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Novel Azole-based Rearrangements

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By

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ABSTRACT

This work describes efforts targeted at the development of novel reactivity modes for the Breslow intermediate, which was proposed by Breslow to explain the mechanism of action of thiamine-dependent enzymes. By employing this intermediate as a hydroxy-substituted N,S-ketene acetal, we successfully captured it via Claisen rearrangement towards the preparation of diaryl tertiary alcohol products that are isomers of the hitherto elusive intermediate. This strategy also constitutes an unusual disconnection for a Claisen rearrangement precursor.

We have also uncovered an unprecedented radical C-N bond scission of a Breslow intermediate when a fluorenyl group is installed on the azolium nitrogen atom. This facile homolysis affords intermediates that lead to products analogous to those previously reported by Oka. This method is useful for the preparation of several medicinally relevant 2-ketoazoles, while efforts are underway for its application towards the derivatization of existing azole drugs and medicinally relevant aldehydes.

ACKNOWLEDGEMENTS

Over the course of my life and pursuits, I have come to know first-hand the impact of people and vital connections. The decision to sojourn over 6000 miles for doctoral studies and ultimately my successful completion of it was made possible by the interplay of these vital connections.

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Kolawole Fola Ayinuola

July 2015

DEDICATION

To my wife Tolulope Olutayo. You are all my reason!

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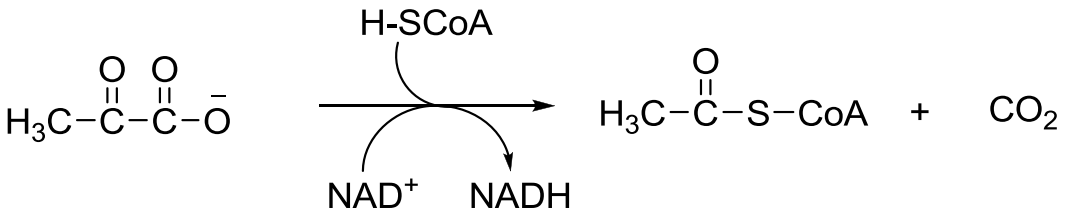
CHAPTER ONE

Novel Azole-based Rearrangements

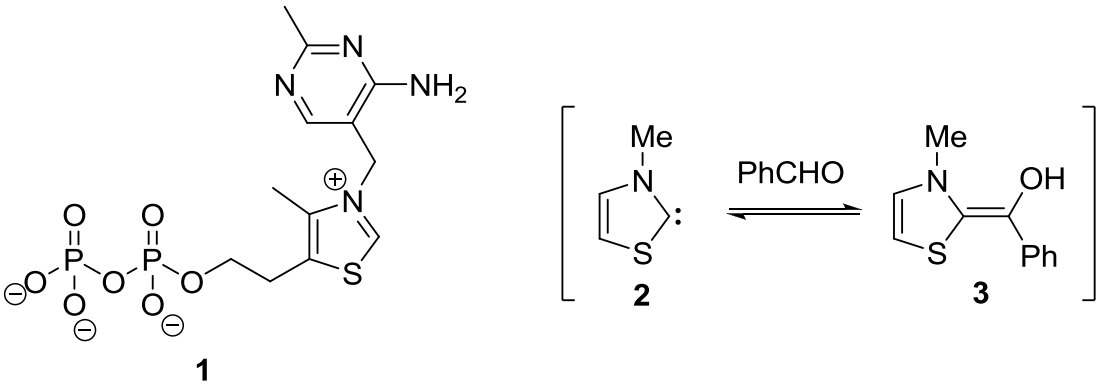
1. Introduction

The discovery of chemical reactions is often inspired by the understanding of some underlying biological process. For example, pyruvate decarboxylation and the subsequent formation of acetyl CoA catalyzed by the pyruvate dehydrogenase complex (PDC) is chemically equivalent to an electrophilic acyl substitution reaction, wherein an acyl carbanion is trapped by an electrophile (**Scheme 1**).[1]



Scheme 1: Decarboxylation of Pyruvate

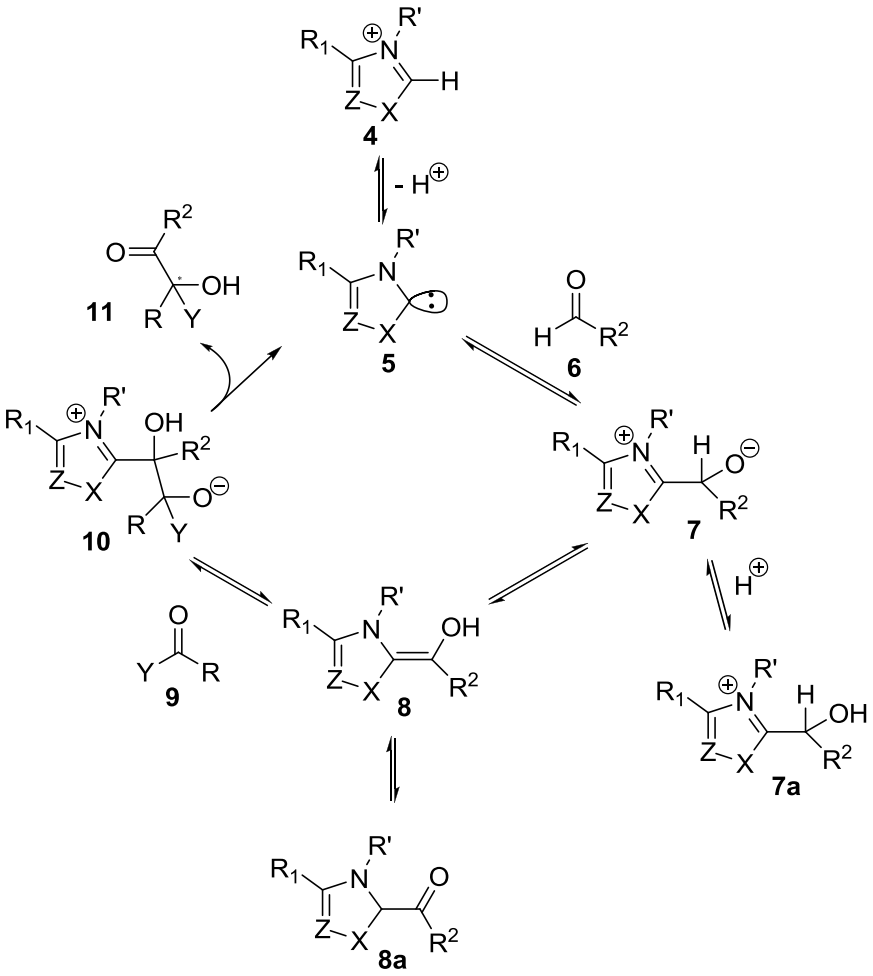
Acyl anions however invariably exist in some stabilized forms e.g. as protected cyanohydrins,[2,3] metalated dithianes,[4,5] or as an “active aldehyde”.[6] Thiamine diphosphate (TDP) **1**, an essential cofactor for several enzymes by means of its thiazole ring,[7] stabilizes acyl carbanions in a variety of enzymatic transformations, especially those occurring near a carbonyl moiety.[8,9] This reactivity observed with TDP in biological systems has since been replicated in many synthetic transformations.[10–12]



Scheme 2: Thiamine diphosphate and the Breslow Intermediate 3

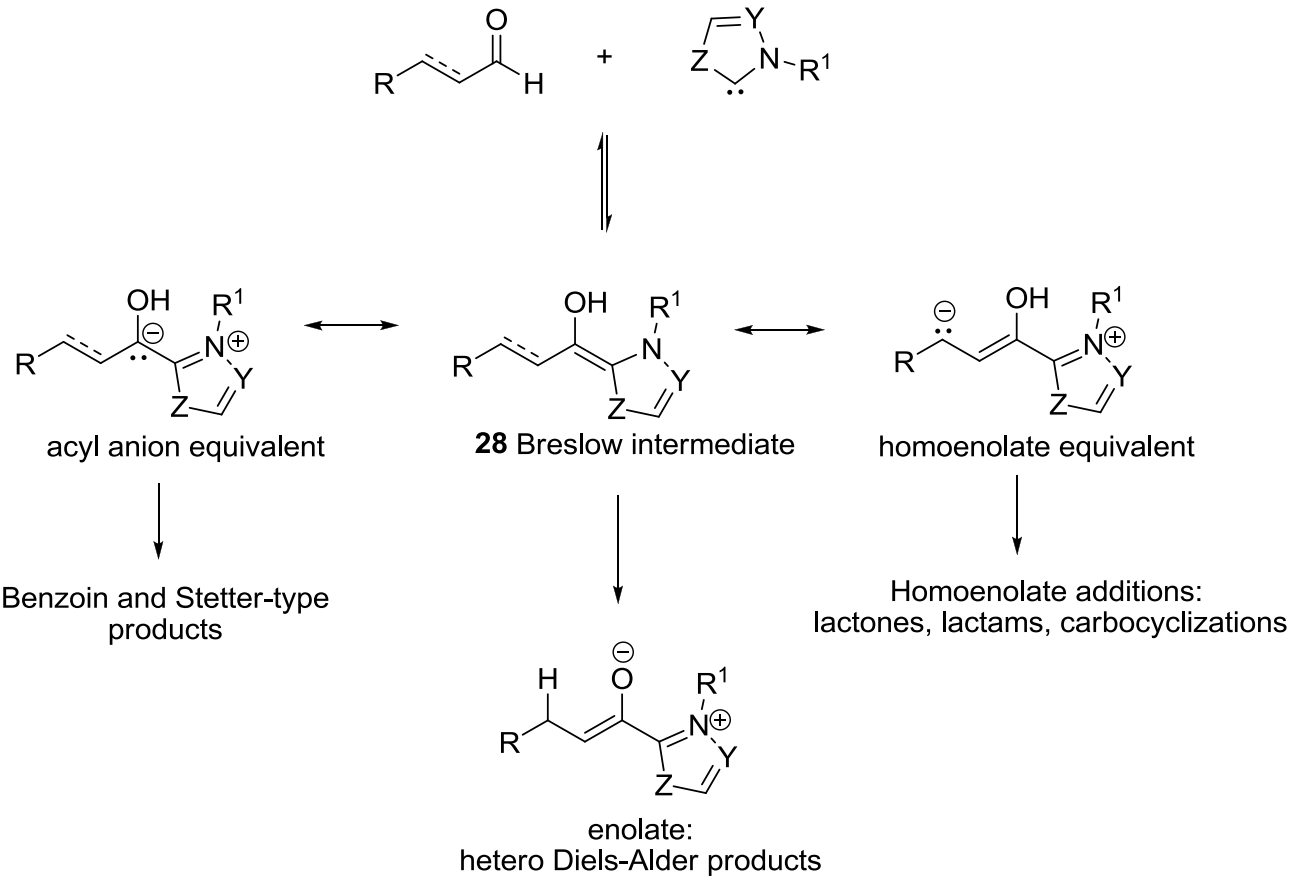
2. Breslow Intermediate and N-Heterocyclic Carbene (NHC) Catalysis

While conducting studies on model systems to investigate TDP catalyzed processes, Breslow proposed carbene **2** and enaminol **3** (**Scheme 2**) as transient intermediates in the thiazolium salt catalyzed benzoin condensation of benzaldehyde.[7] These enaminols, which came to be known as Breslow intermediates, as well as other azole based variants have been the subjects of extensive studies highlighting their roles as catalysts in several NHC catalyzed processes involving aldehydes.[7,10,13] In all these processes, the first step involves deprotonation of an azolium salt precatalyst **4** to give an ylide – the active NHC catalyst **5**. The reaction of **5** with an aldehyde (or some suitable surrogates like α-ketoacids[14,15]) yields a zwitterionic NHC-aldehyde adduct **7** which is then transformed to the Breslow intermediate **8** after proton transfer.[16,17]



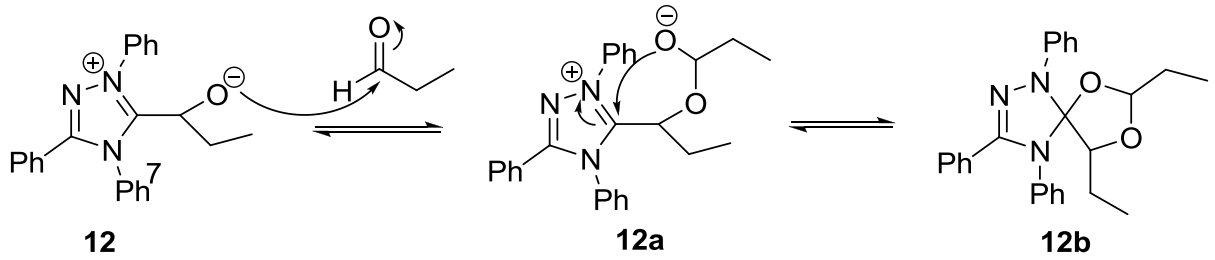
Scheme 3: Catalytic Cycle for Benzoin Condensation as proposed by Breslow

Thus, a reversal of polarity ("umpolung") of the aldehyde substrate ensues thereby opening up reactivity pathways hitherto unavailable at a simple acyl carbon.[11,12,18] These pathways can be broadly divided into two classes: (i) traditional acyl anion equivalent reactivity typified by benzoin and Stetter-type reactions, and (ii) NHC-redox catalysis often initiated by the presence of an activating group adjacent to the aldehyde (**Scheme 4**).[19]



Scheme 4: Reactivity Profile of the Breslow Intermediate (Adapted from Ref 19)

Another feature of NHC catalyzed processes involving aldehydes is the prevalence of reversible elementary reaction steps which gives rise to a number of intermediates, some of which have been isolated and/or identified by spectroscopic methods. For example, the protonated form of the initial zwitterionic NHC-aldehyde adduct (i.e. **7a** cf **Scheme 3**) has been characterized,[6,20–22] supporting Breslow's earlier mechanistic proposal.[7] Berkessel also reported the formation of a spiro-dioxolane (**12b**) as the resting state of the catalytic system when an aliphatic aldehyde is employed, with this intermediate presumably arising from the condensation of NHC-aldehyde adduct **12** with a second aldehyde equivalent (**Scheme 5**).[18]

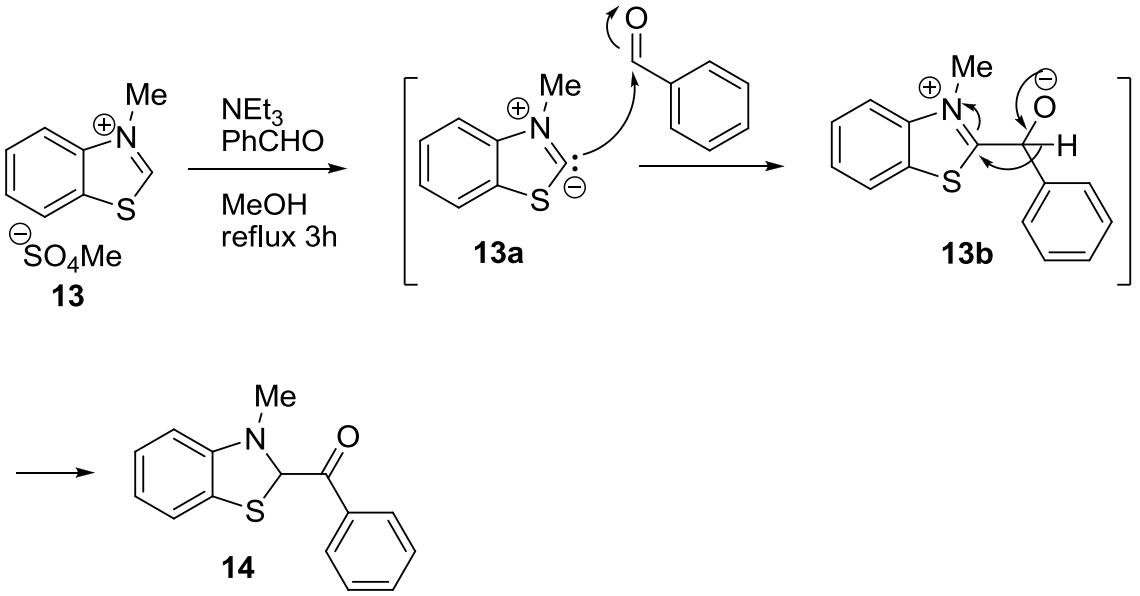


12 **12a** **12b**

Scheme 5: Berkessel's Spirodioxolane Formation

2.1 The Keto form of the Breslow Intermediate

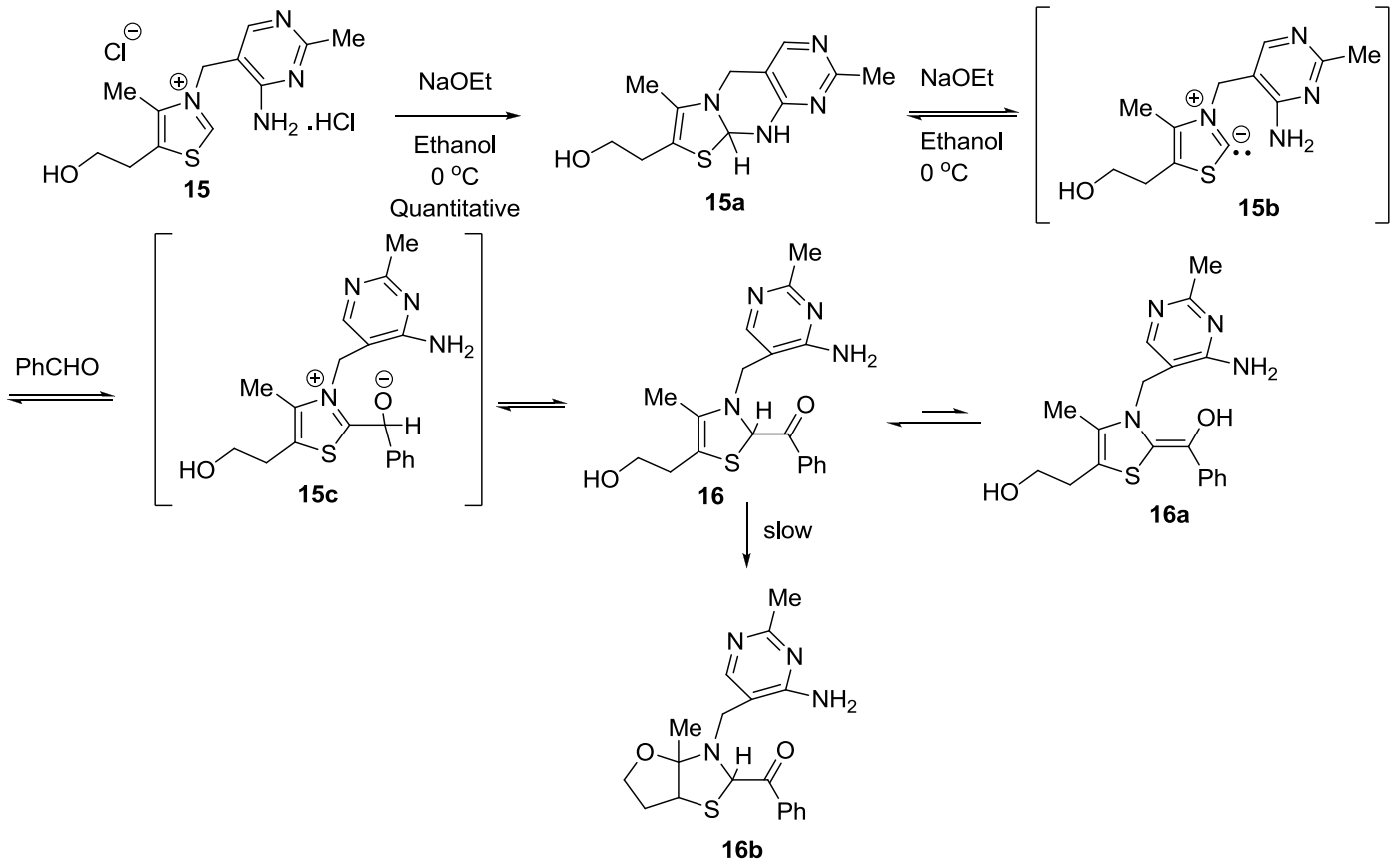
In non-catalytic systems, the keto form of the Breslow intermediate has been isolated. Metzger in 1964 reported the large scale synthesis of ketone **14** in 75% yield from the condensation of benzaldehyde with N-methylbenzothiazolium salt **13** in the presence of triethylamine in refluxing methanol.[23]



Scheme 6: Metzger's Keto-Breslow Intermediate Synthesis

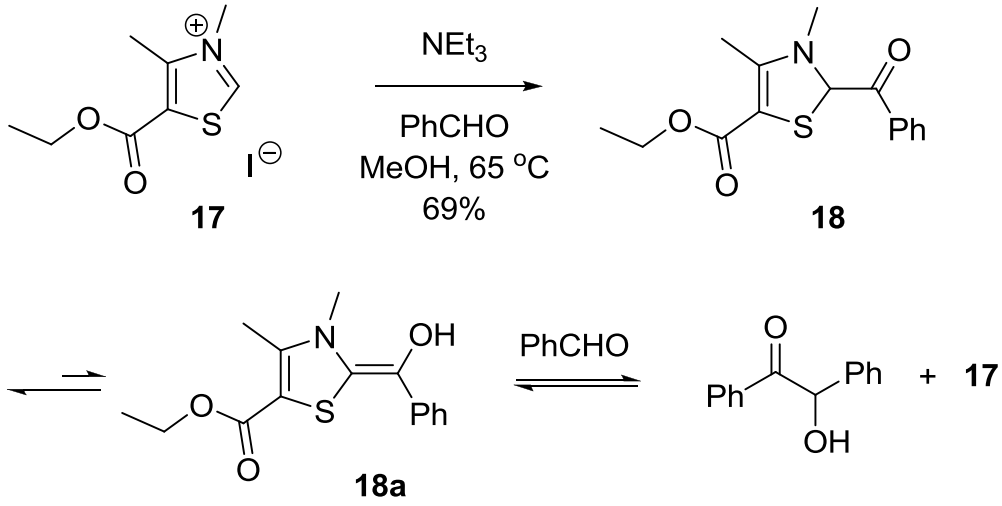
In another report, Metzler observed that when thiamine hydrochloride salt **15** is suspended in basic non-aqueous media, it is converted to the neutral tricyclic form **15a**.[24] Compound **15a** supposedly arises from the intramolecular attack of the amino

group on the pyrimidine ring of **15** on the electrophilic C2 of the thiazole.[24] When **15a** is allowed to persist in basic media, NHC **15b** is formed,[25] so that in the presence of an aldehyde substrate, the same reaction pattern outlined in **Scheme 3** is observed.[26] Based on this, Doughty reported the synthesis of a bicyclic benzoylthiazolidine **16b** when thiamine hydrochloride salt **15** was reacted with excess benzaldehyde in the presence of excess sodium ethoxide in ethanol at 0 ^{o}C.[27] Thiazolidine **16b** is seemingly a thermodynamic sink for the ensuing keto-enol equilibrium between **16** and **16a** (**Scheme 7**).



Scheme 7: Thiamine and its reactivity in Basic Non-aqueous Media

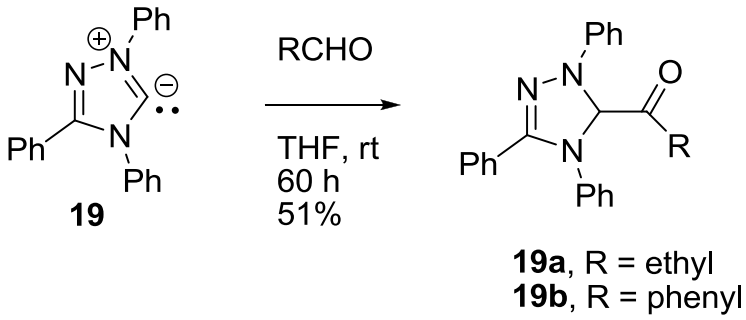
In the same report, Doughty believed he found UV spectroscopic evidence for the existence of an “extensively conjugated system” of which enol **16a** is a type. Thus, avenues to increase the stability of **16a** through increased conjugation in the thiazole were explored. To this end, an electron deficient thiazolium salt **17** with an ester group at the thiazole C-5 was prepared. When salt **17** together with excess benzaldehyde and triethylamine was suspended in refluxing methanol for 1 hour, orange-red crystals of 2-benzoylthiazoline **18** were isolated in 69% yield after the reaction medium was cooled to 0 ^{o}C. TLC and NMR analysis of the mother liquor confirmed the production of benzoin as well as presence of the starting salt **17**. Subsequent NMR experiments confirmed the reaction to form ketone **18** from salt **17** also occurs at room temperature, however the formation of the enol (Breslow intermediate) was not enhanced by the added conjugation in the system.[27]



Scheme 8: Doughty’s Keto-Breslow Intermediate

Keto-Breslow intermediates have also been observed with triazolylidene carbenes. Berkessel reported the synthesis of ketones **19a,b** from the reaction of the stable

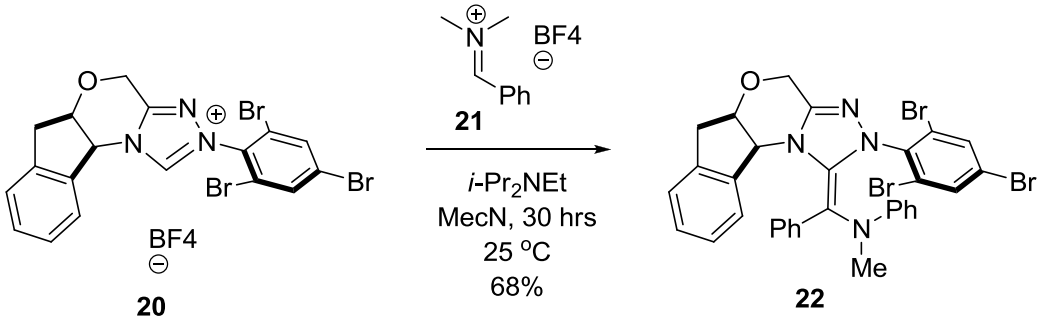
triazolylidene carbene **19**, previously developed by Enders,[28] with both aliphatic and aromatic aldehydes in THF at room temperature.[18]



Scheme 9: Keto-Breslow Intermediates from Triazolylidene Carbene

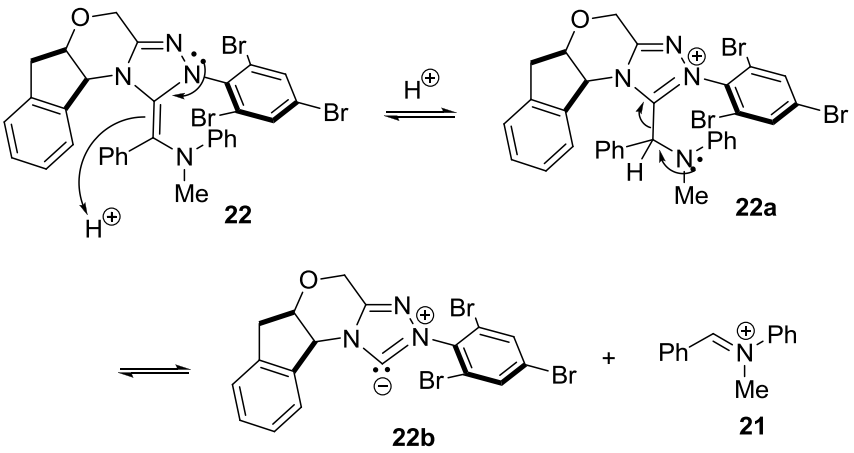
2.2 Isolated Breslow Intermediate Analogs and their Reactivity

Early efforts to drive the keto-enol equilibrium towards the enol were largely unsuccessful, and evidence for the existence of the Breslow intermediate was circumstantial at best. However, analogs of the Breslow intermediate that in some cases show reactivity similar to this elusive intermediate has recently been isolated. In 2012, Rovis disclosed his work on the synthesis of aza-Breslow intermediates derived from chiral triazolylidene carbenes.[29] Therein it was hypothesized that replacing the reactive but transient aldehyde-derived enol with a less reactive but electronically similar enamine group[30] could translate to an isolable Breslow intermediate analog that could retain the reactivity pertinent to the original species.[29] Thus, when chiral NHC precatalyst **20** and iminium salt **21** were suspended in acetonitrile in the presence of diisopropylethylamine at room temperature, a yellow solid confirmed to be the aza-Breslow intermediate **22** crystallized out of the reaction medium after 12 hours. Iminium salt **21** was made *in situ* from the reaction of commercially available *E*-N-benzylideneaniline with trimethyloxonium tetrafluoroborate in acetonitrile.



Scheme 10: Rovis's aza-Breslow Intermediate

In the presence of excess HBF_4, **22** is completely converted to salt **20** (via the carbene **22b**) and iminium salt **21** based on NMR analysis, which imply it could have the requisite catalytic efficiency observed with traditional aldehyde-derived enols.[29]

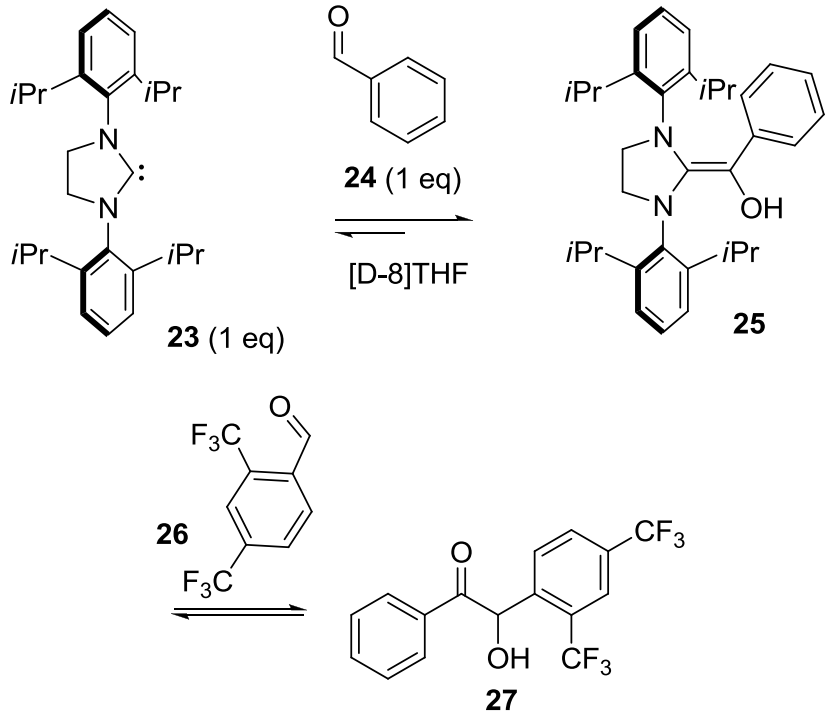


Scheme 11: Fate of Rovis's aza-Breslow Intermediate in Acid Medium

Despite Rovis's structural evidence, the synthesized aza-Breslow intermediate **22** is not thiazole-based and it lacks the requisite reactivity typified by aldehyde-derived Breslow intermediates.

Shortly after Rovis's report, Berkessel disclosed extensive NMR evidence for the characterization of Breslow intermediate analogs derived from imidazolidinyl carbenes.

When commercially available 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene carbene **23** was reacted with several aromatic aldehydes under an inert atmosphere, a variety of imidazolidinyl enols were observed by NMR analysis. In addition, enol **25** was shown to be a competent catalyst for cross-benzoin condensation with the electron-deficient aldehyde **26**.[31]

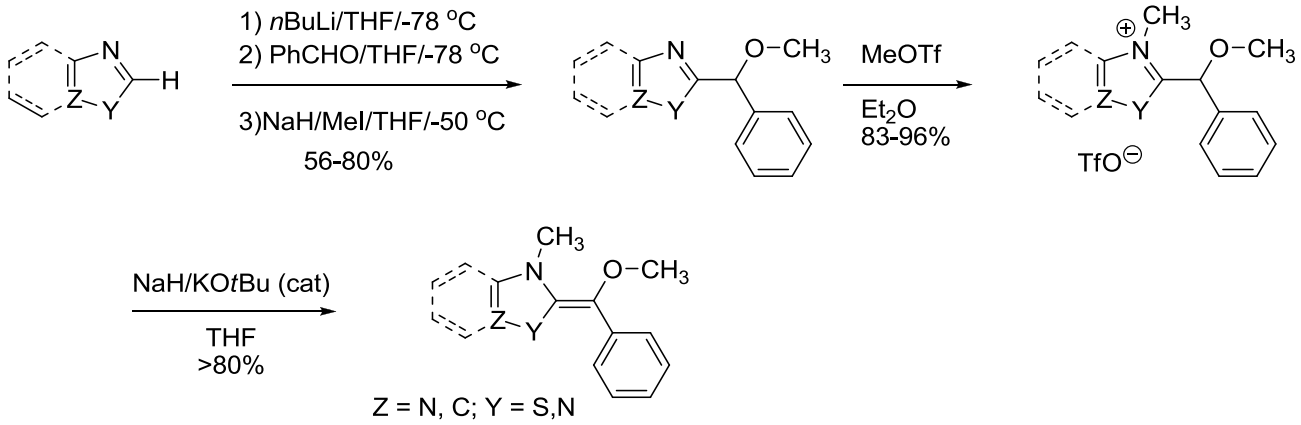


Scheme 12: Berkessel-Teles Imidazolidinyl Breslow Intermediates

As was the case with Rovis's intermediate, Berkessel's intermediates are also not thiazole-based and the reported diamino enols are not fully aromatic.

