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# Investigation of Factors Influencing Recombination Versus Disproportionation of Complex Radicals Formed by C-N Homolysis of Breslow Type Intermediates and Related Compounds

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Investigation of Factors Influencing Recombination Versus Disproportionation of Complex Radicals Formed by C-N Bond Homolysis of Breslow Type Intermediates and Related Compounds

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

by

Taylor Burnett  
University of Arkansas at Monticello  
Bachelor of Science in Chemistry, 2015

July 2021  
University of Arkansas

This dissertation is approved for recommendation to the Graduate Council.

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## Abstract

Electron rich enamines are capable of C-N bond homolysis and subsequent recombination and/or disproportionation. It is unclear what causes these radicals to undergo recombination or disproportionation. Density Functional Theory (DFT) calculations do not provide a transition state for the recombination and disproportionation processes and therefore they cannot be used to predict the favorable reaction. Breslow intermediates formed by deprotonation of thiazolium salts and reaction with aromatic aldehydes are examples of electron rich enamines. These breslow intermediates can undergo C-N bond homolysis to form a radical pair the either recombine or disproportionate. Upon investigation of the factors influencing recombination and disproportionation, it was determined that when fluorene is employed as the nitrogen substituent on thiazole, the reaction favors disproportionation at low and high temperatures.

The biological compound "vitachrome" was synthesized by reacting thiamine HCl with triethylamine in DMF. We hypothesize vitachrome forms through a radical mechanism which is supported by the observation of pyrimidine monomer and dimer in the reaction mixture. An asymmetric dimer can also be formed using this method when diphenylmethylthiazolium bromide salt and diphenylmethylbenzothiazolium bromide salt are used as starting materials.

## **Acknowledgements**

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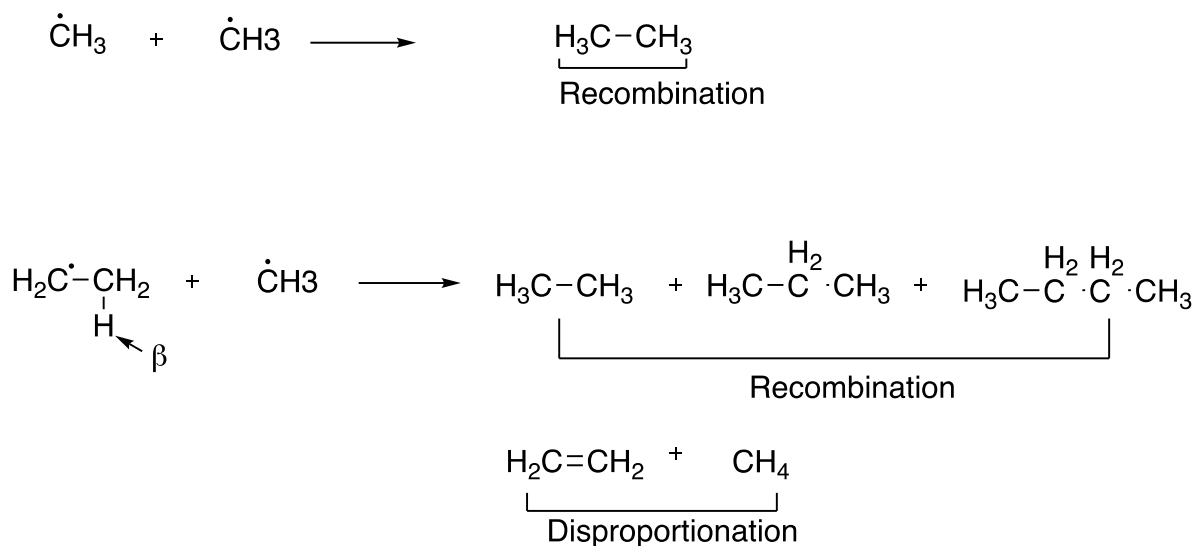
## **Chapter One: Factors Influencing Combination vs Disproportionation of Radicals**

### **1. Introduction**

Understanding the mechanism and reaction conditions necessary for a reaction to occur are critical to the applicability of any reaction in synthesis. While organic radicals are present in many reactions and have biological and industrial applications, their different reactivities provide the problem of predicting which pathway they will undergo in a reaction. Radical recombination and disproportionation have been the focus of many studies, but the pathway of the radicals relies on many different factors including the structure and electronic properties of the radicals. Further complicating the problem, radical recombination and disproportionation are barrierless reactions and theoretical calculations to predict the reaction outcome are not straightforward.

### **2. Recombination and Disproportionation**

Two common reactivity modes of radicals are recombination and disproportionation. Organic free radicals are very reactive and may only exist for a short time due to their propensity to react with other compounds to form stable bonds. When a bond undergoes homolysis to form two unpaired electron species, the two free radicals can recombine to form a diamagnetic compound. If one of the radicals has an abstractable  $\beta$  hydrogen atom, then the two radicals can undergo disproportionation.<sup>1</sup> Disproportionation occurs when one radical abstracts a beta hydrogen atom from another radical compound. The disproportionation results in one of the radicals gaining a hydrogen atom and a pi bond forming in the other compound.<sup>2</sup> For example, methyl radicals only contain hydrogen atoms alpha to the carbon radical center. For this reason, methyl radicals can only undergo recombination with one another. However, in the case of ethyl radicals, there are three hydrogen atoms beta to the carbon radical center, so it is capable of recombination or disproportionation to form ethylene and ethane. The ethyl radical is capable of combination with other ethyl radicals as well as combination with other radicals such as methyl.



**Scheme 1: Radical recombination and disproportionation of methyl and ethyl radicals**

Radical recombination and disproportionation are bimolecular reactions in which the radicals disappear. Since these are both bimolecular processes, the ratio of the percent yields for disproportionation and recombination products can be used to approximate the ratio of rate constants. Rate constants for combination and disproportionation ( $k_d/k_c$ ) can be used to compare reactions and investigate the effect of different factors on the pathway of the radicals.<sup>3</sup> In Gibian's review, he highlights the ratios that have been measured in the gas phase and the dependence on steric and energetic factors. Some measurements in the gas phase and solution indicate that there are very small increases in the  $k_d/k_c$  ratio with a decrease in temperature. However, there are only very small changes in  $k_d/k_c$  ratios over a large range of temperatures. Temperature independent values have been reported for gas phase cyclopentyl (26 to 250° C), n-propyl (18- 150° C), and ethyl (50- 215° C).<sup>2</sup> Consistent and reliable predictions for the combination and disproportionation of radicals are needed to optimize reactions involving radical pairs, especially those possessing structural complexity. By determining what factors cause these radicals to recombine or disproportionate, reactions can be optimized to yield the desired products.



### 3. Theoretical Predictions

Using transition state theory, different chemical reactions can be compared by observing their transition states. The transition state is the point on the reaction coordinate with the highest potential energy. Radical recombination and disproportionation have zero activation enthalpy. This means transition states for these processes cannot be compared to make predictions about reaction outcomes. A “loose” transition state has been developed to represent recombination of methyl radicals. It represents two radicals with 2.6-3 times the normal bonding distance and therefore only experience weak interactions. The normal bonding distance is represented by ( $r_0$ ).  $V_0$  is the potential energy of the bond being formed and  $T$  is the absolute temperature.

$$\frac{r^\ddagger}{r_0} = \left( \frac{6V_0}{RT} \right)^{1/6} \quad (\text{equation 1})$$

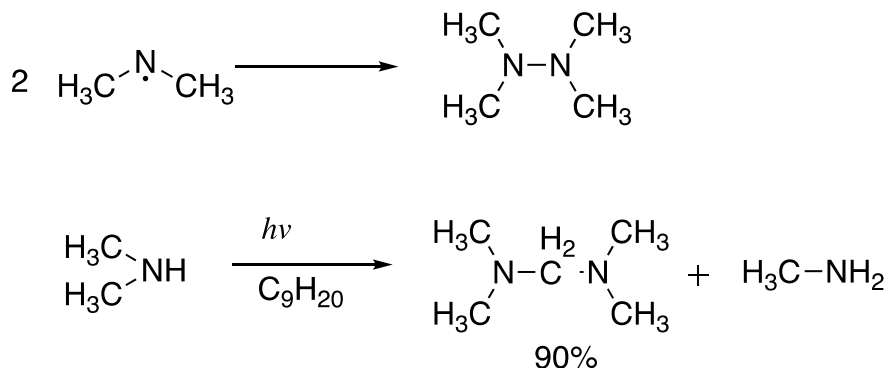
Transition states for the reactions between molecules and radicals are approximated by “tight” transition states. Theoretically, recombination is represented by “loose” transition states and disproportionation is represented by “tight” transition states.<sup>4</sup> Radical recombination and disproportionation reactions are barrierless processes. Therefore, transition states are variable in nature and don’t provide reliable predictions about reaction outcomes. Klippenstein et al did a computational study of saturated alkyl radicals and their combination. He studied combination reactions with ethyl, isopropyl, and *tert*-butyl radicals as well as cross combination reactions with methyl radical. It was determined that steric hindrance had a large effect on the combination rate of the radicals. An increase in the steric bulk resulted in a larger temperature dependence. The combination rate decreased more rapidly for sterically hindered reactants than reactants lacking steric bulk. He only investigated saturated alkyl radicals, so more work would be needed to predict the outcome of larger and more complex radicals.<sup>5, 6</sup> In Smith’s Density-functional theory (DFT) study, he examined the activation enthalpy for the recombination and disproportionation of ethyl, *n*-propyl, and *sec*-propyl radicals in an attempt to elucidate the mechanism of recombination and

disproportionation. In each case, a lower activation enthalpy was observed for recombination than for disproportionation. He determined that the activation enthalpy increased for the hydrogen transfer process when the number of methyl groups increased on the donor radical.<sup>7</sup>

#### 4. Reaction Conditions and Radical Structure Effect on $k_d/k_c$

##### 4.1 Phase of the Reaction

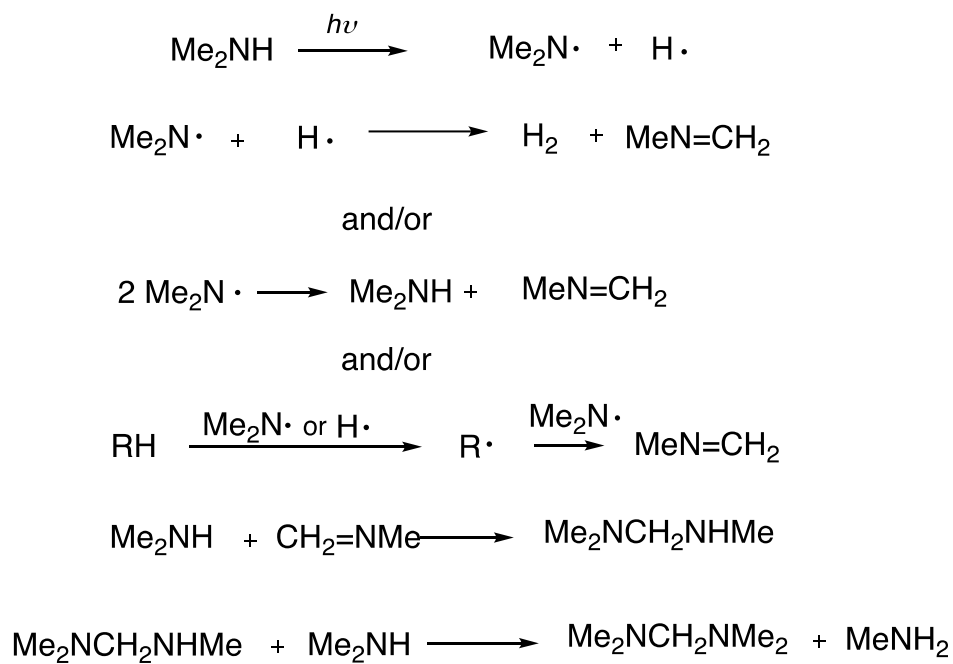
Several studies suggested that whether the reaction occurs in the solid, gas, or liquid phase has an influence on whether the radicals favor recombination or disproportionation. The previous examples have all focused on alkyl radicals but the following reaction occurs with amino radicals. Under gas phase conditions, most of the dimethylamino radicals dimerize to form tetramethylhydrazine. When dimethylamine was irradiated in solution, tetramethylhydrazine was only minimally observed. Instead, the major product formed was diamine.



**Scheme 2: Dimethylamino radical recombination and dimerization**

It is thought that this is due to the origin of the dimethylamino radical. In solution, the radical is generated by photolysis of dimethylamine. After photolysis, the reaction conditions are optimal for disproportionation within the solvent cage or hydrogen transfer with the solvent. In the gas phase, the radicals are generated from tetramethyltetrazene and there is not solvent for hydrogen transfer. For this reason, the diffusion and recombination of the radicals are favored in

the gas phase. The following mechanism is proposed for the formation of the diamine from methylamine. The N-H bond of dimethylamine undergoes bond scission to form the dimethylamino radicals. The radicals can then be oxidized to form *N*-methylenemethylamine by auto disproportionation, bimolecular disproportionation, and/or hydrogen transfer with solvent. Dimethylamine then reacts with *N*-methylenemethylamine to form the trimethylamine which can undergo transamination with dimethylamine to form the major products observed in the reaction.<sup>8</sup>



**Scheme 3: Proposed mechanism for formation of diamine from dimethylamine**

In another study the  $k_d/k_c$  ratios for cycloalkyl radicals were compared in the liquid and gas phases. Cyclopentyl, cyclohexyl, and cycloheptyl radicals had similar  $k_d/k_c$  ratios in the liquid phase.

**Table 1:  $k_d/k_c$  values of cyclopentyl, cyclohexyl and cycloheptyl radicals in gas, liquid and solid phase**

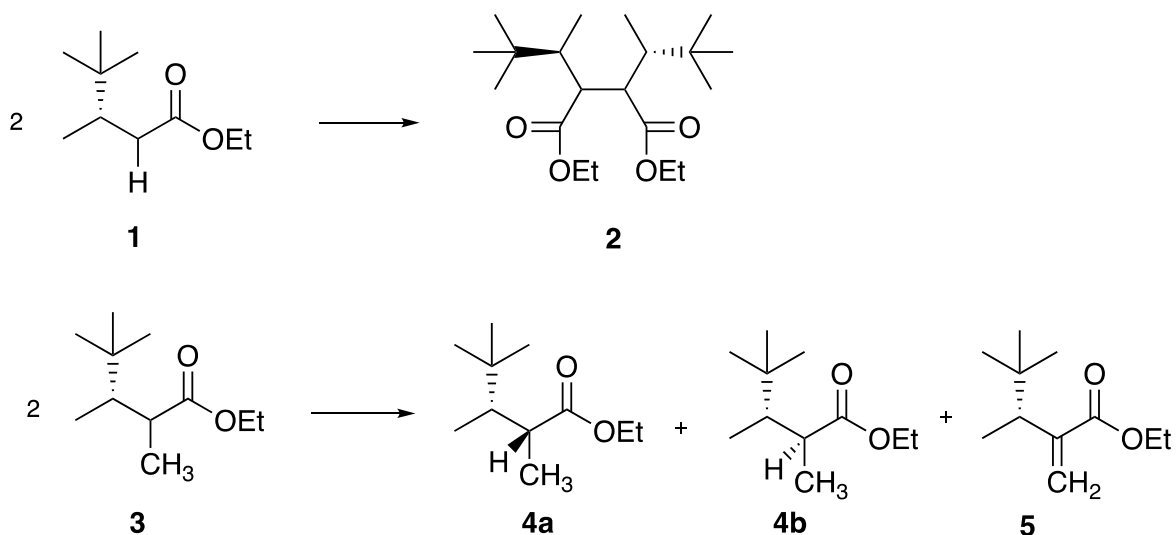
Radicals	Phase	T/K	$k_d/k_c$	Method	Reference
<b>Cyclopentyl</b>	Gas	299-523	1	Mercury	<sup>9</sup>
	Liquid	298	1.5	Aqueous	<sup>10</sup>
	Solid	120	1	Radiolysis	<sup>11, 12</sup>
<b>Cyclohexyl</b>	Gas	302	0.46	Mercury	<sup>13</sup>
	Liquid	298	1.1	Diphenyl	<sup>9</sup>
			1.31-1.47	Mercury	<sup>14</sup>
			1.1	Radiolysis	<sup>15</sup>
	Solid	77-112	4.9-4.5	Hydrogen	
		173-195	0.5-0.8	Alkali	
		186	0.3	Radiolysis	<sup>16</sup>
		186	0.65	Dissolution	
<b>Cycloheptyl</b>	Liquid	298	0.95	Radiolysis	<sup>11, 12</sup>
	Solid	140	1.62	Dissolution	

Lazarou and Papagiannakopoulos reported that in the self-reaction of dimethylaminyl radicals, recombination was completely suppressed under certain conditions in the liquid phase.<sup>17</sup>

## 4.2 Reaction Temperature

It has been speculated that temperature may have an effect on radical combination and disproportionation. Varying results have been observed for different compounds and different phases. The  $k_d/k_c$  ratio for ethyl radicals does not change over the temperature range 173-298 K in the gas phase.<sup>18</sup> There is some evidence that disproportionation increases with decreasing reaction temperature for some radicals in the liquid and gas phase, but the increase is relatively small.<sup>2</sup> In 1976, Schuh and Fischer studied disproportionation and recombination of *tert*-butyl

radicals as a function of temperature in the liquid phase. The radicals recombine to form 2,2,3,3-tetramethylbutane or disproportionate to give isobutane and isobutene. They compared the ratios of disproportionation and recombination for reactions as a function of temperature and solvent viscosity. It was determined that there is only a small dependence on solvent.<sup>19, 20</sup> Ratios have been determined as a function of reaction temperature and viscosity. It is suspected that the effect is dependent on solvent viscosity since the viscosity of the solvent changes with changes in temperature.<sup>21</sup> Porter et al studied recombination and disproportionation reactions between 2-Pentanoate radicals and when an methyl group was attached to the carbon alpha to the carbonyl, disproportionation products were the only products observed over a wide range of temperatures (-78–80° C).<sup>22</sup>



**Scheme 4: Pentanoate radicals recombination and disproportionation**

### 4.3 Caged or Free Radicals

When radicals are formed by homolysis, they form a geminate pair. This means that the two radicals came from the same parent molecule. When homolysis occurs in solution, the radicals exist in a solvent cage for a certain amount of time. While in the solvent cage, the radicals can undergo recombination and disproportionation. When the radicals escape the solvent cage,

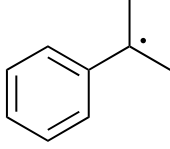

they are termed “free” radicals and are capable of reaction with other compounds. Some studies suggest that whether the termination mechanism occurs in the solvent cage or between free radicals, does not affect the ratio of  $k_d/k_c$ . Photolysis of  $C_2H_5COC_2H_5$  generates a geminate radical pair. All of the other methods of radical generation produce free radicals. The similar  $k_d/k_c$  values for these different methods support the idea that whether radicals are geminate or free, does not influence the ratio of disproportionation vs recombination of ethyl radicals.<sup>23</sup>

**Table 2:  $k_d/k_c$  value for ethyl radicals in solution at 25° C**

Radical generation method	$[C_2H_4]/[C_4H_{10}] = k_d/k_c$
$C_2H_5I + (CH_3)_2CO^\cdot$	0.38
$C_2H_5COC_2H_5$ , photolysis	0.35
$(NH_3)_5CoO_2CC_2H_5^{2+}$ , photolysis	0.31
$V (H_2O)_6^{2+} + C_2H_5C(CH_3)_2OOH$	0.38
$Fe (H_2O)_6^{2+} + C_2H_5C(CH_3)_2OOH$	0.33

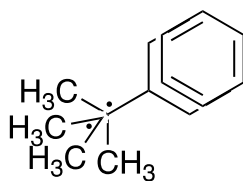
#### 4.4 Steric Effects

The steric hindrance around the radical bearing atom is also suspected to have an influence on the ratio of disproportionation to recombination. Cumyl radicals have a  $k_d/k_c$  value of 0.06 at 60° C and *tert*-butyl radicals have a much higher value of  $k_d/k_c = 5.4$ .

