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Trimethylsilyl trifluoromethanesulfonate-mediated additions to acetals, nitrones, and aminals

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By

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in the Program in Biochemistry and Molecular Biology

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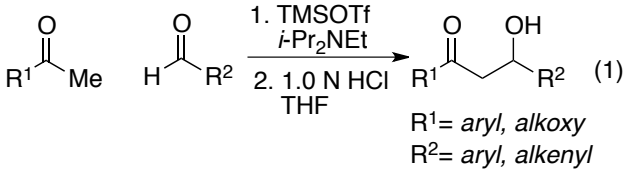
Abstract: One-pot reactions were studied in order to develop procedures for the formation of important carbon-carbon and carbon-nitrogen bonds that are easily reproducible. In the presence of trimethylsilyl triflouromethanesulfonate (TMSOTf), Mukaiyama-aldol and aldol-like reactions occur in one-pot due to TMSOTf acting as a Lewis acid and silylating agent. A variety of reactions, including methoxyalkylation, were performed to form carbon-nitrogen bonds. Here, research involving TMSOTf-mediated additions to acetals, nitrones, and aminals will be discussed.

Chapter I

Organic synthesis is important for discovering new molecules that could be used for pharmaceuticals, especially the development of new carbon-carbon and carbon-nitrogen bond-forming reactions. The reactions focused in my research group are one-pot reactions, which are mediated by TMSOTf. For example, previous work in the Downey group has shown that the addition of aryl methyl ketones and acetate esters to non-enolizable aldehydes provided efficient yields when excess silyl trifluoromethanesulfonate (TMSOTf) was used in the presence of Hunig's base (Eq. 1).[1] These one-pot reactions allow for the formation of a prerequisite enol silane intermediate and secondary products to occur in situ. The tandem enol silane formation-Mukaiyama aldol reaction is made possible due to the ability of TMSOTf to act as a silylating agent and Lewis acid under the chosen reaction conditions. By eliminating the necessity to pre-form and purify the enol silane nucleophile, future time and money needed for this formation can be saved and can benefit pharmaceutical companies.



(1)

Aldehyde and acetal electrophiles have been the main focus of our research. They are reactive in Mukaiyama aldol-type reactions in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf). The trimethylsilyl group is a strong Lewis acid that makes for a good catalyst. The strong Si-O bond in the product drives the reaction and can easily be removed later with acid. Also, the trifluoromethanesulfonate is a great leaving group, with its resonance-stabilized anion that is also stabilized by electronegative fluorines. Based on

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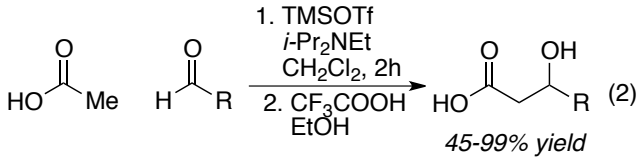
[1] Downey, C. Wade; Johnson, M. W.; Tracy, K. J. *J Org. Chem.* **2008,** *73*, 3299-3302

these attributes, TMSOTf has been a main focus of study and has allowed for numerous successes with Mukaiyama and related reactions.

The Mukaiyama aldol reaction is a popular tool for organic synthesis due to its use with fragment coupling and building block construction.[2] With our development of a new tandem enol silane formation-Mukaiyama aldol, TMSOTf was proven to be a powerful catalyst for Mukaiyama aldol reactions (Eq. 1).[3] Also, the new method discovered by fellow Downey lab members proceeds without preformation and purification of the enol silane nucleophile.

Recently, acetic acid aldol reactions in the presence of TMSOTf were discovered (Eq. 2). Unlike the previous Mukaiyama reactions mentioned, this one-pot process included three steps in order for the acetic acid to undergo aldol addition to non-enolizable aldehydes. In the presence of TMSOTf and trialkylamine base, the three steps include in situ trimethylsilyl ester formation, bis-silyl ketene acetal formation, and TMSOTf-catalyzed Mukaiyama aldol addition, which provide the formation of versatile carboxylic acid products.



(2)

Because the Mukaiyama aldol reaction is versatile and has mild reaction conditions, it is continuously being studied.[1] We have further expanded its scope to include acetals as alipathic aldehyde surrogates (Eq. 3). Various ketones, esters, and amides have been shown to react with a wide range of dimethyl acetals to form β-methoxy carbonyl compound.

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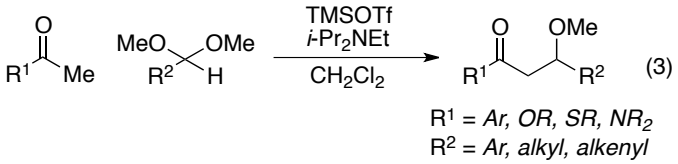
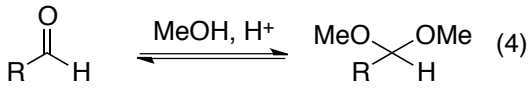
[2] Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509

[3] Downey, C. Wade; Johnson, M. W. *Tetrahedron Lett.* **2007**, *48*, 3559-3562



A review of acetal formation follows. Aldehydes are converted into acetals when an alcohol and acid are present (Eq. 4). As shown in Figure 1, the aldehyde first has to be protonated in order for the alcohol to attack the carbonyl. Then, proton transfer occurs, which allows the methoxy group to form a double bond as water leaves. An additional alcohol attacks the methylated carbonyl to form a protonated acetal. Once the methoxy group is deprotonated, an acetal is formed, which is a carbon with two alkoxy groups.



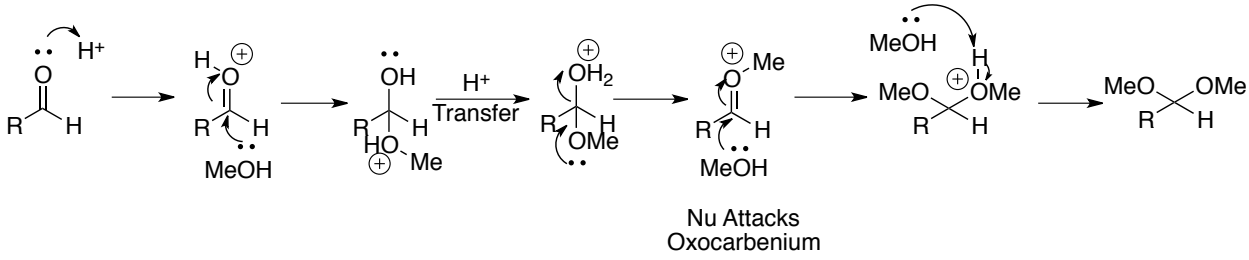


Figure 1. Acetal Formation

Acetal formation usually does not lead to complete product formation, but instead remains in equilibrium with aldehyde. Therefore, acetal breakdown is also occurring at the same time. Acetal breakdown is similar to formation, as shown in Figure 2. First, the methoxy group is protonated, which allows the electrons from the other methoxy group to form a double bond. An alcohol is formed. Water or other nucleophiles used in our research attack the carbonyl. Proton transfer occurs, followed by expulsion of an alcohol. Once the carbonyl is deprotonated,

the aldehyde is formed. In our work, the trimethylsilyl cation plays the same roles as H^+ in acetal breakdown.

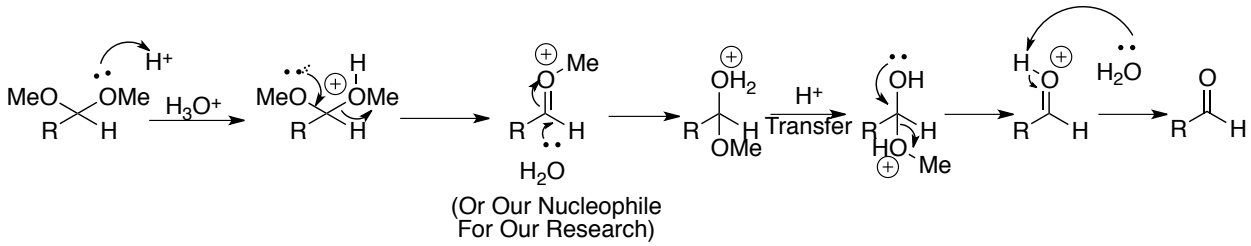


Figure 2. Acetal Breakdown

With the acetal studies summarized in Eq. 3, we thought that more carbon-carbon bond formation reactions could occur for various amides. It was already shown that ketones could form carbon-carbon bonds with an aldol-type addition to acetals. We proposed that a similar reaction would occur for secondary amides in the presence of acetals. However, a C-N bond was formed instead, to form *N,O*-acetals. Accordingly, we set out to establish that this one-pot system is a new method to form carbon-nitrogen bonds (see below).

