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Novel [3,3]- and [1,3]- Rearrangements of Azole-derived N,X-Ketene Acetals

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by

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ABSTRACT

The formation of carbon-carbon bonds in organic chemistry is fundamentally important. One of the major reactions that chemists have widely investigated is the Claisen rearrangement. Based on the fundamental features of this rearrangement, chemists exploited the capability of the transformation and invented their own variations of Claisen-type rearrangements. Our goal in this project is to develop a novel variation of the Claisen rearrangement using azole compounds, which are common heteroaromatic ring systems that are present extensively in the biomedically important natural products. We propose here novel methodologies of preparing 2-substitution azole derivatives using aza-based Claisen rearrangement, N,X-ketene acetals that requires only weak base, possesses broad functional group compatibility, and require no cryogens.

Our strategy employs a Claisen [3,3]-rearrangement of the so-called Breslow intermediate to prepare 2-butenyl benzothiazoles. The precursor N-allyl-N,X-ketene acetals were prepared in situ from the reaction of N-allyl azolium salts with aromatic aldehydes. The details of the approach and the rearrangement results are presented in Chapter 1.

Another novel methodology we discovered to prepare 2-substituted azole derivatives is using radical fragmentation of the Breslow intermediate, which is unprecedented. Preparation of [1,3]-rearrangement products via radical reaction pathways offers possibilities to prepare complex chiral azoles that are not readily accessible via polar methods. It also provides significant information about potential decomposition pathways for Breslow intermediates in N-heterocyclic carbene catalyzed reactions. These investigations are the subject of Chapter 2.

Thiamine (vitamin B1) is an essential human nutrient. In 1970, Oka found that the reaction of thiamine with benzaldehyde afforded the fragmentation products thiazolyl phenyl ketone and 2,5-dimethyl pyrimidin-4-amine along with a small amount of [1,3]-rearrangement product. Kluger proposed that the decomposition of thiamine occurred via the Breslow intermediate in a polar process. We hypothesize that the fragmentation reaction is a radical process. A discussion on this matter is presented in chapter 3.

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All praise is due to Allah, Lord of the Worlds. Prayers and blessing of Allah be upon His last prophets and messengers Mohammed (peace be upon him and his pure progeny). By the grace of Allah and the grace of prayers upon Mohammed and his family, I was able to complete this work.

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TABLE OF CONTENTS

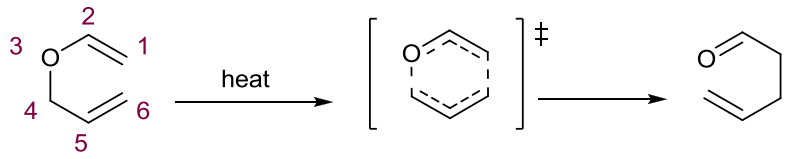
CHAPTER 1

A NOVEL PROCEDURE FOR AZA-BASED CLAISEN REARRANGEMENT

I. INTRODUCTION

The formation of carbon-carbon bonds in organic chemistry is fundamentally important. One of the major reactions that chemists have widely investigated is the Claisen rearrangement, which was discovered in 1912 by Rainer Ludwig Claisen.[1] The Claisen rearrangement is defined as an intramolecular pericyclic [3,3]-sigmatropic rearrangement of allyl vinyl ether **1** to produce 4-pentenal **3** (Scheme 1). Based on this fundamental feature of the rearrangement, chemists exploited the capability of the transformation and invented their own variations of Claisen-type rearrangements.[2-5]

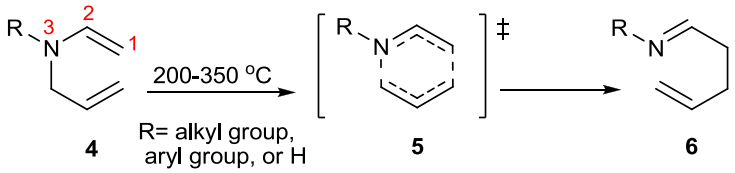
Scheme 1.



1 **2** **3**

One of these versions is the aza-Claisen (amino-Claisen) rearrangement, in which the oxygen in the parent Claisen system is replaced with a nitrogen (Scheme 2).[6] Rearrangement of N-allyl vinyl amine **4** produces the corresponding γ,δ-unsaturated imine product **6**. The thermal aza-Claisen rearrangement usually needs one or more of the following requirements to achieve the rearranged products: (i) higher reaction temperatures (200-350 ^{o}C) compared to the corresponding allylic esters in the Ireland-Claisen system, (ii) in some cases mild to strong Lewis acids are needed as a catalyst, (iii) the nitrogen in the core system has to be quaternary in the precursors (charge acceleration)[7] to allow a significant decrease of the reaction temperature, or (iv) the nitrogen in the core system has to be within an aromatic N-heterocycle system.[8, 9]

Scheme 2.



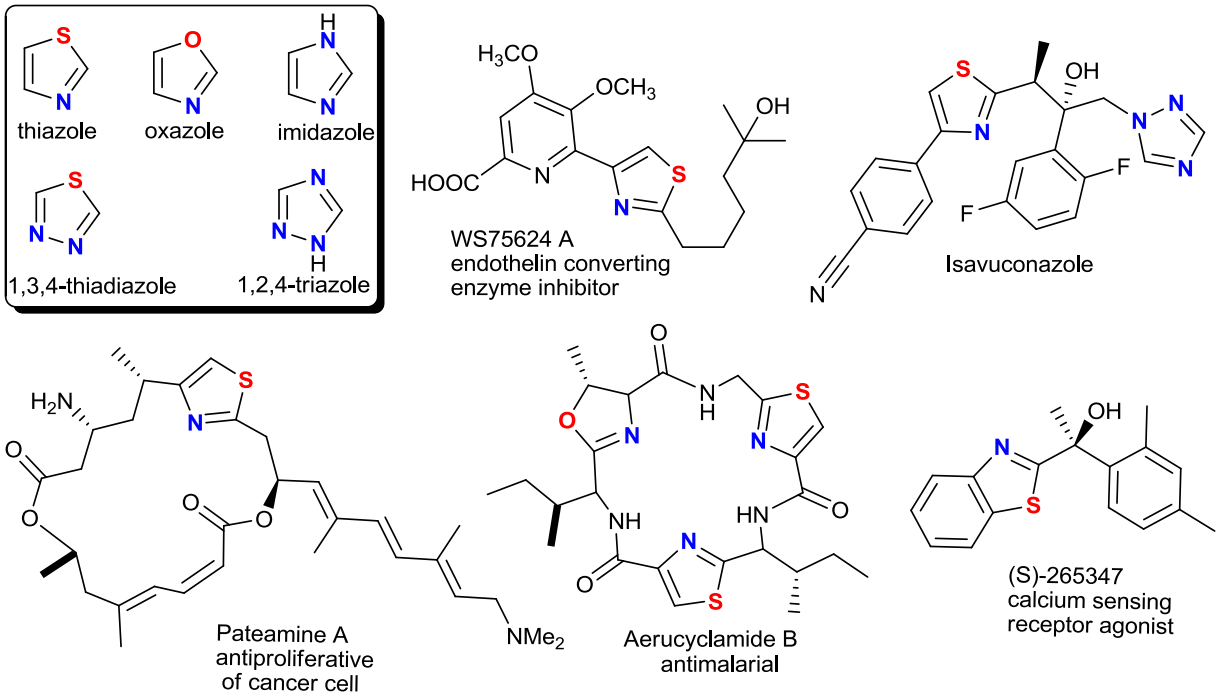
Use of Ireland, aza, and related aliphatic Claisen rearrangements in the synthesis of complex biomedically important molecules are widely employed.[5] Our goal in this project is to develop a novel variation on the Claisen rearrangement that requires only weak base, possesses broad functional group compatibility, and required no cryogens. Successful realization of this goal will provide a practical and scalable method for the synthesis and modification of biomedically important complex molecules. Moreover, avoiding the use of precious metal catalysts or stoichiometric amounts of Lewis acids would allow such rearrangement to be widely employed economically on production scale.

II. BACKGROUND

II.a. Azoles in Natural Products and Pharmaceuticals

Azoles are common heteroaromatic ring systems that are present extensively in the biomedically important natural products.[10-15] Azoles are 5-membered heteroaromatic ring compounds that contain nitrogen and one or more heteroatoms such as S (thiazole), O (oxazole), N (imidazole), S/N (thiadiazole), or N/N (triazole) (Figure 1). A variety of biologically active natural products[16,17] and pharmaceuticals[18, 19] contain azoles. Therefore, suitable access to various substituted azole derivatives is important in the synthesis of these compounds.

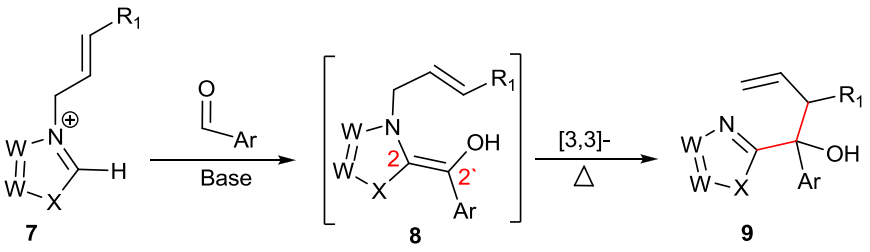
Figure 1.



Our objective here is preparing 2-substituted azole derivatives by employing an aza-based Claisen rearrangement under mild conditions that would be suitable for industrial use. We hypothesized that to prepare 2-substituted azole derivatives such as **9** (Scheme 3) using aza-based Claisen rearrangement, N-allyl-N,X-ketene acetals such as **8** (X= S, O, or N) could be used as precursors. This intermediate **8**,

the so-called Breslow intermediate, is a key intermediate in N-heterocyclic carbene (NHC) catalyzed reactions of aldehydes as well as thiamin catalyzed enzymatic reactions. The Breslow intermediate could be prepared in situ from N-alkyl azolium salts **7**, where N-substituent is allyl group or allyl derivatives.

Scheme 3.



7 **8** **9**

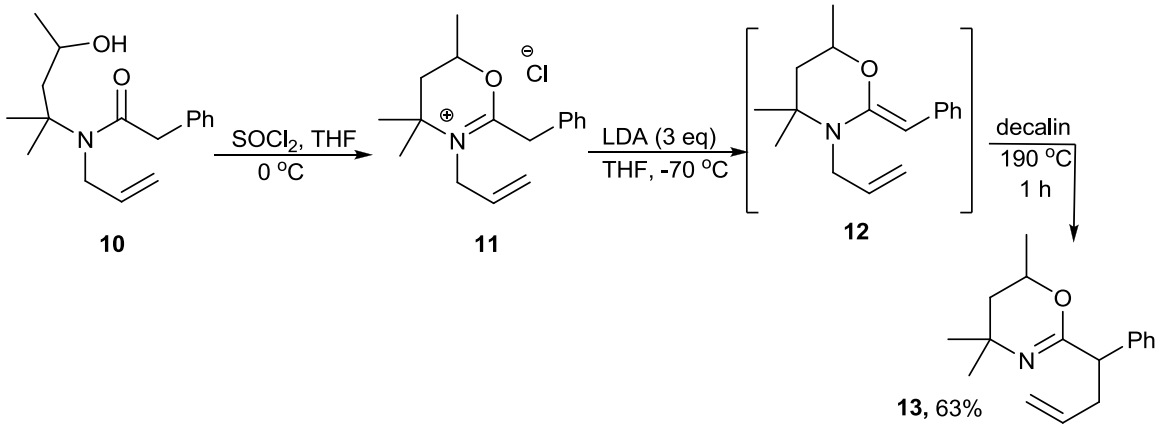
W= CR; X= S, O, NR
R_1=H, Ph

II.b. Reported Examples of Using Ketene N, X- Acetal precursors

II.b.1. Ireland: Oxazine Claisen rearrangement

In 1974, Ireland et al. reported examples of aza-Claisen rearrangement of ketene N,O acetals such as **12** that were obtained from γ-hydroxy amides such as **10** to produce dihydroxazines **13** (Scheme 4).[20] Treatment of γ-hydroxy amide **10** with thionyl chloride in THF at 0 ^{o}C afforded oxazinium salt **11**. Deprotonation of imine salt **11** using excess LDA gave enamine **12**. Then, the reaction mixture was heated for 1 h at 190 ˚C in decalin after the THF and LDA were removed by distillation. Acetal **12** rearranged in situ into a mixture of 2-butenyl oxazine **13** diastereomers in 63% yield.

Scheme 4.

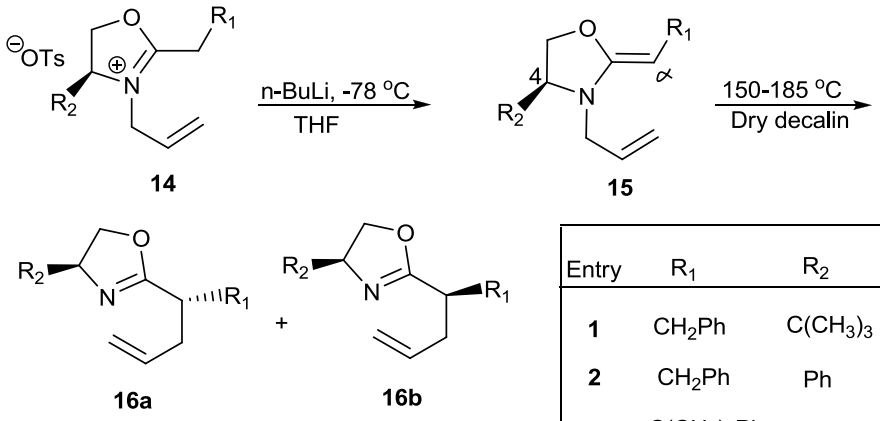


10 **11** **12** **13,** 63%

II.b.2. Kurth: Asymmetric induction and ketene N, O-acetal Claisen rearrangements

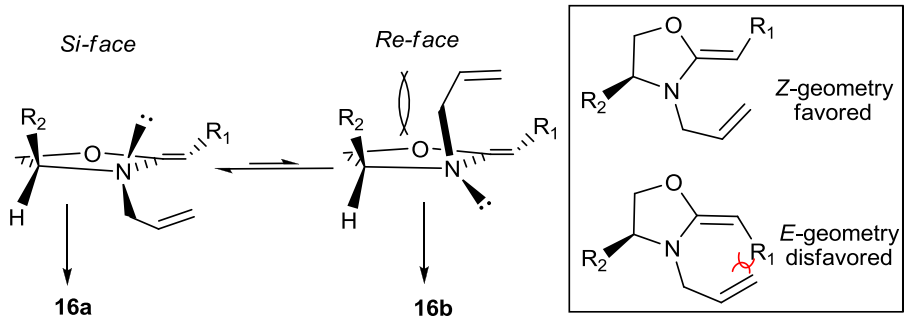
In the mid 80's, Kurth et al. extensively studied the asymmetric induction in Claisen rearrangements of N-allyl *N,O*-ketene acetals of amino acid derived oxazolines (Scheme 5).[21,22] He studied the effect of the substituents on Cα of the acetal olefin and the substituents at C4 of the oxazoline on the stereoselectivity of the rearrangement.[18] He described three parameters that have the significant effects collectively on the diasteroselectivity of this reaction. (i) The size of the substituent at C4 (R_2) had a significant effect on the diastereofacial selectivity of the reaction (entry 1 *vs.* 2). Increasing the size of R_2 led the *Si*-face transition state to be favored, so that the interaction between N-allyl and R_2 would be minimized (Figure 2). (ii) The (*Z*)-*N,O*-acetal olefin geometry of **15** was preferred over the *E*-acetal olefin geometry regardless of the size of the R_1 group because of unfavorable allylic strain between the N-allyl and the R_1 group at Cα in the *E*-isomer (Figure 2). This parameter had a small or no effect on the diastereoselectivity of the products, which suggests that the formation of the minor isomer is due to the incomplete *Re/Si*-face selectivity. (iii) The Cα isomerization of the product oxazoline **16** occurs during the neutralization step in presence of excess n-butyllithium, which is necessary to obtain a good yield or a good diastereoselectivity. These three parameters collectively affect the diastereomer ratio of the products.

Scheme 5.



Entry	R_1	R_2	dr. ratio **16a:16b**	yield %
1	CH_2Ph	$C(CH_3)_3$	98:2	58
2	CH_2Ph	Ph	78:22	34
3	$C(CH_3)_2Ph$	$C(CH_3)_3$	98:2	81

Figure 2.



Kurth extended his studying of asymmetric induction and included C_β induction by examining the effect of *E*/*Z* configuration of N-allyl moiety. He found that the allyl *E*/*Z* geometry played a major role in the observed diasteroselectivity. According to his study, the oxazoline salt with the less stable *Z*-alkene geometry in the N-allyl moiety gave a greater diastereoselectivity compared to the more stable *E*-alkene geometry (Scheme 6).

He proposed that the chair/boat transition state selectivity is a critical parameter in C_β induction. The *E*/*Z* isomers undergo two competing transition states: the boat- and the chair in *E*- and *Z*- isomers (Figure 3). In either alkene geometry, the chair-like transition state is more favorable than the boat-like transition state because the substituents of the nascent C-C bond in chair-like transition state are nearly staggered while in boat-like transition state are approximately eclipsed. However, the energy differences

between the chair/ boat transition states on *Z*-alkene geometry are higher than the energy differences in *E*-alkene geometry. Therefore, greater diastereoselectivity were observed for the thermodynamically less stable *Z*-alkene conformer.

Scheme 6.

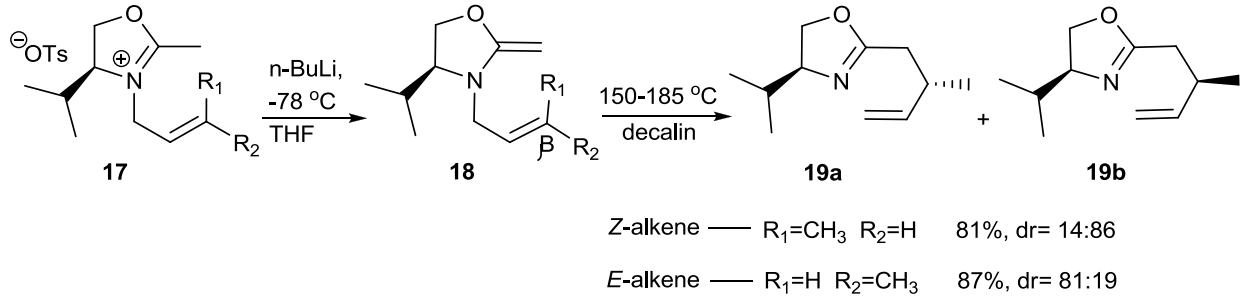
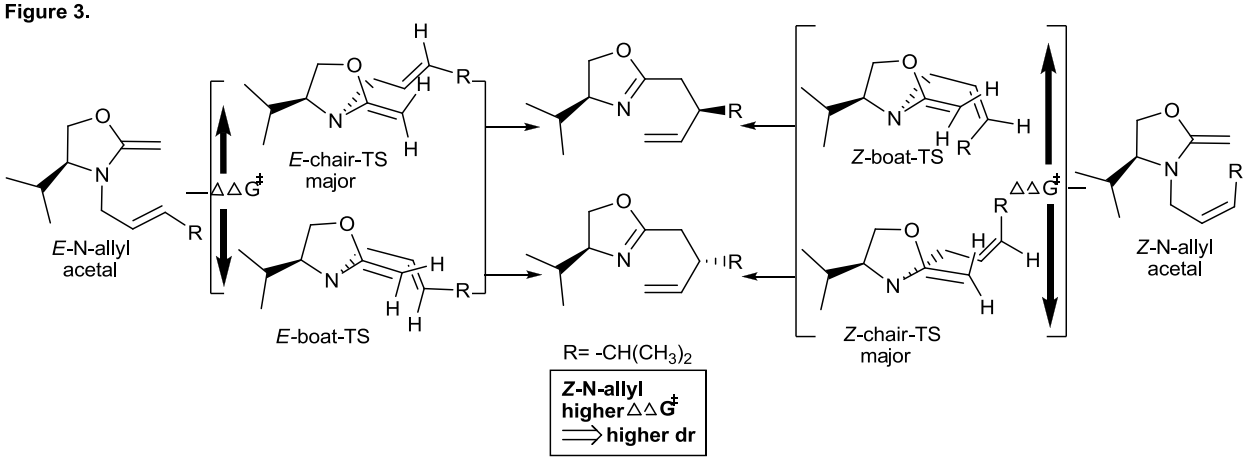


Figure 3.

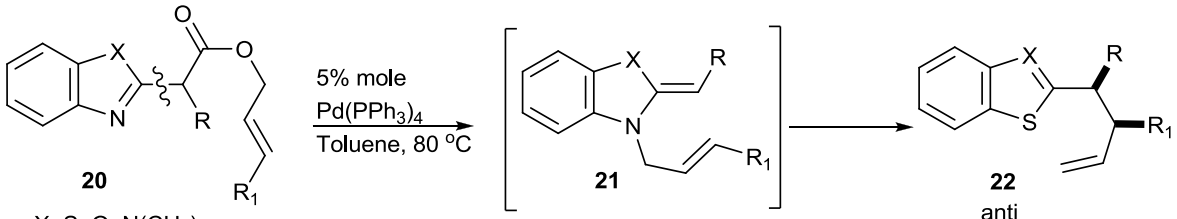


II.b.3. Tunge: N,O-, N,N-, and N,S-ketene acetal Claisen rearrangements

In 2007, Tunge reported preparing 2-butenyl azole derivatives such as **22** with high regio- and modest to high diastereoselectivity using a Pd catalyzed decarboxylative coupling process at temperature of 80– 100 °C that probably proceeded via a Claisen rearrangement (Scheme 7).[23] Tunge tested a range of heteroaromatic substrates (Table 1). He revealed that all substrates with R_1= Ph exhibited high regio- and diastereoselectivity except N-methyl benzimidazole (entry 1-3 *vs.* 4). In comparison with these results, he observed lower diastereomers ratio of the products when R_1= Me (entry 1). He found that the

relative rates of the reactions appeared to depend on the choice of heteroaromatic ring; benzothiazole was the fastest and gave the highest yield (entry 2).

Scheme 7.



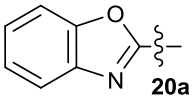
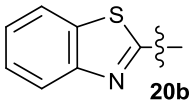
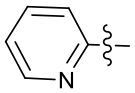
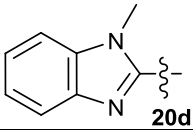
20

X=S, O, N(CH_3)
R= Bn, Me
R_1= Ph, Me

21

22
anti

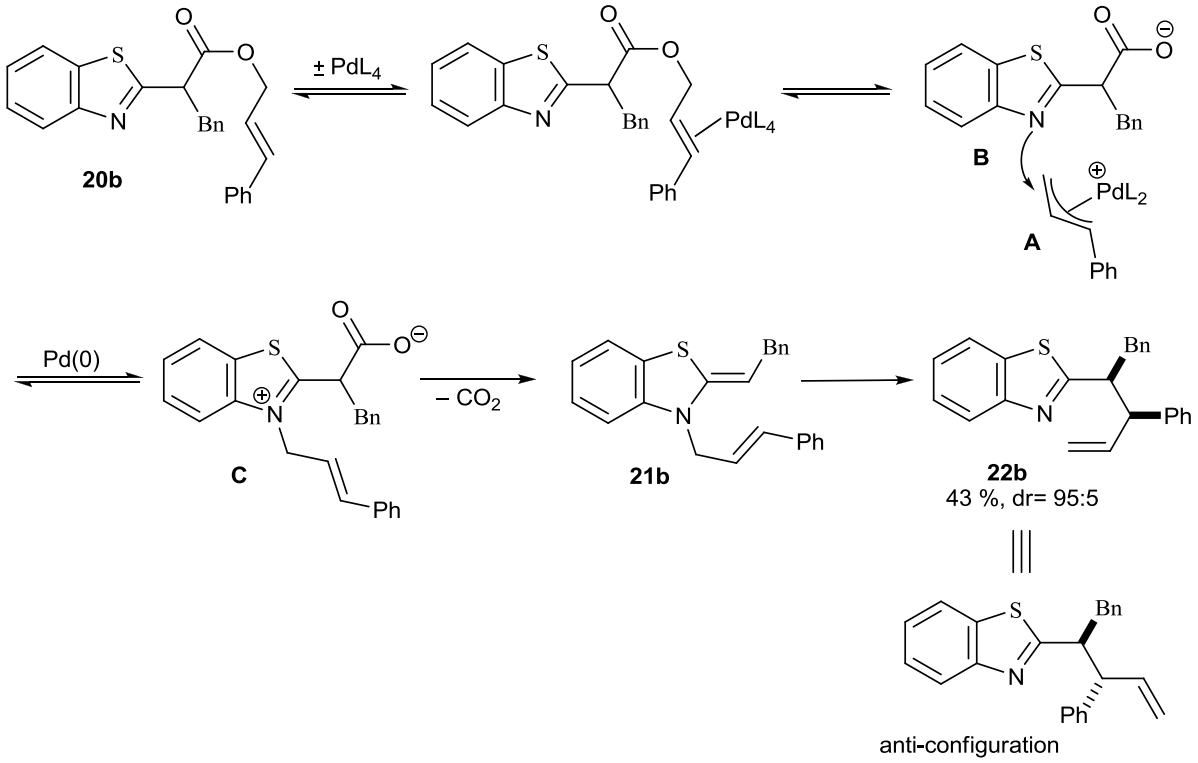
Table 1:

Entry	substrate	R	R_1	time (h)	**22** yield (%) (dr)
1	 **20a**	Bn	Ph	4	66 (>95:5)
		Me	Ph	4	71 (93:7)
		Me	Me	2	61 (73:28)*
2	 **20b**	Bn	Ph	2	75 (>95:5)
3	 **20c**	Bn	Ph	20	53 (>95:5)
4	 **20d**	Bn	Ph	16	52 (74:26)
		Me	Ph	16	43 (69:31)

* Temperature 100 °C

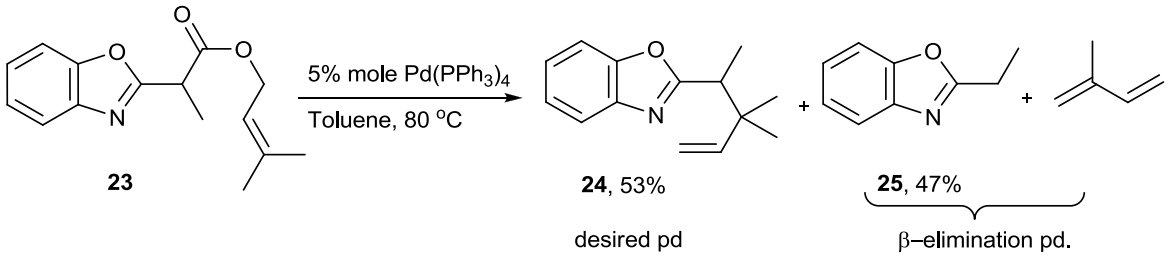
The first step of the proposed mechanism involves nucleophilic attack of Pd(0) on the allyl moiety of ester **20b** to form two fragments: Pd-*π*-allyl complex **A** and α-aryl carboxylate **B** (Scheme 8). Then, these two fragments recombine with the nitrogen in complex **B** attacking the Pd-*π*-allyl **A** at the less substituted allylic carbon to produce zwitterion **C.** Formation of the intermediate **C** will facilitate decarboxylative dearomatization to give N-cinnamyl pyridine ketene acetal **21b**. A subsequent [3,3]-sigmatropic rearrangement of **21b** restores the lost aromaticity and affords the aza-Claisen product **22b**.

Scheme 8.



The decarboxylative coupling strategy revealed by Tunge suffers from some synthetic limitations. Tunge's strategy was reported only with hydrocarbon substituents, so information about functional group compatibility is lacking. Moreover, substrates containing Pd-reactive functional groups such as aryl halides, propargylic esters, or sulfonamides, etc., would presumably be incompatible with the reaction conditions. Furthermore, in several cases where the yields are low, the desired products were formed along with side products that resulting from β-elimination of the π-allylic intermediates (Scheme 9). Therefore, Tunge implied that cinnamyl esters are the most effective substrates for the decarboxylative coupling because the lack of β-hydrogens. An asymmetric variant might also be problematic using Pd (0) as a catalyst since it catalyzed the formation of the ketene acetal rather than the rearrangement itself.

Scheme 9.



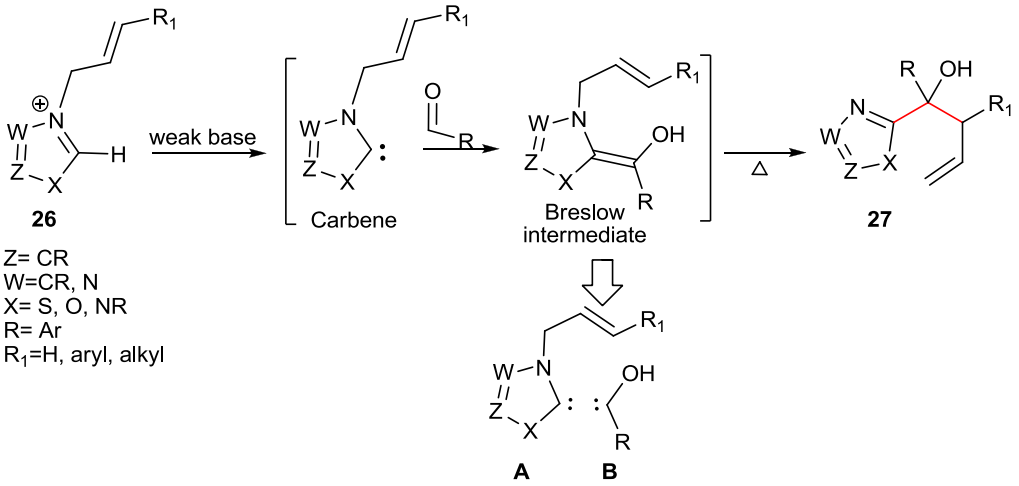
All above examples of preparing 2-substituted azole derivatives subordinate to one or more of the limitations that would avoid its economic use on production scale. Ireland[20] and Kurth[21] examples used stoichiometric amounts of strong bases, required cryogenic conditions, and Tunge strategy employs Pd as a catalyst that has several structural limitations.