Radical	$k_d/k_c$
 <b>6</b>	0.06
 <b>7</b>	5.4

**Figure 1:  $k_d/k_c$  values for cumyl and *tert*-butyl radicals**

It is proposed that the cumyl radicals do not favor disproportionation due to the possible formation of a dimeric association complex, although this complex has not been identified computationally. If this association complex forms during the reaction, the coupling product would be favored rather than disproportionation product due to geometry.<sup>24, 25</sup>

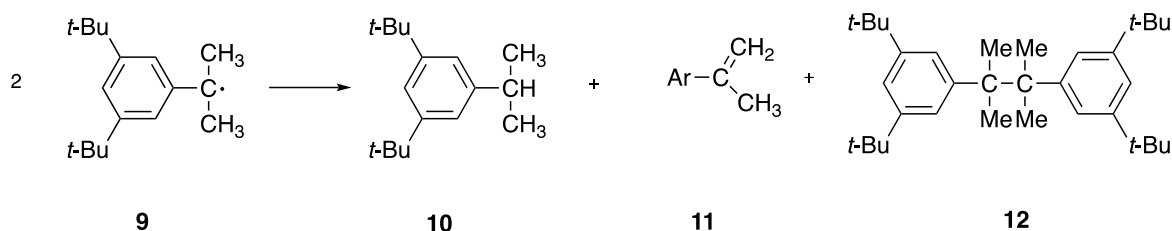


**8**

**Figure 2: Association complex for cumyl radicals**

By adding *tert*-butyl at the 3 and 5 positions of the cumyl group, the association complex will undergo some distortion and therefore result in less recombination and more disproportionation. The  $k_d/k_c$  for cumyl radicals containing *tert*-butyl groups at the 3 and 5 positions was 0.21 and the  $k_d/k_c$  for unsubstituted cumyl radicals was 0.06. Experimentally, the

combination of the radicals was still preferred over disproportionation and they conclude that the *tert*-butyl groups were not large enough to prevent the combination completely.<sup>26, 27</sup>



**Scheme 5: 3,5-di-*tert*-butylcumyl radical combination and disproportionation**

In 1974, Klein and Kelly studied the cross disproportionation of alkyl radicals and did not observe a difference in  $k_d/k_c$  in the temperature range 90-143 K. They were able to form cross-disproportionation products with the alkyl radicals to investigate the mechanism for disproportionation. They concluded that disproportionation is favored when the alkyl radical is more sterically hindered.<sup>28</sup>

#### 4.5 Resonance

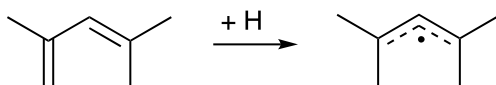
Allylic radicals are thought to be similar to alkyl radicals in that disproportionation is increased at lower temperatures. However, when Klein reacted allylic radicals, only recombination products were observed and he concluded that in the case of allylic-allylic radical reactions, only recombination is possible and not disproportionation. However, an allylic radical can undergo disproportionation and recombination with an alkyl radical.

##### Allylic-allylic radical reactions

For example, when a H atom was added to 1,3-butadiene at 0.3% in propane at 90 K, the methylallyl radical was formed. The reaction mixtures were analyzed by gas chromatography and only the recombination products were observed. Hydrogen atom addition to *cis*-1,3-pentadiene diluted to 0.3% with propane at 90 K produced the 1,3-dimethylallyl radical. If these radicals were



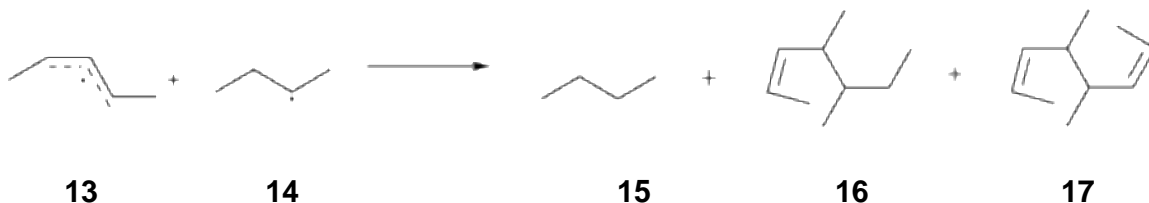
to undergo disproportionation, they would have formed 1- and 2- pentenes. Neither one of these products were observed in the reaction. However, a diene with 10 carbons was detected which is formed by the combination of the 1,3-dimethylallyl radicals. It is known that branching on alkyl radicals influences their recombination/disproportionation. To probe the effect of branching on allylic radicals, 2,4-dimethyl-1,3-pentadiene was used in the reaction. This reaction also favored combination by 99%.



**Figure 3: Formation of 2,4-dimethyl -1,3-pentadiene radical**

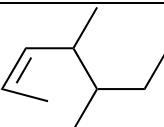
### Allylic-alkyl radical reactions

Disproportionation does occur when an allylic radical is allowed to react with an alkyl radical. Only 15% yield of the reaction mixture resulted from disproportionation. Of this 15%, only 27% resulted from the allyl radical acting as the hydrogen atom acceptor and 73% involved allyl as the H atom acceptor. Using a series of cross-combination/disproportionation experiments, Klein and Kelley showed that allylic radicals do not act as hydrogen acceptors. Therefore, in allylic-allylic radical reactions, only recombination is observed. When 2-butyl radicals are generated with an excess of 1,3-dimethylallyl radicals, the major product is the diene formed by the recombination 1,3-dimethylallyl radicals. Butane and the cross-combination product between the 2-butyl radical and 1,3-dimethylallyl radical were also obtained. Condensed olefins were present as a layer on the bottom of a flask. To generate radicals, the film was bombarded by hydrogen atoms which were produced by thermally dissociating molecular hydrogen on a heated tungsten filament. While Klein and Kelley state that rotation of allylic radicals would not be expected to be observed in the low-temperature region, there is some uncertainty whether the configuration of the dienes were retained.<sup>27</sup>

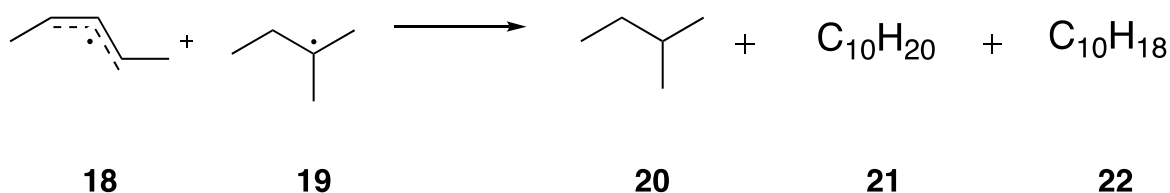


**Figure 4: 1,3-dimethylallyl radical reaction with 2-butyl radical**

**Table 3: Relative yield of products in reaction of 1,3-dimethylallyl radical and 2-butyl radical**

Product	Relative yield of product
$n\text{-C}_4\text{H}_{10}$	25
$1\text{-C}_4\text{H}_8$	<0.5
$t\text{-2-C}_4\text{H}_8$	<0.5
$t\text{-1,3-C}_5\text{H}_8$	<0.1
$2,3\text{-C}_5\text{H}_8$	<0.1
3,4-Dimethylhexane	<0.1
	25
$\text{C}_{10}$ diene	4,000

When 2-methyl-2-butyl and 1,3-dimethylallyl radicals were reacted with one another with 1,3-dimethylallyl radicals in large excess, the combination of the 1,3-dimethylallyl radicals was favored over any disproportionation or cross-combination reactions. In these cross-disproportionation reactions it is interesting that the allyl radical only functions as a hydrogen donor, but not as a hydrogen acceptor. This is the reason given for the lack of disproportionation of allylic radicals.<sup>27</sup>



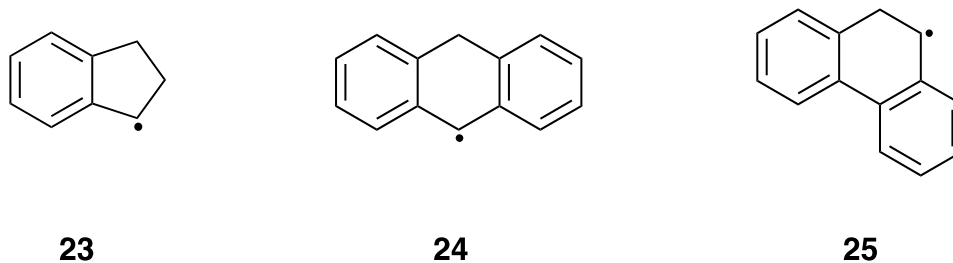
**Figure 5: 1,3-dimethylallyl radical reaction with 2-methyl-2-butyl radical**

**Table 4: Relative yield of products in reaction of 1,3-dimethylallyl radical and 1-methyl-2-butyl radical**

Product	Relative yield of product
2-Methylbutane	1.0
2-Methyl-1-butene	<0.01
<i>n</i> -pentane	<0.02
1-pentene	<0.02
2-pentene	<0.02
C <sub>10</sub> H <sub>20</sub>	1.7
C <sub>10</sub> H <sub>18</sub>	250

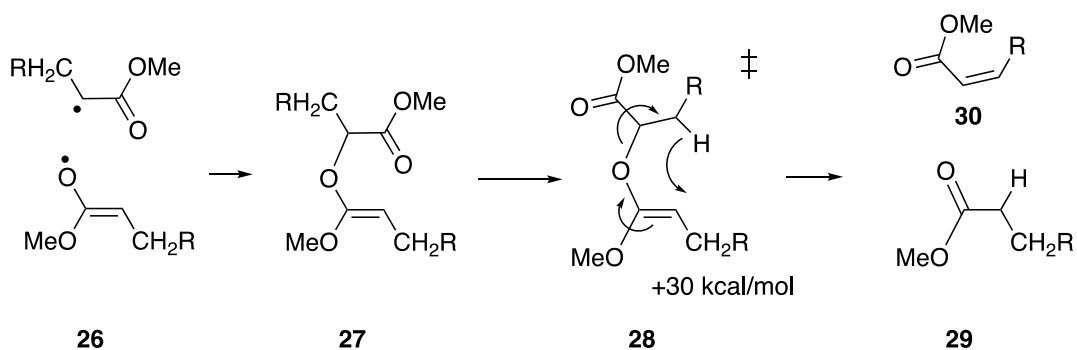
In 1971, Weiner released a report studying the behavior of ketyl radical generated by thermolysis. Benzpinacols undergo thermolysis at temperatures between 80 and 141°C to give benzophenone ketyl radicals. He concludes that more stable radicals are less likely to undergo disproportionation and favor recombination. Also, ketyl radicals containing a *para*-bromine are more stable than the ketyl radicals with a *para* hydrogen atom. A methoxy group in the *para* position destabilizes the radical. More stable radicals were thought to terminate more slowly. However, this is not always the case.<sup>29</sup> Manka and Stein reported experimental  $k_d/k_c$  values for tetrahydronaphthalene, indane, and anthracene radicals which all favored recombination.

Tetrahydronaphthalene and anthracene had smaller  $k_d/k_c$  values of 0.08 and 0.05 respectively. Indane had a slightly higher  $k_d/k_c$  value of 0.12.<sup>30</sup>



**Figure 6: Tetrahydronaphthalene, indane, and anthracene radicals**

Pritchard et al investigated the recombination and disproportionation of alkyl radicals and fluoroalkyl radicals. When  $k_d/k_c$  values were measured for  $n\text{-C}_3\text{F}_7$  and  $\text{CF}_2\text{H}$  radicals, the value was very low ( $k_d/k_c = 0.072$ ). However, when  $\text{CH}_3$  and  $\text{CF}_2\text{H}$  radicals were evaluated, there was an increase in disproportionation ( $k_d/k_c = 0.35$ ). The H-atom from  $\text{CF}_2\text{H}$  is transferred to the alkyl radical. Attempts were made to find a trend correlating to the number of abstractable hydrogen atoms and the resulting  $k_d/k_c$  value. The  $k_d/k_c$  values for the alkyl and fluoroalkyl radicals did not follow any clear trend.<sup>31</sup> In 2016, Yamago et al reported that in the polymerization of acrylates, only disproportionation products are observed but that they form by two different pathways. The first pathway is direct disproportionation and the second pathway is a novel stepwise process that involves the formation of a C-O coupling product which undergoes intramolecular rearrangement.<sup>32</sup> When Asua reevaluated the data from Yamago, the results were heavily influenced by the backbiting reactions which result in disproportionation chains.<sup>33</sup> In certain cases the disproportionation products can be formed through alternate mechanisms so experiments are needed to elucidate the mechanisms behind these reactions.



**Scheme 6: Yamago's stepwise process to form rearrangement products**

#### 4.6 Viscosity

When polymerization reactions for styrene, methyl methacrylate, and methyl acrylate were studied, it was determined that for each of these polymers, disproportionation dominated at lower temperatures ( $< 25^{\circ}\text{C}$ ) and combination dominated at higher temperatures ( $> 60^{\circ}\text{C}$ ). It is thought that this is due to a viscosity effect rather than a temperature effect. Viscosity of the solvent is higher at lower temperatures and prefers disproportionation. Poly methyl methacrylate radicals were generated by photolysis of an organotellurium compound and the combination/disproportionation yields were measured. The reaction was done in benzene, dimethyl sulfoxide (DMSO), and polyethylene glycol (PEG 400). The  $k_d/k_c$  in benzene and DMSO were 1.4 and 3.1 respectively when the reaction was done at room temperature. The  $k_d/k_c$  in PEG 400 at room temperature was increased to 17. Each of the  $k_d/k_c$  values decreased when the reaction temperature was increased to  $60^{\circ}\text{C}$ .<sup>21</sup>

#### 5. Conclusion

The factors that influence the recombination and disproportionation of radicals have been the focus of many experimental and theoretical investigations. However, there is still much to be determined to be able to make confident predictions in these reactions. From these investigations, it is clear that the identity of the radical bearing atom, identity of the atom bearing the abstracted hydrogen, stability of the radicals, solvent, solvent viscosity, steric

hindrance around the radical, cross or homo disproportionation/combination, whether the radicals are allylic or alkyl, reaction temperature and whether the radicals are geminate or free influence the pathway of the radicals.

## Chapter Two: Breslow Intermediates as Electron Rich Enamines and Reactivity

### 1. Introduction

Enamines are valuable organic compounds. Their electronic properties and structure cause them to have several different modes of reactivity.<sup>34</sup>

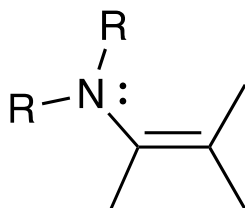
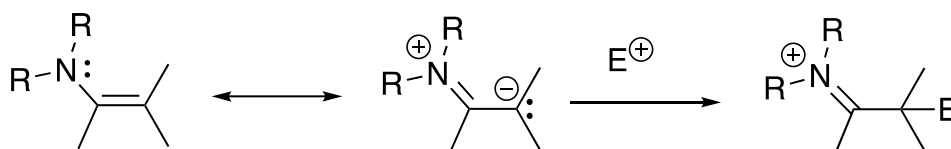


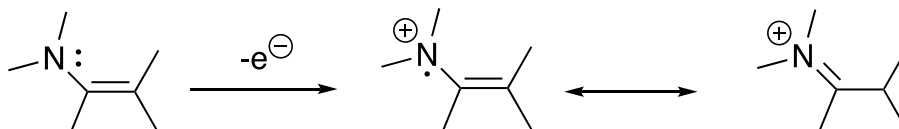
Figure 7: Enamine

Through resonance the enamine contains a double bond between the positively charged nitrogen and the  $\alpha$  carbon. The  $\beta$  carbon possesses a lone pair of electrons and a negative charge causing this carbon to be nucleophilic. This nucleophilic enamine reacts with electrophiles to form positively charged species.



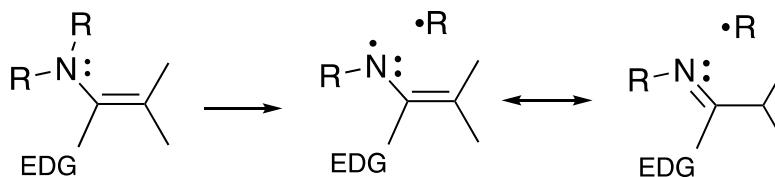
Scheme 7: Resonance form of generic enamine electrophilic addition

Enamines have a second type of reactivity that is not commonly known. The enamine can act as a single electron donor in some reactions producing an enamine radical cation.<sup>34</sup>



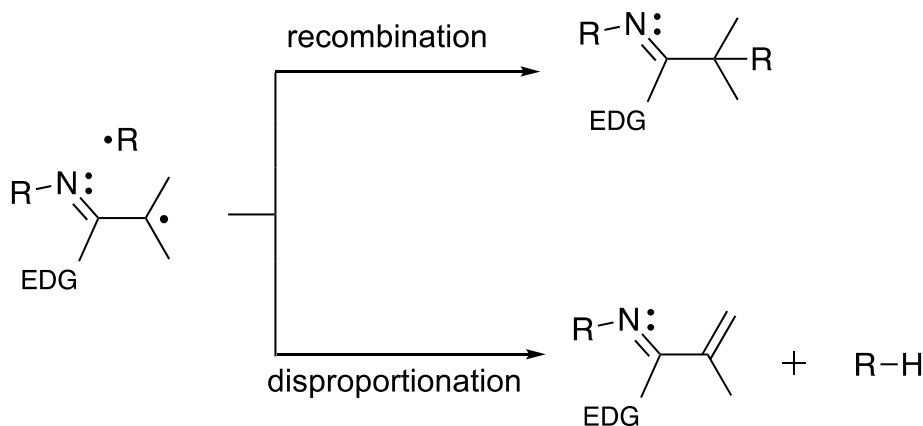
Scheme 8: Enamine as single electron donor

An electron rich enamine with an electron donating group attached at the  $\alpha$  carbon has another type of reactivity. The C-N bond between nitrogen and its substituents can homolyze which produces a nitrogen centered radical and a carbon centered radical.



