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New Thiazolium-Based Strategies for Acyl Anion Addition Reactions

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ABSTRACT

New Thiazolium-Based Strategies for Acyl Anion Addition Reactions

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Two new strategies have been developed to accomplish direct nucleophilic acylation reactions. In the first approach, acylsilanes are added to various electrophiles using *N*-heterocyclic carbenes as catalysts. The second method utilizes *O*-silyl thiazolium carbinols as stoichiometric acyl anion precursors to afford acylated products under mild reaction conditions.

N-heterocyclic carbenes generated in situ from thiazolium salts catalyze the addition of acylsilanes to α,β-unsaturated systems and *N*-phosphinoyl imines in the presence of alcohol additives. The resulting 1,4-diketones and α-amino ketones are isolated in high yields. The use of carbenes in these reactions is novel since it avoids anionic catalysts typically required to access acyl anion reactivity from acylsilanes. Benzoin side product formation is not observed in these processes strongly indicating that the acyl anion intermediate generated in the reaction does not add to another equivalent of acylsilane. Studies conducted to probe the potential reaction pathways of these processes included the independent preparation of an *O*-silyl thiazolium carbinol, a proposed reaction intermediate. All reactions conducted with this species provided evidence that it is an intermediate in the reaction pathway. The results of the experiments

conducted with these unique carbinols demonstrate that these molecules are stable, stoichiometric acyl anion reagents.

O-Silyl thiazolium carbinols operate as stoichiometric acyl anion equivalents when treated with fluoride. The notable features of these unusual acylating agents include their straightforward preparation, stability, and ease of handling. The direct nucleophilic acylation of nitroalkenes has been developed by combining these carbinols with a fluoride anion and thiourea. Importantly, this process has been rendered asymmetric when a chiral thiourea is added to the reaction. Similarly, the synthesis of α-aryl ketones by the direct nucleophilic acylation of *o*-quinone methides has been developed. In this new transformation, two reactive intermediates, acyl anions and *o*-quinone methides, are generated in the same flask upon treatment of the corresponding thiazolium carbinols and silyl-protected phenols with a fluoride source. This strategy has been used to facilitate a short synthesis of demethylmoracin I, a naturally occurring aromatase inhibitor. Finally, further experiments indicate that these carbinols can undergo productive nucleophilic additions to aldehydes for the synthesis of acyloin products.

Thesis Advisor: Professor Karl A. Scheidt

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My parents have been great sources of motivation and I am forever grateful for their encouragement. My husband Brad is an amazing person and friend and I thank him for his constant support. I wish everyone only the best with a future filled with success and happiness.

List of Abbreviations

BINAM	1,1´-binaphthyl-2,2´-diamine
Boc	*tert*-butyloxycarbonyl
Bz	benzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric excess
ee	enantiomeric excess
equiv	equivalents
ESI	electrospray ionization mass spectrometry
GC	gas chromatography
HMPT	hexamethylphosphoramide
HPLC	high performance liquid chromatography
IMES	2,4,6-trimethylphenyl
IPA	isopropanol
KHMDS	potassium hexamethyldisilazane
LRMS	low resolution mass spectroscopy
MALDI-TOF	matrix assisted laser desorption ionization time-of-flight
Ms	mesylate
Mp	melting point
NHC	*N*-heterocyclic carbene

NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMAF	tetramethylammonium fluoride
TMS	trimethylsilyl
Ts	tosylate
TS	thiazolium salt
Tz	thiazolium salt

Dedication

This work is dedicated to Brad, my husband and best friend.

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Chapter 1 Thiazolium-Catalyzed Additions of Acylsilanes

1.1   Umpolung Methods as Useful Synthetic Tools

The development of new methods to form carbon-carbon bonds remains an important area of investigation to provide efficient access to molecules with valuable attributes. Strategies that employ new or unusual modes of reactivity can facilitate the synthesis of useful compounds. The reversal of standard reactivity patterns, or *Umpolung*, is one method that enables unconventional access of important target compounds.[1]   A valuable *Umpolung* tactic is the generation of acyl anion equivalents by the polarity reversal of carbonyl functionalities (Figure 1-1). Acyl, or carbonyl, anion equivalents are potentially useful reactive intermediates able to participate in nucleophilic acylation reactions with numerous electrophiles and for this reason are important intermediates in the synthesis of interesting molecules.[2]
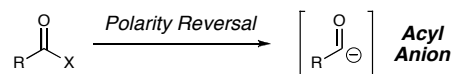
Figure 1-1. Acyl anion generation by the polarity reversal of carbonyl compounds

Acyl anion addition reactions are essential in many biological processes. Nature employs thiamine pyrophosphate, a coenzyme of vitamin B_1, to transform α-keto acids into their corresponding carbonyl anions in important biosynthetic pathways including pyruvate decarboxylation and the citric acid cycle (Figure 1-2). Thiamine pyrophosphate contains a thiazolium heterocycle which exists as the azolium zwitterion. This functions as nature's catalyst for the generation of the carbonyl anions. Inspired by natural chemical transformations,

investigators have sought to utilize *N*-heterocyclic carbenes derived from azolium salts like

thiamine to access acyl anions for use in new carbon-carbon bond forming processes.[3,4]
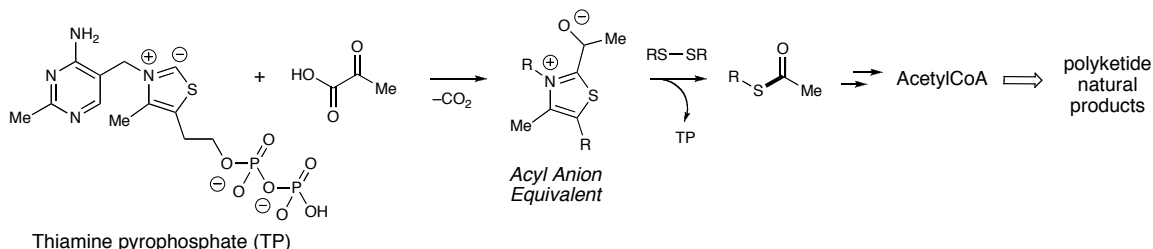
Figure 1-2. Nature's acyl anion

1.2   N-Heterocyclic Carbenes as Umpolung Catalysts

N-Heterocyclic carbenes (NHCs) are a class of stable singlet carbenes that can be isolated,

studied and stored.[3,5]   The key factors that contribute to the overall stability of these interesting

nucleophilies are two heteroatoms, usually sulfur and/or nitrogen, located on the carbon atom.

These substituents offer stabilization to the carbene through their σ withdrawing and π donating

abilities (Figure 1-3).

Three main classes of NHC precursors include thiazoliums, imidazoliums and triazoliums

(Figure 1-3).   While the NHCs resulting from these three classes of heterocycles are closely

related, it is important to note their stability and reactivity differ significantly.   These differences

in reactivity enable certain carbenes to be better suited for one use over another and currently the

optimal NHC for a process is generally determined empirically.   The acidity of the azolium salts

at the C_2 position is one factor that differs significantly between the three classes of NHCs:

thiazolium salts are most acidic with a pKa[DMSO] estimated to be 16[6] while imidazolium salts

are more basic with a pKa[DMSO] ranging from 20-24.[7-9] Data regarding the pKa of triazolium salts have not yet been reported.
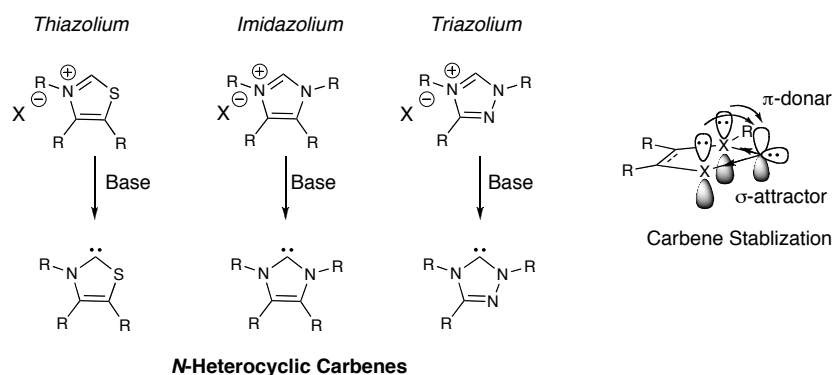
Figure 1-3. Examples of *N*-heterocyclic carbenes

In 1960, Wanzlick reported that the stability of a carbene is substantially increased when adjacent nitrogen substituents are present.[10-12] While Wanzlick demonstrated imidazolium salts can be deprotonated and trapped with phenyl isothiocyanate and mercury salts, he never reported the isolation of the free carbene.[13] Nearly two decades later, Arduengo and coworkers were able to isolate a stable crystalline carbene by deprotonation of 1,3-di-1-adamantylimidazolium chloride with sodium or potassium hydride in the presence of catalytic amounts of potassium *tert*-butoxide or a dimethyl sulfoxide anion (Scheme 1-1).[14,15]