Mayr subsequently reported the synthesis of O-methylated Breslow intermediates derived from thiazoles, imidazoles and triazoles. These species were typically prepared in four steps, starting with the addition of the corresponding 2-lithioazoles to

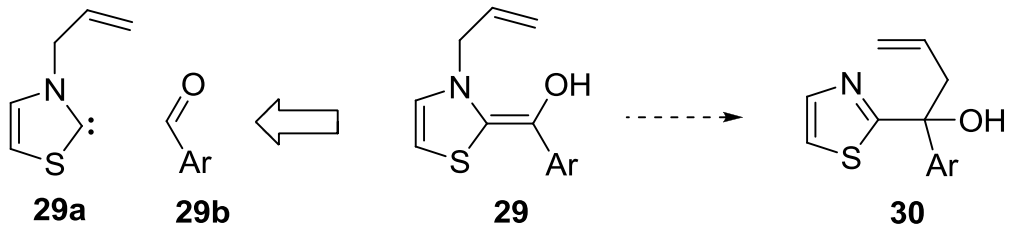
benzaldehyde in THF under cryogenic conditions, followed by deprotonation-alkylation-deprotonation sequences.[16]



Scheme 13: O-methylated Breslow Intermediates

Mayr's O-methylated Breslow intermediates are not readily accessible (**Scheme 13**). Furthermore, they lack the inherent reactivity generally associated with typical Breslow intermediates.[16,31]

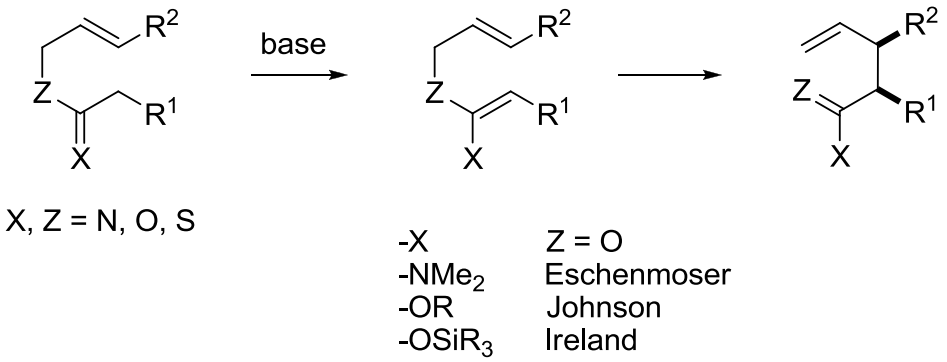
The synthetic utility of the Breslow intermediate is often as NHC catalysts (cf **Schemes 3, 4**), where choice of azole precatalyst, base and alkyl (or aryl) group on the azolium nitrogen has played a role in reaction outcome.[11,12] We however wondered if a novel reactivity mode could be devised whereby this elusive[29,31] intermediate could be captured via Claisen rearrangement. This new reactivity mode would be predicated upon viewing the Breslow intermediate as a hydroxy-substituted N,S-ketene acetal (**29**), which would preferably undergo intramolecular rearrangement (kinetic preference) to give tertiary alcohol **30** rather than intermolecular electrophilic attack. More importantly, this would constitute a novel disconnection for a Claisen rearrangement precursor (**Scheme 13**).[32]



Scheme 14: Novel Disconnection for a Claisen Rearrangement Precursor

3. Claisen Rearrangement

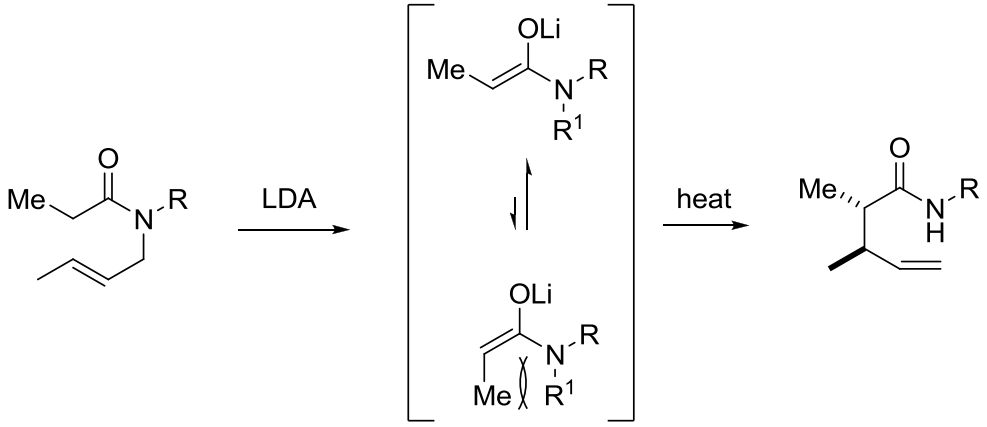
After the seminal report of Ludwig Claisen in 1912, the Claisen rearrangement has undergone a renaissance over the years, revealing further insights about mechanism and the stereochemical course of the reaction. Many important variants have also been developed,[33,34] so that altogether the synthetic organic chemist can draw from an arsenal of some of the most powerful stereoselective carbon-carbon bond forming reactions.



Scheme 15: Some Variants of the Claisen Rearrangement

These reactions have also become very useful in the synthesis of a diverse range of natural products and other targets due to their atom economical nature, as well as high levels of stereocontrol which is a result of the geometry of the cyclic transition state.[34,35] When the parent heteroatom Z = O of a Claisen rearrangement is replaced by a

nitrogen atom (cf. **Scheme 15**), the reaction is referred to as an aza-Claisen rearrangement.[36] Having a nitrogen atom in the central position of the sigmatropic core affords high levels of stereoselectivity in the ketene acetal formation which is as a result of allylic strain.[37]

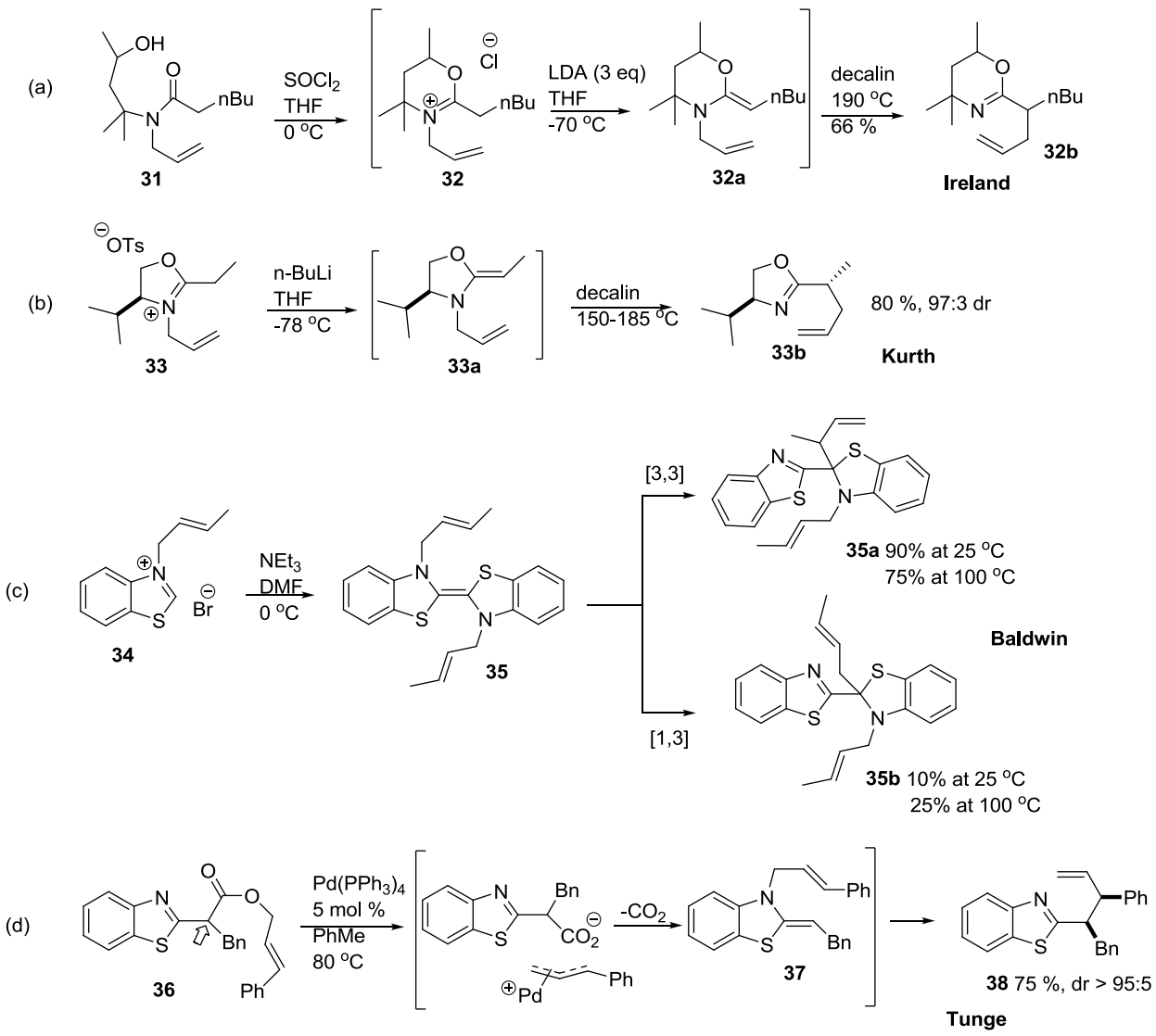


Scheme 16: Tsunoda's aza-Claisen Rearrangement of Amide Enolates

3.1 Aza-Claisen rearrangements of N-allyl-N,X-ketene acetals

The O-allyl Claisen rearrangements are by far more common. However, some examples of Claisen rearrangement of N-allyl-N,X-ketene acetals exist. One of the earliest examples was by Ireland. Therein, oxazinium salts **32** derived from γ-hydroxy N-allyl amides **31** were deprotonated by LDA under cryogenic conditions to generate the *N*-allyl-N,O-ketene acetals **32a**. Heating in decalin at 190 ^{o}C effected the rearrangement (**Scheme 17a**).[38] In a later report, Kurth employed a chiron-mediated approach towards the synthesis of pentenoic acids using amino acid derived oxazolinium salts **33**. The ketene acetal generation and rearrangement conditions were similar to the ones reported by Ireland (**Scheme 17b**).[39] Baldwin studied the rearrangements of the diaminofulvalene **35** derived from treating benzothiazolium salt

34 with triethylamine in DMF at 0 ^{o}C.[40] Therein, it was observed that the reaction pathway was dependent on temperature as well as the azolium N-substituent. Whereas products of [3,3]-rearrangement (**35a**) prevailed at room temperature, [1,3]-rearrangement products (**35b**) were favored at higher temperatures (**Scheme 17c**).[40] Tunge much later effected a Carroll-type rearrangement of azolyl cinnamyl esters **36**, generating N-allyl-N,X-ketene acetals **37** after decarboxylation under palladium catalysis. *In situ* rearrangement at 80 ^{o}C afforded butenyl azoles **38** in good yields and variable diastereoselectivities. However, substrates lacking a substituent α- to the azole (vide infra) failed to give the expected butenyl azole products.[41] (**Scheme 17d**).



Scheme 17: Aza-Claisen rearrangements of N-allyl-N,X-ketene acetals

Unfortunately, each of these variants suffers from one or more limitations. The methods involving the oxazines and oxazolines (**Scheme 17a,b**), employed stoichiometric or superstoichiometric amounts of strong base. The Claisen rearrangement that results from diaminofulvalene **35** has limited utility since the starting material for the reaction is a homodimer (**Scheme 17c**). The Tunge azole variant (**Scheme 17d**) suffers several important structural limitations. The use of Pd(0) catalyst, for instance, raises functional group compatibility issues, as substrates containing terminal alkynes or other moieties

that can engage in oxidative addition like vinyl or aryl halides would not be tolerated. Furthermore, substrates possessing β-hydrogens will not be tolerated since they are prone to β-elimination, hence specially prepared cinnamyl esters are employed as reaction substrates to circumvent this drawback.

We hope to develop an azole-based approach to circumvent some of these limitations of traditional Claisen rearrangements. This will not only lead to a more efficient synthesis, but also provide access to several important substituted azole products.

CHAPTER TWO

Intercepting the Breslow Intermediate via Claisen Rearrangement

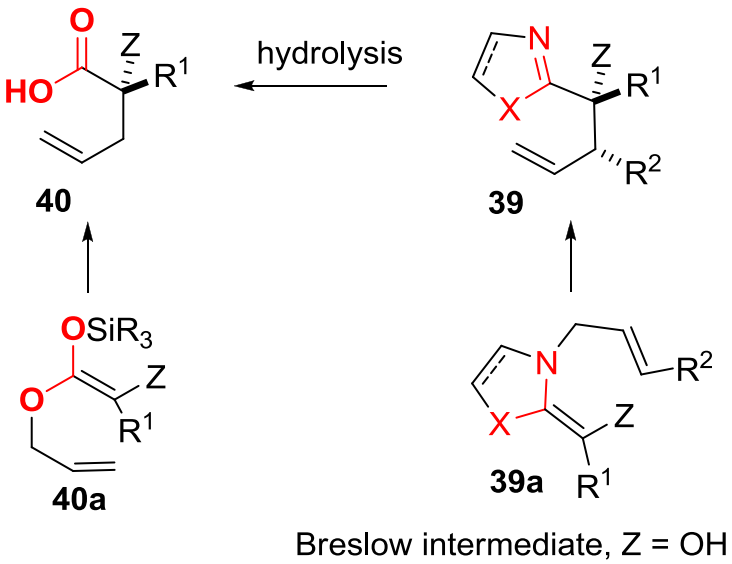
1. Introduction

Aside from the well-established stereochemical outcomes, the ultimate goal of an Ireland-Claisen rearrangement is the synthesis of γ,δ-unsaturated carboxylic acids.[35,42] However, several factors (all of which ultimately come down to economics) limits its potential application towards the production of significant amounts of materials[43,44]

1. Powerful bases such as LDA or K/LHMDS are typically needed, and often in superstoichiometric amounts. The same is true of silylating agents, which may range from the inexpensive TMSCl to the much more expensive TIPSOTf.
2. The use of strong bases in turn necessitates low reaction temperatures that require cryogens, as well as the attendant cost and difficulty in maintaining low reaction temperature on production scale.[45]
3. Strong bases limit functional group compatibility. Alcohols, 1° and 2° amides/sulfonamides, carbonyl groups possessing α-hydrogens, and numerous relatively acidic functionalities would have to be protected and subsequently deprotected, adding at least two steps to the synthesis. Alternatively, still greater equivalents of base would need to be added to compensate for the acidic protons.[46]

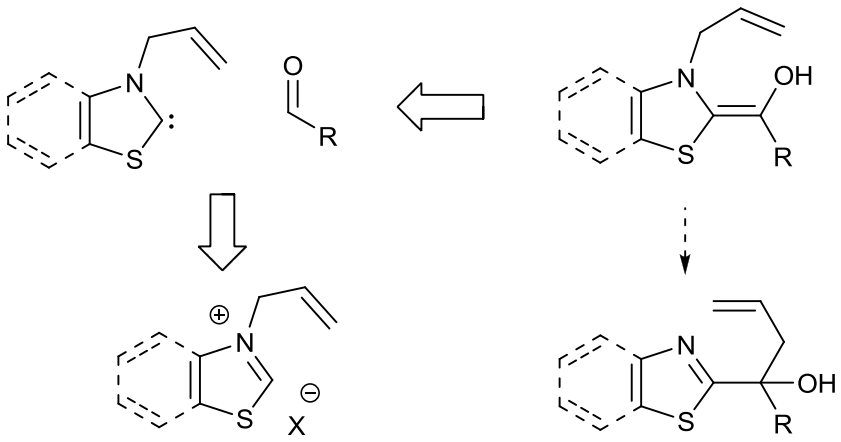
In our opinion, one approach to circumventing these limitations was the development of an azole-based approach to Claisen rearrangement. Therein, we hypothesized that the

carbonyl moiety in a typical Claisen rearrangement product **40** could be masked in an azole ring as **39**, and unveiled (as needed) at a later point in a synthesis via hydrolysis or other synthetic transformations.[47]



Scheme 18

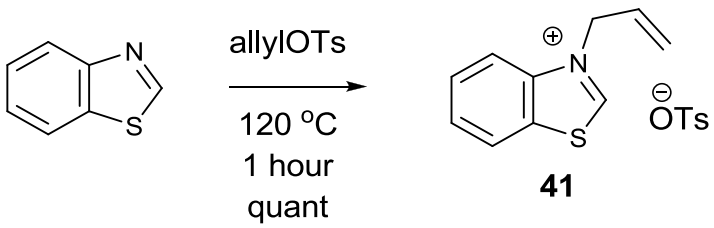
In the case of Z=OH, we considered mild ways to afford these N-allyl hydroxy N,X-ketene acetals (Breslow-type intermediates **39a**) which would efficiently undergo Claisen rearrangement (**Scheme 19**).



Scheme 19

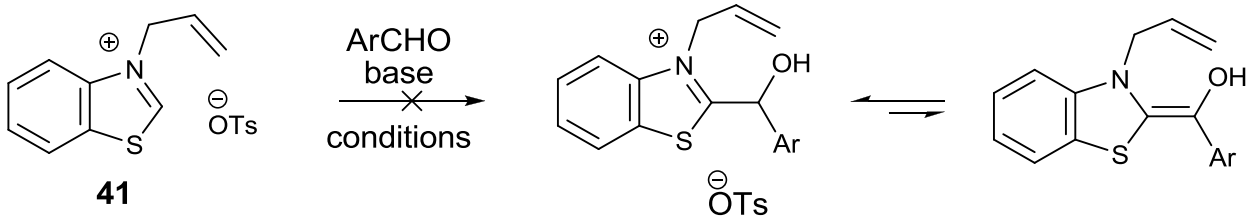
2. Initial Approach

The requisite Breslow intermediate **39a** (cf **Scheme 18**) could arise from deprotonation of an N-allyl azolium salt by a base and subsequent condensation with an aldehyde. Following modification of a reported procedure, N-allyl benzothiazolium tosylate salt **41** was obtained in quantitative yield from heating a neat mixture of benzothiazole and allyl tosylate at 120 ^{o}C for 1 hour.[48]



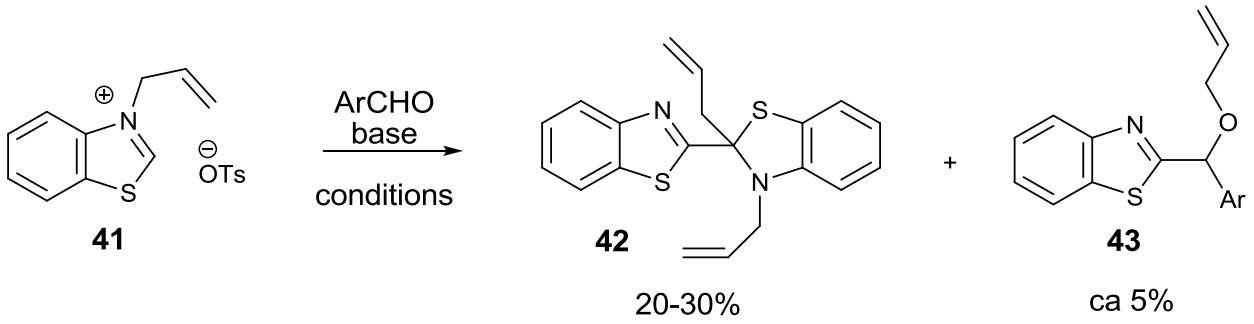
Scheme 20

Subsequent attempts to obtain the Breslow intermediate from the reaction of salt **41** with different aromatic aldehydes in the presence of several bases (diisopropylethyl amine, tetramethylguanidine, KHMDS, NaH) in a variety of aprotic solvents (toluene, MeCN, THF, DCM, DMF, MeCN/THF) either yielded no result or gave complex mixtures.



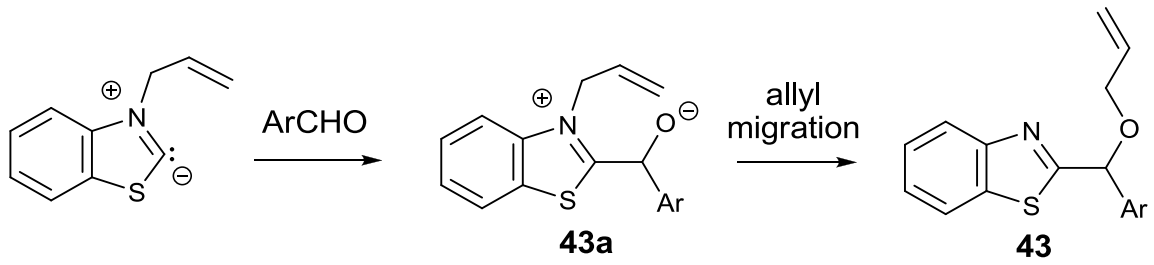
Scheme 21

On further analysis, the complex mixture was composed primarily of homodimer **42** previously reported by Baldwin[40] as well as traces of allyl ether **43**.



Scheme 22

The mechanism of formation of **42** has been extensively studied by Baldwin and others,[40,49–51] and it arises either via carbene dimerization and/or attack of the generated carbene on the electrophilic C2 of salt **41**. Compound **43** could presumably arise from inter- or intramolecular allyl transfer from generated alkoxide **43a** (**Scheme 23**).[47]

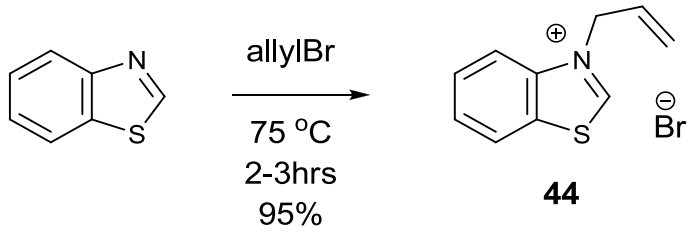


Scheme 23

3. Synthesis of 'Breslow-Ketone' Intermediate and Claisen Rearrangement

We were intrigued by Metzger's report on the synthesis of 2-benzoylbenzothiazoline **14** in 1964 (cf **Scheme 6**), and we wanted to use this as a starting point to explore how we could drive the keto-enol equilibrium towards an irreversible Claisen rearrangement product.

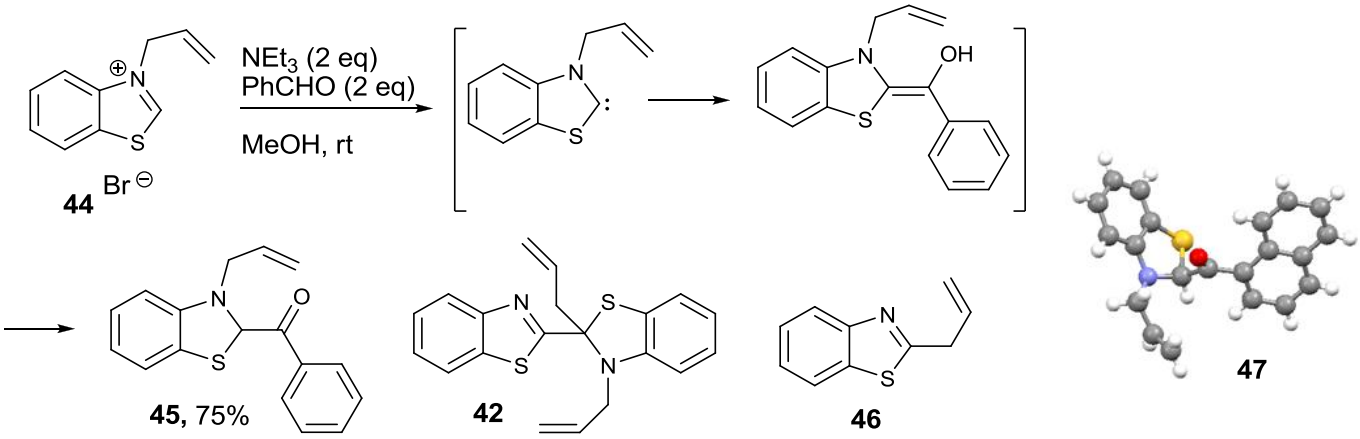
We started by synthesizing N-allylbenzothiazolium bromide salt **44** in 95% yield from heating a neat mixture of benzothiazole and allyl bromide (1.2 eq) to 75 ^{o}C. The brown solid obtained was purified by triturating several times with ether and isolated by filtration.



44

Scheme 24

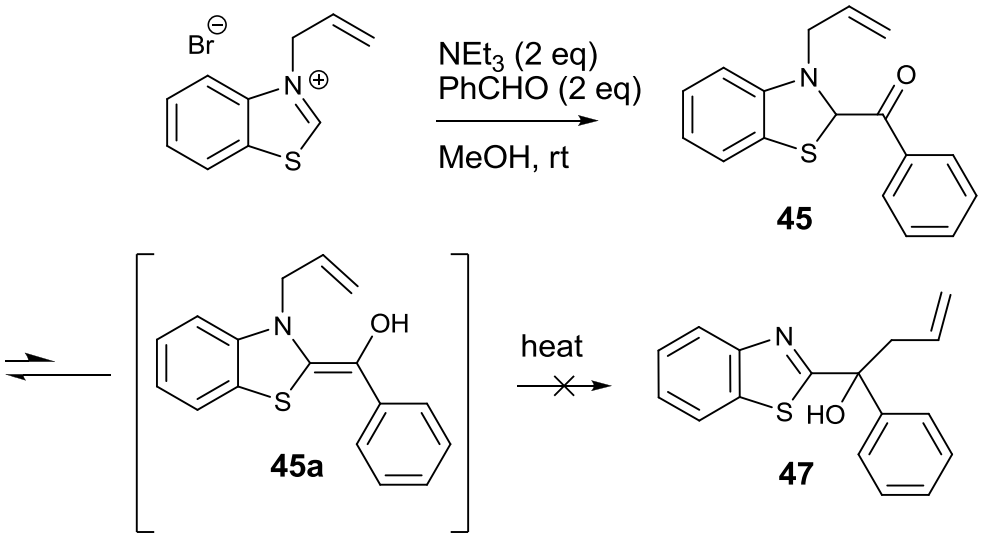
Subsequently, by employing Metzger's conditions, we obtained the allyl analog (**45**) of ketone **14**, surprisingly at room temperature in a similar (75%) yield along with side products which included Baldwin's homodimer **42** and 2-allylbenzothiazole **46**. The identity of the ketone was also confirmed by X-ray crystallography of the 1-naphthyl analog (**47**).



Scheme 25

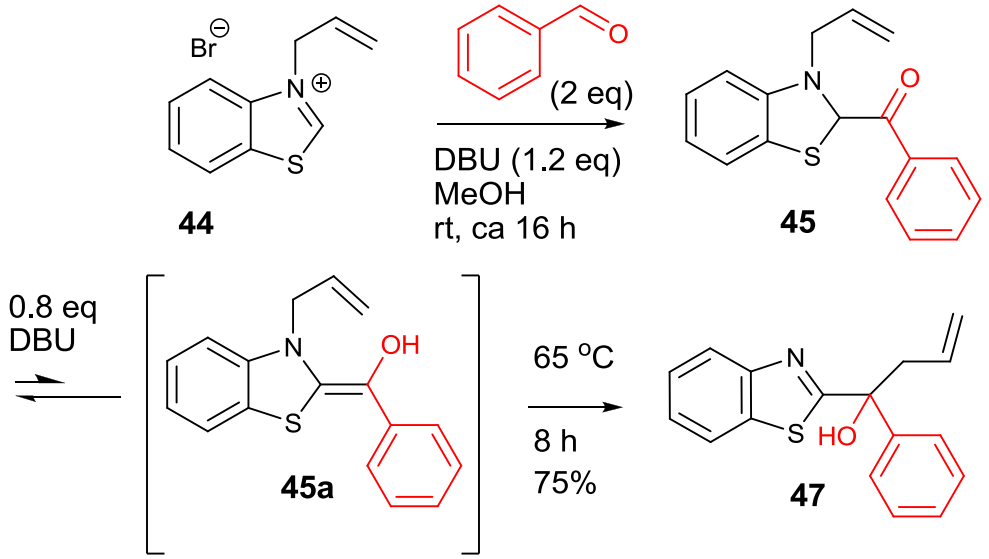
The order of addition, aldehyde equivalents and temperature were important in minimizing side products **42** and **46**, as well as getting a good initial yield of ketone **45**. The methanolic solution of the salt (ca 0.2 M) had to be added slowly (over 20-25 minutes using a syringe pump) to a neat mixture of triethylamine (2 equivalents) and aldehyde (2 equivalents) at room temperature.

After ketone formation, we sought to drive the keto-enol equilibrium towards the enol **45a**, with a view to irreversibly effecting the rearrangement of the resulting ketene acetal to tertiary alcohol **47** (**Scheme 26**). However, after using up to 6 equivalents of triethylamine and heating to 65 ^{o}C, the tertiary alcohol product was not formed at any appreciable rate.



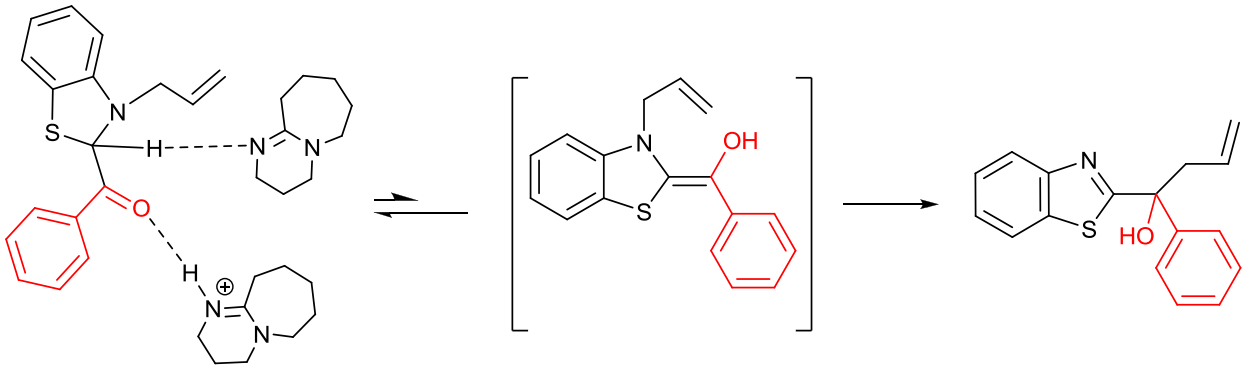
Scheme 26

After further experimentation, it was discovered that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was capable of forming the initial ketone **45**, as well as effecting its rearrangement to the tertiary alcohol **47**. Thus, rather than a two-step Claisen rearrangement procedure, we were able to combine both the ketone formation and rearrangement steps. Following ketone formation at room temperature, a second charge (0.8 equivalents) of DBU was added, and the reaction mixture was heated to 65 ^{o}C to effect the enolization and subsequent rearrangement to tertiary alcohol **47** (**Scheme 27**). More importantly, no benzoin product was detected based on TLC comparison to an authentic sample.



Scheme 27

The specific effect of DBU aside from being non-nucleophilic and a stronger base than triethylamine[52–55] is unknown; however it may be taking part in proton transfer that helps facilitate the keto-enol equilibrium towards Claisen rearrangement (**Scheme 28**).[56,57]We attempted adding substoichiometric amounts of Bronsted acids but there was no noticeable effect on reaction outcome. In some cases, the reaction was inhibited by the addition of acid.



Scheme 28

The extra charge of DBU added after initial ketone formation facilitates the rearrangement. In the absence of excess base, reaction times ranging from a few days to a week were observed.

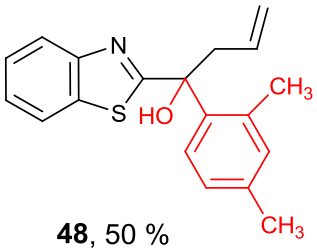
3.1 Scope of Azole-based Claisen Rearrangement

After developing the optimal conditions for the Breslow-ketone intermediate synthesis and its *in situ* rearrangement, we proceeded to explore steric and electronic influences of aromatic and heteroaromatic aldehyde substrates both on the initial ketone formation and the succeeding rearrangement (**Figure 1**). Ortho substituted aldehydes were well tolerated (**48-50, 52, 55**) and even the sterically hindered 1-naphthaldehyde gave tertiary alcohol product (**56**) although the yield was lower. Equal success was observed with electron-rich (**48, 52, 55**) and electron-poor (**49, 50**) aldehydes, though surprisingly 4-nitrobenzaldehyde only afforded Canizzarro-type products.[58,59] Heteroaromatic aldehydes – pyridine-2- and -3-carboxaldehydes as well as furfural underwent smooth ketone formation and subsequent rearrangement in good yields (**51, 54, 57**).

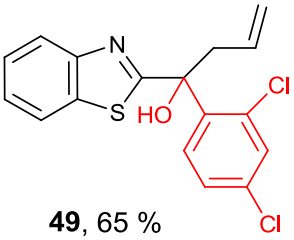
One major drawback in traditional Claisen rearrangement processes is the need to protect any free –OH groups prior to ketene acetal generation and/or rearrangement. We were delighted that this azole-based process tolerated an unprotected phenol (**55**) without any modification of the reaction conditions.

The electron-poor aldehydes were more reactive than their electron- rich counterparts in both the Breslow-ketone formation and the subsequent Claisen rearrangement. For instance, while ketone formation was observed within 30 minutes (based on TLC analysis) with 2-bromobenzaldehyde, ketone formation took at least 24 hours at room

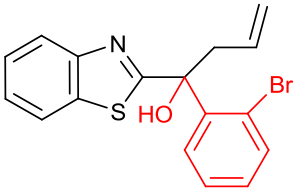
temperature with 2,4-dimethylbenzaldehyde. While the ketones derived from electron rich aldehydes required longer heating times (ca 48 hours at 65°C) and in some cases elevated temperatures (80-85 °C) for rearrangement (compounds **48, 52, 55**), the Breslow ketones derived from electron poor or neutral aldehydes rearranged in 16 hours at 65 °C.



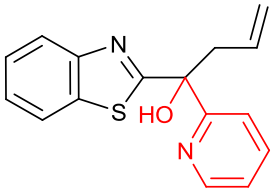
48, 50 %
ortho substitution,
electron rich



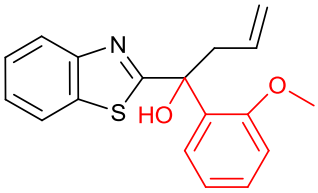
49, 65 %
ortho substitution,
electron poor



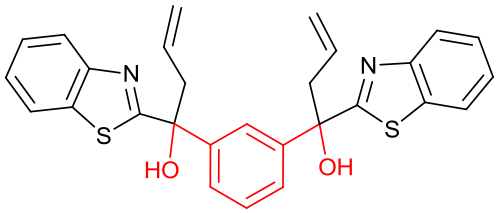
50, 70 %
ortho substitution,
electron poor



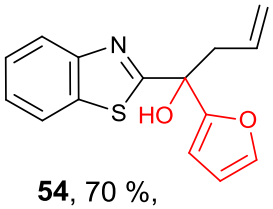
51, 80 %,
heteroaromatic



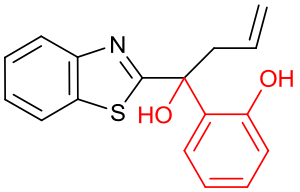
52, 65 %
ortho substitution,
electron rich



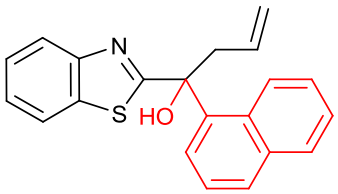
53, 58 %,
Isophthalyl dimer



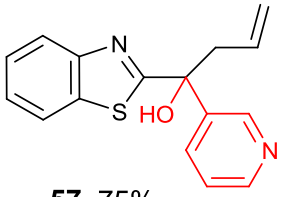
54, 70 %,
heteroaromatic



55, 65 %
unprotected phenol,
ortho substitution,
electron rich



56, 55 %
ortho substitution



57, 75%
heteroaromatic

Figure 1

Since the CR product is simply an isomer of the Breslow intermediate, its capture via Claisen rearrangement lends more structural evidence to the available ones (**Schemes 10, 12**)[29,60] about the existence of this hitherto 'elusive' intermediate.

