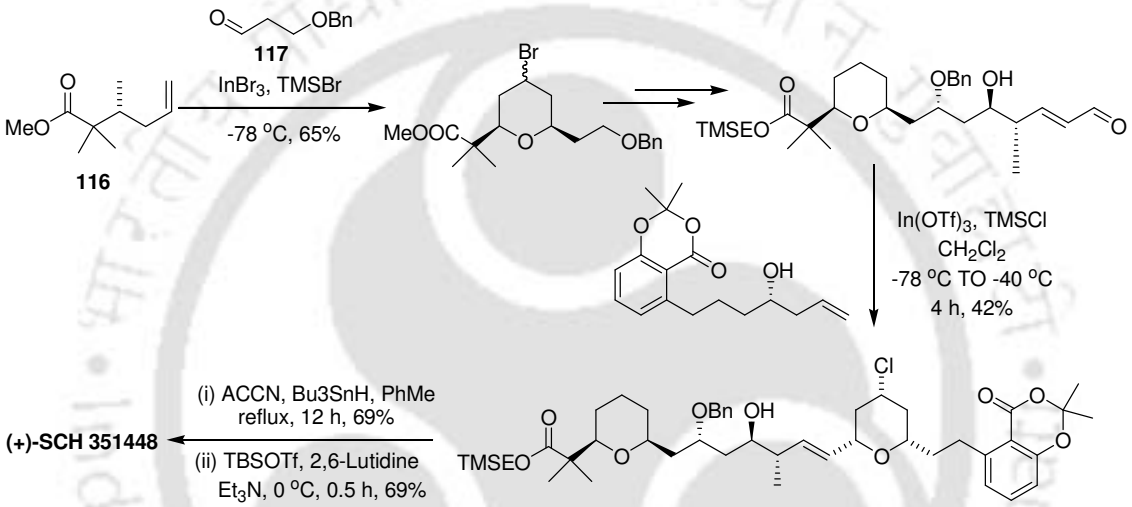
Synthesis of Kendomycin: Kendomycin is an antitumor macrolide antibiotic isolated from the bacteria Streptomyces violaceoruber. It has potent activity as an endothelin receptor antagonist and anti-osteoporosis agent.[70] As shown in *Scheme 1.3.28*, intramolecular macro Prins cyclization using an electron-rich benzaldehyde and a homoallylic alcohol (**114**) efficiently delivered the fully substituted *C*-aryl tetrahydropyranoside (**115**) kendomycin. The selective generation of three new stereocenters in the Prins cyclization facilitated the short and highly convergent assembly of the kendomycin.[71] The reaction was mediated by



Scheme 1.3.28.

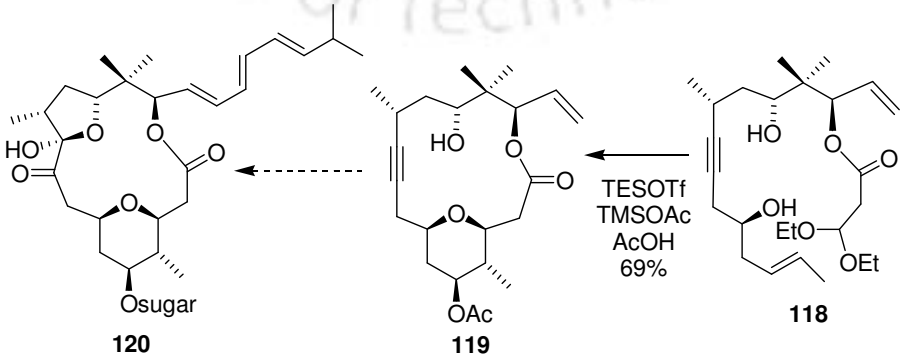
$BF_3{\cdot}OEt_2$ in a heterogeneous non-polar medium. For the electron rich benzaldehyde, the use of acetic acid as a trapping agent is necessary to suppress the side reactions.

Synthesis of (+)-SCH 351448: The dimeric sodiated polyketide (+)-SCH 351448 is the only known selective activator of transcription from the low density lipoprotein receptor. The formal synthesis of (+)-SCH 351448 has been accomplished by Loh and co-workers with the condensation of two complex fragments compound (**116**) and aldehyde (**117**) using catalytic Prins cyclization (*Scheme 1.3.29*).[72]



Scheme 1.3.29.

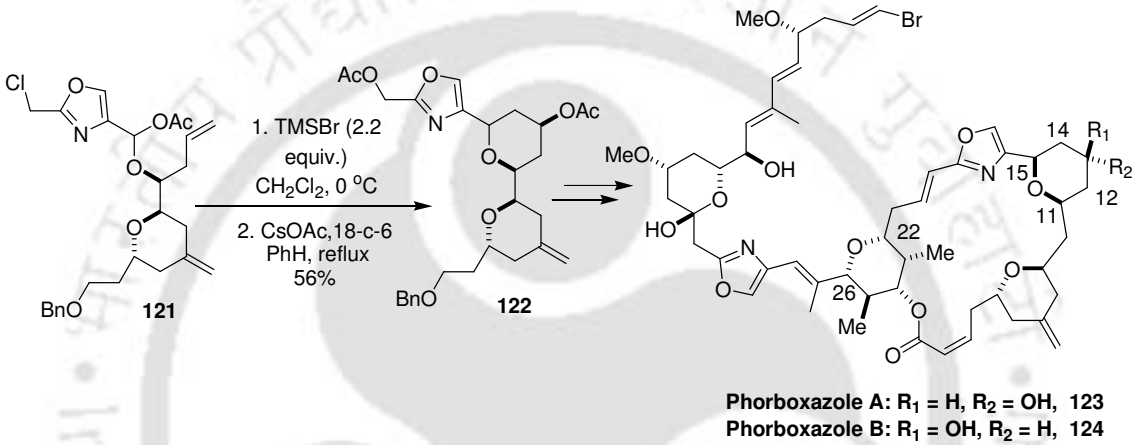
Synthesis of Polycavernoside A: Polycavernoside A (**120**) was isolated by Yasumoto from the edible red alga *Polycavernosa tsudai* as a causative toxin of sudden human intoxication in Guam. An intramolecular Prins macrocyclization strategy was successfully employed by Lee *et al*. for the synthesis of polycavernoside A (*Scheme 1.3.40*).[73] Prins macrocyclization



Scheme 1.3.40.

reaction of **118** proceeded smoothly in the presence of TES triflate, TMS acetate, and acetic acid to give desired macrolactone **119** with 69% yield.

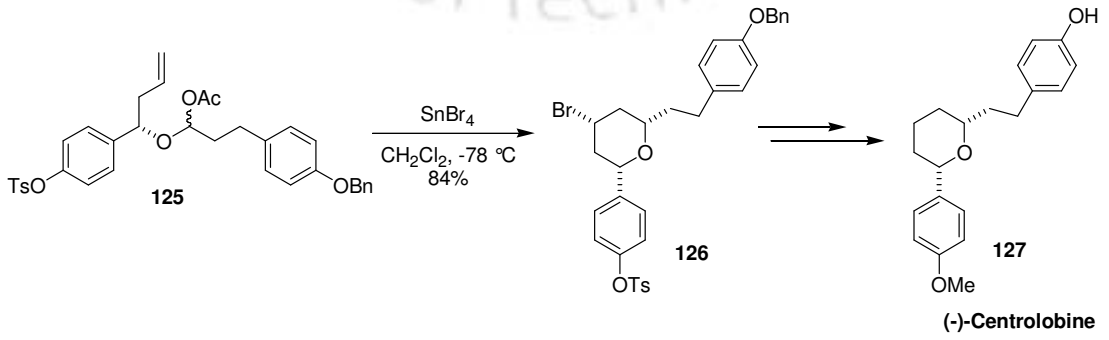
Synthesis of the C3-C19 Segment of phorboxazole B: Phorboxazoles were isolated by Molinski from the Indian Ocean sponge *Phorbas* sp. Phorboxazoles A (**123**) and B (**124**) as a pair of marine macrolides epimeric at C-13. Both possess antifungal activity and are potent antineoplastic agents. Rychnovsky and co-workers[74] have developed a three segment-coupling Prins approaches to the C3-C19 segment of phorboxazole B (*Scheme 1.3.41*). They



Scheme 1.3.41.

utilized a novel TMSBr-mediated cyclization that proceeded with complete axial selectivity. Displacement of bromide with cesium acetate provided the C-13 hydroxyl stereocenter of (**122**). Additionally, treatment of α-acetoxy ether (**121**) with TFA enabled a more concise synthesis of the C3-C19 target (**123**) by allowing direct access to the equatorial alcohol.

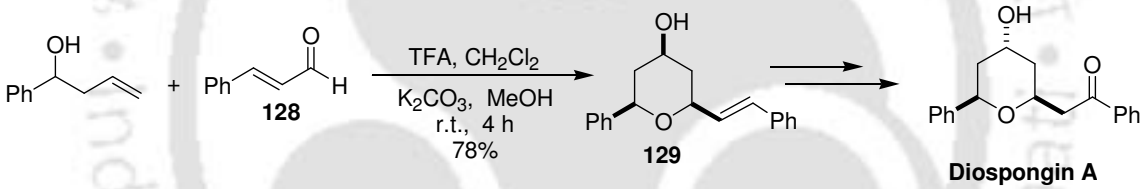
Synthesis of (-)-Centroboline: Several synthesis proceeding via the intermediacy of Prins



Scheme 1.3.42.

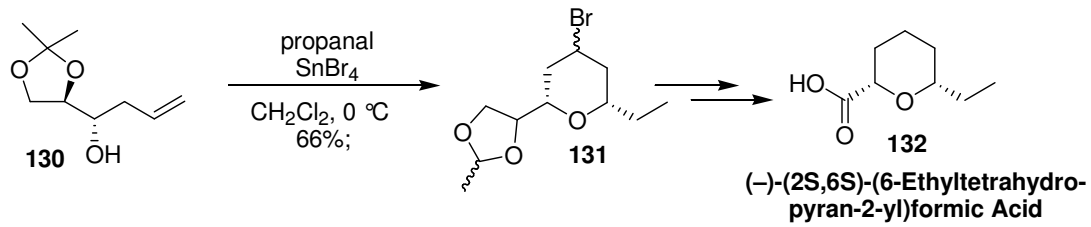
cyclization key steps have been reported for centroboline, an antibiotic isolated from Centrobolium robustum. Loh[75] and Rychnovsky[76] groups have achieved independently the synthesis of (-)-centroboline (**127**). In Rychnovsky strategy, 4-bromo-tetrahydropyran (**125**) was obtained via the reaction of enantiopure α-acetoxy ether (**126**) in the presence of $SnBr_4$ (Scheme **1.3.42**). The racemization takes place through a symmetric 2-oxonia Cope rearrangement that is not observed with α-acetoxy ether precursors.

Synthesis of diospongin A: Piva and coworkers developed a concise and efficient total synthesis of diospongin A using Prins cyclization and enzymatic kinetic resolution as key steps. Many compounds in the diarylheptanoids family exhibit promising biological activities, and diospongin A is active against osteoporosis. 2,4,6-*cis*-Trisubstituted tetrahydropyran ring (**129**) was achieved via a Prins reaction of benzaldehyde and homoallylic alcohol (**128**) (*Scheme 1.3.43*).[78] It enabled control of the relative configuration of the three stereogenic centers contained in the natural product.



Scheme 1.3.43.

Synthesis of (±)-cis-(6-Ethyltetrahydropyran-2-yl)formic acid: (±)-*cis*-(6-Ethyltetrahydropyran-2-yl)formic acid (**132**), is a novel class of non-steroidal analgesic compound. Vasconcello and coworkers described the enantioselective synthesis of (–)-(2*S*,6*S*)-(6-ethyl-tetrahydropyran-2-yl)-formic acid (**132**) in five steps (30% overall yield, 87% ee), from the commercial chiral template (*R*)-2,3-isopropylideneglyceraldehyde (**130**). An efficient Prins cyclization reaction between **130** with propanal mediated by $SnBr_4$ resulted

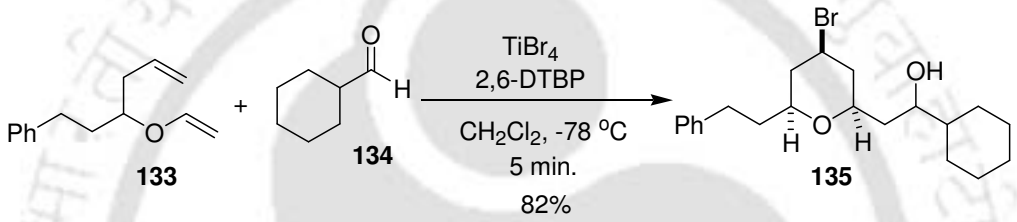


Scheme 1.3.44.

in a mixture of four diastereomers (**131**) (*Scheme 1.3.44*).[79] Reduction of the latter, followed by oxidative cleavage of diol, led to the levo enantiomer of (**132**) in 87% ee.

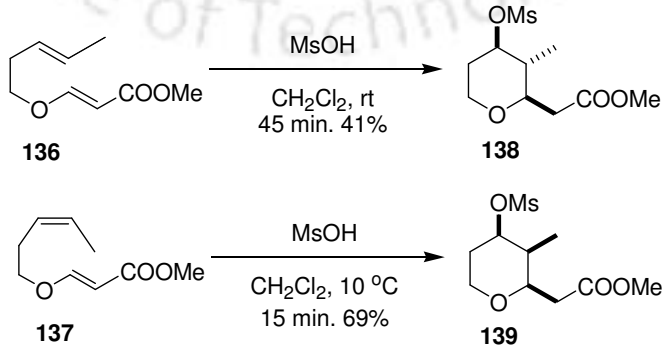
1.3.5. Mukaiyama Aldol–Prins Cyclizations

A new version of the Mukaiyama aldol-Prins (MAP) cyclization has also been developed. Unsaturated enol ethers such as (**133**) were found to couple with aldehydes (**134**) in the presence of $TiBr_4$ to give 4-bromotetrahydropyran (**135**) products (*Scheme 1.3.45*).[80] This cascade reaction sequence leads to the formation of two new carbon-carbon bonds, a ring, and three new stereogenic centers. The same reaction can also be performed with ketone.[81]



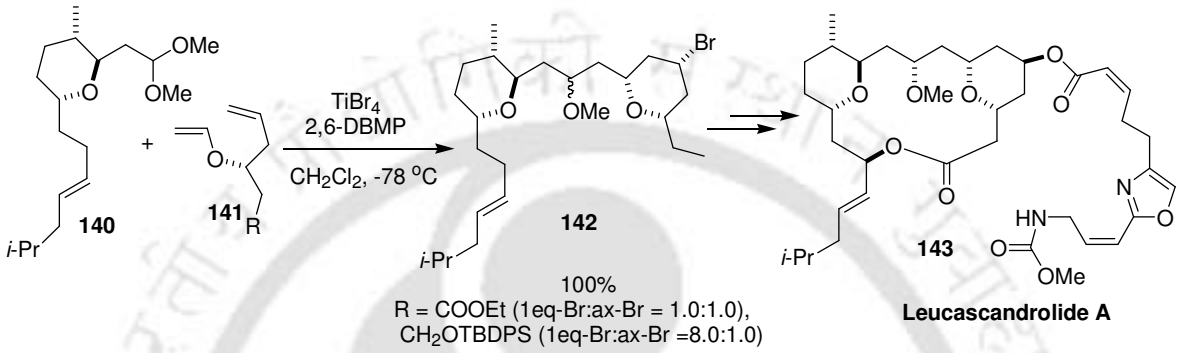
Scheme 1.3.45.

The Mukaiyama-Prins cyclization with *E*- and *Z*-alkenes are shown to be stereospecific. As shown in *Scheme 1.3.46*, the reaction of [(3*E*)-pent-3-enyloxy]acrylate (**136**) in the presence of an excess of MsOH, provided the all-equatorial product (**138**) in 41% yield. Under similar reaction conditions, [(3*Z*)-pent-3-enyloxy]acrylate (**137**) afforded the (2RS,3SR,4RS)-diastereoisomer (**139**) in 69% yield. Hence, it is easily possible to control the configuration at C-3' of the tetrahydro-2*H*-pyran system formed by this Prins-type cyclization of (alk-3-enyloxy)acrylates.[82]



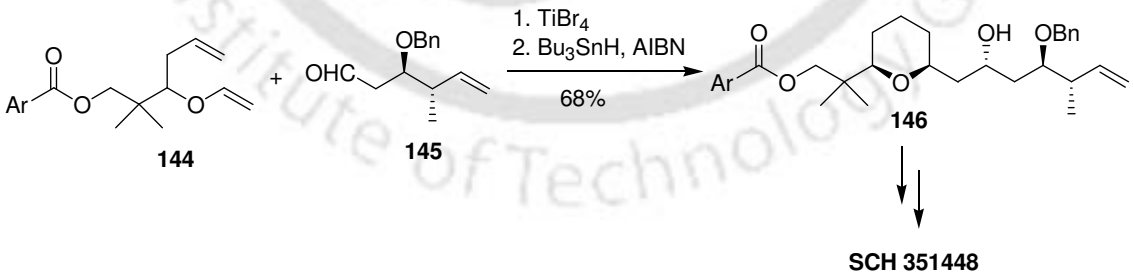
Scheme 1.3.46.

Total Synthesis of Leucascandrolide A: The macrolactone leucascandrolide A (**143**), isolated from the calcareous sponge *L. caveolata*, has both cytotoxic and antifungal activity. The key step in the synthesis of (**142**) reported by Rychnovsky[83] was the stereoselective condensation of the aldehyde (**140**) with homoallyl vinyl ether (**141**) in presence of titanium tetetrabromide (*Scheme 1.3.47*).



Scheme 1.3.47.

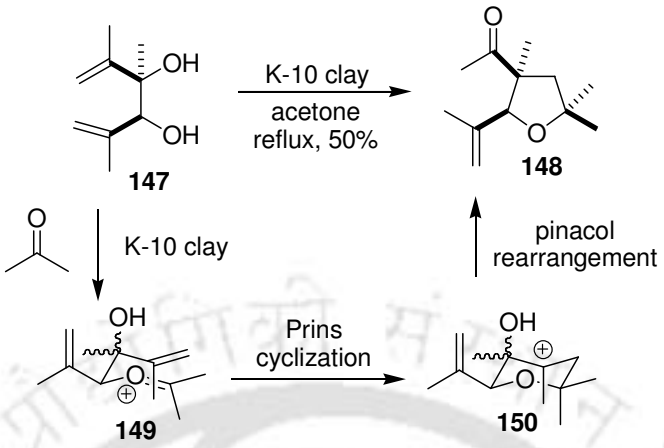
The synthesis and absolute configuration of SCH 351448, an interesting ionophoric natural product, had been reported. Mukaiyama aldol and segment-coupling of Prins reactions were employed to construct the constituent tetrahydropyrans of SCH 351448. The key step in the synthesis of (**146**) was developed from the condensation of the aldehyde (**145**) with homoallyl vinyl ether (**144**) in presence of $TiBr_4$ followed by reduction with Bu_3SnH and AIBN (*Scheme 1.3.48*).[84]



Scheme 1.3.48.

1.3.6. Prins-Pinacol rearrangement

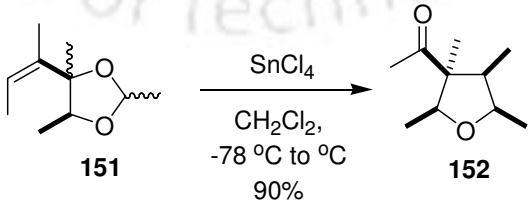
Prins-pinacol reactions are employed to construct a wide variety of oxacyclic ring systems.[85] A wide variety of polysubstituted tetrahydrofurans can be prepared by condensation of allylic diols with aldehydes or ketones in a reaction sequence whose central step is a pinacol-terminated Prins cyclization. Mousset and co-workers discovered this cascade reaction in



Scheme 1.3.49.

an attempt to make the acetonide of meso allylic diol (**147**) by condensation with acetone in the presence of an acidic clay catalyst, these investigators instead obtained tetrahydrofuran (**148**) in high yield (*Scheme 1.3.49*).[85] Condensation of (**147**) and acetone to generate an oxocarbenium ion (**149**) that underwent Prins cyclization via chair conformer, followed by pinacol rearrangement of the resulting hydropyranyl α-hydroxy carbenium ion (**150**) to ultimately generate the tetrahydrofuran product (**148**). In this high-yielding and stereoselective process, two C-C bonds, one C-O bond, and two fully substituted carbon stereocenters were created.

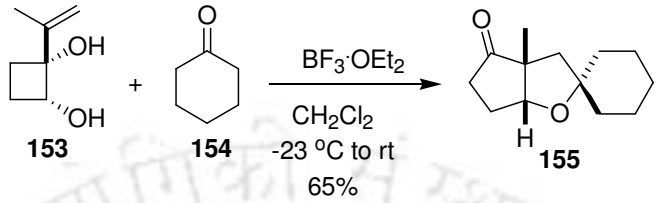
Overman *et al*.[86] synthesized variety of polysubstituted 3-acyltetrahydrofurans. 4-Alkenyl-1,3-dioxolanes undergo pinacol rearrangements to terminate cationic Prins cyclizations which has subsequently been shown to be a powerful strategy for designing stereoselective ring forming cascade reactions. 4-Alkenyl-1,3-dioxolanes (**151**) upon treatment with a slight excess of $SnCl_4$ gave tetrahydrofuran (**152**) in 90% yield (*Scheme 1.3.50*).



Scheme 1.3.50.

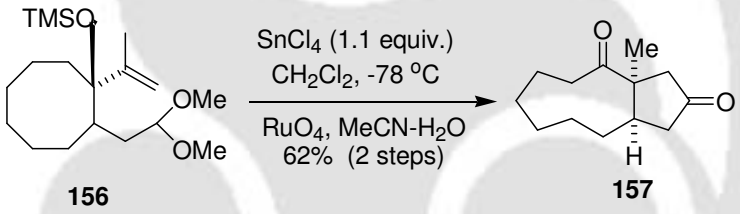
Ring-enlarging tetrahydrofuran: Substituted cycloheptatetrahydrofurans and octahydrobenzo-furans are formed with high levels of stereocontrol by acid-promoted rearrangement of acetals derived from 1-alkenyl-2-hydroxy-cyclohexanols and 1-alkenyl-2-

hydroxycyclopentanols, respectively. Ring-enlarging tetrahydrofuran annulation results from (*Scheme 1.3.51*) the Lewis acid-catalyzed condensation of propenyl cyclobutane diol (**153**) and cyclohexanone (**154**) to gave tricyclic ether (**155**).[87a,b]



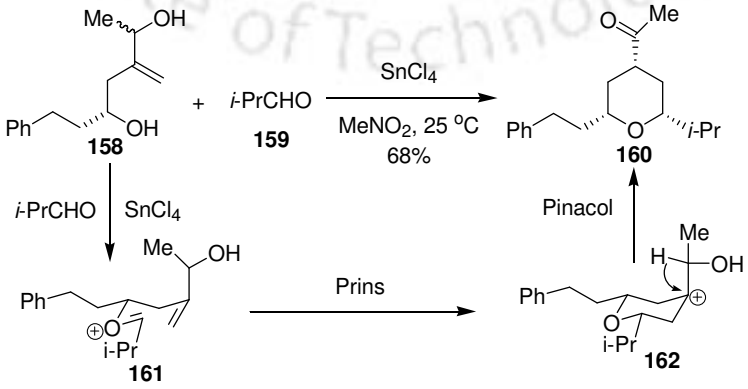
Scheme 1.3.51.

Bicyclo[7.3.0]dodecanediones can be prepared in a similar fashion. The condensation of cyclooctane alkenyl acetal (**156**) with $SnCl_4$ undergoes Prins-pinacol rearrangement to give *cis*-bicyclo[7.3.0]dodecanedione (**157**) in 62% overall yield (*Scheme 1.3.52*).[88]



Scheme 1.3.52.

Overman *et al*. prepared tetrahydropyrans (**160**) conveniently by acid-promoted condensation of 2-methylene-1,4-diols with aldehydes. Although two α-alkoxycarbenium ions can be generated from condensation of an aldehyde (**159**) with unsaturated diol (**158**), preferential

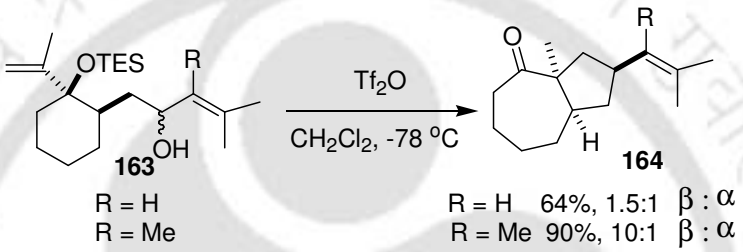


Scheme 1.3.53.

oxonium ion (**161**) forms, as depicted in cyclization of the more stable *E*-oxonium ion

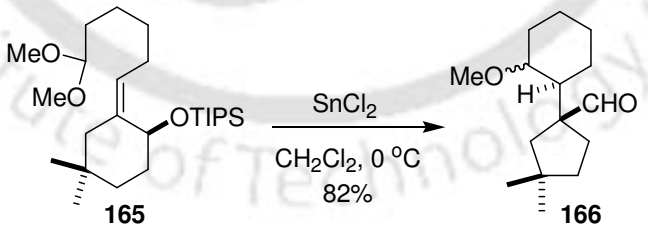
stereoisomer. Prins cyclization of (**161**) would generate cation (**162**). Followed by pinacol shift, occurring with preferential axial hydride delivery, would complete the reaction (*Scheme 1.3.53*).[89]

Allylic alcohols showed to be highly efficacious initiators of cationic cyclization reactions. Overman *et al.*[90] generated an allylic cation from a 1-[2-alkenyl-2-(trialkylsiloxy)-cycloalkyl]- alk-3-en-2-ol (**163**) which initiate ring-expanding cyclopentane annulations to provide a bicyclo[*n*.3.0]alkanone (**164**) product containing a 2-alkenyl side chain on the cyclopentane fragment (*Scheme 1.3.54*).



Scheme 1.3.54.

Overman and coworkers also demonstrated another useful transformation. Prins cyclization of (*E*)-alkylidene cyclohexane (**165**) promoted by $SnCl_4$ followed by pinacolic ring-contraction gave 1-(cyclohexyl)-cyclopentanecarbaldehyde (**166**), as a mixture of methoxy epimers in 82% yield (*Scheme **1.3.55.***).[91]

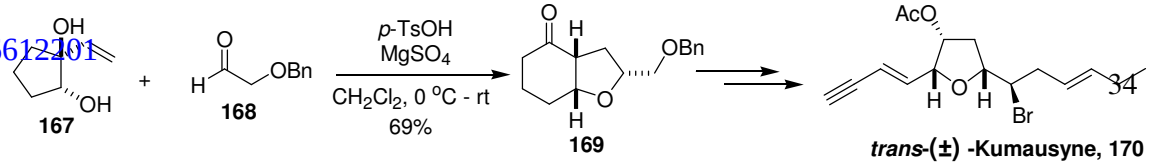


Scheme 1.3.55.

Prins-pinacol Rearrangement in the Synthesis of Natural Products

Prins-pinacol reactions are employed to construct a wide variety of oxacyclic ring systems and extended to synthesis of bioactive natural products.

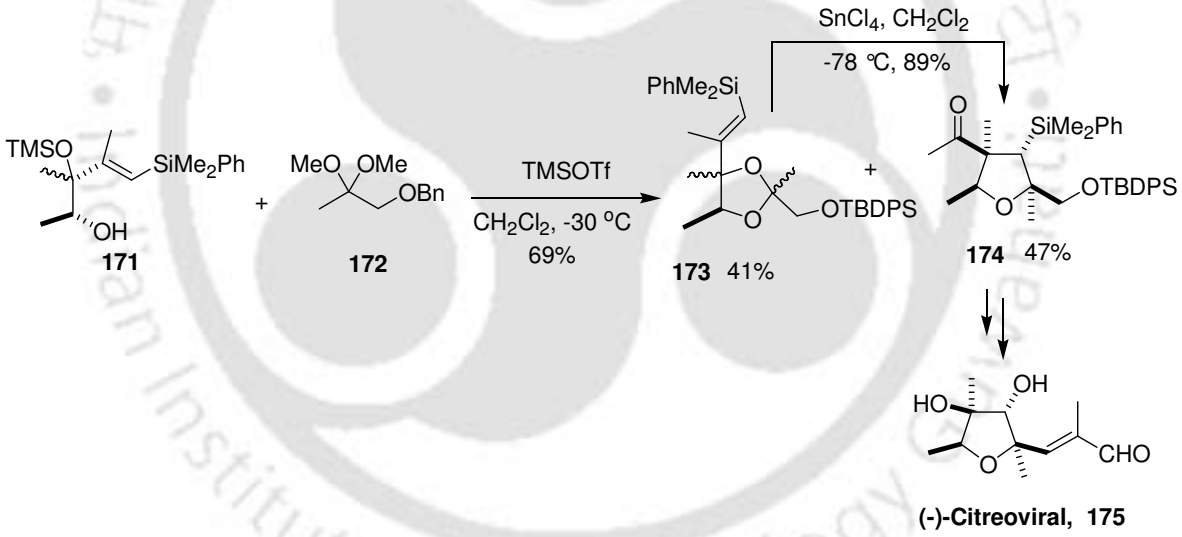
Total Synthesis of ((±)-Kumausyne: A general strategy for the synthesis of C_{15} halogenated



tetrahydrofuranoid lipids from red algae of the genus *Luurenciu* has been developed by Overman and co-workers.[92] The total synthesis of (±)-*trans*-kumausyne from *rac*-**170** was accomplished in 13 steps and >*5%* overall yield. The central step is the convenient formation of (±)-hydrobenzofuranone (**169)** *on* a large scale, and with complete stereocontrol, from the acid-catalyzed condensation of 1 -vinylcyclopentanediol (**167**) and a-(benzy1oxy)acetaldehyde (**168**). Starting with the chiral, nonracemic (lS,2R) diol (**167**), (-)-hydrobenzofuranone (**169)** was also available in good enantiomeric purity. (*Scheme 1.3.56*).

Scheme 1.3.56.

Oveman was the first to present synthesis enantiomer of citreoviral (**175**), in 16 steps and 2.4% overall yield. Moreover, the key step was the synthesis 3-acyltetrahydrofuran (**174**) from condensation of (**171**) with dimethyl ketal (**172**) in the presence of TMSOTf at -30 °C

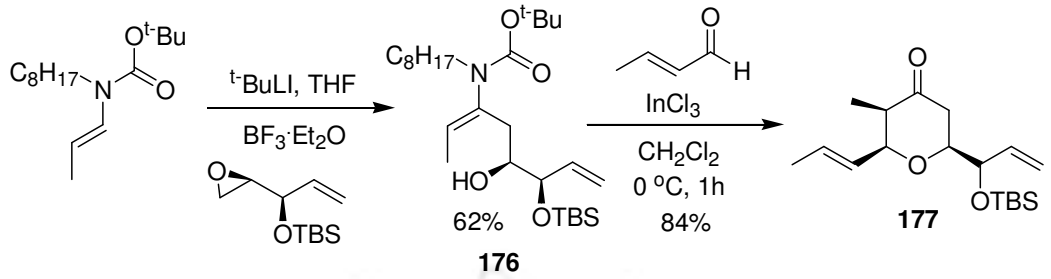


Scheme 1.3.57.

in CH_2Cl_2 in 88% yield with a separable mixture of acetals (**173**). Compound (**173**) could be converted efficiently to (**174**) by exposure to $SnCl_4$ at -78 °C in CH_2Cl_2 (*Scheme 1.3.57*).[93]

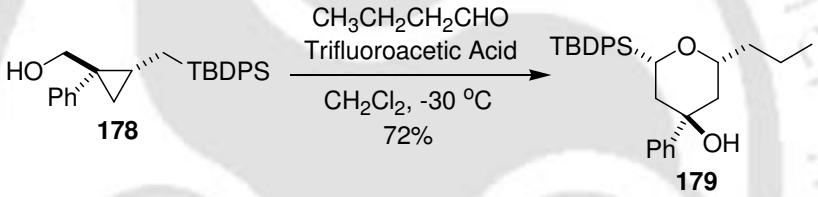
1.3.7. Miscellaneous Prins Cyclization Reactions

Cyclization involving Ene-carbamates: Funk and co-workers developed a diastereoselective synthesis of 2,3,6-trisubstituted tetrahydro-pyran-4-ones via Prins cyclization of enecarbamates.[94] As exemplified in *Scheme 1.3.58*, the reaction of (**176**) with crotonaldehyde led to trisubstituted 2,3,6-*cis,cis*-tetrahydropyran-4-one (**177**).



Scheme 1.3.58.

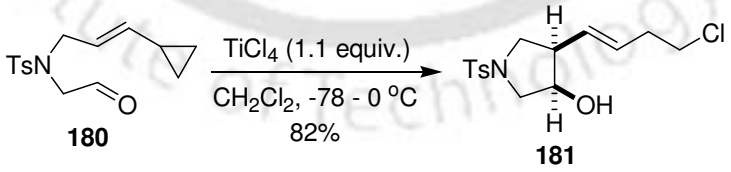
Yadav and co-workers[95] developed a Prins cyclization of a silicon-stabilized homoallyl cation formed from a cyclopropyl carbinol that was vicinally substituted by a silylmethyl function. The reaction was applied to the synthesis of 2,4,6-trisubstituted tetrahydropyran rings in good to excellent yields. As illustrated in *Scheme 1.3.59*, butyraldehyde reacted with (**178**) in the



Scheme 1.3.59.

presence of trifluoroacetic acid in CH_2Cl_2 at -30 °C to furnish compound (**179**) in 72% yield as a single isomer. The reaction introduces three stereogenic centers in the product.

Yu and co-workers developed an intramolecular Prins type cyclization of cyclopropylvinylic aldehydes (**180**) promoted by $TiCl_4$ under mild reaction conditions to form *cis*-cyclic products

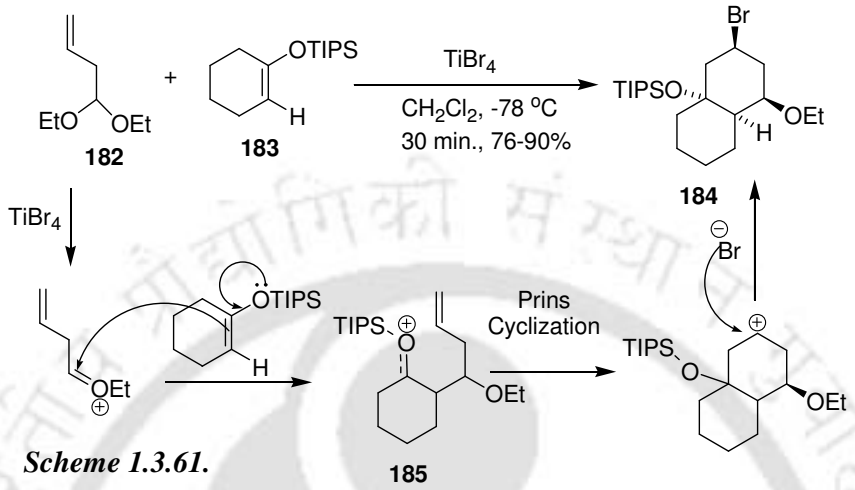


Scheme 1.3.60.

(**181**) in high yield (*Scheme 1.3.60*).[96]

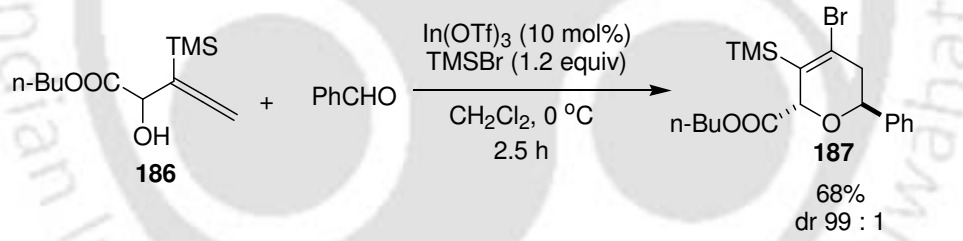
Loh and co-workers[98] established new type Prins cyclization, as shown in *Scheme 1.3.61*. The reaction involves the Mukaiyama-Aldol reaction in presence of $TiBr_4$, silyl enol ether (**183**) with acetal (**182**) via an oxocarbenium intermediate (**185**), which upon trapping by an alkene functionality in an intramolecular Prins cyclization fashion, gives bridged bicyclic ring system (**184**).

Cyclization involving allenes: Loh *et al.*[98] showed an efficient Prins cyclization of carboalkoxyl allenic alcohols with aldehyde. As depicted in *Scheme 1.3.62*, $In(OTf)_3$



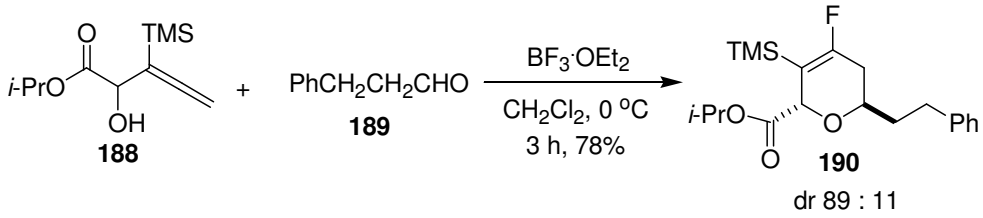
Scheme 1.3.61.

catalyzed the cyclization of carboalkoxyl allenic alcohol (**186**) in the presence of TMSBr to give 2,6-*trans* dihydropyrans (**187**) in 68% yield and high diastereoselectivity.



Scheme 1.3.62.

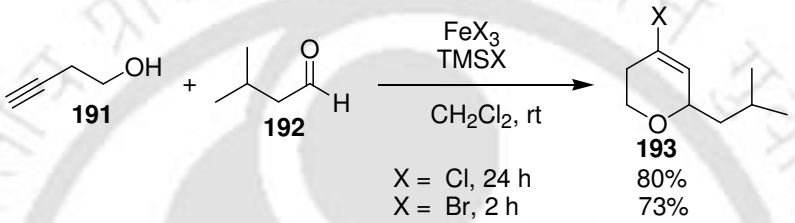
Similarly, fluorinated 2,6-*trans* dihydropyrans were synthesized via $BF_3{\cdot}Et_2O$ promoted Prins cyclization of allenic alcohols (**188**) with aldehydes (**189**). Various 2,6-*trans* fluorodihydropyrans (**190**) were synthesized in moderate to good yields with excellent diastereoselectivities (*Scheme 1.3.63*).[99]



Scheme 1.3.63.

1.3.8. Cyclization involving Homopropargylic alcohol

More recently, Martin has also explored the synthetic potential of cyclization involving homopropargylic alcohols.[100] Reactions of homopropargylic alcohol (**191**) and aldehyde (**192**) mediated by anhydrous $FeCl_3$ or $FeBr_3$ led to 4-halo-2-alkyl-5,6-dihydro-2*H*- pyrans (**193**) in yields ranging from 30 to 98%. Optimization of the experimental conditions has established that the best source of halide anion was TMSX in the presence of 7 mol % of the iron catalyst FeX_3 (*Scheme 1.3.64*). The cyclization could also be mediated with $InCl_3$ and $InBr_3$, but the times of reaction were much longer and the yields were slightly lower.

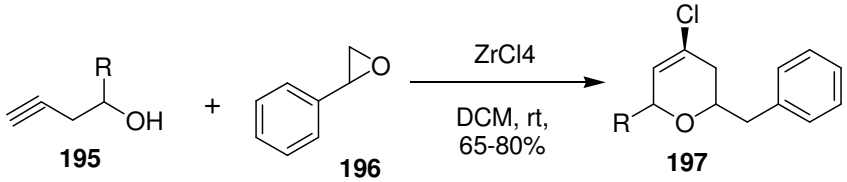


Scheme 1.3.64.

The reaction also catalyzed by $Fe(acac)_3$ to construct the chloro, bromo and iodo heterocycles (**194**), by the suitable combination of iron(III) source, the corresponding trimethylsilyl halide and the solvent, in high yields (*Scheme 1.3.65*).[101]

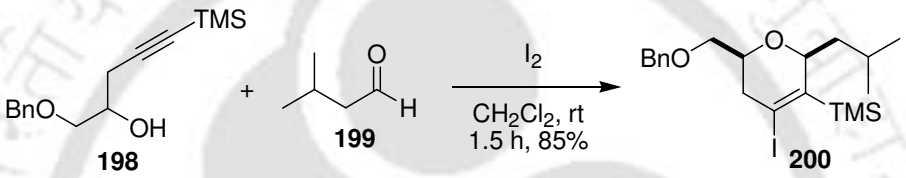
Scheme 1.3.65.

Epoxides (**196**) which function as aldehyde equivalent undergo cyclization with homopropargylic alcohols (**195**) in the presence of zirconium tetrachloride under mild conditions to afford the corresponding dihydropyran derivatives (**197**) in excellent yields under mild conditions (*Scheme 1.3.66*).[102]



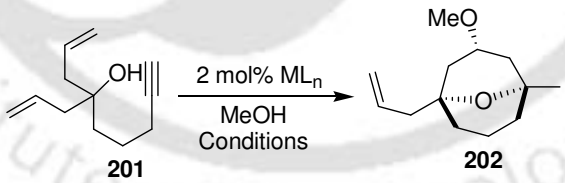
Scheme 1.3.66.

The silylated secondary homopropargylic alcohols (**198**) undergo smooth coupling with aldehydes (**199**) in the presence of molecular iodine under mild reaction conditions to produce 4-iododihydropyrans (**200**) in good yields.[103] This method is highly stereoselective, affording *cis*-dihydropyrans exclusively (*Scheme 1.3.67*).



Scheme 1.3.67.

Tandem gold- or platinum-promoted cycloisomerization/Prins cyclization leading to bridged bicyclic tetrahydropyran has been devised by Barluenga and co-workers.[104] As for example, homoallylic alkynol (**201**) led to bicylic ether (**202**) in 92–94% yield (*Scheme 1.3.68*).

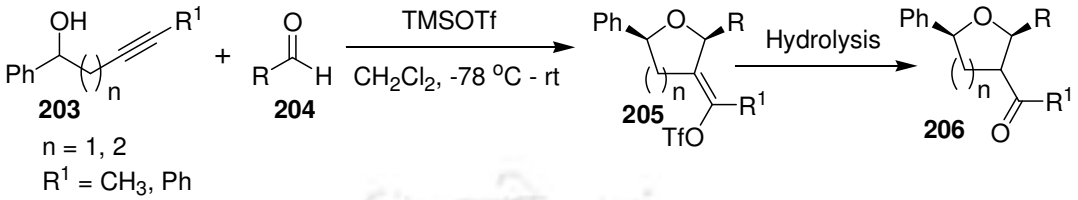


ML_n	Conditions	Yield(%)
$[PtCl_2(cod)]$	65 °C, 12 h	95
$PtCl_4$	65 °C, 0.5 h	96
$AuCl_3$	rt, 1 h	94

Scheme 1.3.68.

3-Furanylidenes and 3-pyranylidens having *cis*-2,5 and *cis*-2,6 substitution were synthesized from terminally substituted alkynyl alcohols (**203**) with various aldehydes (**204**) via Prins-type cyclization.[105] Those 3-furanylidenes and 3-pyranylidenes (**205**) underwent hydrolysis to give the corresponding 3-acyl-substituted products having *all-cis*-configured isomers, such as

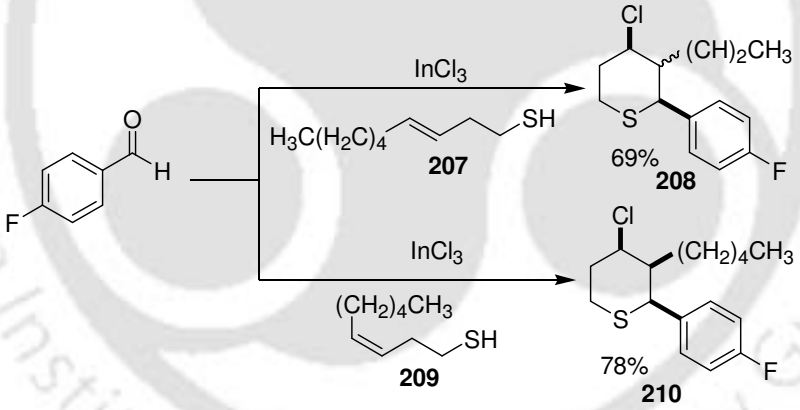
2,3,5-trisubstituted tetrahydrofurans and 2,3,6-trisubstituted tetrahydropyrans (**206**) (*Scheme 1.3.69*).



Scheme 1.3.69.

1.3.9. Thia-Prins cyclization

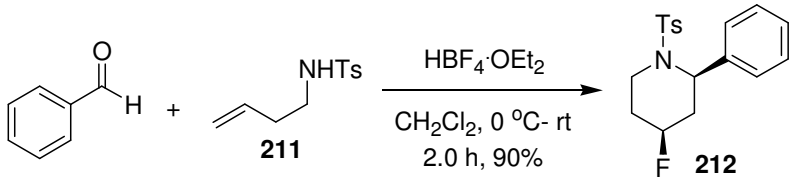
The reaction of *cis*-aliphatic homoallylic mercaptan (**207**) with 4-fluoro-benzaldehyde generated unsymmetrical 2,3,4-trisubstituted thiacyclohexanes (**208**) in 78% yield and with good diastereoselectivity. The diastereoselectivity remains nearly the same in all cases favoring the *cis–trans–cis*-isomers. Similarly *trans*-aliphatic homoallyl mercaptan (**209**) gave compound (**210**) in 69% yield (*Scheme 1.3.70*).[106]



Scheme 1.3.70.

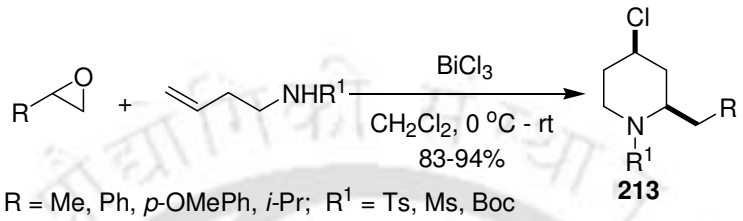
1.3.9. Aza-Prins cyclization

The reaction of aldehydes with N-tosyl homoallylamine (**211**) in the presence of a solution of tetrafluoroboric acid-diethyl ether complex in dichloromethane at ambient temperature gave the 4-fluoropiperidines (**212**) in good yields and with high *cis*-selectivity (*Scheme 1.3.71*).[107]



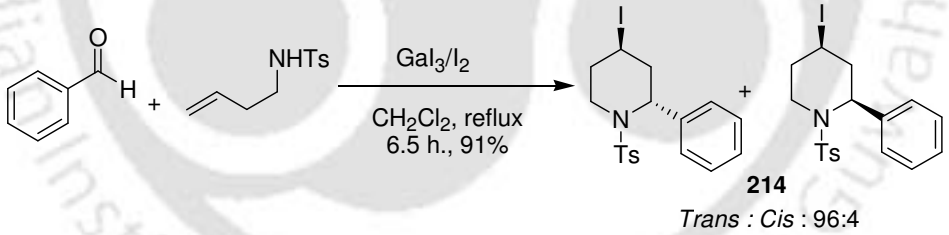
Scheme 1.3.71.

