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Further Studies on the Allylic Diazene Rearrangement

Maha Laxmi Shrestha
University of Arkansas, Fayetteville

FURTHER STUDIES ON THE ALLYLIC DIAZENE REARRANGEMENT

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A dissertation submitted in partial fulfillment
of the requirement for the degree of
Doctor of Philosophy in Chemistry

By

Maha Laxmi Shrestha
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ABSTRACT

Former graduate student Wei Qi and Professor Matt McIntosh have reported diastereoselective reductive 1,3-transpositions of acyclic *α,β*-unsaturated tosyl hydrazones to afford substrates with a 1,4-*syn* or 1,4-*anti* relationship between alkoxy and methyl groups that proceed *via* an ADR (Qi, W.; McIntosh, M. C. *Org. Lett*. **2008**, *10*, 357; Qi, W.; McIntosh, M. C. *Tetrahedron* **2008**, *64*, 7021). In these reports, silica gel was employed to accelerate the reduction. We have found that acetic acid gives the same results with high diastereoselectivity in the reaction. We further optimized the reaction by lowering the amount of catecholborane to 3 eq. Effects of hydrazone *E*/*Z* geometry and implication for reaction mechanism were also investigated.

The dissertation is approved for recommendation to the Graduate Council

Dissertation Director:

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Dr. Matthias C. McIntosh

Dissertation Committee:

_____

Dr. Robert E. Gawley

_____

Dr. Neil Allison

_____

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First of all, I would like to thank my advisor Prof. Matt. McIntosh for giving me an opportunity to work with him. His guidance and cooperation have been tremendously important not only for research but throughout my graduate career. I am really amazed by his professionalism and ability to understand students, despite the language barrier.

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At the end, I have no words to thank my wonderful husband, my best friend, Rajib Man Shrestha for always being there for me.

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CHAPTER 1:FURTHER STUDIES ON THE ALLYLIC DIAZENE REARRANGEMENT

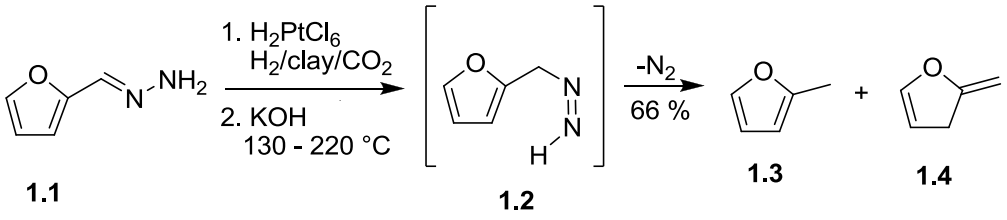
I. INTRODUCTION

A. THE ALLYLIC DIAZENE REARRANGEMENT

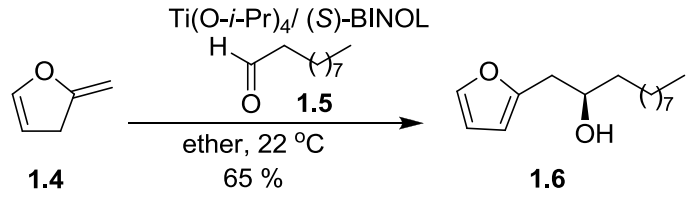
1. Early Developments

1.1 Hydrazone Reduction/ADR

In 1931, Kishner reported the first example of an allylic diazene rearrangement (ADR) by reacting 2-furyl hydrazone (**1.1**) with platinized clay to give 2-methylene-2,3-dihydrofuran (**1.4**) as the major product (Scheme 1, eq. 1).[1] The reaction presumably proceeds *via* 2-furyl diazene (**1.2**). Miles later reinvestigated Kishner's reductive transposition and found that major products were a mixture of 2-methylfuran (**1.3**) and 2-methylene-2,3-dihyrofuran (**1.4**).[2] He also demonstrated its potential as a starting material for 2-substituted furans via using carbonyl ene reactions (Scheme 1, eq. 2)



(1)

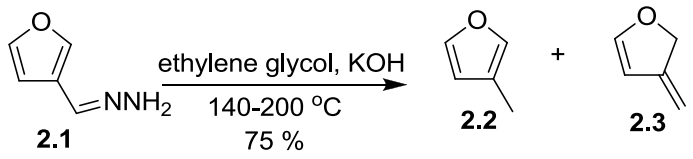


(2)

Scheme 1

Miles also utilized the Huang-Minlon modification of the Wolf-Kishner's reduction, to prepare 3-methylene-2,3-dihydrofuran (**2.3**) from 3-furylhydrazone (**2.1**) (Scheme 2).[3] The Huang-Minlon modification is simpler and more economic compared to other classical modifications of Wolf-Kishner reduction because of the use of sodium or potassium hydroxide

instead of metallic sodium or sodium ehtoxide.[4,5] A 100 % hydrazine was also replaced with a much cheaper 85 % hydrazine hydrate in the Huang-Minlon modification. However, the purification of the product **2.3** involved a significant loss of the compound resulting from isomerization and polymerization.



Scheme 2

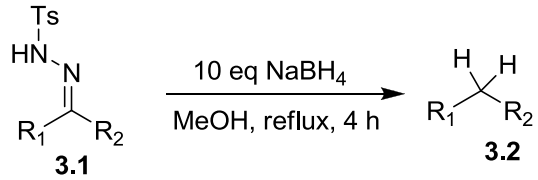
These traditional approaches including the Wolf-Kishner conditions for reductive transposition of hydrazones involves strong base and very high temperatures in which base sensitive functional groups including esters, lactones and ketones are not compatible.[6,7]

2. Tosyl hydrazone Reduction/ADR

2.1 Hydride Reagents

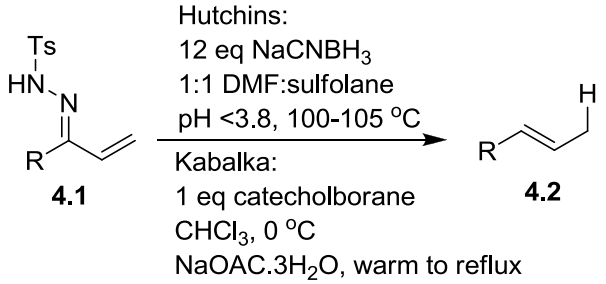
The Wolf-Kishner conditions involved deoxygenation of the aldehydes or ketones *via* base treatment of hydrazone intermediates to afford hydrocarbons. However, the method utilizes tedious reaction conditions; therefore, not suitable for sensitive substrates including hindered molecules. After the Wolf-Kishner reaction, a substantial amount of time and efforts led to the development of a new procedure in which tosyl hydrazones were utilized instead of hydrazones. The harsh reaction conditions of the Wolf-Kishner reduction of hydrazones were avoided by reducing the tosyl hydrazones with a variety of hydride reagents. In 1966, Caglioti utilized lithium aluminium hydride for reduction of tosylhydrazones.[8] Later, he developed the milder

reduction conditions by using sodium borohydride.[9] A variety of ketone tosyl hydrazones **3.1** were reduced with sodium borohydride to obtain hydrocarbons **3.2** (Scheme 3).



Scheme 3

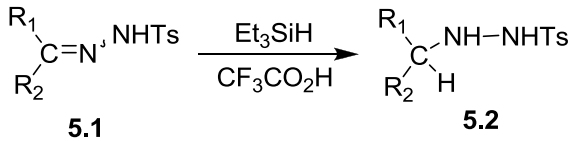
Another procedure for a reduction of tosyl hydrazones using the ADR was developed by Hutchins in the early 1970's, in which an enone was first converted to a tosyl hydrazone **4.1**, then reduced with sodium cyanoborohydride in 1:1 DMF-sulfolane at 100-105 °C to give the reduced rearranged alkene **4.2** (Scheme 4).[10,11,12] Later, Kabalka improved the procedure by introducing catecholborane for the reduction of α,β-unsaturated tosyl hydrazone **4.1**, which offered a number of advantages over sodium borohydride and sodium cyanoborohydride (Scheme 4):[6,13,14] 1) only 1 eq of hydride reagent is required; 2) reduction temperature can be lowered to 0 °C; 3) common organic solvents such as $CHCl_3$ can be utilized instead of DMF:sulfolane system or acetic acid; 4) catecholborane being liquid at room temperature, it may be used without solvent.[15]



Scheme 4

2.2 Hydrosilanes

Other than borane reagents, there are also a few reports on hydrosilane mediated reduction of hydrazones. Wu and coworkers first developed a method for reduction of acyl hydrazones by employing hydrosilane after unsuccessful attempts utilizing the hydride reagents.[16] Triethylsilane is a mild reducing agent, which can be used under acidic conditions to enhance the reactivity of hydrazones.[17,18] Later, the procedure was also employed for the reduction of a variety of tosyl hydrazones (Scheme 5).[19]



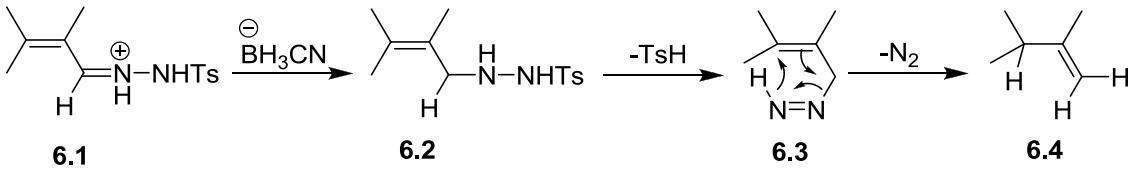
5.1 **5.2**

R_1=H, CH_3, Ph
R_2=CH_3, C_2H_5, Ph, etc.

Scheme 5

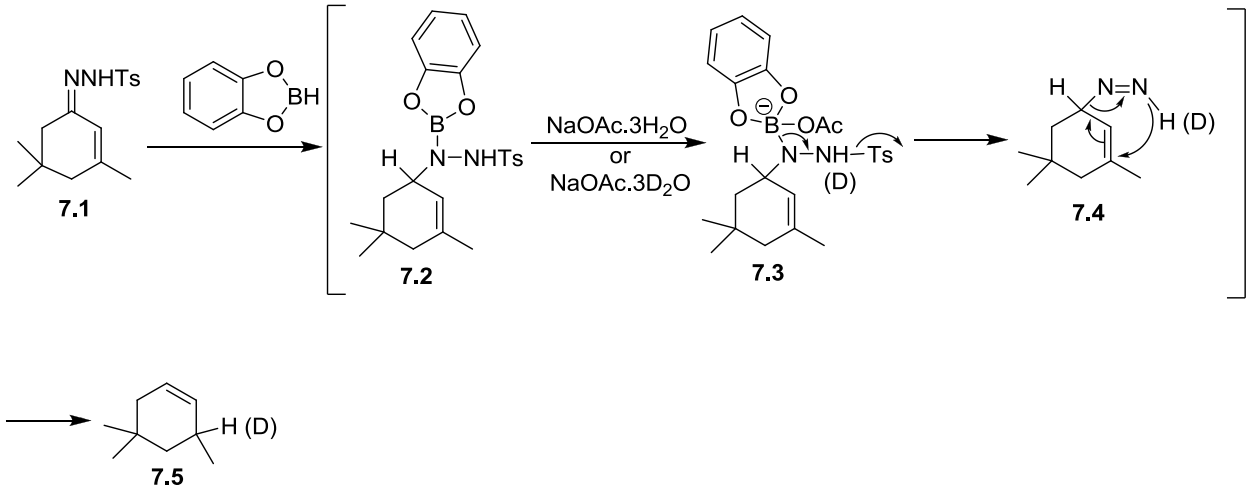
3. Mechanism of Reductive Transposition

There are a number of reports on the possible mechanism of reductive transposition of tosyl hydrazones by using sodium cyanoborohydride or catecholborane. Hutchins proposed that the iminium ion **5.1** formed under acidic conditions and reduces to tosylhydrazine **6.2** when treated with cyanoborohydride (Scheme 6).[12] Elimination of the toluenesulfonyl group forms the diazene intermediate **6.3**, which undergoes ADR. The decomposition occurs by a retro-ene reaction with elimination of nitrogen to give rearranged alkene **6.4**. Therefore, the mechanism of reductive transposition occurs in 3 distinct steps; 1) reduction of hydrazone; 2) formation of diazene intermediate, and 3) allylic diazene rearrangement (ADR).



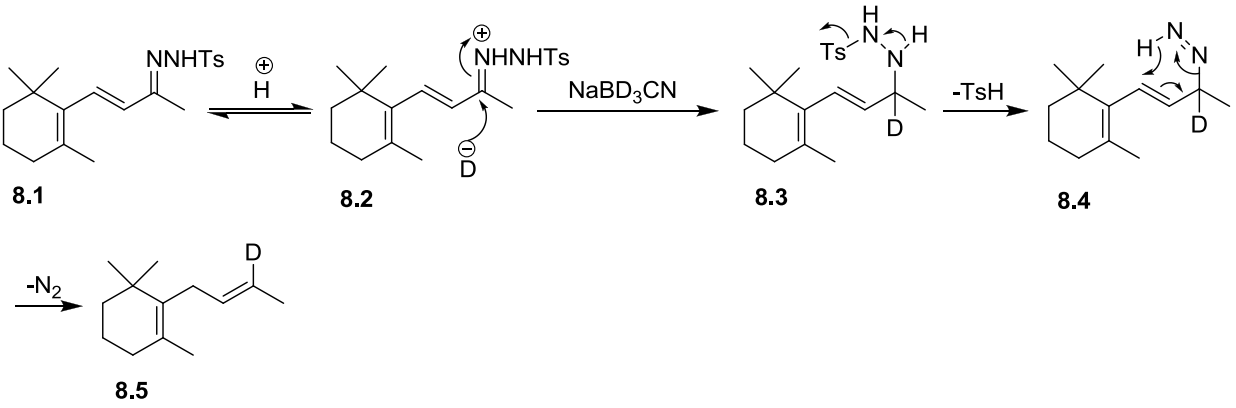
Scheme 6

Later, Kabalka proposed a mechanism for the reduction/ADR of tosyl hydrazones in which tosyl hydrazone **7.1** is reduced to form a hydrazinoborane intermediate **7.2**.[14] Fragmentation of acetoxy catecholborane and tosyl group gives the diazene intermediate **6.4**; ADR of the intermediate affords the desired alkene **7.5** (Scheme 7).[6] The ADR involves decomposition of the diazene intermediate **7.4** through 1,5-hydride shift and elimination of nitrogen in a concerted manner. His experiments with $NaOAc.3D_2O$ afforded deuterium incorporated alkene **7.5** which support the concerted decomposition of the diazene intermediate **7.4**.



Scheme 7

Liu *et al* have performed a mechanistic study of reductive transposition of tosyl hydrazones by utilizing a labeling experiment with $NaCNBD_3$ (Scheme 8).[20,21] Their study revealed that the reaction proceeds *via* formation of an iminium ion **8.2**, followed by hydride attack to give hydrazine **8.3**. Elimination of TsH affords a diazene intermediate **8.4**. The intermediate **8.4** undergoes the decomposition *via* ADR. Alkene **8.5** was identified as the reduced, rearranged product resulting from the ADR of diazene intermediate **8.4**. Thus, all these reports support that the ADR proceeds through a concerted mechanism by decomposition of the diazene intermediate.



Scheme 8

By calculations, Houk has also supported a concerted reaction mechanism for the ADR (Figure 1).[22] The transition state is a half chair in which all atoms are coplanar except C2. The calculated activation energy barrier is only 4.5 kcal/mol. The reaction is highly exothermic at 61 kcal/mol. These results are consistent with those obtained from mechanistic studies. Therefore, the ADR is considered as a thermal concerted retro-ene process that proceeds through a six-membered cyclic transition state (Scheme 9).[23,24,25,26]

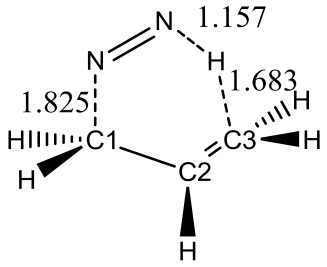
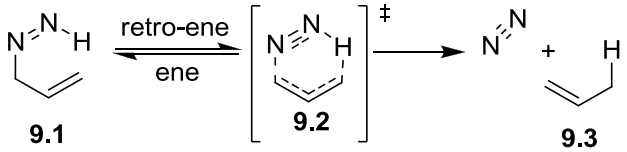


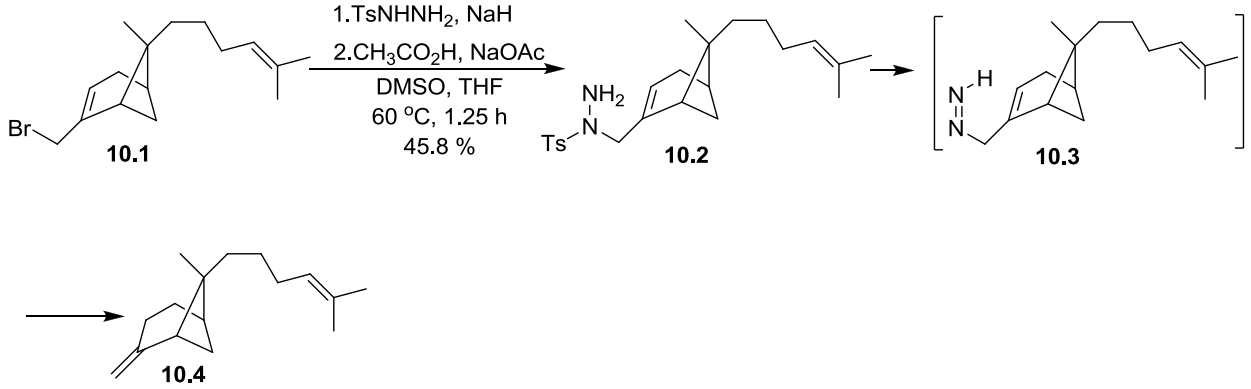
Figure 1



Scheme 9

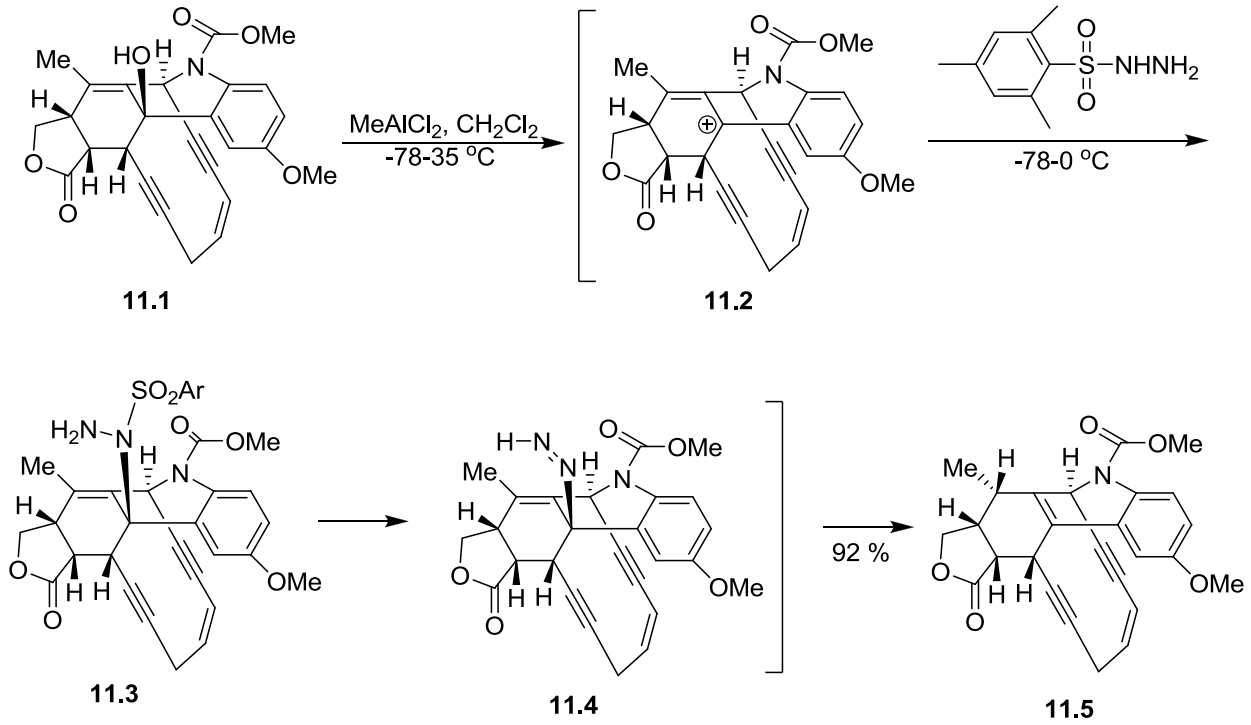
4. Synthetic Applications

In 1971, Corey *et al* reported the application of the ADR in a racemic synthesis of α-trans and β-trans-bergamotene (Scheme 10).[27] Allylic bromide **10.1** was reacted with the sodium salt of tosylhydrazide to give allyl tosylhydrazide **10.2**. Bergamotene (**10.4**) was obtained after elimination of TsH and decomposition of diazene intermediate **10.3** when treated with a buffer of acetic acid and sodium acetate.



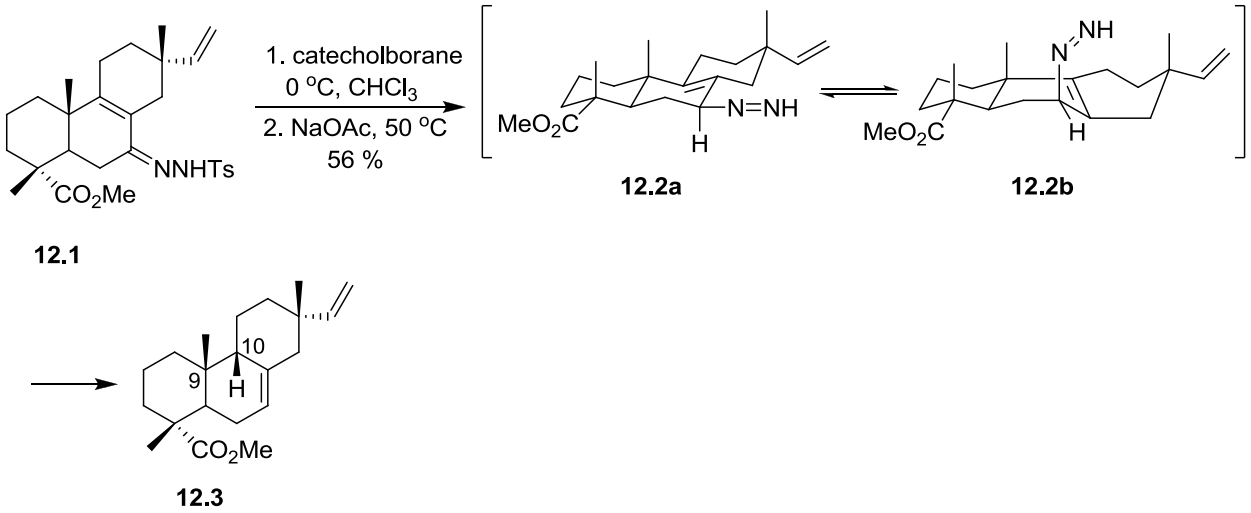
Scheme 10

Several other syntheses have been reported by utilizing variants of the ADR. For instance, Schreiber *et al* employed the ADR in synthesis of the enediyne-bridged tricyclic core of dynemycin A (Scheme 11).[28] Ionization of alcohol **11.1** with $MeAlCl_2$ afforded carbonium ion **11.2** which was trapped with 2,4,6-trimethylsulfonyl hydrazide to give the hydrazine **11.3.** Elimination of the arylsulfonyl group followed by decomposition of the intermediate diazene **11.4** gave the desired product **11.5**.



Scheme 11

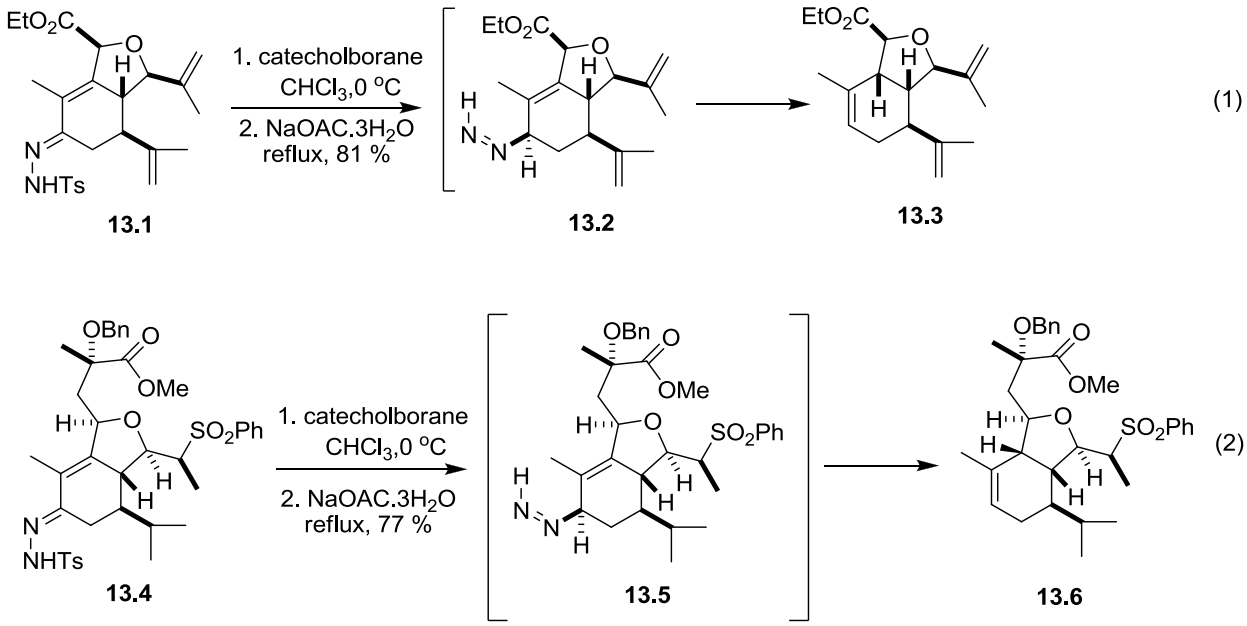
There are a number of reports of synthetic applications of the ADR in the literature in which Hutchins or Kabalka protocols were employed to produce cycloalkenes from cycloalkenones.[29,30,31,32,33,34,35] In general, α,β-unsaturated sulfonyl hydrazones derived from the corresponding cyclohexenones undergo axially selective reduction.[36,37,38] For example, Coates and Chu utilized the ADR in the synthesis of 9,10-diterpenes in which tosyl hydrazone of isopimaradione **12.1** was treated with catecholborane in $CHCl_3$ at 0 °C for ca. 30 min (Scheme 12).[38] The reaction was then heated under reflux with NaOAc for 50 min to afford the desired cycloalkene **12.3**. Formation of the desired product **12.3** with the 9,10 *syn* configuration is rationalized by axial delivery of hydrogen in the ADR which could be possible *via* inversion of a chair conformation **12.2a** to a half-boat **12.2b**.



12.1 **12.2a** **12.2b** **12.3**

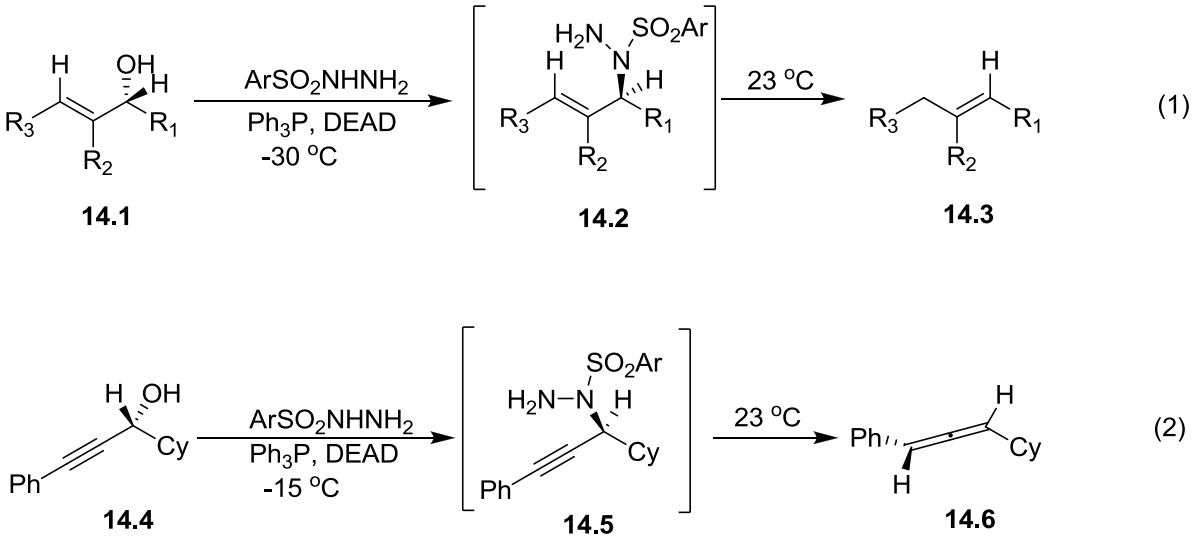
Scheme 12

This variant was also applied in our lab for the synthesis of the isobenzofuran core of eunicellin diterpenes **13.3** (Scheme 13, eq. 1).[39] Further, our group has employed the ADR in synthesis of advanced intermediate **13.6** in a approach to the synthesis of cladiell-11-ene-3,6,7-triol (Scheme 13, eq. 2).[40]



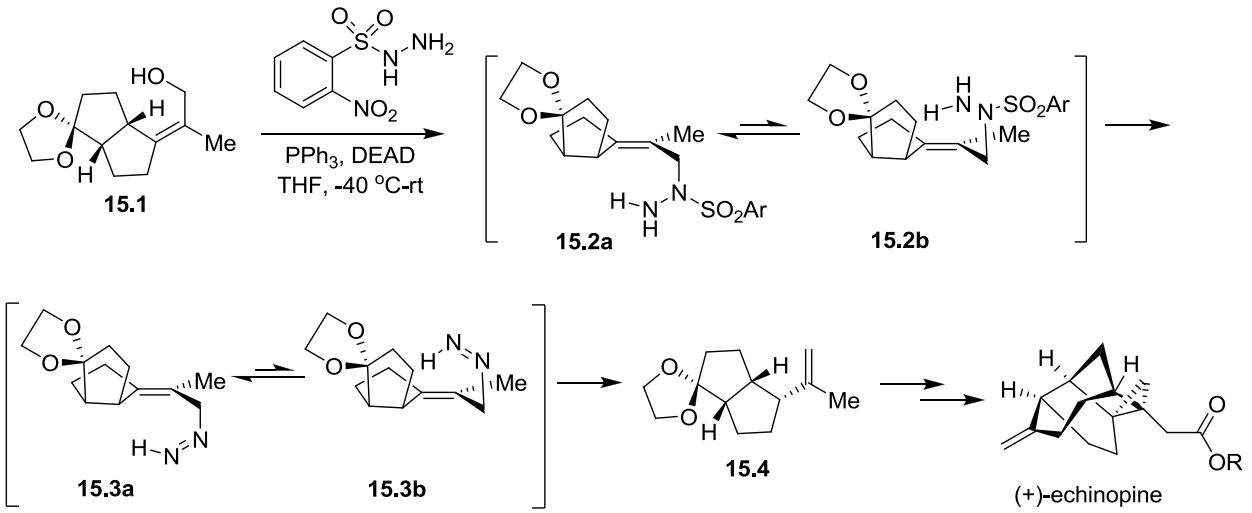
Scheme 13

Another variant of the ADR has been reported by Myers in several applications, as the final step of a reductive transposition.[41,42,43,44,45,46] These reports include Mitsunobu reactions of allyl and propargyl alcohols to form alkenes and allenes, respectively (Scheme 14, eq. 1 and 2). Myers' protocol is important since it stereospecifically affords allenes from reductive transposition of propargylic alcohols, which are readily available in asymmetric form. Although he reported the stereospecific synthesis of allenes, surprisingly, he did not mention any examples of installing sp^3 stereocenters in acyclic systems.



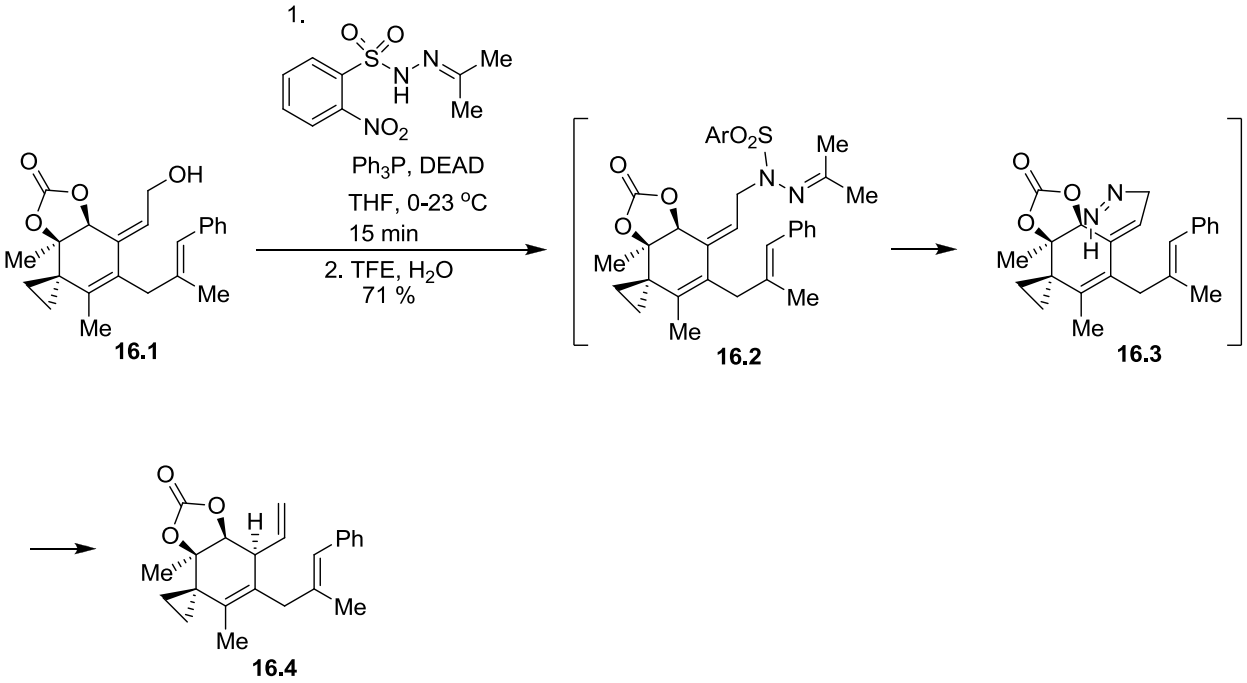
Scheme 14

In 2009, Magauer *et al* employed the Myers protocol as one of the key steps for the total synthesis of (+)-echinopine (Scheme 15).[47] Allylic alcohol **15.1** was treated with 2-nitrobenzenesulfonyl hydrazide (NBSH) under Mitsunobu conditions affording dr 10:1 of isopropenyl compound **15.4** *via* reductive transposition. The formation of the desired isomer was rationalized by the transition state **15.2a** which possesses less steric interaction between cyclopentane ring and hydrazide compared to that of **15.2b**.



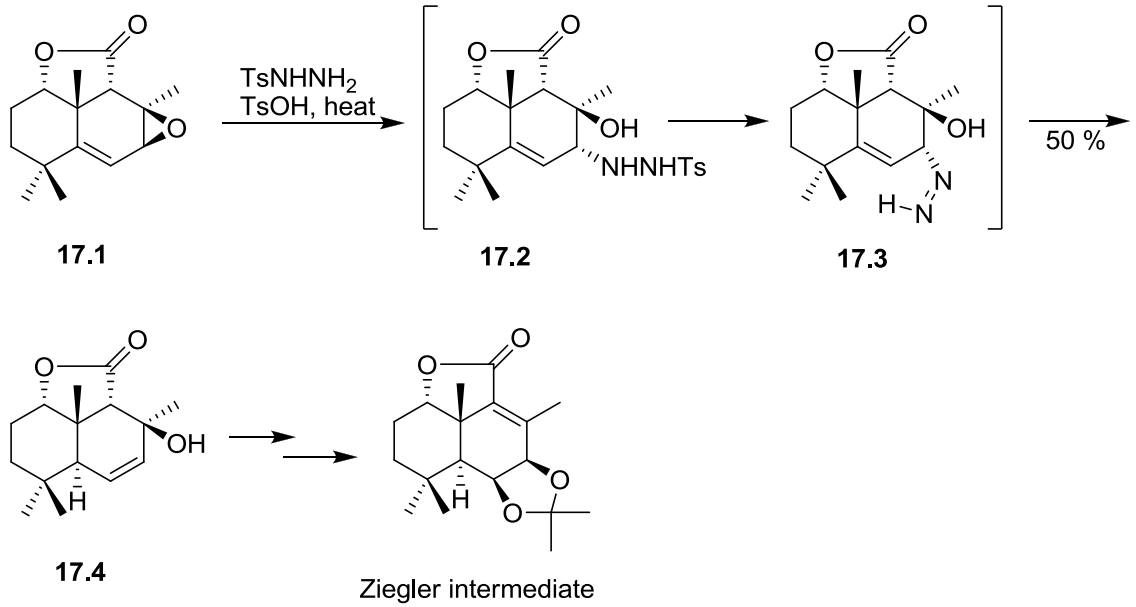
Scheme 15

Movassaghi utilized the ADR in the synthesis of (-)-acylfulvene and (-)-irofulven.[48,49] Mitsunobu displacement of alcohol **16.1** with *N*-isopropylidene-*N*'-2-nitrobenzenesulfonyl hydrazide (IPNBSH) followed by *in situ* hydrolysis and decomposition of diazene intermediate **16.3** provided 71 % of alkene **16.4** (Scheme 16). Only 35-54 % of the desired alkene **16.4** was obtained when 2-nitrobenzenesulfonyl hydrazide (NBSH) was employed for Mitsunobu reaction as in Myers' procedure. These results suggest that the use of IPNBSH may be advantageous over NBSH for reductive transposition of allylic alcohols in some cases.[50]



Scheme 16

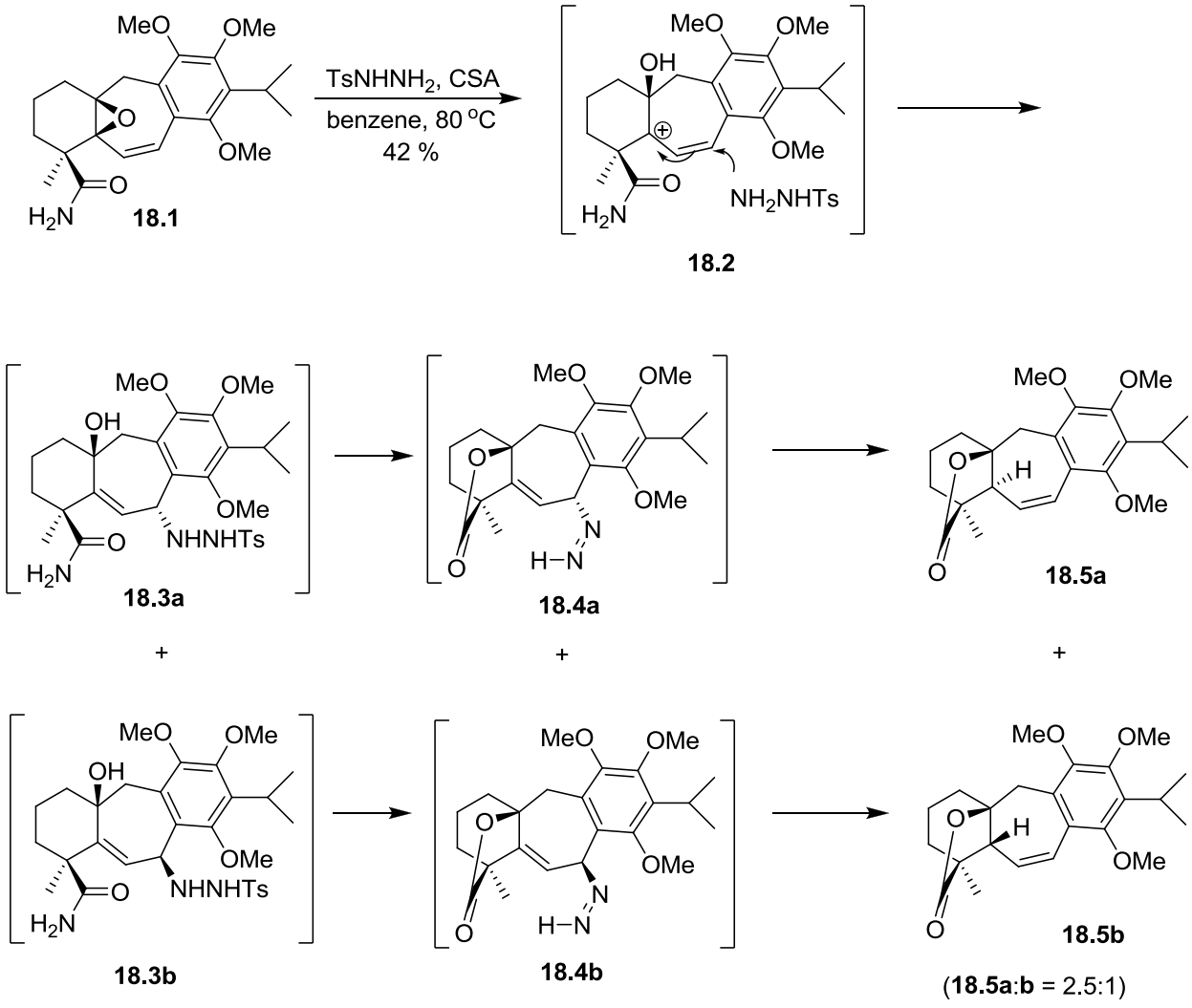
In 2009, Qiu *et al* utilized a stereoselective ADR to afford the Ziegler intermediate in the synthesis of forskolin (Scheme 17).[51] Addition of tosylhydrazide to epoxide **17.1** was catalyzed by *p*-toluenesulfonic acid to give hydrazine **17.2**, which afforded the desired compound **17.4**, presumably *via* diazene intermediate **17.3**.



17.1 **17.2** **17.3** **17.4** Ziegler intermediate

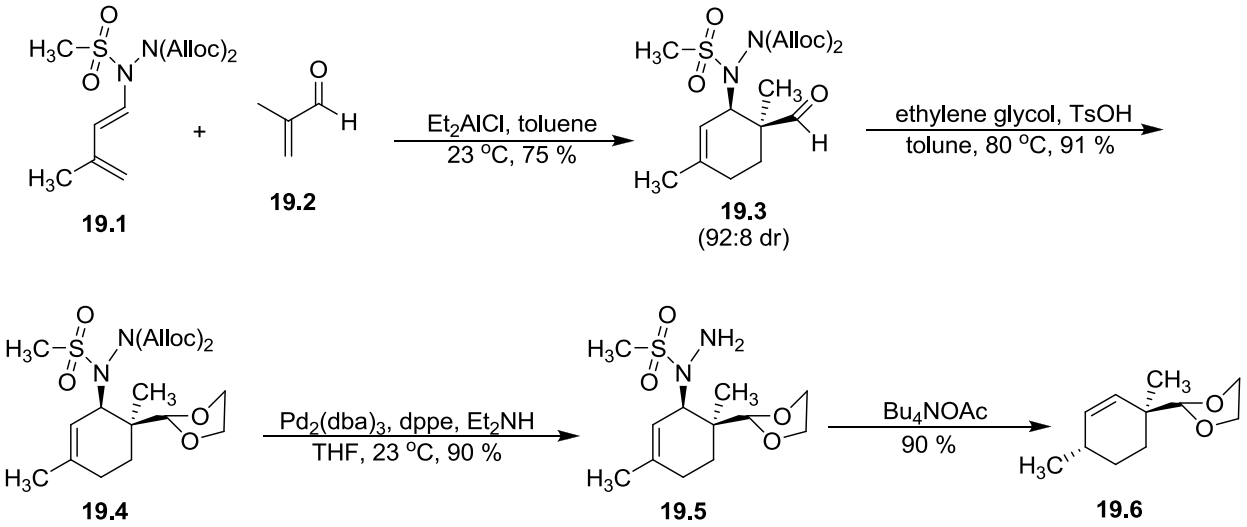
Scheme 17

Similarly, Sarpong employed the stereospecific nature of the diazene rearrangement in an approach to synthesis of (±)-icetexone diterpenoids (Scheme 18).[52] Heating of epoxide **18.1** with tosylhydrazide in the presence of camphorsulfonic acid provided a 2.5:1 mixture of diastereomers **18.5a** and **18.5b**. The reaction presumably occurs through protonation of the epoxide to give allylic cation **18.2**, which was trapped by tosylhydrazide affording a mixture of **18.3a** and **18.3a**. Formation of diazene intermediates **18.4** followed by ADR afforded the desired product **18.5a** as the major diastereomer.



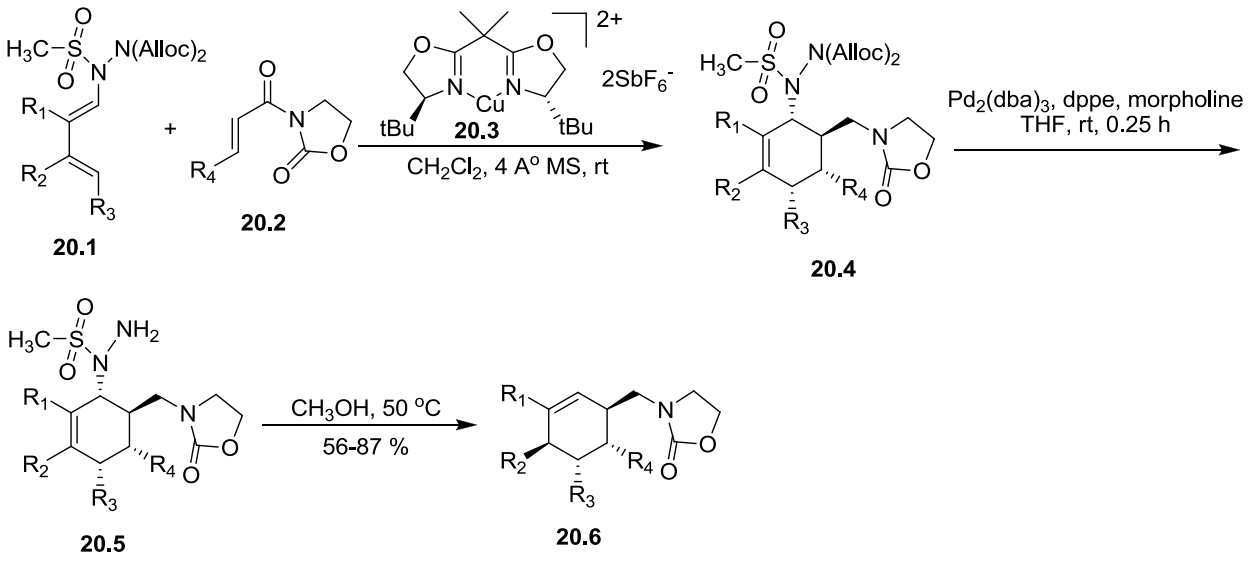
Scheme 18

Sorensen and his group employed reductive transpositions of [4+2] cycloadducts of 1-hydrazinodienes to obtain cyclohexenes with a 1,4-stereorelationships (Scheme 19).[53] Diels-Alder product **19.3** was formed by treating 1-hydrazinodiene **19.1** with dienophile **19.2** under Lewis acid catalysis. Protection of aldehyde **19.3**; followed by deprotection of the Alloc-protected nitrogen provided hydrazine **19.4**. Compound **19.4** afforded the ADR product **19.5** in 90 % yield when heated with tetrabutylammonium acetate.



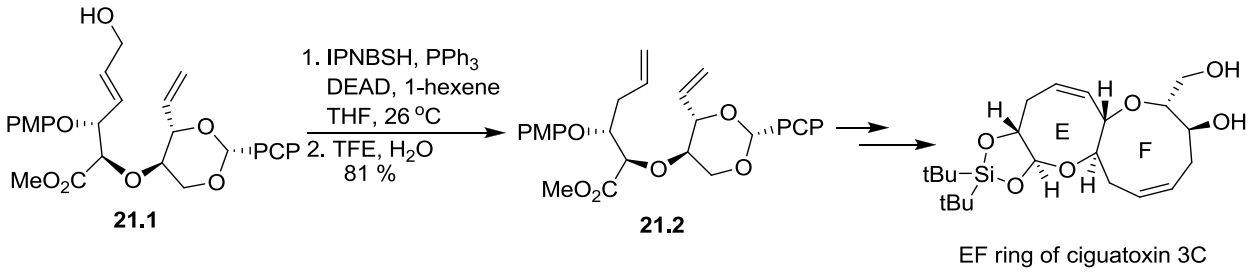
Scheme 19

In 2011, Sorensen subsequently employed the ADR in reductive transpositions of cycloadducts of 1-hydrazino dienes **20.4** (er > 20:1) prepared in catalytic asymmetric Diels-Alder reaction (Scheme 20).[54] Cleavage of the Alloc group followed by ADR afforded cyclohexene **20.6**.