Furthermore, an added benefit of this reaction is easy access to medicinally relevant motifs in a mild and efficient manner. For example, AC-265347 and analogs have been reported to be positive allosteric modulators of the calcium sensing receptor (member of the group C family of G protein-coupled receptors, GPCR).[61,62]

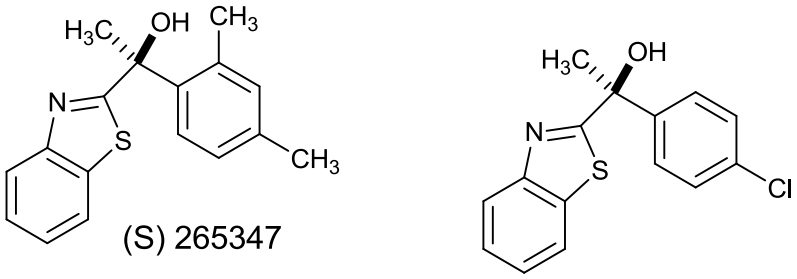


Figure 2

These compounds were made by the addition of 2-lithiobenzothiazole to the corresponding ketones at -78 ^{o}C. Using our azole-based Claisen approach, we were able to make the allyl analogs of these compounds in 50 and 65% yields in two steps from benzothiazole and the corresponding aldehyde.

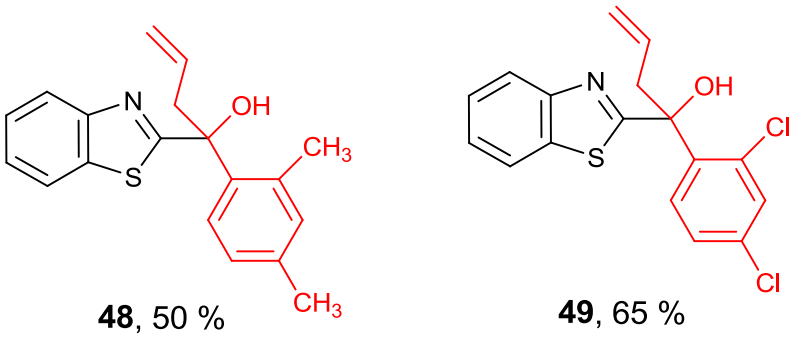
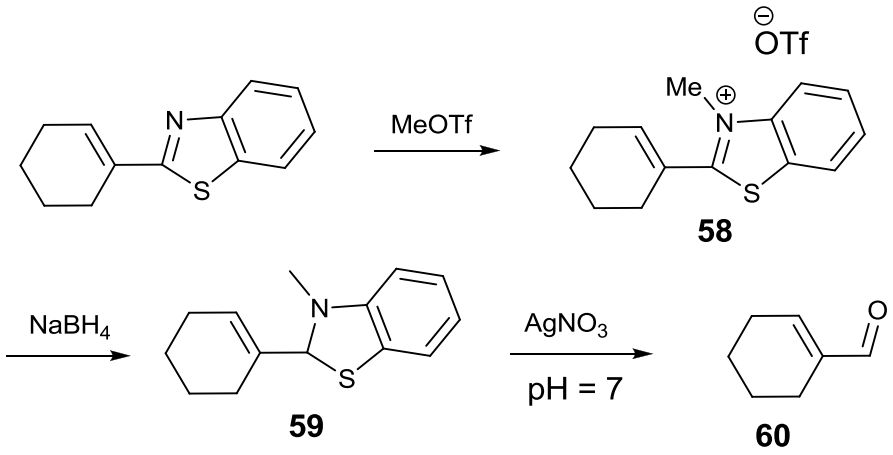


Figure 3

4. Preparation of Pentenoic acids and/or Pentenals via Azole Cleavage

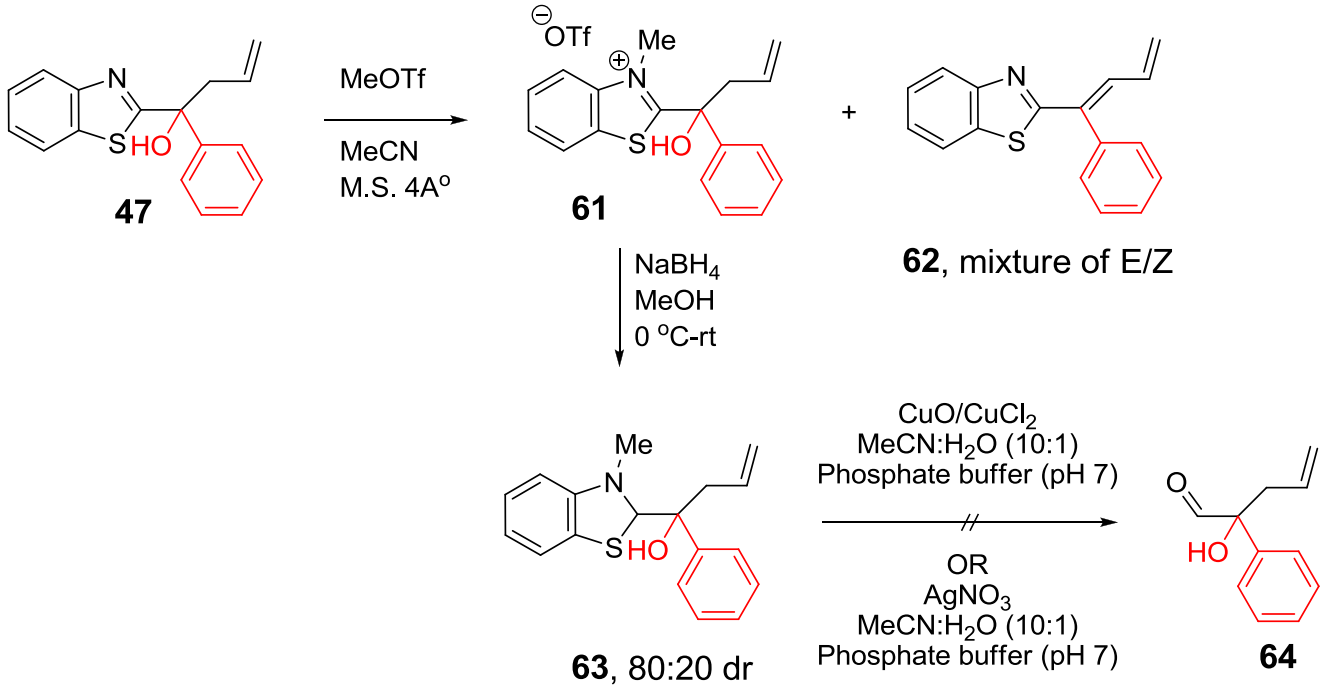
Azoles can serve as carboxylic acid surrogates. A variety of methods are available for their conversion into acids and other carbonyl derivatives. Dondoni and others have reported some methods for the conversion of thiazoles and benzothiazoles into acids and/or aldehydes.[63] The thiazole 'deprotection' typically begins with N-methylation of the azole with strong methylating agents such as methyl triflate or a large excess of methyl iodide to afford the azolium salt **58**. Borohydride reduction of the salt to the thiazoline **59** is followed by metal ($HgCl_2$, $AgNO_3$, or $CuCl_2$/CuO) assisted hydrolysis to provide the aldehyde.[64,65]



Scheme 29

Based on the above, we obtained N-methylated salt **61** along with a side product we have identified as diene **62**. Compound **62** was presumably formed from the triflic acid mediated dehydration of tertiary alcohol **47**. Salt **61** could be formed on gram scale and in an improved 80% yield by mixing tertiary alcohol **47** with methyl triflate in diethyl ether at room temperature. The precipitated white solid salt was then easily isolated by trituration with ether and filtration. $NaBH_4$ reduction of **61** gave benzothiazoline **63** as an

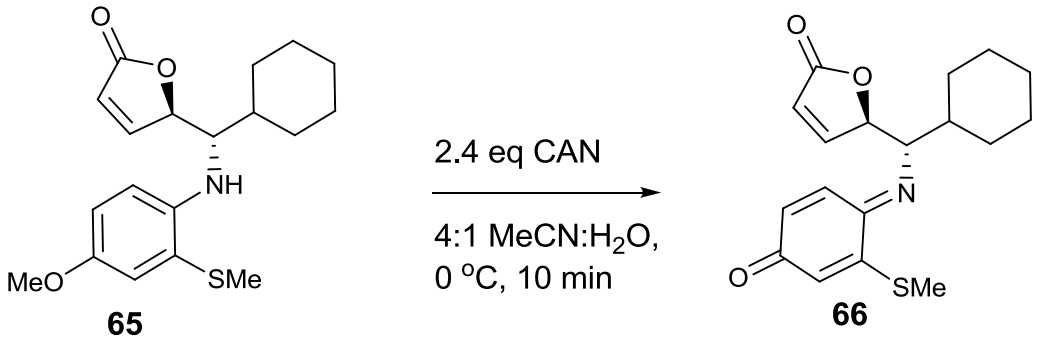
80:20 mixture of diastereomers (based on ^{1}H-NMR analysis). However, hydrolysis of **63** under the reported conditions or other modified conditions either failed to give α-hydroxy aldehyde **64** or formed it in very small amounts. Starting benzothiazoline **63** persisted even after heating to 50 ^{o}C (**Scheme 30**).



Scheme 30

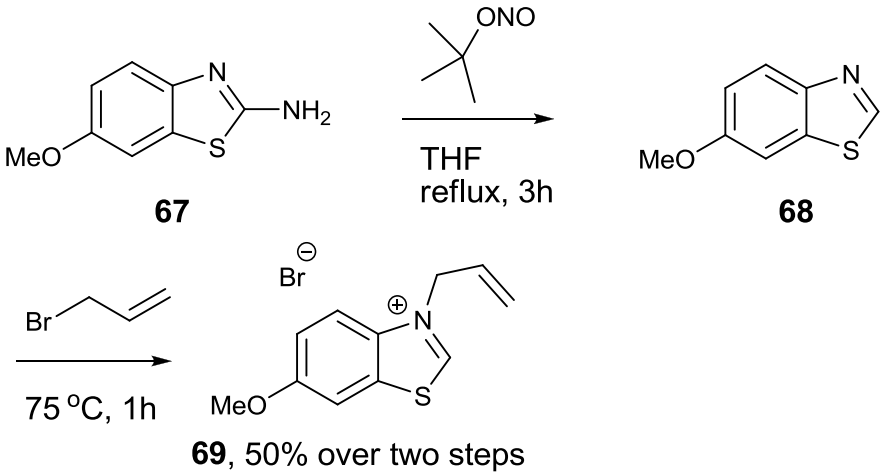
4.1 Oxidative Approach to Azole Cleavage

Hoveyda reported the synthesis of azaquinone **66** from the ceric ammonium nitrate (CAN) oxidation of secondary amine **65** (**Scheme 31**).[66] The methoxy group para to the amine makes the ring electron rich, thus susceptible to oxidative cleavage.



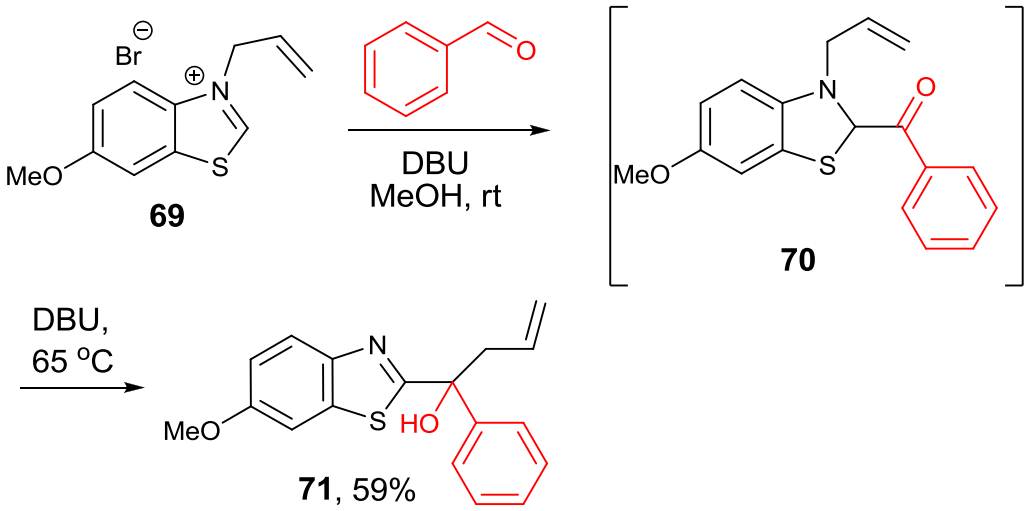
Scheme 31

We sought to develop a similar oxidative strategy towards azole cleavage starting from 6-methoxybenzothiazole tertiary alcohol **71**. Using a reductive deamination procedure reported by Swahn,[67] we obtained 6-methoxybenzothiazole **68** from commercially available 2-aminobenzothiazole **67**. The crude benzothiazole product was treated with neat allyl bromide at 75 °C to obtain salt **69** in 50% yield over two steps after trituration with ether and decantation.



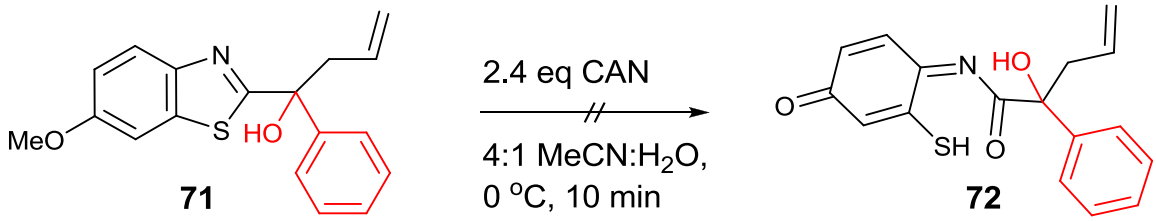
Scheme 32

To our delight, condensation of the N-allyl salt **69** with benzaldehyde and subsequent heating to 65 ^{o}C afforded the 6-methoxy substituted CR product **71** (via the ketone **70,** **Scheme 33**) in 59% yield.



Scheme 33

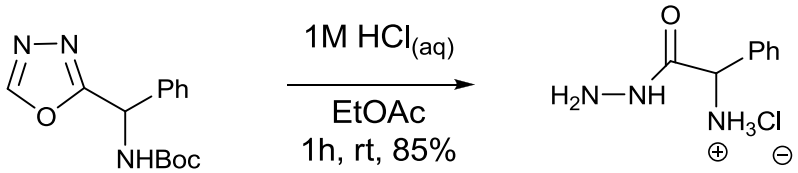
However, subjecting **71** to Hoveyda's conditions yielded no reaction (**Scheme 34**).



Scheme 34

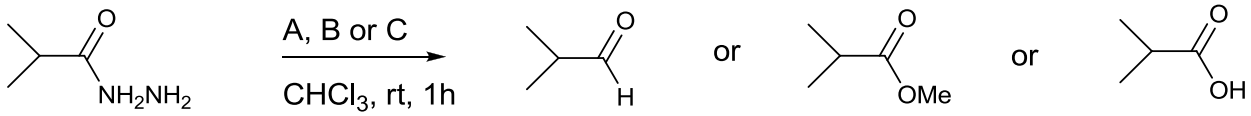
4.2 Use of Thiadiazoles as Masked Carbonyl Derivatives

We sought to extend our developed Claisen methodology to other heterocycles particularly oxadiazoles and thiadiazoles. The use of diazoles offers two unique possibilities: (i) 1,3,4 oxadiazoles on aqueous acid hydrolysis have been reported to yield acyl hydrazides.[68]



Scheme 35

Upon treatment with 2-iodoxybenzoic acid (IBX) under mild conditions, aliphatic acyl hydrazides have been converted into the corresponding aldehydes, esters, and carboxylic acids.[69]

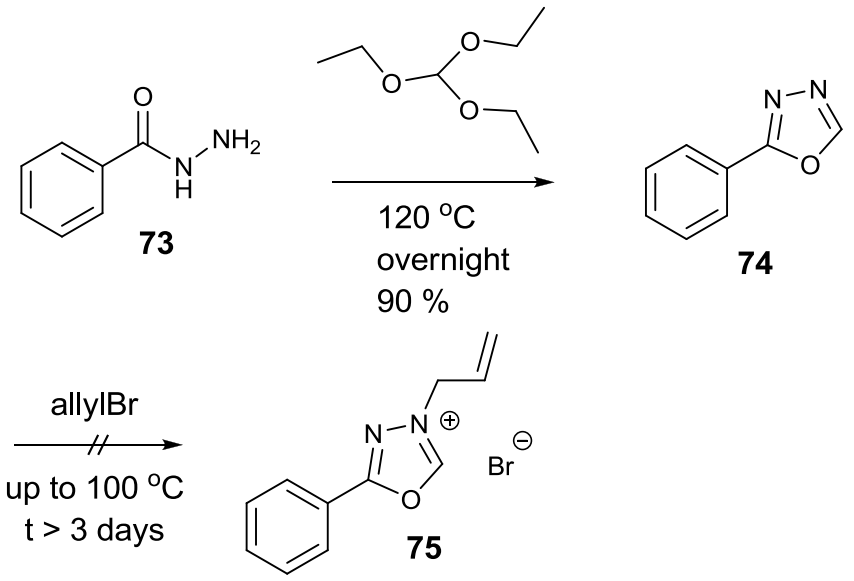


A: 1 eq IBX, NH_3 (10 mol%). B: 2 eq IBX, MeOH. C: 2 eq IBX, H_2O

Scheme 36

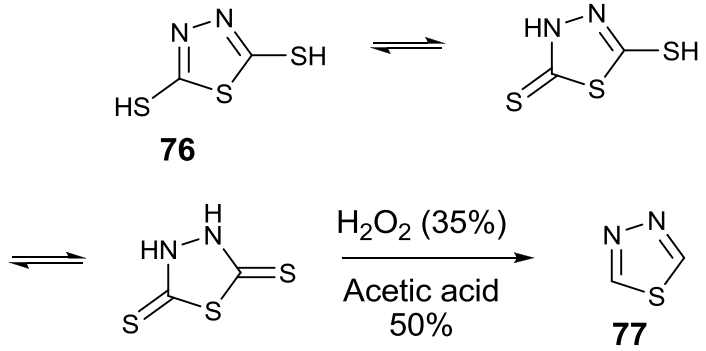
(ii) The presence of an additional Lewis basic nitrogen atom on the diazoles affords a second coordination point for catalysis,[36] thereby increasing the rigidity of the catalyst-substrate complex which we hope could translate into asymmetric induction.

Oxadiazole **74** was readily synthesized by condensation of the commercially available N-acylhydrazide **73** with triethyl orthoformate.[70] However, several attempts to obtain the N-allyl salts **75** failed (**Scheme 37**).



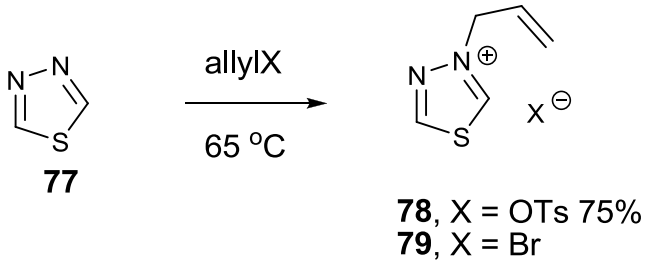
Scheme 37

Subsequently we looked at ways of accessing thiadiazoles instead. Commercially available precursors of thiadiazoles are 2-aminothiadiazole and 2,5-dimercaptothiadiazole. Attempts at reductive deamination of the 2-aminothiadiazole gave intractable product mixtures. Fortunately we were able to adapt a previously reported oxidative desulfurization of imidazolyl-2-thiones[71] to desulfurize 2,5-dimercaptothiadiazole **76**, obtaining thiadiazole **77** in 50% yield.



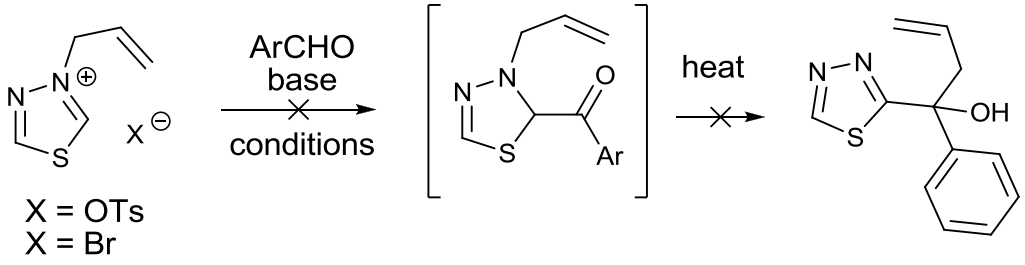
Scheme 38

Reacting **77** with neat allyl tosylate at 65 ^{o}C gave a viscous oil which on agitation in ether gave an off-white solid N-allylthiadiazolium tosylate **78** in 75% (quantitative based on NMR of crude reaction mixture) yield, while the reaction with allyl bromide at 65 ^{o}C gave a brown solid **79** within 30 minutes. Salt **79** was found to be air sensitive, so it was used without further purification.



Scheme 39

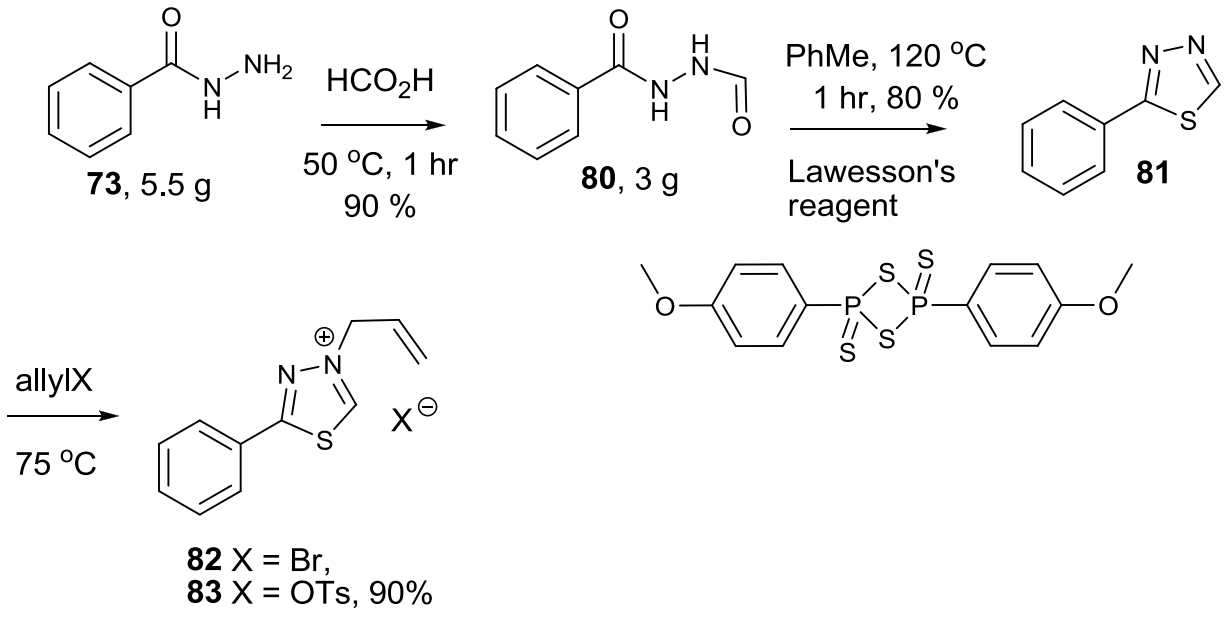
Despite the relative ease of accessing the respective salts, subjecting them to the previously developed Claisen rearrangement conditions or some modifications (different base, solvent, additives – catechol, titanium isopropoxide) consistently gave what seemed to be ring opened products and acyloin derivatives on heating.



Scheme 40

We then explored access to substituted thiadiazoles like phenylthiadiazoles, hoping to arrive at compounds that would be more stable under our Claisen reaction conditions. Starting from commercially available benzoyl hydrazide **73**, we were able to make N-

allyl salts of phenylthiadiazole **81** in three steps. Hydrazide **73** was condensed with neat formic acid at 50 ^{o}C to afford N-formyl benzoyl hydrazide **80** in 90% yield. The resulting hydrazide **80** was refluxed with Lawesson's reagent in toluene (0.04M) for 1-2 hours to obtain 2-phenylthiadiazole **81** in 80% yield (**Scheme 41**).[72]

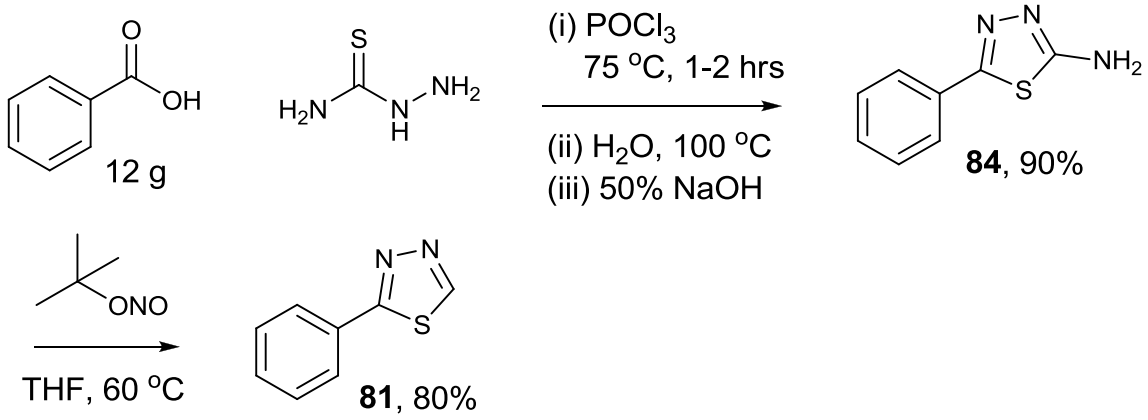


Scheme 41

As observed with the parent thiadiazole, the bromide salt **82** was not very stable at room temperature and was used without further purification while the tosylate salt **83** was obtained in 90% yield after vigorous trituration with ether.

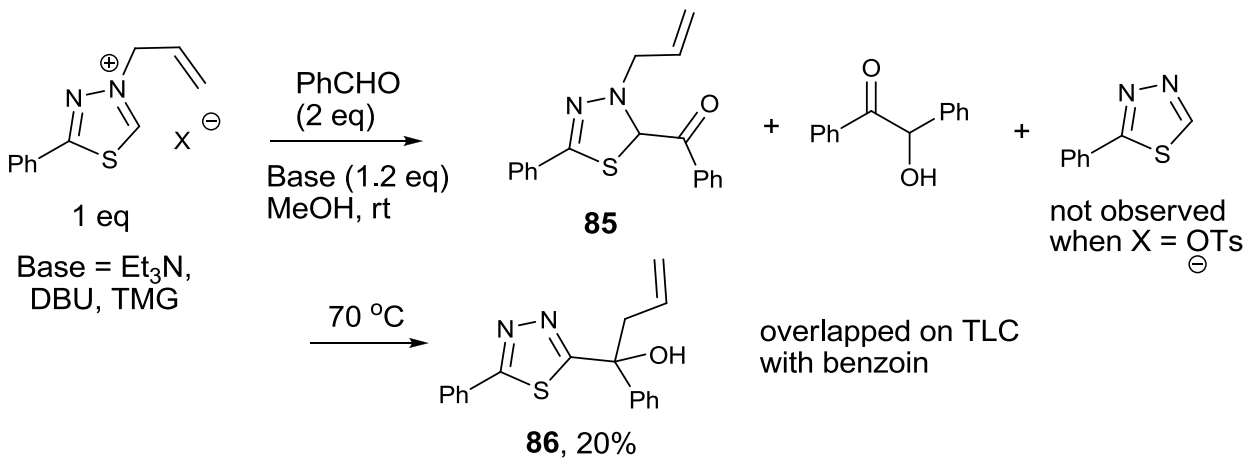
The use of stoichiometric Lawesson's reagent in this reaction has some drawbacks. Some of which includes (i) very poor atom economy – 400 mass units was lost to supply one sulfur (mass = 32) atom (ii) extremely volatile and malodorous thiophosphine side products and (iii) high dilution (0.04M reaction) required.

A more operationally feasible and scalable route for thiadiazole synthesis was thus developed to circumvent the above drawbacks. In addition, several other functionalized thiadiazoles could be readily accessed if needed.[73] Benzoic acid was condensed with N-aminothiourea in the presence of $POCl_3$ at 75 ^oC for 1-2 hours. After further refluxing in water for 4 hours and basifying the reaction mixture, the 2-aminothiadiazole product **84** precipitated out of solution and was purified by recrystallization from ethanol. Phenylthiadiazole was subsequently obtained by employing a previously applied reductive deamination strategy (**Scheme 42**).



Scheme 42

When the N-allylthiadiazolium bromide salt **82** was treated with benzaldehyde in the presence of several bases at room temperature, three major products were observed. In addition to the desired ketone product **85**, products of benzoin condensation as well as de-allylation (i.e. phenylthiadiazole) were obtained regardless of solvent and base. Heating this mixture to 70 ^oC gave the Claisen rearrangement product **86** in ca 20% yield (**Scheme 43**).



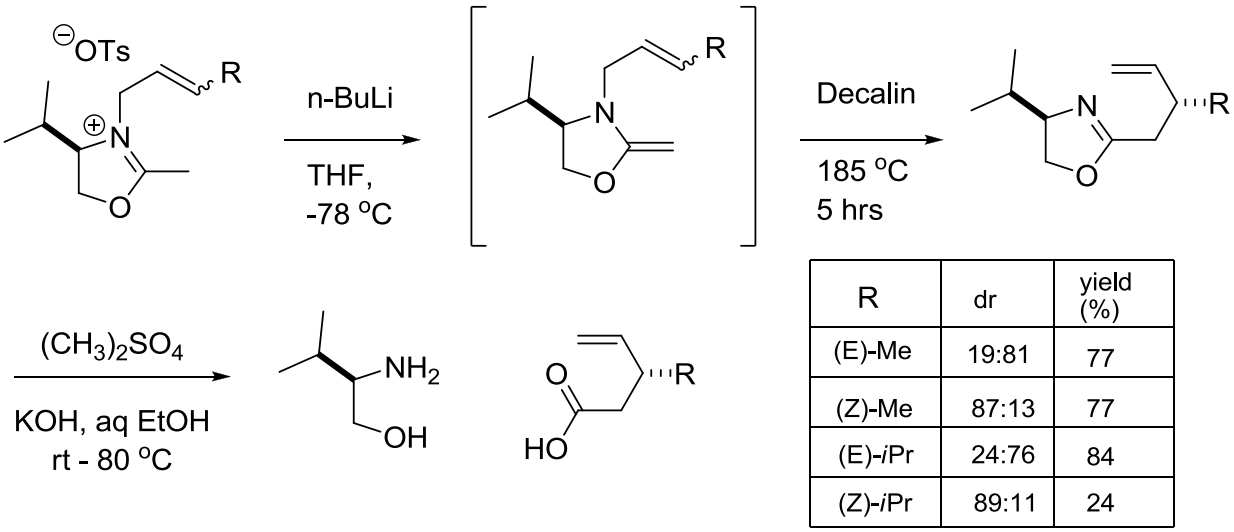
Scheme 43

The deallylation could be circumvented by using salts with a non-nucleophilic counterion like tosylate (salt **83**), but the benzoin product persisted regardless of counterion.

The carbenes obtained from these thiadiazoles are considerably more reactive than their thiazole counterpart on the basis of rate of formation of the key Breslow ketone intermediate as well as observation of products of acyloin condensation. Whereas ketone formation is observed in 0.5-24 hours (depending on how electron deficient the aldehyde substrate is) in the benzothiazole case, it was observed almost immediately (ca 5 minutes) with the thiadiazoles. By contrast, benzoin products were never observed in the benzothiazole case.

4.3 Chiron-mediated Approach to Asymmetric Induction and Azole Cleavage

We attempted to employ amino acid derived oxazolines and thiazolines as chiral auxiliaries towards asymmetric induction, borrowing a leaf from Kurth's approach.[39,74]

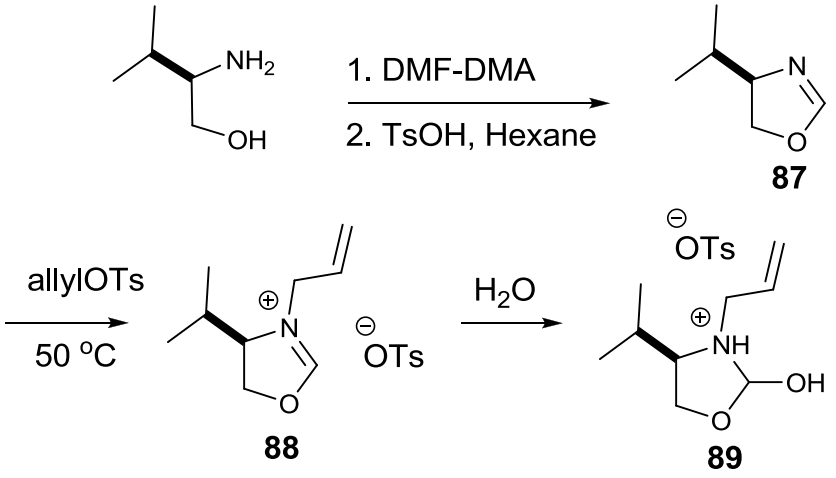


R	dr	yield (%)
(E)-Me	19:81	77
(Z)-Me	87:13	77
(E)-*i*Pr	24:76	84
(Z)-*i*Pr	89:11	24

Scheme 44

Herein the chiral auxiliary also serves as the carbonyl derivative 'mask', and as Kurth demonstrated, these azolines are easier to cleave off to release the necessary carboxylic acid products.