**Scheme 9: Homolysis of enamine to form two radicals**

Through resonance, the nitrogen centered radical can also be found on the  $\beta$  carbon. Once these two radicals are formed, there are two different termination reactions that can occur. The radicals can either undergo recombination or disproportionation. Recombination of the two radicals form a rearrangement product with the nitrogen substituent replaced at the  $\beta$  carbon. Disproportionation of the two radicals occurs through hydrogen atom abstraction, which forms a protonated substituent and a new pi bond between the  $\beta$  carbon and the neighboring atom from which the hydrogen atom was abstracted. It is important to note that for disproportionation to occur between the two radicals, there must be an abstractable hydrogen atom  $\beta$  to one of the radicals.<sup>2</sup>



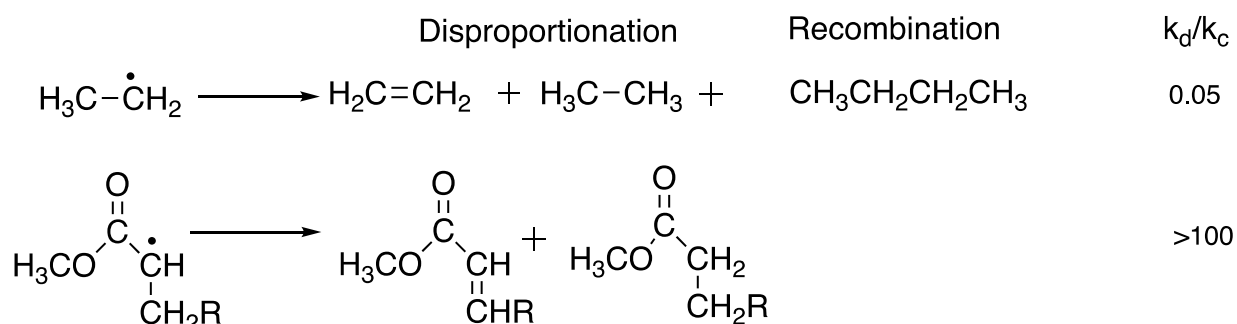
**Scheme 10: Homolyzed radical pair and subsequent recombination or disproportionation**



What causes radicals to favor recombination or disproportionation is often unclear. Since radical recombination and disproportionation are barrierless interactions, comparisons of transition state energies do not provide insight into which pathway is favored. Some experimental studies have been done to determine factors that cause small radicals to recombine or disproportionate, but clear trends have not been determined. The ratio  $k_d/k_c$  is used to compare radical reactions and their preference for recombination or disproportionation.  $k_d/k_c$  is used to represent the ratio of the rate constants for the formation of the disproportionation products and the formation of the recombination products (**Equation 2**).<sup>3</sup>

$$\frac{\text{yield of disproportionation}}{\text{yield of combination}} = \frac{k_d}{k_c} \quad \text{(Equation 2)}$$

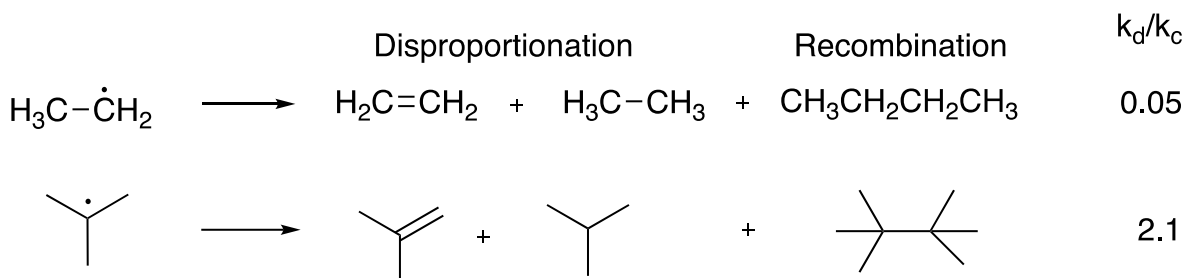
The  $k_d/k_c$  ratio can vary by a large factor. For example, in the case of ethyl radical, the ratio is only 0.05 indicating that radicals favor recombination. However, methyl ester radicals favor disproportionation with a ratio over 100 (**Figure 8**).<sup>2</sup>



**Figure 8:  $k_d/k_c$  values for ethyl radical and methyl ester radical**

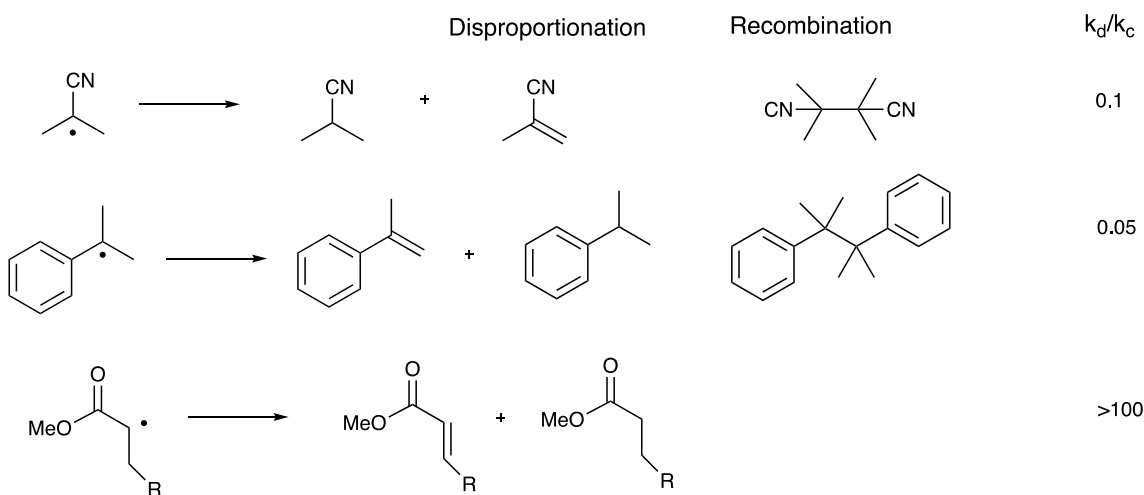
Some experiments have been done to determine if steric hindrance influences the pathway of the radicals. Compared to ethyl radicals, tertiary butyl radicals favor

disproportionation by a small factor in relation to the different ratios for ethyl radicals and methyl ester radicals (**Figure 9**).<sup>2</sup>



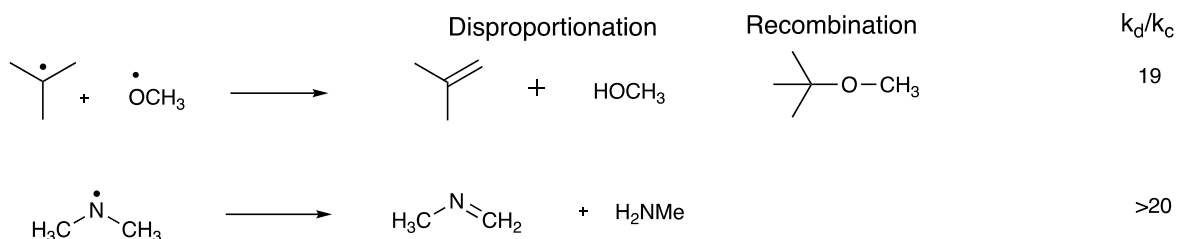
**Figure 9:  $k_d/k_c$  values for ethyl radical and *tert*-butyl radical**

Radicals can also be conjugated with a functional group and some studies have been done to see how this influences  $k_d/k_c$ . When the radicals are conjugated with a nitrile or with a benzene functional group, the radicals favor recombination. However, when the radicals are conjugated with a methyl ester functional group, disproportionation is the favored pathway by a large ratio although it's unclear how general the trend is considering the relative paucity of reports in the literature (**Figure 10**).<sup>2</sup>



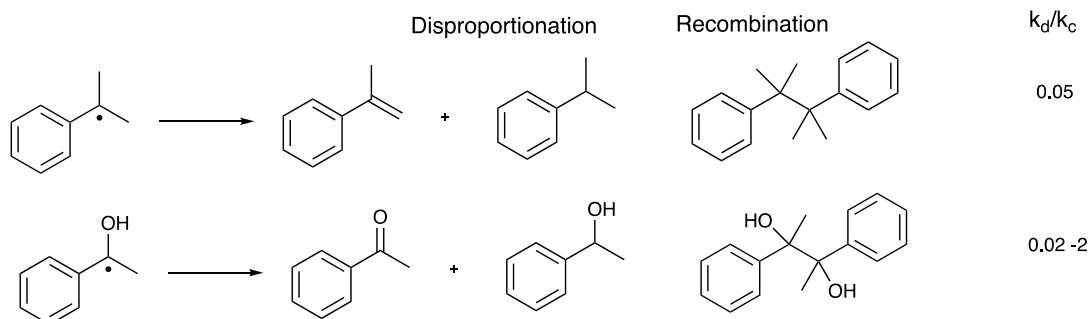
**Figure 10:  $k_d/k_c$  values of nitrile radical, cumyl radical and methyl ester radical**

Some experiments have also been done to determine the outcome when the radical bearing atom is something other than carbon. In the case of nitrogen and oxygen radicals, the favored pathway is disproportionation (**Figure 11**).<sup>2</sup>



**Figure 11:  $k_d/k_c$  for tert-butyl radical with methoxy radical and  $k_d/k_c$  for amine radical**

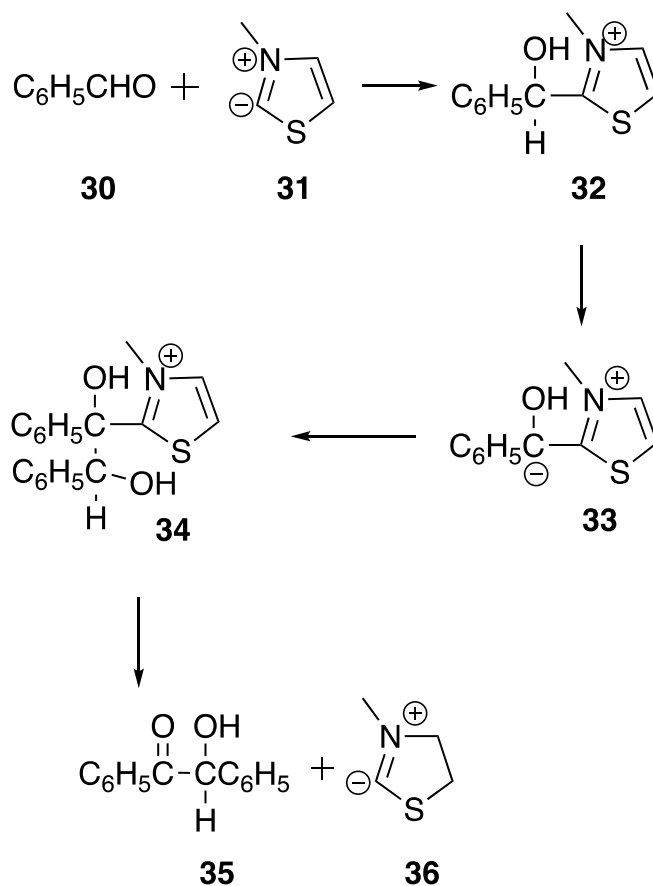
Methyl ester radicals favor disproportionation by a large degree. In methyl ester radicals, the radical is conjugated with an oxygen atom. It is expected that when conjugation with oxygen is present disproportionation would be favored. However, in the case of the benzyl alcohol radical, recombination is still favored (**Figure 12**).<sup>2</sup>



**Figure 12:  $k_d/k_c$  values for cumyl radical and 2-methyl-1-phenylethanol radical**

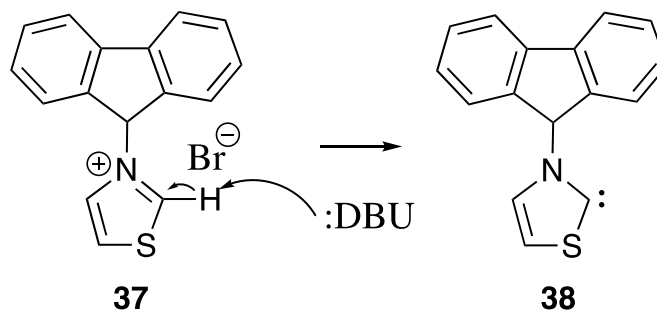
## 2. Breslow Intermediates as Electron Rich Enamines

Breslow intermediates were first proposed by Ronald Breslow in 1958 when studying thiamine catalyzed benzoin condensation of benzaldehyde. He proposed a carbene **31** and enaminol **33** as transient intermediates in the process.<sup>35</sup>



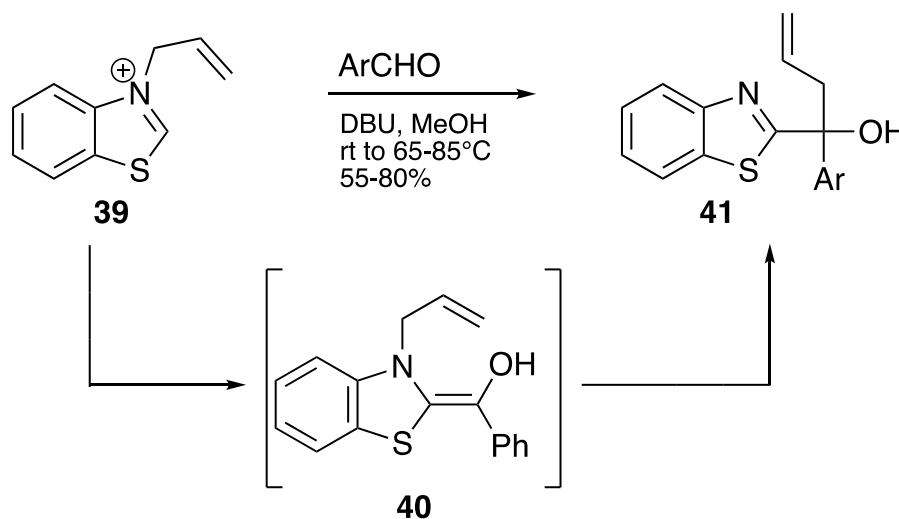
**Scheme 11: Thiamine catalyzed benzoin condensation and Breslow intermediate**

Azole *N*-heterocyclic carbenes can be formed by deprotonation of azolium salts with base. For example, *N*-fluorenylthiazolium salt **37** can be deprotonated with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) to form *N*-fluorenylthiazole carbene **38**.



**Figure 13: Formation of *N*-heterocyclic carbene from azolium salt**

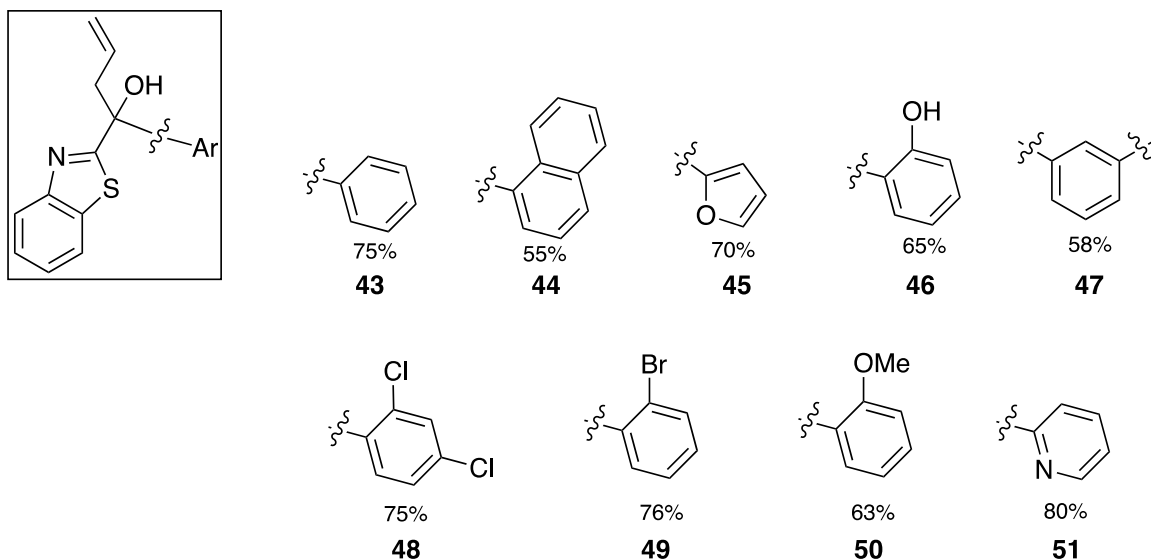
When these types of NHC's are used in reactions with aldehydes, a Breslow intermediate is formed. Breslow intermediates are an example of electron rich enamines capable of the reactivities mentioned previously. In this case, the carbonyl carbon of the aldehyde is also the  $\beta$  carbon of the enamine, which is nucleophilic through umpolung of the aldehyde. This allows attack of another benzaldehyde and formation of benzoin and NHC.<sup>36</sup> Previously, our group found that Claisen rearrangement products could be formed from reaction of *N*-allylbenzothiazolium salt with aldehydes and DBU in methanol (**Scheme 12**). These reactions worked well under mild conditions including low temperature.



**Scheme 12: *N*-allylbenzothiazolium and benzaldehyde form rearrangement product**

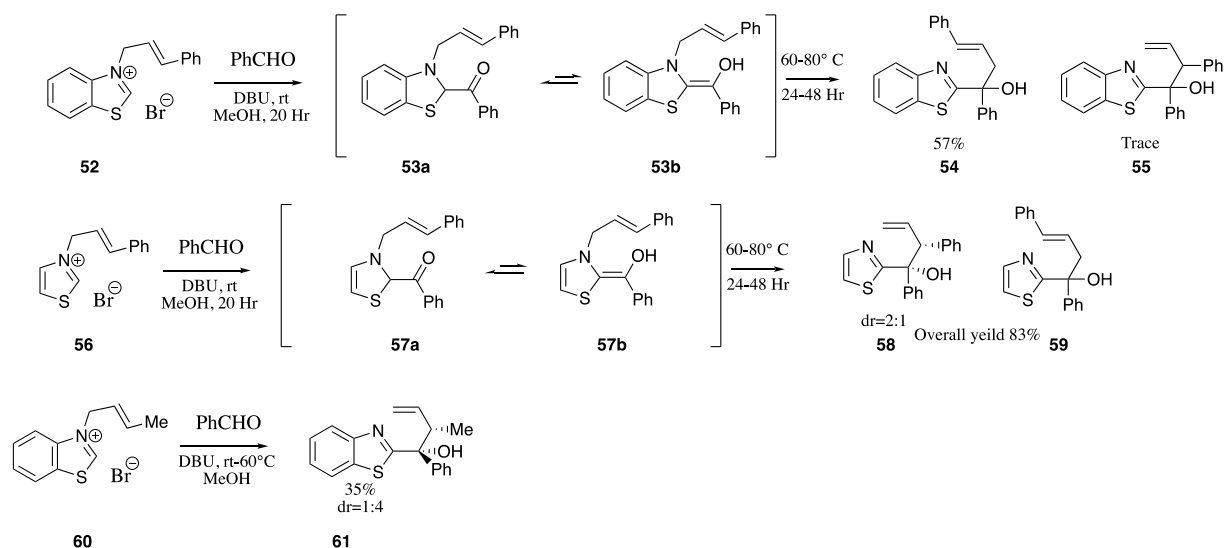
The Breslow intermediate formed **40** can undergo benzoin condensation as well with another molecule of aldehyde, but that is not what was observed under the conditions. The rationale is that since benzoin condensation is an intermolecular process and rearrangement is an intramolecular process, the rearrangement is kinetically favored. The rearrangement worked well with a variety of different aldehydes, including aromatic and heteroaromatic aldehydes (**Figure 14**). Electron-rich and electron-poor aldehydes yield the rearrangement products in

good yields. Pyridine-2-carboxaldehyde and 2-furaldehyde also undergo rearrangement to provide good yields **51** and **45**. An unprotected phenol is even tolerated in the reaction **46**.<sup>37</sup>



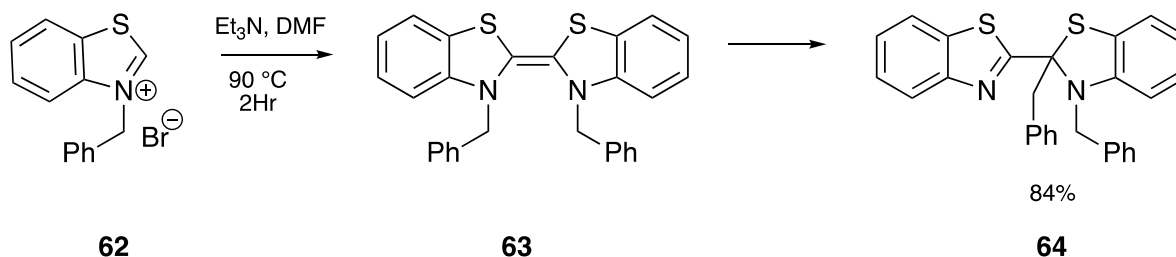
**Figure 14: N-allylbenzothiazolium salt and aromatic aldehydes**

When the *N*-substituent of the azolium salt was changed to an *E*-substituted allyl group, such as cinnamyl or crotyl, there were interesting trends observed. In the case of cinnamylbenzothiazolium salt **52**, deprotonation and nucleophilic attack with benzaldehyde did not form the rearrangement product that was expected. There were trace amounts of the [3,3]-rearrangement product **55** and 57% of a [1,3]-rearrangement product **54** was observed. However, when the *N*-cinnamylthiazolium salt **56** was used in the reaction, equal amounts of the [1,3]-rearrangement and [3,3]-rearrangement were obtained **58** and **59**. In the case of *N*-crotylbenzothiazolium salt **60**, the [3,3] rearrangement product **61** was the only product observed. The rearrangements with the *N*-allylbenzothiazolium salt were all thought to be [3,3]-rearrangements. The product formed from cinnamylbenzothiazolium was the result of an unexpected [1,3]-rearrangement.