Scheme 1-1. First isolation of a stable crystalline carbene
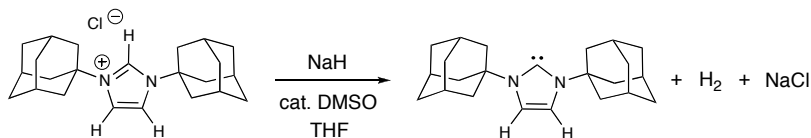
N-Heterocyclic carbenes (NHCs) are emerging as a class of highly useful organic molecules able to participate in a number of diverse reactions.[16] Because of their unusual

electronic characteristics, NHCs are unique molecular architectures for a) the development of new organometallic processes,[17-20] b) catalysts in organocatalytic reactions[3,5,21-33] and c) reagents in multi-component coupling reactions.[34-36] Furthermore, they can be generated in situ from stable precursors, are typically tolerant of air and moisture, and are generally non-toxic. Two well-established and related acyl anion addition reactions that can be catalyzed by NHCs are the benzoin condensation[37,38] and the Stetter reaction.[39]

1.2.1 NHC-Catalyzed Benzoin Condensation

One of the oldest and most well known reactions involving an acyl anion is the benzoin condensation (Scheme 1-2). Investigations into this transformation were first reported in 1832 when it was discovered by Wöhler and Liebig that cyanide is able to catalyze the 1,2-addition of an aldehyde to another aldehyde.[40] In 1903, Lapworth proposed a mechanism for the cyanide-catalyzed process.[41] Over a century after its discovery, Ukai and coworkers reported in 1943 that thiazolium salts are also suitable catalysts for the benzoin condensation.[42] In 1958, a mechanism was proposed by Breslow, based in part on the mechanistic work done by Lapworth, in which the active catalytic species was an NHC derived from a thiazolium salt (Scheme 1-3).[38]

Scheme 1-2. The benzoin condensation
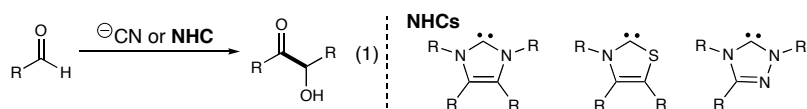
The proposed catalytic cycle begins with deprotonation of the thiazolium salt to generate the catalyst, nucleophilic carbene species **I-I**. Subsequent nucleophilic addition of **I-I** to an aldehyde occurs followed by proton transfer to form the "Breslow intermediate"[38] **I-III**. In this *Umpolung* intermediate, the polarity has been reversed and the once electrophilic carbonyl

carbon is now nucleophilic. The activated aldehyde **I-III** then undergoes an addition to a second equivalent of aldehyde. Finally, formation of the carbonyl regenerates the carbene catalyst and the benzoin product is formed. A more detailed mechanistic study reported by Leeper and coworkers in 2001 supports this catalytic cycle.[43]

Scheme 1-3. Proposed catalytic cycle of the NHC-catalyzed benzoin condensation
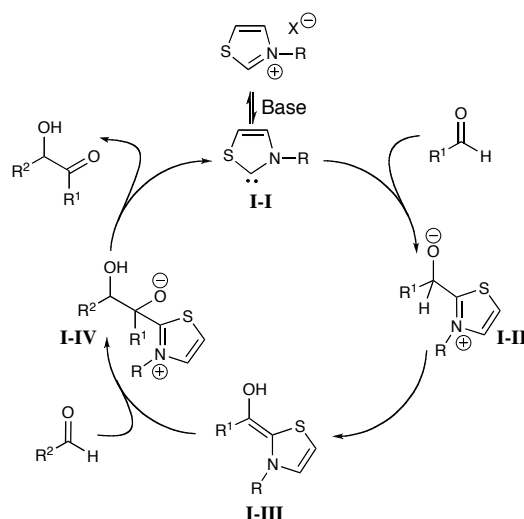
The α-hydroxy ketone product produced from the benzoin condensation contains a newly formed stereogenic center. With the appropriate catalyst and proper reaction conditions it should be possible to control the stereochemical outcome of the bond-forming event. This hypothesis has not gone unnoticed and significant research has been dedicated towards rendering the intermolecular NHC-catalyzed benzoin condensation asymmetric.

Over the past sixty years, a number of investigators have designed, synthesized and tested numerous novel chiral NHC catalysts (Figure 1-3). Beginning in 1966, Sheehan and coworkers were the first to attempt an enantioselective benzoin condensation utilizing an NHC derived from thiazolium salt **I-1**.[44] Unfortunately the success for this early ground breaking work was limited

to a low yield (9%) and low enantiomeric excess (22% ee). Sheehan achieved moderate enantioselectivities (up to 52% ee) employing thiazolium salt **I-2**, derived from (R)-α-methyl napthyl amine; however, the yield remained low (6%).[45] A slight increase in yield was observed when (L)-menthol derived catalyst **I-3** was employed by Tagaki and coworkers, although the enantioselectivity remained low at 35% ee.[46] Bisthiazolium salt **I-4** was examined by Lopez-Calahorra with an observed enantioselectivity of 26% ee.[47] Several chiral thiazolium salts were investigated in the Leeper laboratory, including catalysts **I-5** through **I-8**.[48,49] While yields of up to 50% were observed in some cases, the highest enantiomeric excess reported was only 21% ee. Rawal and coworkers designed the chiral thiazolium salt **I-9**, although the enantioselectivity observed was only 30% ee.[50] Most recently in 2004, the planar chiral thiazolium salt developed by Bach and coworkers **I-14** showed an improvement in yield however the enantioselectivity remained moderate at 40% ee.[51]

A significant breakthrough in the enantioselective NHC-catalyzed intermolecular benzoin condensation was realized by Enders and Breur when they discovered that chiral triazolium salt **I-11** provided moderate yields of product with enantioselectivities of up to 75% ee.[52] Further optimization of the triazolium structure was pursued in the Leeper laboratory.[53] They found bicyclic triazolium salt **I-12** generated the corresponding product in moderate enantioselectivity (63% ee). Finally in 2002, Enders and Kallfass accomplished the first high yielding, highly enantioselective intermolecular benzoin condensation with triazolium salt **I-13** as the precatalyst.[54]

I-1
1966, Sheehan
9% yield
22% ee

I-2
1974, Sheehan
6% yield
52% ee

I-3
1980, Tagaki
20% yield
35% ee

I-4
1993, Lopez-Calahorra
21% yield
26% ee

I-5
1997, Leeper
34% yield
20% ee

I-6
1997, Leeper
20% yield
11% ee

I-7
1997, Leeper
50% yield
21% ee

I-8
1997, Leeper
31% yield
13% ee

I-9
1998, Rawal
18% yield
30% ee

I-10
1998 Leeper
45% yield
80% ee

I-11
1996,Enders
66% yield
75% ee

I-12
1998, Leeper
22% yield
63% ee

I-13
2002, Enders
83% yield
90% ee

I-14
2004, Bach
85% yield
40% ee

Figure 1-4. Examples of chiral azolium salts utilized as NHC precursors in asymmetric intermolecular benzoin condensation reactions

1.2.2 NHC-Catalyzed Stetter Reaction

In 1976, Stetter reported the 1,4-addition of an aldehyde to an α,β-unsaturated system to generate 1,4-dicarbonyl compounds (Scheme 1-4).[39] This transformation has proven to be a useful carbon-carbon bond forming reaction that has attracted the attention of investigators interested in method development and natural product synthesis.[55,56] The reactive nucleophile is proposed to be the same as within the benzoin condensation (i.e. the Breslow intermediate) with addition at the β-position of the electrophile, rather than addition to the carbonyl carbon. The

resulting 1,4-dicarbonyl products are valuable building blocks in organic synthesis that can be

easily manipulated to afford useful compounds such as substituted furans and pyrroles.[57,58]

Scheme 1-4. Stetter reaction
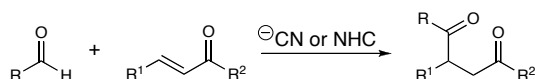
In a manner similar to the α-hydroxy ketones produced in the benzoin condensation, the

1,4-diketone products contain a new stereogenic center. An appropriate catalyst and suitable

reaction conditions should be able to render this transformation asymmetric. Indeed, substantial

efforts have been put forth by several research groups to accomplish this task. In a seminal

paper, Enders and coworkers demonstrated aldehydes (**I-15**) can be added to α,β-unsaturated

systems in an intramolecular fashion with high yields and good levels of enantioselectivity using

chiral NHC catalysts derived from triazolium salt **I-11** (Scheme 1-5).[59] The Rovis laboratory has

more recently disclosed that triazolinyilidene carbene **I-17** affords enhanced yields and

enantioselectivities in transforming **I-15** to **I-16**.[60] While a number of successes have been

reported in the development of highly enantioselective intramolecular Stetter reactions using

chiral imidazolium and triazolium derived carbenes as catalysts, the development of an

asymmetric intermolecular Stetter has proven to be a far more difficult task.[59-62]

Scheme 1-5. Asymmetric intramolecular Stetter reaction
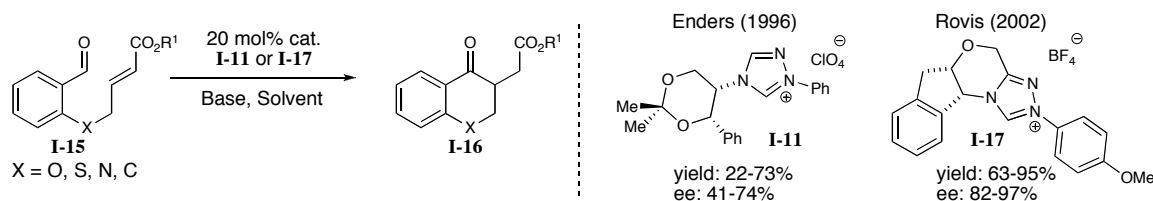
In the both benzoin condensation and Stetter reaction, an aldehyde has been successfully utilized as an acyl anion precursor. A major limitation associated with these reactions is the undesired side reactions that can occur, reducing the overall utility of the transformations. Specifically, due to the highly reactive nature of an aldehyde, uncontrollable additions of the acyl anion to the acyl anion precusor (the aldehyde) leads to undesired side products. For this reason, alternate acyl anion precursors have been explored to address this problem.