Scheme 20

More recently Fujiwara employed a slightly modified Movasaaghi's procedure[49,50] for the reductive transposition of allylic alcohol **21.1** to diene **21.2** (Scheme 21).[55] The diene was utilized for the synthesis of the EF ring of ciguatoxin 3C.

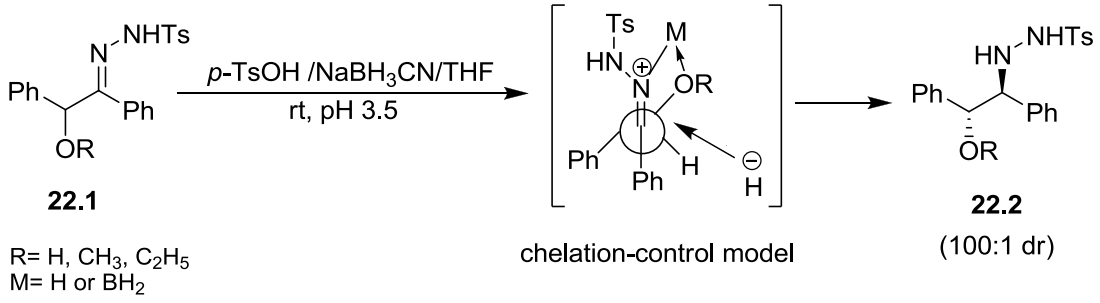


Scheme 21

B. DIASTEREOSELECTIVE REDUCTION OF THE IMINE BOND OF TOSYL HYDRAZONES AND OXIMES IN ACYCLIC SYSTEM

1. Imine Bond of Tosyl Hydrazones

A key step in the reductive transposition of α,β-unsaturated tosyl hydrazones is the reduction of the imine bond. As discussed earlier, many reaction conditions have been utilized towards the development of optimum conditions for C=N bond reduction including Hutchins and Kabalka's conditions.[6,8,9,10,11,12] However, reports on diastereoselective reduction of tosyl hydrazones is still scarce. Therefore, Rosini's work on tosylhydrazone reduction using sodium cyanoborohydride is noteworthy. Initially, Rosini reported the reduction of tosylhydrazones by converting them into *N*,*N*'-mercurio-bis-tosylhydrazone and then treating them with sodium cyanoborohydride.[56] Later, he simplified the procedure by reducing tosylhydrazone **22.1** directly with sodium cyanoborohydride and *p*-toluenesulfonic acid in THF at room temperature and isolated the reduction product **22.2** (Scheme 22).[57] Although he did not report the *E*/*Z* configuration of hydrazones **22.1**, he provided the coupling constant values for *anti* (3-5 Hz) and *syn* (8-11 Hz) diastereomers of the hydrazines. The 1,2-*anti* hydrazines **22.2** were obtained from the reduction of α-alkoxy hydrazones **22.1**, presumably *via* to chelation control.[58]

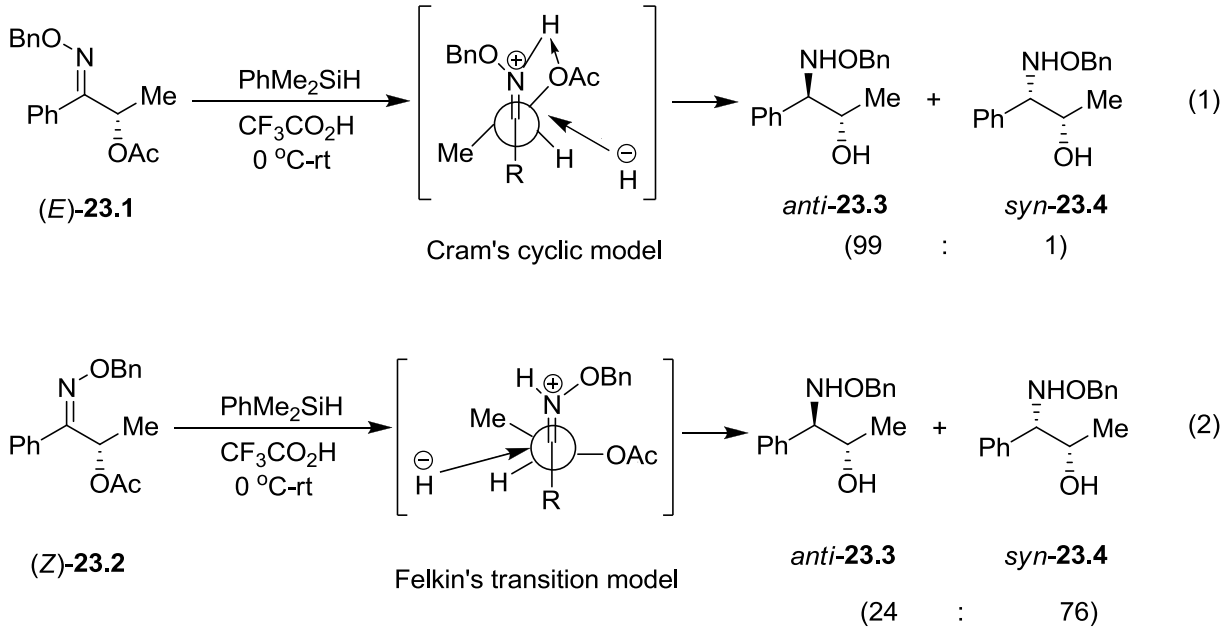


Scheme 22

Due to the paucity of reports on the diastereoselective reduction of tosyl hydrazones in acyclic system, we also reviewed C=N bond reduction in oximes as analogs of hydrazones.

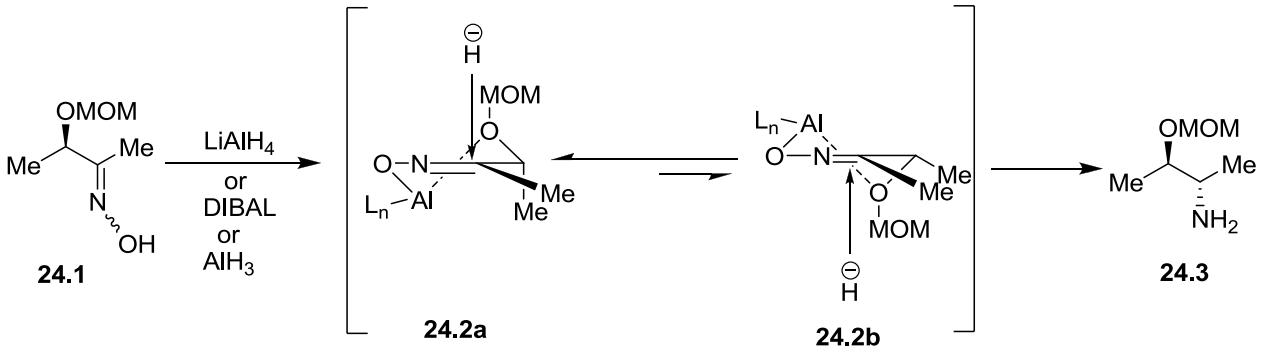
2. Imine Bond of α-Alkoxy Oximes

There are numerous reports on reduction of a variety of oximes; however, only the representative examples of oximes derived from α-alkoxy or α-hydroxy ketones will be discussed. Diastereoselective reduction of the C=N bond in *E*- and *Z*-α-acetoxy oximes **23.1** can be achieved by utilizing acid catalyzed hydrosilylation (Scheme 23).[59] The reaction gave 99:1 *anti*:*syn* (**23.3** and **23.4**) products when *E*-oxime **23.1** was used (Scheme 23, eq. 1). The observed *anti*-selectivity was presumably due to a proton-bridged Cram's cyclic model. However, low diastereoselectivity was observed in case of *Z*-oxime **23.2**, most likely due to the lack of formation of the cyclic transition state. The author also rationalized the preference of *syn* selectivity through Felkin's transition model; however, the selectivity is low (Scheme 23, eq. 2).



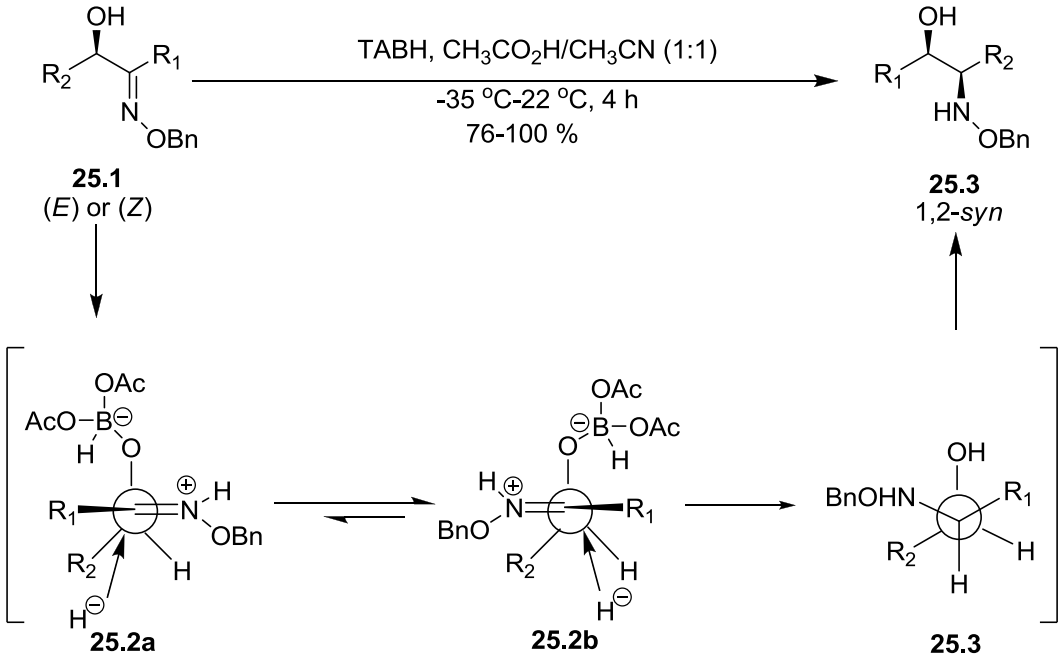
Scheme 23

Another type of diastereoselective reduction of imine bond has been reported by Kibayashi *et al* (Scheme 24).[60] The authors proposed the transition states **24.2a** and **24.2b** to rationalize the diastereoselectivity of the reduction. Stereocontrolled reduction of α-alkoxy oximes **24.1** with aluminium hydride reagents gave *anti* amino alcohols **24.3** preferentially due to chelation control; however, the configuration of the oximes **24.1** was not disclosed. Transition state analysis suggests that **24.2a** is favored since **24.2b** suffers from steric interaction between two methyl groups.



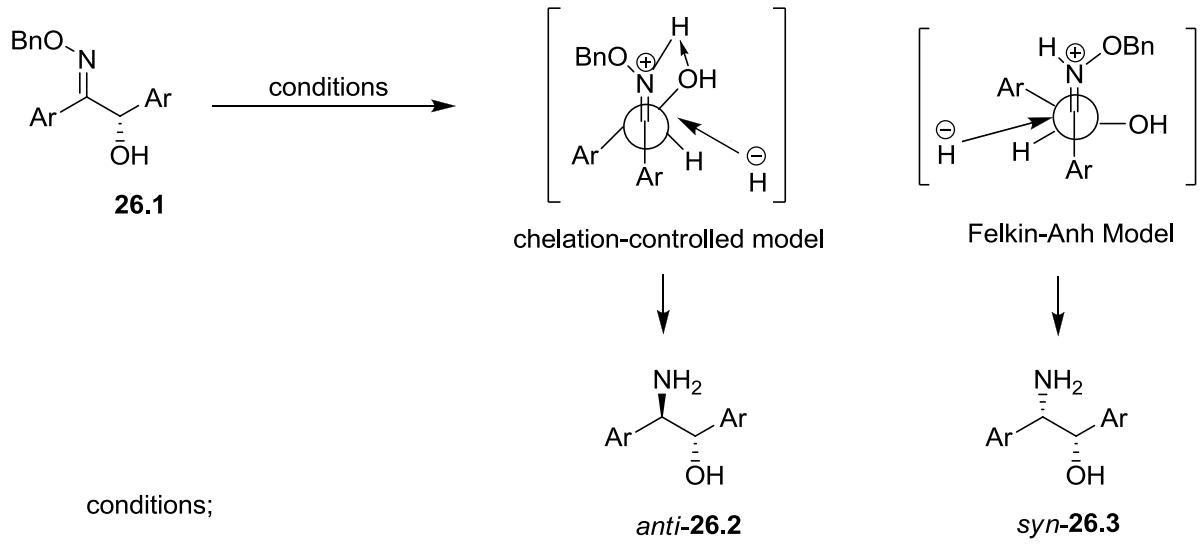
Scheme 24

Contrary to the above reports of *anti*-selectivity, Williams *et al* obtained *syn*-1,2-benzyloxy amino alcohols **25.3** from diastereoselective hydride reduction of α-hydroxy oximino ethers **25.1** when tetramethylammonium triacetoxyborohydride (TABH) was used (Scheme 25).[61] The authors hypothesized the preference for the *syn* product by a Felkin-Anh transition state. External hydride addition to rotamer **25.2b** would provide the *syn* isomer. The diastereoselectivity of the reduction was not dependent upon the *E*/*Z* geometry of oximes. However, it was not clear why the authors did not mention the possibility of the reduction by the adjacent diacetoxy borohydride that could give a 1,2-*anti* product.



Scheme 25

Fujisawa *et al* also investigated the diastereoselective reduction of α-hydroxy oximes under a variety of conditions (Scheme 26).[62] For this purpose, he utilized three different reducing agents; $Na[AlH_2(OCH_2CH_2OCH_3)_2]$, $LiAlH_4$, and Pd-C/H_2. Reduction of oxime **26.1** under first two sets of reaction conditions gave *syn* product **26.3** predominantly, which was rationalized by the Felkin-Anh Model. *Anti*-selectivity was preferred when Pd-C/H_2 in EtOH was employed, perhaps due to chelation of the hydroxyl proton to the imine nitrogen. However, the authors did not address this issue and they have shown the *anti*-selectivity in the *E*-oximes only. Nevertheless, they concluded that the selectivity depends on the conditions used for the reduction and not on the configuration of the starting oximes.



conditions;

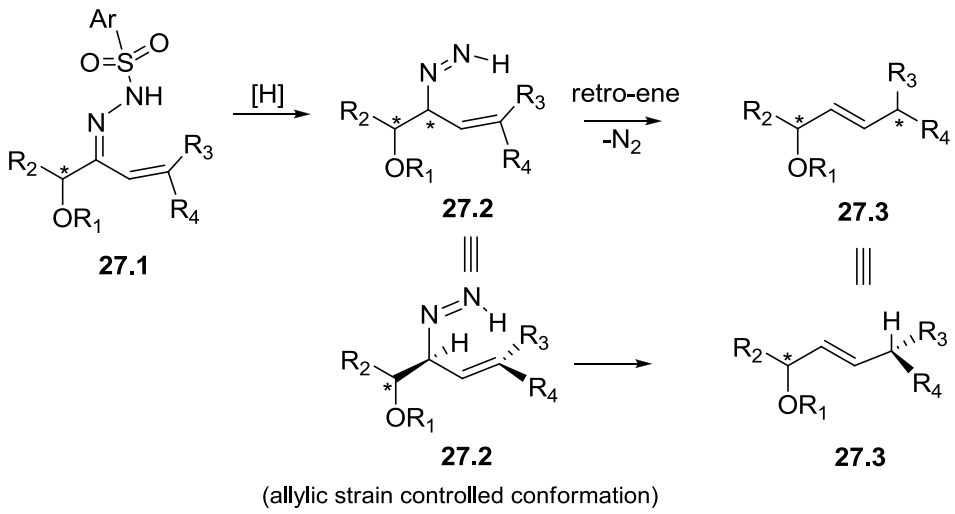
1. $Na[AlH_2(OCH_2CH_2OCH_3)_2]$, THF, -30 °C-reflux, 59 %, (2 : 98)
2. $LiAlH_4$, DME, 0 °C-reflux, 56 %, (12 : 88)
3. 10 % Pd-C/H_2, EtOH, rt, 96 %, (96 : 4)

Scheme 26

Based on all these results obtained from diastereoselective reduction of oximes, formation of *anti* and *syn* products can be rationalized by Cram's chelation-controlled model or the Felkin-Anh model respectively.

C. ACYCLIC STEREOCONTROL IN THE ADR

There are many examples of the ADR in cyclic systems; however, there were no reports of ADR on installation of sp^3 stereocenters in acyclic systems prior to Qi and McIntosh's work.[63] If the terminal carbon of the alkene of a α,β-unsaturated hydrazone is prochiral, the ADR can be employed to install a stereocenter. Therefore, this variant of the ADR expanded the scope of this transformation. Diastereoselective 1,2-reduction of a α,β-unsaturated tosylhydrazone **27.1** can be achieved under the influence of an α'-alkoxy stereocenter (Scheme 27). The hydrazone imine of an unsaturated tosylhydrazone in principle can undergo either Felkin-Anh or Cram chelation controlled reduction. The transfer of hydrogen to the prochiral alkene is the result of the suprafacial nature of the rearrangement along with the allylic strain induced conformational constraints.[44,64] This type of 1,4-*syn* and 1,4-*anti* stereorelationship can be found in many marine natural products (Figure 2).[65,66,67,68]



Scheme 27

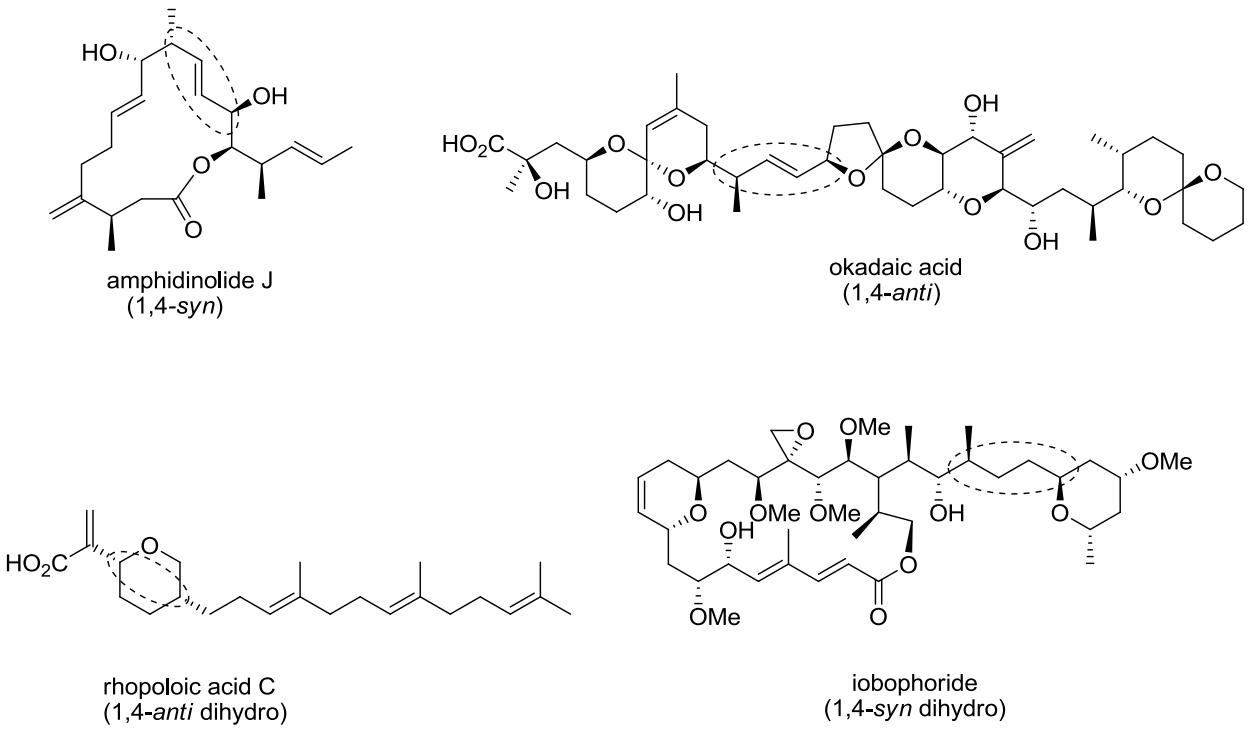
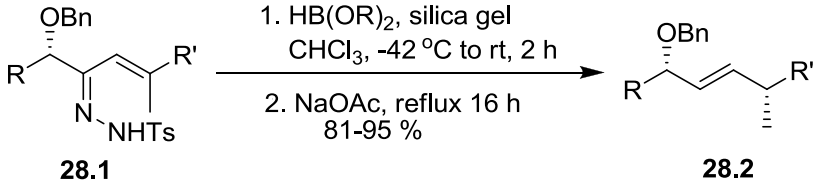


Figure 2

The first report of use of an ADR to install an sp^3 stereocenter in acyclic systems was published in 2008 by Qi and McIntosh (Scheme 28).[63] A variety of α,β-unsaturated tosyl hydrazones were employed as precursors for reductive transposition to give corresponding alkenes with high diastereoselectivity. In a representative example, tosyl hydrazone **28.1** was treated with ca. 6 eq of catecholborane and 2 wt. eq of silica gel at low temperature. After 2 h, $NaOAc.3H_2O$ was added and the reaction mixture was heated to reflux for ca.16 h. The reaction gave 81-95 % yields, depending upon the R and R' substitutions.

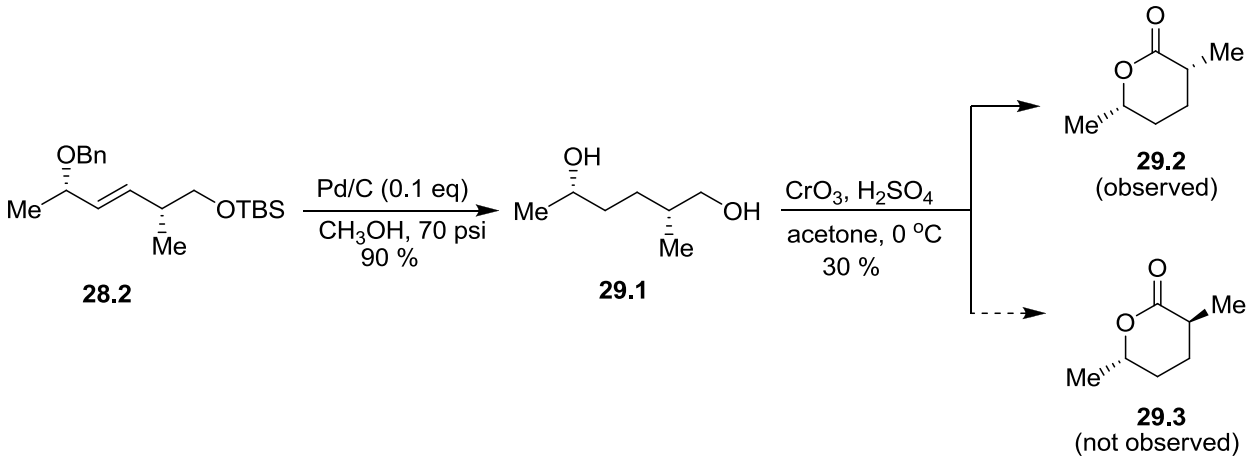


28.1 **28.2**

R= Me, Ph
R'= CH_2OTBS, CH_2CH_2OTBS, $CH{=}CH_2$

Scheme 28

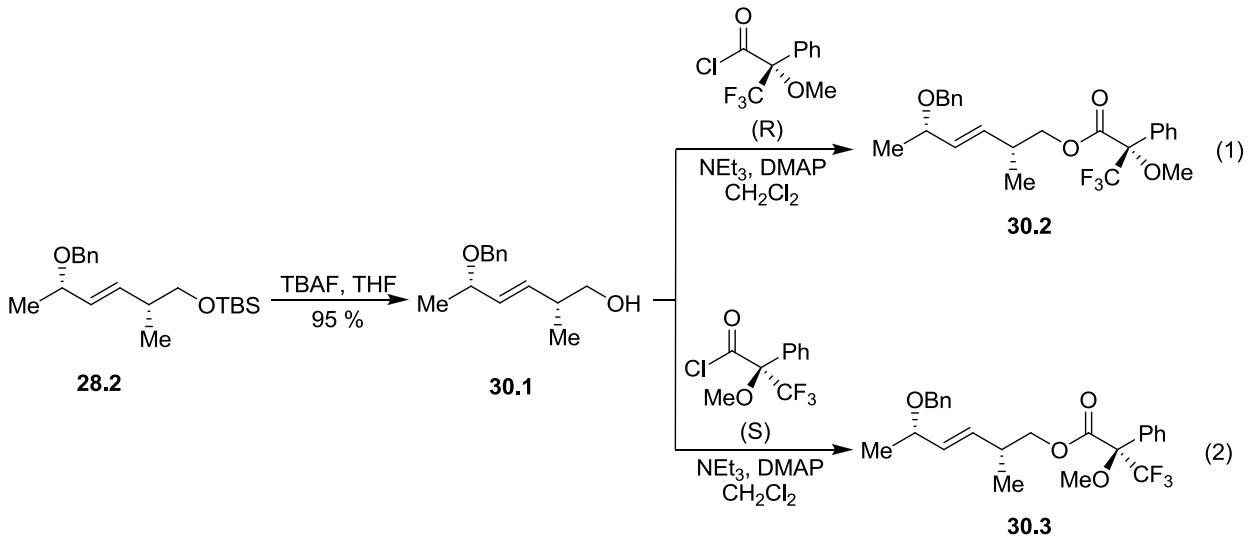
The relative configuration of the 1,4-*syn* alkene **28.1** was confirmed by converting it to the known lactone **29.2** via hydrogenolysis followed by oxidation (Scheme 29).[69] Lactone **29.3** would have been observed if the 1,4-*anti* alkene were obtained from reduction/ADR.



28.2 **29.1** **29.2** (observed) **29.3** (not observed)

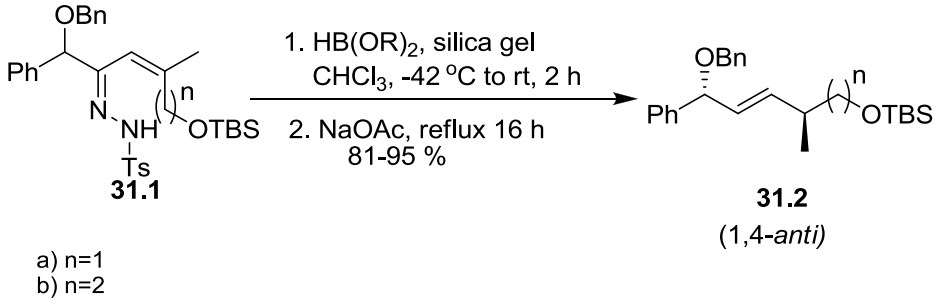
Scheme 29

Mosher ester analysis of alcohol **30.1** derived from (*S*)-(+)-lactic acid also showed only a diastereomer based on NMR spectroscopy (Scheme 30).[63,70,71] These results suggest that no racemization occurred at the α'-alkoxy stereocenter and the integrity of *syn* stereochemistry was maintained throughout the reaction.



Scheme 30

Furthermore, Qi and McIntosh also reported two examples of 1,4-*anti* alkenes obtained from *Z*-alkene α,β-unsaturated *E*-hydrazones (Scheme 31).[63] These results are significant since both 1,4-*syn* alkenes and 1,4-*anti* alkenes could be prepared by employing appropriate alkene geometry of α,β-unsaturated *E*-hydrazones.



Scheme 31

This methodology was subsequently utilized for the synthesis of a model of the C22-C34 fragment of antascomicn B (Figure 3, Scheme 32, eq. 1).[72] More recently, McIntosh *et al* have also reported the successful completion of the fully substituted C21-C34 fragment of antascomicin B by reduction/ADR of the corresponding hydrazone (Figure 3, Scheme 3, eq. 2).[73]

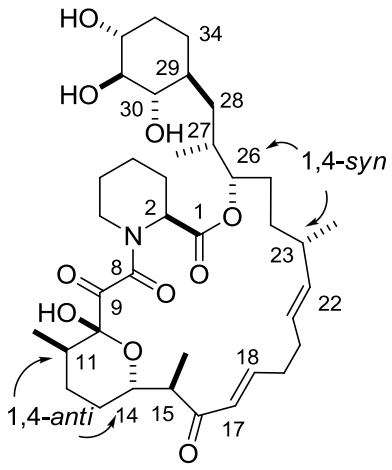
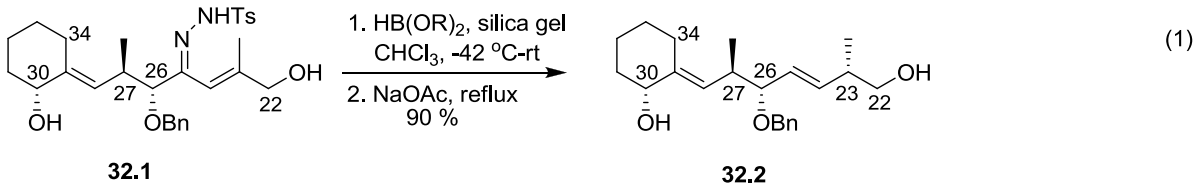
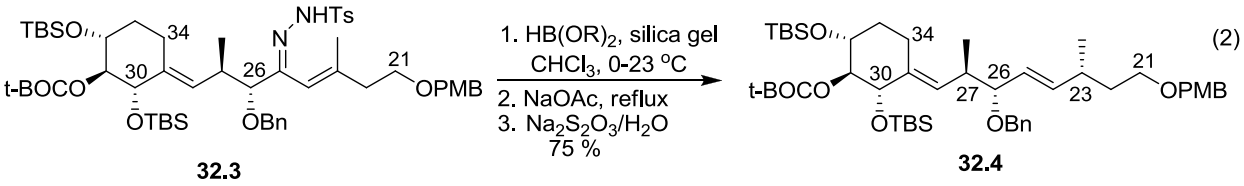


Figure 3: Antascomicin B



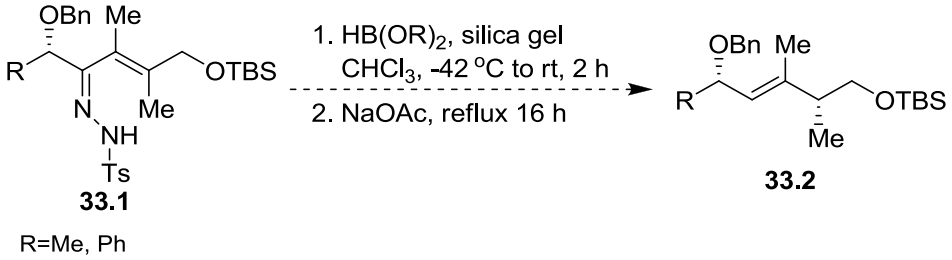
32.1 **32.2**



32.3 **32.4**

Scheme 32

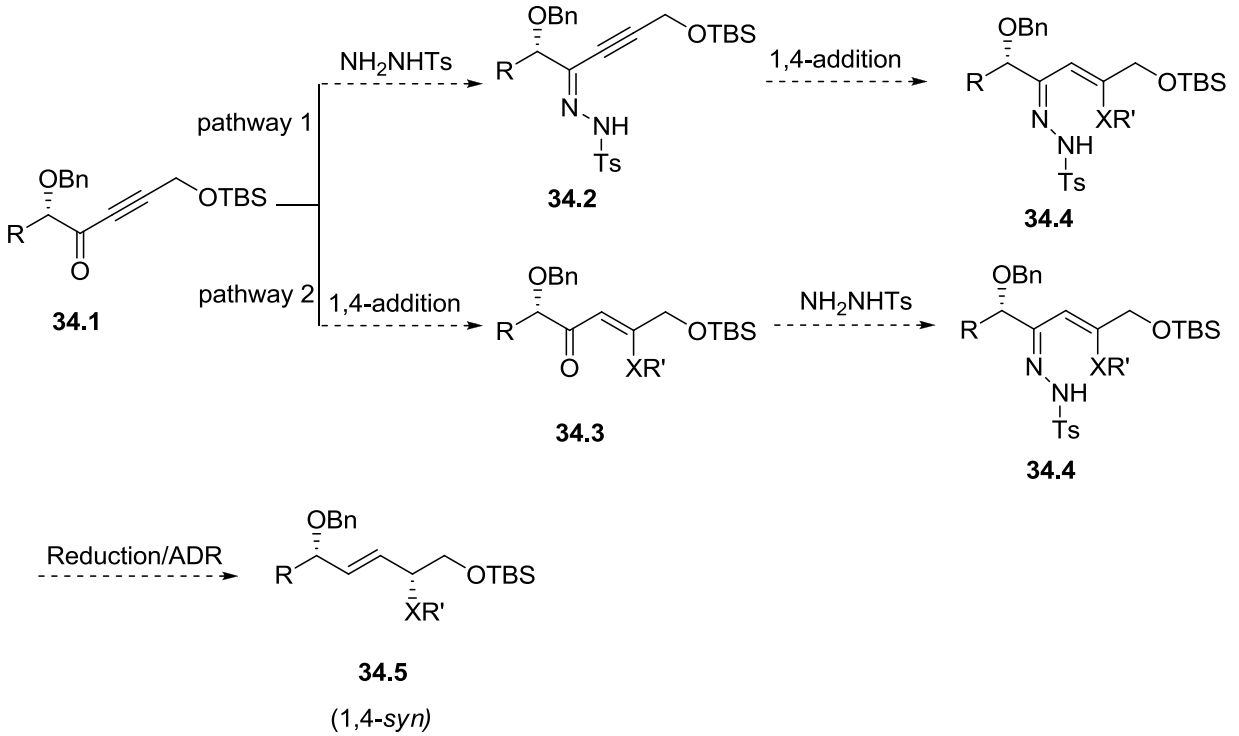
Based on these results, we expected that the extension of the method would afford 1,4-*syn* trisubstituted alkenes **33.2** from tetrasubstituted α,β-unsaturated *E*-hydrazones **33.1**, which could find potential application in the synthesis of natural products.



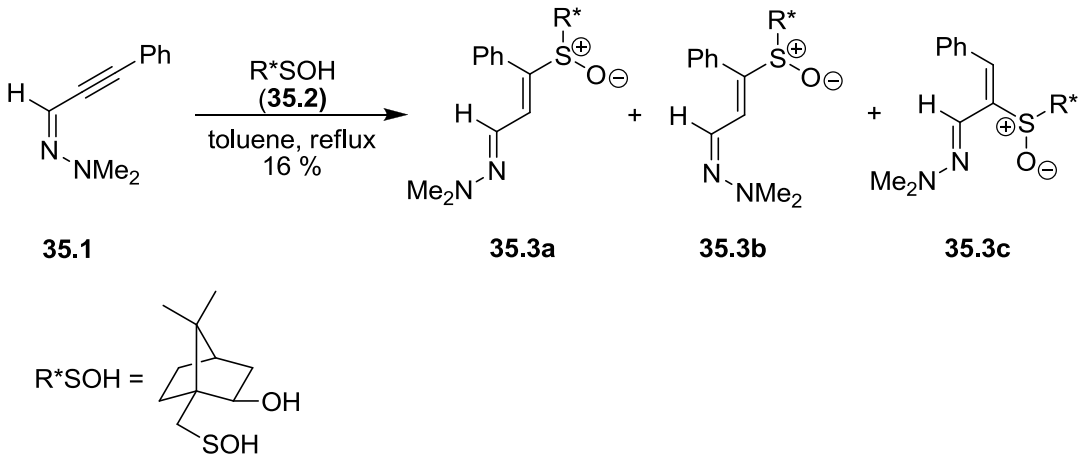
Scheme 33

D. FURTHER EXTENSION OF THE METHODOLOGY IN ACYCLIC SYSTEM

Further extension of the asymmetric reduction/ADR in acyclic system could provide 1,4-*syn* alkenes **34.5** with heteroatom functionality such as alkoxy, amine or alcohol (Scheme 34). We designed two pathways to obtain alkenes **34.5** from the reductive transposition of α,β-unsaturated enone hydrazone **34.4** (Scheme 34). In pathway 1, we expected to obtain α,β-unsaturated enone hydrazone **34.4** from ynone **34.1** by hydrazonation and subsequent 1,4-addition of a heteroatom nucleophile. However, we were able to find only one literature report for conjugate addition to ynone hydrazone **35.1** in which sulfenic acid **35.2** was utilized as a nucleophile (Scheme 35).[74] Further, the reaction suffered from a very low yield providing a mixture of products. Therefore, the alternative pathway 2 was proposed to prepare the same hydrazone **34.4** simply by reversing the order of reaction i.e. 1,4-adddition to ynone **34.1** followed by hydrazonation of the resulting enone **34.3**.

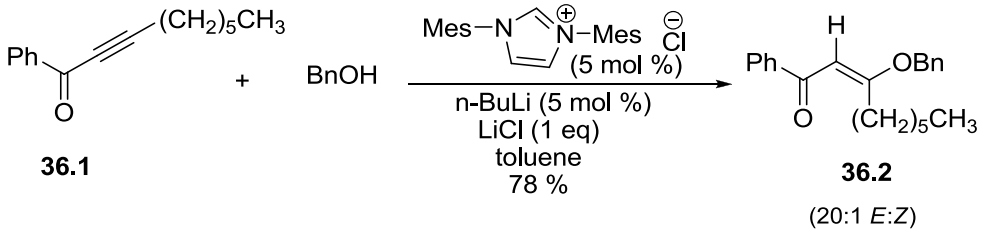


Scheme 34



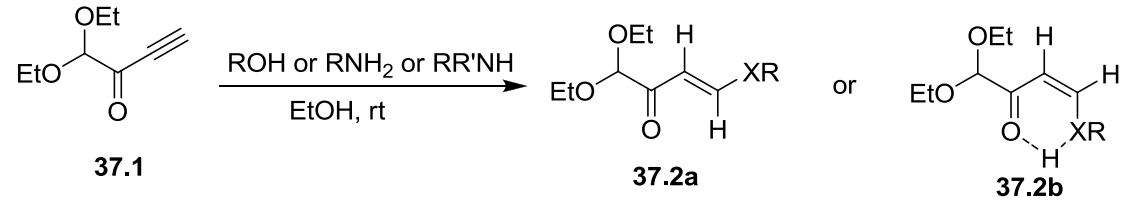
Scheme 35

Despite the lack of examples of the 1,4-addition to the ynone hydrazones, there are a number of close precedents of the conjugate addition to α,β-unsaturated ynones. For example, Scheidt reported *N*-heterocyclic carbene (NHC) catalyzed conjugate addition of benzyl alcohol to obtain enone **36.2**, the *E*-configuration being the major isomer (Scheme 36).[75]



Scheme 36

Recently Sydnes and Sengee reported 1,4-conjugate addition to butynone **37.1** by utilizing various nucleophiles, including primary and secondary amines (Scheme 37).[76] The reaction preferentially provided the *E*-isomer **37.2a**, as a 1,4-adduct. The reaction afforded the *Z*-isomers **37.2b** when primary amines were utilized as nucleophiles perhaps due to the favorable hydrogen bonding in the product.

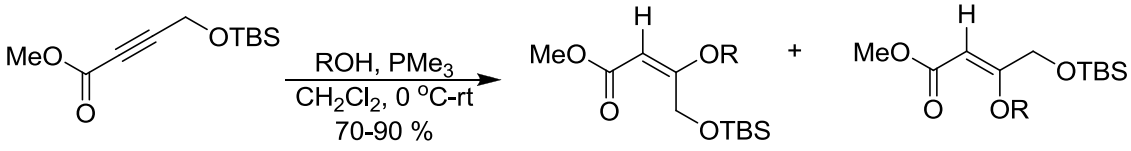


37.1 **37.2a** **37.2b**

X=OH, NH_2, NH

Scheme 37

Another example of 1,4- addition reaction was reported by Paintner in which a variety of alcohols were added to the known butynoate **38.1** in the presence of the nucleophilic catalyst trimethylphosphine to give enol ethers (Scheme 38).[77] The reaction gave up to 90 % product yield with *E*/*Z* ratio ca. 97:3.



38.1 ***E*-38.2a** ***Z*-38.2b**

R= Me, Bn, *i*-Pr, (1R)-menthyl,
$TMSCH_2CH_2$, p-$MeOC_6H_4CH_2$, CH_2=$CHCH_2$

Scheme 38

Therefore, we envisioned to prepare alkenes **34.4** bearing 1,4-stereocenters at the allylic position from reductive transposition of the corresponding hydrazones **34.4** (*cf*. Scheme 34). This type of stereorelationship is commonly found in marine natural products such as nigricanosides that possesses 1,4-diol and a 1,4-diether (Figure 4).[78]

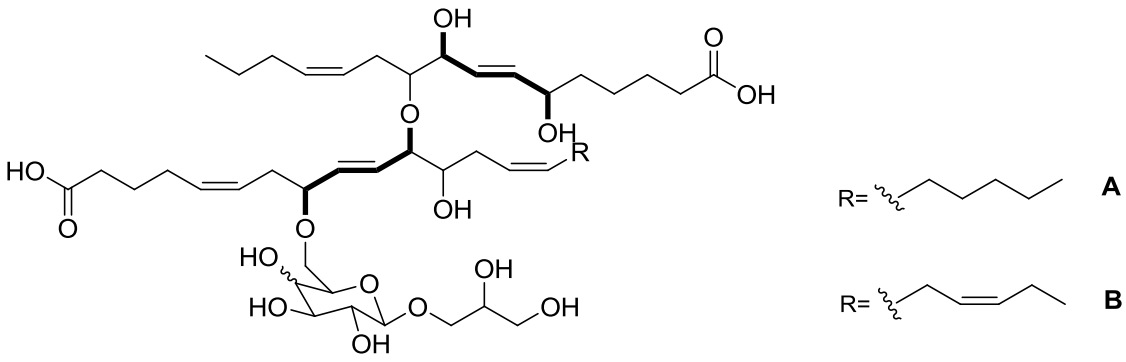
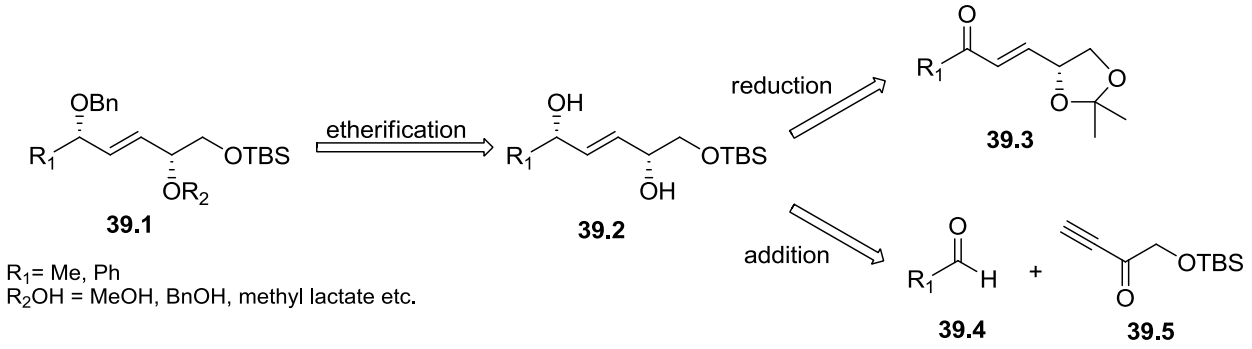


Figure 4

Asymmetrical 1,4-diols are commonly prepared by asymmetric reduction of chiral γ-hydroxy ketones,[79] or addition reactions of 1-alkyne-3-ols.[80] However these methodologies may not be practical in total synthesis because two different chiral sources may be required to establish the stereocenters. Further, these diols could be employed to obtain alkoxy alcohol or dialkoxy alkenes by the standard etherification procedure i.e. Williamson's ether synthesis (Scheme 39).[81] However, the major complication of the reaction may arise due to the competition with the base catalyzed elimination when secondary alcohol such as, methyl lactate is used as a nucleophile.[82]



Scheme 39

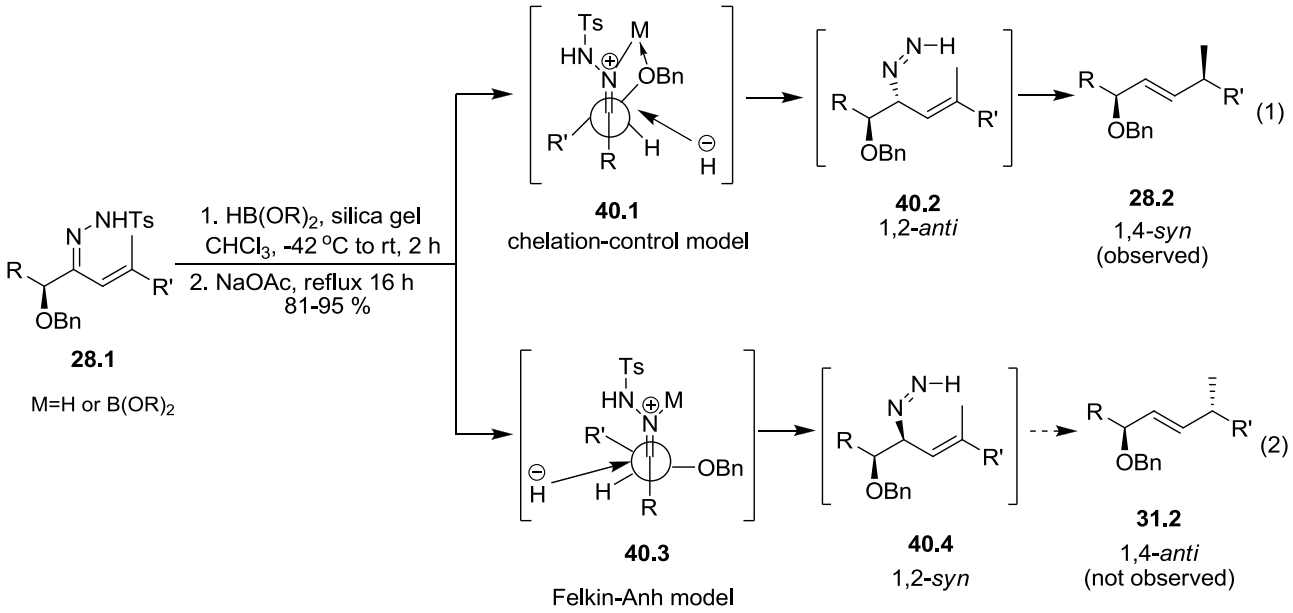
It could be possible to avoid these complications and synthesize the acyclic 1,4-alkoxy alcohol or 1,4-dialkoxy alkenes **34.5** by using asymmetric reduction/ADR of the corresponding hydrazones (*cf*. Scheme 34). The methodology may provide alkenes with varying 1,4-functionality including hydroxyl amines and hydroxyl ethers. The expansion of the asymmetric reduction/ADR in acyclic system depends upon the appropriate configuration of the precursor hydrazones. Therefore, stereoselective hydrazone preparation is the key step towards the successful transformation to the desired alkenes. Details on hydrazone preparation involving tetrasubstituted hydrazones and ynone hydrazones will be discussed in the next chapter.

II. RESULTS AND DISCUSSION

A. DIASTEREOSELECTIVITY IN REDUCTION/ADR OF TOSYL HYDRAZONES

1. α,β-Unsaturated Tosyl hydrazones

As mentioned previously, Qi and McIntosh developed a procedure for reductive transposition of trisubstituted hydrazones to afford disubstituted *E*-alkenes with alkoxy and alkyl stereocenters at the allylic positions (*cf*. Scheme 28).[63] Since 1,4-*syn* alkenes were obtained in the reduction/ADR of α,β-unsaturated *E*-hydrazones, the 1,2-*anti* isomer must have been produced in the hydrazone reduction step (Scheme 40). A chelation control model can be used to rationalize the formation of the 1,2-*anti* product from the reduction. Chelation with either proton or $B(OR)_2^+$ is possible. According to this model, hydride attacks from the less hindered side of the chelate ring to give the 1,2- *anti* product. The 1,4-*syn* alkene was obtained as a result of suprafacial delivery of the hydrogen atom in the ADR. If the reaction followed the Felkin-Anh model, the hydride would attack from the opposite side affording the 1,2-*syn* product **40.4** and we would have obtained 1,4-*anti* alkene after the ADR (Scheme 40, eq. 2).