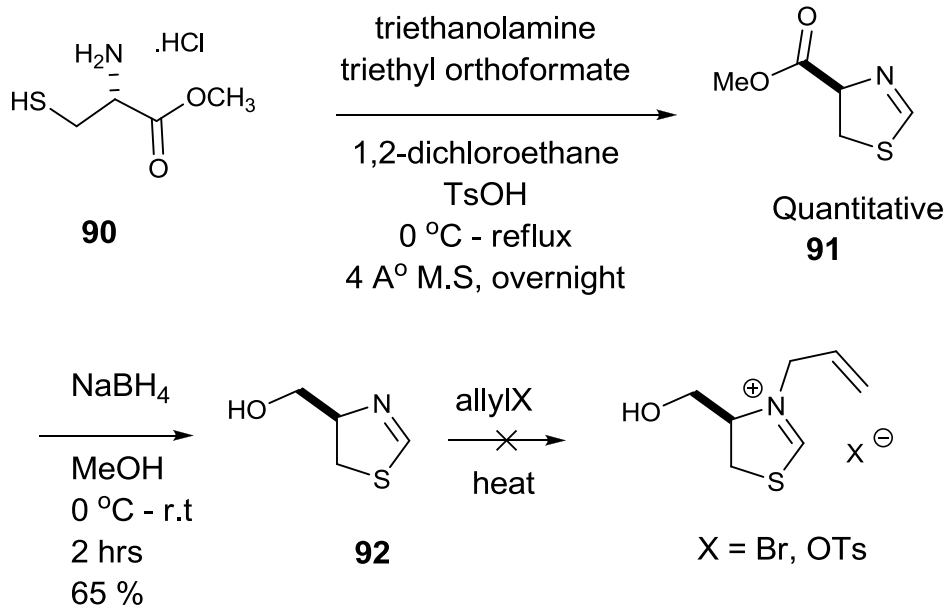
Starting from valinol and dimethylformamide-dimethylacetal, we obtained oxazoline **87** in 47% yield.[75] Heating to 50 °C with neat allyl tosylate gave a highly moisture sensitive salt **88** isolated as a mixture with the hydrate **89**.



Scheme 45

Treating this salt-hydrate mixture with base and aldehyde under our parent Claisen rearrangement conditions (or modified conditions) gave no reaction at room temperature or at elevated temperatures.

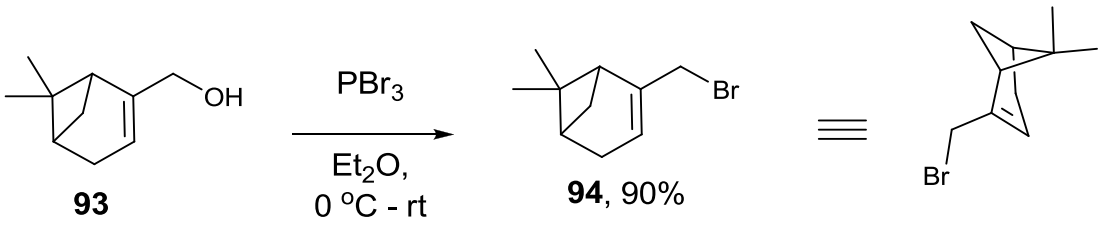
Subsequently, we looked at thiazolines to see if we could get some success. Following a reported procedure, we obtained thiazolinyl methyl ester **91** in quantitative yield from the condensation of the hydrochloric salt of cysteine methyl ester **90** with triethyl orthoformate in the presence of TsOH.[76] Sodium borohydride reduction of methyl ester **91** gave primary alcohol **92** in 65% yield.[77] However several attempts to allylate thiazolinyl methanol **92** only gave complex reaction mixtures.



Scheme 46

4.3.1 Substrate Control

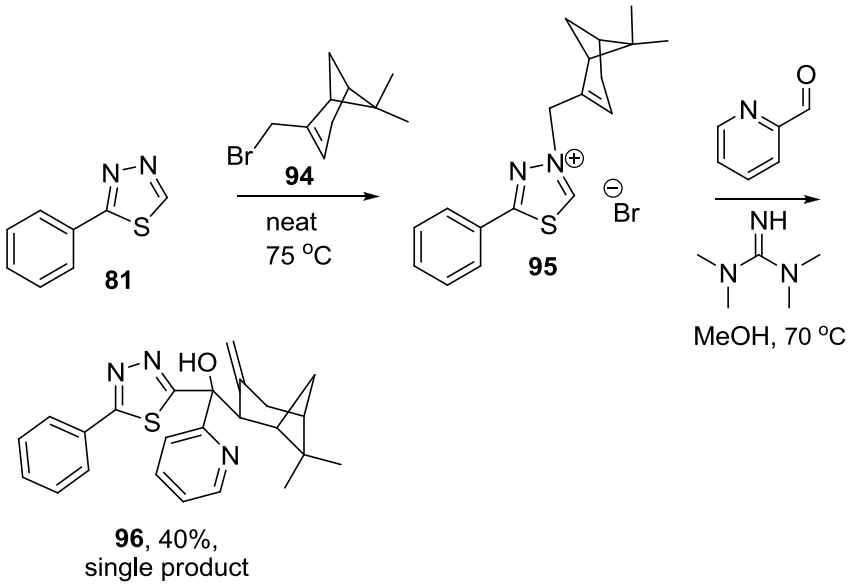
We subsequently attempted the use of chiral allylating agents to see if there could be any chirality transfer from the chiral salt to the rearranged tertiary alcohol. Myrtenol **93** is a commercially available terpene which was easily converted to the bromide **94** by the reaction with PBr_3 in 90% yield.[78]



Scheme 47

To our delight, bromide **94** effectively alkylated phenylthiadiazole **81** at 75 °C to produce N-myrtenylthiadiazolium bromide salt **95** in 80% yield. Subjecting salt **95** to our Claisen

condition (using tetramethylguanidine, TMG as base instead of DBU) gave tertiary alcohol **96** as the single product in 40% yield, with the configuration yet unknown.



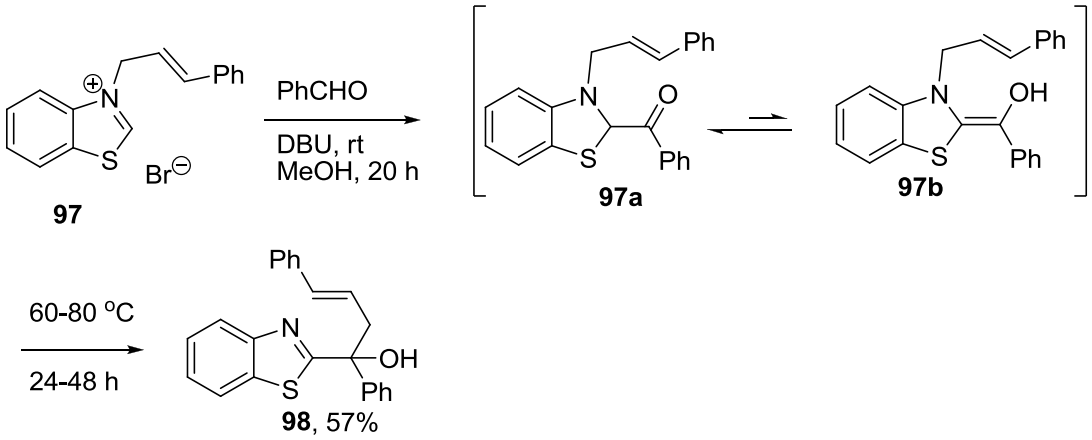
Scheme 48

CHAPTER THREE

Azole-Aldehyde Coupling: Mild and Efficient C2-Acylation of Azoles via Breslow Intermediate

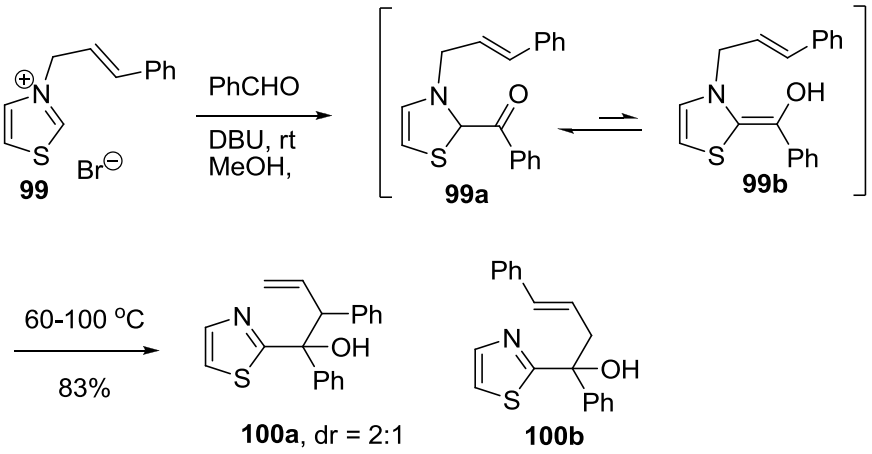
1. Introduction

While investigating the internal diastereoselection of our previously developed azole-based Claisen rearrangement (cf **Scheme 27**, Chapter 2), we observed some interesting trends especially when azolium salts with *E*-substituted *N*-allyl groups like cinnamyl or crotyl were employed **(Schemes 49-51)**. When the *N*-cinnamyl salts were employed, the outcomes with benzothiazole and thiazole were markedly different. In the benzothiazole case, the expected [3,3]-rearrangement product was only obtained in trace amounts. Rather, the major product observed pointed to a formal [1,3]-rearrangement.[79]



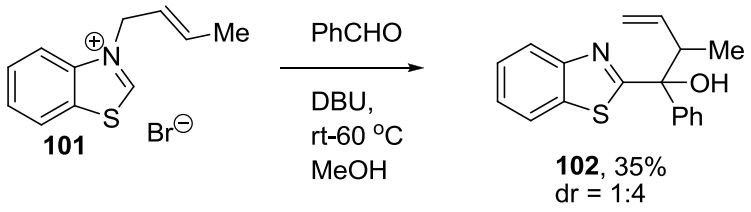
Scheme 49: [1,3]-Rearrangement of *N*-cinnamylbenzothiazolium Salts

When *N*-cinnamylthiazolium bromide salt **99** was subjected to the same reaction conditions, a mixture of [3,3]- and [1,3]-rearrangement products was obtained in approximately equal yields (overall yield = 83%).[79]



Scheme 50: [3,3]- and [1,3]-Rearrangement of *N*-cinnamylthiazolium Salts

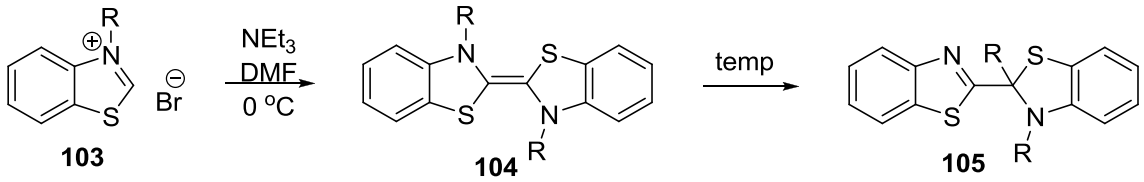
On the other hand, when *N*-crotylbenzothiazolium bromide salt **101** (used as a 3:1 E/Z mixture) was subjected to the same conditions, the [3,3]-rearrangement product was obtained in a modest 35% yield and 4:1 diastereomeric ratio, while no significant amount of [1,3]-product was observed.[79]



Scheme 51: [3,3]-rearrangement of *N*-crotylbenzothiazolium Salts

These results are consistent with Baldwin's report in 1974, wherein it was disclosed that depending on reaction temperature and the azolium *N*-substituent, two competing reaction pathways were in effect in the rearrangement of diaminofulvalenes derived from benzothiazolium salts. Reactions conducted at room temperature yielded predominantly [3,3]-rearrangement products when the azolium *N*-substituents were allylic (**Scheme 52**, cf **Scheme 17** Chapter 2). When the reactions were run at higher

temperatures, the yield of [1,3]-rearrangement products increased. While in situations where [3,3]- rearrangement was not possible (e.g. with *N*-benzyl salts), [1,3]-rearrangement products were exclusively observed (**Scheme 4**).[40]

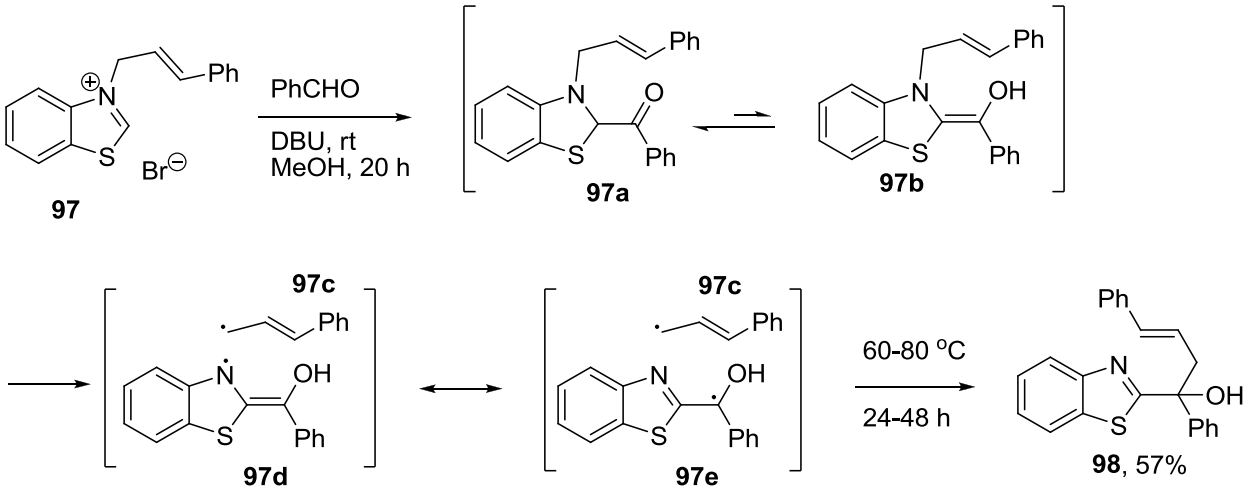


% Yield of [3,3]-Rearrangement

R	25 °C	75 °C	100 °C
$CH_2CH=CD_2$	100		
$CH_2CH=CHCH_3$	90	85	75
$CH_2CH=C(CH_3)_2$	60		30

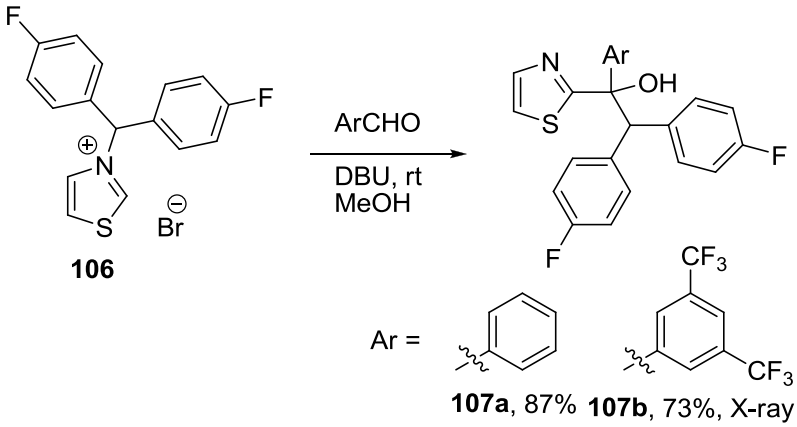
Scheme 52: Baldwin's [3,3]- and [1,3]-rearrangement of Electron-rich Olefins

Baldwin proposed a radical mechanism for the formation of the observed [1,3]-rearrangement products (cf **Scheme 52**),[49] and we believe the same mechanism is in effect in our systems (cf **Schemes 49 and 50**). C-N bond homolysis of the Breslow intermediate **97b** leads to the formation of resonance stabilized radicals: a nitrogen-centered radical **97d** and a carbon-centered radical **97c**. The final product **98** thus arises from radical recombination of **97c** and **97e** (**Scheme 53**).



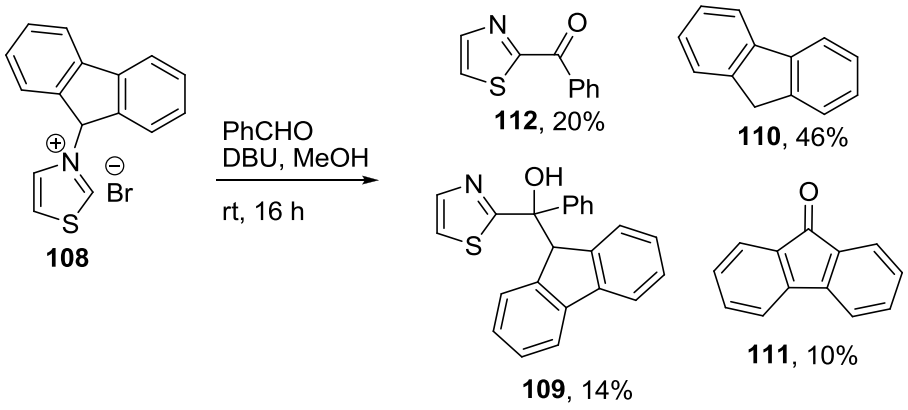
Scheme 53: Radical Fragmentation of a Breslow-type Intermediate

To exclude the possibility of the [3,3]-rearrangement, we sought to employ non-allylic azolium *N*-substituents that could still yield stable carbon-centered radical intermediates. Thus, when a methanolic solution of diphenylmethylthiazolium salt **106** was added to a mixture of an aromatic aldehyde and DBU at room temperature, products of [1,3]-rearrangement **107a,b** were obtained in modest to excellent yields.[79]



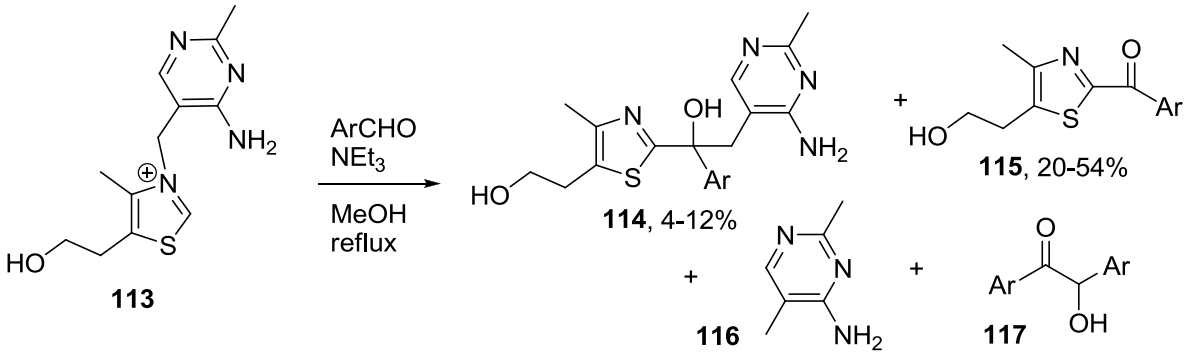
Scheme 54: [1,3]-Rearrangement of Diphenylmethylthiazolium Salt

Next, we sought to examine how a more radical stabilizing group like fluorene would fare in the reaction. On subjecting *N*-fluorenylthiazolium salt **108** to the previous reaction conditions with benzaldehyde at room temperature, a mixture of products was observed. One of the products precipitated out of methanol at room temperature and was isolated by filtration. This brown solid obtained was confirmed to be the [1,3]-rearrangement product **109**, isolated in 14% yield. Three other products were isolated from the filtrate by column chromatography: a white solid (Rf value 0.9 in 2% ethyl acetate in hexane) confirmed to be fluorene **110**, isolated in 46% yield, a yellow oil confirmed to be fluorenone **111** (Rf value 0.75 in 2% ethyl acetate in hexane), isolated in 10% yield and thiazolyl phenyl ketone **112** (Rf value 0.3 in 2% ethyl acetate in hexane) isolated in 20% yield (**Scheme 55**).



Scheme 55: Fragmentation Reaction of *N*-fluorenylthiazolium Salt

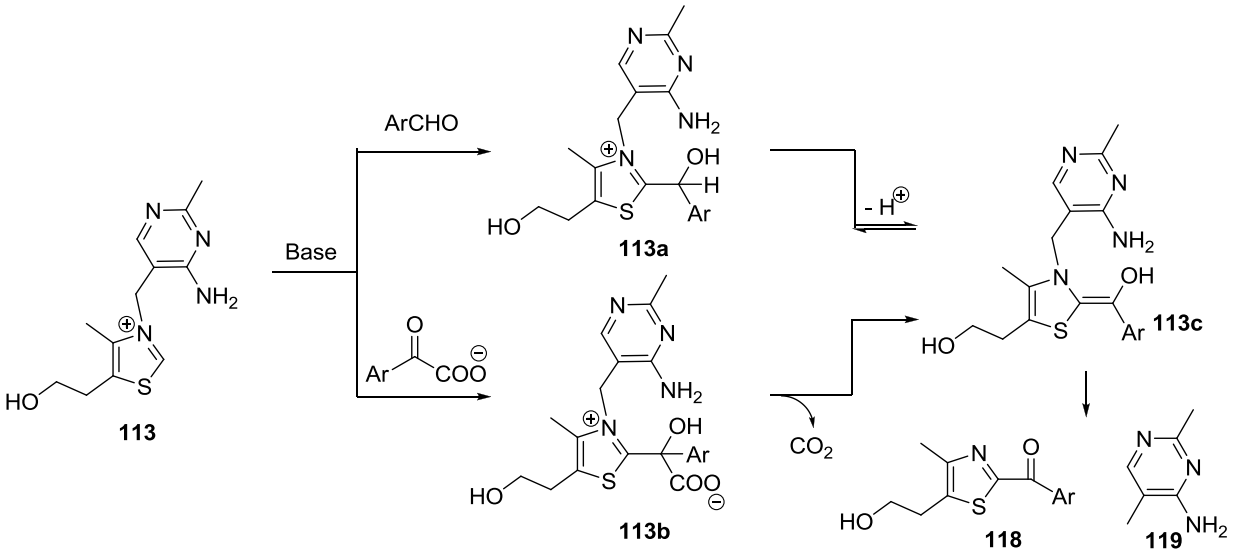
These observations seemed consistent with Oka's report in 1970, wherein he disclosed that upon adding an aromatic aldehyde to a refluxing mixture of thiamine hydrochloride salt **113** and triethylamine in methanol, low yields of rearrangement product **114**, fragmentation products ketone **115** and pyrimidine **116**, as well as significant amounts of benzoin product **117** were obtained (**Scheme 56**).[80,81]



Scheme 56: Oka Fragmentation of Thiamine

Given that the reactivity of thiamine especially in the presence of base and aldehyde has been extensively studied,[6,7,20,22] the mechanism proposed by Oka for the formation of these products seemed rather far-fetched.[81]

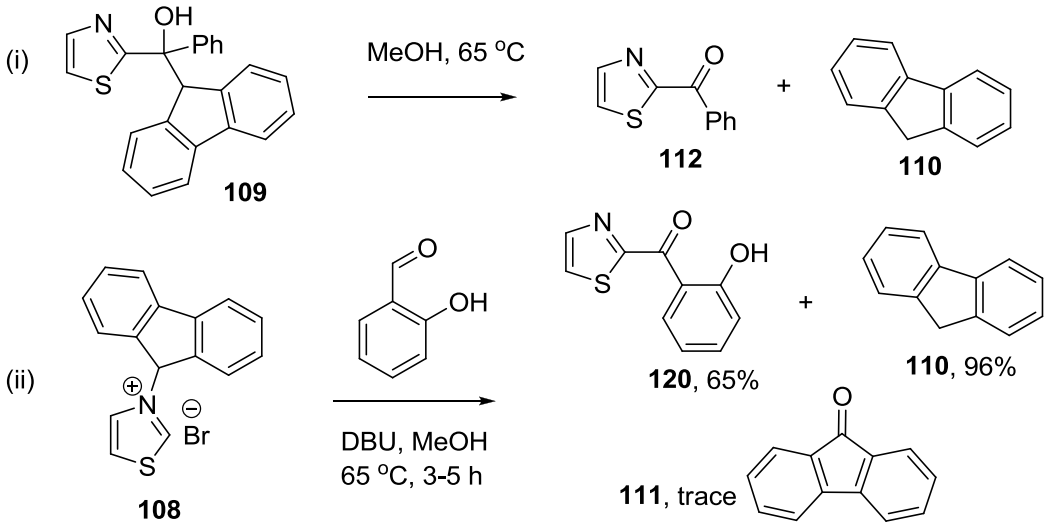
After a few years, Kluger embarked on an in-depth analysis of the Oka fragmentation and postulated that the cleavage occurred via an enamine (Breslow) intermediate, regardless of how this enamine was formed.[15,82,83]



Scheme 57: Oka Fragmentation via Breslow Intermediate

In his reports, Oka asserted that the amino group on the pyrimidine moiety was necessary for the fragmentation of **113c** into products **118** and **119**, as none of these products were observed when either the amino group was modified or when a different group altogether was placed on the azolium nitrogen.[80] This is contrary to our observation (cf **Scheme 55**), as we obtained analogous fragmentation products when an all-carbon based *N*-substituent, fluorine, was employed.

Despite several experimentations, the maximum yield of rearrangement product **109** obtained was modest at best. Thus, we wondered if perhaps compound **109** was unstable under the reaction conditions, and was rather fragmenting into the diaryl ketone **112** and fluorene **110**. To investigate this, we heated compound **109** in refluxing methanol in the absence of base, and indeed observed the formation of thiazolyl phenyl ketone **112** and fluorene **110** based on TLC analysis of authentic samples. Moreover, treatment of *N*-fluorenyl thiazolium bromide salt **108** with salicyaldehyde and DBU in refluxing methanol for a few hours exclusively provided the thiazolyl salicyl ketone **120** in 65% yield and fluorene **110** in 96% yield, with no precipitation/appearance of [1,3]-rearrangement product observed, and only trace amount of fluorenone **111**.



Scheme 58: Fragmentation of 13 and Azole-aldehyde Coupling Procedure

2. Background and Significance

Azoles are extremely common ring systems. In fact, a Scifinder substructure search for each of the parent azoles yielded over five million compounds (**Figure 4**). This high number of available azole substructure is partly reflected in their synthetic utility both as carboxylic acid surrogates[63] and bioisosteres.[84] For example, Dondoni and others have developed procedures for converting thiazoles and benzothiazoles to carbonyl derivatives,[64,65] while thiazoles are considered amide isosteres and are often important in drug development, when certain properties/effects are desired.[85]

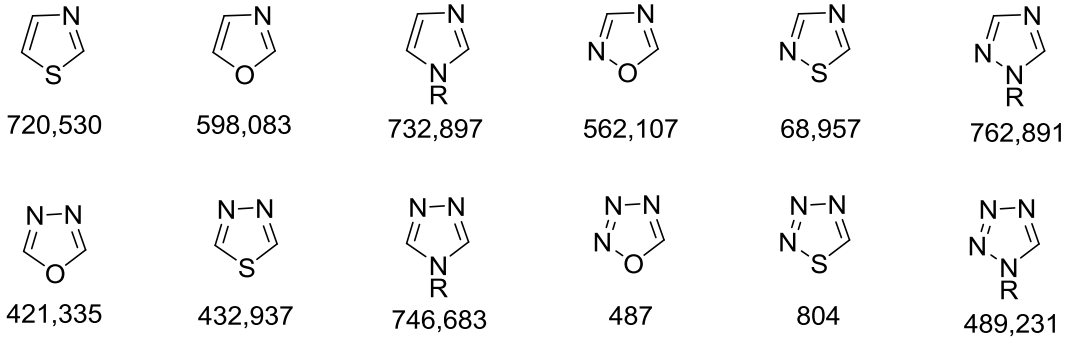


Figure 4: Scifinder Conventional Substructure Search Results

Azoles are also present in a large class of pharmaceutical and biomedical targets.[86–89] Over 50% of new chemical entities (NCEs) launched into the market in the last five years contain nitrogen heterocycles.[89–94] Thus any method that provides access to functionalized azoles in a mild and efficient manner will be attractive.

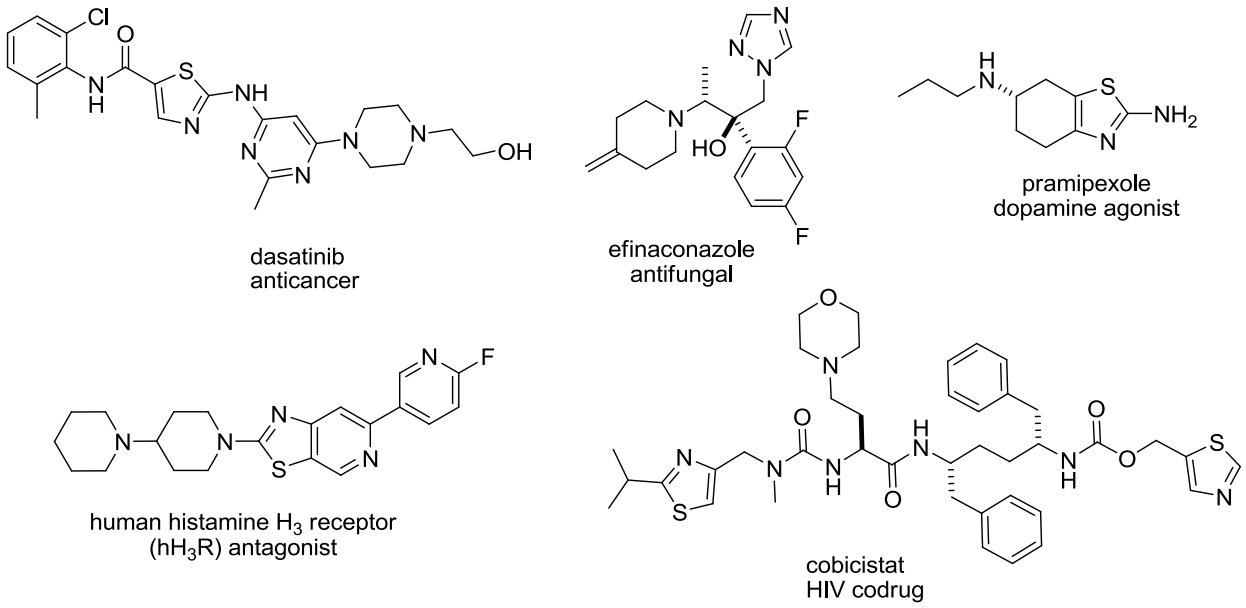


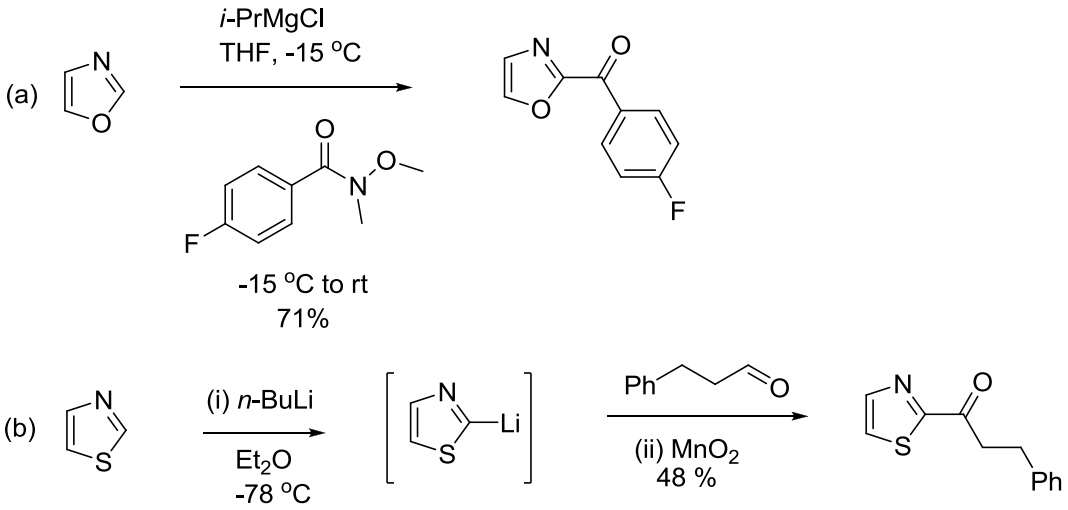
Figure 5: Some Azole-containing Drugs and Pharmaceutical Targets

Azolyl ketones, particularly thiazolyl and benzothiazolyl ketones, have been the subject of several medicinal chemistry efforts.[95–101] Thiazolyl ketones have shown potent activity as inhibitors of group IVA cytosolic phospholipase A_2 (GIVA $cPLA_2$) – an anti-inflammatory target.[96,97] In addition, they show useful activities in histone deacetylase inhibition, which is important in the process of DNA expression.[98,99] They are also precursors to (methoxyalkyl)thiazoles which are the core structure of a series of "potent, selective, and orally active 5-lipoxygenase Inhibitors".[102] Benzothiazolyl ketones on the other hand have been shown to be inhibitors of 17β-hydroxysteroid dehydrogenase 1

(17β-HSD1) - a novel therapeutic target for the treatment of estrogen dependent diseases like breast cancer.[103]

2.1 Azolyl Ketone Synthesis

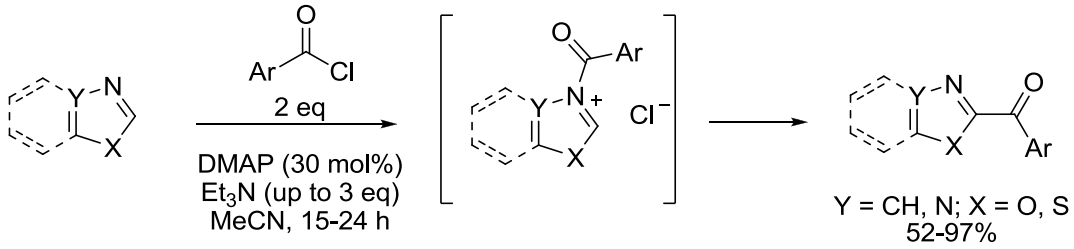
Azolyl ketones are often prepared by the addition of an organo Li or Mg reagent to a carbonyl containing precursor, e.g. a Weinreb amide,[104] or an aldehyde that is subsequently oxidized to a ketone.[105]



Scheme 59: Traditional Azolyl Ketone Synthesis

The use of strongly basic and nucleophilic organometallic reagents in traditional ketone synthesis has some major drawbacks, mostly due to functional group compatibility. In addition, unless the substituent is a simple, commercially available organometallic reagent, it must in turn be prepared by deprotonation,[63] metal-halogen exchange,[106] or transmetallation,[107] typically from an organostannane.[108] Finally, use of highly reactive nucleophiles typically requires the use of cryogenic conditions. On a production scale, this requires expensive reactor equipment and careful monitoring of reaction temperature due to the danger of exotherms.