Several N-protected homoallyl amines and epoxides were subjected to an aza-Prins cyclization. A rapid and efficient $BiCl_3$ promoted stereoselective synthesis of *trans*-2,4-disubstituted piperidine derivatives (**213**) was also reported (*Scheme 1.3.72*).[108]



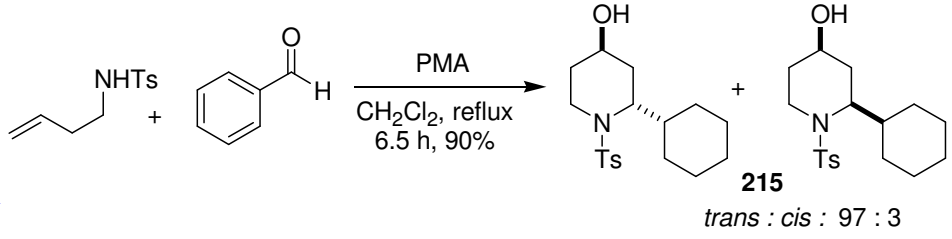
Scheme 1.3.72.

4-Iodopiperidines were prepared with high selectivity by means of aza-Prins-cyclization using a catalytic amount of gallium(III) iodide and a stoichiometric amount of iodine.[109] The treatment of benzaldehyde with N-tosylhomoallyl amine in the presence of 10 mol % of GaI_3 and a stoichiometric amount of molecular iodine at ambient temperature over 6.5 h gave the corresponding 4-iodo-2-phenylpiperidine (**214**) in 91% yield with *trans*-selectivity (*Scheme 1.3.73*).



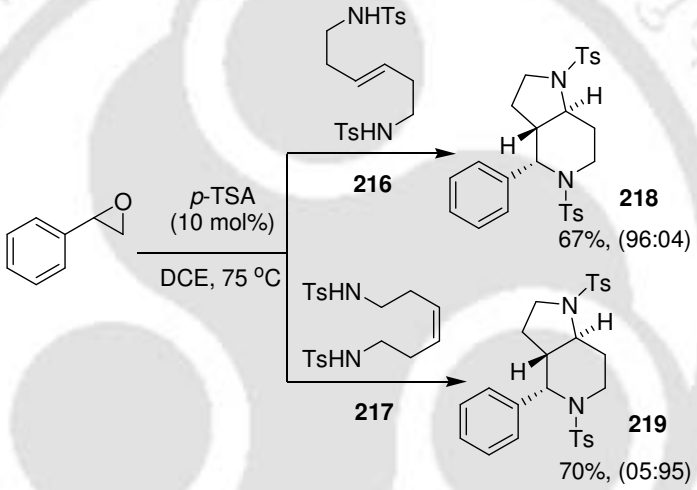
Scheme 1.3.73.

Yadav *et al*. first reported the synthesis of 4-hydroxypiperidines via aza-Prins-cyclization. They attempted the coupling of benzaldehyde with N-tosyl homoallylic amine in the presence of 10 mol % phosphomolybdic acid in refluxing dichloromethane. The reaction went to completion in 6.5 h and the corresponding 4-hydroxy-2-phenylpiperidine (**215**) was obtained in 90% yield with *trans*-selectivity (*Scheme 1.3.74*).[110]



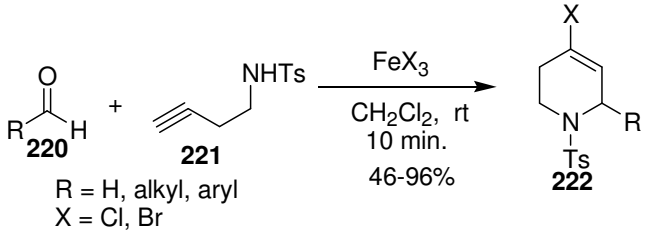
Scheme 1.3.74.

Aryl epoxides undergo coupling smoothly with (*E*)-hex-3-ene-1,6-ditosylamide (**216**) in the presence of 10 mol% *p*-TSA in 1,2-dichloroethane at 75 ^{o}C to produce the corresponding 1,5-ditosyl-octahydro-1*H*-pyrrolidino-[3,2-*c*]pyridines (**218**) in good yields with high *trans*-selectivity, whereas the coupling of (*Z*)-hex-3-ene-1,6-ditosylamide (**217**) gave *cis*-fused octahydro-1*H*-pyrrolidino[3,2-*c*] pyridines predominantly (**219**) (*Scheme 1.3.75*).[111]



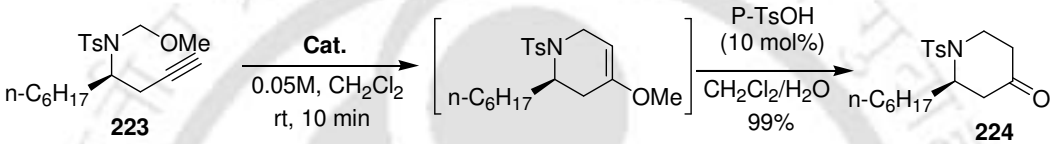
Scheme 1.3.75.

Martin and Juan group developed a $FeCl_3$ catalyzed alkyne-Prins cyclization[111] by using homopropargyl derivatives (**220**) and aldehyde (**221**) to give the unsaturated six membered ring heterocycles (**222**) using TMSCl as the halide source in the presence FeX_3 in CH_2Cl_2 at room tempereature (*Scheme 1.3.76*). They also used $Fe(acac)_3$ as catalyst the related iron species was as efficient as $FeCl_3$.[112]



Scheme 1.3.76.

A new gold(I)-catalyzed cycloisomerization to access highly substituted piperidines has been developed by Rhee *et al*..[113] Combining a conceptually new way of generating iminium ions using cationic gold(I) complexes and an efficient cyclization reaction that can minimize a potentially competing aza-Cope rearrangement, the proposed reaction successfully circumvents a long-standing problem in the classical aza-Prins reaction. The gold(I)-catalyzed cycloisomerization of tosyl-protected homopropargylic amines (**223**) was easily converted into (**224**) in 99% yield under acidic conditions (*Scheme 1.3.77*).



Cat. = [Au(P(C6F5)3)]SbF6 (5 mol%) / 2,6-di-tert-butylpyridine (4 mol%)

Scheme 1.3.77.

1.4. Conclusion

The Prins reaction is a very interesting route to form carbon-carbon bonds. The different acid catalysts have been studied in order to control the outcome of the reaction. The Prins cyclization is the powerful and versatile tools for the synthesis of functionalized tetrahydropyran skeletons that are commonly encountered in a wide range of biologically active natural products. Most of the cases good control of stereoselectivity is observed. Finally, the Prins cyclization and the corresponding tandem reaction have become a key strategic process in the total synthesis of heterocyclic and carbocyclic natural products. In combination with Prins cyclization other reactions such as pinacol rearrangement, Mukaiyama aldol, Friedel-Crafts have been developed. In combination with other tandem reactions Barbier-Prins and Sakurai-Prins have also been developed. Extensive mechanistic studies have led to a clear understanding of the most subtle aspects of the reaction. There are plenty of refinements in the recent literature. These results overcome oxonia-cope side reaction and racemization in the cyclization. Progress is such that the building of more and more complex substitution patterns, and the enantioselective synthesis of complex targets may now be achieved.

A few examples of the extension to the synthesis of analogous sulfur-containing heterocycles have been reported. Aza-Prins cyclizations, involving cyclization onto iminium ions less electrophilic than oxocarbenium ions, have received much less attention. However, as

exemplified by selected applications, the latter reaction enables access to complex aza-polycyclic skeletons in a single step.

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CHAPTER 2

Stereoselective Synthesis of 4-Amidotetrahydropyrans

2.1. Importance and Applications

4-Aminotetrahydropyran skeleton is a core structure in a number of bioactive molecules[1] and natural products such as ambruticins VS, glycamino acid, sialic acid and others.[2] The compound **1**[3] (*Figure 2.1.1*) is a heat-developable photosensitive material used in photographic films. Compound **2** (*Figure 2.1.1*) is a non-macro cyclic supramolecule showed appreciable binding with alkali metals[4] (Li^+, Na^+, and K^+) with association constants (*K*a) greater than 10^7-10^8 and compound **3** (*Figure 2.1.1*) is a melanocortin receptor agonist.[5]

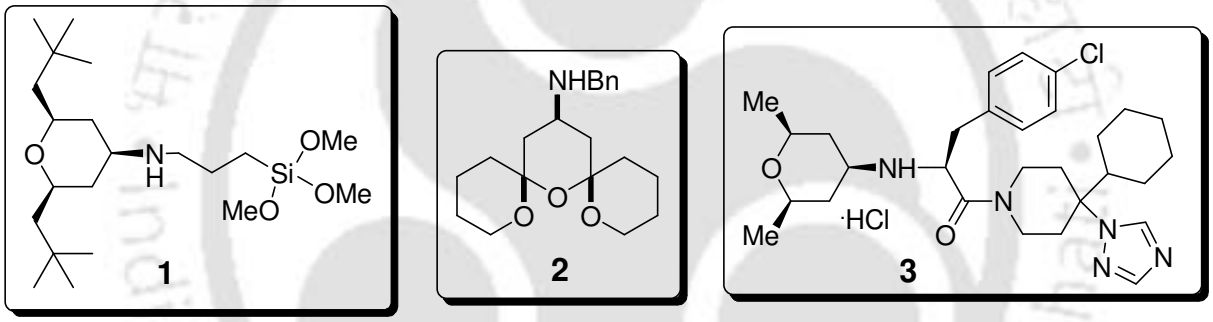


Figure 2.1.1. *Examples of some biologically active 4-amino-tetrahydropyran derivatives*

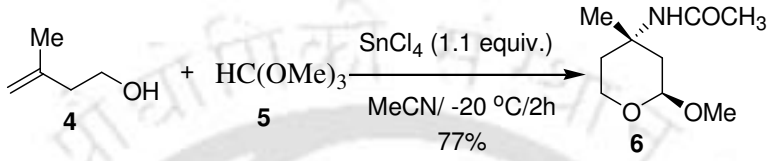
2.2 An Overview of Relevant Synthetic Methods

Review of literature reveals that several strategies were developed for the synthesis of 4-amido-*six*-membered heterocycles. Prins cyclization followed by Ritter reaction received considerable attention and showed a significant progress to develop a 4-amidotetrahydropyrans. They are summarized below and have already been discussed in introduction.

Tandem Prins–Ritter reaction: amide formation: Using Prins cyclization 'N' heteroatomic group selectively incorporated at 4th-position of tetrahydropyranyl cation. There are rather few examples of 4-tetrahydropyranyl carbocation trapping by nitrogen-centered nucleophiles in the literature. Owing to their basicity, most of them are incompatible with the presence of strong

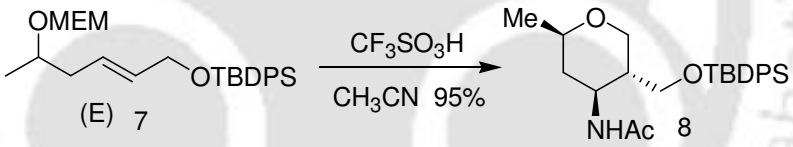
Lewis acids. The most frequently encountered examples of C–N bond formation involve the Ritter reaction.

Perron and Albizati first to develop a Prins cyclization and Ritter sequence.[6] They had prepared diastreoselective 4-acetamidopyranoside (**6**) from the reaction of trimethoxymethane (**5**) with 3-methylbut-3-en-1-ol (**4**) in acetonitrile mediated by $SnCl_4$ in 77% yield (*Scheme 2.2.1*).



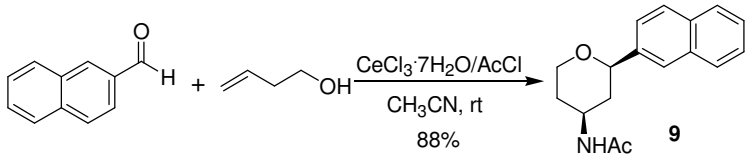
Scheme 2.2.1.

Willis and co-workers[7] developed a 4-amidotetrahydropyrans (**8**) by using Prins-Ritter reaction. They had treated homoallylic acetal (**7**) with triflic acid in acetonitrile to give 4-amido derivative in excellent yield (95%) with total control of the diastereoselectivity (*Scheme 2.2.2*).



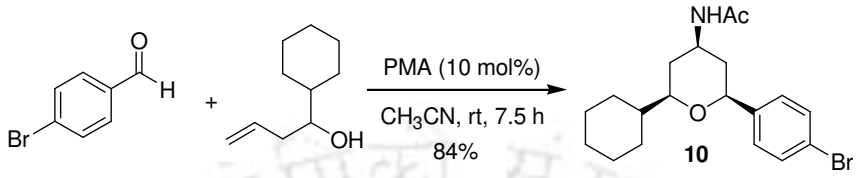
Scheme 2.2.2.

Yadav and co-workers[8] described a Prins–Ritter reaction sequence for the synthesis of 4-amido tetrahydropyrans from homoallylic alcohols with various carbonyls in nitrile solvent and acetyl chloride promoted by $CeCl_3$. As illustrated in *Scheme 2.2.3*, the reaction of 2-naphthaldehyde with but-3-en-1-ol in acetonitrile in the presence of 10 mol % of $CeCl_3{\cdot}7H_2O$ and 1.5 equiv of acetyl chloride at ambient temperature gave 4-acetamido tetrahydropyran (**9**) in 88% yield with all *cis*-selectivity.



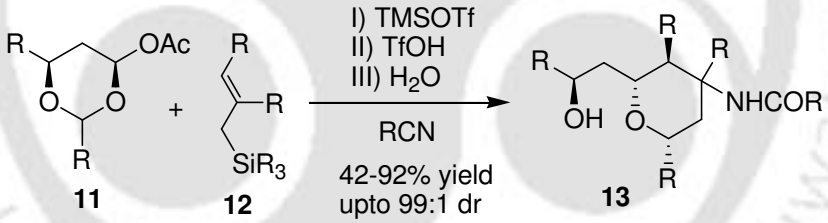
Scheme 2.2.3.

Recently, Prins-Ritter reaction was explored with efficient catalysts such as PMA,[9a] $Bi(OTf)_3$[9b] and $Ce(SO_4)_2$.[9c] Yadav and coworkers described an efficient protocol for the synthesis of 4-Amidotetrahydropyrans (**10**) by using PMA as solid acid catalyst (*Scheme 2.2.4*).



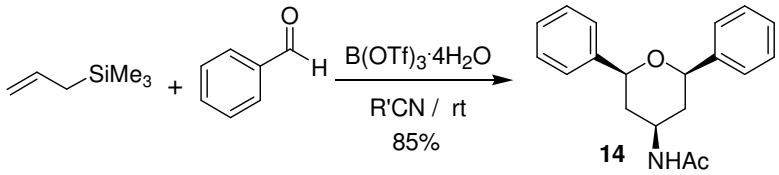
Scheme 2.2.4.

Rovis and Epstein developed a one-pot, three component reaction for the synthesis of 4-amido-tetrahydropyran (**13**) from the reaction of 4-acetoxy-1,3-dioxane (**11**) with allyltrimethylsilane (**12**) in the presence of TMSOTf, TfOH and acetonitrile in good yield and high diastereoselectivities. This multicomponent reaction enables the introduction of structural diversity at C-4. A large number of nitriles and allyl silane were examined (*Scheme 2.2.5*).[10]



Scheme 2.2.5.

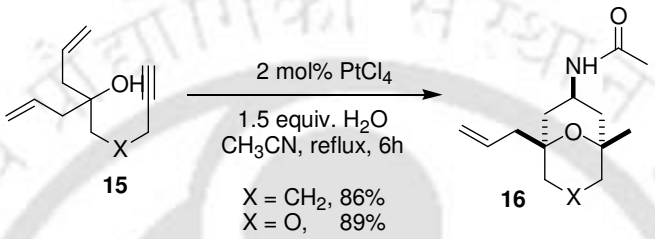
The multicomponent Sakurai-Prins-Ritter reaction was promoted by $Bi(OTf)_3$ catalyst.[11] As illustrated in *Scheme 2.2.6*, two equivalents of benzaldehyde when treated with allyltrimethylsilane in acetonitrile in the presence of 10 mol % $Bi(OTf)_3.4H_2O$ at room



Scheme 2.2.6.

temperature, resulted in 4-acetamido-2,4-diphenyl tetrahydropyran (**14**) in 85% yield with high diastereoselectivity.

The Prins-Ritter reaction is also possible on alkynols (**15**) in acetonitrile with H_2O in the presence of 2 mol% of $PtCl_4$ under reflux.[12] Under these conditions, amide derivatives (**16**) were isolated in very high yields and as single diastereoisomers. The same reaction also carried out with 2 mol% of $AuCl_3$ as the catalyst.

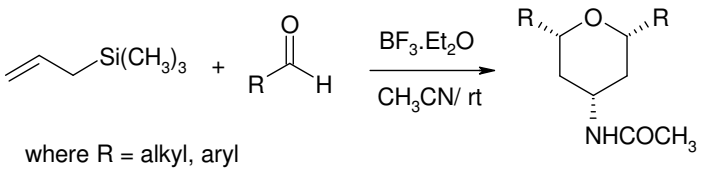


Scheme 2.2.7.

2.3 Results and Discussion:

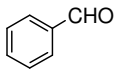
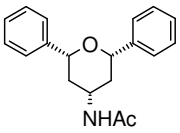
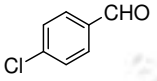
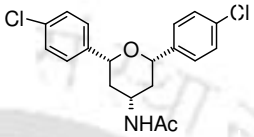
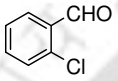
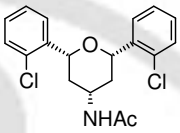
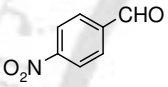
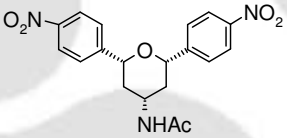
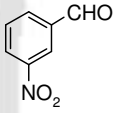
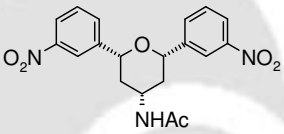
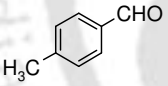
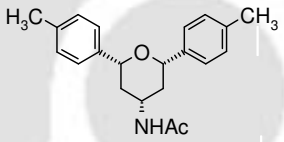
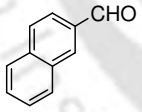
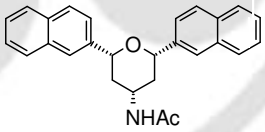
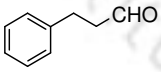
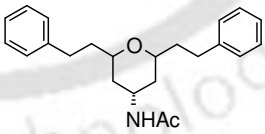
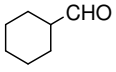
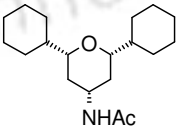
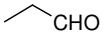
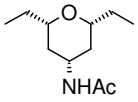
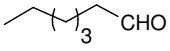
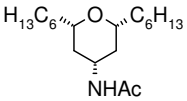
An important objective of contemporary synthesis endeavors is the development of new transformations that rapidly evolve molecular complexity in a stereo controlled fashion. One approach towards this goal is to combine two or more distinct reactions into a single transformation, producing a process often referred to as a sequential, tandem, cascade, or domino reaction. In this chapter, we discuss the development of one such tandem reaction, the acid catalyzed Prins cyclization.

We developed a one-pot, four component synthesis of 2,6-dialkyl- or 2,6-diaryl-4-amidotetrahydropyrans using Hosami-Sakurai-Prins-Ritter reaction involving allyltrimethyl-silane and aldehyde in the presence of a variety of nitriles promoted by $BF_3{\cdot}Et_2O$ (*Scheme 2.3.1*). When benzaldehyde was subjected to react with allyltrimethylsilane in acetonitrile in presence of



Scheme 2.3.1*. Synthesis of 4-acetamidotetrahydropyran*

***Table 2.3.1**: Synthesis of 4-amidotetrahydropyrans*

Sl No.	Substrate (a)	Time/h	Product (b)	Yield[a] (%)
1		24		70
2		24		74
3		24		89
4		24		70
5		27		63
6		36		60
7		36		45
8		12		85
9		12		99
10		12		98
11		12		91

[a] Yields refer to isolated yield. Compounds are characterized by ^{1}H, ^{13}C NMR and IR spectra.

boron trifluoride etherate provided 4-acetamido-2,6-diphenyltetrahydropyan streoselectively in 70% yield. The reaction were screened with various Lewis acids such as $Sc(OTf)_3$, $In(OTf)_3$ and TMSOTf to mediate the Prins cyclization, but they were failed to give the desired product. By using the above optimized reaction conditions, a variety of aldehydes and nitriles were selected to construct the 2,6-disubstituted-4-amidotetrahydropyran rings and it was found that products were obtained in moderate to good yields with excellent stereoselectivities. The results are summarized in *Tables 2.3.1 and 2.3.2.* In all the cases studied 4-acetamidotetrahydropyran *(Table 2.3.1)* could be obtained in high purity without any side products. Both aliphatic and aromatic aldehydes give good yield with high diasteroselectivity as determined from the ^1H and ^{13}C NMR spectrum of the crude product. The substituent on the aromatic ring has promising effect on this reaction. The electron-withdrawing and simple aldehydes gave good yields compared to electron-donating groups on the ring. Entries **9-11** demonstrated that aliphatic aldehydes are more reactive than the aromatic aldehydes, and only a single diastereomer was obtained from each reaction, which was determined by ^1H and ^{13}C NMR and comparison of the authentic samples.[13]

The conformations of the compounds are in the chair form and all the three substituent's are in equatorial position. The substituent's at the 2-, 4-, and 6-positions of the tetrahydropyran ring are in a *cis* relationship and are equatorial. This is revealed from the coupling constants of the 2,6-H

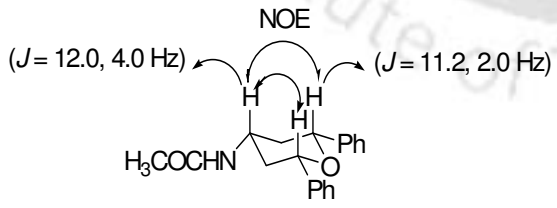


Figure 2.3.1. Coupling constants and NOE of Compound 1b

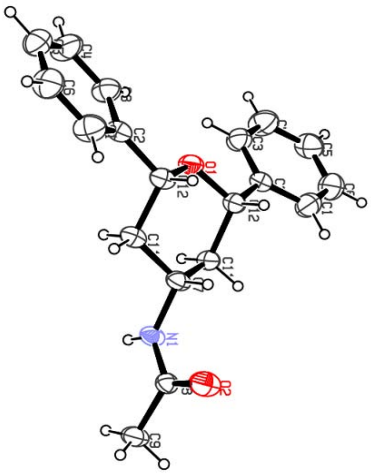
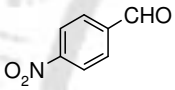
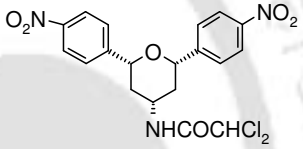
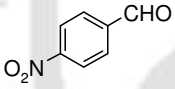
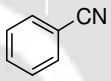
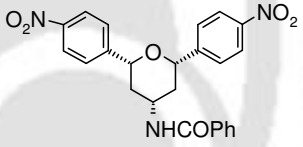
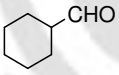
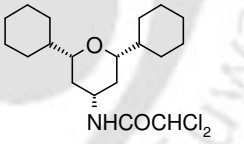
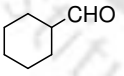
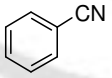
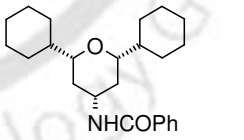
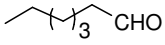
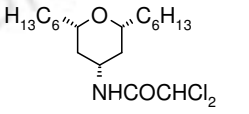
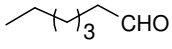
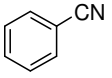
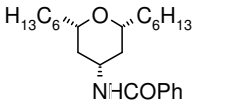


Figure 2.3.2. The ORTEP structure of 4 - acetamido-2,6-diphenyltetrahydropyran 1b

(J = 11.2 and 2.0 Hz) and the 4-H (J = 12.0 and 4.0 Hz) hydrogen atoms of compound **1b** (*Figure 2.3.1*). This is further confirmed by NOE experiment and single crystal X-ray analysis (*Figure 2.3.2*).[14]

This three-component coupling sequence allows the installation of added diversity at the 4-position. Indeed, a variety of nitriles successfully participate in the one-pot Sakurai-Prins- Ritter reaction (*Table 2.3.2*) to give substituted amides **1-6d** in good yield and excellent diastereoselectivity.

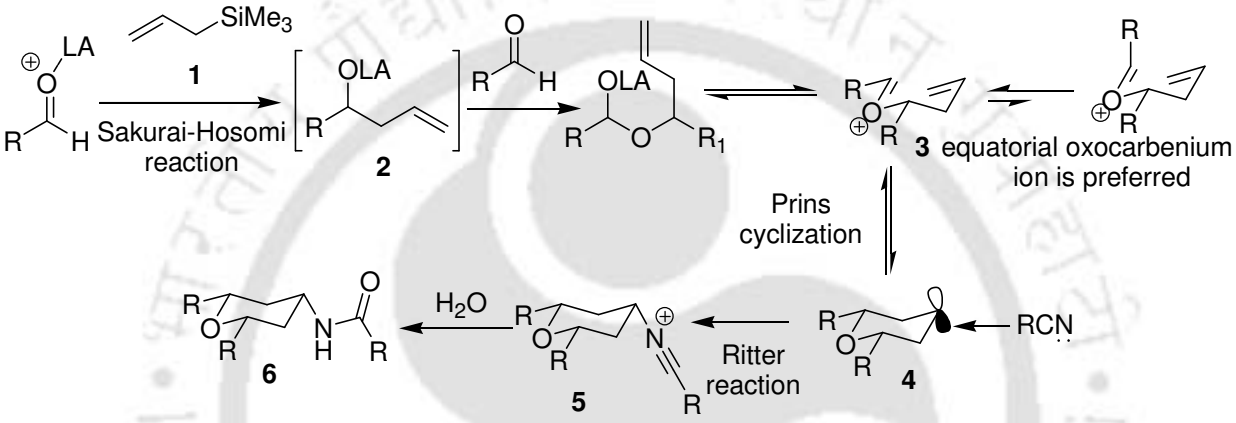
Table 2.3.2: *Synthesis of 4-dichloroacetamido- and 4-benzamidotetrahydropyran*

Sl No.	Aldehyde (c)	Nitrile	time/h	Product (d)	Yield[a] (%)
1		Cl_2CHCN	12		92
2			12		67
3		Cl_2CHCN	8		65
4			8		61
5		Cl_2CHCN	8		76
6			8		65

[a]Yields refer to isolated yield. Compounds are characterized by ^1H, ^{13}C NMR and IR spectra.

The mechanism of the reaction can be explained as follows. In the presence of Lewis acid aldehyde and allyltrimethylsilane (**1**) undergoes Hosami-Sakurai allylation reaction to afford

intermediate (**2**) (*Scheme 2.3.2*). The intermediate (**2**) reacts with another molecule of aldehyde to give oxocarbenium ion (**3**), which under goes Prins cyclization to give tetrahydropyranyl cation (**4**), which has an increased stability relative to the open-chain oxocarbenium ion due to delocalization of cation, tetrahydropyranyl cation (**4**) in the presence of neucleophile, CH_3CN undergoes Ritter reaction to form nitrilium ion (**5**). This upon hydrolysis gives the 4-acetamidotetrahydropyran (**6**).



Scheme 2.3.2. Mechanism of the reaction

Conclusion

A multicomponent Hosomi-Sakurai-Prins-Ritter reaction was developed for the efficient synthesis of 2,6-disubstituted 4-amidotetrahydropyran. The current work would be extremely useful due to its readily available and easily accessible starting materials, excellent yield, mild conditions, and its high diastreoselectivity. To our knowledge this is the first method for the synthesis of symmetric 2,6-disubstituted 4-acetamidotetrahydropyrans in a single step.

2.4. Experimental Section

2.4.1 Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed

in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded with a Büchi B-540 melting point apparatus. Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer. Fourier transform-infra red (FT-IR) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ or/with [D_6] DMSO with tetramethylsilane as the internal standard for ^1H (400 MHz) or ^{13}C (100 MHz). Crystal Data were collected with Bruker Smart Apex-II CCD diffract meter using graphite monochromatic Mock$_\alpha$ radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

2.4.2 General procedure

To a mixture of aldehyde (1.0 equiv), allyltrimethylsilane (0.6 equiv), and nitrile (5.0 mL), was added borontrifluoride etherate (1.2 equiv) drop by drop at rt. The reaction mixture was stirred at rt for specified time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

*4-Acetamido-2,6-diphenyltetrahydropyran (**1b**, Table 1):* To a mixture of benzaldehyde, **1a** (0.10 mL, 1.0 mmol), allyltrimethylsilane (0.10 mL, 0.6 mmol.), and acetonitrile (5.0 mL), boron trifluoride etherate (0.15 mL, 1.2 mmol) added drop by drop at rt. The reaction mixture was stirred at rt for 24h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with

aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give 4-acetamido-2,6-diphenyltetrahydropyran **1b** (207 mg, 70%) as a crystalline solid with m.p. 223-224 ^oC.

*2.2 N-[2,6-bis-(4-nitro-phenyl)-tetrahydro-pyran-4-yl-benzamide (**2d**, Table 2):* To a mixture of nitrobenzaldehyde, **2c** (151 mg, 1.0 mmol), allyltrimethylsilane (0.10 mL, 0.6 mmol.), and benzonitrile (5.0 mL) was added boron trifluoride etherate (0.15 mL, 1.2 mmol) drop by drop at rt. The reaction mixture was stirred at rt for 12h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give N-[2,6-bis-(4-nitro-phenyl)-tetrahydro-pyran-4-yl-benzamide **2d** (300 mg, 67%) as a crystalline solid with m.p. 263-264 ^oC. The product **2d** is characterized by spectrometric methods.

2.5 Reference and Notes

(1) (a) Gopalsamy, A.; Moore, W. J.; Kern, J. C.; Molinari, A. J.; Shi, M.; Welmaker, G. S.; Wilson, M. A.; Krishnamurthy, G.; Commons, T. J.; Webb, M. B.; Woodworth, R. P. PCT. Int. Appl. WO 2006124875 A2, 2006, 516 pp. (b) Braun, A.; Courtemanche, G.; Crespin, O.; Fett, E.; Pascal, C. Fr. Demande FR 2873690 A1, 2006, 59 pp. (c) Bandiera, T.; Lombardi Borgia, A.; Polucci, P.; Villa, M.; Nesi, M.; Angiolini, M.; Varasi, M. PCT. Int. Appl. WO 2007068619 A1, 2007, 238 pp. (d) Duan, J.; King, B. W.; Decicco, C.; Maduskuie, T. P.; Voss, M. E. US Patent Appl. US 2004072802 A1, 2004, 150 pp.

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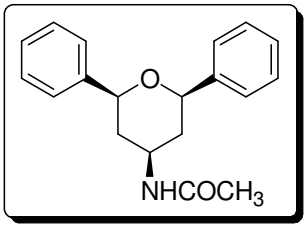
(15) Crystallographic data for compound CMR-2 has been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 658766.

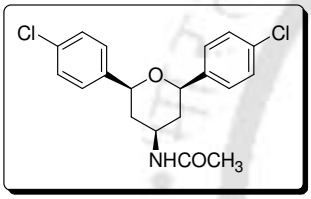
2.6 Spectral data

4-Acetamido-2,6-diphenyltetrahydropyran (1b):



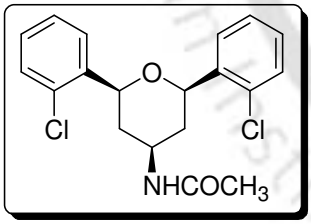
Solid**, M.P.:** 223-224 °C**; 1H NMR** (400 MHz, $CDCl_3$): δ 1.38-1.48 (m, 2 H), 1. 96 (s, 3 H), 2.25-2.30 (m, 2 H), 4.32-4.44 (m, 1 H), 4.65 (dd, *J*=11.2 and 2.0 Hz, 2 H), 5.60 (d, *J*= 8.0 Hz, 1 H), 7.25-7.43 (m, 10 H)[1]; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6, 40.6, 46.8, 78.5, 125.9, 127.7, 128.5, 142.2, 169.6. **IR:** 3296, 2922, 2846, 1640, 1543, 1493, 1446, 1282, 1114, 1064 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.42; H, 7.20; N, 4.69.

4-Acetamido-2,6-di(4-chlorophenyl)-tetrahydropyran (2b):



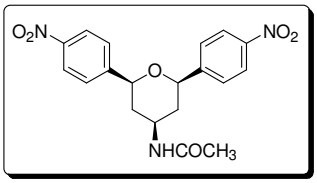
Solid**, M.P.:** 203-204 °C**; ^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33-1.43 (m, 2 H), 1. 97 (s, 3 H), 2.24-2.28 (m, 2 H), 4.30-4.41 (m, 1 H), 4.61 (dd, *J*=11.2 and 2.0 Hz, 2 H), 5.52 (d, *J*= 7.6 Hz, 1 H), 7.26-7.37 (m, 8 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6, 40.4, 46.7, 77.8, 127.3, 128.8, 133.5, 140.5, 169.7**. IR:** 3304, 3071, 2950, 2843, 1638, 1539, 1489, 1079, 1004, 820 cm^{-1}. **Anal. Calcd** for $C_{19}H_{19}Cl_2NO_2$: C, 62.65; H, 5.26; N, 3.85. Found: C, 62.70; H, 5.24; N, 3.79.

4-Acetamido-2,6-di(2-chlorophenyl)-tetrahydropyran (3b):



Solid**, M.P.:** 201-202 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25-1.35 (m, 2 H), 1. 95 (s, 3 H), 2.40-2.43 (m, 2 H), 4.38-4.50 (m, 1 H), 5.03 (dd, *J*=11.2 and 2.0 Hz, 2 H), 5.64 (d, *J*= 8.0 Hz, 1 H), 7.18-7.23 (m, 2 H), 7.26-7.33 (m, 4 H), 7.67 (d, *J* = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6, 38.8, 46.4, 75.7, 127.3, 128.8, 129.6, 131.6, 139.7, 169.6**. IR**: 3427, 2927, 1647, 1548, 1438, 1281, 1082, 1042, 987, 755 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.46; H, 7.25; N, 4.78.

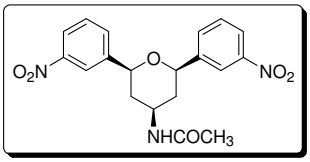
4-Acetamido-2,6-di(4-nitrophenyl)-tetrahydropyran (4b):



Solid**, M.P.:** 258-260 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.38-1.48 (m, 2 H), 2. 00 (s, 3 H), 2.36-2.40 (m, 2 H), 4.40-4.50 (m, 1 H), 4.81 (dd, *J*=10.0 and 2.0 Hz, 2 H), 5.45 (d, *J*= 8.0 Hz, 1 H), 7.60 (d, *J* = 8.8 Hz, 4 H), 8.24 (d, *J* = 8.8 Hz, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6, 40.1, 46.6, 77.8, 124.0, 126.6, 147.7, 148.7, 169.8. IR: 3294, 3075, 2929, 2848, 1642,

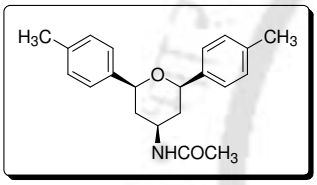
1519, 1346, 1092, 849 cm^{-1}. **Anal. Calcd** for $C_{19}H_{19}N_3O_6$: C, 59.22; H, 4.97; N, 10.90. Found: C, 59.34; H, 5.12; N, 10.87.

4-Acetamido-2,6-di(3-nitrophenyl)-tetrahydropyran (5b):



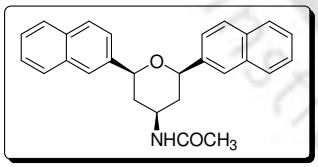
Solid**, M.P.:** 212-216 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.46-1.55 (m, 2 H), 2. 01 (s, 3 H), 2.38-2.42 (m, 2 H), 4.40-4.52 (m, 1 H), 4.81 (dd, *J*=10.0 and 2.0 Hz, 2 H), 5.52 (d, *J*= 7.2 Hz, 1 H), 7.54-7.58 (m, 2 H), 7.75-7.80 (m, 2 H), 8.16-8.19 (m, 2 H), 8.25-8.32 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6, 40.0, 46.6, 77.8, 121.0, 123.0, 129.8, 132.2, 143.6, 148.6, 169.8. IR: 3408, 2928, 2854, 1643, 1530, 1349, 1075 cm^{-1}. **Anal. Calcd** for $C_{19}H_{19}N_3O_6$: C, 59.22; H, 4.97; N, 10.90. Found: C, 59.40; H, 5.18; N, 11.12.

4-Acetamido-2,6-ditolyltetrahydropyran (6b):



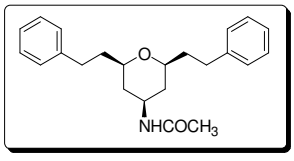
Solid**, M.P.:** 192-194 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.36-1.45 (m, 2 H), 1. 97 (s, 3 H), 2.22-2.26 (m, 2 H), 2.32 (s, 6 H), 4.30-4.41 (m, 1 H), 4.60 (dd, *J*=10.4 and 2.0 Hz, 2 H), 5.52 (d, *J*= 8.0 Hz, 1 H), 7.08-7.15 (m, 4 H), 7.24-7.30 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 23.6, 40.5, 46.9, 78.3, 128.9, 129.2, 137.3, 139.3, 169.8. **IR**: 3428, 2936, 2863, 1643, 1551, 1446, 1369, 1291, 1078 cm^{-1}. **Anal. Calcd** for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 77.85; H, 7.93; N, 4.50.

4-Acetamido-2,6-di(2-naphthyl)-tetrahydropyran (7b):



Solid**, M.P.:** 213-244 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.50-1.60 (m, 2 H), 1. 98 (s, 3 H), 2.37-2.40 (m, 2 H), 4.42-4.58 (m, 1 H), 4.86 (dd, *J*=11.2 and 2.0 Hz, 2 H), 5.60 (d, *J*= 8.4 Hz, 1 H), 7.43-7.61 (m, 7 H), 7.70-7.95 (m, 7 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.7, 40.5, 47.1, 78.8, 124.4, 124.7, 126.1, 126.3, 128.0, 128.4, 132.0, 133.2, 133.5, 139.6, 169.9; IR: 3291, 3056, 2922, 2844, 1642, 1545, 1438, 1367, 1299, 1113, 1073 cm^{-1}. **Anal. Calcd** for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 82.14; H, 6.20; N, 3.68.

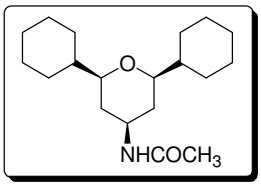
4-Acetamido-2,6-diphenylethyltetrahydropyran (8b):



Solid**, M.P.:** 84-87 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01-1.10 (m, 2 H), 1.67-1.76 (m, 2 H), 1.83-1.90 (m, 2 H), 1.93 (s, 3 H), 2.60-2.96 (m, 2 H), 3.30-3.35 (m, 2 H), 3.89-4.00 (m, 1 H), 5.59 (d, *J*= 7.6 Hz, 1 H), 7.16-7.36 (m, 10 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.4, 31.9, 37.9, 38.5, 46.3, 5.1,125.9,

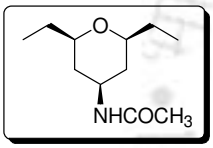
128.5, 128.5, 142.1, 169.7. IR: 3278, 3072, 3028, 2927, 2850, 1648, 1548, 1502, 1445, 1070, 812 cm^{-1}. **Anal. Calcd** for $C_{23}H_{29}NO_2$: C, 78.60; H, 8.32; N, 3.98. Found: C, 78.77; H, 8.38; N, 4.12.

4-Acetamido-2,6-dicyclohexyltetrahydro-pyran (9b):



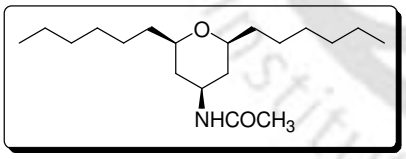
Solid**, M.P.:** 202-203 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89-1.00 (m, 6 H), 1.12-1.23 (m, 6 H), 1.27-1.36 (m, 2 H), 1.63-1.71 (m, 8 H), 1.90-1.93 (m, 2 H), 1.95 (s, 3 H), 2.96-3.00 (m, 2 H), 3.92-3.96 (m, 1 H), 5.28 (d, *J*= 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6, 26.2, 26.4, 26.8, 29.0, 29.3, 36.0, 43.2, 47.1, 80.5, 169.5; IR: 3278, 2922, 2853, 1643, 1556, 1439, 1363, 1303, 1147, 1003 cm^{-1}. **Anal. Calcd** for $C_{19}H_{33}NO_2$: C, 74.22; H, 10.82; N, 4.56. Found: C, 74.30; H, 10.95; N, 4.67.

4-Acetamido-2,6-diethyltetrahydropyran (10b):



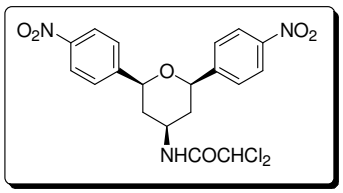
Semisolid**; ^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94 (t, *J*=7.6 Hz, 6 H), 1.40-1.50 (m, 2 H), 1.50-1.60 (m, 2 H), 1.90-1.95 (m, 2 H), 1.97 (s, 3 H), 3.23-3.29 (m, 2 H), 3.96-4.06 (m, 1 H), 5.31 (d, *J*= 6.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 10.2, 23.7, 29.2, 38.4, 46.6, 77.6, 169.6; IR: 3270, 2987, 2850, 1645, 1455, 1144, 1008, 997, 766 cm^{-1}. **Anal. Calcd** for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.34; H, 10.71; N, 7.15.

4-Acetamido-2,6-dihexyltetrahydro-pyran (11b):



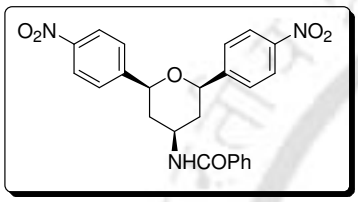
Solid**, M.P.:** 82-84 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J*=7.6 Hz, 6 H), 0.93-1.02 (m, 2 H), 1.20-1.35 (m, 14 H), 1.36-1.48 (m, 4 H), 1.48-1.58 (m, 2 H), 1.90-1.95 (m, 2 H), 1.96 (s, 3 H), 3.28-3.34 (m, 2 H), 3.96-4.10 (m, 1 H), 5.28 (d, *J*= 7.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.8, 23.7, 25.8, 29.4, 32.0, 36.4, 38.9, 46.6, 76.3, 169.5. IR: 3275, 3080, 2928, 2854, 1724, 1648, 1548, 1456, 1375, 1149, 1079, 1050 cm^{-1}. **Anal. Calcd** for $C_{19}H_{37}NO_2$: C, 73.26; H, 11.97; N, 4.50. Found: C, 73.50; H, 12.10; N, 4.57.

N-[2,6-bis-(4-nitro-phenyl)-tetrahydro-pyran-4-yl]-2,2-dichloro-acetamide (1d):



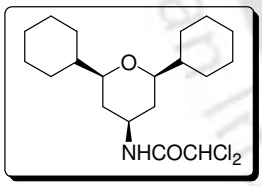
Solid**, M.P.: 2**82-284 °C; **^{1}H NMR** (400 MHz, $CDCl_3$/DMSO-d_6): δ 1.52-1.61 (m, 2 H), 2.31-2.35 (m, 2 H), 4.30-4.45 (m, 1 H), 4.84-4.86 (m, 2 H), 6.10 (s, 1 H), 7.65-7.67(d, *J* = 8.8 Hz, 2 H), 8.24-8.25 (d, *J* = 8.8 Hz, 2 H), 8.35 (d, *J* = 6.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$/DMSO-d_6): δ 37.8, 46.1, 65.7, 76.2, 122.6, 125.7, 146.2, 148.1, 162.7; IR : 3274, 3087, 2923, 2840, 1673, 1602, 1558, 1516, 1350, 1284, 1207, 1127, 1084, 850, 809, 746 cm^{-1}. **Anal. Calcd** for $C_{19}H_{17}Cl_2N_3O_6$: C, 50.24; H, 3.77; N, 9.25. Found: C, 50.35; H, 3.81; N, 9.18.

N-[2,6-bis-(4-nitro-phenyl)-tetrahydro-pyran-4-yl-benzamide (2d):



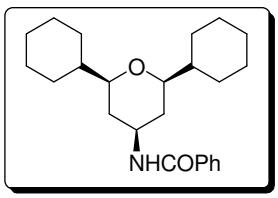
Solid**, M.P.:** 263-264 °C; **^{1}H NMR** (400 MHz, $CDCl_3$/DMSO-d_6): δ 1.64-1.73 (m, 2 H), 2.39-2.42 (m, 2H), 4.58-4.70 (m, 1 H), 4.88-4.91 (m, 2 H), 7.40-7.43 (m, 2 H), 7.48-7.53 (m, 2 H), 7.66-7.68 (m, 4 H), 7.83-7.85 (m, 2 H), 7.92-7.94 (d, *J* = 7.6 Hz, 1 H), 8.23-8.26(m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$/DMSO-d_6) : δ 39.1, 46.4, 76.9, 123.3, 126.2, 127.1, 127.9, 131.0, 134.3, 146.9, 148.8, 166.9; IR: 3286, 3060, 2945, 2849, 1632, 1602, 1579, 1516, 1490, 1347, 1283, 1159, 1094, 855, 747, 701 cm^{-1}. **Anal. Calcd** for $C_{24}H_{21}N3O_6$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.45; H, 4.87; N, 9.50.

2,2-dichloro-N-(2,6-dicyclohexyl-tetrahydro-pyran-4-yl)-acetamide (3d):



Solid**, M.P.:** 140- 142 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.91-0.94 (m, 4 H), 1.00-1.09 (m, 2 H), 1.12-1.22 (m, 6 H), 1.30-1.36(m, 2 H), 1.58-1.71(m, 10 H), 1.93-1.98 (m, 2 H), 2.97-3.02 (m, 2 H), 3.91-3.98 (m, 1H), 5.87 (s, 1 H), 6.25-6.27(d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.2, 26.3, 26.7, 29.0, 29.3, 35.3, 43.1, 48.3, 66.7, 80.4, 163.5; **IR**: 3258, 2918, 2851, 1667, 1635, 1567, 1434, 1396, 1146, 1105, 1091, 1083, 811, 743 cm^{-1}. **Anal. Calcd** for $C_{19}H_{31}Cl_2NO_2$: C, 60.63; H, 8.30; N, 3.72. Found: C, 60.72; H, 8.25; N, 3.81.