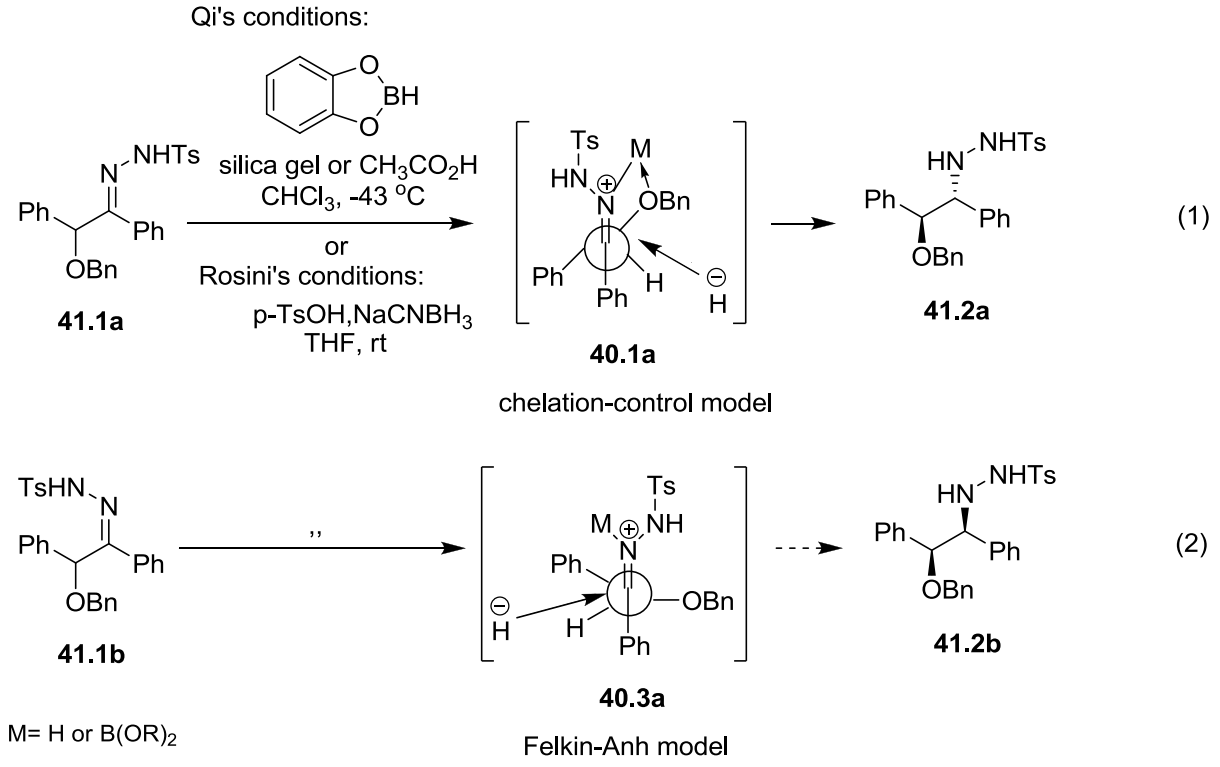


Scheme 40

2. O-Benzyl Benzil Hydrazones

If the *E*-hydrazone undergoes reduction to afford 1,2-*anti* product, it could be also possible to obtain the 1,2-*syn* product from the reduction of the *Z*-hydrazone *via* Felkin-Anh pathway. We hypothesized that the *E*/*Z* configuration of the hydrazones may affect the diastereoselectivity of the reduction. Furthermore, it could be noteworthy to isolate the intermediate after the reduction and determine its configuration. To alleviate these issues, we examined the effect of the *E*/*Z* configuration of the O-benzyl benzil hydrazones in the diastereoselective reduction. O-Benzyl benzil hydrazones were chosen since the phenyl substituent of the hydrazone prevents the ADR from occurring which enables us to determine the diastereoselectivity of the reduction product by isolating the intermediate.

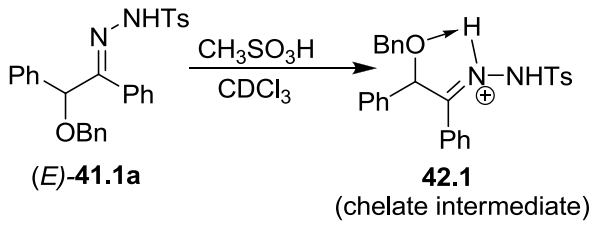
Reduction of the *E*-hydrazone **41.1** afforded 1,2-*anti* product **41.2** under both Rosini's[57] Qi's conditions (Scheme 41, eq. 1).[63] Although we were unable to obtain a pure 1,2-*anti* reduction product **41.2**, we were able to determine the configuration of the product based on the coupling constants provided in Rosini's report.[57] We also expected to obtain the 1,2-*syn* product when the *Z*-hydrazone **41.1b** was subjected for the reduction (Scheme 41, eq. 2). However, we could only recover the starting material from the reaction. According to the conformational analysis, the *Z*-hydrazone is unreactive presumably due to the sterically hindered substrate, blocking the hydride attack. These results suggest that the configuration of the hydrazones is important in reduction since only the *E*-hydrazone undergoes reduction providing 1,2-*anti* product. The stereoselectivity of the reduction in the *E*-hydrazone is most likely controlled by chelation.



Scheme 41

3. Proof of Chelation

We also performed NMR experiments to study the chelation effect that facilitates the 1,2-*anti* reduction of the O-benzyl benzil *E*-hydrazone. Firstly, a solution was prepared by adding O-benzyl benzil *E*-hydrazone **41.1a** and methanesulfonic acid (1:1) in $CDCl_3$ (Scheme 42). Methanesulfonic acid was used instead of toluenesulfonic acid because of its higher solubility in $CDCl_3$. The proton NMR showed the disappearance of the sulfonamide proton of the *E*-hydrazone immediately after mixing the sample (Figure 5). The methyl, benzylic and methine protons were shifted downfield compared to that of the *E*-hydrazone. These results suggest that an intermediate **42.1** may possibly form by chelation of hydrazone with proton.



(*E*)-**41.1a** **42.1** (chelate intermediate)

Scheme 42

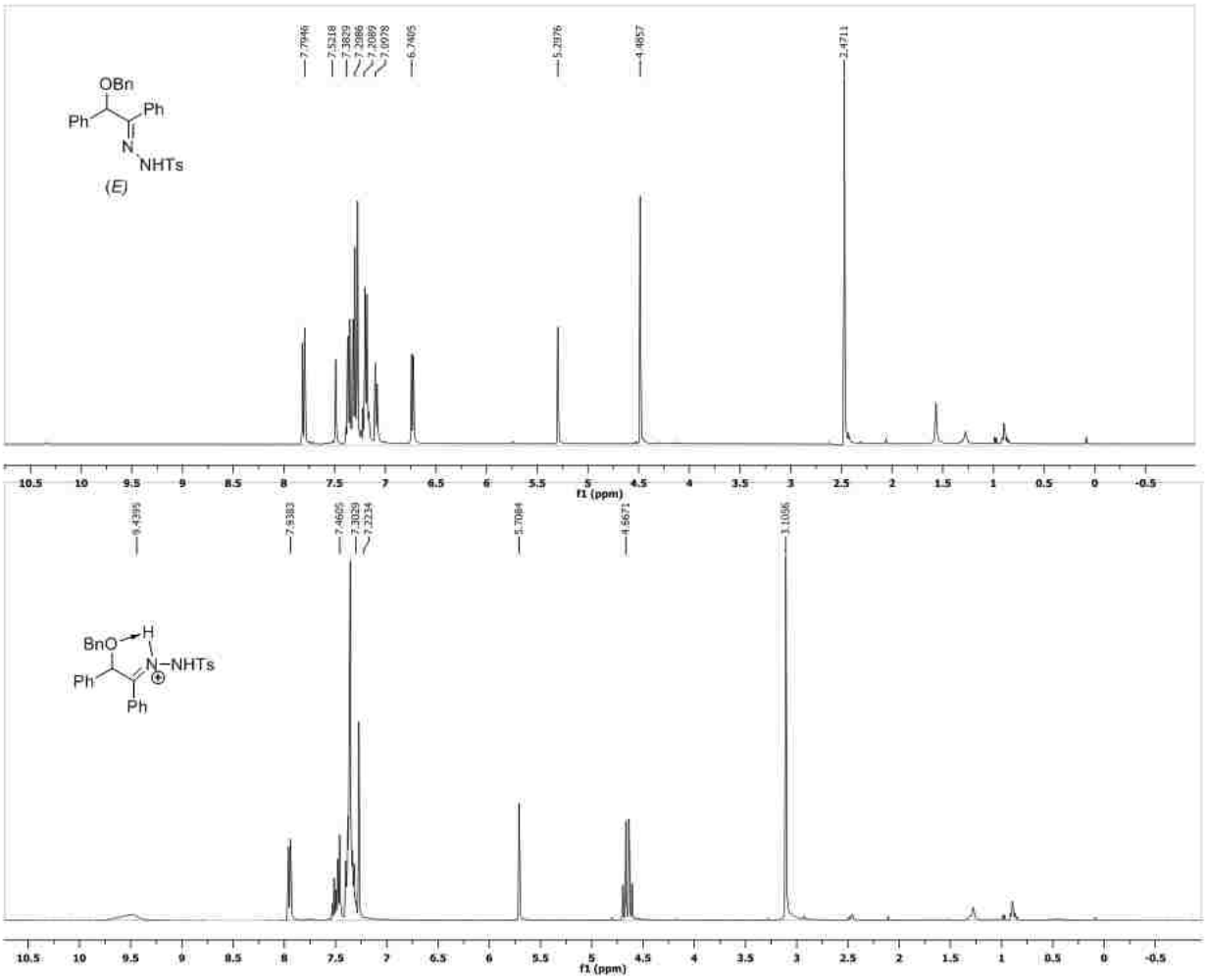
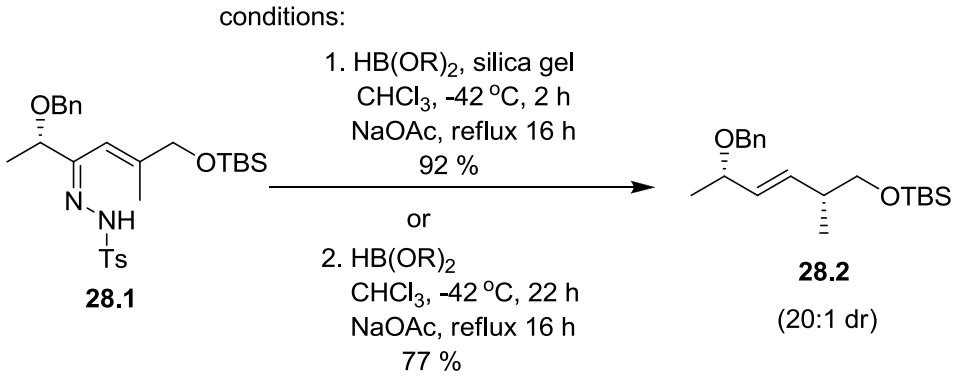


Figure 5: ^{1}H NMR of the reaction between *E*-hydrazone and methanesulfonic acid

B. EFFECTS OF SILICA GEL AND PROTIC ACIDS

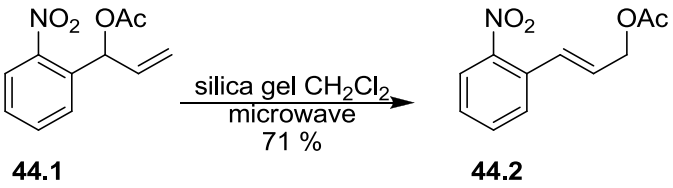
Qi has found that the reductive transposition of hydrazones in the presence of silica gel gave high yield with ≥ 20:1 diastereoselectivity.[63] We reexamined this result and found that the reaction gave very high yield when silica gel was utilized for the reduction, whereas the reaction with no silica gel gave moderate yield and much longer reaction time was required.



Scheme 43

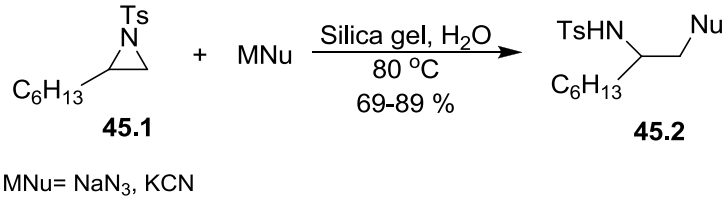
These results clearly demonstrate that silica gel not only accelerates the reduction but also gives better product yield. However the role of silica gel was unclear. The pK_a value of the silanol group of silica gel has been determined to be 7.1 ± 0.5.[83] The silica gel used in our lab was purchased from SORBENT and the pH range of the silica gel was specified as 6.5-7.0.

There are numerous examples of organic reactions utilizing silica gel as an acidic catalyst.[83,84] In one example, silica gel was used as an acidic catalyst for the rearrangement of the allylic acetate **44.1** (Scheme 44).[85]



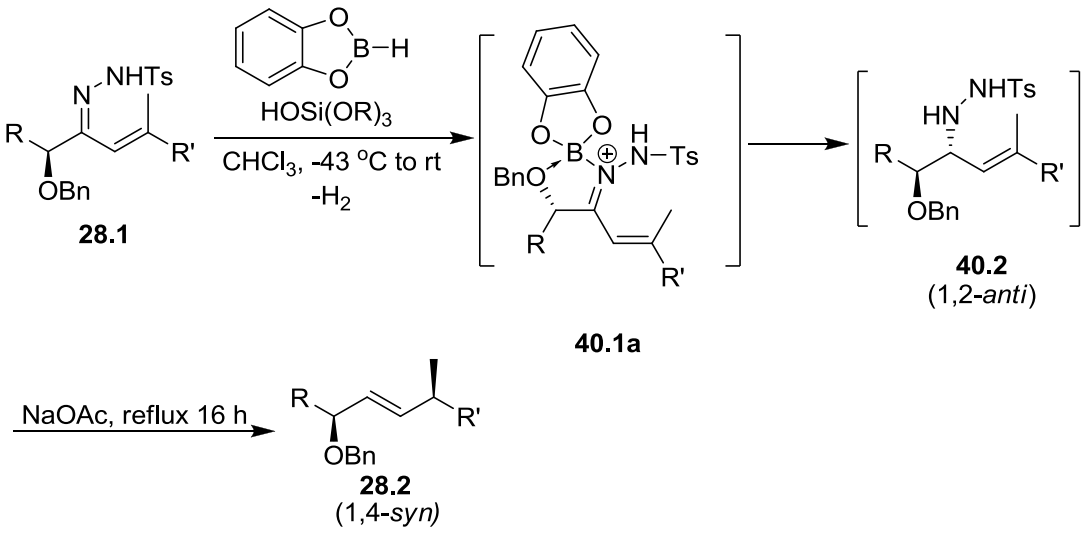
Scheme 44

Another example reported by Minakata also showed that acidic nature of silica gel facilitated the ring opening of the aziridine **45.1**.[86] The reaction did not proceed without silica gel (Scheme 45).



Scheme 45

Therefore, we speculated two possible roles of silica gel in reduction/ADR of the hydrazones due to a weakly acidic nature of the silica gel: 1) formation of a chelating boronium ion **40.1a** *via* elimination of H_2 (Scheme 46). The boronium ion **40.1a** is similar in structure to the known boronium ion (Figure 6); in both cases the boron is covalently bonded to two phenolic oxygens, an imine nitrogen, and possesses a dative bond to an ether oxygen.[87,88]



Scheme 46

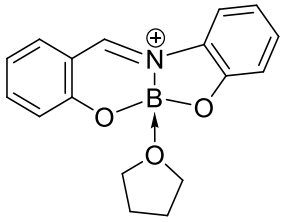
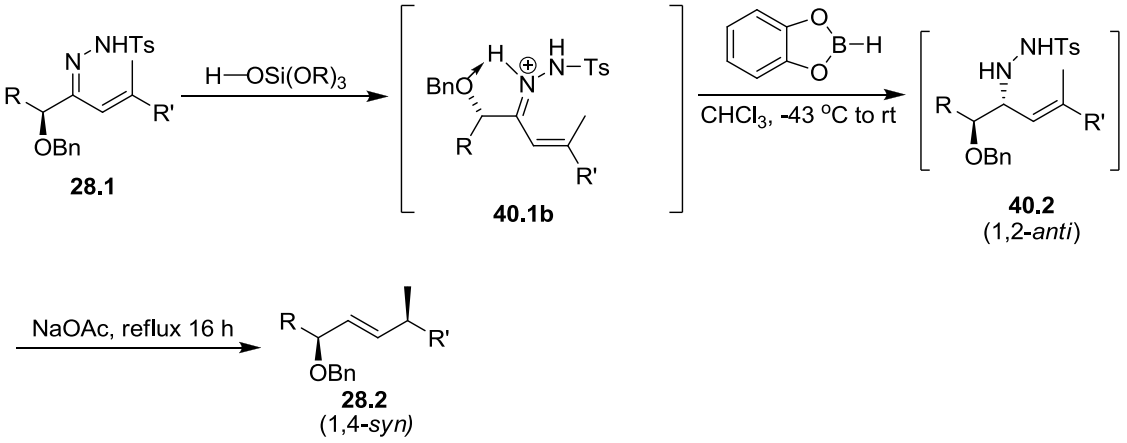


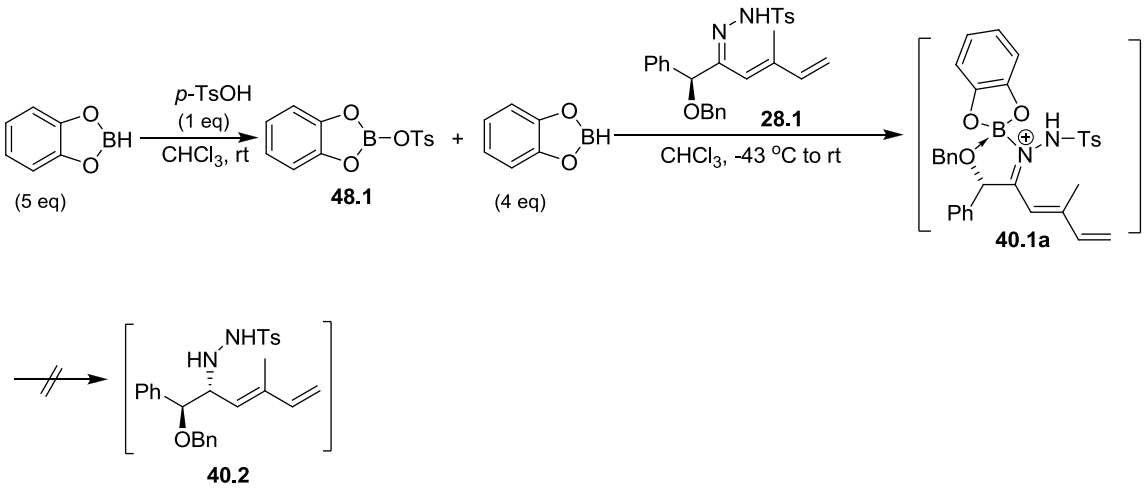
Figure 6: Boronium ion

2) formation of a 5-membered chelate intermediate with a proton from silica gel so that hydride would attack iminium ion **40.1b** to afford 1,2 *anti*-product **40.2** from reduction (Scheme 47).



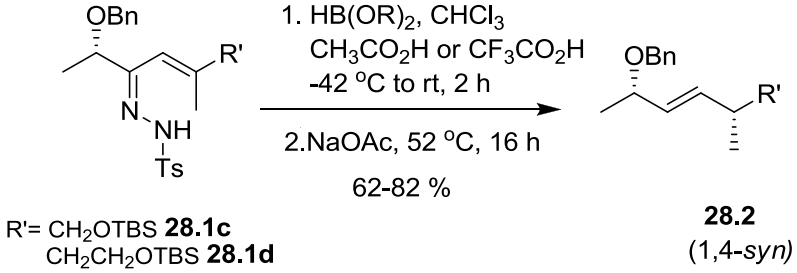
Scheme 47

The first hypothesis was tested by reacting 5 eq of catecholborane with 1 eq of *p*-toluenesulfonic acid followed by addition of hydrazone (Scheme 48). When catecholborane was treated with *p*-toluenesulfonic acid, bubbling occurred presumably due to evolution of H_2 gas. After cessation of bubbling, diene *E*-hydrazone **28.1** was added; however, the intermediate **40.2** was not observed by TLC analysis. Starting material **28.1** was recovered from the mixture. Under these conditions, protonation of the substrate should not be possible since all of the acid had reacted with catecholborane and a catecholborane-derived species would have to serve as the chelating agent. This result suggests the silica gel serves as an acid to provide a 5-membered chelate intermediate **40.1b**.



Scheme 48

The second hypothesis was tested by replacing silica gel with a protic acid in reduction/ADR. Although the reductive transposition of hydrazones in the presence of silica gel gave high yield with 20:1 diastereoselectivity,[63] it would be preferable to replace insoluble silica gel[89] with a soluble well defined protic acid such as acetic acid. Another drawback of using silica gel is that it might not be practical to use stoichiometric amounts (2 wt. eq) of silica gel in large-scale preparations. When 6-10 eq of acetic acid was used instead of silica gel in Qi's conditions, trisubstituted alkene *E*-hydrazones **28.1c** and **28.1d** gave good yields (Scheme 49, Table 1, entry 1,3). However, the reaction gave lower yield when trifluroacetic acid was used with substrate **28.1c**. (Table 1, entry 2). These results demonstrate that acetic acid can be an alternative to silica gel for chelation to facilitate the reduction.

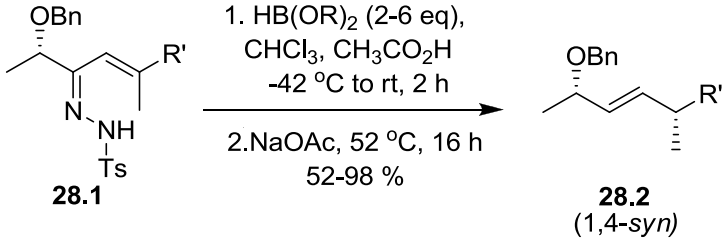


Scheme 49

Entry	Substrate	Protic acids	Yield (%)
1.	**28.1c**	CH_3CO_2H	82
2.	„	CF_3CO_2H	62
3.	**28.1d**	CH_3CO_2H	62-80

Table 1: Reductive transposition by using protic acids

We next sought to optimize the reaction conditions by lowering the amount of catecholborane in 0.040 g scale reaction. Previously, 5.85-6 eq of catecholborane were used for reductive transposition of hydrazones. We found that there were no differences in product yield when 6 eq or 3 eq of catecholborane was used (Table 2, entry 1-3). The amount of catecholborane could be further decreased to 2 eq, but gave lower yield and required longer reaction time (Table 2, entry 6 and 7).



Scheme 50

Entry	**$HB(OR)_2$ (eq)**	**Time (h)**	**Yield (%)**
1.	6	2	97-98
2.	4	,,	,,
3.	3	4	98
4.	2.5	2	96
5.	2.2	,,	93
6.	2	4	75
7.	2	22	52

Table 2: Optimization by lowering the amount of catecholborane

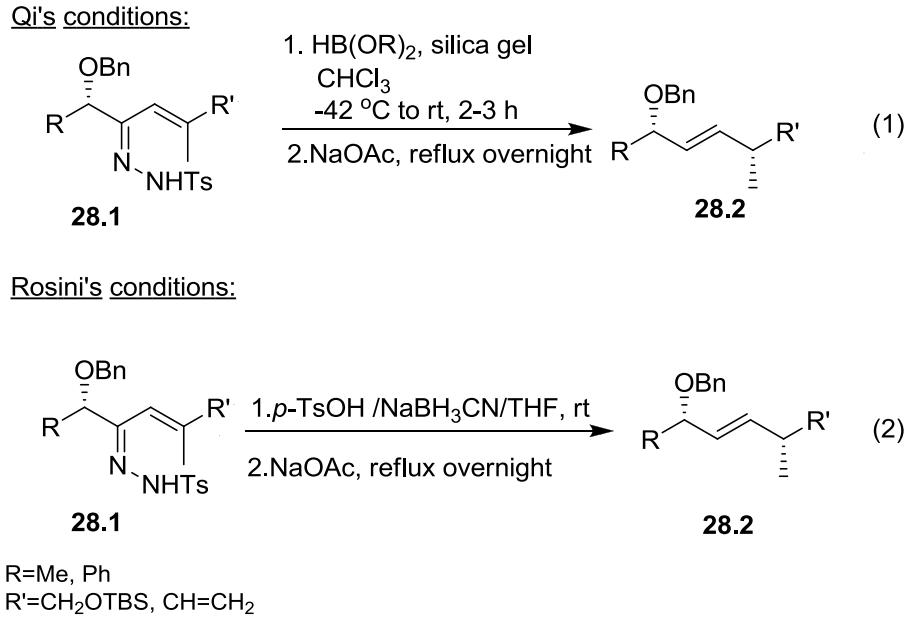
Scaling up the reaction by using 0.100 g of the substrate **28.1c** also gave similar results (Table 3, entry 1-4). The use of 2.5 eq or 3 eq of catecholborane did not show any significant difference. The reaction gave high yield after 4 h reduction followed by ADR. Therefore, 3 eq of catecholborane and 4 h reduction time were utilized as the optimum conditions. We have also demonstrated the usefulness of the reaction by further scaling up the reaction to 0.4 g (entry 5).

Entry	**Rxn scale (g)**	**$HB(OR)_2$ (eq)**	**Time (h)**	**Yield (%)**
1.	0.100	2.5	2	82
2.	,,	,,	4	92
3.	,,	3	2	80-82
4.	,,	,,	4	92
5.	0.400	,,	4	85

Table 3: Optimization by scaling up the reaction

C. COMPARISIONS OF CONDITIONS FOR REDUCTION

During the course of optimization, we have also utilized different reaction conditions for the reductive transposition of α,β-unsaturated hydrazones and compared the results. For this purpose, we have employed four different substrates **28.1a-d** (Figure 7).[63] Firstly we examined Qi's conditions (Scheme 51, eq. 1)[63] and Rosini's conditions (Scheme 51, eq. 2)[57] for reduction/ADR.



Scheme 51

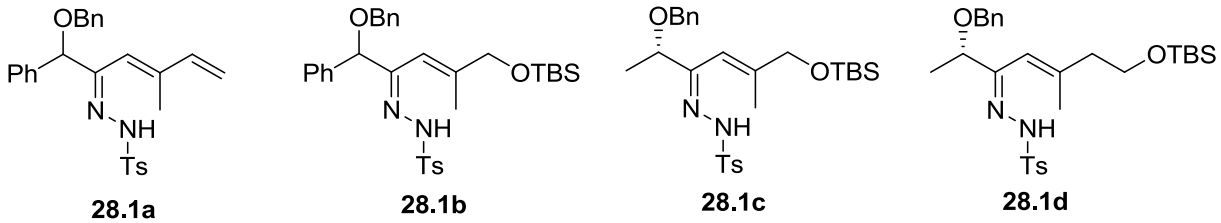


Figure 7

Substrate **28.1a** gave similar results (85-90 %) under both Qi's and Rosini's conditions (Table 4). However, Qi's conditions gave higher yield with substrate **28.1b**. When silica gel was replaced with *p*-toluenesulfonic acid in Qi's condition, only the decomposition of the starting material occurred. Further, the reaction gave a much lower yield from the reduction/ADR of hydrazone **28.1c** compared to that of Qi's conditions when acetic acid was utilized instead of *p*-toluenesulfonic acid in Rosini's conditions (Table 4, entry 7)

Entry	**Substrate**	**Our conditions**	**No. of runs**	**Results/ Yield (%)**	**Rosini's Conditions**	**No. of runs**	**Results/ Yield (%)**
1.	**28.1a**	Silica gel/$CHCl_3$	3	90	*p*-TsOH/THF	2	85-90
2.	,,	*p*-TsOH/$CHCl_3$	2[a]	No product[b]	-	-	-
3.	,,	*p*-TsOH/THF	1[a]	,,	-	-	-
4.	**28.1b**	Silica gel/$CHCl_3$		88[c]	*p*-TsOH/THF	2	40
5.	,,	*p*-TsOH/$CHCl_3$	1	No product[b]	-	-	-
6.	,,	*p*-TsOH/THF	,,	,,	-	-	-
7.	**28.1c**	Silica gel/$CHCl_3$		92[c]	CH_3CO_2H	1	58

Table 4: Comparative results of reduction /ADR by using Rosini's conditions and Our conditions

Note:

a = Catecholborane and *p*-TsOH were stirred at room temperature for about 6 h and then substrate was added.

b = Desired product was not formed. The reaction gave decomposition of the starting material or an unidentified side product.

c = Results from Qi and McIntosh's paper.

These results clearly show that Rosini's conditions could be useful for diene hydrazone **28.1a** reduction; however, not suitable for the hydrazone **28.1b** presumably due to strongly acidic conditions (Table 4 and 5). Furthermore, we compared the cost effectiveness of the reducing agents i.e.; sodium cyanoborohydride and catecholborane. Although, Rosini's conditions offer more economic procedure using sodium cyanoborohydride, our conditions could be beneficial for the reduction/ADR of the acid sensitive substrates.

	Reagent	**Cost of Reagent**	**Acidity**
Our conditions	$HB(OR)_2$	$491.06/mol	mild
Rosini's conditions	$NaCNBH_3$	$153.97/mol	strong

Table 5: Comparisions of conditions for reduction

III. CONCLUSION

We have developed the procedure for acyclic reductive transposition of α,β-unsaturated tosyl hydrazones to obtain alkenes with 1,4-stereocenters by successfully replacing silica gel with a well-defined protic acid. Reaction optimization was also satisfactory since only 3 eq of catecholborane can be used to get high yield. We have also demonstrated that this reaction would be useful for bigger scale preparation.

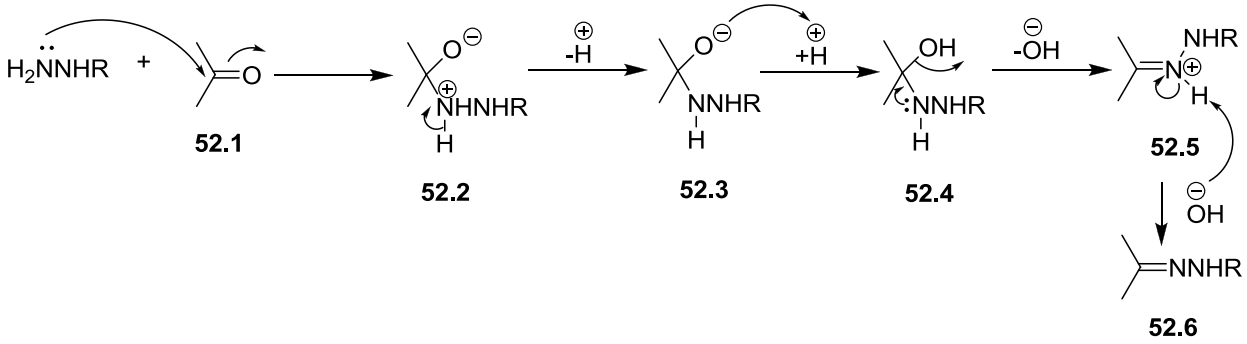
CHAPTER 2:PREPARATION OF HYDRAZONES FROM CARBONYL COMPOUNDS

I. INTRODUCTION

A. MECHANISM OF HYDRAZONE FORMATION

Hydrazones are synthetic precursors to generate diazene intermediates in a number of organic reactions, including Wolf-Kishner reduction,[1] allylic diazene rearrangement[3] and Bamford-Stevens reaction.[90]

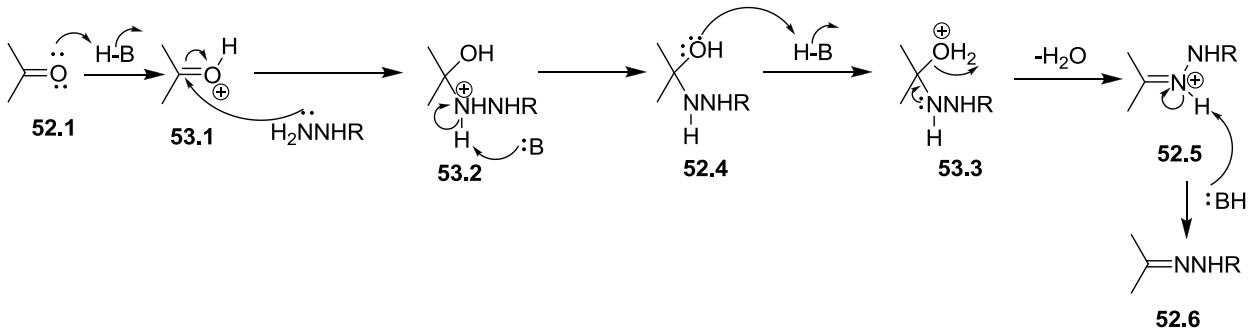
Hydrazones are generally prepared by reacting aldehydes or ketones with hydrazine or an *N*-substituted hydrazine. The mechanism of hydrazone formation follows the general scheme of the carbonyl addition reaction.[91] The reaction mechanism depends on whether the conditions used are acidic, basic or neutral.[92,93,94] Under neutral conditions, the reaction proceeds through attack of the hydrazine on to the carbonyl carbon to provide zwitterionic tetrahedral intermediate **52.2** (Scheme 52).[92] Proton transfer affords hemiaminal **52.4**. The rate determining step in the reaction involves loss of hydroxide affording hydrazone **52.5**.



Scheme 52

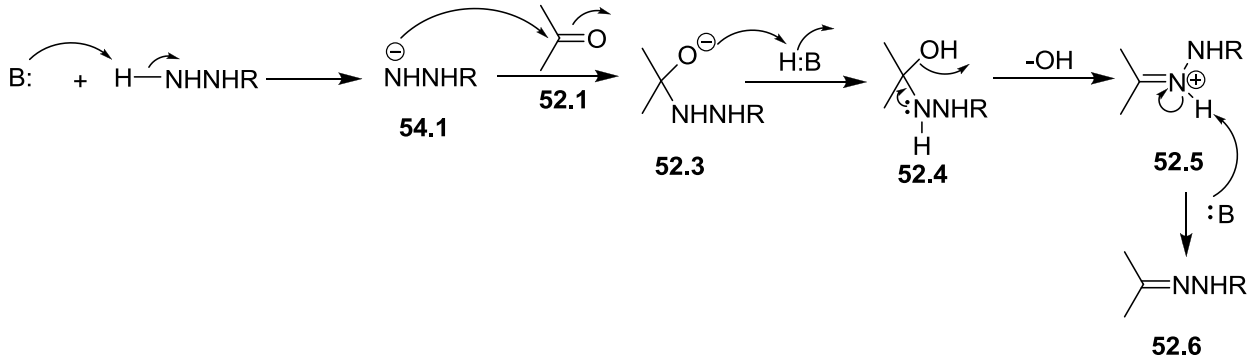
The reaction mechanism of acid or base catalyzed hydrazonation is slightly different from that of uncatalyzed hydrazonation. In the case of acid catalyzed reactions, protonation at the carbonyl oxygen takes place first, which facilitates carbonyl addition of the nucleophile (Scheme 53).[92,95,96] Deprotonation of intermediate **53.2** followed by dehydration gives the hydrazone **52.6**. The dehydration is the rate determining step of the reaction. The acid catalyzed

dehydration step is faster than that of the uncatalyzed step, resulting the change in rate determining step of the reaction.



Scheme 53

Similarly, the mechanism for base catalyzed hydrazonation is as follows (Scheme 54).[92] The pK_a of hydrazine (R=H) is ca. 8.1, therefore base catalysis is preferable to enhance the nucleophilicity of the hydrazine.[97] The reaction proceeds through deprotonation of hydrazine which subsequently attacks to the carbonyl group of **52.1** to give the intermediate **52.3**. Protonation to **52.3** followed by dehydration forms hydrazone **52.6**. The rate determining step of the reaction is the loss of hydroxide of the tetrahedral intermediate **52.4**.

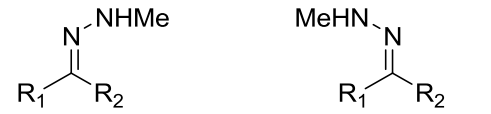


Scheme 54

B. NMR ANALYSIS OF *E*- AND *Z*-HYDRAZONES

Hydrazonation of ketones generally gives a mixture of *E* and *Z* isomers. The *E*/*Z* selectivity of the hydrazones depends upon the reaction conditions and priorities. The

configuration of hydrazones can be determined either by ^{1}H NMR or ^{13}C NMR spectroscopy. In 1967, Karabatos determined the configuration of *N*-methyl hydrazones by utilizing ^{1}H NMR (Figure 8, Table 6).[98] The *E*- and *Z*-geometry of aldehyde and ketone hydrazones were determined based on the chemical shifts of *anti* and *syn* protons attached to the corresponding carbon atom. For example, the α-methyl and *N*-methyl substituents of the *E*-hydrazones appear upfield of the *Z*-hydrazones due to α-methyl group *syn* the NH group of hydrazone (Table 6). Likewise, the β-methyl substituent of the *E*-hydrazones shift upfield compared to that of the *Z*-hydrazones.



E-hydrazone **8a** *Z*-hydrazone **8b**

Figure 8

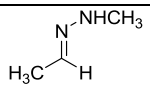
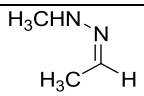
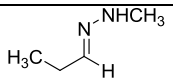
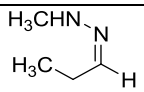
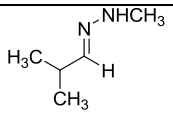
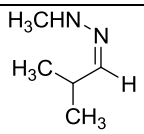
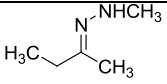
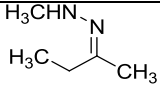
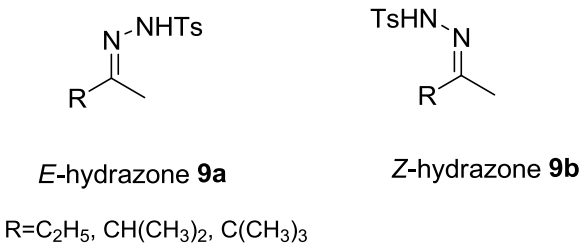
Entry	*E*-hydrazone	Chemical shifts			*Z*-hydrazone	Chemical shifts		
		αCH_3	βCH_3	NCH_3		αCH_3	βCH_3	NCH_3
1.		8.22	-	7.16		8.36	-	7.32
2.		-	9.04	7.17		-	9.25	7.32
3.		-	8.98	7.19		-	9.04	7.33
4.		8.35	9.01	-		8.22	9.24	-

Table 6: Chemical shifts of *E*- and *Z*-methyl hydrazones

Similarly, the configuration of methyl ketone tosyl hydrazones can be determined by ^{1}H NMR based on the chemical shift of the methyl substituent.[98,99] For *Z*-hydrazones of methyl ketones **9b**, the α-methyl group resonates at 1.75-1.80 ppm while for *E*-hydrazones **9a**, it is at ca. 1.92 ppm (Figure 9).

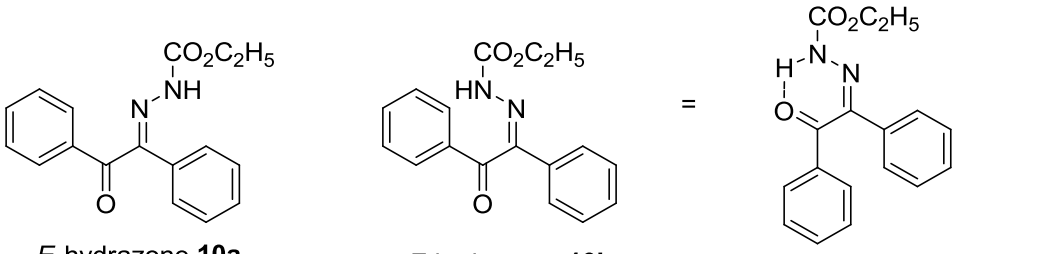


E-hydrazone **9a** *Z*-hydrazone **9b**

R=C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$

Figure 9

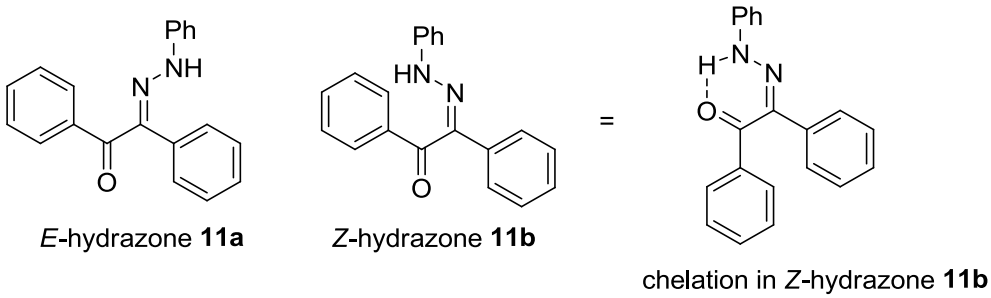
Further, ^{1}H NMR can be utilized to differentiate between *E*/*Z* geometry of carbethoxy α-keto hydrazones (Figure 10).[100] The NH proton of the *Z*-hydrazone **10b** is more deshielded and shifted downfield compared to that of the *E*-hydrazone **10a** due to the internal hydrogen bonding. Therefore, the ^{1}H NMR of NH is the diagnostic feature for the configuration of the hydrazones.



E-hydrazone **10a** *Z*-hydrazone **10b** H-bonding in Z-hydrazone **10b**

Figure 10

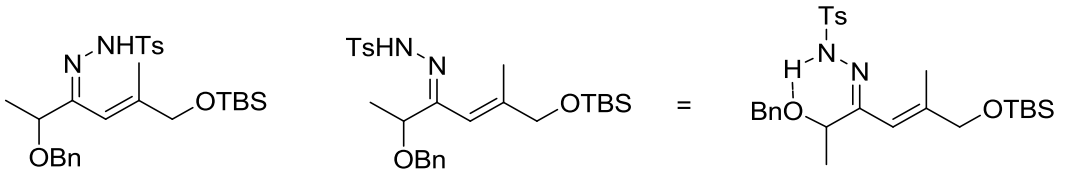
The configuration of monophenyl hydrazones of benzoin were also determined by differentiating the chemical shift values of the NH proton (Figure 11).[101] The NH proton of the *E*-hydrazone **11a** resonates at ca. 8 ppm whereas that of the *Z*-hydrazone **11b** shifts downfield due to the chelation of the NH proton with oxygen.



E-hydrazone **11a** *Z*-hydrazone **11b** chelation in *Z*-hydrazone **11b**

Figure 11

Based on these chemical shift differences of the NH in *E*- and *Z*-hydrazones, our group has been able to differentiate the geometry of the α,β-unsaturated trisubsituted hydrazones (Figure 12).[63] The sulfonamide proton of *E*-hydrazone **12a** is found at ca. 8 ppm while that of *Z*-hydrazone **12b** is at ca. 10 ppm due to the hydrogen bonding in the *Z*-hydrazone.



E-hydrazone **12a** *Z*-hydrazone **12b** H-bonding in *Z*-hydrazone **12b**

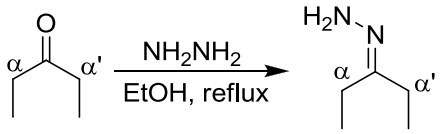
Figure 12

Another important tool to determine the geometry of a variety of ketone hydrazones is ^{13}C NMR. The chemical shift of the α-carbon *syn* to the imino group lies at 12-15 ppm while the α-carbon *anti* to the imino group shifts upfield and resonates at 3-6 ppm (Scheme 55).[102,103] The configuration of hydrazones are therefore determined by taking the difference of the chemical shift of α-carbon of the corresponding ketone and the hydrazone.

Δδ for *syn*-hydrazone=(δC α ketone)-(δC α imine)

Δδ for *anti*-hydrazone=(δC α' ketone)-(δC α' imine)

Thus calculated chemical shift difference for the α-carbon *anti* to the imino group is between 13.7-15.5 ppm whereas it is ca. 10 ppm for the carbon *syn* to the imino group.

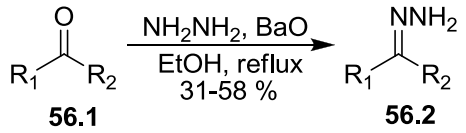


55.1 **55.2**

Scheme 55

C. HYDRAZONES

Traditionally, simple hydrazones were prepared from carbonyl compounds by Curtius and Pflug's procedure.[104] According to the procedure, a solution of anhydrous NH_2NH_2 in EtOH was added slowly to a stirring mixture of the ketone **56.1** and barium oxide, which was used as a dehydrating reagent for hydrazone preparation (Scheme 56).[105,106] The reaction mixture was then heated under reflux for 5-14 h, depending on the substrate used. The ketone hydrazones **56.2** were obtained after extraction followed by distillation. The low product yield (31-58 %) is presumably due to a side product azine, formed by condensation of 2 eq of ketone with 1 eq of hydrazine. However, the author did not suggest a reason for obtaining low yield. The configuration of the asymmetric ketone hydrazone was not reported (Table 7, entry 3).



56.1 **56.2**

Scheme 56

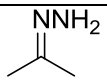
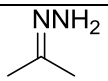
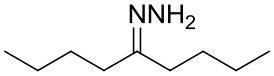
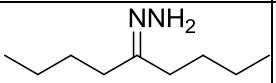
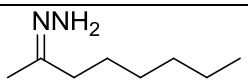
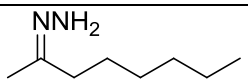
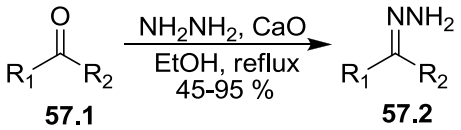
Entry	Ketones	Hydrazones	Yield %
1.			31
2.			38
3.			58

Table 7: Ketone hydrazones

Freshly heated calcium oxide can be utilized instead of barium oxide as a dehydrating agent. Szmant and McGinnis prepared hydrazones of a variety of benzophenones by heating a mixture of calcium oxide, ketone and hydrazine in EtOH under reflux, under the conditions of continuous removal of H_2O (Scheme 57, Table 8).[91] After completion of the reaction, traces of

calcium oxide were removed by filtration and the solution was concentrated to obtain the diaryl hydrazones. The electron rich benzophenone, Michler ketone (Table 8, entry 3) gave very high yield compared to other diaryl hydrazones. The *E/Z* geometry of the hydrazone derived from asymmetric ketone was not reported (Table 8, entry 5).