III. RESULTS AND DISCUSSION

In our research, we have developed novel methods of azole alkylation that are highly functional group tolerant and do not require strong bases, heavy metals, or protecting groups. The method employs novel nitrogen-based rearrangements to form two new carbon-carbon single bonds. The essence of this method is to facilitate the access to substituted azole derivatives that are not easily available by existing methods. Moreover, this method will be amenable to the industrial scale synthesis of azole containing pharmaceuticals.

We started with the hypothesis that we could prepare 2-butenyl azole derivatives **27** via Clasien rearrangement of a so-called Breslow intermediate (Scheme 10). This unstable intermediate N, X-ketene acetal could be prepared by treatment of N-allyl azolium salt **26** with a weak base to provide an N-hetero-cyclic carbene which could then condense with an aldehyde to provide the Breslow intermediate.[24] The Breslow intermediate could be viewed as a new disconnection that formally derived from N-heterocyclic carbene **A** and α-hydroxy carbene **B**.

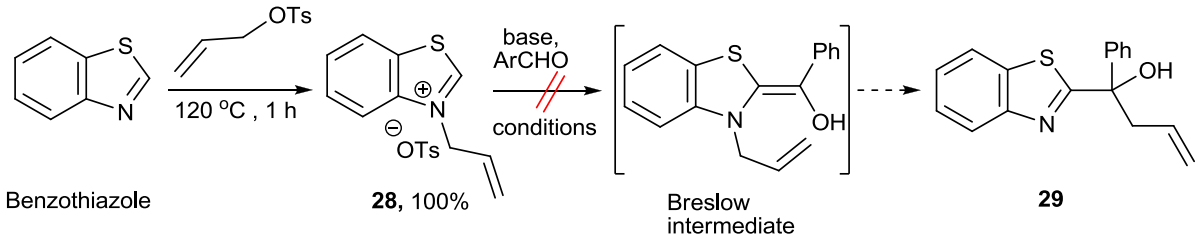
Scheme 10.



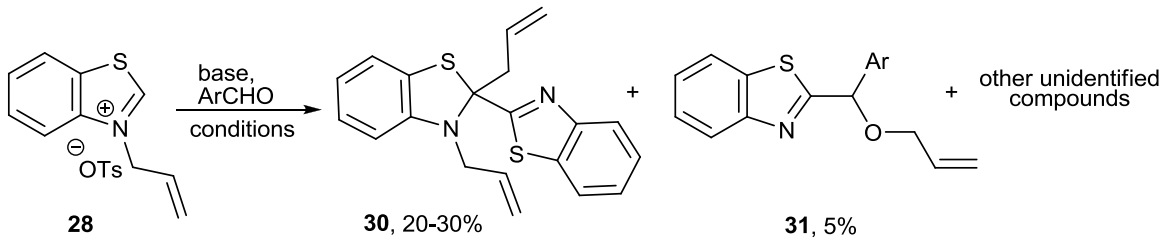
The allylation of benzothiazole to form N-allyl benzothiazolium salt **28** was made in quantitative yield (Scheme 11).[25] However, the reaction of the salt **28** with benzaldehyde initially did not succeed.[26]

Different reaction conditions were inspected in order to form Breslow intermediate; several bases were examined (TMG, KHMDS, DIPEA, and NaH) in several aprotic solvents (THF, DCM, Toluene, DMF, MeCN/THF, and DMF/THF); nevertheless, no reaction or complex mixtures were obtained in all of above conditions. The observed complex mixture was analyzed (Scheme 12) and found to contain homodimer **30** (20-30%), allyl ether **31** (5%), and along with unidentified compounds.

Scheme 11.

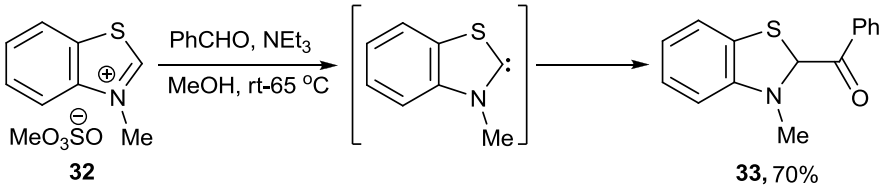


Scheme 12.



In 1964, Metzger et al reported a condensation reaction of N-methyl benzothiazolium salt **32** with benzaldehyde in the presence of NEt_3 in methanol. Under such conditions ketone **33** was produced in 75% yield (Scheme 13).[27]

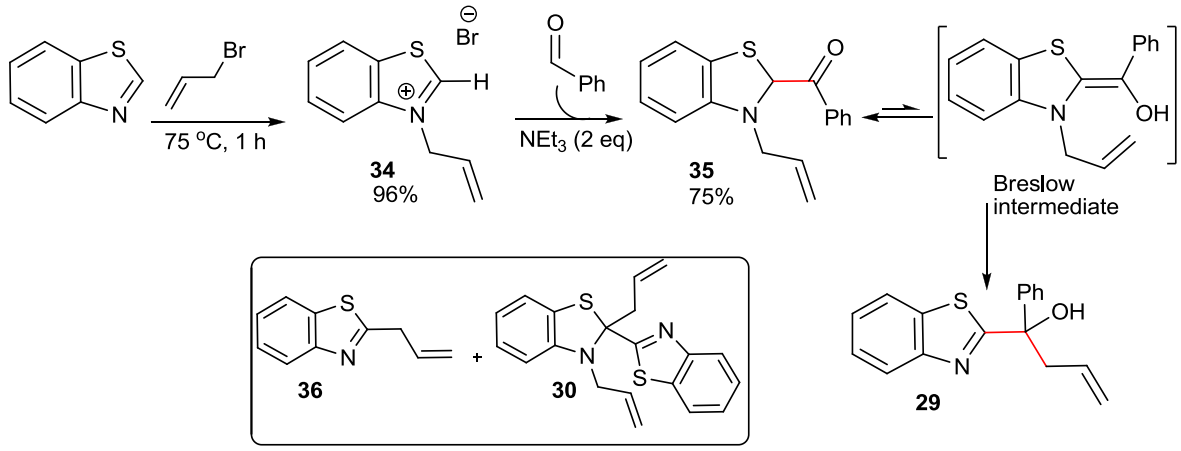
Scheme 13.



Based on Metzger's report, in an analogous fashion, we hypothesized that N-allyl benzothiazolium salt **34** would provide ketone **35** upon treatment with triethylamine in MeOH (Scheme 14). We also hypothesized that ketone **35** would be in equilibrium with the ketene acetal (Breslow intermediate), to some degree. Moreover, the **intra**molecular rearrangement should be faster than **inter**molecular NHC-catalyzed benzoin condensation.[28] Hence, the Breslow intermediate would rearrange to afford azole **29**.

We have prepared N-allyl benzothiazolium salt **34** by the addition of commercially available benzothiazole to neat ally bromide. Heating this mixture at 75 ˚C for 1 hour solidifies the mixture. Trituration with diethyl ether gave salt **34** in 96% yield as brown grains. Using Metzger's conditions (NEt_3, benzaldehyde, and methanol) at rt provided ketone **35** in 75% yield along with small amount of byproducts, C2-allyl benzothiazole **36** and homodimer **30** that was observed in previous conditions (see Scheme 12).

Scheme 14.



Attempts at optimization of the reaction (Scheme 15) yielded the following conclusions: (i) heating the reaction mixture in the presence of excess base increased the amount of byproducts **36**, **30**, and decreased the yield of ketone **35**. (ii) Using benzaldehyde as the limiting reagent had little to no effect on the yield of ketone at rt; however, at 60 °C the dimer **30** became the major product. (iii) Using ethanol as solvent and heating the reaction at 75 °C hydrolyzed the benzothiazole ring and gave ring opening product (vide infra) as a major component; however, at rt ketone **35** was produced in 52% yield. (iv) MeOH is the best choice of alcohol solvent and 23 °C is the optimal temperature. We also found that the

order of addition of the reagents played an important role in the byproduct formation. Adding a mixture of base and aldehyde to the dissolved salt gave the dimer **30** in large quantities. Therefore, the dissolved salt must be added slowly to a mixture of base and aldehyde to minimize the dimer formation. Carbenes readily react with the salt species to form homodimer **30**. This dimerization mechanism has been investigated.[29-32] Thus, keeping the carbene concentration very low in the reaction mixture helps to minimize the byproduct formation, especially the dimer, and to increase the yield of ketone up to 75% (entry 7 vs 2). Hence, to obtain the optimal yield, the dissolved salt **34** in MeOH (0.2 M) is added dropwise to a mixture of base and aldehyde at ambient temperature.

Scheme 15.

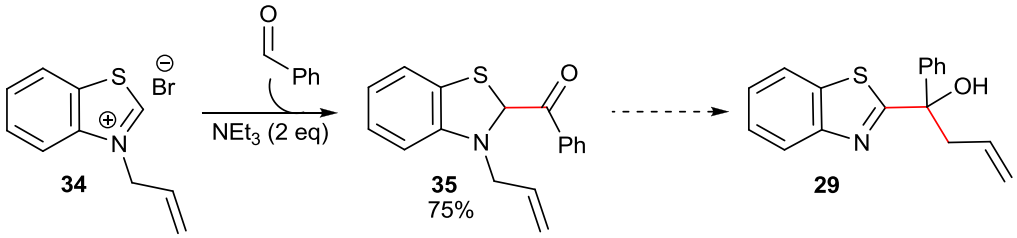
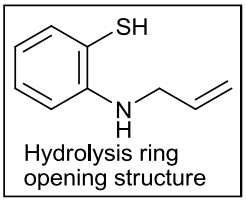


Table 2:

Entry	Solvent	PhCHO eq	Conditions	Yield% **35**[a]
1	MeOH	2	12 h, 60 °C	45%
2	"	2	12 h, rt	59%
3	"	0.5	24 h, 60 °C	28%
4	"	0.5	24 h, rt	55%
5	allylOH	2	12 h, rt	50%
5	EtOH	2	24 h, 75 °C	hydrolysis pd.
6	EtOH	2	12 h, rt	52%
7	MeOH	2	12 h, rt	75%*

[a] mixture of base and aldehyde was added to disolved salt in MeOH

* dissolved salt in MeOH was added dropwise to a mixture of base and aldehyde.

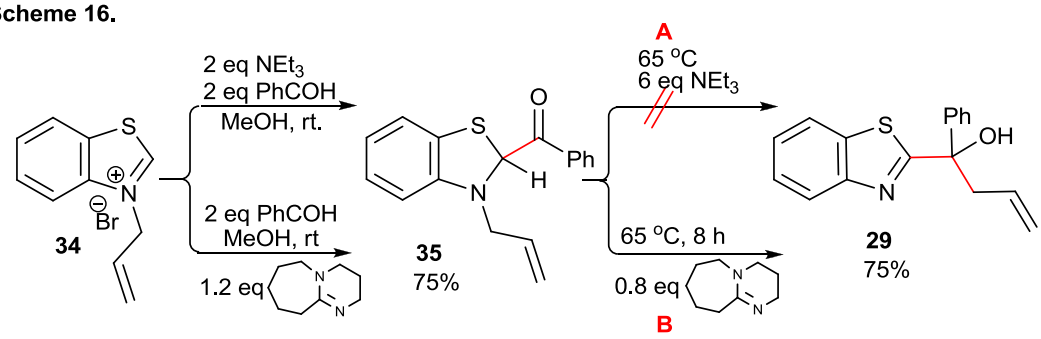


After ketone formation, the rearranged product **29** did not form at an appreciable rate even after using 6 eq of NEt_3 and heating the mixture to 65 °C (Scheme 16, A). Therefore, we decided to survey different bases for the rearrangement step. We used 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a

starting point. Fortunately, we obtained the respective rearranged product **29** in a good yield (75%) within a few hours (Scheme 16, B). Since DBU was good enough to afford the rearranged product, we decided to use it in the first step to form the ketone instead of using NEt_3. It is known that DBU base is somewhat stronger than NEt_3 (in DMSO $^{+}NEt_3H$, $pK_a = 9$ *vs.* $^{+}HDBU$, $pK_a = 12$).[33] DBU base is also non-nucleophilic and bulkier than NEt_3. These facts about DBU might be a reason among others that makes DBU to be a better base than NEt_3 for the rearrangement step. Moreover, we observed that an additional charge of DBU in the second step was needed to obtain the rearranged product **29** within a few hours.

We also carried out the reaction in DMF and we detected the ketone and the rearranged product by TLC; however, the rate of formation of rearranged product was very low compared to the methanol case.

Scheme 16.

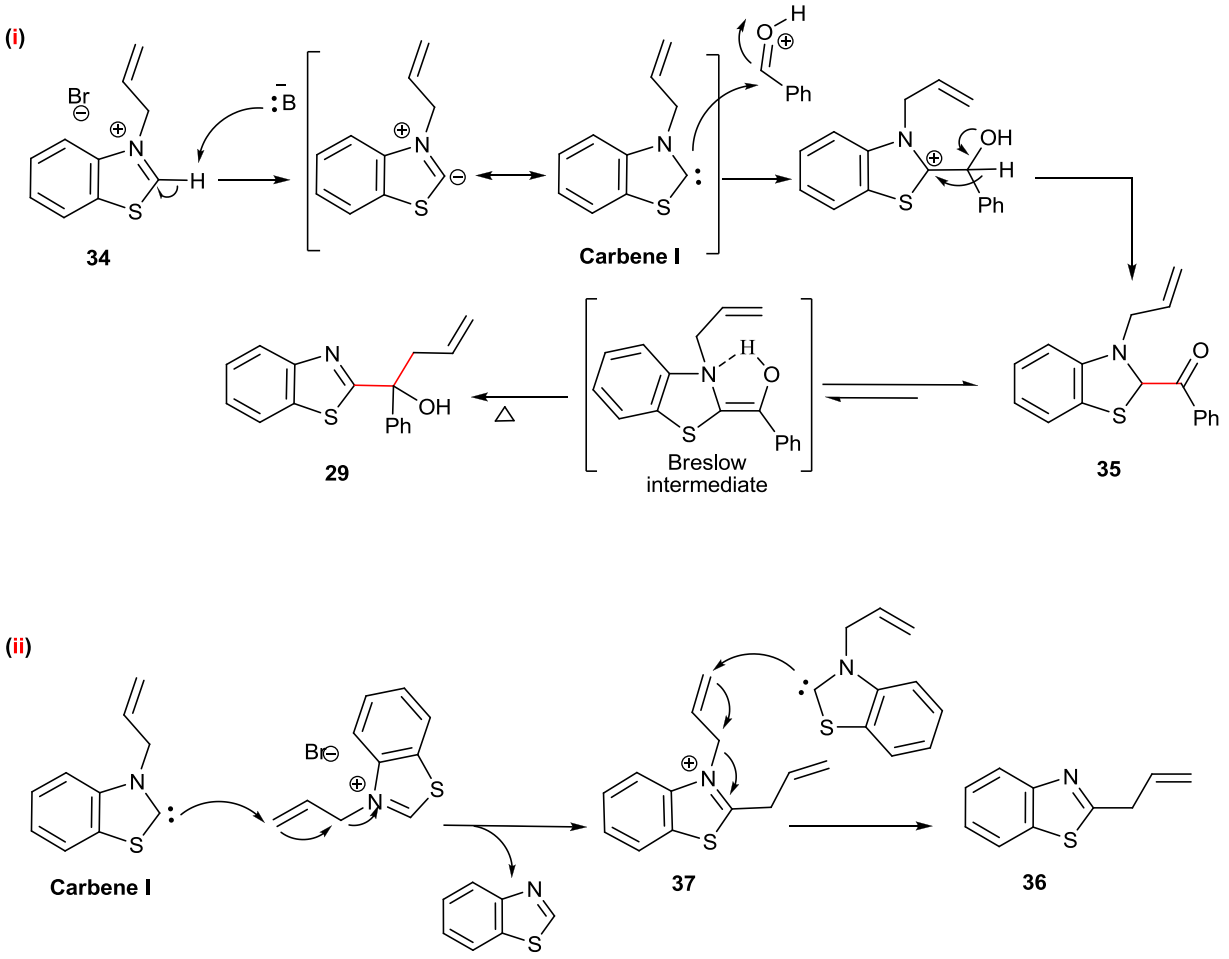


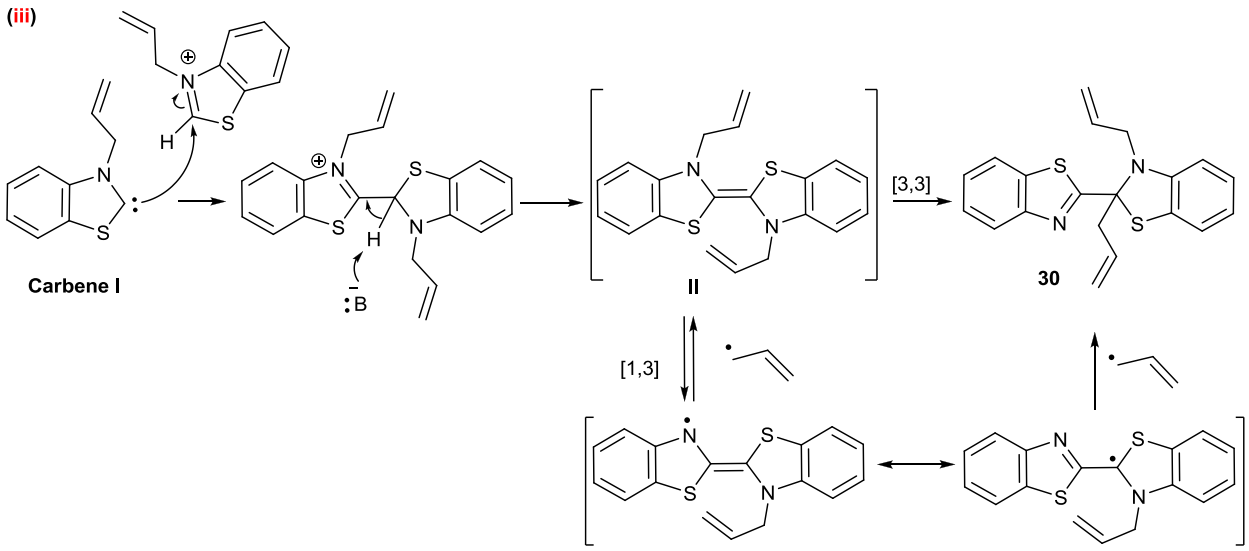
III.a. Plausible Mechanisms for the [3,3]-Product and the Byproducts

A reasonable mechanisms for the formation of [3,3]-rearranged product and the byproducts observed in this reaction are presented. Once the dissolved salt **34** was added to the base, carbene **I** will be produced (Scheme 17). This carbene can undergo at least three competing reactions: (**a**) nucleophilic attack on to the aldehyde to form ketone **35**. This ketone is in tautomerization with enol that rearranged under subsequent heating to form product **29** (Scheme 17, part i). (**b**) Nucleophilic attack on the allyl group of molecule of salt, generating diallyl benzothiazolium salt **37**, which can undergo deallylation to produce 2-allyl benzothiazole **36** (part ii). This byproduct could not be avoided completely by any means.

(**c**) The third reaction is nucleophilic attack by the carbene **I** on to molecule of salt to form unstable dimer **II** which can undergo an in situ [3,3]-rearrangement or [1,3]-rearrangement to form stable dimer **30** (part iii).[34]

Scheme 17.





III.b Scope of The [3,3]-Rearrangement Reaction

We continued our investigation of the steric and electronic influences on the rearrangement reaction by surveying a variety of aromatic and heteroaromatic aldehydes (Scheme 18). We found that ortho substituted aldehydes behaved well under these reaction conditions (**29a**-**h**). Both electrons-poor (**29b**-**c**) and electron-rich (**29f**-**g**) aldehydes participated in the reaction. Moreover, heteroaromatic aldehydes such as pyridine-2-carboxaldehyde and 2-furfuraldehyde also provided good yields of rearrangement products (**29d**-**e**). We also found that an unprotected phenol was tolerated under the reaction conditions (**29g**).[35]

This aza Claisen rearrangement has several practical benefits for the synthesis of 3^{o} alcohols such as **29**. For example, AC-265347 and analogs thereof have been reported to be calcium sensing receptor agonists (Figure 4).[36] It was prepared in the traditional fashion by addition of 2-lithiobenzothiazole to the corresponding ketones at -78 ^{o}C. By contrast, we prepared allyl analog **29i** in 50% yield over two steps from benzothiazole using our approach.

Scheme 18.

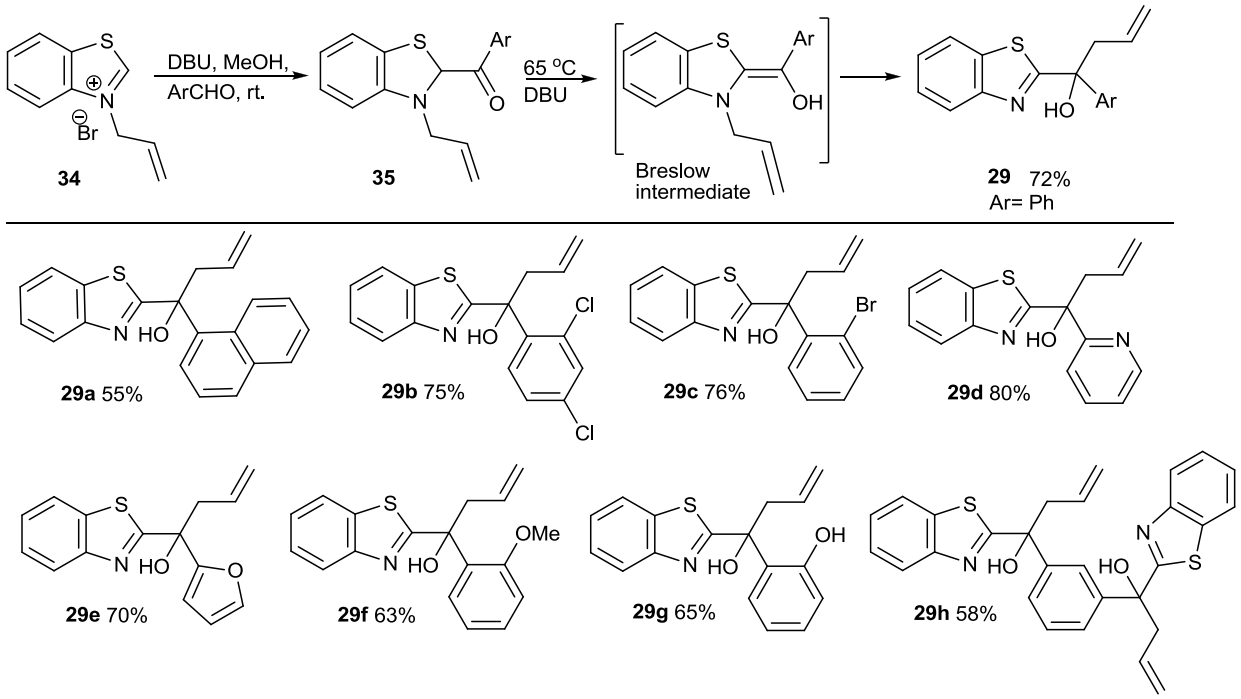
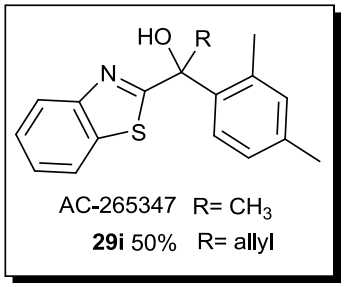
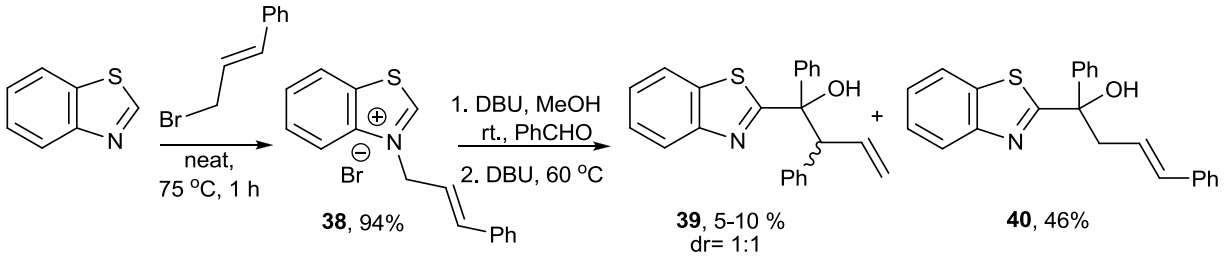


Figure 4.



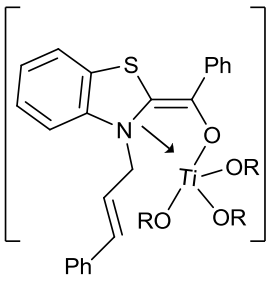
We next investigated the internal diastereoselection of the rearrangement. We started by preparing N-allyl substituted benzothiazolium salt **38** by adding cinnamylbromide to the benzothiazole and heating the mixture neat at 75 °C for 1 h to provide N-cinnamyl benzothiazolium salt **38** in 94 % yield (Scheme 19). Then, we applied the previous conditions of the rearrangement reaction (1.2 eq DBU, 2 eq PhCHO, 0.2 M MeOH) at ambient temperature to form the ketone, subsequently heating the mixture at 65 °C after adding 0.8 eq of DBU to obtain rearranged product **39**. However, the reaction produced only trace amounts of [3,3]-Claisen rearrangement product **39** and instead provided the formal [1,3]-rearrangement product **40** as the major product in 46% yield.

Scheme 19.



To continue our investigation on [3,3]-rearrangement formation, we did a preliminary examination using catalysts. We hypothesized that using catalyst might suppressed the formation of [1,3]-product **40** and increase the formation of [3,3]-product **39**. We chose Ti(IV) catalysts because of their low cost, their extensive employment as Lewis acids, and the ready availability of chiral ligands.[37] We speculated that such a catalyst would chelate the nitrogen and oxygen in the ketene acetal intermediate to form a five membered ring[38] (Figure 5). Also, the addition of Lewis acids to the ketene acetal could accelerate the Claisen rearrangement and increase the diastereoselectivity.[39]

Figure 5.



From our preliminary results we found that performing the reaction with 10% or 100% mol of Ti(O-iPr)$_4$ formed the product of [3,3]-rearrangement **39** in 26% yield and a dr=1:2.5 (Scheme 20, Table 3, entry 1 & 2) along with small quantity of an inseparable mixture of [1,3]-rearrangement product **40** and transposed product **41**. Moreover, using catalytic or stoichiometric amounts of catalyst gave identical dr= 1:2.5. Furthermore, addition of a mixture of Ti(O-iPr)$_4$ and a chiral ligand such as, L-diethyl tartrate (L-DET)[40] or (±)-1,1-binaphthol[41] reduced the reaction time from 2 weeks to 3 days, and also reversed the diastereoselectivity of product **39** while retaining similar yield (Table 3, entry 1-2 vs. 4-6).

Scheme 20.

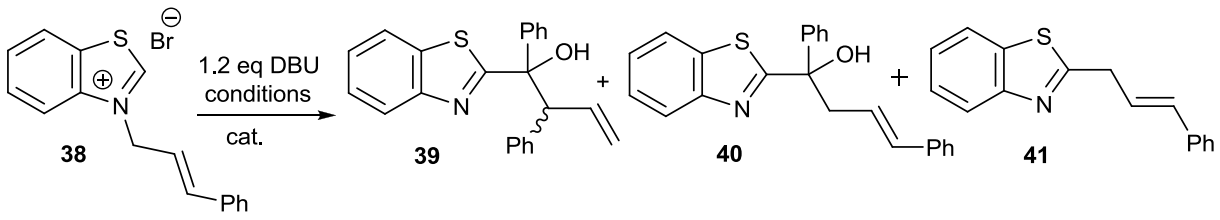


Table 3:

Entry	Solvent	Catalyst	Ligand	Conditions	yield % of **39**
1	MeOH	10% $Ti(O\text{-}iPr)_4$	------	2 weeks, rt	26% , dr=1:2.5
2	"	100% $Ti(O\text{-}iPr)_4$	------	2 weeks, rt	26 %, dr=1:2.5
3	"	-------	-------	2 week, rt	complex mixture
4	MeOH, then DCM	10% $Ti(O\text{-}iPr)_4$	12% L-DET/ 3A^{o} sieves	3 days, -20 ^{o}C- rt	23%, dr= 1.8:1
5	"	10% $Ti(O\text{-}iPr)_4$	20 % L-DET/ 3A^{o} sieves,	3 days, -20 ^{o}C- rt	23%, dr= 1.5:1
6	MeOH then THF	10% $Ti(O\text{-}iPr)_4$	20% BINOL	3 days, rt	24%, dr= 1.4:1

The low diastereoselectivity in the Claisen rearrangement could be accounted for three reasons: (i) the low selectivity of chair/boat transition states, (ii) mixture of *E*/*Z* ketene acetals, or (iii) epimerization. Two of these reasons can be ruled out; epimerization cannot occur since compound **39** contains a quaternary center and *E*-ketene acetal is predominant in cinnamyl case. Therefore, the low selectivity of chair/boat transition state is the only reason for low diastereoselectivity.

We believe that with the appropriate conditions, choice of catalyst, and ligands we can improve the yield of [3,3]-rearrangement product and its diastereoselectivity which will be a subject of further studies in our lab.

CHAPTER 2

RADICAL FRAGMENTATION OF THE BRESLOW INTERMEDIATE

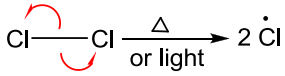
I. INTRODUCTION

In this chapter of the dissertation, we will take a detour into a corner of organic chemistry where bonds are formed by the combination of single electrons and bonds break through the homolytic cleavage. These are generally referred to as free radical reactions. Organic free radical reactions that were discovered by Moses Gomberg in 1900[42] nowadays plays an important role in many chemical fields.[43, 44]

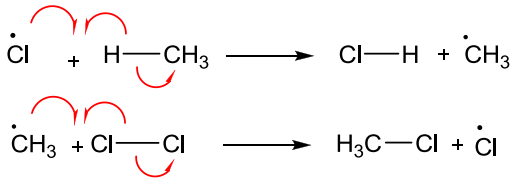
Free radical reactions fall into two main categories: radical chain reactions and radical nonchain reactions.[45] The mechanism of radical chain reactions consist of three main steps: initiation, propagation, and termination. For instance, the chlorination mechanism of methane undergoes radical reaction in presence of light or heat (Scheme 21).[46]

Scheme 21.