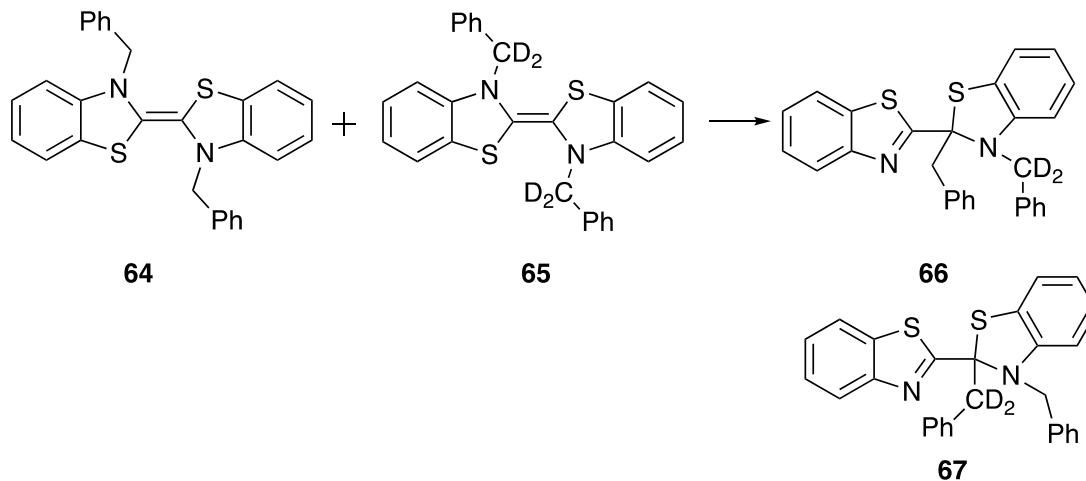
**Scheme 13: Formation of [1,3]-rearrangement product with cinnamyl salt**

This [1,3]-rearrangement has been observed in other systems. In 1974, Baldwin reported that when *N*-allylbenzothiazolium salts react with triethylamine, they are deprotonated and dimerize in solution. Once they dimerize, a rearrangement occurs. There are two competing pathways for this rearrangement. Rearrangement can either occur through a [3,3]-Sigmatropic rearrangement or [1,3]-rearrangement. He found that [3,3]-rearrangement products were favored at room temperature and [1,3]-rearrangements were favored at higher temperatures. When *N*-benzylbenzothiazolium **62** salt reacts with triethylamine, a [1,3]-rearrangement product is observed **64**. The benzyl substituent is not capable of undergoing a [3,3]-rearrangement. Later, he noticed that there was an increase in the rate of rearrangement with *p*-nitrobenzyl derivative versus the benzyl derivative. This is indicative of a radical mechanism.



**Scheme 14: [1,3]-rearrangement of N-phenylbenzothiazolium salt**

He used deuterium labeling experiments to show that it was indeed a radical mechanism. He prepared a mixture of deuterium labeled *N*-benzylbenzothiazole salt **65** and unlabeled *N*-benzylbenzothiazole salt **64**. The mixture was then mixed with base. A rearranged dimer containing a mixture of labeled and unlabeled benzyl groups **66** was observed. The formation of this crossover product is consistent with a radical mechanism. When the reactions were carried out, they obtained a rearrangement product that contained a labeled benzyl group and a non-labeled benzyl group. This product only accounted for 28% of the total. An intermolecular migration would give 50% yield of this mixed product, but Baldwin attributes this to a cage effect in the radical dissociation-recombination reaction.<sup>38</sup>

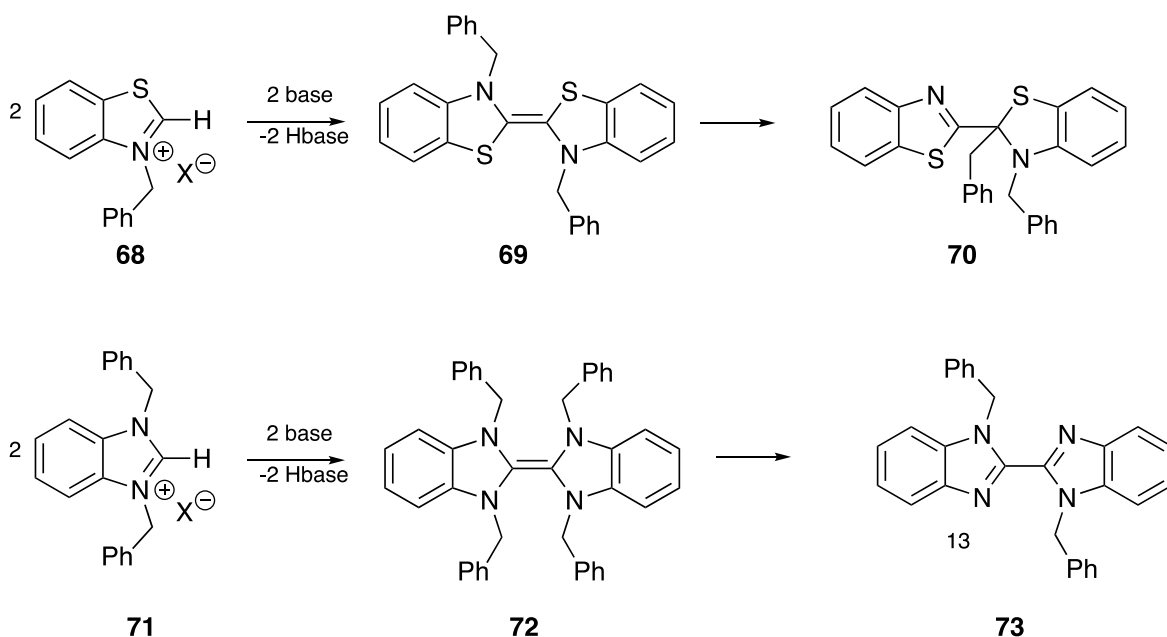


**Scheme 15: Baldwin's deuterium labeling experiment**

To rule out the possibility of an intermolecular crossover before the [1,3]-benzyl shift, a mixture of methyl benzothiazole salt was mixed with unmethylated benzothiazole salt and rearranged under normal reaction conditions. If this crossover were occurring before the [1,3]-benzyl shift, then a monomethyl dimer would have formed. However, it was undetectable by mass spectrometry. Bibenzyl was also detected in the crude product, which supports the radical mechanism for this rearrangement. They owe the [1,3]-benzyl migration to the resonance stabilization of the bibenzothiazoline radical.<sup>39</sup>



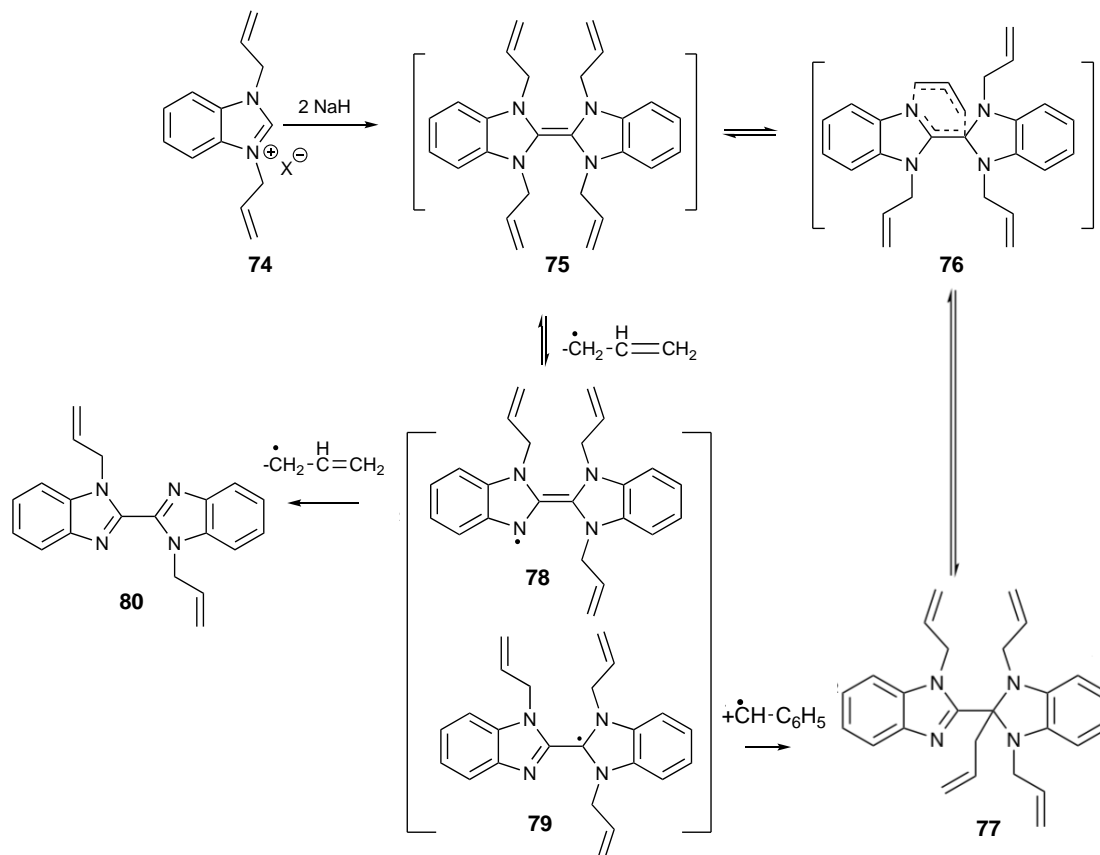
When *N,N'*-dibenzylidibenzodiazadithiofulvalene (**69**) is heated in the presence of base, a rearrangement product is formed (**70**). However, when tetrabenzylidibenzotetraazafulvalene (**72**) is employed, the double debenzylated product (**73**) is the only product detected. In 2006, Hahn used experimental and computational studies to investigate the mechanism behind this rearrangement with different substituents on dibenzotetraazafulvalenes.



**Scheme 16: Rearrangement or second homolysis depending on azolium salt**

When the *N*-substituents of the dibenzotetraazafulvalene are all allyl groups (**75**), the rearrangement product can be formed through a 3-aza-Cope rearrangement or a radical rearrangement. In the radical pathway, the C-N bond between the imidazole and the allyl group homolyze; forming a radical pair (**78** and **79**). The radical pair can undergo recombination at the C2 position to form the rearrangement product (**77**). In the 3-aza-Cope rearrangement, a six-membered transition state (**76**) is formed which also leads to the rearrangement product. Using experiments and DFT calculations, Hahn showed that the rearrangement of benzannulated *N*-heterocyclic carbenes favors a [1,3]-radical decomposition pathway. By comparing the energy of the six-membered transition state and the energy required to form the radical pair, it can be

determined which pathway is energetically favorable. He found that for this system the radical pathway is favored by 27.8 kcal/mol. When two of the substituents are exchanged for benzyl groups and the other two substituents remain allyl groups, experiments yield a decomposition product in which double debenzylation occurs giving product (**80**).

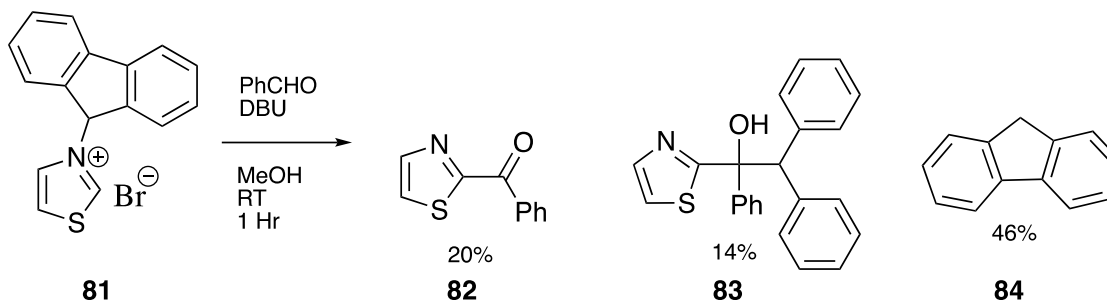


**Scheme 17: N-allyl substituent capable of rearrangement or second homolysis**

The formation of the [1,3]-rearrangement product was unexpected, but these examples of [1,3]-rearrangement from Baldwin and Hahn demonstrate a similar rearrangement under the reaction conditions.<sup>38-40</sup>

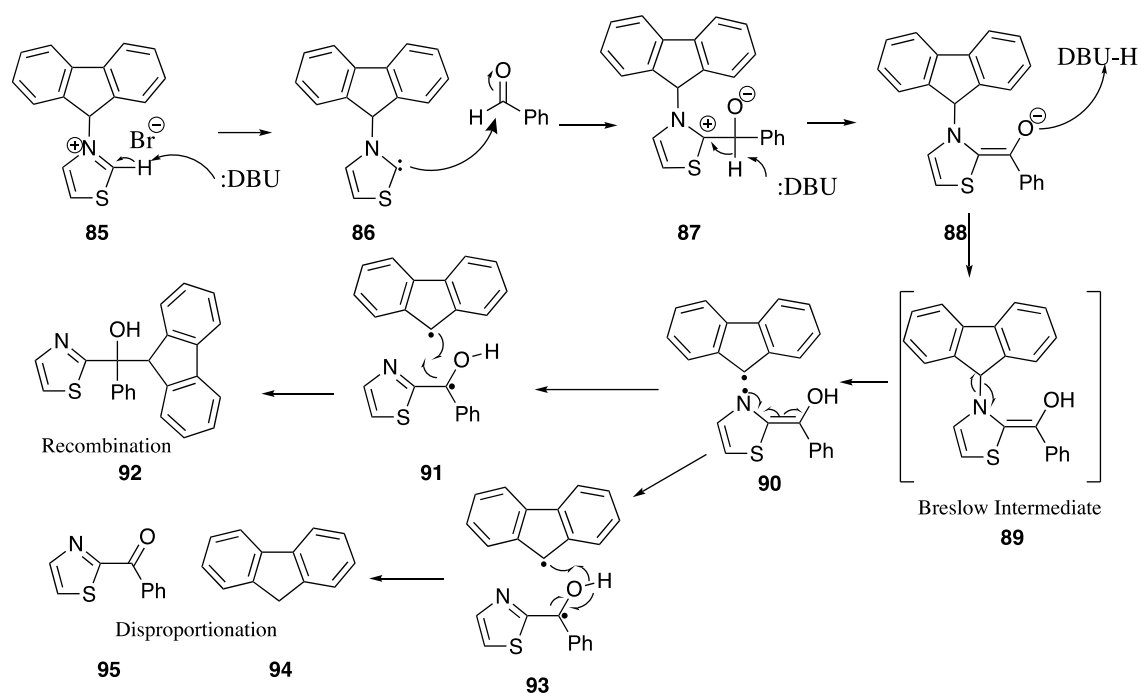
The [1,3]-rearrangement was investigated further by employing *N*-substituents that were not capable of a [3,3]-rearrangement. When fluorene was used in the reaction, another

unexpected result occurred. In an attempt to obtain the [1,3]-rearrangement product **83** similar to the cinnamyl reaction, it was interesting that this reaction provided the [1,3]- rearrangement product as well as a thiazolyl ketone **82** in a slightly higher yield.



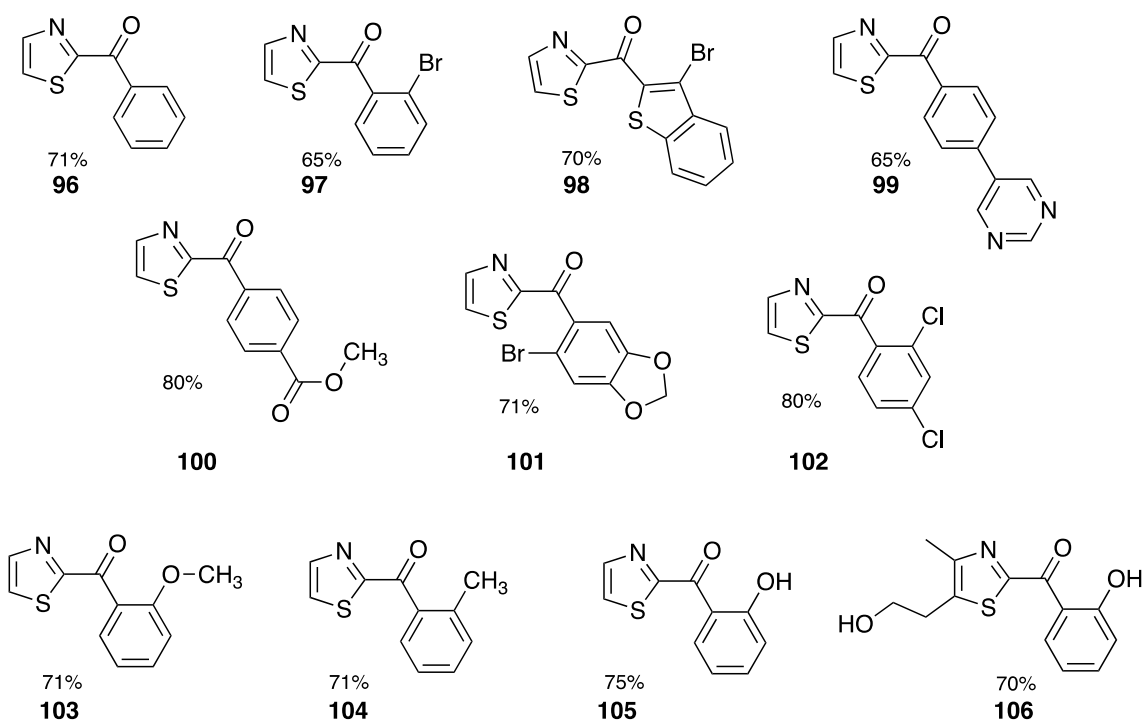
**Scheme 18: N-fluorenylthiazolium salt and formation of keto azole.**

The products formed in this reaction can form by deprotonation of the *N*-fluorenylthiazolium salt **85** with DBU to give the carbene **86**. The carbene can then attack the benzaldehyde, forming the Breslow intermediate **89**, which is an electron rich enamine. After C-N homolysis of the fluorene nitrogen bond, a fluorene radical forms, as well as a nitrogen centered radical **90**. Through resonance, the nitrogen centered radical can place the radical on the carbon adjacent to the hydroxyl oxygen atom **93**. At this point, the two radicals can either recombine to give the [1,3]-rearrangement product **92** or undergo disproportionation to give the azolyl ketone **95** and fluorene **94**.