57.1 **57.2**

Scheme 57

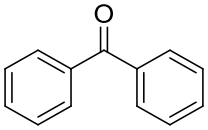
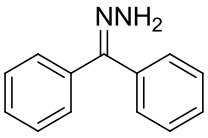
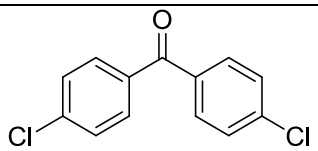
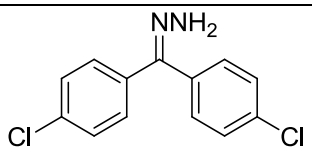
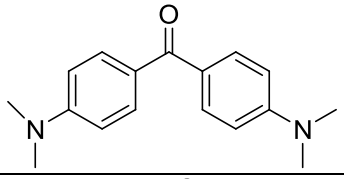
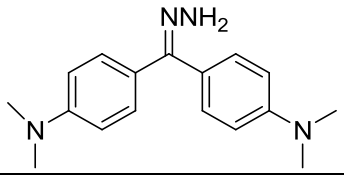
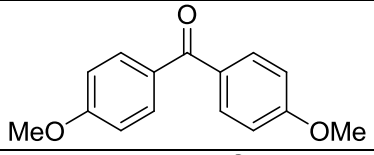
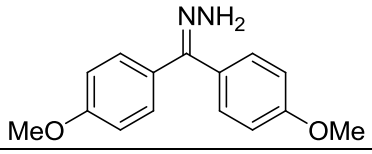
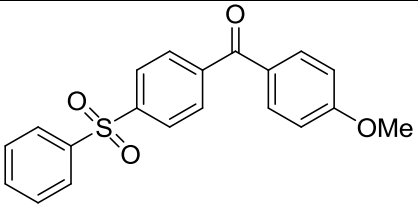
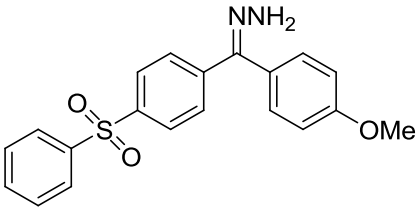
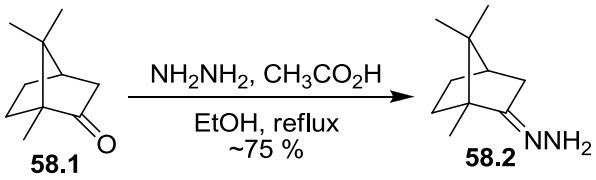
Entry	**Ketone**	**Hydrazone**	**Yield %**
1.			88
2.			45
3.			95
4.			50
5.			50

Table 8: Benzophenone derived diaryl hydrazones

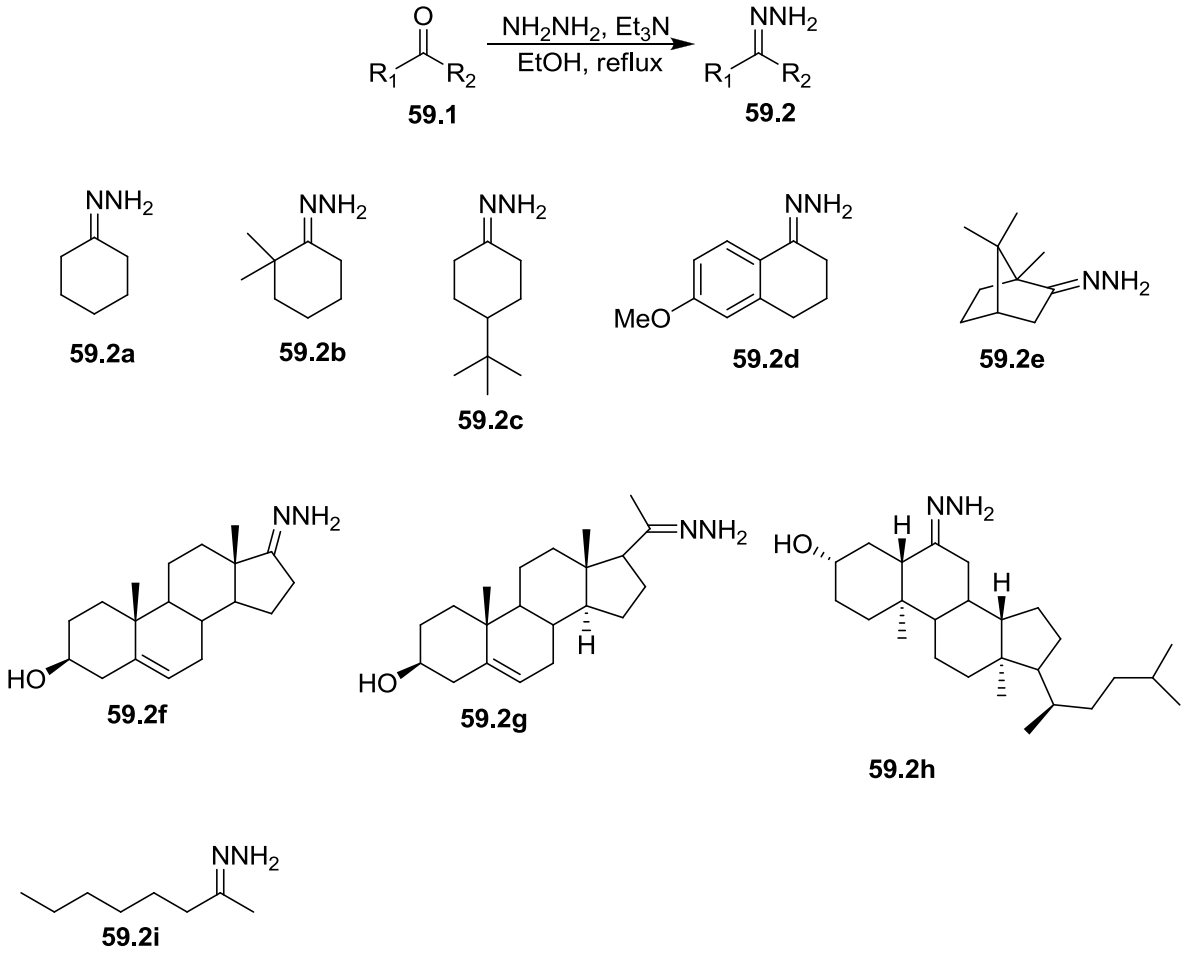
Another variant of hydrazone preparation uses acid catalysis. A variety of acids including CH_3CO_2H, *p*-TsOH, HCl, BF_3.OEt have been used.[107] This type of acid catalyzed hydrazonation was employed with cyclic and acyclic ketones including hindered bicyclic ketones

such as camphor (Scheme 58).[108] In a typical procedure, camphor hydrazone was prepared by mixing *d*-camphor (**58.1**), hydrazine and acetic acid in EtOH and heating under reflux for 4 h. After completion of the reaction, EtOH was removed under reduced pressure and the residue was diluted with ether. Extractive work up followed by distillation under reduced pressure afforded ca. 75 % of hydrazone **58.2**; presumably the *E* hydrazone due to steric reason.[109]



Scheme 58

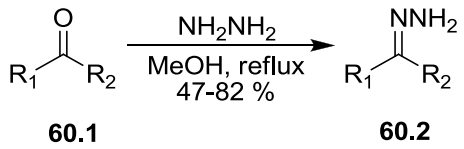
Hydrazones have also been prepared by using triethylamine as a catalyst. Barton reported the preparation of a wide range of cyclic and acyclic ketone hydrazones **59.2** by treating the corresponding ketone **59.1** and hydrazine with triethylamine in EtOH (Scheme 59).[110] The hydrazones were obtained after evaporation of solvent and drying over sodium sulfate followed by recrystallization; however, he did not report the yield or the configuration of these hydrazones.



Scheme 59

Unlike the hydrazone preparations using dehydrating reagents or acid or base catalysts, cyclic and acyclic ketone hydrazones were also prepared by simply heating a solution of hydrazine and corresponding ketone under reflux in absolute MeOH (Scheme 60, Table 8).[111]

Extractive work up followed by distillation gave the pure hydrazones, but the author did not report the *E*/*Z* selectivity of the hydrazone formation (Table 9, entry 2-3). The reaction most likely afforded the sterically favored *E*-hydrazone as the major isomer.



60.1 **60.2**

Scheme 60

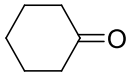
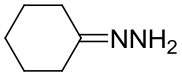
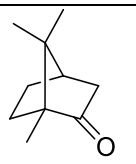
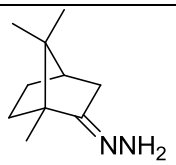
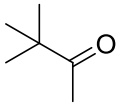
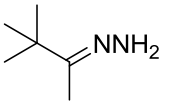
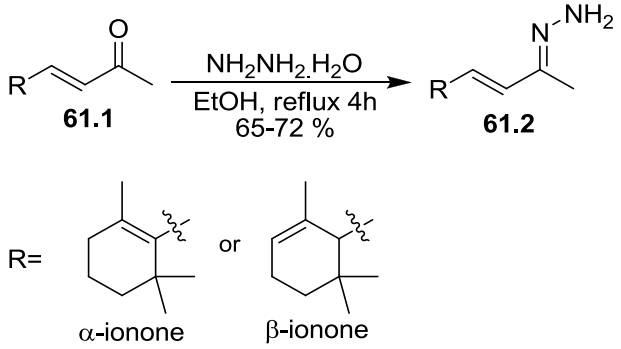
Entry	**Ketones**	**Hydrazone**	**Yield %**
1.			63
2.			47
3.			82

Table 9: Ketone hydrazones derived from cyclic and acyclic ketones

By utilizing a similar procedure, α,β-unsaturated hydrazones such as α-ionone and β-ionone hydrazones were also obtained (Scheme 61).[102] After heating a mixture of the corresponding ionone and hydrazine hydrate under reflux in EtOH, the reaction mixture was extracted with ether and dried with magnesium sulfate. Evaporation of the solvent followed by recrystallization in MeOH afforded only the *E*-hydrazones. The configuration of the *E*-hydrazones **61.2** was determined by using ^{13}C NMR as described previously.



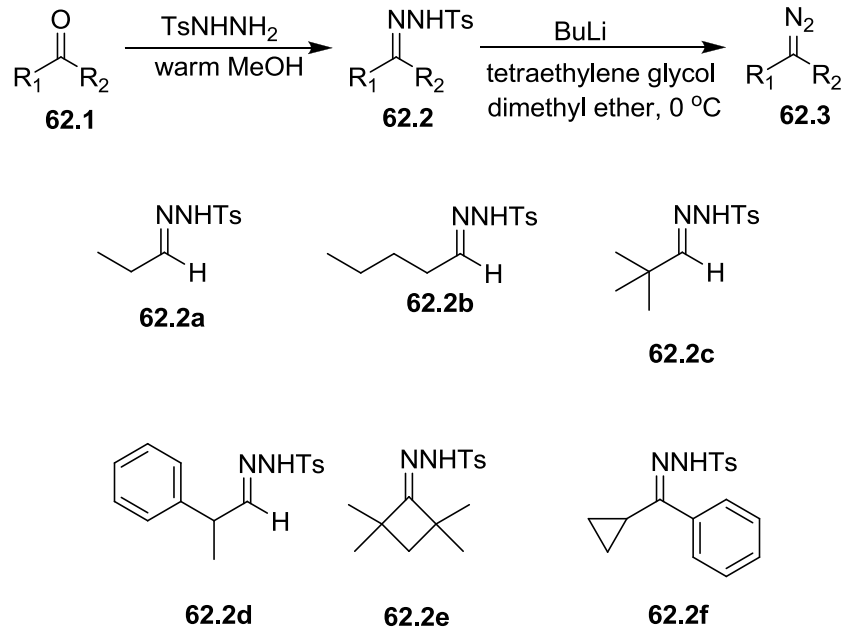
Scheme 61

These results demonstrate that preparation of unsubstituted hydrazones is possible either in presence or in absence of added acidic or basic catalyst.

D. ARYLSULFONYL HYDRAZONES

Similar to the simple hydrazones, arylsulfonyl hydrazones are also useful synthetic intermediates and have been used in organic chemistry for almost 60 years.[112] Aryl sulfonyl hydrazones such as tosyl hydrazones are commonly prepared from carbonyl compounds and tosylhydrazide without using any acidic or basic catalyst. In 1965, Shechter developed a procedure for aldehyde and ketone tosyl hydrazone preparation by warming a mixture of tosylhydrazide and the corresponding carbonyl compound in MeOH (Scheme 62).[113] The product formed was recrystallized from MeOH. Pure hydrazone was obtained after cooling the

reaction mixture to -70 °C and washing with petroleum ether. The procedure worked for both cyclic and acyclic systems; however, some acyclic aldehyde tosyl hydrazones such as **62.2b** decomposed on recrystallization. Product yield and the configuration of the hydrazones were not reported since these hydrazones were directly utilized to prepare diazo compounds *via* lithium salt of tosyl hydrazones. Nevertheless, these aldehyde hydrazones **62.a-d** were likely obtained as the *E*-configuration due to sterically favored isomer.



Scheme 62

A variety of alkyl aryl or diaryl ketone tosyl hydrazones were also obtained by heating an equimolar mixture of corresponding carbonyl compound and tosylhydrazide in MeOH to 50 °C for 12 h (Table 10).[56] The tosylhydrazones crystallized upon cooling and were isolated by filtration. These hydrazones were utilized for the reduction without purification; therefore the product yields and the *E*/*Z* selectivity of the hydrazones were not reported.

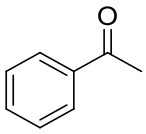
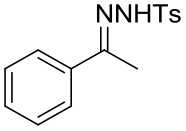
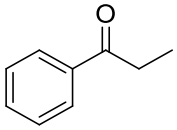
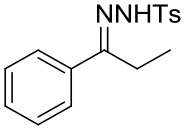
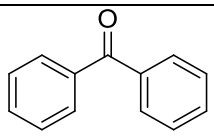
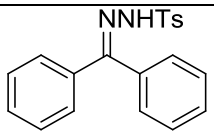
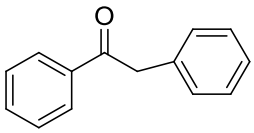
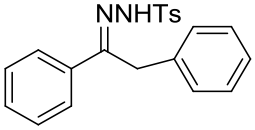
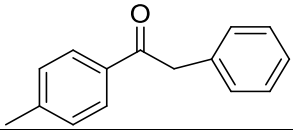
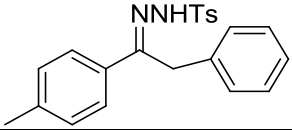
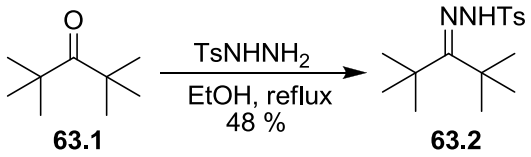
Entry	**Ketones**	**Hydrazones**
1.		
2.		
3.		
4.		
5.		

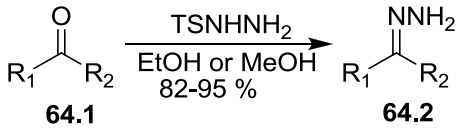
Table 10: Alkyl aryl or diaryl ketone hydrazones

Hutchins' report on hydrazone preparation is noteworthy since he demonstrated that hydrazone formation in DMF-sulfolane was very slow even at high temperature when hindered ketones such as di-t-butyl ketone were used as precursors.[11] However, simply heating the ketone **63.1** and tosylhydrazide in EtOH under reflux provided the corresponding hydrazone (Scheme 63). After cooling the reaction mixture, highly pure crystalline hydrazone was obtained. These results suggest that protic solvent facilitates the hydrazone preparation, presumably due to hydrogen bonding to C=O, making the carbonyl group more electrophilic and the rate determining dehydration step faster.[95,96]



Scheme 63

Rosini prepared a series of aldehyde and ketone tosylhydrazones by utilizing MeOH or EtOH (Scheme 64, Table 11).[114] These hydrazones were obtained in very high yield when a solution of tosylhydrazide and corresponding carbonyl compound were heated in MeOH or EtOH; however, he did not report *E*/*Z* configurations of the hydrazones.



64.1 **64.2**

Scheme 64

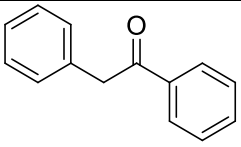
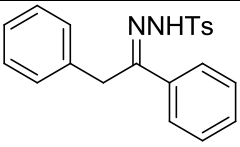
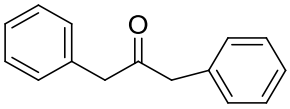
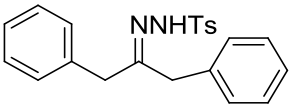
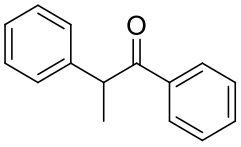
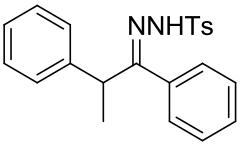
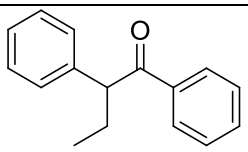
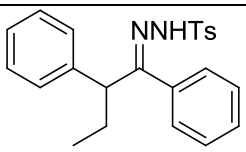
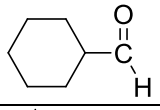
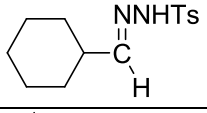
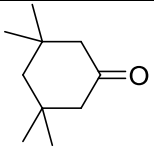
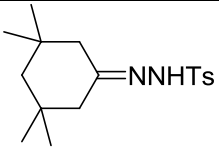
Entry	Aldehyde or Ketone	Tosylhydrazones	Yield %
1.			87
2.			85
3.			82
4.			84
5.			95
6.			87

Table 11: Tosyl hydrazones prepared by Rosini

Surprisingly, Bertz and Dabbagh obtained only a 34 % yield of cyclohexanecarboxyaldehyde tosylhydrazone (*cf*. Table 11, entry 5) when Rosini's procedure

was used.[115] Further, they obtained only 16-36 % yield when Shechter's conditions[113] (warming a methanolic solution of tosylhydrazide and corresponding aldehyde or ketone) were followed for preparation of tosyl hydrazones from 3-methylpentanal and pivaldehyde (Table 12, entry 3-4). Therefore, they investigated different solvents or solvent combinations for hydrazone preparation and recrystallization. A 91 % pure cyclohexanecarboxaldehyde tosylhydrazone was obtained when Bertz's improved procedure was employed (Table 12, entry 1).[115] According to the improved procedure, the recommended solvent for aldehyde hydrazone preparation is MeOH or THF; however, THF gave the best result. Similarly, ketone hydrazones were best prepared in diethyl ether so that they crystallize directly in analytically pure form. These results clearly show that proper choice of solvent is necessary for hydrazone formation. Further, bulkier hydrazones such as trimyl hydrazones (2,4,6-trimethylbenzenesulfonyl hydrazones) and trisyl hydrazones (2,4,6-triisopropylbenzenesulfonyl hydrazones) were also prepared by utilizing a variety of aldehydes or ketones. A mixture of *E*- and *Z*-isomers were also reported in some cases (entry 3-5), however, the ratio of these isomers were not mentioned.

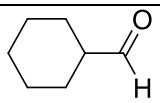
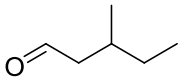
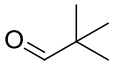
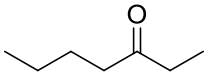
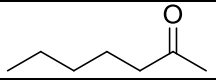
Entry	**Aldehyde or Ketone**	**Hydrazone**	**Yield %**
1.		tosylhydrazone trimylhydrazone	91 57
2.		tosylhydrazone	72
3.		tosylhydrazone	95
4.		trisylhydrazone	65
5.		trisylhydrazone	63

Table 12: Arylsulfonyl hydrazones prepared by Bertz's improved procedure

Similar to Bertz's procedure, Reese reported the preparation of aldehyde and ketone arylsulfonyl hydrazones.[116] Aldehyde arylsulfonyl hydrazones were obtained simply by stirring a solution of aldehyde and corresponding hydrazide in methanol at room temperature. However, a catalytic amount of concentrated HCl was added for ketone hydrazone preparation (Table 13). Acid catalysis was required for ketone hydrazone preparation due to decrease in reactivity of ketone compared to that of aldehyde. Reported yields were a mixture of *E*- and *Z*-hydrazones; however, the ratio of these isomers was not reported.

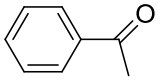
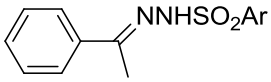
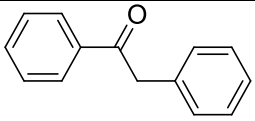
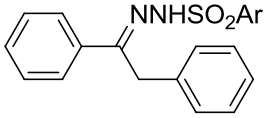
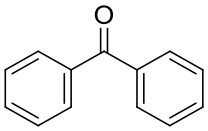
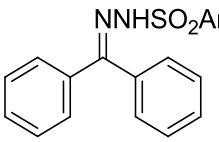
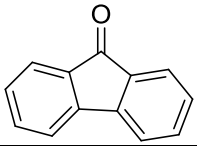
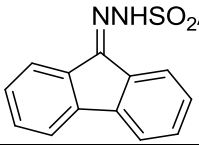
Entry	**Ketone**	**Aryl sulfonyl hydrazone**	**Yield %**
1.			90
2.			95
3.			92
4.			90

Table 13: Aryl sulfonyl hydrazones prepared by Reese

Reese also found that the preparation of trisyl hydrazones afforded more stable hydrazones compared to tosyl hydrazones or trimyl hydrazones presumably due to bulkiness of the aryl substituent.

This type of HCl-catalyzed ketone hydrazone preparation in acyclic systems has also been reported in 1970's (Table 14).[99] Both *E* and *Z* hydrazones were produced from hydrazonation, the *E* hydrazone being the major isomer in case of unsymmetrical ketones. The *E*/*Z* ratio was determined by ^{1}H NMR.[98]

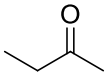
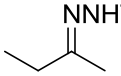
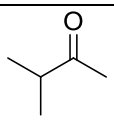
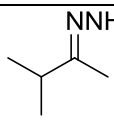
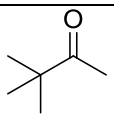
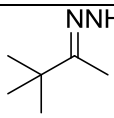
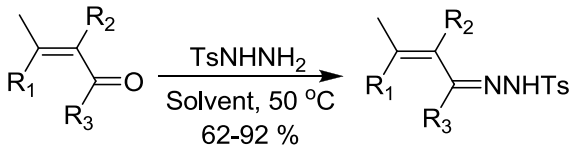
Entry	**Ketone**	**Hydrazone**	***E*/*Z* ratio**
1.			-
2.			83:17
3.			92:8
4.			100:0

Table 14: Diastereoselectivity in ketone hydrazones

Thus, methods to prepare a variety of cyclic and acyclic aldehyde or ketone hydrazones have been developed by using different solvents, acid or base catalyst or heat.

1. Tosyl Hydrazones from α,β-Unsaturated Carbonyl Compounds

There are several reports in the literature describing the preparation of sulfonyl hydrazones of α,β-unsaturated ketones. For example, Closs obtained α,β-unsaturated ketone tosyl hydrazones by heating a mixture of carbonyl compound and tosylhydrazide in MeOH, EtOH or benzene not exceeding 50 °C (Scheme 65, Table 15).[117] These hydrazones were directly employed for synthesis of alkylcyclopropenes *via* base induced pyrolysis; no attempts were made to assign *E*/*Z* configuration of the hydrazones.



65.1 **65.2**

Scheme 65

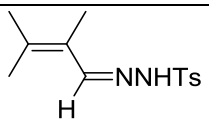
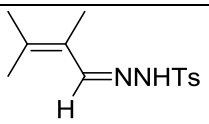
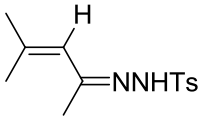
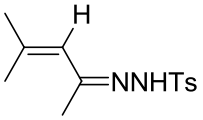
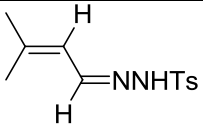
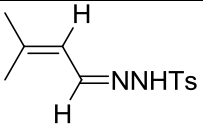
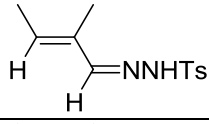
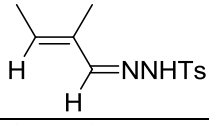
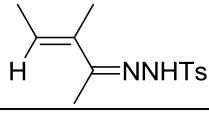
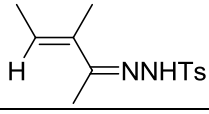
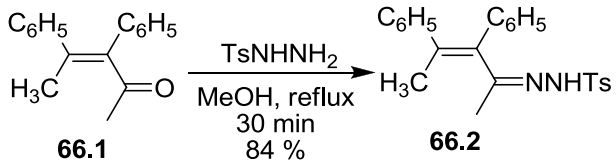
Entry	Aldehyde or ketone	Hydrazones	Yield %
1.			79
2.			70
3.			75
4.			92
5.			62

Table 15: Tosyl hydrazones from α,β-unsaturated carbonyl compounds

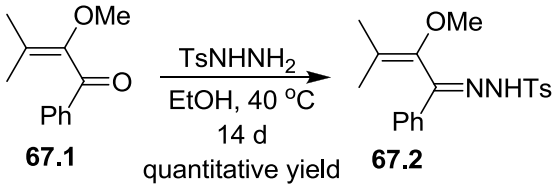
Sato and Watanabe also prepared α,β-unsaturated tosyl hydrazones from the corresponding carbonyl compounds.[118] Mesitylene oxide hydrazone (Table 15, entry 2) was obtained by following Closs procedure (Scheme 65).[117] Similarly, dyphone tosylhydrazone **66.2** was obtained by heating a 1:1 mixture of dyphone **66.1** and tosylhydrazide in MeOH under reflux with a catalytic amount of concentrated HCl for 30 min (Scheme 66). After cooling the solution to room temperature, filtration and recrystallization provided 84 % yield of pure hydrazone; however, the configuration of the hydrazone was not reported.



66.1 **66.2**

Scheme 66

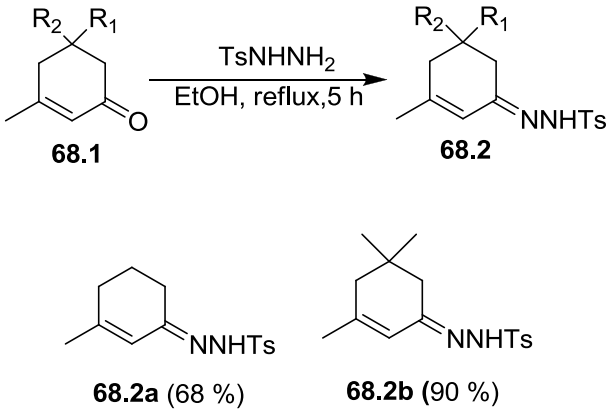
In 1975, Hamon reported tosylhydrazone formation by heating a methanolic solution of 2-methoxy-3-methyl-1-phenylbut-2-en-1-one and tosylhydrazide at 40 °C for 14 days (Scheme 67).[119] Despite the fact that the hydrazone formation was extremely sluggish, the report is significant for providing an α,β-unsaturated tosylhydrazone bearing a OMe substituent at the α-position. The author did not report any other attempts to obtain the hydrazone or provide any reasons for such a slow hydrazone formation.



67.1 **67.2**

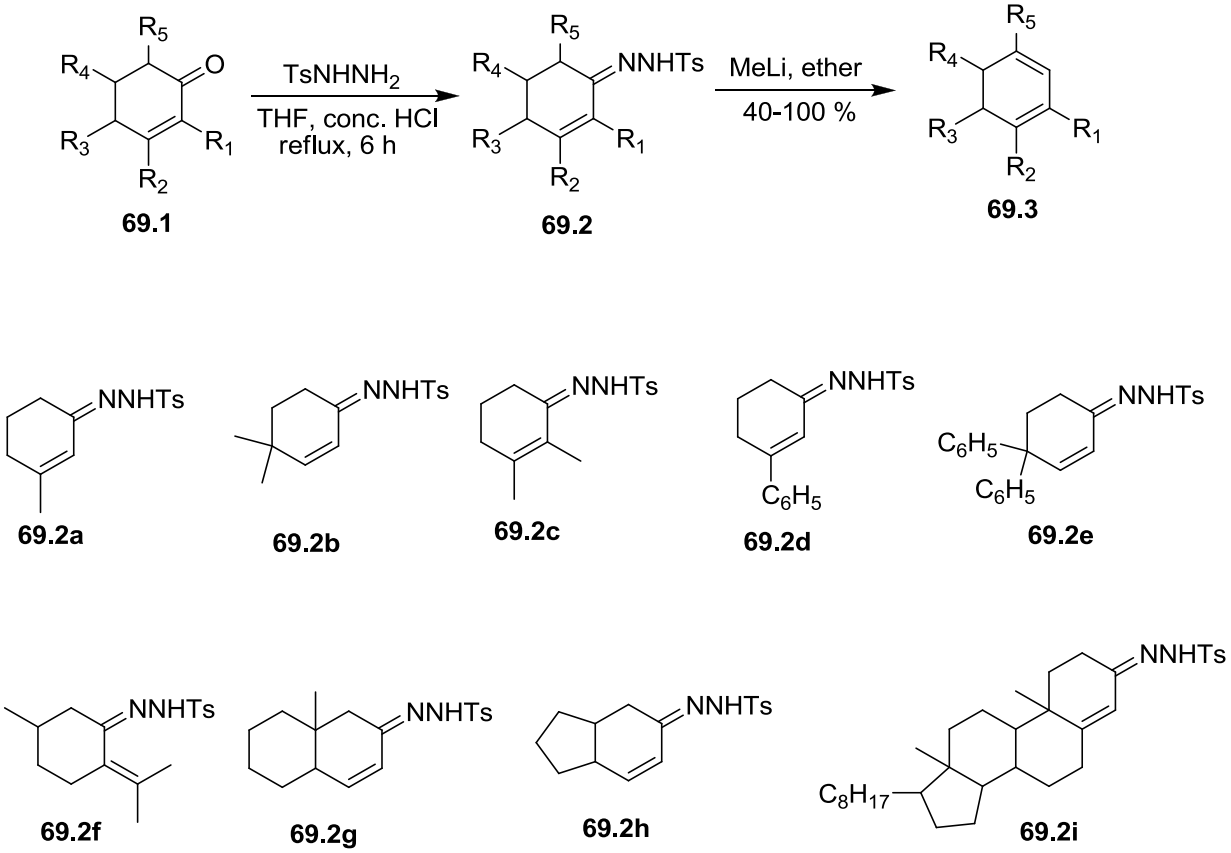
Scheme 67

Similar to the acyclic α,β-unsaturated ketone hydrazones, Freeman prepared cyclic α,β-unsaturated hydrazones by using cyclic ketones (Scheme 68).[120] For this purpose, a methanolic solution of tosylhydrazide and corresponding carbonyl compound was heated for 5 h under reflux. Then water was added to the warm reaction mixture and it was cooled to room temperature. A precipitate was formed upon cooling which was separated by vacuum filtration. The reaction afforded 68-90 % yield as a mixture of the *E*- and *Z*-hydrazones; however, the ratio of these isomers were not reported. The reaction most likely afforded 1:1 *E*/*Z* mixture.



Scheme 68

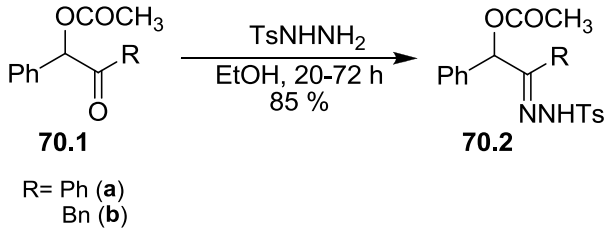
Shapiro *et al* also obtained a variety of α,β-unsaturated tosyl hydrazones by heating a solution of the corresponding cyclic ketone, tosylhydrazide and a catalytic amount of HCl in THF under reflux (Scheme 69).[121] The hydrazones were utilized *in situ* for the synthesis of conjugated dienes *via* treatment with alkyllithium reagents. The yield and the configuration of the hydrazones were not determined; but was likely a mixture of the *E*- and *Z*-hydrazones.



Scheme 69

2. Tosyl Hydrazones from α-Hydroxy and α-Alkoxy Carbonyl Compound

There are also a number of reports of tosyl hydrazones derived from α-hydroxy or α-acetoxy ketones in organic synthesis. In early 1970, Rosini prepared α-acetoxybenzoin tosylhydrazone (**70.2a**) by allowing a solution of α-acetoxydeoxybenzoin (**70.1a**) and tosylhydrazide in EtOH to stand for 3 days (Scheme 70).[122] However, α-acetoxy-1,3-diphenylpropan-2-one tosyl hydrazone (**70.2b**) was obtained after 20 h, presumably due to less hindered substrate compared to α-acetoxybenzoin.



70.1

R= Ph (**a**)
Bn (**b**)

70.2

Scheme 70

Rosini subsequently prepared a variety of α-hydroxy and α-alkoxy benzoin tosyl hydrazones by heating methanolic solutions of benzoins and tosyl hydrazide (Table 16).[57] He did not report the *E*/*Z* configuration of these hydrazones.

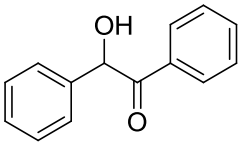
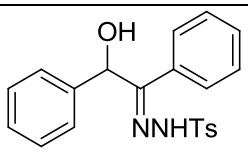
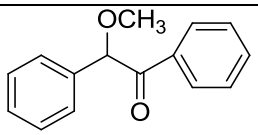
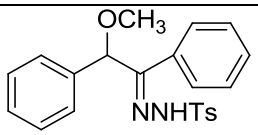
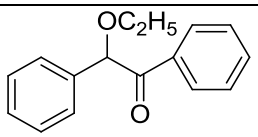
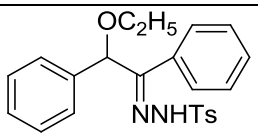
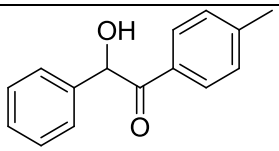
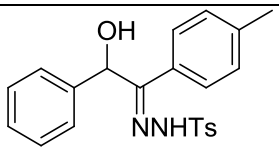
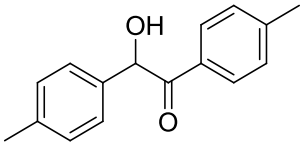
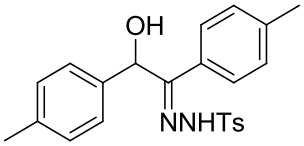
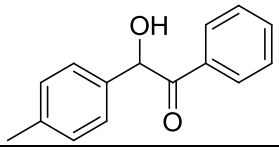
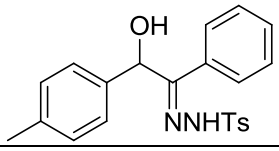
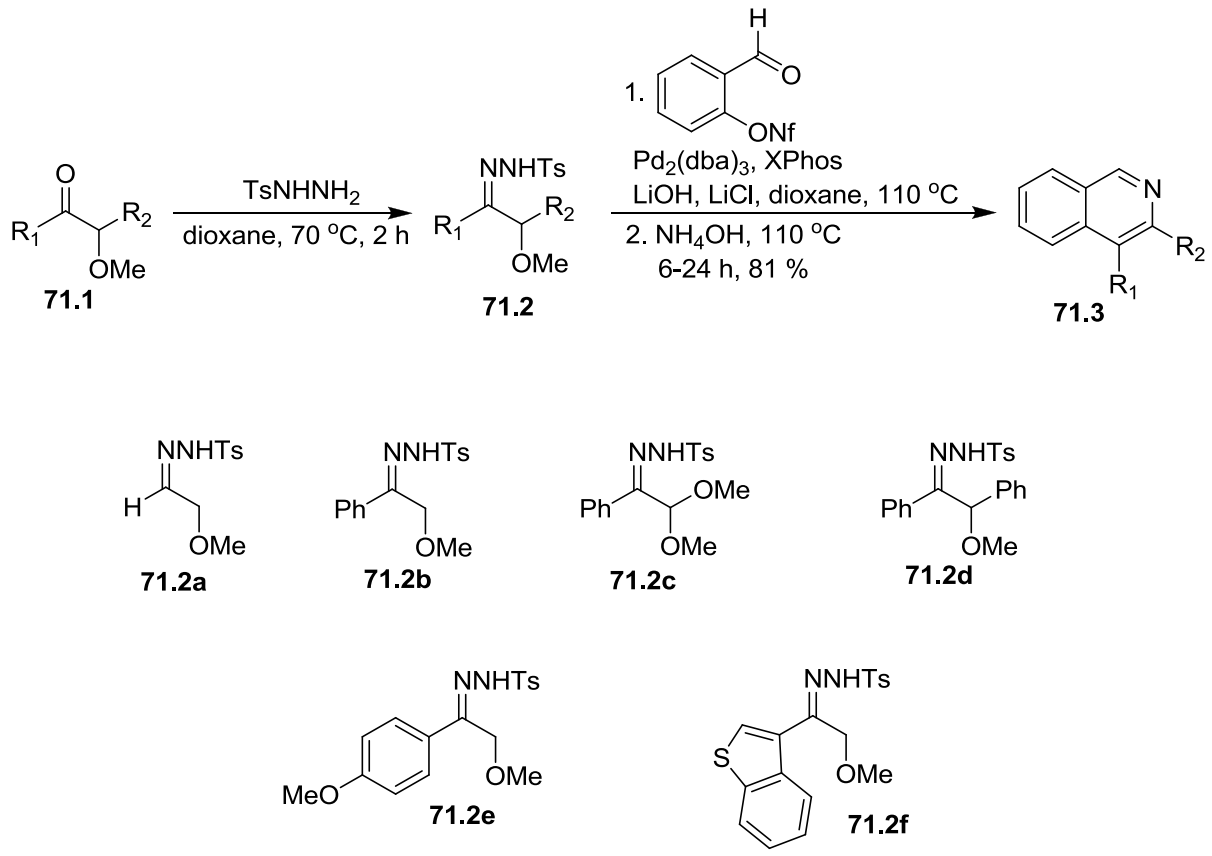
Entry	**Carbonyl compound**	**Hydrazone**	**Yield %**
1.			85
2.			78
3.			95
4.			87
5.			87
6.			94

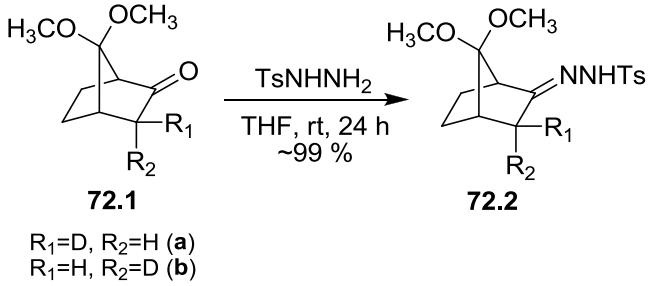
Table 16: α-hydroxy and α-alkoxy hydrazones

More recently Valdes prepared a variety of α-alkoxy tosyl hydrazones by stirring the α-alkoxy ketone and tosylhydrazide for 2 h in dioxane at 70 °C (Scheme 71).[123,124] The *in situ* generated tosyl hydrazones were subjected to the cross coupling reactions to afford polysubstituted isoquinolines. The *E*/*Z* configurations of the hydrazones were not reported.



Scheme 71

Unlike the previously discussed procedures by using acid or base catalyst or heat, Lightner *et al* prepared hindered dialkoxy tosylhydrazone **71.2** by stirring ketone **72.1** and tosylhydrazide in anhydrous THF with 5 A° molecular sieves at room temperature for 24 h (Scheme 72).[125] The method is noteworthy since it showed no epimerization and no deuterium loss during hydrazonation when deuterium labeled precursor was used. They also found that racemic tosyl hydrazone was more easily crystallized compared to either of the enantiomers.



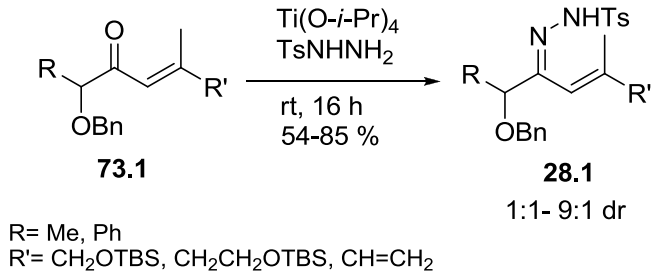
72.1 **72.2**

R_1=D, R_2=H (**a**)
R_1=H, R_2=D (**b**)

Scheme 72

3. α'-Alkoxy or α'-Hydroxy Tosyl Hydrazones from Ketones

Recently, Qi and McIntosh prepared α'-alkoxy α,β-unsaturated hydrazones by reacting enones and tosylhydrazide in Ti(O-*i*-Pr)$_4$ at room temperature (Scheme 73, Table 17).[63] The reactions gave mixtures of *E*- and *Z*-hydrazones in ratios from 1:1-99:1.



Scheme 73

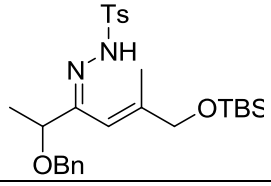
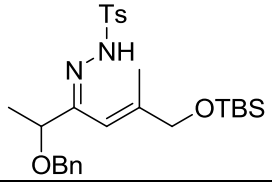
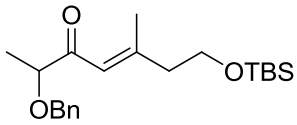
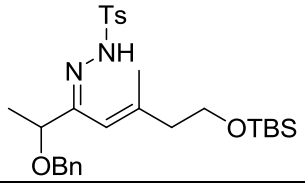
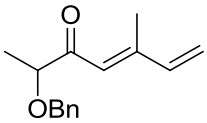
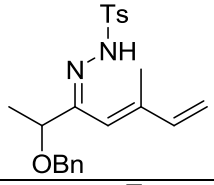
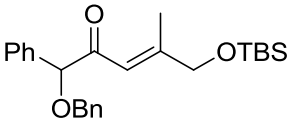
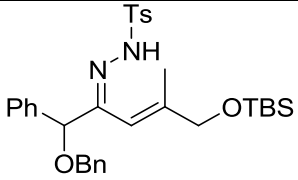
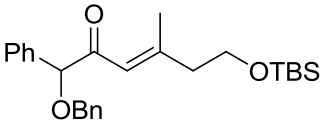
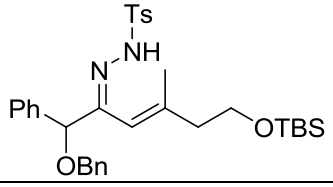
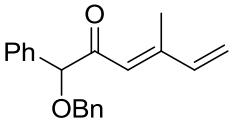
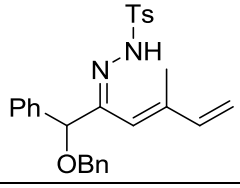
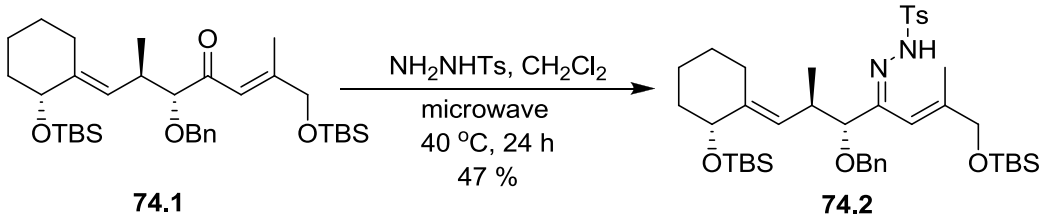
Entry	Ketones	Hydrazones	Yield %	*E*:*Z*
1.			72	60:40
2.			71	79:21
3.			50	50:50
4.			85	90:10
5.			63	80:20
6.			67	99:1

Table 17: Tosyl hydrazones from α'-alkoxy α,β-unsaturated ketones

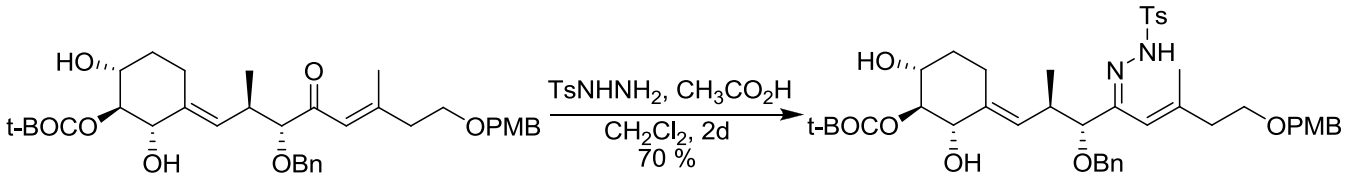
Qi and McIntosh also reported one example of hydrazone preparation using microwave irradiation without any catalyst by reacting enone **74.1** with tosyl hydrazide in CH_2Cl_2 (Scheme 74).[72] The reaction gave only the *E*-hydrazone though the yield was a moderate 47%.



74.1 **74.2**

Scheme 74

Further, McIntosh *et al* obtained the *E*-hydrazone only by reacting the enone **75.1** with tosylhydrazide and acetic acid in dichloromethane for 2 days (Scheme 75).[73] The reaction provided 70 % yield of the *E*-hydrazone.

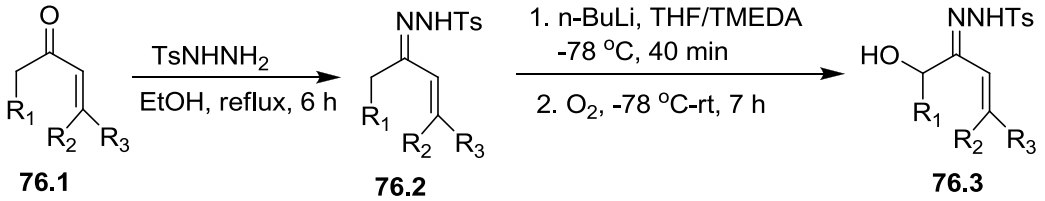


75.1 **75.2**

Scheme 75

A different method has been used for the synthesis of α'-hydroxy α,β-unsaturated tosyl hydrazones. Baptistella and Aleixo reported the preparation of a variety of α'-hydroxy α,β-unsaturated tosyl hydrazones **76.3** by first preparing the α,β-unsaturated tosyl hydrazones **76.2** by heating the mixture of corresponding ketone **76.1** and tosylhydrazide in EtOH under reflux (Scheme 76, Table 18).[126] Then the tosyl hydrazones **76.2** were lithiated with n-BuLi and exposed with molecular oxygen to obtain the desired α'-hydroxy α,β-unsaturated tosyl hydrazones. The reaction afforded the *Z*-hydrazones in most cases presumably due to the hydrogen bonding (Table 18, entry 1-2,4). The diastereomeric ratios of the products were reported as below (Table 18, entry 1-3). Although this procedure provided the α'-hydroxy α,β-

unsaturated tosyl hydrazones, the reaction requires an organolithium reagent and cryogenic conditions, therefore may not be suitable for preparation of the highly functionalized substrates such as **74.2** and **75.2** (*cf*. Scheme 74-75).



76.1 **76.2** **76.3**

Scheme 76

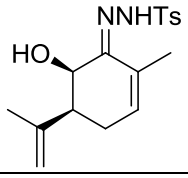
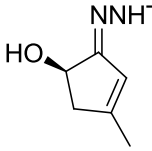
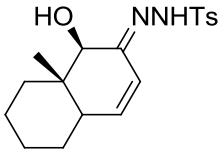
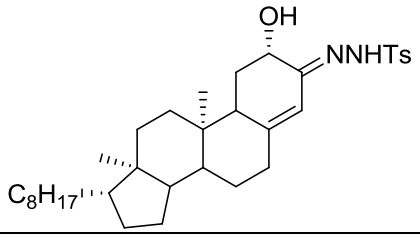
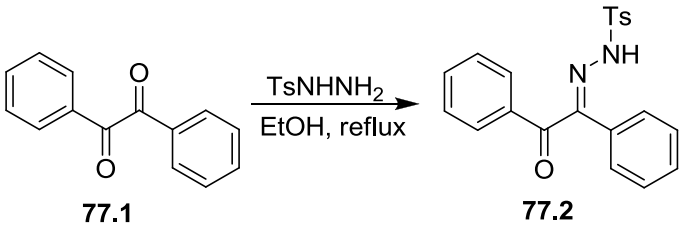
Entry	**Hydrazone**	**Yield %**	***E*/*Z***	**dr**
1.		85	0:100	1:3
2.		78	0:100	-
3.		45	4:1	1:1.5 (only for *E*)
4.		35	0:100	-

Table 18:α'-hydroxy α,β-unsaturated hydrazones

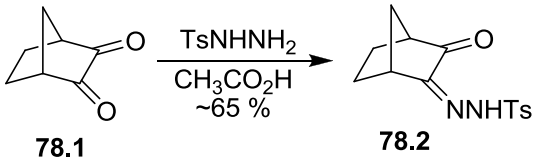
4. Tosyl Hydrazones from Dicarbonyl Compounds

Arylsulfonyl hydrazones derived from dicarbonyl compounds such as diketones, α-keto esters or β-keto esters are also important class of hydrazones in synthesis. Butler prepared benzil tosyl hydrazone (**77.2**) by using a known procedure in which a mixture of benzil and tosylhydrazide was heated under reflux in EtOH (Scheme 77).[127,128] The pure *E*-hydrazone **77.2** was obtained simply by recrystallization in EtOH. The geometry of the hydrazone was determined by ^{1}H NMR analysis.



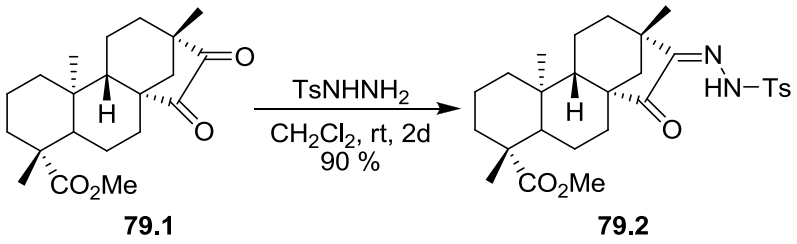
Scheme 77

Colby reported the synthesis of the acyl tosyl hydrazone from norcamphorquinone by adding a solution of tosylhydrazide and hot glacial acetic acid to the cold mixture of diketone **78.1** and acetic acid (Scheme 78).[129] The precipitated hydrazone **78.2** was obtained after overnight cooling. The crude product was purified by washing with water and recrystallization in MeOH or acetonitrile. The *E*/*Z* geometry of the hydrazone was not reported.



Scheme 78

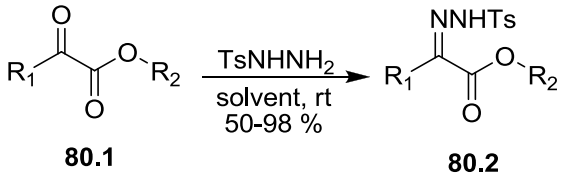
Acyl tosyl hydrazone derivative **79.2** was formed by simply stirring a solution of an equimolar amount of tosylhydrazide and the diketone **79.1** in dichloromethane at room temperature for 2 days (Scheme 79).[130] The reaction gave 90 % of the acyl *Z*-hydrazone **79.2** which was utilized as an intermediate for the synthesis of isosteviol derivatives.



79.1 **79.2**

Scheme 79

Hayes *et al* prepared a wide range of arylsulfonyl hydrazones **80.2** from inexpensive dicarbonyl compounds by using Reese's protocol,[116] i.e. stirring a methanolic solution of tosylhydrazide and corresponding dicarbonyl compound **80.1** at room temperature (Scheme 80, Table 19).[131] Toluene or EtOH was also used as solvent in some cases. Without determining *E*/*Z* configuration, these hydrazones were utilized to access α-alkoxy or α-amino acid derivatives through diazo intermediates.