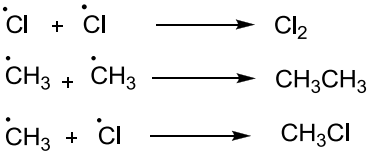
step 1: initiation step to produce radicals



step 2: propagation sequence to form products and propagate chain



step 3: termination step to destroy the radicals and form closed shell products



The initiation step involves reactions that produce radicals that participate in the propagation steps. The propagation cycle consists of two or more reactions where the products are formed and radicals are formed that serve as reactants in another step of the propagation sequence. In the termination step, the reaction stops by destroying the radicals through radical-radical recombination to form closed shell compounds.

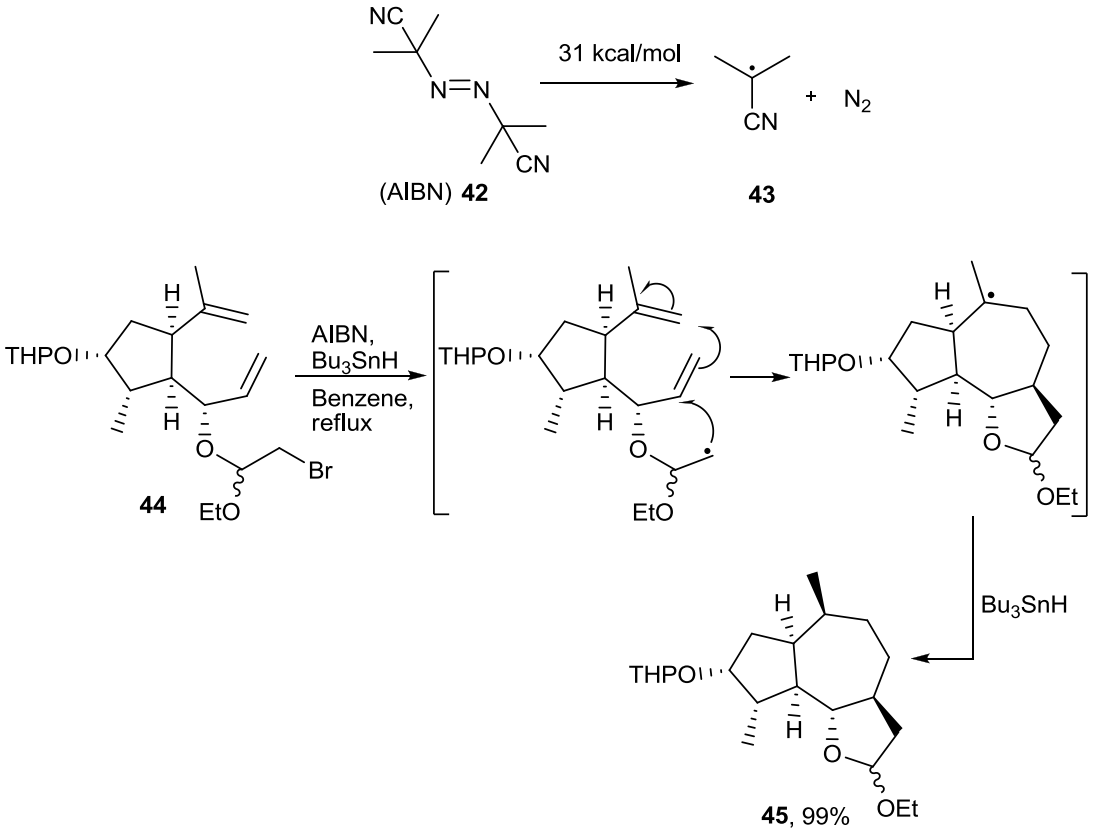
The radicals in the initiation step are formed by homolytic cleavage of a covalent bond, which is normally initiated by thermolysis or photolysis. Some radical reactions are performed in the presence of thermal initiators which consist of weak bonds such as peroxides,[47] N-haloamides,[48] azo compounds, and molecular halogens,[49] etc.

II. BACKGROUND

II.a. Thermal Initiators

Radical initiators are substances bearing one or more weak bonds with BDE ~30-40 kcal/mol.[50] These initiators are relatively stable at room temperature and decompose homolytically under temperatures below 150 ^{o}C to produce free radicals. These radicals can initiate (chain or nonchain) radical reactions. For example, azobisisobutyronitrile (AIBN) **42** has weak C-N bounds with BDE around 31 kcal/mol, and it has been widely used in organic synthesis as thermal radical initiator (Scheme 22).[50, 51]

Scheme 22.



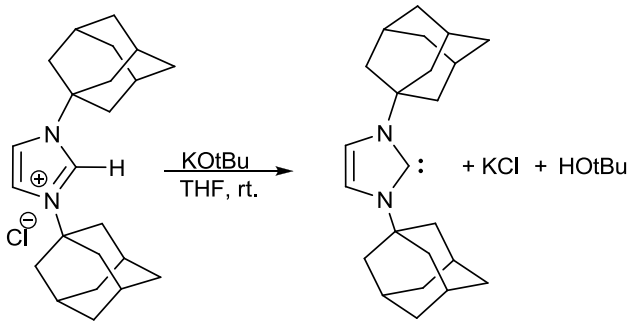
II.b. Stable N-Heterocyclic Carbenes

The reactivity and applications of N-Heterocyclic carbenes (NHCs) in modern chemistry are categorized into three sections: NHCs as ligands for transition metals,[52, 53] as coordination to p-block elements,[54] or as organocatalysts.[55, 56] In this section, we will discuss in brief the stability and the use of HNCs as organocatalysts and provide some examples form literature.

II.b.1. First Example of a Stable Carbene

In 1991, Arduengo et al. reported the first example of a stable carbene **48** (Scheme 23).[57] The deprotonation of 1,3-di-1-adamantylimidazolium chloride **47** at room temperature with potassium tert-butoxide in THF produce colorless crystals of carbene **48** in 96% yield.

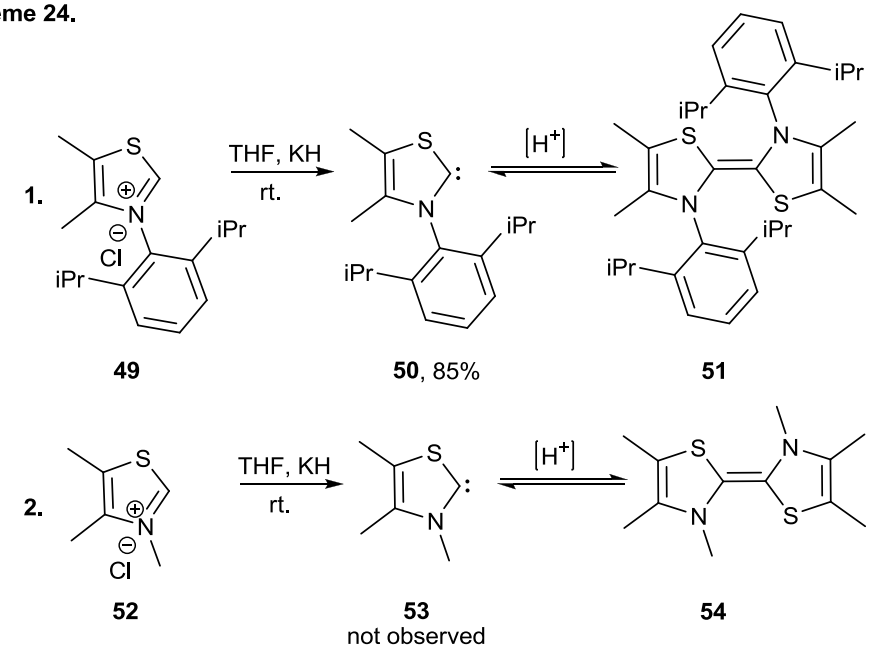
Scheme 23.



47 **48**, 96%

A few years later, Arduengo et al. reported the first example of an isolable, stable thiazolium carbene N-(2,6-diisopropylphenyl)thiazol-2-yliden **50** and its corresponding olefin dimer **51** (Scheme 24, eq 1).[58] When potassium hydride was added to a dissolved salt N-(2,6-diisopropylphenyl)-4,5-dimethylthiazolium chloride **49** in THF at room temperature, stable carbene **50** was formed along with KCl and H_2. Filtration and removal of THF in vacuo produced the crude carbene in 88% yield. Recrystallization of the carbene from hexane yielded carbene **50** in 85% yield as colorless crystalline solid. This carbene was believed to be kinetically stable because of the bulky group at the nitrogen atom. The structure of this carbene was determined by an X-ray diffraction study. It can undergo a reversible dimerization to the olefin dimer **51**. Arduengo reported that the dimerization of **50** proceeds smoothly under acidic conditions to form *E*-dimer **51** as red solid. However, in the absence of acid catalysts no dimerization was detected on a time scale of weeks. The author reported that when the N-substituent is a methyl group, the carbene **53** was not detectable and the dimer product **54** was obtained directly upon the deprotonation of the salt **52** (Scheme 24, eq 2).

Scheme 24.

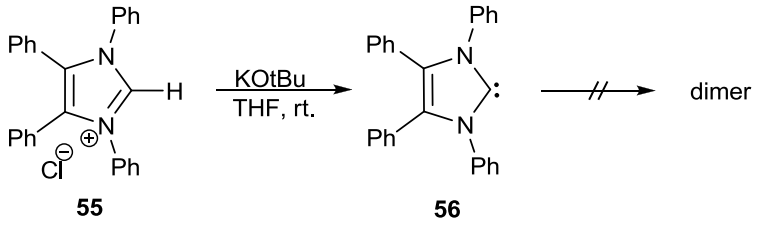


Arduengo concluded that the N-substituent's size play a major rule in the equilibrium. If the N-substitiuent is sterically less demanding such as methyl, then the equilibrium will lie toward dimerization, whereas sterically demanding N-substitiuents will shift the equilibrium toward the free carbene.

II.b.2. First Example of Stable Carbene Substituted Imidazolium

In 1970, Wanzlick et al. tried to synthesize carbene **56** (Scheme 25), but his attempts were unsuccessful.[59] In 1998, Arduengo et al. slightly modified the synthetic approach to the carbene **56** and were able to prepare the free carbene.[59] In Arduengo's procedure, the salt **55** was prepared using Wanzlick's procedure; however, he converted the counterion from hydrogensulfate to chloride. Moreover, Arduengo noted that the unsaturated imidazolium carbene of type **56** had no tendency for dimerization.[60] Arduengo reported the synthesis and isolation of a series of stable carbenes that could be stored at room temperature under a nitrogen atmosphere.[61]

Scheme 25.

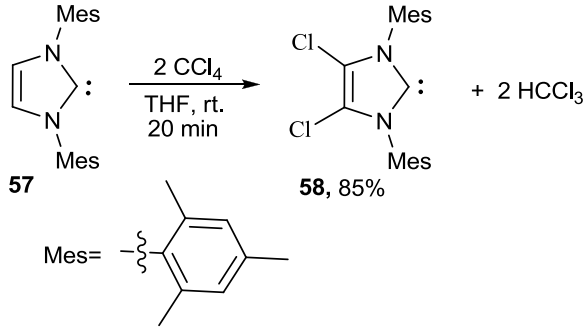


55 **56**

II.b.3. First Example of an Air Stable Carbene

In 1997, Arduengo synthesized the first air stable carbene 1,3-dimesityl-4,5-dichloroimidazol-2-ylidene **58** via chlorination reaction of carbene **57** (Scheme 26).[62] Carbene 1,3-dimesitylimidazol-2-ylidene **57**[63] reacts rapidly with carbon tetrachloride in THF at room temperature to produce carbene **58** and chloroform. Adruengo stated that halogenation of the imidazole ring increased the stability of the carbene compared to unhalogenated analog. Carbene **58** exhibits enhanced stability toward air, moisture, and acidic halogenated solvents such as chloroform. Nowadays, there are huge numbers of free carbenes reported in the literature that are easily prepared.[64-66]

Scheme 26.

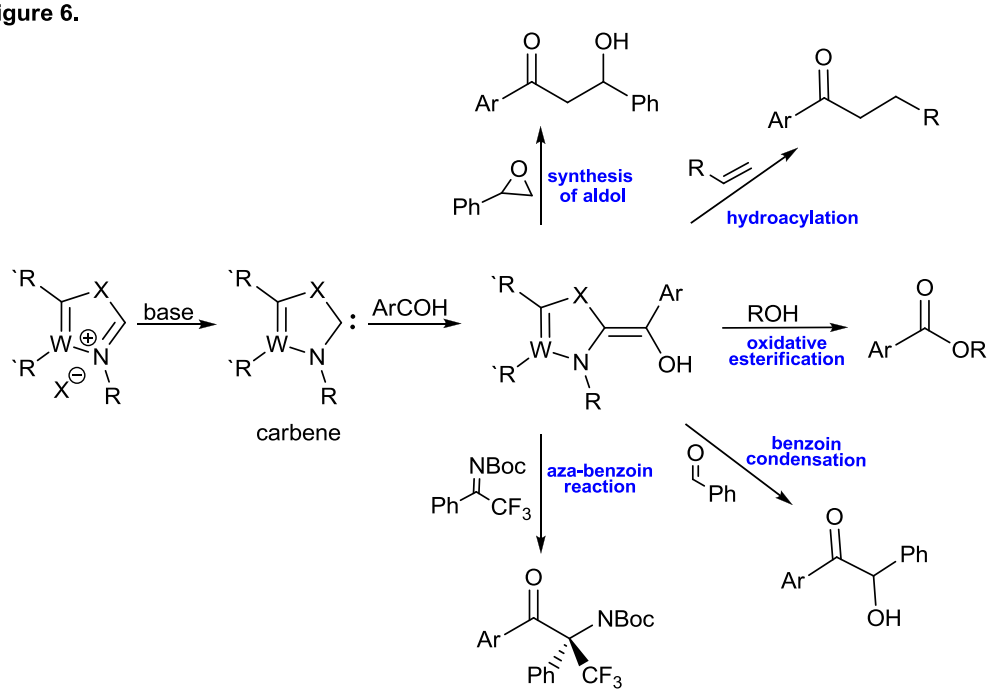


57 **58,** 85%

II.c. Reactivity of The Carbenes

The stable carbenes mentioned above have been reported to act as catalysts in a large number of carbonyl reactions. A few examples of these reactions are aldol,[67] hydroacylation,[68] oxidative esterification,[69] benzoin condensation,[28] aza-benzoin reaction,[70] and so forth. The mechanism for all these types of reactions engages a key intermediate that is so called-Breslow intermediate (Figure 6) after the well-established mechanism for benzoin condensation catalyzed by thiazolium salts that was first proposed by Breslow.[24]

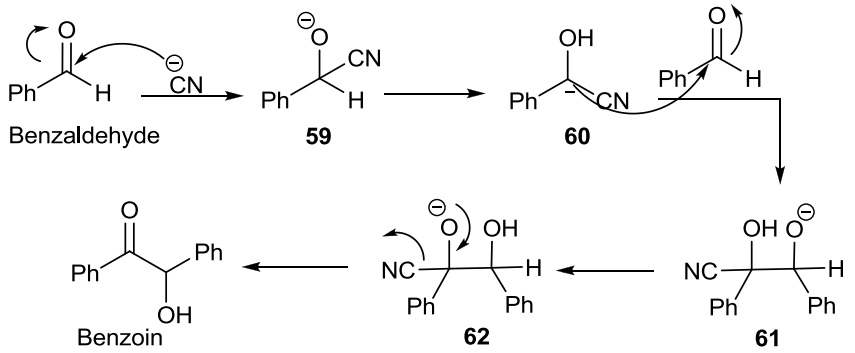
Figure 6.



II.c.1. Benzoin Condensation

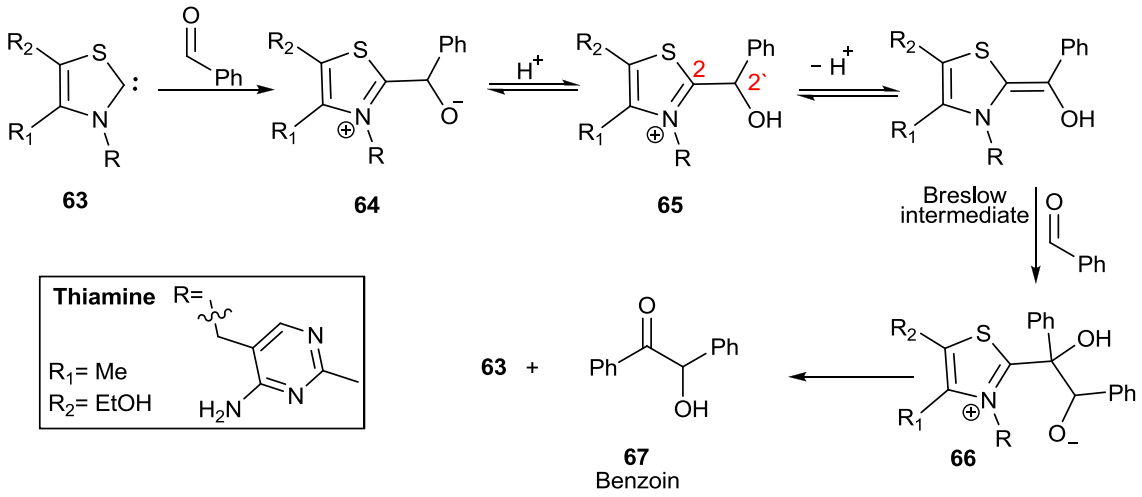
Benzoin condensation is a C-C bound formation reaction. Benzoin was originally prepared by the reaction of two molecules of aldehyde catalyzed by cyanide ion (Scheme 27).[71] In this reaction, the cyanide ion activate the first aldehyde molecule to form the intermediate cyanohydrin adduct **59** that rearranged to the nucleophilic carbanion species **60**, which then adds to another aldehyde molecule to finally deliver benzoin.

Scheme 27.



An analogous reaction to benzoin condensation occurs in our body, which is catalyzed by the thiazolium moiety of the co-enzyme thiamine pyrophosphate (TPP). [72] Breslow proposed that the benzoin condensation mechanism could proceed via the carbene **63** (Scheme 28).[28] In the mechanism, carbene **63** acts as a nucleophile and attacks the aldehyde to form intermediate **64**, which is converted to alcohol **65** upon protonation. Upon deprotonation at C2`, the Breslow intermediate is generated. This nucleophilic enol intermediate reacts with a second molecule of aldehyde to form intermediate **66**, which is followed by release of benzoin **67** to regenerate carbene **63**. Breslow stated that the enol is most consistent with the mild base conditions that are relevant to biochemical and biological systems. Several benzoin-type condensation reactions are catalyzed by enzymes that use thiamine (Vitamin B1) as a coenzyme (vide infra, chapter 3).

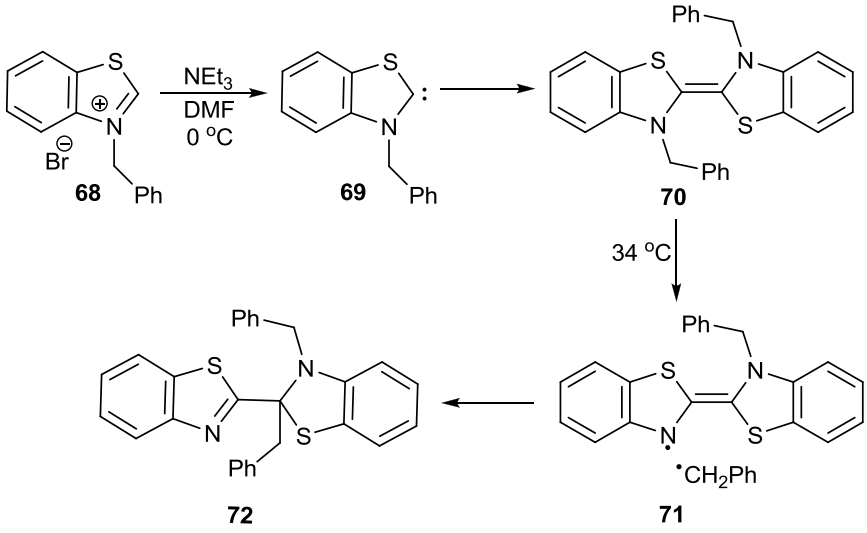
Scheme 28.



II.d. Baldwin's Studies

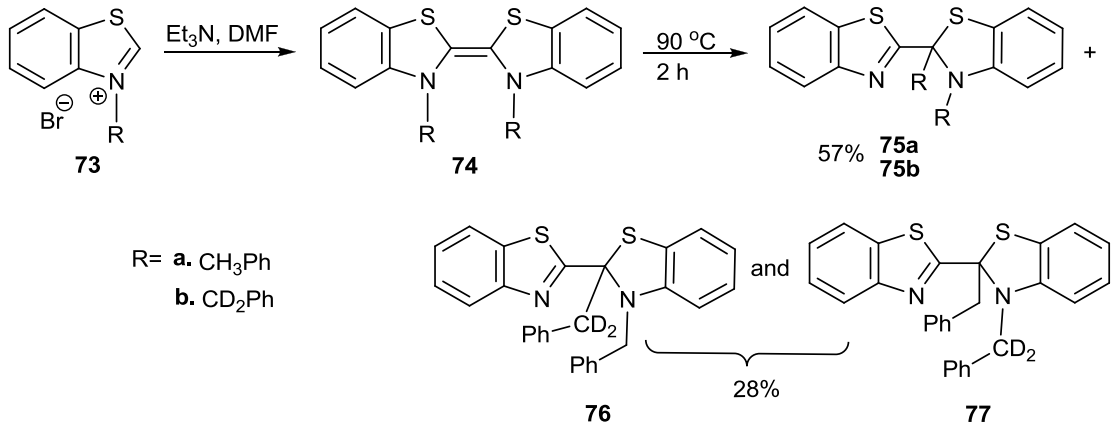
In 1974, Baldwin et al reported the [1,3]-rearrangement of a dimer arising from N-benzyl benzothiazolium salt **68**. This dimer **70** was not stable and rearranged to form compound **72** (Scheme 29).[73] Baldwin reported that benzothiazole dimer **70** underwent C-N bond homolysis to afford products of formal 1,3-rearrangement **72**.

Scheme 29.



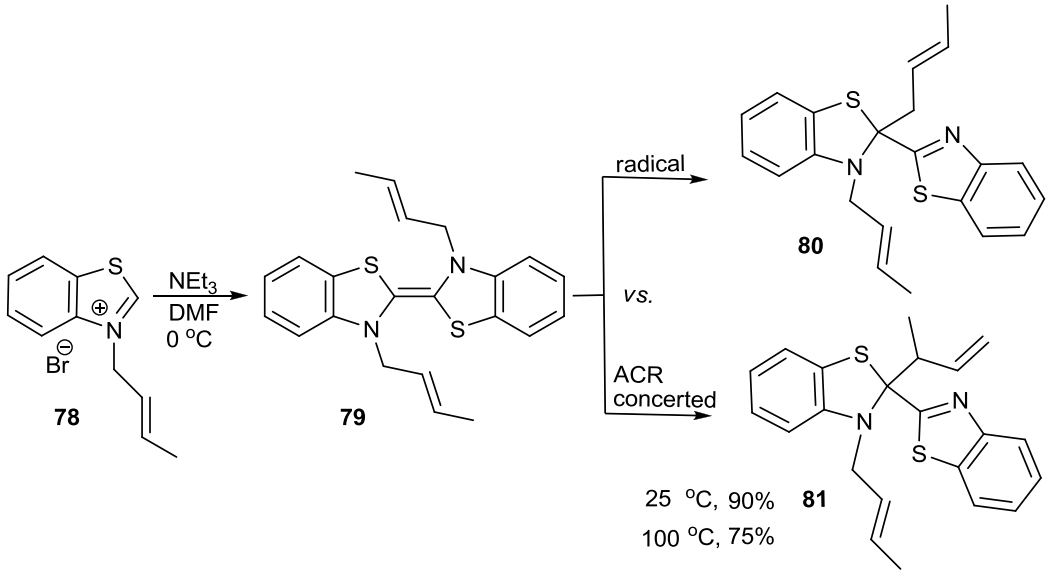
A crossover reaction with deuterium labeled benzyl groups demonstrated that a bimolecular mechanism was responsible for the formation of product **72** (Scheme 30).[74] A significant amount proportion of the mixture of the dideuterio dimers **76** and **77** was formed. The products ratios were determined by mass spectroscopic analysis to be 28 ± 2% of the total yield. He also obtained a moderate yield of **intra**molecular recombination products **75a** and **75b** in 57 ± 4% yield. The authors suggested that low yield of the **inter**molecular crossover products was a result of a solvent cage effect in the radical dissociation-recombination process, and the formal [1,3]-rearrangement products probably resulted from fast recombination of the two radical components within the solvent cage.[75]

Scheme 30.



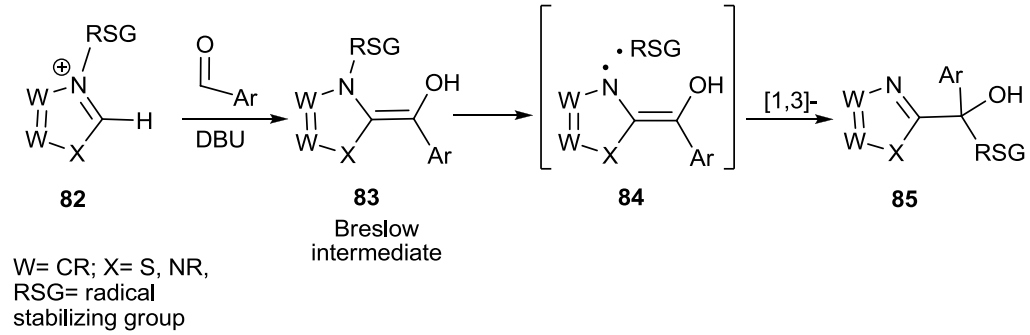
Baldwin also studied the rearrangement of N-crotyl benzothiazole dimer **79** (Scheme 31). He reported that competing reactions, concerted [3,3]- and radical [1,3]- occurred depending upon the reaction temperature and the nature of the N-substituent. At higher temperature, a radical pathway becomes competitive. Additionally, more highly radical stabilizing N-alkyl groups favor the radical pathway of the rearrangement.

Scheme 31.



All the carbene-carbonyl type reactions mentioned above (Figure 6) are polar processes. In the present work, we describe a new methodology to prepare formal [1,3]-rearrangement products that form by radical fragmentation of the Breslow intermediate (Scheme 32). This new approach would offer possibilities to prepare complex chiral azoles that are not readily accessible via polar methods. Radical reactions have several advantages over polar processes. From a synthetic point of view, (i) radical processes generally have high functional group tolerance. (ii) Beta elimination is less common in radical compared to carbanionic pathways. (iii) Carbocation intermediate suffer 1,2-shifts, which is very rare in the radical intermediate.

Scheme 32.



The primary objective of this part of the project is to explore unprecedented radical reaction pathways for the Breslow intermediate, which is a valuable precursor to radical based C-C bond forming reactions. Additionally, understanding the radical chemistry of the Breslow intermediate would provide significant data about potential decomposition pathways for Breslow intermediates in N-heterocyclic carbene catalyzed reactions. Moreover, radical pathways are more functional group tolerant and provide a means of preparing chiral azoles.

III. RESULTS AND DISCUSSION

III.a Rearrangement of N-Cinnamyl Benzothiazolium Salt 38

We had so far found that Claisen Rearrangement of Breslow intermediates derived from N-allyl benzothiazolium salts **34** and aromatic aldehydes were possible (see Scheme 18, Chapter 1). We next turned our attention to thiazolium and benzothiazolium salts bearing terminally substituted N-allyl groups such as crotyl and cinnamyl. Salt **38** was treated at ambient temperature with 2 eq of DBU, 2 eq PhCHO, and 0.15 M in MeOH (Scheme 33). The reaction mixture was heated at 60 ˚C for 1 d after stirring at rt for 20 h. The reaction produced only trace amounts of [3,3]-Claisen rearrangement product **39** with dr=1:1 along with 2-cinnamylbenzothiazole **41**. It provided also the formal [1,3]-rearrangement product **40a** as the major product in 46% yield (entry 1). By increasing the reaction time and temperature, a higher 57% yield of the [1,3]-product was obtained (entry 2). The structure of compound **40a** was confirmed by X-ray crystallographic analysis.

Scheme 33.

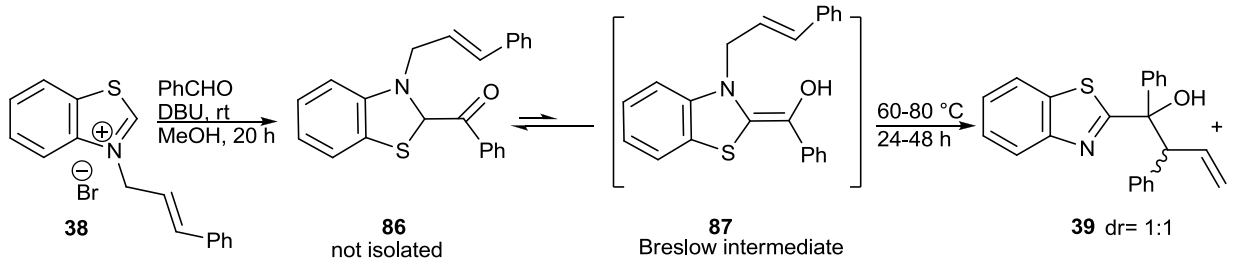
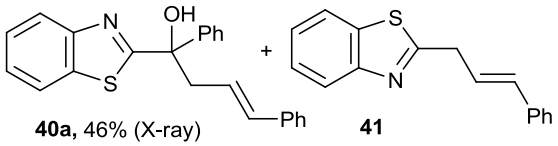


Table 4.