Chapter II

I. Amides[4]

As previously mentioned, Mukaiyama aldol reactions have been studied with tertiary amides serving as the enolate precursor.[1] When a secondary amide was used instead, methoxyalkylation was observed at the amide nitrogen instead of at the α carbon, forming an *N,O*-acetal, a carbon singly bound to both a nitrogen and an oxygen (Eq. 5). With this discovery and the recognition that the reaction products could serve as *N*-acyliminium ion sources, the optimization of this *N,O*-acetal formation reaction was pursued.

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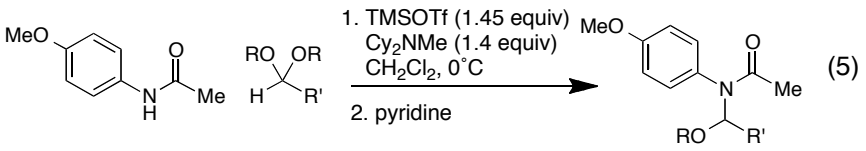
[4] Research was in collaboration with Alan S. Fleisher, James T. Rague, and Megan E. Venable



(5)

The formation of *N,O*-acetals shows that nitrogen of a secondary amide acts like the α-carbon of a ketone when base and TMSOTf are present to form a silyl imidate. With the hydrogen available on the secondary amide, the silyl imidate is formed and attacks the oxocarbenium electrophile. This is significant because removal of the hydrogen at the secondary amide allows a carbon-nitrogen bond to form, which is important for pharmaceutical production.

A brief survey of reaction conditions was conducted. The substitution of *i*-Pr_2NEt with Cy_2NMe allowed for better product yields. Also, an excess of TMSOTf (1.45 equiv) compared to acetal (1.4 equiv) was used to make certain that a catalytic amount of silylating agent was left in solution after the acetal was converted to the oxocarbenium ion. Once the reaction was finished, the unpurified reaction mixture was quenched with pyridine, which quenched any remaining TMSOTf. This was necessary because residual TMSOTf appeared to contribute to product decomposition during purification.

A proposed mechanism for this one-pot silyl imidate formation-*N,O*-acetal formation is outlined in Figure 3. With TMSOTf and a trialkyl amine, the secondary amide is deprotonated and a silyl imidate forms. In addition, the TMSOTf interacts with the acetal substrate to produce an oxocarbenium electrophile, which is later attacked by the siyl imidate through a Mukaiyama aldol-like addition. In order to reach the final product, a silyl transfer to an additional acetal occurs and produces another oxocarbenium ion.

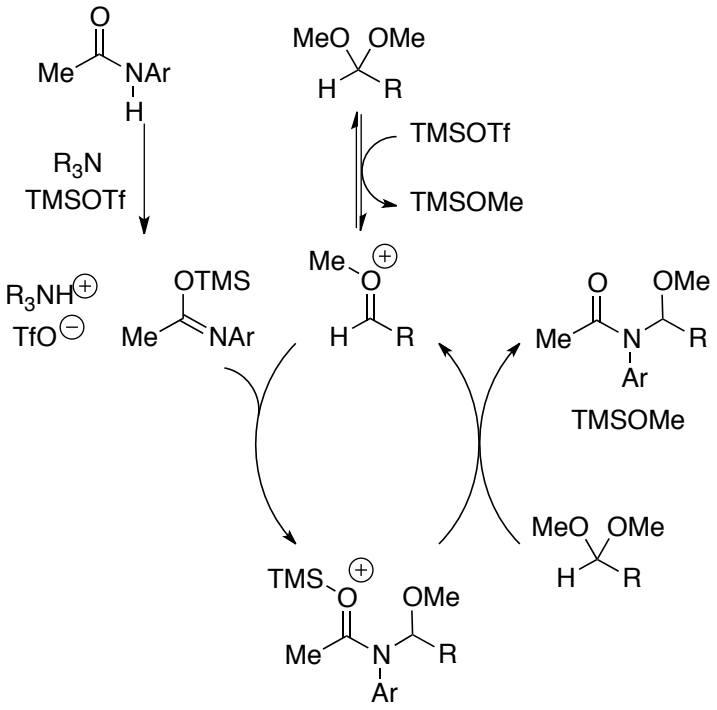
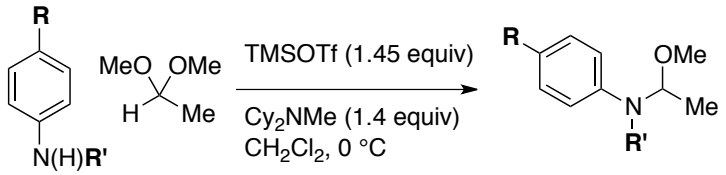
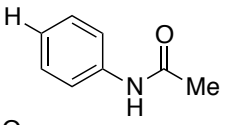
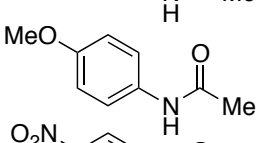
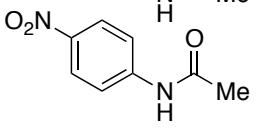
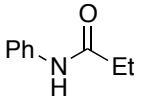
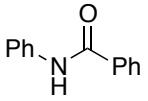
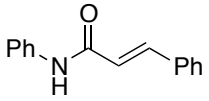


Figure 3. Proposed Mechanism

Based on this proposed mechanism, the secondary amide reaction was studied with two representative acetals. First, condensations with acetaldehyde dimethyl acetal were studied (Table 1). This sample acetal is a challenging substrate because its oxocarbenium derivative is readily enolized, which may lead to undesired side reactions. Both the electron-rich and -poor secondary amides produced favorable yields. However, the parent acetanilide had poor reactivity (41%), which could not be explained. When the acetyl group was replaced with other acyl groups (propionyl, benzoyl, and cinnamoyl), good yields of *N,O*-acetals were produced. So far, this reaction only seems optimal for *N*-aryl secondary amides. This reaction with other silyl imidate precursors led to either no reactivity (*N*-alkyl) or unidentifiable byproducts (*N*-allyl or -benzyl).

Table 1. Condensation of various anilides with acetaldehyde dimethyl acetal[a]



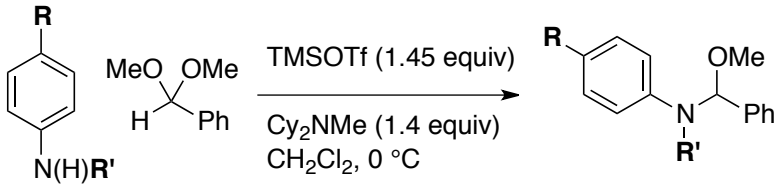
amide	yield (%)[b]
	41
	68
	65
	65
	88
	93

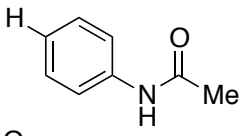
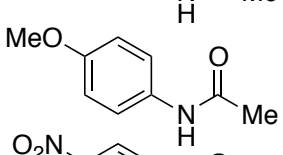
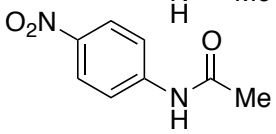
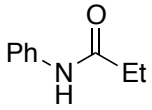
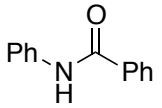
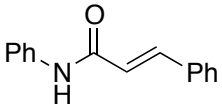
[a] Standard reaction conditions: amide (1.00 mmol), acetal (1.40 mmol), TMSOTf (1.45 mmol), Cy_2NMe (1.40 mmol), CH_2Cl_2 (5 mL), 0˚C, 2 h.
[b] Isolated yield after chromatography

In addition to acetaldehyde dimethyl acetal acting as an electrophile, benzaldehyde dimethyl acetal was studied with various secondary amides and produced similar and sometimes better results (Table 2). One difference was that benzaldehyde dimethyl acetal produced better results with the acetanilide (74% yield). In addition, this held true for propionanilide with the benzaldehyde dimethyl acetal (89% vs. 65%). The remaining anilides researched reacted similarly. Note that the oxocarbenium ion derived in situ from acetaldehyde dimethyl acetal was able to be deprotonated to produce an enol ether, which could potentially explain the decrease in

yield and formation of byproduct. This is not possible for benzaldehyde dimethyl acetal because the bendaldehyde oxocarbenium derivative is not acidic.