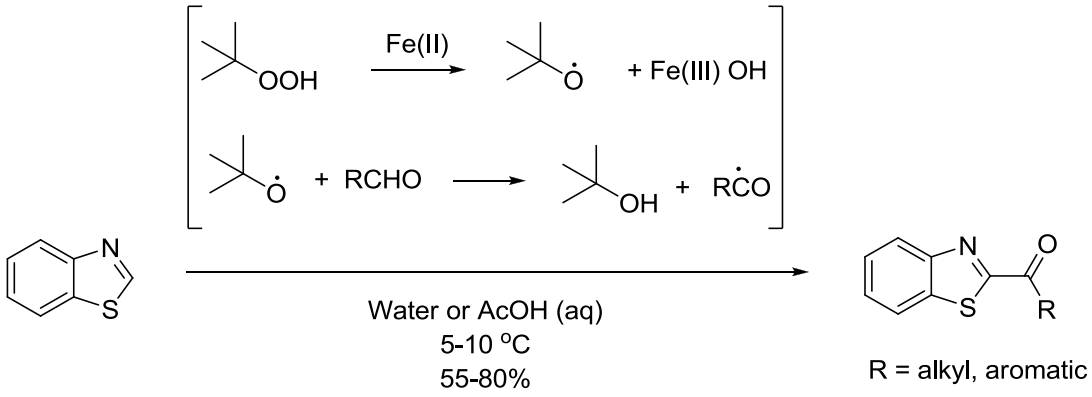
Regel reported a metal-free direct C-2 aroylation of azoles when he serendipitously discovered that the reaction of imidazoles with acid chlorides in the presence of a base gave C-2 acylated products rather than the expected *N*-acyl derivatives.[109,110] Hoarau improved on Regel's work by employing DMAP as catalyst. This led to an improvement in yield and reactivity especially with less basic azoles.[111]



Scheme 60: Regel-type Direct Aroylation of Azoles

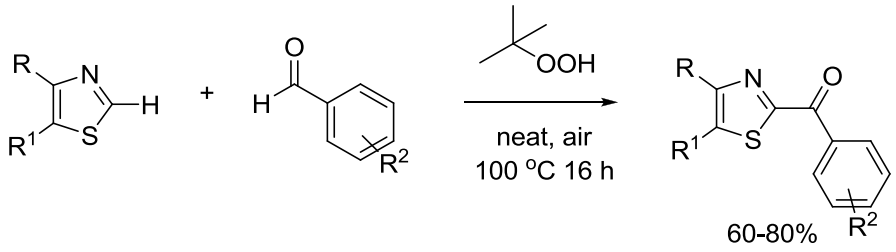
This method was effective for the aroylation of a variety of azoles including thiazoles, oxazoles, diazoles and benzazoles. However, a significant drawback is lack of tolerance for any acid sensitive functionality, free alcohols and amines.

In the presence of superstoichiometric amounts of ferrous sulphate and t-butyl hydroperoxide (TBHP), Minisci reported the generation of acyl radicals from aldehydes. He subsequently demonstrated that these radicals were capable of homolytically acylating heteroaromatic bases with good selectivities.[112,113]



Scheme 61: Minisci's Homolytic Acylation of Benzothiazoles with Aldehydes

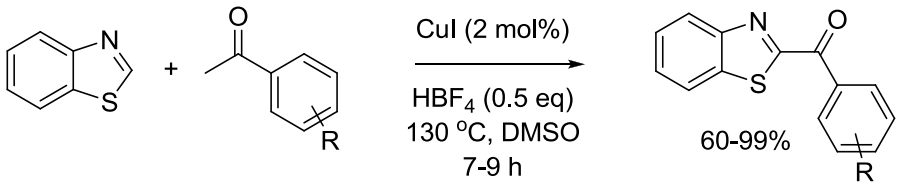
Bhanage reported a metal-free Minisci reaction for the synthesis of thiazolyl ketones. This methodology required heating the neat mixture of thiazole, aldehyde and t-butyl hydroperoxide to 100 ^{o}C under an air atmosphere.[114]



Scheme 62: TBHP Promoted Radical Aroylation of Thiazoles

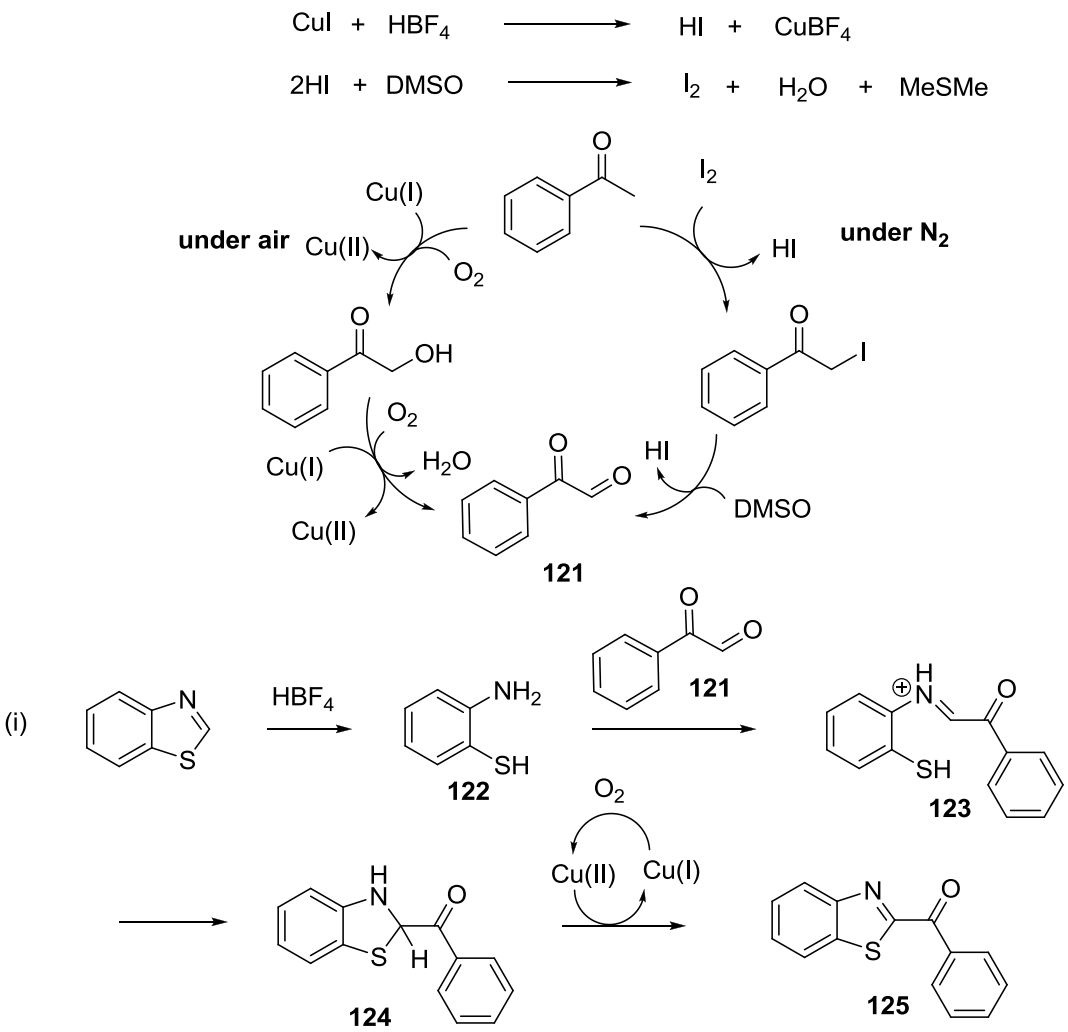
The thiazolyl ketones were formed presumably from the combination of a thiazolyl radical with an aldehyde acyl radical. Both radicals were generated in the presence of TBHP under air atmosphere.

Very recently, Song and Feng effected the acid-mediated aroylation of benzothiazoles with acetophenone in the presence of 2 mol% CuI in DMSO at 130 ^{o}C.[115]



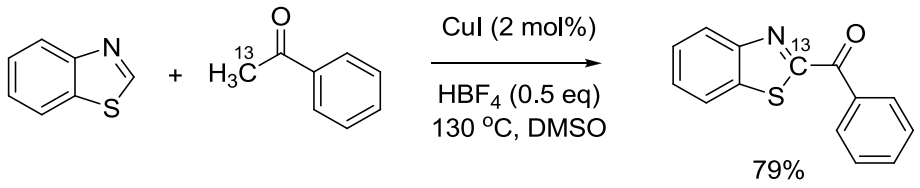
Scheme 63: Cu-catalyzed Acylation of Benzothiazoles with Acetophenones

Acid-mediated opening of the benzothiazole ring (to an o-aminothiophenol **122**) is followed by condensation with a phenylglyoxal, **121** – an oxidation product of acetophenone – to form an iminium ion **123**.



Scheme 64: Song's Benzothiazole and Acetophenone Coupling

Nucleophilic attack by the thiol on the iminium is followed by oxidation of the resultant benzothiazoline **124** to afford ketone **125**. The reaction was successful both under air or nitrogen atmosphere, with the difference in each case being the reactive intermediate that leads to the crucial glyoxal intermediate **121**. Deuterium labelling studies supports the ring-opening of the benzothiazole (**Scheme 65**).



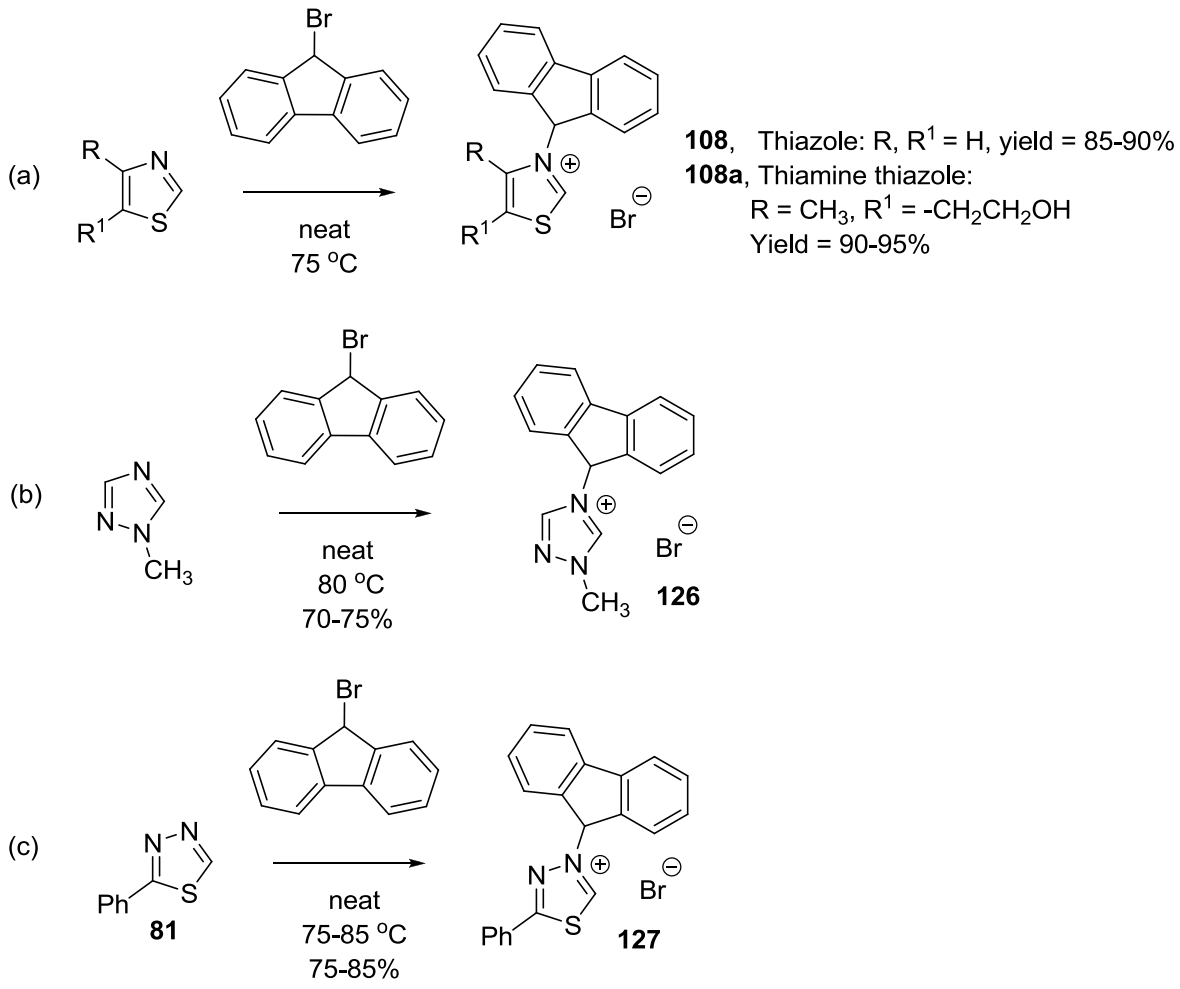
Scheme 65: Deuterium labelling Studies

The Minisci reaction and Song's method are limited to simple thiazoles and benzothiazoles. Furthermore, they will not be amenable to acid-sensitive and/or oxidizable functionalities or the presence of an azole with no substitution at C2.

3. Azole-Aldehyde Coupling via Breslow Intermediate.

3.1 *N*-fluorenyl Azolium Salt Formation

N-Fluorenyl azolium salts were readily synthesized by heating a neat mixture of the corresponding azole and commercially available 9-bromofluorene for a few hours at 75-85 ^{o}C. The solid obtained is subsequently triturated several times with diethyl ether and filtered or decanted. In the case where the starting azole is a solid, the reaction is carried out in acetonitrile and the salts are precipitated with diethyl ether.

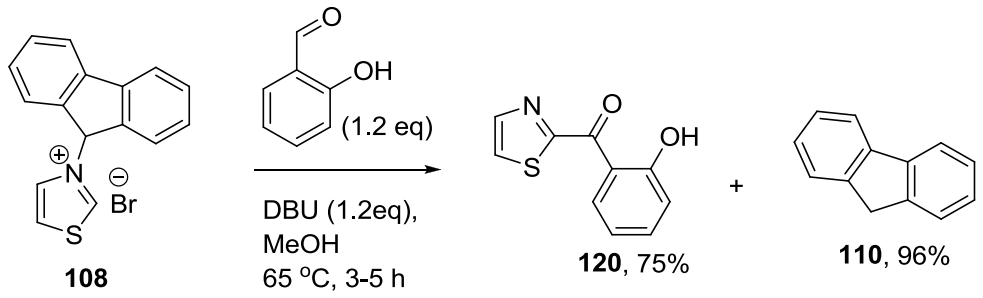


Scheme 66: Preparation of *N*-fluorenylazolium Salts

3.2 Reaction Optimization

On further experimentation, we discovered that 1.2 equivalents of aldehyde was sufficient to react with *N*-fluorenylthiazolium salt **108** to furnish the desired ketone product. Furthermore, after exploring several bases (Cs_2CO_3, K_2CO_3, tetramethylguanidine - TMG and triethylamine) and solvents (DMF, THF and MeCN), we discovered that the reactions with DBU in methanol or THF were the most consistent and reproducible. In THF, protonated DBU salt precipitated out of the reaction and was filtered out or carefully decanted with rinsing several times with THF, prior to product

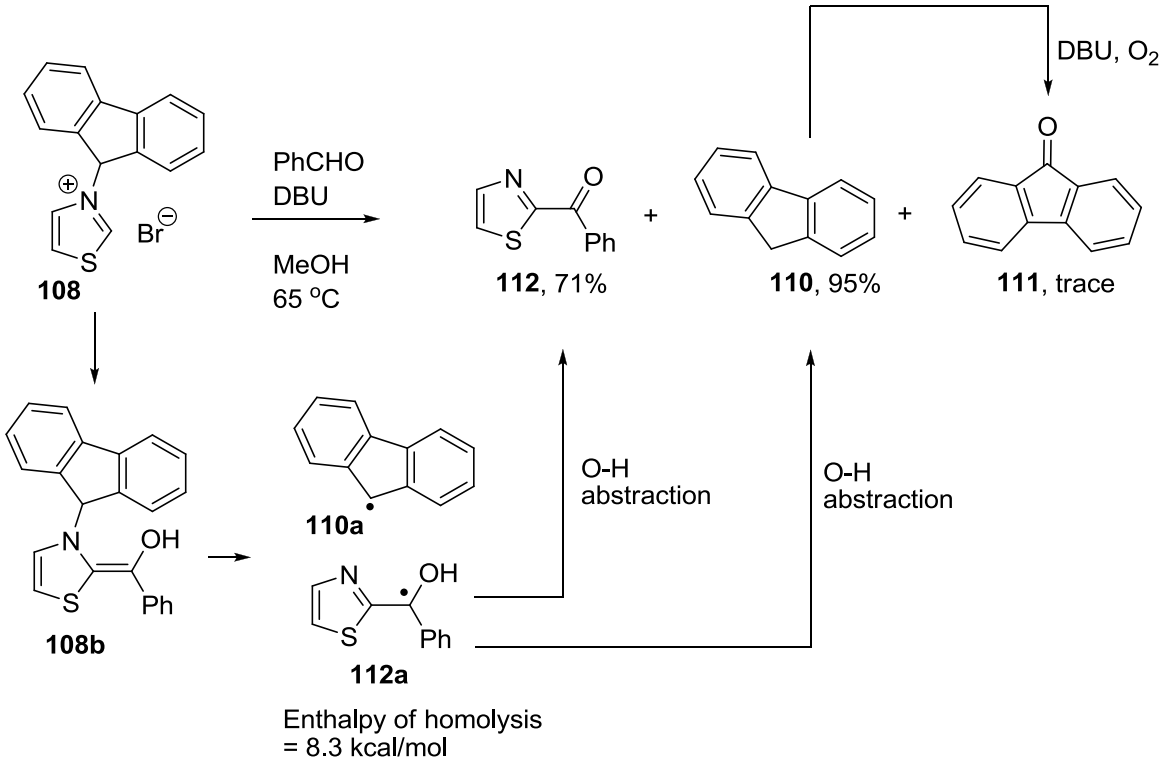
purification. Under this optimized conditions (1.2 eq of DBU added to a mixture of salt and 1.2 eq aldehyde in solvent, 0.15 M at 65 ^{o}C, stirred for 3-5 hours), the thiazolyl salicyl ketone was isolated in an improved 75 % yield (**Scheme 67**).



Scheme 67: Optimized Conditions for 2-ketothiazole Synthesis

3.3 Mechanism of Azolyl Ketone Formation

Following the formation of the Breslow intermediate **108b** from the reaction of salt **108** with benzaldehyde in the presence of DBU, a facile C-N bond homolysis of the *N*-fluorenyl bond occurs, leading to the formation of two stabilized radical intermediates **110a** and **112a**. DFT calculations (B3LYP/6-31g*) predicts the ΔH for the C-N bond homolysis to be 8.3 kcal/mol. We believe that O-H abstraction from **112a** affords the thiazolyl phenyl ketone **112**, subsequently fluorene is formed after this O-H abstraction by the fluorenyl radical **110a**. Fluorenone presumably arises from the oxidation of the fluorenyl anion.



Scheme 68: Mechanism of Azole-Aldehyde coupling

3.4 Reaction Scope: Thiazolyl Ketones

The *N*-fluorenylthiazolium bromide salt reacted with both electron neutral and electron poor aldehydes to afford 2-thiazolyl ketones in good yields. Slightly higher yields were observed with the more electron poor aldehydes **130** and **132**. For substrates containing an ester or other hydrolyzable groups, performing the reaction in MeOH resulted in hydrolysis and ester exchange, and no ketone formation was observed. In such situations, the reaction was performed in THF instead and it proceeded smoothly (e.g. compound **130**)

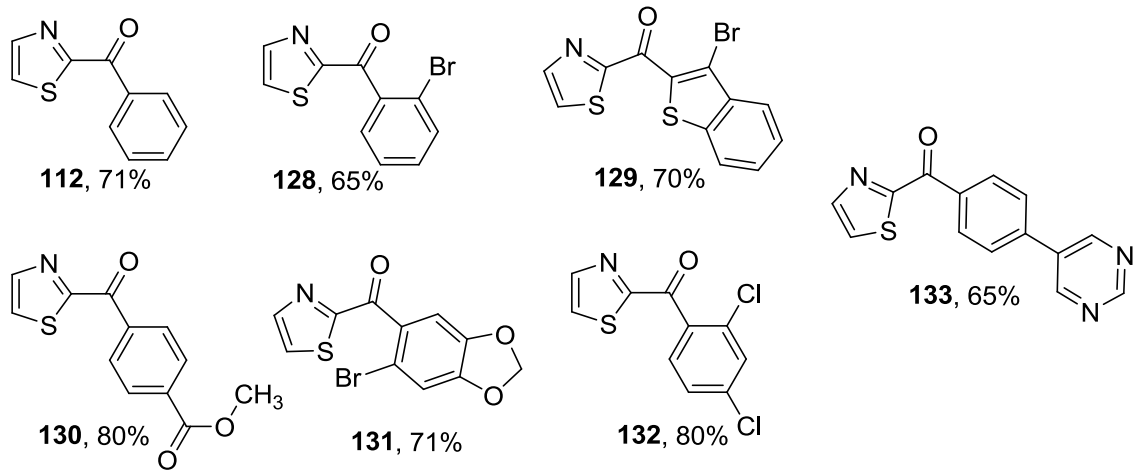


Figure 6: 2-Thiazolyl Ketones from Electro*n*-neutral and –poor Aldehydes

The reaction also works well with electron rich aldehydes, affording 2-aroylated thiazole products in very good yields. In fact an unprotected phenol was tolerated (cf **Scheme 67**). Ketone **120** will take more steps to make using the previously discussed traditional ketone synthesis (cf **Scheme 59**) or by Regel's method (cf **Scheme 60**). The fluorenyl salt obtained from thiamine-derived thiazole (**108a**, cf **Scheme 66 equation a**) containing an unprotected primary alcohol also reacted with salicyaldehyde to furnish ketone product **136** in 70% yield.

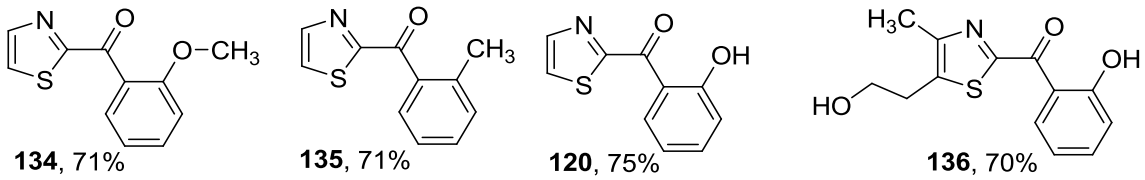
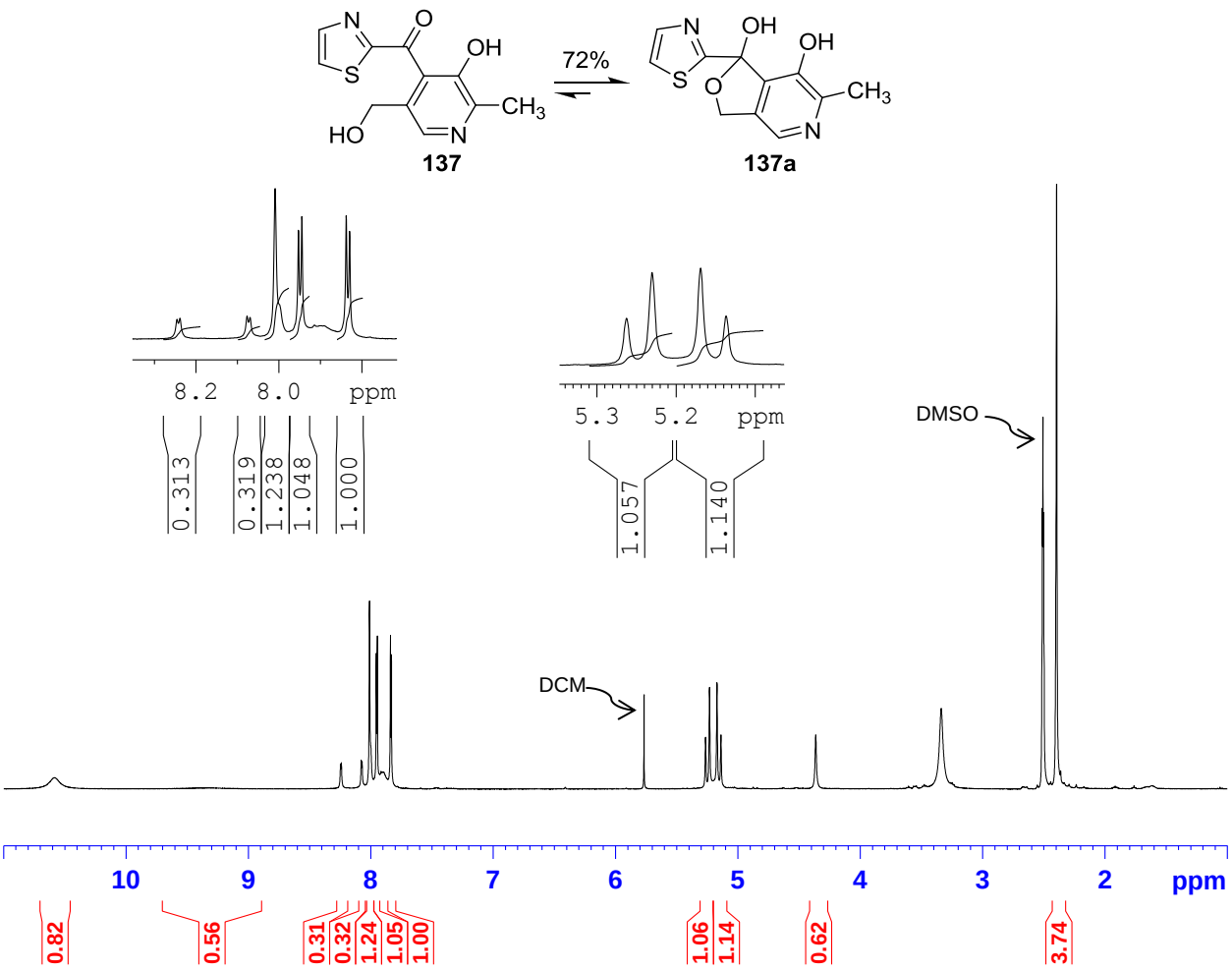


Figure 7: 2-Thiazolyl Ketones from Electron-rich Aldehydes and Thiamine-thiazole

We were delighted that pyridoxal – a form of vitamin B_6 (containing both a phenolic and aliphatic -OH) was tolerated. Interestingly, the product was isolated almost exclusively as the hemiacetal, presumably from the attack of the aliphatic -OH on the ketone.



Scheme 69: Thiazolyl Pyridoxal Ketone and Hemiacetal

We believe H-bonding existing between the carbonyl group and the 'phenolic' –OH renders the ketone C=O more susceptible to nucleophilic attack. On adding deuterated trifluoroacetic acid to a DMSO-D_6 solution of the ketone-hemiacetal mixture, signals corresponding to the ketone were more pronounced, but the equilibrium still largely favored the hemiacetal.

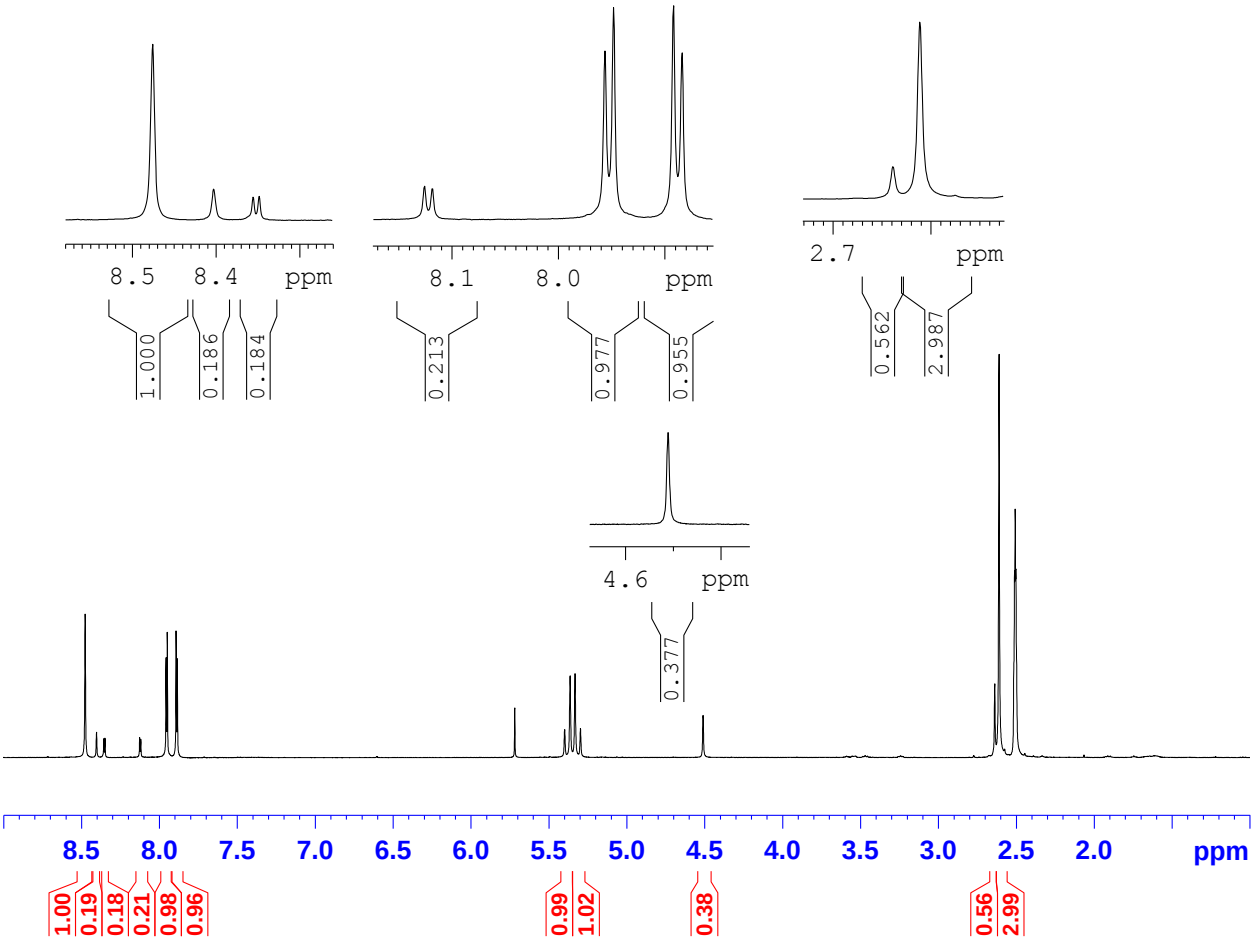
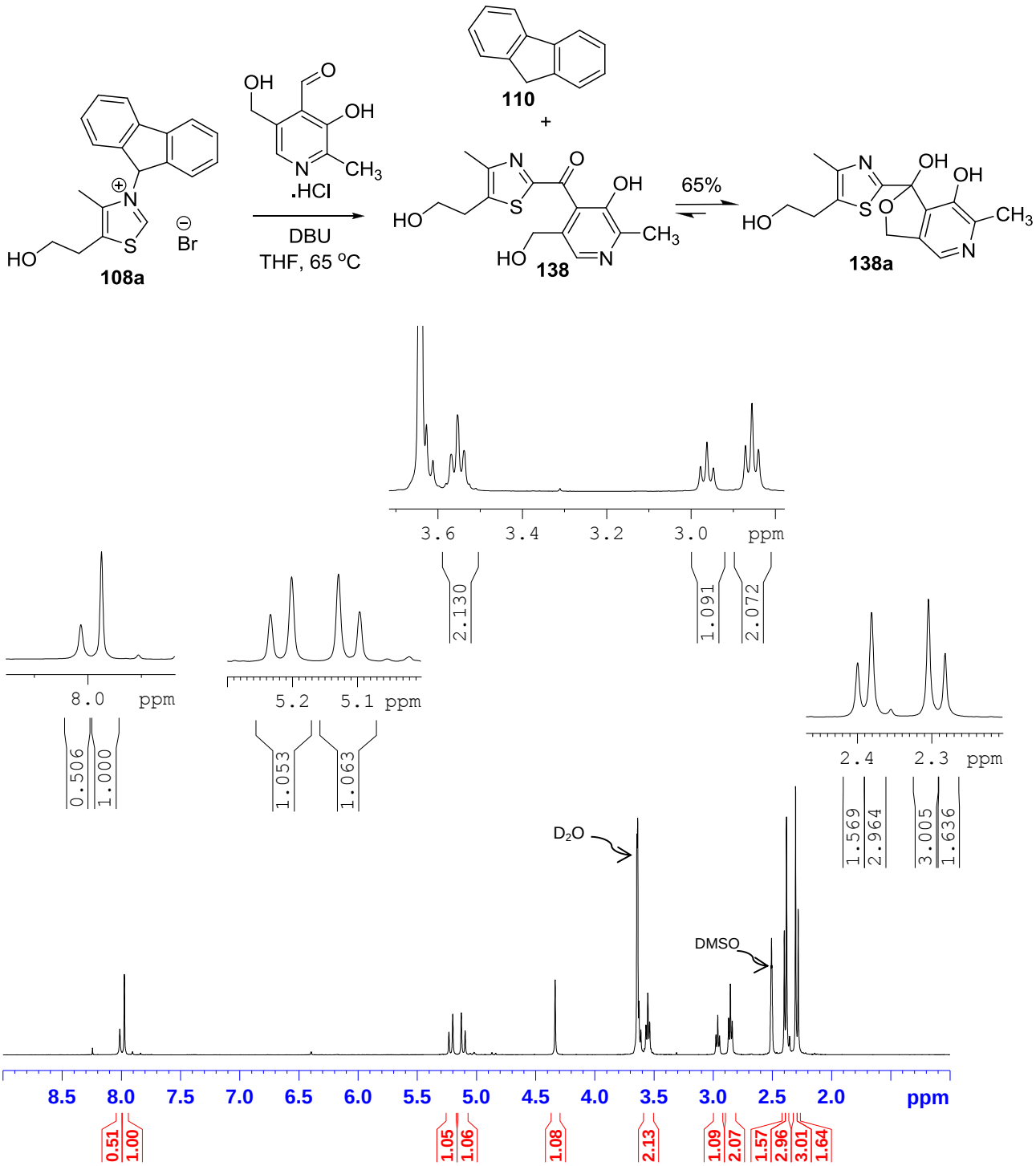


Figure 8: Thiazolyl Pyridoxal Ketone and Hemiacetal with TFA-D

We subsequently attempted coupling thiamine-derived thiazole (**108a** cf **Scheme 66 equation a**) with pyridoxal – thus having two vitamin B analogs (B_1 and B_6) in a single compound. As observed with thiazole, the ketone product **138** was obtained in the hemiacetal form (**138a**) when salt **108a** was combined with pyridoxal under the reaction conditions. Addition of D_2O led to the appearance of ^{1}H-NMR signals corresponding to ketone **138**.