Entry	DBU (eq)	Time / (°C)	Results **40a/ 39**
1.	1.2 eq/0.8 eq	20 h, rt/ 1 d, 60 °C	46% / tace
2.	1.2 eq/0.8 eq	1 d, rt/ 2 d, 80 °C	57% / trace
3.	2-3 eq	14 d, rt	complex mixture on TLC

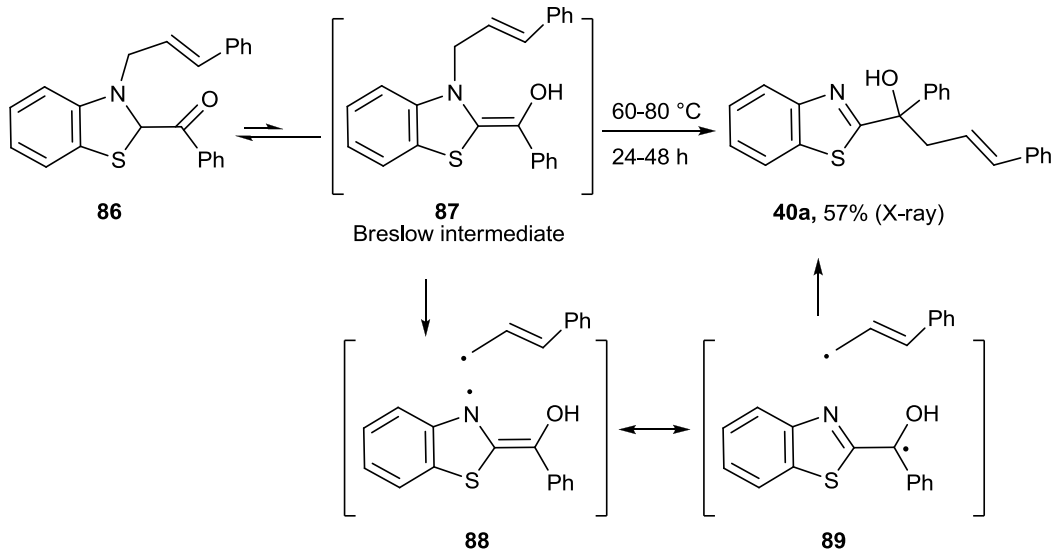


40a, 46% (X-ray) **41**

The attempts to isolate ketone **86** of this system were unsuccessful. When dissolved salt **38** in MeOH was treated at rt with a mixture of (DBU, PhCHO), a complex mixture of products was observed based on TLC analysis (entry 3). The isolation of ketone **86** was not important by itself, but it was a way to follow the progress of the reaction.

A reasonable way to form product **40a** would be through a radical pathway via C-N bond scission of the Breslow intermediate **87** to form two radical species: benzothiazole radical intermediate **88** and cinnamyl radical (Scheme 34). The [1,3]-product **40a** would be generated upon recombination of cinnamyl radical with the radical intermediate **89** with simultaneous rearomatization of benzothiazole. DFT calculations (B3LYP/6-31g*) predict an unusually low C-N homolytic bond dissociation enthalpy for Breslow intermediate **87** of 13.2 kcal/mol which explains the remarkable result of this system.

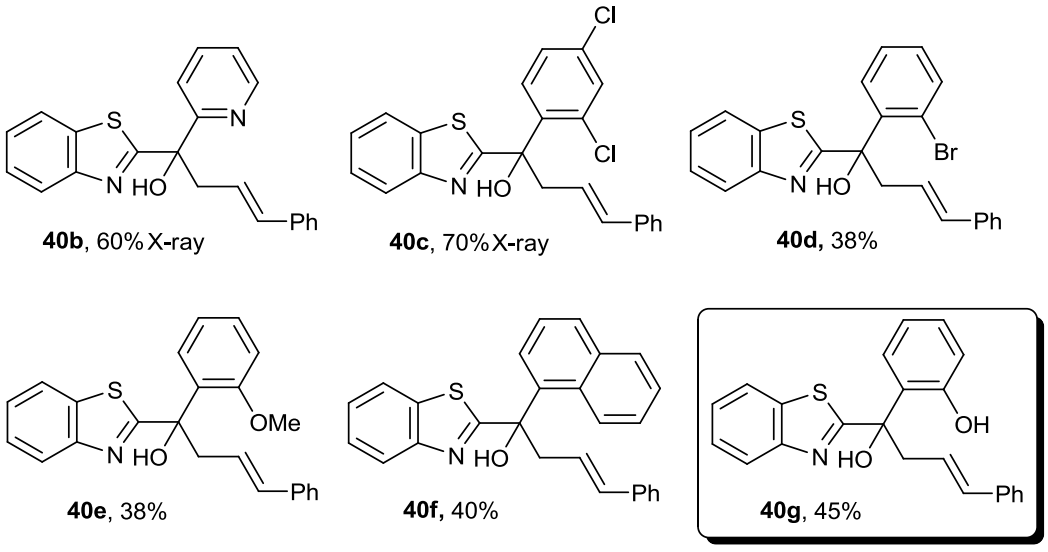
Scheme 34.



At this point, we were motivated to examine different aromatic and heteroaromatic aldehydes to determine the scope of this reaction (Figure 7). We found that ortho-substituted aldehydes are tolerated under the reaction conditions (**a**-**g**). Heteroaromatic aldehyde such as pyridine-2-carboxaldehyde reacted smoothly and provided 60% yield of [1,3]-product **40b**. Moreover, using electron poor aldehydes such as 2,4-dichlorobenzaldhyde and 2-bromo-benzaldehyde gave good to moderate 70-38% yield of [1,3]-product **40c** and **40d**, respectively. Furthermore, the radical reaction tolerated the ortho-substituted electron rich aldehyde such as 2-methoxybenzaldehyde to provide moderate yield 38% of the [1,3]-product **40e**. The radical reaction also tolerated 1-naphthaldehyde and gave product **40f** in 40% yield. The 2-hydroxybenzaldehyde was a special case (inset).

For unclear reasons, sometimes [1,3]-product **40g** was obtained (~ 45% yield) and other times the Claisen rearrangement product was obtained in similar yield with dr=1:1. Besides that, this example was the only one in which the product precipitated out of the reaction mixture and by simple filtration and washing with MeOH we obtained pure product whether it was [1,3]- or [3,3]-rearrangement. These interesting results of this system suggested that the ortho-hydroxyl group might add more stability to the Breslow intermediate because of increasing the hydrogen bonding within the molecule. Thus, the differences in the activation energies of the transition states for [1,3]- and [3,3]- would presumably be very small.

Figure 7.

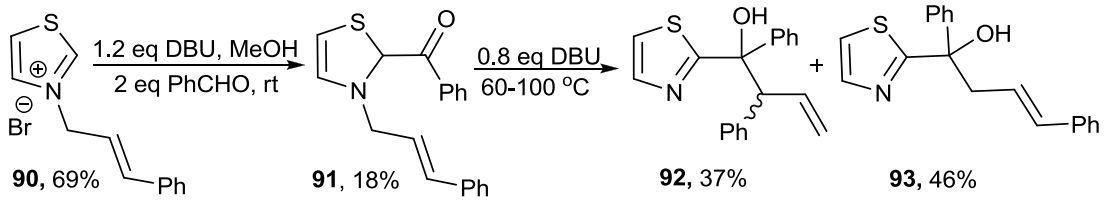


The above results with N-cinnamyl benzothiazolium salt encouraged us to strive to examine variables associated with the radical stability, and determine how they would affect either pathway. These variables are (i) using catalysis (see page 19, Ch1), (ii) using less highly conjugated thiazole core instead of benzothiazole, or (iii) using the less radical stabilizing N-crotyl group instead of the N-cinnamyl group.

III.b Rearrangement Using N-Cinnamyl Thiazolium Salt 90

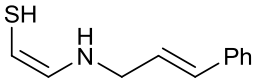
Thiazolium salt **90** was synthesized in an analogous fashion to the previous salts. Mixing the commercially available thiazole with cinnamyl bromide neat and heating to 75 ^{o}C for 12 hours provided salt **90** in 69% yield. Under the reaction conditions (2 eq DBU, 2 eq aldehyde, 0.15 M MeOH, reflux), a mixture of products were obtained. After purifying via column chromatography, the products were [3,3]-rearrangement product **92** (37% yield) with dr=1:2, and [1,3]-rearrangement product **93** (46% yield) (Scheme 35). The same reaction was performed again and the mixture was heated at higher temperatures (100 ^{o}C) for 12 hours after degassing to examine the effect of the higher temperature on the products yield. The 1,3-product **93** was obtained in a similar yield along with ring opening product **94** in 18% yield, and 18% of recovered ketone **91**. We then tried to run the rearrangement reaction on the microwave after forming the ketone at rt for 12 hours. We only tried two conditions but there was no reaction detected by TLC.

Scheme 35.



Microwave cons.

40 power,60 ^{o}C, 30 pressure, for 2.5 h	No reaction
60 power,60 ^{o}C, 30 pressure, for 14 h	No reaction



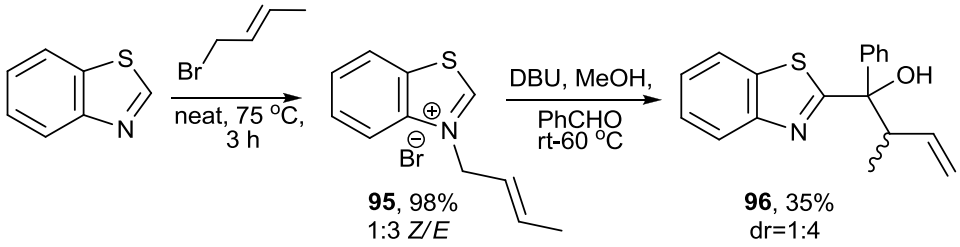
94, 18% ring opening structure

III.c Rearrangement Using N-Crotyl Benzothiazolium Salt 95

We synthesized N-crotyl benzothiazolium salt **95** by adding the commercially available crotyl bromide to benzothiazole and heating the neat reaction mixture at 75 ˚C for 3 hours to obtain the salt in 98% as a 1:3 *Z*/*E* mixture (Scheme 36). The rearrangement reaction was carried out using 2 eq of DBU and 2 eq of benzaldehyde to form ketone first at rt, then heated the reaction mixture at 60 ˚C for 2-3 days

to obtain the rearranged products. A separable mixture of [3,3]-diastereomers **96** was obtained in 35% yield and dr=1:4 based on ^{1}H NMR analysis. However, [1,3]-product was not detected by ^{1}H NMR of crude mixture.

Scheme 36.



Our objective here was to probe the boundaries of the radical pathway and determine to what extent the radical stability of the azole core and N-substituent affected the reaction pathway. From the above results, we concluded that using more radical stabilizing N-substituent group will increase the yield of [1,3]-product (N-cinnamyl *vs* N-crotyl). Moreover, using highly conjugated azole core brings more stability to radical intermediate (benzothiazole *vs* thiazole).

The above results with N-cinnamyl benzothiazolium salt prompted us to examine different N-aryl radical stabilizing groups that would increase the radical pathway. Moreover, being capable of manipulating the reaction pathway to either a radical or concerted would constitute novel chemistry.

III.d Rearrangement Using N-Benzyl Salt 97

The known N-benzyl benzothiazolium salt **97**[76] was synthesized by adding benzylbromide to benzothiazole, then heating the mixture at 60 °C for 7 h to obtain salt **97** in approximately quantitative yield (Scheme 37). A methanolic solution of salt **97** was added to a mixture of 2 eq DBU and 2 eq PhCHO, and the reaction mixture was maintained at rt for 12 h. During this time, a bright yellow spot was observed on the TLC plate, which proved to be ketone **98**. The mixture was then heated at 60 °C until the ketone disappeared, which required 6 days. A low yield 28% of [1,3]-rearrangement product **99** was isolated (Table 5, entry 1). In an attempted to improve the yield of [1,3]-product, the ketone formation

reaction was maintained at rt for a longer period of time (24 h). There was slightly or no improvement in the yield of [1,3]-product (entry 2). The rearrangement reaction then was carried out at a higher temperature (120 ^{o}C) for 20 h after degassing the reaction mixture; however, the yield of rearrangement product did not improve (entry 3).

Consequently, we separated the ketone and the rearrangement steps to determine if one step was responsible for the observed low yield. Doing so, we found that the ketone formation step required at least 4 days to produce ketone **98** in 71% yield. Thus, the ketone formation step was implemented and sustained at rt for 4 days, then heated the mixture at 60 ^{o}C for 3 days until all ketone disappeared by TLC. Unfortunately, low yield was again obtained after purification (entry 4). The rearrangement step was also performed using pure ketone **98** in MeOH and 0.8 eq DBU, but similar yield was obtained. Therefore, the above results elucidate that the rearrangement step was problematic.

Scheme 37.

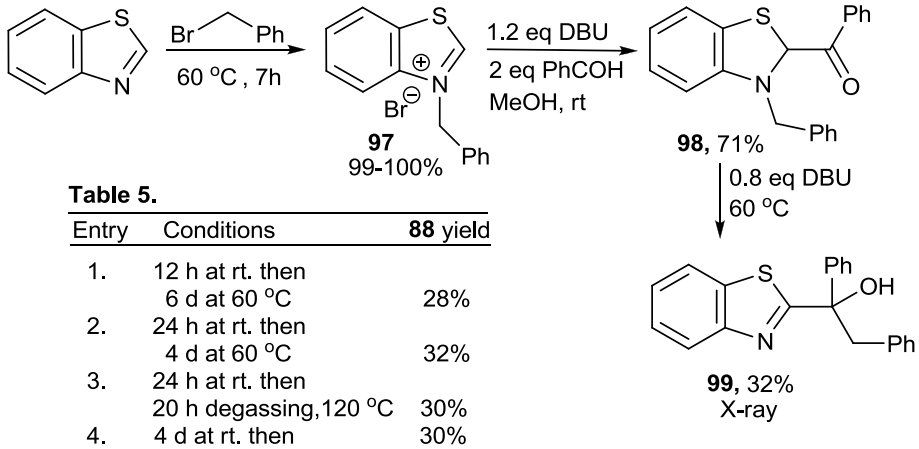
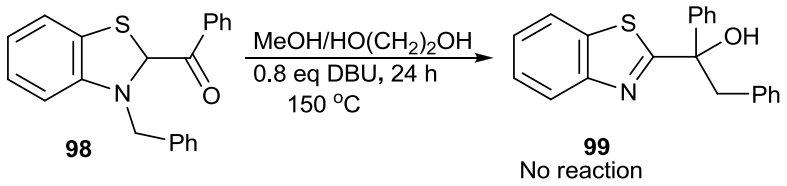


Table 5.

Entry	Conditions	**88** yield
1.	12 h at rt. then 6 d at 60 ^{o}C	28%
2.	24 h at rt. then 4 d at 60 ^{o}C	32%
3.	24 h at rt. then 20 h degassing,120 ^{o}C	30%
4.	4 d at rt. then 3 d at 60 ^{o}C	30%

We performed the reaction again starting with ketone **98** and a mixture of solvents methanol/ ethylene glycol so that we could raise the temperature of the reaction mixture to 150 ^{o}C; however, no reaction was detected by TLC (Scheme 38). After these dissatisfying results, we stopped working with this salt.

Scheme 38.



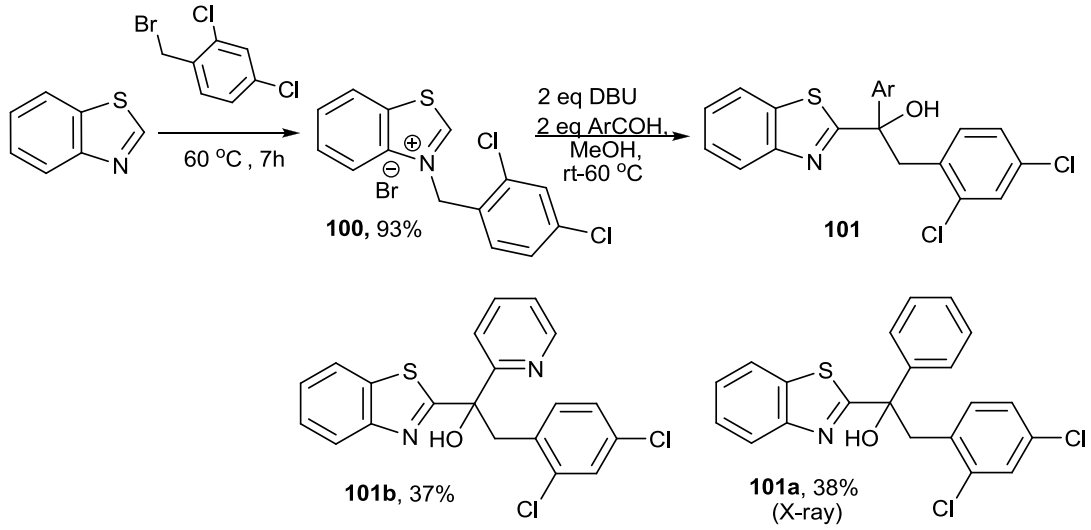
98 **99**
No reaction

III.e Rearrangement Using N-(2,4-dichlorobenzyl) Benzothiazolium Salt 100

We continued our investigation on [1,3]-rearrangement reaction using N-2,4-dichlorobenzyl benzothiazolium salt **100** (Scheme 39). It was synthesized by mixing 2,4-dichlorobenzyl chloride with benzothiazole neat and heated at 80-170 ^{o}C for 2-4 days; however, we obtained only trace amounts of the salt. Therefore, dichlorobenzyl chloride was converted to the bromide by heating the chloride with NaBr in acetone at reflux for 4 days.[77] Heating a mixture of benzothiazole with 2,4-dichloro-benzyl bromide at 65 ^{o}C for 7 hours delivered the salt **100** in 93% yield.

Submitting this salt to the standard conditions (2 eq DBU, 0.15 M MeOH) using 2 eq of benzaldehyde and/or 2-pyridinecarboxaldehyde gave the rearrangement product **101a** in 38% yield and **101b** in 37% yield, respectively. In these examples, the ketones formed after 12 h at rt based on TLC analysis. Then, another charge 0.8 eq of DBU was added and the reaction mixture was heated to 60 ^{o}C for 12 h.

Scheme 39.



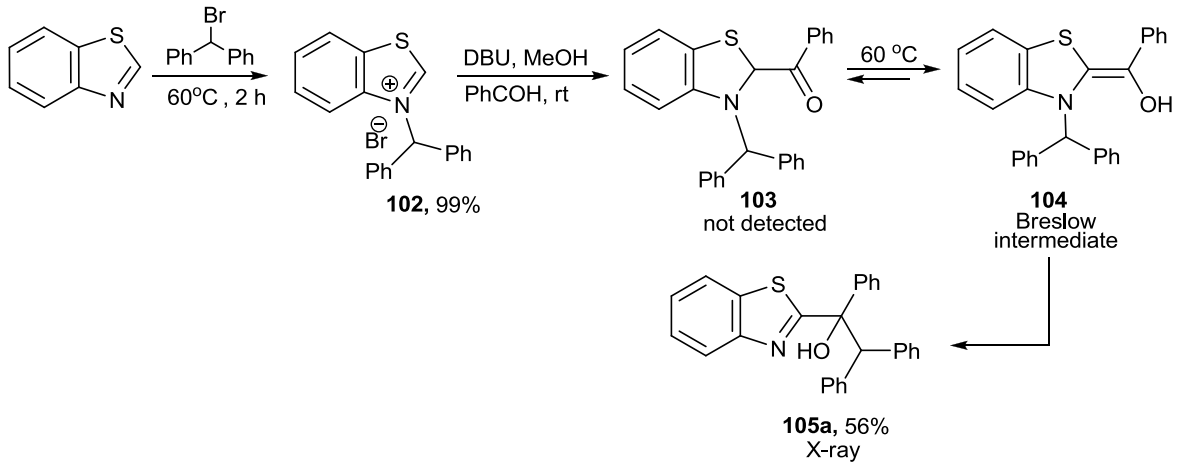
III.f. Benzhydryl And Substituted Benzhydryl Groups

Benzhydryl moiety and its derivatives are common species in pharmaceuticals.[78-82] It would be interesting to study the behavior of such species in the [1,3]-rearrangement process.

III.f.1. Rearrangement Using N-(benzhydryl) Benzothiazolium Salt 102

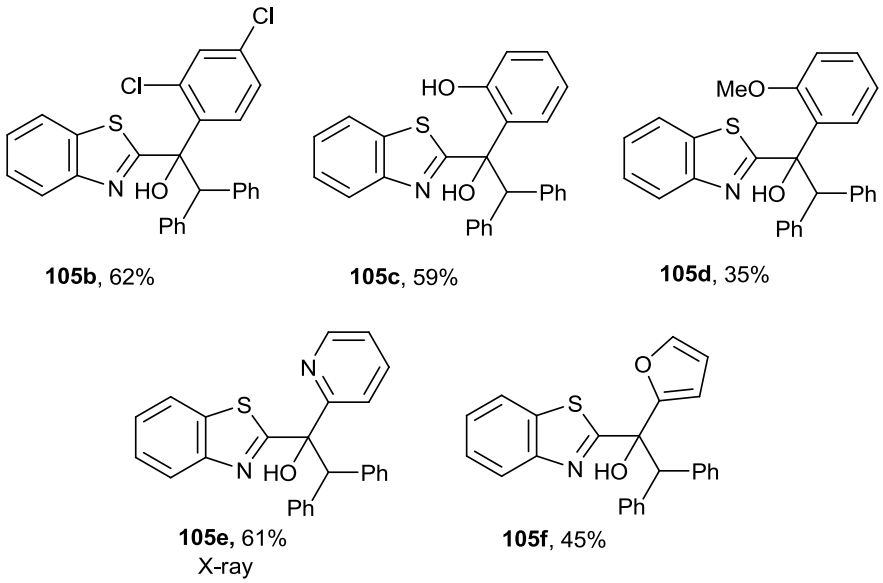
The N-benzhydryl benzothiazolium salt **102** was synthesized by heating a neat mixture of commercially available benzhydryl bromide and benzothiazole at 65 °C for 2 h to obtain the salt in approximately quantitative yield (Scheme 40). The reaction was carried out by adding a methanolic solution of salt **102** to a mixture of (2 eq DBU, 2 eq benzaldehyde, rt). Ketone **103** could not be detected by TLC even after 24 h. The reaction mixture was then heated at 60 °C for 12 h. A white precipitate formed in the flask. Filtration, washing with MeOH, and recrystallization with dichloromethane afforded [1,3]-rearrangement product **105a** in 56 % yield as white needle-like crystals. The structure of this compound was confirmed by X-ray crystallographic analysis.

Scheme 40.



Different aromatic and heteroaromatic aldehydes were investigated under the same reaction conditions (Figure 8). The results showed that electron-poor aldehyde such as 2,4-dichlorobenzaldehyde worked well under this reaction conditions and gave [1,3]-product **105b** in a moderate yield 62%. Likewise, using 2-substituted electron-rich aldehydes such as 2-hydroxy or 2-methoxy benzaldehyde gave a good to moderate yield of the rearrangement products **105c** (59%) and **105d** (35%), respectively. Moreover, carrying out the rearrangement reaction using heteroaromatic aldehydes 2-pyridiencarbox-aldehyde and 2-furfuraldehyde gave product **105e** in 61% (x-ray) and **105f** in 45% yield. Although the ketones were not detected on this system, the [1,3]-products were obtained in good to moderate yield. Moreover, in this system no column chromatography was needed since the rearrangement products precipitated from the reaction mixture.

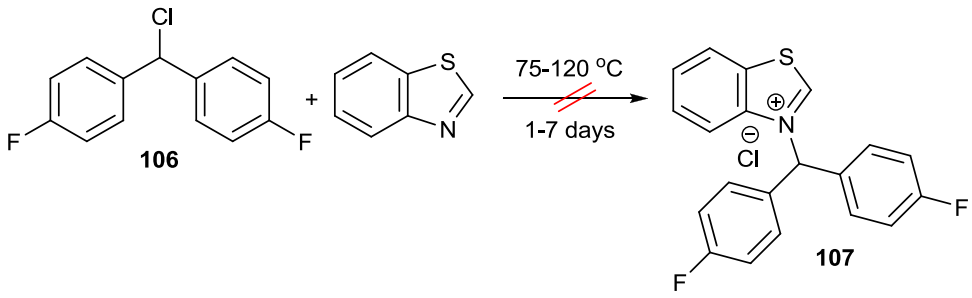
Figure 8.



III.f.2 Rearrangement Using N-(bis(4-fluorophenyl)methyl) thiazolium salt 110

Mixing the commercially available bis(4-fluorophenyl)methyl) chloride **106** and the benzothiazole neat at 75 ^{o}C for 24 h provided only 5% conversion to the product (Scheme 41). The reaction temperature was increased to 120 ^{o}C and the reaction progresses were monitored by ^{1}H NMR for 7 d. Approximately 40% conversion to the product was obtained, which was hard to purify.

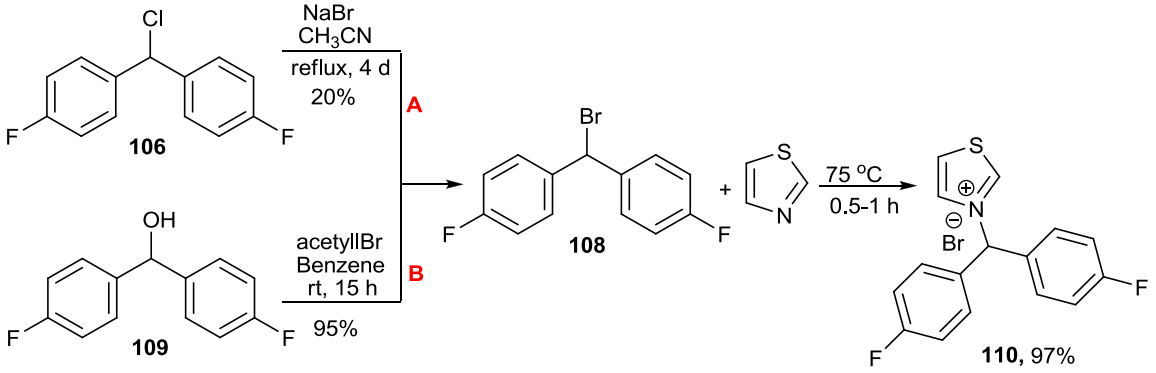
Scheme 41.



We decided then to find another practical way to make the target salt. Therefore, bis(4-fluorophenyl) methyl chloride **106** was converted to methyl bromide **108** (Scheme 42). The initial attempt was by

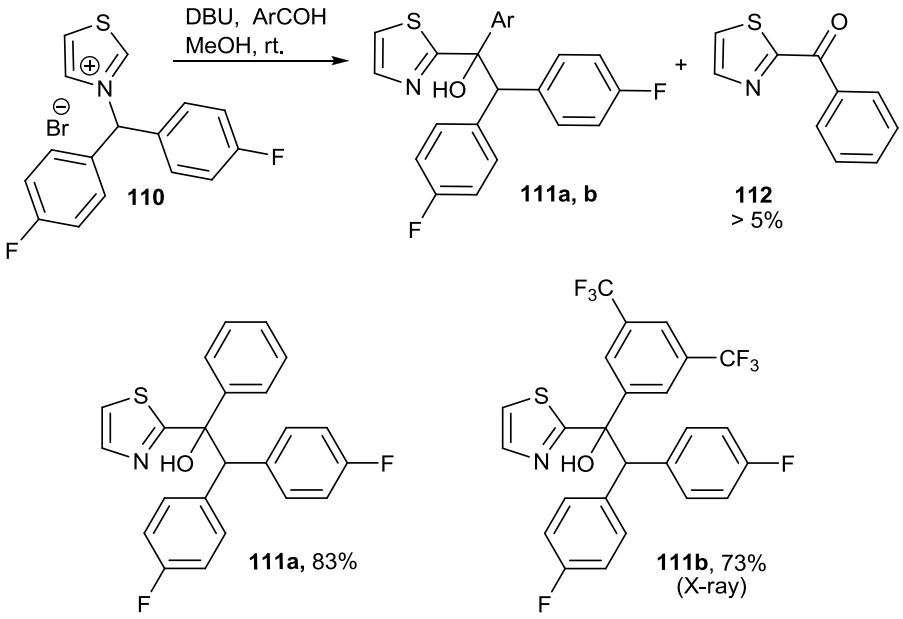
mixing bis(4-fluorophenyl)methyl chloride **106** with NaBr in acetonitrile and refluxing the mixture for 4 d (Route A). This route provided only 20% of the product methyl bromide **108**. A literature search provided a procedure to make such compound starting from the commercially available bis(4-fluorophenyl)methanol **109** (route B).[83] Mixing fluorophenylmethanol **109** and acetyl bromide in benzene at ambient temperature for 6 h produced the desired product **108** in 71% yield. It was later found that increasing the reaction time (15 h) provided 95% yield of the product **108**. To prepare the salt **110**, a mixture of bis(4-fluorophenyl)methyl bromide **108** with thiazole was heated at 75 ^{o}C for 0.5-1 h, until the mixture solidified to obtain salt **110** in 97% yield.

Scheme 42.



With this salt in hand, the conditions of rearrangement reaction were applied by adding the methanolic solution of the salt **110** to a mixture of DBU (2 eq) and benzaldehyde (2 eq) at ambient temperature (Scheme 43). The rearrangement proceeded well with thiazolium salt **110** and provided [1,3]-rearrangement product **111a** in 93% yield within 1 h. Thiazolium ketone **112** was also isolated in less than 5% yield. Thiazolium salt **110** worked also well with very electron-poor aldehyde such as 3,5-bis(trifluoromethyl)benzaldehyde and provided the formal [1,3]-product **111b** in 73% yield within minutes at ambient temperature. Ketone **112** is a well-known compound in literature.[84, 85]

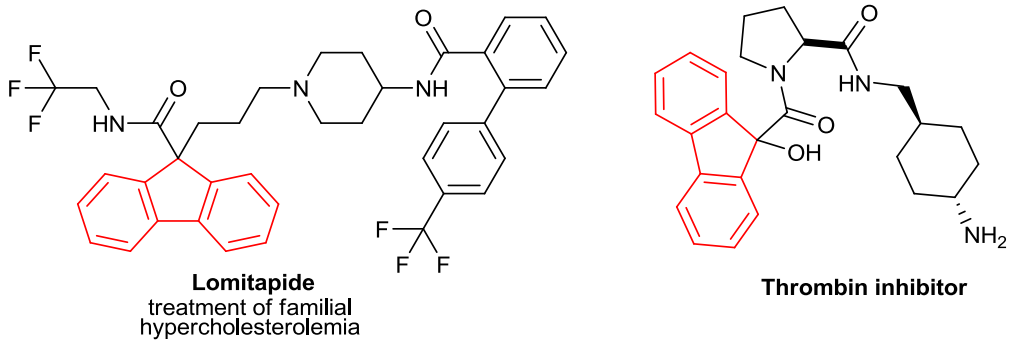
Scheme 43.



