Recent Studies of Stereoselective Synthesis of Dihydropyran Tetrahydropyran-4-Ones Using Vinyl Compound Via Prins Cyclization

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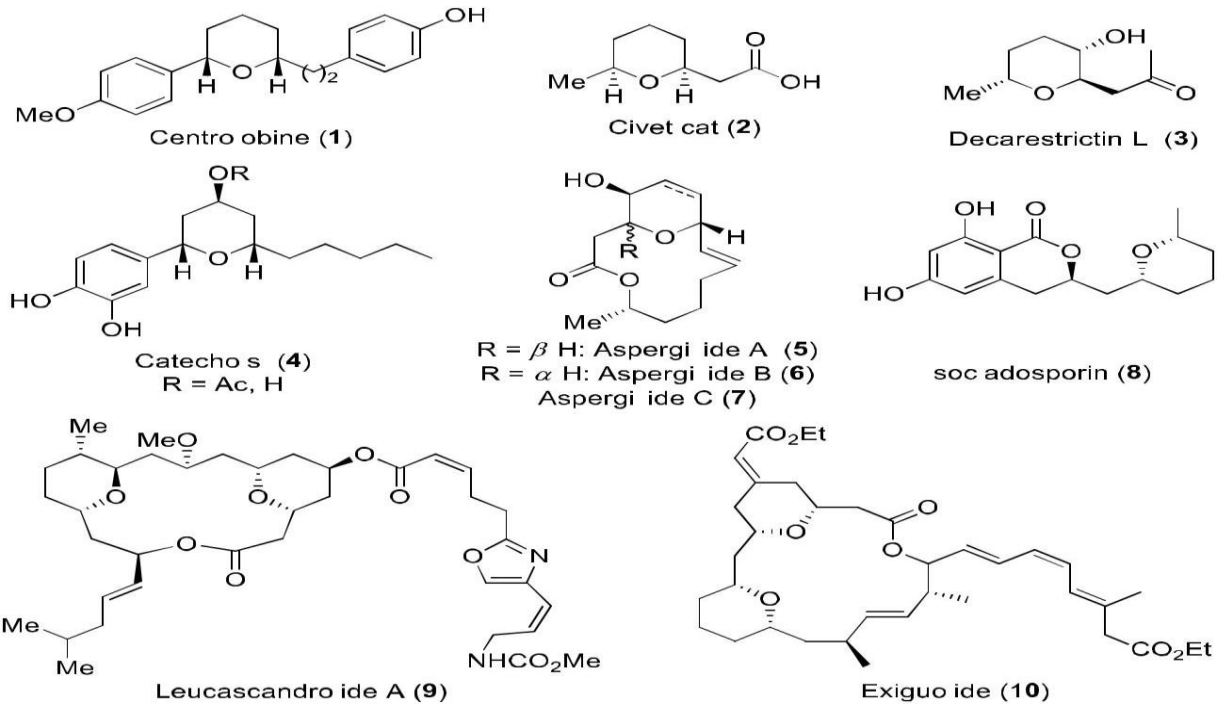
1. INTRODUCTION

The tetrahydropyrans (THPs), dihydropyrans (DHPs) and tetrahydropyran-4-ones (THPOs) are ubiquitous in nature. They form part structures of many important bioactive cyclic ether natural products.[1] For example, substituted THPs form core structure of centrolobine (**1**), civet cat (**2**), leucascandrolide A (**9**), where as DHP is core structure aspergillide C (**7**) (Fig.1). Traditionally, cyclic ethers are most commonly prepared by Williamson's etherification involving C-O bond formation. While useful, this method has several limitations due to harsh reaction conditions one needs to employ. Over the last three decades, synthesis of cyclic ethers using C-C bond formation as a key step to close the ring has emerged as a complementary approach. Amongst these, those which generate C=C functionality are particularly attractive as they give scope for further functionalization of cyclic ether rings.[2]