Table 2. Addition of various anilides to benzaldehyde dimethyl acetal[a]



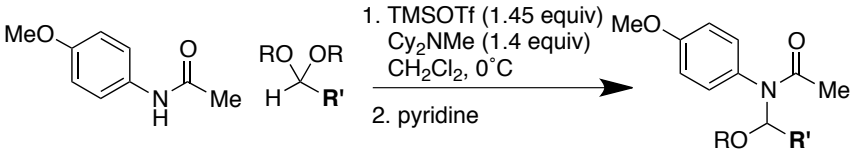
amide	yield (%)[b]
	74
	73
	69
	89
	76
	93

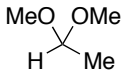
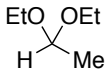
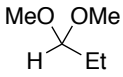
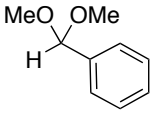
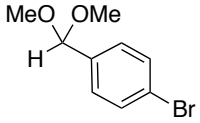
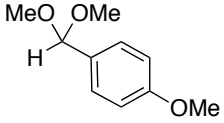
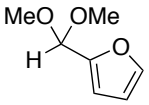
[a] Standard reaction conditions: amide (1.00 mmol), acetal (1.40 mmol), TMSOTf (1.45 mmol), Cy_2NMe (1.40 mmol), CH_2Cl_2 (5 mL), 0˚C, 2 h.
[b] Isolated yield after chromatography

The production of *N*-acyl-*N,O*-acetals with various acetals was then studied. The representative amide *p*-methoxyacetanilide was chosen for reaction optimization (Table 3). Some electron-rich substrates resulted in competitive reduction of acetals to aryl methyl ethers

when Cy_2NMe was used, as discussed later in this thesis. Thus, 2,6-lutidine was used instead for the indicated substrates, for reasons described later. Acetals derived from aromatic or heteroaromatic aldehydes produced the most favorable results. Lower yields occurred for the aliphatic acceptors, which can be explained by the competing enol ether formed by deprotonation of the oxocarbenium ion.

Table 3. Condensation of *p*-methoxyacetanilide with various acetals[a]

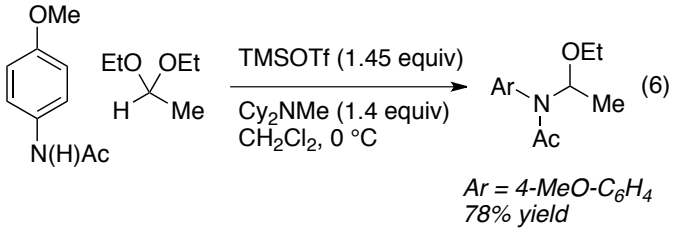


Acetal	yield (%)[b]
	68
	78
	52
	73
	99[c]
	77[c]
	61

[a] Standard reaction conditions: amide (1.00 mmol), acetal (1.40 mmol), TMSOTf (1.45 mmol), Cy_2NMe (1.40 mmol), CH_2Cl_2 (5 mL), 0˚C, 2h.
[b] Isolated yield after chromatography.
[c] 2,6-Lutidine was used instead of Cy_2NMe.

Unfortunately, the re-optimized reaction conditions were not favorable for other problematic acetals. For instance, 2-thiophene carboxaldehyde dimethyl acetal seemed to react, but we were unable to purify the compound since it appeared to be unstable to chromatography.

However, the reaction was favorable for the more hindered diethyl acetal of acetaldehyde resulting in a 78% yield (Eq. 6)



Benzyl methyl ether production was a major side reaction during the condensation reactions for some aryl acetals. We suspected that the ether formation occurred by a hydride transfer from the trialkylamine base to the oxocarbenium ion (Figure 4). The ether byproduct was frequently observed when Cy_2NMe or *i*-Pr_2NEt were used, but not when the reaction was treated when 2,6-lutidine as a base. One explanation for this finding is that 2,6-lutidine has no hydrogens α to nitrogen to be transferred to oxocarbenium ion. Also, no reaction occurred when amine was removed from the reaction, i.e. when only dimethyl acetal was stirred with TMSOTf. Finally, a similar reduction to the methyl ether was found when cyclohexadiene (hydride donor) was used instead of an amine base.

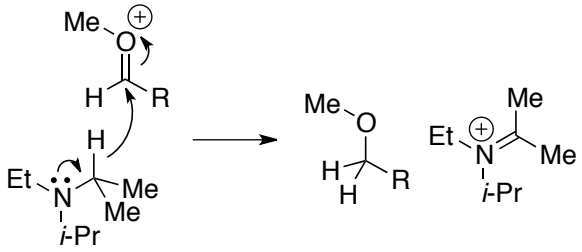


Figure 4: Reduction of oxocarbenium ion by *i*-Pr_2NEt

These findings are somewhat precedented in the literature. Silyl triflates have been found to catalyze the reduction of dimethyl acetals with silanes.[5] Our efforts toward a similar reaction performed with *i*-Pr_2NEt as the hydride source are summarized in Table 4. Electron-rich *p*-anisaldehyde produced higher conversions than the aromatic dimethyl acetals tested. However, these yields, compared to the conversions observed by ^1H NMR spectroscopy, dropped considerably when the compound was purified. Overreduction of the acetal carbon to the corresponding methyl group did occur but did not account for the major loss in yield. Neither could the reaction be optimized for reduction to the methyl group. In order to eliminate product volatility as a source of error, 2-napthaldehyde dimethyl acetal was studied under normal reaction conditions. Even with an observed conversion of 95%, the yield continued to be poor at 32%. Thus, volatility was not a contributor to the low yields observed and further studies of this reduction reaction were suspended.

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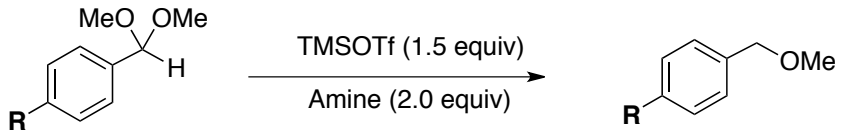
[5] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979**, *20,* 4679-4680

Table 4. Reduction of dimethyl acetals to methyl ethers[a]

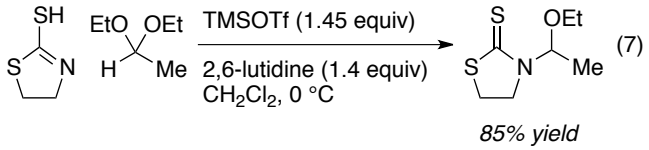


Amine	Solvent	R	Conv (%)[b]	Yield (%)[c]
i-Pr_2NEt	CH_2Cl_2	OMe	67	20
***i*-Pr_2NEt**	**Et_2O**	**OMe**	**94**	**23**
Cy_2NMe	Et_2O	OMe	81	ND[d]
Et_3N	Et_2O	OMe	<5	ND[d]
2,6-Lutidine	**Et_2O**	**OMe**	**<5**	**ND[d]**
i-Pr_2NEt	Et_2O	H	69	ND[d]
i-Pr_2NEt	Et_2O	Br	65	27
i-Pr_2NEt	Et_2O	Cl	57	ND[d]
i-Pr_2NEt	Et_2O	2-napthyl	95	32

[a]Standard reaction conditions: acetals (1.00 mmol), TMSOTf (1.50 mmol), *i*-Pr_2NEt (2.00 mmol), solvent (2.5 mL), rt, 1h.
[b]Determined by ^1H NMR spectroscopy of unpurified reaction mixture.
[c]Isolated yield after chromatography.
[d]ND= Not Determined

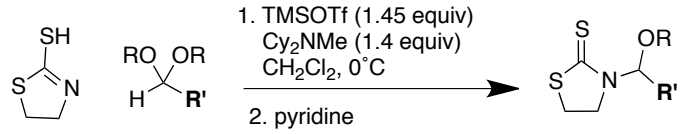
Nonetheless, the methoxyalkylation scope could be successfully expanded further. To wit, the anilide study was expanded to study the *N,O*-acetal formation with 2-mercaptothiazoline. The products of the reaction are *N*-(1-alkoxy)alkylated thiazolidinethiones, which are found in Table 5. These thione products may be useful in total synthesis. In order to further confirm the structure of the products, X-ray crystallographic analysis was employed, which confirmed that alkylation occurred at nitrogen and not at sulfur. From Table 5, the yields were high, but sometimes 2,6-lutidine was necessary to produce higher yields. For instance, condensation of 2-mercaptothiazoline with diethyl acetal of acetaldehyde under normal conditions had to compete with enol ether formation. To fix this competition, Cy_2NMe was replaced with the less basic