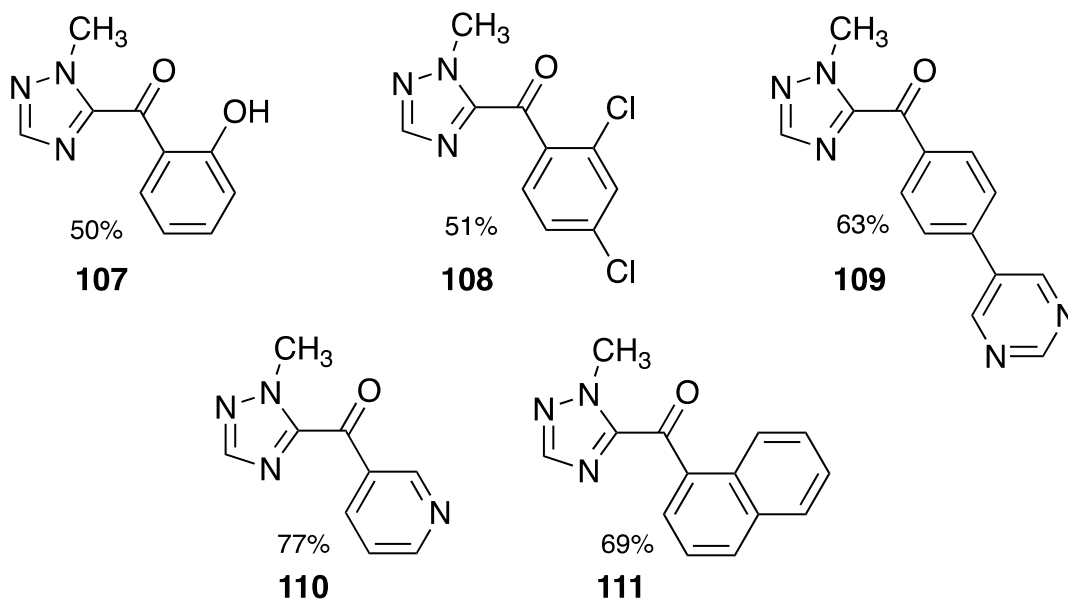
**Scheme 19: Disproportionation and recombination mechanism**

Once the fluorene reaction was heated to 65° C, the yield of the disproportionation product was increased to 75% yield in the case of the *N*-fluorenylthiazolium salt and salicylaldehyde. Under these optimized conditions, the reaction worked well with a variety of different azoles and aldehydes. The azolyl ketone formation from the Breslow intermediate is possible with a variety of aldehydes, including electron neutral and electron poor aldehydes. Aldehydes with an ester functional group resulted in hydrolysis when reaction was carried out in methanol and no ketone was formed. To avoid this problem, tetrahydrofuran was used and successfully produced the azolyl ketone.



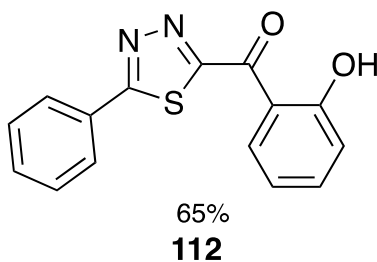
**Figure 15: Keto azoles formed from *N*-fluorenylthiazole salt and aromatic aldehydes**

The reaction also worked with electron rich aldehydes and tolerated an unprotected phenol group from salicylic acid. It was also observed that the reaction proceeded with aliphatic aldehydes, but only produced the thiazolyl alkyl ketone in smaller yields. Attempts were made to use other azoles to form azolium salts with fluorene. Benzoxazole and oxadiazole could not be functionalized by the 9-bromofluorene. 1-methyl-1,2,4-triazole reacted with 9-bromofluorene to form the 4-fluorenyltriazolium salt.



**Figure 16: Acyl azoles formed from *N*-fluorenylthiazolium salt and aromatic aldehydes**

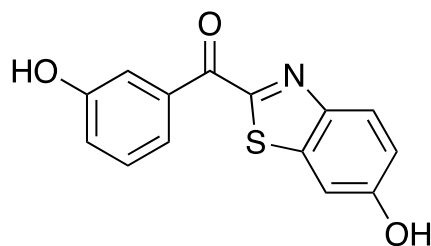
The reaction with 4-fluorenylthiazolium salt, aldehyde, and base in THF produced the 5-ketotriazole product. 3-fluorenyl-5-phenyl-1,3,4- thiadiazolium bromide also produced the 2-ketothiadiazole product.



**Figure 17: Acyl azole formed from 3-fluorenyl-5-phenyl-1,3,4-thiadiazolium salt**

Azoles are a very common class of heterocycles including, imidazole, thiazole, benzothiazole, triazole, and many others. These azoles have important uses in pharmaceuticals, natural products, and agriculture.<sup>41</sup> 244,000 tons of fungicides were sold worldwide in 1997 and in Switzerland, 40 tons of azoles are sold per year. This represents about 5% of the active ingredients in fungicides. Azoles are also useful in treating human

diseases, have fewer side effects and are less expensive than other alternatives.<sup>42</sup> If the factors that influence radicals from the Breslow intermediate to disproportionate, then reactions can be driven towards the formation of the desired azolyl ketones using a mild and efficient method. Certain benzothiazolyl compounds have been found to inhibit target compounds, such as 17 $\beta$ -HSD<sub>1</sub> **113**, that increase formation of estradiol in estrogen-dependent diseases.<sup>43</sup>



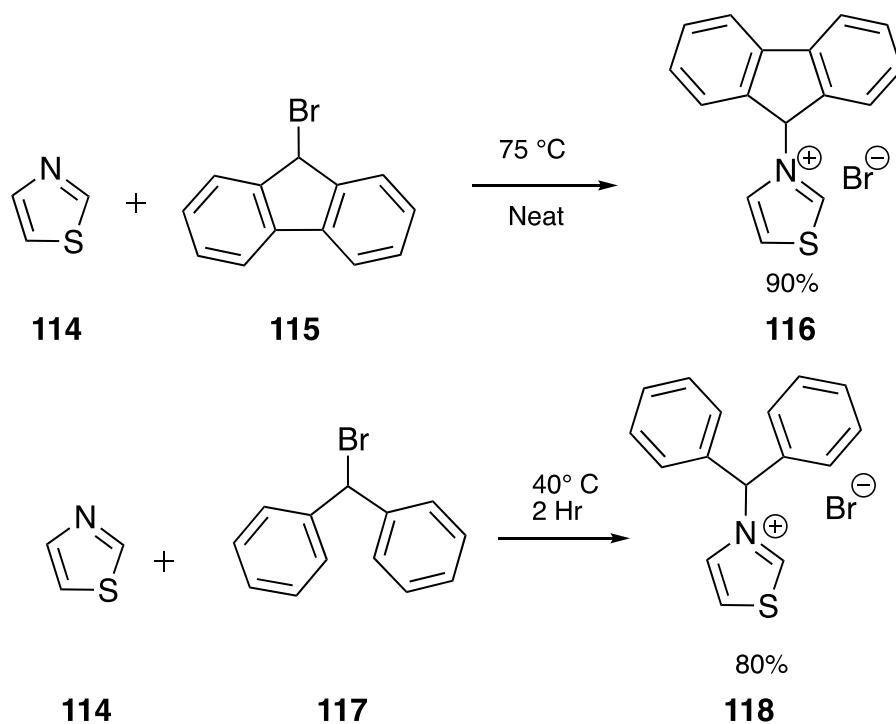
**113**

**Figure 18: 17 $\beta$ -HSD<sub>1</sub>**

Many of the methods used to synthesize the 2-acyl azoles require catalysts, long reaction times, strong bases, and/or cryogenic conditions. These methods don't provide functional group compatibility for unprotected alcohols.<sup>44-46</sup> By determining the factors that lead to this radical disproportionation or recombination of the radicals derived from homolysis of Breslow intermediates, this and other reactions can be influenced to form the desired product.

### 3. Thiazole N-Substituent and $k_d/k_c$

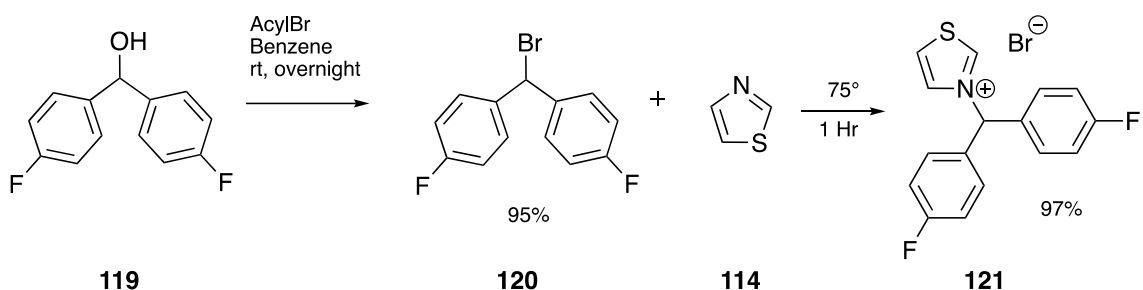
The thiazolium salts were produced using previously established conditions. To form *N*-fluorenylthiazolium salt **116**, thiazole **114** was mixed with a slight excess of 9-bromofluorene **115** then stirred and heated to 75° C for at least 5 hours until solidified. The solid was then triturated with diethyl ether overnight. The diethyl ether was then decanted and the solid was dried with nitrogen gas. The *N*-fluorenylthiazolium salt was obtained in 90% yield.



**Scheme 20: Formation thiazolium salts**

To obtain *N*-diphenylmethylthiazolium salt **118**, thiazole **114** and 1.2 Eq of bromodiphenylmethane **117** were added to a pressure tube and heated to 40° C for two hours. The solid was triturated with diethyl ether overnight. The diethyl ether was decanted and the solid was dried using nitrogen gas to obtain the salt in 80% yield. To form *N*-4,4'-difluorodiphenylthiazolium salt **121**, first bromodifluorodiphenylmethane **120** had to be synthesized by mixing difluorodiphenylmethanol **119** with acetyl bromide in benzene. The mixture was stirred overnight at room temperature to give 95% of bromodifluorodiphenylmethane. Thiazole could then be mixed with (1.2) Eq of bromodifluorodiphenylmethane and heated to 75 ° C for 1 hour to form a solid. After triturating with diethyl ether, the *N*-4,4'-difluorodiphenylthiazolium salt **121** was obtained in 97% yield.



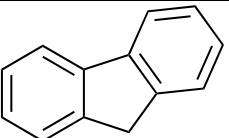
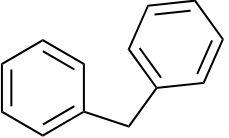


**Scheme 21: Formation of *N*-4,4'-difluorodiphenylthiazolium salt**

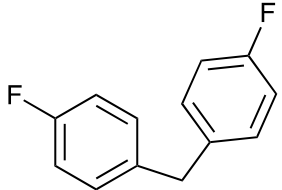
### 3.1 Fluorene *N*-Substituent and Disproportionation

Under the optimized conditions each salt was used in the reaction at ambient temperature and 65° C. The *N*-diphenylmethylthiazolium and the *N*-4,4'-difluorodiphenylthiazolium favor recombination at ambient temperature and 65° C. However, the fluorenylthiazolium salt favors disproportionation at ambient temperature. When the fluorenylthiazolium salt is heated to 65° C, very little to no recombination product forms and the yield for the disproportionation product is increased to 67%. The fluorene substituent is unique in the fact that it favors disproportionation at ambient temperature and the  $k_d/k_c$  increases with an increase in temperature.

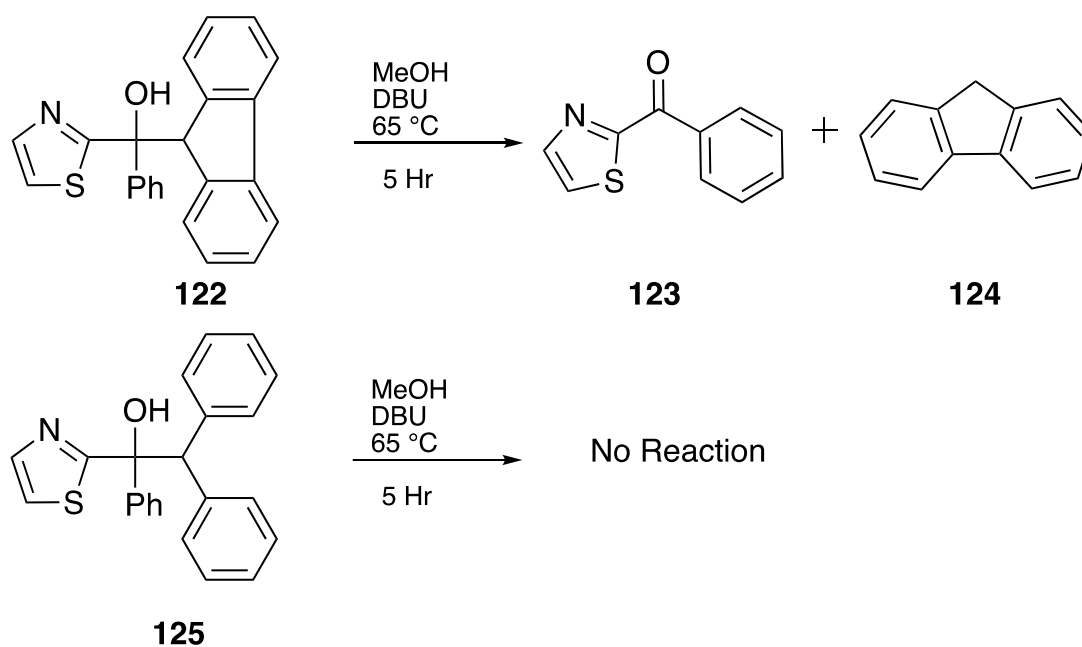
**Table 5:  $k_d/k_c$  as a function of temperature and *N*-substituent on thiazole salt**

R	Temperature (° C)	Recombination %	Disproportionation %	$k_d/k_c$
	25	23	61	<b>2.6</b>
	65	2	67	<b>33</b>
	25	25	17	<b>0.68</b>
	65	34	24	<b>0.70</b>

**Table 5:  $k_d/k_c$  as a function of temperature and N-substituent on thiazole salt Cont.**

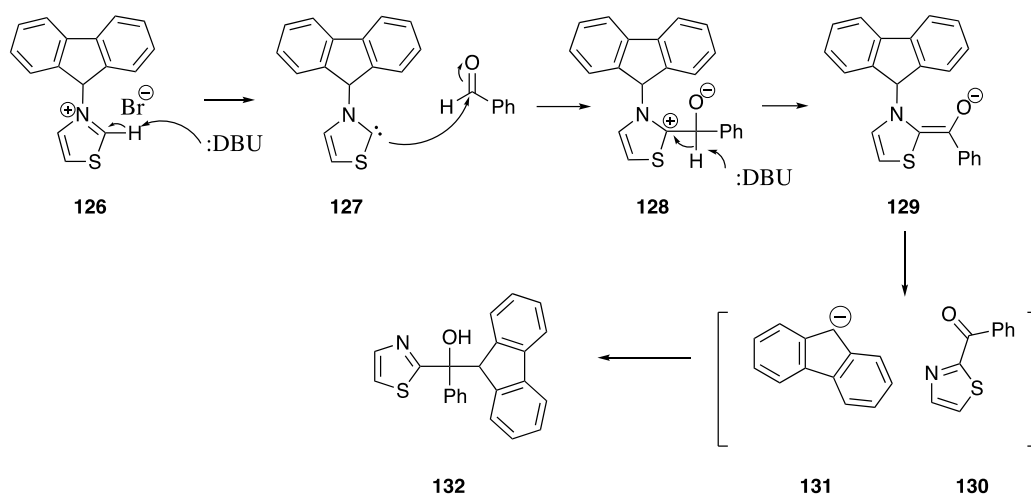
	25	37	18	<b>0.76</b>
	65	45	20	<b>0.44</b>

It was hypothesized that the recombination product could undergo a retro-Knoevenagel reaction under the reaction conditions to provide an alternative route to the ketone product. When the recombination product was mixed with DBU and heated in methanol, the proton NMR of the product showed only the azolyl ketone and fluorene (**Scheme 22**). When the same reaction was done with the recombination product from the *N*-diphenylmethylthiazolium reaction, it did not decompose into diphenylmethane and the azolyl ketone. This was interesting given the structural similarities to the two products. However, the pKa values for fluorene and diphenylmethane are very different. Fluorene has a pKa value of 22.6 in water and diphenylmethane has a pKa value of 33.<sup>47</sup> The differences in their pKa values is most likely due to the fact that when fluorene is deprotonated, it is aromatic and diphenylmethane is not. This makes fluorene more stable. The decomposition of the fluorene recombination product increases the observed yield of the disproportionation product and gives a higher net  $k_d/k_c$ . The electronic properties of the *N*-substituent influence the ratio of the  $k_d/k_c$ , but the difference may not be a direct result of recombination and disproportionation of the radicals.



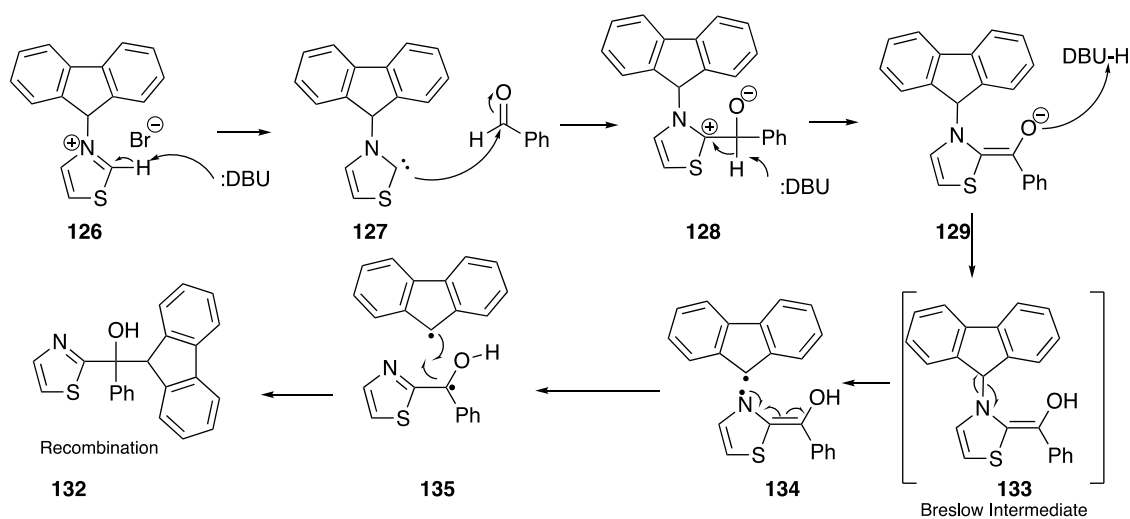
**Scheme 22: Fluorene nitrogen substituent and diphenylmethane substituent effect**

We considered that the [1,3]-rearrangement product could also form by an ionic mechanism rather than through the proposed radical mechanism. It is thought that the thiazole salt **126** can be deprotonated with base. The carbene **127** can then react with benzaldehyde to give the zwitterion **128**. After a second deprotonation, the thiazolyl ketone **130** and fluorene anion **131** are formed by heterolytic bond breaking of the C-N bond between thiazole nitrogen and fluorene. The two intermediates can then undergo nucleophilic addition to give the [1,3]-rearrangement product **132**.



**Scheme 23: Proposed ionic mechanism for rearrangement product formation**

The radical mechanism that we believe is occurring, also involves the carbene **127** reacting with benzaldehyde to form the zwitterion. Through tautomerization, the Breslow intermediate **133** is formed. The Breslow intermediate then undergoes C-N homolysis to form two radicals **134**. The fluorene radical can recombine at the carbon adjacent to the oxygen atom and form the [1,3]-rearrangement product **132**.