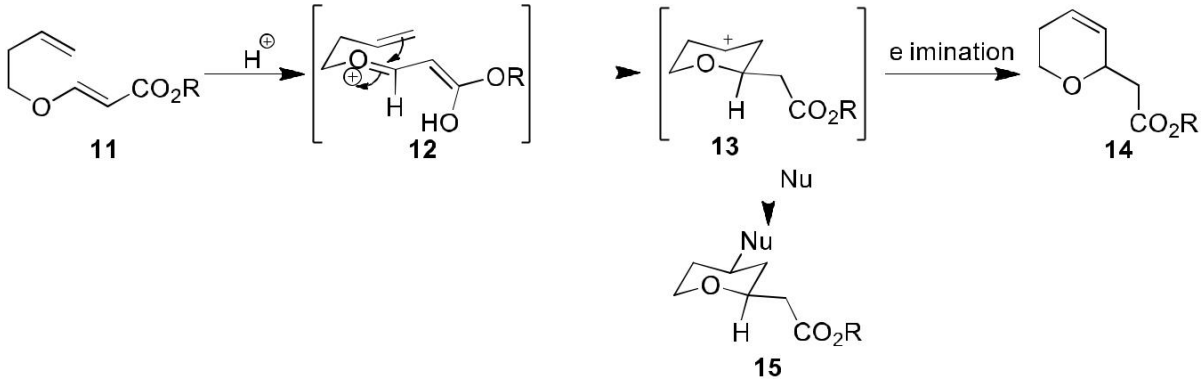


2 ACID CATALYSED PRINS CYCLIZATION

In this context,Prins type cyclization is one of the most popular approaches for the synthesis of THP and DHP derivatives. Over the years, a variety of approach have been studied for gaining access to oxonium ion required in the Prins cyclization. To keep the present work inperspective, a brief account of the synthesis of cyclic ethers using olefin Prins type cyclization of an oxonium ion generated from a vinylogous carbonate is described here.

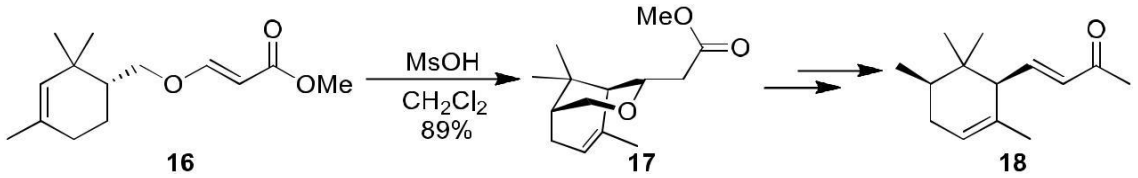
Vinylogous carbonates have been shown to give access to oxonium ions under the influence of Lewis and Bronsted acids. Intramolecular trapping of these oxonium ions thus generated with appropriate nucleophiles lead to cyclic ethers. One important example of this type of cyclization is Prins cyclization which involves an oxonium ion **12** formed from (alk-3-enyloxy)acrylate**11** upon treatment with acid by protonation of the carbonyl oxygen-atom. Direct protonation of the enol ether C=C bond is also possible but energetically less favourable. The oxonium ion **12** cyclizes to the carbenium ion **13**, which is either trapped by a nucleophile -to afford 2,4-disubstituted THP **15** or undergoes elimination to result in the formation of a 3,6-dihydro-2H-pyran **14** (Scheme 1).[3]