1.3   *Acylsilanes as Acyl Anion Precursors*

Acylsilanes are interesting compounds that have been employed as useful acyl anion precursors.[63-65]   A seminal report by Brook in 1957 describes the first isolation and characterization of an acylsilane.[66] The early studies of acylsilanes initially focused mainly on their interesting spectroscopic properties, such as the lowering of the carbonyl stretch in the infrared spectra when compared to simple ketones and the downfield shift of the carbonyl carbon in the ^{13}C NMR spectrum.   In addition to their unusual spectroscopic properties, these compounds can participate in interesting chemical transformations.   With the appropriate catalyst, acylsilanes can undergo a Brook rearrangement (1,2-silyl shift from carbon to oxygen) to generate an acyl anion equivalent in situ (Scheme 1-6). Furthermore, no addition of the acyl

anion equivalent to the acylsilane, the acyl anion precursor, is observed. The reason this side reaction is avoided may be because acylsilanes are more sterically congested due to substitution on the silicon.

Scheme 1-6. Generation of an acyl anion equivalent from an acylsilane
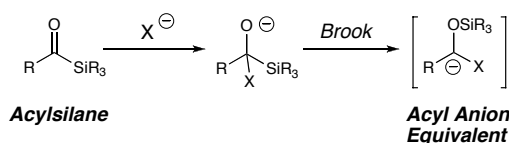
Many investigators have applied the *Umpolung* reactivity of acylsilanes towards the development of new chemical transformations. In the early 1980s, two groups, Ricci and coworkers[67] along with Schinzer and Heathcock,[68] independently described the fluoride-catalyzed addition of aryl acylsilanes to alkyl halides to afford the corresponding ketones in moderate yields (Scheme 1-7). Ricci and coworkers found ketones can be prepared from the reaction of benzoyltrimethylsilane with organic halides in the presence of KF and 18-crown-6. Heathcock and coworkers found acylsilanes add to methyl iodide and *n*-butyl iodide to afford the corresponding ketones in moderate yields. Several years later, in 1987, Degl'Innocenti, a coauthor on the Ricci publication described above, reported 1,4-additions acylsilanes to α,β-unsaturated electrophiles, such as cyclohexenone, using cyanide as a catalyst (Scheme 1-8).[69]

Scheme 1-7. Fluoride-catalyzed addition of aryl acylsilanes to alkyl halides
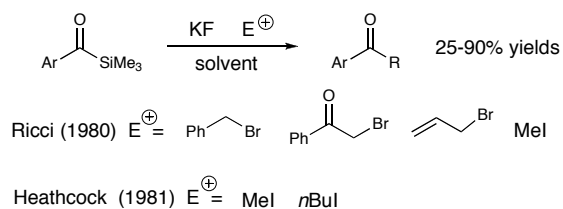
Scheme 1-8. Cyanide-catalyzed additions of acylsilanes to cyclohexenone
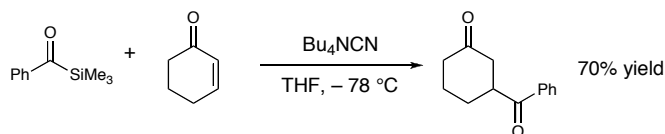
Concurrent with the studies from the Scheidt group, the Johnson group has reported more recent advances in the area of catalytic acylsilane addition reactions (Scheme 1-9). Both alkyl and aryl acylsilanes have been employed in cross-benzoin reactions with cyanide as the catalyst.[70] The resulting unsymmetrical α-hydroxy ketones are isolated in moderate to high yields (51-95%) with excellent regiocontrol. Johnson has also reported an asymmetric variant of the cross-benzoin catalyzed by a chiral metallophosphite that affords the desired products in good yields (65-86%) and moderate to high enantioselectivities (41-91%).[71]

Scheme 1-9. Acylsilane additions to aldehydes using cyanide or metallophosphites as catalysts
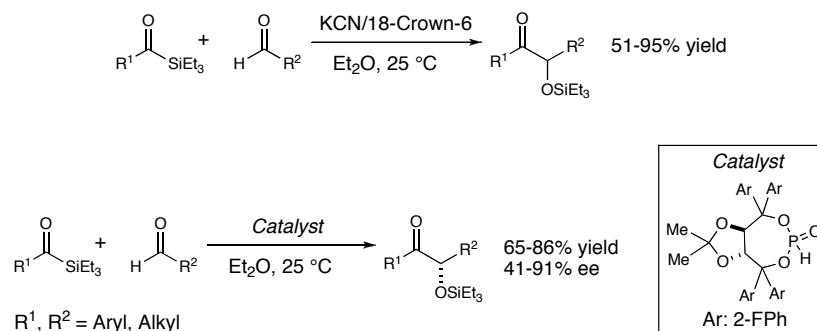
Johnson and coworkers have also employed metallophosphites to catalyze the addition of aryl acylsilanes to α,β-unsaturated amides (Scheme 1-10).[72] The resulting α-silyl-γ-ketoamides were isolated in good yields (62-91%) with diastereoselectivities ranging from 1.3:1 to 11:1 (*anti/syn*). The authors were able to demonstrate the reaction can be rendered asymmetric with good enantioselectivities reported (60% and 74% ee).

Scheme 1-10. Acylsilane additions to α,β-unsaturated amides catalyzed by metallophosphites
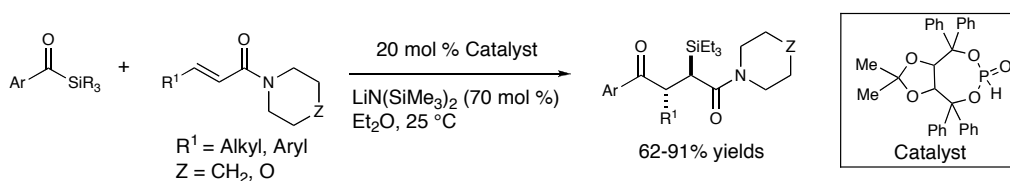
As is evident from previous publications in the area (vide supra), standard methods to convert acylsilanes to acyl anion equivalents typically employ strongly anionic catalysts, like fluoride and cyanide. At the onset of our investigation into acylsilane addition reactions, we sought to develop strategies to access acyl anion equivalents under more mild reaction

conditions. It is well known that both aldehydes and acylsilanes can be converted into acyl

anion equivalents using cyanide (Scheme 1-11). Additionally, it is well established that NHC-

catalysis can be used to generate acyl anion equivalents from aldehydes. We reasoned that it

might be possible for an NHC to catalyze acyl anion additions of acylsilanes. In this process, an

NHC would undergo a nucleophilic addition to an acylsilane and promote a 1,2-silyl group shift

(Brook rearrangement) from carbon to oxygen to render the carbonyl carbon nucleophilic

(Scheme 1-12). When compared to small nucleophiles like fluoride and cyanide, it was not clear

whether a larger five-membered heterocycle would add to the carbonyl carbon of an acylsilane.

Indeed, heteroazolium carbenes/zwitterions had not been used to promote Brook rearrangements

of acylsilanes prior to our investigation.