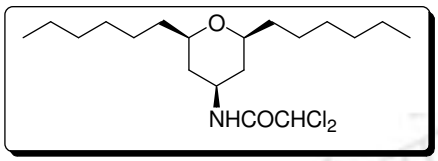
N-(2,6-dicyclohehyl-tetrahydro-pyran-4-yl)-benzamide (4d):



Solid**, M.P.:** 82-85 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95-1.01 (m, 4 H), 1.03-1.12 (m, 2 H), 1.15-1.35 (m, 6 H), 1.40-1.49 (m, 2 H), 1.64-1.77 (m, 6 H),1.92-1.95(m, 2 H), 2.06-2.10 (m, 2 H), 2.29-2.37 (m, 2 H), 3.05-3.09 (m, 2 H), 4.12-4.17 (m, 1 H), 5.95-5.97 (d, *J* = 8.0 Hz, 1 H), 7.41-7.50 (m, 2 H), 7.59-7.67 (m, 2 H), 7,73-7.75 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.2, 26.4, 26.8, 29.1, 29.4, 36.1, 43.2, 47.6, 80.6, 127.0, 128.8, 131.6, 135.0, 167.0; **IR** : 3273, 2918,

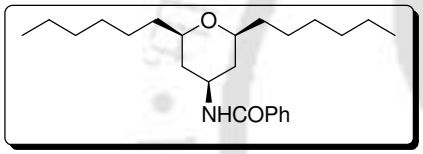
2850, 1632, 1578, 1539, 1489, 1445, 1360, 1315, 1148, 1102, 1089, 995, 693 cm^{-1}. **Anal. Calcd** for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; N, 3.79. Found: C, 78.12; H, 9.34; N, 3.85.

2,2-dichloro-N-(2,6-dihexyl-tetrahydro-pyran-4-yl)-acetamide (5d):



Solid**, M.P.:** 202-203 ^oC; **^{1}H NMR** (400 MHz, CDCl3): δ 0.83-0.86 (d, *J*= 6.4 Hz, 6 H), 1.02-1.11 (m, 2 H), 1.20-1.36 (m, 12 H), 1.34-1.42 (m, 4 H), 1.45-1.58 (m, 4 H), 1.92-1.96 (m, 2 H), 3.30-3.37 (m, 2 H), 3.94-4.10 (m, 1 H), 5.90 (s, 1 H), 6.29 (d, *J*= 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.8, 25.7, 29.4, 32.0, 36.3, 38.1, 47.8, 66.6, 76.2, 163.6; **IR**: 3264, 2955, 2926, 2858, 1679, 1645, 1572, 1468, 1380, 1336, 1212, 1151, 1084, 814, 721 cm^{-1}. **Anal. Calcd** for $C_{19}H_{35}Cl_2NO_2$: C, 59.99; H, 9.25; N, 3.68. Found: C, 60.12; H, 9.44; N, 3.71.

N-(2,6-dihexyl-tetrahydro-pyran-4-yl)-benzamide (6d):

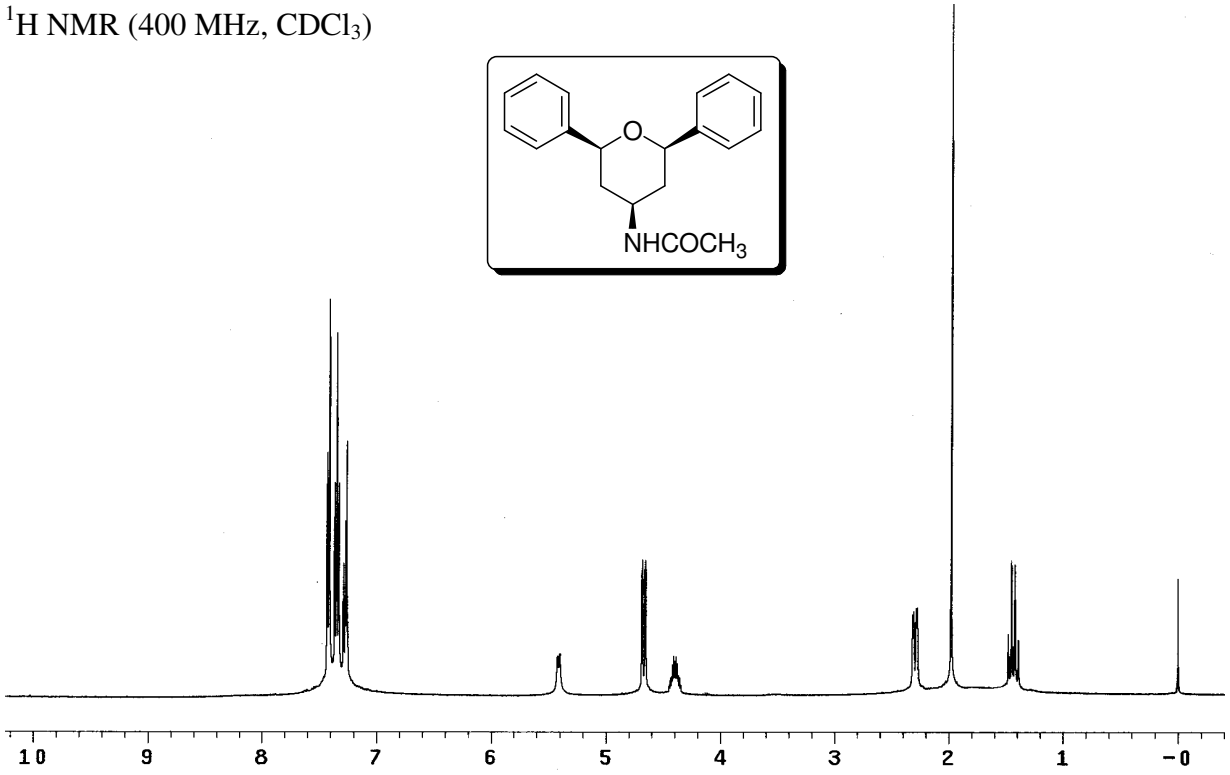


Solid**, M.P.:** 225-226 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (m, 6 H), 1.05-1.14 (m, 2 H), 1.28 (m, 12 H), 1.42 (m, 4 H), 1.52-1.59 (m, 4 H), 2.02- 2.06 (m, 2 H), 3.37-3.39 (m, 2 H), 4.19-4.23 (m, 1 H), 6.05-6.07 (d, *J* = 7.6 Hz, 1 H), 7.41-7.51 (m, 3 H), 7.73-7.75 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.8, 25.8, 29.4, 32.0, 36.3, 38.8, 47.1, 76.3, 127.0, 128.7, 131.6, 134.8, 167.0; **IR**: 3294, 3063, 3031, 2925, 2855, 1634, 1604, 1579, 1540, 1491, 1467, 1378, 1332, 1261, 1148, 1084, 923, 856, 800, 697 cm^{-1}. **Anal. Calcd** for $C_{24}H_{39}NO_2$: C, 77.16; H, 10.50; N, 3.75. Found: C, 77.18; H, 10.37; N, 3.87.

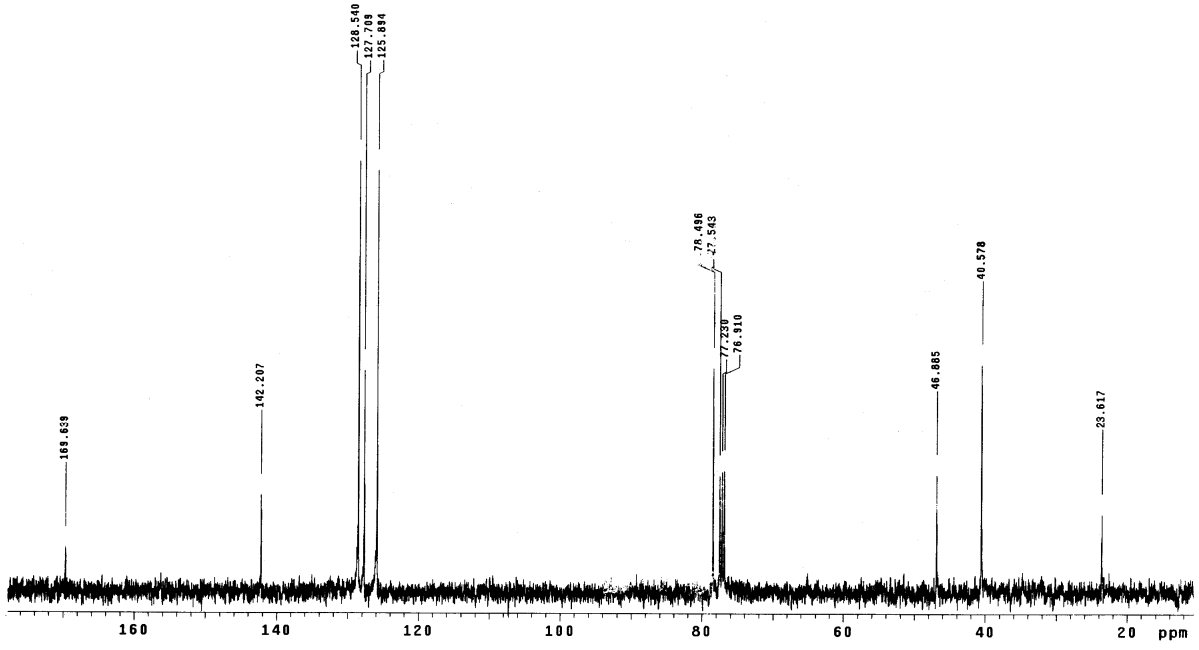
2.7 Selected Spectra of 4-amidotetrahydropyrans

4-Acetamido-2,6-diphenyltetrahydropyran (1b):

^{1}H NMR (400 MHz, $CDCl_3$)

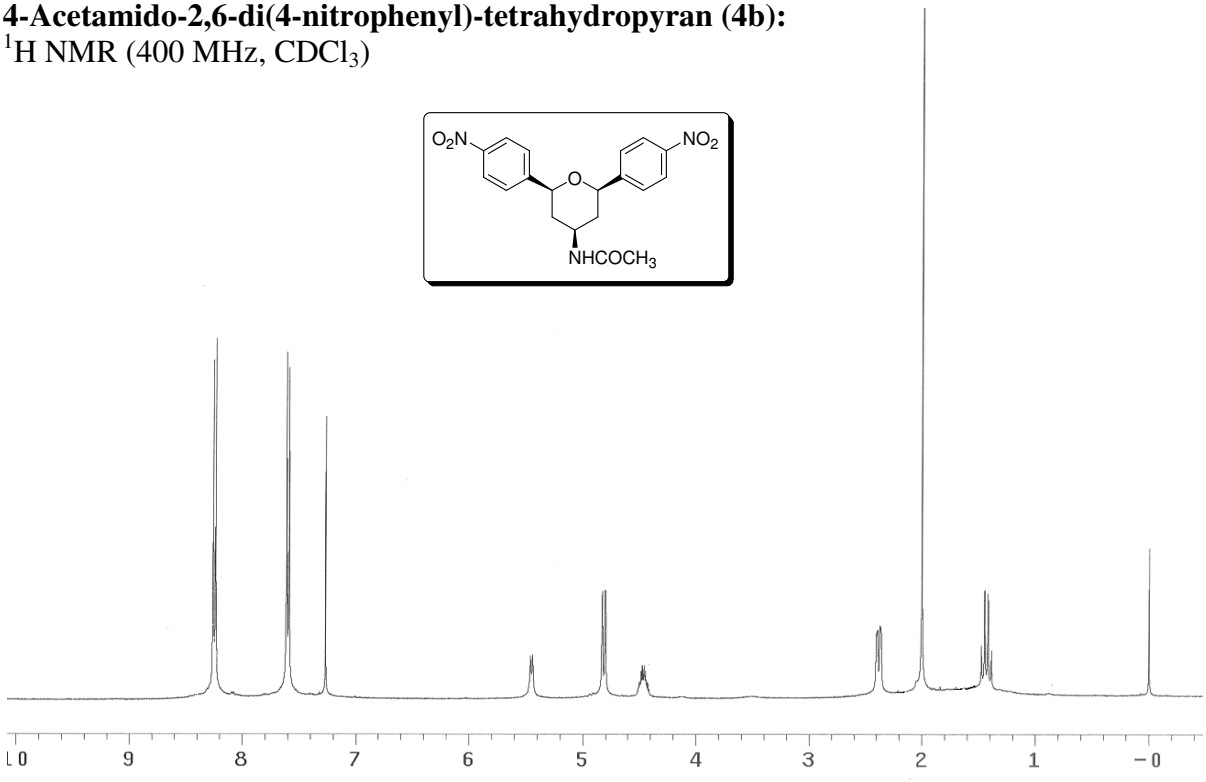


^{13}C NMR (100 MHz, $CDCl_3$)

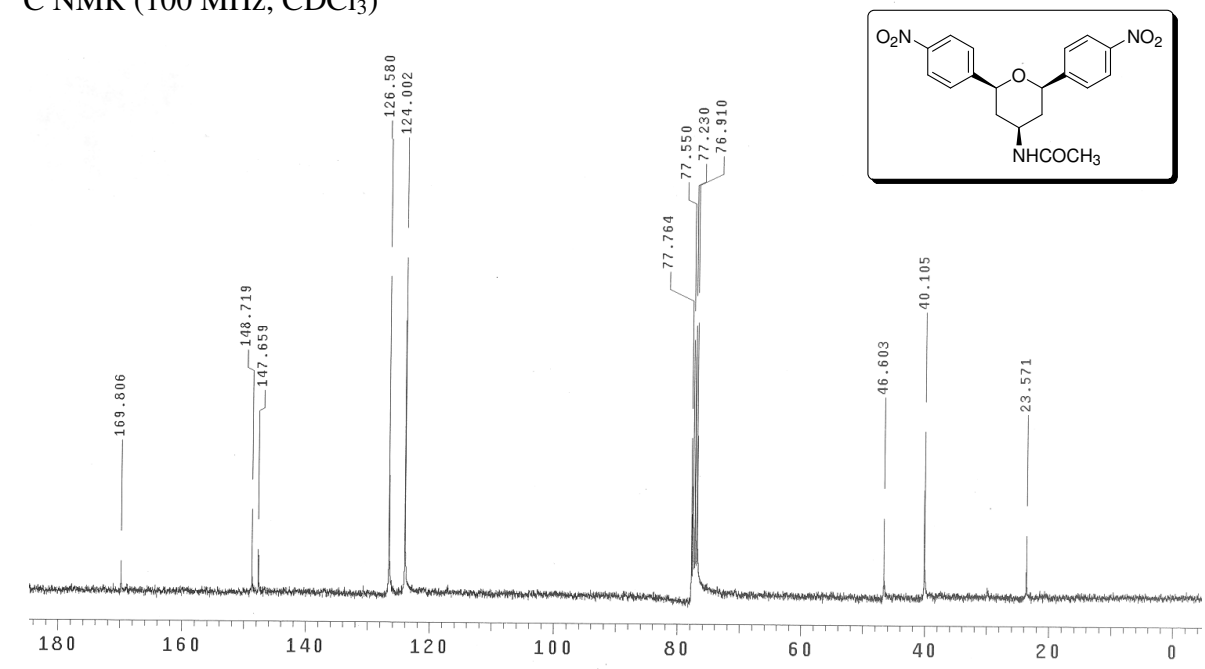


4-Acetamido-2,6-di(4-nitrophenyl)-tetrahydropyran (4b):

^{1}H NMR (400 MHz, $CDCl_3$)

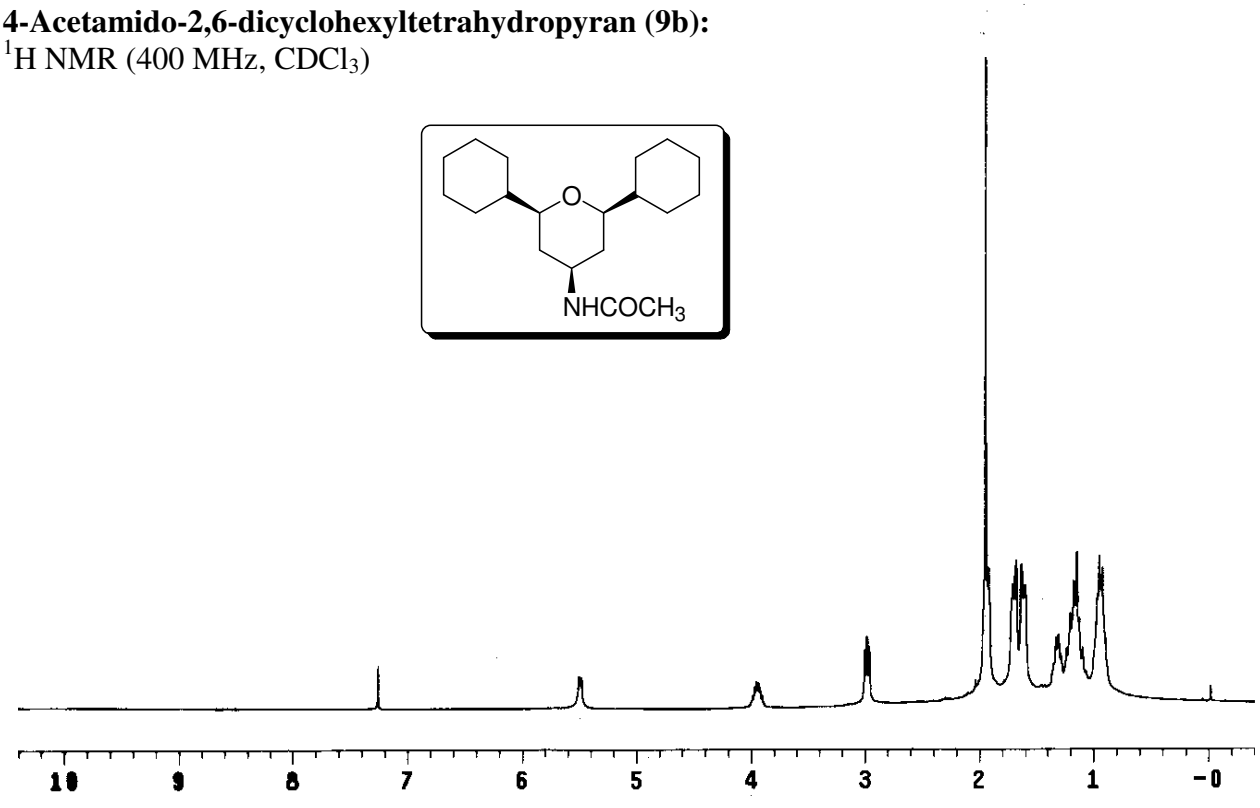


^{13}C NMR (100 MHz, $CDCl_3$)

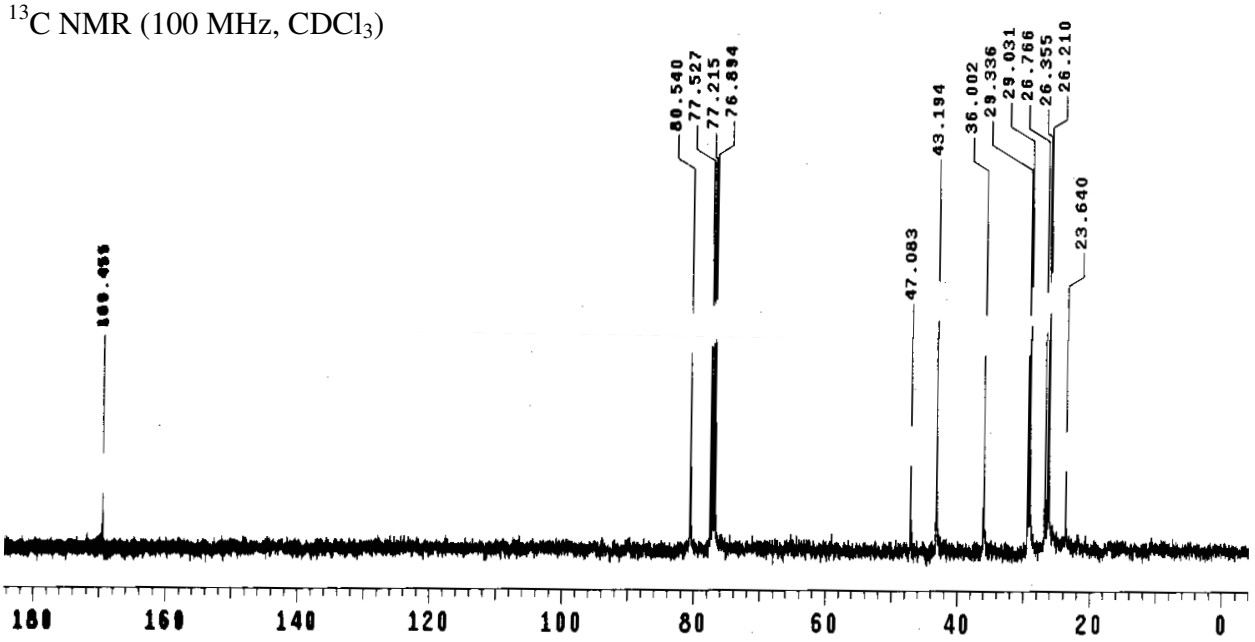


4-Acetamido-2,6-dicyclohexyltetrahydropyran (9b):

^{1}H NMR (400 MHz, $CDCl_3$)

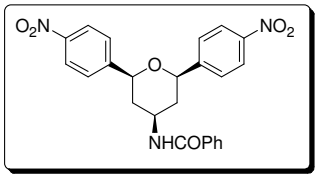


^{13}C NMR (100 MHz, $CDCl_3$)

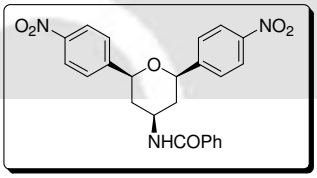


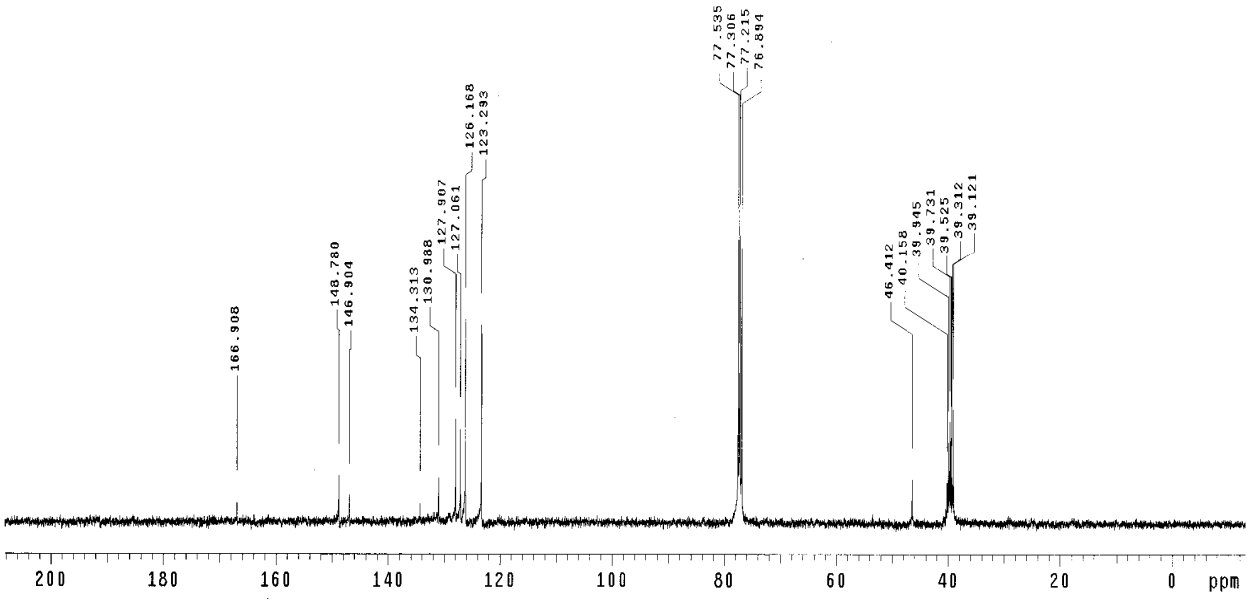
N-[2,6-bis-(4-nitrophenyl)-tetrahydropyran-4-yl-benzamide (2d):

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





The crystal parameters of compound 1b.

Parameters	**1b** (CMR-2; CCDC 658766)
Formula	$C_{19}H_{21}NO_2$
Formula weight	295.37
T/K	296(2)
Crystal system	Orthorhombic
Space group	Pnma
a/Å	20.0166(7)
b/Å	16.6428(6)
c/Å	4.83180(10)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	1609.63(9)
Z	4
Abs. Coeff./mm^{-1}	0.079
Abs. Correction	None
GOF on F^2	0.998
Final *R* indices	*R1* = 0.0488,
[$I > 2\sigma(I)$]	*wR2* = 0.1089
R indices [all data]	*R1* = 0.0822,
	wR2 = 0.1253

CHAPTER 3

Stereoselective Synthesis of Symmetrical 4-Aryltetrahydropyrans

3.1. Importance and Applications

The synthesis of the tetrahydropyran unit is important because of its presence in many natural products.[1] The all-*cis* 2,6-disubstituted-4-aryltetrahydropyrans are found to be biologically active, for example compound **1** (*Figure 3.1.1*) has olfactory properties[2] and compound **2** (*Figure **3.1.1***) shows nonredox 5-lipoxygenase inhibiting properties.[3]

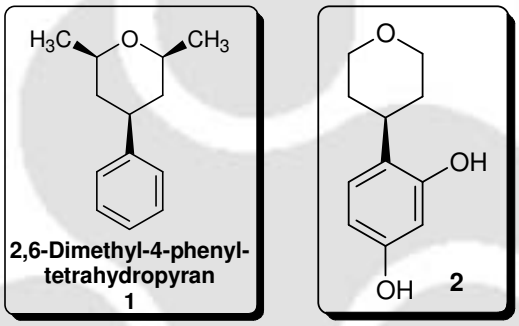


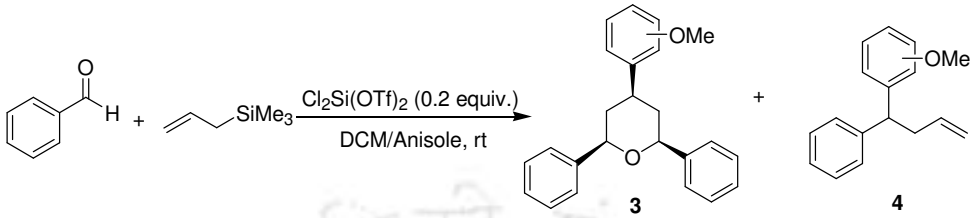
Figure 3.1.1. *Some important symmetrical 4-aryl-tetrhydropyran*

3.2. Synthetic Methods

There are few examples of 4-tetrahydropyranyl carbocation trapping by carbon-centered nucleophiles in the literature. Most of the cases, carbon nuclephiles are incompatible or in sufficient nucleophiles in the presence of Lewis acid. The valuable 4-aryltetrahydropyrans are synthesized by using tandem Sakurai-Prins-Friedel-Crafts reaction and other methods such as Grignard reaction on tetrahydro-pyran-4-one and Micheal addition reactions.

Tandem Sakurai-Prins-Friedel-Crafts Reaction: Shiina *et al.* observed Sakurai-Prins-Friedel-Crafts reaction product, while trying to develop a three-component coupling reaction using aromatic aldehydes, allyltrimethylsilanes and aromatic nucleophiles in order to directly synthesise tetrahydropyran (**4**) by using $Cl_2Si(OTf)_2$. However, a regioisomeric mixture of the corresponding 4-aryltetrahydropyran (**3**) was mainly obtained (*Scheme 3.1.1*).[4] The reaction

using $Hf(OTf)_4$ and $Sc(OTf)_3$ gave complex mixtures of several by-products, and TMSOTf did not promote the desired reaction.

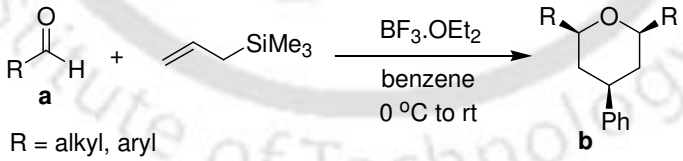


Scheme 3.1.1.

3.3. Results and Discussion

In our previous chapter we have described a methodology for the synthesis of 2,6-disubstituted-4-amidotetrahydropyrans by using Sakurai–Hosomi–Prins–Ritter reaction. In this chapter the synthesis of 4-aryltetrahydropyrans from the reaction of aldehydes, allyltrimethylsilane, and arenes by Lewis acid is presented.

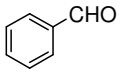
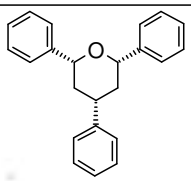
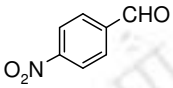
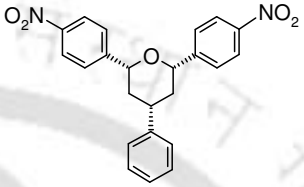
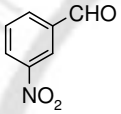
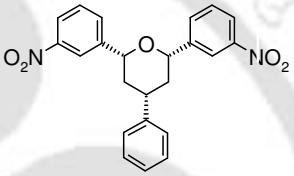
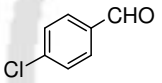
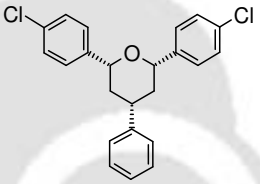
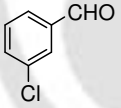
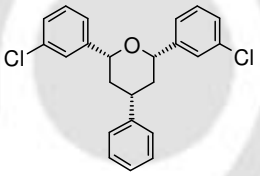
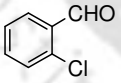
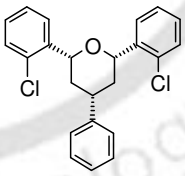
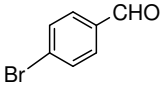
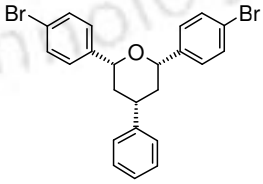
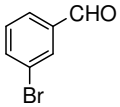
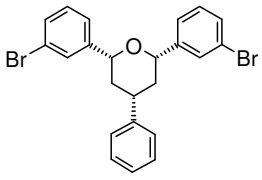
Initially, benzaldehyde (1.0 mmol) was treated with allyltrimethylsilane (0.6 mmol) in benzene (5.0 mL) in the presence of $BF_3{\cdot}Et_2O$ (1.2 mmol) at 0 °C, and then warmed to room temperature. 2,4,6-Triphenyltetrahydropyran was obtained in 74% yield. To prove the general applicability of this reaction, a variety of alkyl and aryl aldehydes were investigated as shown in *Scheme 3.3.1*. The results are summarized in *Table 3.3.1*.



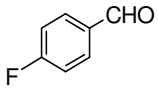
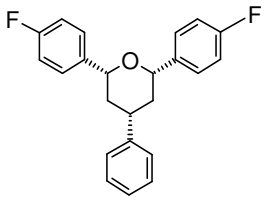
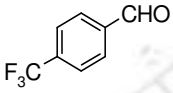
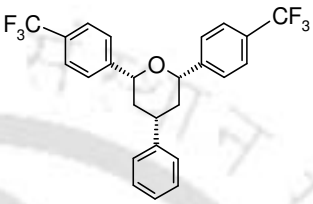
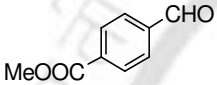
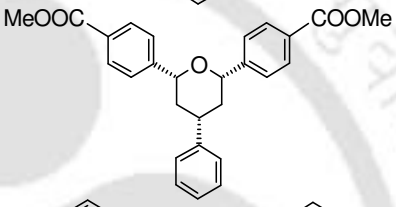
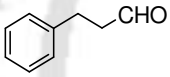
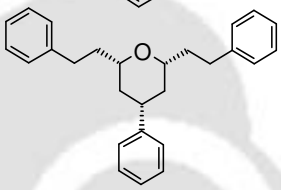
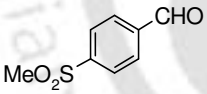
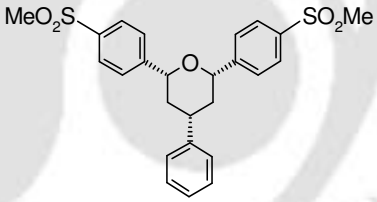
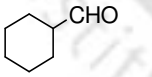
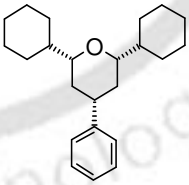
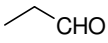
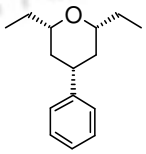
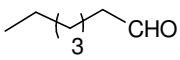
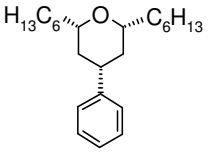
Scheme 3.3.1. *Synthesis of symmetrical 2,6-disubstituted-4-aryltetrahydropyran*

In all the cases studied, 4-aryltetrahydropyrans (**1b–16b**) (*Table 3.3.1*) could be obtained in high purity without any side products. Both aliphatic and aromatic aldehydes gave good yields with high diastereoselectivity, as determined from the ^{1}H and ^{13}C NMR spectra of the crude products. The substituents on the aromatic ring play an important role in this reaction; electron-

Table 3.3.1. *Synthesis of 2,6-disubstituted-4-phenyltetrahydropyran*

Sl No.	Substrate (a)	Time/h	Product (b)	Yield[a](%)
1		14		74
2		8		93
3		8		95
4		12		80
5		7		85
6		12		60
7		12		85
8		6.5		90

Continue...

Sl No.	Substrate (a)	Time/h	Product (b)	Yield[a](%)
9		8		85
10		16		80
11		8		87
12		16		80
13		8		88
14		16		72
15		16		50
16		16		85

[a]Yields refer to isolated yield. Compounds are characterised by ^{1}H, ^{13} NMR and IR spectroscopy.

withdrawing substituent's and simple aldehydes gave better yields than those obtained when electron-donating groups were on the ring. Aliphatic aldehydes were found to be better substrates for this reaction. The substituent's at the 2-, 4-, and 6-positions of the tetrahydropyran ring are in a *cis* relationship and are equatorial. This is revealed from the coupling constants of the 2, 6-H (J = 11.2 and 2.0 Hz) and the 4-H (J = 11.2 and 2.0 Hz) hydrogen atoms of compound **2b** (*Figure 3.3.1*). This was also confirmed by an NOE experiment and single-crystal X-ray analysis(*Figure 3.3.2*).[5]

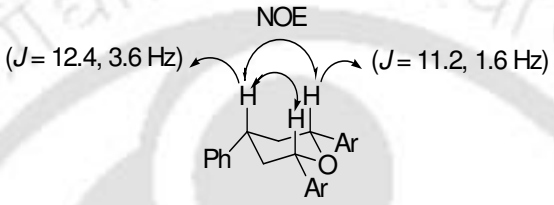


Figure 3.3.1. *Coupling constants and NOE of Compound* ***2b***

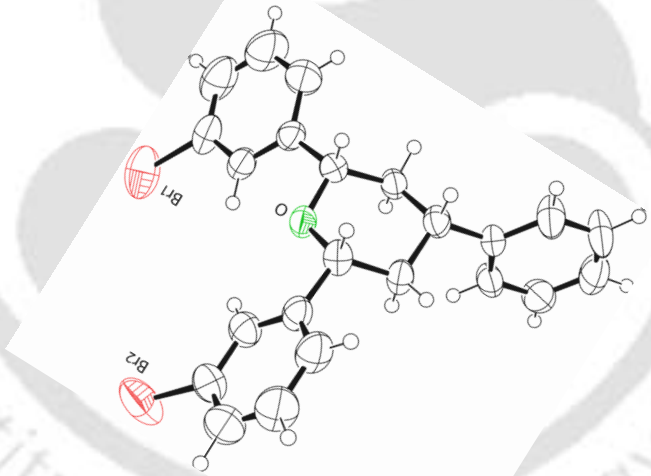
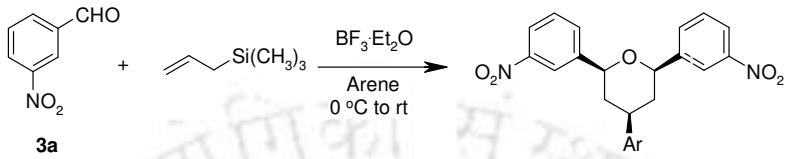


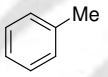
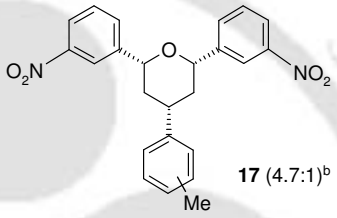
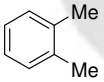
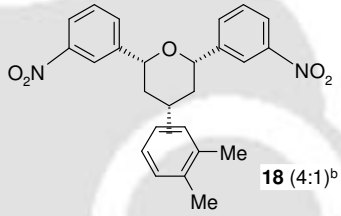
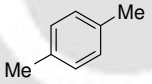
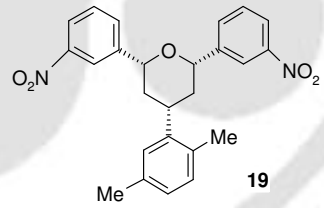
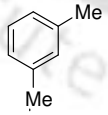
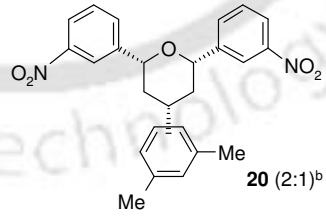
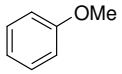
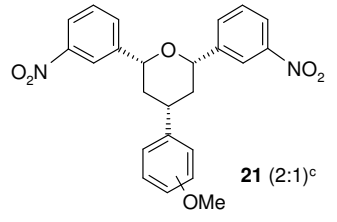
Figure 3.3.2: *ORTEP diagram of 4-Phenyl-2, 6-di(3- bromophenyl)-tetrahydropyran (**2b**)*

To explore further utility of the method, other arenes were also studied as nucleophiles as shown in *Table 3.3.2*. Thus, the reaction of *m*-nitrobenzaldehyde (**3a**) in toluene gave product **17** as an inseparable mixture of two regioisomers with a ratio of 4.7:1 and 97% overall yield. *o*-Xylene gave product **18** as an inseparable mixture of two regioisomers with a ratio of 4:1 and 100% overall yield. In contrast, *p*-xylene gave single product **19** with 100% yield. Similarly, *m*-xylene

gave product **20** as an inseparable mixture of two regioisomers with a ratio of 1:2 and 100% overall yield. Anisole is a good nucleophile, as it gave **21**with 95% yield within 30 min.

Table 3.3.2. *Reaction of m-nitrobenzaldehyde with other aromatic nucleophiles*



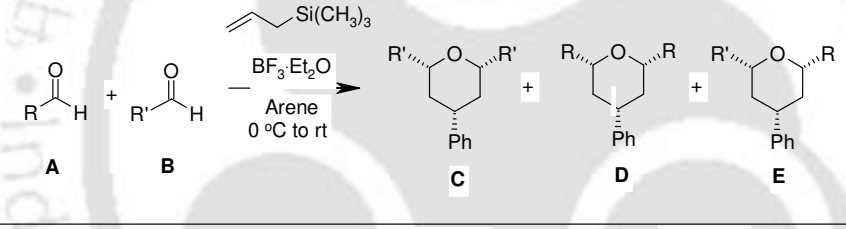
Sl No.	Nucleophiles (Arenes)	Time/h	Product	Yield[a](%)[a]
1		2	 **17** (4.7:1)[b]	99
2		1	 **18** (4:1)[b]	100
3		1	 **19**	100
4		1	 **20** (2:1)[b]	100
5		0.5 18[d]	 **21** (2:1)[c]	95 90[b]

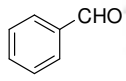
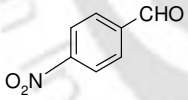
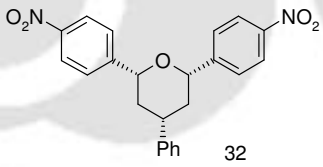
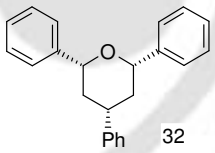
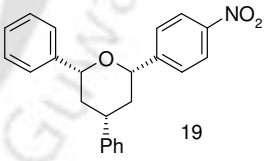
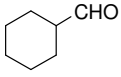
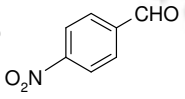
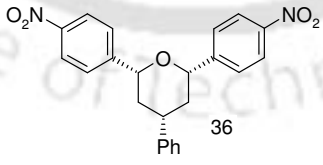
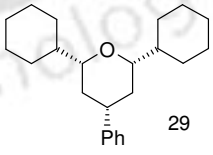
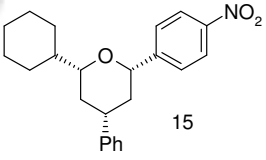
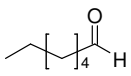
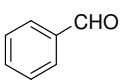
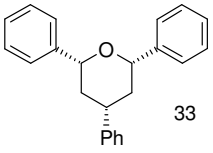
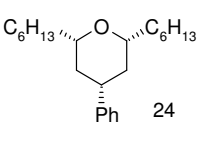
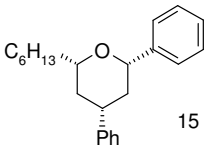
[a]Yields refer to isolated yield. [b]Inseparable regioisomers. Ratio is determined by ^{1}H NMR.
[c]*o/p*-isomers are separated and their ratio is 2:1 [d]Reaction with 5.0 equivalents of anisole.

(**21*p*/21*o***, 1:2). Even at a low concentration of anisole in dichloromethane a good yield was obtained (90%, *Table 3.3.2*). Electron-deficient aromatic compounds such as halobenzenes and nitrobenzene do not act as nucleophiles in the Friedel–Crafts reaction. Aromatic compounds having electron-donating groups, such as methyl and methoxy groups, behave as strong nucleophiles in comparison to benzene, which is evident from their reaction times and yields (*Tables 3.3.1 and 3.3.2*). Other aromatic compounds like naphthalene, 2-methoxynaphthalene, and other fused-ring aromatic compounds were inactive under these reaction conditions. This might be due to steric hindrance.

The reaction was also carried out with two different aldehydes. The reaction was performed by allowing aldehyde **A** to react with allyltrimethylsilane for 1 h, followed by the addition of aldehyde **B**. The reaction was not selective and gave three different products, cross product **E**

Table 3.3.3. *Reaction with mixed aldehydes*



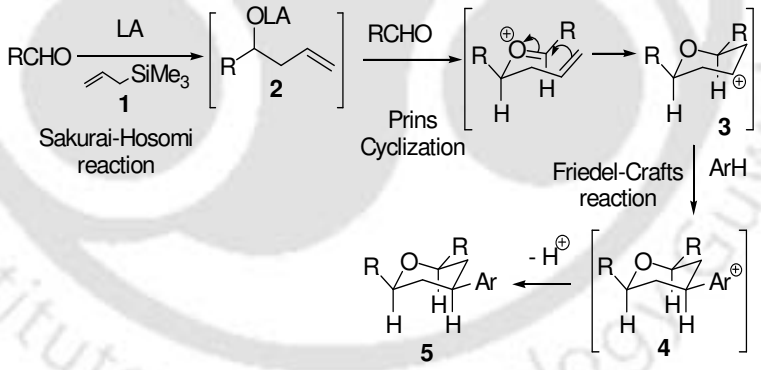
Sl No.	R	R¹	Time/h	Product (% Yield) C	Product (% Yield) D	Product (% Yield) E
1			2	 32	 32	 19
2			1	 36	 29	 15
3			1	 33	 24	 15

[a]Yields refer to isolated yield. Compounds are characterised by ^{1}H, ^{13}C NMR and IR spectroscopy.

symmetric products **C** and **D** and (*Table 3.3.3*). The yield of the cross product was always less than that of the symmetric products. Allowing the first aldehyde to react with allyltrimethylsilane for a longer time period resulted in lower amounts of cross products. This indicates that the rate of formation of homoallylic alcohol (Sakurai–Hosomi reaction) is slower than the Prins Cyclization reaction. That is, all the molecules of aldehyde **A** do not form the homoallylic alcohol intermediate so that aldehyde **B** can take part in Prins cyclization to give the cross product. The possibility of allyl transfer from the initially formed homoallyloxy intermediate (species **2**, *Scheme 3.3.2*) to the second aldehyde cannot be ruled out.

The mechanism of the reaction can be explained as follows: In the presence of Lewis acid allyltrimethylsilane (**1**) reacts with the aldehyde to afford intermediate **2** (*Scheme 3.3.2*). Intermediate **2** reacts with another molecule of the aldehyde to give tetrahydropyranyl cation **3**, which in the presence of an aryl nucleophile, gives intermediate **4**. Species **4** after deprotonation gives 2,6-disubstituted-4-aryltetrahydropyran **5**.

Scheme 3.3.2. *Mechanism of the reaction*



Conclusion

An efficient, highly diastereoselective, onepot method for the synthesis of 2,6-disubstituted-4-aryltetrahydropyrans in good yields has been developed. The advantages of the protocol are mild reaction conditions, high yields of products.

3.4. Experimental Section

3.4.1. Instrumentation and Characterization

As described in Chapter 2, Section 2.5.1.

3.4.2. General procedure

To a mixture of aldehyde (1.0 mmol) and boron trifluoride etherate (1.2 mmol) in aryl compound (3.0 mL), was added allyltrimethylsilane (0.6 mmol) in aryl compound (2.0 mL) drop by drop at 0 °C and slowly increasing the temperature to rt in 1h. The reaction mixture was stirred at rt for specified time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

*Procedure for the synthesis of 2,4,6-Triphenyltetrahydropyran (**1b**, Table 3.3.1):* To a mixture of benzaldehyde, **1a** (0.10 mL, 1.0 mmol), benzene (3.0 mL), and boron trifluoride etherate (0.15 mL, 1.2 mmol), was added allyltrimethylsilane (0.10 mL, 0.6 mmol.) in benzene (2.0 mL) drop by drop at 0 °C and slowly increasing the temperature to rt in 1h. The reaction mixture was stirred at rt for 14h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane (EtOAc:Hexane; 1:9) as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give 2,4,6-triphenyltetrahydropyran **1b** (116 mg, 74%) as a gum. The product **1b** is characterized by spectrometric methods.