III.g. Rearrangement Using N-fluorenyl thiazolium salt 114

Fluorene is used as a precursor to other fluorene derivatives that have important applications.[86-89] For instance, fluorene-9-carboxylic acid is a precursor to pharmaceuticals such as Lomitapide which is used as treatment for familial hypercholesterolemia (Figure 9).[90] Moreover, 9-hydroxyazafluorenes are used as thrombin inhibitors.[91] Therefore, it would be very interesting to include fluorene and study the reactivity of such group in this investigation.

Figure 9.



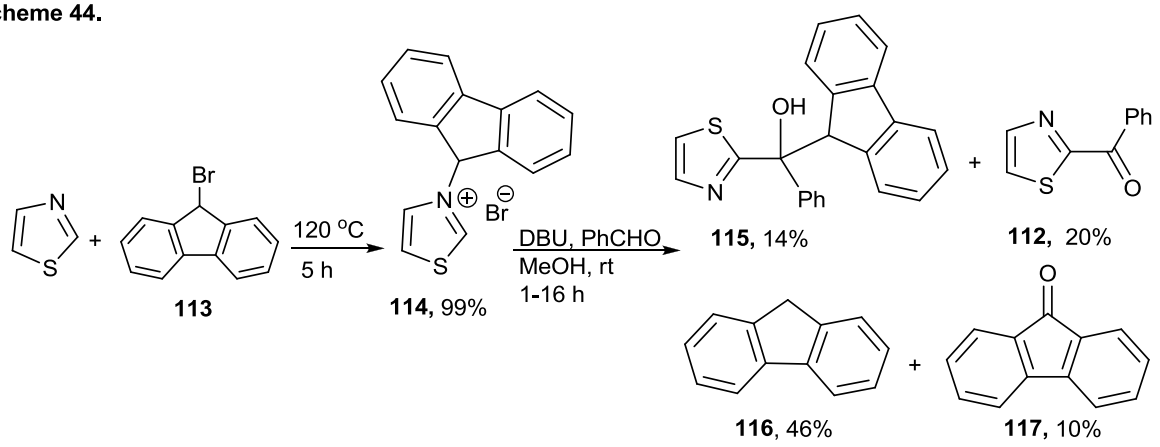
Lomitapide
treatment of familial hypercholesterolemia

Thrombin inhibitor

N-Fluorenyl thiazolium bromide salt **114** was made by mixing the commercially available fluorenyl bromide **113** with thiazole neat and heating the mixture at 120 ^{o}C for 5 h (Scheme 44). Making this salt required high reaction temperatures because the fluorenylbromide crystals are not soluble at lower temperatures. The reaction mixture solidified after 1 h at 120 ^{o}C; however, increasing the reaction time to 5 h increased the yield to obtain salt **114** to approximately quantitative.

The rearrangement reaction of salt **114** was carried out using standard conditions (2 eq DBU, 2 eq benzaldehyde, 0.13 M MeOH, rt). Once the methanolic solution of the salt was added to a mixture of DBU and benzaldehyde, precipitation started to occur in the flask. Three new spots were detected by TLC. After 1 h of the reaction time, the precipitate was isolated by simple filtration, and the three products were separated by column chromatography. The ^{1}H NMR of these products revealed that the precipitate was the [1,3]-rearrangement product **115** which was obtained in 14% yield (Scheme 44). The three spots represented thiazolium ketone **112** (obtained in 20% yield), fluorene **116** (obtained in 46% yield), and fluorenone **117** (obtained in 10% yield). Leaving the reaction mixture to stir at rt for 5 minutes or for 16 h did not change the yield of the [1,3]-product **115**. The rearrangement reaction was performed again with the aldehyde as the limiting reagent (0.5 eq), which increased the yield of the [1,3]-product **115** to 37%, but the other side products were still detected.

Scheme 44.



The formation of these four products are rationalized as follows. After homolytic cleavage of the C-N bond in the Breslow intermediate **118** (Scheme 45), two radical species formed: fluorene radical **119** and phenyl-2-thiazolyl-methanol radical **120**. (i) Recombination of those radical species generates the [1,3]-rearrangement product **115**. (ii) Abstracting hydrogen atom from the OH of phenyl-2-thiazolyl-methanol radical **120** generates the phenyl thiazolium ketone **112** and fluorene **116**. (iii) Fluorenone product **117** could be auto-oxidation product of the fluorenyl radical upon reaction with molecular oxygen or reaction of oxygen with fluorenyl anion generated by reaction with DBU.

We have calculated homolytic bond dissociation enthalpy for Breslow intermediate derived from thiazole and fluorenyl bromide. The remarkably low calculated bond dissociation enthalpy (8.3 kcal/mol) explains the spontaneous fragmentation at ambient temperature in this case (Figure 10). A typical C-N single bond dissociation energy is 73 kcal/mol.[92]

Scheme 45.

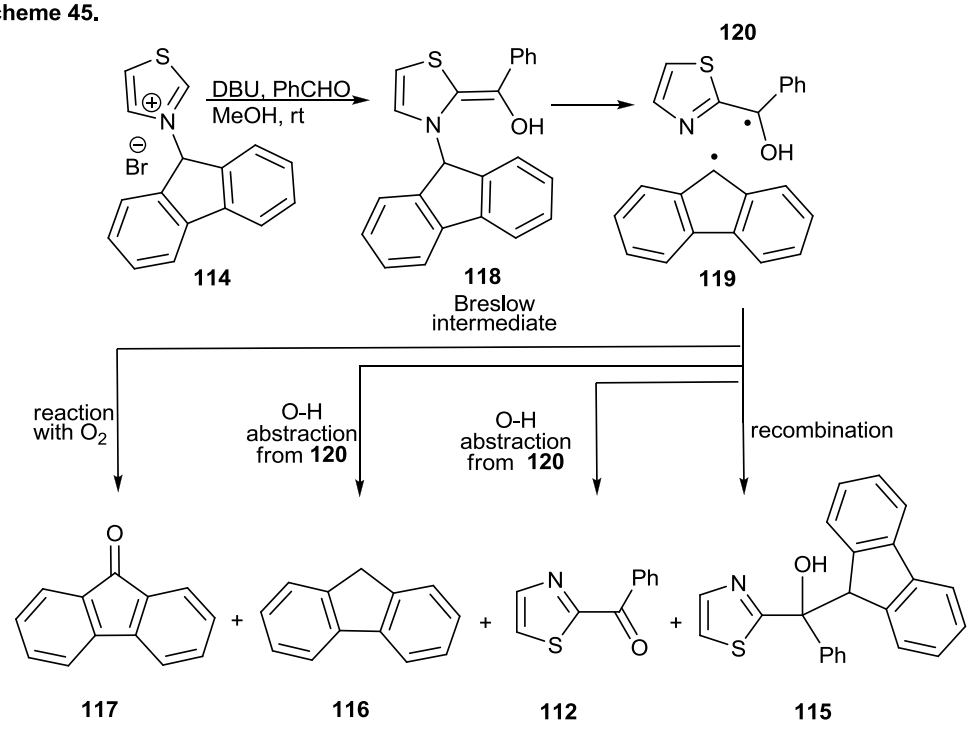
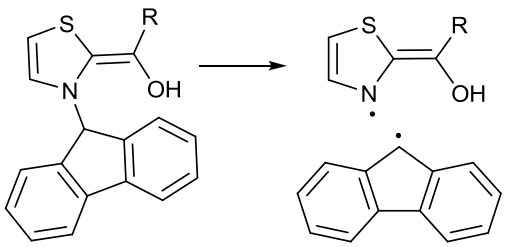


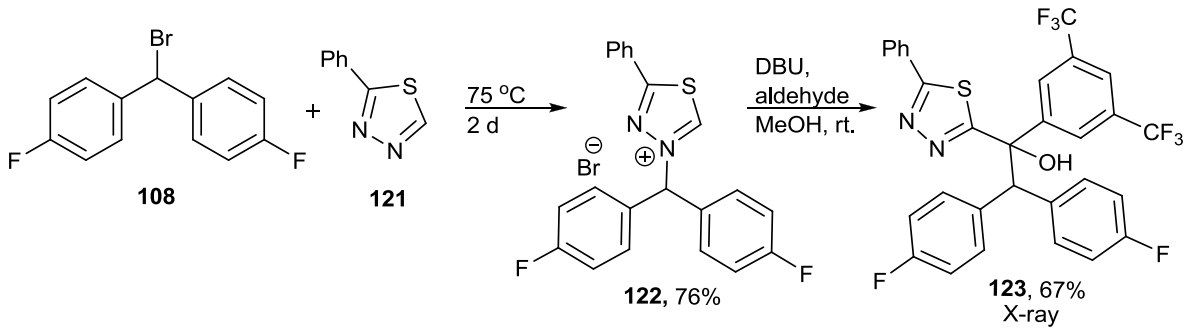
Figure 10.



III.h. Rearrangement Using N-(bis(4-fluorophenyl)methyl)-thiadiazolium bromide salt 122

At this stage of our investigation of the radical reaction of the Breslow intermediate, we became interested to study different azoles and comprehend how general the reaction might be. Hence, thiadiazolium bromide salt **122** (Scheme 46) was synthesized. Mixing bis(4-fluorophenyl)methyl bromide **108** (prepared previously, see Scheme 41) with 5-phenyl-1,3,4-thiadiazole **121** and heating the mixture at 75 ^{o}C for 2 d, provided salt **122** in 76% yield. The rearrangement reaction was performed by adding the dissolved salt in MeOH to a mixture of DBU (2 eq) and aldehyde (2 eq) at rt. The rearrangement reaction proceeded well and provided the [1,3]-rearrangement product **123** in 67% yield at ambient temperature within 9 h.

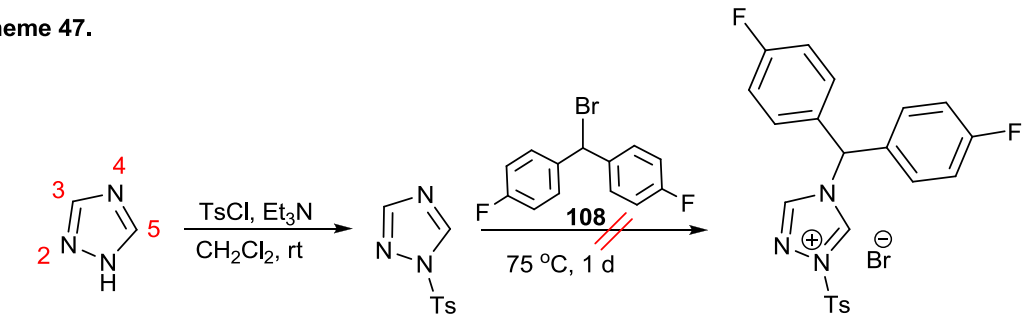
Scheme 46.



III.i. Rearrangement Using 1,4-bis(di(4-fluorophenyl)methyl)-4H-1,2,4-triazolium salt 129

Many reactions of carbonyl compounds utilized NHC catalysts that based on 1,2,4-triazoles.[93-99] Hence, it was important to examine whether such azoles would undergo the radical fragmentation. When we started planning to synthesize a triazolium salt, we hypothesized that placing a tosylate group on N1 and alkylating N4 would make the proton at C5 sufficiently acidic to deprotonate with a weak base. Following a literature procedure, mixing triethylamine with the triazole and tosyl chloride in DCM at ambient temperature, N-tosyl triazole **124** was obtained in 64% yield (Scheme 47).[100] Forming the next step by mixing di(4-fluorophenyl)methyl bromide **108** with compound **124** did not afford the desired product **125**. Consequently, we planned to find an alternative way to make the triazolium salt.

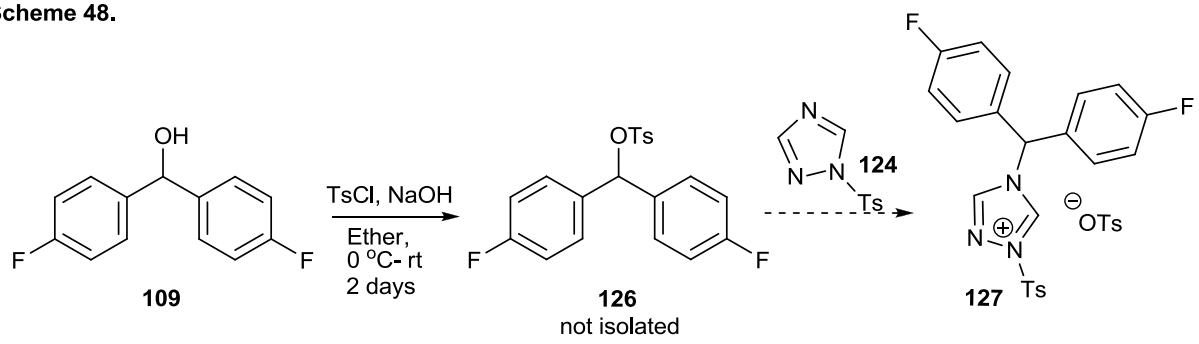
Scheme 47.



1H-1,2,4-triazole **124**, 64% **125**

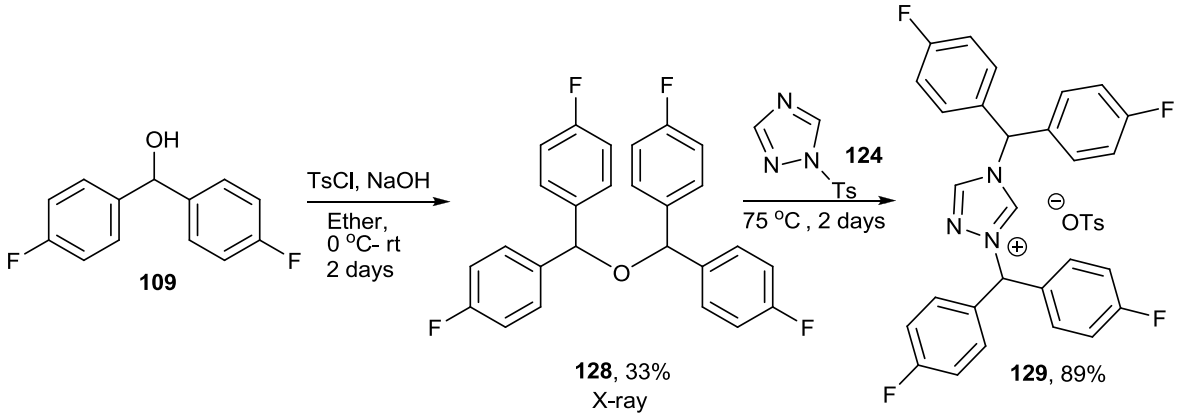
In the alternative route, we planned to form di(4-fluorophenyl)methyl tosylate **126** and use it to make triazolium salt **127** having the OTs group as a counterion (Scheme 48). The commercially available di(4-fluorophenyl)methanol **109** was added to a mixture of tosyl chloride and NaOH in ether at 0 °C. After 2 d, a precipitate formed that was isolated by simple filtration. Purifying the product by column chromategraphy and analyzing it by ^{1}H NMR and ^{13}C NMR revealed that it was not the expected product **126**.

Scheme 48.



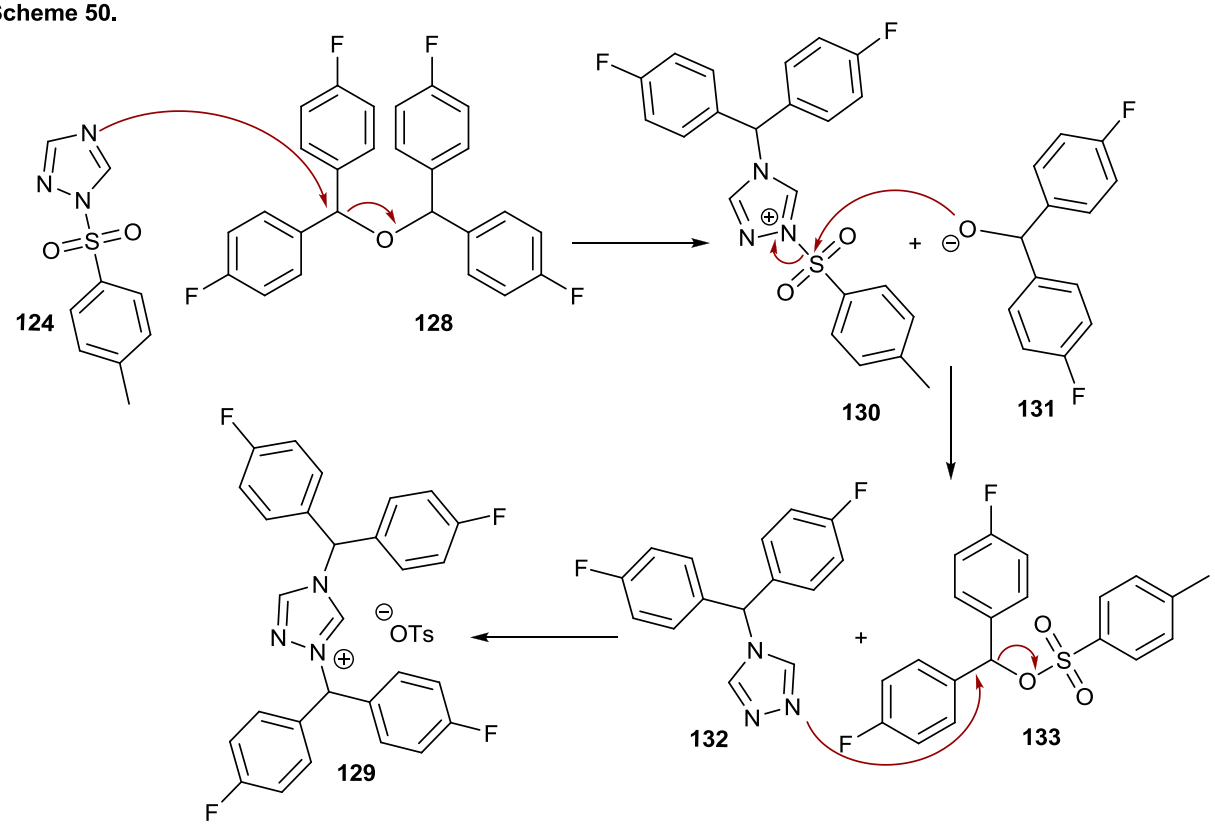
At that point, we could not determine its identity. Subsequent recrystallization and X-ray crystallography structure of the unidentified compound showed that it was symmetric ether **128** (Scheme 49).[101] We decided to use this symmetric ether **128** in the alkylation step. Mixing ether **128** with N-tosyl triazole **124** neat at 75 °C for 2 d afforded triazolium salt **129** in 89% yield.

Scheme 49.



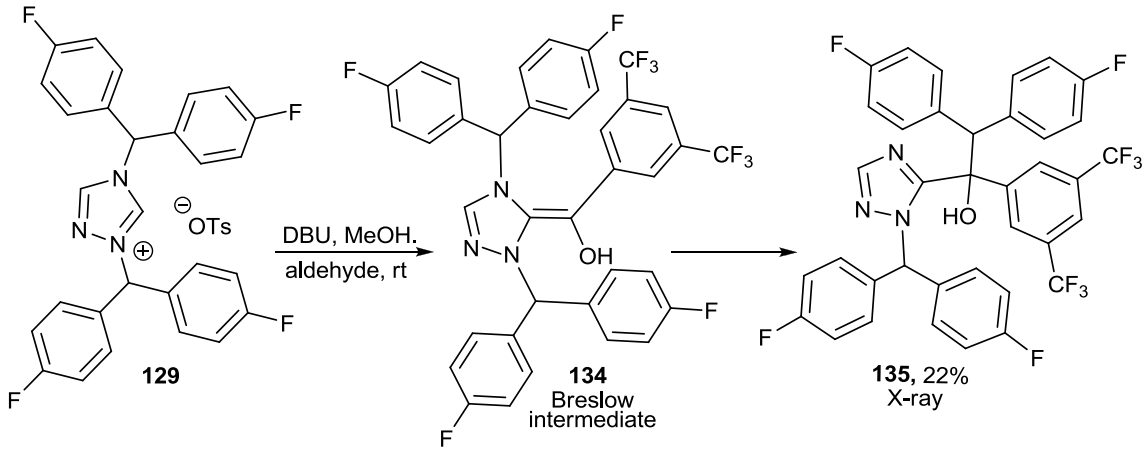
The postulated mechanism for the formation of this salt is described as follows (Scheme 50). The N4 of N-tosyl triazole **124** attacks the carbon of ether **128**, breaking the C-O bond to form compound **130** and alkoxide **131**. Alkoxide **131** then attacks the sulfonate group to form sulfonate **133** and releases N-alkyl triazole **132**. Then, N1 of the triazole **132** attacks the carbon of **133** to form triazolium salt **129** with the tosyl group as a counterion.

Scheme 50.



The rearrangement reaction of triazolium salt **129** using 2 eq of bis (3,5-trifluoromethyl) benzaldehyde and 1.2 eq of DBU produced [1,3]-rearrangement triazole product **135** at ambient temperature (Scheme 51). Fragmentation presumably occurred via Breslow intermediate, which suggests that 1,2,4-triazoles bearing radical stabilizing N-substituents would be poor choices for NHC catalysts in reactions with aldehydes.

Scheme 51.



A plausible mechanism for all above mentioned examples of [1,3]-rearrangement products involve Breslow intermediates. The preliminary data for these [1,3]-products provide strong evidence that Breslow-type intermediates can undergo C-N bond scission to a radical pair which can recombine with high efficiency to form 1,3-rearrangement products. Moreover, increasing the radical stability nature of N-substituents led to greater stabilization of the resulting radical products, which were observed herein on the experimental studies.

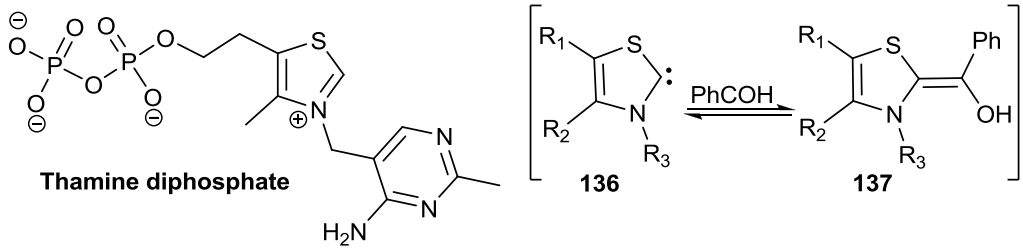
CHAPTER 3

Thiamine (Vitamin B1)

I. INTRODUCTION

Thiamine (vitamin B1) is an essential cofactor in all organisms.[102-104] The active form, thiamine diphosphate (Figure 11), is a coenzyme for a number of important biochemical enzymatic reactions such as pyruvic decarboxylation to form acetaldehyde,[105] transketolase reaction,[106] oxidative decarboxylation,[107] α-ketoglutarate dehydrogenase.[108] Thiamine can also be utilized as an alternative to cyanide to catalyze the formation of benzoin from benzaldehyde.[24] All these thiamine reactions with aldehydes share a key intermediate, which is Breslow intermediate **137**.

Figure 11.



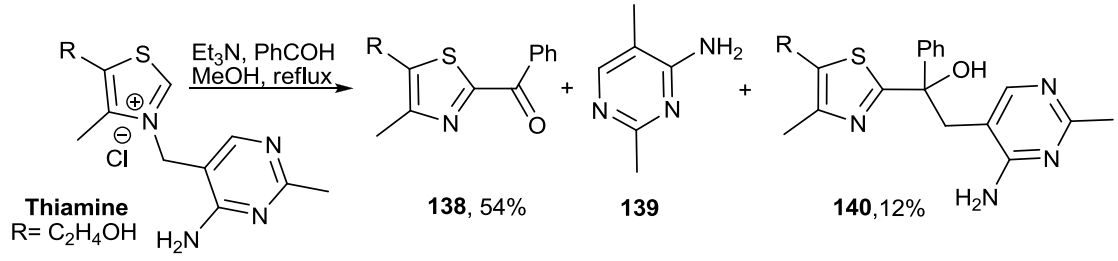
II. BACKGROUND

II.a. Oka Fragmentation

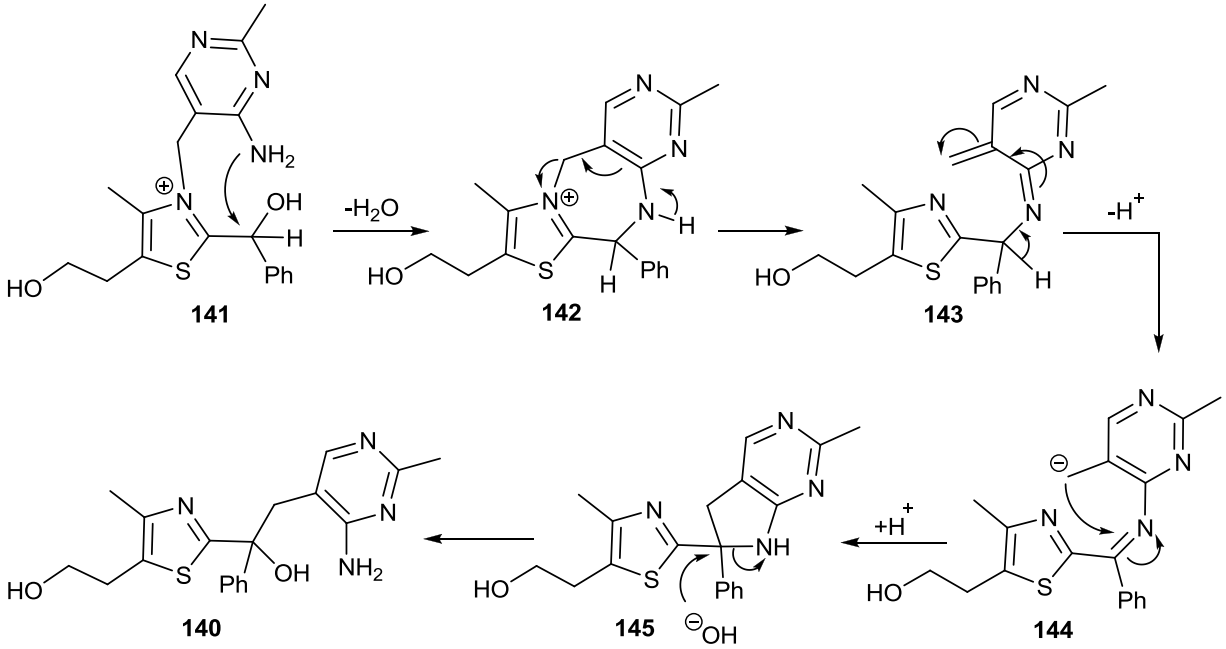
As a part of an investigation of thiamine mechanism with benzaldehyde in non-enzymatic reaction, Oka et al reported in 1970 that treatment of a mixture of thiamine and benzaldehyde with triethylamine in refluxing methanol afforded fragmentation products thiazolyl ketone **138** and pyrimidine **139** along with a small amount of 1,3-rearranged product **140** (Scheme 52).[109] The authors proposed an implausible mechanism to account for the rearrangement product (Scheme 53).[110] They came up with this mechanism because they presumed that 4-amino group in the pyrimidine ring has an essential role for both the cleavage process that lead to the fragmentations **138** and **139**, and the rearrangement process that lead to [1,3]-product **140**. This assumption was made based on experimental results in which the 4-

amino group in thiamin was replaced by hydroxyl group, the reaction failed. This reaction also suffered some limitations, which is only working with aromatic aldehydes.[109]

Scheme 52.



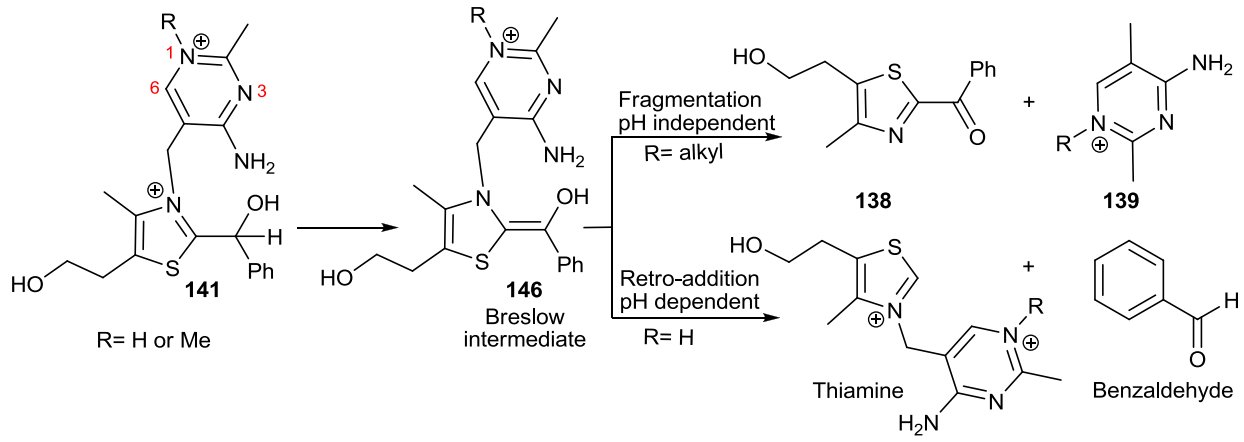
Scheme 53.