Scheme 1-11. Cyanide and NHC-catalyzed generation of acyl anions from aldehydes and acylsilanes
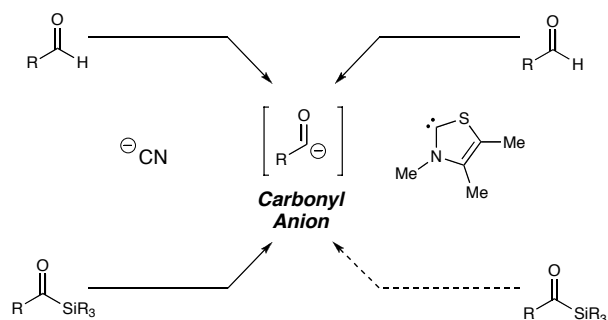
Scheme 1-12. Proposed NHC-catalyzed generation of acyl anion equivalents from acylsilanes
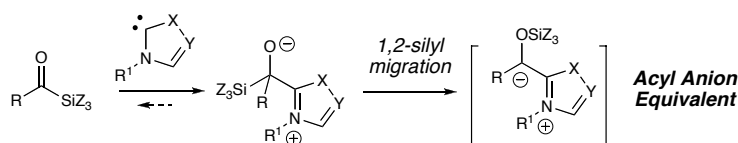
1.4 Thiazolium-Catalyzed Additions of Acylsilanes to α,β-Unsaturated Systems

1.4.1 Preparation of Acylsilanes

To begin our investigations we first required efficient methods to access both aryl and alkyl acylsilanes. Aryl acylsilanes were prepared according to previously published procedures reported by Yamamoto and coworkers (Scheme 1-13).[73] In this approach, an acid chloride is subjected to allyl palladium chloride dimer and triethyl phosphite in hexamethyldisilane to afford the corresponding aryl acylsilane. This reaction requires careful monitoring by gas chromatography to ensure all starting acid chloride is consumed prior to work up. If any acid chloride remains, it is extremely difficult to separate from the desired acylsilane product. Once the reaction is complete, the desired acylsilane can be easily purified by distillation on multigram scale.

Scheme 1-13. Preparation of aryl acylsilanes

X= Me, Cl, H

X= Me, 46%
    Cl,   42%
    H,   55%
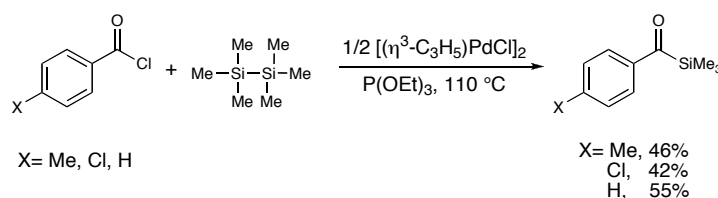
The synthesis of alkyl acylsilanes was accomplished according to a method developed in the Scheidt laboratory.[74] The addition of dimethylphenylsilyl lithium to an alkyl morpholine amide in THF at −78 °C provides good to excellent yields of the corresponding acylsilane after purification (Scheme 1-14). This method cannot be applied to the synthesis of aryl acylsilanes

due to undesired side reactions that occur, presumably from competing Brook rearrangement

pathways.

Scheme 1-14. Preparation of alkyl acylsilanes

60-85% yields
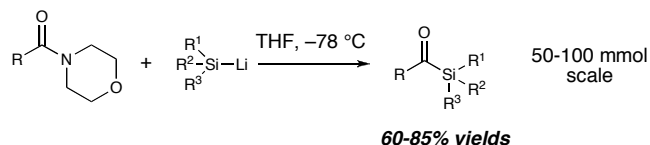
1.4.2 Development NHC-Catalyzed Additions of Acylsilane to Chalcone

Our investigation of NHC-catalyzed acyl anion additions began with a survey of reaction

conditions to carry out 1,4-additions of acylsilanes to 1,3-diphenyl-1-propen-3-one (chalcone).

Our choice of pursuing the synthesis of 1,4-dicarbonyl compounds via a carbonyl anion addition

was driven by the utility of these molecules in organic synthesis. After significant

experimentation with the structure of the electrophile, we discovered that a stoichiometric

amount of thiazolium salt **I-20a** and DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) successfully

promotes the addition of benzoyltrimethylsilane **I-18a** to chalcone to produce 1,4-dicarbonyl **I-21** in a good yield after 12 h by heating to reflux in THF (71%, entry 1, Table 1-1). With the

desired bond-forming process realized, a brief survey of bases and solvents indicated that DBU

and THF were optimal. Methylene chloride provided only a 39% yield product, most likely due

to the low reaction temperature (entry 4). The use of toluene as a solvent resulted in a

heterogeneous mixture that afforded no product (entry 5).

Table 1-1. Optimization of acylsilane addition to chalcone with stoichiometric thiazolium

entry	base	solvent	yield (%)
1	DBU	THF	71
2	NEt$_3$	THF	40
3	KOt-Bu	THF	0
4	DBU	CH$_2$Cl$_2$	39
5	DBU	PhCH$_3$	0

After successful formation of **I-21** in the stoichiometric process, we focused on developing a catalytic acylsilane addition reaction. Based on our knowledge of the Stetter reaction, we suspected that the process should potentially be catalytic in thiazolium salt. However, when the amount of **I-20a** was reduced from 1 equiv to 30 mol %, only a 41% yield of the product was isolated (Scheme 1-15). A more surprising result was obtained when no product was observed with a stoichiometric amount catalyst **I-20b**.

Scheme 1-15. Acylsilane addition to chalcone with catalytic thiazolium
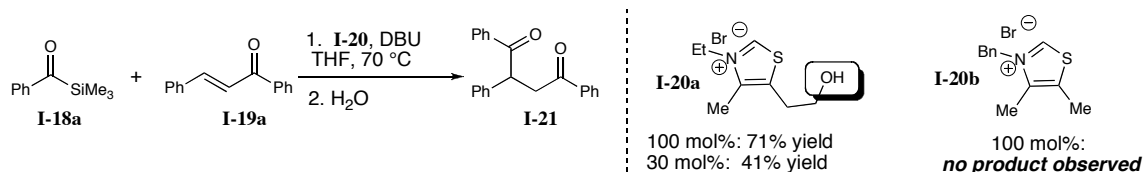
A comparison of catalysts **I-20a** and **I-20b** reveals that the free alcohol (an artifact of the conversion of thiamine into structures such as **I-20a**) may be the cause for the significant difference in reactivity. To explore whether a free alcohol was necessary for the reaction, 4 equivalents of isopropanol were added to an acylsilane addition reaction containing 30 mol % of

I-20a (Scheme 1-16). We were pleased to find the straightforward addition of alcohol improved the yield of **I-21** to 77% with only 30 mol % of **I-20a**. Further confirmation of the importance of an alcohol additive was observed when thiazolium **I-20c** was employed with 4 equivalents of isopropanol: these reaction conditions provided the same yield as with **I-20a.**

Scheme 1-16. Catalytic sila-Setter with protic additive

with **I-20a**: 77% yield
with **I-20c**: 77% yield
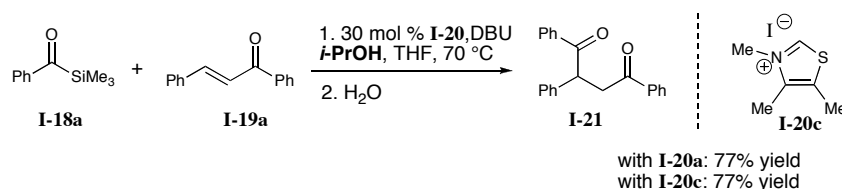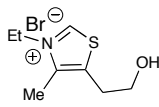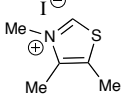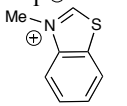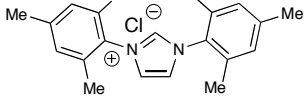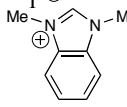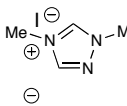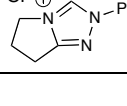
1.4.3   Examination of NHC Catalyst Structure

A key variable of interest in the process described above was the structure of the heteroazolium catalyst. Since the reactivity of an NHC can significantly be affected by steric and electronic properties, an examination of potential catalysts was carried out determine the best NHC to catalyze the desired conjugate addition. To our surprise, NHCs derived from anything besides thiazolium salts (i.e. imidazolium and triazolium compounds) fail to deliver significant amounts of the desired product **I-21** (Table 1-2). Surprisingly, the catalyst derived from benzothiazolium **I-20d** does *not* provide any of desired product, thereby underscoring the subtle electronic effects that control the interaction of the heteroazolium-derived carbene with the acylsilane as well as the carbon-carbon bond forming process. Additionally, no decomposition of the chalcone or acylsilane is observed with **I-20d**. There is also no product formation with the sterically hindered IMES (1,3-bis(2,4,6-trimethylphenyl)) catalyst resulting from imidazolium salt **I-20e**, although the acylsilane is consumed. Interestingly, benzaldehyde is the only product

resulting from the reaction catalyzed by **I-20e**, no benzoin products were observed by gas chromatography. The benzimidazolium derived catalyst (**I-20f)** affords nearly complete conversion of the acylsilane but only 5% yield of 1,4-diketone **I-21** is observed. Triazolium derived catalysts **I-20g** and **I-20h** had similar results, with little product formation and little recovered acylsilane. These observations taken en masse emphasize how slight perturbations in the heteroazolium core and nitrogen substitution can cause drastic differences in reactivity for the sila-Stetter.