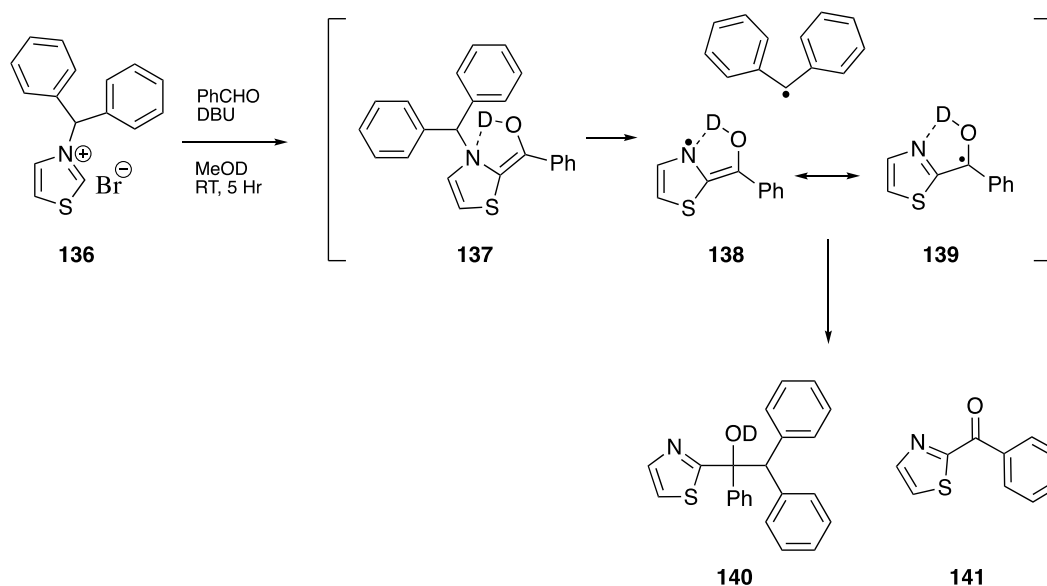


**Scheme 24: Proposed radical mechanism for rearrangement product formation**

We have found that the [1,3]-rearrangement product of *N*-fluorenylthiazolium carbene and benzaldehyde can form up to 14% yield in only one hour at rt.. To determine if the product is forming through the radical mechanism, the thiazolyl ketone was reacted with fluorene and DBU at ambient temperature for 5 hours. The reaction was monitored by thin layer chromatography (TLC) and proton nuclear magnetic resonance (NMR). After 5 hours, no recombination product had formed and there was only azolyl ketone, DBU and fluorene in the reaction mixture. This indicates that the [1,3]-rearrangement product observed in this reaction is forming through the proposed radical mechanism and not the proposed ionic mechanism.

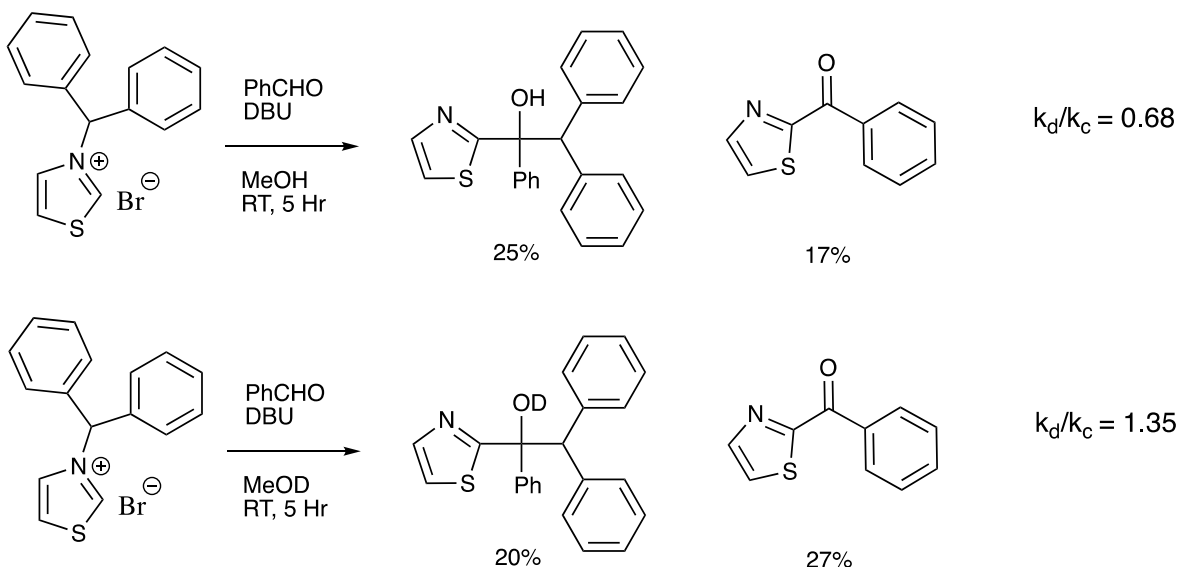
#### **4. Hydrogen Bonding and Recombination vs Disproportionation**

The nitrogen atom of the Breslow intermediate is capable of hydrogen bonding with the enol hydrogen atom. An increase in the hydrogen bonding between the two atoms will strengthen the oxygen- hydrogen bond and make it more difficult to break or undergo hydrogen atom abstraction. By strengthening this bond, the yield of the recombination product is expected to increase and the yield of the disproportionation products are expected to decrease. This effect can be investigated by exchanging the enol hydrogen atom with a deuterium **137**. The reaction between *N*-diphenylmethylthiazolium salt, benzaldehyde and DBU was done in deuterated methanol (MeOD). We hypothesize that the deuterated enamine would be expected to undergo disproportionation more slowly.<sup>48</sup>



**Scheme 25: Hydrogen bonding and Deuterium bonding in recombination product formation**

It was expected for the  $k_d/k_c$  ratio to decrease. However, the opposite effect was observed. The  $k_d/k_c$  ratio increased to favor disproportionation when the hydrogen was exchanged for a deuterium. This could be due to the stability of the diphenylmethane formed by disproportionation with the O-D bond. However, the actual cause is unknown.

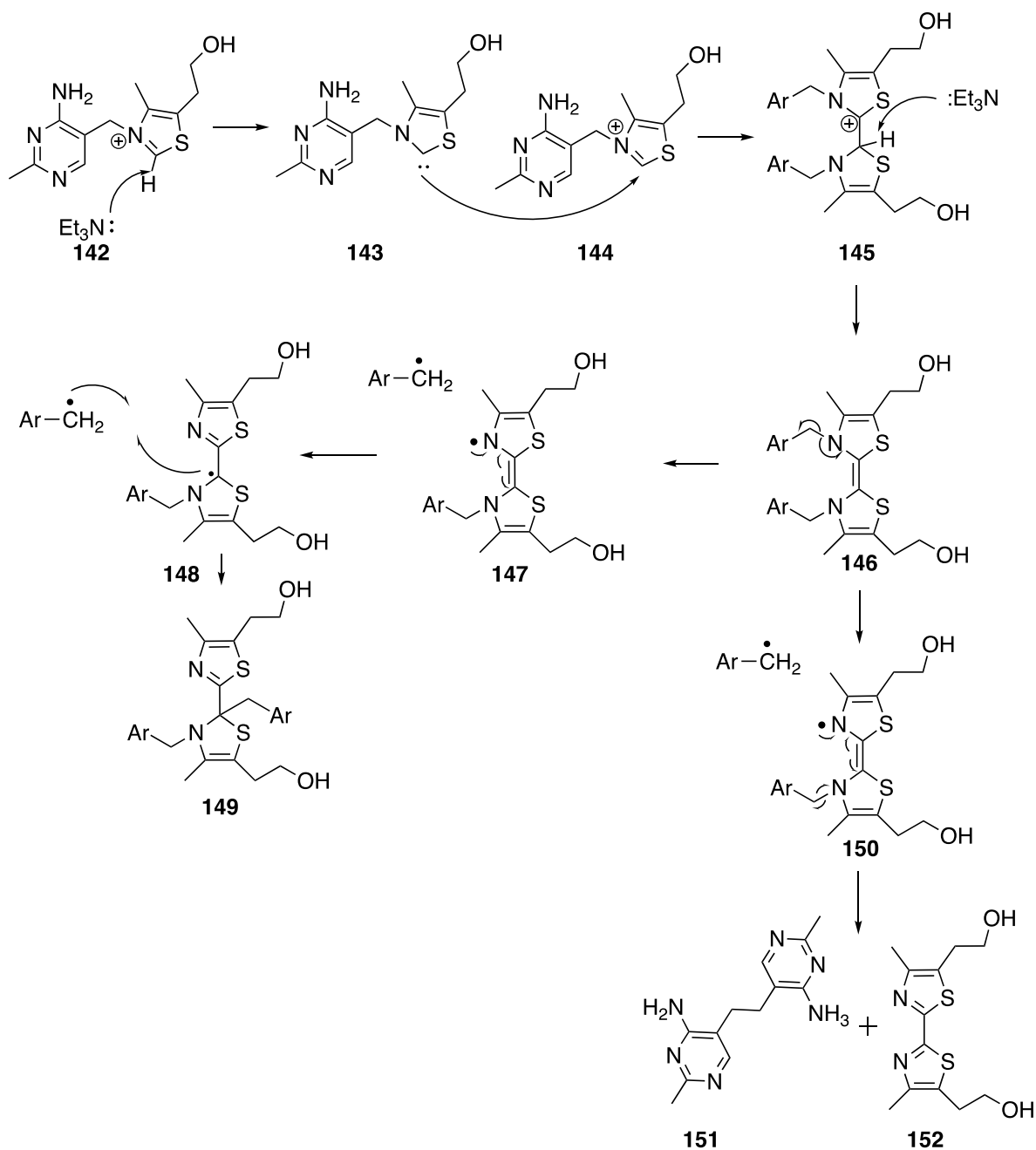


**Scheme 26:  $k_d/k_c$  of *N*-diphenylmethylthiazolium salt reacted with benzaldehyde in methanol and deuterated methanol**

## Chapter Three: Dimerization of NHC's and Azolium Salts

### 1. Introduction

Breslow type intermediates can form when NHCs react with a second molecule of azolium salt. As mentioned in Hahn's paper in chapter 2, a second homolysis is possible when electron rich enamines form between NHCs and azolium salts. For example, after deprotonation of thiamine HCl **142** at the C-2 position, the carbene formed can react with a protonated molecule of thiamine at C-2' to form a dimer **145**. After a second deprotonation, an electron rich enamine forms **146**, which is capable of C-N homolysis to form a pyrimidine radical as well as a radical on the nitrogen of the thiazole dimer. These dimers can either undergo recombination to form a rearranged dimer **149** or undergo a second C-N homolysis to form vitachrome **152** and two pyrimidine radicals. These two pyrimidine radicals can combine to form a dimer of pyrimidine **151** also.



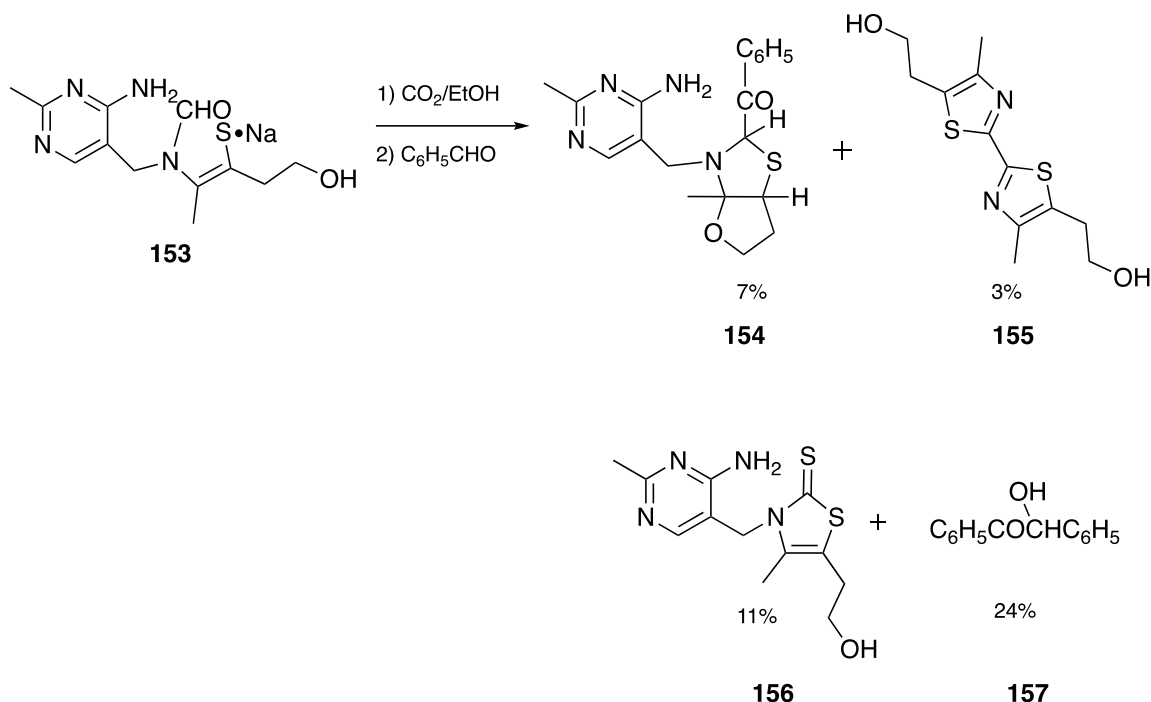
**Scheme 27: Proposed mechanism for vitachrome formation and rearranged dimer**

## 2. Vitachrome

In 1967, Takamizawa was studying the reactivity of thiamine with aldehydes and obtained a dimer of the azole portion of thiamine. Thiamine-sodium salt was dissolved in ethanol in the presence of dry carbon dioxide and reacted with benzaldehyde to form several



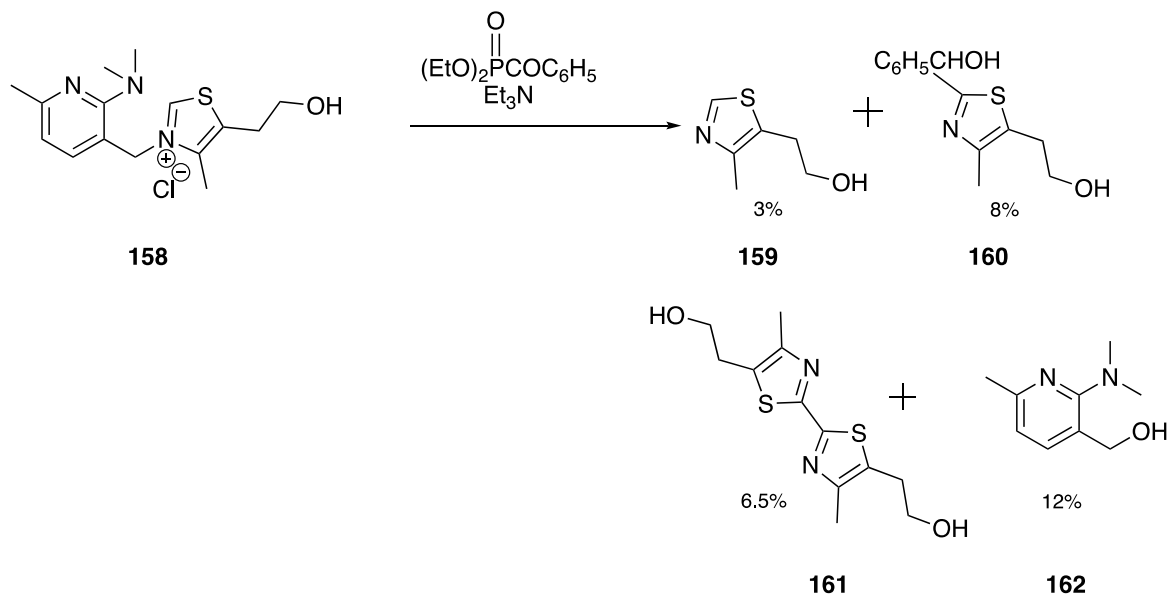
products. He obtained a cyclized form of thiamine and benzaldehyde **154**, 3-(2-methyl-4-aminopyrimidin-5-yl-methyl)-4-methyl-5-(1-hydroxy-ethylthiazoline)-2-thione **156**, benzoin **157**, and a dimer of the thiazole portion of thiamine **155**. This dimer had an absorption maximum at 347 m $\mu$  in its ultraviolet absorption spectrum. Also, after reaction with acetic anhydride-pyridine, a diacetate was formed. These properties aligned with the dimer, vitachrome, which was found by Karrer and coworkers.<sup>49</sup> Vitachrome was obtained by irradiation of 4-methyl-5-oxyethyl thiazole with a mercury vapor lamp. It's fluorescence is compared with thiochrome, but thiochrome is only fluorescent in basic solutions, while vitachrome is fluorescent in basic and acidic solutions.<sup>50</sup>



**Scheme 28: Thiamine sodium salt reaction with benzaldehyde to form vitachrome**

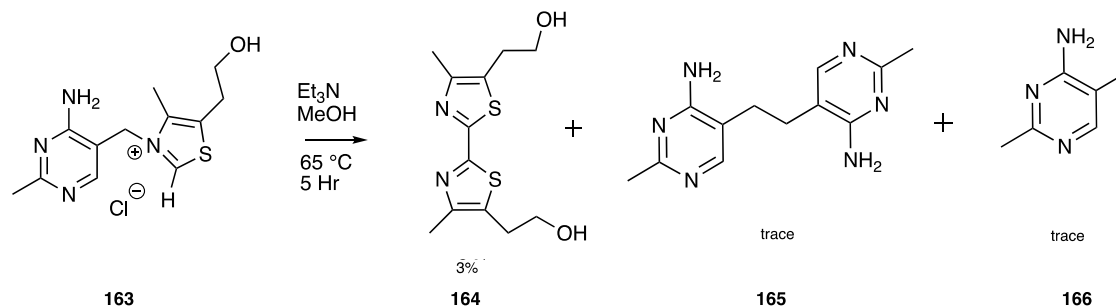
In another report by Takimizawa, he observed this dimer of thiazole when studying the reactivity of the C-2 position of different thiamine analogues and benzoylphosphonate. When a nitrogen atom in the pyrimidine ring was replaced with a carbon, the reaction yielded vitachrome **161** in about 7%. Takamizawa does not propose a mechanism for the formation of this dimer in

either of these experiments.<sup>51</sup> We hypothesize that the thiazole dimer, known as vitachrome, is forming through a radical mechanism in these reactions.



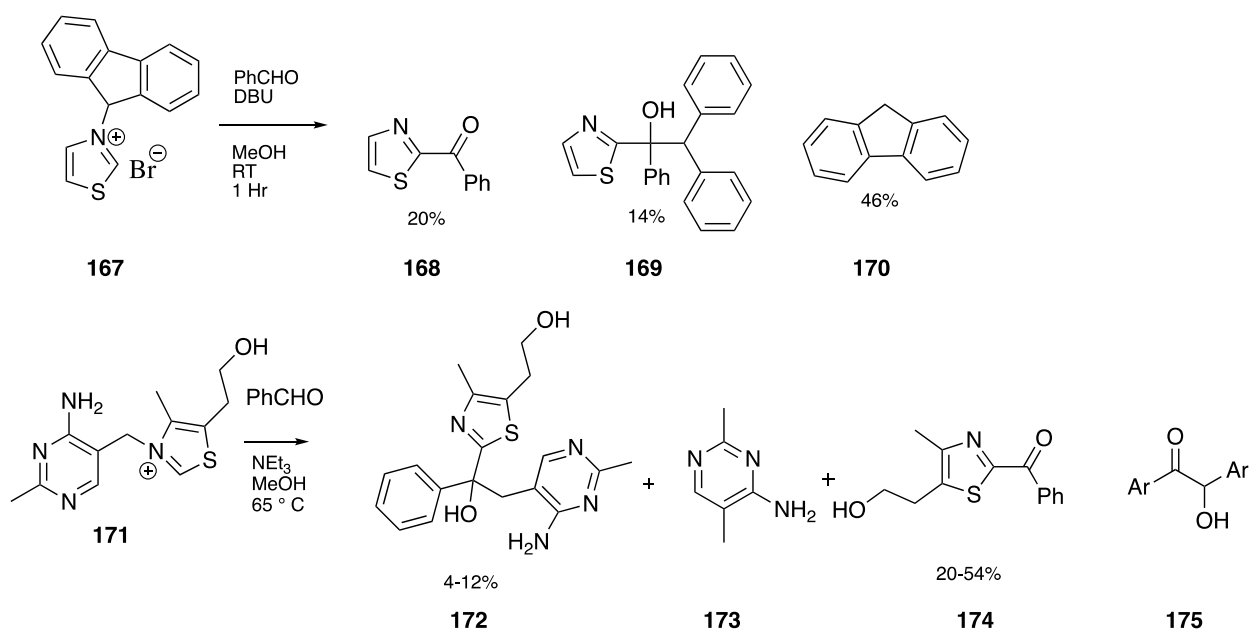
**Scheme 29: Thiamine analogue reaction with benzoylphosphonate**

To investigate this mechanism, thiamine HCl **163** was dissolved in methanol at 65° C and 2 Eq of triethylamine were added to the mixture and reacted for 5 hours. The mixture was separated by PTLC and vitachrome **164** was observed by proton NMR and liquid chromatography-mass spectrometry (LCMS). The pyrimidine monomer **166** and dimer **165** were also observed by proton NMR indicating that the pyrimidine functional group is capable of C-N homolysis when part of an electron rich enamine. The formation of vitachrome under these conditions and the formation of pyrimidine monomer and dimer contradicts the claims made by Kluger that pyrimidine is not a sufficient leaving group for C-N homolysis from thiazole.