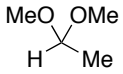
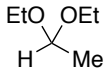
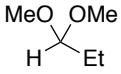
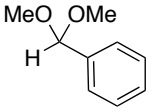
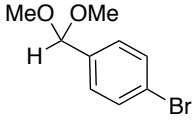
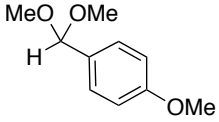
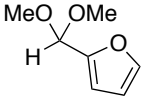
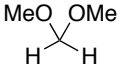
2,6-lutidine, which allowed an 85% yield to arise (Eq. 7). However, even with 2,6-lutidine as base, byproduct formation occurred with formaldehyde dimethyl acetal. We proposed that the byproduct was a methylene-bridged bis-thiazolidinethione instead of a reduced acetal. Further studies on the optimization of the observed byproduct will be discussed later in this thesis.



(7)

Table 5. Condensation of 2-mercaptothiazoline with various acetals[a]



Acetal	yield (%)[b]
	97
	85[c]
	85
	88
	98
	89[c]
	83
	68[c,d]

[a] Standard reaction conditions: amide (1.00 mmol), acetal (1.40 mmol), TMSOTf (1.45 mmol), Cy_2NMe (1.40 mmol), CH_2Cl_2 (5 mL), 0˚C, 2h.
[b] Isolated yield after chromatography.
[c] 2,6-Lutidine was used instead of Cy_2NMe.
[d] Product was contaminated with approximately 5 mol% side product (see text).

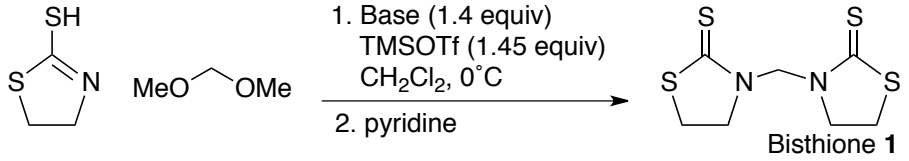
In conclusion, TMSOTf mediates the one-pot silyl enol ether formation-*N,O*-acetal formation reactions of secondary amides. Two roles for TMSOTf occur for this reaction: it silylates an alkoxy group on the acetal and activates the amide to lead to deprotonation.

Chapter III

I. Bisthione Synthesis

As previously noted, a byproduct was found in the formaldehyde dimethyl acetal reaction with 2-mercaptothiazoline and 2,6-lutidine as the base. The byproduct was tentatively identified as Bisthione **1**, a potentially useful iminium ion precursor. In order to amplify formation, optimization reactions were performed (Table 6). Conversion to bisthione increased with more equivalents of acetal. Also, 2,6-lutidine provided a 52% conversion to bisthione, which shows that a hindered, weaker base was more favorable. Despite further optimization studies (data not shown), product formation did not exceed 52% conversion.

Table 6. Base optimization reactions[a]



Bisthione **1**

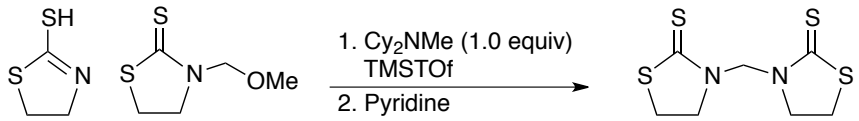
Base	Equiv Acetal	Conv (%)[b] Bisthione:	Unknown:	S.M.
Cy_2NMe	0.5	16	16	68
Cy_2NMe	0.7	37	10	52
i-Pr_2NEt	0.7	31	39	30
2,6-Lutidine	**0.7**	**52**	**15**	**33**

[a]Standard reaction conditions: amide (0.20 mmol), base (0.28 mmol), TMSOTf (0.29 mmol), CH_2Cl_2 (1 mL), rt, 15 min.; acetal (0.14 mmol), 0˚C, 2 h.; pyridine (0.20 mmol).
[b]Determined by ^1H NMR spectroscopy of unpurified reaction mixture.

In order to simplify the process, we decided to attempt bisthione formation from the previously synthesized Reactant **2** (Table 7). First, Cy_2NMe was used instead of 2,6-lutidine because previous experiments suggested that Cy_2NMe produced better results for the replacement of a single methoxy group. An increase in TMSOTf stoichiometry increased the

conversion to bisthione, which means that more TMSOTf was needed when compared to base. Also, the temperature affected the conversion. For instance, 0 ˚C reaction conditions were favorable with 1.0 equiv of Reactant **2**, but increasing concentration of the reactant caused the room temperature conditions to be more favorable. It was found that 60 ˚C was the most suitable temperature, providing 87% conversion at 1 hour. However, when the reaction was purified by silica gel chromatography, the bisthione could not be separated from the unknown product. Due to the complications of purification, further development of this reaction was postponed.

Table 7. Optimization Conditions for Bisthione Formation[a]



Reactant **2** Bisthione **1**

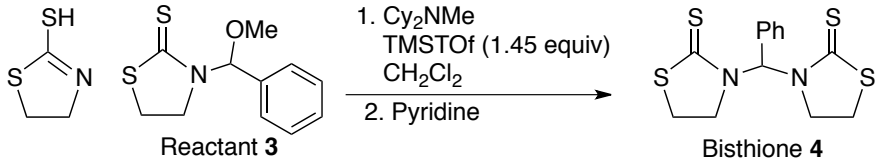
Equiv Reactant 2	Equiv TMSOTf	Solvent	Temperature	Time (hr)	Conv (%)[b] Bisthione:	Unknown:	S.M.
1.0	1.25	CH_2Cl_2	RT	1	26	63	11
1.0	1.45	CH_2Cl_2	0˚C	1	86	75	16
1.0	1.45	CH_2Cl_2	RT	1	36	53	11
1.2	1.45	CH_2Cl_2	0˚C	1	10	68	22
1.2	1.45	CH_2Cl_2	RT	1	44	55	1
1.2	1.45	CH_2Cl_2	50˚C	1	84	16	-
1.2	1.45	$CHCl_3$	60˚C	0.5	81	19	-
1.2	**1.45**	**$CHCl_3$**	**60˚C**	**1**	**87**	**13**	**-**
1.2	1.45	$CHCl_3$	60˚C	2	85	11	4
1.2	1.45	$(CH_2Cl)_2$	85˚C	1	65	33	2
1.2	1.65	CH_2Cl_2	RT	1	66	33	1

[a]Standard reaction conditions: amide (0.20 mmol), reactant 2 (0.20 mmol), Cy_2NMe (0.20 mmol), TMSOTf (0.29 mmol), solvent (1 mL), 1 h.; pyridine (0.20 mmol).
[b]Determined by ^1H NMR spectroscopy of unpurified reaction mixture.

In order to access a more controllable reaction pathway, Reactant **3** was used instead of dimethoxymethane, as shown in Table 8. No reaction occurred when the equivalents of base

exceeded or was similar to the amount of TMSOTf, in accordance with previous studies. Thus, 1.2 equiv of Cy_2NMe was found to produce a 95% conversion when 1.5 equiv of TMSOTf was present. A small-scale column showed that the product could be purified. However, due to the continued complications of purification for this product, further development of this reaction was postponed.

Table 8. Optimization of Base Stoichiometry with Methoxythiazolidine (Reactant **3**)[a]



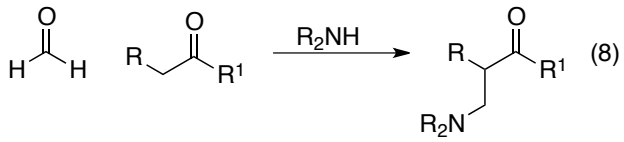
Reactant **3** — Bisthione **4**

Base	Equiv base	Conv (%)[b]
Cy_2NMe	1.6	No Rxn
Cy_2NMe	1.4	No Rxn
Cy_2NMe	**1.2**	**95**
2,6-Lutidine	1.2	34
i-Pr_2NEt	1.2	31
Pyridine	1.2	16

[a]Standard reaction conditions: amide (0.20 mmol), reactant **3** (0.20 mmol), base, TMSOTf (1.45 mmol), CH_2Cl_2 (1 mL), rt, 1 h.; pyridine (0.20 mmol).
[b]Determined by ^1H NMR spectroscopy of unpurified reaction mixture.