Scheme 1



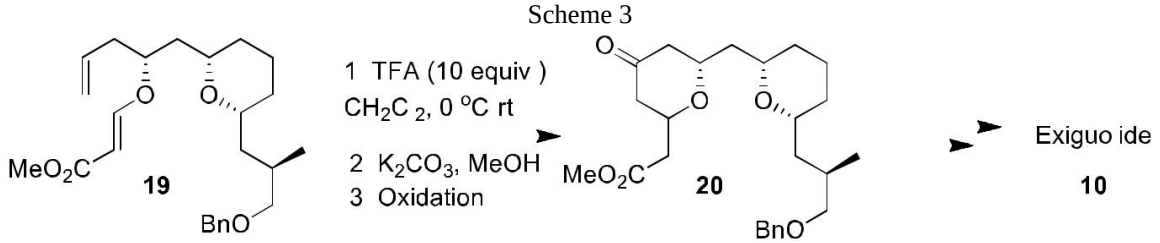
The Prins cyclization was first employed in a stereoselective synthesis of the orris odorant (±)-*cis*-□-irone**18**. The vinylogous carbonate **16** when treated with catalytic amount of methane sulphonic acid resulted in the formation of the THP derivative **17**which was further transformed into (±)-*cis*-□-irone**18** (Scheme 2).[4]

Scheme 2



The trifluoroacetic acid-mediated Prins cyclization followed by subsequent hydrolysis of the trifluoroacetate has been widely applied in natural product syntheses. These experimental conditions were applied by Lee and co-workers on the vinylogous carbonate **19** for the synthesis of THP derivative **20** in the total synthesis of exiguolide**10** (Scheme 3).[5]

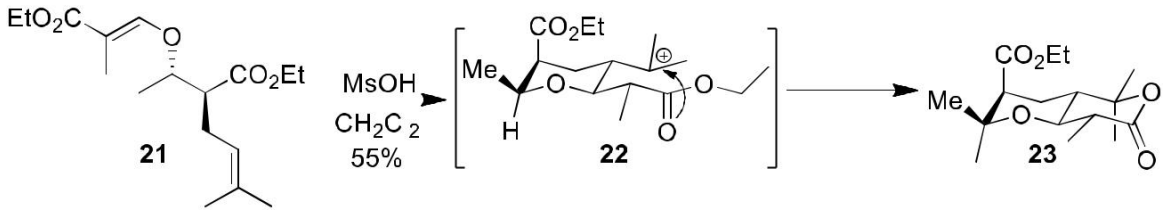
Scheme 3



Frater *et al.* used geminally dimethyl-substituted C=C bond tethered vinylogous carbonate **21** for Prins cyclization, expecting the oxonium ion generated in the reaction to cyclize in such a way that the tertiary

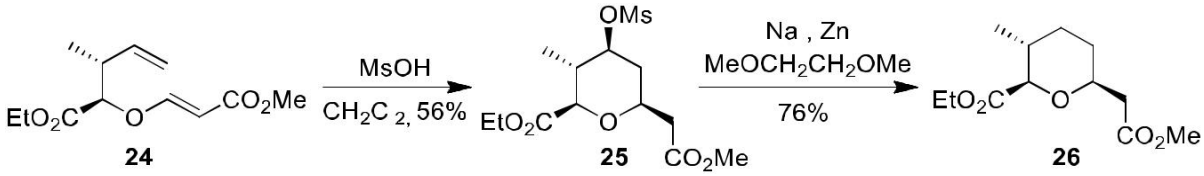
carbocation **22** would be formed, which could further react intramolecularly with the ester moiety. Indeed, the reaction proceeded as expected with threefold excess of MsOH at room temperature for 3 days and the bicyclic-pyranolactone**23** was obtained in 55% yield (Scheme 4).[4]

Scheme 4



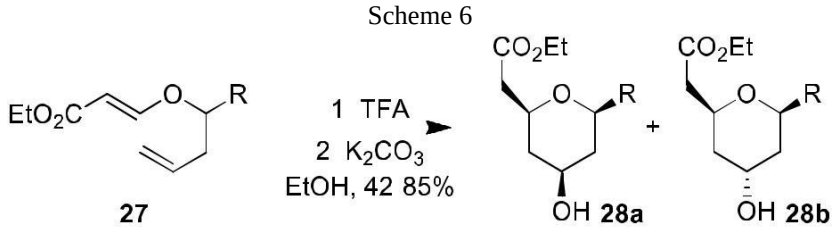
Vinylogous carbonate **24** upon reaction with excess of MsOH at room temperature was shown to give the tetrahydro-2H-pyran **25**. The diastereoselective synthesis of the pyran diester **26** was completed by reductive removal of the methylsulfonyl group of with NaI/Zn in 1,2-dimethoxyethane at room temperature (Scheme 5).[4]