Scheme 70: Thiamine-thiazole Pyridoxal Coupling

To introduce additional functionality, derivatives of salicyaldehyde were prepared so as to further emphasize the mildness of this method as compared to previously reported

methods for 2-ketoazole synthesis (vide supra). For instance, the metal-mediated radical acylation of azoles with aldehydes developed by Minisci, along with other reported variants will not tolerate aldehyde substrates containing azoles unsubstituted at C2 (e.g. **139**). The reaction also tolerates a terminal alkyne (**140**), while a sugar substituted salicyaldehyde reacted to give ketone **141.**

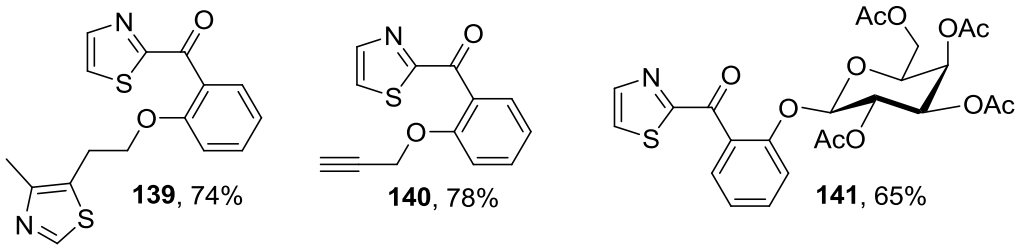


Figure 9: 2-Thiazolyl Ketones from Salicyl Derivatives

N-Fluorenylthiazolium salt also reacted with aliphatic aldehydes to give thiazolyl alkyl ketones however in diminished yields. Oka had indicated that aliphatic aldehydes only yielded α-hydroxy alkylthiazoles.[80]

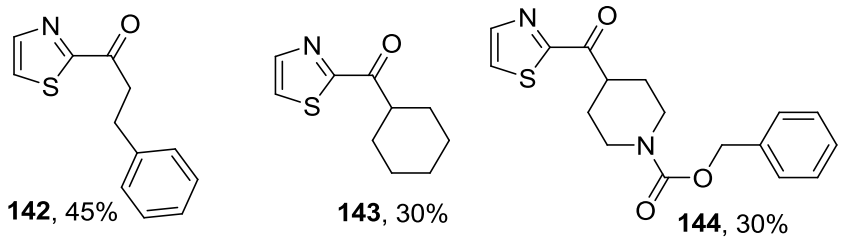


Figure 10: 2-Thiazolyl Ketones from Aliphatic Aldehydes

3.5 Other Azoles

We explored the synthesis of other azoles to examine the generality of the method . The less basic benzoxazoles and oxadiazole could not be alkylated with 9-bromofluorene after several attempts and modifications. When 1-methyl imidazole was reacted with 9-

bromofluorene, the requisite 3-fluorenyl salt was obtained. However, this salt was extremely moisture sensitive. A one-pot salt formation and acylation procedure was attempted, but this only gave complex reaction mixtures and products of benzoin condensation regardless of choice of base or solvent.

In contrast, 1-methyl-1,2,4-triazole gave very stable and easily isolable 4-fluorenyltriazolium salts **126** (cf **Scheme 66 equation b**). Subjecting this salt to the reaction conditions in methanol gave complex mixtures, but the reaction in THF gave clean 5-ketotriazole products.

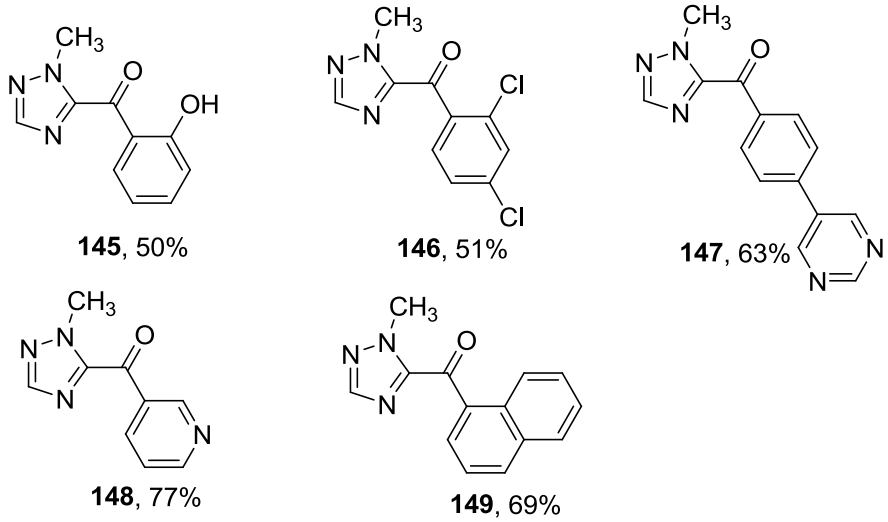
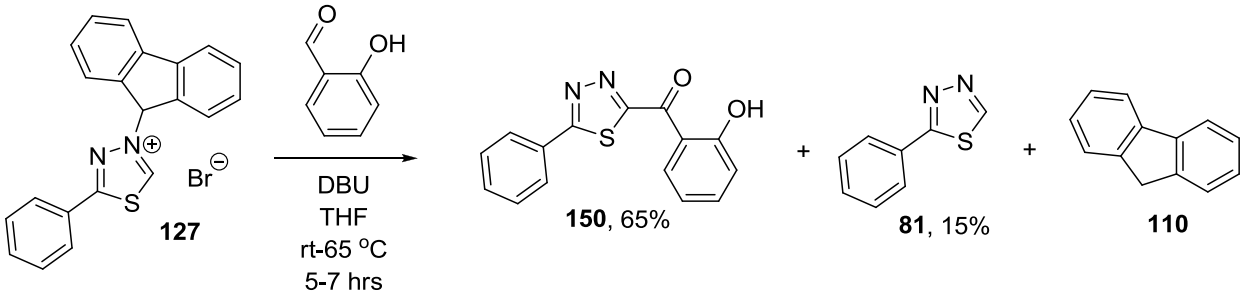


Figure 11: 5-Ketotriazoles from 1-Methyl-4-fluorenyltriazolium Salts

The reaction of 3-fluorenyl-5-phenyl-1,3,4-thiadiazolium bromide salt **127** (cf **Scheme 66 equation c**) also gave 2-ketothiadiazole product **150**. The reaction was stirred at room temperature for 5 hours followed by heating to 65 ^{o}C for ca 2 hours (**Scheme 20**). Phenylthiadiazole **81** was also isolated in 15% yield and this is due to ‘de-fluorenation’

of the salt **127**. This was also observed in the Claisen rearrangement project (cf **Scheme 50** Chapter 2).



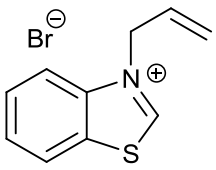
Scheme 71: 2-Ketothiadiazole formation from 3-Fluorenylthiadiazolium Salt

Experimental:

General Information

All reactions were conducted under a N_2 atmosphere using standard Schlenk techniques. Apart from this, no other scrupulous attempt was made to exclude air or moisture. Methanol was used without drying for azole-based Claisen rearrangement reactions, and was dried under 4Å molecular sieves for azole-aldehyde coupling reactions. THF, ether and dichloromethane were dried under an alumina packed column, while other commercially available reagents were used without additional purification unless otherwise indicated. Compound purification was effected by flash chromatography using 230x400 mesh, 60 Å porosity obtained from Sorbent Technologies; and by recrystallization from indicated solvents. Melting points were taken using a Stuart SMP 10 and a Fisher-Johns melting point apparatuses. Proton and ^{13}C NMR spectra were obtained on a 400 MHz Bruker Avance spectrometer. Structural assignments were based on ^{1}H, ^{13}C, and IR spectroscopies and X-ray crystallography. Elemental analyses were performed by Atlantic Microlab, Inc.

Procedure for the Preparation of Compounds

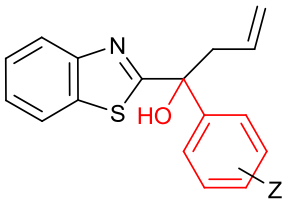


Salt **44**: This is a slight modification of the procedure reported by Hor et al: Yen, S. K.; Koh, L. L.; Huynh, H. V.; Hor, T. S. A. *Dalton Trans.* **2007**, 3952-3958.

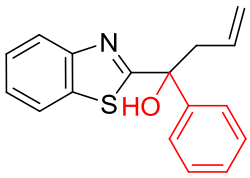
Benzothiazole was mixed neat with a slight excess (1.2 eq) of allyl bromide and the mixture was maintained at 75 °C until the reaction mixture solidified (45-60 min). The

resulting salt was then triturated twice with acetone for 10 min. The solvent was decanted and the solid dried in vacuo for 30 min to yield **44** in 85% yield. Data matched that reported by Hor et al.

Tertiary Benzothiazolyl Aryl Alcohols (47-57):



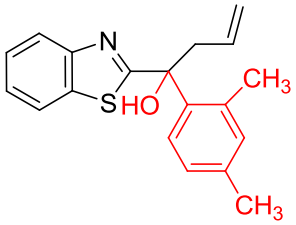
A 0.2 M methanolic solution of salt **44** (200 mg salt in 4 mL of MeOH) was added over 20 min to a neat mixture of aldehyde (2 eq) and DBU (1.2 eq) at room temperature. After TLC analysis indicated that ketone formation was complete (16-48 h), a second charge of DBU (0.8 eq) was added and the mixture was heated to 60-80 °C for 16-72 h. Solvent was removed in vacuo and product was purified using column chromatography using hexanes/ethyl acetate as eluent. Where possible, the product was recrystallized from Et_2O, petroleum ether or hexanes.



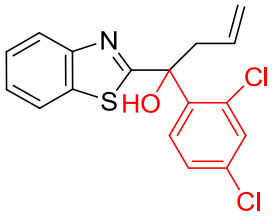
47: Data matched that reported by Troisi et al: Capriati, V.; Florio, S.; Ingrosso, G.; Granito, C.; Troisi, L. *Eur. J. Org. Chem.* **2002**, 478-484.

Eluent: 98:2 hexanes/EtOAc; colorless crystals (petroleum ether), m.p. 55-58 °C. ^{1}H, NMR (400 MHz, CDCl3) δ 3.11 (dd, 1H, *J* = 7.9, 13.9 Hz, RCH*H*R^1), 3.47 (dd, 1H, *J* = 6.6, 13.9 Hz RC*H*HR^1), 3.65 (br. s, 1 H, exchanges with D_2O), 5.27 (m, 2H, H_2C=CHR), 5.77 (ddt, 1H, *J* = 7.2, 10, 17 Hz, RC*H*=CH_2), 7.28 (m, 1H, Het Ar CH), 7.37 (m, 3H, overlapping Ar CHs), 7.48 (ddd, 1H, *J* = 1.3, 7.3, 8.2 Hz, Het Ar CH), 7.73 (app d, 2H, *J*

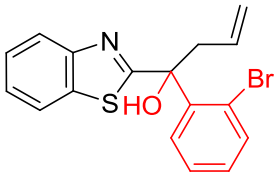
= 7.9 Hz, Ar CH), 7.85 (d, 1H, *J* = 9.9 Hz, Het Ar CH), 8.04 (d, 1H, *J* = 8.1 Hz, Het Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 47.3 (=CH*C*H2R), 77.74 (quat *C*-OH), 121.3 (H_2C=CHR), 121.7 (R*C*H=CH2), 123.2 (Ar CH), 125.0 (Ar CH), 125.4 (Ar CH), 125.9 (Het Ar CH), 127.7 (Het Ar CH), 128.4 (Het Ar CH),132.5 (Het Ar CH), 135.7 (quat. Ar C), 143.4 (quat. Ar C), 153.1 (quat. Ar C), 177.9 (SC=N). IR (CH_2Cl_2) υ_{max}: 3427 (br), 3069, 2921, 1658, 1502. Elemental Analysis: calcd for $C_{17}H_{15}NOS$: C 72.57 H, 5.37 N 4.98, found C 72.34 H, 5.55 N 5.08.



48: Eluent: 98:2 hexanes/EtOAc; brown solid, m.p. 109-111 °C. ^{1}H, NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H, $PhCH_3$), 2.32 (s, 3H, $PhCH_3$), 3.31 (m, 2H, RCH_2 R[1]), 3.67 (s, 1H, exchanges with D_2O), 5.23 (m, 2H, CH_2=CHR), 5.84 (ddt, 1H, J = 7.2, 10.2, 14.4 Hz, RC*H*=CH_2), 6.98 (s, 1H, Ar CH), 7.06 (d, 1H, J = 8.0 Hz, Ar CH), 7.37 (t, 1H, J = 7.6 Hz, Het Ar CH), 7.48 (t, 1H, J = 7.7 Hz, Het Ar CH), 7.53 (d, 1H, J = 8.0 Hz, Ar CH), 7.82 (d, 1H, J = 7.9 Hz, Het Ar CH), 8.03 (d, 1H, J = 8.0 Hz, Het Ar CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.88 ($PhCH_3$), 21.55 ($PhCH_3$), 46.27 (=CH*C*H2R), 77.99 (quat C-OH), 120.65 (H_2C=CHR), 121.70 (R*C*H=CH_2), 123.26 (Ar CH), 125.07 (Ar CH), 125.94 (Ar CH), 126.30 (Het Ar CH), 126.45 (Het Ar CH), 132.64 (Het Ar CH), 133.52 (Het Ar C), 135.99 (quat Ar C), 137.40 (quat Ar C), 137.90 (quat Ar C), 138.07 (quat Ar C), 152.37 (quat Ar C), 178.12 (SC=N); IR (CH_2Cl_2) υ_{max}: 3434 (br), 1636, 1504; Elemental Analysis: calcd for $C_{19}H_{19}NOS$: C 73.75 H, 6.19 N 4.53, found C 73.47 H, 6.23 N 4.41.

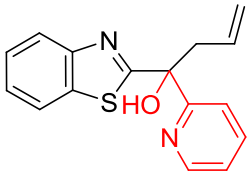


49: Eluent: 95:5 hexanes/EtOAc; colorless crystals (petroleum ether), m.p. 108-110 °C. ^{1}H, NMR (400 MHz, CDCl3) δ 3.42 (dd, 1H, *J* = 7.0, 14.2 Hz, RCH*H,* R^{1}), 3.51 (dd, 1H, *J* = 7.2, 14.2 Hz RC*H*HR^{1}), 3.70 (br. s, 1 H, exchanges with D_2O), 5.18 (dd, 1H, *J* = 1.0, 10.2 Hz H_a), 5.23 (dd, 1H, *J* = 1.1, 17.2 Hz H_b), 5.81 (ddt, 1H, *J* = 7.1, 10.2, 17.2 Hz, RC*H*=CH_2), 7.33 (dd, 1H, J = 2.0, 8.6 Hz Ar CH), 7.38 (d, 1H, J = 1.8 Hz Ar CH) 7.41 (d, 1H, J = 7.9 Hz, Ar CH), 7.49 (t, 1H, J = 7.7 Hz, Het Ar CH), 7.79 (d, 1H, *J* = 8.5 Hz, Het Ar CH), 7.86 (d, 1H, *J* = 8.0 Hz, Het Ar CH), 8.03 (d, 1H, *J* = 8.0 Hz, Het Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 43.8 (=CH*C*H2R), 120.5 (H_2C=CHR), 121.8 (R*C*H=CH2), 123.5 (Ar CH), 125.4 (Ar CH), 126.1 (Ar CH), 127.0 (Het Ar CH), 129.6 (Het Ar CH), 131.1 (Het Ar CH), 132.0 (Het Ar CH), 134.8 (quat. Ar C), 135.7 (quat. Ar C), 138.9 (quat. Ar C), 139.0 (quat. Ar C), 152.4 (quat. Ar C), 175.7 (SC=N). IR (CH_2Cl_2) υ_{max}: 3399 (br), 3074, 2292, 1642, 1586. Elemental Analysis: calcd for $C_{17}H_{13}Cl_2NOS$: C 58.29 H, 3.74 N 4.00, found C 58.36 H, 3.88 N 4.01.

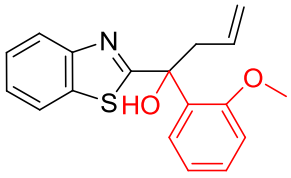


50: Eluent: 95:5 hexanes/EtOAc; white solid m.p. 124-126 °C. ^{1}H, NMR (400 MHz, $CDCl_3$) δ 3.44 (dd, 1H, J = 7.2, 14.2 Hz RC*H*H, R^{1}), 3.59 (dd, 1H, J = 7.2, 14.2 Hz RCH*H,* R^{1}), 3.82 (br. s, 1 H, exchanges with D_2O), 5.17 (m, 1H, H_a), 5.24 (dd, 1H, J = 1.6, 17.2 Hz, H_b), 5.84 (ddt, 1H, J = 7.0, 10.2, 17.2 Hz, RC*H*=CH_2), 7.23 (m, 1H, Ar CH), 7.40 (td, 2H, J = 1.1, 7.8 Hz, Ar CHs), 7.49 (td, 1H, J = 1.7, 7.7 Hz, Ar CH), 7.60 (dd, 1H, J = 1.3, 7.9 Hz, Het Ar CH), 7.81 (dd, 1H, J = 1.7, 8.0 Hz, Het Ar CH),

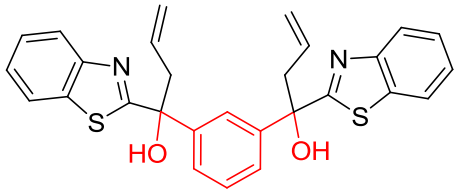
7.87 (d, 1H, J = 8.0 Hz, Het Ar CH), 8.05 (d, 1H, J = 8.2 Hz, Het Ar CH,); ^{13}C NMR (100 MHz, CDCl3) δ 44.1 (=CH*C*H2R), 78.3 (quat C-OH), 120.2 (H_2C=CHR), 121.8 (R*C*H=CH_2), 122.1 (quat Ar C), 123.5 (Ar CH) 125.3 (Ar CH), 126.0 (Ar CH), 127.4 (Ar CH), 129.0 (Het Ar CH), 129.8 (Het Ar CH), 132.4 (Het Ar CH), 135.0 (Het Ar CH), 135.9 (quat Ar C), 141.6 (quat Ar C), 152.5 (quat Ar C), 176.5 (SC=N); IR (CH_2Cl_2) υ_{max}: 3397 (br), 3070, 2919, 1639, 1502; Elemental Analysis: calcd for $C_{17}H_{14}BrNOS$: C 56.67 H, 3.92 N 3.81, found C 56.94 H, 4.07 N 3.75.



51: Eluent 95:5 hexanes/EtOAc; colorless crystals (Et_2O), m.p. 117-120 °C. ^{1}H, NMR (400 MHz, $CDCl_3$) δ 3.18 (dd, 1H, J = 7.6, 14.1 Hz, RCH*H,* R^1), 3.30 (dd, 1H, J = 6.6, 14.1 Hz, RC*H*H, R^1), 5.02 (app d, 1H, J = 10.3 Hz, H_a), 5.11 (dd, 1H, J = 1.5, 17.2 Hz, H_b), 5.72 (ddt, 1H, J = 6.8, 10.0, 16.8 Hz, RC*H*=CH_2), 6.92 (s, 1H, exchanges with D_2O), 7.25 (m, 1H, Pyridyl CH), 7.35 (t, 1H, J = 7.1 Hz, Pyridyl CH), 7.46 (td, 1H, J = 1.1, 7.8 Hz, Het Ar CH), 7.76 (td, 1H, J = 1.7, 7.8 Hz, Het Ar CH), 7.86 (d, 1H, J = 8.0 Hz, Pyridyl CH), 7.98 (d, 1H, J = 8.0 Hz, Het Ar CH), 8.02 (d, 1H, J = 8.2 Hz, Het Ar CH), 8.52 (d, 1H, J = 5.0 Hz, Pyridyl CH); ^{13}C NMR (100 MHz, CDCl3) δ 46.85 (=CH*C*H2R), 77.95 (quat C-OH), 119.15 (H_2C=CHR), 121.53 (R*C*H=CH_2), 121.79 (Pyridyl CH), 122.95 (Pyridyl CH), 123.01 (Het Ar CH), 124.72 (Het Ar CH), 125.74 (Pyridyl CH), 132.21 (Het Ar CH), 135.52 (quat Ar C), 137.54 (Het Ar CH), 146.79 (Pyridyl CH), 154.00 (quat Ar C), 158.95 (quat Ar C), 178.53 ((SC=N); IR (CH_2Cl_2) υ_{max}: 3402 (br), 3072, 2915, 2097, 1642, 1593, 1509; Elemental Analysis: calcd for $C_{16}H_{14}N_2OS$: C 68.06 H, 5.00 N 9.92, found C 67.90 H, 5.14 N 9.86.

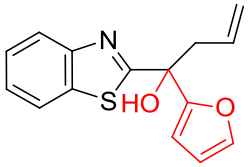


52: Eluent: 95:5 hexanes/EtOAc; colorless oil. ^{1}H, NMR (400 MHz, $CDCl_3$) δ 3.26 (dd, 1H, J = 7.0, 14.2 Hz, RCH*H,* R^{1}), 3.32 (dd, 1H, J = 6.9, 14.3 Hz, RC*H*H, R^{1}), 3.78 (s, 3H, OCH_3), 5.09 (dd, 1H, J = 1.2, 10.2 Hz, H_a), 5.16 (dd, 1H, J = 1.6, 17.1 Hz, H_b), 5.42 (s, 1H, exchanges with D_2O), 5.92 (ddt, 1H, J = 7.0, 10.3, 17.2 Hz, RC*H*=CH_2), 6.93 (d, 1H, J = 8.2 Hz, Ar CH), 7.02 (t, 1H, J = 7.5 Hz, Ar CH), 7.33 (ddd, 2H, J = 4.4, 8.4, 11.4 Hz, overlapping Ar CHs), 7.45 (t, 1H, J = 7.3 Hz, Het Ar CH), 7.57 (dd, 1H, J = 1.6, 7.8 Hz, Het Ar CH), 7.87 (d, 1H, J = 8.0 Hz, Het Ar CH), 8.00 (d, 1H, J = 8.2 Hz, Het Ar CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.10 (=CH*C*H2R), 55.61 (O-CH_3), 78.66 (quat C-OH), 111.78 (H_2C=CHR), 118.61 (R*C*H=CH_2), 121.31 (Ar CH), 121.60 (Ar CH), 123.14 (Ar CH), 124.71 (Ar CH), 125.64 (Het Ar CH), 127.74 (Het Ar CH), 129.44 (Het Ar CH), 133.24 (Het Ar CH), 133.40 (quat Ar C), 135.55 (quat Ar C), 153.18 (quat Ar C), 156.68 (quat Ar C), 179.00 (SC=N); IR u_{max}: 3486 (br), 2922, 1593.

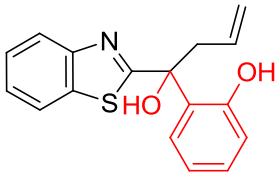


53: Eluent: 95:5 hexanes/EtOAc; white foam (presumed to be ca. 1:1 mixture of *d,l*- and *meso*-). ^{1}H, NMR (400 MHz, $CDCl_3$) δ 3.09 (dd, 1H, J = 7.8, 12.9 Hz, RC*H*H, R^{1}), 3.43 (m, 1H, RCH*H,* R^{1}), 3.71 (d, 1H, J = 3.0, exchangeable with D_2O), 5.20 (dd, 1H, J = 2.3, 10.2 Hz, H_a), 5.28 (m, 1H, H_b), 5.73 (m, 1H, RC*H*=CH_2), 7.34 (m, 2H, overlapping Ar CHs), 7.46 (ddd, 1H, J = 2.0, 5.0, 8.2 Hz, Ar CH), 7.63 (m, 1H, Het Ar CH), 7.81 (dd, 1H, J = 8.0, 12.2 Hz, Het Ar CH), 7.99 (t, 1H, J = 8.8 Hz, Het Ar CH), 8.13 (m, 0H); ^{13}C NMR (100 MHz, CDCl3) δ 47.43 (=CH*C*H2R),

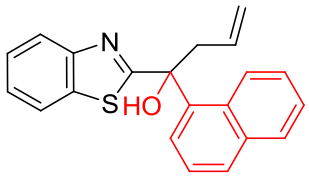
77.68 (quat. C-OH), 121.27 (H_2C=CHR), 121.70 (RCH=CH_2), 122.69 (Ar CH), 123.17 (Ar CH), 124.90 (Ar CH), 125.05 (Het Ar CH), 125.92 (Het Ar CH), 128.25 (Het Ar CH), 132.62 (Het Ar CH), 135.78 (quat Ar C), 143.76 (quat Ar C), 153.22 (quat. Ar C), 177.79 (SC=N); IR (CH_2Cl_2) υ_{max}: 3527, 3415 (br), 3070, 2978, 2922, 1639, 1600, 1502; Elemental Analysis: calcd for $C_{28}H_{24}N_2O_2S_2$: C 69.39 H, 4.99 N 5.78, found C 69.26 H, 5.03 N 5.68.



54: Eluent: 98:2 hexanes/EtOAc; brown solid, m.p. 81-84 °C. ^{1}H, NMR (400 MHz, $CDCl_3$) δ 3.20 (dd, 1H, J = 7.2, 14.0 Hz, RCH*H,* R^1), 3.26 (dd, 1H, J = 7.3, 14.1 Hz, RCH*H,* R^1), 3.96 (s, 1H, exchanges with D_2O), 5.19 (m, 1H, H_a), 5.26 (ddd, 1H, J = 1.4, 3.1, 17.2 Hz, H_b), 5.77 (ddt, 1H, J = 7.2, 10.0, 17.2 Hz, RC*H*=CH_2), 6.36 (dd, 1H, J = 1.8, 3.3 Hz, Ar CH), 6.42 (dd, 1H, J = 0.8, 3.3 Hz, Ar CH), 7.41 (m, 2H, overlapping Het Ar CH), 7.49 (ddd, 1H, J = 1.3, 7.3, 8.3 Hz, Ar CH), 7.89 (dd, 1H, J = 0.6, 8.0 Hz, Het Ar CH), 8.04 (d, 1H, J = 8.3 Hz, Het Ar CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.08 (=CH*C*H2R), 75.11 (quat C-OH), 107.25 (H_2C=CHR), 110.51 (R*C*H=CH_2), 120.80 (Ar CH), 121.77(Ar CH), 123.32(Het Ar CH), 125.19 (Het Ar CH), 126.08 (Ar CH), 131.54 (Het Ar CH), 135.7 (quat Ar C), 142.71 (Het Ar CH), 152.58 (quat Ar C), 155.08 (quat Ar C), 174.79 (SC=N); IR (CH_2Cl_2) υ_{max}: 3413 (br), 3072, 2924, 2857, 1670, 1505; Elemental Analysis: calcd for $C_{15}H_{13}NO_2S$: C 66.40 H, 4.83 N 5.16, found C 66.90 H, 5.04 N 4.94.

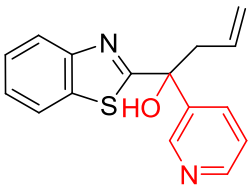


55: Eluent: 95:5 hexanes/EtOAc; white solid, m.p. 145 – 147 °C. ^{1}H, NMR (400 MHz, $CDCl_3$) δ 3.35 (d, 2H, J = 7.3 Hz, RCH_2R^1), 3.82 (s, 1H, exchanges with D_2O), 5.30 (m, 2H, C*H*$_2$=CHR), 5.61 (td, 1H, J = 7.3, 17.3 Hz, RC*H*=CH_2), 6.93 (t, 1H, J = 7.6 Hz, Ar CH), 7.00 (d, 1H, J = 8.0 Hz, Ar CH), 7.25 (dd, 1H, J = 6.8, 14.1 Hz, Ar CH), 7.41 (t, 1H, J = 7.6 Hz, Ar CH), 7.53 (m, 2H, overlapping Het Ar CH), 7.88 (d, 1H, J = 8.0 Hz, Het Ar CH), 8.01 (d, 1H, J = 8.2 Hz, Het Ar CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.40 (=CH*C*H2R), 78.18 (quat C-OH), 119.62 (H_2C=CHR), 120.18 (R*C*H=CH_2), 121.85 (Ar CH), 122.24 (Ar CH), 122.61(Ar CH), 125.50 (Ar CH), 126.23 (Het Ar CH), 126.53 (Het Ar CH), 127.70 (quat Ar C), 129.92 (Het Ar CH), 131.78 (Het Ar CH), 134.53 (quat Ar C), 151.50 (quat Ar C), 156.13 (quat Ar C), 180.02 (SC=N); IR ($CHCl_3$) υ_{max}: 3418 (br), 2099, 1642; Elemental Analysis: calcd for $C_{17}H_{15}NO_2S$: C 68.66 H, 5.08 N 4.71, found C 68.73 H, 4.94 N 4.73



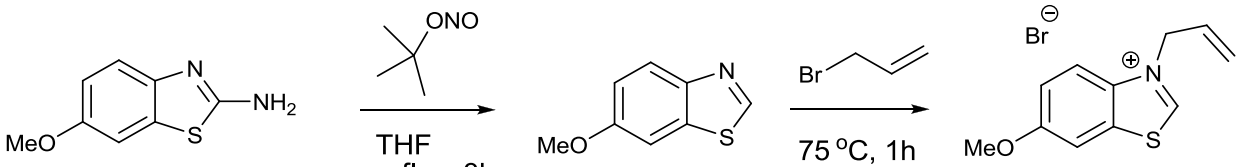
56: Eluent: 98:2 hexanes/EtOAc; white foam. ^{1}H, NMR (400 MHz, CDCl3) δ 3.55 (app d, 1H, *J* = 7.2 Hz, RC*H*$_2$ R^1), 3.84 (br. s, 1 H, exchanges with D_2O), 5.28 (m, 2H, *H*$_2$C=CHR), 5.85 (ddt, 1H, *J* = 7.2, 10, 17.2 Hz, RC*H*=CH_2), 7.38 (m, 3H, overlapping Ar CHs), 7.49 (dt, 2H, J = 4.4, 8.5, overlapping Het Ar CH), 7.80 (d, 1H, *J* = 7.9 Hz, Ar CH), 7.86 (dd, 3H, J = 4.3, 10.5 Hz, overlapping Ar CHs), 8.07 (d, 1H, *J* = 8.2 Hz, Het Ar CH), 8.43 (d, 1H, *J* = 8.5 Hz, Het Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 46.4 (=CH*C*H2R), 78.3 (quat *C*-OH), 121.0 (H_2C=CHR), 121.8 (R*C*H=CH2), 123.3 (Ar

CH), 124.7 (Ar CH), 124.8 (Ar CH), 125.1 (Het Ar CH), 125.3 (Het Ar CH), 125.96 (Ar CH),126.0 (Ar CH), 126.1 (Ar CH), 129.0 (Ar CH), 129.9 (Het Ar CH), 131.0 (quat Ar C), 132.5 (Het Ar CH), 134.7 (quat. Ar C), 136.0 (quat. Ar C), 138.2 (quat. Ar C), 152.5 (quat. Ar C), 178.1 (SC=N). IR (CH_2Cl_2) u_{max}: 3519 (br), 3433, 3060, 2978, 2926, 1637, 1599, 1506. Elemental Analysis: calcd for $C_{21}H_{17}NOS$: C 76.10 H, 5.17 N 4.23, found C 76.20 H, 5.01 N 4.35.



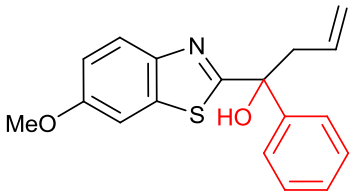
57: Eluent: 80:20 hexanes/EtOAc; colorless viscous oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 3.07 (ddt, J = 13.9, 8.2, 1.0 Hz, 1H), 3.47 (ddt, J = 13.8, 6.4, 1.2 Hz, 1H), 4.17 (s, 1H), 5.28 (m, 2H), 5.73 (dddd, J = 16.8, 10.1, 8.1, 6.4 Hz, 1H), 7.28 (m, 1H), 7.38 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 7.49 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.86 (dt, J = 7.9, 0.9 Hz, 1H), 8.04 (m, 2H), 8.50 (dd, J = 4.8, 1.6 Hz, 1H), 8.99 (d, J = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, CDCl3) δ 177.01, 153.24, 148.75, 147.33, 138.96, 135.49, 133.48, 131.79, 126.10, 125.15, 123.26, 123.09, 121.87, 121.77, 47.35.