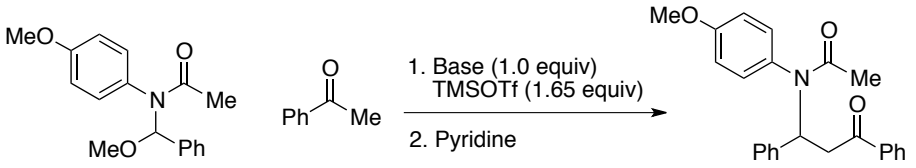
II. Reaction with other *N,O*-acetals

In aldol reactions, an enolate ion attacks the carbonyl of the ketone or aldehyde in order to produce a *β*-hydroxycarbonyl. The Mannich reaction is analogous to the aldol, but produces a *β*-aminocarbonyl. In Mannich reactions, an enol or enolate functions as a nucleophile and attacks an electrophilic iminium ion, which comes from the condensation of a second carbonyl with an amine (Eq. 8). In a Mukaiyama-Mannich reaction, the nucleophile is an enol silane.



After no successful optimization conditions were found for the formation of the bisthione, we elected to study the addition of acetophenone to the *N,O*-acetals we previously formed from secondary amides.[6] Such a reaction would provide one-pot access to Mukaiyama-Mannich products. As shown in Table 9, *i*-Pr_2NEt and CH_2Cl_2 constituted the most favorable reaction conditions, providing an 82% conversion to Putative Product **6**.

Table 9. Optimization Reactions[a]



Reactant **5** — Putative Product **6**

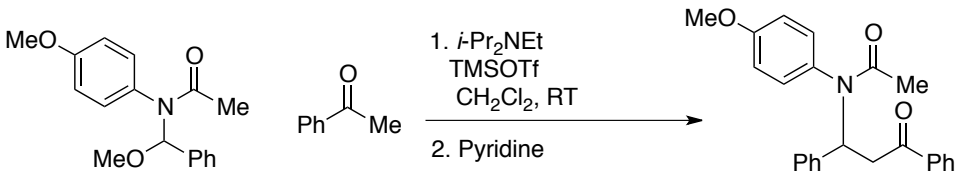
Base	Solvent	Conv (%)[b] Product 2: Enol Silane: PhCOMe		
Cy_2NMe	CH_2Cl_2	54	17	28
2,6-Lutidine	CH_2Cl_2	75	2	23
***i*-Pr_2NEt**	**CH_2Cl_2**	**82**	**-**	**18**
i-Pr_2NEt	THF	46	-	54
i-Pr_2NEt	Toluene	15	11	74
i-Pr_2NEt	Et_2O	11	35	53

[a]Standard reaction conditions: reactant **5** (0.40 mmol), acetophenone (0.20 mmol), base (0.20 mmol), TMSOTf (0.33 mmol), solvent (1 mL), rt, 1 h.; pyridine.
[b]Determined by ^1H NMR spectroscopy of unpurified reaction mixture.

[6] Downey, C. Wade; Fleisher, A. S.; Rague, J. T.; Safran, C. L.; Venable, M. E.; Pike, R. D. *Tetrahedron Lett.* **2011**, *52*, 4756-4759

With solvent and base optimization reactions completed, optimization of the ratio of *i*-Pr_2NEt to TMSOTf was performed. A larger amount of TMSOTf than base was found to be favorable as shown in Table 10. However, the purified product after column chromatography was not the desired product, but rather a previously synthesized compound from our lab (Eq. 9), as confirmed by ^1H NMR spectroscopy.

Table 10. Ratio of *i*-Pr_2NEt to TMSOTf



Reactant **5** Putative Product **6**

Equiv TMSOTf	Equiv *i*-Pr_2NEt	Conv (%)[b] Product 2:	Enol Silane:	PhCOMe
1.2	1.0	39	18	43
1.2	1.1	24	48	29
1.45	1.0	57	10	33
1.65	**1.0**	**82**	**-**	**18**
1.65	1.55	37	61	1
1.65	1.75	3	89	8

[a]Standard reaction conditions: reactant **5** (0.40 mmol), acetophenone (0.20 mmol), base, TMSOTf, solvent (1 mL), rt, 1 h.; pyridine.
[b]Determined by ^1H NMR spectroscopy of unpurified reaction mixture.

The mechanism for this undesired product formation is illustrated in Figure 5. Two preliminary reactions occur simultaneously: the carbonyl from the amide attacks a TMSOTf while the carbonyl from a ketone attacks an additional TMSOTF. The acetal methoxy group on the amide expels the amide to form a silyl imidate and an oxocarbenium ion. Also, a base attacks the ketone to form an enol silane. The enol silane then attacks the oxocarbenium ion. Thus, a Mukaiyama aldol-type reaction, as previously described (Eq. 9),[1] occurred.

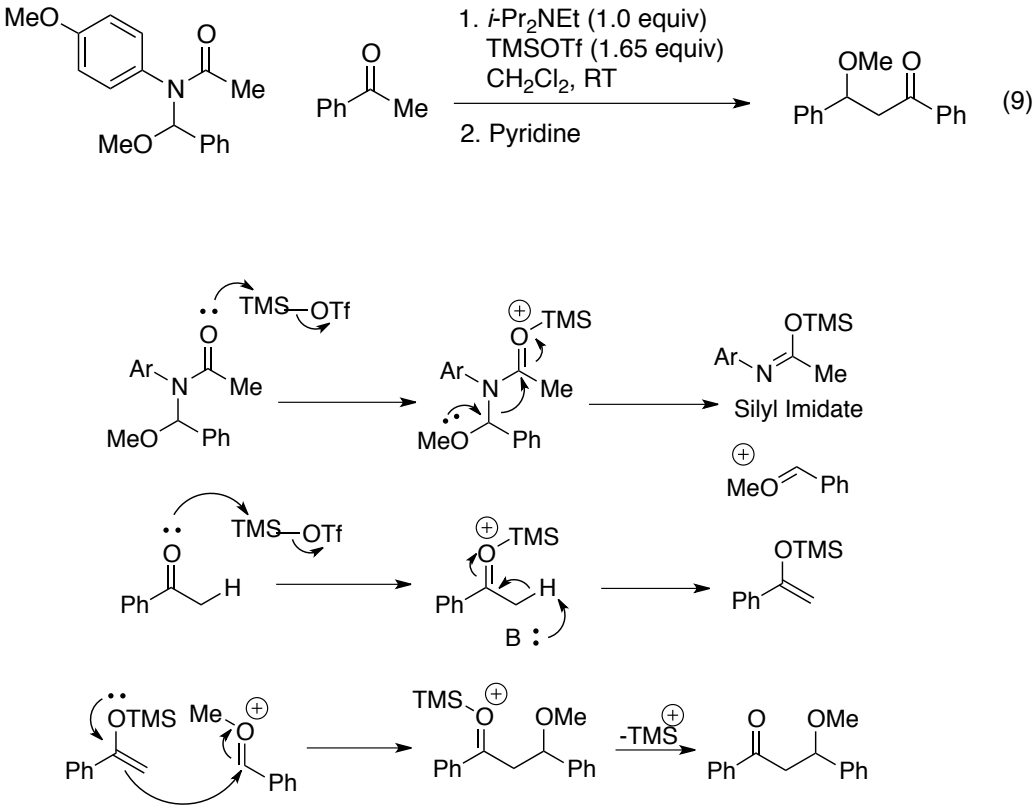


Figure 5. Actual Mechanism

Since formation of desired product did not occur, we decided to mask the carbonyl as an enol silane to prevent breakdown, as shown in Eq. 10. This required formation of the enol silane in situ. When Hunig's base and TMSOTf were used for enol silane formation, a 1:1 ratio of desired product to undesired was the most optimal conversion produced. In an attempt to improve conversion to the enol silane, bis-trimethylsilyl amides (K, Li, Na) were used as non-nucleophilic bases (Table 11). However, NaHMDS produced poorer results than the *i*-Pr_2NEt while no reaction occurred for KHMDS and LiHMDS. With no significant conversions produced through optimization reactions, the project was abandoned.