*Procedure for the synthesis of 2,6-bis(3-nitrophenyl)-4-(methoxyphenyl) tetrahydropyran (**17**, Table 3.3.2)*: To a solution of m-nitrobenzaldehyde, **3a** (302 mg, 2.0 mmol) and boron trifluoride etherate (0.30 mL, 2.4 mmol) in dichloromethane (2.0 mL) was added a solution of allyltrimethylsilane (0.22 mL, 1.4 mmol.) and anisole (1.10 mL, 10.0 mmol) drop by drop at 0 °C and slowly increasing the temperature to rt in 1h. The reaction mixture was stirred at rt for 24h.

The progress of the reaction was monitored by TLC using ethyl acetate and hexane (EtOAc:Hexane; 1:9) as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by thin layer chromatography over silica gel to give **21*o*** and **21*p*** with the ratio 2:1 (390 mg, 90% of overall yield) as a solid. The products **21*o*** and **21*p*** are characterized by spectroscopic methods.

General procedure for crossed 2,6-disubstituted-4-phenyltetrahydropyran (Table 3.3.3): To a mixture of aldehyde (1.0 mmol) and boron trifluoride etherate (1.2 mmol) in benzene (2.0 mL) was added allyltrimethylsilane (0.6 mmol) in benezene (1.0 mL) drop by drop at 0 °C. The reaction mixture was stirred for 1h at the same temparature, then added another aldehyde (1.2 mmol), boron trifluoride etherate (1.4 mmol) in benzene (2 mL) drop by drop at same temparature. After that the temperature was slowly brought to rt in 1h. The reaction mixture was stirred at rt for specified time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude products, which was purified by short column chromatography over silica gel to give the title compounds.

*Synthesis of 6-(4-Nitro-phenyl)-2,4-diphenyltetrahydropyran (**1E**, Table 3.3.3):* To a mixture of benzaldehyde (106 mg, 1.0 mmol) and boron trifluoride etherate (0.15 mL, 1.2 mmol) in benzene (2.0 mL) was added allyltrimethylsilane (0.10 mL, 0.6 mmol) in benezene (1.0 mL) drop by drop at 0 °C. The reaction mixture was stirred for 1h at the same temparature, then added *p*-nitro-benzaladehyde (181 mg, 1.2 mmol) and boron trifluoride etherate (1.8 mg, 1.4 mmol) in benzene (2 mL) drop by drop at same temparature. The temperature was slowly brought to rt in 1h. The reaction mixture was stirred at rt for specified time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude products, which was purified by short column chromatography

over silica gel to give the compounds **1b** (100 mg, 32%), **2b** (129 mg, 32%), **1E** (68 mg, 19%), which are characterized by spectrometric methods..

3.5 Reference and Notes

(1) (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, VCH, Weinhein, **1996.** (b) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4130-4133. (c) Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 1843-1857. (d) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420-8421. (e) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670-13671. (f) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485-3488. (g) Bahnck, K. B.; Rychnovsky, S. D. *Chem. Commun.* **2006**, 2388-2390. h) Tian, X. T.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem*. **2006**, *71*, 3176-3183. (i) Smith, III, A. B.; Fox, R. J.; Razler, T. M *Acc. Chem. Res*., **2008***, 41*, 675-678.

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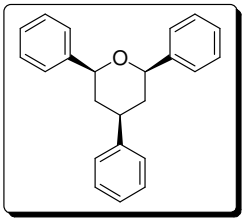
(5) **8b** has been deposited with Cambridge Crystallographic Data Centre as a supplementary publication number CCDC 692425.

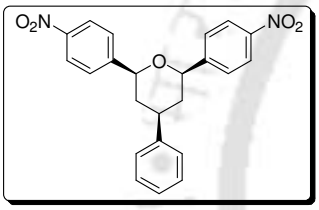
3.6. Spectral Data

2,4,6-Triphenyltetrahydropyran (1b, *Table 3.3.1*):



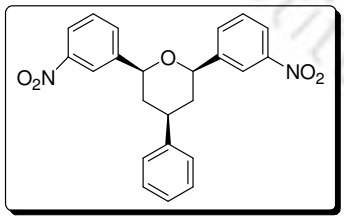
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 1.76-1.85 (m, 2 H, 3ax,5ax-CH), 2.16-2.20 (m, 2 H, 3eq,5eq- CH), 3.17 (tt, $J_{4ax,(3,5)ax}$ = 12.0, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 4.75 (dd, $J_{2ax,3ax}$ =11.2, $J_{2ax,3eq}$ = 2.0 Hz, 2 H, 2ax,6ax-CH), 7.19-7.37 (m, 12 H, ArH), 7.47-7.49 (m, 3 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.4, 42.6, 80.0, 126.0, 126.6, 126.9, 127.5, 128.5, 128.7, 143.1, 145.3. **IR**: 3063, 2915, 2874, 1598, 1573, 1476, 1443, 1208, 1133, 1079, 1051, 1035, 753 cm^{-1}. **Anal. Calcd** for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 87.68; H, 7.21.

4-Phenyl-2,6-di(4-nitrophenyl)-tetrahydropyran (2b):



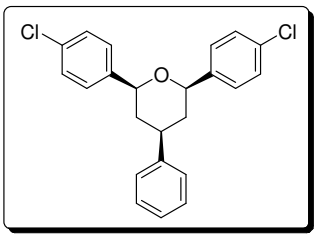
Solid, M.P.: 224-225 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.74-1.83 (m, 2 H, 3ax,5ax-CH), 2.23-2.26 (m, 2 H, 3eq,5eq-CH), 3.25 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$= 3.6 Hz, 1 H, 4ax-CH), 4.89 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ =11.2, $J_{2ax,3eq}$ = $J_{6ax,5eq}$ =1.6 Hz, 2 H, 2ax,6ax-CH), 7.24-7.35 (m, 5 H, ArH), 7.65 (d, *J* = 8.8 Hz, 4 H, ArH), 8.24 (d, *J* = 8.8 Hz, 4 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.0, 42.3, 79.2, 123.9, 126.6, 126.9, 127.2, 129.0, 144.0, 147.5, 149.6; **IR**: 3085, 2915, 2846, 1600, 1512, 1344, 1103, 1091, 850 cm^{-1}. **Anal. Calcd** for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.39; H, 5.10; N, 6.87.

4-Phenyl-2,6-di(3-nitrophenyl)-tetrahydropyran (3b):



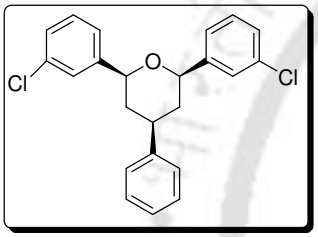
Solid, M.P.: 169-171 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.80-1.89 (m, 2 H, 3ax,5ax-CH), 2.24-2.27 (m, 2 H, 3eq,5eq-CH), 3.25 (tt, $J_{4ax,(3,5)ax}$ = 12.4, , $J_{4ax,(3,5)eq}$ = 3.6 Hz 1 H, 4ax-CH), 4.89 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ =10.0, $J_{2ax,3eq}$ = $J_{6ax,5eq}$ = 2.0 Hz, 2 H, 2ax,6ax-CH), 7.22-7.36 (m, 5 H, ArH), 7.55-7.59 (m, 2 H, ArH), 7.83 (d, *J* = 6.8 Hz, 2 H, ArH), 8.17 (d, *J* = 8.4 Hz, 2 H, ArH), 8.34 (s, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.9, 42.3, 79.2, 121.1, 122.8, 126.9, 127.1, 129.0, 129.7, 132.1, 144.1, 144.4, 148.5; **IR**: 3080, 2953, 2839, 1603, 1525, 1347, 1107, 1071 cm^{-1}. **Anal. Calcd** for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.42; H, 5.09; N, 6.85.

4-Phenyl-2,6-di(4-chlorophenyl)-tetrahydropyran (4b):



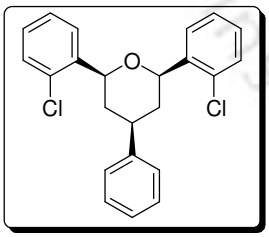
Solid, M.P.: 111-114 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.69-1.78 (m, 2 H, 3ax,5ax-CH), 2.11-2.15 (m, 2 H, 3eq,5eq = CH), 3.14 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax- CH), 4.70 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 11.2 and $J_{2ax,3eq}$ = $J_{6ax,5eq}$ = 1.6 Hz, 2 H, 2ax,6ax-CH), 7.19-7.24 (m, 4H, ArH), 7.28-7.33 (m, 5 H, ArH), 7.36-7.40 (m, 4 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.2, 42.4, 79.4, 126.8, 126.9, 127.4, 128.7, 128.8, 133.3, 141.4, 144.8; **IR**: 3027, 2907, 2837, 1600, 1489, 1084, 1013, 822 cm^{-1}. **Anal. Calcd** for $C_{23}H_{20}Cl_2O$: C, 72.07; H, 5.26. Found: C, 72.15; H, 5.20.

4-Phenyl-2,6-di(3-chlorophenyl)-tetrahydropyran (5b):



Solid, M.P.: 77-78 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.71-1.80 (m, 2 H, 3ax,5ax-CH), 2.12-2.17 (m, 2 H, 3eq,5eq-CH), 3.14 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz 1 H, 4ax-CH), 4.70 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 11.2, $J_{2ax,3eq}$ = $J_{6ax,5eq}$ = 1.6 Hz, 2 H, 2ax,6ax-CH), 7.21-7.26 (m, 6 H, ArH), 7.29-7.33 (m, 5 H, ArH), 7.46 (s, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.1, 42.3, 79.4, 124.1, 126.2, 126.8, 126.9, 127.7, 128.8, 129.8, 134.4, 144.7, 144.8; **IR**: 2875, 1599, 1475, 1428, 1320, 1110, 1075, 885, 782 cm^{-1}. **Anal. Calcd** for $C_{23}H_{20}Cl_2O$: C, 72.07; H, 5.26. Found: C, 72.10; H, 5.18.

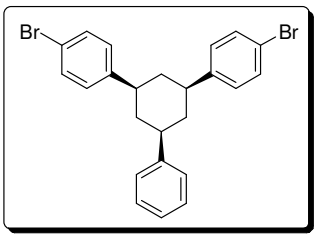
4-Phenyl-2,6-di(2-chlorophenyl)-tetrahydropyran (6b):



Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.61-1.71 (m, 2 H, 3ax,5ax-CH), 2.36-2.40 (m, 2 H, 3eq,5eq-CH), 3.28 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 5.20 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 11.2, $J_{2ax,3eq}$ = $J_{6ax,5eq}$ = 1.6 Hz, 2 H, 2ax,6ax-CH), 7.19-7.24 (m, 4 H, ArH), 7.28-7.33 (m, 5 H, ArH), 7.36-7.40 (m, 4 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.2, 42.4, 79.4, 126.8, 126.9, 127.4, 128.7, 128.8, 133.3, 141.4, 144.8; **IR**: 2921, 2851, 1596, 1473, 1443, 1100, 1083, 1034, 752 cm^{-1}. **Anal. Calcd** for $C_{23}H_{20}Cl_2O$: C, 72.07; H, 5.26. Found: C, 72.21; H, 5.17.

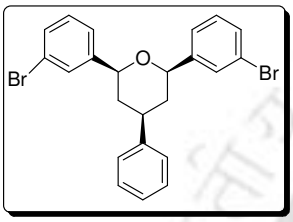
4-Phenyl-2,6-di(4-bromophenyl)-tetrahydropyran (7b):

Solid**,** M.P**.:** 120-121 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.66-1.75 (m, 2 H, 3ax,5ax-CH), 2.00-2.12 (m, 2 H, 3eq,5eq-CH), 3.11 (tt, $J_{4ax,(3,5)ax}$ = 12.0, $J_{4ax,(3,5)eq}$ =3.6 Hz, 1 H, 4ax-CH), 5.64 (dd,



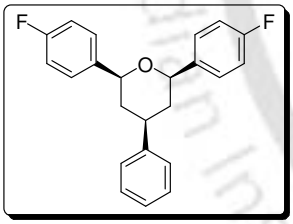
$J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 11.2, $J_{2ax,3eq}$ = $J_{6ax,5eq}$ = 1.6 Hz, 2 H, 2ax,6ax-CH), 7.19-7.22 (m, 4 H, ArH), 7.27-7.31 (m, 5 H, ArH), 7.44-7.46 (m, 4 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.1, 42.3, 79.3, 121.3, 126.8, 126.9, 127.7, 128.8, 131.6, 141.8, 144.8; **IR**: 2931, 2852, 1590, 1485, 1084, 1070, 1009, 819, 757 cm^{-1}. **Anal. Calcd** for $C_{23}H_{20}Br_2O$: C, 58.50; H, 4.27. Found: C, 58.62; H, 4.16.

4-Phenyl-2,6-di(3-bromophenyl)-tetrahydropyran (8b):



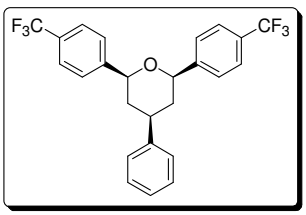
Solid**,** M.P.**:** 108-112 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.72-1.81 (m, 2 H, 3ax,5ax- CH), 2.13-2.17 (m, 2 H, 3eq,5eq-CH), 3.16 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 4.69 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 11.2, $J_{2ax,3eq}$ = $J_{6ax,5eq}$ = 1.2 Hz, 2 H, 2ax,6ax-CH), 7.21-7.25 (m, 4H, ArH), 7.31-7.33 (m, 3 H, ArH), 7.37-7.42 (m, 4 H, ArH), 7.61 (s, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.00, 42.2, 79.3, 122.6, 124.6, 126.8, 126.9, 128.8, 129.1, 130.1, 130.6, 144.9; **IR**: 2920, 2873, 1596, 1473, 1113, 1076, 885, 698 cm^{-1}. **Anal. Calcd** for $C_{23}H_{20}Br_2O$: C, 58.50; H, 4.27. Found: C, 58.64; H, 4.32.

4-Phenyl-2,6-di(4-fluorophenyl)-tetrahydropyran (9b):



Solid**,** M.P.**:** 98-101 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.72-1.82 (m, 2 H, 3a,5a-CH), 2.12-2.16 (m, 2 H, 3eq,5eq-CH), 3.15 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 4.71 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 11.2, $J_{2ax,}$3eq = $J_{6ax,5eq}$ = 1.6 Hz, 2 H, 2ax,6ax-CH), 7.00-7.10 (m, 4H, ArH), 7.20-7.33 (m, 5 H, ArH), 7.40-7.44 (m, 4 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.3, 42.3, 79.4, 115.24 (d, $^{2}J_{C-F}$ = 21.4 Hz), 126.7, 126.9, 127.6 (d, $^{3}J_{C-F}$ = 7.6 Hz), 128.7, 138.7, 144.9, 162.2 (d, $^{1}J_{C-F}$ = 243 Hz); ^{19}F NMR (376 MHz, C_6F_6): 46.38-46.45 (m, 2F); **IR**: 2916, 2820, 1605, 1505, 1377, 1219, 1155, 1106, 1068, 836, 701 cm^{-1}.

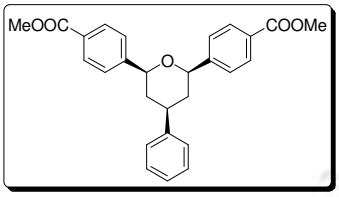
2,6-bis(4-(trifluoromethyl)phenyl)-tetrahydro-4-phenyl-2H-pyran(10b):



Semisolid**; ^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.73-1.82 (m, 2 H, 3ax,5ax-CH), 2.18-2.22 (m, 2 H, 3eq,5eq-CH), 3.20 (tt, $J_{4ax,(3,5)ax}$ = 12.0, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 4.81 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 10.4, $J_{2ax,3eq}$ = $J_{6ax,5eq}$ = 2.0 Hz, 2 H, 2ax,6ax-CH), 7.20-7.35 (m, 5 H, ArH), 7.53-7.64 (m, 8 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.2, 42.4, 79.4, 124.4 (q, $^{1}J_{C-F}$ =

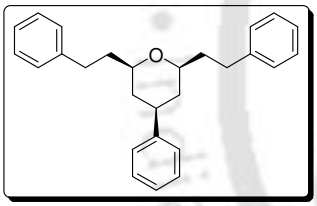
270.7 Hz), 125.5, 126.2, 126.9, 127.0, 128.9, 130.0 (q, $^{2}J_{C\text{-}F}$ = 32 Hz), 144.6, 146.7; ^{19}F NMR (376 MHz, C_6F_6): 99.30 (s, 6F); **IR**: 2916, 2848, 1622, 1416, 1326, 1164, 1124, 1067, 837, 700 cm^{-1}.

4-Phenyl-2,6-di(4-methoxycarbonylphenyl)-tetrahydropyran (11b):



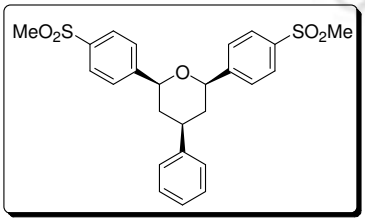
Solid**,** M.P**.:** 162-163 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.71-1.82 (m, 2 H, 3ax,5ax-CH), 2.16-2.21 (m, 2 H, 3eq,5eq-CH), 3.20 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 3.93 (s, 3 H, -OCH_3), 4.81 (dd, $J_{2ax,3ax} = J_{6ax,5ax}$ = 10.4, $J_{2ax,3eq} = J_{6ax,5eq}$ = 2.0 Hz, 2 H, 2ax,6ax-CH), 7.20-7.33 (m, 5 H, ArH), 7.54 (d, *J*=8.4 Hz, 4 H, ArH), 8.00 (d, *J* = 8.4 Hz, 4 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.2, 52.3, 79.6, 125.8, 126.9, 127.0, 128.8, 129.4, 130.0, 144.7, 147.8, 167.1; **IR**: 2950, 2870, 1714, 1609, 1434, 1276, 1107, 1074, 768 cm^{-1}. **Anal. Calcd** for $C_{27}H_{26}O_5$: C, 75.33; H, 6.09. Found: C, 75.45; H, 7.17.

4-Phenyl-2,6-diphenylethyltetrahydropyran (12b):



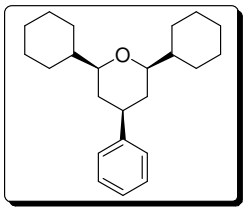
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.42-1.51 (m, 2 H, 3ax,5ax-CH), 1.75-1.83 (m, 4 H, -CH_2-), 1.93-2.00 (m, 2 H, 3eq,5eq-CH), 2.75-2.83 (m, 4 H, -CH_2-), 2.91 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 3.40-3.45 (m, 2 H, 2ax,6ax -CH), 7.20-7.33 (m, 15 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 32.1, 38.1, 39.5, 41.9, 76.4, 125.9, 126.4, 126.9, 128.5, 128.6, 128.7, 142.5, 146.0; **IR**: 2931, 2857, 1603, 1495, 1454, 1376, 1324, 1117, 1077, 1060, 751, 698 cm^{-1}. **Anal. Calcd** for $C_{27}H_{30}O$: C, 87.60; H, 8.22. Found: C, 87.75; H, 8.36.

Tetrahydro-2,6-bis(4-(methylsulfonyl)phenyl)-4-phenyl-2H-pyran (13b):



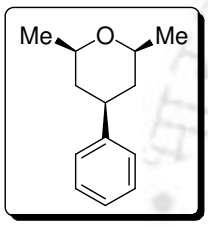
Solid**,** M.P**.:** 105-119 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.74-1.83 (m, 2 H, 3ax,5ax-CH), 2.22-2.25 (m, 2 H, 3ex,5ex-CH), 3.10 (s, 3 H, -SO_2CH_3), 3.23 (tt, $J_{4ax,(3,5)ax}$ = 12.0, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 4.87 (dd, $J_{2ax,3ax} = J_{6ax,5ax}$ = 10.4, $J_{2ax,3eq} = J_{6ax,5eq}$ = 2.0 Hz, 2 H, 2ax,6ax-CH), 7.24-7.34 (m, 5 H, ArH), 7.67-7.68 (d, *J* = 8.4 Hz, 4 H, ArH), 7.96 (d, *J* = 8.4 Hz, 4 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.1, 42.3, 44.8, 79.4, 126.8, 126.9, 127.1, 127.8, 128.9, 139.8, 144.2, 148.7; **IR**: 2925, 2857, 1602, 1508, 1404, 1310, 1149, 1089, 957, 768 cm^{-1}. **Anal. Calcd** for $C_{25}H_{26}O_5S_2$: C, 63.81; H, 5.57. Found: C, 63.95; H, 5.64.

4-Phenyl-2,6-dicyclohexyltetrahydropyran (14b):



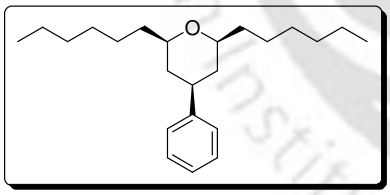
Semisolid**; ^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.86-1.00 (m, 6 H, 3x-CH_2-), 1.20-1.46 (m, 14 H, 2x-CH_2-), 1.53-1.65 (m, 4 H, 2x-CH_2-), 1.79-1.83 (m, 2 H, 3eq,5eq-CH), 2.78 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 3.40 (m 2 H, 2ax,6ax -CH), 7.18 (m, 3 H, ArH) 7.29-7.33 (m, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.8, 25.9, 29.5, 32.1, 36.6, 39.6, 42.2, 77.7, 126.4, 127.0, 128.6, 146.3; **IR**: 2929, 2857, 1604, 1465, 1377, 1325, 1136, 1083, 698 cm^{-1}. **Anal. Calcd** for $C_{23}H_{34}O$: C, 84.60; H, 10.50. Found: C, 84.74; H, 10.68.

4-Phenyl-2,6-dimethyltetrahydropyran (15b):



Semisolid**; ^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (d, J = 6.0 Hz, 6 H, 2x-CH_3), 1.31-1.43 (m, 2 H, 3ax,5ax-CH), 1.78-1.82 (m, 2 H, 3eq,5eq-CH), 2.78 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 3.58-3.66 (m, 2 H, 2ax,6ax-CH), 7.19-7.22 (m, 3 H, ArH), 7.29-7.33 (m, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.3, 40.8, 42.0, 73.7, 126.4, 127.0, 128.7, 146.1; **IR**: 2930, 1643, 1375, 1142, 1027, 756, 699 cm^{-1}. **Anal. Calcd** for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.24; H, 9.45.

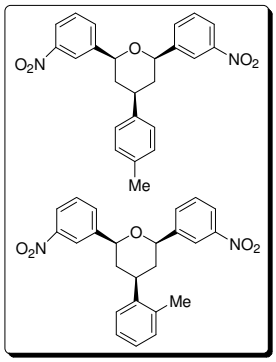
4-Phenyl-2,6-dihexyltetrahydropyran (16b):



Solid**,** M.P.**:** 86-89 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.98 (t, J=7.6 Hz, 6 H, 2x-CH_3), 1.11-1.44 (m, 16 H, 8x-CH_2-), 1.63-1.75 (m, 4 H, 2x-CH_2-), 1.83-1.87 (m, 2 H, 3eq,5eq- CH), 2.04-2.10 (m, 2 H, -CH_2-), 2.7 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 3.04-3.10 (m, 2 H, 2ax,6ax-CH), 7.18-7.22 (m, 3 H, ArH), 7.29-7.32 (m, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.3, 26.4, 26.9, 29.2, 29.6, 36.7, 42.5, 43.5, 82.2, 126.4, 127.1, 128.7, 146.8; **IR**:2927, 2853, 1601, 1448, 1388, 1119, 1087, 998, 697 cm^{-1}. **Anal. Calcd** for $C_{23}H_{38}O$: C, 83.57; H, 11.59. Found: C, 83.50; H, 11.70.

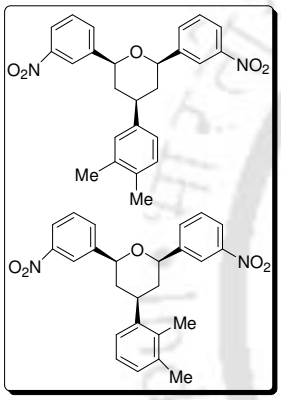
Tetrahydro-2,6-bis(3-nitrophenyl)-4-o-tolyl-2H-pyran and Tetrahydro-2,6-bis(3-nitrophenyl)-4-p-tolyl-2H-pyran (inseparable mixture 1:4.7) (17):

Solid, **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.80-1.89 (m, 2 H, 3ax,5ax-CH), 2.15-2.34 (m, 2 H, 3eq,5eq-CH), 2.43 (s, 0.5 H, -CH_3), 2.47 (s, 2.5 H, -CH_3), 3.20 (tt, J = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz,



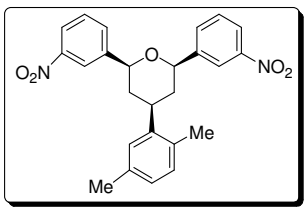
0.2 H, 4ax-CH), 3.44-3.51 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 0.8 H, 4ax-CH), 4.87-4.93 (m, 2 H, 2ax,6ax-CH), 7.12-7.20 (m, 4 H, ArH), 7.54-7.59 (m, 2 H, ArH), 7.84 (d, *J* = 7.6 Hz, 2 H, ArH), 8.16 (d, *J* = 7.6 Hz, 2 H, ArH), 8.33 (s, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.7, 37.8, 40.2, 79.2, 79.4, 121.1, 122.8, 125.6, 126.7, 129.7, 130.8, 132.2, 135.2, 142.0, 144.4, 148.5; **IR**: 3085, 2915, 2855, 1521, 1348, 1099, 1069, 905, 738, 686 cm^{-1}.

Tetrahydro-4-(2,3-dimethylphenyl)-2,6-bis(3-nitrophenyl)-2H-pyran and Ttetrahydro-4-(3,4-dimethylphenyl)-2,6-bis(3-nitrophenyl)-2H-pyran (inseparable mixture 1:4)(18):



Solid**,** M.P.**:** 82-84 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.80-1.89 (m, 2 H, 3ax,5ax-CH), 2.16-2.26 (m, 2 H, 3ex,5ex-CH), 2.25 (s, 0.60 H, -CH_3), 2.27 (s, 0.60 H, -CH_3), 2.32 (s, 2.40 H, -CH_3), 2.36 (s, 2.40 H, -CH_3), 3.20 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 0.20 H, 4ax- CH), (3.54 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 0.80 H, 4ax- CH), 4.87 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 10, $J_{2ax,3eq}$ = $J_{6ax,5eq}$ = 1.2 Hz, 0.40 H, 2ax,6ax-CH), 4.92 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 10, $J_{2ax,3eq}$ = $J_{6ax,5eq}$ = 1.2 Hz, 1.60 H, 2ax,6ax-CH), 7.00-7.10 (m, 3 H, ArH), 7.55-7.60 (m, 2 H, ArH), 7.83 (d, J = 7.6 Hz, 2 H, ArH), 8.17 (d, J = 8.4 Hz, 2 H, ArH), 8.4 (s, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.0, 19.5, 20.0, 21.3, 38.1, 40.4, 41.0, 41.8, 79.2, 79.4, 121.1, 122.8, 123.3, 124.2, 126.1, 128.1, 128.5, 129.7, 130.1, 132.1, 133.8, 135.3, 137.1, 137.4, 141.7, 141.8, 144.5, 148.5; **IR**: 2919, 2856, 1528, 1477, 1347, 1109, 1070, 810, 738 cm^{-1}. **Anal. Calcd** for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.50; H, 5.70; N, 6.57.

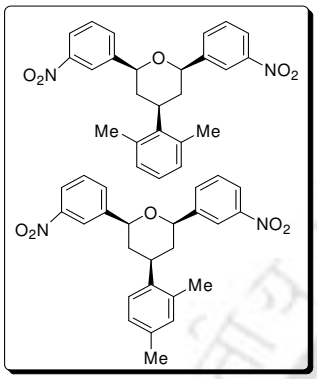
Tetrahydro-4-(2,5-dimethylphenyl)-2,6-bis(3-nitrophenyl)-2H-pyran(19):



Solid**,** M.P.**:** 174-176 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.80-1.89 (m, 2 H, 3ax,5ax-CH), 2.14-2.17 (m, 2 H, 3eq,5eq-CH), 2.28 (s, 3 H, -CH_3), 2.42 (s, 3 H, -CH_3), 3.44 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 4.91 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ =10.4, $J_{2ax,3eq}$ = $J_{6a,5eq}$ = 2.0 Hz, 2 H, 2ax,6ax-CH), 6.93-7.10 (m, 3 H, ArH), 7.54-7.58 (m, 2 H, ArH), 7.84 (d, J= 7.6 Hz, 2 H, ArH), 8.17 (d, J= 7.2 Hz, 2 H, ArH), 8.35 (s, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.2, 21.3, 37.7, 40.2, 79.4, 121.1, 122.8, 126.3, 127.4, 129.7, 130.8, 131.9, 132.2, 136.1, 141.8, 144.5,

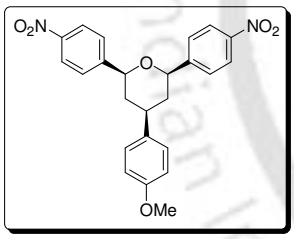
148.5; **IR**: 2940, 2866, 1525, 1348, 1108, 1071, 810 cm^{-1}. **Anal. Calcd** for $C_{25}H_{24}N2O_5$: C, 63.43; H, 5.59; N, 6.48. Found: C, 63.49; H, 5.65; N, 6.55.

Tetrahydro-4-(2,6-dimethylphenyl)-2,6-bis(3-nitrophenyl)-2H-pyran and Tetrahydro-4-(2,4-dimethylphenyl)-2,6-bis(3-nitrophenyl)-2H-pyran (inseparable mixture 1:2.8) (20):



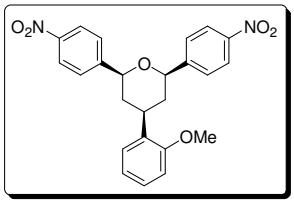
Solid, **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.78-1.87 (m, 0.54 H, 3ax,5ax-CH), 2.05-2.17 (m, 2 H, 3eq,5eq-CH), 2.25-2.34 (m, 1.46 H, 3ax,5ax-CH), 2.43 (s, 1.6 H, $-CH_3$), 2.48 (s, 4.4 H, $-CH_3$), 3.44 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 0.27 H, 4ax-CH), 3.75 (tt, J = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 0.73 H, 4ax-CH), 4.86-4.92 (m, 2 H, 2ax,6ax-CH), 6.93-7.10 (m, 3 H, ArH), 7.55-7.60 (m, 2 H, ArH), 7.84 (d, J = 7.6 Hz, 2 H, ArH), 8.17 (d, J = 7.2 Hz, 2 H, ArH), 8.33 (s, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.2, 21.3, 37.7, 40.2, 79.4, 121.1, 122.8, 126.3, 127.4, 129.7, 130.8, 131.9, 132.2, 136.1, 141.8, 144.5, 148.5; 2930, 2876, 1529, 1476, 1347, 1103, 1063, 811, 737, 685 cm^{-1}.

Tetrahydro-4-(4-methoxyphenyl)-2,6-bis(3-nitro-phenyl)-2H-pyran (21p):



Solid, M.P.: 164-168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.74-1.84 (m, 2 H, 3ax,5ax-CH), 2.21-2.25 (m, 2 H, 3eq,5eq-CH), 3.20 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 3.78 (s, 3 H, $-OCH_3$), 4.88 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 10, $J_{2ax,3eq}$ = $J_{6a,5eq}$ =1.2 Hz, 2 H, 2ax,6ax-CH), 6.86 (d, J = 8.4 Hz, 2 H, ArH),7.18 (d, J = 8.4, 2 H, ArH), 7.56 (m, 2 H, ArH), 7.83 (d, J = 7.6 Hz, 2 H, ArH), 8.15(d, J = 8.0 Hz, 2 H, ArH), 8.34 (s, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.2, 41.4, 55.5, 79.2, 114.3, 121.1, 122.8, 127.8, 129.7, 132.1, 136.3, 144.5, 148.5, 158.6; **IR**: 2933, 2853, 1528, 1350, 1250, 1103, 1072, 810, 737 cm^{-1}. **Anal. Calcd** for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.50; H, 5.27; N, 6.57.

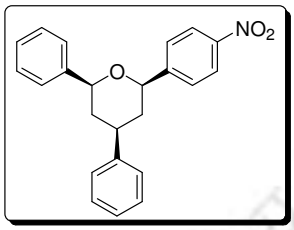
Tetrahydro-4-(2-methoxyphenyl)-2,6-bis(3-nitrophenyl)-2H-pyran (21-o):



Solid, M.P.: 124-128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.73-1.85 (m, 2 H, 3ax,5ax-CH), 2.20-2.24 (m, 2 H, 3ex,5ex-CH), 3.69 (tt, $J_{4ax,(3,5)ax}$ = 12.4, $J_{4ax,(3,5)eq}$ = 3.6 Hz, 1 H, 4ax-CH), 3.90 (s, 3 H, $-OCH_3$), 4.92 (dd, $J_{2ax,3ax}$ = $J_{6ax,5ax}$ = 10, $J_{2ax,3eq}$ = $J_{6a,5eq}$ = 1.2 Hz, 2 H, 2ax,6ax-CH), 6.88-6.95 (m, 2 H, ArH), 7.16-7.24 (m, 2 H, ArH), 7.56 (m, 2 H, ArH), 7.84 (d, J

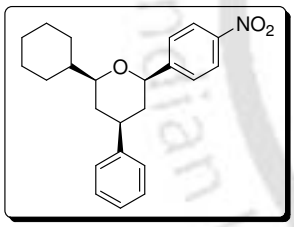
= 7.6 Hz, 2 H, ArH), 8.14-8.17 (m, 2 H, ArH), 8.33 (s, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 35.1, 39.6, 55.6, 79.4, 110.7, 121.0, 121.1, 122.7, 126.6, 127.8, 129.6, 132.2 (2C), 144.7, 148.5, 156.9; **IR**: 2920, 2850, 1528, 1348, 1241, 1102, 1070, 810, 736 cm^{-1}. **Anal. Calcd** for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.52; H, 5.23; N, 6.49.

6-(4-Nitro-phenyl)-2,4-diphenyltetrahydropyran (1E, Table 3):



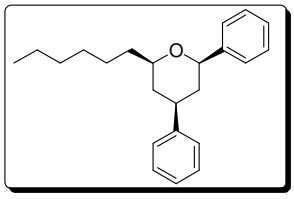
Solid, M. P.: 101-103 °C; **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C)): δ 1.70 (q, *J* = 12.4 Hz, 1 H), 1.80 (q, *J* = 12.8 Hz, 1 H), 2.15-2.18 (m, 2 H), 3.17 (tt, *J* = 12.0 and 3.6 Hz, 1 H), 4.73 (dd, *J* = 11.2 and 2.0 Hz, 1 H), 4.80 (dd, *J* = 11.2 and 2.0 Hz, 1 H), 7.18-7.39 (m, 8 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 8.16 (d, *J* = 8.8 Hz, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.0, 41.2, 42.3, 78.9, 80.1, 123.7, 125.9, 126.3, 126.6, 126.9, 127.7, 128.6, 128.8, 142.5, 144.6, 147.2, 150.3. **IR**: 3062, 3029, 2941, 2849, 1602, 1516, 1495, 1345, 1287, 1102, 1078, 1030, 987, 851, 748 cm^{-1}. **Anal. Calcd** for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90 Found: C, 76.92; H, 5.78; N, 3.88.

2-Cyclohexyl-6-(4-nitro-phenyl)-4-phenyltetrahydropyran (2E):



Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.05-1.32 (m, 5 H), 1.48-1.62 (m, 4 H), 1.67-1.80 (m, 3 H), 1.90-1.94 (m, 1 H), 1.98-2.00 (m, 1 H), 2.10-2.14 (m, 1 H), 2.97 (tt, *J* = 12.0 and 4.0 Hz, 1 H), 3.42 (ddd, J = 11.2, 6.4 and 2.0 Hz, 1 H), 4.61 (dd, *J* = 11.2 and 2.0 Hz, 1 H), 7.22-7.26 (m, 3 H), 7.30-7.33 (m, 2 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 8.19 (d, *J* = 8.4 Hz, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.3, 26.4, 26.8, 28.9, 29.1, 35.6, 41.3, 42.2, 43.2, 78.2, 82.3, 123.6, 126.4, 126.6, 126.9, 128.7, 145.4, 147.0, 150.9. **IR**: 2927, 2849, 1600, 1523, 1507, 1449, 1346, 1103, 1079, 852, 747, 696 cm^{-1}. **Anal. Calcd** for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83 Found: C, 75.66; H, 7.57; N, 3.87.

2-Hexyl-4,6-diphenyltetrahydropyran (3E):



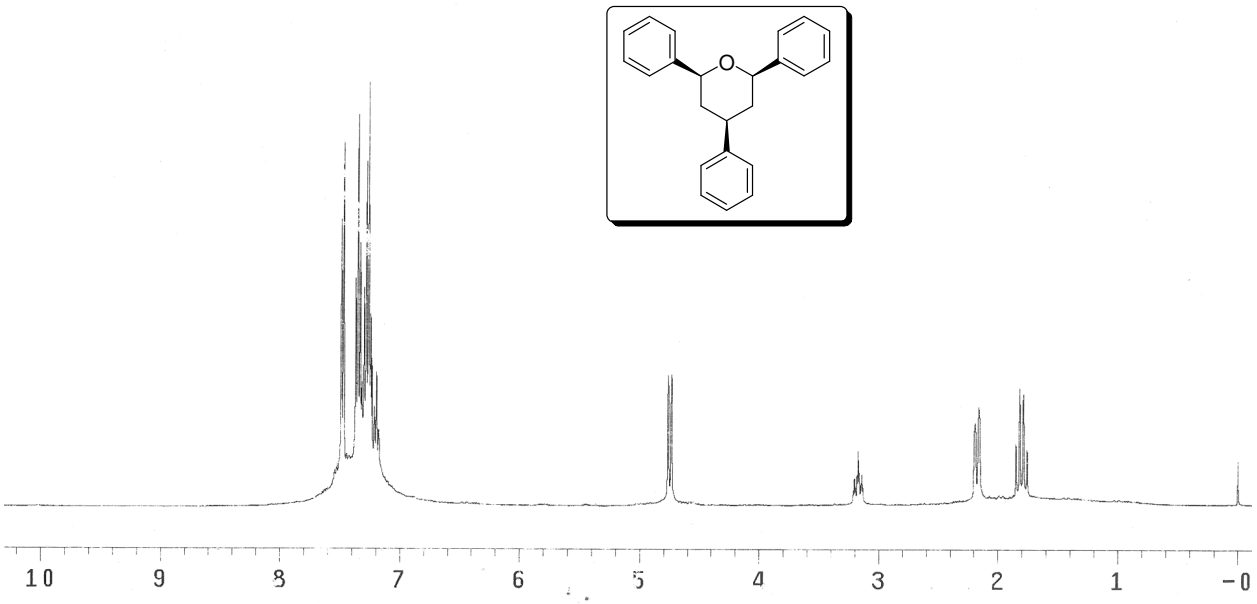
Semisolid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3 H, -CH_3), 1.20-1.37 (m, 6 H, 3x-CH_2), 1.40-1.60 (m, 4 H, 2x-CH_2), 1.63-1.74 (m, 2 H, 3eq,5eq-CH), 1.89 (dq, J_{3ax} = 12.8 and 2.0 Hz, 1 H, -CH), 2.08 (dq, J_{5ax} = 12.8 and 2.0 Hz, 1 H, -CH), 2.96 (tt, J_{4ax} = 11.6 and 3.2 Hz, 1 H, -CH), 3.58-3.66 (m, 1 H, 2ax-CH), 4.52 (dd, J_{4ax} = 11.2 and 1.6 Hz, 1 H, 6ax-CH),

7.17-7.25 (m, 5 H, ArH), 7.27-7.34 (m, 3 H, ArH), 7.39 (d, *J* = 7.2 Hz, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.8, 25.7, 29.6, 32.0, 36.6, 39.1, 41.2, 42.4, 78.2, 79.3, 126.0, 126.5, 127.0, 127.3, 128.4, 128.7, 143.3, 145.8. **IR**: 2929, 2856, 1603, 1495, 1453, 1375, 1132, 1080, 1066, 750, 697 cm^{-1}. **Anal. Calcd** for $C_{23}H_{30}O$: C, 85.66; H, 9.38; Found: C, 85.58; H, 9.32.