Table 1-2. Examination of catalyst structure

entry	catalyst		I-18a conversion	I-19a conversion	yield
1		**I-20a**	100%	100%	77%
2		**I-20c**	100%	100%	77%
3		**I-20d**	0%	0%	0%
4		**I-20e**	50%	31%	0%
5		**I-20f**	74%	9%	5%
6		**I-20g**	100%	53%	7%
7		**I-20h**	93%	27%	0%

1.4.4 *Examination of Acylsilane Additions to α,β-Unsaturated Systems*

We proceeded to examine the scope of the addition reaction of various acylsilanes to α,β-unsaturated systems after the key conditions had been identified. After our initial success with chalcone (**I-19a**), we examined numerous unsaturated amides and esters as electrophiles with no sign of formation of the desired product (Figure 1-5). A current requirement of our acylsilane conjugate additions is the electrophile needs to be an α,β-unsaturated ketone or highly reactive ester. Utilizing an unsaturated acyl pyrrole as the electrophile produced only decomposed starting material. No desired product was observed when maleic anhydride (**I-22**) or *N*-methylmaleimide (**I-23**) were used as potential conjugate acceptors. Only decomposition of both starting materials was observed when fumaronitrile and coumarin were employed as electrophiles. When alkylidene malonates (**I-25**) were employed as electrophiles low yields of product were obtained because of poor conversion. Experiments with nitroalkenes (**I-26**) as electrophiles failed because the starting materials decomposed under these reaction conditions. NHCs are good nucleophiles and it is possible that some substrates are not successful because the NHC may add directly to the electrophile thus preventing the desired reaction from occurring.

| I-22 | I-23 | I-24 | I-25 | I-26 |
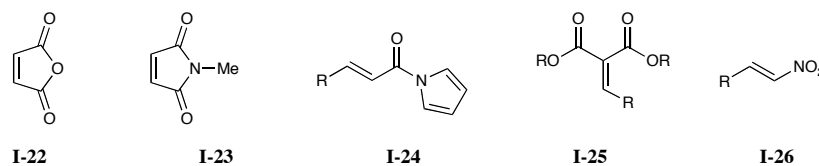
Figure 1-5. Examples of electrophiles screened with our NHC and acylsilane system

Our investigations of the α,β-unsaturated ketone scope began with an examination of various substituted derivatives (Table 1-3). The addition reaction can tolerate both electron-donating and electron-withdrawing substituents on either aryl group, delivering good to high yields of product in all cases (66-82%, entries 1-9). A free hydroxyl group at the para position provides the desired 1,4-diketone **I-36**, albeit in a slightly reduced yield because of reduced levels of conversion (50%, entry 10). Importantly, since isopropanol is a key constituent in the reactions, there are no stringent precautions to exclude moisture in any of these reactions.

Table 1-3. Catalytic sila-Stetter reaction with acylsilane **I-18a** and β-aryl unsaturated phenyl ketones

entry	R^1	R^2	yield (%)	product
1	Ph	4-ClPh	82	**I-27**
2	Ph	4-OMePh	80	**I-28**
3	1-Napth	Ph	72	**I-29**
4	4-BrPh	Ph	66	**I-30**
5	4-ClPh	Ph	74	**I-31**
6	2-ClPh	Ph	68	**I-32**
7	4-MePh	Ph	84	**I-33**
8	3-OMePh	Ph	75	**I-34**
9	4-OMePh	Ph	77	**I-35**
10	4-HOPh	Ph	50	**I-36**

The influence of acylsilane structure on the reaction was also examined (Table 1-4). Since the addition of a thiazolium-derived carbene/zwitterions to an acylsilane is an important step in a successful reaction, the substitution of the silyl group should influence the reactivity of the acylsilane. Accordingly, both alkyl and substituted aryl acylsilanes were investigated as acyl

anion precursors. Acylsilane **I-18b** containing an electron withdrawing substituent in the para position provided the best results, generating **I-37** in an 82% yield (entry 2). Acylsilanes with alkyl group at R^1 (**I-18e** and **I-18f**) are successful substrates and generate 1,4-diketone products **I-39** and **I-40** in good yields (entries 5 and 6). These entries indicate that the reaction can accommodate acylsilanes with enolizable protons without observing aldol or Michael chemistry. Additionally, dimethylphenyl acylsilane **I-18d** proved to be a suitable acyl anion precursor yielding 61% of **I-21** (entry 4).
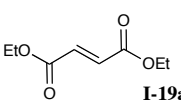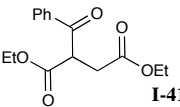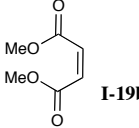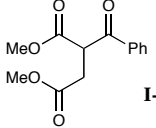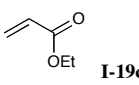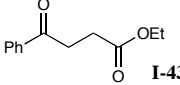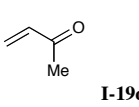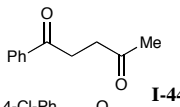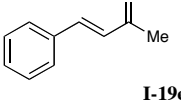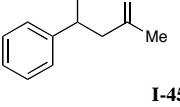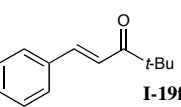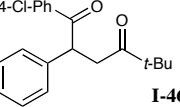
Table 1-4. Catalytic sila-Stetter reaction with acylsilane **I-18** and β-aryl unsaturated phenyl ketones

entry	acylsilane	R^1	R^2	yield (%)	product
1	**I-18a**	Ph	CH_3	77	**I-21**
2	**I-18b**	4-ClPh	CH_3	82	**I-37**
3	**I-18c**	4-CH_3Ph	CH_3	70	**I-38**
4	**I-18d**	Ph	Ph	61	**I-21**
5	**I-18e**	CH_3	Ph	70	**I-39**
6	**I-18f**	Cyclohexyl	Ph	63	**I-40**

The scope of the sila-Setter was further examined by employing various classes of α,β-unsaturated carbonyl electrophiles (eq 7, Table 1-5). Even with multiple nucleophilic species in solution (e.g. DBU, isopropanol, thiazolium carbene/zwitterion) a surprising number of highly reactive conjugate acceptors that are typically prone to polymerization provide moderate yields of 1,4-dicarbonyl products. For example, diethyl fumarate and dimethyl maleate are competent substrates generating the corresponding products **I-41** and **I-42** in good yield (entries 1 and 2). Highly reactive substrates lacking substitution in the β-position such as ethyl acrylate (**I-19c**) and methyl vinyl ketone (**I-19d**) undergo these nucleophilic acylation reactions to generate **I-43** and

I-44 in 72% and 75% yields (entries 3 and 4). Finally, additions to alkyl chalcone derivatives

I-19e and **I-19f** produce the desired 1,4-diketones in moderate yields (entries 5 and 6). It is of

interest to note that the reactions of **I-19e** and **I-19f** failed to proceed to completion and this

could potentially be due to the conformation of these molecules. Aryl chalcone derivatives are

planar, however, this may not be the case for the alkyl variants and might be affecting the

reactivity of these substrates.

Table 1-5. Acylsilane additions to α,β-unsaturated esters and ketones

entry	Acylsilane	I-19	product	yield
1	**I-18a**	I-19a	I-41	65%
2	**I-18a**	I-19b	I-42	72%
3	**I-18a**	I-19c	I-43	72%
4	**I-18a**	I-19d	I-44	75%
5	**I-18b**	I-19e	I-45	63%[a]
6	**I-18b**	I-19f	I-46	48%[b]

[a]64% conversion [b]59% conversion

1.4.5 Asymmetric Acylsilane Additions

Once the reaction scope had been established, a new potential direction was the development of an asymmetric variant of this reaction (Scheme 1-17). Unfortunately, all attempts to add benzoyltrimethylsilane to chalcone under standard reaction conditions using **I-2** and **I-5** as the catalysts only resulted in the recovery of starting material along with a small amount of decomposition. There was no formation of the desired 1,4-diketone. A potential explanation for the lack of reactivity in this system may be that the chiral catalysts are too sterically congested to add to the acylsilane. Furthermore, during the course of our investigation into an asymmetric variant it became clear that the synthesis of chiral thiazolium salts is a significant challenge. Several steps are required with impractical overall yields and for this reason the testing of additional chiral thiazoliums was limited. While chiral imidazolium and triazolium salts are more attainable synthetically, the salts examined to date afford no desired product (no reaction was observed with **I-10**).