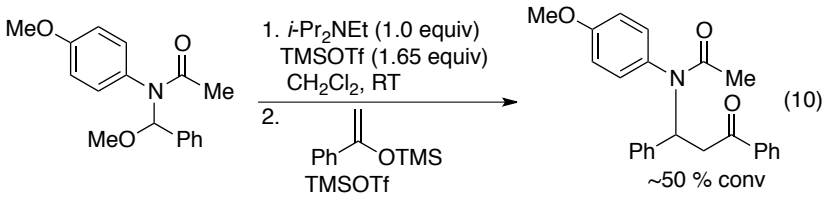
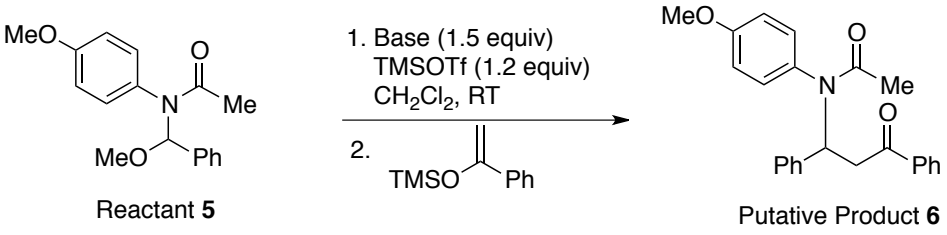


Table 11. Optimization Reaction with Bis-trimethylsilyl Amides[a]



Reactant **5** Putative Product **6**

Base	Conv (%)[b] Desired: Undesired
NaHMDS	33 66
KHMDS	No Rxn
LiHMDS	No Rxn

[a]Standard reaction conditions: reactant **5** (0.20 mmol), NaHMDS (0.6 M in Toluene); KHMDS (0.5 M in Toluene); LiHMDS (1.0 M in Toluene)**,** TMSOTf (0.24 mmol), rt, 2 h.; 1-phenyl-1-trimethylsiloxyethylene (0.22 mmol), TMSOTf (0.10 mmol),
[b]Determined by ^{1}H NMR spectroscopy of unpurified reaction mixture

Chapter V

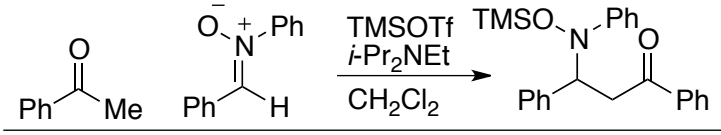
I. Additions to Nitrones[7]

In order to find a more feasible Mannich reaction, we turned to the addition of ketones to ntirones under our silylating conditions. It was found that the reaction proceeded cleanly with Hunig's base, TMSOTf, and methylene chloride. As shown in Table 12, a 59% conversion was found with 1.2 equiv of *i*-Pr_2NEt and 1.5 equiv of TMSOTf. However, when more Hunig's base than TMSOTf was present, the conversion to product decreased significantly, which agrees with previous studies. It was also found that with very limited amounts of base (0.2 equiv) no

[7] Research was in collaboration with Odamea Akomah '09

reaction occurred. This shows that a small excess of TMSOTf relative to base was needed in order for the nitrone to be silylated.

Table 12. Stoichiometry of Base and TMSOTf[a]

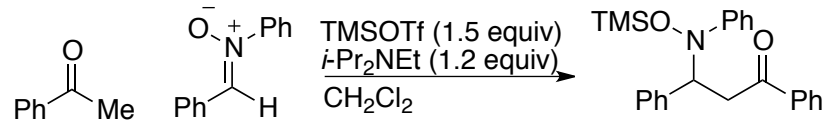


Equiv Base	Equiv TMSOTf	Conv (%)[b]
0.2	1.5	No Rxn
1.2	1.5	59
1.5	1.2	18

[a]Standard reaction conditions: nitrone (0.24 mmol), acetophenone (0.20 mmol), *i*-Pr_2NEt, TMSOTf, solvent (1 mL), rt, 1 h.
[b]Determined by ^1H NMR spectroscopy of unpurified reaction mixture.

In addition to the stoichiometry of base and TMSOTf, the order of addition in the reaction was studied. It was found that adding the nitrone last drastically increased the conversion to greater than 95%, as shown in Table 13. Also, the addition of nitrone after TMSOTf was not time dependent, because no change in conversion was found when nitrone was added immediately after all other reagents, as opposed to waiting 20 minutes to add nitrone.

Table 13. Optimization Reactions Dependent on Time and Order[a]

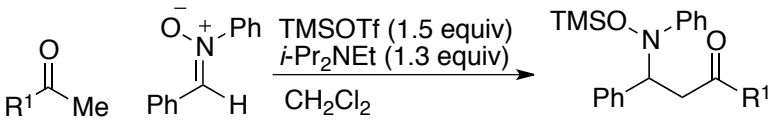


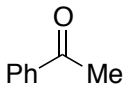
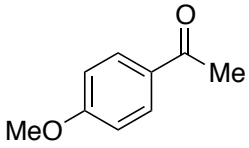
Order	Time (min)	Conv (%)[b]
Nitrone First	None	59
Nitrone Last	20	> 95
Nitrone Last	None	> 95

[a]Standard reaction conditions: : acetophenone (0.20 mmol), *i*-Pr_2Net (0.24 mmol), TMSOTf (0.26 mmol), nitrone (0.24 mmol), solvent (1 mL), rt, 1 h.
[b]Determined by ^{1}H NMR spectroscopy of unpurified reaction mixture.

Once the reaction conditions were optimized, the reaction was performed on a 1.0 mmol scale and the product was purified with silica column chromatography. The acetophenone-derived product was purified to produce a yield of 94%. With an electron-donating methoxy group present on the aromatic ring of the ketone, the reaction was able to proceed in high yield as well.

Table 14. Formation of Silylated Nitrones with Various Ketones[a]



Ketone	Conv (%)[b]	Yield (%)[c]
	> 95	94
	> 95	89

[a]Standard reaction conditions: : acetophenone (1.0 mmol), *i*-Pr_2Net (1.20 mmol), TMSOTf (1.30 mmol), nitrone (1.20 mmol), solvent (5 mL), rt, 1 h.
[b]Determined by ^{1}H NMR spectroscopy of unpurified reaction mixture.
[c]Isolated yield after chromatography.

II. Future Work

With success in synthesizing and purifying nitrone-based products, expansion of the reaction scope is planned for the near future. In order to fully probe the generality of the reaction, more ketones, nitrones, and other nitrogen electrophiles will be studied. Also, with the TMS group still present in the product, desilylation conditions will be studied, which may lead to more interesting product structures.

Chapter V

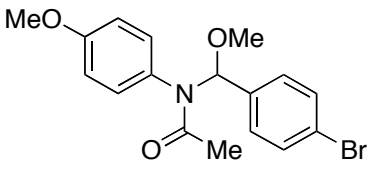
I. *N,O*-acetal Experimental Section

General Information. Reactions were carried out under an atmosphere of nitrogen with a septum cap in oven-dried glassware with magnetic stirring. CH_2Cl_2 was purified by passage through a bed of activated alumina.[8] Amines were distilled and stored under inert atmosphere (*i*-Pr_2NEt and 2,6-lutidine) or used as received from Aldrich Chemical Company (Cy_2NMe and

[8]Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

pyridine). TMSOTf from Aldrich Chemical Company was stored in a Schlenk flask under inert atmosphere. Amides were used as received from Aldrich Chemical Company (acetanilide), TCI (*p*-nitrolacetanilide), or Alfa Aesar (*p*-methoxyacetanilide, benzanilide), or were synthesized by reaction of aniline with the appropriate acid chloride (cinnamanilide, propionanilide). Acetals were used as received from Aldrich Chemical Company (acetaldehyde dimethyl acetal, acetaldehyde diethyl acetal, benzaldehyde dimethyl acetal, *p*-bromobenzaldehyde dimethyl acetal), TCI (prionaldehyde dimethyl acetal, dimethoxymethane), or Fluka (*p*-anisaldehyde dimethyl acetal), or were synthesized via literature precedent[9] (2-furan carboxaldehyde dimethyl acetal). Purification of reaction products was carried out by flash chromatography using Merck grade 9385 silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on J.T. Baker Baker-Flex Silica Gel IB-F plate. Visualization was accomplished with UV light and either ceric ammonium nitrate stain or anisaldehyde stain, followed by heating. Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Bruker Avance 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.28 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Bruker Avance 500 (500 MHz) or Bruker Avance 300 (300 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). High-resolution mass spectra were obtained by electrospray ionization. Mass spectra were obtained via a Shimadzu GC-17A gas chromatograph/mass spectrometer, except high-resolution mass spectra, which were obtained on Bruker Daltonios BioTOF-Q spectrometer. Melting points were determined using a Thomas Hoover Uni-Melt capillary melting point apparatus.