II.b. Kluger studies

A few years later, Kluger began to study the so-called Oka fragmentation because the decomposition of the thiamine in non-enzymatic reaction is analogous to the dependent enzyme and has general implications for the mechanism.[111] Over several years, Kluger performed extensive kinetic studies on the Oka fragmentation, although his studies focused exclusively on the formation of the fragmentation products. He did not explicitly address the formation of the [1,3]-rearrangement product. Kluger studies revealed that the fragmentation process occurred via the Breslow intermediate **146** (Scheme 54). He proposed that the decomposition of the adduct of thiamine and benzaldehyde **141** could undergo either of two pathways: (i) a retro-addition process to produce benzaldehyde and thiamine or (ii) a fragmentation process to produce ketone **138** and pyrimidine **139**, depending on the conditions to which adduct **141** was exposed.[112, 113]

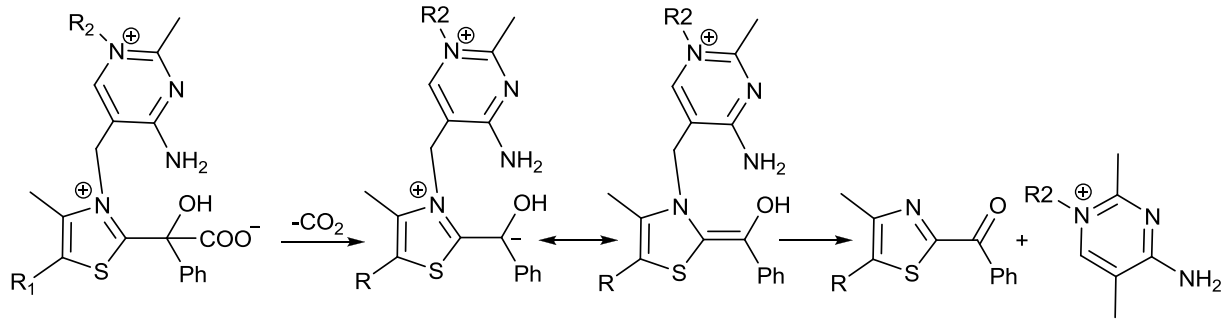
Scheme 54.



In 2004, Kluger postulated that the fragmentation process was promoted by a positive charge at N1 on pyrimidine ring of thiamine. In neutral solution when R= H (protonated at N1), the rate of fragmentation was 1000 times faster than the rate of elimination.[114] However, if R= alkyl group, fragmentation products formed exclusively. In a subsequent publication, he excluded the necessity of the positive charge at N1 of the pyrimidine ring to promote the fragmentation step.[115] He rejected the former conclusion after his studies on the mandelylthiamin (MT) **147** decarboxylation (Scheme 55). Loss of

carbon dioxide from **147** produced the conjugate base **148**, which is a resonance structure with the enamine **146**. The yields of fragmentation products **138** and **139** were similar in both cases (protonated at N1 or methylated at N1) over a wide range of buffer concentrations.

Scheme 55.

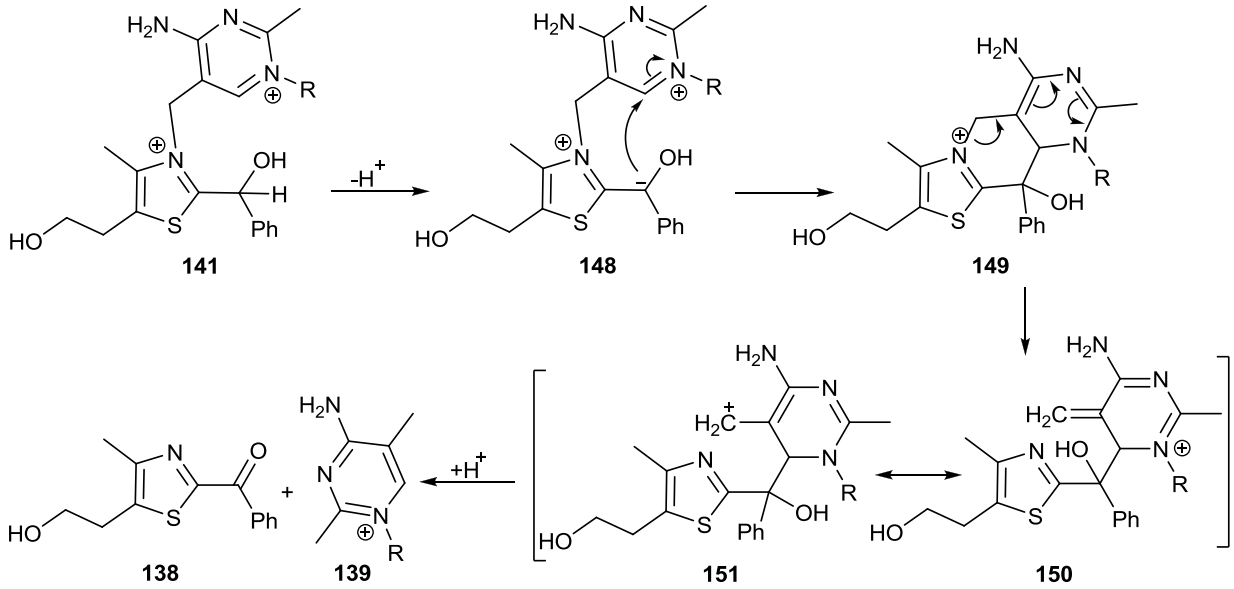


III.c. Proposed Mechanisms of Fragmentation Formation

II.c.1. Stepwise Rearrangement Mechanism

In early studies of Kluger reported in 2000, he proposed a stepwise mechanism to account for the observed fragmentation products.[116] The mechanism involved formation of carbanion intermediate **148** (Scheme 56), followed by **intra**molecular attack of the C2α carbanion at the C6 position of the pyrimidine ring to form cyclic compound **149**. Subsequent cleavage of C-N bound gave the resonance-stabilized cation **151**, which cleaved at C2α-C6 to produce the fragmentation products. As a part of testing this hypothesis, Kluger used azide ion as trapping agent for the cationic intermediate **150**. However, the azidopyrimidine product did not form. Thus, he ruled out the carbocationic intermediates and the stepwise mechanism.

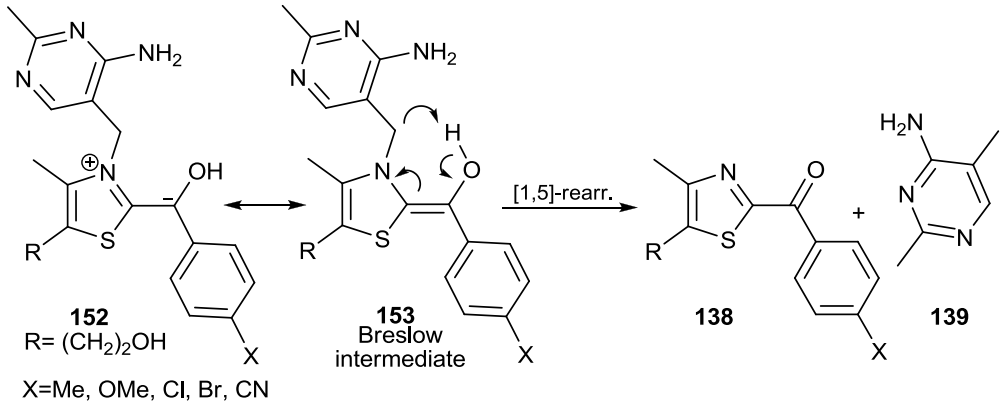
Scheme 56.



II.c.2. [1,5]-Shift Mechanism

Another kinetic study by Kluger in 2000 advocated that the Breslow intermediate must be involved in the fragmentation mechanism.[117] He suggested that a proton transfer from the hydroxyl group of the Breslow intermediate to the methylene bridge might be involved in the mechanism (Scheme 57).

Scheme 57.

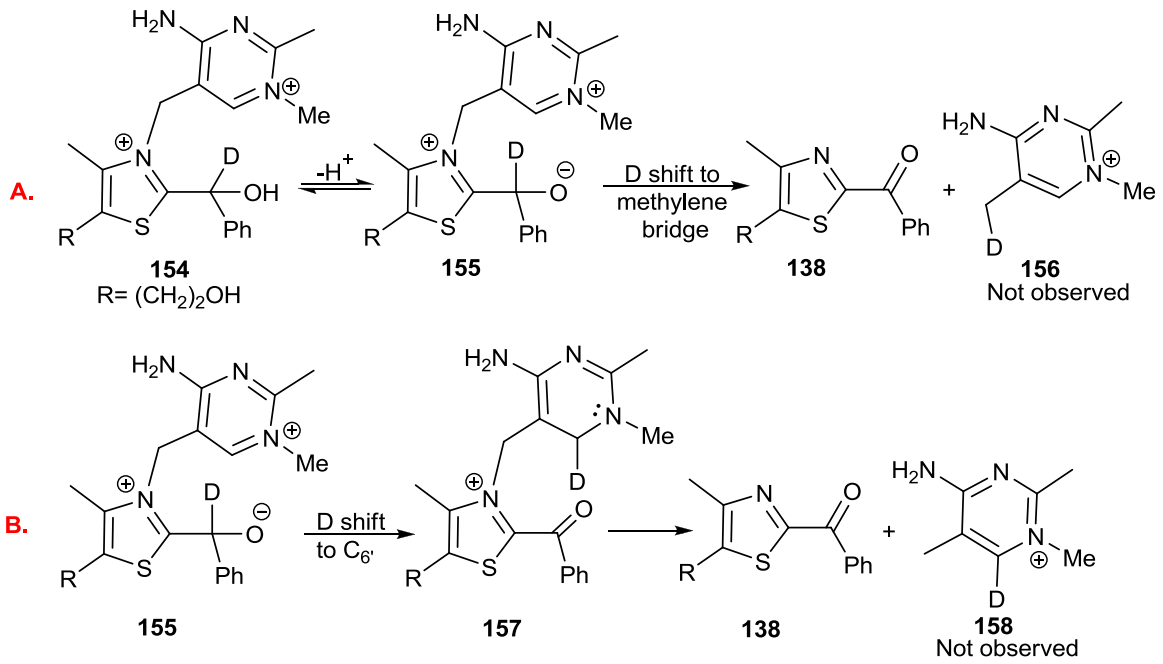


However, in 2002, kinetic studies by Kluger on the effects of para-substituent of the benzaldehyde on the rate of fragmentation process revealed that the fragmentation reaction of the Breslow intermediate **153** is very fast compared to the rate of proton transfer from the hydroxyl group to the methylene bridge.[118] He concluded that C-N cleavage is insensitive to the nature of the substituent on the benzaldehyde and fragmentation products occurred rapidly. Moreover, for this transformation to occur, "the hydroxyl group must rotate out of plane to accommodate the necessary overlaps" which is geometrically impossible.

II.c.3. Internal Hydride Shift Mechanisms

In 2005, Kluger proposed two mechanisms to account for the fragmentation in which an internal hydride transfers from C2α to the methylene bridge (Scheme 58, A) or to C6 on the pyrimidine (Scheme 58, B).[119] However, deuterium-labeling studies revealed that there was no deuterium incorporated into the pyrimidine products **156** and **158** when the reaction was performed in water. He explained that the loss of deuterium must come from the initial reaction. Therefore, Kluger demonstratively ruled out hydride shift mechanisms (A and B).

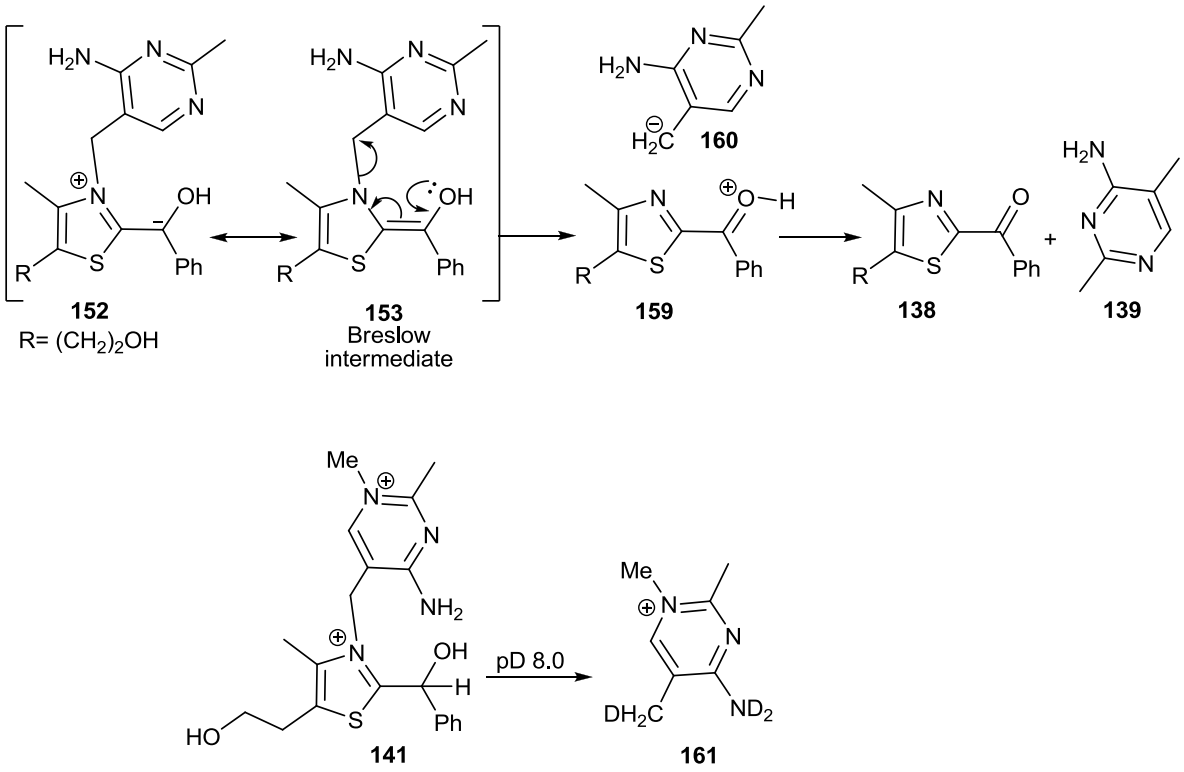
Scheme 58.



II.c.4. Polar Mechanism

In 2004, Kluger proposed an ionic fragmentation of the Breslow intermediate in which the pyrimidine moiety **160** left as a carbanion (Scheme 59).[115] Deuterium labeling study of this fragmentation in deuterium oxide produced monodeuteration of the pyrimidine **161** in which the deuterium here comes from the solvent. In all Kluger mechanisms mentioned above, only Oka fragmentation products were addressed.

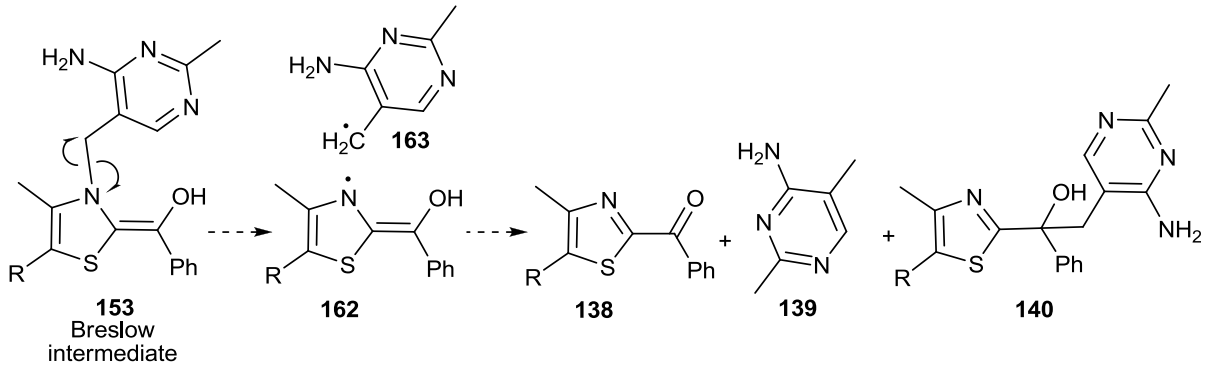
Scheme 59.



III. RESULTS AND DISCUSSION

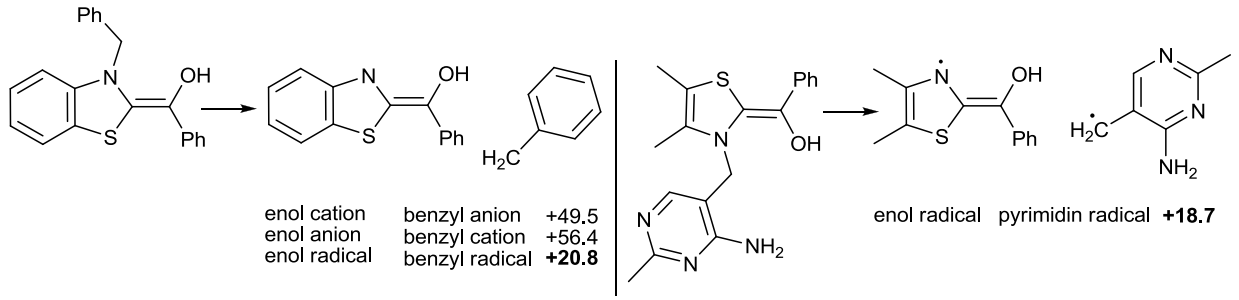
Based on our data that were presented in Chapter 2, we hypothesized that the Breslow intermediate **153** derived from thiamine is mechanistically identical to the radical chemistry observed above. Thus, it is likely to undergo C-N bond scission to produce fragmentation products and [1,3]-rearrangement product (Scheme 60). Kluger deuterium labeling does not rule out the radical mechanism. The hydroxyl proton in the thiazole moiety **159** (see Scheme 59) can be exchanged with the deuterium from the solvent. Abstraction of that deuterium would results the monodeuteration that Kluger observed in pyrimidine moiety **161**. In fact, in one of his papers he stated that a homolytic process might be involved in the mechanism but "we see no route that generates radicals readily".[118] Our results in (Scheme 43 & 44, Ch 2) showed that the [1,3]-rearrangement product could be obtained within a few minutes at rt which presumably accrue via a radical pathway.

Scheme 60.



Calculation of the enthalpy of reaction for the homolysis or heterolysis of the Breslow intermediate (Figure 12) showed that the polar pathways for benzothiazole were at least 2.5 times higher in energy than the radical pathway. Moreover, the calculation showed that the homolysis energy using the thiamine analog was even lower than the calculated benzothiazole homolysis (18.7 kcal/mol vs 20.8 kcal/mol).

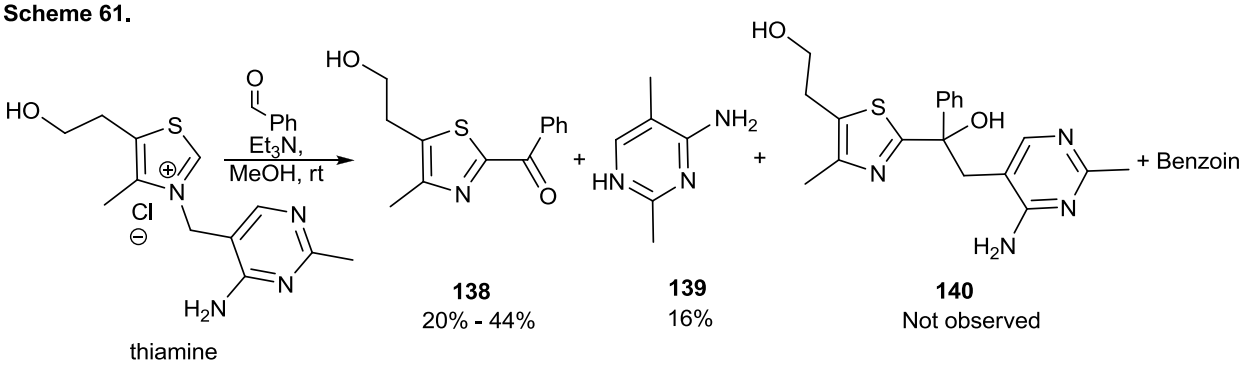
Figure 12.



All values in kcal/mol B3LYP/6-31g* in H_2O, solvent continuum model

Experimentally, we have found that using the Oka conditions (2 eq benzaldehyde, 2 eq Et_3N) in 0.4 M methanol at room temperature provides a mixture of benzoin and fragmentation products ketone **138** and pyrimidine **139** (Scheme 61). However, in other hands the [1,3]-product was not observed. We previously observed a very fast fragmentation reaction in fluorene case (see Scheme 44, Ch 2). All products in fluorene example were fully consistent with a radical pathway and directly analogous to the three products first reported by Oka.[109]

Scheme 61.

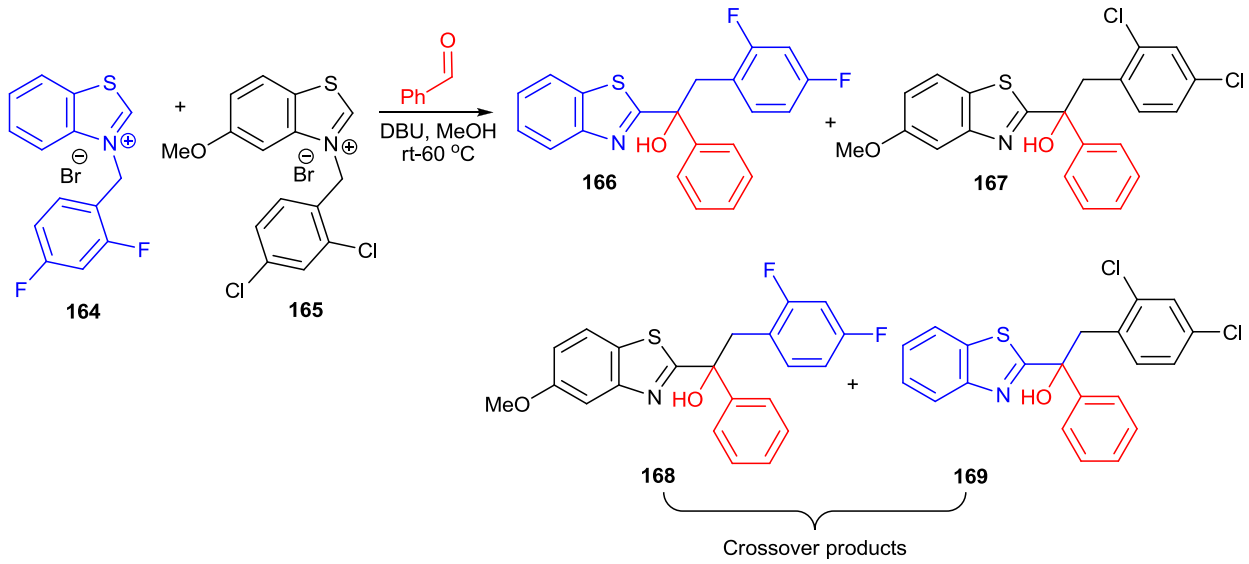


IV. FUTURE WORK

We have strong evidences that the N-substituent radical stabilizing group (RSG) thiazolium derived Breslow intermediate undergoes radical C-N homolysis. We will continue on this project to provide additional evidence for the radical mechanism by using appropriate radical trapping agent, ESR technique analysis, deuterium labeling, or crossover experiment.

Crossover experiments are useful in studying the reaction mechanism. The structure of the result products help to determine whether they formed via self or cross recombination. If a mixture of salts **164** and **165** (Scheme 62) was applied to the reaction conditions (DBU, PhCHO, in MeOH, rt-reflux), a predictable mixture of products would be obtained. These predictable products are **Intra**molecular (self-recombination) products **166** and **167** that formed within the solvent cage, and **inter**molecular (cross-recombination) products **168** and **169** that formed by escaping the radical species from the solvent cage. If crossover products **168** and **169** were obtained, then this would be a conclusive evident for the radical mechanism.

Scheme 62.



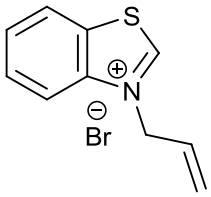
Providing support for the radical mechanism would help resolve the mechanism of the Oka fragmentation and give scientists the necessary information to investigate how the native enzyme avoids the radical fragmentation pathway.

EXPERIMENTAL SECTION

General Information

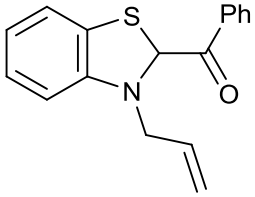
All reactions were carried out under a blanket of nitrogen. No other scrupulous attempt was made to exclude air or moisture. The commercially available compounds were purchased from Sigma-Aldrich Corporation, Alfa Aesar Organics, and TCI America and used as received without additional purification unless otherwise specified. Flash column chromatography employed 230X400 mesh, 60 Å porosity silica gel purchased from Sorbent Technologies. Melting points were taken using Fisher-Jonhs 352 melting point apparatus. All ^{1}H and ^{13}C spectra were obtained on a 400 MHz Bruker Avance spectrometer. X-ray crystallography was carried out on a Bruker SMART X2S spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc.

Purification for all salts was by trituration of the solid with the indicated solvent and then filtration over filter paper. The collected solid was dried under vacuum. Work-up for all the rearrangement products is defined as concentration of the solvent in vacuo and purification directly by column chromatography.

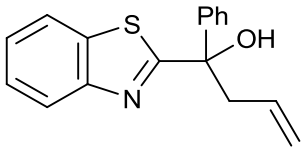


N-Allybenzothiazolium bromide salt 34. Adapted from Hor et al: Yen, S. K.; Koh, L. L.; Huynh, H. V.; Hor, T. S. A. *Dalton Trans*. **2007**, 3952-3958.

A mixture of benzothiazole (3 mL, 27.47 mmol) and allyl bromide (2.85 mL, 32.96 mmol) in a pressure tube was stirred for 1 h at 75 ^{o}C. Trituration of the resulting solid with Et_2O provided salt **36** as a fine brown solid (6.47 g, 92%). Data matched that reported by Hor et al. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.19 (s, 1H), 8.36 (d, J=8.1 Hz, 1H), 8.11 (d, J=8.3 Hz, 1H), 7.88 (t, J=7.4 Hz, 1H), 7.82 (t, J=7.8 Hz, 1H), 6.19 (m, 1H),), 5.87 (d, J=5.3 Hz, 2H), 5.60 (d, J= 17 Hz, 1H), 5.54 (d, J= 10 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.40, 140.27, 131.40, 130.15, 129.10, 128.82, 125.24, 123.16, 117.18, 55.68.



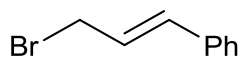
N-Allyl-benzothiazolyl ketone 35. To a mixture of benzaldehyde (0.16 mL, 1.56 mmol) and DBU (0.14 mL, 0.94 mmol) was added dropwise a solution of salt **34** (0.2 g, 0.78 mmol) in MeOH (4 mL) at rt. The mixture was stirred at rt. for 15 h. The reaction was concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give ketone **35** as thick yellow oil (0.165 g, 75%). IR (film) 1679.9 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J= 8.5 Hz, 2H), 7.60 (tt, J= 7.4, 1.2 Hz, 1H), 7.48 (m, 2H), 7.04 (td, J= 7.7, 1.3 Hz, 1H), 6.98 (d, J= 7.5 Hz, 1H), 6.68 (t, J= 7.5 Hz, 1H), 6.56 (d, J= 8 Hz, 1H), 6.25 (s, 1H), 5.92 (m, 1H), 5.31, (d, J= 17 Hz, 1H), 5.22 (d, J= 10 Hz, 1H), 4.15 (dd, J= 17, 5 Hz, 1H), 3.76 (dd, J= 16, 7 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 190.60, 185.26, 147.34, 133.57, 132.85, 128.80, 128.63, 126.36, 121.88, 119.10, 118.67, 108.05, 69.45, 50.85.



Alcohol 29, To a mixture of benzaldehyde (0.16 mL, 1.56 mmol) and DBU (0.14 mL, 0.94 mmol) was added dropwise a solution of salt **34** (0.2 g, 0.78 mmol) in MeOH (4 mL, 0.2M) at rt. The reaction mixture was stirred at rt. for 15 h. Then, a second charge of DBU (0.09 mL, 0.62 mmol) was added to the mixture and heated at 65 ^{o}C for 15 h. The reaction then was concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/ hexane (1:99) to give rearranged product **29** as colorless crystals (0.16 g, 73%). M.P. 55-58 ^{o}C. IR (film) 3456.3 cm^{-1}. Data matched that reported by Troisi et al: Capriati, V.; Florio, S.; Ingrosso, G.; Granito, C.; Troisi, L. *Eur. J. Org. Chem.* **2002**, 478-484.

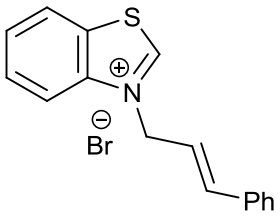
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J=8.2 Hz, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.76 (app d, J=7.9 Hz, 2H), 7.48 (t, J=7.6 Hz, 1H), 7.37 (m, 3H), 7.28 (m, 1H), 5.79 (m, 1H), 5.30 (d, J= 17.2 Hz, 1H), 5.23 (d, J= 10.1 Hz, 1H), 3.66 (s, 1H, exchange with D_2O), 3.46 (dd, J=6.5, 13.6 Hz, 1H), 3.11 (dd, J= 8, 13.8 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 177.82, 153.14, 143.37, 135.67, 132.52, 128.39, 127.67, 125.92, 125.43, 124.95, 123.18, 121.72, 121.31, 77.73, 47.25.

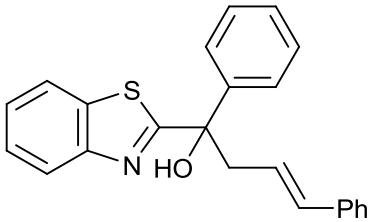


Cinnamyl bromide. This compound is commercially available; however, it is very expensive. In the literature, there is only one procedure proposed by Zhang et al to prepare such compound starting from cinnamylchloride and using Rhodium as a catalyst. Wang, J.; Tong, X.; Xie, X.; Zhang, Z. *Org. Lett*. **2010**, 12, 5370-5373. It was prepared here in a new and convenient way.