Scheme 80

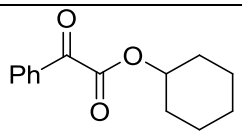
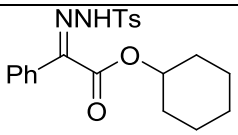
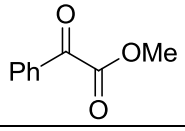
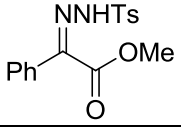
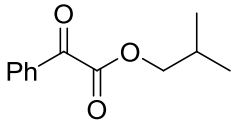
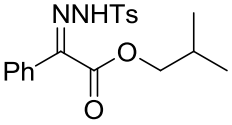
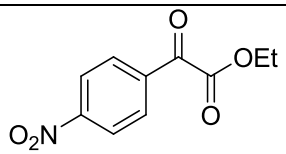
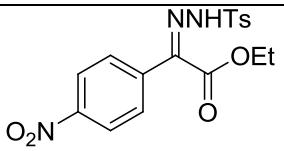
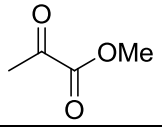
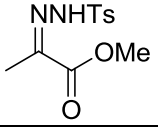
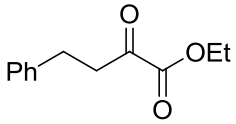
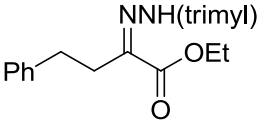
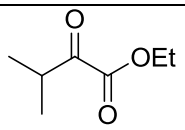
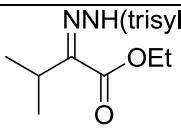
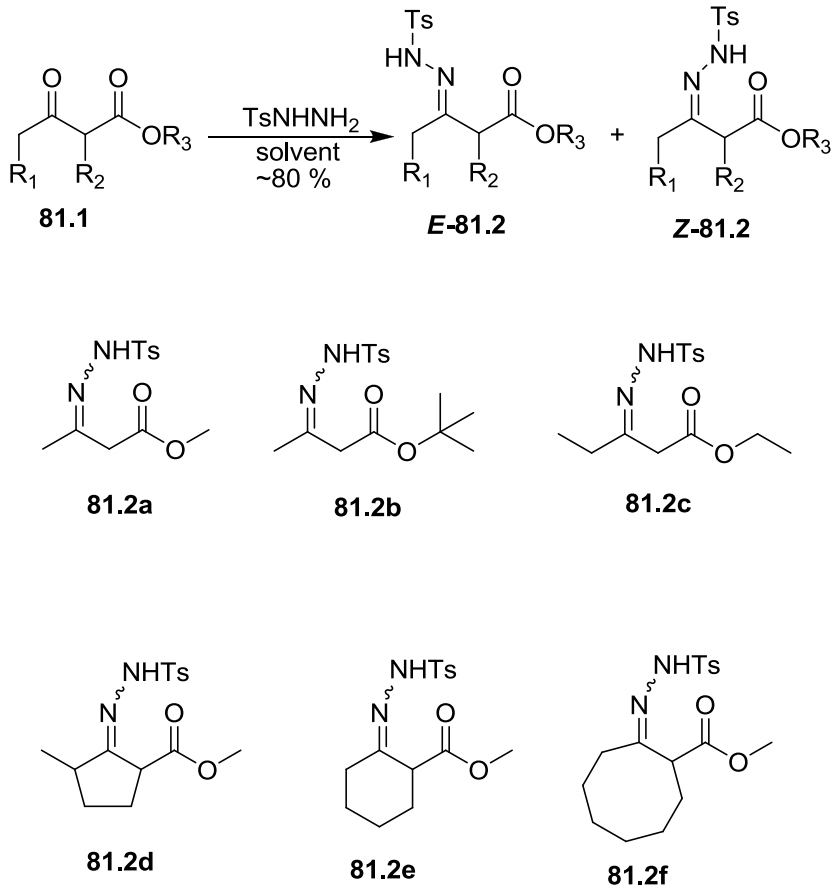
Entry	Keto esters	Hydrazone	Yield %
1.			75
2.			60
3.			63
4.			70
5.			51
6.			81
7.			98

Table 19: Hydrazones derived from dicarbonyl compounds

Similarly, a variety of tosyl hydrazones of β-keto esters **81.1** were obtained by treating their corresponding carbonyl compounds with tosylhydrazide in ether, methanol or ethanol (Scheme 81).[132] The reaction afforded a mixture of *E*-**81.2a** and *Z*-**81.2b** hydrazones, however the ratios of these isomers in the mixture were not reported.



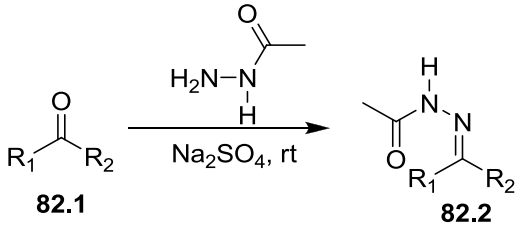
Scheme 81

E. ACYL HYDRAZONES

Similar to the tosyl hydrazones, the acyl hydrazones are commonly prepared by the condensation of aldehyde or ketones and acylhydrazines in presence or in absence of a catalyst.[133] These compounds are purified easily by recrystallization. A variety of acyl

hydrazones can be obtained by employing different acylhydrazines such as acetylhydrazine, phenylhydrazine, etc.[134]

Acetyl hydrazones **82.2** were prepared by treating the ketones **82.1** with acetylhydrazide and sodium sulfate at room temperature (Scheme 82, Table 20).[135] After completion of the reaction, the mixture was treated with dichloromethane and sodium sulfate was separated by filtration. Concentration of the solution in vacuo provided crystals of the acetyl hydrazones. The configuration of the acyl hydrazones were determined by crystallography; however, the *E*/*Z* ratio of some hydrazones (entry 2) was not reported.



82.1 **82.2**

Scheme 82

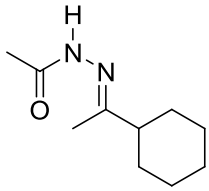
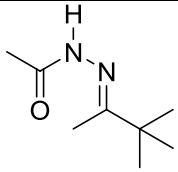
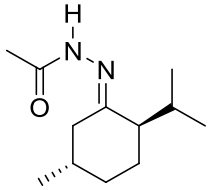
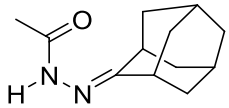
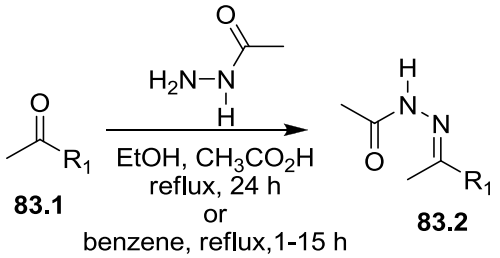
Entry	**Hydrazone**	**Yield %**	***E*/*Z***
1.		91	100:0
2.		99	-
3.		84	5:1
4.		69	-

Table 20: Acetyl hydrazones

Warkentin prepared a variety of acyl *E*-hydrazones by employing two different sets of the reaction conditions (Scheme 83, Table 21).[136,137] The acyl hydrazones **83.2a-c** were obtained by heating a mixture of corresponding ketones with acylhydrazine in EtOH and 5 mol % of acetic acid. Acyl hydrazones **83.2d-h** were prepared from the mixture of ketones and acylhydrazine under the conditions of the continuous removal of water by using Dean-Stark trap. These reactions afforded 70-95 % of the product yield.



83.1 **83.2**

Scheme 83

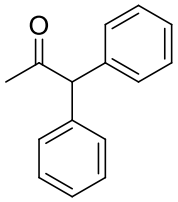
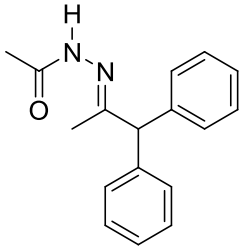
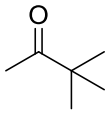
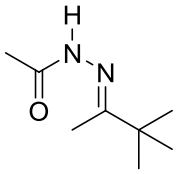
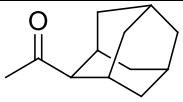
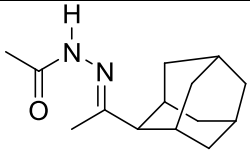
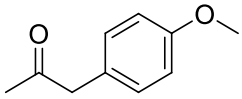
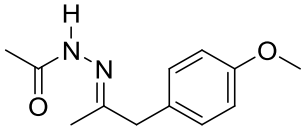
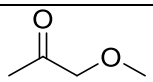
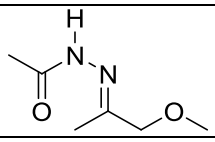
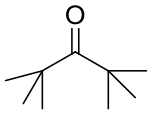
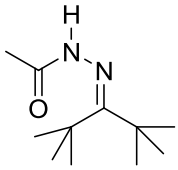
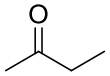
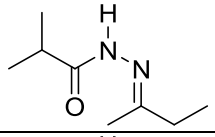
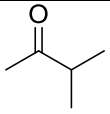
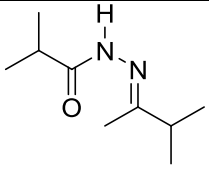
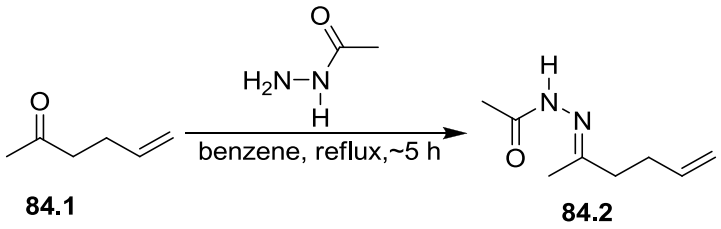
Entry	Ketones	Hydrazones	Yield %
1.			73
2.			75
3.			75
4.			90
5.			74
6.			75
7.			70
8.			75

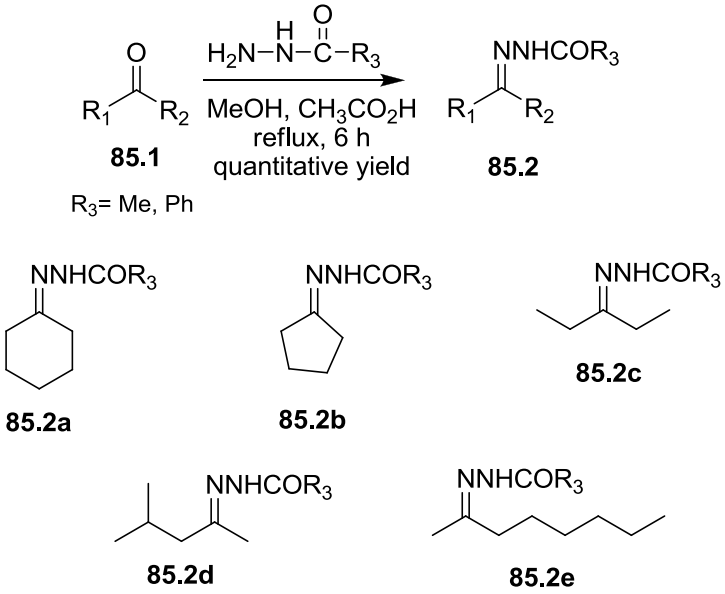
Table 21: Acyl hydrazones

Tiecco *et al* prepared the ketone acyl hydrazone **84.2** by heating the mixture of ketone **84.1** with acylhydrazine and molecular sieves in benzene under reflux for ca. 5 h (Scheme 84).[138] The *E*-isomer was obtained as a pure product simply after removal of the solvent; however, the author did not report the product yield.



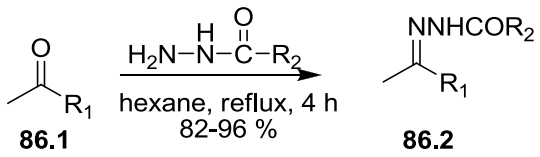
Scheme 84

In 1989, Chiba prepared benzoyl and acetyl hydrazones **85.2** by mixing ketones **85.1**, hydrazine and a few drops of acetic acid in MeOH and heating to reflux for about an hour (Scheme 85).[139,140] The crystalline acyl hydrazones **85.2** were obtained in quantitative yield after recrystallization in MeOH or in the mixture of benzene and petroleum ether. The *E*/*Z* configurations of these hydrazones were not reported.



Scheme 85

Wu also prepared acetyl hydrazones and benzoyl hydrazones from aliphatic ketones by heating the mixture of the ketone and the corresponding hydrazine in hexane under reflux for 4 h (Scheme 86, Table 22).[16] The reaction provided 82-96 % product yield; however, the author did not report the configuration of these hydrazones.



86.1 **86.2**

Scheme 86

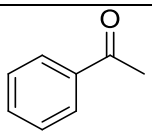
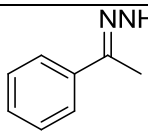
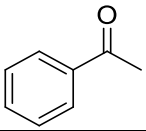
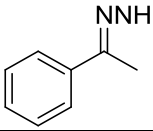
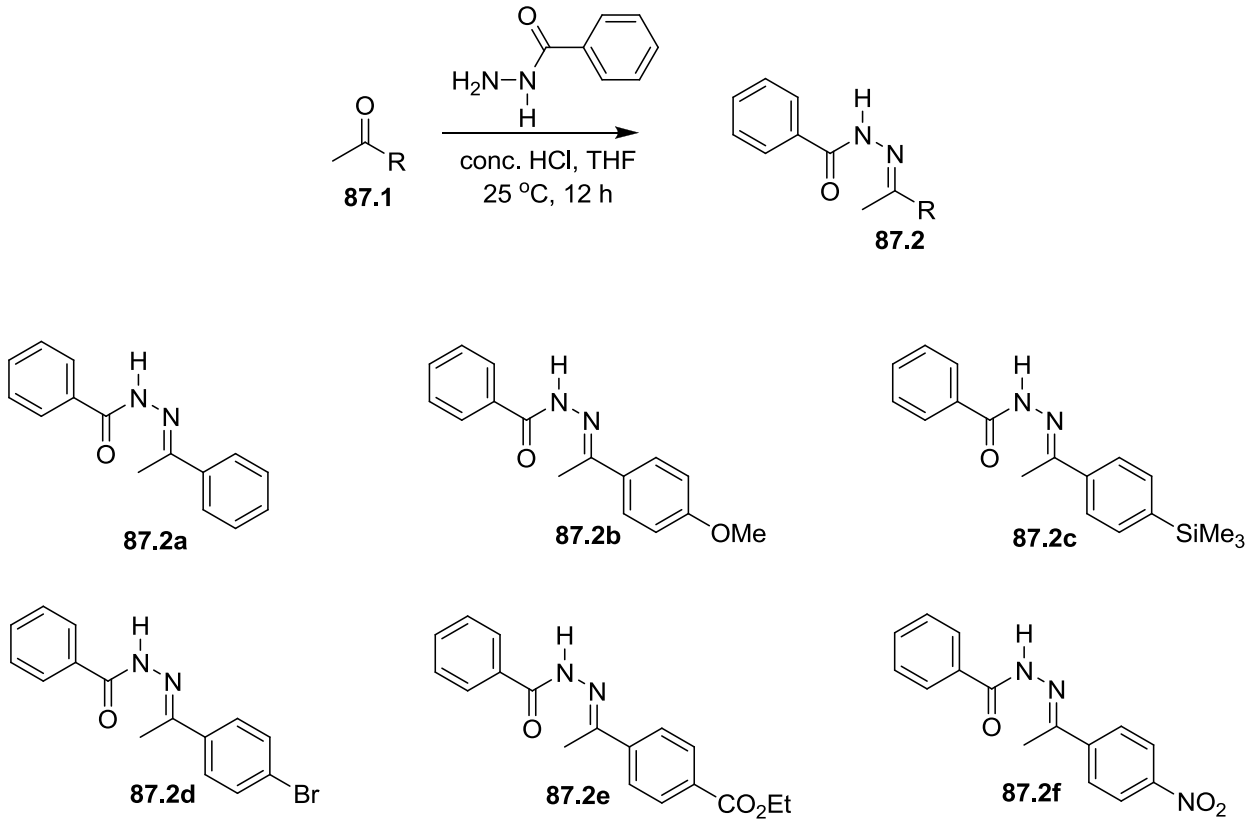
Entry	**Ketones**	**Hydrazones**	**Yield %**
1.			91
2.			82
3.			96
4.			91

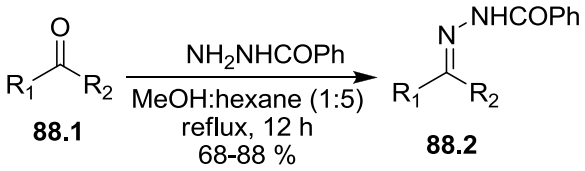
Table 22: Acetyl and Benzoyl hydrazones

Burk *et al* prepared a series of benzoyl hydrazones from the reaction of ketones and benzoylhydrazide with a catalytic amount of concentrated HCl in THF (Scheme 87).[141,142] The precipitate was filtered and washed with THF, ether and pentane to obtain the hydrazones. The reaction gave 64 % of hydrazone **87.2a** as a 5:1 *E*:*Z* mixture. However, the authors did not provide the yields and the *E*/*Z* ratios of the other hydrazones, but they were likely similar.



Scheme 87

Leighton obtained a variety of benzoyl hydrazones by preparing a solution of the ketones, benzoyl hydrazide and acetic acid in 1:5 mixture of methanol: hexane (Scheme 88).[143] The reaction mixture was heated under reflux for 12 h. Recrystallization with toluene provided the *E*-hydrazones in most cases (Table 23, entry 1-5); however, the reaction provided a 3.8:1 *E*/*Z* mixture in a few cases (Table 23, entry 6-7).



Scheme 88

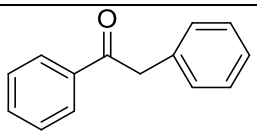
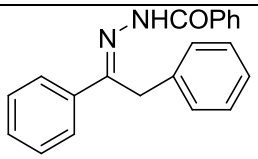
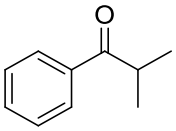
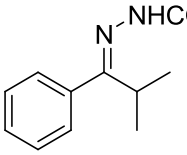
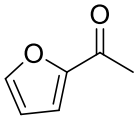
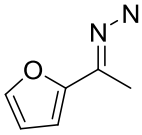
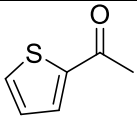
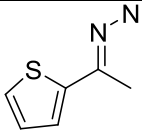
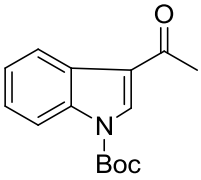
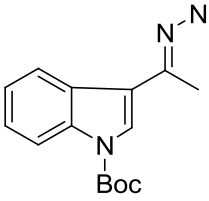
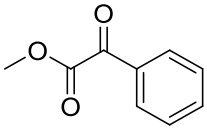
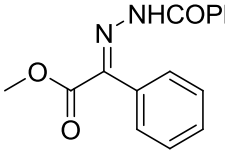
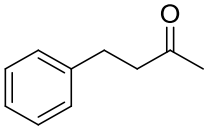
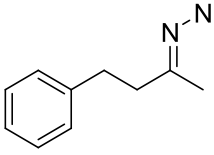
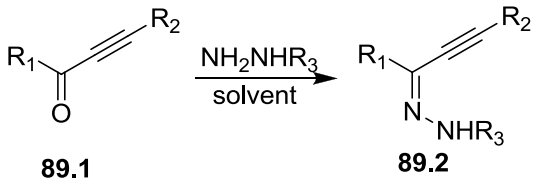
Entry	Ketones	Hydrazones	Yield %
1.			88
2.			68
3.			77
4.			85
5.			87
6.			70
7.			82

Table 23: Benzoyl hydrazones

F. YNONE HYDRAZONES

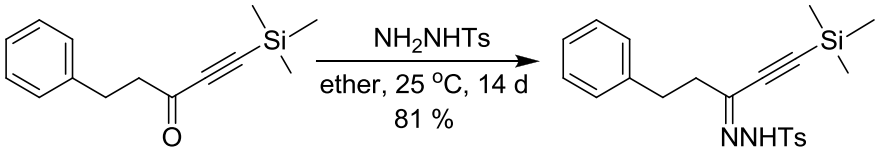
Ynone hydrazones are readily prepared by the reaction of acetylenic ketones (or ynones) with hydrazines (Scheme 89).[144] Ynone hydrazones are commonly used as intermediates in the synthesis of pyrazoles, which have been studied for more than a century.



89.1 **89.2**

Scheme 89

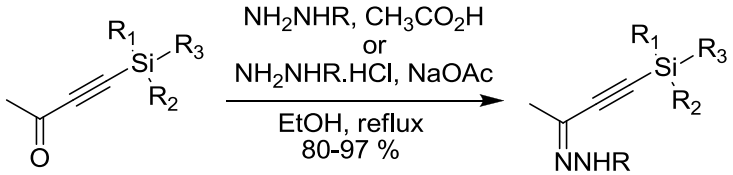
In 1982, Danheiser *et al* reported the preparation of an ynone hydrazone by stirring a mixture of the silylated acetylenic ketone and tosylhydrazide in ether at 25 °C for 14 days (Scheme 90).[145] Crystals of the ynone hydrazones were obtained after recrystallization in 95 % EtOH. However the authors did not specify the *E*/*Z* configuration of the hydrazone. The reaction most likely provided the *Z*-configuration of the hydrazone **90.2** because the hydrazone **90.2** was later utilized for synthesis of pyrazole derivatives.



90.1 **90.2**

Scheme 90

A variety of silylated ynone hydrazones were also prepared by heating an ethanolic solution of the corresponding ketones and methylhydrazine or phenylhydrazine under reflux (Scheme 91, Table 24).[146] Either acetic acid or sodium acetate was used as a catalyst for the reaction. The completion of the reaction was monitored by TLC and extracted with a mixture of dichloromethane and water. Purification by column chromatography provided the desired hydrazones. The *E*/*Z* configuration of the ynone hydrazones was not determined.



91.1 **91.2**

Scheme 91

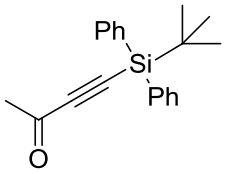
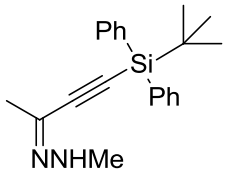
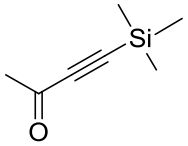
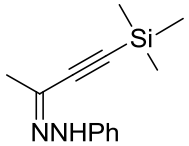
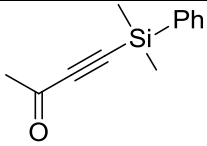
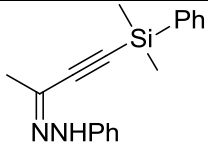
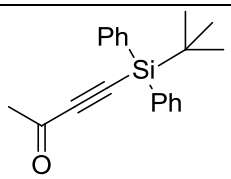
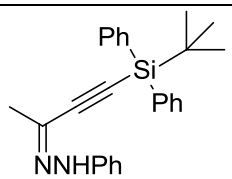
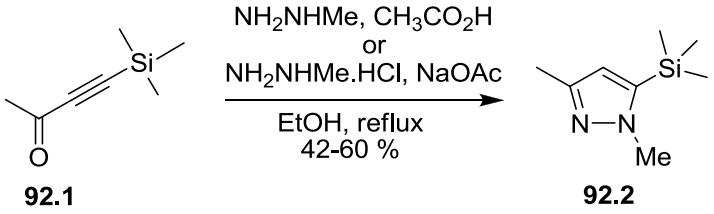
Entry	**Ynones**	**Hydrazones**	**Yield %**
1.			64
2.			80
3.			86
4.			97

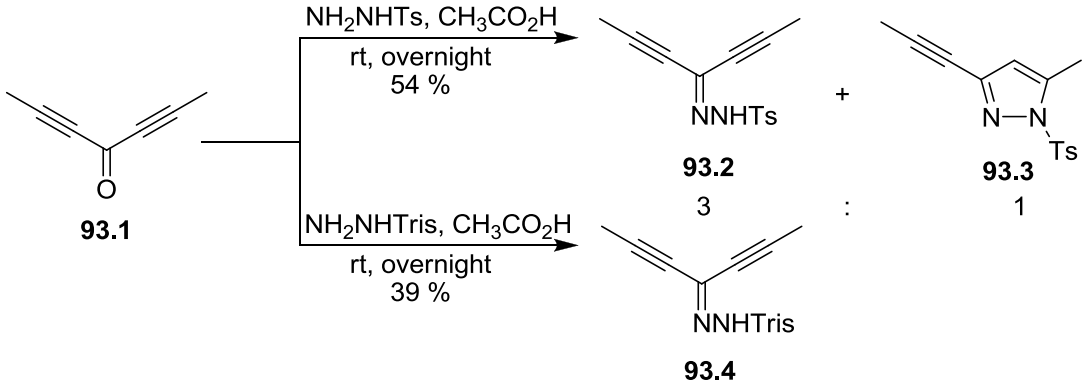
Table 24: Methyl and Phenyl ynone hydrazones

Although the reaction of silylated acetylenic ketone with hydrazine provided the ynone hydrazones, the reaction was complicated by formation of a pyrazole when methylhydrazine was used (Scheme 92). The cyclization was avoided by utilizing the bulkier phenylhydrazine (*cf*. Table 24, entry 2). Further, a bulkier silyl group was used to suppress pyrazole formation (*cf*. Table 24, entry 1, 3-4). The formation of the pyrazole derivatives or the ynone hydrazones depends upon the nature of the substituents of the hydrazine or the silyl group.



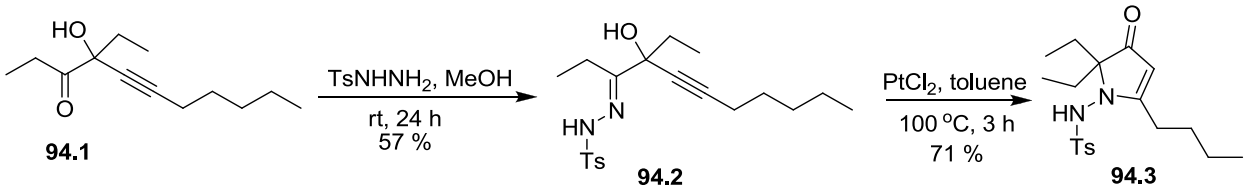
Scheme 92

McMohan also demonstrated that the use of the bulkier substituent in the hydrazonation of acetylenic ketone **93.1** prevented the cyclization (Scheme 93).[147,148] The reaction of the ketone with tosylhydrazide afforded 54 % yield with 3:1 ratio of the ynone hydrazone **93.2** and the pyrazole derivative **93.3**. Whereas, the reaction provided only the ynone hydrazone **93.4** when the bulkier trisyl hydrazide (2,4,6-triisopropylbenzenesulfonyl hydrazide) was utilized. However, the product yield was only 39 % with bulkier substituents.



Scheme 93

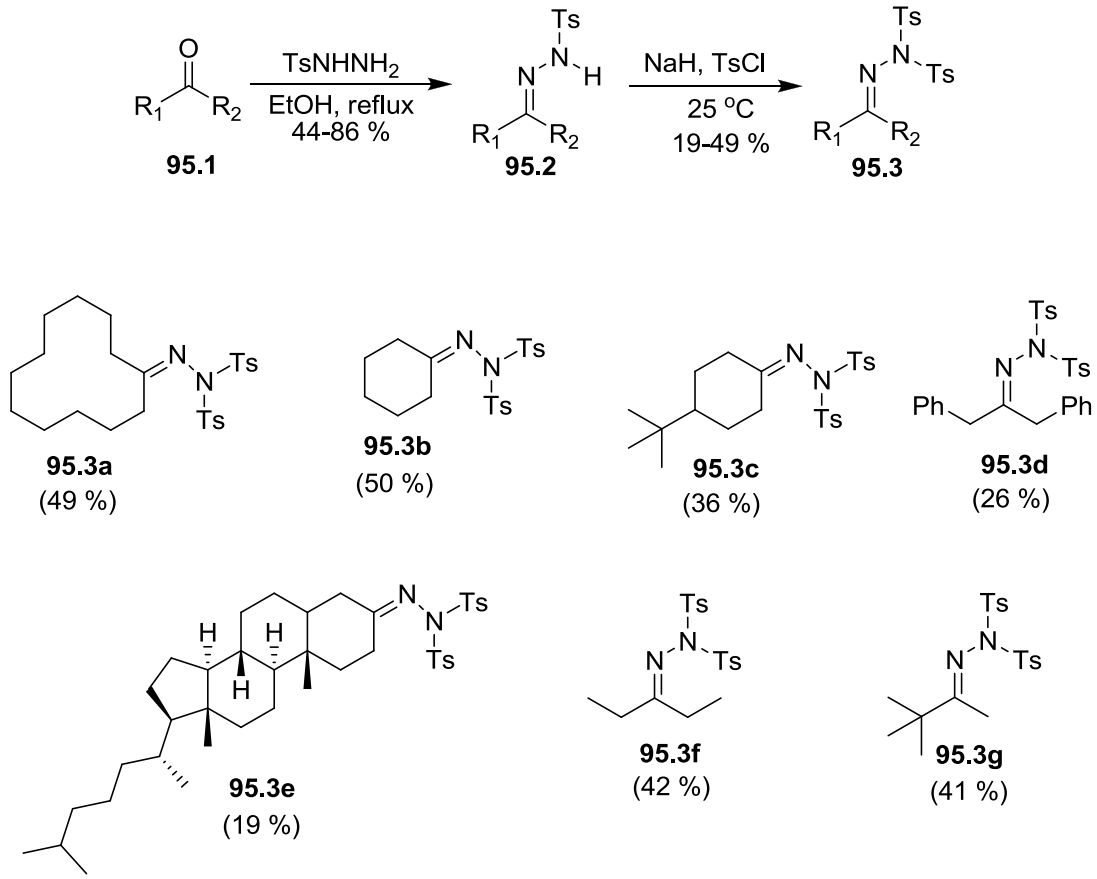
Sarpong *et al* prepared the more functionalized α-hydroxy β,γ-unsaturated ynone hydrazone by stirring a solution of the ketone and tosylhydrazide in MeOH for 24 h (Scheme 94).[149,150] The pure *E*-hydrazone was obtained after column chromatography. Thus prepared hydrazone was utilized for Pt(II)-catalyzed hetereocyclization/1,2-migration to obtain pyrrolone **94.3**.



Scheme 94

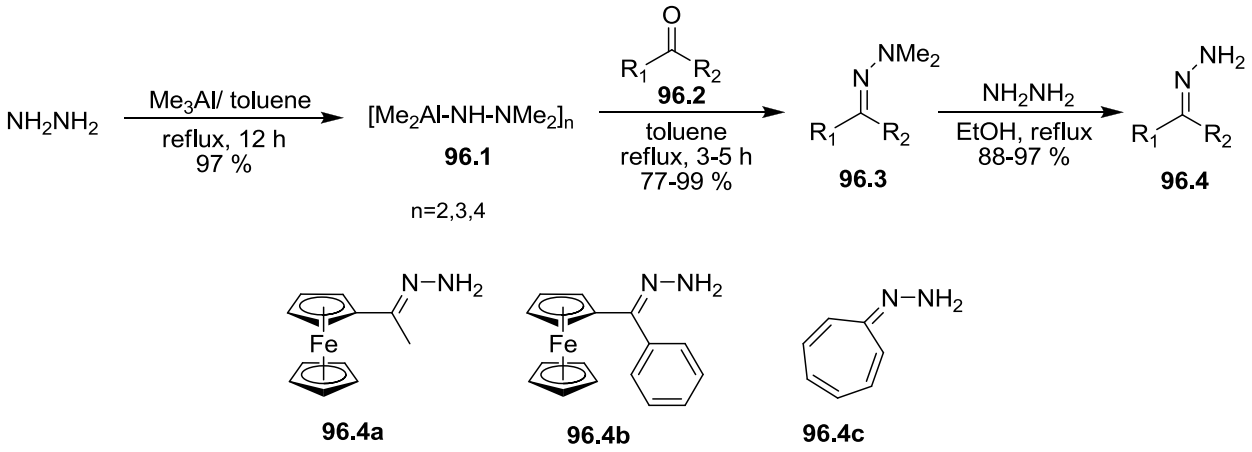
G. *N*-DISUBSTITUTED HYDRAZONES

Similar to other hydrazones including simple hydrazones, arylsulfonyl hydrazones and acyl hydrazones, *N*-disubstituted hydrazones have also been in use in organic chemistry. A variety of *N*,*N*-ditosyl hydrazones were obtained by first preparing monotosylhydrazones from the corresponding ketones (Scheme 95).[151] Then the monotosyl hydrazones **95.2** were treated with sodium hydride and toluenesulfonyl chloride at room temperature. The reactions gave only 19-49 % yields; however, these results were reported without further optimization. The *E*/*Z* configuration of the hydrazones **95.3e**,**3g** were not reported. These hydrazones were utilized to afford hydrocarbons by treating with alkyllithium reagent.



Scheme 95

Another method for *N*-disubstituted hydrazone preparation was developed by Bildstein, in which a dimer or oligomer of *N*-dimethylaluminium *N'*,*N*'-dimethylhydrazide **96.1** was obtained first from a reaction of trimethylaluminium with hydrazine in toluene (Scheme 96).[152] Heating a solution of *N*-dimethylaluminium *N'*,*N'*-dimethylhydrazide **96.1** and ferrocenyl ketone **96.2** in toluene under reflux gave the disubstituted hydrazones **96.3**. Further treatment of hydrazone **96.3** with anhydrous NH_2NH_2 afforded *N*-unsubstituted hydrazone **96.4**. Although this method utilizes the pyrophoric trimethylaluminium reagent, it is useful to prepare hydrazones from stubborn ketones such as ketone **96.2**. The method was developed after all other attempts to prepare the hydrazone such as acid or base catalysis, high temperatures, anhydrous conditions, etc. failed.



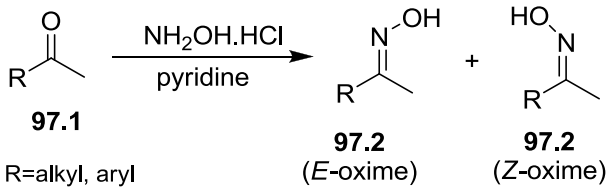
Scheme 96

Different reaction conditions have been developed for hydrazone preparation, such as acid or base catalysis, anhydrous reaction conditions, high temperature, different solvents, etc. However a general stereoselective synthesis of *E*- or *Z*-hydrazones from unsymmetrical ketones is yet to be established. Therefore, it would be noteworthy to overview oxime preparation for unsymmetrical ketones due to their structural similarity to hydrazones.

H. OXIMES

1. Preparation of *E*- and *Z*-Oximes

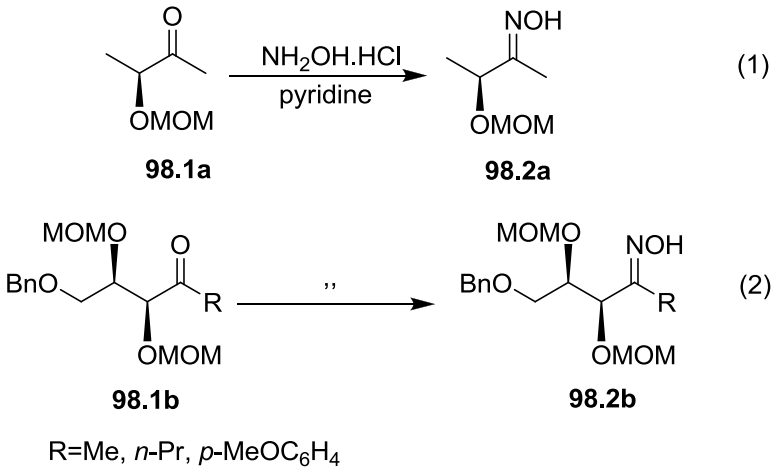
Similar to hydrazones, oximes are readily obtained from carbonyl compounds. Both cyclic and acyclic oximes are commonly prepared by treating the carbonyl compound with $NH_2OH.HCl$ and pyridine or sodium acetate (Scheme 97).[153] Usually, both *E*- and *Z*-oximes are obtained with unsymmetrical ketones.



Scheme 97

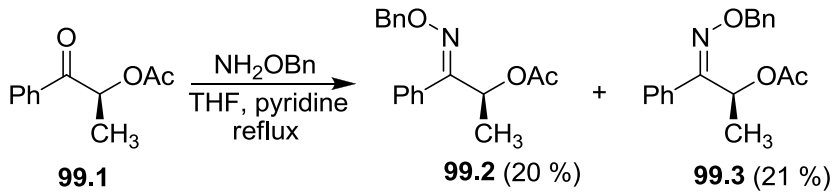
Since *E*- and *Z*-oximes have different physical properties and biological activities,[154] it may be necessary to obtain the desired isomer specifically. Generally, the desired isomer is isolated by chromatography or recrystallization. There are a numerous reports on oxime preparation using the procedure described above. Following are some of the representative examples of oxime preparation.

In 1987, Kibayashi prepared acyclic alkoxy ketone oximes by treating the corresponding ketone with $NH_2OH.HCl$ and pyridine at room temperature (Scheme 98).[60] The reaction worked for both α-alkoxy ketone and α,β-dialkoxy ketones. However, he reported neither the product yield nor *E*/*Z* configuration of oximes.



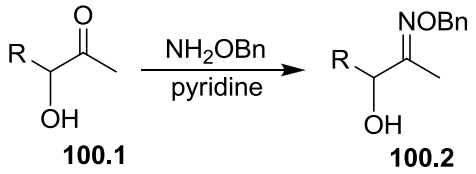
Scheme 98

Hiyama and Fujita obtained a 1:1 ratio of *E*-**99.2** and Z-**99.3** oximino ethers from a reaction between 2-acetoxy-1-phenyl-1-propanone **99.1** and pyridine in THF (Scheme 99).[59] After extractive work up, these isomers were separated by preparative TLC and the geometry of *E*- and *Z*-isomers were determined by ^1H NMR. Chemical shifts of the CH_3 group of *E*-oxime **99.2** and *Z*-oxime **99.3** are found to be at 1.39 ppm and 1.60 ppm respectively. In general, the methyl protons of the *Z*-oximes **99.3** resonate downfield due to the CH_3 group *syn* to oximino group.



Scheme 99

Williams *et al* reported the preparation of various α-hydroxy oximino ethers by treating α-hydroxyl ketone with NH_2OBn (Scheme 100, Table 25).[61] After chromatographic separation, the *E*- and *Z*-geometry of the pure isomers were established by ^{13}C NMR. The chemical shifts of the α-carbon *syn* to the benzyloxy group shifts upfield compared to the α-carbon *anti* to the benzyloxy group due to steric compression. The reaction afforded only the *E*-oximes in some cases (entry 4, 6-7). The ratios of other oximes are not provided in the paper.



Scheme 100

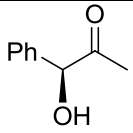
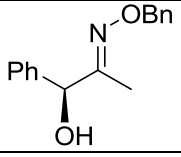
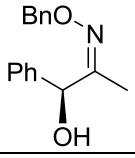
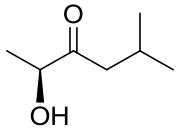
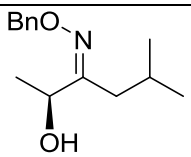
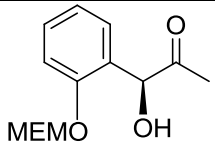
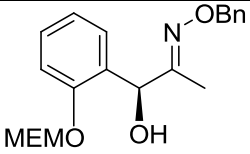
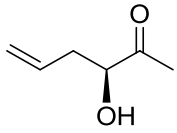
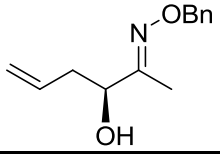
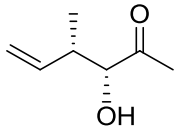
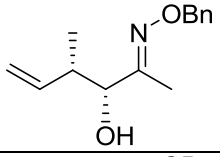
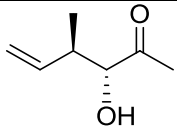
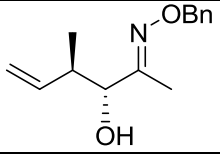
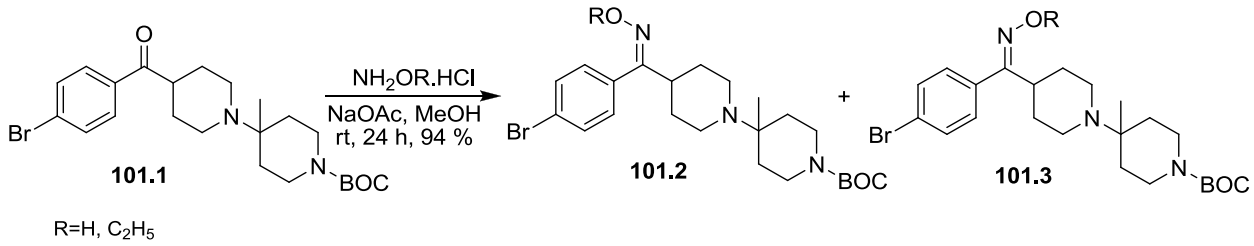
Entry	Ketone	Oxime	*E*/*Z*
1.			-
2.	,,		-
3.			-
4.			100:0
5.			-
6.			100:0
7.			100:0

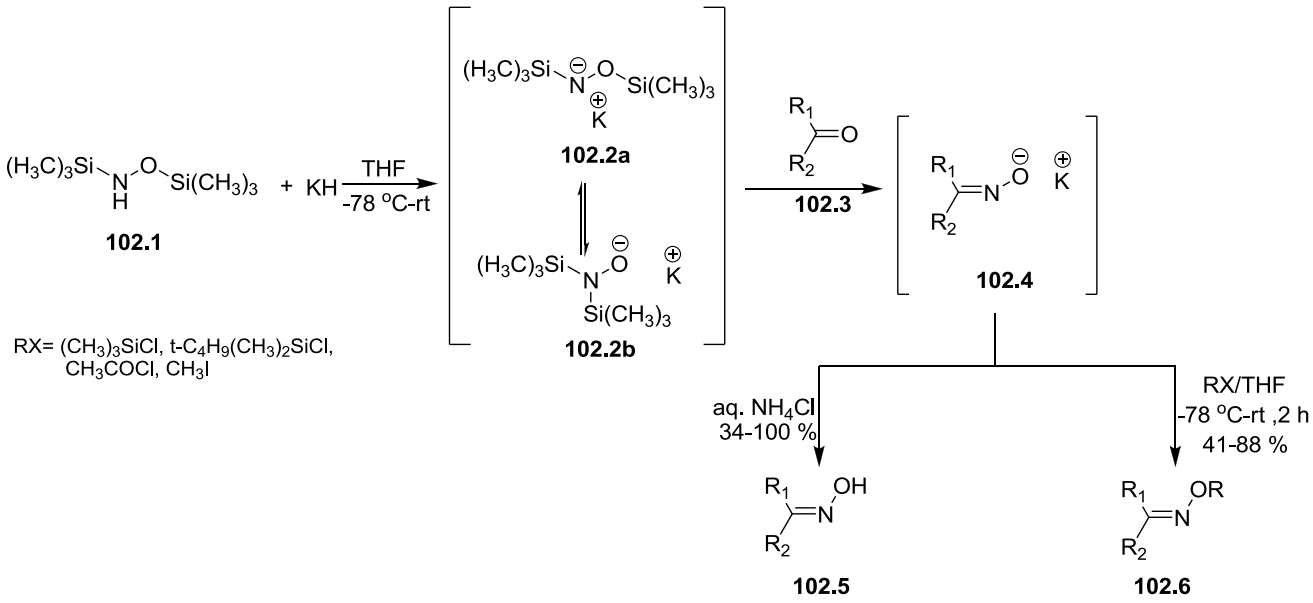
Table 25: Oximes obtained from α-hydroxy carbonyl compounds

Palani prepared oximes by stirring a mixture of ketone **101.1**, $NH_2OR.HCl$ and sodium acetate in MeOH at room temperature for 24 h (Scheme 101).[155] The reaction gave a 94 % of the mixture of the *E*- and the *Z*-oximes; however, the ratio of these isomers were not reported. The desired *Z*-oxime **101.2** was isolated by chromatography. Then it was utilized as an intermediate for the synthesis of oximino-piperidino-piperidine amides, a potentially new candidate for treatment of HIV-1 infection.



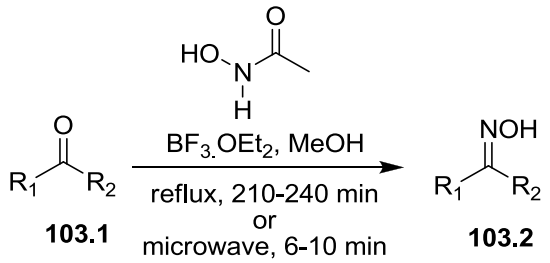
Scheme 101

Hoffman developed a method for the synthesis of oximes in which carbonyl compounds **102.3** were reacted with potassium salt of *N*,*O*-bis(trimethylsilyl)hydroxylamine **102.2** to give oximate anions **102.4** (Scheme 102).[156] The anions **102.4** could be protonated to make oximes **102.5** or trapped in situ with electrophiles to give *O*-substituted oxime derivatives **102.6**. The author did not determine the *E*/*Z* configuration of these oximes.



Scheme 102

A recent develpement in oxime preparation was reported by Sridhar in which microwave heating was utilized (Scheme 103).[157,158] Various oximes were prepared by microwave heating of a methanolic solution of carbonyl compound, acetoxyhydroxamic acid (AHA) and Lewis acid such as $BF_3.Et_2O$ as catalyst (Table 26). Although he did not report the *E*/*Z* configuration of the oximes, he compared the results obtained from microwave heating with that of conventional heating. The reactions using microwave irradiation were complete within a few minutes and provided better product yields. These results suggest that microwave heating may be a better alternative for some oxime preparations.



Scheme 103

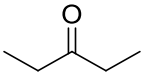
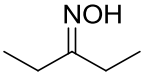
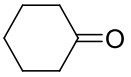
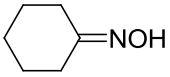
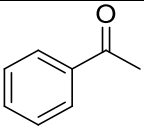
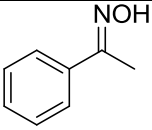
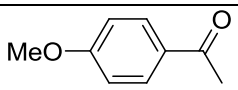
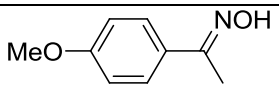
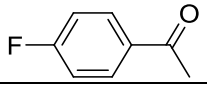
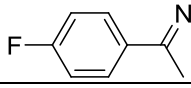
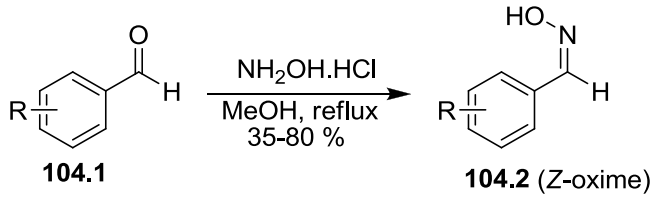
Entry	Carbonyl compound	Oxime	Conventional heating		Microwave heating	
			yield %	min	yield %	min
1.			80	240	87	7
2.			80	270	87	,,
3.			85	210	93	,,
4.			80	240	86	8
5.			83	,,	90	,,

Table 26: Comparative study of conventional heating and microwave heating

There are also a few examples of stereoselective synthesis of oximes reported. Heller and Zvilichovsky described the preparation of *Z*-oxime **104.2** by simply heating a solution of aryl aldehyde **104.1** and hydroxylamine hydrochloride under reflux in MeOH (Scheme 104).[159] After completion of reaction, the reaction mixture was treated with cold water and recrystallized from ether. Only 35 % *Z*-benzaldoxime (R=H) was obtained from benzaldehyde while 70 % and 80 % *Z*-oximes were formed from 4-methoxybenzaldehyde and 2,4-dimethoxybenzaldehyde respectively. A low product yield in benzaldoxime preparation could be due to the low basicity of hydrochloride of benzaldoxime.