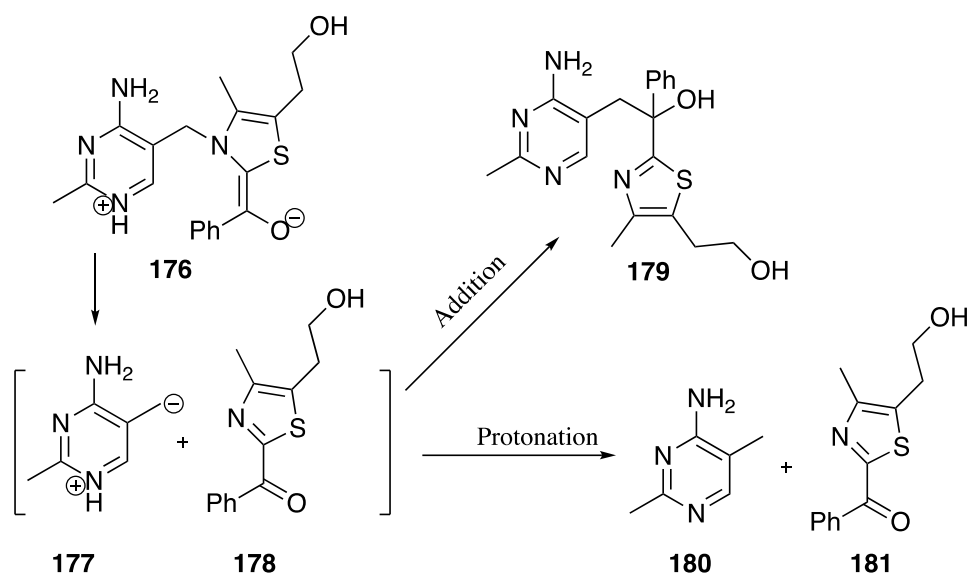
**Scheme 30: Thiamine reaction with base yields vitachrome and pyrimidine products**

In a report from 1970, Oka was investigating the reactivity of thiamine HCl with aldehydes (**scheme 31**) when he reacted it with excess base and benzaldehyde. From this reaction, he obtained pyrimidine **173**, thiazolyl ketone **174**, rearrangement product **172** and benzoin **175**. He proposed that the pyrimidine and azolyl ketone form by fragmentation of the 3° alcohol. When investigating the scope of this reaction, it was observed that when alkyl aldehydes were used instead of aromatic aldehydes, only the alpha hydroxyalkylthiamin was formed. The reaction did work with aromatic aldehydes and when the substituents on the thiazole ring were changed. However, when the pyrimidine was modified, the results varied and when the 4-amino group of the pyrimidine was substituted for a hydroxy group, the reaction failed. From this he concluded that the amino group on pyrimidine was essential for the formation of the azolyl ketone and pyrimidine.<sup>52</sup>

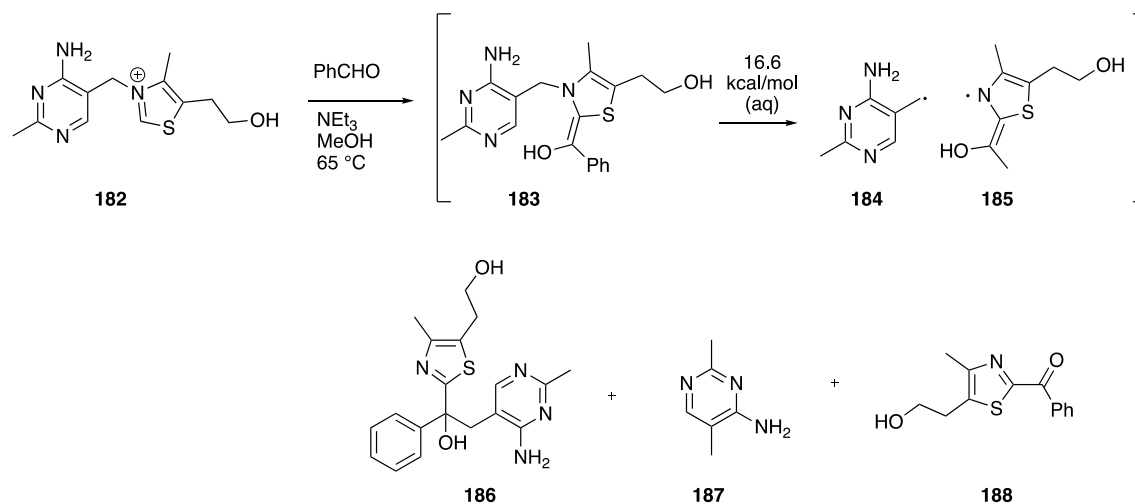


**Scheme 31: Products formed from thiamine HCl reaction with base and benzaldehyde**

Kluger and his group have studied the mechanism for the formation of these products extensively.<sup>53-56</sup> In his reports, Kluger argues that the formation of these products does form through an ionic mechanism, but first passes through a Breslow intermediate. He proposed that the C-N bond between pyrimidine and the thiazole ring break heterolytically to give a negatively charged  $sp^3$  carbon on pyrimidine. Then, he proposed that the thiazolyl ketone and pyrimidine undergo nucleophilic addition to form the 3° alcohol or simple protonation to obtain the thiazolyl ketone and pyrimidine.<sup>56</sup>



**Scheme 32: Proposed ionic mechanism for rearrangement, keto azole and pyrimidine**



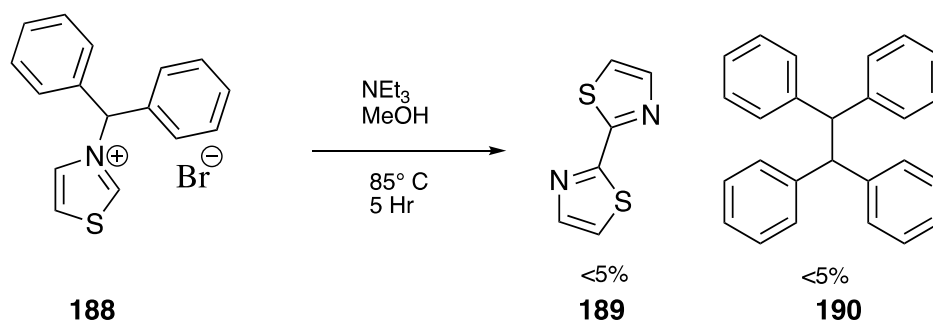
**Scheme 33: Proposed radical mechanism for rearrangement, keto azole, and pyrimidine**

It is possible for these products to through a radical mechanism, similar to the one observed in our system as well as others. The pyrimidine should be capable of C-N homolysis from the thiazole portion of thiamine, since the homolysis enthalpy is only 16.6 kcal/mol. Our results from the experiment with thiamine HCl and triethylamine indicate that the C-N bond between the azolium nitrogen and pyrimidine substituent is capable of C-N homolysis under the reaction

conditions. Once the radical pair is formed, recombination yields the rearrangement product. Disproportionation leads to pyrimidine monomer and thiazole ketone.

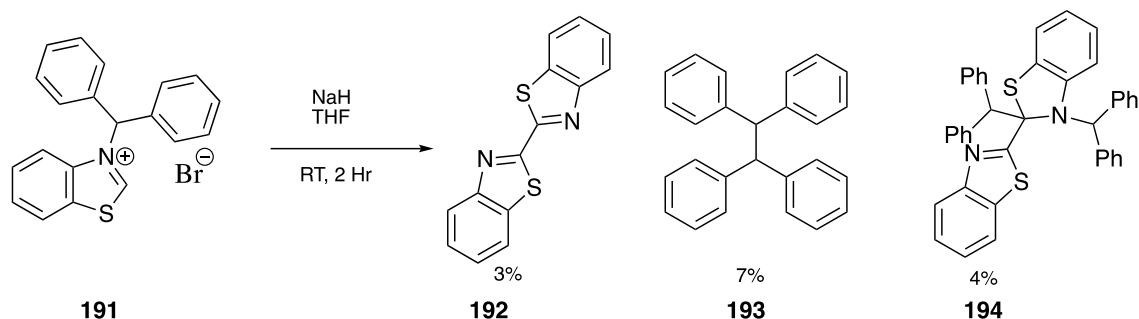
### 3. Dimerization of Other Azoles

Interestingly, this double homolysis was observed in other systems as well. When the *N*-diphenylmethylthiazolium salt **188** was dissolved in methanol and heated to 85° C in a pressure tube with triethylamine, a dimer of thiazole **189** and a dimer of diphenylmethane **190** were formed in very small yields.



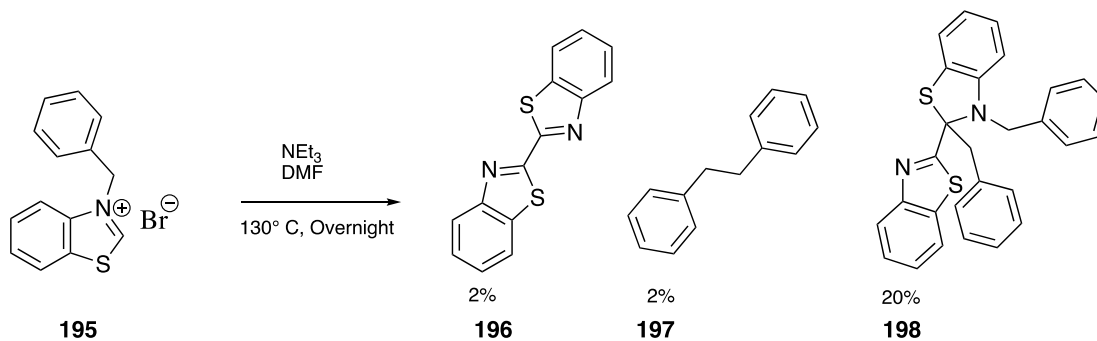
**Scheme 34: Thiazole dimer formation from *N*-diphenylmethylthiazolium salt**

The reaction also worked when the diphenylmethane substituent was placed on benzothiazole instead of thiazole. Under the conditions used in Hahn's paper for benzoimidazole, the benzothiazole dimer and diphenylmethane dimer were formed. Interestingly, the rearranged dimer formed under these conditions as well. When this reaction is heated and triethylamine is used, instead of sodium hydride, the rearrangement product is not observed.



**Scheme 35: Formation of benzothiazole dimer from *N*-diphenylmethylbenzothiazolium salt**

It is known that the dimerization of NHC's is more likely with less bulky substituents. By replacing the diphenylmethane substituent with a benzyl substituent, the dimerization of the NHC was expected to increase. When the *N*-benzylbenzothiazole salt **195** was dissolved in DMF with triethylamine and heated to 130° C overnight, the benzothiazole dimer **196** and benzyl dimer **197** formed in very small yields, while the rearranged dimer **198** was the major product observed.

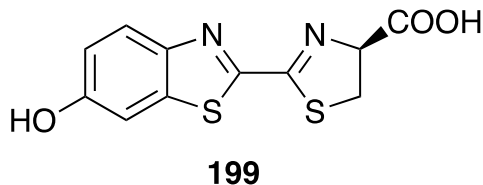


**Scheme 36: Formation of benzothiazole dimer and rearranged dimer**

#### 4. Asymmetric Azole Dimers

Asymmetrical biheteroaryls are found in many drugs and biological compounds. Asymmetrical azole dimers are also found in biological systems. The most popular example of these unsymmetrical dimers is firefly luciferin. Firefly luciferin is oxidized by the enzyme luciferase to form oxyluciferin and carbon dioxide. The structure of firefly luciferin consists of a

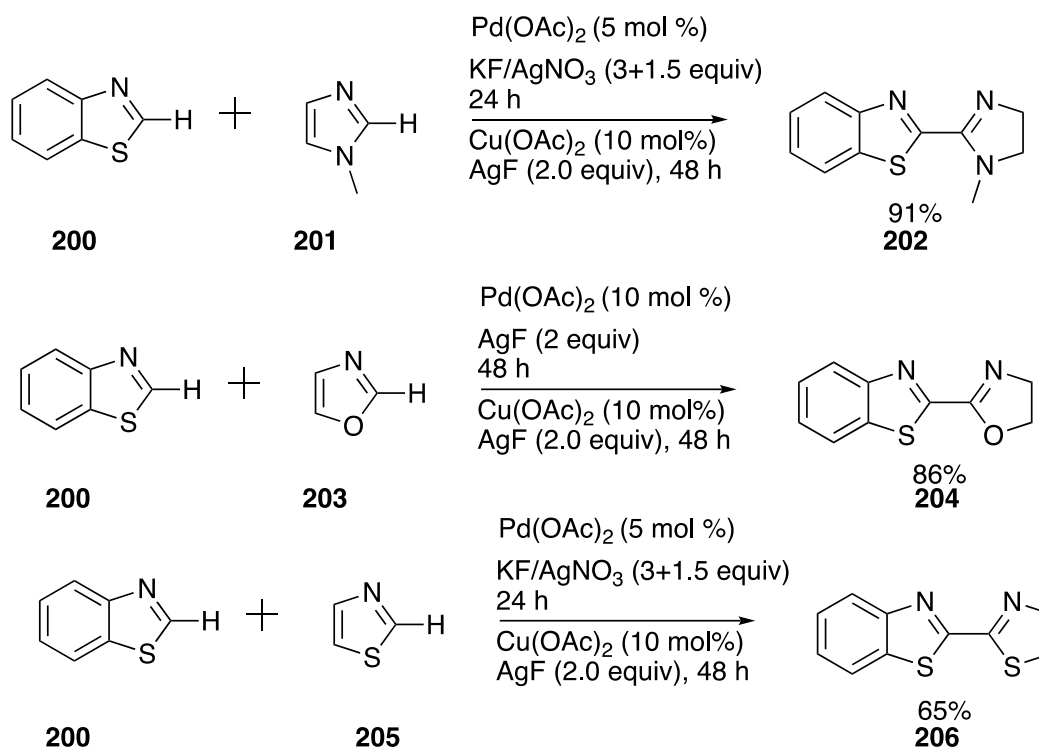
thiazole and benzothiazole ring with a C-C bond between their C-2 carbons. There is a carboxylic acid group at the C-4 position on thiazole and an alcohol group at the 6' position on the benzene ring of benzothiazole.<sup>57</sup>



**Figure 19: Firefly Luciferin**

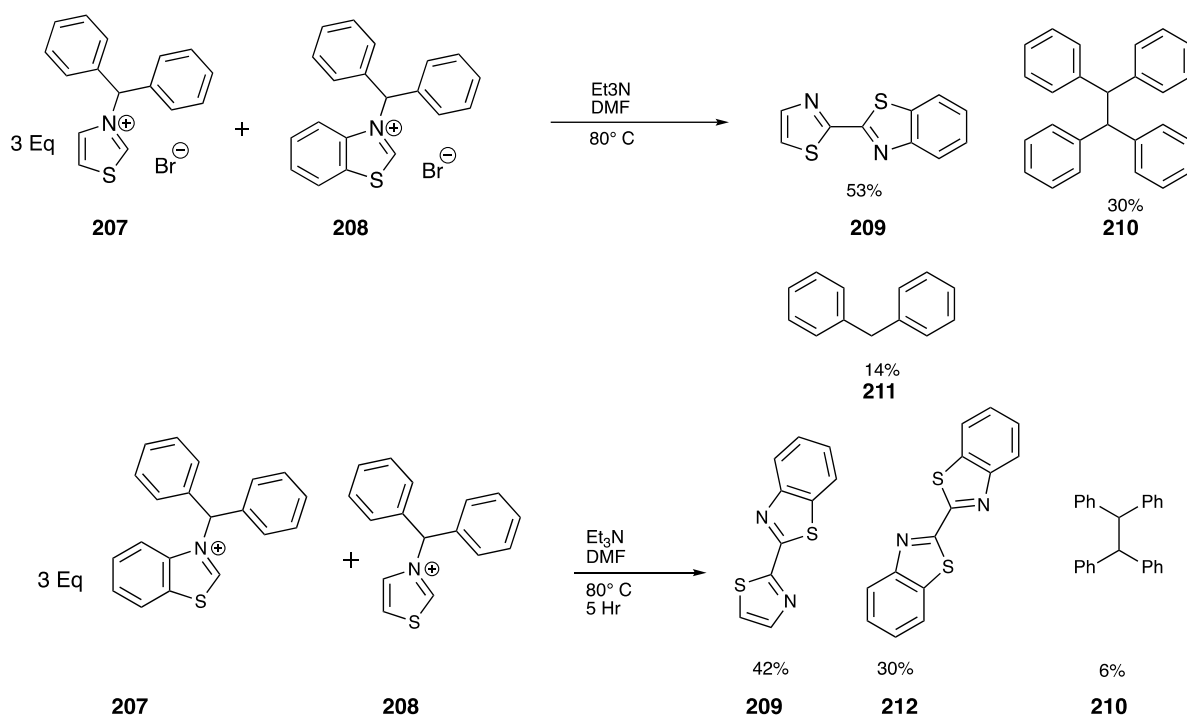
The current methods to form a carbon-carbon bond between azoles require transition metal catalysts and long reaction times.<sup>58-61</sup> The ability to couple different azoles to form heterodimers is challenging, because azoles tend to form homodimers. Han's group was able to couple different azoles such as, benzothiazole, imidazole, oxazole and thiazole. This was accomplished using palladium-catalyzed dehydrogenative cross coupling.<sup>58</sup> These reactions require expensive transition metal catalysts and long reaction times to obtain the asymmetric azole dimers.