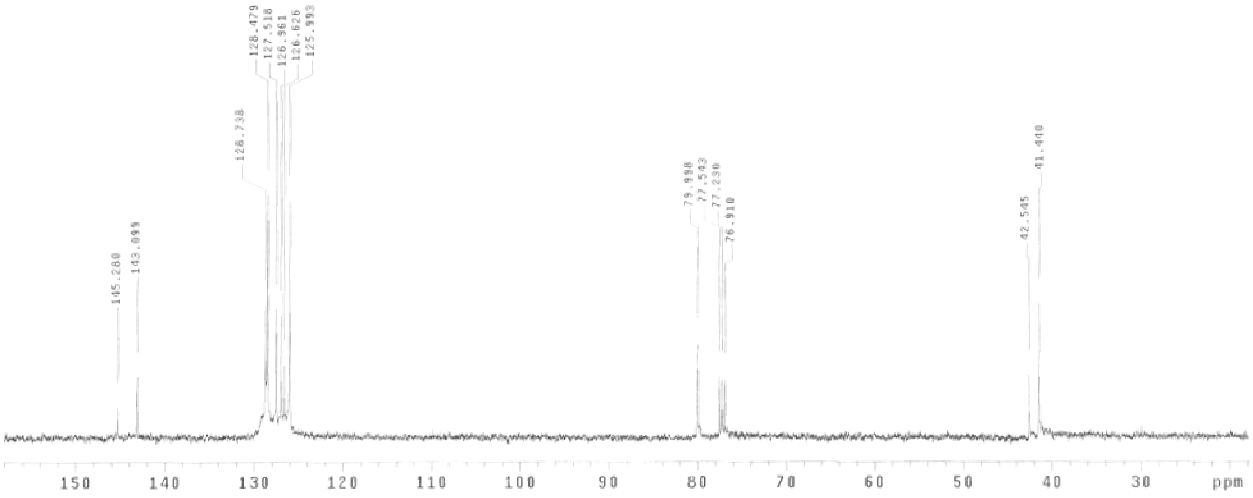
3.7 Selected Spectra of symmetrical 4-aryltetrahydropyrans

2,4,6-Triphenyltetrahydropyran (1b):

^{1}H NMR (400 MHz, $CDCl_3$)

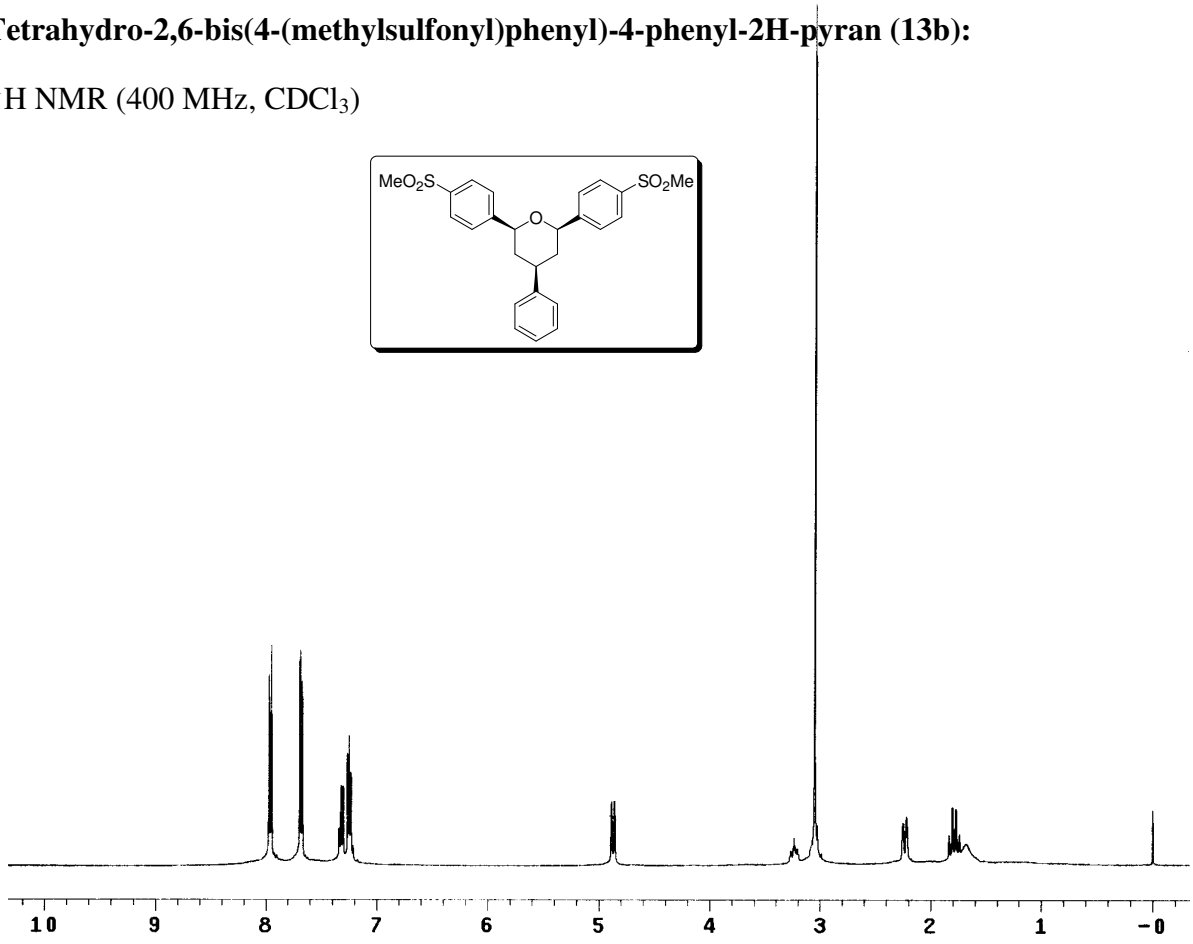


^{13}C NMR (100 MHz, $CDCl_3$)

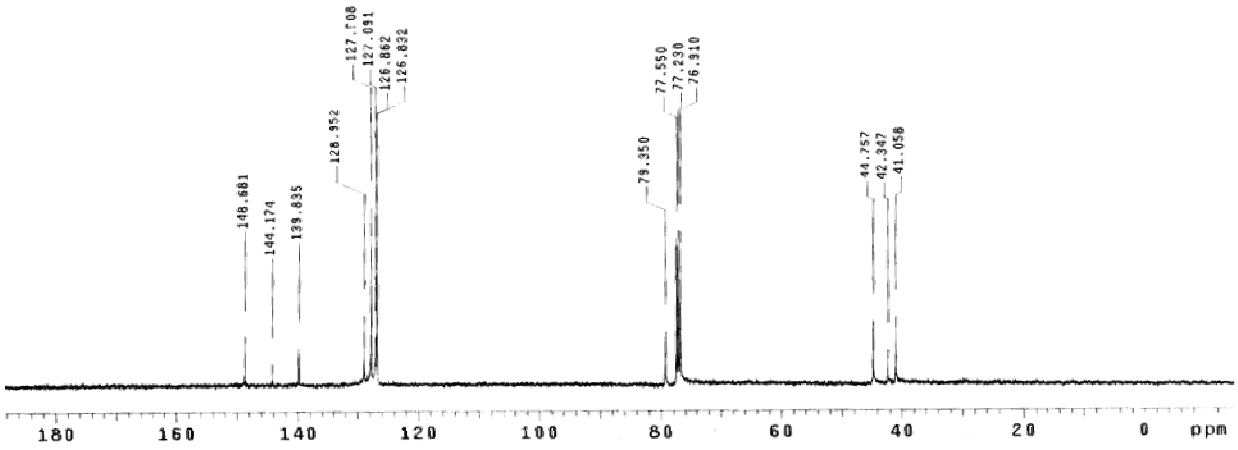


Tetrahydro-2,6-bis(4-(methylsulfonyl)phenyl)-4-phenyl-2H-pyran (13b):

^{1}H NMR (400 MHz, $CDCl_3$)

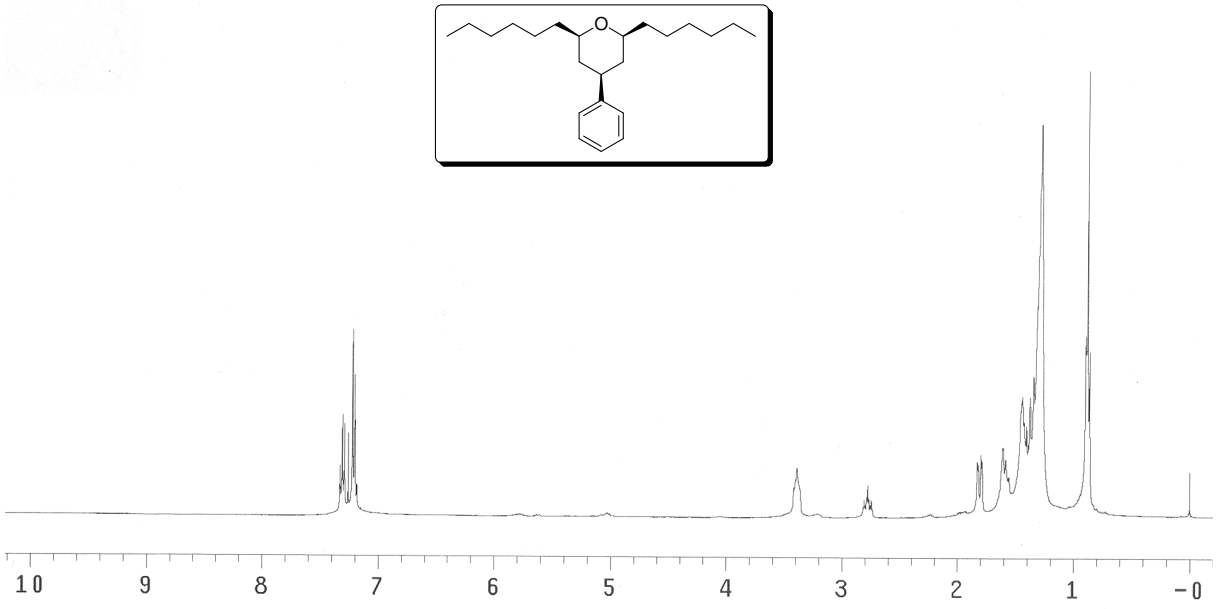


^{13}C NMR (100 MHz, $CDCl_3$)

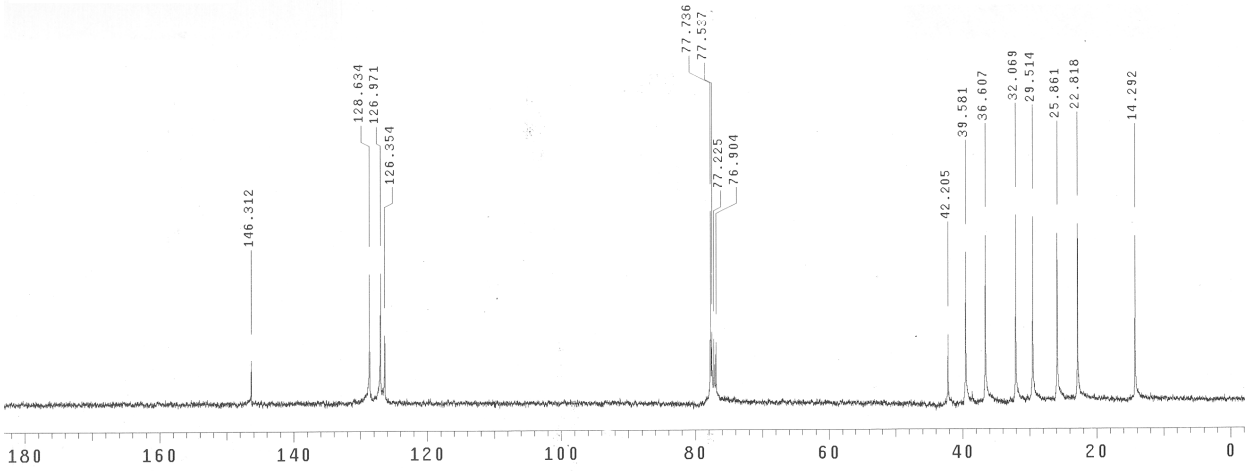


4-Phenyl-2,6-dihexyltetrahydropyran (16b):

^{1}H NMR (400 MHz, $CDCl_3$)

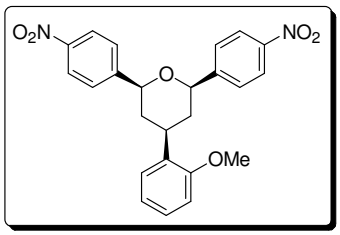


^{13}C NMR (100 MHz, $CDCl_3$)

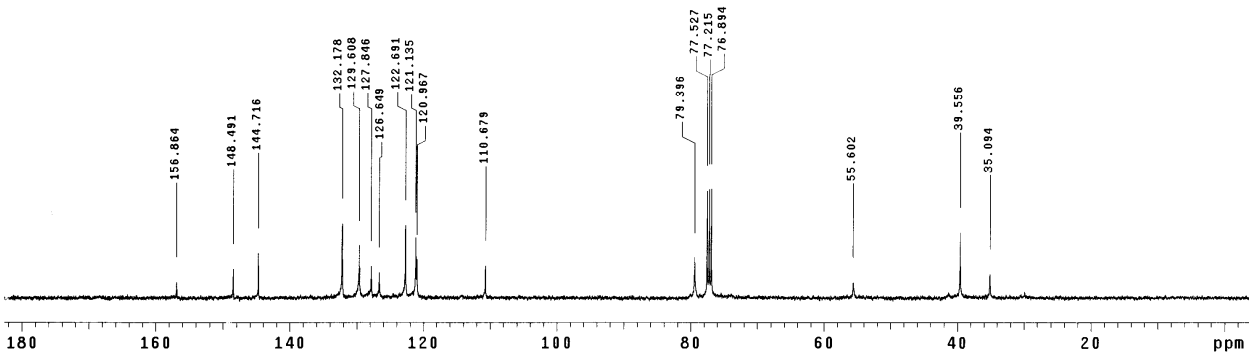


Tetrahydro-4-(2-methoxyphenyl)-2,6-bis(3-nitrophenyl)-2H-pyran (21-*o*):

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



2.8 The Crystal Parameters of Compound 1b.

Crystal Parameters	**8b** (VCR_mbba_Om; CCDC 692415)
Formula	C23 H20 Br2 O
Formula weight	472.21
T/K	296(2)
Crystal system	Orthorhombic
Space group	'P2(1)2(1)2(1) '
a/Å	8.6692(8)
b/Å	13.8031(13)
c/Å	17.0157(16)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	2036.1(3)
Z	4
Abs. Coeff./mm^{-1}	3.990
Abs. Correction	None
GOF on F^2	0.946
Final *R* indices	*R1* = 0.0372
[$I > 2\sigma(I)$]	*wR2* = 0.0732
R indices [all data]	*R1* = 0.1110,
	wR2 = 0.0898

CHAPTER 4

Stereoselective Synthesis of Unsymmetrical 4-Aryltetrahydropyrans

4.1.1. Importance and Applications

The 4-aryl tetrahydropyrans are core units of many naturally occurring biologically active compounds such as calyxins **1** & **2** (*Figure 4.1.1*)[1], and they show interesting antiproliferative activity against carcinoma cells. Epicalyxin F is the most potent member of these class and show ca. 1 *t*M activity against human HT-1080 fibro sarcoma and murine 26-L5 carcinoma. (-)-Sugiresinol **3** (*Figure 4.1.1*),[2] a norlignan isolated from heartwood of *Cryptomeria japonica* by Funaoka *et al*., has potent antifungal activity and inhibits cyclic AMP phosphodiesterase in addition to the growth of *C. shiitake* hyphae.

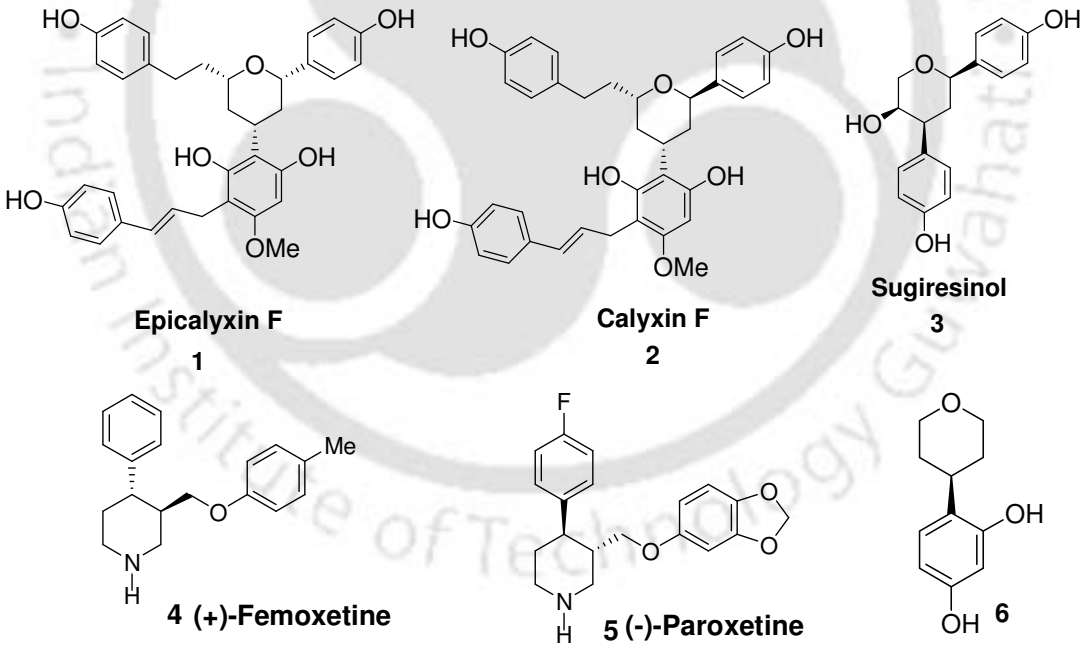


Figure 4.1.1. *Some biologically active 4-aryl-tetrhydropyran and piperidine derivatives*

3-Substituted-4-arylpiperidines such as (+)-femoxetine **4**, (-)-paroxetine **5** (*Figure 4.1.1*),[3] and their analogues are a significantly important class of serotonin (5-

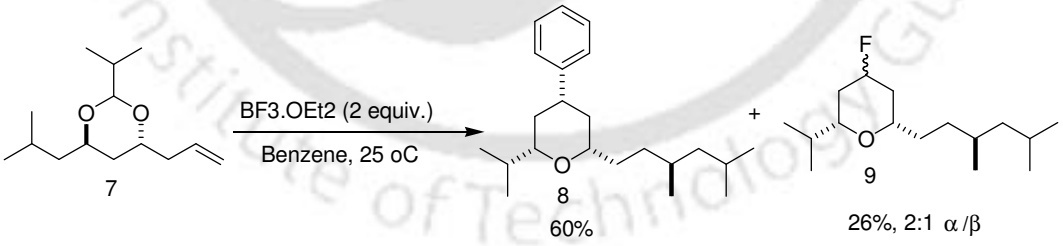
hydroxytryptamine) reuptake inhibitors. 4-(Tetrahydro-pyran-4-yl)-benzene-1,3-diol derivatives **6** (*Figure4.1.1*)[4] exhibits tyrosinase enzyme-inhibiting activity and show a very low cytotoxicity. These compounds find use in human medicine, particularly in dermatology and cosmetics.

4.2. An Overview of Relevant Synthetic Methods and its Applications

Review of the literature reveals that several strategies were developed for the synthesis 4-aryl six-membered heterocycles. Prins cyclization followed by Friedel-Crafts reaction[5] received a considerable attention and showed significant progress to develop 4-aryl-tetrahydropyrans. While there are some other approaches available for making 4-aryltetrahydropyrans, most of them are Hetero-Diels-Alder followed by coupling reaction and metal catalyzed aryl addition to tetrahydropyran-4-ones.

4.2.1. Tandem Prins-Friedel-Crafts Reactions

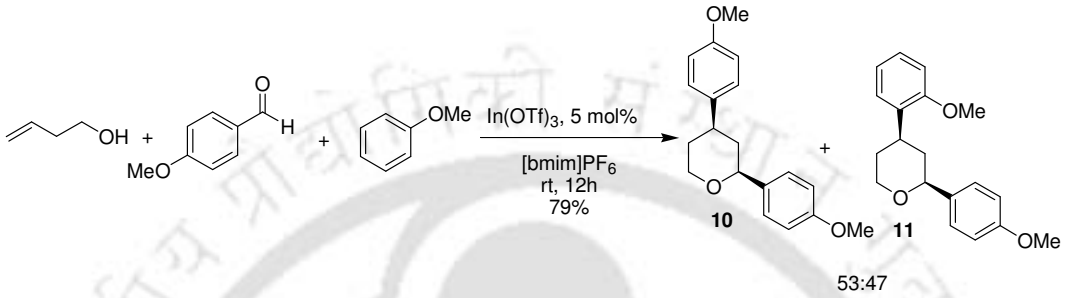
Rychnovsky and co-workers[6] observed the Prins-Friedel-Crafts product, while studying the reactivity of 4-allyl-6-isobutyl-2-isopropyl-[1,3]-dioxane (**7**) with excess of $BF_3{\cdot}OEt_2$ in benzene. During the reaction 4-phenyl-tetrahydropyran (**8**) and 4-fluoro-tetrahydropyran (**9**) were isolated in 60% and 26% yields respectively (*Scheme 4.2.1*). The formation of byproduct and lack of selectivity are the major drawback of the reaction.



Scheme 4.2.1

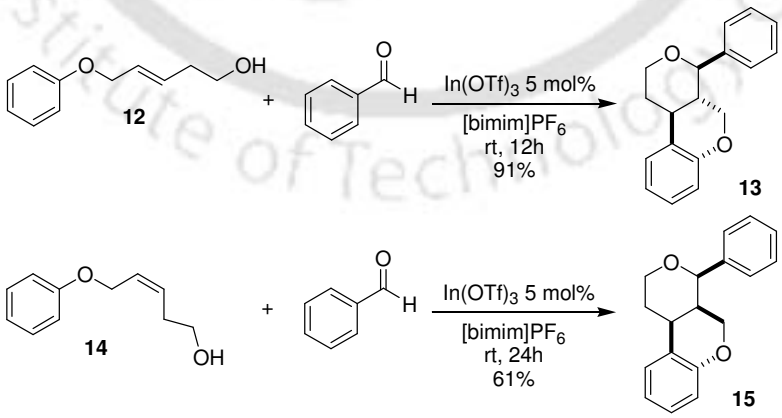
Li and coworkers had developed a one-pot Prins-Friedel-Crafts reaction for the synthesis of 4-aryl-tetrahydropyrans.[7] The reaction of *p*-methoxybenzaldehyde, 3-buten-ol, and an excess amount of anisole with catalytic amount of indium triflate in ionic liquid

[bmim]PF_6 at room temperature provided desired *ortho*- and *para*-regioisomers (**10** and **11**) with a ratio of 53:47 in 79% overall yield (*Scheme 4.2.2*). The method is limited to aromatic nucleophiles having a methoxy group on the ring. The presence of ionic liquid as solvent is another requirement.



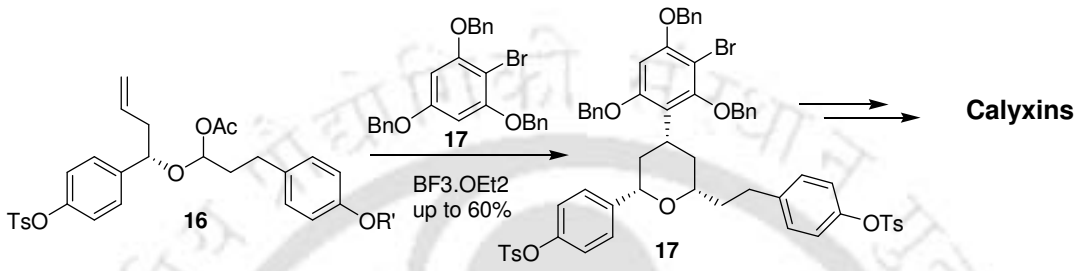
Scheme 4.2.2

An intramolecular Friedel–Crafts reaction of *trans*-homoallyl alcohol (**12**) and benzaldehyde proceeded smoothly in ionic liquid under similar conditions to yield tricyclic compound (**13**) in 91% yield (*Scheme 4.2.3*)[7], which contains two *trans*-fused tetrahydropyran rings with all substituents at the equatorial position. This is a direct analogue of calyxine I. Cyclization of the *cis*-homoally alcohol (**14**), proceeded at a slower rate and gave lower yield (61%) in comparison to *trans*-homoallyl alcohol. The cyclized product **(15),** is an epimer of calyxine F.



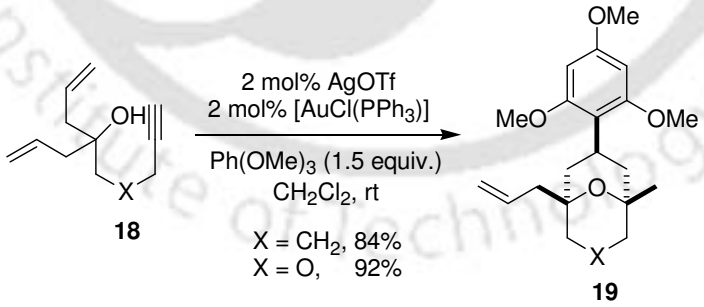
Scheme 4.2.3

Rychnovsky applied tandem Prins-Friedel-Crafts reaction to prepare the core structures of calyxin natural products.[8] As illustrated in *Scheme 4.2.4*, the reaction of α-acetoxy ether (**16**) and electron-rich arene in presence of $BF_3{\cdot}OEt_2$ gave the core structures of calyxin (**17**) natural product in 60% yield.



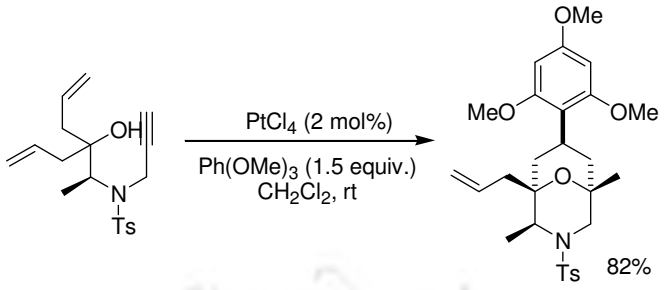
Scheme 4.2.4

Barluenga and co-workers developed a Prins cyclization to prepare bridged bicyclic tetrahydropyrans.[9] Treatment of alkynol (**18**) with 2 mol% of [AuCl (PPh_3)]/AgOTf in the presence of the 1,3,5-trimethoxy benzene in dichloromethane gave a bicyclic tetrahydropyrans (**19**) in high yield (*Scheme 4.2.5*). For this reaction electron-rich aromatic compounds were appropriate reagents.



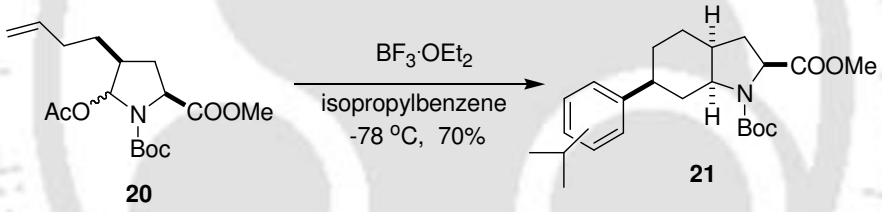
Scheme 4.2.5

The above reaction was extended to nitrogen-centered alkynols, where $PdCl_4$ was used as catalyst instead of [AuCl (PPh_3)]/AgOTf (*Scheme 4.2.6*).



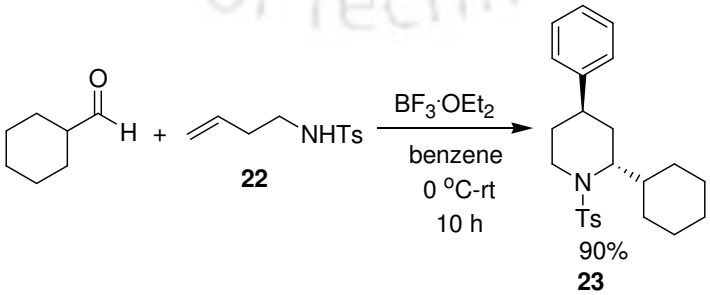
Scheme 4.2.6

Hanessian group reported a related Azonia-Prins/Friedel-Crafts reaction based on *N*-acyloxyiminium ion cyclizations.[10] As illustrated in *Scheme 4.2.7*, $BF_3{\cdot}OEt_2$ mediate the facile Friedel-Crafts-type tandem carbocyclization of compound (**20**) in isopropylbenzene to give the product (**21**) as an *o/p*-mixture in 70% yield .



Scheme 4.2.7

Recently Yadav *et al.* reported an *aza*-Prins-Friedel–Crafts reaction for the synthesis of 4-arylpiperidines from aldehydes and N-tosyl homoallyl amine by using boron trifluoride etherate under mild conditions.[11] As shown in *Scheme 4.2.8*, the coupling of cyclohexane



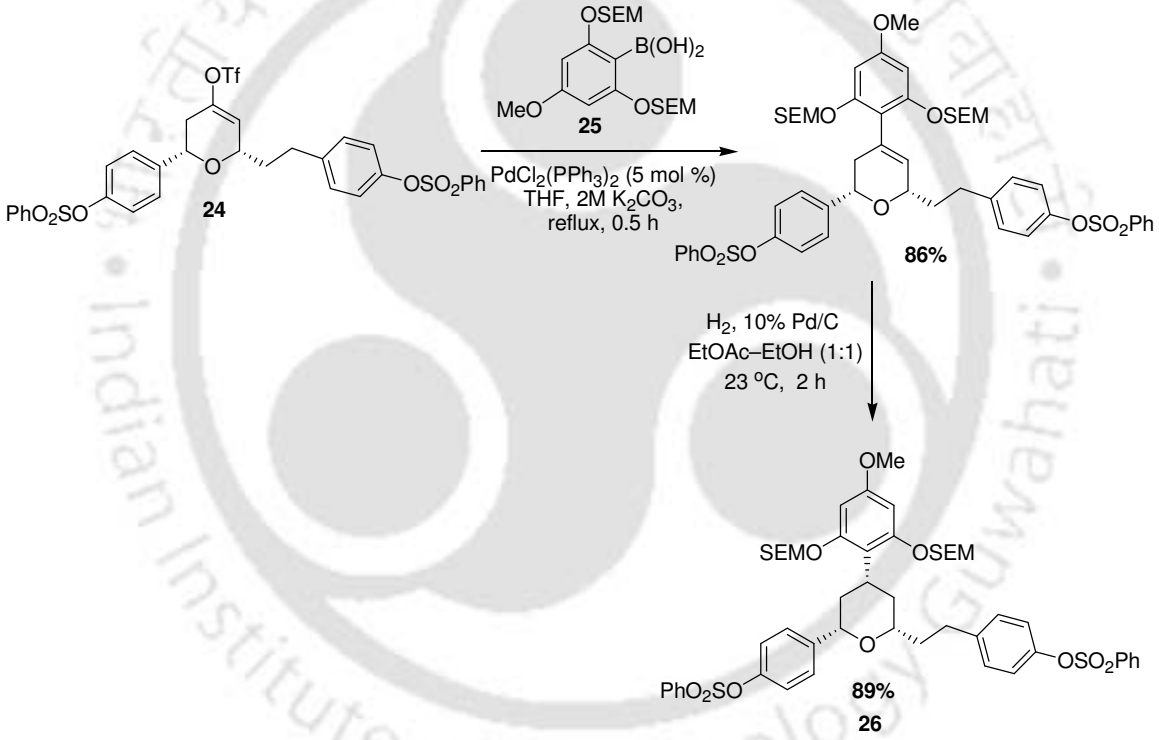
Scheme 4.2.8

carboxaldehyde with N-tosylhomoallyl amine (**22**) in the presence of 1.2 equiv. of boron trifluoride etherate in benzene at room temperature gave 4-arylpiperidines (**23**) in 90% yield and trans-selectivity.

4.2.2 Synthesis of Tetrahydropyrans by using Metal Catalyst

a) Reduction of Dihydropyrans

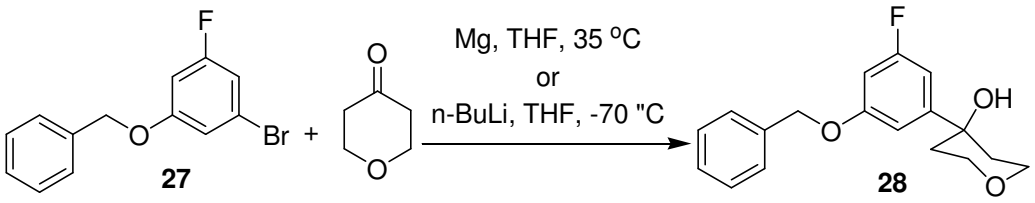
All-*cis*-2,4,6-trisubstituted tetrahydropyran (**26**) could be prepared by using Suzuki–Miyaura coupling of enol triflate (**24**) with 2,4,6-trialkoxyphenylboronic acid (**25**), followed by catalytic hydrogenation in a stereo controlled manner (*Scheme 4.2.9*).[12]



Scheme 4.2.9

b) From the Reaction of Grignard or Lithium Reagent

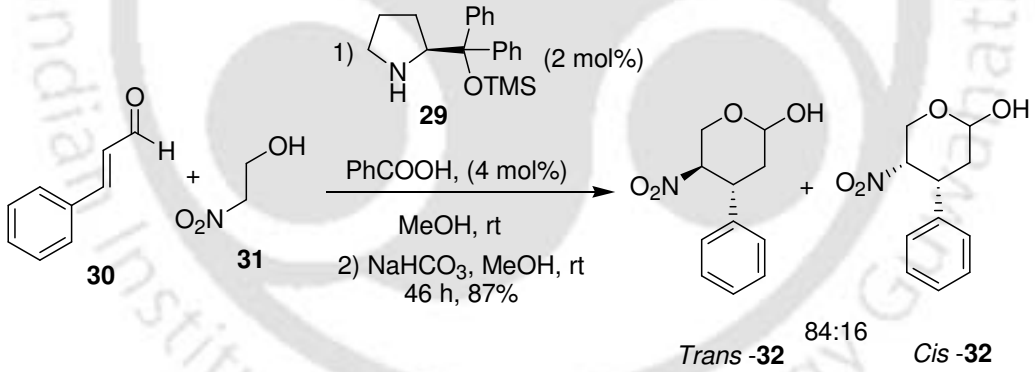
Tetrahydropyran derivative (**28**) were also prepared from the reaction of organomagnesium or lithium reagents generated from compound (**27**) and tetrahydropyran-4-one (*Scheme 4.2.10*) with high diastreoselectivity.[13]



Scheme 4.2.10

4.2.3 Michael Reaction for the Synthesis of THPs

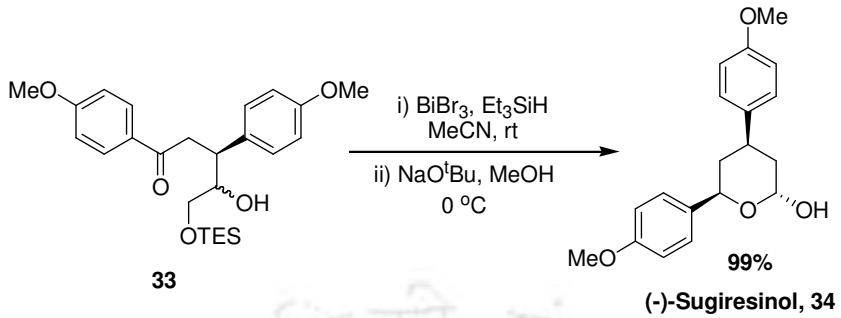
The reaction of nitroethanol with α,β-unsaturated aldehyde generates the Michael adduct, γ-nitroaldehyde, which was cyclize to afford substituted tetrahydropyrans. Diphenylprolinol trimethylsilyl ether (**29**) catalysed the reaction of cinnamaldehyde (**30**) and nitroethanol (**31**) in the presence of benzoic acid in MeOH to give *Trans*-**32** and *cis*-**32** isomers.[14] When these mixture was treated with inorganic base $NaHCO_3$ in MeOH, afford the *trans*-**32** isomer predominantly (*Scheme 4.2.11*).



Scheme 4.2.11

4.2.4 Other Methods

The compound (**33**) was subjected to reductive etherification with bismuth tribromide and triethylsilane, followed by treatment with NaO^tBu, an *insitu* deprotection of the acetyl group, afford (-)-sugiresinol dimethyl ether (**34**) in 99% yield, with 19:1 diastereoselectivity (*Scheme 4.2.12*).[15]

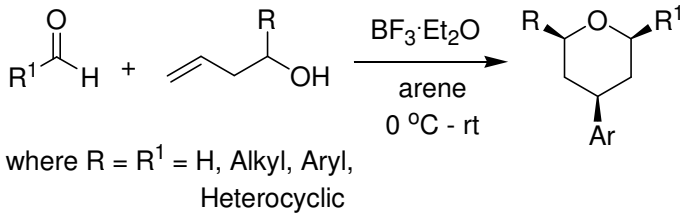


Scheme 4.2.12

4.3. Results and Discussion

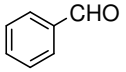
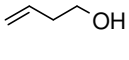
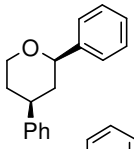
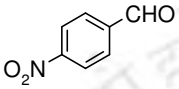
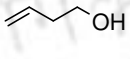
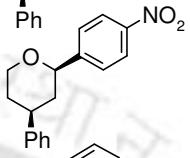
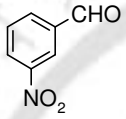
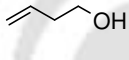
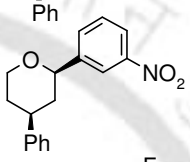
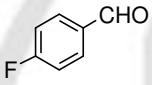
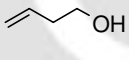
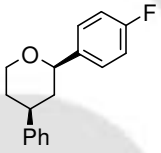
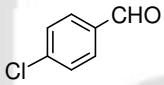
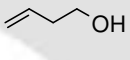
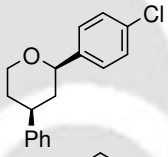
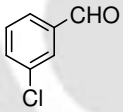
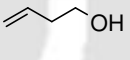
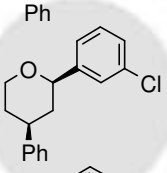
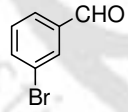
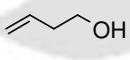
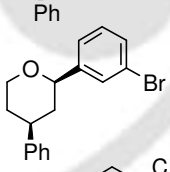
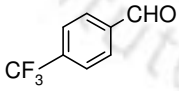
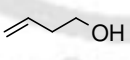
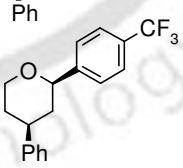
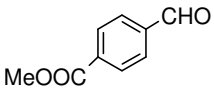
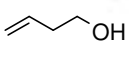
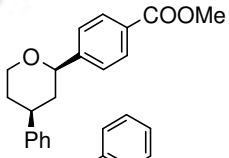
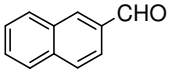
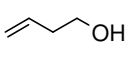
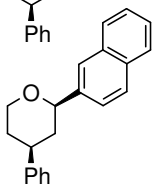
In our previous chapter we had described a methodology for the synthesis of 4-aryl-tetrahydropyran by using Sakurai-Hosomi-Prins-Friedel-Crafts reaction. Although the Sakurai-Hosomi-Prins-Friedel-Crafts reaction provides symmetrical 4-aryl tetrahydropyran with excellent stereochemistry, but it fails to afford unsymmetrical 2,6-disubstituted 4-aryl-tetrahydropyran. Here we report an efficient method for the synthesis of unsymmetrical 2,6-disubstituted 4-aryl tetrahydropyran from carbonyl compound, homoallyl alcohol and arene mediated by boron trifluoride etherate in excellent yield and stereochemistry.

Initially benzaldehyde was reacted with homoallyl alcohol in the presence of boron trifluoride etherate in benzene at rt. The product 2,4,-diphenyltetrahydropyran was obtained with 75% yield in 6 h. The reaction is stereoselectve and both the substituents are in *cis* position. $BF_3{\cdot}OEt_2$ was found to be the most effective Lewis acid for the reaction as several other non-halogenated Lewis acids such as TMSOTf, $In(OTf)_3$,

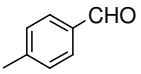
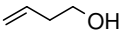
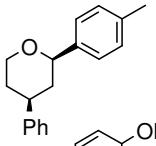
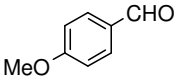
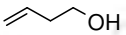
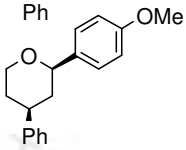
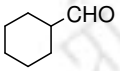
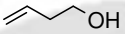
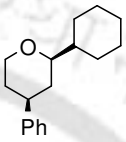
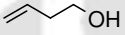
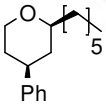
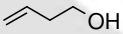
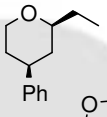
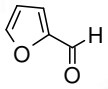
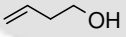
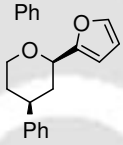
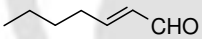
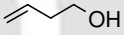
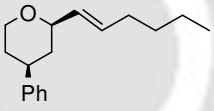
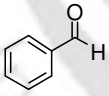
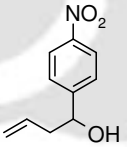
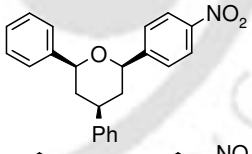
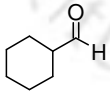
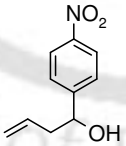
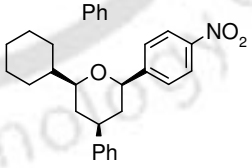
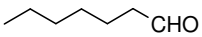
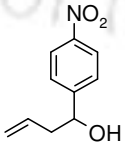
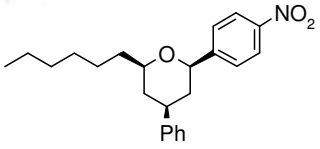
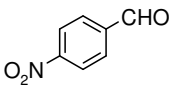
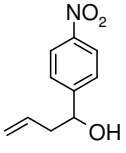
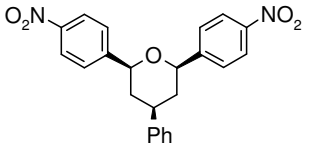


Scheme 4.3.1. *Synthesis of 2,6-disubstituted 4-phenyl tetrahydropyran*

Table 4.3.1. *Synthesis of 2,6-disubstituted 4-aryl tetrahydropyran*

Sl No.	Aldehyde (a)	Homoallyl alcohol	Time /h	Product (b)	Yield[a] (%)
1			6		75
2			4		90
3			4		90
4			4		95
5			4		88
6			4		92
7			4		80
8			4		93
9			4		90
10			9		60

continue...

Sl No.	Aldehyde (a)	Homoallyl alcohol	Time / h	Product (b)	Yield[a] (%)
11			9		70
12			10		65
13			4		80
14			4		85
15			5		70
16			6		63
17			6		65
18			3		75
19			3		85
20			3		90
21			3		92

[a]Yields refers to isolated yield.

$Bi(OTf)_3$ and $Sc(OTf)_3$ were found to be either less effective or not effective at all. The reaction can be generalized as shown in *scheme 4.3.1*.

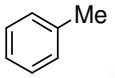
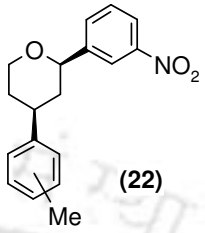
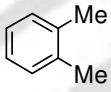
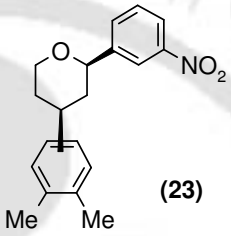
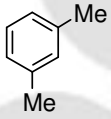
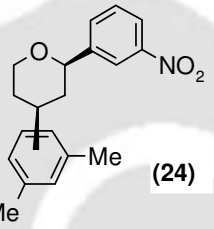
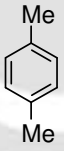
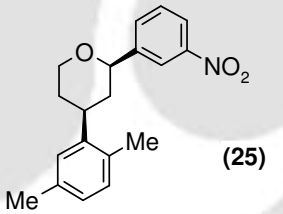
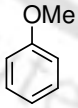
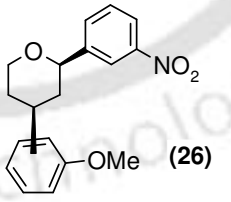
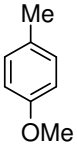
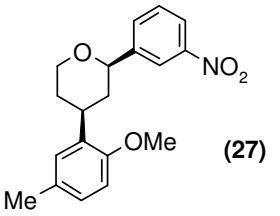
In order to prove its general applicability, aliphatic, aromatic, unsaturated, and hetrerocyclic aldehydes were examined and found that all types of aldehydes give good yields and stereochemistry (*Table 4.3.1*)

In all the cases studied, 4-aryl tetrahydropyran **1b-21b** (*Table 4.3.1*) could be obtained in high purity without any side products. Both aliphatic and aromatic aldehydes give good yield with high degree of diastereoselectivity as determined from the ^{1}H and ^{13}C NMR spectrum of the crude product. The substituent on the aromatic ring has promising effect on this reaction. The electron-withdrawing and simple benzaldehydes gave good yields compared to electron donating groups. Aliphatic aldehydes are found to be better substituents for this reaction.

To extend the utility of this method various arens, as nucleophile, were systematically investigated under these reaction conditions. It was observed that methyl and methoxy substituted benzene reacts faster than benzene. Thus the reaction with toluene gave **22** as an inseparable regioisomers with a ratio of 4.7:1 and 97% overall yield. Similarly *ortho* and *meta*-xylene gave products **23** (85% yield) and **24** (80% yield) as mixture of two regioisomers with a ratio of 2:1 and 80% overall yield (*Table 4.3.2*). On the other hand 1-methoxy-4-methyl benzene gave single isomer **27** with 82% yield. But fused ring aromatic compounds, for example, naphthalene, 2-methoxy naphthalene and deactivated aromatic compounds were remained uncreative.

The conformation of the compounds is in the chair form and all the three substituents are in equatorial position. The substituent's at the 2-, 4-, and 6-positions of the tetrahydropyran ring are in a *cis* relationship and are equatorial. This is revealed from the two inseparable regioisomers with a ratio of 1:1.2 and 1:2.7, respectively. On the other hand *para* xylene gave **25** as a single isomer with 88% yield. Anisole gave **26** as *ortho*/*para* coupling constants of the 2-H (J = 10.8 and 1.6 Hz), 6-H (J = 11.6 and 2.8 Hz) and the 4-H (J = 12.4 and 3.6 Hz) hydrogen atoms of compound **2b** (*Figure 4.3.1*).

Table 4.3.2. *Reaction of 3-buten-1-ol and m-nitro-benzaldehyde with other nucleophiles (Arenes)*

S.No.	Arene	Time (/h)	Product	%Yield[a]
1		1.5	 **(22)**	90
2		1	 **(23)**	85
3		1	 **(24)**	88
4		1	 **(25)**	80
5		6	 **(26)**	80
6		6	 **(27)**	82

[a]Yields refer to isolated yield

This was confirmed by NOE experiment and single-crystal X-ray analysis of 2-(4-Nitro-phenyl)-4-phenyl-tetrahydropyran (*Figure 4.3.2*).[16]

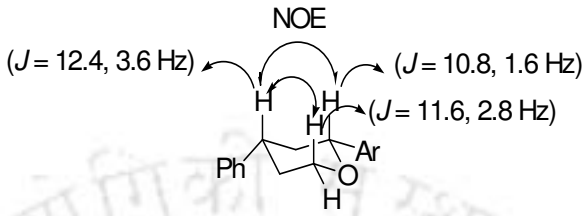


Figure 4.3.1. *Coupling constants and NOE of Compound (**2b**)*

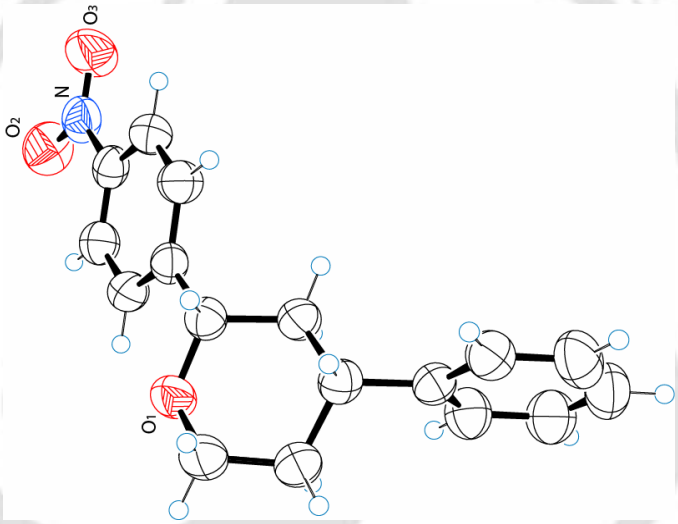
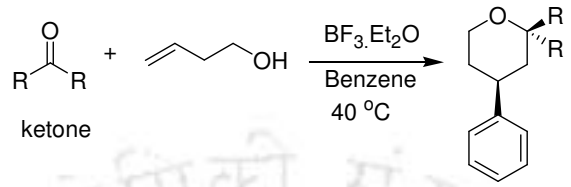


Figure 4.3.2. *ORTEP diagram of 2-(4-Nitro-phenyl)-4-phenyl-tetrahydropyran (**2b**)*

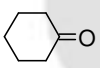
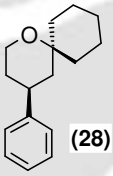
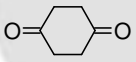
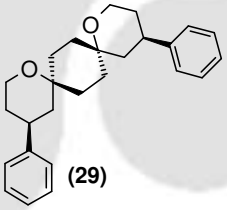
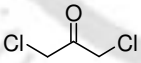
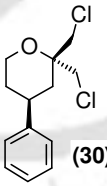
We were naturally tempted to gauge the efficacy of the above protocol for the construction of tetrahydropyran ring, and thus we attempted the reaction with ketones as well (*Scheme 4.3.2*). The reactions proceeded smoothly to generate the desired products in good yields (*Table 4.3.3*). But, the reaction requires high temperature (40 ^{o}C) and takes longer reaction time. Thus, the reaction with cyclohexanone and 1,4-cyclohexanedione gave spirocyclic product **28** and **29** with 46% and 30% respectively at 40 ^{o}C. On the other hand symmetrical dichloroacetone gave 2,2-bis-chloromethyl-4-phenyl-tetrahydropyran

30 with 40% yield. Thus, it is evident that this reaction has widespread application for the synthesis of novel bicyclic heterocycles.



Scheme 4.3.2 *Reaction of 3-buten-1-ol with ketone*

Table 4.3.3. *Reaction with Ketones*

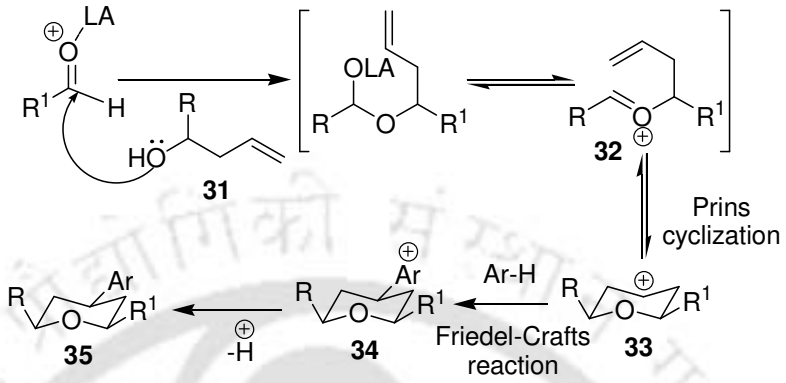
Ketone	Time /h	Product	Yield[a]
	8	 **(28)**	46
	24	 **(29)**	30
	8	 **(30)**	40

[a]Yields refers to isolated yield

The major advantage of this reaction is that in a single step, two reactions primarily Prins cyclisation and Friedel-Crafts reaction can be performed without any difficulties.

The mechanism of the reaction can be explained as follows (*Scheme 4.3.3*). In the presence of Lewis acid homoallyl alcohol **31** reacts with aldehyde to afford oxocarbenium ion **32**. The intermediate **32** undergoes Prins cyclization to give tetrahydropyranyl cation **33**, which in the presence of aryl neucleophile, gives

intermediate **34**. The species **34** after deprotonation gives the 2,6-disubstituted-4-aryltetrahydropyran **35**.



Scheme 4.3.3 *Mechanism of the reaction*

Conclusion:

An efficient, highly diastereoselective one-pot method has been developed for the synthesis of unsymmetrical 2,6-disubstituted 4-aryl tetrahydropyran. The same method can be used for the synthesis of spirocyclic compound in good yields. This method holds good for aldehydes, ketones and will be of immense importance in natural product synthesis.

4.4. Experimental Section

4.4.1. Instrumentation and Characterization

As described in Chapter 2, Section 2.5.1.