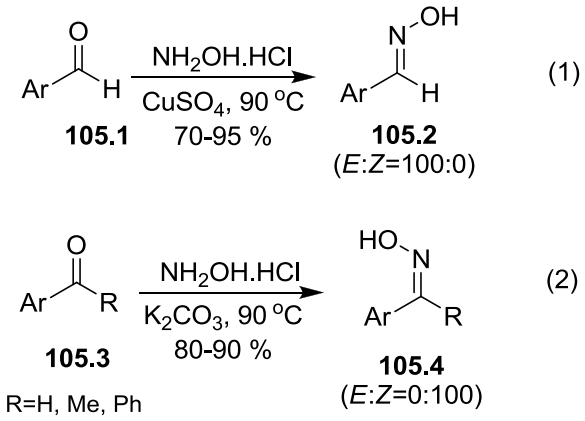


104.1 **104.2** (*Z*-oxime)

R=H,4-methoxy, 2,4-dimethoxy

Scheme 104

More importantly, Sharghi selectively synthesized *E*-oxime **105.2** (aryl group *anti* to OH) and *Z* oximes **105.3** (aryl group *syn* to OH) by using $CuSO_4$ and K_2CO_3 respectively (Scheme 105).[160] However, the author did not provide any reason for the selectivity. The preparation of the *E*-oxime **105.2** by using $CuSO_4$ was successful only when the aryl aldehyde **105.1** was utilized (Scheme 105, eq. 1). There was no reaction when the same reaction conditions were employed for the preparation of the keto oximes; presumably due to steric reasons.



Scheme 105

Rusisnka-Roszak *et al* performed various computational methods including HF/6-31G** to study the hydrogen bonding in different configuration of a simple oxime.[161,162] These calculations predicted that **1a** is more stable than **2a** by 1.09 kcal/mol (Figure 13), suggesting that *E*-oxime **1** is thermodynamically preferred over *Z*-oxime **2**.

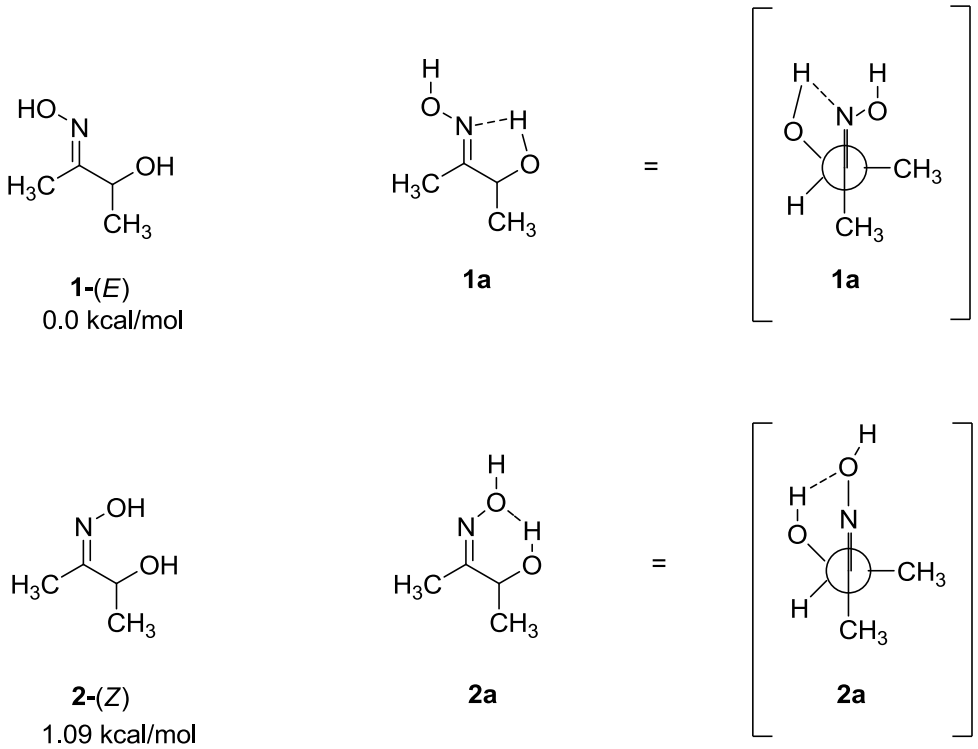


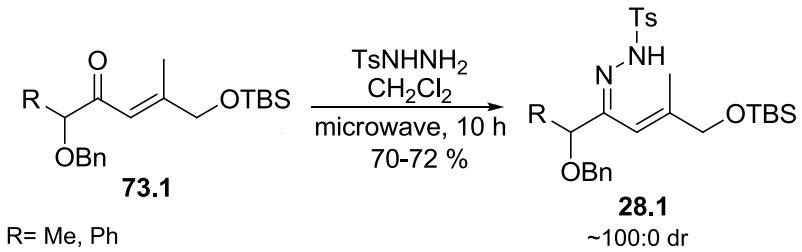
Figure 13

II. RESULTS AND DISCUSSION

A. PREPARATION AND DIASTEREOSELECTIVITY OF TRISUBSTITUTED ALKENE HYDRAZONES

As discussed previously, Qi and McIntosh reported the preparation of trisubstituted alkene hydrazones by employing two different sets of reaction conditions. The most general procedure for the preparation of hydrazones **28.1** involved the reaction of the enone with tosyl hydrazide and neat Ti(O-*i*-Pr)$_4$ at room temperature (*cf*. Scheme 73).[63] The resulting hydrazones were mixtures of *E*- and *Z*-isomers, *E*- being the major isomer. Furthermore, Qi and McIntosh prepared a hydrazone **74.2** using microwave irradiation without any catalyst by reacting the enone **74.1** with tosyl hydrazide in CH_2Cl_2 (*cf*. Scheme 74).[72] The reaction was noteworthy since it gave only the *E*-hydrazone.

Since microwave irradiation provided better diastereoselectivity in hydrazone preparation, we utilized the microwave conditions for preparation of hydrazones **28.1** from trisubstituted alkene enones **73.1** (Scheme 106).[63] The reaction gave only the *E*-hydrazone, therefore provided better selectivity compared to the hydrazones prepared from Ti(O-*i*-Pr)$_4$ catalyzed reaction, although the generality of the process has not been demonstrated (*cf*. Scheme 73).



Scheme 106

In order to better understand the reasons for the observed *E*-selectivity, molecular modeling of simplified hydrazones was performed. To avoid confusion due to priority changes, the sulfonamide group *anti* to R group will be referred to the *trans*-hydrazones whereas the sulfonamide group *syn* to R group as the *cis*-hydrazones. Hartree-Fock calculations (HF/6-31G*) of the simplified trisubstituted hydrazones show that *cis*-hydrazone is by far the higher energy isomer for R=Me due to the steric interaction caused by the isopropyl group and the sulfonamide group, which means the *trans*-hydrazone would be thermodynamically favored (Figure 14). However, the *cis*-hydrazone is slightly preferred for R=OMe, presumably due to internal hydrogen bonding. Thus, these calculations suggest that hydrazone formation for the α-alkoxy enones under either set of reaction conditions is under kinetic control.

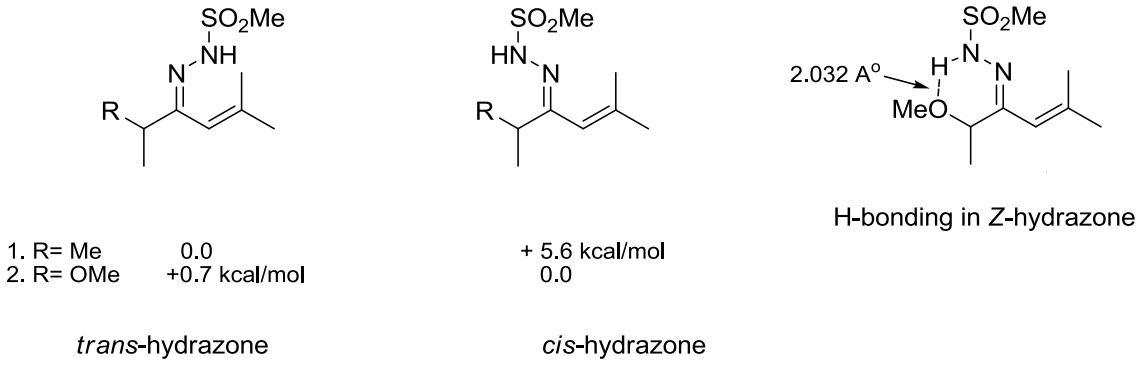
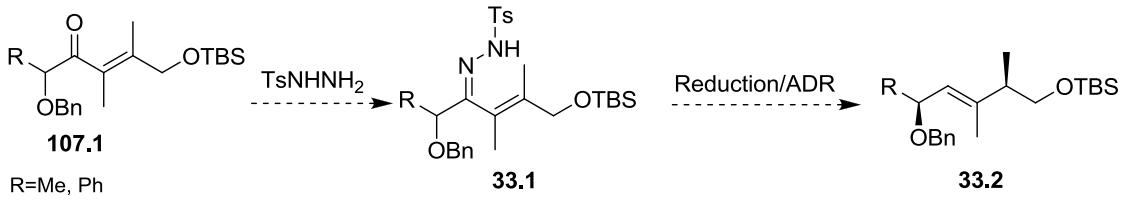


Figure 14

B. TETRASUBSTITUTED ALKENE HYDRAZONES

As discussed previously in the first chapter, Qi and McIntosh prepared hydrazones of trisubstituted enones and utilized them to afford disubstituted *E*-alkenes with alkoxy and alkyl stereocenters at the allylic positions (*cf*. Scheme 28).[63] Either 1,4-*syn* or 1,4-*anti* diastereomers can be prepared by using the appropriate alkene stereoisomers of the hydrazones. The extension of the method to tetrasubstituted α,β-unsaturated hydrazones would afford trisubstituted alkenes

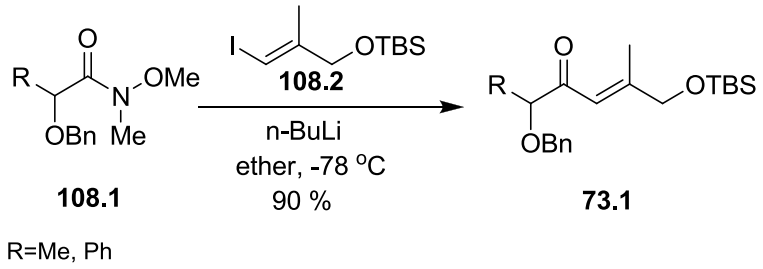
in the reduction/ADR (Scheme 107). We anticipated obtaining tetrasubstituted hydrazones **33.1** from the corresponding tetrasubstituted enones **107.1**.



Scheme 107

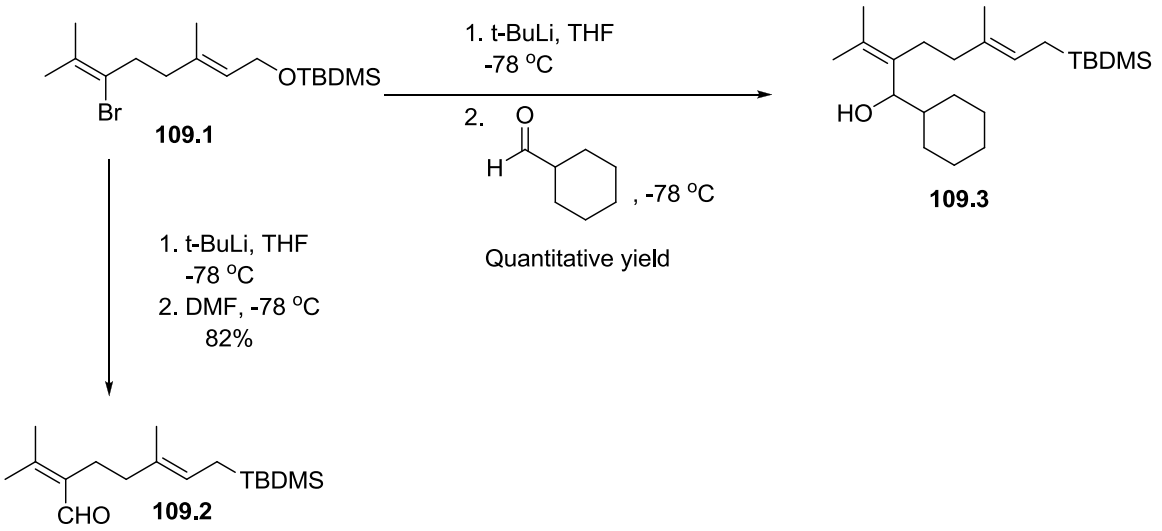
1. Synthesis of Tetrasubstituted Enones

Qi and McIntosh used lactic acid and mandelic acid derived Weinreb amides **108.1** and trisubstituted *Z*-iodide **108.2** for the preparation of α,β-unsaturated enones in very high yield (Scheme 108).[63]



Scheme 108

Stork *et al* have reported the reaction of a tetrasubstituted vinyl bromide **109.1** with t-BuLi at –78 °C to give the corresponding vinyl lithium intermediate (Scheme 109).[163] Addition of dimethylformamide gave an unsaturated aldehyde **109.2** in 82 % yield. Similarly, cyclohexanecarboxaldehyde was added to the vinyl lithium intermediate to obtain the corresponding carbinol **109.3**.

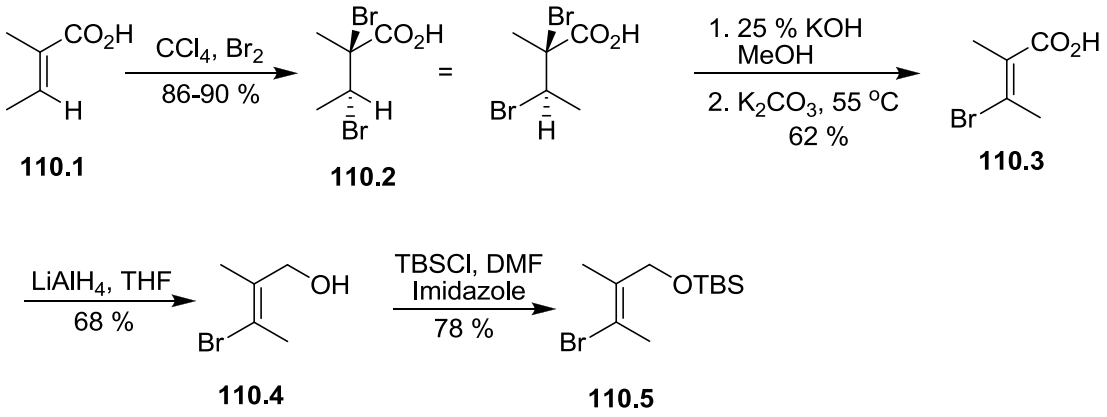


Scheme 109

Therefore we attempted to prepare tetrasubstituted enones from an *E*-bromide by metal-halogen exchange with t-BuLi followed by reaction with Weinreb amides (vide infra). The *E*-bromide and Weinreb amides were prepared first to make the corresponding enones.

1.1 Preparation of *E*-Bromide

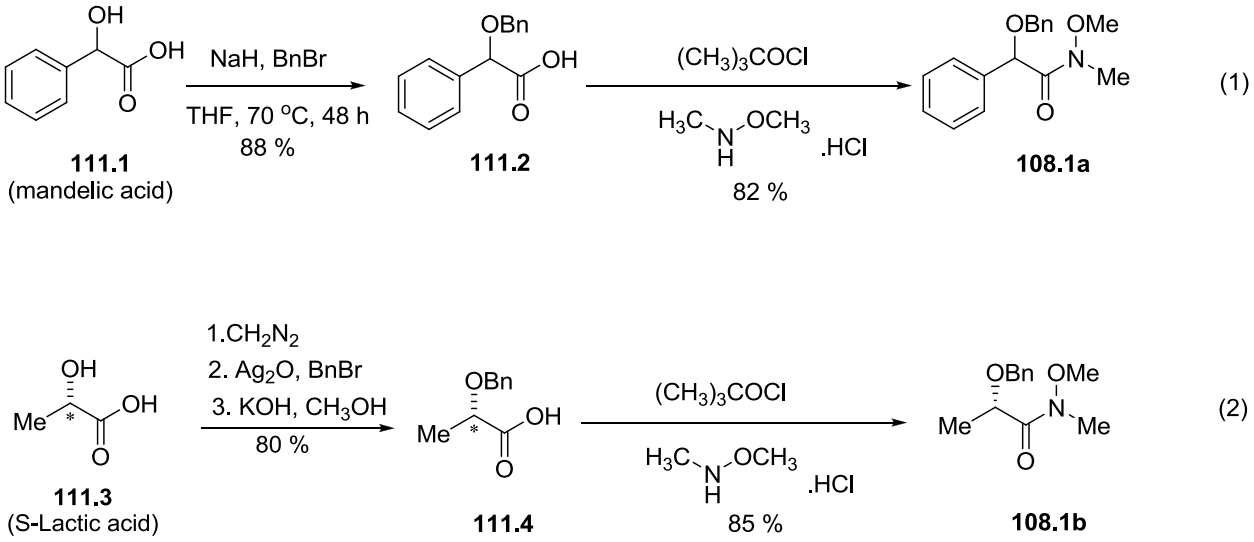
The *E*-bromide **110.5** was prepared in 4 steps in an overall yield of 29 % (Scheme 110). The first two steps are known reactions.[164] Tiglic acid undergoes bromination to give α,β-dibromo-α-methylbutyric acid **110.2** in 86-90 % yield after crystallization. Dehydrobromination of dibromide **110.2** gave β-bromoangelic acid **110.3**. $LiAlH_4$ reduction of the carboxylic acid gave alcohol **110.4** and protection of the TBS ether gave silyl ether **110.5**.



Scheme 110

1.2. Preparation of Weinreb Amides

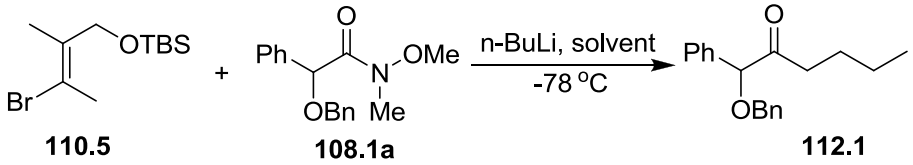
Weinreb amides **108.1a** and **108.1b** were prepared using known procedures (Scheme 111).[63] Firstly, the alcohol oxygen was protected as the benzyl ether. The resulting ester was converted to the amide *via* the mixed anhydride. In the case of lactic acid derived amide **108.1b**, Ag_2O was used as a base to avoid racemization.



Scheme 111

1.3 Attempts to prepare the Enones

The reaction of vinyl bromide **110.5** with n-BuLi at –78 °C followed by addition of Weinreb amide **108.1a** afforded only the ketone **112.1** resulting from addition of BuLi to the Weinreb amide (Scheme 112). Even after 4 h of exposure of vinyl bromide **110.5** to n-BuLi at –78 °C, no metal-halogen exchange product was observed.

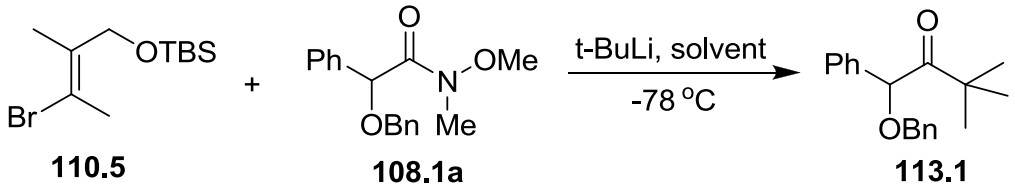


Scheme 112

Entry	n-BuLi (eq)	Results
1.	1.1	**112.1**
2.	,,	,,
3.	1.0	,,
4.	2.0	No reaction

Table 27: Reaction of vinyl bromide **110.5** with n-BuLi

Similarly, the addition of Weinreb amide **108.1** to a mixture of vinyl bromide **110.5** and t-BuLi gave the t-butyl ketone side product **113.1** (Scheme 113). Vinyl bromide **110.5** was also treated with t-BuLi under a variety of reaction conditions. The reaction was carried out between –78 °C to room temperature. However, there was no metal-halogen exchange between vinyl bromide and t-BuLi. No product of Li/Br exchange was ever isolated (Table 17, 28). Vinyl bromide **110.5** was invariably recovered from the reaction mixture.



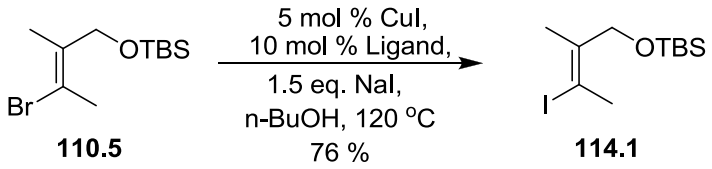
Scheme 113

Entry	t-BuLi (eq)	Amide 108.1a (eq)	Solvent	Temp.(°C)	Results
1.	2	1	Ether	-78	**113.1**
2.	,,	,,	THF	,,	,,
3.	,,	-	Ether	0	No reaction
4.	,,	-	THF	,,	,,
5.	,,	-	Ether	-78	,,
6.	,,	-	THF	,,	,,
7	2.5	0.5	Ether	,,	**113.1**
8.	,,	,,	THF	,,	,,
9.	,,	1.5	Ether	,,	,,
10.	,,	-	,,	-78 to rt	,,

Table 28: Reaction of vinyl bromide **110.5** with t-BuLi

1.4 Preparation of *E*-Iodide

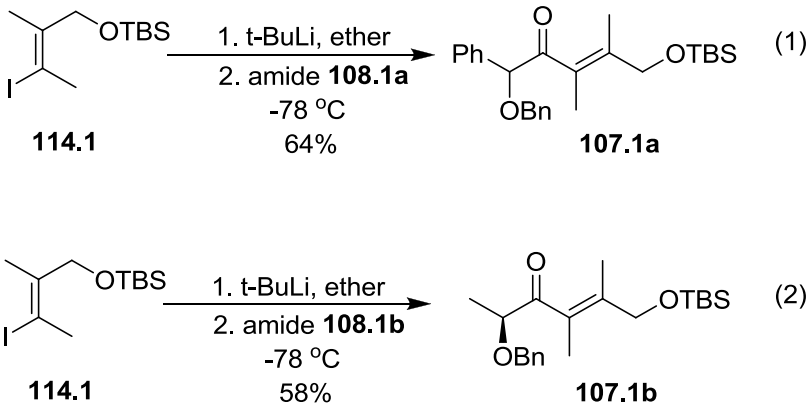
Due to the lack of reactivity of *E*-bromide **110.5**, we converted it to the more reactive *E*-iodide **114.1** (Scheme 114).[165] The reaction was carried out in a Schlenk tube with 5 mol % of CuI, 10 mol % of *N*,*N*-dimethyethylene diamine, 1.5 eq of NaI and n-BuOH as a solvent at 120 °C for 24 hours. The formation of the *E*-iodide was confirmed by TLC, and ^{1}H and ^{13}C NMR.



Scheme 114

1.5 Preparation of the Enones

Gratifyingly, the α,β-unsaturated enones were prepared by metal-halogen exchange of *E*-iodide **114.1** with t-BuLi followed by the addition of Weinreb amide **108.1a** or **108.1b** to give tetrasubstituted enones **107.1a** and **107.1b** respectively (Scheme 115).



Scheme 115

2. Attempts to make Tetrasubstituted Alkene Hydrazones

As mentioned previously, the experimental results from trisubstituted hydrazone preparation and Hartree-Fock calculations (HF/6-31G*) of the simplified trisubstituted hydrazones showed that the preference of *E*-selectivity is under kinetic control (*cf*. Figure 14). We also utilized molecular modeling for the tetrasubsituted hydrazone preparation and compared the results with that of the trisubsituted hydrazones (Figure 15). The trisubstituted *trans*-hydrazone is lower in energy than the *cis*-hydrazone by 2.0 kcal/mol. Similarly, the *trans*-hydrazone is favored by 2.3 kcal/mol over the corresponding *cis*-hydrazone in tetrasubstituted alkenes (R=Me). This evidence suggests that the hydrazone formation reaction would afford *E*-hydrazone as a major isomer in tetrasubstituted alkenes as well.

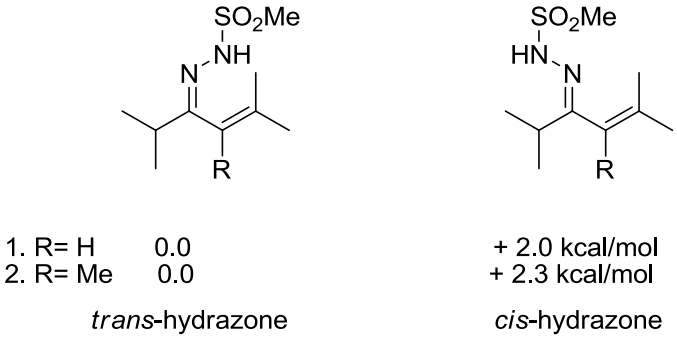
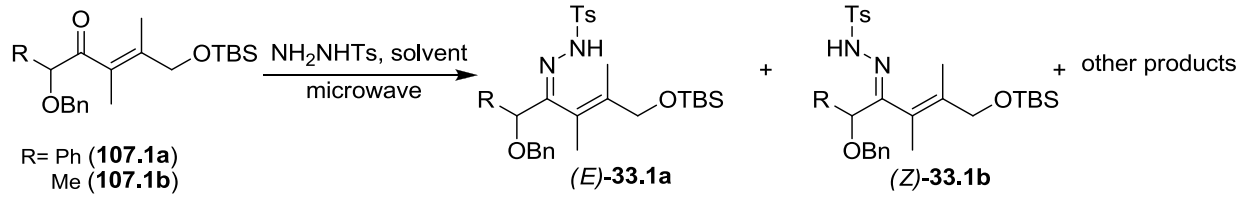


Figure 15

Based on these results, we reasoned that the same kinetic selectivity as in trisubstituted alkene hydrazones for the *E*-isomer would occur for the reaction with tetrasubstituted enones. We initially utilized microwave irradiation for tetrasubsituted hydrazone preparation (Scheme 116). When a mixture of enone **107.1a** and tosylhydrazide in CH_2Cl_2 was irradiated under microwave at 40 °C for 30 minutes, no reaction occurred. After 18-24 h, the reaction afforded a 1:1 mixture of *E*- and *Z*-hydrazone and another unidentified product. We next treated enone

107.1a treated with 1.1 eq of Ti(O-*i*-Pr)$_4$ and tosyl hydrazide under microwave irradiation for 24 h. The reaction provided the same mixture as before.

Proton NMR was used to identify the *E*- and *Z*-hydrazones. The chemical shifts of sulfonamide proton in the *E*- and *Z*-isomers were approximately at 8 ppm and 10 ppm, respectively.[100] However, we were unable to separate the *E*- or *Z*-isomers. NMR data also showed other inseparable impurities. Several different reaction conditions were utilized for hydrazone preparation; however, all of them gave the same mixture (Table 29).

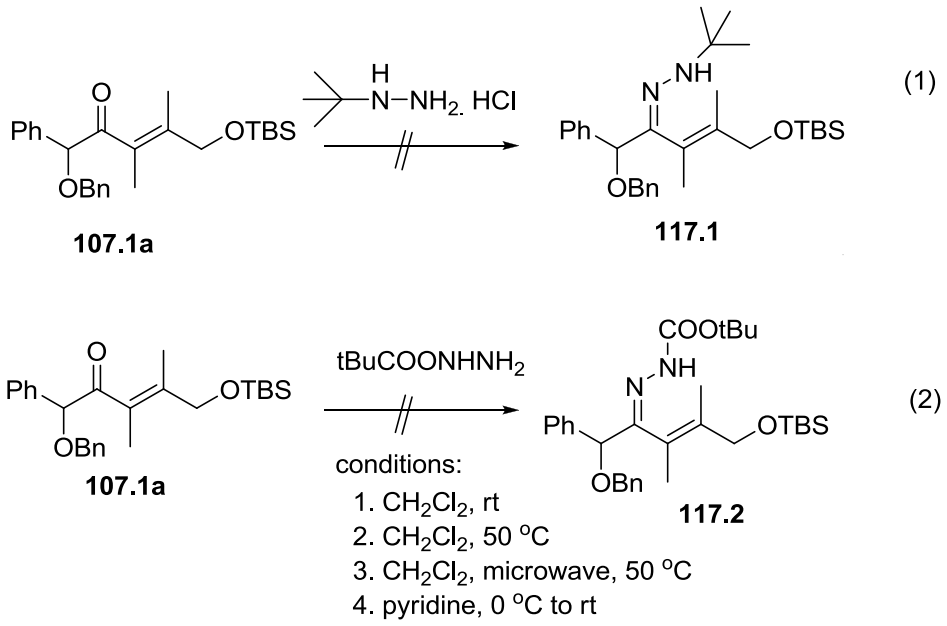


Scheme 116

Entry	Time (h)	Temp. (°C)	Power (w)	Solvent	Ti(O-*i*-Pr)$_4$ (eq)	Results
1.	0.5	40	30	CH_2Cl_2	0	Starting material recovered
2.	18	,,	,,	,,	,,	Mixture
3.	24	,,	,,	,,	,,	,,
4.	,,	60	,,	EtOH	,,	,,
5.	,,	,,	200	,,	,,	,,
6.	,,	40	30	,,	1.1	,,
7.	,,	60	,,	neat	-	,,
8.	,,	,,	,,	,,	1.1	,,

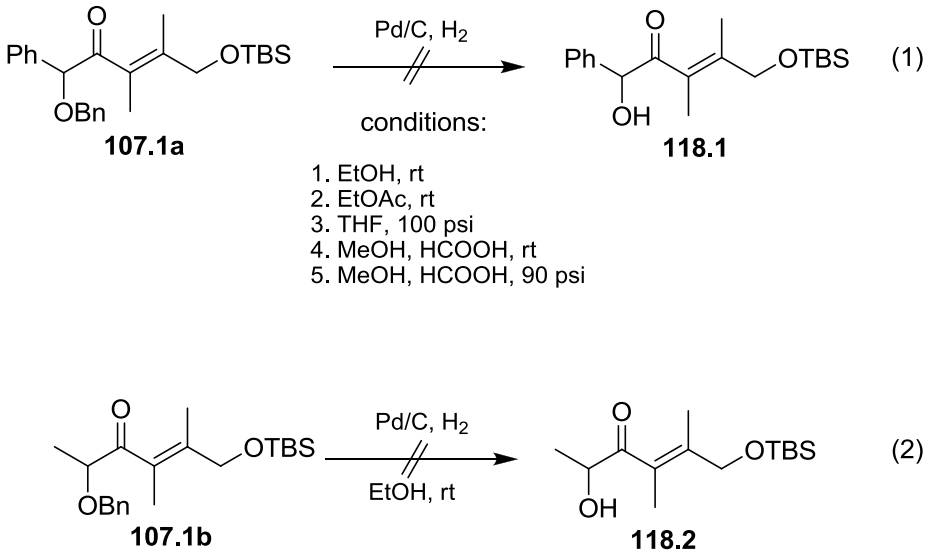
Table 29: Hydrazone formation reactions

We have also attempted to make hydrazones by using other hydrazides such as the more nucleophilic t-butyl hydrazine hydrochloride and t-butyl carbazides (Scheme 117).[166] Different reaction conditions mentioned below were tried; however, none of them gave the desired product. The reaction gave a mixture of several products, which we were unable to separate. The highly sterically hindered nature of the carbonyl group is the probable reason for the failure.



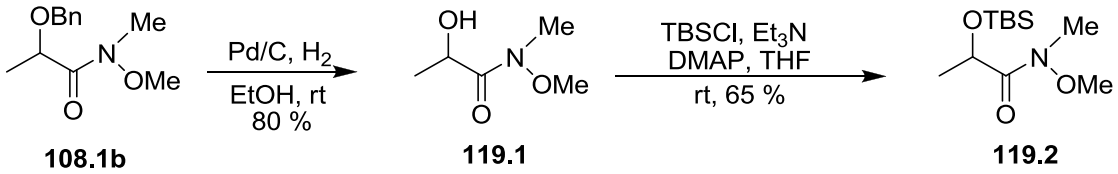
Scheme 117

We reasoned that removal of the benzyl group might help to overcome the steric issues in hydrazone formation. In addition to this, the hydrogen bonding between the sulfonamide nitrogen and hydroxyl group might help to form the hydrazone. Therefore we attempted hydrogenolysis of enones **107.1a** or **107.1b** over Pd/C; however, we recovered only starting material from the reaction (Scheme 118).[167,168,169]



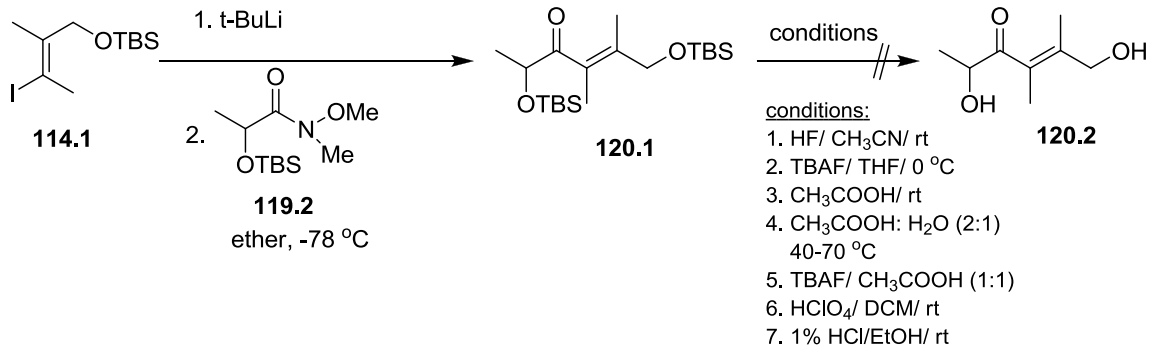
Scheme 118

Another strategy to prepare the hydroxy ketone was by using a more easily removable protecting group. Therefore our next step was preparation of TBS protected amide **119.2**. First, hydroxy amide **119.1** was prepared by debenzylation of amide **108.1b**[168,169] and protected with TBSCl (Scheme 119). Enone **120.1** was prepared by using amide **119.2** and vinyl iodide **114.1** (Scheme 120). However, cleavage of the TBS group was not successful under a variety of reaction conditions, providing only a complex mixture of products.[170,171]



108.1b **119.1** **119.2**

Scheme 119



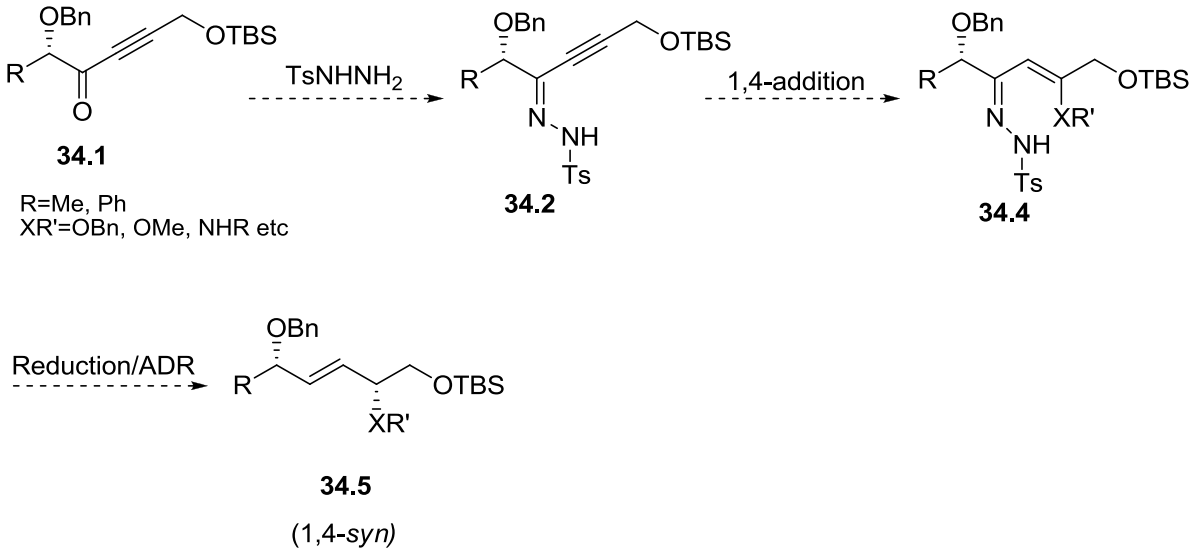
114.1 **119.2** **120.1** **120.2**

Scheme 120

After several attempts to prepare and purify the tetrasubstitued hydrazones, we realized that the low yield and stereoselectivity in forming the hydrazone presumably due to the highly sterically hindered nature of the molecule, would make the method unsatisfactory in applications involving enones. The project was therefore abandoned.

C. α,β-UNSATURATED YNONE HYDRAZONES

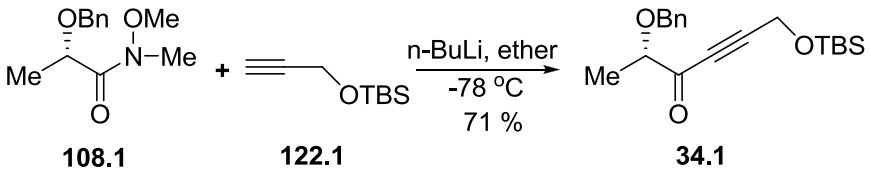
As described in the first chapter, our next strategy was to utilize α,β-unsaturated ynone hydrazones to further expand the ADR methodology in acyclic system. We anticipated that ynone hydrazone **34.2** could be used as an intermediate for the synthesis of (bis)-alkoxy alkene, alkoxy amine alkene or diol alkene **34.5** with 1,4-stereocenters (Scheme 121). Ynone hydrazones **34.2** could be readily prepared from condensation of α,β-unsaturated ynones **34.1** and tosylhydrazide.[144]



Scheme 121

1. Preparation of α,β-Unsaturated Ynone

Firstly, α,β-unsaturated ynones **34.1** were prepared by deprotonation of TBS protected propargylic alcohol **122.1** with n-BuLi followed by treatment with Weinreb amides (Scheme 122). The reaction gave good yield.

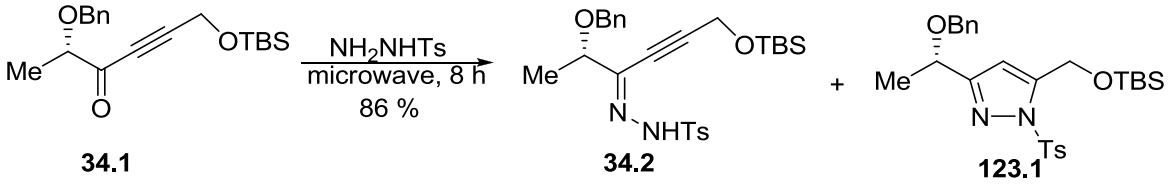


108.1 **122.1** **34.1**

Scheme 122

2. Preparation of α,β-Unsaturated Ynone Hydrazones

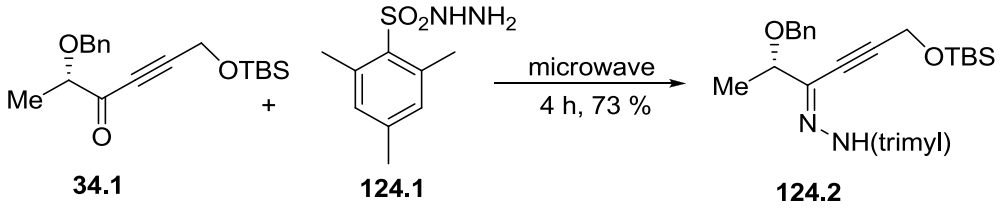
Based on the literature, the reaction between α,β-unsaturated ynones and hydrazine may give a mixture of the ynone hydrazone and a pyrazole.[144,145] Nevertheless, we sought to prepare the hydrazones by utilizing microwave irradiation of a mixture of ynone **34.1** and tosylhydrazide in CH_2Cl_2 (Scheme 123). The reaction afforded a mixture of α,β-unsaturated ynone hydrazone **34.2** and pyrazole **123.1** as a side product.[172] After chromatography, we obtained ca. 5:1 ratio of the ynone hydrazone **34.2** and pyrazole **123.1**.



34.1 **34.2** **123.1**

Scheme 123

The formation of ynone hydrazone and pyrazole depends on the nature of the substituents of the hydrazine and silyl group.[146,147] In general, bulkier substituents help to prevent cyclisation of hydrazones. Therefore, we utilized trimylhydrazide (2,4,6-trimethyl sulfonylhydrazide) to prepare the ynone hydrazone **124.2** (Scheme 124). The formation of ynone trimyl hydrazone was faster compared to that of ynone tosyl hydrazones (*cf*. Scheme 123).

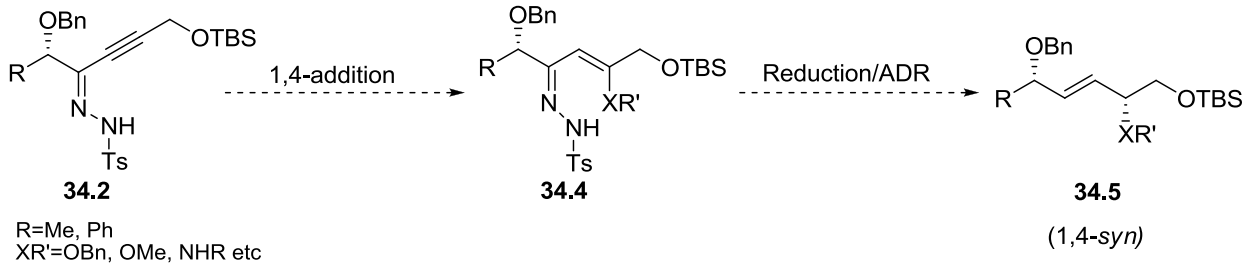


34.1 **124.1** **124.2**

Scheme 124

D. ATTEMPTS TO PREPARE β-ALKOXY AND β-AMINO α,β-UNSATURATED ENONE HYDRAZONES FROM α,β-UNSATURATED YNONE HYDRAZONES

After preparing the ynone hydrazones, our next step was to employ them in 1,4-additions to prepare α,β-unsaturated enone hydrazones **34.4**, precursors to alkenes **34.5** (Scheme 125). Although we were unable to find close precedent for the 1,4-addition to ynone hydrazones, we decided to attempt conjugate addition to the ynone hydrazone also.



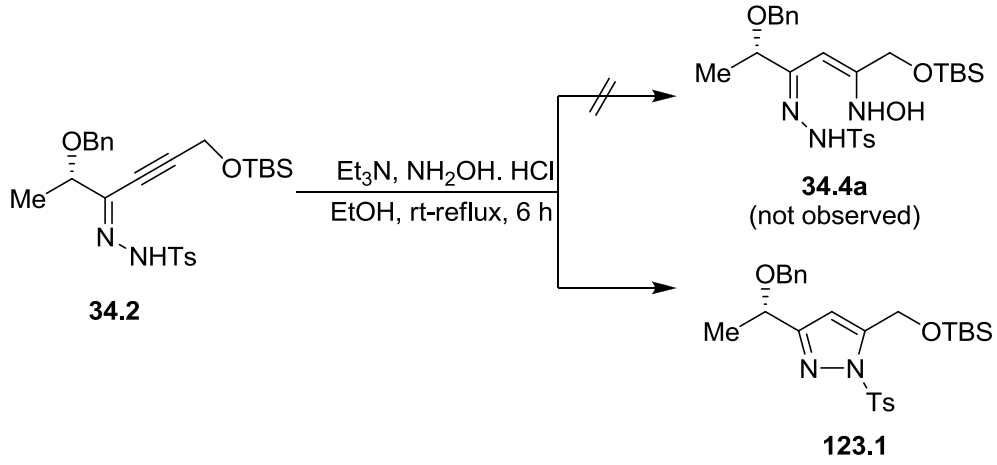
34.2 **34.4** **34.5**

R=Me, Ph
XR'=OBn, OMe, NHR etc

(1,4-*syn)*

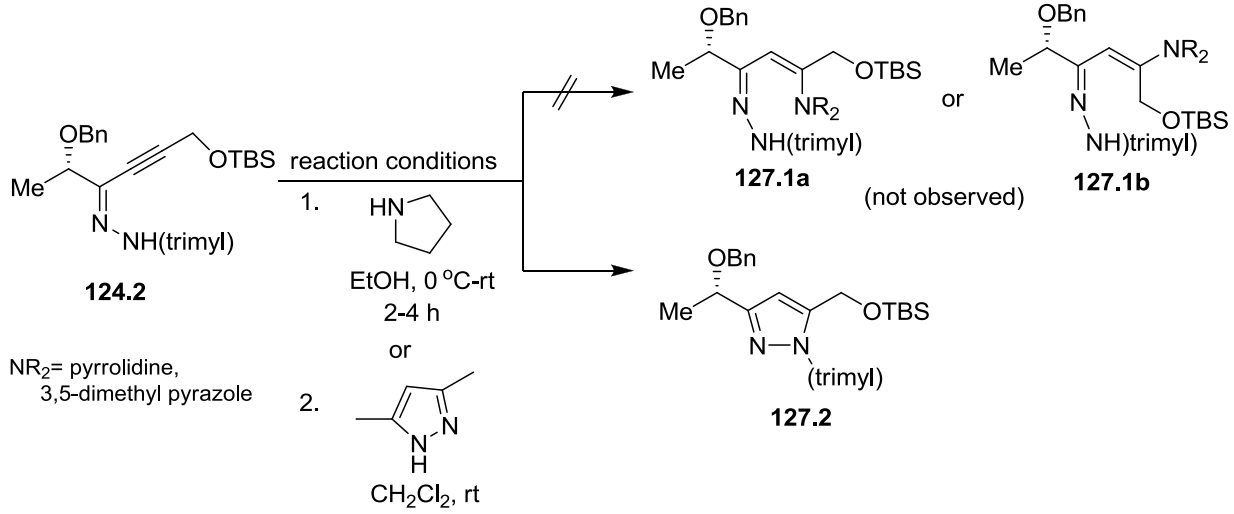
Scheme 125

At first, we treated α,β-unsaturated ynone hydrazone **34.2** with $NH_2OH.HCl$ in the presence of base in the hope of obtaining the addition product **34.4a** (Scheme 126)**.** However, the reaction only gave pyrazole derivative **123.1**.



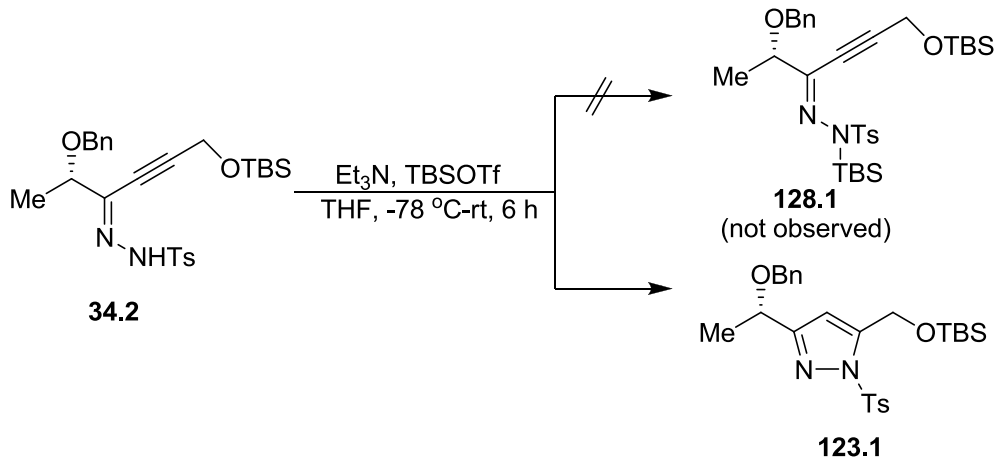
Scheme 126

We also utilized trimyl hydrazone **124.2** hoping to obtain the 1,4-addition product (Scheme 127). However, both pyrrolidine and 3,5-dimethyl pyrazole gave only pyrazole derivative **127.2**.[173]



Scheme 127

To avoid the cyclisation of ynone hydrazone, we attempted to protect the sulfonamide nitrogen with a TBS group by following Myers' protocol (Scheme 128).[45] The reaction gave only the pyrazole **123.1** instead.

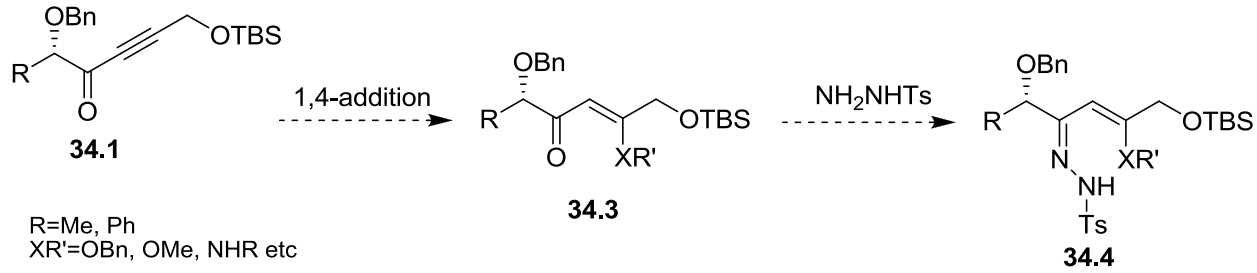


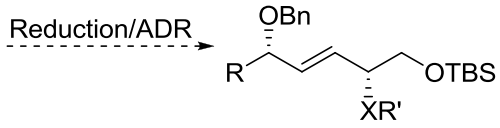
Scheme 128

Pyrazole formation might be due to the acidity of the sulfonamide proton. McMahon reported cyclisation of acetylenic tosylhydrazones as a general problem even during chromatography by using silica gel, acidic or basic alumina.[147,148] Considering the fact that the cyclisation of ynone hydrazones is a common problem, we decided to utilize an alternative method to prepare α,β-unsaturated enone hydrazones.