Scheme 1-17. Investigation of asymmetric acylsilane additions
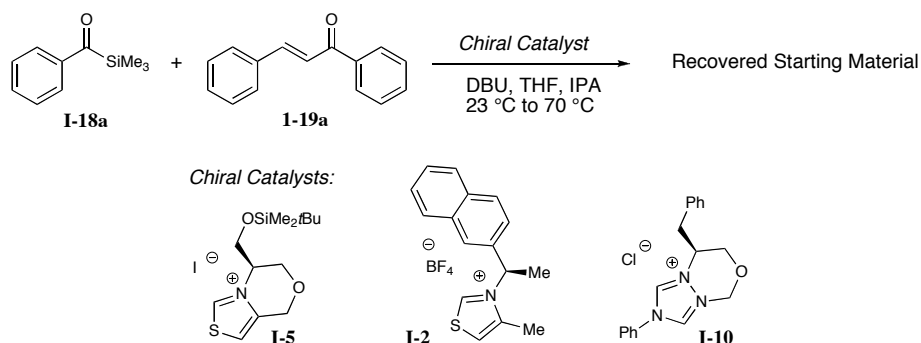
An additional aspect to consider with the enantioselective version is the ease of epimerization of the newly formed stereogenic center. Due to the nature of the reaction under development, this asymmetric carbon is always alpha to a carbonyl and thus even mildly harsh conditions (basic conditions and/or elevated temperatures) will likely cause the product to racemize. In light of this challenging aspect of direct asymmetric nucleophilic acylation reactions, we decided more mild reaction conditions for the acylsilane additions would be required in order for the process to occur with useful levels of enantioselectivity.

1.5 Thiazolium-Catalyzed Additions of Acylsilanes to N-Phosphinoyl Imines

1.5.1 Optimization of Acylsilane Additions to N-Phosphinoyl Imines

The successful conjugate additions from the previous study (vide supra) confirmed that NHCs promote carbonyl anion reactions of acylsilanes. After exploring different unsaturated ketones as electrophiles in these 1,4-additions, we turned our attention towards developing the related 1,2-addition manifold. Acylsilane additions to activated imines would enable the direct preparation of α-aminoketone products, valuable compounds in synthetic and medicinal chemistry.[75-77] While powerful methods exist to generate α-amino acids from imines, such as the Strecker reaction,[78-80] the options to directly synthesize protected α-aminoketones are limited. In a recent report, the process group at Merck Research Laboratories described the synthesis of α-amido ketones (**I-49**) using thiazolium salt derived catalysts to add aldehydes (**I-47**) to tosylamides (**I-48**) (Scheme 1-18).[81]

Scheme 1-18. Synthesis of α-amido ketones using thiazolium-catalysis

R¹= Aryl, Me,   R²= Aryl, H
BnOCH₂,   R³= H, CH₃, Aryl
PhCH=CH   OBn, O*t*Bu, cyclohexyl

yield: 58-98%
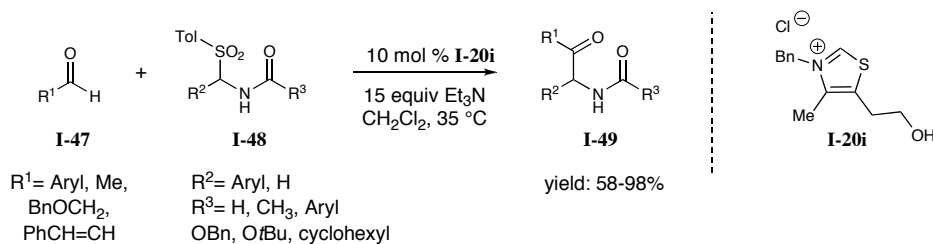
Table 1-6. Optimization of acylsilane additions to *N*-phosphinoyl imines

entry	Y	catalyst	solvent	alcohol	yield (%)
1	SO₂Ph	**I-20a**	THF	*i*-PrOH	N.R.
2	POPh₂	**I-20a**	THF	*i*-PrOH	69
3	POPh₂	**I-20a**	CH₂Cl₂	*i*-PrOH	41
4	POPh₂	**I-20a**	CHCl₃	*i*-PrOH	79
5	POPh₂	**I-20a**	CHCl₃	*t*-BuOH	74
6	POPh₂	**I-20c**	CHCl₃	*i*-PrOH	93

The optimal conditions were determined to be a similar to those developed for the 1,4-addition reactions. With chloroform as the solvent and isopropanol as an additive, the carbene derived from thiazolium salt **I-20c** and DBU provided an excellent yield of α-aminoketone **I-51** (93%, Table 1-6, entry 6). Notably, thiazolium **I-20c** provides significantly higher yields than **I-20a** (entry 4 vs. entry 6). Although the reason for this is not clear at this time, we have observed decomposition of **I-20a** while **I-20c** appears to be more stable under the reaction conditions.

The *N*-phosphinoyl imines were prepared by the condensation of the corresponding phosphoramide with an aldehyde in the presence of titanium tetrachloride.[82] It is important to

note that the phosphinoyl protecting group is crucial for success in these reactions. Other imines surveyed (*N*-benzyl , *N*-sulfinyl, *N*-sulfonyl) were unsuccessful in this process. For these nucleophile-catalyzed reactions, a careful balancing of reactivity must be present: the ultimate electrophile (conjugate acceptor or imine) must interact reversibly with the nucleophilic catalysts. The characteristics of *N*-phosphinoylimines in these acylsilane additions vs. other imines underscores this key design point for nucleophilic catalysis.

Table 1-7. Effect of acylsilane structure on addition to imines

entry	R^1	R^2	product		yield
1	Ph	Me		I-51	93%
2	4-ClPh	Me		I-52	90%
3	4-MePh	Me		I-53	81%
4	Me	Ph		I-54	87%
5	(CH$_2$)$_3$OBn	Ph		I-55	63%

1.5.2 Reaction Scope of Acylsilane Additions to N-Phosphinoyl Imines

We examined the scope of this 1,2 addition reaction with regard to acylsilane structure and imine substitution. The impact of acylsilane structure on the reaction was examined. Similar to the previous conjugate additions, this second reaction type accommodates both alkyl and aryl acylsilanes, producing high yields of product in all cases (Table 1-7). An acylsilane with a protected alcohol is a competent acyl anion precursor in the reactions (entry 5).

Various aromatic substituted *N*-phosphinoylimines were also examined as electrophiles in the acylsilane additions reactions (Table 1-8). Imines containing electron-withdrawing substituents on the aryl ring, such as 4-Cl and 2-Cl are suitable substrates generating high yields of the corresponding α-aminoketone products (entries 2 and 9). The imine derived from *p*-anisaldehyde produced an excellent yield of **I-61** (86%, entry 6). The reaction can also successfully incorporate heterocycles, such as thiophene, into the final product in high yield (80%, entry 10). The use of *N*-phosphinoyl imines derived from saturated aldehydes could not be investigated since the presence of an enolizable proton allows for a facile conversion to the more stable enamide tautomer and thus the imines could not be isolated. In an attempt to avoid this problem by generating only small concentrations of reactive imine during the reaction, Charette's method using sulfinic acid adducts of imines was employed (Scheme 1-19).[83] Unfortunately, no desired products were observed using the imine precursors.

Table 1-8. Examination of acylsilane additions to *N*-phosphinoyl imines

entry	R²	yield (%)	product
1	4-FPh	89	**I-56**
2	4-ClPh	85	**I-57**
3	4-BrPh	82	**I-58**
4	4-MePh	94	**I-59**
5	3-MePh	83	**I-60**
6	4-MeOPh	86	**I-61**
7	2-Napthal	80	**I-62**
8	3,4-DiClPh	67	**I-63**
9	2-ClPh	77	**I-64**
10	Thiophene	80	**I-65**

Scheme 1-19. Attempt to add acylsilane to alkyl imines generated in situ
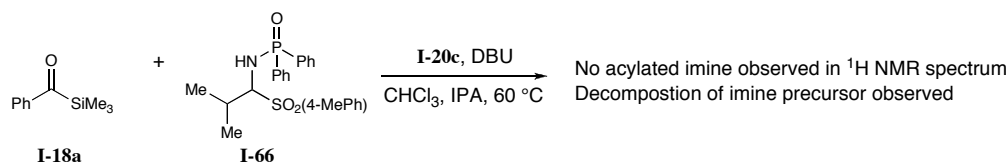
1.5.3   Utility of α-Amino Ketones

An attractive feature of this catalytic acyl anion process is the resulting protected amines can be easily manipulated (Scheme 1-20). For example, the exposure of **I-51** to acid followed by (Boc)₂O smoothly modulates the nitrogen protecting group. Additionally, treatment with a reducing agent (BH₃•DMS) produces the *trans*-1,2–amido alcohol **I-68** with high diastereoselectivity (15:1 dr) and yield (70%). The selectivity in this reaction may result from the hydride adding to a specific face of the carbonyl according to the potential transition state depicted in Scheme 1-20.