4.4.2. General Procedure for the Synthesis of Compounds 1b-21b and 22-25

Aldehyde (1.0 equiv) was dissolved in arene (3.0 mL) and then added borontrifluoride etherate (1.2 equiv). It was cooled to 0 ^{o}C and added homoallyl alcohol (1.0 equiv) in aryl compound (2.0 mL) drop by drop over 10 min. The temperature was slowly increased to rt in 1h. The reaction mixture was stirred at rt for specified time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was washed with aqueous sodium bicarbonate, extracted with ethyl acetate and finally washed with brine and water. The

organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

Synthesis of 2,4,6-triphenyltetrahydropyran (1b, Table 4.3.1)*:* Benzaldehyde **1a** (0.20 mL, 2.0 mmol) was dissolved in benzene (3.0 mL) and then added borontrifluoride etherate (0.30 mL, 2.4 mmol). It was cooled to 0 ^oC and added buten-1-ol (144 mg, 2.0 mmol) in benzene (2.0 mL) drop by drop over 10 min. The temperature was slowly increased to rt in 1h. The reaction mixture was stirred at rt for 6h. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give 2,4,6-triphenyltetrahydropyran **1b** (414 mg, 75%) as a gum.

4.4.3. General Procedure by using Different Arenes

m-Nitrobenzaldehyde (1.0 equiv) was dissolved in CH_2Cl_2 (2.0 mL) and then added borontrifluoride etherate (1.2 equiv). It was cooled to 0 ^oC and added homoallyl alcohol (1.0 equiv) and nucleophile (arene) in CH_2Cl_2 (1.0 mL) drop by drop over 10 min. and the temperature is slowly increased to rt in 1h. The reaction mixture was stirred at rt for specified time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

4-(2-Methoxy-phenyl)-2-(3-nitro-phenyl) tetrahydro-pyran and 4-(4-Methoxy-phenyl)-2-(3-nitro-phenyl) tetrahydro-pyran (26, Table 4.3.2)*:* *m*-Nitrobenzaldehyde (0.20 mL, 2.0 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and then added borontrifluoride etherate (0.30 mL, 2.4 mmol). It was cooled to 0 ^oC and added 3-buten-1-ol (144 mg, 2.0 mmol) and anisole (0.65 mL, 6 mmol) in CH_2Cl_2 (1.0 mL) drop by drop over 10 min. The temperature was then slowly increased to rt in 1h. The reaction mixture was stirred at rt for 6h. After completion of the reaction, the reaction mixture was treated with aqueous

sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give **25** as two regioisomers with a ratio 2:1 (501 mg, 80%).

4.4.4. General Procedure for the Three Component Reaction with Ketone 28-30

Ketone (1 equiv) and 3-beten-ol (1 equiv) were dissolved in benzene and added boron trifluoride etherate (1.2 equiv) and then reaction mixture was stirred for the specified time at 40 ^oC. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel. The product were characterized by spectrometric methods.

Synthesis of 4-Phenyl-1-oxa-spiro[5.5]undecane (28, Table 4.3.3)*:* Cyclohexanone (196 mg, 2.0 mmol) and 3-buten-1-ol (144 mg, 2.0 mmol) was dissolved in benzene (5.0 mL) and then added borontrifluoride etherate (0.30 mL, 2.4 mmol. Then reaction mixture was stirred at 40 ^oC for 8h. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give 4-Phenyl-1-oxa-spiro[5.5]undecane **28** (212 mg, 46%) as a gum.

4.5. Reference and Notes

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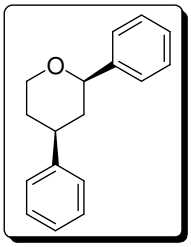
(16) Crystallographic data for compound VCR-pnb has been deposited with Cambridge Crystallographic Data Centre as a supplementary publication number CCDC 687645.

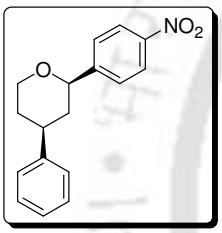
4.6. Spectral Data

2,4,6-Triphenyltetrahydropyran (1b):



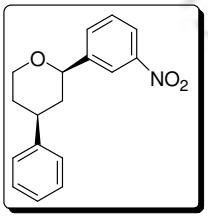
Gum.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.73-1.82 (m, 1 H), 1.85-1.95 (m, 2 H), 2.05-2.12 (m, 1 H), 2.93-2.30 (m, 1 H), 3.74-3.81 (m, 1 H), 4.27-4.32 (m, 1 H), 4.48 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.19-7.40 (m, 10 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.3, 41.5, 42.0, 68.5, 79.8, 125.7, 126.4, 126.7, 127.4, 128.3, 128.5, 142.9, 145.4. **IR**: 3061, 3029, 2938, 2845, 1494, 1452, 1374, 1252, 1128, 1088, 1041, 961, 918, 751, 701 cm^{-1}. **Anal. Calcd** for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.55; H, 7.78.

2-(4-Nitro-phenyl)-4-phenyltetrahydropyran(2b):



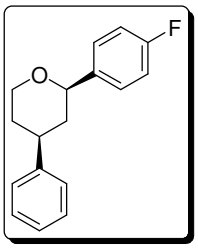
Solid, M. P.: 77-78 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.60-1.70 (m, 1 H), 1.85-1.95 (m, 2 H), 2.08-2.12 (m, 1 H), 2.94-3.02 (m, 1 H), 3.73-3.80 (m, 1 H), 4.28-4.33 (m, 1 H), 4.57 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.19-7.33 (m, 5 H) 7.53 (d, J=8.8 Hz, 2 H), 8.17 (d, J=8.8 Hz, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.2, 41.7, 42.0, 68.7, 78.8, 123.7, 126.5, 126.7, 126.8, 128.8, 145.0, 147.2, 150.3. **IR**: 3085, 2941, 2848, 1633, 1603, 1520, 1347, 1130, 1106, 1088, 850, 748 cm^{-1}. **Anal. Calcd** for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.18; H, 6.21; N, 4.88.

2-(3-Nitro-phenyl)-4-phenyltetrahydropyran (3b):



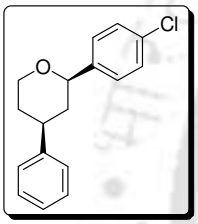
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.67-1.76 (m, 1 H), 1.86-1.98 (m, 2 H), 2.12-2.15 (m, 1 H), 2.96-3.03 (m, 1 H), 3.76-3.82 (m, 1 H), 4.33 (dd, J = 10.0 and 2.8 Hz, 1 H), 4.58-4.61 (m, 1 H), 7.21-7.36 (m, 5 H), 7.48-7.52 (t, J=8.0 Hz, 1 H), 7.71(d, J =8.0 Hz, 1 H), 8.12 (d, J=8.0 Hz, 1 H), 8.29 (s, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.1, 41.6, 41.9, 68.7, 78.5, 120.9, 122.3, 126.6, 126.8, 128.7, 129.3, 131.9, 145.0, 145.1, 148.3. **IR**: 3086, 3062, 3028, 2917, 2848, 1602, 1526, 1349, 1130, 1091, 845, 807, 759 cm^{-1}. **Anal. Calcd** for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.18; H, 6.18; N, 5.03.

2-(4-Fluoro-phenyl)-4-phenyltetrahydropyran (4b):



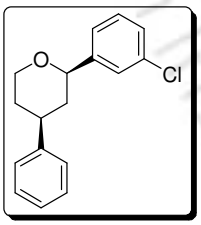
Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.68-1.77 (m, 1 H), 1.80-1.93 (m, 2 H), 2.02-2.07 (m, 1 H), 2.91-2.99 (m, 1 H), 3.72-3.79 (m, 1 H), 4.25-4.30 (m, 1 H), 4.45 (dd, J = 9.2 and 2.0 Hz, 1 H), 6.99-7.05 (m, 2 H), 7.19-7.25 (m, 3 H), 7.29-7.37 (m, 4 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.2, 41.5, 41.9, 68.4, 79.0, 115.0 (d, J = 20.6 Hz), 126.4, 126.7, 127.3 (d, J = 7.6 Hz), 128.5, 138.8, 145.3, 162.2 (d, J = 243 Hz). ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ 46.44-46.51 (m, 1 F). **IR**: 3062, 3029, 2918, 2846, 1604, 1509, 1374, 1252, 1223, 1157, 1128, 1086, 833, 777, 758, 700 cm^{-1}.

2-(4-Chloro-phenyl)-4-phenyltetrahydropyran (5b):



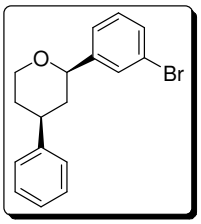
Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.65-1.74 (m, 1 H), 1.80-1.93 (m, 2 H), 2.00-2.10 (m, 1 H), 2.90-2.98 (m, 1 H), 3.71-3.78 (m, 1 H), 4.25-4.30 (m, 1 H), 4.45 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.18-7.33 (m, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.4, 41.6, 42.1, 68.7, 79.2, 126.6, 126.9, 127.3, 128.6, 128.7, 133.1, 141.5, 145.4. **IR**: 3060, 3028, 2916, 2845, 1601, 1491, 1374, 1129, 1088, 825, 758, 699 cm^{-1}. Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.86; H, 6.28. Found: C, 74.77; H, 6.37.

2-(3-Chloro-phenyl)-4-phenyltetrahydropyran (6b):



Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.66-1.76 (m, 1 H), 1.81-1.93 (m, 2 H), 2.04-2.10 (m, 1 H), 2.91-2.99 (m, 1 H), 3.72-3.78 (m, 1 H), 4.26-4.31 (m, 1 H), 4.46 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.19-7.33 (m, 8 H), 7.40 (s, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.1, 41.4, 41.8, 68.4, 78.8, 123.8, 125.9, 126.4, 126.7, 127.3, 128.5, 129.5, 134.1, 145.0, 145.1. **IR**: 3062, 3028, 2917, 2939, 2845, 1600, 1575, 1429, 1355, 1130, 1086, 863, 784, 758, 699 cm^{-1}. Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.86; H, 6.28. Found: C, 74.91; H, 6.17.

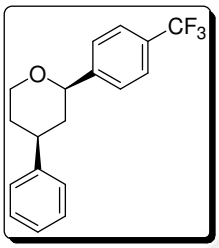
2-(3-Bromo-phenyl)-4-phenyltetrahydropyran (7b):



Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.66-1.75 (m, 1 H), 1.81-1.93 (m, 2 H), 2.03-2.08 (m, 1 H), 2.90-2.98 (m, 1 H), 3.71-3.77 (m, 1 H), 4.26-4.30 (m, 1 H), 4.44 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.17-7.40 (m, 8H), 7.56 (s, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.0, 41.3, 41.7,

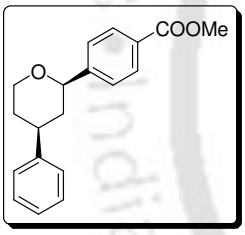
68.3, 78.6, 122.3, 124.3, 126.3, 126.6, 128.4, 128.7, 129.8, 130.2, 145.0, 145.2. **IR**: 3062, 3028, 2939, 2846, 1597, 1568, 1426, 1372, 1129, 1084, 884, 783, 758, 697 cm^{-1}. Anal. Calcd for $C_{17}H_{17}BrO$: C, 64.37; H, 5.40. Found: C, 64.45; H, 5.55.

4-Phenyl-2-(4-trifluoromethyl-phenyl)-tetrahydropyran (8b):



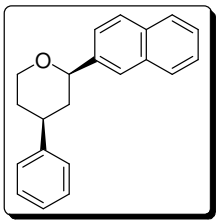
Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.65-1.74 (m, 1 H), 1.82-1.94 (m, 2 H), 2.03-2.10 (m, 1 H), 2.93-3.01 (m, 1 H), 3.73-3.80 (m, 1 H), 4.28-4.32 (m, 1 H), 4.53 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.19-7.33(m, 5 H), 7.48 (d, J = 8.4, 2 H), 7.58 (d, J = 8.4, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.3, 41.7, 42.1, 68.6, 79.1, 124.4 (q, J = 270.7 Hz), 125.2, 126.1, 126.6, 126.8, 128.7, 129.5 (q, J = 32.1 Hz), 145.3, 147.1. **^{19}F NMR** (376 MHz, $CDCl_3/C_6F_6$): δ 99.36 (s, 3F).**IR**: 3064, 3030, 2919, 2848, 1622, 1416, 1326, 1164, 1127, 1091, 1067, 838, 760, 700 cm^{-1}.

4-(4-Phenyl-tetrahydropyran-2-yl)-benzoic acid methyl ester (9b):



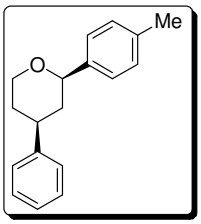
Solid; M. P. 61.2-63.4 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.66-1.75 (m, 1 H), 1.82-1.95 (m, 2 H), 2.04-2.11 (m, 1 H), 2.94-3.00 (m, 1 H), 3.73-3.80 (m, 1 H), 3.90 (s, 3 H), 4.28-4.32 (m, 1 H), 4.54 (dd, J = 11.2 and 2.4 Hz, 1 H), 7.19-7.33 (m, 5 H) 7.45 (d, J = 7.6 Hz, 2 H), 8.02 (d, J = 7.6 Hz, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.3, 41.6, 42.1, 52.1, 68.7, 79.4, 125.7, 126.6, 126.8, 128.7, 129.2, 129.8, 145.3, 148.0, 167.0. **IR**: 3061, 3029, 2950, 2845, 1722, 1611, 1435, 1279, 1112, 1089, 855, 757, 701 cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.12; H, 6.75.

2-Naphthalen-1-yl-4-phenyl-tetrahydropyran (10b):



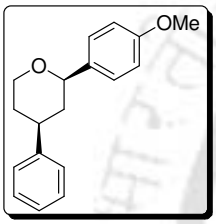
Gum**, ^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.79-1.97 (m, 3 H), 2.14-2.18 (m, 1 H), 2.95-3.01 (m, 1 H), 3.77-3.83 (m, 1 H), 4.31-4.34 (m, 1 H), 4.61-4.64 (m, 1 H), 7.18-7.32 (m, 5 H), 7.42-7.50 (m, 3 H), 7.80-7.84 (m, 4 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.6, 41.6, 42.3, 68.9, 80.1, 124.4, 124.5, 125.9, 126.2, 126.6, 127.0, 127.8, 128.2, 128.4, 128.7, 133.1, 133.6, 140.4, 145.6. **IR**: 3027, 3057, 2938, 2844, 1633, 1602, 1507, 1494, 1452, 1373, 1252, 1127, 1088, 962, 856, 819, 757, 700 cm^{-1}. **Anal. Calcd** for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.55; H, 7.12.

4-Phenyl-2-p-tolyl-tetrahydropyran (11b):



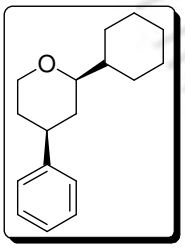
Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.73-1.93 (m, 3 H), 2.03-2.08 (m, 1 H), 2.32 (s, 3 H), 2.91-2.99 (m, 1 H), 3.72-3.79 (m, 1 H), 4.25-4.30 (m, 1 H), 4.45 (dd, J = 10.8 and 1.6 Hz, 1 H), 7.13-7.33 (m, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 33.4, 41.6, 42.1, 68.6, 79.7, 125.8, 126.4, 126.7, 128.5, 129.0, 136.9, 139.9, 145.6. **IR**: 3059, 3027, 2937, 2844, 1602, 1515, 1453, 1374, 1252, 1129, 1086, 814, 758, 700 cm^{-1}. **Anal. Calcd** for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.78; H, 8.14.

2-(4-Methoxy-phenyl)-4-phenyl-tetrahydro-pyran (12b):



Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.73-1.93 (m, 3 H), 2.01-2.06 (m, 1 H), 2.89-2.96 (m, 1 H), 3.71-3.7m (m, 1 H), 3.77 (s, 3 H), 4.24-4.28 (m, 1 H), 4.42 (dd, J = 10.8 and 2.0 Hz, 1 H), 6.87 (d, J = 8.8 Hz, 2 H), 7.18-7.33 (m, 7 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.5, 41.4, 42.2, 55.3, 68.8, 79.7, 113.8, 126.5, 126.9, 127.3, 128.7, 135.2, 145.7, 159.1. **IR**: 3060, 3001, 2936, 2838, 1612, 1513, 1453, 1375, 1248, 1176, 1108, 1128, 1084, 1036, 829, 758, 700 cm^{-1}. **Anal. Calcd** for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.67; H, 7.45.

2-Cyclohexyl-4-phenyl-tetrahydro-pyran (13b):

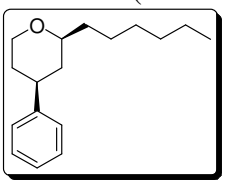


Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95-1.08 (m, 2 H), 1.11-1.28 (m, 3 H), 1.36-1.49 (m, 2 H), 1.64-1.78 (m, 5 H), 1.81-1.86 (m, 1 H), 1.90-1.94 (m, 1 H), 1.98-2.12 (m, 1 H), 2.69-2.76 (m, 1 H), 3.13-3.18 (m, 1 H), 3.51-3.57 (m, 1 H), 4.10-4.15 (m, 1 H), 7.19-7.33 (m, 5 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.4, 26.5, 26.8, 28.9, 29.3, 33.9, 36.6, 42.2, 43.4, 68.5, 82.4, 126.4, 127.0, 128.6, 146.3. **IR**: 3062, 3028, 2927, 2851, 1603, 1496, 1451, 1254, 1127, 1090, 757, 699 cm^{-1}. **Anal. Calcd** for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.46; H, 9.97.

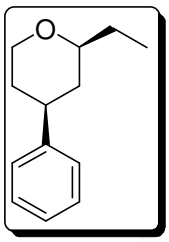
2-Hexyl-4-phenyl-tetrahydropyran (14b):

Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.2 Hz, 3 H), 1.26-1.35 (m, 6 H), 1.38-1.47 (m, 4 H), 1.54-1.61 (m, 1 H), 1.72-1.78 (m, 2 H), 1.80-1.85 (m, 1 H), 2.72-2.89 (m, 1 H), 3.36-3.42 (m, 1 H), 3.53-3.59 (m, 1 H), 4.10-4.14 (m, 1 H), 7.19-7.33 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 25.6, 29.6, 32.0, 33.8, 36.7, 39.7, 42.0, 68.3, 78.0, 126.4, 126.9, 128.6, 146.1. **IR**: 3063, 3029, 2931, 2857, 1604, 1496, 1454, 1379, 1252, 1135, 1088, 757, 699 cm^{-1}. **Anal. Calcd** for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.79; H, 10.57.

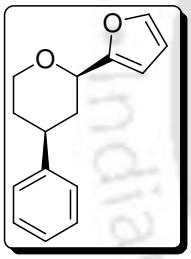


2-Ethyl-4-phenyl-tetrahydropyran (15b):



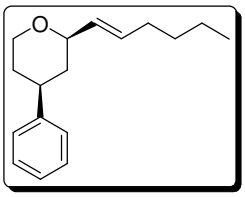
Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.6 Hz, 3 H), 1.37-1.66 (m, 3 H), 1.73-1.79 (m, 2 H), 1.82-1.87 (m, 1 H), 2.72-2.89 (m, 1 H), 3.29-3.35 (m, 1 H), 3.53-3.60 (m, 1 H), 4.10-4.15 (m, 1 H), 7.19-7.33 (m, 5 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 10.1, 29.5, 33.8, 39.3, 42.0, 68.4, 79.4, 126.5, 127.0, 128.7, 146.2. **IR**: 3063, 3029, 2936, 2842, 1495, 1454, 1380, 1251, 1138, 1086, 756, 699 cm^{-1}. **Anal. Calcd** for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.14; H, 9.64.

2-Furan-2-yl-4-phenyl-tetrahydropyran (16b):



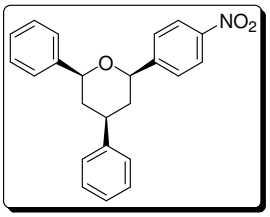
Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.79-1.95 (m, 2 H), 1.97-2.14 (m, 2 H), 2.87-2.95 (m, 1 H), 3.72-3.79 (m, 1H), 4.21-4.26 (m, 1 H), 4.55 (dd, J = 11.6 and 2.0 Hz, 1 H), 6.27-6.30 (m, 1 H), 6.32-6.34 (m, 1 H), 7.21-7.35 (m, 5 H), 7.38-7.39 (m, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.3, 37.3, 41.8, 68.8, 73.3, 106.5, 110.3, 126.7, 127.0, 128.8, 142.3, 145.4, 154.9. **IR**: 3062, 3029, 2942, 2847, 1627, 1497, 1353, 1252, 1124, 1081, 1013, 807, 739, 700 cm^{-1}. **Anal. Calcd** for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.88; H, 7.18.

2-Hex-1-enyl-4-phenyltetrahydropyran (17b):



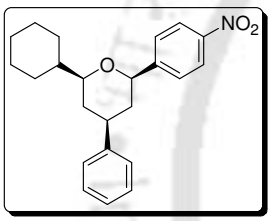
Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$):): δ 0.88 (t, J = 7.2 Hz, 3 H), 1.26-1.42 (m, 4 H), 1.52-1.63 (m, 1 H), 1.74-1.8 (m, 2 H), 1.83-1.88 (m, 1 H), 2.00-2.10 (m, 2 H), 2.78-2.86 (m, 1 H), 3.60-3.66 (m, 1 H), 3.85-3.92 (m, 1 H), 4.13-4.18 (m, 1 H), 5.48-5.54 (m, 1 H), 5.68-5.76 (m, 1 H), 7.19-7.34 (m, 5 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0, 22.3, 31.3, 32.1, 33.3, 39.9, 41.8, 68.2, 78.3, 126.4, 126.8, 128.6, 130.8, 132.2, 145.8. **IR**: 3062, 3028, 2930, 2853, 1603, 1496, 1454, 1377, 1252, 1125, 1084, 1035, 969, 756, 699 cm^{-1}. **Anal. Calcd** for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.68; H, 10.06.

2-(4-Nitro-phenyl)-4,6-diphenyl tetrahydropyran (18b):



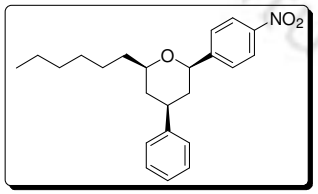
Solid, M. P.: 101-103 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.65-1.74 (m, 1 H), 1.76-1.85 (m, 1 H), 2.15-2.18 (m, 2 H), 3.14-3.20 (m, 1 H), 4.72-4.73 (dd, J = 11.2 and 2.0 Hz, 1 H), 4.80 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.18-7.39 (m, 8 H), 7.46 (d, J = 8.8 Hz, 2 H), 7.59 (d, J = 8.4 Hz, 2 H), 8.16 (d, J = 8.8 Hz, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.0, 41.2, 42.3, 78.9, 80.1, 123.7, 125.9, 126.3, 126.6, 126.9, 127.7, 128.6, 128.8, 142.5, 144.6, 147.2, 150.3. **IR**: 3062, 3029, 2941, 2849, 1602, 1516, 1495, 1345, 1287, 1102, 1078, 1030, 987, 851, 748 cm^{-1}. **Anal. Calcd** for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90 Found: C, 76.92; H, 5.78; N, 3.88.

2-Cyclohexyl-6-(4-nitro-phenyl)-4-phenyl-tetrahydropyran (19b):



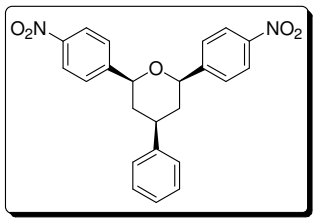
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.05-1.32 (m, 5 H), 1.48-1.62 (m, 4 H), 1.67-1.80 (m, 3 H), 1.90-1.94 (m, 1 H), 1.98-2.00 (m, 1 H), 2.10-2.14 (m, 1 H), 2.92-3.00 (m, 1 H), 3.40-3.45 (m, 1 H), 4.61 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.22-7.26 (m, 3 H), 7.30-7.33 (m, 2 H), 7.56 (d, J = 8.4 Hz, 2 H), 8.19 (d, J = 8.4 Hz, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.3, 26.4, 26.8, 28.9, 29.1, 35.6, 41.3, 42.2, 43.2, 78.2, 82.3, 123.6, 126.4, 126.6, 126.9, 128.7, 145.4, 147.0, 150.9. **IR**: 2927, 2849, 1600, 1523, 1507, 1449, 1346, 1103, 1079, 852, 747, 696 cm^{-1}. **Anal. Calcd** for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83 Found: C, 75.66; H, 7.57; N, 3.87.

2-Hexyl-6-(4-nitro-phenyl)-4-phenyltetrahydropyran (20b):



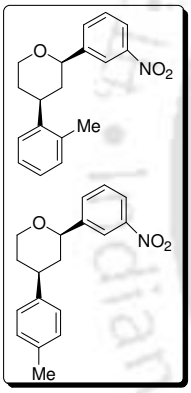
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3 H), 1.26-1.39 (m, 8 H), 1.41-1.64 (m, 3 H), 1.66-1.75 (m, 1 H), 1.90-1.95 (m, 1 H), 2.08-2.13 (m, 1 H), 2.96-3.03 (m, 1 H), 3.63-3.69 (m, 1 H), 4.62 (dd, J = 11.2 and 2.0 Hz, 1 H), 7.21-7.34 (m, 5 H), 7.56 (d, J = 8.4 Hz, 2 H), 8.19 (d, J = 8.8 Hz, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 22.8, 25.6, 29.5, 31.9, 36.4, 38.7, 41.3, 42.1, 78.2 (2C), 123.6, 126.5, 126.6, 126.8, 128.7, 145.2, 147.1, 150.7. **IR**: 3063, 3029, 2930, 2856, 1602, 1519, 1454, 1346, 1132, 1083, 1014, 853, 748, 698 cm^{-1}. **Anal. Calcd** for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81 Found: C, 75.24; H, 7.88; N, 3.90.

4-Phenyl-2,6-di(4-nitrophenyl)-tetrahydropyran (21b):



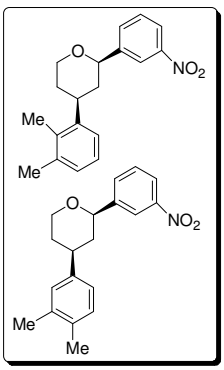
Solid, M.P.: 224-225 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.74-1.83 (m, 2 H), 2.23-2.26 (m, 2 H), 3.25 (tt, J = 12.4, and 3.6 Hz, 1 H), 4.89 (dd, J =11.2 and 1.6 Hz, 2 H), 7.24-7.35 (m, 5 H), 7.65 (d, J = 8.8 Hz, 4 H), 8.24 (d, J = 8.8 Hz, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.0, 42.3, 79.2, 123.9, 126.6, 126.9, 127.2, 129.0, 144.0, 147.5, 149.6; **IR**: 3085, 2915, 2846, 1600, 1512, 1344, 1103, 1091, 850 cm^{-1}. **Anal. Calcd** for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.39; H, 5.10; N, 6.87.

2-(3-Nitro-phenyl)-4-o-tolyl tetrahydropyran and 2-(3-Nitro-phenyl)-4-p-tolyl tetrahydropyran (22; two ortho/para regioisomers: 3:3.4):



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64-1.96 (m, 3 H), 2.00-2.13 (m, 1 H), 2.32 (s, 1.4 H), 2.41 (s, 1.6 H), 2.91-3.00 (m, 0.54 H), 3.18-3.26 (m, 0.46 H), 3.74-3.85 (m, 1 H), 4.28-4.35 (m, 1 H), 4.56-4.63 (m, 1 H), 7.03-7.24 (m, 4 H), 7.47-7.51 (m, 1 H), 7.69-7.72 (m, 1 H), 8.10-8.13 (m, 1 H), 8.28 (s, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.4, 21.0, 32.5, 33.1, 33.2, 37.6, 40.7, 41.5, 41.6, 41.8, 68.7, 68.9, 78.5, 78.7, 120.8, 122.3, 123.8, 125.5, 126.3, 126.5, 126.6, 127.4, 127.5, 128.5, 129.2, 129.3, 130.6, 131.9, 135.1, 136.1, 138.0, 142.8, 145.0, 148.3. **IR**: 3020, 2919, 2848, 1605, 1529, 1349, 1130, 1087, 1042, 810, 737 cm^{-1}. **Anal. Calcd** for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.85; H, 6.59; N, 4.66.

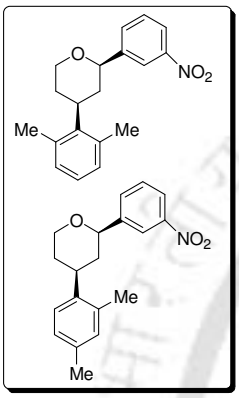
4-(2,3-Dimethyl-phenyl)-2-(3-nitro-phenyl)-tetrahydropyran and 4-(3,4-dimethyl-phenyl)-2-(3-nitro-phenyl)-tetrahydropyran (23; two regioisomers 1:1.2):



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64-1.74 (m, 1 H), 1.78-1.94 (m, 2 H), 2.00-2.12 (m, 1 H), 2.23 (s, 1.4 H), 2.25 (s, 1.6 H), 2.30 (s, 3 H), 2.89-2.97 (m, 0.54 H), 3.25-3.33 (m, 0.46 H), 3.74-3.86 (m, 1 H), 4.29-4.35 (m, 1 H), 4.56-4.64 (m, 1 H), 6.96-7.10 (m, 3 H), 7.47-7.52 (m, 1 H), 7.70-7.72 (m, 1 H), 8.10-8.13 (m, 1 H), 8.28 (s, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.8, 19.4, 19.9, 21.2, 32.8, 33.4, 38.0, 41.1, 41.5, 41.8, 68.7, 68.9, 78.6, 78.8, 120.6, 122.0, 123.0, 123.9,

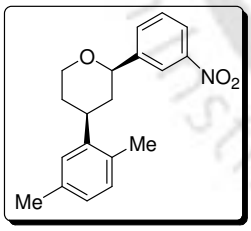
125.7, 127.9, 129.0, 129.7, 131.7, 133.5, 134.4, 136.6, 136.8, 142.4, 142.5, 145.0, 145.1, 148.1. **IR**: 2941, 2848, 1633, 1529, 1442, 1350, 1130, 1090, 1041, 807, 737, 693 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.45; H, 6.94; N, 4.56.

4-(2,4-Dimethyl-phenyl)-2-(3-nitro-phenyl)-tetrahydropyran and 4-(2,6-dimethyl-phenyl)-2-(3-nitro-phenyl)-tetrahydropyran (24; two regioisomers: 2:1):



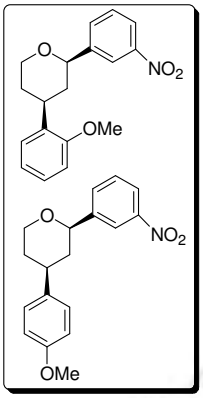
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67-1.80 (m, 1 H), 1.82-1.96 (m, 1 H), 2.00-2.04 (m, 1 H), 2.14-2.23 (m, 1 H), 2.28 (s, 3 H), 2.37 (s, 0.66 H), 2.45 (s, 0.34 H), 3.14-3.22 (m, 0.66 H), 3.47-3.54 (m, 0.34 H), 3.74-3.84 (m, 1 H), 4.30-4.36 (m, 1 H), 4.56-4.62 (m, 1 H), 7.00 (d, J = 5.2 Hz, 2 H), 7.10 (d, J = 7.6 Hz, 1 H), 8.10-8.13 (m, 1 H), 8.28 (s, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.1, 20.7, 21.2, 21.7, 29.3, 32.5, 33.0, 37.5, 37.7, 38.7, 40.7, 41.5, 41.6, 68.6, 69.2, 78.5, 79.0, 120.5, 120.6, 122.0, 124.5, 125.2, 126.1, 126.9, 129.0, 131.2, 131.6, 131.7, 134.7, 135.4, 136.0, 137.8, 139.7, 139.8, 145.1, 148.1. **IR**: 2941, 2848, 1633, 1529, 1442, 1130, 1090, 1041, 807, 737, 692 cm^{-1}. . Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.35; H, 6.88; H, 4.61.

4-(2,5-Dimethyl-phenyl)-2-(3-nitro-phenyl)-tetrahydropyran (25):



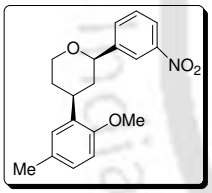
Gum, **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.68-1.80 (m, 2 H), 1.84-1.95 (m, 1 H), 2.00-2.05 (m, 1 H), 2.29 (s, 3 H), 2.36 (s, 3 H), 3.15-3.23 (m, 1 H), 3.78-3.84 (m, 1 H), 4.30-4.35 (m, 1 H), 4.60 (dd, J = 11.2 and 2.0 Hz, 1 H), 6.92-6.94 (m, 1 H), 7.02,-7.10 (m, 2 H), 7.50 (t, J = 8.0 Hz, 1 H), 7.71 (d, J = 7.6 Hz, 1 H), 8.10-8.13 (m, 1 H), 8.30 (s, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.0, 21.2, 32.6, 37.6, 40.8, 68.9, 78.8, 120.9, 122.3, 126.3, 127.0, 129.3, 130.5, 131.9, 132.0, 135.8, 142.6, 145.2, 148.3. **IR**: 3077, 3017, 2945, 2848, 1614, 1528, 1441, 1348, 1131, 1082, 1043, 808, 739, 695 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.55; H, 6.89; N, 4.65.

4-(2-Methoxy-phenyl)-2-(3-nitro-phenyl) tetrahydropyran and 4-(4-Methoxy-phenyl)-2-(3-nitro-phenyl) tetrahydropyran (26):



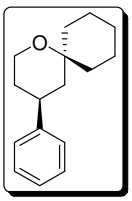
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.62-1.71 (m, 1 H), 1.80-1.94 (m, 2 H), 2.08-2.12 (m, 0.67 H), 2.26-2.35 (m, 0.33 H), 2.94-2.99 (m, 0.33 H), 3.40-3.50 (m, 0.67 H), 3.77-3.82 (m, 1 H), 3.85 (s, 3 H), 4.28-4.32 (m, 1 H), 4.62 (dd, J = 11.2 and 2.0 Hz, 1 H), 6.83-7.00 (m, 3 H), 7.17-7.24 (m, 2 H), 7.48 (t, J = 8.0 Hz, 1 H), 7.71 (d, J = 7.6 Hz, 1 H), 8.10 (d, J = 8.4 Hz, 1 H), 8.28 (s, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 31.8, 34.9, 40.4, 55.5, 69.1, 78.9, 110.7, 114.3, 121.0, 121.2, 122.5, 124.3, 126.8, 127.6, 129.4, 130.4, 132.2, 133.2, 145.5, 148.6, 157.0, 158.3. **IR**: 3067, 3000, 2938, 2839, 1608, 1524, 1439, 1349, 1241, 1102, 1083, 1031, 845, 810, 753 cm^{-1}. **Anal. Calcd** for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.08; H, 6.17; N, 4.56.

4-(2-Methoxy-5-methyl-phenyl)-2-(3-nitro-phenyl)-tetrahydropyran (27):



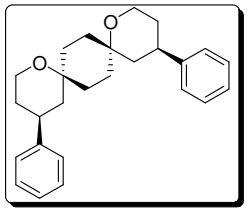
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65-1.74 (m, 1 H), 1.78-1.98 (m, 2 H), 2.00-2.10 (m, 1 H), 2.33 (s, 3 H), 3.15-3.22 (m, 1 H), 3.77 (s, 3 H), 3.80-3.86 (m, 1 H), 4.30-4.35 (m, 1 H), 4.61 (dd, J = 11.2 and 2.0 Hz, 1 H), 6.66-6.69 (m, m, 1 H), 6.76 (d, J = 2.0 Hz, 1 H), 7.00 (d, J = 8.9 Hz, 1 H), 7.50 (t, J = 8.0, 1 H), 7.71 (d, J = 7.6 Hz, 1 H), 8.12 (d, J = 8.0 Hz, 1 H) 8.28 (s, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 18.7, 32.5, 38.0, 40.8, 55.4, 69.0, 78.9, 111.1, 112.1, 121.1, 122.5, 127.2, 129.4, 131.5, 132.0, 144.2, 145.1, 148.5, 158.5. **IR**: 3086, 2926, 2851, 1610, 1529, 1463, 1251, 1109, 1085, 1041, 806, 738 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47 N, 4.28. Found: C, 69.85; H, 6.55; N, 4.33.

4-Phenyl-1-oxa-spiro[5.5]undecane (28):



Gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.26-1.80 (m, 13 H), 2.10-2.14 (m, 1 H), 2.90-2.97 (m, 1 H), 3.73-3.85 (m, 1 H), 7.18-7.23 (m, 3 H), 7.28-7.33 (m, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 21.8, 26.3, 29.7, 33.7, 36.7, 40.5, 43.6, 60.7, 72.4, 126.3, 126.8, 128.5, 146. **IR**: 3027, 2927, 2855, 1603, 1492, 1445, 1375, 1175, 1101, 1079, 974, 910, 759, 698 cm^{-1}.**Anal. Calcd** for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.54; H, 9.54.

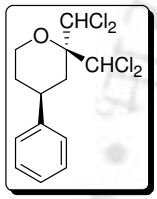
4,13-Diphenyl-1,10-dioxa-dispiro [5.2.5.2] hexadecane (29):



Solid; M.P. 195.0-198.0 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.37-1.84 (m, 14 H), 2.23-2.28 (m, 2 H), 2.94-3.04 (m, 2 H), 3.68-3.75 (m, 2 H), 3.81-3.88 (m, 2 H), 7.19-7.23 (m, 3 H), 7.29-7.33 (m, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ. 23.7, 24.1, 33.8, 35.0, 35.4, 36.8, 37.0, 44.7, 61.2, 72.3, 126.4, 127.0, 128.7, 146.3. **IR**: 3026, 2929, 2853, 1600, 1491, 1452, 1375, 1108, 1084, 996, 757, 698 cm^{-1}. **Anal. Calcd** for $C_{26}H_{32}O_2$: C, 82.94; H, 8.57. Found: C, 82.87; H, 8.65.

2,2-Bis-chloromethyl-4-phenyl-tetrahydropyran (30):

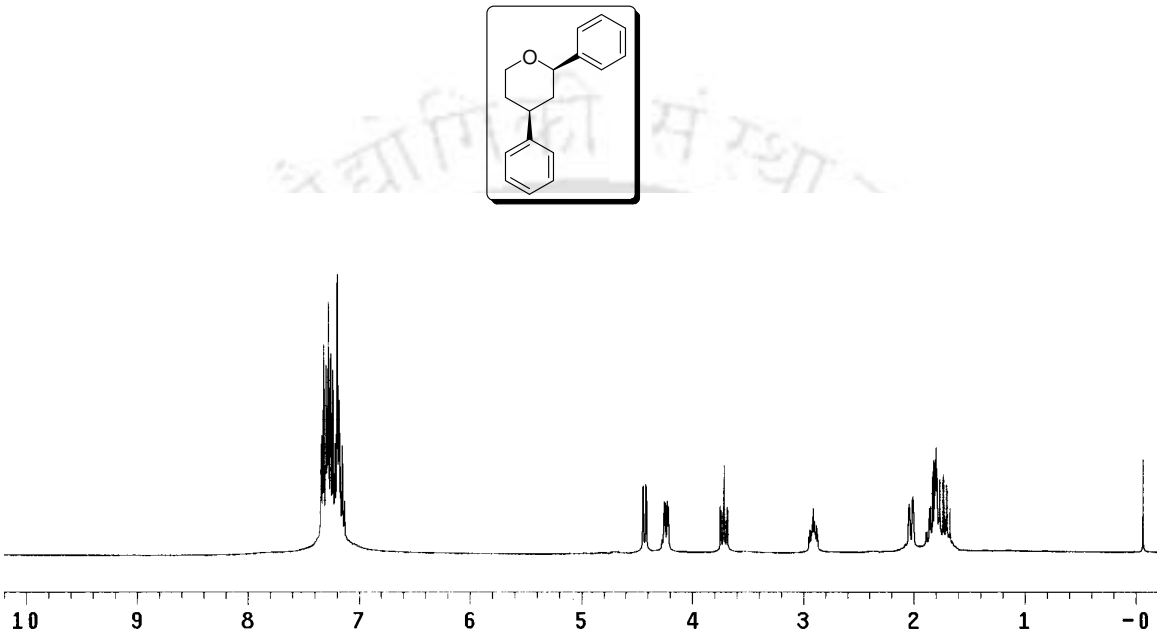
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.56-1.66 (m, 1 H), 1.75-1.82 (m, 2 H), 2.12 (dd, J = 14.00 and 3.2 Hz, 1 H), 2.80-2.90 (m, 1 H), 3.62 (q, J_{AB} = 11.2 Hz, 2 H), 3.60-3.78 (m, 2 H), 3.92 (q, J_{AB} = 12.0 Hz, 2 H), 7.21-7.25 (m, 3 H), 7.31-7.35 (m, 2 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ. 32.5, 36.8, 41.9, 49.8, 62.8, 75.2, 126.8, 126.9, 128.9, 144.5. **IR**: 2943, 2833, 1602, 1495, 1441, 1257, 1120, 1082, 783, 750, 699 cm^{-1}. **Anal. Calcd** for $C_{13}H_{16}Cl_2O$: C, 60.25; H, 6.22. Found: C, 60.32; H, 6.16.