Two-step Synthesis of Salt 69

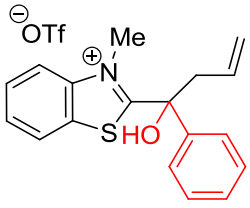


Compound **68** is known and was made following a reported procedure.[67] To a refluxing THF (20 ml) solution of *t*-butyl nitrite (10.9 mmol) was added a solution of 2-

aminobenzothiazole (5.5 mmol) in 10 ml THF very slowly (evolution of N_2 gas visible). The reaction was refluxed for 3 hours and monitored by TLC. After 2-aminobenzothiazole was completely consumed, all volatiles were rotovapped off. Subsequently, allyl bromide (11 mmol) was added to the residue and the mixture was heated to 75 ^{o}C for 1 hour. The brown solid obtained was triturated severally with diethyl ether and carefully decanted. The resulting salt **69** was dried overnight under nitrogen, and was obtained in 50% yield based on starting 2-aminobenzothiazole (1 g of **67** yielded 0.801 g of **69**, ca 51% yield).



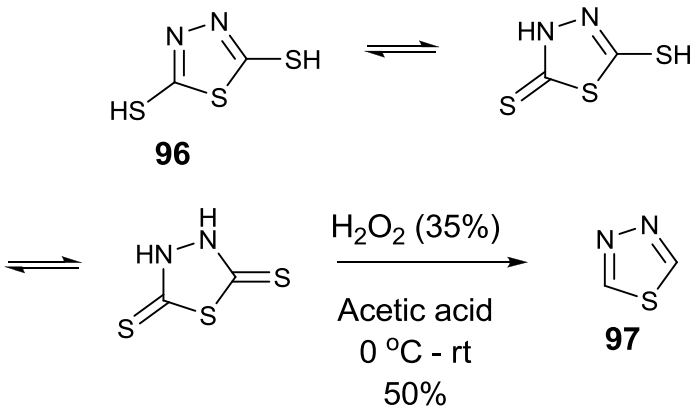
Alcohol **71** was obtained using the general procedure (vide supra) in 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (m, 2H), 3.44 (ddt, J = 13.9, 6.6, 1.2 Hz, 1H), 3.62 (s, 1H), 3.87 (s, 3H), 5.28 (m, 3H), 5.77 (dddd, J = 16.9, 10.2, 7.9, 6.7 Hz, 2H), 7.08 (dd, J = 9.0, 2.6 Hz, 1H), 7.29 (m, 4H), 7.37 (m, 2H), 7.71 (dt, J = 8.2, 1.1 Hz, 3H), 7.92 (d, J = 9.0 Hz, 1H).



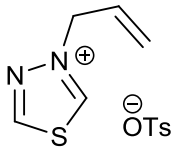
Salt **61**: To a solution of tertiary alcohol **47** (0.97 g, 3.4 mmol) in dry ether (10 ml) at room temperature was added methyl triflate (1 ml, 8.8 mmol) with stirring. The reaction mixture went cloudy after 5 minutes followed by precipitation of salt **61** almost instantaneously. The suspension was left to stir for 1 hour at room temperature after which the solid was triturated several times with dry ether and

carefully decanted. The white solid obtained was dried under nitrogen (80% yield; 0.97 g of **47** yielded 1.2 g of **61**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (m, 1H), 3.55 (ddt, J = 13.2, 6.6, 1.3 Hz, 1H), 4.21 (d, J = 0.9 Hz, 3H), 5.17 (m, 2H), 5.66 (ddt, J = 17.2, 10.4, 6.9 Hz, 1H), 6.67 (s, 1H), 7.43 (m, 4H), 7.84 (dddd, J = 22.6, 8.3, 7.1, 1.2 Hz, 2H), 7.93 (m, 1H), 8.18 (dd, J = 7.8, 1.3 Hz, 1H).

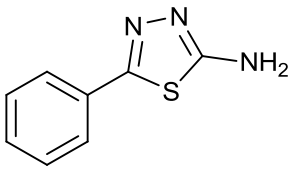
Desulfurization of Dithiol 96



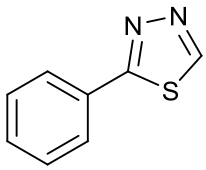
Following procedure reported by Schantl and Lagoja.[71] To a cooled (0 °C) suspension of dithiol (33.5 mmol) in glacial acetic acid (150 ml) was added 35% hydrogen peroxide (29 ml) dropwise after which a yellow suspension ensues. The ice bath was removed and stirring was continued for 2 hours, by which time the reaction mixture was off-white. The reaction mixture was filtered and the filtrate was basified with 15% sodium hydroxide and organic product was extracted into DCM. The DCM layer was dried with $MgSO_4$, filtered and solvent evaporated in-vacuo to give the desulfurized dithiol **97** in 54% yield as a colorless oil which crystallized on standing (5 g of dithiol **96** yielded 1.55 g of **97**). ^{1}H NMR (400 MHz, CDCl3) δ 9.25; ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.12



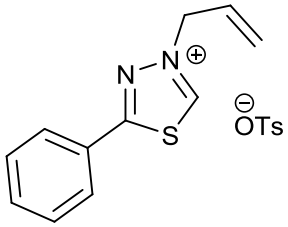
Salt **98**: Thiadiazole **97** was mixed neat with allyl tosylate (1:1), and the mixture was heated to 65 ^{o}C overnight after which the initially clear mixture became a brown viscous oil. On vigorous trituration in ether, the viscous oil solidified to give an off-white solid which was carefully decanted and dried under nitrogen. Salt **98** was isolated in 75% yield (100% based on crude NMR analysis). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 5.32 (d, J = 6.6 Hz, 2H), 5.51 (m, 2H), 6.08 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 9.97 (s, 1H), 11.42 (s, 1H); ^{13}C NMR (101 MHz, CDCl3) δ 163.17, 160.12, 142.46, 140.16, 128.96, 128.09, 125.84, 124.31, 59.93, 21.33.



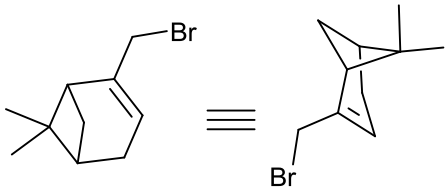
Compound **84**: According to procedure reported by Guan et al.[73] Benzoic acid (12.20 g, 100 mmol) was mixed with thiosemicarbazide (9.1 g, 100 mmol) in $POCl_3$ and the mixture was heated to 75 ^{o}C for 2 hours. After cooling to room temperature, 110 ml of water was added and the reaction was refluxed for a further 4 hours, after which it was brought to room temperature. The reaction was basified (till pH 8) with 50% NaOH and the precipitated amino compound **84** was filtered off and air dried overnight. 12.2 g of benzoic acid yielded 15.95 g of aminothiadiazole **84** (ca 90% yield). Data matched Guan's report.



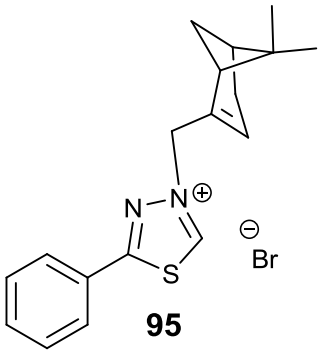
Compound **81**: Solid aminothiadiazole **84** (3 g, 16.9 mmol) was slowly added to a THF (90 ml) solution of *t*-butyl nitrite (25 mmol) at room temperature. The mixture was heated to 60 ^{o}C and monitored by TLC (5-7 hours). Alternatively the reaction could be carried out at room temperature for 24-48 hours. The volatiles were rotovapped off and the residue was purified by column chromatography (10% diethyl ether in DCM or 40% EtOAc in hexane) to obtain phenylthiadiazole **81** in 80% yield (ca 2.2 g). Data matched Gierczyk and Zalas's report.



Compound **83**: Phenylthiadiazole **81** was mixed neat with allyl tosylate (1:1.2), and the mixture was heated to 75 ^{o}C for 3-5 hours to obtain a reddish-brown viscous oil. On vigorous trituration in ether, the viscous oil solidified to give a brown solid which was carefully decanted and dried under nitrogen. Salt **83** was isolated in 85% yield (1.42 g of phenylthiadiazole afforded 2.79 g of salt **83**). ^{1}H NMR (400 MHz, CDCl3) δ 2.32 (s, 3H), 5.50 (d, J = 6.7 Hz, 2H), 5.55 (d, J = 10.2 Hz, 1H), 5.66 (d, J = 16.7 Hz, 1H), 6.20 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H), 7.13 (d, J = 7.9 Hz, 3H), 7.58 (dd, J = 8.4, 7.1 Hz, 2H), 7.67 (m, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 7.2 Hz, 1H), 11.81 (s, 1H). ^{13}C NMR (101 MHz, CDCl3) δ 171.59, 163.56, 142.94, 139.61, 134.01, 129.88, 128.72, 128.31, 127.98, 126.25, 125.97, 124.41, 77.36, 77.24, 77.04, 76.72, 60.64, 21.27.

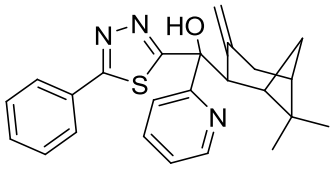


Myrtenyl bromide **94** was made from a reported procedure.[78] Phosphorus tribromide (0.32 ml, 3.4 mmol) was added to a cooled solution of Myrtenol (0.8 ml, 5 mmol) in diethyl ether (7 ml) and was stirred at 0 ^{o}C for 1.5 hours. Reaction was quenched with saturated $NaHCO_3$ and organic product extracted into ether. Organic layer was dried with $MgSO_4$, filtered and solvent evaporated in-vacuo to obtain bromide **94** which was used without further purification. Data matched those reported by Araki et al.



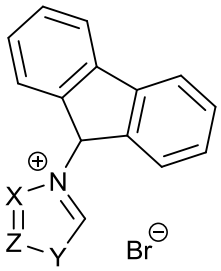
95

Phenylthiadiazole (0.61 g, 3.8 mmol) was mixed neat with bromide **94** (0.75 g, 3.5 mmol) and the mixture was heated to 75 ^{o}C. Reaction mixture solidified into a gel in 45 mins, from which a brown solid was obtained after trituration with ether, decantation and drying under nitrogen in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (s, 3H), 1.23 (d, *J* = 8.7 Hz, 1H), 1.27 (s, 3H), 2.13 (d, *J* = 3.2 Hz, 1H), 2.39 (m, 7H), 5.57 (q, *J* = 13.9 Hz, 3H), 6.05 (s, 1H), 7.59 (m, 3H), 7.69 (m, 2H), 7.95 (d, *J* = 7.8 Hz, 2H), 12.29 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.68, 163.88, 139.21, 134.15, 130.02, 128.27, 127.91, 126.26, 77.35, 77.24, 77.03, 76.71, 63.13, 43.91, 40.22, 38.29, 31.67, 31.52, 25.91, 21.10.



Compound **96**: A methanolic solution of salt **95** (107 mg, 0.3 mmol) was added dropwise to a mixture of pyridine-2-carboxaldehyde (0.03 ml, 0.32 mmol) and tetramethylguanidine (TMG, 0.04 ml, 0.32 mmol) at room temperature, and the reaction was stirred for 3-5 hours. Single yellow ketone spot was observed by TLC, after which a second charge of TMG (0.03 ml) was added and the reaction was heated from 65 ^{o}C – 70 ^{o}C for ca 4 hours at which point yellow ketone spot had been consumed. The volatiles were rotovapped and the residue was purified by prep TLC (10% EtOAc in hexane) to obtain alcohol **96** in 40% yield as a single product. ^{1}H NMR (400 MHz, CDCl3) δ 0.77 (s, 3H), 1.24 (s, 3H), 1.29 (m, 1H), 1.93 (m, 2H), 2.05 (m, 1H), 2.27 (m, 3H), 3.19 (d, J = 1.4 Hz, 1H), 4.13 (m, 1H), 4.40 (s, 1H), 7.19 (s, 1H), 7.31 (m, 1H), 7.47 (dd, J = 5.1, 1.9 Hz, 3H), 7.79 (td, J = 7.8, 1.7 Hz, 1H), 7.94 (m, 2H), 8.25 (d, J = 8.0, 1.1 Hz, 1H), 8.54 (d, J = 4.9, 1.3 Hz, 1H);^{13}C NMR (101 MHz, CDCl3) δ 159.20, 149.59, 146.43, 137.28, 130.91, 130.30, 129.10, 127.68, 123.25, 123.09, 110.74, 80.66, 77.33, 77.02, 76.70, 53.36, 44.94, 40.71, 40.43, 29.17, 27.21, 25.87, 21.65.

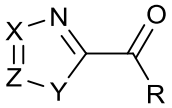
General procedure for the preparation of fluorenylazolium bromide salts (108, 108a, 126, 127):



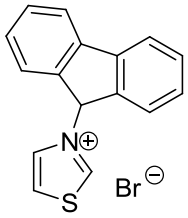
The corresponding azole was mixed neat with a slight excess (1.2 eq) of 9-bromofluorene and the mixture was maintained at 75-85°C until the reaction mixture

solidified (4-6 hours). The resulting solid was then triturated three times with diethyl ether, allowing the salt to stir for 30 mins per time. The solvent was decanted and the solid dried under nitrogen to yield the corresponding azolium salts in 70-95% yield.

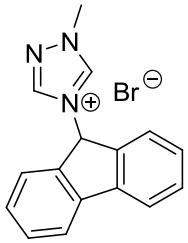
General procedure for the preparation of 2-ketoazoles:



To a mixture of fluorenylazolium bromide salt and aldehyde (1.2-1.5 eq) in solvent (0.15 M in methanol or THF) at 65^{o}C was added DBU (1.2-1.5 eq) and the reaction was stirred at 65 ^{o}C for 4-5 hours. The solvent was rotovapped off and the residue was purified by flash chromatography with indicated solvent systems.

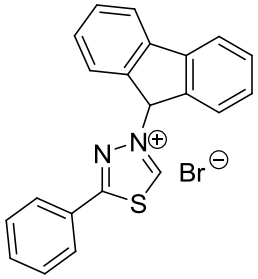


108: Heated to 85 ^{o}C, white solid obtained in 90% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (s, 1H), 7.42 (td, J = 7.5, 1.1 Hz, 2H), 7.60 (m, 4H), 8.05 (m, 3H), 8.32 (dd, J = 3.8, 2.4 Hz, 1H), 10.63 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.1, 140.9, 140.1, 135.2, 131.1, 129.1, 128.8, 126.1, 121.7, 67.7.

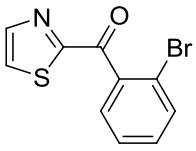


126: Heated to 75 ^{o}C. Salt obtained as a white solid in 70% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.04 (s, 3H), 6.97 (s, 1H), 7.45 (td, J = 7.5, 1.0 Hz, 2H), 7.60 (td, J = 7.6, 1.0 Hz, 2H), 7.67 (dt, J = 7.6, 0.9 Hz, 2H), 8.04 (d, J = 7.6 Hz, 2H), 9.40 (s, 1H),

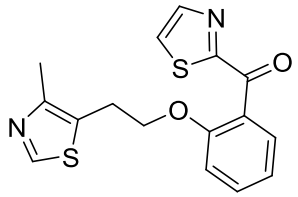
10.15 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 144.4, 143.0, 140.8, 139.9, 130.9, 129.8, 128.9, 128.7, 126.8, 126.2, 121.5, 61.6



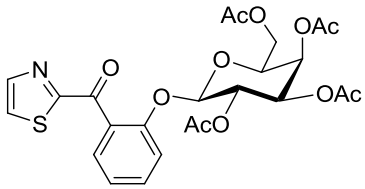
127: Heated to 75 ^{o}C. Brown powdery solid obtained in 81% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (m, 3H), 7.58 (dt, *J* = 15.6, 7.6 Hz, 4H), 7.69 (m, 3H), 7.84 (m, 2H), 8.04 (d, *J* = 7.6 Hz, 2H), 11.36 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.2, 165.0, 141.1, 139.4, 134.2, 131.0, 130.3, 129.8, 128.8, 128.7, 128.5, 126.8, 126.6, 126.4, 121.5, 121.1, 70.2.



128: Eluent: 95:5 to 90:10 hexanes/EtOAc; yellow oil, solidified on standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (td, 1H, *J* = 2, 9.6 Hz, Ar CH), 7.47 (td, 1H, *J* = 1.2, 8.8 Hz Ar CH), 7.64 (dd, 1H, *J* = 2, 7.6 Hz Ar CH), 7.70 (dd, 1H, *J* = 0.8, 8.0 Hz, Ar CH), 7.80 (d, 1H, *J* = 2.8 Hz Ar CH), 8.08 (d, 1H, *J* = 3.2 Hz Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 120.2 (Ar C), 127.07 (Ar CH), 127.12 (Ar CH), 130.2 (Ar CH), 132.2 (Ar CH), 133.6 (Ar CH), 133.6 (Ar CH), 138.4 (Ar C), 145.5 (Ar CH), 166.38 (SC=N), 187.0 (C=O); IR (CH_2Cl_2) υ_{max}: 3105, 2950, 1662, 1585, 1382.

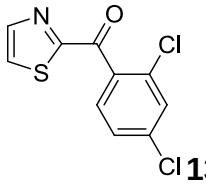


139: Eluent: 1:1 to 1:2 Hexanes/EtOAc; yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 2.34 (s, 3H, CH_3), 3.03 (t, 2H, *J* = 6.4, 12.8 Hz **H_2*C***-Het), 4.17 (t, 2H, *J* = 6.8, 13.2 Hz O***C*H$_2$***C*H2-Het), 7.00 (d, 1H, *J* **=** 8.4 Hz Ar CH), 7.11 (app t, 1H, *J* **=** 7.6, 14.8 Hz Ar CH), 7.51 (td, 1H, *J* = 2.0, 8.2 Hz, Ar CH), 7.61 (dd, 1H, *J* = 2.4, 7.6 Hz Ar CH), 7.71 (d, 1H, *J* = 2.8 Hz Ar CH) 7.99 (d, 1H, *J* = 3.2 Hz, Ar CH), 8.53 (s, 1H, SCH=N); ^{13}C NMR (100 MHz, CDCl3) δ 14.9 (Het-CH_3), 26.3 (H_2***C***-Het), 68.5 (O***C***H_2*C*H2-Het), 112.8 (Ar CH), 121.0 (Ar CH), 126.0 (Ar CH), 126.9 (Ar C) 127.3 (Ar C), 130.3 (Ar CH), 133.1 (Ar CH), 144.8 (Ar CH), 149.6 (Ar C), 149.9 (Ar CH), 157.0 (SCH=N), 167.8 (SC=N), 187.3 (C=O). IR (CH_2Cl_2) υ_{max}: 3150, 2850, 1654, 1597, 1448, 1382.

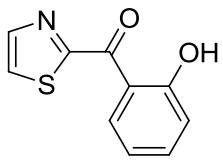


141: Eluent: 2:1 to 1:1 Hexanes/EtOAc; off-white foam. ^{1}H NMR (400 MHz, CDCl3) δ 1.98 (app d, 3H, *J* = 2.4 Hz, CH_3C=O), 2.04 (app d, 3H, *J* = 2.8 Hz, CH_3C=O), 2.08 (app d, 3H, *J* = 2.8 Hz, CH_3C=O) 2.16 (app d, 3H, *J* = 2.8 Hz, CH_3C=O), 4.04 (app t, 1H, *J* **=** 6.4, 13.2 Hz CHOAc), 4.13 (m, 1H, CHOAc), 4.21 (m, 1H, CHOAc), 5.03 (m, 2H, CH_2OAc) 5.31 (td, 1H, *J* = 2.4, 12.8 Hz, CHOAc), 5.42 (app d, 1H, *J* = 2 Hz anomeric CH); 7.23 (m, 1H, Ar CH), 7.28 (app t, 1H, *J* **=** 4.4, 8.4 Hz Ar CH), 7.50 (m, 1H, Ar CH), 7.61 (app d, 1H, *J* = 7.6 Hz Ar CH), 7.75 (dd, 1H, *J* = 1.6, 3.2 Hz Ar CH) 8.04 (app t, 1H, *J* = 2.8, 5.6 Hz, Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 20.55 (CH_3C=O) 20.66 (CH_3C=O), 20.69 (CH_3C=O), 61.3 (CHOAc), 66.8 (CHOAc), 68.1

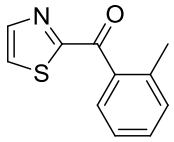
(CHOAc), 70.8 (CH_2OAc), 71.0 (CHOAc), 100.4 (anomeric C) 117.6 (Ar CH), 123.2 (Ar CH), 126.6 (Ar CH), 128.9 (Ar C), 129.9 (Ar CH), 132.5 (Ar CH), 145.2 (Ar CH), 154.8 (Ar C), 167.3 (SC=N), 169.2 ($CH_3C=O$), 170.1 ($CH_3C=O$), 170.2 ($CH_3C=O$), 170.4 ($CH_3C=O$), 186.1 (C=O). IR (CH_2Cl_2) υ_{max}: 3111, 2857, 1747, 1670, 1367, 1215.



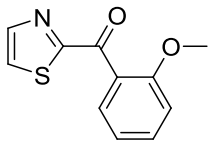
132: Eluent: 98:2 to 95:5 Hexanes/EtOAc; off-white solid m.p. 81-82 ^oC. ^1H, NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, 1H, *J* = 2, 8.4 Hz, Ar CH), 7.54 (app d, 1H, *J* = 2 Hz Ar CH), 7.66 (d, 1H, *J* = 8.0 Hz Ar CH), 7.81 (app d, 1H, *J* = 3.2 Hz, Ar CH), 8.08 (app d, 1H, *J* = 3.2 Hz Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 120.1 (Ar C), 126.9 (Ar CH), 127.3 (Ar CH), 130.5 (Ar CH), 131.5 (Ar CH), 133.4(Ar C), 134.5 (Ar C), 137.9 (Ar C), 145.4(Ar CH), 166.4 (SC=N), 185.1 (C=O); IR (CH_2Cl_2) υ_{max}: 3118, 2860, 1662, 1581, 1552, 1467, 1367.



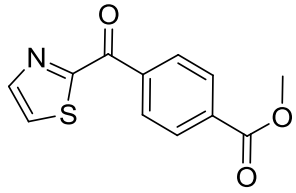
120: Eluent: 98:2 to 95:5 Hexanes/EtOAc; yellow solid. m.p. 64-65 ^oC ^1H, NMR (400 MHz, CDCl3) δ 7.05 (m, 2H Ar CH), 7.58 (td, 1H, *J* = 1.6, 9.9 Hz, Ar CH), 7.78 (app d, 1H, *J* = 3.0 Hz, Ar CH), 8.14 (app d, 1H, *J* = 3.1 Hz, Ar CH), 9.20 (dd, 1H, *J* = 1.7, 8.2 Hz, Ar CH) 12.19 (s, 1H, exchanges with D_2O, Ar-OH); ^{13}C NMR (100 MHz, CDCl3) δ 118.0 (Ar C), 118.4 (Ar CH), 119.4 (Ar CH), 126.5 (Ar CH), 133.9 (Ar CH), 137.2 (Ar CH), 144.9 (Ar CH), 164.1 (Ar C), 167.9 (SC=N),186.5 (C=O). IR (CH_2Cl_2) υ_{max}: 3086 (br), 2922, 1620, 1585, 1440, 1477, 1388.



135: Eluent: 98:2 – 95:5 hexanes/EtOAc; yellow oil ^{1}H NMR (400 MHz, CDCl3) δ 2.49 (s, 3H, CH_3), 7.35 (m, 2H Ar CH), 7.47 (td, 2H, *J* = 1.2, 7.8 Hz, Ar CH), 7.75 (d, 1H *J* = 3 Hz, Ar CH), 7.88 (app d, 1H, *J* = 8.5 Hz), 8.08 (app d, 1H *J* = 3 Hz) ; ^{13}C NMR (100 MHz, CDCl3) δ 20.5 (Ar-CH_3), 125.3 (Ar CH), 126.5 (Ar CH), 130.7 (Ar CH), 131.4 (Ar CH), 131.7 (Ar CH), 135.6 (Ar C), 138.5 (Ar C), 145.1 (Ar CH), 168.3 (SC=N),188.2 (C=O); IR (CH_2Cl_2) υ_{max}: 3061, 3022, 1654, 1448, 1263, 715.

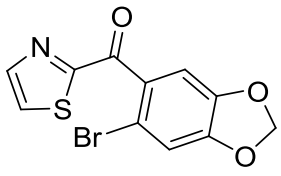


134: Eluent: 85:15 to 80:20 hexanes/EtOAc; yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 3.82 (s, 3H, OCH_3), 7.05 (app d, 1 H *J* = 8.5 Hz, Ar CH), 7.06 (app d, 1H, *J* = 8 Hz, Ar CH), 7.53 (td, 1H, *J* = 1.6, 9 Hz, Ar CH), 7.67 (dd, 1H, *J* = 1.6, 7.6 Hz, Ar CH), 7.70 (app d, 1H, *J* = 3.2 Hz, Ar CH), 8.03 (app d, 1H, *J* = 3.2 Hz, Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 55.9 (OCH_3), 111.9 (Ar CH), 120.3 (Ar CH), 126.0 (Ar CH), 126.6 (Ar C), 130.6 (Ar CH), 133.2 (Ar CH), 144.9 (Ar CH), 158.3 (Ar C), 168.0 (SC=N),187.0 (C=O); IR (CH_2Cl_2) υ_{max}: 3109, 3080, 1654, 1597, 1265, 1246.

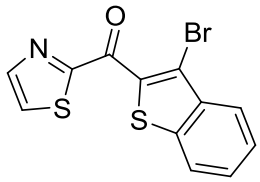


130: Eluent: 95:5 to 90:10 Hexanes/EtOAc; white solid m.p. 107-108 ^{o}C. ^{1}H, NMR (400 MHz, CDCl3) δ 3.99 (s, 3H, OCH_3), 7.79 (d, 1 H *J* = 3.1 Hz, Ar CH), 8.14 (d, 1H, *J* = 3.0 Hz, Ar CH), 8.19 (s, 1H, Ar CH), 8.21 (s, 1H, Ar CH), 8.53 (s, 1H, Ar CH), 8.55 (s, 1H, Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 52.51 (OCH_3), 126.8 (Ar

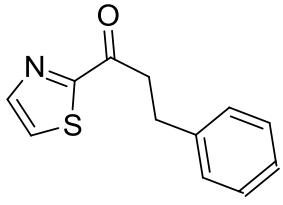
CH), 129.5 (Ar CH), 131.0 (Ar CH), 126.6 (Ar C), 134.1 (Ar C), 138.6 (Ar C), 145.1 (Ar CH), 166.3 (ester C=O), 167.3 (SC=N), 183.7 (C=O). IR (CH_2Cl_2) υ_{max}: 3115, 3084, 2958, 1720, 1635, 1500, 1566, 1483.



131: Eluent: 85:15 to 80:20 Hexanes/EtOAc; yellow solid m.p. 129-132 ^{o}C. ^{1}H, NMR (400 MHz, CDCl3) δ 6.09 (s, 2H, OCH_2O), 7.14 (s, 1 H, Ar CH), 7.21 (s, 1H, Ar CH), 7.78 (d, 1H, *J* = 3.2 Hz Ar CH), 8.07 (d, 1H, *J* = 3.2 Hz Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 102.5 (OCH_2O), 110.7 (Ar CH), 113.3 (Ar C), 114.0 (Ar CH), 127.0 (Ar CH), 131.0 (Ar C), 145.2 (Ar CH), 147.0 (Ar C), 150.7 (Ar C), 166.7 (SC=N), 185.6 (C=O). IR (CH_2Cl_2) υ_{max}: 3109, 2916, 1662, 1610, 1500, 1473, 1384.

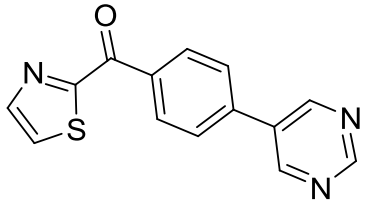


129: Brown solid, precipitated and triturated with MeOH m.p. 140-143 ^{o}C. ^{1}H, NMR (400 MHz, $CDCl_3$) δ 7.56 (app quintet, 2H, *J* = 7.2, 15.2 Hz, Ar CH), 7.79 (app d, 1H, *J* = 3.2 Hz Ar CH), 7.90 (d, 1H, *J* = 7.6 Hz Ar CH), 8.10 (app d, 1H, *J* = 7.6 Hz, Ar CH), 8.15 (app d, 1H, *J* = 2.8 Hz Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 117.8 (Ar C), 122.7 (Ar CH), 125.76 (Ar CH), 125.83 (Ar CH), 127.1 (Ar CH), 128.8 (Ar CH), 129.3 (Ar C), 138.0 (Ar C), 142.2 (Ar C), 1144.6 (Ar CH) 167.7 (SC=N), 176.6 (C=O); IR (CH_2Cl_2) υ_{max}: 3177, 3142, 1631, 1475, 1390.

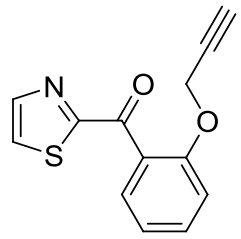


Data matched those reported by Klumpp et al. *J. Org. Chem.*, **2014**, *79* (12), pp 5852–5857

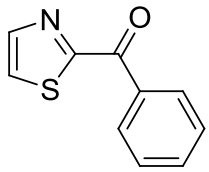
142: Eluent: 95:5 to 90:10 Hexanes/EtOAc; yellow oil. ^{1}H, NMR (400 MHz, $CDCl_3$) δ 3.12 (t, 2H, *J* = 7.2, 15.2 Hz CH_2Ph), 3.54 (t, 2H, , *J* = 8.0, 15.6 Hz $C(=O)CH_2$), 7.23 (m, 1H, Ar CH), 7.31 (m, 4H, Ar CH) 7.69 (d, 1H, J = 3.2 Hz, Th CH), 8.01 (d, 1H, J = 2.8 Hz, Th CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8 (CH_2Ph), 40.11 ($C(=O)CH_2$), 126.2 (Ar CH), 126.23 (Ar CH), 128.47 (Ar CH), 128.50 (Ar CH), 140.7 (Ar C), 144.7 (Ar CH), 167.0 (SC=N), 193.0 (C=O); IR (CH_2Cl_2) υ_{max}: 3050, 2900, 1681, 1550 1479, 1388.



133: Brown solid, precipitated and triturated with MeOH. m.p. 170-171 ^{o}C ^{1}H, NMR (400 MHz, CDCl3) δ 7.7 (app d, 1H, *J* = 1.6 Hz Ar CH), 7.80 (app d, 2H *J* = 3.2 Hz, Ar CH), 8.16 (d, 1H, *J* = 2.8 Hz, Ar CH), 8.67 (app d, 2H, *J* = 8.4 Hz Ar CH), 9.06 (s, 2H, Ar CH), 9.30 (s, 1H, Ar); ^{13}C NMR (100 MHz, CDCl3) δ 126.7 (Ar CH), 127.0 (Ar CH), 132.1 (Ar CH), 133.4 (Ar C), 135.5 (Ar C), 139.1 (Ar C), 145.03 (Ar CH), 155.1 (Ar CH), 158.2 (NC=N), 167.6 (SC=N), 183.4 (C=O). IR (CH_2Cl_2) υ_{max}: 3068, 1639, 1604, 1550, 1481, 1402.

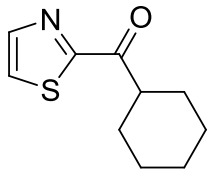


140: Eluent: 90:10 to 80:20 Hexanes/EtOAc; yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 2.49 (t, 1H, *J* = 2.4, 4.8 Hz alkyne CH), 4.71 (d, 2H *J* = 2.4 Hz, propargyl CH_2), 7.15 (td, 1H, *J* = 0.8, 8 Hz, Ar CH), 7.21 (d, 1H, *J* = 8 Hz, Ar CH), 7.55 (td, 1H, *J* = 1.6, 8.8 Hz, Ar CH), 7.69 (dd, 1H, *J* = 1.6, 7.6 Hz, Ar CH), 7.72 (d, 1H, *J* = 2.8 Hz, Ar CH) 8.04 (d, 1H *J* = 3.2 Hz, Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 56.8 (alkyne CH), 75.9 (propargyl CH_2), 78.1 (alkyne C) 113.8 (Ar CH) 121.4 (Ar CH), 126.0 (Ar CH), 127.5 (Ar C), 130.7 (Ar CH), 133.0 (Ar CH), 144.9 (Ar CH), 156.4 (Ar C), 167.8 (SC=N),186.7 (C=O). IR (CH_2Cl_2) υ_{max}: 3294, 2950, 2121, 1658, 1597, 1485, 1448.

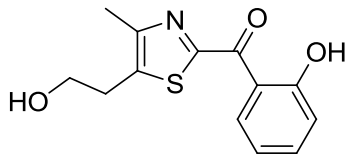


Data matched those reported by Hoarau et al. *Synlett.* **2013**, 2233–2240

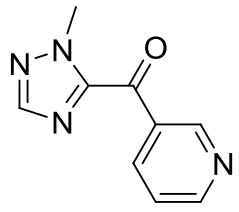
112: Eluent: 98:2 to 95:5 Hexanes/EtOAc; yellow oil. ^{1}H, NMR (400 MHz, CDCl3) δ 7.54 (app t, 2H, *J* = 7.5, 15.4 Hz, Ar CH), 7.65 (app t, 1H, *J* = 7.5, 14.8 Hz, Ar CH), 7.74 (app d, 1H, *J* = 3.0 Hz, Ar CH), 8.11 (app d, 1H, *J* = 3.1 Hz, Ar CH), 8.47 (dd, 2H, *J* = 1.5, 8.8 Hz, Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 126.3 (Ar CH), 128.4 (Ar CH), 131.1 (Ar CH), 133.6 (Ar CH), 135.2 (Ar C), 144.9 (Ar CH), 167.9 (SC=N), 184.2 (C=O). IR (CH_2Cl_2) υ_{max}: 3050, 1635, 1597, 1477, 1446, 1382, 1286.



143: Eluent: 95:5 Hexanes/EtOAc; yellow oil. ^{1}H, NMR (400 MHz, CDCl3) δ 1.29 (qt, *J* = 14.9, 4.8 Hz, 1H), 1.49 (m, 4H), 1.75 (dddt, *J* = 13.3, 5.3, 3.5, 1.8 Hz, 1H), 1.86 (m, 2H), 2.01 (m, 2H), 3.63 (tt, *J* = 11.4, 3.4 Hz, 1H), 7.67 (d, *J* = 3.0 Hz, 1H), 8.02 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.93, 167.12, 144.58, 126.11, 45.92, 28.85, 25.87, 25.62.