Scheme 1-20. Reduction and deprotection of α-aminoketone products
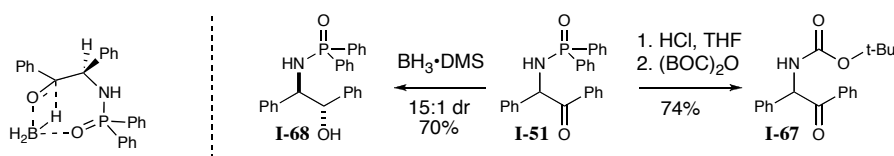
Scheme 1-21. Proposed reaction pathway
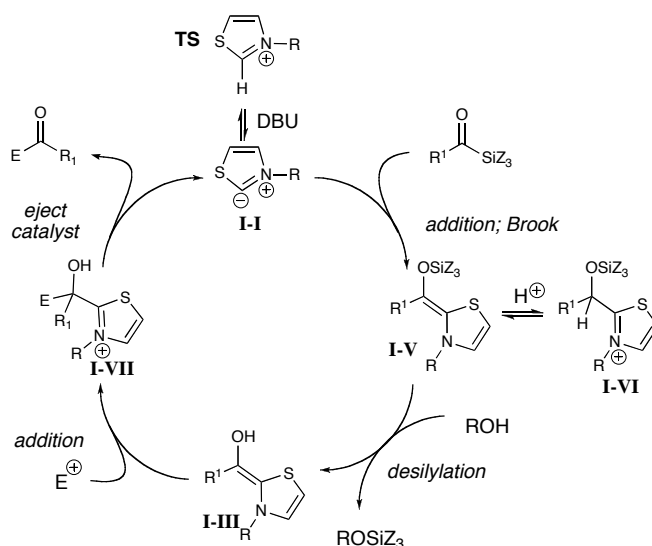
1.6 Investigation of Proposed Reaction Pathway
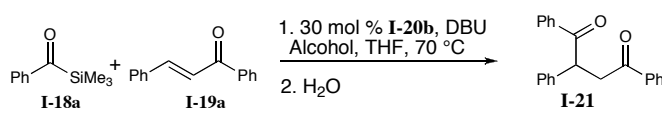
With successful development of 1,2 and 1,4 acylsilane addition reactions, we became interested in a deeper understanding of the mechanism of these NHC-catalyzed processes. We have advanced a plausible reaction pathway based on the mechanism proposed for the benzoin condensation (Scheme 1-21).[38,43,84-88] The deprotonation of the thiazolium salt (**TS**) yields the nucleophilic carbene catalyst. The addition of the NHC to an acylsilane generates a tetrahedral intermediate which undergoes a 1,2-silyl group migration from carbon to oxygen (1,2 Brook rearrangement). This thermodynamically driven migration produces acyl anion equivalent **I-V** (after electronic reorganization). The carbon with the silyloxy group appended is now

nucleophilic by virtue of the connecting enamine and is most likely in equilibrium with **I-VI** when in the presence of an available proton. All attempts to observe and/or isolate compounds such as **I-V** have been fruitless (vide infra). While the reactive characteristics of a species such as *O*-silyl heterocycle **I-V** remain uncertain, the geminal subsitution on the nucleophilic carbon **I-V** renders a nucleophilic addition energetically unfavorable due to steric hindrance. Instead, it is plausible that a desilylation of **I-V** occurs in the presence of DBU and an alcohol (such as isopropanol) to yield **I-III**, a less encumbered acyl anion equivalent able to undergo additions reactions with greater facility. Enol/enamine structures similar to **I-III** were first invoked as the carbonyl anion nucleophile in the seminal work on the mechanism of the benzoin reaction by Breslow and thus termed "Breslow intermediates." The nucleophilic addition of **I-III** to the electrophile forms the key carbon-carbon bond that is followed by collapse of a second tetrahedral intermediate to the carbonyl to regenerate the thiazolium catalyst and produce the acylated product.

In order to gain an improved understanding of the addition reactions described above, we investigated the role of the alcohol in the reaction as well as carried out a synthesis and investigation of potential intermediate **I-VI**. We were initially puzzled by the observation that when thiazolium salts such as **I-20b** lacking a hydroxyl group afforded *no* product without isopropanol. However, after determining that a full equivalent of a hydroxyl group must be present on the thiazolium or as an additive for the reaction to proceed to 100% conversion, we concluded that the alcohol is involved in the generation of the carbonyl anion and not catalyst turnover. Isopropanol had been the alcohol of choice; however a more thorough investigation revealed that the alcohol structure had only a moderate effect on the yield (Table 1-9). A survey of various alcohol additives for the process indicates that the reaction is highly tolerant of

alcohol structure and acidity in terms of conversion and length of reaction. The substitution of

the alcohol (1°, 2° or 3°) does not significantly affect the overall process (entries 1, 2, and 3). In

fact, the reaction is slightly better over 17 hours with *t*-butyl alcohol. Surprisingly, the acidity of

the hydroxyl moiety does not seem to perturb the outcome of the reaction either. The presence

of acidic protons in the reaction system has the potential to protonate the reactive intermediates;

however, this does not seem to be a problem because the yields remain high despite the pKa.

The gas chromatography yield of the reaction using phenol (pKa[DMSO] = 18) as the additive

(81%) is not much different than when *t*-butyl alcohol is employed (pKa[DMSO] = 29, GC yield

= 99%). Although mildly controversial, the acidity (pKa) value of thiazolium salts has been

reported to be approximately 16 (DMSO). From these data and in accordance with the

observations from our reaction, it is evident that DBU (pKa[DMSO] = 12) in the reaction should

favor the generation of the thiazolium carbene (zwitterions) rather than deprotonation of the

alcohol additive.

Table 1-9. Effect of alcohol on acylsilane additions to chalcone

entry	alcohol	pKa (DMSO)	yield(%)
1	EtOH	28	56
2	*i*-PrOH	29	85
3	*t*-BuOH	29	99
4	(CF$_3$)$_2$CHOH	18	70
5	Phenol	18	81

Based on experiments monitored by GC, the alcohol additive is acting as a silyl acceptor.

This was accomplished by employing 3-octanol (R_t = 3.3 min) as the additive and monitoring the

formation of 3-(trimethylsilyloxy)octane (R_t = 3.9 min) by gas chromatography during the

reaction (Figure 1-4). The peak at 3.9 min in the reaction spectrum clearly corresponds to the

retention time of an authentic sample of 3-(trimethylsilyloxy)octane. The starting material

chalcone (R_t = 8.4 min) and product **I-18** (R_t = 10.9 min) are also observed. These data support

the hypothesis that the alcohol additive promotes desilylation of **I-V**: enolsilanes are known to be

mild silylating agents while silyl ethers (such as *O*-silylated versions of **I-VII)** are less prone to

donate a silyl group.[89-91] However, this observation does not confirm that intermediates such as

I-V undergo desilylation since silyl group transfer after addition of **I-V** to an electrophile cannot

be ruled out at this time. The elusive nature of compounds such as **I-V** (vide infra) has made the

delineation of the exact role of the alcohol additive inconclusive.
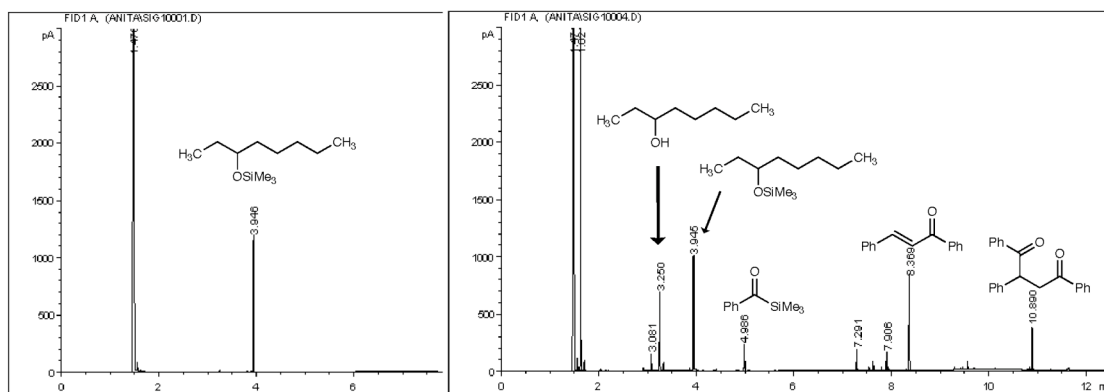
Figure 1-6. Gas chromatography traces of 3-trimethylsilyoxy-octane (left) and a catalytic sila-Stetter reaction (right) with chalcone and benzoyltrimethylsilane with 3-octanol as the alcohol additive (4 equiv).

To further probe the mechanism of these acylsilane additions, we attempted to synthesize

a silylated "Breslow intermediate" with a structure similar to **I-V** in our proposed reaction

pathway. Access to compounds like **I-V** would allow us to assess their ability to undergo

addition reactions with or without an alcohol present. This species is invoked in our reaction

pathway and could be produced in a manner very similar to the first steps in the proposed catalytic cycles of the benzoin condensation and Stetter reaction. In these *Umpolung* processes, the addition of a thiazolium-derived catalyst to the aldehyde followed by an intermolecular proton transfer to generate the acyl anion equivalent occurs. We suspected that a similar sequence is occurring in our addition reactions in which the interaction of a thiazolium carbene/zwitterion with acylsilane generates intermediate **I-V**. To probe whether **I-V** was involved as an intermediate in the reaction, an independent synthesis was required. This was attempted by lithiation of 4,5-dimethylthiazole at the 2-position using *n*-butyllithium then reacting with an aldehyde (Scheme 1-22).[92] The resulting carbinol was purified by simple recrystallization (ethyl acetate/hexanes) then protected with a trimethylsilyl group (TMS) in the presence of triethylamine. Finally, the thiazolium salt was prepared by straightforward alkylation with neat iodomethane at 80 °C. Confirmation of the synthesis of desired intermediate **I-VI** was obtained by ^{1}H and ^{13}C NMR spectroscopy. We anticipated that intermediate **I-V** could be generated by deprotonation of the protected thiazolium carbinol **I-VI**. Unfortunately, upon addition of base (DBU, Et$_3$N, *i*Pr$_2$EtN, KHMDS) to the thiazolium carbinol only decomposition was observed by thin layer chromatography or ^{1}H NMR spectroscopy. However, due to the nature of the acylsilane addition reactions we speculated thiazolium salt **I-VI** may be an intermediate in the process. As depicted in Scheme 1-21, this thiazolium salt (**I-VI**) could be in equilibrium with **I-V** and this pathway would provide a different entry into the catalytic cycle.