Scheme 5



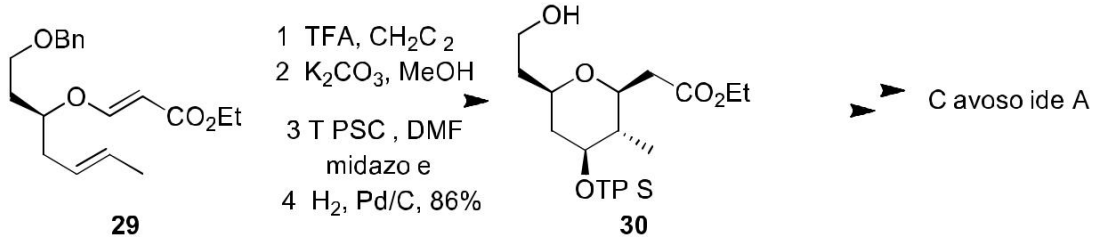
Hart*et al.* developed the synthesis of 4-hydroxy-tetrahydropyrans **28** using Prins type cyclization of the vinylogous carbonates **27** followed by hydrolysis. Diastereoselectivities ranged from ≥ 19:1 to 1:1 depending on the nature of the substituents (Scheme 6).[6]

Scheme 6



The first total synthesis of clavosolide A, isolated from *Myriastraclavosa*marine sponge, was reported by Willis and co-workers.[7] Their strategy was based on the construction of the central tetrahydropyranic unit **30** *via*Prins cyclization of the alkoxyacrylate**29**. The latter proved again to be highly effective to introduce three additional stereogenic centres with complete stereocontrol. The key subunit **30** was dimerized after functional-group interconversions to set up the lateral chains in thetotal synthesis of clavosolide A (Scheme 7).[8]

Scheme 7



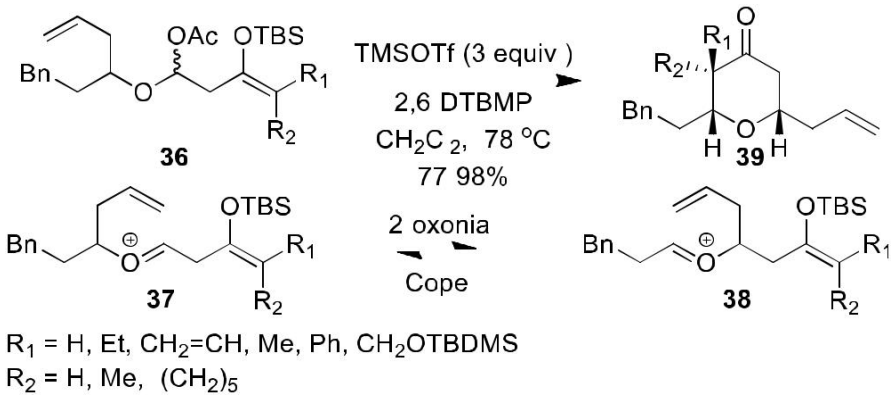
2.1 Prins cyclization involving heteroatom substituted double bonds

More nucleophilic than simple alkenes, functionalized double bonds like enol ethers, ene-carbamates, allylsilanes and vinylsilanes have also been shown to

be excellent partners in Prins cyclization. Depending on the nature of the double bond, the reaction can lead to pyranones, DHPs or methylenetetrahydropyrans.

A general route to tetrahydropyranones**39** using enol ethers **36** was devised by Rychnovsky.[9] The oxonium ions **37** and **38** generated from acetoxyethers**36** were shown to be in equilibrium owing to an oxonia-Cope rearrangement (Scheme 10).