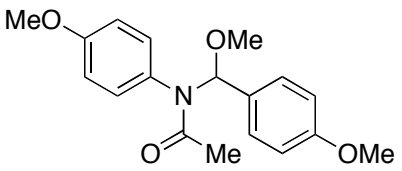
General Procedure for One-Pot Silyl Imidate Formation-*N*,*O*-Acetal Formation Reaction: To an oven-dried round-bottomed flask under N_2 atmosphere was added the silyl imidate precursor (1.00 mmol). The flask was charged with CH_2Cl_2 (5mL) and cooled to 0 °C, then amine (1.40 mmol) and TMSOTf (262μL, 322 mg, 1.45 mmol) were added. The mixture was stirred for fifteen minutes at 0°C, then acetal (1.4 mmol) was added. The mixture was stirred for 2 h and pyridine (82 μL, 80 mg, 1.0 mmol) was added. The mixture was passed though a plug of silica (1.0 cm x 3.0 cm) with Et_2O. The solvent was removed in vacuo, and the residue was purified by column chromatography (10-80% Et_2O/hexanes).



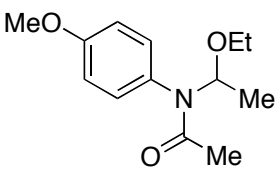
***N*-((4-Bromophenyl)(methoxy)methyl)-*N*-(4-methoxyphenyl)acetamide** The title compound was prepared according to the General Procedure, using 4-methoxyacetanilide (166.6 mg, 1.01 mmol), 2,6-lutidine (164 μL, 151 mg, 1.40 mmol), and 4-bromobenzaldehyde dimethyl acetal (234 μL, 324 mg, 1.40 mmol). The product was isolated as a yellow-green oil (99% yield). IR (film) 2924, 2846, 2361, 2341, 1658, 1510, 1374, 1304, 1297, 1238, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J=8.5 Hz, 2H), 6.96 (d, J=8.5 Hz, 2H), 6.94 (s, 1H) 6.66 (ap bs, 4H), 3.66 (s, 3H), 3.52 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 172.2, 159.2, 137.4, 131.0, 130.9, 130.4, 128.4, 121.8, 114.0, 84.0, 56.2, 55.3, 23.1; HRMS (ESI) exact mass calcd for $C_{17}H_{18}O_3NBrNa$

[9] Clerici, A.; Pastori, N.; Obretta, P. *Tetrahedron* **1998**, *54*, 15679-15690.

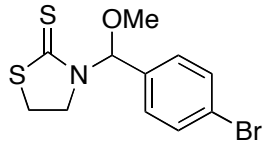
[M+Na] 386.0368 and 388.0347, found 386.0367 and 388.0344; GCMS exact mass calcd for $C_{17}H_{18}O_3NBr$ [M+] 363, 365, found 363, 365.



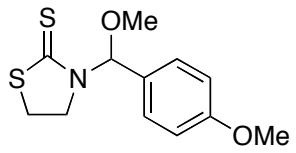
***N*-(Methoxy(4-methoxyphenyl)methyl)-*N*-(4-methoxyphenyl)acetamide** The title compound was prepared according to the General Procedure, using 4-methoxyacetanilide (166.2 mg, 1.01 mmol), 2,6-lutidine (164 μL, 151 mg, 1.40 mmol), and *p*-anisaldehyde dimethyl acetal (238 μL, 255 mg, 1.40 mmol). The product was isolated as a yellow oil (77% yield). IR (film) 2357, 2333, 1662, 1506, 1300, 1246, 1168, 1091, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16-6.95 (m, 4H), 6.80-6.65 (m, 5H), 3.72 (s, 5H), 3.71 (s, 1H), 3.55 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 159.2, 159.1, 131.2, 130.8, 130.4, 127.8, 113.8, 113.2, 84.5, 56.1, 55.3, 55.1, 29.7, 23.2; HRMS (ESI) exact mass calcd for $C_{18}H_{21}O_4NNa$ [M+Na] 338.1368, found 338.1377; GCMS exact mass calcd for $C_{18}H_{21}O_4N$ [M+] 315, found 315



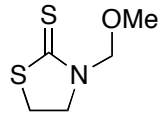
***N*-(1-Ethoxyethyl)-*N*-(4-methoxyphenyl)acetamide** The title compound was prepared according to the General Procedure, using 4-methoxyacetanilide (165.7 mg, 1.00 mmol), Cy_2NMe (297 μL, 273 mg, 1.40 mmol), and acetaldehyde diethyl acetal (200 μL, 165 mg, 1.40 mmol). The product was isolated as pale yellow oil (78% yield). IR (film) 2974, 1658, 1506, 1390, 1366, 1316, 1238, 1079 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 7.5 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 6.18 (q, J = 6.3, 1H), 3.85 (s, 3H), 3.79-3.72 (m, 1H), 3.69-3.62 (m, 1H), 1.85 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 159.3, 130.9, 130.7, 114.3, 78.7, 63.4, 55.4, 23.3, 19.8, 15.0; HRMS (ESI) exact mass calcd for $C_{13}H_{19}O_3NNa$ [M+Na] 260.1263, found 260.1275; GCMS exact mass calcd for $C_{13}H_{19}O_3N$ [M+] 237, found 237.



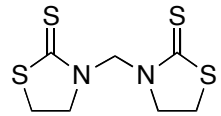
3-((4-Bromophenyl)(methoxy)methyl)thiazolidine-2-thione (21) The title compound was prepared according to the General Procedure, using 2-mercaptothiazoline (120.2 mg, 1.01 mmol), Cy_2NMe (297 μL, 273 mg, 1.40 mmol), and 4-bromobenzaldehyde dimethyl acetal (234 μL, 324 mg, 1.40 mmol). The product was isolated as a white solid (98% yield). mp: 77-79 °C; IR (film) 2936, 2882, 2823, 1476, 1410, 1285, 1216, 1080, 1006, 983, 874, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.315 (d, J = 8.4 Hz, 2H), 6.97 (s, 1H), 3.96-3.90 (m, 1H), 3.52-3.46 (m, 1H), 3.48 (s, 3H), 3.32-3.26 (m, 1H), 3.20-3.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 135.6, 132.0, 127.8, 122.8, 86.1, 56.8, 50.3, 28.3, 15.4; HRMS (APCI) exact mass calcd for $C_{11}H_{13}ONS_2Br$ [M+H] 317.9616 and 319. 9602, found 317.9621 and 319.9600; GCMS exact mass calcd for $C_{11}H_{12}ONS_2Br$ [M+] 317, 319, found 317, 319. X-ray analysis of this compound was performed upon a single crystal grown via slow diffusion of hexanes into a methylene chloride solution. X-ray data have been deposited at the Cambridge Crystallographic Database have been assigned the number CCDC 824052. See Appendices below for ORTEP diagram and X-ray data tables.



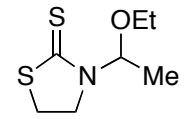
3-(Methoxy(4-methoxyphenyl)methyl)thiazolidine-2-thione The title compound was prepared according to the General Procedure, using 2-mercaptothiazoline (121.1 mg, 1.02 mmol), 2,6-lutidine (164 μL, 151 mg, 1.40 mmol), and *p*-anisaldehyde dimethyl acetal (238 μL, 255 mg, 1.40 mmol). The product was isolated as a white solid (89% yield). mp: 84-87 °C; IR (film) 2928, 2823, 1607, 1510, 1409, 1293, 1238, 1133, 1083, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.8 Hz, 2H), 6.98 (s, 1H), 6.87 (d, *J* = 8.8, 2H), 3.98-3.93 (m, 1H), 3.79 (s, 3H), 3.58-3.52 (m, 1H), 3.49 (s, 1H), 3.31-3.25 (m, 1H), 3.17-3.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 159.9, 128.6, 127.0, 113.9, 86.7, 56.7, 55.4, 50.4, 28.2; HRMS (ESI) exact mass calcd for $C_{12}H_{15}O_2NS_2Na$ [M+Na] 292.0442, found 292.0437; GCMS exact mass calcd for $C_{12}H_{15}O_2NS_2$ [M+] 269, found 269.