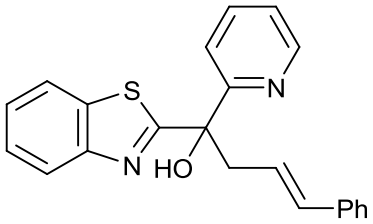
A mixture of cinnamylchloride (3 mL, 21.5 mmol) and sodium bromide (6.65 g, 6.46 mmol) in acetone (15 mL) was heated under reflux for 4 d. The reaction then was filtered to remove solids and the filtrate was concentrated in vacuo to produce cinnamylbromide (3.87 g, 91%) as a light brown oil. Analytical data matched a commercial sample.



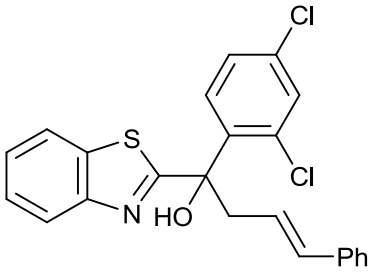
N-Cinnamyl benzothiazolium bromide salt 38. A mixture of benzothiazole (0.34 mL, 3.11 mmol) and cinnamyl bromide (0.74 g, 3.73 mmol) in a pressure tube was stirred for 1.5 h at 75 ^{o}C. Trituration of the resulting solid with Et_2O provided salt **41** as fine tan solid (0.98 g, 95%). M.P. 148 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 1H), 8.36 (d, J= 8 Hz, 1H), 8.24 (d, J= 8.2 Hz, 1H), 7.83 (t, J=7.4 Hz, 1H), 7.73 (t, J=7.8 Hz, 1H), 7.35 (m, 2H), 7.23 (m, 3H), 7.08 (d, J=15.5 Hz, 1H), 6.50 (m, 1H), 6.02 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.25, 140.06, 137.93, 134.79, 131.33, 130.11, 128.92, 128.78, 128.58, 126.92, 125.30, 119.44, 117.37, 55.23.



Alcohol 40a. To a mixture of benzaldehyde (0.12 mL, 1.20 mmol) and DBU (0.13 mL, 0.90 mmol) was added dropwise a solution of salt **38** (0.2 g, 0.60 mmol) in MeOH (4 mL) at rt. After 15 h at rt, a second charge of DBU (0.075 mL, 0.48 mmol) was then added. The reaction mixture was heated at 80 ^{o}C in a sealed tube for 2 d, concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **40a** as yellow crystals (0.12 g, 57%). M.P. 131-133 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J= 8.1 Hz, 1H), 7.86 (d, J= 8.1 Hz, 1H), 7.78 (d, J= 8.1 Hz, 2H), 7.50 (t, J= 7.3 Hz, 1H), 7.40 (m, 3H), 7.30 (m, 6H), 6.65 (d, J= 15.9 Hz, 1H), 6.18 (td, J= 15.3, 7.5 Hz, 1H), 3.77 (s, 1H, exchange with D_2O), 3.65 (dd, J= 13.8, 6.7 Hz, 1H), 3.28 (dd, J= 13.8, 8.1 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.90, 153.22, 143.48, 136.65, 136.22, 135.74, 128.56, 128.47, 127.75, 126.41, 125.98, 125.46, 125.02, 123.53, 123.26, 121.80, 78.19, 46.67. IR (CH_2Cl_2) υmax: 3418.66, 3029.51, 2924.94. Elemental Analysis: calcd for $C_{23}H_{19}NOS$: C 77.28, H 5.36 found C 77.03, H 5.43. The structure was confirmed by X-ray crystallographic analysis.

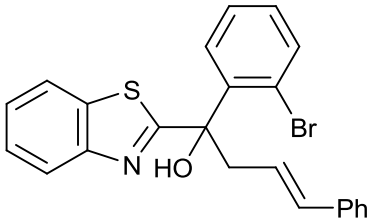


Alcohol 40b. To a mixture of pyridine-2-carboxaldehyde (0.12 mL, 1.20 mmol) and DBU (0.14 mL, 0.93 mmol) was added dropwise a solution of salt **38** (0.2 g, 0.602 mmol) in MeOH (4 mL) at rt. After 15 h at rt, a second charge of DBU (0.07 mL, 0.48 mmol) was then added. The reaction mixture was heated at 60 ^{o}C for 2 d, concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **40b** as white crystals (0.13 g, 60%). M.P. 129-131 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J= 4.9 Hz, 1H), 8.04 (app t, J= 9 Hz, 2H), 7.88 (d, J= 8.0 Hz, 1H), 7.78 (td, J= 7.7, 1.7 Hz, 1H), 7.48 (ddd, J= 8.3, 7.2, 1.2 Hz, 1H), 7.36 (ddd, J = 8.1, 7.2, 1.0 Hz, 1H), 7.25 (m, 5H), 7.17 (m, 1H), 6.99 (s, 1H, exchange with D_2O), 6.47 (dt, J = 15.8, 1.3 Hz, 1H), 6.13 (dt, J= 15.8, 6.8 Hz, 1H), 3.45 (ddd, J= 14.2, 6.9, 1.5 Hz, 1H), 3.36 (ddd, J= 14.2, 7.6, 1.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.65, 158.99, 154.13, 146.91, 137.54, 137.38, 135.61, 134.08, 128.37, 127.15, 126.22, 125.78, 124.77, 123.95, 123.07, 123.00, 121.84, 121.49, 78.24, 46.20. IR (CH_2Cl_2) υmax: 3313.6, 3048.2, 2926.3. Elemental Analysis: calcd for $C_{22}H_{18}N_2OS$: C 73.71, H 5.06 found C 73.42, H 5.10. The structure was confirmed by X-ray crystallographic analysis.

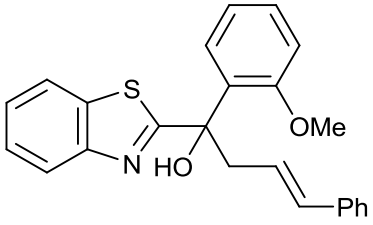


Alcohol 40c. To a mixture of 2,4-dichlorobenzaldehyde (0.21 g, 1.20 mmol) and DBU (0.14 mL, 0.93 mmol) was added dropwise a solution of salt **38** (0.2 g, 0.602 mmol) in MeOH (4 mL) at rt. After 15 h at rt, a second charge of DBU (0.07 mL, 0.48 mmol) was then added. The reaction mixture was heated at 60 ^{o}C for 2 d, concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **40c** as white crystals (0.18 g, 70%). M.P. 132-136 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J= 6.6 Hz, 1H), 7.88 (d, J= 6.5 Hz, 1H), 7.84 (d, J= 8.6 Hz, 1H), 7.51 (app td, J= 8.3, 1.3 Hz, 1H), 7.42 (td, J= 2.2, 1.3 Hz, 2H), 7.35 (dd, J= 8.6, 2.2 Hz, 1H), 7.31 (s, 2H), 7.29 (m, 2H), 7.24 (ddd, J= 8.2, 4.2, 2.6 Hz, 1H), 6.57 (dt, J= 15.9, 1.4 Hz, 1H), 6.22 (dt, J= 15.7,

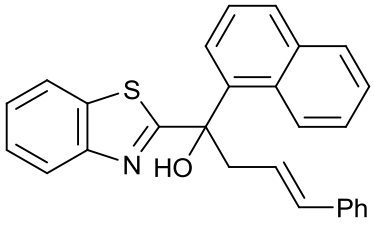
7.2 Hz, 1H), 3.88 (s, 1H, exchange with D_2O), 3.63 (dd, J= 14.5, 7.4 Hz, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 175.89, 152.45, 139.14, 136.90, 135.67, 135.19, 134.81, 133.30, 131.09, 129.67, 128.53, 127.58, 127.11, 126.34, 126.13, 125.46, 123.51, 123.37, 121.81, 77.70, 43.04. IR (CH_2Cl_2) υmax: 3389.55, 3055.18, 1581.68. Elemental Analysis: calcd for $C_{23}H_{17}Cl_2NOS$: C 64.79, H 4.02 found C 64.73, H 4.15. The structure was confirmed by X-ray crystallographic analysis.



Alcohol 40d. To a mixture of 2-bromobenzaldehyde (0.14 mL, 1.20 mmol) and DBU (0.14 mL, 0.93 mmol) was added dropwise a solution of salt **38** (0.2 g, 0.602 mmol) in MeOH (4 mL) at rt. After 15 h at rt, a second charge of DBU (0.07 mL, 0.48 mmol) was then added. The reaction mixture was heated at 60 ^oC for 2 d, concentrated in vacuo, and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **40d** as off-white solid (0.1 g, 38%). M.P. 122-125 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J= 8.2 Hz, 1H), 7.87 (app t, J= 8.2 Hz, 2H), 7.63 (dt, J= 7.8, 1.6 Hz, 1H), 7.51 (tt, J= 9.1, 1.8 Hz, 1H), 7.42 (app t, J= 7.6 Hz, 2H), 7.35 (m, 6H), 6.58 (d, J= 16 Hz, 1H), 6.25 (td, J= 15.0, 7.3 Hz, 1H), 3.96 (s, 1H, exchange with D_2O), 3.75 (dd, J= 14.0, 7.2 Hz, 1H), 3.63 (dd, J= 14.2, 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.57, 152.58, 141.68, 137.06, 135.88, 135.04, 134.90, 129.85, 129.05, 128.48, 127.44, 126.32, 126.01, 125.30, 123.85, 123.49, 122.08, 121.80, 78.66, 43.35. M.P. 123-125 ^oC. IR (CH_2Cl_2) υmax:3330.5, 3064.3, 2934. Elemental Analysis: calcd for $C_{23}H_{18}BrNOS$: C 63.31, H 4.16 found C 63.5, H 4.37.

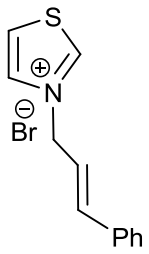


Alcohol 40e. To a mixture of 2-methoxybenzaldehyde (0.145 mL, 1.20 mmol) and DBU (0.14 mL, 0.93 mmol) was added dropwise a solution of salt **38** (0.2 g, 0.602 mmol) in MeOH (4 mL) at rt. After 15 h at rt, a second charge of DBU (0.07 mL, 0.48 mmol) was then added. The reaction mixture was heated at 60 ^{o}C for 2 d, concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **40e** as brown solid (0.09 g, 38%). M.P. 108-110 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J= 8.5 Hz, 1H), 7.88 (d, J= 6.6 Hz, 1H), 7.60 (dd, J= 8.99, 1.6 Hz, 1H), 7.47 (t, J= 7.6 Hz, 1H), 7.36 (m, 6H), 7.18 (t, J= 6.5 Hz, 1H), 7.04 (t, J= 7.6 Hz, 1H), 6.95 (d, J= 8.2 Hz, 1H), 6.51 (d, J= 16 Hz, 1H), 6.36 (td, J= 16, 6.9 Hz 1H), 5.51 (s, 1H, exchange with D_2O), 3.79 (s, 3H), 3.48 (dd, J= 14.5, 6.3 Hz, 1H), 3.41 (dd, J= 14.3, 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.99, 156.71, 153.22, 137.51, 135.58, 133.50, 131.27, 129.47, 128.36, 127.77, 127.06, 126.21, 125.67, 124.91, 124.74, 123.17, 121.65, 121.39, 111.81, 79.02, 55.67, 44.43. IR (CH_2Cl_2) υmax: 3470.75, 3045.5, 1593.64. Elemental Analysis: calcd for $C_{24}H_{21}NO_2S$: C 74.39, H 5.46 found C 73.26, H 5.5.

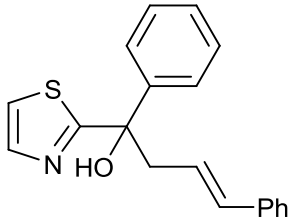


Alcohol 40f. To a mixture of 1-naphthaldehyde (0.16 mL, 1.20 mmol) and DBU (0.14 mL, 0.93 mmol) was added dropwise a solution of salt **38** (0.2 g, 0.602 mmol) in MeOH (4 mL) at rt. After 15 h at rt, a second charge of DBU (0.07 mL, 0.48 mmol) was then added. The reaction mixture was heated at 60 ^{o}C for 2 d, concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **40f** as brown solid (0.1 g, 40%). M.P. 83-85 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J= 8.5 Hz, 1H), 8.11 (d, J= 8.1 Hz, 1H), 7.89 (m, 3H), 7.83 (d, J= 8 Hz, 1H), 7.56 (m, 2H), 7.40 (m, 3H), 7.28 (m, 5H), 6.66 (d, J= 16 Hz, 1H), 6.25 (td, J= 16, 7.3 Hz, 1H), 3.88 (s, 1H, exchange with D_2O), 3.73 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.24, 152.58, 138.29,

136.88, 136.04, 135.79, 134.82, 131.01, 129.99, 129.10, 128.54, 127.63, 126.40, 126.22, 126.08, 126.03, 125.45, 125.22, 124.92, 124.81, 123.77, 123.42, 121.83, 78.81, 45.72. IR (CH_2Cl_2) υmax: 3394.5, 3042.76, 2925.31, 1715.5.

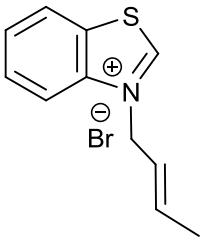


N-Cinnamyl thiazole salt 90. A mixture of thiazole (0.2 mL, 2.82 mmol) and cinnamyl bromide (0.64 g, 3.24 mmol) in a pressure tube was stirred for 12 h at 75 ^{o}C. Trituration of the resulting solid with dichloromethane (DCM) provided salt **90** as fine tan solid (0.55 g, 69.3%). M.P. 108-110 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 8.50 (d, J=3.2 Hz, 1H), 8.26 (s, 1H), 7.42 (m, 2H), 7.31 (m, 3H), 7.04 (d, J=15.7 Hz, 1H), 6.46 (td, J= 14.6, 7.1 1H), 5.70 (d, J=7 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.67, 139.29, 136.41, 134.72, 129.23, 128.85, 127.17, 126.79, 119.46, 57.52.



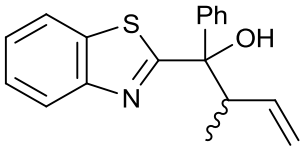
Alcohol 93. To a mixture of benzaldehyde (0.07 mL, 0.71 mmol) and DBU (0.06 mL, 0.42 mmol) was added dropwise a solution of salt **90** (0.1 g, 0.35 mmol) in MeOH (2 mL) at rt. After 15 h at rt, the mixture was degassed and heated at 100 ^{o}C in a sealed tube for 2 d. The mixture was then concentrated and purified by flash chromatography over silica gel with ethyl acetate/hexane (5:95) to give alcohol **93** as white crystals (0.05 g, 46%). M.P. 105-107 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J= 3.2 Hz, 1H), 7.68 (app d, J= 7.8 Hz, 2H), 7.37 (app t, J= 7.3 Hz, 2H), 7.29 (m, 5H), 7.27 (s, 2H), 6.59 (d, J= 15.8 Hz, 1H), 6.05 (td, J= 15.4, 7.3 Hz, 1H), 3.49 (s, 1H, exchange with D_2O and overlapping with CH_2 peak), 3.48 (ddd, J= 13.9, 7.6, 1.3 Hz, 1H), 3.20 (ddd, J= 13.8, 7.8, 1.1 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.17, 144.03, 142.41, 136.69, 135.97, 128.54, 128.40, 127.69, 127.59, 126.34, 125.32, 123.67, 119.66,

77.46, 46.96. IR (CH_2Cl_2) υmax 3377.3 cm^{-1}. Elemental Analysis: calcd for $C_{19}H_{17}NOS$: C 74.23, H 5.57 found C 73.95, H 5.61.



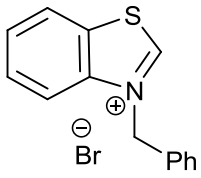
N-Crotyl benzothiazole salt 95. This compound was described by Baldwin et al but no procedure or data were reported in his paper. Baldwin, J. E.; Walker, J. A., *J. Amer. Chem. Soc.* **1974**, 96, 596-7.

A mixture of benzothiazole (1 mL, 9.15 mmol) and crotyl bromide (mixture of *Z/E*, 1:6) (1.13 mL, 10.98 mmol) in a pressure tube was stirred for 3 h at 75 ^{o}C. Trituration of the resulting solid with acetone provided salt **95** in a mixture of Z/E isomers with 1:3 ratio as brown solid (2.42 g, 98%). M.P. 140-143 ^{o}C. Data for the major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.93 (s, 1H), 8.43 (d, J=8.2 Hz, 1H), 8.15 (d, J=8.2 Hz, 1H), 7.85 (t, J=7.1 Hz, 1H), 7.78 (t, J=7.5 Hz, 1H), 6.25 (m, 1H), 5.79 (s, 1H), 5.73 (app s, 2H), 1.73 (d, J=6.2 Hz, 3H).

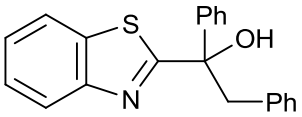


Alcohol 96. To a mixture of benzaldehyde (0.15 mL, 1.48 mmol) and DBU (0.13 mL, 0.88 mmol) was added dropwise a solution of salt **95** (0.2 g, 0.74 mmol) in MeOH (4 mL) at rt. After 38 h at rt, a seconed charge of DBU (0.088 mL, 0.59 mmol) was then added. The reaction mixture was heated at 60 ^{o}C for 3 d, concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give a separable mixture of diastereomers alcohol **96** (dr=1:1.5) as yellow solid (0.07 g, 32%). Data for one of these isomers: M.P. 62-64 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J=8.3 Hz, 1H), 7.82 (d, J=8.4 Hz, 2H), 7.48 (t, J=7.4 Hz, 1H), 7.34 (q, J=7.1 Hz, 3H), 7.25 (s, 2H), 5.9 (ddd, J=7.0, 6.5, 4.1 Hz, 1H), 5.21 (dd, J=10.7, 17.5 Hz, 2H), 3.77 (q, J=7.0 Hz, 1H), 3.70 (s, 1H, exchange with D_2O), 0.97 (d, J=7.0 Hz,

3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.41, 152.87, 143.25, 138.25, 135.53, 128.25, 127.43, 125.90, 125.88, 125.84, 124.90, 123.11, 121.65, 117.43, 80.77, 47.34, 13.80.



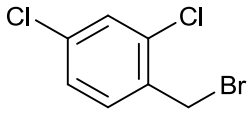
N-Benzylbenzothiazolium bromide 97. Adapted from Hor et al. Yen, S. K.; Koh, L. L.; Hahn, F. E.; Huynh, H. V.; Hor, T. S. A., *Organometallics* **2006,** *25*, 5105-5112. A mixture of benzothiazole (1 mL, 9.15 mmol) and benzyl bromide (1.09 mL, 9.15 mmol) in a pressure tube was stirred for 7 h at 60 ^{o}C. Trituration of the resulting solid with ether provided off-white powder of salt **97** (2.80 g, 100%). M.P. 190-192 ^{o}C. The published data by Hor was taken in 300 MHz NMR. Data presented here was taken in 400 MHz NMR. ^{1}H NMR (400 MHz, CD_3OD) δ 10.57 (s, 1H), 8.4 (d, J= 7.8 Hz, 1H), 8.31 (d, J= 8.2 Hz, 1H), 7.92 (t, J= 7.7 Hz, 1H), 7.85 (t, J= 8 Hz, 1H), 7.54 (m, 2H), 7.46 (m, 3H), 6.13 (s, 2H). 13C NMR (100 MHz, $CDCl_3$) δ 163.58, 140.40, 131.88, 131.81, 129.91, 129.39, 129.27, 128.84, 128.39, 124.80, 117.91, 56.20.



Alcohol 99. Preparation of this compound was reported by Miyashita et al. Suzuki, Y.; Takemura, Y.; Iwamoto, K.-i.; Higashino, T.; Miyashita, A., *Chem. Pharm. Bull.* **1998,** *46*, 199-206. The authors used Grignard reagents in their procedure and started from benzothiazolyl ketone. A different procedure is reported here.

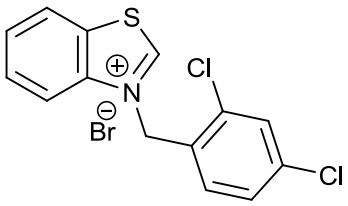
To a mixture of benzaldehyde (0.13 mL, 1.30 mmol) and DBU (0.12 mL, 0.78 mmol) was added dropwise a solution of salt **97** (0.2 g, 0.65 mmol) in MeOH (4 mL) at rt. After 24 h at rt, a second charge of DBU (0.07 mL, 0.52 mmol) was then added. The mixture was then degassed and heated at 100 ^{o}C for 24 h, concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **99** as yellow crystals (0.07 g, 32%). The data presented here was taken in 400 MHz NMR. M.P. 98-101 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J= 8.1 Hz, 1H), 7.83 (d, J= 8 Hz, 1H),

7.77 (app d, J= 7.2 Hz, 2H), 7.49 (dt, J= 7.9, 1.1 Hz, 1H), 7.37 (m, 3H), 7.30 (m, 1H), 7.20 (m, 3H), 7.11 (m, 2H), 4.13 (d, J= 13.6 Hz, 1H), 3.59 (d, J= 13.6 Hz, 1H), 3.36 (s, 1H, exchange with D_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.10, 153.17, 143.63, 135.68, 134.96, 130.83, 128.47, 128.33, 127.68, 127.27, 125.92, 125.49, 124.91, 123.21, 121.74, 78.78, 48.47. IR (CH2Cl2) υmax: 3420.6, 1653.4. The structure was confirmed by X-ray crystallographic analysis.

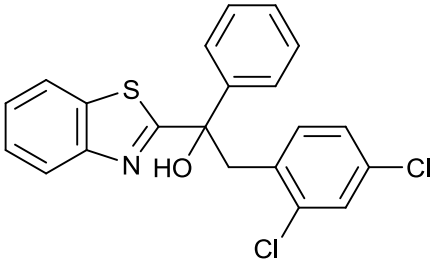


1-(Bromomethyl)-2,4-dichlorobenzene. This compound is commercially available; however, it is very expensive. There is only one reported procedure to prepare the compound starting from chloromethyl 2,4-dichlorobenzene by Kopka el at. Kopka, I.; Li, B.; Hagmann, W. Patent: US2005/0245554 A1, **2005**. However, he used 2 eq of Ceric ammonium nitrate (CAN) in his procedure. A different and easier procedure is reported here.

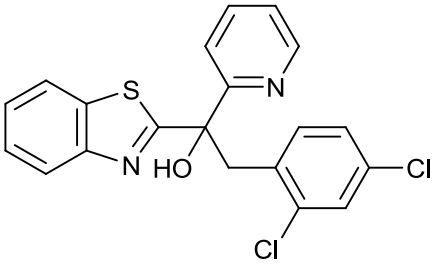
A mixture of chloromethyl 2,4-dichlorobenzene (2 mL, 14.4 mmol) and sodium bromide (4.45 g, 43.21 mmol) in acetone (10 mL) was refluxed for 3 d. The reaction then was filtered to remove solids and the filtrate was concentrated in vacuo to produce 2,4-dichlorobenzyl bromide (3.17 g, 92%) as a colorless liquid. ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.39 (d, J= 8.2 Hz, 1H), 7.25 (dd, J= 8.2, 2.0 Hz, 1H), 4.56 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.17, 135.01, 134.03, 131.98, 129.88, 127.66, 29.53.



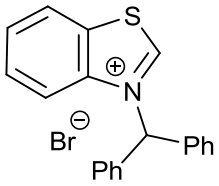
N-(2,4-Dichlorobenzyl)benzothiazolium bromide salt 100. A mixture of benzothiazole (0.76 mL, 6.95 mmol) and 2,4-dichlorobenzyl bromide (2.02 g, 8.41 mmol) in a pressure tube was stirred for 5-6 h at 75 ^{o}C. Trituration of the resulting solid with ether provided off white solid of salt **100** (2.45 g, 93%). M.P. 223-227 ^{o}C. ^{1}H NMR(400 MHz, C_2D_6OS) δ 10.75 (s, 1H), 8.65 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.89 (td, J = 15.7, 7.3 Hz, 2H), 7.81 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 6.27 (s, 2H). ^{13}C NMR (101 MHz, C_2D_6OS) δ 166.95, 140.64, 135.25, 134.39, 132.38, 132.12, 130.35, 130.12, 129.86, 129.04, 128.66, 126.17, 117.59, 53.41.



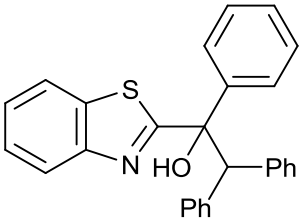
Alcohol 101a. To a mixture of benzaldehyde (0.11 mL, 1.06 mmol) and DBU (0.09 mL, 0.64 mmol) was added dropwise a solution of salt **100** (0.2 g, 0.53 mmol) in MeOH (4 mL) at rt. After 24 h at rt, a second charge of DBU (0.06 mL, 0.42 mmol) was then added. The reaction mixture was heated at 60 ^{o}C for 24 h, concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **101a** as colorless crystals (0.08 g, 38%). M.P. 153-156 ^{o}C. ^{1}H NMR (400 MHz, C_2D_6OS) δ 7.96 (d, J= 8.0 Hz, 1H), 7.83 (d, J= 7.9 Hz, 1H), 7.49 (app d, J= 7.5 Hz, 2H), 7.42 (dt, J= 8.3, 1.2 Hz, 1H), 7.31 (m, 2H), 7.16 (m, 4H), 6.99 (dd, J= 8.3, 2.2 Hz, 1H), 6.73 (s, 1H, exchange with D_2O), 4.01 (d, J= 14.5 Hz, 1H), 3.76 (d, J= 14.6 Hz, 1H). ^{13}C NMR (101 MHz, C_2D_6OS) δ 180.32, 153.25, 143.54, 135.84, 135.43, 134.11, 133.84, 132.07, 128.60, 128.26, 127.80, 126.82, 126.56, 126.16, 125.56, 123.28, 122.66, 78.49, 42.85. IR (CH_2Cl_2) υmax: 3415.83, 2256.44, 1656.55. Elemental Analysis: calcd for $C_{21}H_{15}Cl_2NOS$: C 63.01, H 3.78 found C 61.62, H 3.94. The structure was confirmed by X-ray crystallographic analysis.



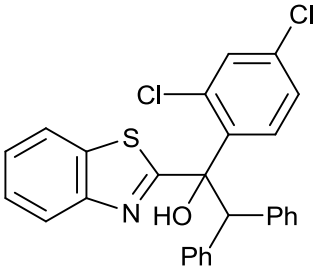
Alcohol 101b. To a mixture of picolinaldehyde (0.1 mL, 1.06 mmol) and DBU (0.09 mL, 0.64 mmol) was added dropwise a solution of salt **100** (0.2 g, 0.53 mmol) in MeOH (4 mL) at rt. After 24 h at rt, a second charge of DBU (0.06 mL, 0.42 mmol) was then added. The reaction mixture was heated at 60 ^{o}C for 24 h, concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **101b** as off-white solid (0.08 g, 37%). M.P. 162-165 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (app d, J= 4.8 Hz, 1H), 8.13 (dd, J= 9.1, 8.0 Hz, 2H), 7.87 (d, J= 7.9 Hz, 1H), 7.74 (td, J= 7.6, 1.7 Hz, 1H), 7.50 (td, J= 7.2, 1.2 Hz, 1H), 7.37 (td, J= 8.0, 1.1 Hz, 1H), 7.24 (m, 3H), 7.02 (dd, J= 8.3, 2.1 Hz, 1H), 6.95 (s, 1H, exchange with D_2O), 4.06 (d, J= 14.2 Hz, 1H), 3.90 (d, J= 14.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.10, 158.35, 153.95, 146.74, 137.37, 136.03, 135.70, 133.12, 132.91, 132.50, 129.02, 126.42, 125.88, 124.93, 123.23, 123.13, 121.98, 121.85, 78.38, 43.73. IR (CH_2Cl_2) υmax: 3352.34, 2930.45, 1683.79. Elemental Analysis: calcd for $C_{20}H_{14}Cl_2N_2OS$: C 59.86, H 3.52 found C 59.73, H 3.59.



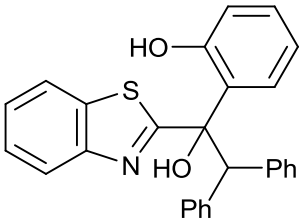
N-Benzhydrylbenzothiazolium bromide salt 102. A mixture of benzothiazole (2 mL, 18.3 mmol) and benzhydryl bromide (5.43 g, 21.9 mmol) in a pressure tube was stirred for 3 h at 75 ^{o}C. Trituration of the resulting solid with ether provided brown solid of salt **102** (6.95 g, 99%). M.P. 197-199 ^{o}C. ^{1}H NMR (400 MHz, CD_3OD) δ 9.87 (s, 1H), 8.47 (app s, 1H), 8.14 (app s, 1H), 7.90 (s, 1H), 7.86 (m, 2H), 7.52 (s, 6H), 7.39 (s, 4H). ^{13}C NMR (101 MHz, CD_3OD) δ 163.26, 140.66, 134.75, 132.23, 129.89, 129.70, 129.53, 129.02, 128.54, 124.88, 118.04, 70.56.



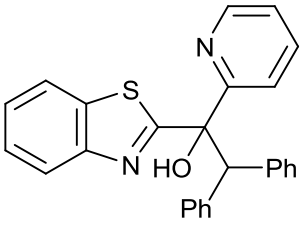
Alcohol 105a. To a mixture of benzaldehyde (0.11 mL, 1.04 mmol) and DBU (0.09 mL, 0.63 mmol) was added dropwise a solution of salt **102** (0.2 g, 0.52 mmol) in MeOH (4 mL) at rt. After 5 h at rt. the reaction mixture was heated at 60 ^{o}C for 8 h. Collecting of the formed precipitation, washing it with MeOH, and recrystallize it with DCM to give alcohol **105a** as white crystals (0.12 g, 56%). M.P. 215-218 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J= 8.1 Hz, 1H), 7.78 (m, 3H), 7.43 (m, 3H), 7.32 (m, 3H), 7.23 (t, J= 7.5 Hz, 2H), 7.13 (m, 7H), 5.68 (s, 1H), 4.11 (s, 1H, exchange with D_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.71, 152.68, 142.78, 140.15, 139.56, 135.72, 130.20, 130.12, 128.39, 128.02, 128.00, 127.12, 126.84, 126.25, 126.09, 125.87, 124.82, 123.12, 121.67, 81.46, 60.25. IR (CH_2Cl_2) υmax: 3411.37, 1642.64. Elemental Analysis: calcd for $C_{27}H_{21}NOS$: C 79.57, H 5.19 found C79.07, H5.28. The structure was confirmed by X-ray crystallographic analysis.