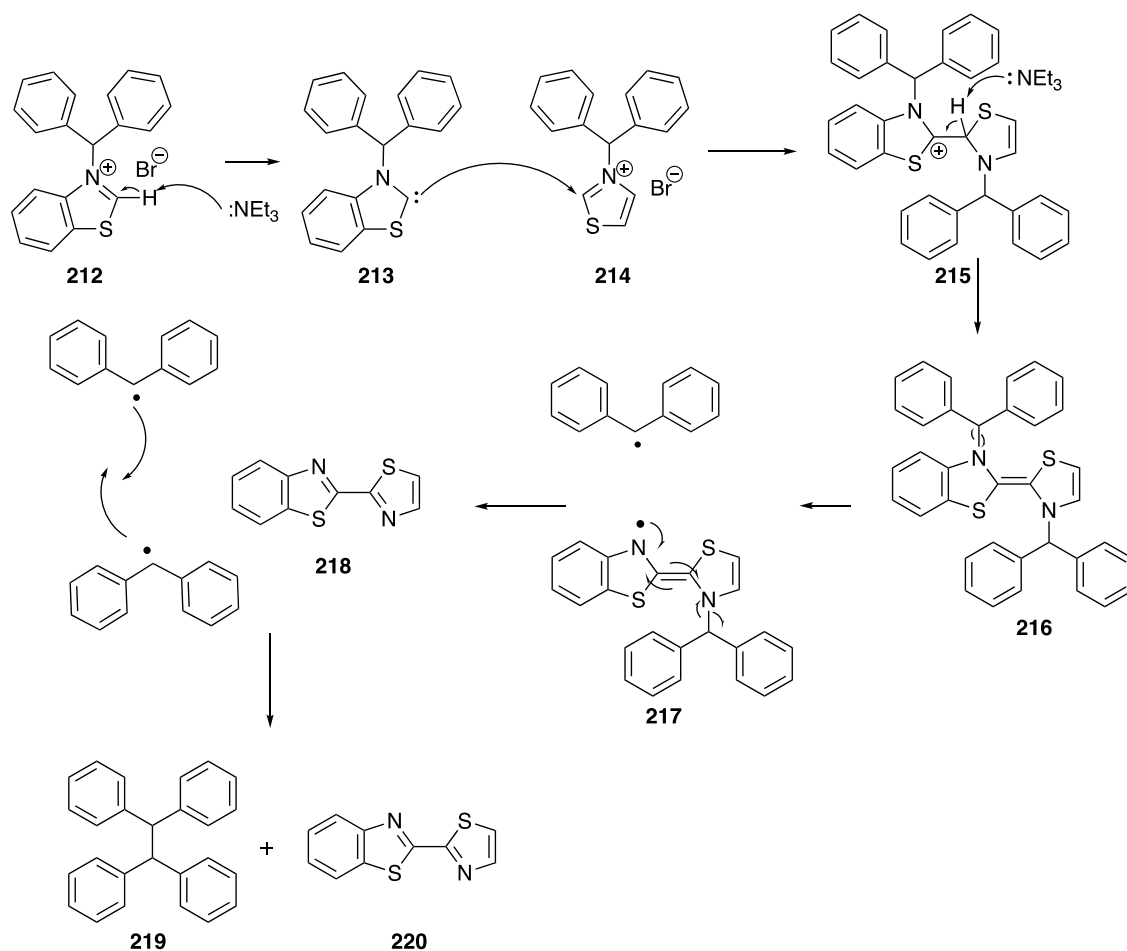
**Scheme 37: Transition metal catalyzed methods to form asymmetric azole dimers**

A sulfur (IV) mediated synthesis has been developed to form asymmetrical heterocycle dimers also. The synthesis works well for a wide variety of heterocycles, including azoles and pyridine compounds. However, this method requires the use of Grignard reagents and cryogenic conditions.<sup>62</sup>



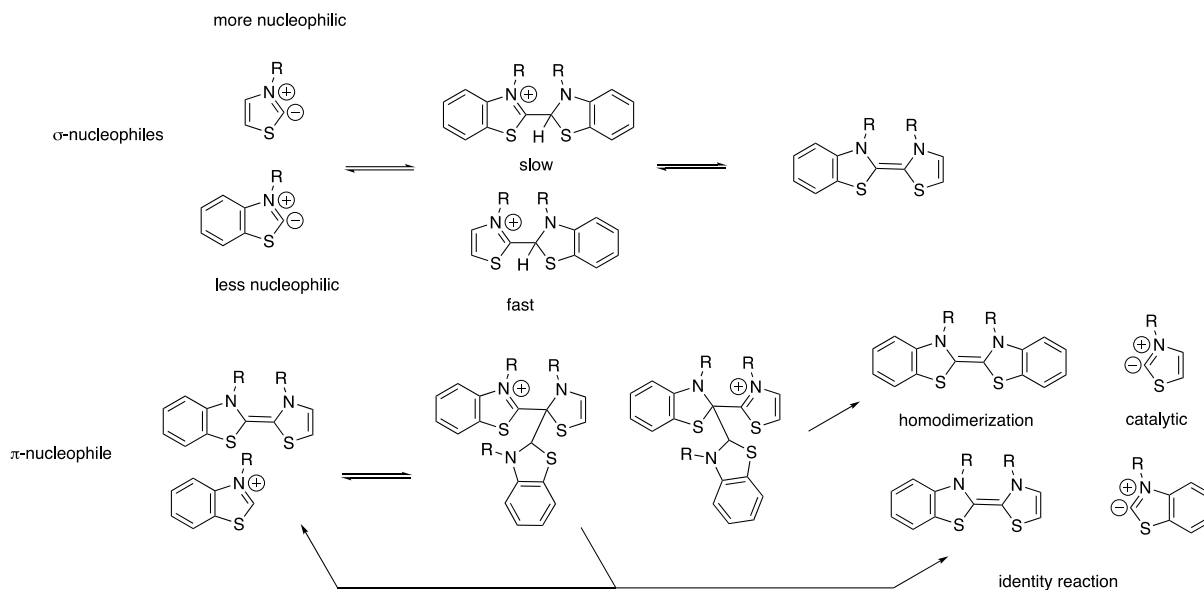
**Scheme 38: Asymmetric azole dimer formation under mild conditions**

Since it was possible to form a symmetrical heterocyclic dimer using our method with base and heat, we wanted to see if this method could be used to form an asymmetric heterocyclic dimer. It was possible to form the symmetric dimer of thiazole as well as the symmetric dimer for benzothiazole, when they contained a diphenylmethane substituent on the azole nitrogen atom. It was desired to dimerize two different azoles. The dimerization worked well when 3 equivalents of the *N*-diphenylmethylthiazole salt and 1 Eq of the *N*-diphenylmethylbenzothiazole salt were dissolved in dimethylformamide (DMF) and heated to 80° C. Once the salts dissolved, triethylamine was added to the mixture and heated for 5 hours. After PTLC with 1:9 ethyl acetate: hexanes, the heterodimer **209**, tetraphenylethane **210**, and diphenylmethane **211** were obtained. It is possible for the asymmetric azole dimer to form through a radical mechanism similar to the formation of the symmetric azole dimers.



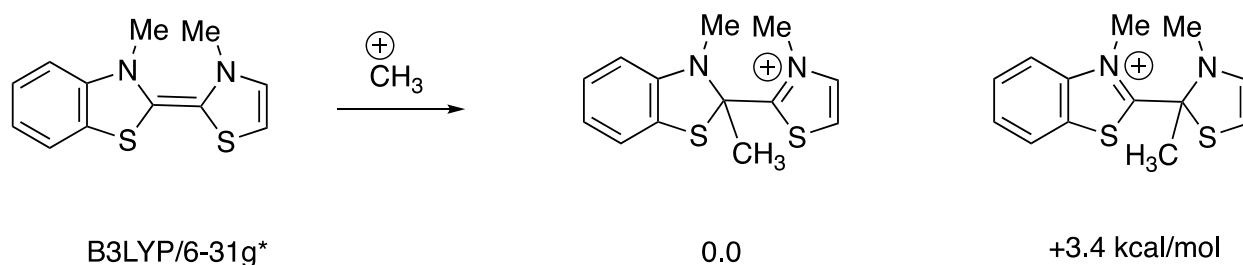
**Scheme 39: Proposed mechanism for formation of asymmetric azole salt**

When the reaction was repeated with an excess of diphenylmethylthiazolium salt, the heterodimer and tetraphenylethane were observed. The benzothiazole homodimer was obtained in 30% yield. This is much higher than the previously observed 3% yield. The presence of the thiazole salt lead to an increase in the yield of the benzothiazole homodimer. It is possible that the thiazole carbene catalyzed the formation of the benzothiazole homodimer.



**Scheme 40: Carbene catalysis of dimerization**

The azolium salts are deprotonated to form the thiazole carbene and benzothiazole carbene. The thiazole carbene is a stronger nucleophile than the benzothiazole carbene, so the dimerization of the thiazole carbene and excess benzothiazole salt is favored. After the second deprotonation, the electron rich alkene is formed, which reacts with another equivalent of the benzothiazole salt. The benzothiazole salt can form a C-C bond at the C2 position of thiazole or C2 of benzothiazole. When the bond forms at the C2 position of benzothiazole, the homodimer is formed and the thiazole carbene is regenerated. The benzothiazole salt can also be bound to the C2 of the thiazole which leads to the heterodimer and regeneration of the benzothiazole carbene. DFT calculations (B3LYP/6-31g\*), predicts that it is energetically favorable for a methyl substituent to bind at the C2 position of benzothiazole instead of the C2 position of thiazole. For simplification, methyl substituents are attached at the azole nitrogen atom instead of diphenylmethane.



**Scheme 41: DFT Calculation (B3LYP/6-31g\*) Stability of C2 Bond with Methyl Group**

To investigate this mechanism further, the experiment should be repeated with 10% *N*-methylthiazolium salt. The methyl substituent is less bulky and therefore less likely to undergo C-N homolysis to form the heterodimer. If a higher yield of the benzothiazole homodimer is still observed under these conditions, it is possible that the thiazole carbene is catalyzing this process.

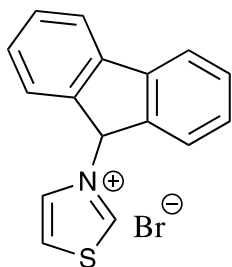
### Future Work

We have found evidence for the C-N homolysis of electron rich enamines, specifically Breslow intermediates. There is also evidence for their subsequent recombination and disproportionation. While the electronic effects, including the stability of the radicals, have an effect on the  $k_d/k_c$ , this will continue to be studied by employing different *N*-substituents on thiazole rings. The effect of the hydrogen bonding between nitrogen and the enol hydrogen do seem to play a part in the outcome of the reaction and this will be investigated further. By determining how these and other factors influence the  $k_d/k_c$  of the reaction, better predictions can be made for the outcome of these types of reactions. Attempts will be made to form asymmetric azole dimers with other azole compounds.

## Experimental

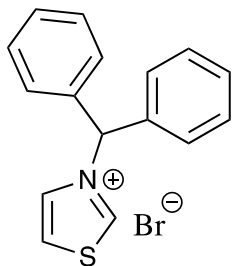
All reactions were conducted under a N<sub>2</sub> atmosphere using standard Schlenk techniques. Commercially available reagents were used without additional purification unless otherwise indicated. Compound purification was accomplished by preparatory plate chromatography. Proton and carbon NMR spectra were obtained on a 400 MHz Bruker Advance spectrometer. Structural assignments were based on proton, carbon, and liquid chromatography-mass spectrometry measurements.

### Procedure for the Preparation of fluorenylthiazolium bromide salts



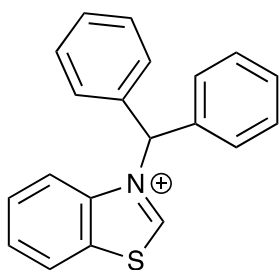
#### 116

Thiazole was mixed neat with a slight excess (1.2 eq) of 9-bromofluorene and the mixture was maintained at 85° C until the reaction mixture solidified. The solid was triturated with diethyl ether. The excess ether was decanted and the salt was dried under nitrogen to yield the fluorenylthiazolium salt in 90% yield. Heated to 85 C, white solid obtained in 90% yield. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 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). <sup>13</sup>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.



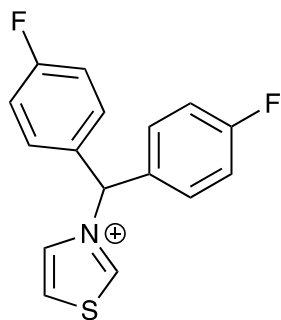
### 118

Thiazole was mixed neat with a slight excess (1.2 eq) of bromodiphenylmethane and the mixture was maintained at 40° C until the reaction mixture solidified. The solid was triturated with diethyl ether. The excess ether was decanted and the salt was dried under nitrogen to yield the diphenylmethylthiazolium salt in 90% yield.  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  71.9, 128.5, 129.8, 135.7, 135.8, 159.8.



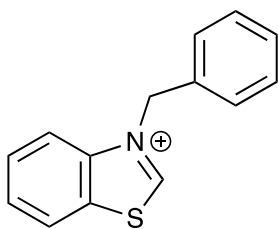
### 191

Benzothiazole was mixed neat with a slight excess (1.2 eq) of bromodiphenylmethane and the mixture was maintained at 40° C until the reaction mixture solidified. The solid was triturated with diethyl ether. The excess ether was decanted and the salt was dried under nitrogen to yield the diphenylmethylbenzothiazolium salt in 90% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.16 (s, 1H), 7.50 (m, 10H), 7.97 (d, 2H), 8.48 (d, 2H), 10.13 (s, 1H).  $^{13}\text{C}$  NMR  $\delta$  71.7, 120.8, 128.6, 128.7, 129.1, 130.0, 130.2, 131.5, 132.7, 134.0, 140.6, 165.6.



## 121

Parafluorophenylmethanol was mixed with acetyl bromide in benzene and stirred overnight at ambient temperature. The benzene was evaporated by nitrogen. The solid was then triturated with diethyl ether. The solid was then dried by nitrogen. This resulted in 95% of the bis(4-fluorophenyl)methyl bromide. Thiazole was mixed neat with a slight excess (1.2 eq) of bis(4-fluorophenyl)methyl bromide and the mixture was maintained at 75° C until the reaction mixture solidified. The solid was triturated with diethyl ether. The excess ether was decanted and the salt was dried under nitrogen to yield the bis(4-fluorophenyl)methylthiazolium salt in 97% yield. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 7.25 (m, 8H), 7.53 (s, 1H), 8.32 (s, 1H), 8.42 (s, 1H), 9.99 (s, 1H). <sup>13</sup>C NMR (300 MHz, DMSO-D<sub>6</sub>) δ 70.3, 115.2, 128.1, 131.8, 133.1, 137.5, 161.1, 165.0



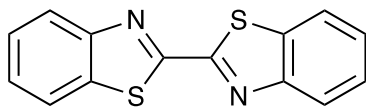
## 195

Benzothiazole was mixed neat with a slight excess (1.2 eq) of benzyl bromide and the mixture was maintained at 65° C until the reaction mixture solidified. The solid was triturated with diethyl ether. The excess ether was decanted and the salt was dried under nitrogen to yield the



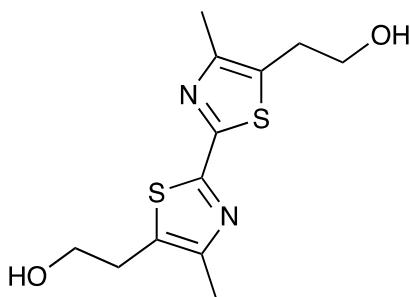
benzylbenzothiazole salt in 90% yield.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  6.25 (s, 2H), 7.65 (m, 7H), 8.5 (m, 2H), 10.93 (s, 1H). Data matched that reported by Baldwin et al.<sup>38</sup>

### **Dimers**



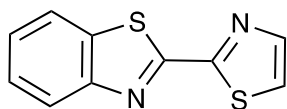
**192**

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (t,  $J = 7.08$ , 2H), 7.59 (t,  $J = 7.12$ , 2H), (d,  $J = 8.1$ , 2H), 8.07 (d,  $J = 8.1$ , 2H).



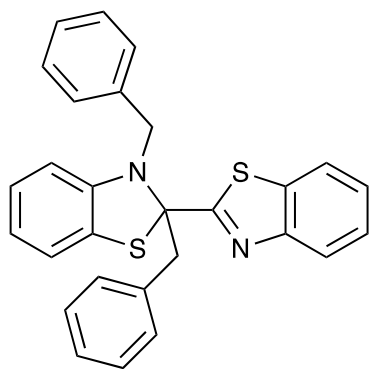
**185**

$^1\text{H}$  NMR (300 MHz, DMSO- $D_6$ )  $\delta$  2.43 (s, 6H), 3.05 (t,  $J = 5.9$ , 4H), 3.88 (t,  $J = 6.4$ , 4H).  $^{13}\text{C}$  NMR (300 MHz, DMSO- $D_6$ )  $\delta$  15.9, 30.3, 61.8, 132.1, 149.9, 165.8.



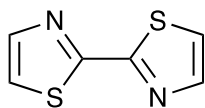
**206**

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (t,  $J = 7.12$ , 1H), 7.53 (m,  $J = 1.0$ , 2H), 7.96 (d,  $J = 8.0$ , 1H), 8.01 (d,  $J = 3.08$ , 1H), 8.12 (d,  $J = 8.12$ , 1H).  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  121.9, 122.2, 123.7, 126.2, 126.7, 135.3, 144.3, 153.5, 161.3, 161.7.



**198**

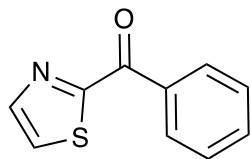
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.05 (q,  $J=13$ , 2H), 4.70 (q,  $J=17$ , 2H), 7.05 (m, 18H).



**189**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.90(d,  $J=3.1$ , 2H), 7.44 (d,  $J=3.1$ , 2H).

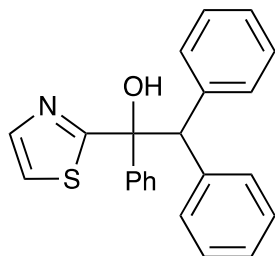
### Ketone



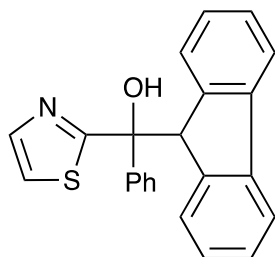
**123**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 (t,  $J = 7.5$ , 2H), 7.65 (t,  $J = 7.5$ , 1H), 7.74 (d,  $J = 3.0$ , 1H), 8.11 (d, 1H, 3.1) 8.47 (dd,  $J=1.5$ , 8.8, 2H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  126.3, 128.4, 131.1, 133.6, 135.2, 144.9, 167.9 (SC=N), 184.2 (C=O).

## Recombination products

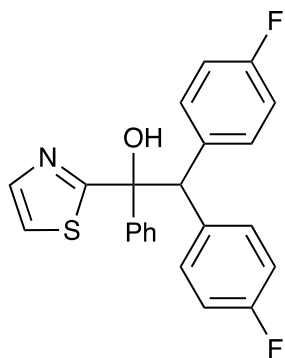


$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.94 (s, 1H), 7.14 (m, 12H), 7.38 (d,  $J = 4.1$ , 2H), 7.6 (d,  $J = 3.25$ , 1H) 7.73 (d,  $J=7.56$ , 2H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  54.8, 80.4, 120.3, 126.3, 127.6, 128.2, 128.7, 129.0, 141.6, 143.1, 162.0.



### 132

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.5 (s, 1H), 6.13 (d,  $J = 7.72$  1H), 6.31 (d,  $J = 7.72$ , 1H), 6.95 (t,  $J = 7.2$ , 1H) 7.05 (t,  $J = 7.2$ , 1H), 7.39 (m, 6H), 7.74 (dd,  $J = 7.6$ , 2H), 7.89 (d,  $J = 7.56$ , 2H), 7.96 (d,  $J = 3.24$ , 1H).  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 58.4, 80.4, 119.6, 119.8, 119.9, 124.7, 125.3, 125.6, 125.7, 126.6, 126.7, 126.9, 127.3, 127.4, 127.5, 127.8, 141.6, 141.7, 142.3, 142.6, 142.8, 143.1, 177.7



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.07 (s, 1H), 6.85 (m,  $J = 8.8$  4H), 7.23 (m, 8H), 7.61 (d,  $J = 3.28$ , 1H) 7.70 (d,  $J = 7.68$ , 2H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  55.13, 81.2, 115.4, 119.9, 125.8, 127.3, 128.2, 129.8, 141.6, 141.7, 162.9, 163.3. Matched data reported by Alwarsh et al.<sup>66</sup>

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