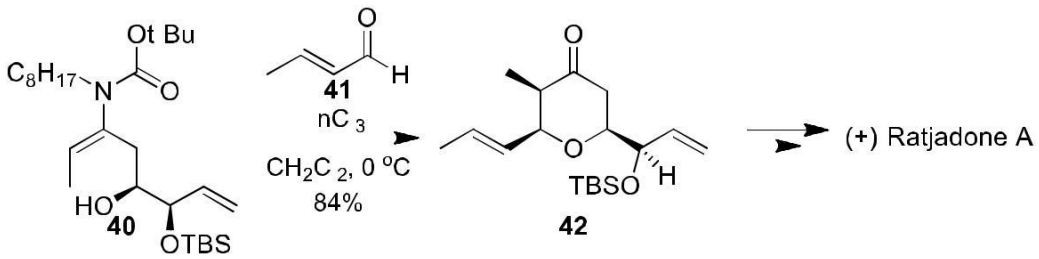
Scheme 10



The Prins cyclization process involving the enol ether moiety is much faster than that involving the terminal alkene. The reaction proceeds, *via* the former, to give the pyranone. It must be emphasized that the tandem oxonia-Cope-Prins cyclization pathway implies inversion of the stereogeniccenter.

Funk and co-workers showed that the ene-carbamate**40** can participate in a Prins cyclization leading to the synthesis of 2,3,6-*cis*,*cis*-tetrahydropyran-4-one **42**.[10] The ene-carbamate moiety of **40** reacted much faster than the olefin. The higher diastereoselectivity observed was attributed to the preferred *E* configuration of the ene-carbamate and from the favoured chair transition state for the cyclization of the oxocarbenium ion. Further transformations on the pyranone**42** lead to a formal synthesis of (+)-ratjadone A (Scheme 11).

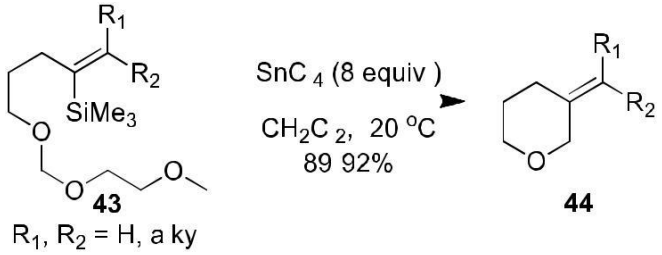
Scheme 11



Overman was the first to investigate the intramolecular cyclization of vinylsilanes**43** with MEM acetal derived oxonium ions in the presence of SnCl4 which led to alkylidene THP derivatives **44** (Scheme 12).[11]

Similarly, Speckamp and co-workers have reported the intramolecular cyclization of vinyl silane onto □-acetoxyethers.[12]

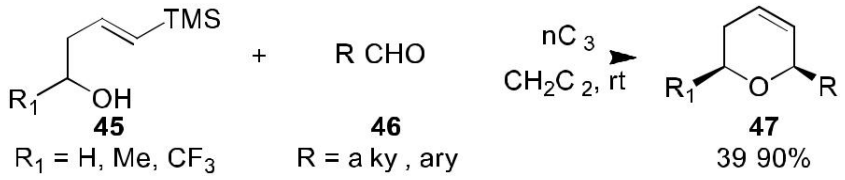
Scheme 12



Dobbs and Martinovic have extended the silyl-Prins methodology to various aldehydes (Scheme 13).[13] The reaction can be carried out at room temperature, in the presence of indium trichloride that can be used either in a stoichiometric or catalytic amount. As in the previously cited Li's report, these authors have shown

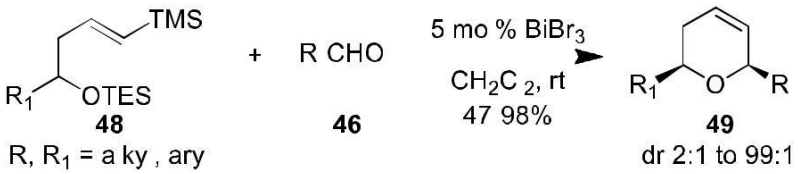
that the use of an epoxide as starting material is an alternative of an aldehyde.