E. ATTEMPTS TO PREPARE α,β-UNSATURATED ENONE HYDRAZONES FROM α,β-UNSATURATED ENONES

An alternative strategy could be used to prepare alkenes **34.5** by employing α,β-unsaturated enone hydrazone (Scheme 129). Enone hydrazone **34.4** could be obtained by first preparing α,β-unsaturated enone **34.3** from 1,4-addition to ynone **34.1** and then utilizing the enone **34.3** for hydrazonation.





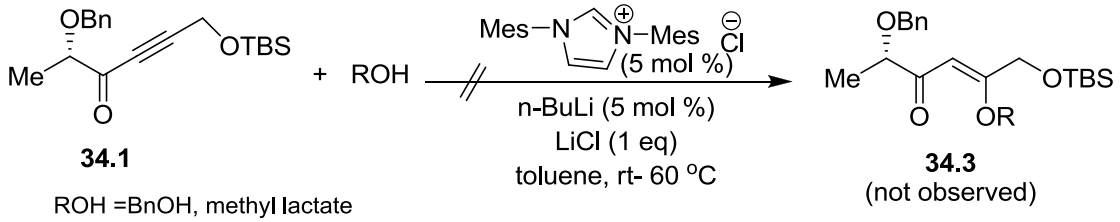
34.5

(1,4-*syn*)

Scheme 129

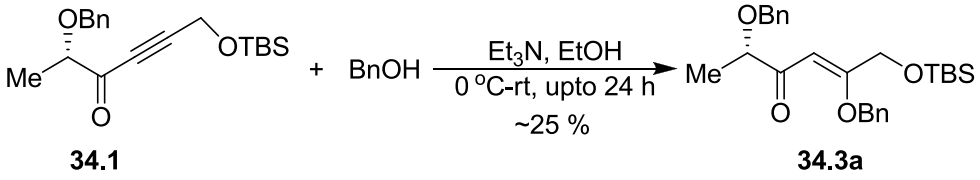
1. Preparation of α,β-Unsaturated Enone from Ynone

Synthesis of α,β-unsaturated enone **34.3** could be possible by 1,4-conjugate addition to α,β-unsaturated ynone **34.1**. There is also a close precedent for this type of reaction reported by Scheidt in which an *N*-heterocyclic carbene (NHC) was utilized as a catalyst (*cf*. Scheme 36).[75] We employed the same reaction conditions to prepare the desired enone **34.3** from ynone **34.1** and BnOH (Scheme 130). No reaction was observed at room temperature. The reaction gave a complex mixture of products on heating to 60 °C. Similarly, a complex mixture was formed when methyl lactate was used as a nucleophile at room temperature.



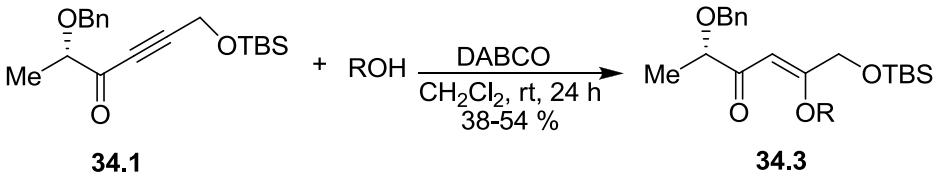
Scheme 130

However, the desired product **34.3a** was obtained simply by stirring a reaction mixture of ynone **34.1** and BnOH under basic conditions at room temperature (Scheme 131).[75] The reaction gave only ca. 25 % yield with some impurities even after purification. Optimization of the reaction conditions by using lower temperature, -78 to 0 °C, did not improve the yield. The reaction was not complete even after 4 days at room temperature.



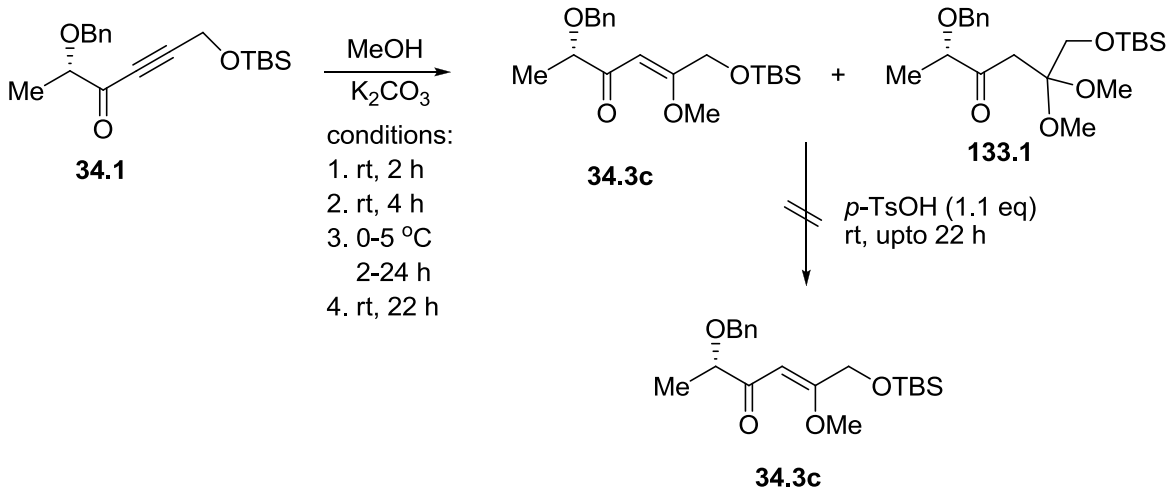
Scheme 131

Another 1,4-addition reaction was reported in which a variety of alcohols were added to butynoate **38.1** by using trimethylphosphine as a nucleophilic catalyst (*cf*. Scheme 38).[77] The reaction provided ca. 97:3 mixture of the *E*- and *Z*-isomers. Based on these results, we decided to attempt a DABCO (1,4-diazabicyclo[2.2.2] octane) catalyzed conjugate addition to our substrate **34.1** (Scheme 132).[174] BnOH and (*S*)-Methyl lactate were employed for this purpose. The reactions gave better yield compared to the previous conditions using triethylamine (*cf*. Scheme 131).



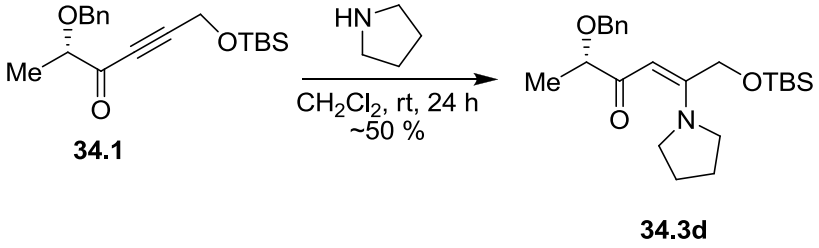
Scheme 132

Our next strategy was to use MeOH simply to study the behavior of our substrate **34.1** towards conjugate addition of common alcohols. Conjugate addition of methanol[175] to ynone **34.1** with K_2CO_3 at room temperature gave the desired adduct **34.3c**; however, the product was accompanied by ketal **133.1** resulting from double addition of MeOH to α,β-unsaturated ynone **34.1** (Scheme 133). We were not able to isolate the desired product by chromatography. Lower temperature (0-5 °C) and shorter reaction time (2-4 h) were also tried to avoid the side product; but all of them gave a mixture. However, longer reaction time (22 h) afforded ketal **133.1** as the only product. We also attempted acid catalyzed elimination to obtain pure **34.3c**, but the reaction gave a complex mixture. Proton NMR of the crude reaction mixture showed cleavage of the TBS group with other side products.



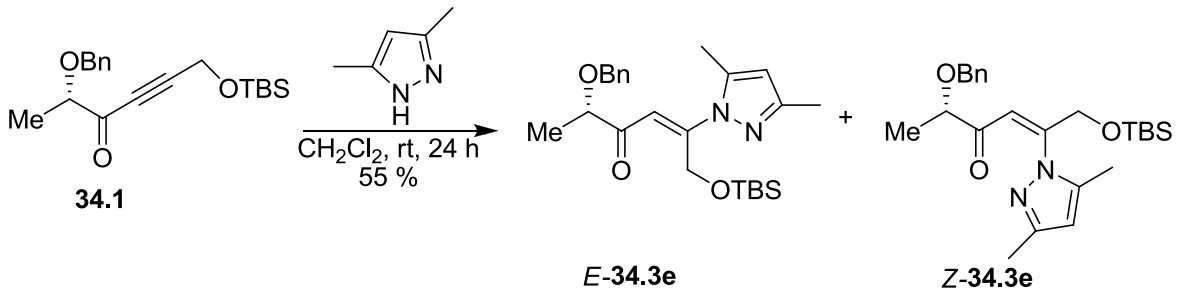
Scheme 133

We have also utilized nitrogen containing nucleophiles such as pyrrolidine and 3,5-dimethyl pyrazole.[173] Stirring a solution of ynone **34.1** and pyrrolidine in CH_2Cl_2 for 24 h afforded the corresponding enone **34.3d** but only ca. 50 % yield (Scheme 134). Proton NMR showed the presence of only isomer; however, the *E*/*Z* configuration of the product was not determined.



Scheme 134

The reaction with 3,5-dimethyl pyrazole gave a mixture of two isomers, presumably *E*- and *Z*-isomers (Scheme 135) which were separated by chromatography. The configuration of the isomers was not assigned.

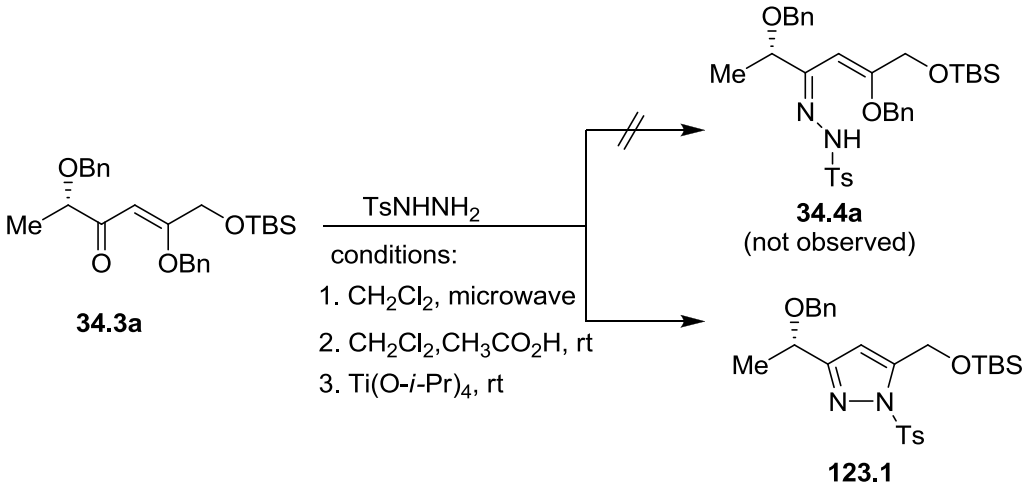


E-**34.3e** *Z*-**34.3e**

Scheme 135

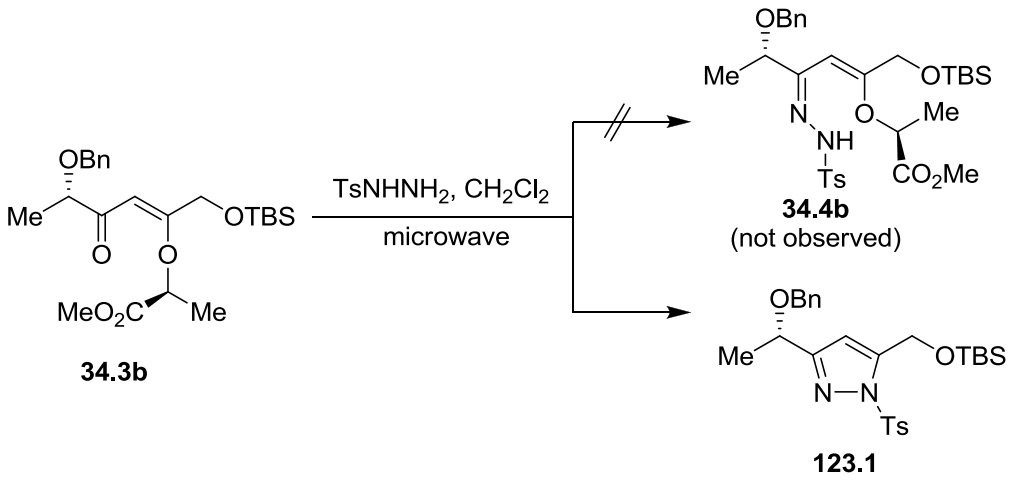
2. Attempts to Prepare α,β-Unsaturated Hydrazone from α,β-Unsaturated Enone

After preparing α,β-unsaturated enones, we envisioned utilizing the corresponding enones for hydrazonation (Scheme 136). At first, we attempted to prepare α,β-unsaturated hydrazone **34.4** by treating enone **34.3a** with tosylhydrazide under microwave irradiation. We obtained only the pyrazole product **123.1** instead of the desired hydrazone. Further, the acid catalyzed hydrazonation with acetic acid or Ti(O-*i*-Pr)$_4$ did not provide the expected product. All of these conditions gave only the side product pyrazole.



Scheme 136

We also employed α,β-unsaturated enone **34.3b** for hydrazone preparation under microwave irradiation; however, only pyrazole **123.1** was isolated with recovery of ca. 12 % starting material (Scheme 137).

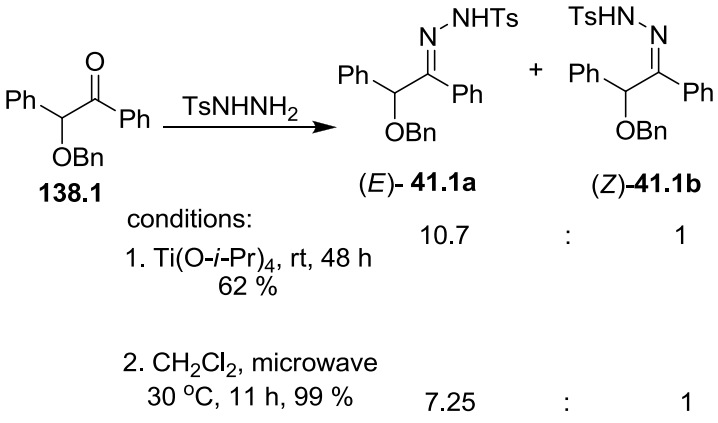


Scheme 137

All the attempts to prepare α,β-unsaturated hydrazone were unsuccessful due to competing pyrazole formation during either hydrazonation or conjugate addition reactions.

F. REEXAMINATION OF THE HYDRAZONE PREPARATION

As mentioned earlier in the first chapter, the *E*/*Z* configuration of the hydrazone is important in reductive transpositions, since only the *E*-hydrazone underwent reduction using catecholborane or sodium cyanoborohydride. We surveyed a variety of reaction conditions in the hope of maximizing the *E*-selectivity. Firstly, O-benzyl benzil hydrazone was prepared by treating O-benzyl benzil with tosyl hydrazide and Ti(O-*i*-Pr)$_4$ (Scheme 138). Secondly, O-benzyl benzil hydrazone was prepared by microwave irradiation of a mixture of O-benzyl benzil and tosyl hydrazide in CH_2Cl_2. These reactions gave a *E*/*Z* mixture of hydrazones, ***E*-41.1a,** being the major isomer. These results are consistent with those we obtained in preparation of the α,β-unsaturated trisubstituted alkene hydrazones (*cf*. Scheme 73-74).[63]



Scheme 138

The *E*-selectivity in the hydrazone formation under first set of reaction conditions may result from a titanium chelated intermediate (Figure 16). Related bidentate chelated intermediates have been proposed in other Lewis acid mediated reactions. For example, Yamamoto proposed the formation of chelated intermediate from the reaction of α-imino ester **139.1** with Ti(O-*i*-Pr)$_4$ (Scheme 139).[176]

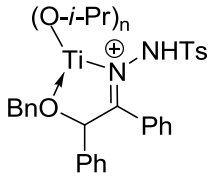
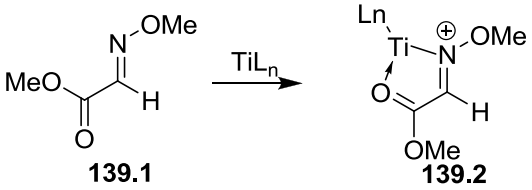


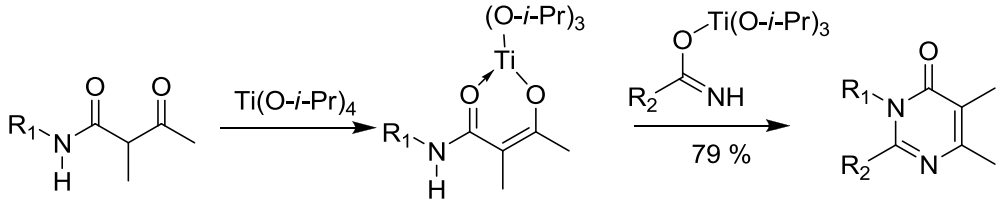
Figure 16



139.1 **139.2**

Scheme 139

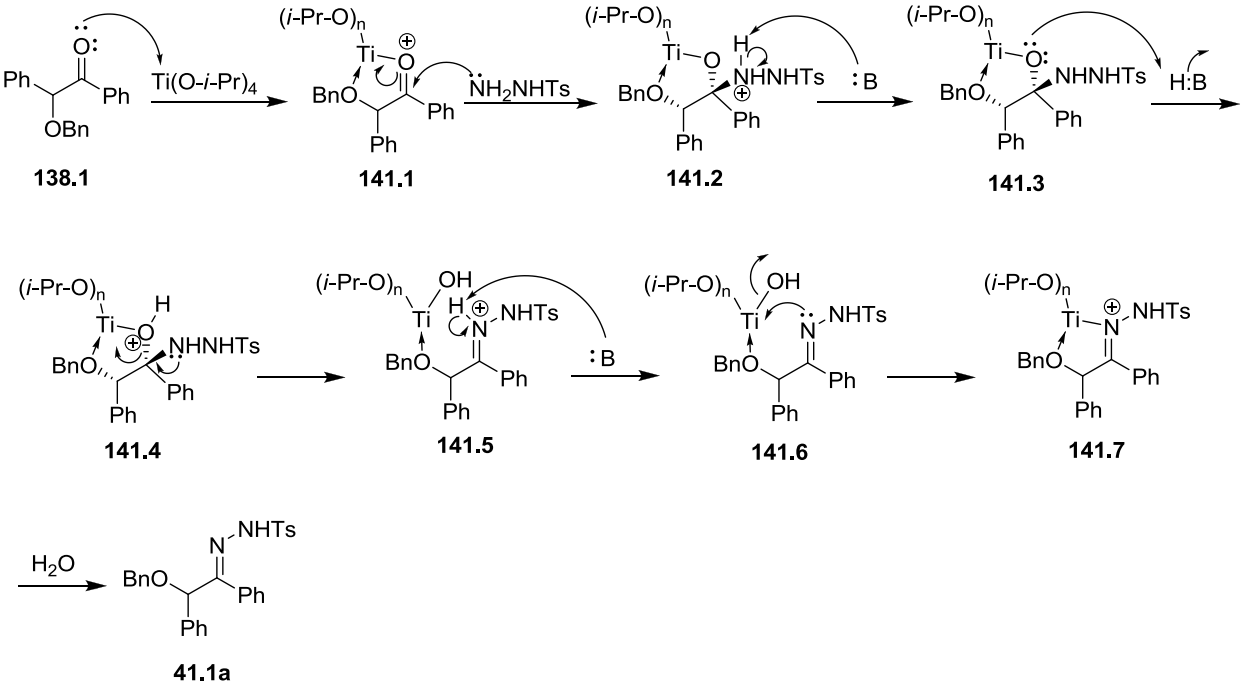
Titanium chelate **140.2** was proposed by Ramanjulu, as an intermediate in the formation of pyrimidine-4-ones in the presence of Ti(O-*i*-Pr)$_4$ (Scheme 140).[177]



140.1 **140.2** **140.3**

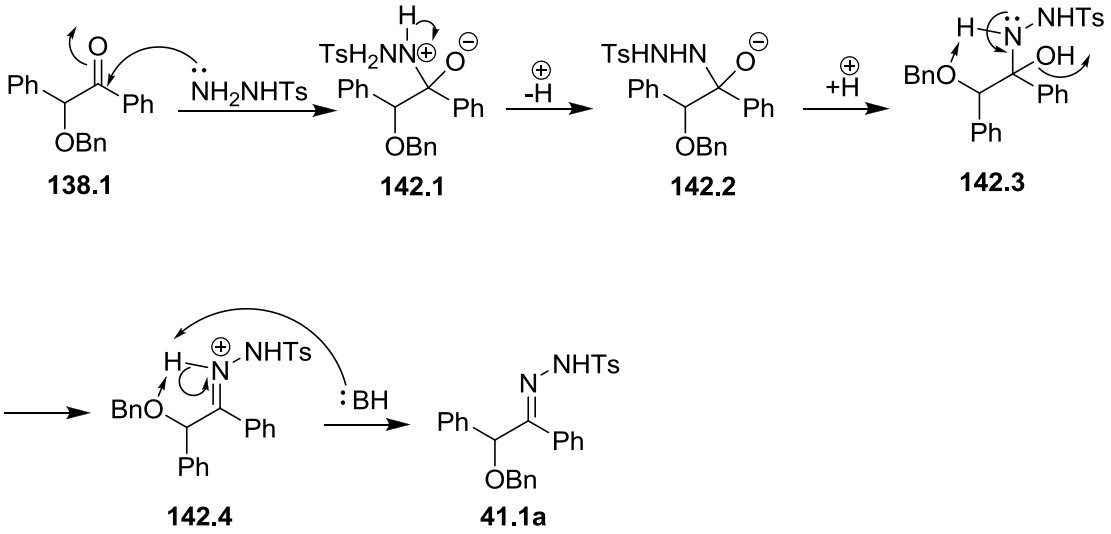
Scheme 140

The hydrazonation under Ti(O-*i*-Pr)$_4$ mediated reaction likely follows a general Lewis acid catalyzed mechanism.[178,179,180] The titanium chelated intermediate **141.7** could possibly form by coordination of titanium with nitrogen and oxygen atoms resulting the *E*-hydrazone (Scheme 141).



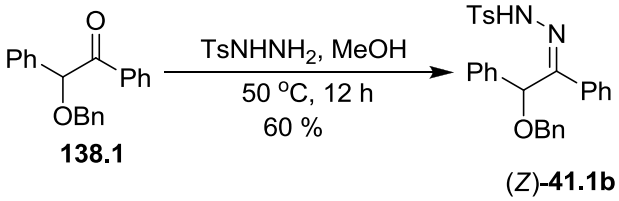
Scheme 141

Similarly, hydrazone stereoselectivity using tosylhydrazide in dichloromethane under microwave irradiation could be due to the formation of the chelated intermediate **142.4** (Scheme 142).



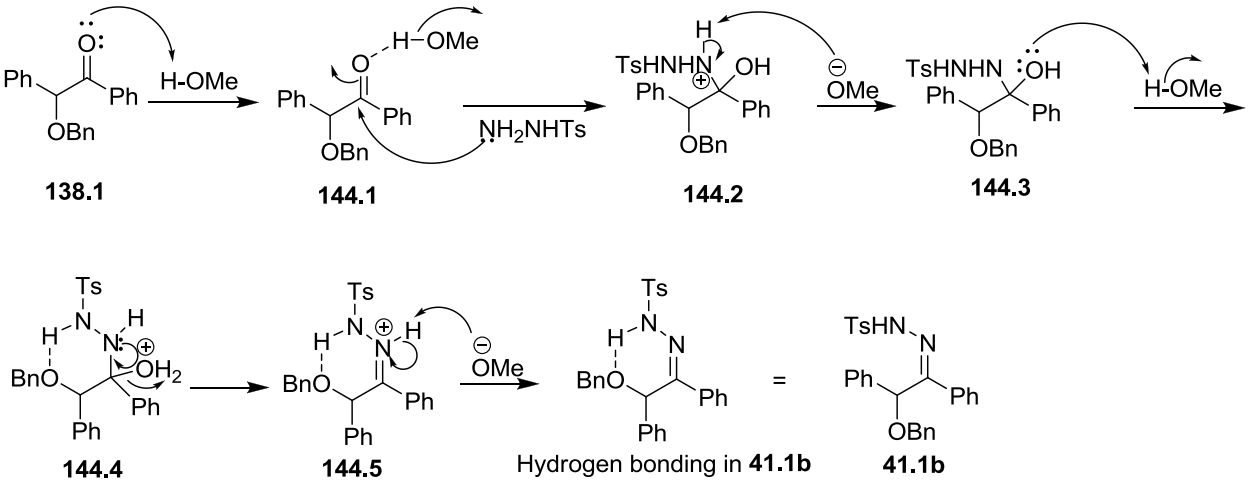
Scheme 142

We also used Rosini's method to prepare O-benzyl benzil hydrazone by heating O-benzyl benzil with tosyl hydrazide in methanol (Scheme 143).[57] Surprisingly, the reaction gave only the *Z*-hydrazone **41.1b**. Rosini *et al* did not report the *E*/*Z* configurations of very similar hydrazones.



Scheme 143

The *Z*-selectivity of the hydrazone preparation under Rosini's conditions can be explained by following reaction mechanism (Scheme 144). Protic solvent, methanol facilitates the addition reaction by protonation which makes the ketone more electrophilic. The *Z*-hydrazone may result from the lack of chelation. Hydrogen bonding of the sulfonamide proton and O-benzyl group as in **41.1b** may possibly the reason for providing the *Z*-isomer.



Scheme 144

These experimental results were compared with the results of DFT calculations (Figure 17). HF/6-31G* calculations of simplified *cis* and *trans*-hydrazones predicted that the *trans*-hydrazone (sulfonamide group *anti* to the R group) is thermodynamically more favored than the *cis*-hydrazone (sulfonamide group *syn* to the R group) for R=Me. The *cis*-hydrazone possesses higher energy conformation presumably due to interaction between isopropyl moiety and the sulfonamide group. By contrast, the *cis*-hydrazone is more favored for R=OMe which is likely due to hydrogen bonding. These results strongly suggest that the O-benzyl benzil hydrazone formation under first two sets of reaction conditions i.e; Ti(O-*i*-Pr)$_4$ mediated conditions and microwave irradiation (*cf*. Scheme 138) is kinetically controlled. Further, given the result of the HF/6-31G* calculations, O-benzyl benzil hydrazone preparation under Rosini's conditions (*cf*. Scheme 143) is likely the result of thermodynamic control.

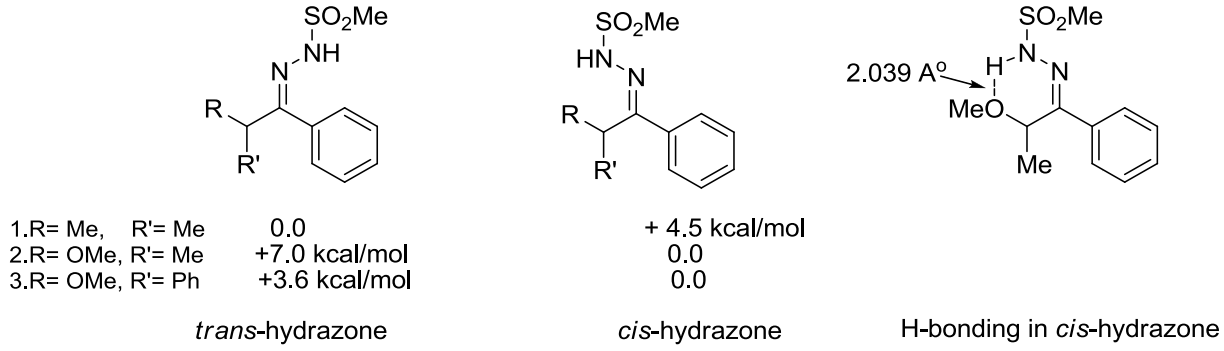
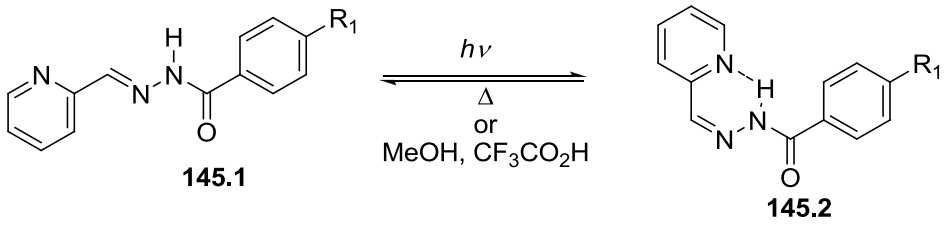


Figure 17

G. *E*/*Z* ISOMERIZATION OF HYDRAZONES

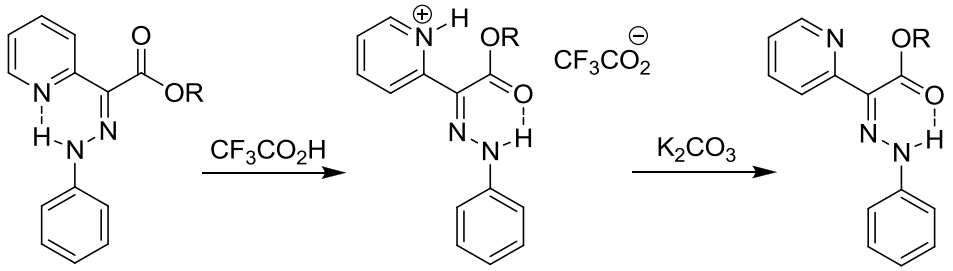
It has been known that the C=N bond of hydrazones can undergo isomerization under photochemical, thermal and acidic conditions. Lehn and coworkers reported the isomerization of the *E*-acyl hydrazone **145.1** to the *Z*-acyl hydrazone **145.2** upon irradiation with UV light Scheme 145).[181] The *Z*-hydrazone **145.2** was reverted to the *E*-hydrazone **145.1** when heated under reflux or acid catalysis.



145.1 145.2

Scheme 145

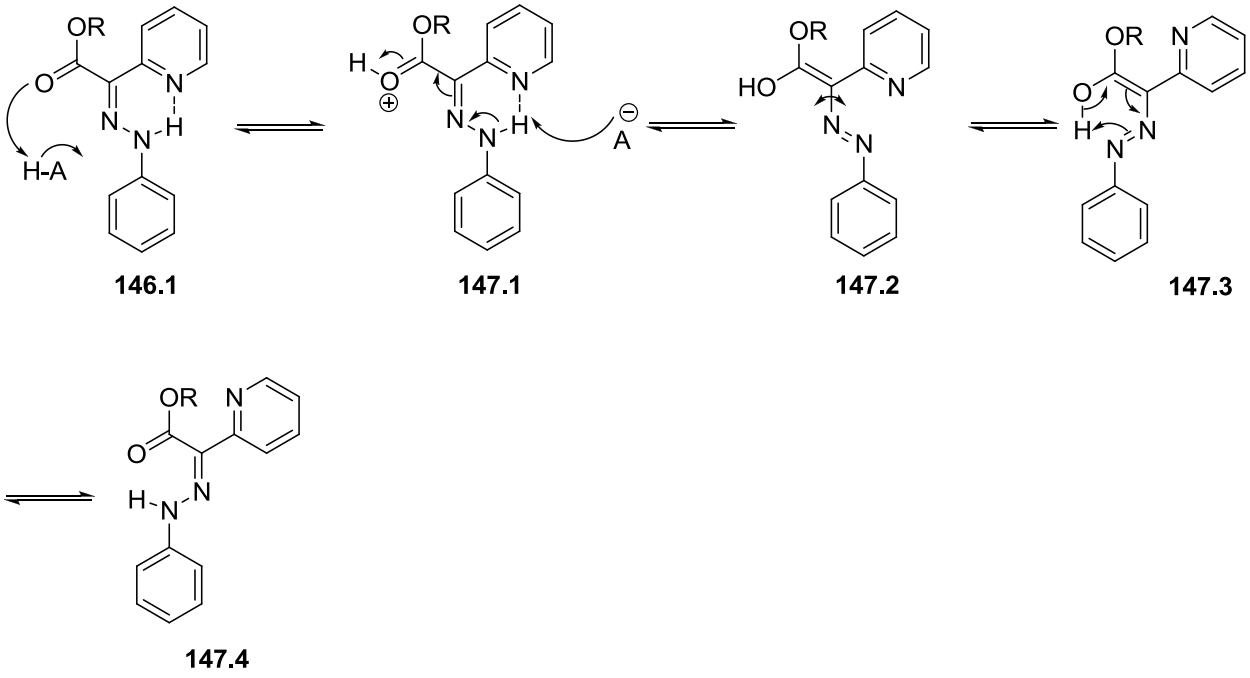
Another example of the acid catalyzed *E*/*Z* isomerization of the hydrazone was reported by Aprahamian *et al* in which the *E*-phenyl hydrazone **146.1** was isomerized to the *Z*-phenyl hydrazone **146.3** (Scheme 146).[182,183] A trifluoroacetic acid salt **146.2** was initially formed from the reaction of the *E*-phenyl hydrazone **146.1** with trifluoroacetic acid. The *Z*-phenyl hydrazone **146.3** was isolated after treatment with potassium carbonate.



146.1 146.2 146.3

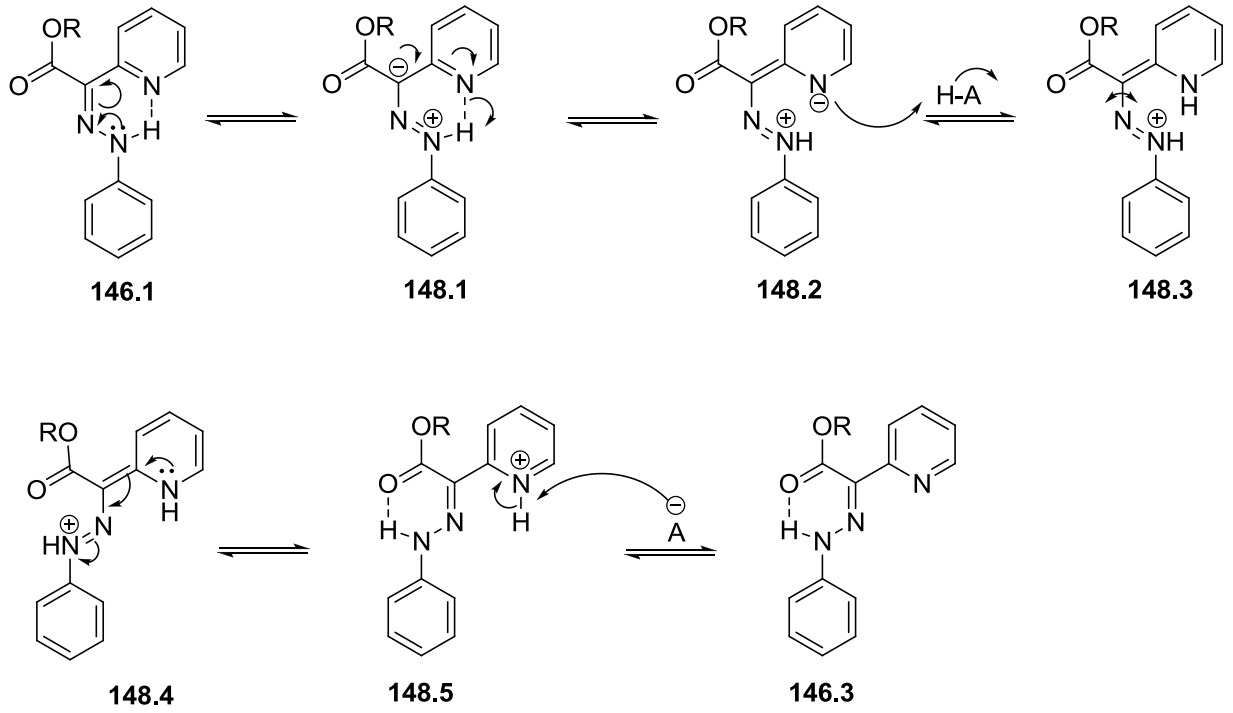
Scheme 146

A mechanism for the isomerization of **146.1** to **146.3** has been proposed, in which the phenyl hydrazone **146.1** first reacted with the acid catalyst to give the protonated intermediate **147.1** (Scheme 147).[182] The isomerization involved tautomerization followed by rotation around C-N single bond to afford the *Z*-hydrazone **146.3**. The isomerization under these conditions provided ca. 3:97 mixture of the *E*- and *Z*-isomers after the *Z*-hydrazone was equilibrated. A 65-93 % of the Z-hydrazones **146.3** were obtained in a pure form after chromatography.



Scheme 147

However, an alternative mechanism can be drawn as follows; since the *E*/*Z* isomerization most likely proceeds through protonation of nitrogen (Scheme 148). The intermediate **148.5** was also detected from proton NMR when the *E*-hydrazone was treated under acidic conditions.

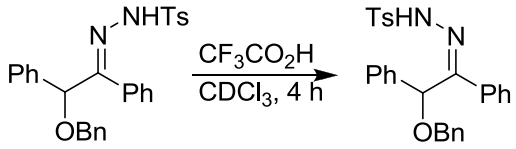


Scheme 148

We utilized a variety of protic acids to study the isomerization of the O-benzyl benzil *E*-hydrazone. Firstly, we performed an NMR tube experiment by preparing a solution of O-benzyl benzil *E*-hydrazone **41.1a** and methanesulfonic acid (1:1) in $CDCl_3$. Proton NMR showed the disappearance of *E*-hydrazone immediately after mixing the sample. A white precipitate was formed after leaving the solution at room temperature for about 20 h. The precipitate was filtered and attempted to analyze through the NMR spectroscopy. However, we were unable to dissolve the precipitate even by using solvents including CD_3CN. Therefore, NMR analysis could not be performed to confirm the isomerization of the *E*-hydrazone to the *Z*-hydrazone. Another NMR sample was prepared by mixing O-benzyl benzil *E*-hydrazone with

methanesulfonic acid in CD_3CN; however, the same white precipitate appeared after 15 minutes. The use of *p*-toluenesulfonic acid with *E*-hydrazone also gave the insoluble precipitation.

We then utilized the less acidic trifluoroacetic acid with the *E*-hydrazone in $CDCl_3$ (Scheme 149). After 4 h, NMR showed a presence of *Z*-hydrazone **41.1b** along with the *E*-hydrazone **41.1a** and the O-benzyl benzyl ketone **138.1** (Figure 18). The *Z*-hydrazone was isolated and its configuration was confirmed by NMR spectroscopy. These results suggested that acidic conditions can be useful for isomerization of *E*-hydrazone to *Z*-hydrazone.



(*E*)- **41.1a** (*Z*)-**41.1b**

Scheme 149

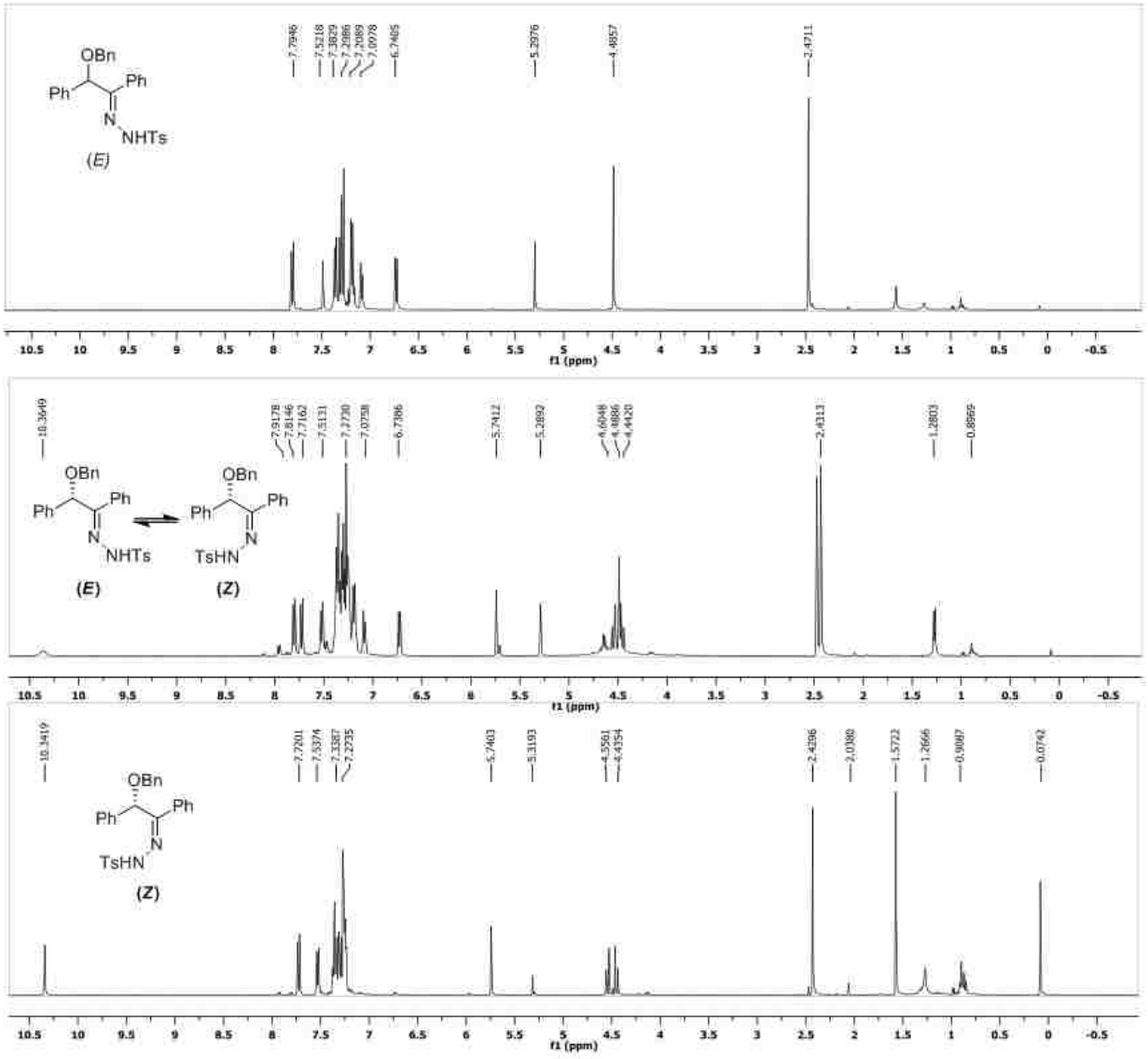
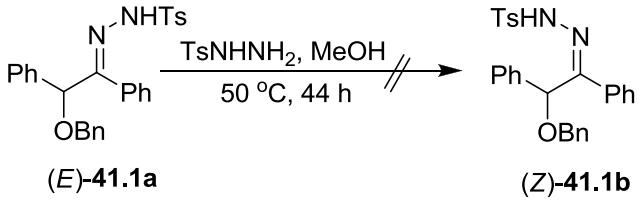


Figure 18: ^{1}H NMR showing Isomerization of *E*-hydrazone to *Z*-hydrazone

Another strategy for *E*/*Z* isomerization was employed by heating a mixture of O-benzyl benzil *E*-hydrazone and tosylhydrazide in MeOH (Scheme 150). We added 1 eq of tosylhydrazide to the reaction mixture hoping that transimination reaction could accelerate the isomerization by chemical exchange.[181] However, no isomerization occurred even after 44 h and the reaction gave a complex mixture of several products.



(*E*)-**41.1a** (*Z*)-**41.1b**

Scheme 150

III. CONCLUSIONS

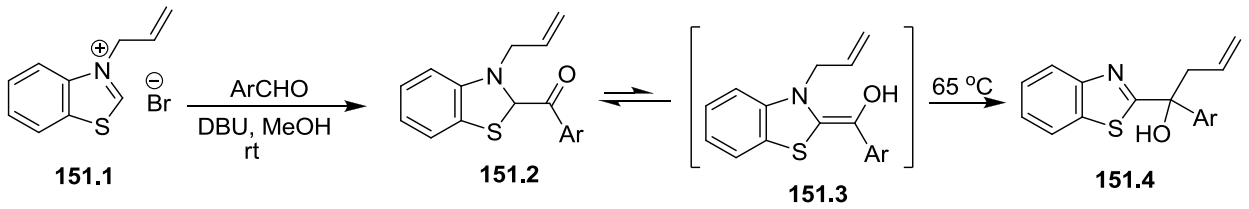
A variety of hydrazones were prepared using different reaction conditions including microwave irradiation. The hydrazone preparations under microwave irradiation and $Ti(O\text{-}i\text{-}Pr)_4$ conditions are kinetically controlled, providing the *E*-hydrazones preferentially. Thermodynamically preferred *Z*-hydrazones can be obtained from heating a solution of ketones and tosyl hydrazide in MeOH.

CHAPTER 3:DBU RECOVERY

I. INTRODUCTION

A. AZA-CLAISEN REARRANGEMENT FOR PREPARATION OF TERTIARY ALCOHOL

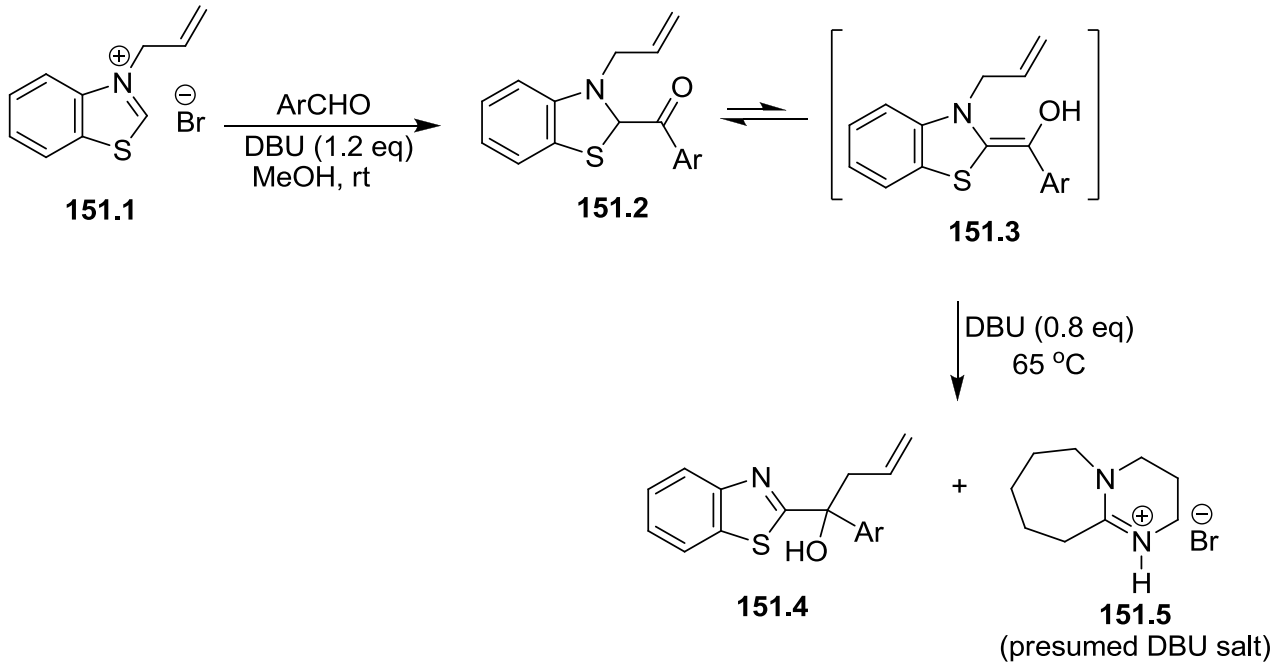
Recently, our group has successfully developed a method to obtain benzothaizolium bearing allyl aryl alcohol by modifying the Metzger conditions[184] i.e.; replacing NEt_3 with DBU (Scheme 151).[185] Deprotonation of benzothiazole salt followed by condensation with benzaldehyde afforded ketone **151.2**. Tertiary alcohol **151.4** was formed upon heating the reaction mixture possibly *via* trapping Breslow intermediate **151.3**,[186,187] which subsequently underwent Claisen rearrangement.



Scheme 151

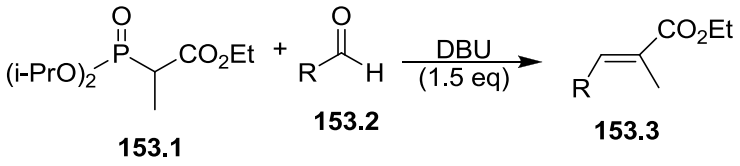
B. DBU RECOVERY

DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) is a base which catalyzes many organic reactions. We have utilized DBU in aza-Claisen rearrangement for the preparation of benzothiazolium derived tertiary alcohols (Scheme 152).[185] We sought to separate and recover DBU from the reaction mixture since 2 eq (1.2 eq + 0.8 eq) of the base was employed as a catalyst to obtain the ACR product. Furthermore, it is equally important to recycle the base to ensure the viability in industrial scale preparation.