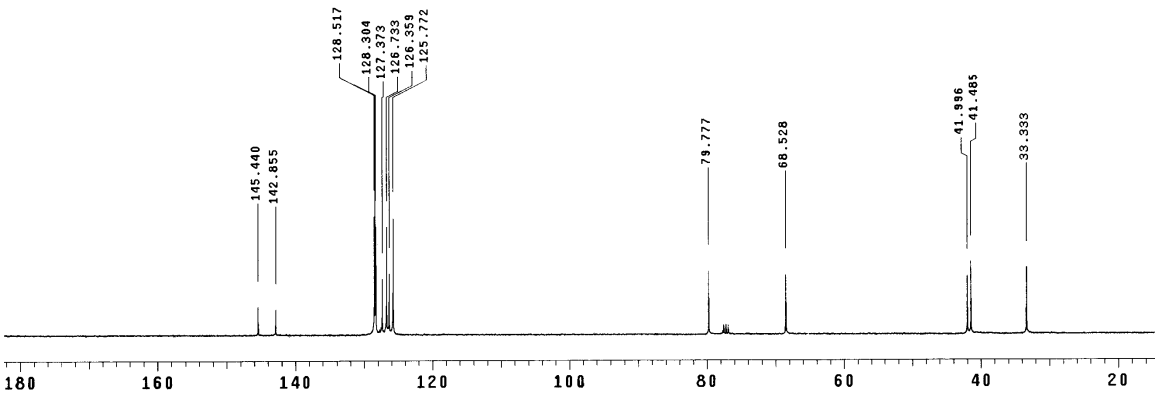
4.7 Selected Spectra of unsymmetrical 4-aryltetrahydropyrans

2,4,6-triphenyltetrahydropyran (1b):

^{1}H NMR (400 MHz, CDCl3)

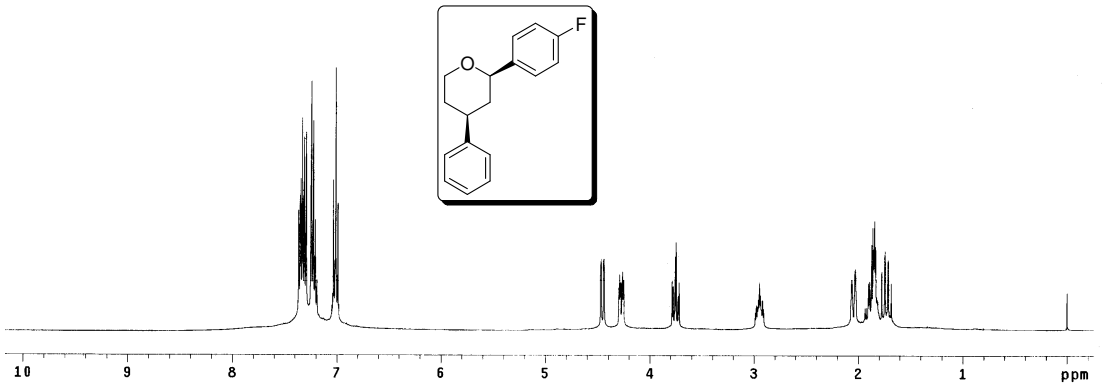


^{13}C NMR (100 MHz, CDCl3)

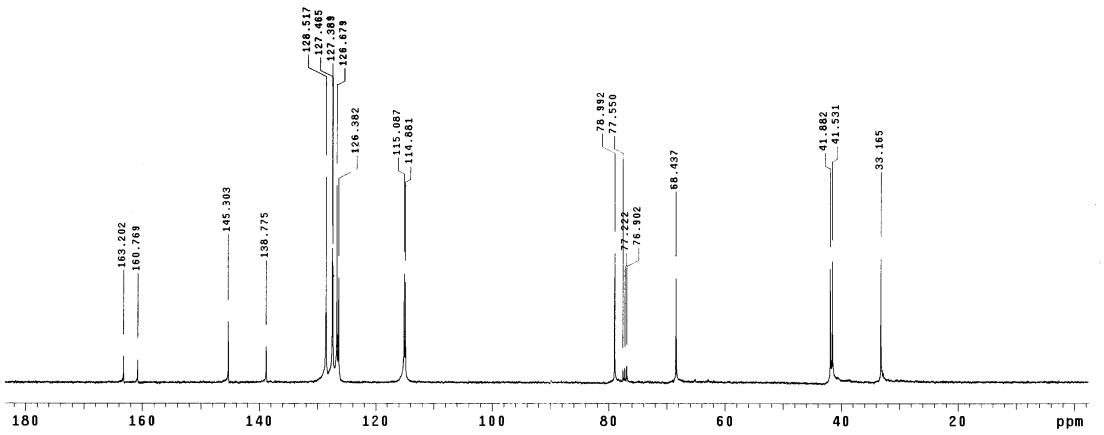


2-(4-Fluoro-phenyl)-4-phenyltetrahydropyran (4b):

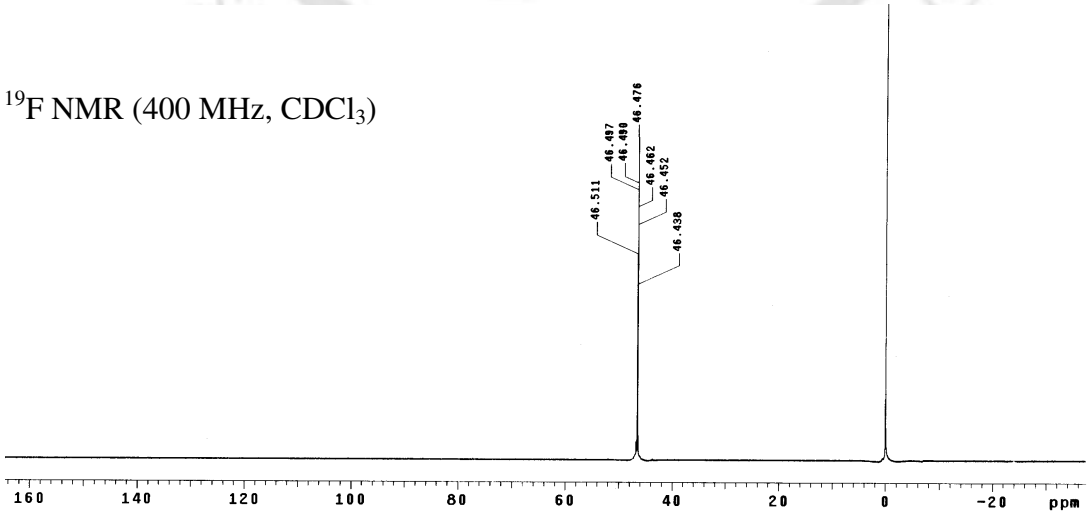
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

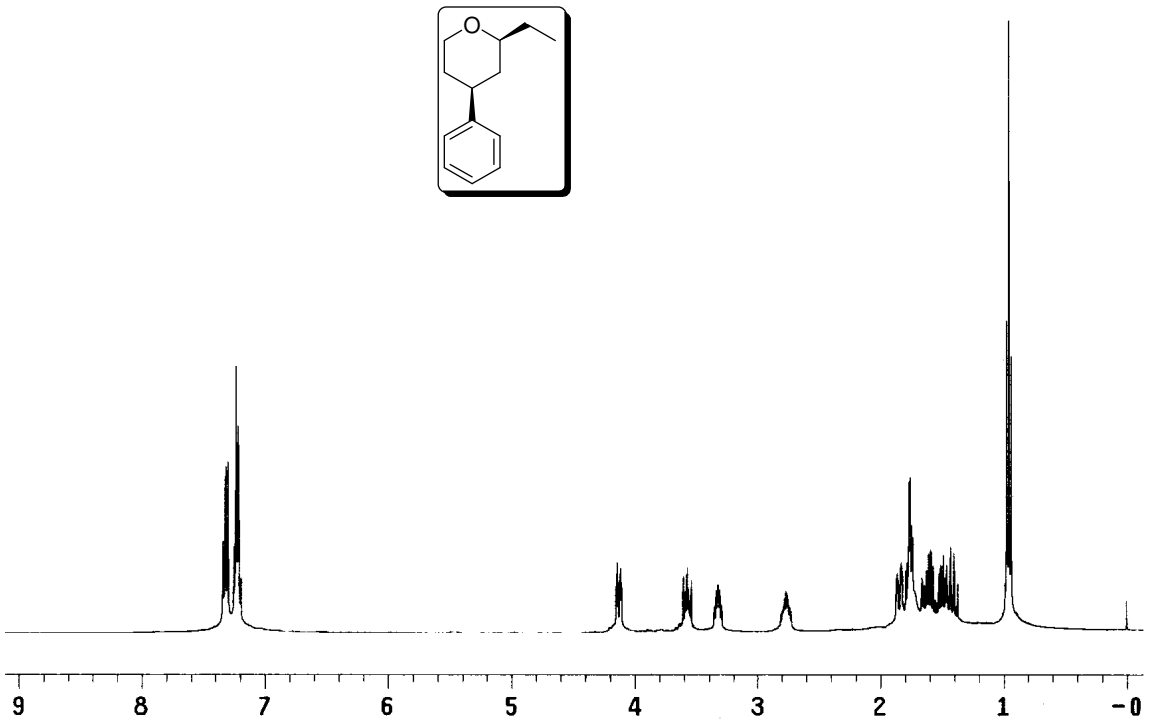


^{19}F NMR (400 MHz, $CDCl_3$)

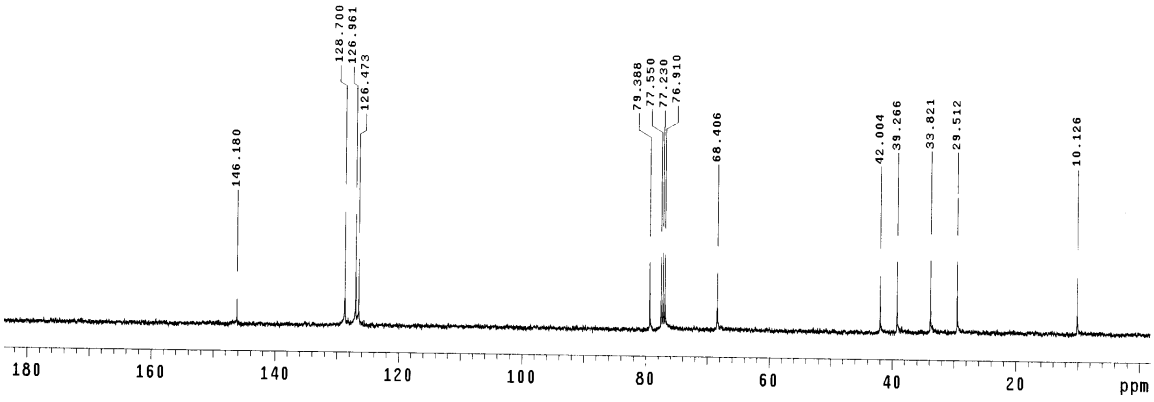


2-Ethyl-4-phenyl-tetrahydropyran (15b):

^{1}H NMR (400 MHz, $CDCl_3$)

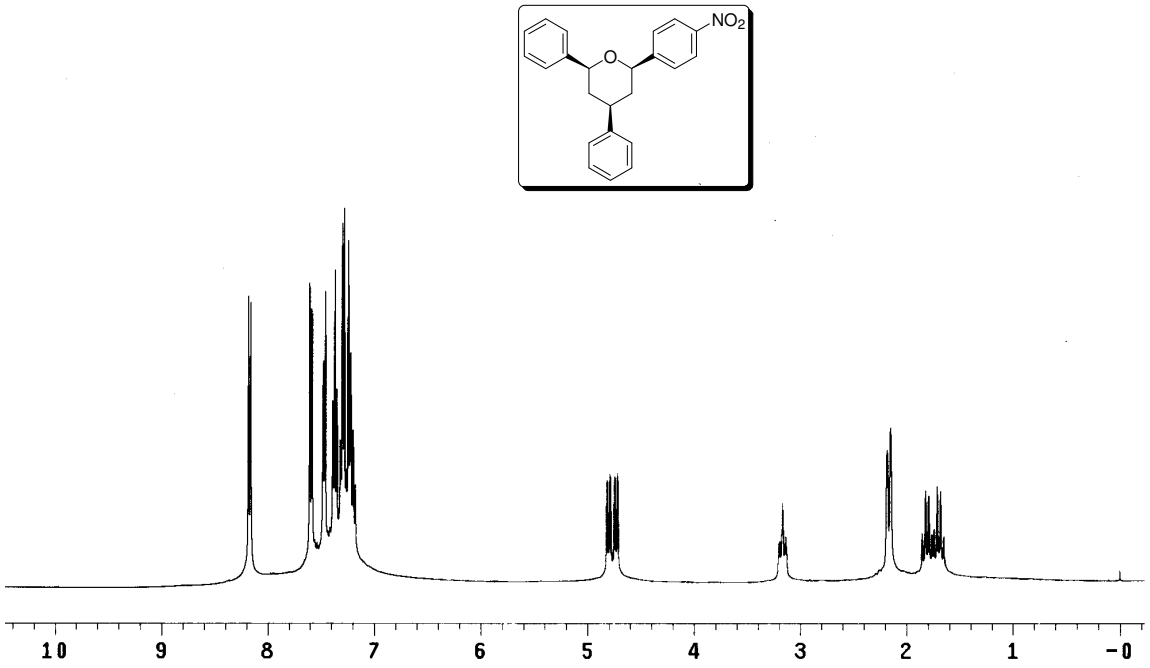


^{13}C NMR (100 MHz, $CDCl_3$)

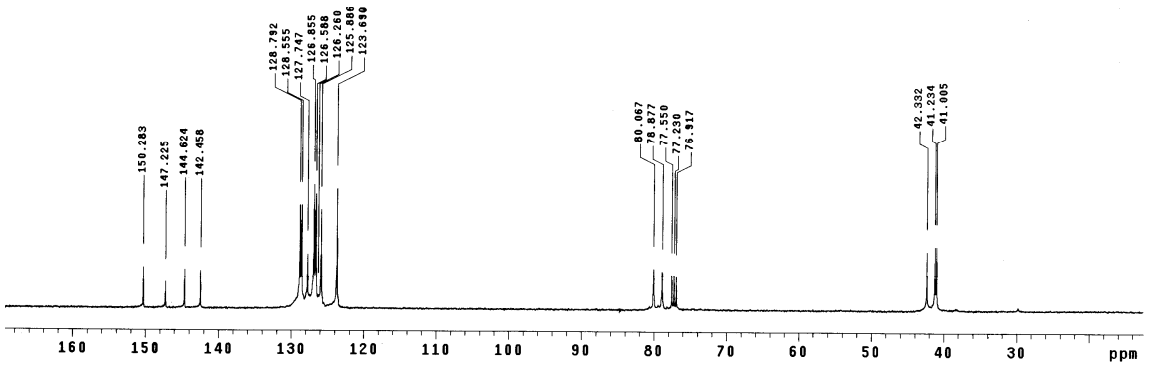


2-(4-Nitro-phenyl)-4,6-diphenyl tetrahydropyran (18b):

^{1}H NMR (400 MHz, $CDCl_3$)

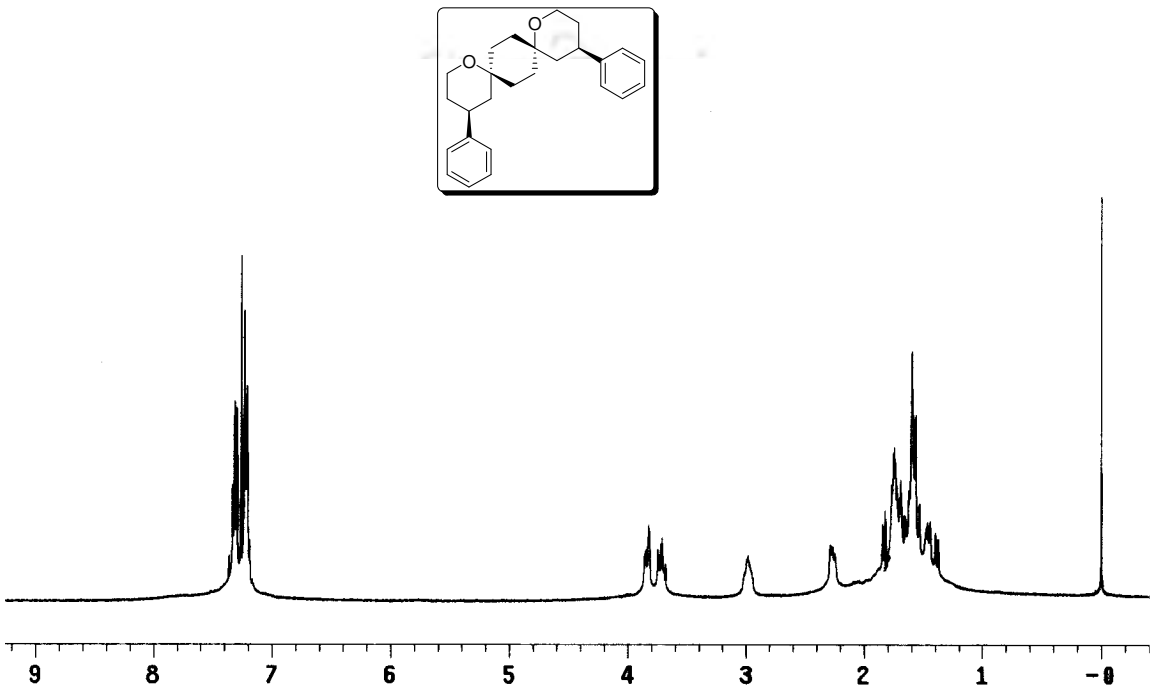


^{13}C NMR (100 MHz, CDCl3)

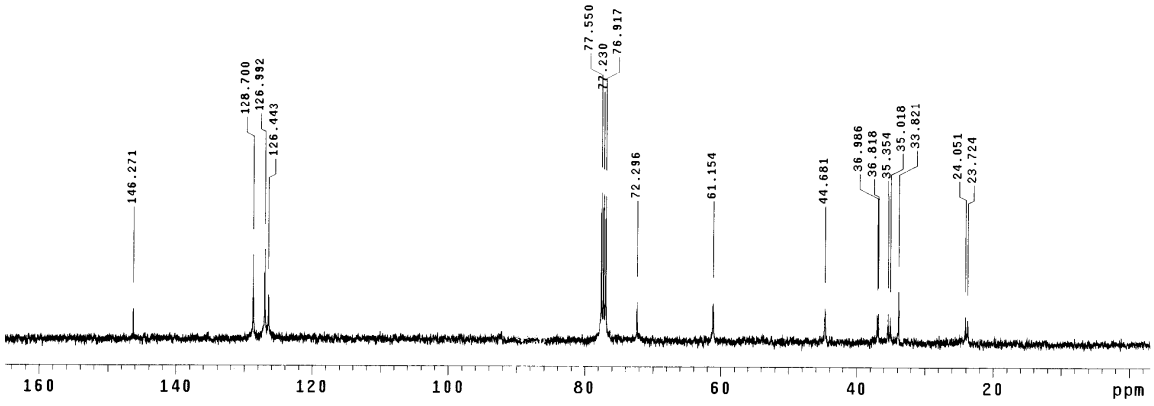


4,13-Diphenyl-1,10-dioxa-dispiro [5.2.5.2] hexadecane (29):

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



2.8 The Crystal Parameters of Compound 2b

Crystal Parameters	**2b** (CMR-2; CCDC 658766)
Formula	$C_{17}H_{17}NO_3$
Formula weight	283.32
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)/c
a/Å	15.0086(18)
b/Å	5.5608(7)
c/Å	18.443(2)
α/º	90.00
β/º	105.738(3)
γ/º	90.00
V/Å^3	1481.6(3)
Z	4
Abs. Coeff./mm^{-1}	0.087
Abs. Correction	None
GOF on F^2	0.968
Final *R* indices	*R1* = 0.0434
[$I > 2\sigma(I)$]	*w*R2 = 0.0996
R indices [all data]	R2 = 0.0984
	*w*R2 = 0.1218

CHAPTER 5

Synthesis of Substituted 4-Aryl-5,6-dihydro-2*H*-pyrans

5.1. Importance and Applications

The synthesis of 5,6-dihydropyran is synthetically attractive since the olefin function can be further functionalized to obtain polysubstituted tetrahydropyrans.[1] 2-Alkyl-4-aryldihydropyrans **1 & 2** (*Figure 5.1.1*) are used as flavoring and aroma agents.[2] The oxazolidinone[3] **3** (*Figure 5.1.1*) exhibits anti bacterial activity. It is also active against Gram-positive pathogens and resistance to vacomycin.

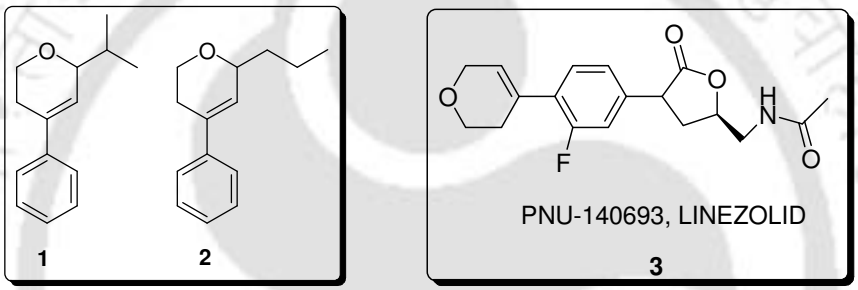


Figure 5.1.1. *Examples of some biologically active 4-aryl-dihydropyran derivatives*

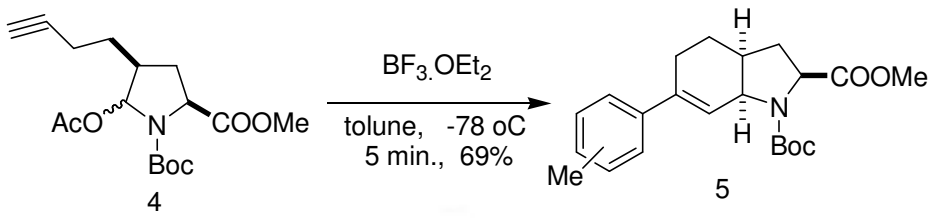
5.2. An Overview of Relevant Synthetic Methods and its Applications

There are several methods for the synthesis of dihydropyrans in the literature. Among these Prins cyclization is the most convenient because it provides the desired product in a single step. Usually Lewis acid is used for this reaction and, in most of the cases, the product is a 4-halosubstituted dihydropyran, but the synthetic access to 4-aryldihydropyrans is limited. The existing methods have limitations such as formation of side products, low yield, and use of multistep processes. These are also prepared by using Hetero-Diels-Alder followed by coupling reaction and Grubbs olefine metathesis. These are summarized below and briefly discussed in the previous sections.

5.2.1 Tandem Prins-Friedel-Crafts Reaction

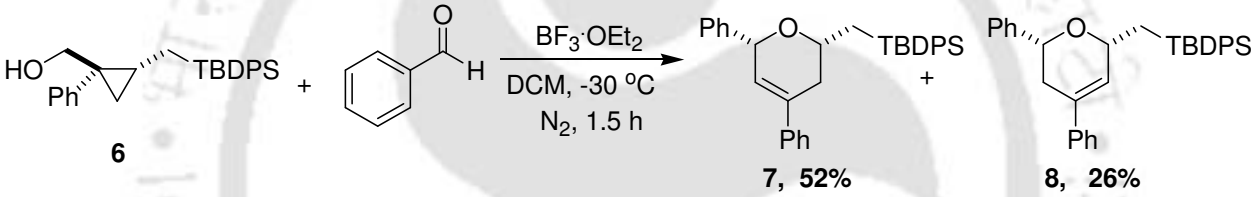
Hanessian and Coworkers[4] developed an alkyne Prins cyclization reaction. As exemplified in *scheme 5.2.1*, compound (**4**) with $BF_3{\cdot}OEt_2$ in toluene gave the vinylic 6-tolyl adducts (**5**), as an

o/*p*-mixture in 69% yield.



Scheme 5.2.1

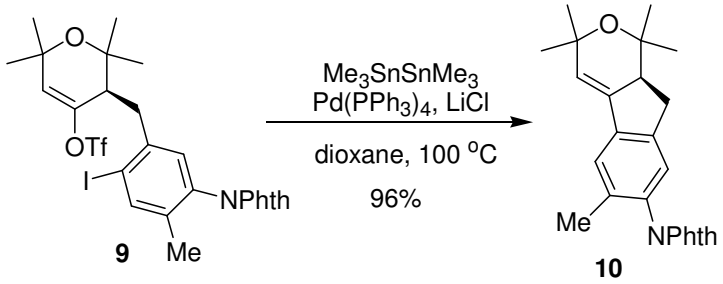
Yadav and Vijaya Kumar developed a Prins cyclization from the reaction of cyclopropyl carbinols.[5] As illustrated in *Scheme 5.2.2*, the reaction of benzaldehyde with (**6**) in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at -30 ^oC gave 2:1 mixture of (**7**) and (**8**) in 78% overall yield. Among the several Lewis acids that were used, $BF_3{\cdot}OEt_2$ was found to be the most effective.



Scheme 5.2.2

5.2.2 Coupling Reactions

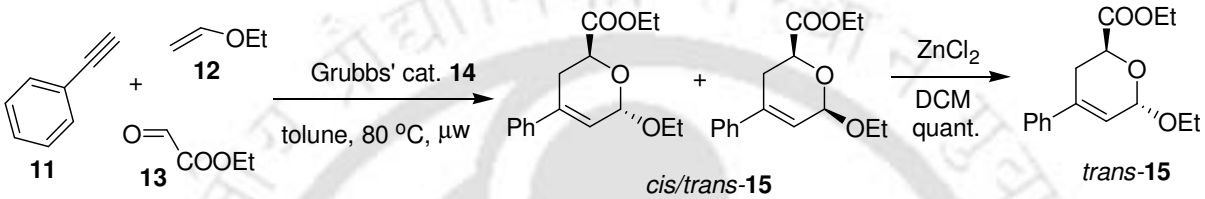
Coupling reactions such as Suzuki-Miyaura, Heck or Stille reactions are a useful and practical alternative to the tandem Friedel-Crafts-Prins cyclization. 4-Aryldihydropyrans were prepared by using tandem Stille ring closure.[6] As shown in *Scheme 5.2.3*, the intramolecular cross-coupling of compound (**9**) catalyzed by $Pd(PPh_3)_4$, in the presence of $Me_3SnSnMe_3$ and LiCl in 1,4-dioxane solvent achieved the envisioned tandem sequence through the aryl stannane followed by ring closure gave the tricycle compound (-)-**10** in 96% yield.



Scheme 5.2.3

5.2.3 Reaction with Grubb's 2nd Generation catalyst

The microwave irradiation of alkyne (**11**) with ethyl vinyl ether (**12**) and ethyl glyoxalate (**13**) in toluene and in the presence of Grubb's 2nd generation catalyst gave the 2,3-dihydropyrans (**15**) as a mixture of *cis*/*trans* diastereoisomers (*Scheme 5.2.4*).[7] The dihydropyrans (**15**) were then equilibrated in the presence of $ZnCl_2$. The presence of a Lewis acid led to the formation of *trans*-**15** compound as the only product in quantitative yield.

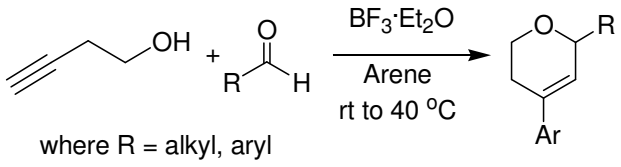


Scheme 5.2.4

5.3. Results and Discussion

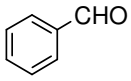
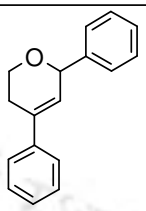
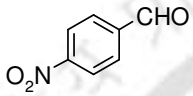
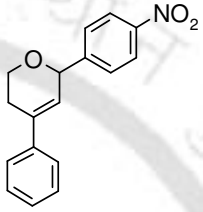
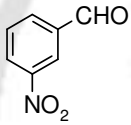
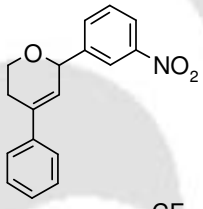
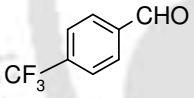
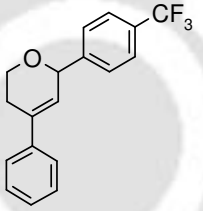
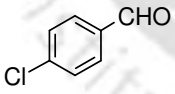
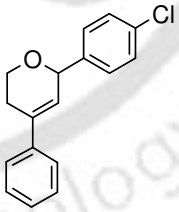
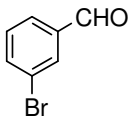
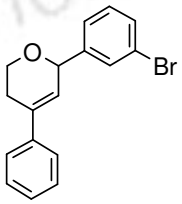
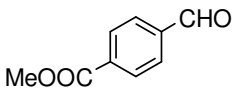
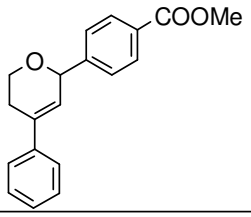
In our previous chapter we described a methodology for the synthesis of 4-aryl-tetrahydropyran using Prins-Friedel-Crafts reaction starting with homoallyl alcohols, carbonyl compounds in presence of arene nucleophiles. Here we extended above method to prepare 4-Aryl-5,6-dihydropyran from carbonyl compounds or epoxides, homopropargyl alcohols, and arenes mediated by boron trifluoride etherate by using alkyne-Prins–Friedel–Crafts Reaction.

To start, benzaldehyde reacted with homopropargyl alcohol in the presence of boron trifluoride etherate in benzene at room temperature. The product, 2,4-diphenyl-5,6-dihydropyran, was obtained in 45% yield. Other non-halogenated Lewis acids such as TMSOTf, $Sc(OTf)_3$, $In(OTf)_3$, and $Bi(OTf)_3$ were found to be inefficient for this reaction. The general conversion is shown in *Scheme 5.3.1*.

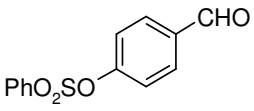
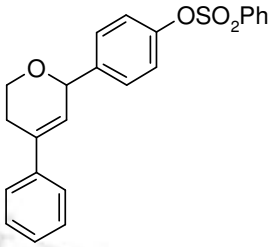
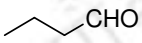
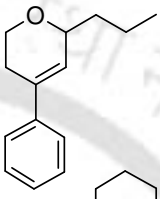
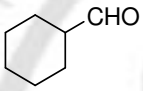
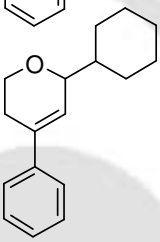
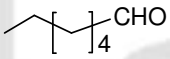
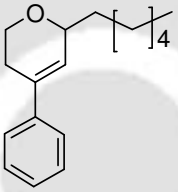
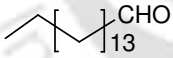
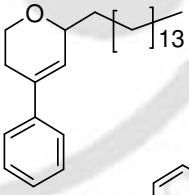
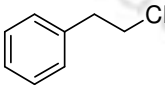
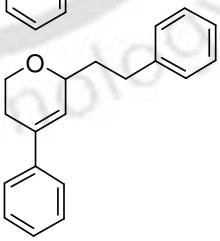
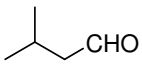
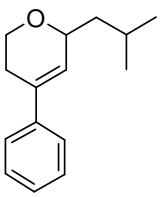


Scheme 5.3.1. *Synthesis of 4-aryldihydropyran*

Table 5.3.1. *Synthesis of 4-aryldihydropyran*

Sl No.	Aldehyde (a)	Time /h	Temp./°C	Product (b)	Yield[a] (%)
1		8	40		45
2		8	40		61
3		8	40		63
4		7	40		66
5		8	40		54
6		8	40		64
7		8	40		67

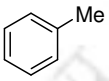
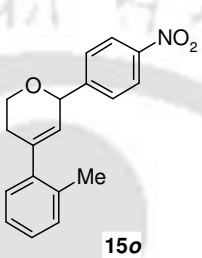
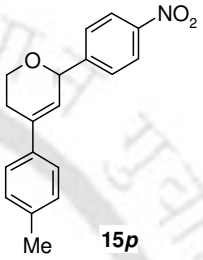
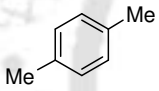
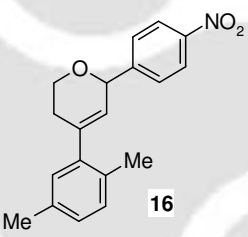
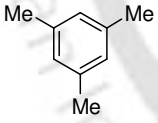
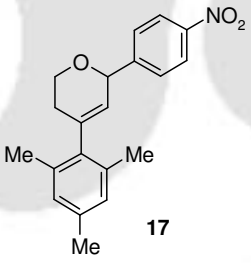
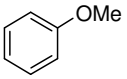
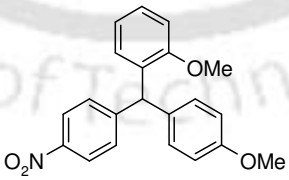
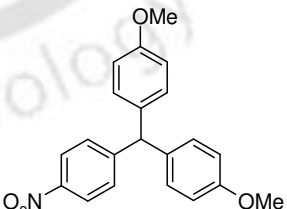
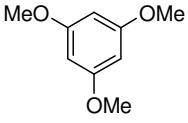
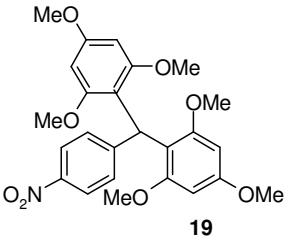
continue...

Sl No.	Aldehyde (a)	Time /h	Temp./°C	Product (b)	Yield[a] (%)
8		9	40		72
9		8	rt		95
10		8	rt		95
11		7	rt		87
12		7	rt		81
13		8	rt		92
14		8	rt		75

[a]Yields refer to isolated yield. Compounds are characterized by IR, NMR and mass spectroscopy.

The scope of the reaction was examined by considering a range of aldehydes as shown in *Table 5.3.1.* It was observed that the reaction holds good for simple aromatic aldehydes and aldehydes having electron-withdrawing groups on the aromatic ring. Aromatic aldehydes having electron-

Table 5.3.2. *Reaction of 3-butyn-1-ol with p-nitrobenzaldehyde with other arenes*

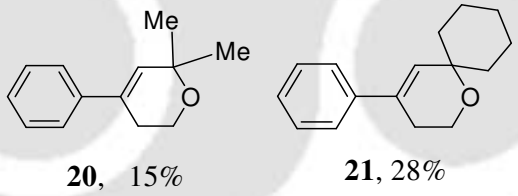
Sl No.	Arene	Time/h	Product	Yield(%)[b]
1		5	 **15*o***  **15*p***	72
2		5	 **16**	78
3		5	 **17**	94
4		6	 **18o**  **18*p***	76
5		4	 **19**	82

[a]Yields refers to isolated yields. Compound characterized by IR, NMR and mass spectroscopy.

donating groups such as anisaldehyde failed to give products. This can be attributed to the stability of the benzylic carbocation due to the presence of methoxy group on the aromatic ring, which leads to oxonia-[3,3]-sigmatropic rearrangement.[8] On the other hand aliphatic aldehydes were very good substrates and give good yields.

To extend the utility of this method, various arenes as nucleophiles were investigated under these reaction conditions. The results are summarized in *Table 5.3.2*. It was observed that methyl-substituted arenes gave good yields in comparison to benzene. Thus, the reaction with toluene gave *o-/p*-**15** as an inseparable mixture of regioisomers with a ratio of 2:1 and 72% overall yield. Similarly, *p*-xylene and mesitylene gave single isomers **16** and **17** in 78% and 92% yields, respectively. On the other hand methoxy substituted benzenes such as anisole gave regioisomeric triarylmethane adducts *o*-**18** and *p*-**18** with a ratio of 4:1and 76% overall yield. Similarly, 1,3,5-trimethoxybenzene gave triarylmethane adduct **19** in 82% yield.

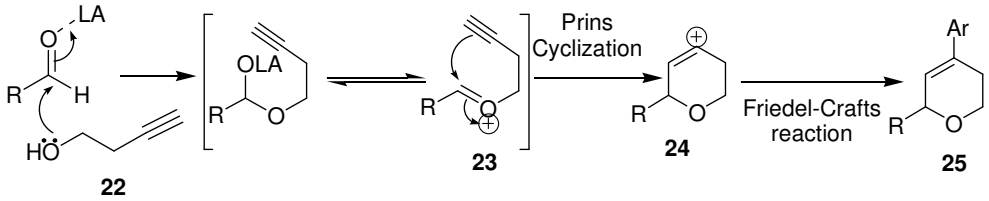
The reaction with ketone was not satisfactory. Thus, the reaction of acetone and cyclohexanone with homopropargyl alcohol in benzene gave spirocyclic compounds **20** and **21** (*Figure 5.3.1*) in 13% and 28% yields, respectively. This is due to the lower reactivity of the ketones than aldehydes.



20, 15% **21**, 28%

Figure 5.3.1.

The mechanism of the reaction can be explained as follows (*Scheme 5.3.2*). Lewis acid activates the aldehyde for nucleophilic attack by the homopropargyl alcohol **22** to give oxocarbenium ion **23**. The intermediate **23** after Prins cyclization forms carbocation **24**, which undergoes Friedel–Crafts reaction to give dihydropyran **25**.

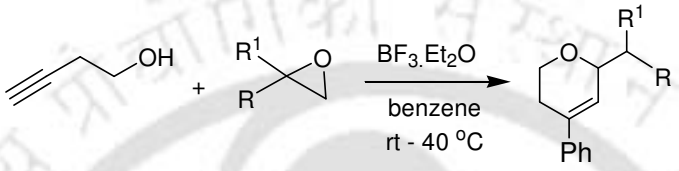


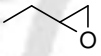
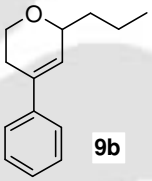
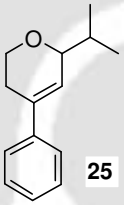
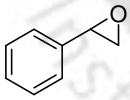
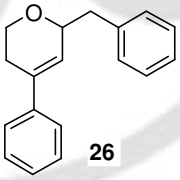
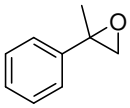
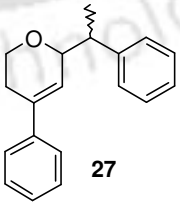
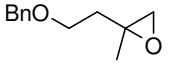
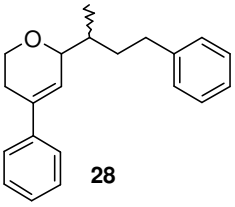
22 **23** **24** **25**

Scheme 5.3.2. *Mechanism of the reaction*

The same dihydropyran can also be prepared using epoxides as aldehyde equivalents, as shown in *Table 5.3.3.* The reactivity of epoxides varies from 2,2-disubstituted to monosubstituted epoxides. In the case of monosubstituted epoxides only a trace amount of dihydropyran was detected. On the other hand styrene oxide gave better yields than the aliphatic epoxides.[10]

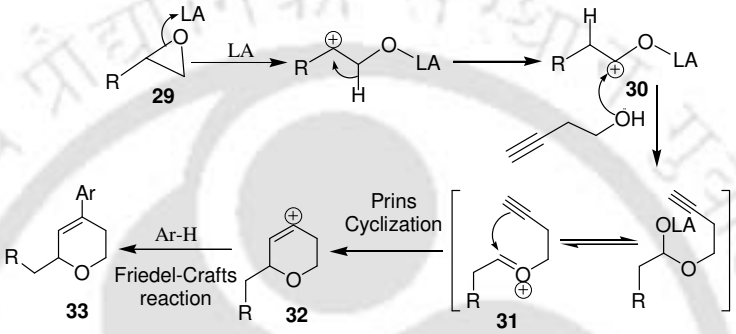
Table 5.3.3. *Reaction of 3-butyn-1-ol with epoxides*



Sl No	Epoxide	Time/h	Product	Yield(%)[a]
1		6	 **9b**	Trace
2		5	 **25**	45
3		5	 **26**	60
4		5	 **27**	75[b]
5		5	 **28**	45[b]

[a]Yields refer to isolated yield. Compounds are characterized by IR, NMR and mass spectroscopy. [b]Mixture of two inseparable isomers with a ratio of 2:3.

The mechanism of the reaction with epoxide can be explained (*Scheme 5.3.3*) by considering the already reported fact that epoxide (**29**) after opening with Lewis acid rearranges to intermediate (**30**). Here the intermediate (**30**) is attacked by homopropargyl alcohol to give oxocarbenium ion (**31**), which after Prins cyclization gives carbocation (**32**). The carbocation (**32**) undergoes Friedel-Crafts reaction to give dihydropyran (**33**).[11]



Scheme 5.3.3. *Mechanism of the Prins cyclization reaction with epoxide*

Conclusion

Dihydropyrans are useful intermediates, particularly for the synthesis of tetrahydropyrans.[12] The current work should prove to be extremely useful as it is initiated with readily available and easily accessible starting materials, proceeds in adequate to excellent yields, use mild conditions, and gives products that are not halogenated. Furthermore, this method can be extended to epoxide where aldehydes are not easily accessible. Although the reaction is also successful for ketones, the yields of products are very poor.

5.4 Experimental Section

5.4.1 Instrumentation and Characterization

As described in Chapter 2, Section 2.5.1.

5.4.2 General procedure for the synthesis of 4-aryldihydropyran from carbonyl compounds 1b-14b and 15-21

To a mixture of aldehyde (1.0 equiv) and homopropargyl alcohol (2.0 equiv) in dry arene (2.0 mL) was added freshly distilled boron trifluoride etherate (1.2 equiv) under nitrogen atmosphere.

The reaction mixture was stirred at specified temperature. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

*Synthesis of 2,4-Diphenyl-5,6-dihydro-2H-pyran (**1b**)*: To a mixture of benzaldehyde (0.10 mL, 1.0 mmol) and homopropargyl alcohol (140 mg, 2.0 mmol) in dry arene (2.0 mL) was added freshly distilled boron trifluoride etherate (0.15 mL, 1.2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 40 °C for 8 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the 2,4-Diphenyl-5,6-dihydro-2*H*-pyran **1b** (106 mg, 45% yield) as a liquid.

*6-Isopropyl-4-phenyl-5,6-dihydro-2H-pyran (**22**)*: To a mixture of 1,2-epoxy-2-methylpropane (0.09 mL, 1.0 mmol) and homopropargyl alcohol (140 mg, 2.0 mmol) in dry benzene (3.0 mL) was added freshly distilled $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at r.t. for 5 h. The progress of the reaction was monitored by TLC with EtOAc and hexane as eluents. After completion of reaction, the reaction mixture was treated with aq $NaHCO_3$, and the product was extracted with Et_2O, and then the combined organic extracts washed with brine and H_2O. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel.

5.5.3. General procedure for the synthesis of compounds 9b, 25-28

To a mixture of epoxide (1.0 equiv) and homopropargyl alcohol (2.0 equiv) in dry benzene (3.0 mL) was added freshly distilled boron trifluoride etherate (1.2 equiv) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried

(Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

*4-Phenyl-2-isopropyl-5,6-dihydro-2H-pyran (**25**):* To a mixture of 1,2-epoxy-2-methylpropane (0.09 mL, 1.0 mmol) and homopropargyl alcohol (140 mg, 2.0 mmol) in dry benzene (3.0 mL) was added freshly distilled boron trifluoride etherate (0.15 mL, 1.2 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate and the product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the 4-Phenyl-2-isopropyl-5,6-dihydro-2H-pyran (**25**) (90 mg, 45 % yield) as a liquid.

5.6. References and Notes

(1) (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963-3008. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309-3362. (c) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911-913. (d) Li, C.-J.; Zhang, W.-C. *Tetrahedron* **2000**, *56*, 2403-2411. (e) Schmidt, B.; Westhus, M. *Tetrahedron* **2000**, *56*, 2421-2426.

(2) Vinals, J. F.; Kiwala, J.; Hruza, D. E.; Hall, J. B.; Vock, M. H. A. US 4070491, 1978.

(3) (a) Xua, J.; Golshania, A.; Aokia, H.; Remmeb, J.; Chosayc, J.; Shinabargerd, D. L.; Ganoza, M. C. *Biochem. Bioph. Res. Co.* **2005**, *328,* 471–476. (b). Michael, Barry, M. G. WO 97/30995, 1997.

(4) Hanessian, S.; Tremblay, M. *Org. Lett.* **2004**, *6*, 4683-4686.

(5) Yadav, V. K., Kumar, N. V. *J. Am. Chem. Soc.* **2004**, *126*, 8652-8653.

(6) Smith, III, A. B.; Davulcu, A. H.; Kurti, L. *Org. Lett.* **2006**, *8*, 1669-1672.

(7) Castagnolo, D.; Botta, L.; Botta, M. *Tetrahedron Lett.* **2009**, *50*, 1526–1528.

(8) Liu, F.; Loh, T.-P. *Org. Lett.* **2007**, *9*, 2063-2066.

(9) Podder, S.; Choudhury, J.; Roy, U. K.; Roy, S. *J. Org. Chem.* **2007**, *72*, 3100-3103.

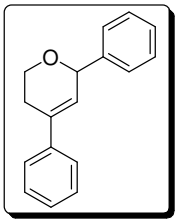
(10) The product **26** was sensitive to silica gel. While purifying the compound by column chromatography, it was decomposed. Therefore, the silica gel of the column chromatography was impregnated with 3% Et_3N in hexane during the purification.

(11) (a) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212-8216. (b) Li, J.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 793-796.

(12) Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 1843-1857.

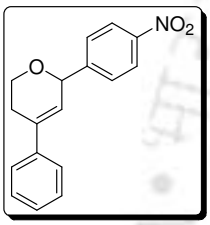
5.7. Spectral data

2,4-Diphenyl-5,6-dihydro-2*H*-pyran (1b):



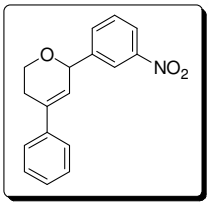
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45-2.52 (m, 1 H), 2.70-2.80 (m, 1 H), 3.92 (ddd, *J* = 11.6, 8.8 and 4.0 Hz, 1 H), 4.18 (ddd, *J* = 11.6, 5.2 and 3.6 Hz, 1 H), 5.30 (d, *J* =2.4 Hz, 1 H), 6.22 (d, *J* = 1.2 Hz, 1 H), 7.23-7.45 (m, 10 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.3, 63.6, 72.4,124.3, 124.4, 125.1, 27.9, 128.6 (2C), 129.6, 133.4, 135.5, 136.9, 139.9, 148.5. **IR**: 3029, 2923, 2854, 1600, 1493, 1453, 1273, 1119, 1075, 1029, 886, 749, 698 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{17}H_{16}O$: $(M+H)^+$ 237.1279, found 237.1258.

4-Phenyl-2-(4-nitro-phenyl)-5,6-dihydro-2*H*-pyran (2b):



Solid; M. P. 105-108 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.47-2.55 (m, 1 H), 2.74-2.84 (m, 1 H), 3.96 (ddd, *J* = 11.6, 9.2 and 4.0 Hz, 1 H), 4.22 (ddd, *J* = 11.6, 5.6 and 3.2 Hz, 1 H), 5.41 (d, *J* = 2.0 Hz, 1 H), 6.14 (d, *J* = 1.2 Hz, 1 H), 7.28-7.38 (m, 3 H), 7.41-7.43 (m, 2 H), 7.60 (d, *J* = 8.8 Hz, 2 H), 8.23 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.1, 63.8, 76.9, 125.1, 125.5, 127.7, 127.8, 128.1, 128.6, 28.7, 135.1, 140.3, 141.5. **IR**: 3059, 2928, 2858, 1600, 1520, 1346, 1273, 1107, 1061, 854, 748, 695 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{17}H_{15}NO_3$: M^+ 281.1052, found 281.1021.

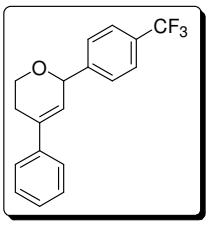
4-Phenyl-2-(3-nitro-phenyl)-5,6-dihydro-2*H*-pyran (3b):



Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.44-2.52 (m, 1 H), 2.70-2.82 (m, 1 H), 3.94 (ddd, *J* = 11.2, 9.2 and 4.0 Hz, 1 H), 4.19 (ddd, *J* = 11.6, 5.6 and 3.2 Hz, 1 H), 5.38 (d, *J* = 2.0 Hz, 1 H), 6.15 (d, *J* = 1.2 Hz, 1 H), 7.24-7.29 (m, 1 H), 7.34 (t, *J* = 7.2 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.51 (t, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 1 H) , 8.13 (d, *J* = 8.0 Hz, 1 H) , 8.28 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.1, 63.7, 75.8, 122.4, 122.9, 124.0, 125.1, 128.0, 128.7, 129.6, 133.6, 136.2, 139.7, 143.9, 148.5. **IR**: 3086, 2963, 2859, 1528, 1495, 1349, 1266, 1123, 1062, 908, 811, 756, 693 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{17}H_{15}NO_3$: M^+ 281.1052, found 281.1033.

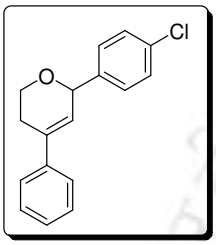
4-Phenyl-2-(4-trifluoromethyl-phenyl)-5,6-dihydro-2*H*-pyran (4b):

Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.45-2.52 (m, 1 H), 2.71-2.80 (m, 1 H), 3.93 (ddd, *J* = 11.6, 9.2 and 4.0 Hz, 1 H), 4.19 (ddd, *J* = 11.2, 5.6 and 3.2 Hz, 1 H), 5.34 (d, *J* = 2.0, 1 H),



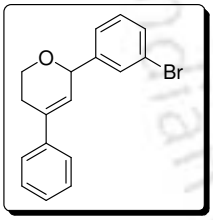
6.16 (d, *J* = 1.6, 1 H), 7.25-7.43 (m, 5 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.2, 63.8, 76.3, 124.4 (q, *J* = 270.7 Hz, -CF3), 124.6, 125.1, 125.6, 127.8, 128.0, 128.7, 130.2 (q, *J* = 32.1 Hz, C-CF3), 135.7, 140.0, 145.6. ^{19}F NMR (376 MHz, CDCl3/C6F6): δ 99.27 (s, -CF3). **IR**: 3034, 2927, 2857, 1620, 1325, 1165, 1125, 1107, 1067, 1018, 839, 696 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{18}H_{15}F_3O$: $(M+H)^+$ 305.1153, found 305.1155.

2-(4-Chloro-phenyl)-4-phenyl-5,6-dihydro-2*H*-pyran (5b):



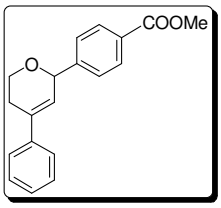
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.46- 2.53 (m, 1 H), 2.71-2.81 (m, 1 H), 3.93 (ddd, *J* = 11.2, 8.8 and 4.0 Hz, 1 H), 4.19 (ddd, *J* = 11.2, 5.2 and 3.2, 1 H), 5.29 (d, *J* = 2.8 Hz, 1 H), 6.17 (d, *J* = 2.0 Hz, 1 H), 7.26-7.45 (m, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.2, 63.6, 76.2, 125.0, 125.1, 127.9, 128.7, 128.9, 129.7, 133.9, 135.5, 140.1. **IR**: 3058, 2925, 2855, 1598, 1490, 1269, 1119, 1088, 1014, 827, 752, 694 cm^{-1}. **HRMS** (APCI) m/z calcd for $C_{17}H_{15}ClO$: $(M+H)^+$ 271.0890, found 271.0863.

2-(3-Bromo-phenyl)-4-phenyl-5,6-dihydro-2*H*-pyran (6b):



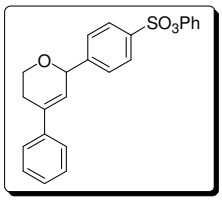
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.42- 2.49 (m, 1 H), 2.69-2.78 (m, 1 H), 3.89 (ddd, *J* = 11.6, 9.6 and 3.6 Hz, 1 H), 4.15 (ddd, *J* = 11.2, 5.2 and 3.2 Hz, 1 H), 5.24 (d, *J* = 2.8 Hz, 1 H), 6.14 (d, *J* = 2.0 Hz, 1 H), 7.18-7.42 (m, 8 H), 7.56 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.1, 63.6, 76.1, 122.8, 124.7, 125.1, 126.3, 127.9, 128.6, 130.2, 130.7, 131.1, 135.5, 139.9, 143.9. **IR**: 3059, 2924, 2856, 1594, 1569, 1473, 1426, 1266, 1120, 1070, 784, 754, 692 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{17}H_{15}BrO$: $(M+H)^+$ 315.0384, found 315.0352.