Scheme 13



The silyl-Prins methodology was also adapted by Hinkle in the synthesis of DHPs **49** using □-triethylsilyloxy-vinyltrimethylsilanes**48** and aldehydes **46** in the presence of BiBr3 as the catalyst (Scheme 14).[14] Both the diastereoselectivity and yield depended strongly on the structure of the aldehyde. While aliphatic aldehydes gave generally good to high diastereoselectivity and yield, aromatic aldehydes showed variations depending on the substitutions of the aryl ring. In a similar approach, Furman *et al.* demonstrated that (*Z*)-vinylstannanes too participated in a highly diastereoselective Prinscyclizations*en route* to 2,6-disubstituted dihydropyrans.[15]

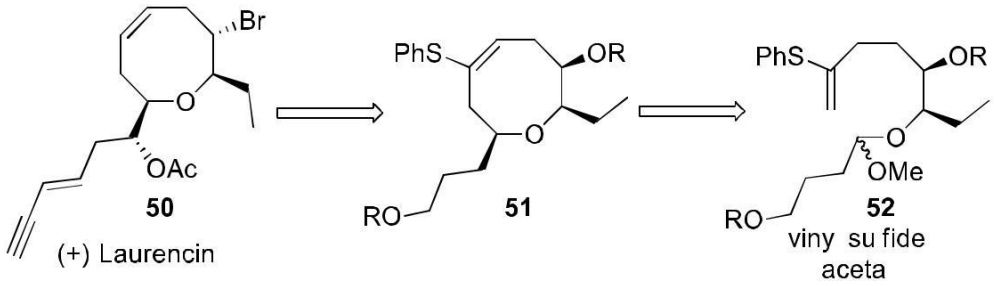
Scheme14



2.2 Prins cyclization involving vinyl sulfide

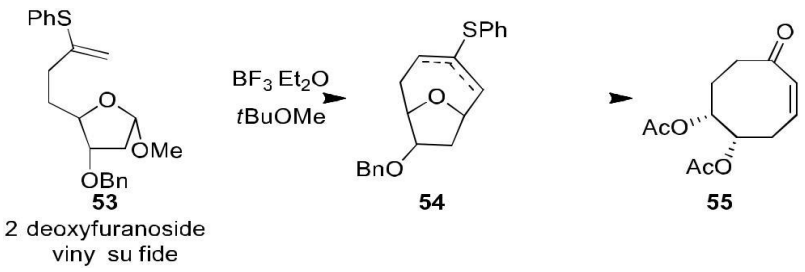
In their total synthesis of (+)-Laurencin **50**, Overman and co-workers used Prins cyclization of acetal**52** to generate the eight membered cyclic ether **51**. The reaction relied on using vinyl sulfide moiety of **52** as nucleophile whereas the oxonium ion was obtained from the acetal moiety (Scheme 15).[16]

Scheme 15



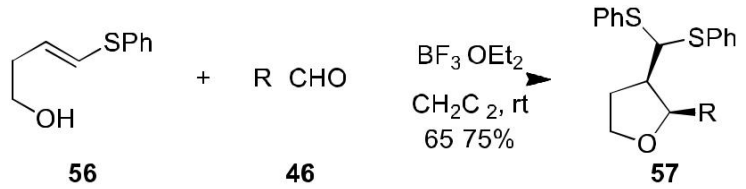
Maier group observed that the oxonium ion generated from the acetal**53**in the presence of Lewis acid participated in a Prins type of cyclization with the vinyl sulfide moiety to furnish the bicyclic product **54** (Scheme 16).[17] The bicyclic ether derivative **54** was elaborated to the ketone **55**. While this is an interesting approach, installation of vinyl sulfide group may require lengthy reaction sequence. Further, in many a cases regioselectivity of the vinyl sulfide formation is poor.