Alcohol 105b. To a mixture of 2,4-dichlorobenzaldehyde (0.18 g, 1.04 mmol) and DBU (0.09 mL, 0.63 mmol) was added dropwise a solution of salt **102** (0.2 g, 0.52 mmol) in MeOH (4 mL) at rt. After 5 h at rt, the reaction mixture was heated at 60 ^{o}C for 12 h. The precipitate was washed with MeOH, and recrystallized with DCM to give alcohol **105b** as white solid (0.16 g, 62%). M.P. 173-175 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (app t, J= 8.5 Hz, 2H), 7.79 (d, J= 7.8 Hz, 1H), 7.53 (app d, J= 7.6 Hz, 2H), 7.45 (td, J= 7.3, 1.2 Hz, 1H), 7.35 (m, 3H), 7.18 (m, 8H), 5.80 (s, 1H), 4.79 (s, 1H, exchange with D_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.96, 151.55, 140.53, 139.58, 139.13, 135.91, 134.12, 132.70, 131.13, 130.96, 130.84, 130.03, 128.14, 128.08, 126.90, 126.45, 125.99, 125.24, 123.29, 121.64, 81.46, 58.53. IR (CH_2Cl_2) υmax: 3535.28, 3062.12, 3027.11. Elemental Analysis: calcd for $C_{27}H_{19}Cl_2NOS$: C 68.07, H 4.02 found C 68.09, H 4.15.

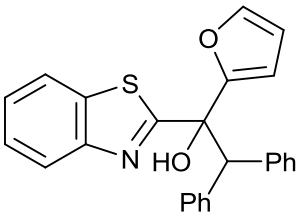


Alcohol 105c. To a mixture of 2-hydroxybenzaldehyde (0.11 mL, 1.04 mmol) and DBU (0.09 mL, 0.63 mmol) was added dropwise a solution of salt **102** (0.2 g, 0.52 mmol) in MeOH (4 mL) at rt. After 5 h at rt, the reaction mixture was heated at 60 ^{o}C for 5 h. The precipitate was washed with MeOH to give alcohol **105c** as white solid (0.1 g, 45%). M.P. 205-209 ^{o}C. ^{1}H NMR (400 MHz, C_2D_6OS) δ 10.80 (s, 1H, exchange with D_2O), 7.92 (t, J= 8.2 Hz, 2H), 7.62 (s, 1H, exchange with D_2O, overlap with d, J= 6 Hz, 1H), 7.52 (d, J= 7.2 Hz, 2H), 7.40 (m, 3H), 7.33 (t, J= 7.4 Hz, 1H), 7.06 (m, 7H), 6.73 (t, J= 7.8 Hz, 1H), 6.67 (d, J= 8.0 Hz, 1H), 5.45 (s, 1H). ^{13}C NMR (101 MHz, C_2D_6OS) δ 181.49, 154.54, 152.81, 142.12, 141.53, 135.14, 130.82, 130.33, 129.18, 129.08, 128.76, 128.12, 127.88, 126.41, 126.37, 126.31, 125.19, 122.80, 122.44, 119.81, 117.28, 82.96, 59.31. IR (CH_2Cl_2) υmax: 3312.17 (s), 3062.88, 2541.56 (br), 1579.20. Elemental Analysis: calcd for $C_{27}H_{21}NO_2S$: C 76.57, 5.0 found C 75.80, H 5.15.

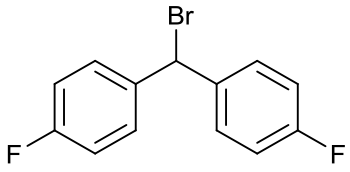


Alcohol 105e. To a mixture of pyridine-2-carboxaldehyde (1 mL, 1.05 mmol) and DBU (0.09 mL, 0.63 mmol) was added dropwise a solution of salt **102** (0.2 g, 0.52 mmol) in MeOH (4 mL) at rt. After 5 h at rt, the reaction mixture was heated at 60 ^{o}C for 8 h. The precipitate was washed with MeOH and recrystallized with DCM to give alcohol **105e** as white crystals (0.13 g, 61%). M.P. 200-203 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (app d, J= 4.8 Hz, 1H), 8.25 (d, J= 8.0 Hz, 1H), 8.00 (d, J= 8.3 Hz, 1H), 7.77 (d, J= 8.0 Hz, 1H), 7.69 (td, J= 7.8, 1.7 Hz, 1H), 7.64 (app d, J= 7.5 Hz, 2H), 7.45 (s, 1H, exchange with D_2O), 7.41 (m, 1H), 7.30 (m, 3H), 7.08 (m, 7H), 5.48 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.14, 158.57, 154.09, 146.23, 140.68, 140.10, 137.19, 135.57, 130.00, 129.92, 127.87, 127.74, 126.24, 125.54, 124.47, 122.89, 122.67, 122.10, 121.70, 81.05, 61.11. IR (CH_2Cl_2) υmax: 3429, 3233, 3061.94, 1591.76. Elemental Analysis: calcd for

$C_{26}H_{20}N_2OS$: C 76.44, H 4.93, N 6.86, S 7.85 found C 76.01, H 4.87, N 6.79, S 7.69. The structure was confirmed by X-ray crystallographic analysis.



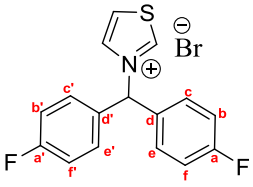
Alcohol 105f. To a mixture of furfuraldehyde (0.08 mL, 1.04 mmol) and DBU (0.09 mL, 0.63 mmol) was added dropwise a solution of salt **102** (0.2 g, 0.52 mmol) in MeOH (4 mL) at rt. After 30 min at rt, the reaction mixture was heated at 60 ^{o}C for 2 days. Precipitation started to form after cooling down the reaction mixture. It was collected and washed with MeOH to give alcohol **105f** as white solid (0.1 g, 48%). M.P. 160-162 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J= 8.1 Hz, 1H), 7.81 (d, J= 7.9 Hz, 1H), 7.45 (m, 5H), 7.34 (m, 2H), 7.22 (m, 3H), 7.10 (m, 3H), 6.34 (app d, J= 3.3 Hz, 1H), 6.23 (m, 1H), 5.32 (s, 1H), 4.52 (s, 1H, exchange with D_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.35, 154.47, 151.86, 142.08, 139.96, 139.28, 135.78, 129.89, 129.59, 128.07, 126.66, 126.63, 125.90, 124.99, 123.14, 121.68, 110.70, 107.75, 79.53, 59.86. IR (CH_2Cl_2) υmax: 3164, 3059.36, 3028.93, 1598.79. Elemental Analysis: calcd for $C_{25}H_{19}NO_2S$: C 75.54, H 4.82 found C 75.32, H 4.93.



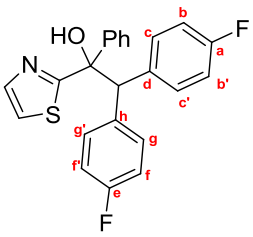
4,4'-(Bromomethylene)bis(fluorobenzene) 108. Adapted from Mohan et al. Padmanaban, M.; Biju, A. T.; Glorius, F. *Org. Lett.* **2011,** *13*, 98-101. A slight modification was made in the procedure. Increasing the reaction time from 6 h to 15 h produced better yield.

Amixture of acetyl bromide (6.04 mL, 81.73 mmol) and di(4-fluorophenyl)methanol **109** (4 g, 18.16 mmol) in benzene (55 mL) was stirred at rt. for 15 h. The reaction mixture was then concentrated in vacuo,

washed with $NaHCO_3$ (25 mL x 2), brine (45 mL), and extracted with ether (25 mL x 2). The collected organic layer was dried over $MgSO_4$ and the filtrate was concentrated in vacuo to provide compound **108** (4.89 g, 95%) as tan oil. Data matched to that reported by Mohan.

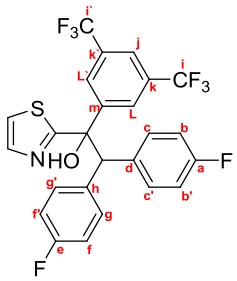


N-(Di(4-fluorophenyl)methyl)thiazolium bromide salt 110. A mixture of thiazole (3 mL, 4.22 mmol) and compound **108** (1.41 g, 4.98 mmol) in a pressure tube was stirred for 2 h at 75 ^{o}C. Trituration of the resulting solid with ether provided tan solid of salt **110** (1.55 g, 99%). M.P. 220-223 ^{o}C. ^{1}H NMR (400 MHz, C_2D_6OS) δ 10.19 (s, 1H), 8.58 (dd, J= 3.8, 1.3 Hz, 1H), 8.48 (dd, J= 3.5, 2.3 Hz, 1H), 7.82 (s, 1H), 7.37 (m, 8H). ^{13}C NMR (101 MHz, C_2D_6OS) δ 162.85 (d, $^{1}J_{CF}$= 246.5 Hz, $C_{a/a`}$), 160.63, 136.97, 132.80 (d, $^{4}J_{CF}$= 3 Hz, $C_{d/d`}$), 131.32 (d, $^{3}J_{CF}$= 8.6 Hz, $C_{c/c`}$, $C_{e/e`}$), 128.70, 116.75 (d, $^{2}J_{CF}$= 21.9 Hz, $C_{b/b`}$, $C_{f/f`}$), 69.71.

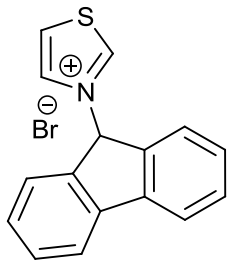


Alcohol 111a. To a mixture of benzaldehyde (0.11 mL, 1.08 mmol) and DBU (0.09 mL, 0.65 mmol) was added dropwise a solution of salt **110** (0.2 g, 0.54 mmol) in MeOH (4 mL) at rt. After 1-2 h at rt, the reaction was concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give product **111a** as a light pink solid (0.18 g, 84%). M.P. 120-122 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (app d, J= 8.0 Hz, 2H), 7.62 (d, J= 3.3 Hz, 1H), 7.34 (m, 2H), 7.26 (m, 4H), 7.17 (m, 2H), 6.86 (td, J= 17.7, 8.7 Hz, 4H), 5.43 (s, 1H), 4.10 (s, 1H, exchange with D_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.44, 161.65 (d, $^{1}J_{CF}$= 246 Hz, C_a), 161.32 (d, $^{1}J_{CF}$= 245.4 Hz, C_e), 143.13 (Ar), 141.59, 135.86 (d, $^{4}J_{CF}$= 3.3 Hz, C_d), 135.47 (d, $^{4}J_{CF}$= 3 Hz, C_h), 131.53 (d, $^{3}J_{CF}$= 7.6 Hz, $C_{c/c`}$), 131.49 (d, $^{3}J_{CF}$= 8.1 Hz, $C_{g/g`}$), 128.19 (Ar), 127.26 (Ar), 125.76 (Ar), 119.93, 115,09 (d, $^{2}J_{CF}$= 20.8 Hz, $C_{b/b`}$), 114.89 (d, $^{2}J_{CF}$= 20.7 Hz, $C_{f/f`}$), 81.19,

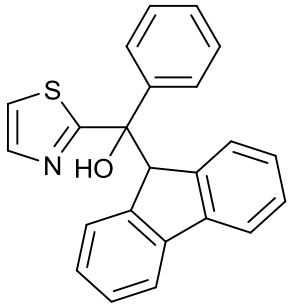
59.70. IR (CH_2Cl_2) υmax: 3231, 3069.54, 2925.21, 1958.86, 1892.24, 1737.8, 1649.19, 1602.45. Elemental Analysis: calcd for $C_{23}H_{17}F_2NOS$: C70.21, H 4.36 found C 70.36, H 4.33.



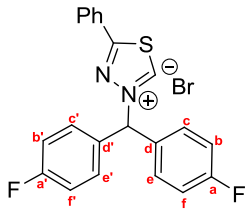
Alcohol 111b. To a mixture of 3,5-bis(trifluoromethyl) benzaldehyde (0.18 mL, 1.08 mmol) and DBU (0.09 mL, 0.65 mmol) was added dropwise a solution of salt **110** (0.2 g, 0.54 mmol) in MeOH (4 mL) at rt. After 15 minutes at rt, the reaction was concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **111b** as colorless crystals (0.22 g, 73%). M.P. 139-142 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 2H), 7.76 (d, J= 3.2 Hz, 1H), 7.64 (s, 1H), 7.35 (app dd, J= 8.8, 5.4 Hz, 2H), 7.28 (d, J= 3.0 Hz, 1H), 7.21 (dd, J= 8.7, 5.3 Hz, 2H), 6.91 (app t, J= 8.6 Hz, 2H), 6.85 (app t, J= 8.7 Hz, 2H), 5.49 (s, 1H), 4.03 (s, 1H, exchange with D_2O). ^{13}C NMR (101 MHz, CD_3OD) δ 177.34, 161.68 (d, $^1J_{CF}$= 244 Hz, C_a), 161.58 (d, $^1J_{CF}$= 244 Hz, C_e), 147.11 (Ar), 142.36, 135.97 (d, $^4J_{CF}$=3.3, C_d), 135.75 (d, $^4J_{CF}$= 3.4, C_h), 131.60 (d, $^3J_{CF}$= 8 Hz, $C_{c/c`}$, $C_{g/g`}$), 130.40 (q, $^2J_{CF}$= 33.2 Hz, $C_{k/k`}$), 126.97 (q, $^3J_{CF}$= 3.7 Hz, $C_{L/L`}$), 123.42 (q, $^1J_{CF}$= 272 Hz, $C_{i/i`}$), 120.32 (pent, $^3J_{CF}$= 3.8 Hz, $C_j$), 119.59, 114.11 (d, $^2J_{CF}$= 21.3 Hz, $C_{b/b`}$), 113.96 (d, $^2J_{CF}$= 21 Hz, $C_{f/f`}$), 81.07, 61.52. IR (CH_2Cl_2) υmax: 3269.40, 1736.55, 1605.44. Elemental Analysis: calcd for $C_{25}H_{15}F_8NOS$: C 56.71, H 2.86 found C 56.91, H 2.90. The structure was confirmed by X-ray crystallographic analysis.



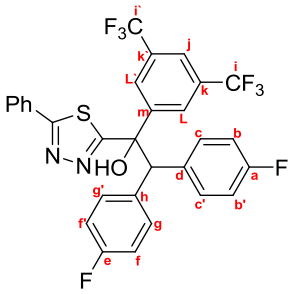
N-(9H-fluorenyl)-thiazolium bromide salt 114. A mixture of thiazole (0.17 mL, 2.39 mmol) and 9-bromo-9H-fluorene **113** (0.7 g, 2.87 mmol) in a pressure tube was stirred for 3 h at 120 ^{o}C. Trituration of the resulting solid with ether provided tan salt **114** (0.77 g, 99%). M.P. 222-225 ^{o}C. ^{1}H NMR (400 MHz, CD_3OD) δ 10.48 (s, 1H), 8.27 (s, 1H), 8.03 (s, 1H), 7.97 (m, 2H), 7.60 (m, 4H), 7.43 (m, 2H), 7.10 (s, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 161.09, 140.90, 140.04, 135.12, 131.13, 129.09, 128.90, 126.09, 121.70, 67.67.



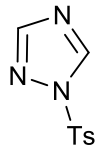
Alcohol 115. To a mixture of benzaldehyde (0.12 mL, 1.21 mmol) and DBU (0.11 mL, 0.73 mmol) was added dropwise a solution of salt **114** (0.2 g, 0.60 mmol) in MeOH (4.6 mL) at rt. After 5 minutes at rt, precipitation started to occur. The precipitate was collected and washed with MeOH to give alcohol **115** as tan solid (0.03 g, 14%). M.P. 126-129 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.89 (d, J= 7.4 Hz, 2H), 7.74 (dd, J= 12.0, 7.7 Hz, 2H), 7.37 (m, 6H), 7.06 (t, J= 7.3 Hz, 1H), 6.96 (t, J= 7.5 Hz, 1H), 6.32 (d, J= 7.3 Hz, 1H), 6.14 (d, J= 7.4 Hz, 1H), 5.49 (s, 1H), 2.64 (s, 1H, exchange with D_2O). ^{13}C NMR (101 MHz, CDCl3) δ 177.68, 143.10, 142.81, 142.62, 142.26, 141.73, 141.60, 128.31, 128.25, 128.00, 127.82, 126.95, 126.55, 126.52, 126.32, 125.74, 119.87, 119.79, 119.56, 80.44, 58.40. IR (CH_2Cl_2) υmax: 3451.53, 3065.8. Elemental Analysis: calcd for $C_{23}H_{17}NOS$: C 77.72, H 4.82 found C 77.06, H 4.81.



N-(Di(4-fluorophenyl)methyl)-5-phenyl-1,3,4-thiadiazolium bromide salt 122. A mixture of 5-phenyl-1,3,4-thiadiazole **121** (0.4 g, 2.46 mmol) and compound **108** (0.83 g, 2.96 mmol) in a pressure tube was stirred for 2 d at 75 ^{o}C. Trituration of the resulting solid with ether provided tan solid of salt **122** (0.83 g, 76%). M.P. 101-105 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.75 (s, 1H), 8.80 (s, 1H), 7.89 (d, J= 7.4 Hz, 2H), 7.64 (m, 5H), 7.55 (m, 2H), 7.08 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.35, 165.20, 163.11 (d, $^{1}J_{CF}$= 250 Hz, $C_{a/a`}$), 134.23, 131.37 (d, $^{4}J_{CF}$= 3.3 Hz, $C_{d/d`}$), 131.07 (d, $^{3}J_{CF}$= 8.5 Hz, $C_{c/c`}$, $C_{e/e`}$), 129.99 (Ar), 128.01(Ar), 126.35 (Ar), 116.12 (d, $^{2}J_{CF}$= 21.8 Hz, $C_{b/b`}$, $C_{f/f`}$), 72.12.

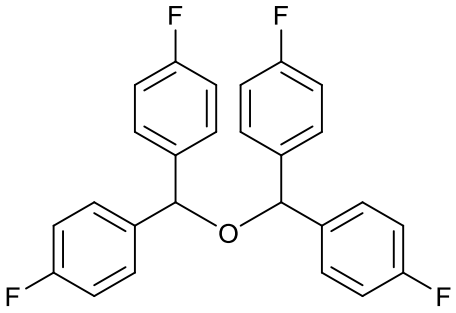


Alcohol 123. To a mixture of 3,5-bis(trifluoromethyl) benzaldehyde (0.15 mL, 0.90 mmol) and DBU (0.08 mL, 0.54 mmol) was added dropwise a solution of salt **122** (0.2 g, 0.45 mmol) in MeOH (3.3 mL) at rt. After 9 h at rt, the reaction mixture was concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give product **123** as white crystals (0.16 g, 67%). M.P. 160-163 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 2H), 7.89 (d, J= 7.4 Hz, 2H), 7.67 (s, 1H), 7.47 (m, 3H), 7.39 (dd, J= 8.7, 5.3 Hz, 2H), 7.33 (dd, J= 8.7, 5.3 Hz, 2H), 6.97 (t, J= 8.6 Hz, 2H), 6.87 (t, J= 8.6 Hz, 2H), 5.66 (s, 1H), 4.01 (s, 1H, exchange with D_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.19, 170.22, 162.16 (d, $^{1}J_{CF}$= 248 Hz, C_a), 161.69 (d, $^{1}J_{CF}$= 247 Hz, C_e), 144.55 (C_m), 134.05 (d, $^{4}J_{CF}$=3.2 Hz, C_d), 133.20 (d, $^{4}J_{CF}$=2.6 Hz, C_h), 131.65 (d, $^{3}J_{CF}$= 8.3 Hz, C_g/$_{g`}$), 131.58, 131.54 (q, $^{2}J_{CF}$=33.4 Hz, $C_k$/$_{k`}$), 131.26 (d, $^{3}J_{CF}$= 7.8 Hz, C_c/$_{c`}$), 129.50 (app s, $C_L$/$_{L`}$), 129.25, 127.86, 126.38, 123.06 (q, $^{1}J_{CF}$= 273 Hz, C_i/$_{i`}$), 121.56 (pent, $^{3}J_{CF}$= 3.6 Hz, $C_J$), 116.10 (d, $^{2}J_{CF}$= 21.3 Hz, $C_b$/$_{b`}$), 115.53 (d, $^{2}J_{CF}$= 21.3 Hz, C_f/$_{f`}$), 79.99, 59.30. IR (CH_2Cl_2) υmax: 3389.63, 3040.81, 2921.50, 1604.90. Elemental Analysis: calcd for $C_{30}H_{18}F_8N_2OS$: C 59.41, H 2.99 found C 59.32, H 3.05. The structure was confirmed by X-ray crystallographic analysis.

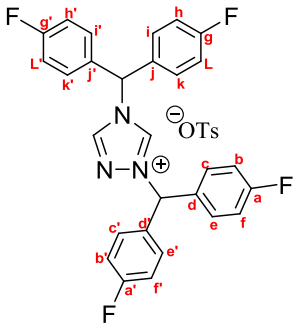


1-Tosyl-1H-1,2,4-triazole 124. Adapted from Ho et al. Law, H.; Baussanne, I.; Garcia Fernandez, J. M.; Defaye, J., *Carbohydr. Res.* **2003,** *338*, 451-453.

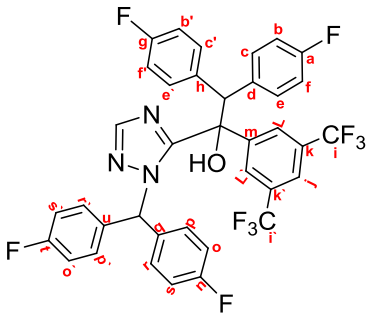
To a mixture of 1,2,4-triazole (2 g, 28.95 mmol) and triethylamine Et_3N (4.44 mL, 31.85 mmol) in DCM (20 mL) was added dropwise a solution of *p*-toluenesulfonyl chloride (6.07 g, 31.85 mmol) in DCM (38 mL) at 0 ^oC. After 24 h at rt, the reaction mixture was filtered to remove the solids and washed with H_2O three times. The collected organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography over silica gel with ethyl acetate/hexane (5:95) to provide product **124** as white crystals (4.16 g, 64%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.02 (s, 1H), 7.97 (t, J=8.12 Hz, 2H), 7.39 (t, J=7.94 Hz, 2H), 2.45 (d, J=4.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.23, 147.27, 144.52, 132.65, 130.41, 128.74, 21.85.



Bis(di(4-fluorophenyl)methyl) ether 128. To a solution of di(4-fluorophenyl)methanol **109** (3 g, 13.62 mmol) and *p*-toluenesulfonyl chloride (2.59 g, 13.62 mmol) in diethyl ether (20 ml) was slowly added sodium hydroxide NaOH (1.52 g, 38.14 mmol) at 0 ^oC. After 2 d at rt, the reaction mixture was filtered to remove the solids and the filtrate was concentrated in vacuo. The residue was purified by column chromatography over silica gel with ethyl acetate/hexane (1:99) to give product **128** as white crystals (1.87 g, 33%). Data matched to that reported by Brahmachari et al. Brahmachari, G.; Banerjee, B., *Org. Med. Chem. Lett*. **2013**, 3, 1-7 pp.

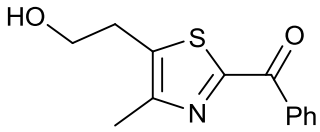


1,4-Bis(di(4-fluorophenyl)methyl)-4H-1,2,4-triazolium tosylate salt 129. A mixture of tosylate triazole **124** (0.28 g, 1.25 mmol) and ether **128** (0.63 g, 1.50 mmol) in a pressure tube was stirred for 2.5 d at 120 ^{o}C. Trituration of the resulting solid with ether provided a white solid **129** (1.27 g, 88%). M.P. 160-163 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.82 (s, 1H), 7.64 (d, J= 8 Hz, 2H), 7.55 (s, 1H), 7.48 (s, 1H), 7.28 (m, 8H), 7.10 (d, J= 7.8 Hz, 2H), 6.94 (m, 8H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.04 (d, $^{1}J_{CF}$= 250.7 Hz, $C_{a/a`}$), 162.91 (d, $^{1}J_{CF}$= 249.6 Hz, $C_{g/g`}$), 144.18, 143.95, 143.25, 139.86, 131.49 (d, $^{4}J_{CF}$= 3 Hz, $C_{d/d`}$), 131.21 (d, $^{4}J_{CF}$= 3 Hz, $C_{j/j`}$), 130.45 (d, $^{3}J_{CF}$= 8.4 Hz, $C_{e/e`}$, $C_{c/c`}$), 130.24 (d, $^{3}J_{CF}$= 8.6 Hz, $C_{i/i`}$, $C_{k/k`}$), 128.77, 125.77, 116.62 (d, $^{2}J_{CF}$= 22 Hz, $C_{b/b`}$, $C_{f/f`}$), 116.07 (d, $^{2}J_{CF}$= 21.4 Hz, $C_{L/L`}$, $C_{h/h`}$), 68.15, 64.97, 21.26.



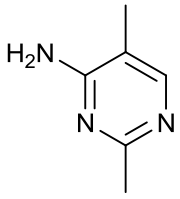
Alcohol 135. To a mixture of 3,5-bis(trifluoromethyl) benzaldehyde (0.1 mL, 0.62 mmol) and DBU (0.05 mL, 0.37 mmol) was added dropwise a solution of salt **129** (0.2 g, 0.31 mmol) in MeOH (2.4 mL) at rt. After 2 d at rt, the reaction mixture was concentrated in vacuo and purified by flash chromatography over silica gel with ethyl acetate/hexane (1:99) to give alcohol **135** as colorless crystals (0.06 g, 22.5%). M.P. 44-46 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.86 (s, 2H), 7.56 (s, 1H), 7.42 (dd, J= 7.7, 5.3 Hz, 2H), 7.29 (s, 1H), 7.14 (dd, J= 7.7, 5.4 Hz, 2H), 6.96 (m, 6H), 6.83 (t, J= 8.1 Hz, 2H), 6.77 (t, J= 8.5 Hz, 2H), 6.64 (dd, J= 8.3, 5.3 Hz, 2H), 5.82 (s, 1H), 3.38 (s, 1H, exchange with D_2O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.33 (d, $^{1}J_{CF}$= 249 Hz, C_n), 162.08 (d, $^{1}J_{CF}$= 248 Hz, C_t), 162.00 (d, $^{1}J_{CF}$= 248 Hz, C_a), 161.74 (d, $^{1}J_{CF}$= 248 Hz, C_g), 156.18, 150.14, 144.03 (C_m), 134.71 (d, $^{4}J_{CF}$= 3.3 Hz, C_d), 133.89 (d, $^{4}J_{CF}$= 3.5 Hz, C_h), 133.75 (d, $^{4}J_{CF}$=2.7 Hz, C_q), 133.72 (d, $^{4}J_{CF}$=3 Hz, C_u), 131.68 (d, $^{3}J_{CF}$= 7.9 Hz, $C_{p/p`}$), 131.45 (q, $^{2}J_{CF}$= 33.3 Hz,

$C_k/_{k`}$), 131.37 (d, $^3J_{CF}$= 7.8 Hz, $C_r/_{r`}$), 129.69 (d, $^3J_{CF}$= 8.1 Hz, $C_e/_{e`}$, $C_c/_{c`}$), 126.09 (q, $^3J_{CF}$= 3.9 Hz, $C_L/_{L`}$), 122.87 (q, $^1J_{CF}$= 273 Hz, $C_i/_{i`}$), 121.28 (sept, $^3J_{CF}$= 3.9 Hz, C_j), 115.89 (d, $^2J_{CF}$= 21.4 Hz, $C_o/_{o`}$), 115.65 (d, $^2J_{CF}$= 21.8 Hz, $C_s/_{s`}$), 115.56 (d, $^2J_{CF}$= 21.9 Hz, $C_b/_{b`}$), 115.34 (d, $^2J_{CF}$= 22.4 Hz, $C_f/_{f`}$), 78.86, 65.33, 58.28. IR (CH_2Cl_2) υmax: 3518.37, 2928.55, 1606.19. The structure was confirmed by X-ray crystallographic analysis.



(5-(2-Hydroxyethyl)-4-methyl-2-thiazolyl)(phenyl)methanone (138). To a mixture of benzaldehyde (0.6 mL, 5.93 mmol) and Et_3N (0.83 mL, 5.93 mmol) was added dropwise a solution of thiamine hydrochloride hydrate (1 g, 2.96 mmol) in MeOH (7.4 mL) at rt. After 12 h at rt, the reaction mixture was filtered to remove the solids (benzoin) and the filtrate was concentrated in vacuo. The residue was purified by column chromatography over silica gel with ethyl acetate/hexane (5:95) to give product **138** as yellow solid (0.3 g, 41%). Data matched to that reported by Kluger et al.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J= 7.7 Hz, 2H), 7.60 (t, J= 7.2 Hz, 1H), 7.45 (m, 2H), 3.83 (td, J= 6.2, 2.8 Hz, 2H), 3.03, (td, J= 6.3, 2.7 Hz, 2H), 2.87 (s, 1H, exchange with D_2O), 2.45, (d, J= 2.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.22, 163.34, 152.20, 137.78, 135.35, 133.41, 131.06, 128.35, 62.44, 30.23, 15.33.



2,5-Dimethylpyrimidin-4-amine (139). This compound was isolated by column chromatography over silica gel with ethyl acetate. Data matched to that reported by Kluger et al. ^{1}H NMR (400 MHz, C_2D_6OS) δ 7.74 (s, 1H), 6.32 (s, 2H), 2.27 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (101 MHz, C_2D_6OS) δ 164.70, 162.68, 154.17, 109.93, 25.41, 13.83.

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