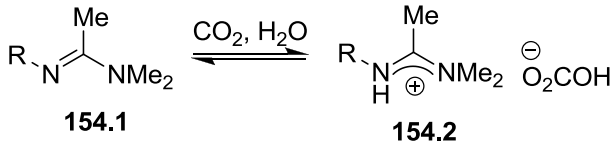
Scheme 152

There are only a few reports that describe recovery of DBU from the reaction mixture. Ando and Yamada recovered 90 % DBU from a Horner-Wadsworth reactions (Scheme 153).[188] The desired product **153.3** was separated first by flash chromatography then DBU was eluted with MeOH. Further treatment of the eluate with NaOH followed by extraction provided DBU. However, we sought to avoid column chromatography, so we did not consider the procedure.



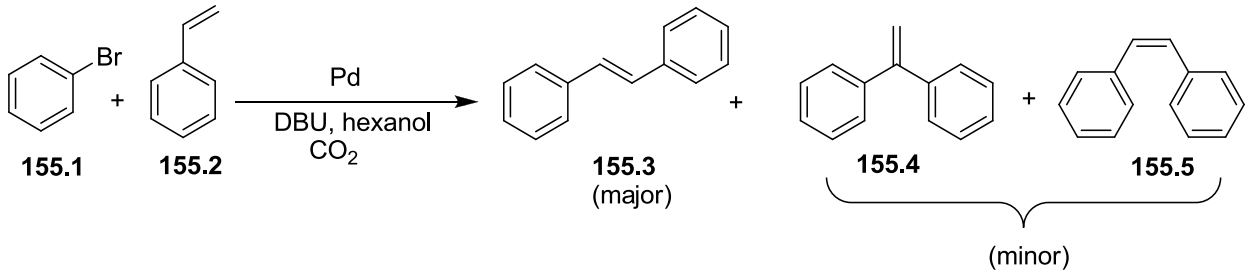
Scheme 153

We were also motivated by the fact that amidine **154.1** reacts with CO_2 and H_2O to form amidinium bicarbonate salt **154.2** (Scheme 154).[189] The bicarbonate salt can be easily reconverted to amidine **154.1** by bubbling argon through the solution. The formation of bicarbonate was also confirmed by conductivity experiment. The conductivity of the solution increased when CO_2 was bubbled and decreased on bubbling argon.



Scheme 154

Similar techniques have been utilized in reversible ionic liquids in which a molecular liquid is switched to ionic liquid on addition of CO_2.[190] In a two-component reversible ionic liquid system, CO_2 was bubbled through an equimolar solution of DBU and MeOH. Ionic liquid containing DBU carbonate salt was separated from a reaction mixture and converted back to DBU by bubbling argon. This technique has been successfully used to recover stoichiometric amount of HBr salt of DBU from a Heck reaction (Scheme 155).



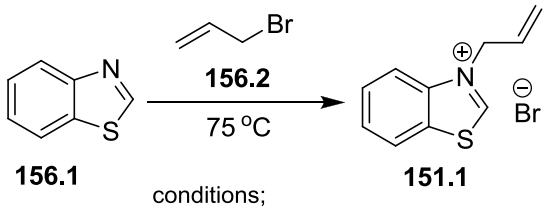
Scheme 155

II. RESULTS AND DISCUSSION

A. PREPARATION OF *N*-ALLYL BENZOTHIAZOLIUM SALT

Allyl benzothiazolium salt **151.1** is the precursor to benzothiazolium derived allyl aryl tertiary alcohol, an ACR product (*cf*. Scheme 151).[186] Previously, our group has prepared the salt **151.1** by heating a mixture of benzothiazole (**156.1**) and allyl bromide (**156.2**) at 75 °C in a pressure tube (Scheme 156). We expected to get the same product **151.1**, avoiding pressure tube so that the methodology could be useful for industrial process. Therefore, we reasoned to obtain the salt **151.1** by simply refluxing 1M solution of reaction mixture in acetone. At first we performed a 10 g scale reaction by preparing a solution of 0.07 mole benzolthiazole and 0.11 mole allyl bromide in acetone. Temperature of the reaction mixture was carefully monitored. After 4 h, the product formed was triturated with acetone and dried in high vacuum; however, the

yield was only ca. 22 %. We attempted to increase the yield by preparing a more concentrated, 2M solution in same reaction scale, but we obtained only 48 % yield. However, heating a neat reaction mixture of benzothiazole (**156.1**) and allyl bromide (**156.2**) provided 90 % benzothiazole salt **151.1** without any exotherm being observed. Then we performed another successful reaction under same conditions by utilizing 0.5 mole of benzothiazole. Further scaling up to a mole of the substrate gave 88-90 % yield after 5 h. These results suggested that still larger scale preparations of bezothiazole salts can safely be performed.



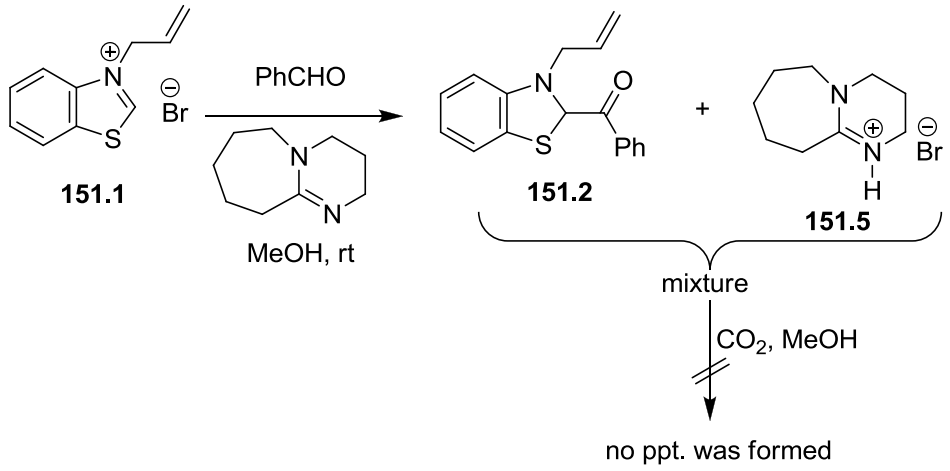
conditions;

1. pressure tube, 1 h, 90 % (10 g scale)
2. acetone, 1M solution, 4h, 22 % (10 g scale)
3. acetone, 2M solution, 8 h, 48 % (10 g scale)
4. 4 h, 90 % (10 g scale)
5. 4-5 h, ~90 % (68 g and 136 g scale)

Scheme 156

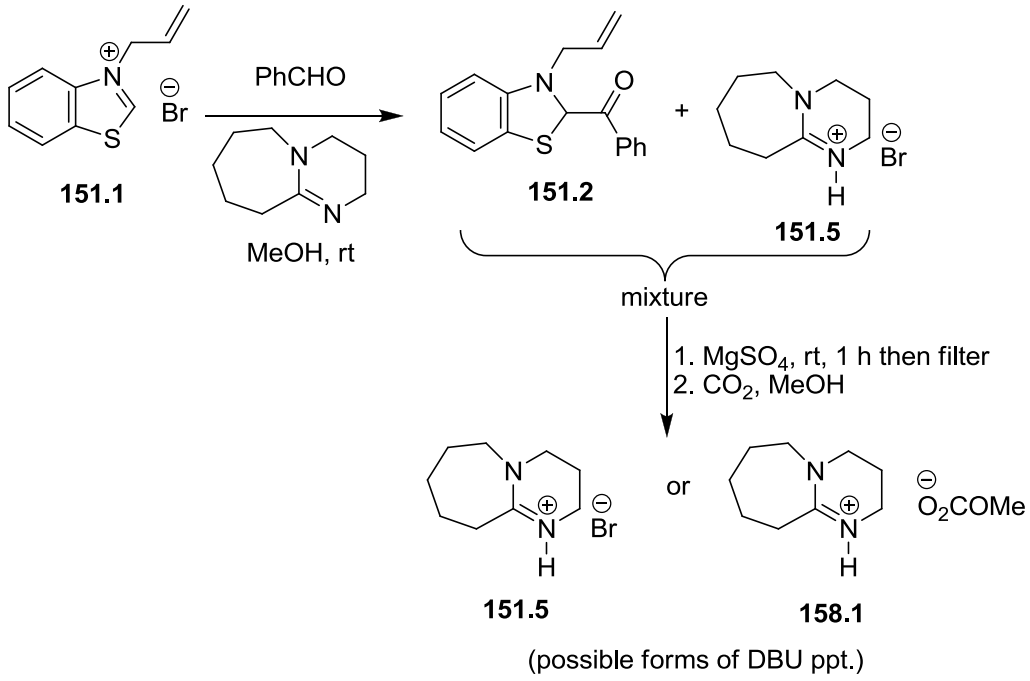
B. DBU RECOVERY

As mentioned previously, it should be possible to separate $DBUH^+Br^-$ from the reaction mixture by precipitating with appropriate solvent. Initially, ketone **151.2** was prepared by reacting benzothiazole salt with benzaldehyde and DBU in methanol (Scheme 157). The reaction mixture was then treated with THF, hoping to obtain the $DBUH^+Br^-$ salt; however, we did not observe any precipitation. Different organic solvents including ether, hexane, dichloromethane, etc. were also tried, but $DBUH^+Br$ did not precipitate. Then, we utilized a reversible ionic liquid technique,[189] assuming that DBU may precipitate as a carbonate salt (Scheme 157). CO_2 was bubbled through a methanolic solution of the reaction mixture at room temperature. However, precipitate of the carbonate salt of DBU was not formed even after 4 h.



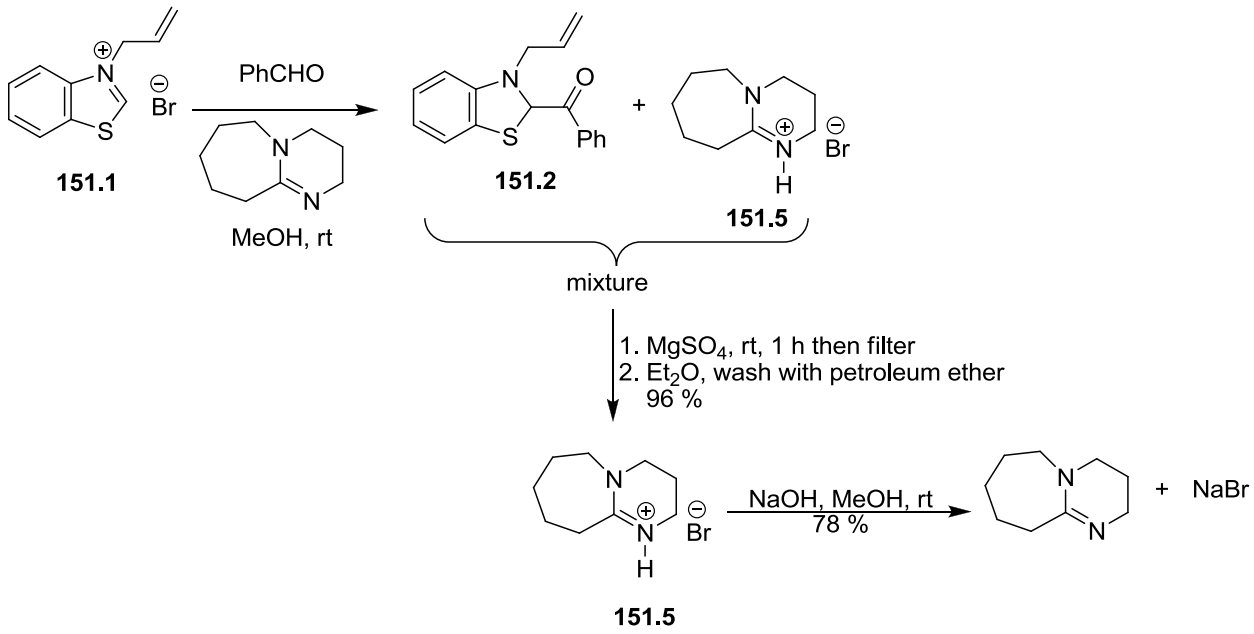
Scheme 157

After all above mentioned attempts failed, we stirred the reaction mixture from ketone preparation with magnesium sulfate (Scheme 158). After 1 h, magnesium sulfate was separated by filtration. The filtrate was then subjected for carboxylation by bubbling CO_2 and the solvent was concentrated in vacuo. Precipitates of DBU were formed when ether was added to the reaction mixture. However, thus formed precipitate could be the DBU salt of HBr **151.5** or the carbonate **158.1**.



Scheme 158

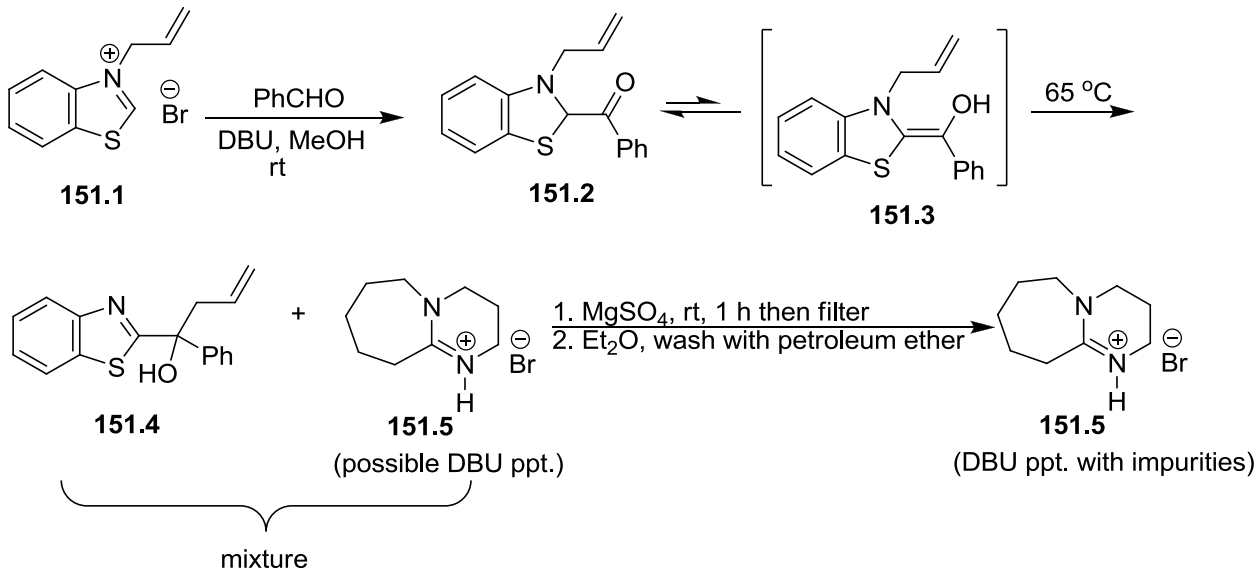
Since DBU could possibly form $DBUH^+Br^-$ *in situ* while preparing the ketone from benzolthiazole salt and benzaldehyde, it could be worth attempting to recover the precipitates directly without carboxylation. Therefore, the reaction mixture was dried directly with magnesium sulfate, filtered then concentrated (Scheme 159). The concentrated reaction mixture provided yellowish-white precipitation when treated with ether. After washing with petroleum ether, pure HBr salt of DBU was obtained with 96 % recovery. Formation of $DBUH^+Br^-$ was confirmed by NMR comparisons with literature data.[189] These results suggested that drying with magnesium sulfate is a necessary step to recover the DBU salt most likely due to undistilled MeOH used in ketone preparation. Further, $DBUH^+Br^-$ salt was reconverted to DBU by treating with NaOH solution. A precipitate of NaBr was separated by filtration. The filtrate was concentrated and dried in high vacuum to give pure DBU.



Scheme 159

Furthermore, we also attempted to recover DBU from the reaction mixture of ACR product **151.4** (Scheme 160). After completion of the reaction, the reaction mixture was stirred with magnesium sulfate at room temperature for an hour. Magnesium sulfate was separated by

filtration and the solution was concentrated in vacuo. A viscous precipitate was obtained when treated with ether. Proton NMR of the precipitate showed the presence of $DBUH^{+}Br^{-}$ but with impurities.

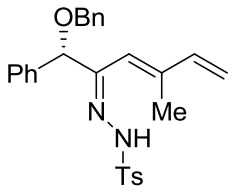


Scheme 160

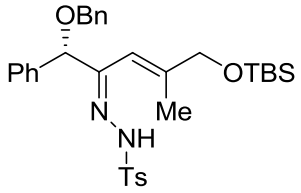
III. CONCLUSION

In conclusion, we have demonstrated a large scale preparation of benzothiazole salt, useful for industrial process without any exothermic conditions. Further, we successfully developed a method to recover DBU by precipitation.

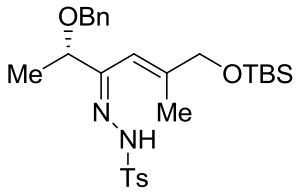
EXPERIMENTAL SECTION



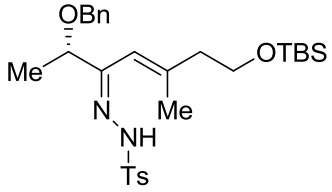
1. α'-Alkoxy alkyl α,β-unsaturated hydrazone 28.1a Titanium (IV) isopropoxide (0.44 mL, 1.71 mmol) was added to a solution of ketone (0.25 g, 0.855 mmol) and tosylhydrazide (0.20 g, 1.11 mmol) at room temperature and stirred for 48 h. The reaction was quenched by adding water and precipitation was separated by filtration. Extractive work up followed by purification provided hydrazone **28.1a** (yield 67 %). Data same as the previous report.[63]



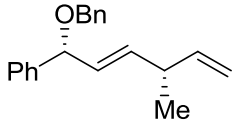
2. α'-Alkoxy alkyl α,β-unsaturated hydrazone 28.1b A solution of tosylhydrazide (0.05 g, 0.271 mmol) and ketone **73.1** (0.1 g, 0.226 mmol) in CH_2Cl_2 (0.5 mL) was irradiated under microwave at 30 °C, 30 W for 9 h. Pure *E*-hydrazone was obtained via flash chromatography with 17:1 hexane/EtOAc (yield 72 %). Data same as the previous report.[63]



3. α'-Alkoxy alkyl α,β-unsaturated hydrazone 28.1c Prepared as above for hydrazone **28.1b** by using microwave (yield 73 %). Data same as the previous report.[63]



4. α'-Alkoxy alkyl α,β-unsaturated hydrazone 28.1d Prepared as above for hydrazone **28.1a** by using Ti(O-*i*-Pr)$_4$ (yield 50 %). Data same as the previous report.[63]

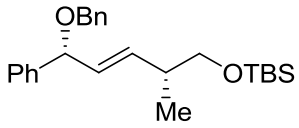


5. α'-Alkoxy Alkyl Alkene 28.2a

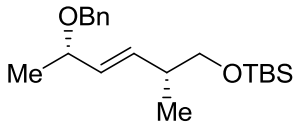
a) Rosini's Procedure A mixture of hydrazone **28.1a** (0.03 g, 0.065 mmol), $NaCNBH_3$ (0.016 g, 0.260 mmol) and a few mg of Bromocresol green in THF (0.65 mL) was stirred at room temperature. A solution of *p*-TsOH (0.05 g, mmol) in THF (0.65 mL) was added slowly to maintain pH 3.5 indicated by a tan color. After 6 h, $NaOAc.3H_2O$ (0.13 g, 0.975 mmol) was added and the reaction mixture was refluxed for 16 h. Extractive work up followed by flash chromatography gave alkene **28.2a** in 85-90 % yield.

b) Qi's Procedure Catecholborane (0.62 mL, 0.588 mmol) was added slowly to a solution of hydrazone **28.1a** (0.045 g, 0.098 mmol) and silica gel (0.090g, 2 wt. eq) in $CHCl_3$ (1.2 mL) at -42 °C. After 2 h, $NaOAc.3H_2O$ (0.20 g, 1.47 mmol) was added and the solution was refluxed for 16 h. The reaction mixture was extracted and purified by column chromatography to obtain alkene **28.2a** (yield 90 %).

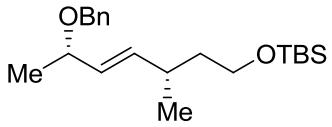
c) Modified Procedure To a mixture of hydrazone **28.1a** (0.04 g, 0.087 mmol) and CH_3CO_2H (0.04 mL, 0.69 mmol) in freshly distilled $CHCl_3$ (1 mL), catecholborane (0.055 mL, 0.522 mmol) was added dropwise at -42 °C. After 2 h, $NaOAC.3H_2O$ was added and the reaction mixture was heated upto 55 °C for 16 h. After completion of the reaction, the mixture was poured into water and extracted with ether. The crude material was purified by flash chromatography over silica gel with 32:1 hexane/EtOAc to obtain pure alkene **28.2a** as colorless oil (yield 98 %). Data same as previous report.[63]



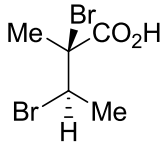
6. α'-Alkoxy alkyl alkene 28.2b Prepared as above for alkene **28.2a** following Rosini's procedure and Qi's procedure. Data same as the previous report.[63]



7. α'-Alkoxy alkyl alkene 28.2c Prepared as above for alkene **28.2a** by following a modified procedure. Data same as the previous report.[63]

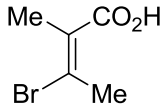


8. α'-Alkoxy alkyl alkene 28.2d Prepared as above for alkene **28.2a** by modified procedure. Data same as the previous report.[63]



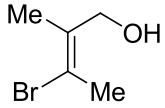
9. α,β-Dibromo-α-methyl butyric acid 110.2 A mixture of α,β-dimethyl acrylic acid (10 g, 100 mmol) in anhydrous CCl_4 (20 mL) and Br_2 (16 g, 100 mmol) was allowed to stand overnight. It was heated under reflux until the solution became light orange in color. Solvent was evaporated and dried under vacuum. The residue was crystallized from petroleum ether to give dibromide **110.2,** in 86-90% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (d, *J*=7.2, 3H), 2.01 (s, 3H), 4.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.92, 51.04, 61.32, 110.01, 141,14, 175.47.



10. β-Bromoangelic acid 110.3 To a solution of dibromide **110.2** (23.40 g, 90 mmol) in MeOH (12.6 mL), a 25% solution of KOH in methanol (126 g) was added slowly. Anhydrous K_2CO_3 (2.34 g) was also added. The temperature of the reaction mixture was increased to 55 °C and held for 2 hours. Excess KOH was removed by bubbling the CO_2 through the reaction mixture. The mixture was filtered while warm and washed with warm MeOH. The methanol solutions were combined and solvent removed in vacuo. The residue was dissolved in water and acidified with 6M HCl to congo red. It was then filtered, dried and recrystallized in petroleum ether to obtain angelic acid **110.3** (62%).

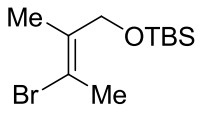
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.85, 28.58, 127.29, 140.44, 171.82.



11. Alcohol 110.4 To a cooled and stirred solution of acid **110.3** (7.16 g, 40.0 mmol) in THF (85 mL), $LiAlH_4$ (1.52 g, 40.0 mmol) was added slowly. The reaction mixture was stirred for 16 hours at room temperature. Additional $LiAlH_4$ (0.152 g, 4.0 mmol) was added to the reaction mixture and stirred for about 30 minutes, then cooled to 0 °C. Excess $LiAlH_4$ was quenched with saturated solution of Na_2SO_4 (2.2 mL) and ether (55 mL) was added. The mixture was poured into 2M H_2SO_4 (81.8 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were concentrated and the remaining oil was dissolved in CH_2Cl_2 and washed with 10% aqueous solution of K_2CO_3 (28 mL). The aqueous

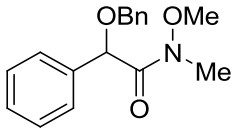
layer was re-extracted with CH_2Cl_2. The combined organic layers were concentrated and dried in vacuo. The residue was recrystallized from ether to give alcohol **110.4** (68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.40 (s, 3H), 4.20 (s, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 21.30, 25.21, 62.59, 121.80, 133.38.



12. TBS-ether 110.5 A solution of alcohol **110.4** (1.494 g, 9.05 mmol) in DMF (4.5 mL), TBSCl (1.63 g, 10.86 mmol) and imidazole (0.736 g, 10.86 mmol) was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with hexane to give ether **110.5** (78%).

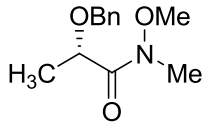
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 1.92 (s, 3H), 2.36 (s, 3H), 4.18 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.43, 23.20, 25.74, 29.82, 30.74, 67.58, 81.90, 124.33, 138.80.



13. Amide 108.1a NaH (4.0 g, 60% in mineral oil, 100 mmol) was washed with hexane to remove mineral oil. THF (110 mL) was added to the washed NaH under N_2 and stirred the reaction mixture. Mandelic acid (5.0 g, 32.85 mmol) was added slowly to the mixture followed by addition of benzyl bromide (11.24 g, 7.8 mL, 66 mmol). It was then heated under reflux at 70 ^{o}C for 48 hours. Distilled H_2O was added to the reaction mixture to dissolve the product. The aqueous layer was extracted 3 times with EtOAc. The aqueous layer was acidified with

concentrated HCl and again extracted with EtOAc. The product was concentrated in vacuo to give ether **111.2** (88%).

Ether **111.2** (7.033 g, 29.05 mmol) was dissolved in CH_2Cl_2 (20 mL) and stirred at 0 °C. NEt_3 (4.45 mL, 31.95 mmol) was added and followed after15 minutes by trimethylacetyl chloride (3.50 g, 3.58 mL, 29.05 mmol). After 1 hour *N*,*O*-dimethylhydroxylamine hydrochloride (3.11 g, 31.95 mmol) was added followed by dropwise addition of NEt_3 (6.90 mL, 49.40 mmol). The reaction mixture was maintained for about 48 hours and quenched with 1 eq of concentrated HCl. Distilled water was added to the reaction mixture and aqueous phase was extracted with EtOAc. The combined organic layers were concentrated and the product was purified by silica gel chromatography with 3:1 hexane/ EtOAc. 1 eq of NEt_3 was added to the column before the addition of the crude product for better purification. The pure product was dried in vacuo to give amide **108.1a** (82%). Data same as previous report.[63]

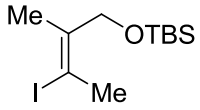


14. Amide 108.1b Lactic acid derived Weinreb amide **108.1b** was prepared by using a known procedure.[63] A solution of diazomethane in ether was added to a stirring solution of *S*- (+)- lactic acid (1 g, 11 mmol) in ether (10 mL) at 0 °C. After the disappearance of the starting material the solution was concentrated in vacuo to give *S*-lactic methyl ester (100 %).

A mixture of Ag_2O (3.1 g, 13.2 mmol), benzyl bromide (2.3 g, 13.2 mmol) and ester (1.1 g, 10.6 mmol) in CH_2Cl_2 (20 mL) was stirred for 48 h. The reaction mixture was filtered and the solution was concentrated in vacuo to give benzyl ether.

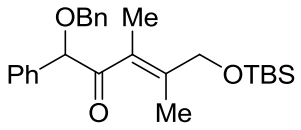
An aqueous solution of KOH (0.6 g, 10.6 mmol in 10 mL H_2O) was added dropwise to a solution of benzyl ether in ethanol (10 mL) at 0 °C. The reaction mixture was stirred for 30 minutes and extracted with ether (10 mL x 2). The aqueous phase was neutralized with 12 N HCl and was extracted with ether (10 mL x 2). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo to give *O*-benzyl- (*S*)- lactic acid **111.4** (80%).

Trimethyl acetyl chloride (1.1 g, 8.9 mmol) was added to a stirring solution of acid **111.4** (1.5 g, 8.5 mmol) and NEt_3 (0.9 g, 8.9 mmol) at 0 oC. After 30 minutes, *N*,*O*-dimethyl-hydroxylamine hydrochloride (0.87 g, 8.9 mmol) was added, followed by NEt_3 (1.8 g, 17.8 mmol). The reaction mixture was allowed to warm to rt and stirred for 16 h. After extractive work up, the crude product was purified by flash chromatography to give amide **108.1b** (85%). Data same as previous report.[63]



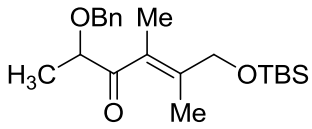
15. Vinyl iodide 114.1 A Schlenk tube was evacuated and backfilled with N_2. The tube was charged with CuI (191 mg, 1.0 mmol), NaI (4.5 g, 30 mmol), *N*,*N*-dimethylethylenediamine (213 µL, 2.0 mmol), bromide **110.5** (5.586 g, 20 mmol) and *n*-BuOH (10 mL) under N_2.[165] The Schlenk tube was sealed with the stopper and the reaction mixture was stirred at 120 °C for 24 hours. The resulting mixture was allowed to cool to room temperature and poured into ethyl acetate (100 mL). The mixture solution was washed with 30 % aq. NH_4OH (5 mL) in water (100 mL) followed by water (3X100 mL). The organic phase was dried with $MgSO_4$ and concentrated in vacuo to give liquid vinyl iodide **114.1** (yield 76 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.97 (s, 3H), 2.58 (s, 3H), 4.21 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$)) δ 5.32, 13.71, 18.33, 25.66, 27.03, 29.80, 34.97, 60.78, 62.71, 98.15, 139.79.



16. Tetrasubstituted enone 107.1a t-BuLi (13.28 mL, 1.5 M in pentane, 20 mmol) was added slowly to a solution of vinyl iodide **114.1** (3.263 g, 10 mmol) in ether at –78 °C. After 30 minutes, a solution of amide **108.1a** (2.851 g, 10 mmol) in ether was added dropwise. After 2 hours, the reaction mixture was quenched with acetic acid at 0 °C. After extractive work up with hexane, crude product was purified by flash chromatography to give enone **107.1a** (64 %).

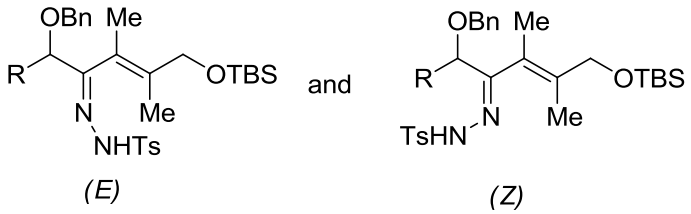
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.91 (s, 10 H), 1.60 (s, 6H), 2.18 (s, 2H), 4.54 (d, J=3.6 Hz, 1H), 4.70 (d, J=3.6 Hz, 1H), 5.17 (s, 1H), 7.35 (m, 10H) ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.08, 14.0, 16.90, 18.28, 25.84, 62.08, 70.76, 84.60, 127.90, 128.67, 130.48, 135.64, 137.44, 138.27, 205.32.



17. Tetrasubstituted enone 107.1b Enone **107.1b** was prepared as above-mentioned procedure by using amide **108.1b**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.40 (d, J=6.8 Hz, 3H), 1.78 (s, 3H), 1.83 (s, 3H), 4.20 (s, 2H), 4.28 (m, 1H), 4.49 (d, J=12.8 Hz), 4.67 (d, J=10.8 Hz), 7.32 (m, 5H);

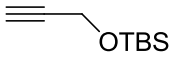
^{13}C NMR (100 MHz, $CDCl_3$) δ -5.34, 14.70, 17.10, 17.49, 18.30, 25.75, 26.41, 29.70, 62.97, 71.65, 78.58, 127.83, 128.43, 148.50.



(E) *(Z)*

18. Tetrasubstituted alkene hydrazones 33.1a and 33.1b

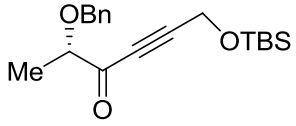
p-Toluene sulfonyl hydrazide (0.323 g, 2 mmol) was added to a solution of enone **107.1** (0.424 g, 1 mmol) in CH_2Cl_2. The solution was irradiated under microwave at 40 °C at 30 W for 18 hours. Purification was carried out via flash chromatography.



19. TBS-Ether 122.1

Prepared as above for TBS-ether **110.5**

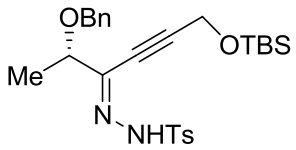
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.89 (s, 9H), 2.34 (s, 1H), 4.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.19, 18.32, 51.59, 72.70, 82.47; IR (film) cm^{-1} 3311, 2933, 1474



20. α,β-Unsaturated ynone 34.1 To a solution of TBS-ether **122.1** (0.9 g, 5.28 mmol) in ether (4 mL) was added n-BuLi (2.26 mL, 2.8 M in hexane, 6.33 mmol) at -78 ^{o}C. After 1 h, a solution of amide **108.1b** (0.59 g, 2.64 mmol) in ether (4 mL) was added slowly and stirred for about 2 h.

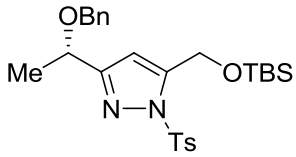
The reaction mixture was quenched with CH_3CO_2H and extracted with ether. Flash chromatography of the crude product provided 71 % ynone **34.1** as white oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.94 (s, 6H), 4.05 (q, J= Hz, 1H), 4.40 (d, J= Hz, 1H), 5.40 (s, 2H), 4.71 (d, J=Hz, 1H), 7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.98, 18.0, 51.69, 71.98, 81.55, 83.09, 94.57, 128.27, 128.50, 136.69, 188.76; IR (film) cm^{-1} 2937, 1607, 1454, 1254, 1125, 841.



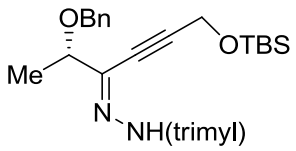
21. α,β-Unsaturated ynone hydrazone 34.2 A mixture of α,β-unsaturated ynone **34.2** (0.1 g, 0.30 mmol) and tosylhydrazide (0.067 g, 0.36 mmol) in CH_2Cl_2 (0.5 mL) was irradiated under microwave at 30 ^{o}C, 30 W for 8 h. The reaction gave ynone hydrazone **34.2** (71 %) and pyrazole **123.1** (15 %) after purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.89 (s, 9H), 1.36 (d, J= Hz, 3H), 2.39 (s, 3H), 4.16 (q, J= Hz, 1H), 4.17 (d, J= Hz, 1H), 4.18 (d, J= Hz, 1H), 4.55 (s, 2H), 7.13 (d, J= Hz, 2H), 7.28 (m, 5H), 7.84 (d, J= Hz, 2H), 8.42 (s, 1H)



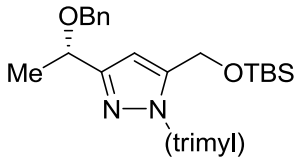
22. Pyrazole 123.1 ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.95 (s, 6H), 1.45 (d, J=6.7 Hz, 3H), 2.40 (s, 3H), 4.28 (s, 2H), 4.60 (q, J=6.6 Hz, 1H), 5.01 (s, 2H), 7.19 (d, J=8.0 Hz, 2H), 7.27 (m, 5H), 7.87 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.18, 21.69, 25.90, 29.78,

58.92, 70.05 71.22, 106.51, 127.84, 128.33, 128.53, 130.47; IR (film) cm^{-1} 2933, 1457, 1382, 1258, 1188, 1120, 840.

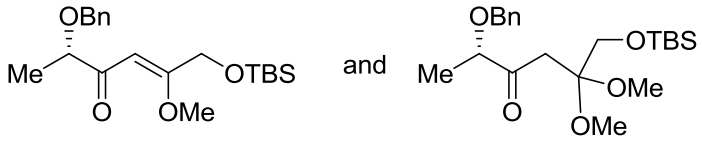


23. α,β-Unsaturated ynone hydrazone 124.2 α,β-unsaturated ynone **34.1** (0.108 g, 0.32 mmol) was reacted with mesylhydrazide (0.084 g, 0.39 mmol) in CH_2Cl_2 (0.5 mL) under microwave at 30 ^oC, 30 W for 4 h. Flash chromatography of the crude product gave a pure mesitylene hydrazone **124.2** (73 %)

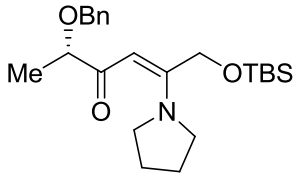
^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 6H), 0.95 (s, 9H), 1.32 (d, J=6.5 Hz, 3H), 2.26 (s, 3H), 2.69 (s, 6H), 4.02 (m, 2H), 4.17 (d, J=11.9 Hz, 1H), 4.58 (s, 2H), 6.79 (s, 3H), 7.12 (d, J= Hz, 2H), 7.29 (s, 2H), 8.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.37, 18.98, 21.49, 23.28, 26.15, 52.30, 70.92, 128.59, 128., 128. , 132.53, 140.77; IR (film) cm^{-1} 3209, 2937, 1601, 1345, 1167, 1095, 838.



24. Pyrazole 127.2 ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.99 (s, 9H), 1.44 (d, J=6.5 Hz, 3H), 2.31 (s, 3H), 2.54 (s, 6H), 4.23 (d, J=11.8 Hz, 1H), 4.36 (d, J=11.7 Hz, 1H), 4.49 (q, J=6.5 Hz, 1H), 5.00 (s, 2H), 6.43 (s, 1H), 6.96 (s, 2H), 7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.69, 18.50, 21.06, 22.48, 26.47, 58.34, 70.01, 70.29, 104.73, 127.56, 128.02, 128.28, 132.62, 138.02, 141.15, 145.14, 149.41, 157.94; IR (film) cm^{-1} 2937, 2860, 1606, 1471, 1370, 1116.

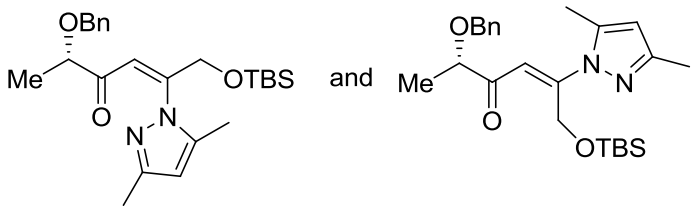


25. α,β-Unsaturated enone 34.3c A mixture of α,β-unsaturated ynone **34.2** (0.13 g, 0.41 mmol) and K_2CO_3 (0.005 g, 0.038 mmol) in MeOH (30 mL) was stirred at room temperature. After consumption of the starting material, the reaction mixture was concentrated partially in rotory evaporator and diluted with ether. Then the solution was treated with $MgSO_4$, filtered, concentrated and dried in vacuo to obtain a mixture of **34.3c** and **133.1**.



26. α,β-Unsaturated enone 34.3d A solution of α,β-unsaturated ynone **34.1** (0.1 g, 0.3 mmol) and pyrrolidine (0.036 mL, 0.45 mmol) in CH_2Cl_2 (0.3 mL) was stirred at room temperature for 24 h. A pure enone **34.3d** was obtained after chromatography (yield ca. 50 %).

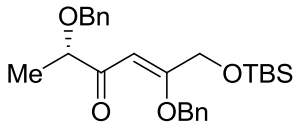
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.94 (s, 6H), 1.37 (d, J=6.8 Hz, 3H), 1.98 (s, 4H), 3. 24 (s, 2H), 3.74 (s, 2H), 3.83 (dd, J=6.7, 13.5 Hz, 1H), 4.42 (d, J=11.7 Hz, 1H), 4.66 (d, J=11.8 Hz, 1H), 5.12 (d, J=12.4 Hz, 1H) 5.31 (t, J=5.4 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.33, 20.07, 25.89, 48.50, 48.75, 58.34, 71.36, 89.14, 127.24, 127.65, 128.31; IR (film) cm^{-1} 2935, 1724, 1724, 1623, 1454, 1104



27. α,β-Unsaturated enone 34.3e Enone **34.3e** was prepared as above mentioned procedure by using 2,3-dimethyl pyrazole. The reaction gave 2 different isomes in 55 % overall yield (major isomer 35 % and minor isomer 20 %).

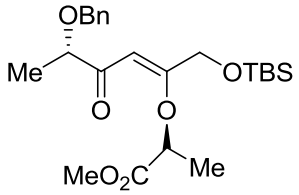
Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.81 (s, 9H), 1.25 (d, J=6.9 Hz, 3H), 2.17 (s, 3H), 2.26 (s, 3H), 3.67 (s, 2H), 3.90 (q, J=6.8 Hz, 1H), 4.36 (d, J=11.5 Hz, 1H), 4.47 (d, J=11.5 Hz, 1H), 5.77 (s, 1H), 6.26 (s, 1H), 7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.30, 6.75, 11.45, 13.42, 16.92, 25.38, 39.65, 71.86, 80.58, 104.25, 127.83, 128.35, 136.72; IR (film) cm^{-1} 2933, 1723, 1213, 840.

Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.92 (s, 6H), 1.34 (d, J=6.9 Hz, 3H), 1.61 (s, 4H), 3.86 (q, J=6.8 Hz, 1H), 4.41 (d, J=11.7 Hz, 1H), 4.48 (dd, J=1.6, 6.3 Hz, 2H), 4.60 (d, J=11.7 Hz, 1H), 5.99 (s, 1H), 6.99 (s, 1H), 7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.47, 11.28, 14.01, 17.77, 25.98, 64.60, 71.78, 80.67, 106.64, 115.19, 127.83, 128.42; IR (film) cm^{-1} 2931, 1724, 1217, 839.



28. α,β-Unsaturated enone 34.3a To a solution of ynone **34.2** (0.19 g, 0.57 mmol) and DABCO (0.006 g, 0.057 mmol) in CH_2Cl_2 (0.6 mL) was added BnOH (0.09 mL, 0.86 mmol) slowly. The reaction mixture was stirred for 24 h at room temperature. Flash chromatography of the crude product gave enone **34.3a** in 38.5 %.

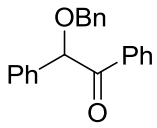
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.91 (s, 9H), 1.34 (d, J=6.9 Hz, 3H), 3.89 (q, J=6.9 Hz, 1H), 4.43 (d, J=11.8 Hz, 1H), 4.53 (d, J=11.8 Hz, 1H), 4.94 (m, 4H), 6.05 (s, 1H), 7.39 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.54, 13.85, 19.74, 22.51, 25.62, 31.51, 61.98, 70.0, 72.02, 82.06, 94.18, 128.82, 129.0, 135.39, 138.50, 174.52, 202.22; IR (film) cm^{-1} 2932, 1579, 1100, 840



29. α,β-Unsaturated enone 34.3b Above mentioned procedure for Enone **34.3a** was used with (*S*)-methyl lactate as a nucleophile. Enone **34.3b** was obtained after purification by using column chromatography (yield 53.5 %)

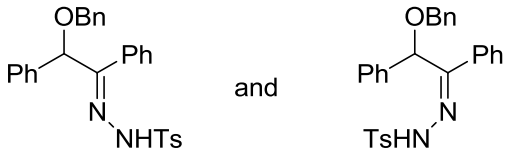
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.93 (s, 9H), 1.29 (d, J=8.0 Hz, 3H), 1.61 (d, J=8.0 Hz, 3H), 3.76 (s, 3H), 3.85 (dt, J=5.8, 6.8 Hz, 1H), 4.44 (d, J=11.7 Hz, 1H), 4.55 (d, J=11.8 Hz, 1H), 4.65 (q, J=6.8 Hz, 1H), 4.75 (dd, J=0.8, 15.7 Hz, 1H), 5.01 (dd, J=9.2, 9.8 Hz, 1H), 5.78 (s, 1H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.82, 17.21, 18.59, 26.51, 52.33, 61.28,

71.68, 72.64, 81.59, 94.33, 127.03, 128.45, 137.36, 200.36; IR (film) cm^{-1} 2938, 1754, 1583, 1100, 841.



30. O-Benzyl benzil ketone 138.1 To a stirred solution of amide (1.00 g, 3.53 mmol) in ether (9 mL) at -78 °C, phenyllithium (4.91 mL, 8.83 mmol) was added dropwise. Completion of the reaction was monitored by TLC. Then the reaction mixture was allowed to warm to room temperature and quenched with acetic acid. Extractive work up followed by flash chromatography provided ketone (yield 82 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 2H), 5.65 (s, 1H), 7.36 (m, 13 H), 7.98 (d, J=Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.0, 83.4, 127, 128, 130, 134; IR (film) cm^{-1} 3061, 2360, 1688, 1449, 1100, 695; calcd for $C_{21}H_{18}O_2$ C, 83.42, H, 6.00; found C, 83.22, H, 5.88.



(*E*) (*Z*)

31. O-Benzyl benzil *E*-hydrazone 41.1a and *Z*-hydrazone 41.1b

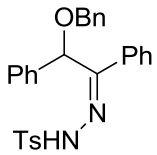
a) Tosyl hydrazide (0.605 g, 3.21 mmol) and titanium(IV) isopropoxide (1.971 g, 2.03 mL, 7.89 mmol) were added to the O-benzyl-benzil ketone **138.1** (0.60 g, 1.98 mmol). The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was quenched by adding water followed by extractive work up. *E*-hydrazone and *Z*-hydrazone were isolated by flash chromatography using 15:1 hexane:ethyl acetate (62 %).

E-hydrazone **41.1a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 4.51 (s, 2H), 5.36 (s, 1H), 6.74 (d, *J*= 7.66, 2H), 7.27 (m, 15 H), 7.80 (d, *J*=8.10, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.63, 70.78, 83.58, 126.50, 127.39, 128.08, 128.42, 129.10, 129.65, 130.06, 135.33, 137.66, 144.23, 156.96; IR (film) cm^{-1} 3224, 3060, 2918, 1602, 1357, 1166, 1085; calcd for $C_{28}H_{26}N_2O_3S$ C, 71.46, H, 5.57, N, 5.95; found C, 71.27, H, 5.59, N, 6.01; mp 168 °C.

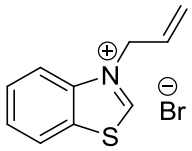
Z-hydrazone **41.1b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.44 (d, J= 9.24), 4.51 (d, J=9.24), 5.74 (s, 1H), 7.30 (m, 15H), 7.72 (d, J=8.96, 2H), 10.34 (s, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.60, 28.14, 71.82, 80.40, 126.43, 127.36, 127.85, 128.10, 128.47, 128.96, 129.58, 135.13, 136.24; IR (film) cm^{-1} 3200, 3027, 1347, 1164; calcd for $C_{28}H_{26}N_2O_3S$ C, 71.46, H, 5.57, N, 5.95; found C, 71.34, H, 5.63, N, 6.01; mp 168 °C.

b) A microwave reaction of O-benzyl benzyl ketone **138.1** (0.10 g, 0.33 mmol) with tosylhydrazide (0.074 g, 0.39 mmol) in CH_2Cl_2 (0.5 mL) for 8 h gave a mixture of *E*-hydrazone

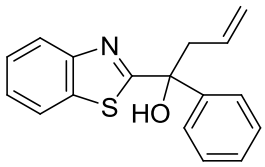
and *Z*-hydrazone. Flash chromatography over silica gel provided 99 % yield with 7.25:1 ratio of pure *E*-**41.1a** and *Z*-**41.1b** hydrazones.



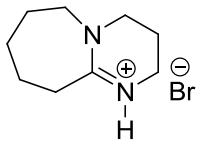
32. O-Benzyl benzil *Z*-hydrazone 41.1b The solution of tosyl hydrazide (0.074 g, 0.39 mmol) and O-benzyl-benzil ketone (0.108 g, 0.35 mmol) in MeOH was stirred at 50 °C for 12-28 h. The reaction mixture was filtered and pure *Z*-hydrazone was obtained (60 %) without purification.



33. N-Allyl benzothiazolium bromide salt 151.1 A mixture of benzothiazole (110 mL, 1.0 mol) and allyl bromide (130.8 mL, 1.5 mol) was refluxed at 75 °C for 5 h. Pure salt was obtained after trituration with acetone. Data same as previous report.[185]



34. Benzothiazole derived tertiary alcohol 151.4 A 0.2 M methanolic solution of benzothiazole salt (5.33 g, 20.80 mmol) was added dropwise to a mixture of benzaldehyde (4.20 mL, 41.60 mmol) and DBU (3.73 mL, 24.96 mmol). After stirring at room temperature for 24 h, 0.8 eq DBU (2.48 mL, 16.64 mmol) was added to the reaction mixture and heated upto 65 ^{o}C for h. Purification by flash chromatography provided alcohol. Data same as the previous report.[185]



35. DBUH^{+}Br^{-} precipitate 151.5

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (m, 6H), 2.09 (m, 2H), 3.09 (s, 2H), 3.54 (m, 6H), 10.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.82, 24.00, 27.47, 29.56, 32.69, 37.91, 49.38, 54.60, 166.24

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