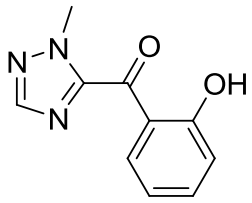


136: Eluent: 50:40 to 45:55 Hexanes/EtOAc; yellow viscous oil (solidified on standing) ^{1}H NMR (400 MHz, CDCl3) δ 1.91 (br S, exchanges with D_2O - OH), 2.52 (s, 3H, CH_3) 3.09 (t, 2H, *J* = 6.2, 12.5 Hz **H_2C**-Het), 3.90 (t, 2H, *J* = 6.2, 12.5 Hz O***CH_2***CH2-Het), 6.99 (m, 2H Ar CH), 7.53 (td, 1H, *J* = 1.7, 8.6 Hz, Ar CH), 9.1 (dd, 1H, *J* = 1.7, 8.2 Hz, Ar CH), 12.43 (s, 1H, exchanges with D_2O, Ar-OH); ^{13}C NMR (100 MHz, CDCl3) δ 15.32 (CH_3) 30.13 (CH_2) 62.57 (CH_2) 118.4 (Ar CH), 119.3 (Ar CH), 133.9 (Ar CH), 136.8 (Ar CH), 137.9 (Ar C) 152.1 (Ar C), 163.5 (Ar C), 163.8 (SC=N),186.0 (C=O). IR (CH_2Cl_2) u_{max}: 3404 (br), 2964, 1620,1581, 1427, 1303, 1247.

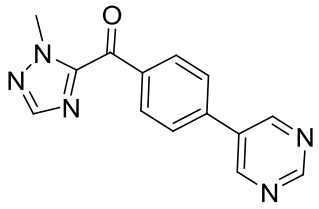


148: Eluent: 50:50 Hexanes/EtOAc; off-white solid. m.p. 72-73 ^{o}C. ^{1}H NMR (400 MHz, CDCl3) δ 4.3 (app d, *J* = 2.8 Hz, N-CH_3), 7.48 (m, 1H, Ar CH) 8.03 (app d, 1H, *J* = 2.4 Hz Ar CH), 8.68 (m, 1H, Ar CH), 8.85 (m, 1H Ar CH), 9.54 (s, 1H, Ar

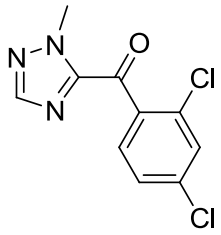
CH), ^{13}C NMR (100 MHz, CDCl3) δ 39.1 (CH_3) 123.3 (Ar CH) 131.5 (Ar C) 138.2 (Ar CH), 148.5 (Ar C), 150.1 (Ar CH), 152.0 (Ar CH), 154.0 (Ar CH),181.8 (C=O). IR (CH_2Cl_2) u_{max}: 3400, 3100, 1662, 1583, 1467, 1269.



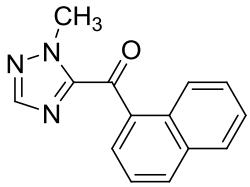
145: Eluent: 90:10 to 80:20 Hexanes/EtOAc; light yellow solid ^{1}H NMR (400 MHz, CDCl3) δ 4.25 (s, N-CH_3), 7.00 (td, 1H, *J* = 1.1, 8.7 Hz, Ar CH) 7.08 (dd, 1H, *J* = 0.9, 8.4 Hz Ar CH), 7.57 (td, 1H, *J* = 1.7, 9.4 Hz, Ar CH), 8.05 (s, 1H Ar CH), 8.72 (dd, 1H, *J* = 1.7, 8.2 Hz Ar CH) 11.96 (s, 1H, exchanges with D_2O, Ar-OH), ^{13}C NMR (100 MHz, CDCl3) δ 39.0 (N-CH_3) 118.5 (Ar CH) 119.0 (Ar C) 119.5 (Ar CH), 134.1 (Ar CH), 137.8 (Ar CH), 149.0 (Ar C), 149.8 (Ar CH), 164.0 (Ar C) 186.6 (C=O). IR (CH_2Cl_2) u_{max}: 3119 (br), 3084, 1624, 1608, 1469, 1296.



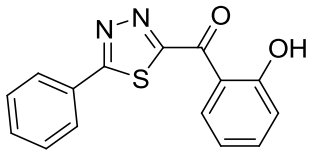
147: precipitated with MeOH and filtered; lilac solid. m.p. 173-175 ^{o}C. ^{1}H NMR (400 MHz, CDCl3) δ 4.32 (s, N-CH_3), 7.78 (d, 2H, *J* = 8.0 Hz, Ar CH) 8.06 (s, 1H, Ar CH), 8.55 (d, 2H, *J* = 8.0 Hz, Ar CH), 9.04 (s, 2H Ar CH), 9.30 (s, 1H, Ar CH) ^{13}C NMR (100 MHz, CDCl3) δ 39.1 (N-CH_3) 127.1 (Ar CH) 132.0 (Ar CH) 133.2 (Ar C), 136.1 (Ar C), 139.5 (Ar C), 148.9 (Ar C), 150.0 (Ar CH), 155.1(Ar CH), 158.3 (Ar CH), 182.4 (C=O). IR (CH_2Cl_2) u_{max}: 3101, 3035, 1643, 1606.7, 1550, 1490, 1448, 1357.



146: Eluent: 90:10 to 80:20 Hexanes/EtOAc; off-white solid. m.p. 122-125 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, N-CH_3), 7.41 (dd, 1H, *J* = 1.9, 8.3 Hz, Ar CH), 7.52 (app d, 1H, *J* = 1.9 Hz Ar CH), 7.65 (d, 1H, *J* = 8.3 Hz Ar CH), 7.97 (s, 1H, Ar CH); ^{13}C NMR (100 MHz, CDCl3) δ 38.8 (N-CH_3) 127.1 (Ar CH), 130.6 (Ar CH), 131.5 (Ar CH), 133.5 (Ar C), 134.7 (Ar C), 138.5 (Ar C), 148.9 (Ar C), 150.5 (Ar CH), 183.3 (C=O); IR (CH_2Cl_2) υ_{max}: 3100, 1676, 1581, 1465, 1363, 1274.



149: Eluent: 80:20 to 70:30 Hexanes/EtOAc; off-white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.38 (d, J = 0.6 Hz, 3H), 7.61 (m, 3H), 7.95 (m, 1H), 8.02 (d, J = 0.7 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 7.3, 0.9 Hz, 1H), 8.54 (d, J = 8.5, 0.8 Hz, 1H); ^{13}C NMR (101 MHz, CDCl3) δ 185.72, 150.09, 134.01, 133.89, 132.88, 132.07, 130.93, 128.72, 128.25, 126.64, 125.17, 124.18, 38.96; IR (CH_2Cl_2) υ_{max}: 3049, 2954, 1655, 1508, 1278, 1058.



150: Eluent: 98:2 to 95:5 Hexanes/EtOAc; yellow solid. m.p. 125-126 ^{o}C ^{1}H NMR (400 MHz, CDCl3) δ 7.08 (m, 2H, Ar CH) 7.60 (m, 4H, Ar CH), 8.11 (dd, 2H, *J* = 1.8, 8.3 Hz, Ar CH), 9.24 (dd, 1H, *J* = 1.5, 8.2 Hz Ar CH), 11.89 (s, 1H, exchanges with D_2O, Ar-OH), ^{13}C NMR (100 MHz, CDCl3) δ 117.9 (Ar C) 118.4 (Ar CH)

119.8 (Ar CH), 128.5 (Ar CH), 129.3 (Ar C), 129.5 (Ar CH), 132.3 (Ar CH), 134.0 (Ar CH), 138.1 (Ar CH), 164.4 (Ar C), 169.0 (Ar C), 172.8 (Ar C) 186.2 (C=O). IR (CH_2Cl_2) υ_{max}: 3061 (br), 1620, 1595, 1483, 1408, 1336, 1257.

Literature Cited:

(1) *Thiamin Diphosphate Catalysis: Enzymic and Nonenzymic Covalent Intermediates*. Kluger, R.; Tittmann, K. *Chem. Rev.* **2008**, *108*, 1797–1833.

(2) *Reactions of Acyl Anion Equivalents Derived from Cyanohydrins, Protected Cyanohydrins and α-Dialkylaminonitriles*. Albright, J. D. *Tetrahedron* **1983**, *39*, 3207–3233.

(3) *Anions of Protected Cyanohydrins as Acyl Carbanion Equivalents and Their Use in a New Synthesis of Ketones*. Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286–5287.

(4) *Carbanions of 1,3-Dithianes. Reagents for C-C Bond Formation by Nucleophilic Displacement and Carbonyl Addition*. Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075–1077.

(5) *Synthesis of 1,n-Dicarbonyl Derivates Using Carbanions from 1,3-Dithianes*. Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1077–1078.

(6) *Reactions of Benzaldehyde with Thiazolium Salts in Me2SO: Evidence for Initial Formation of 2-(.alpha.-Hydroxybenzyl)thiazolium by Nucleophilic Addition, and for Dramatic Solvent Effects on Benzoin Formation*. Chen, Y.-T.; Barletta, G. L.; Haghjoo, K.; Cheng, J. T.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 7714–7722.

(7) *On the Mechanism of Thiamine Action. IV.1 Evidence from Studies on Model Systems*. Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

(8) *A New Perspective on Thiamine Catalysis*. Pohl, M.; Sprenger, G. A.; Müller, M. *Curr. Opin. Biotechnol.* **2004**, *15*, 335–342.

(9) *Thiamine Models and Perspectives on the Mechanism of Action of Thiamine-Dependent Enzymes*. Malandrinos, G.; Louloudi, M.; Hadjiliadis, N. *Chem. Soc. Rev.* **2006**, *35*, 684–692.

(10) *Organocatalysis by N-Heterocyclic Carbenes*. Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.

(11) *On the Mechanism of N-Heterocyclic Carbene-Catalyzed Reactions Involving Acyl Azoliums*. Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696–707.

(12) *Exploiting Acyl and Enol Azolium Intermediates via N-Hetero- Cyclic Carbene-Catalyzed Reactions of α-Reducible Aldehydes*. Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617–1639.

(13) *Aspects of Nucleophilic Carbene Chemistry*. Wanzlick, H. W. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 75–80.

(14) *α'-Hydroxyenones as Mechanistic Probes and Scope-Expanding Surrogates for α,β-Unsaturated Aldehydes in N-Heterocyclic Carbene-Catalyzed Reactions*. Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714–8718.

(15) *Fragmentation of the Conjugate Base of 2-(1-Hydroxybenzyl)thiamin: Does Benzoylformate Decarboxylase Prevent Orbital Overlap To Avoid It?* Hu, Q.; Kluger, R. *J. Am. Chem. Soc.* **2004**, *126*, 68–69.

(16) *Structures and Reactivities of O-Methylated Breslow Intermediates*. Maji, B.; Mayr, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 10408–10412.

(17) *On the Organocatalytic Activity of N-Heterocyclic Carbenes: Role of Sulfur in Thiamine*. Hollóczki, O.; Kelemen, Z.; Nyulászi, L. *J. Org. Chem.* **2012**, *77*, 6014–6022.

(18) *Aldehyde Umpolung by N-Heterocyclic Carbenes: NMR Characterization of the Breslow Intermediate in Its Keto Form, and a Spiro-Dioxolane as the Resting State of the Catalytic System*. Berkessel, A.; Elfert, S.; Etzenbach-Effers, K.; Teles, J. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 7120–7124.

(19) *Synthesis of an N-Mesityl Substituted Chiral Imidazolium Salt for NHC-Catalyzed Reactions*. Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957–960.

(20) *The Thiazolium Catalyzed Benzoin Condensation with Mild Base Does Not Involve a "dimer" Intermediate*. Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699–702.

(21) *Investigating Organocatalytic Reactions: Mass Spectrometric Studies of a Conjugate Umpolung Reaction*. Schrader, W.; Handayani, P. P.; Burstein, C.; Glorius, F. *Chem. Commun.* **2007**, No. 7, 716–718.

(22) *Kinetics of the Thiazolium Ion-Catalyzed Benzoin Condensation*. White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124–5131.

(23) *Behavior and Reactivity of Heterocyclic Ammonium Compounds in the Synthesis of Cyanine and Carbocyanine Dyes. I. Benzothiazolium Derivatives*. Metzger, J.; Larive, H.; Dennilauler, R.; Baralle, R.; Gaurat, C. *Bull. Soc. Chim. Fr.* **1964**, 2857–2867.

(24) *Structures of Thiamine in Basic Solution1*. Maier, G. D.; Metzler, D. E. *J. Am. Chem. Soc.* **1957**, *79*, 4386–4391.

(25) *Studies on the Aminopyrimidinyl Group of Thiamine*. Doughty, M. B.; Risinger, G. E. *J. Chem. Soc. Chem. Commun.* **1985**, No. 22, 1551–1553.

(26) *The Chemistry of Thiamine: Studies on the Dimerization of Thiazolium Salts*. Doughty, M. B.; Risinger, G. E. *Bioorganic Chem.* **1987**, *15*, 1–14.

(27) *Chemistry of the Tricyclic Form of Thiamine with Aldehydes in Basic Ethanol*. Doughty, M. B.; Risinger, G. E.; Jungk, S. J. *Bioorganic Chem.* **1987**, *15*, 15–30.

(28) *Preparation, Structure, and Reactivity of 1,3,4-Triphenyl-4,5-Dihydro-1H-1,2,4-Triazol-5-Ylidene, a New Stable Carbene*. Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021–1023.

(29) *Isolable Analogues of the Breslow Intermediate Derived from Chiral Triazolylidene Carbenes*. DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143–6145.

(30) *Equilibrium Acidities in Dimethyl Sulfoxide Solution*. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

(31) *Umpolung by N-Heterocyclic Carbenes: Generation and Reactivity of the Elusive 2,2-Diamino Enols (Breslow Intermediates)*. Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J.-M.; Schlörer, N. E.; Teles, J. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 12370–12374.

(32) *Intercepting the Breslow Intermediate via Claisen Rearrangement: Synthesis of Complex Tertiary Alcohols without Organometallic Reagents*. Alwarsh, S.; Ayinuola, K.; Dormi, S. S.; McIntosh, M. C. *Org. Lett.* **2013**, *15*, 3–5.

(33) Claisen Rearrangements. In *Comprehensive Organic Synthesis II (Second Edition)*; Martín-Castro, A. M.; Tortosa, M. ; Knochel, P., Ed.; Elsevier: Amsterdam, 2014; pp 912–977.

(34) *Claisen Rearrangement over the Past Nine Decades*. Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002.

(35) The Ireland–Claisen Rearrangement (1972–2004). In *The Claisen Rearrangement*; McFarland, C. M.; McIntosh, M. C. ; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA, 2007; pp 117–210.

(36) Aza-Claisen Rearrangement. In *The Claisen Rearrangement*; Nubbemeyer, U. ; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA, 2007; pp 461–523.

(37) *Aza-Claisen Rearrangement of Amide Enolates. Stereoselective Synthesis of 2,3-Disubstituted Carboxamides*. Tsunoda, T.; Sasaki, O.; Itô, S. *Tetrahedron Lett.* **1990**, *31*, 727–730.

(38) *Claisen Rearrangement of N-Allylketene O, N-Acetals*. Ireland, R. E.; Willard, A. K. *J. Org. Chem.* **1974**, *39*, 421–424.

(39) *Asymmetric Induction in the Claisen Rearrangement of N-Allylketene N,O-Acetals*. Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443–448.

(40) *Competing [1-3]- and [3,3]-Sigmatropic Rearrangements of Electron-Rich Olefins*. Baldwin, J. E.; Walker, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 596–597.

(41) *Regio- and Diastereoselective Decarboxylative Coupling of Heteroaromatic Alkanes*. Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138–4139.

(42) *Claisen Rearrangement of Allyl Esters*. Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.

(43) *The Claisen Rearrangement: Methods and Applications . Edited by Martin Hiersemann and Udo Nubbemeyer*. Knight, J. *Org. Process Res. Dev.* **2008**, *12*, 1016–1016.

(44) *Unification of Reaction Metrics for Green Chemistry II: Evaluation of Named Organic Reactions and Application to Reaction Discovery*. Andraos, J. *Org. Process Res. Dev.* **2005**, *9*, 404–431.

(45) *Chemical Process Engineering: Design And Economics*, Silla, H. ; Chemical Industries; Marcel-Dekker: New York, 2003.

(46) *Highly Stereoselective Allylic Alkylations of Peptides*. Kazmaier, U.; Deska, J.; Watzke, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4855–4858.

(47) Studies Directed toward the Synthesis of Sclerophytin-A Novel N-Based Rearrangements. Ph.D., Dormi, S. S. , University of Arkansas: United States -- Arkansas, 2012.

(48) *Pd(II) Complexes of N,S-Heterocyclic Carbenes with Pendant and Coordinated Allyl Function and Their Suzuki Coupling Activities*. Yen, S. K.; Koh, L. L.; Huynh, H. V.; Hor, T. S. A. *Dalton Trans.* **2007**, No. 35, 3952–3958.

(49) *The Radical Nature of the [1,3]-Sigmatropic Rearrangements of Electron-Rich Olefins*. Baldwin, J. E.; Branz, S. E.; Walker, J. A. *J. Org. Chem.* **1977**, *42*, 4142–4144.

(50) *New Evidence Supporting Bis(thiazolin-2-Ylidene)s as the Actual Catalytic Species in the Benzoin Condensation.* Castells, J.; Domingo, L.; López-Calahorra, F.; Martí, J. *Tetrahedron Lett.* **1993**, *34*, 517–520.

(51) *Reactivity of the Thiazolium C2 Ylide in Aprotic Solvents: Novel Experimental Evidence for Addition rather than Insertion Reactivity*. Chen, Y. T.; Jordan, F. *J. Org. Chem.* **1991**, *56*, 5029–5038.

(52) Bordwell pKa Table (Acidity in DMSO) http://www.chem.wisc.edu/areas/reich/pkatable/.

(53) *Basicity of Substituted 2-Phenyl-1,1,3,3- Tetramethylguanidines and Other Bases in Acetonitrile Solvent*. Leffek, K. T.; Pruszynski, P.; Thanapaalasingham, K. *Can. J. Chem.* **1989**, *67*, 590–595.

(54) *Acidities of Some Substituted Ammonium Ions in DimethylSulfoxide†*. Crampton, M. R.; Robotham, I. A. *J. Chem. Res. Synop.* **1997**, No. 1, 22–23.

(55) *Basicities of Strong Bases in Water: A Computational Study*. Kaupmees, K.; Trummal, A.; Leito, I. *Croat. Chem. Acta* **2014**, *87*, 385–395.

(56) *Mechanistic Insights on N-Heterocyclic Carbene-Catalyzed Annulations: The Role of Base-Assisted Proton Transfers*. Verma, P.; Patni, P. A.; Sunoj, R. B. *J. Org. Chem.* **2011**, *76*, 5606–5613.

(57) *Catalytic Asymmetric Intermolecular Stetter Reaction of Enals with Nitroalkenes: Enhancement of Catalytic Efficiency through Bifunctional Additives*. DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402–10405.

(58) *Lithium Bromide as a Flexible, Mild, and Recyclable Reagent for Solvent-Free Cannizzaro, Tishchenko, and Meerwein−Ponndorf−Verley Reactions*. Mojtahedi, M. M.; Akbarzadeh, E.; Sharifi, R.; Abaee, M. S. *Org. Lett.* **2007**, *9*, 2791–2793.

(59) *Protonation of Homoenolate Equivalents Generated by N-Heterocyclic Carbenes*. Maki, B.; Chan, A.; Scheidt, K. *Synthesis* **2008**, *2008*, 1306–1315.

(60) *Umpolung by N-Heterocyclic Carbenes: Generation and Reactivity of the Elusive 2,2-Diamino Enols (Breslow Intermediates) (Angew. Chem. Int. Ed. 49/2012)*. Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J.-M.; Schlörer, N. E.; Teles, J. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 12135–12135.

(61) *Discovery of a Class of Calcium Sensing Receptor Positive Allosteric Modulators; 1-(benzothiazol-2-Yl)-1-Phenylethanols*. Gustafsson, M.; Jensen, J.; Bertozzi, S. M.; Currier, E. A.; Ma, J.-N.; Burstein, E. S.; Olsson, R. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5918–5921.

(62) *Characterization of Highly Efficacious Allosteric Agonists of the Human Calcium-Sensing Receptor*. Ma, J.-N.; Owens, M.; Gustafsson, M.; Jensen, J.; Tabatabaei, A.; Schmelzer, K.; Olsson, R.; Burstein, E. S. *J. Pharmacol. Exp. Ther.* **2011**, *337*, 275–284.

(63) *Thiazole-Mediated Synthetic Methodology*. Dondoni, A.; Marra, A. *Chem. Rev.* **2004**, *104*, 2557–2600.

(64) *General Reactivity of 2-Lithiobenzothiazole to Various Electrophiles and the Use as a Formyl Anion Equivalent in the Synthesis of α-Hydroxy Carbonyl Compounds*. Chikashita, H.; Ishibaba, M.; Ori, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3637–3648.

(65) *Benzothiazoles as Carbonyl Equivalents*. Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, *19*, 5–8.

(66) *Three-Component Ag-Catalyzed Enantioselective Vinylogous Mannich and Aza-Diels−Alder Reactions with Alkyl-Substituted Aldehydes*. Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961–17969.

(67) *Synthesis and Evaluation of 2-Pyridylbenzothiazole, 2-Pyridylbenzoxazole and 2-Pyridylbenzofuran Derivatives as 11C-PET Imaging Agents for β-Amyloid Plaques*. Swahn, B.-M.; Wensbo, D.; Sandell, J.; Sohn, D.; Slivo, C.; Pyring, D.; Malmström, J.; Arzel, E.; Vallin, M.; Bergh, M.; et al. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1976–1980.

(68) *An Efficient Synthesis of New 2-Aminomethyl-1,3,4-Oxadiazoles from Enantiomeric Phenylglycine Hydrazides*. Kudelko, A.; Zieliński, W. *Tetrahedron* **2009**, *65*, 1200–1206.

(69) *Selective Oxidation of Hydrazides Using O-Iodoxybenzoic Acid to Carboxylic Acids, Esters, and Aldehydes*. Takale, B. S.; Telvekar, V. N. *Chem. Lett.* **2010**, *39*, 546–547.

(70) *Copper-Mediated C–H Activation of 1,3,4-Oxadiazoles with 1,1-Dibromo-1-Alkenes Using PEG-400 as a Solvent Medium: Distinct Approach for the Alkynylation of 1,3,4-Oxadiazoles*. Reddy, G. C.; Balasubramanyam, P.; Salvanna, N.; Das, B. *Eur. J. Org. Chem.* **2012**, *2012*, 471–474.

(71) *1-Arylamino-1H-Imidazoles by "Oxidative Reduction" --- Conversion of 1-Arylamino-2,3-Dihydro-1H-Imidazole-2-Thiones*. G. Schantl, J.; M. Lagoja, I.

Heterocycles **1998**, *48*, 929.

(72) *Synthesis of Substituted 1,3,4-Thiadiazoles Using Lawesson's Reagent*. Gierczyk, B.; Zalas, M. *Org. Prep. Proced. Int.* **2005**, *37*, 213–222.

(73) *Design, Synthesis and Preliminary Bioactivity Studies of 1,3,4-Thiadiazole Hydroxamic Acid Derivatives as Novel Histone Deacetylase Inhibitors*. Guan, P.; Sun, F.; Hou, X.; Wang, F.; Yi, F.; Xu, W.; Fang, H. *Bioorg. Med. Chem.* **2012**, *20*, 3865–3872.

(74) *Concomitant C(.alpha.),C(.beta.)-Asymmetric Induction in the Aza-Claisen Rearrangement of N-Allylketene N,O-Acetals*. Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1986**, *51*, 1377–1383.

(75) *A Rapid and Efficient Synthesis of Chiral 2-Hydro-2-Oxazolines*. Leonard, W. R.; Romine, J. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 1961–1963.

(76) *Stereoselective Synthesis of Optically Active Bicyclic β-Lactam Carboxylic Acids That Target Pilus Biogenesis in Pathogenic Bacteria*. Emtenäs, H.; Carlsson, M.; Pinkner, J. S.; Hultgren, S. J.; Almqvist, F. *Org. Biomol. Chem.* **2003**, *1*, 1308–1314.

(77) *Lithiation of D2-Thiazolines: The C2-Anion Approach to 2-Substituted Derivatives and Their Reactivity*. M. J. Tronchet, J.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Heterocycles* **1993**, *36*, 473.

(78) *Preparation and Some Reactions of Allylic Indium Reagents*. Araki, S.; Shimizu, T.; Johar, P. S.; Jin, S. J.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538–2542.

(79) Novel [3,3] and [1,3]-Rearrangement of Azole-Derived N,X-Ketene Acetals. Ph.D., Alwarsh, S. , University of Arkansas: United States -- Arkansas, 2015.

(80) *Studies on Vitamin B1 and Related Compounds. CIX. A Novel Cleavage of Thiamin and Its Homologues by the Reaction with Aromatic Aldehydes*. Oka, Y.; Kishimoto, S.; Hirano, H. *Chem. Pharm. Bull. (Tokyo)* **1970**, *18*, 527–533.

(81) *Studies on Vitamin B1 and Related Compounds. CX. Rearrangements of α-Hydroxybenzylthiamin and Its Homologues*. Oka, Y.; Kishimoto, S.; Hirano, H. *Chem. Pharm. Bull. (Tokyo)* **1970**, *18*, 534–541.

(82) *Destruction of Vitamin B1 by Benzaldehyde. Reactivity of Intermediates in the Fragmentation of N1'-Benzyl-2-(1-Hydroxybenzyl)thiamin*. Kluger, R.; Moore, I. F. *J. Am. Chem. Soc.* **2000**, *122*, 6145–6150.

(83) *Reactivity of Intermediates in Benzoylformate Decarboxylase: Avoiding the Path to Destruction*. Hu, Q.; Kluger, R. *J. Am. Chem. Soc.* **2002**, *124*, 14858–14859.

(84) *Bioisosterism: A Rational Approach in Drug Design*. Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147–3176.

(85) *Antagonists of Inhibitor of Apoptosis Proteins Based on Thiazole Amide Isosteres*. Cohen, F.; Koehler, M. F. T.; Bergeron, P.; Elliott, L. O.; Flygare, J. A.; Franklin, M. C.; Gazzard, L.; Keteltas, S. F.; Lau, K.; Ly, C. Q.; et al. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2229–2233.

(86) *2-Aminothiazole as a Novel Kinase Inhibitor Template. Structure−Activity Relationship Studies toward the Discovery of N-(2-Chloro-6-Methylphenyl)-2-[[6-[4-(2-Hydroxyethyl)-1- Piperazinyl)]-2-Methyl-4-Pyrimidinyl]amino)]-1,3-Thiazole-5-Carboxamide (Dasatinib, BMS-354825) as a Potent Pan-Src Kinase Inhibitor*. Das, J.; Chen, P.; Norris, D.; Padmanabha, R.; Lin, J.; Moquin, R. V.; Shen, Z.; Cook, L. S.; Doweyko, A. M.; Pitt, S.; et al. *J. Med. Chem.* **2006**, *49*, 6819–6832.

(87) *Azole Derivatives as Histamine H3 Receptor Antagonists, Part I: Thiazol-2-Yl Ethers*. Walter, M.; Coburg, Y. von; Isensee, K.; Sander, K.; Ligneau, X.; Camelin, J.-C.; Schwartz, J.-C.; Stark, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5879–5882.

(88) *The Biology and Chemistry of Antifungal Agents: A Review*. Kathiravan, M. K.; Salake, A. B.; Chothe, A. S.; Dudhe, P. B.; Watode, R. P.; Mukta, M. S.; Gadhwe, S. *Bioorg. Med. Chem.* **2012**, *20*, 5678–5698.

(89) *Synthetic Approaches to the 2013 New Drugs*. Ding, H. X.; Leverett, C. A.; Kyne Jr., R. E.; Liu, K. K.-C.; Fink, S. J.; Flick, A. C.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2015**, *23*, 1895–1922.

(90) *Synthetic Approaches to the 2009 New Drugs*. Liu, K. K.-C.; Sakya, S. M.; O'Donnell, C. J.; Flick, A. C.; Li, J. *Bioorg. Med. Chem.* **2011**, *19*, 1136–1154.

(91) *Synthetic Approaches to the 2010 New Drugs*. Liu, K. K.-C.; Sakya, S. M.; O'Donnell, C. J.; Flick, A. C.; Ding, H. X. *Bioorg. Med. Chem.* **2012**, *20*, 1155–1174.

(92) *Synthetic Approaches to the 2011 New Drugs*. Ding, H. X.; Liu, K. K.-C.; Sakya, S. M.; Flick, A. C.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2013**, *21*, 2795–2825.

(93) *Synthetic Approaches to the 2012 New Drugs*. Ding, H. X.; Leverett, C. A.; Kyne Jr., R. E.; Liu, K. K.-C.; Sakya, S. M.; Flick, A. C.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2014**, *22*, 2005–2032.

(94) *Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals*. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.

(95) *Inhibitors of Proteases and Amide Hydrolases That Employ an α-Ketoheterocycle as a Key Enabling Functionality*. Maryanoff, B. E.; Costanzo, M. J. *Bioorg. Med. Chem.* **2008**, *16*, 1562–1595.

(96) *Inhibition of Group IVA Cytosolic Phospholipase A2 by Thiazolyl Ketones in Vitro, Ex Vivo, and in Vivo*. Kokotos, G.; Feuerherm, A. J.; Barbayianni, E.; Shah, I.; Sæther, M.; Magrioti, V.; Nguyen, T.; Constantinou-Kokotou, V.; Dennis, E. A.; Johansen, B. *J. Med. Chem.* **2014**, *57*, 7523–7535.

(97) *Design of Novel and Potent cPLA2α Inhibitors Containing an α-Methyl-2-Ketothiazole as a Metabolically Stable Serine Trap*. Mete, A.; Andrews, G.; Bernstein, M.; Connolly, S.; Hartopp, P.; Jackson, C. G.; Lewis, R.; Martin, I.; Murray, D.; Riley, R.; et al. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3128–3133.

(98) *A Novel Series of Histone Deacetylase Inhibitors Incorporating Hetero Aromatic Ring Systems as Connection Units*. Dai, Y.; Guo, Y.; Curtin, M. L.; Li, J.; Pease, L. J.; Guo, J.; Marcotte, P. A.; Glaser, K. B.; Davidsen, S. K.; Michaelides, M. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3817–3820.

(99) *Heterocyclic Ketones as Inhibitors of Histone Deacetylase*. Vasudevan, A.; Ji, Z.; Frey, R. R.; Wada, C. K.; Steinman, D.; Heyman, H. R.; Guo, Y.; Curtin, M. L.; Guo, J.; Li, J.; et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3909–3913.

(100) Benzophenones as Inhibitors of Reverse Transcriptase. Andrews, C.; Chan, J.; Freeman, G.; Romines, K.; Tidwell, J. . WO0117982 (A1), March 15, 2001.

(101) Novel Aminophenyl Ketone Derivatives. Havez, S. . WO02083622 (A2), October 24, 2002.

(102) *(Methoxyalkyl)thiazoles: A New Series of Potent, Selective, and Orally Active 5-Lipoxygenase Inhibitors Displaying High Enantioselectivity*. Bird, T. G. C.; Bruneau, P.; Crawley, G. C.; Edwards, M. P.; Foster, S. J.; Girodeau, J. M.; Kingston, J. F.; McMillan, R. M. *J. Med. Chem.* **1991**, *34*, 2176–2186.

(103) *Optimization of Hydroxybenzothiazoles as Novel Potent and Selective Inhibitors of 17β-HSD1*. Spadaro, A.; Frotscher, M.; Hartmann, R. W. *J. Med. Chem.* **2012**, *55*, 2469–2473.

(104) *Reactions between Weinreb Amides and 2-Magnesiated Oxazoles: A Simple and Efficient Preparation of 2-Acyl Oxazoles*. Pippel, D. J.; Mapes, C. M.; Mani, N. S. *J. Org. Chem.* **2007**, *72*, 5828–5831.

(105) *Cyclodehydrations Leading to Indene Products Having N-Heterocyclic Substituents*. Boblak, K. N.; Klumpp, D. A. *J. Org. Chem.* **2014**, *79*, 5852–5857.

(106) *The Mechanism of the Lithium - Halogen Interchange Reaction : A Review of the Literature*. Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1–46.

(107) *Efficient Synthesis of Functionalized Organozinc Compounds by the Direct Insertion of Zinc into Organic Iodides and Bromides*. Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044.

(108) Organic Synthesis: Tin/Lithium Transmetallation, the Stille Reaction, and the Removal of Tin Residues. In *Organotin Chemistry*; Davies, A. G. ; Wiley-VCH Verlag GmbH & Co. KGaA, 2004; pp 373–382.

(109) *C-Acylation of 5-Membered N-Heterocycles, I. — Acylation at C-2 of Imidazoles and Benzimidazoles*. Regel, E.; Büchel, K.-H. *Justus Liebigs Ann. Chem.* **1977**, *1977*, 145–158.

(110) *C-Acylation of 5-Membered N-Heterocycles, II. — Acylation of 1-Acylimidazoles, Thiazoles and Oxazoles, and Preparation of N-Unsubstituted C-Acylazoles*. Regel, E. *Justus Liebigs Ann. Chem.* **1977**, *1977*, 159–168.

(111) *DMAP-Catalyzed Regel-Type Direct C-2 (Hetero)Aroylation of Oxazoles and Thiazoles Derivatives with Acid Chlorides*. Lassalas, P.; Marsais, F.; Hoarau, C. *Synlett* **2013**, *24*, 2233–2240.

(112) *Nucleophilic Character of Acyl Radicals: A New Selective Type of Aromatic Acylation*. Caronna, T.; Gardini, G. P.; Minisci, F. *J. Chem. Soc. Chem. Commun.* **1969**, No. 5, 201–201.

(113) *Homolytic Acylation of Benzothiazole. A Diagnostic Criterion for the Presence of Acyl Radicals*. Caronna, T.; Galli, R.; Malatesta, V.; Minisci, F. *J. Chem. Soc. C Org.* **1971**, No. 0, 1747–1750.

(114) *Direct C-2 Acylation of Thiazoles with Aldehydes via Metal- and Solvent-Free C–H Activation in the Presence of Tert-Butyl Hydroperoxide*. Khemnar, A.; Bhanage, B. *Synlett* **2013**, *25*, 110–114.

(115) *Chemoselective Copper-Catalyzed Acylation of Benzothiazoles with Aryl Methyl Ketones*. Feng, Q.; Song, Q. *Adv. Synth. Catal.* **2014**, *356*, 2445–2452.