Scheme 16



Reddy *et al*. demonstrated a method for coupling of aldehydes **46** with 4-(phenylthio)but-3-en-1-ol **56** in the presence of BF3˙OEt2 in CH2Cl2 at room temperature to afforded 2,3-disubstitued tetrahydrofurans**57** in good yields with excellent selectivity (Scheme 17).[18]

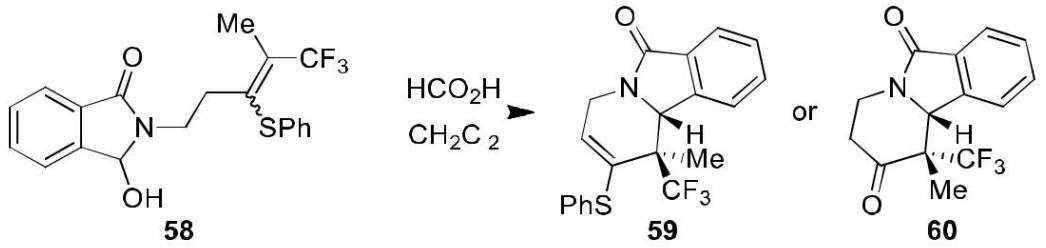
Scheme 17



56 **46** **57**

Very recently, Zard and co-workers have expanded the use of vinyl sulfide as nucleophile to reaction with iminium ions in the synthesis of nitrogen-containing polycyclic structures.Thus, when hemiaminal**58** was reacted with formic acid, the lactam **59** and **60** was formed in good yield with excellent diastereoselectivity (Scheme 18). Interestingly, the stereoselectivity of the reaction was found to be dependent on the geometry of the vinyl sulfide **58**. However, only limited numbers of examples were demonstrated and synthesis of vinyl sulfide required lengthy sequence of reactions.[19]

Scheme 18



58 **59** **60**

from (Z) isomer 61%, dr ≥ 95:5

from (E) isomer 70%, dr ≥ 95:5

A complete literature survey revealed that, many Prins reaction suffers hydrolysis of oxa carbenium as side reaction, Even though Prins type cyclization on vinylogous carbonates is successfully demonstrated, these methodologies suffer with a drawback of formation of 4-hydroxy tetrahydropyrans and corresponding ethers or counter ion act as nucleophile[20].Moreover, presently known reaction conditions are not regioselective. To overcome these problems, surprisingly, trapping of oxonium ion generated from vinylogous carbonates or by intermolecular reaction of aldehyde with doubly activated electron rich (*Z*)-vinyl bis-sulfide for the synthesis of oxygen-based heterocycles is still not explored in literature. With this background, our group has initiated a program directed at expanding the synthetic utility of vinylogous carbonates. Towards this, focus was on studying the Prins cyclization of the (*Z*)-vinyl *bis*-sulfide onto vinylogous carbonates as surrogate of oxonium ion under acidic conditions leading tothe synthesis of various 2,6-disubstituted dihydropyrans and THP derivatives.

3. OBJECTIVE

The main objectives of the present work is to combine a concise approach for the highly regio and diastereosective synthesis of DHP and THP derivatives products.

4. SUMMARY AND OUTLOOK

organic chemists have developed a vast array of synthetic methodologies based on different intermediates. Older synthetic conversion is constantly evolving. New approaches, catalysts, and substrates continue to be developed. Moreover, these classical reactions are being utilized in state-of-the-art total syntheses projects, a testimony to the value and scope of these Prins cyclization-based reactions. We also continue to see synthetic organic chemists develop new and innovative methods, especially those produced in a chiral environment. In the years ahead, challenges will include advancing the asymmetric synthetic methodologies, developing more robust catalysts, and finding more environmentally friendly conditions for reactions.

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