3-(Methoxymethyl)thiazolidine-2-thione The title compound was prepared according to the General Procedure, using 2-mercaptothiazoline (119.2 mg, 1.00 mmol), 2,6-lutidine (164 μL, 151 mg, 1.40 mmol), and dimethoxymethane (124 μL, 107 mg, 1.40 mmol). The product was isolated as a pale yellow oil (68% yield). IR (film) 2917, 1486, 1425, 1283, 1220, 1166, 1100, 1052, 1024, 973, 891, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (s, 2H), 4.10 (t, *J* = 7.8 Hz, 2H), 3.34 (s, 3H), 3.30 (t, *J* = 8.1, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 78.4, 57.1, 54.6, 27.8; HRMS (APCI) exact mass calcd for $C_5H_{10}ONS_2$ [M+H] 164.0198, found 164.0200 GCMS exact mass calcd for $C_5H_9ONS_2$ [M+] 163, found 163.



^1H NMR spectrum was contaminated with 5 mol% of a compound tentatively identified as the methylene-bridged bisthione: 5.72 (s, 2H), 4.22 (t, *J* = 7.8 Hz, 4H), 3.29 (t, *J* = 8.1Hz, 4H). (Tentative structure)



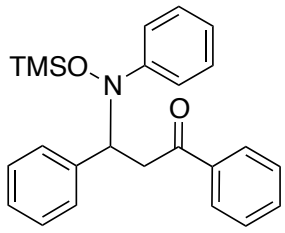
3-(1-Ethoxyethyl)thiazolidine-2-thione (25) The title compound was prepared according to the General Procedure, using 2-mercaptothiazoline (120.8 mg, 1.01 mmol), Cy_2NMe (297 μL, 273 mg, 1.40 mmol), and acetaldehyde diethyl acetal (200 μL, 165 mg, 1.40 mmol). The product was isolated as a yellow oil (85% yield). IR (film) 2978, 2897, 2869, 1475, 1413, 1293, 1211, 1157, 1106, 1091, 1060, 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.13 (q, *J* = 6.3 Hz, 1H), 4.12-4.06 (m, 1H), 4.02-3.94 (m, 1H), 3.60-3.53 (m, 2H), 3.40-3.25 (m, 2H), 1.56 (s, 1H), 1.41 (d, *J* = 6.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 83.2, 64.5, 50.1, 28.3, 18.5, 15.0; HRMS (APCI) exact mass calcd for $C_7H_{14}ONS_2$ [M+H] 192.0511, found 192.0505; GCMS exact mass calcd for $C_7H_{13}ONS_2$ [M+] 191, found 191.

II. Nitrones Experimental Section

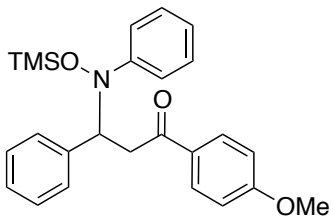
General Information. Reactions were carried out under an atmosphere of nitrogen with a septum cap in oven-dried glassware with magnetic stirring. CH_2Cl_2 was purified by passage through a bed of activated alumina.[VII] Amines were distilled and stored under inert atmosphere (*i*-Pr_2NEt). TMSOTf from Aldrich Chemical Company was stored in a Schlenk flask under inert atmosphere. Nitrones were used as received from Alfa Aesar (*N*,α-diphenyl nitrone). Phenones were used as received from Aldrich Chemical Company (acetophenone). Purification of reaction products was carried out by flash chromatography using Merck grade 9385 silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on J.T. Baker Baker-Flex Silica Gel IB-F plate. Visualization was accomplished with UV light. Infrared spectra were

recorded on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Bruker Avance 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.28 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Bruker Avance 500 (500 MHz) or Bruker Avance 300 (300 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). High-resolution mass spectra were obtained by electrospray ionization. Mass spectra were obtained via a Shimadzu GC-17A gas chromatograph/mass spectrometer, except high-resolution mass spectra, which were obtained on Bruker Daltonios BioTOF-Q spectrometer. Melting points were determined using a Thomas Hoover Uni-Melt capillary melting point apparatus.

General Procedure for One-Pot Nitrone Reaction: To an oven-dried round-bottomed flask under N_2 atmosphere was added the ketone (1.00 mmol). The flask was charged with CH_2Cl_2 (5 mL) and then *i*-Pr_2NEt (1.20 mmol), TMSOTf (235 μL, 288.94 mg, 1.3 mmol), and nitrone (1.2 mmol) were added. The mixture was stirred for 1 h. The mixture was passed though a plug of silica (1.0 cm x 3.0 cm) with Et_2O. The solvent was removed in vacuo, and the residue was purified by column chromatography (1-5% EtOAc/hexanes).



1,3-diphenyl-3-(phenyl((trimethylsilyl)oxy)amino)propan-1-one The title of the compound was prepared according to the General Procedure, using *N*,α-diphenyl nitrone (236.7 mg, 1.2 mmol) and acetophenone (117 μL, 120.2 mg, 1.0 mmol). The product was isolated as a yellow solid (94%). mp: 70-73˚C; IR (film) 3065, 3031, 2955, 1682, 1594, 1492, 1445, 1245, 1220, 1201, 919, 878, 840, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 6.5 Hz, 2H), 7.34-7.26 (m, 5H), 7.21 (d, *J* = 7.5 Hz, 2H), 5.20 (dd, *J* = 5 Hz, 8.4 Hz, 1H), 3.81 (dd, *J* = 8.4 Hz, 17.2 Hz, 1H), 3.68 (dd, *J* = 5 Hz, 17.2 Hz, 1H), -0.047 (s, (9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 152.4, 138.9, 137.2, 133.0, 129.6, 129.5, 128.2, 128.1, 127.9, 127.6, 123.5, 120.3, 69.5, 37.7, -0.63; HRMS (ESI) exact mass calcd for $C_{24}H_{27}NO_2Si$ [M+] 412.1703, found 412.1705.



1-(4-methoxyphenyl)-3-phenyl-3-(phenyl((trimethylsilyl)oxy)amino)propan-1-one The title compound was prepared according to the General Procedure, using *N*,α-diphenyl nitrone (236.7 mg, 1.2 mmol) and methoxy acetophenone (150.2 mg, 1.0 mmol). The product was isolated as a yellow oil (89%). IR (film) 2955, 1679, 1597, 1575, 1508, 1486, 1306, 1252, 1166, 1024, 922, 881, 837, 758, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 11.6 Hz, 2H), 7.37 (d, *J* = 6.8 Hz, 2H), 7.32-7.25 (m, 5H), 7.21 (d, *J* = 7.5 Hz, 2H), 6.94 (d, *J* = 7.2 Hz, 2H), 5.19 (dd, *J* = 5.3 Hz, 8.8 Hz, 1H), 3.86 (s, 3H), 3.77 (dd, *J* = 8.4 Hz, 16.9, 1H), 3.61 (dd, *J* = 4.7 Hz, 16.9 Hz, 1H), -0.049 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 163.4, 152.5, 130.3, 129.6, 128.5, 127.9, 127.6, 123.5, 120.3, 113.7, 69.6, 55.4, 37.3, -0.58; HRMS (ESI) exact mass calcd for $C_{25}H_{29}NO_3Si$ has yet to be determined.

Chapter VI

References

1. Downey, C. Wade; Johnson, M. W.; Tracy, K. J. *J Org. Chem.* **2008,** *73*, 3299-3302
2. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509
3. Downey, C. Wade; Johnson, M. W. *Tetrahedron Lett.* **2007**, *48*, 3559-3562
4. Research was in collaboration with Alan S. Fleisher ‘11, James T. Rague ‘11, and Megan E. Venable ‘11
5. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979**, *20,* 4679-4680
6. Downey, C. Wade; Fleisher, A. S.; Rague, J. T.; Safran, C. L.; Venable, M. E.; Pike, R. D. *Tetrahedron Lett.* **2011**, *52*, 4756-4759
7. Research was in collaboration with Odamea Akomah ‘09
8. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.
9. Clerici, A.; Pastori, N.; Obretta, P. *Tetrahedron* **1998**, *54*, 15679-15690.