2-(4-Phenyl-5,6-dihydro-2*H*-pyran-2-yl)-benzoic acid methyl ester (7b):



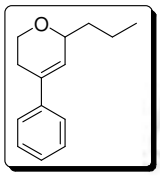
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.46-2.53 (m, 1 H), 2.73-2.82 (m, 1 H), 3.91 (s, 3 H), 3.95 (ddd, *J* = 11.6, 9.2 and 4.0 Hz, 1 H), 4.20 (ddd, *J* = 11.6, 5.2 and 3.2 Hz, 1 H), 5.36 (d, *J* = 2.4 Hz, 1 H), 6.18 (d, *J* = 2.0 Hz, 1 H), 7.26-7.44 (m, 5 H), 7.50 (d, *J* = 7.6 Hz, 2 H), 8.04 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.1, 52.2, 63.7, 76.3, 124.7, 125.0, 127.4, 127.8, 128.6, 129.7, 130.0, 135.4, 140.0, 146.6, 167.0. **IR**: 3028, 2927, 2855, 1719, 1610, 1435, 1278, 1113, 1062, 1019, 910, 753, 709, 696 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{19}H_{18}O_3$: $(M+H)^+$ 295.1334, found 295.1310.

Benzenesulfonic acid 2-(4-phenyl-5,6-dihydro-2*H*-pyran-2-yl)-phenyl ester (8b):



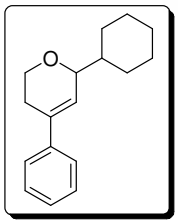
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.41-2.49 (m, 1 H), 2.68-2.78 (m, 1 H), 3.89 (ddd, *J* = 11.2, 9.2 and 4.0 Hz, 1 H), 4.14 (ddd, *J* = 11.2, 5.2 and 3.2 Hz, 1 H), 5.25 (d, *J* = 2.4 Hz, 1 H), 6.11 (d, *J* = 2.0 Hz, 1 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 7.28 (t, *J* = 7.2 Hz, 1 H), 7.32-7.36 (m, 4 H), 7.38-7.42 (m, 2 H), 7.50 (*t*, *J* = 8.4 Hz, 2 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.83 (d, *J* = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.2, 63.7, 76.1, 122.5, 124.9, 125.0, 127.9, 128.7, 128.9, 129.3, 131.6, 134.3, 135.5, 135.7, 140.0, 140.7, 149.3. **IR**: 3062, 2925, 1600, 1499, 1375, 1199, 1153, 1093, 868, 754, 687 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{23}H_{20}O_4S$: $(M+H)^+$ 393.1161, found 393.1177.

4-Phenyl-2-propyl-5,6-dihydro-2*H*-pyran (9b):



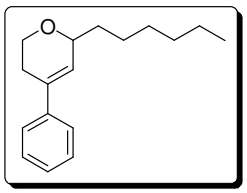
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.2 Hz, 3 H), 1.43-2.64 (m, 4 H), 2.29-2.37 (m, 1 H), 2.60-2.70 (m, 1 H), 3.76 (ddd, *J* = 10.8, 9.6 and 3.6 Hz, 1 H), 4.14 (ddd, *J* = 11.6, 5.6 and 2.8 Hz, 1 H), 4.2-4.25 (m, 1 H), 6.03-6.05 (m, 1 H), 7.23-7.41 (m, 5, H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 18.7, 27.4, 37.8, 63.8, 74.3, 124.9, 126.7, 127.4, 128.5, 134.5, 140.5. **IR**: 3058, 2959, 2871, 1645, 1447, 1361, 1269, 1128, 1095, 1060, 753, 697 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{14}H_{18}O$: M^+ 202.1358, found 202.1343.

2-Cyclohexyl-4-phenyl-5,6-dihydro-2*H*-pyran (10b):



Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.10-1.30 (m, 5 H), 1.53-1.81 (m, 6 H), 2.27-2.33 (m, 1 H), 2.60-2.70 (m, 1 H), 3.73 (dt, *J* = 10.8 and 3.2 Hz, 1 H), 4.02-4.06 (m, 1 H), 4.15 (ddd, *J* = 11.2, 5.6 and 2.0 Hz, 1 H), 6.08-6.09 (m, 1 H), 7.26 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.5, 26.7, 27.5, 27.1, 28.3, 29.0, 43.2, 64.0, 78.8, 124.8, 125.2, 127.3, 128.5, 135.1, 140.6. **IR**: 3028, 2925, 2852, 1621, 1447, 1360, 1128, 1082, 1032, 753, 698 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{17}H_{22}O$: $(M+H)^+$ 243.1749, found 243.1745.

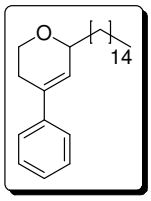
4-Phenyl-2-hexyl-5,6-dihydro-2*H*-pyran (11b):



Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.25-1.38 (m, 6 H), 1.40-1.51 (m, 2 H), 1.57-1.64 (m, 2 H), 2.29-2.37 (m, 1 H), 3.75 (ddd, *J* = 11.2, 10.0 and 3.6 Hz, 1 H), 3.75 (ddd, *J* = 11.2, 5.6 and 1.6 Hz, 1 H), 6.03-6.04 (m, 1 H), 7.23-7.41 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.9, 25.7, 27.6, 29.6, 32.0, 35.8, 63.9, 74.6, 125.0, 126.8, 127.5, 128.6, 134.6, 140.7. **IR**:

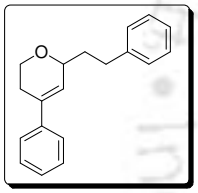
3062, 2955, 2858, 1620, 1447, 1283, 1222, 1178, 1088, 1051 760, 691 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{17}H_{24}O$: $(M+H)^+$ 245.1905, found 245.1906.

2-Pentadecyl-4-phenyl-5,6-dihydro-2*H*-pyran (**12b**):



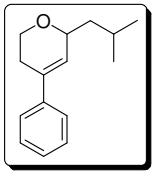
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.20-1.38 (m, 24 H), 1.41-1.51 (m, 2 H), 1.58-1.65 (m, 2 H), 2.30-2.35 (m, 1 H), 2.60-2.71 (m, 2 H), 3.76 (ddd, *J* = 11.2, 10.0 and 3.6 Hz, 1 H), 4.14 (ddd, *J* = 11.6, 6.0 and 2.4 Hz, 1 H), 4.19-4.25 (m, 1 H), 6.03-6.05 (m, 1 H), 7.24-7.28 (m, 1 H), 7.32-7.36 (m, 2 H), 7.38-7.41 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.9, 25.6, 27.5, 29.6, 29.9 (9C), 32.1, 35.8, 63.8, 74.6, 124.9, 126.7, 127.4, 128.5, 134.5, 140.5. **IR**: 2923, 2853, 1646, 1464, 1361, 1216, 1114, 1079, 1053, 751, 696 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{26}H_{42}O$: $(M+H)^+$ 371.3314, found 371.3312.

2-Phenethyl-4-phenyl-5,6-dihydro-2*H*-pyran (13b):



Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.87-1.99 (m, 2 H), 2.32-2.38 (m, 1 H), 2.64-2.88 (m, 3 H), 3.78 (ddd, *J* = 11.2, 10.0 and 4.0 Hz, 1 H), 4.19 (ddd, *J* = 11.6, 6.0 and 2.4 Hz, 1 H), 4.24-4.29 (m, 1 H), 6.04 (m, 1 H), 7.18-7.41 (m, 10 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.5, 31.7, 37.4, 63.8, 73.7, 125.0, 126.0, 126.4, 127.5, 128.5, 128.6, 128.7, 135.0, 140.5, 142.4. **IR**: 3026, 2924, 2853, 1601, 1495, 1454, 1361, 1124, 1079, 1054, 869, 750, 697 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{19}H_{20}O$: $(M+H)^+$ 265.1592, found 265.1576.

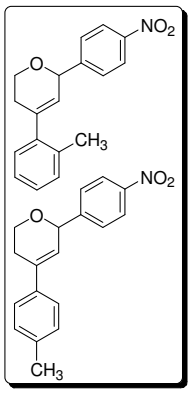
4-Phenyl-2-isobutyl-5,6-dihydro-2*H*-pyran (14b):



Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.96 (d, *J* = 6.4 Hz, 6 H), 1.31-1.38 (m, 1 H), 1.55-1.62 (m, 1 H), 1.85-1.95 (m, 1 H), 2.29-2.37 (m, 1 H), 2.60-2.69 (m, 1 H), 3.75 (ddd, 11.2, 6.0 and 4.0 Hz, 1 H), 4.14 (ddd, *J* = 11.2, 5.6 and 2.8 Hz, 1 H), 4.26-4.31 (m, 1 H), 6.00 (m, 1 H), 7.23-7.27 (m, 1 H), 7.30-7.35 (m, 2 H), 7.37-7.41 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.4, 23.6, 24.7, 27.5, 44.7, 63.7, 72.7, 124.9, 127.1, 127.4, 128.6, 134.4, 140.6. **IR**: 3032, 2924, 2867, 1600, 1466, 1446, 1364, 1106, 1076, 1059, 751, 696 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{15}H_{20}O$: M^+ 216.1514, found 216.1581.

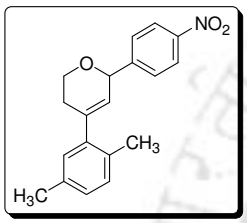
2-(4-Nitro-phenyl)-4-*o*-tolyl-5,6-dihydro-2*H*-pyran and 2-(4-Nitro-phenyl)-4-*p*-tolyl-5,6-dihydro-2H-pyran (15*o/p*):

Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.25-2.31 (m, 0.62 H), 2.31 (s, 1.85 H), 2.34 (s, 1.15 H), 2.45-2.52 (m, 0.38 H), 2.59-2.68 (m, 0.62 H), 2.69-2.80 (m, 0.38 H), 3.90-3.99 (m, 1 H),



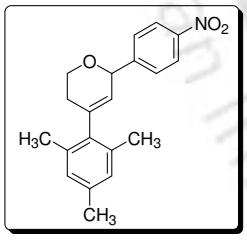
4.13-4.22 (m, 1 H), 5.36-5.38 (m, 1 H), 5.66 (d, *J* = 1.2 Hz, 0.62 H), 6.10 (d, *J* = 8.4 Hz, 0.38 H), 7.09-7.32 (m, 5 H), 7.56-7.60 (m, 2 H), 8.18-8.22 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.0, 21.6, 27.2, 29.9, 63.8, 75.5, 75.9, 122.2, 123.0, 123.9, 124.9, 125.8, 125.9, 126.1, 127.5, 128.0, 128.1, 128.6, 128.8, 129.4, 130.5, 134.8, 138.7, 141.7, 147.6, 149.1. **IR**: 2926, 2858, 1601, 1520, 1348, 1267, 1108, 1060, 855, 753, 702 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{18}H_{17}NO_3$: M^+ 295.1208, found 295.1261.

4-(2,5-Dimethyl-phenyl)-2-(4-nitro-phenyl)-5,6-dihydro-2*H*-pyran (16):



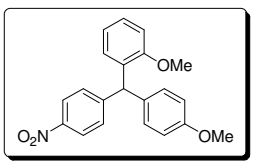
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.26 (s, 3 H), 2.31 (m, 3 H), 2.59-2.75 (m, 1 H), 3.97 (ddd, J = 11.6, 9.2 and 4.0 Hz, 1 H), 4.15 (ddd, J = 11.2, 5.2 and 3.2 Hz, 1 H), 5.39 (d, *J* = 2.4 Hz, 1 H), 5.56 (d, *J* = 2.0 Hz, 1 H), 6.93 (s, 1 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 7.60 (d, *J* = 8.8 Hz, 2 H), 8.23 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.6, 21.0, 29.9, 63.8, 75.5, 123.9, 125.9, 128.0, 128.2, 128.8, 130.4, 131.6, 135.4, 138.7, 141.5, 147.5, 149.1. **IR**: 2961, 2857, 1606, 1522, 1347, 1267, 1118, 1059, 848, 701, 667 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{19}H_{19}NO_3$: M^+ 309.1365, found 309.1360.

2-(4-Nitro-phenyl)-4-(2,4,6-trimethyl-phenyl)-5,6-dihydro-2*H*-pyran (17):



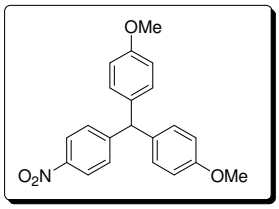
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.09-2.16 (m, 1 H), 2.18 (s, 3 H), 2.25 (s, 3 H), 2.27 (s, 3 H), 2.49-2.58 (m, 1 H), 3.99 (ddd, *J* = 11.6, 9.2 and 4.0 Hz, 1 H), 4.19 (ddd, *J* = 10.8, 5.2 and 2.8 Hz, 1 H), 5.39 (d, *J* = 2.4 Hz, 1 H), 5.56 (d, *J* = 1.6 Hz, 1 H), 6.86 (s, 1 H), 6.89 (s, 1 H), 7.60 (d, *J* = 8.8 Hz, 2 H), 8.23 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.8, 19.9, 21.1, 29.3, 63.9, 75.7, 124.0, 126.1, 128.0, 128.5, 128.5, 135.1, 135.2, 136.9, 137.7, 138.2, 147.6, 149.2. **IR**: 2922, 2855, 1603, 1523, 1347, 1118, 1055, 853, 701 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{20}H_{21}NO_3$: $(M+H)^+$ 323.1521, found 323.1557.

Triarylmethane (18*o*):



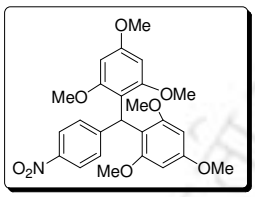
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.71 (s, 3 H), 3.79 (s, 3 H), 5.91 (s, 1 H), 6.79-6.90 (m, 6 H), 6.97 (d, *J* = 8.4 Hz, 2 H), 7.22-7.27 (m, 2 H), 8.10 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 49.2, 55.5, 55.7, 111.0, 114.1, 120.7, 123.6, 128.4, 130.1, 130.2, 130.6, 131.6, 134.4, 146.6, 152.6, 157.1,158.5. **IR**: 2930, 2837, 1605, 1511, 1490, 1346, 1245, 1179, 1030, 828, 755 cm^{-1}.

Triarylmethane (18*p*):



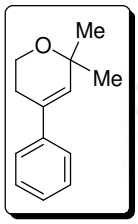
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.78 (s, 6 H), 5.53 (s, 1 H), 6.83 (d, *J* = 8.8 Hz, 4 H), 6.98 (d, *J* = 8.4 Hz, 4 H), 7.26 (d, *J* = 8.8 Hz, 2 H), 8.11 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, CDCl3): δ 55.1, 55.2, 55.3, 114.1, 123.6 130.1 130.3, 134.9, 146.4, 152.5, 158.5. **IR**: 2995, 2837, 1607, 1583, 1505, 1463, 1345, 1250, 1178, 1034, 1015, 823, 740, 566 cm^{-1}.

Triarylmethane (19):



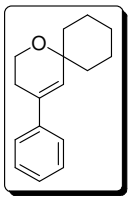
Solid; M. P. 149.7-150.7 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.52 (s, 12 H), 3.79 (s, 6 H), 6.11 (s, 4 H), 6.27 (s, 1 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 8.00 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 37.4, 55.4, 56.0, 91.6, 112.4, 122.7, 128.5, 145.1, 155.0, 159.6, 159.7. **IR**: 2997, 2938, 2837, 1594, 1506, 1492, 1334, 1203, 1122, 1060, 1040, 952, 812, 737 cm^{-1}.

2,2-Dimethyl-4-phenyl-5,6-dihydro-2*H*-pyran (20):



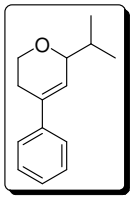
Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.34 (s, 6 H), 2.45 (dt, *J* = 5.2, 1.6 Hz, 2 H), 3.94 (t, *J* = 5.2 Hz, 2 H), 6.00 (s, 1 H), 7.23-7.27 (m, 1 H), 7.32-7.35 (m, 2 H), 7.37-7.41(m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.2, 27.8, 59.9, 72.4, 125.0, 127.4, 128.5, 131.2, 132.9, 140.6. **IR**: 2972, 2863, 1669, 1357, 1274, 1159, 1095, 876, 752, 694 cm^{-1}. **HRMS** (APCI) *m/z* calcd for C13H16O: $(M+H)^+$ 189.1279, found 189.1254.

4-Phenyl-1-oxaspiro[5.5]undec-4-ene (21):



Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25-1.36 (m, 2 H), 1.45-1.55 (m, 4 H), 1.60-1.69 (m, 2 H), 1.70-1.78 (m, 2 H), 2.46 (dt, *J* = 5.2 and 1.6 Hz, 2 H), 3.91 (t, *J* = 5.6 Hz, 2 H), 6.04 (s, 1 H), 7.23-7.27 (m, 1 H), 7.31-7.35 (m, 2 H), 7.38-7.41 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.9, 25.8, 27.7, 35.8, 59.2, 73.0, 125.1, 127.4, 128.6, 131.1, 133.4, 140.9. **IR**: 2931, 2857, 1644, 1445, 1358, 1177, 1092, 909, 748, 693 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{16}H_{20}O$: M^+ 228.1514, found 228.1512.

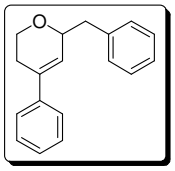
4-Phenyl-2-isopropyl-5,6-dihydro-2*H*-pyran (25):



^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J* = 6.8 Hz, 6 H), 1.82-1.93 (m, 1 H), 2.27-2.40 (m, 1 H), 2.60-2.71 (m, 1 H), 3.73 (dt, *J* = 10.4 and 3.2 Hz, 1 H), 4.00-4.06 (m, 1 H), 4.16 (ddd, *J* = 10.8, 5.6 and 1.6 Hz, 1 H), 6.10 (m, 1 H), 7.24-7.28 (m, 1 H), 7.30-7.36 (m, 2 H), 7.38-7.42 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 18.1, 18.6, 27.7, 33.3, 64.2, 79.4, 125.0 (2C), 127.5, 127.7, 135.6, 140.8. **IR**: 2960, 2853, 1645, 1494, 1363,

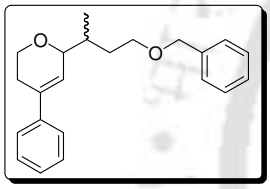
1115, 1089, 880, 751, 699 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{14}H_{18}O$: $(M+H)^+$ 203.1436, found 203.1431.

2-Benzyl-4-phenyl-5,6-dihydro-2*H*-pyran (26):



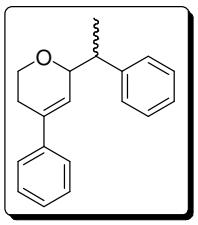
Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.30-2.37 (m, 1 H), 2.61-2.70 (m, 1 H), 2.83 (dd, *J* = 13.2 and 6.4 Hz, 1 H), 3.00 (dd, *J* = 13.6 and 7.2 Hz, 1 H), 3.76 (ddd, *J* = 11.2, 9.6 and 4.0 Hz, 1 H), 4.15(ddd, *J* = 11.2, 5.6 and 2.8 Hz, 1 H),4.45-4.50 (m, 1 H), 6.04 (m, 1 H), 7.22-7.37 (m, 10 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.4, 42.2, 63.8, 75.6, 125.1, 125.5, 125.6, 126.6, 127.6, 128.6, 129.7, 135.2, 138.4, 140.5. **IR**: 2956, 2856, 1603, 1495, 1361, 1126, 1078, 1029, 752, 699 cm-1. **HRMS** (APCI) *m/z* calcd for $C_{18}H_{18}O$: $(M+H)^+$ 251.1436, found 251.1427.

2-(3-Benzyloxy-1-methyl-propyl)-4-phenyl-5,6-dihydro-2*H*-pyran (27):



Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.8 Hz, 1.8 H), 0.99 (d, *J* = 6.8 Hz, 1.2 H), 1.47-1.60 (m, 1.8 H), 1.84-2.00 (m, 2.2 H), 2.23-2.27 (m, 1 H), 2.60-2.70 (m, 1 H), 3.48-3.58 (m, 2 H), 3.65-3.74 (m, 1 H) 4.12-4.17 (m, 2 H), 4.44-4.53 (m, 2 H), 6.00 (bs, 0.6 H), 6.10 (bs, 0.4 H), 7.24-7.39 (m, 10 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.8, 16.0, 27.5, 31.9, 32.9, 35.1, 35.2, 64.2, 64.3, 68.8, 68.9, 72.9, 23.0, 77.9, 78.7, 124.9, 125.3, 127.4, 127.6, 127.7, 127.8, 128.5, 128.5, 135.6, 135.8, 138.8, 140.5. **IR**: 2962, 2871, 1645, 1453, 1364, 1111, 1089, 752, 697 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{22}H_{26}O_2$: M^+ 322.1933, found 322.1979.

2-(1-Phenyl-ethyl)-4-phenyl-5,6-dihydro-2*H*-pyran (28):

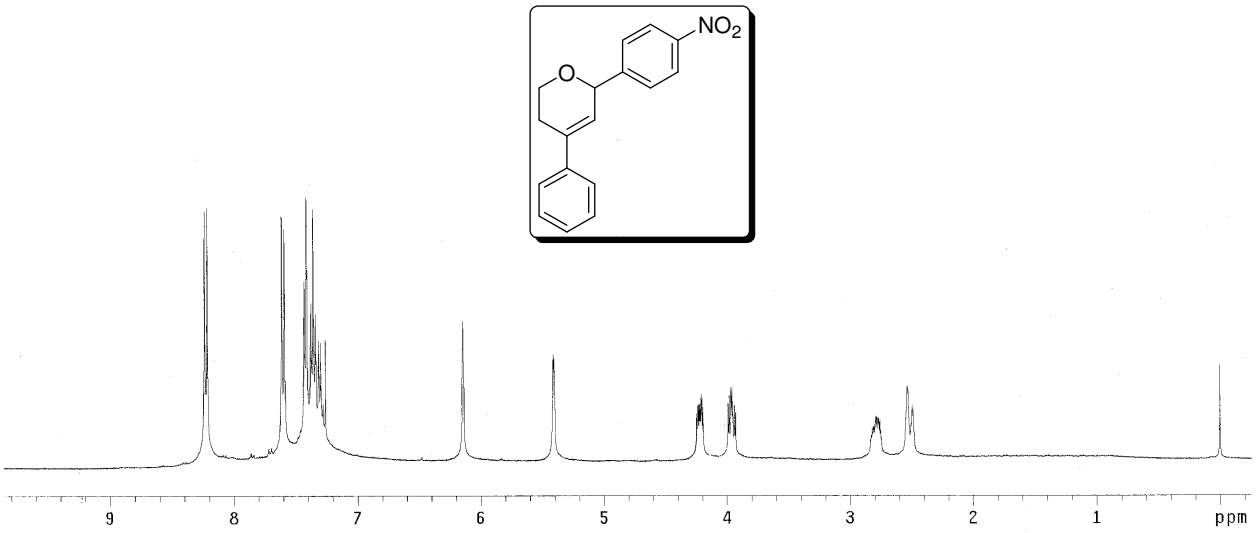


Liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33 (d, *J* = 6.8 Hz, 1.5 H, -CH3), 1.38 (d, *J* = 6.8 Hz, 1.5 H, -CH3), 2.22-2.34 (m, 1 H), 2.55-2.65 (m, 1 H), 2.90 (p, *J* = 6.8 Hz, 0.5 H), 3.12 (dt, *J* = 6.8 and 1.2 Hz, 0.5 H), 3.67-3.77 (m, 1 H), 4.11-4.18 (m, 1 H), 4.29-4.33 (m, 0.5 H), 4.39-4.43 (m, 0.5 H), 5.87 (d, *J* = 0.8 Hz, 0.5 H), 6.02(d, *J* = 1.6 Hz, 0.5 H), 7.20-7.26 (m, 2 H, ArH), 7.28-7.34 (m, 8 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.7, 17.5, 27.3, 27.4, 44.3, 45.3, 63.8, 64.1, 78.9, 79.0, 123.6, 124.9, 125.0, 125.3, 126.5, 126.6, 127.4, 128.2, 128.4, 128.5, 135.2, 136.1, 140.5, 140.6, 143.6, 144.3; **IR**: 2964, 2853, 1600, 1494, 1361, 1135, 1076, 1017, 751, 700 cm^{-1}. MS: (CI) *m/z* 266

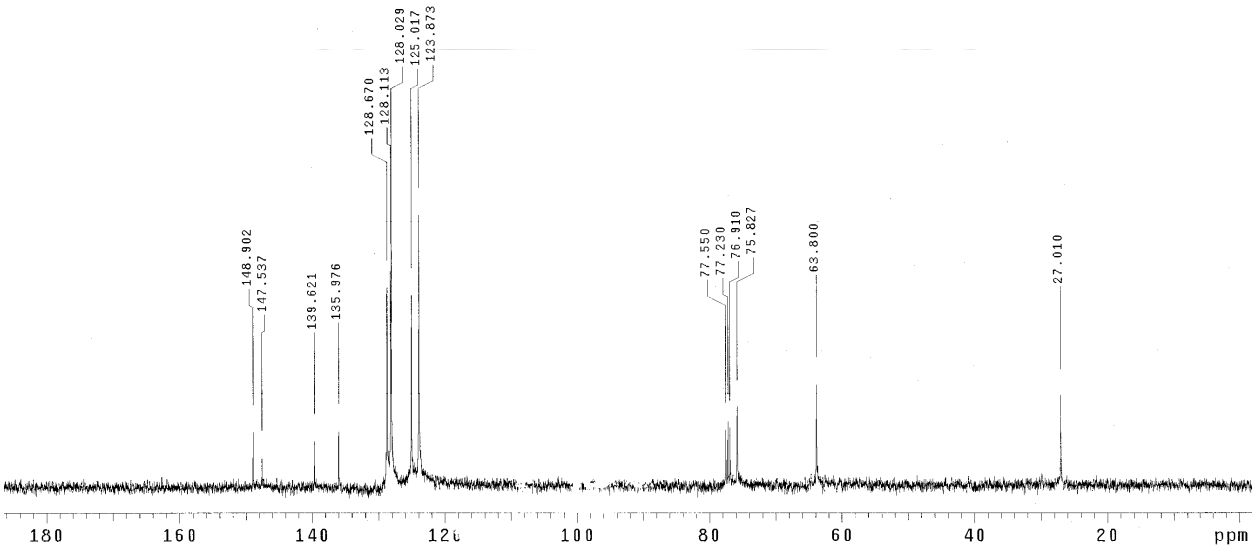
5.8 Selected Spectra of 4-Aryldihydropyrans

4-Phenyl-2-(4-nitro-phenyl)-5,6-dihydro-2*H*-pyran (2b):

^{1}H NMR (400 MHz, $CDCl_3$)

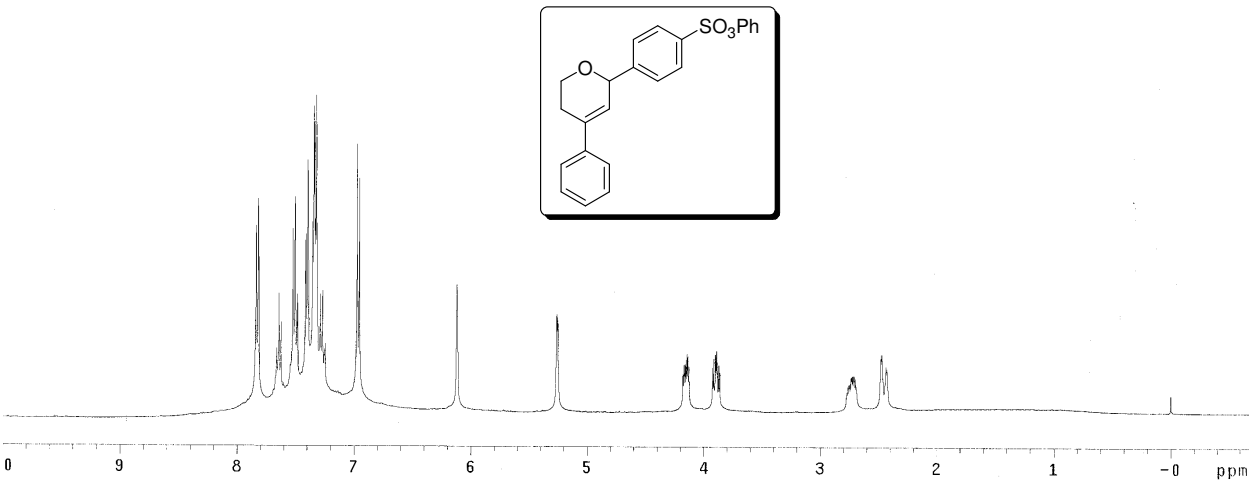


^{13}C NMR (100 MHz, $CDCl_3$)

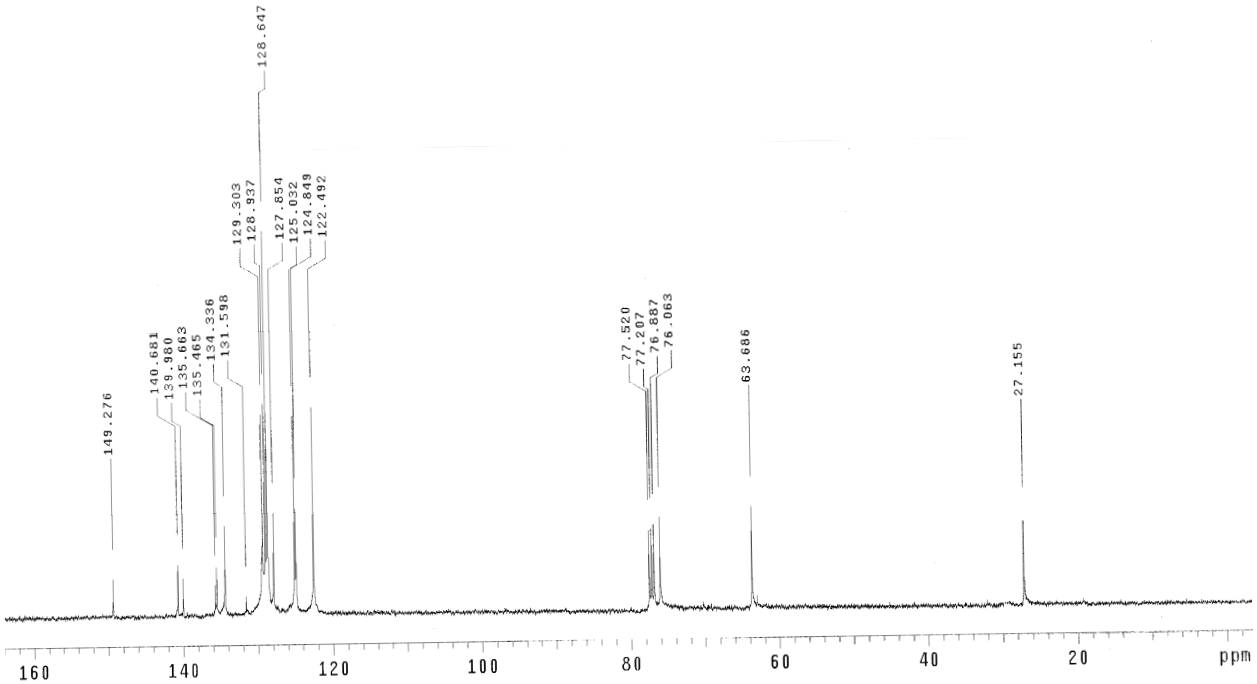


Benzenesulfonic acid 2-(4-phenyl-5,6-dihydro-2*H*-pyran-2-yl)-phenyl ester (8b):

^{1}H NMR (400 MHz, $CDCl_3$)

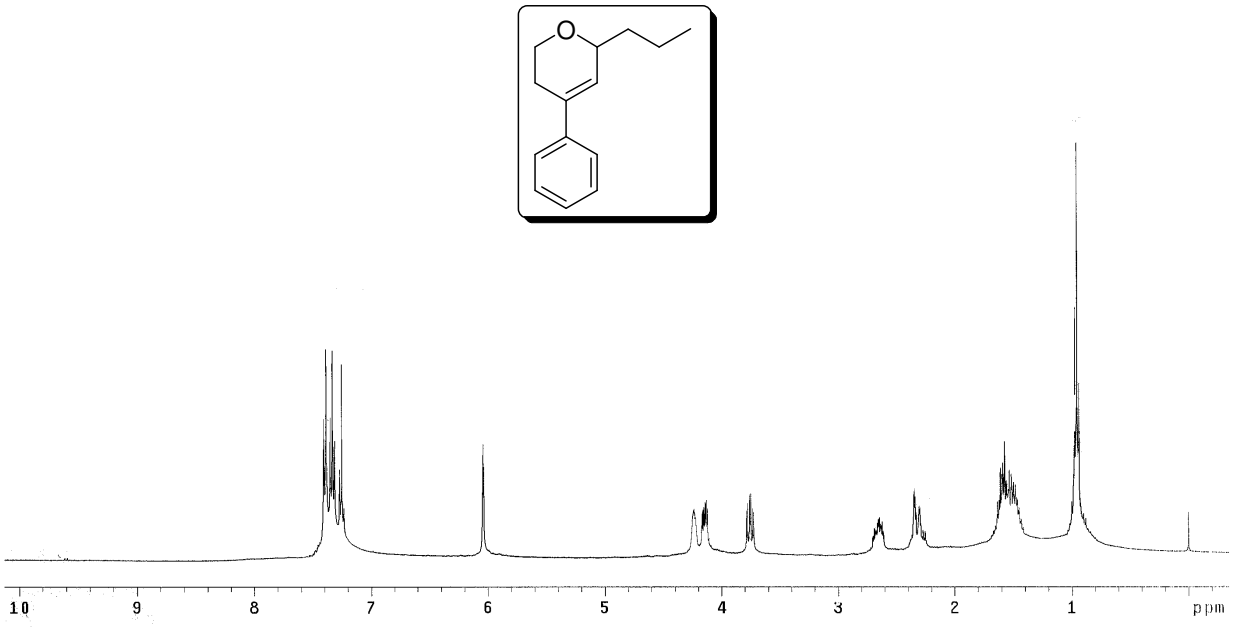


^{13}C NMR (100 MHz, $CDCl_3$)

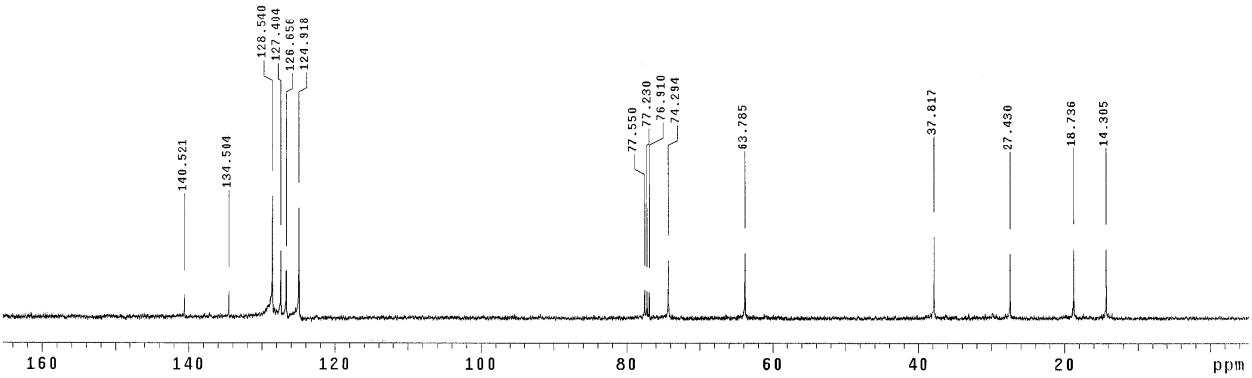


4-Phenyl-2-propyl-5,6-dihydro-2*H*-pyran (9b):

^{1}H NMR (400 MHz, $CDCl_3$)

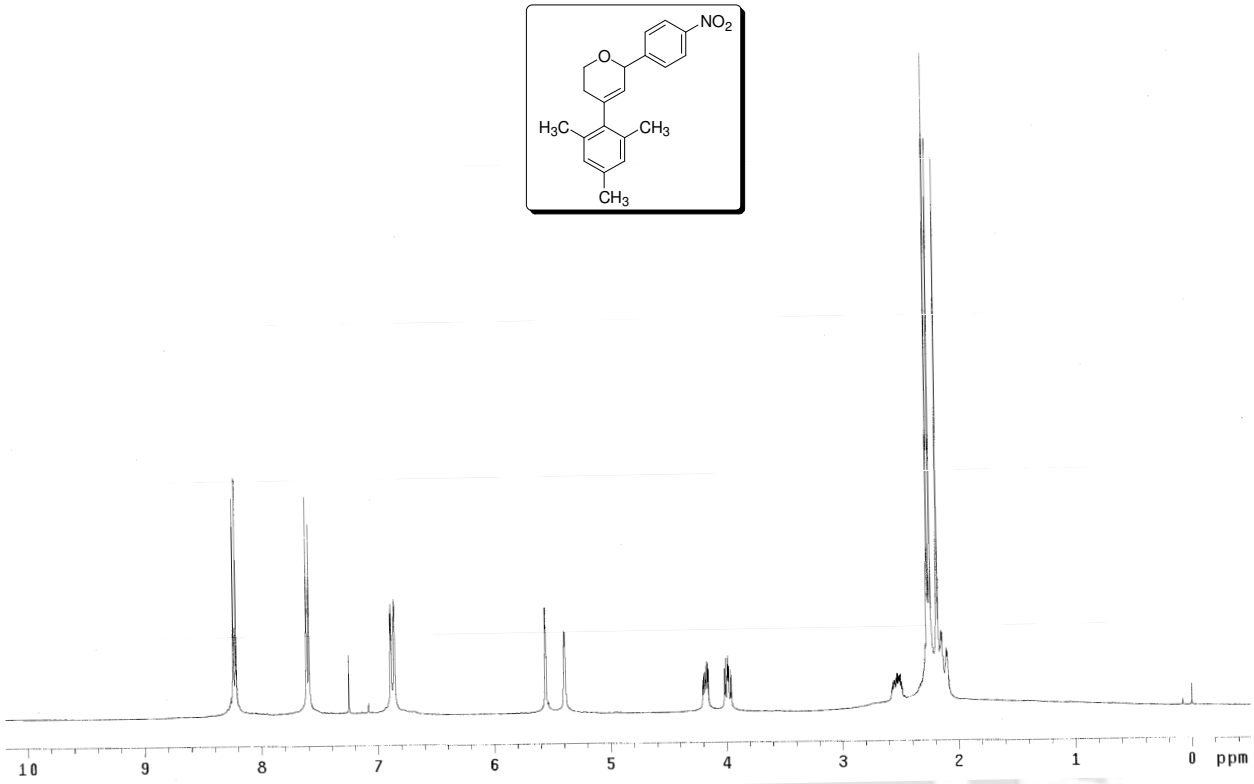


^{13}C NMR (100 MHz, $CDCl_3$)

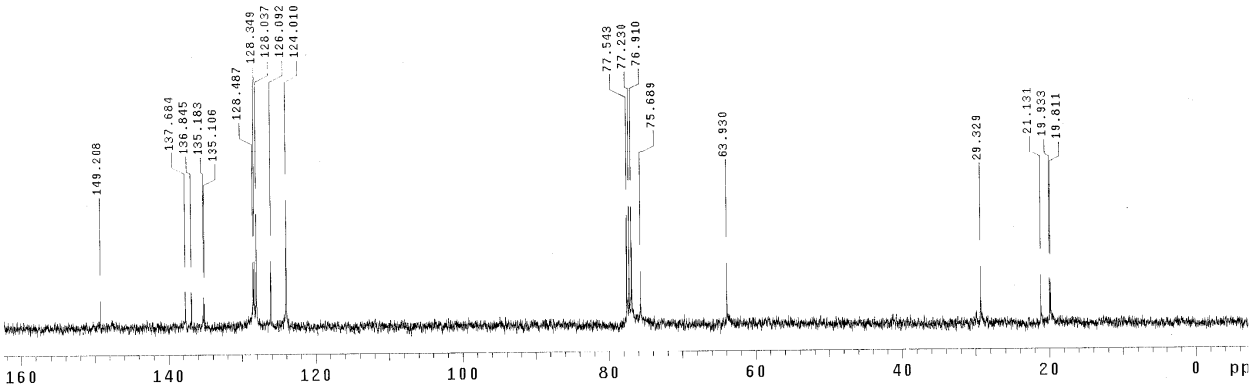


2-(4-Nitro-phenyl)-4-(2,4,6-trimethyl-phenyl)-5,6-dihydro-2*H*-pyran (17):

^{1}H NMR (400 MHz, $CDCl_3$)

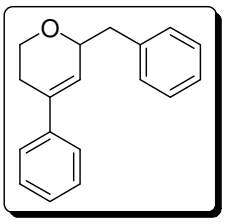


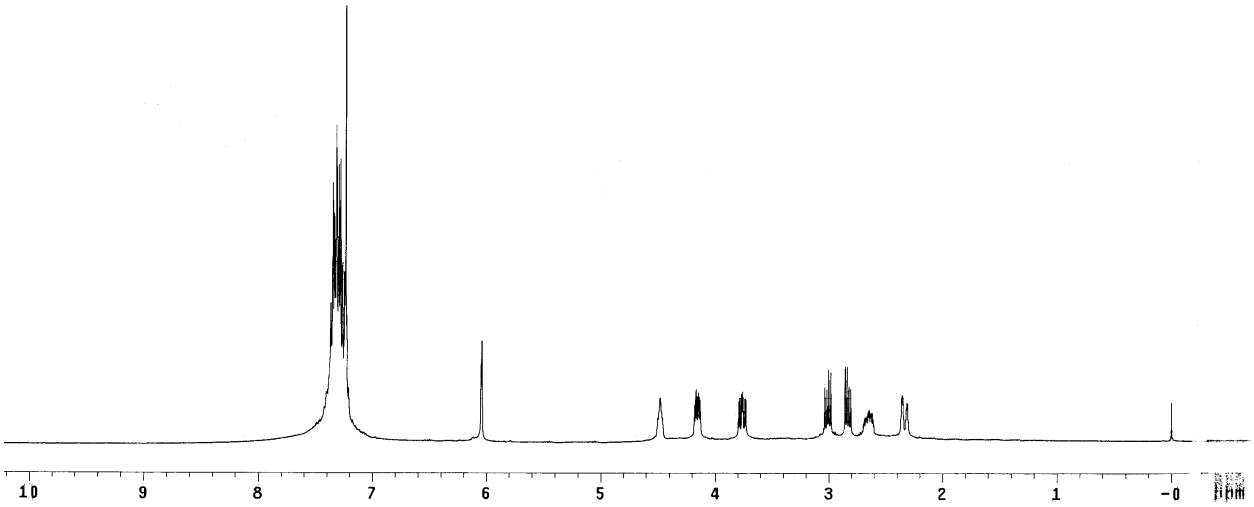
^{13}C NMR (100 MHz, $CDCl_3$)



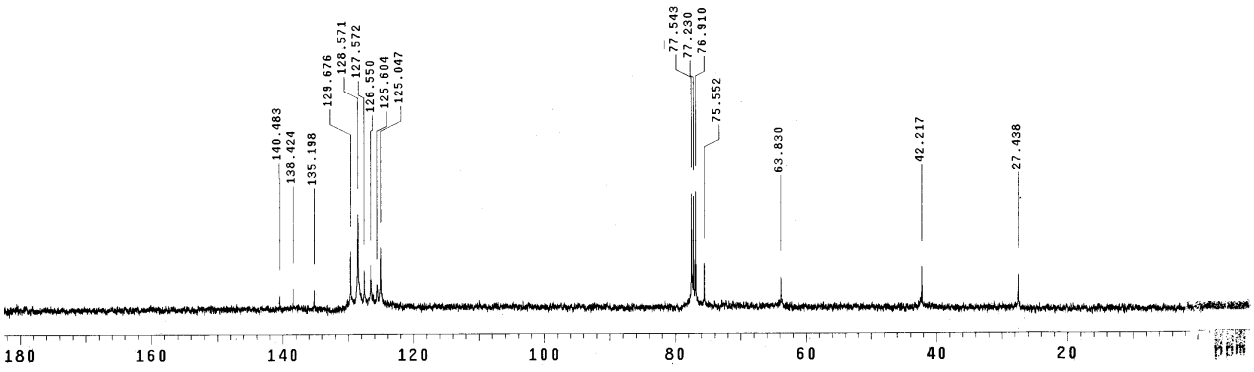
2-Benzyl-4-phenyl-5,6-dihydro-2*H*-pyran (26):

^{1}H NMR (400 MHz, $CDCl_3$)





^{13}C NMR (100 MHz, $CDCl_3$)



List of Publications

1) "Stereoselective One-Pot, Three-Component Synthesis of 4-Amidotetrahydropyrans" **Reddy, U. C.**; Raju, B. R.; Kumar, E. K. P.; Saikia, A. K. *J. Org. Chem.* **2008**, *73*, 1628–1630.
2) "A Stereoselective One-Pot, Three-Component Synthesis of 4-Aryltetrahydropyrans via Prins-Friedel-Crafts Reaction" **Reddy, U. C.**; Bondalapati, S.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605-608.
3) "Stereoselective Synthesis of 2,6-Disubstituted-4-Aryltetrahydropyrans Using Sakurai–Hosomi–Prins–Friedel–Crafts Reaction" **Reddy, U. C.**; Bondalapati, S.; Saikia, A. K. *Eur. J. Org. Chem.* **2009**, 1625–1629.
4) "Cerium(IV) triflate-catalyzed selective oxidation of sulfides to sulfoxides with aqueous hydrogen peroxide" Raju, B. R.; Sarkar, S.; **Reddy, U. C.**; Saikia, A. K. *J. Mol. Catal. A: Chem.* **2009,** *308,* 169-173.
5) "Titanium tetrafluoride: An efficient Lewis acid and fluorinating agent for stereoselective synthesis of 4-fluorotetrahydropyrans" Bondalapati, S.; **Reddy, U.C.;** Kundu D.S.; and Saikia A. K. *J. Fluor. Chem.* **2010,** *131*, 320-324.
6) "One-Pot, Three-Component Synthesis of 4-Aryl-5,6-dihydropyrans via Prins–Friedel–Crafts Reaction" **Reddy, U. C.**; Saikia, A. K. *Synlett.* **2010,** 1027-1032.
7) "A Novel Synthesis of Oxabicyclo-[3.3.1]-nonanone via (3,5)-Oxonium-Ene Reaction" Saha, P; **Reddy, U. C.;** Bondalapati, S.; Saikia A. K. *Org. Lett.*, **2010,** *12*, 1824-1826.
8) "An Efficient Synthesis of 2,3-dihydropyran and 4-methylene tetrahydropyran via Oxonium-Ene Cyclization Reaction" Bondalapati, S.; **Reddy, U. C.**; Saha, P.; Saikia, A. K. (*communicated*).