Scheme 1-22. Attempted synthesis of proposed intermediate **I-V**
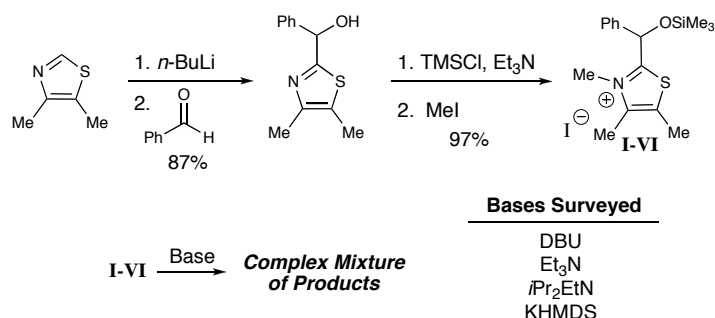
To probe this possibility, thiazolium carbinol **I-VI** was employed in two separate reactions, with chalcone (**I-19a**) and *N*-phosphinoylimine **I-50a** using previously established reaction conditions (Scheme 1-23). In both cases, *the desired product was observed in good yield at 23 °C lending support to the hypothesis that **I-VI** is an intermediate in these addition reactions.* Interestingly, the reactions readily occurred at 23 °C, as opposed to the standard 70 °C. In a second set of experiments, the thiazolium carbinol was added to the reaction in place of the NHC precursor (Scheme 1-24). Gratifyingly, both reactions generated the desired products in good yield providing additional evidence for intermediate **I-VI** participating in the reaction.

Scheme 1-23. Examination of **I-VI** in addition reactions
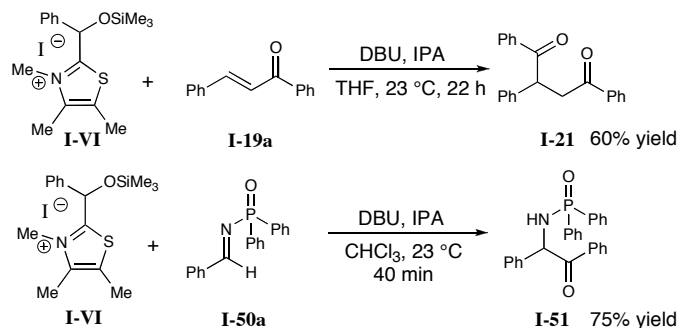
Scheme 1-24. Examination of **I-VI** in addition reactions
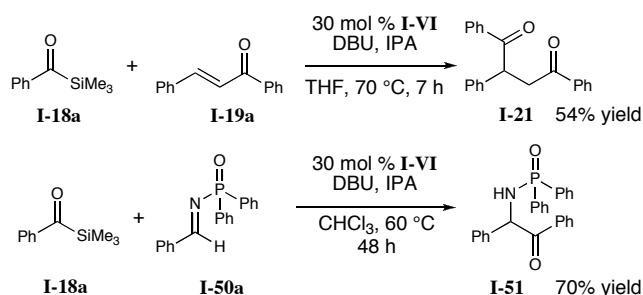
1.7   *Summary*

A new strategy has been developed to generate carbonyl anion equivalents from acylsilanes. We have demonstrated that in the presence of an alcohol additive, neutral NHCs generated in situ from commercially available thiazolium salts successfully catalyze the addition of acylsilanes to α,β-unsaturated systems and *N*-phosphinoylimines. In these processes, the corresponding 1,4-diketones and α-aminoketones are prepared in good to excellent yields. Benzoin side product formation is not observed in these processes, strongly indicating that the acyl anion equivalent does not add to the acylsilane, the acyl anion precursor. To probe the mechanism of these new bond-forming reactions, a protected thiazolium carbinol, a proposed reaction intermediate was independently synthesized and examined under a variety of conditions. The expected products are observed in all cases when this potential intermediate is subjected to a variety of reaction conditions providing substantial evidence for the proposed reaction pathway. Finally, an investigation of the alcohol additive revealed that it is necessary for successful generation of carbonyl anions with acylsilanes and thiazolium salts and also plays the role of the final silyl group acceptor. This new NHC-catalyzed method is a powerful addition to *Umpolung* strategies involving acyl anions since it utilizes neutral carbenes as catalysts, minimizes side

product formation, and enables the use of new electrophiles to produce valuable organic compounds.

1.8 Experimental Section

General Information. All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. THF, Et$_2$O, CH$_2$Cl$_2$, DMF and toluene were purified by passage through a bed of activated alumina. Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[93] Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and anisaldehyde, ceric ammonium nitrate stain, potassium permangenate, or phosphomolybic acid followed by heating. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) or Mercury 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 7.26 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 Varian Inova 500 (125 MHz) or Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 77.0 ppm). Mass spectra data were obtained on a Varian 1200 Quadrupole Mass Spectrometer. α,β-Unsaturated ketones were prepared according to the general procedure of Murphy and Wattansin.[94]

1.8.1 Preparation of Acylsilanes

Benzoyltrimethylsilane **(I-18a)**, *p*-chlorobenzoyltrimethylsilane **(I-18b)**, and *p*-toluoyltrimethylsilane **(I-18c)** were prepared according to the procedure of Yamamoto and

coworkers.[73] Alkylacylsilanes (**I-18e** and **I-18f**) were prepared according to the procedure of

Scheidt et al.[74] and benzoyldimethylphenylsilane (**I-18d**) was prepared using the procedure

developed by Fleming and coworkers.[95]

Typical Procedure for the Synthesis of Aryl Acylsilanes:

A dry 50 mL round bottom flask containing a magnetic stir bar was charged with allyl palladium

chloride (500 mg, 2.74 mmoles) in a nitrogen-filled glove box. The flask was fitted with septa,

removed from box and put under a positive pressure of nitrogen. Next, triethylphosphite (0.94

mL, 5.48 mmoles) was added then hexamethyldisilane (11.8 mL, 58.6 mmoles). The resulting

yellow suspension was stirred from 5 min. Last, distilled benzoyl chloride (6.3 mL, 54.3

mmoles) was added. The flask was fitted with a condenser and the reaction was heated to 110

°C and stirred overnight. The reaction was monitored by gas chromatography for consumption

of benzoyl chloride. This reaction must go to completion or purification is extremely difficult.

After all acid chloride had been consumed (20 h) the reaction was cooled to 23 °C. The crude

reaction mixture was then immediately subject to purification of silica gel using 1% to 4%

ether/hexanes as eluent. The fractions containing the product (a bright yellow oil) were

combined and concentrated. Last, bulb to bulb distillation afforded the desired product as a

yellow oil (5.3g, 55%).

1.8.2 NHC-Catalyzed Acylsilane Additions to α,β-Unsaturated Systems

1.8.2.1 General Procedure for Thiazolium-Catalyzed Acylsilane Additions

A screw-capped test tube was charged with the thiazolium salt (30 mg, 0.119 mmol) in a

nitrogen-filled drybox. The test tube was removed from the box and placed under a positive

pressure of nitrogen. Benzoyltrimethylsilane (140 mg, 0.768 mmol) in THF (0.25 mL) was

added by syringe to the test tube followed by the addition of DBU (17 μL, 0.119 mmol).   The

reaction mixture was heated to 70 °C after which the chalcone (0.384 mmol) in THF (0.25 mL)

was added by syringe followed by the addition of isopropanol (120 μL, 1.56 mmol).   The

reaction was allowed to stir at 70   °C for 24 hours.   Upon completion by thin layer

chromatrography (40% ether/hexanes), the reaction was cooled to room temperature, diluted

with ethyl acetate (20 mL) and washed with water (20 mL). The aqueous layer was washed with

ethyl acetate (3x30 mL) and the combined organic extracts were dried over sodium sulfate,

filtered, and concentrated *in vacuo*.   The resulting residue was purified by flash column

chromatography on silica gel.

1.8.2.2   1,4-Diketone Characterization
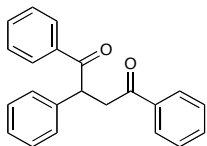
1,2,4-Triphenylbutane-1,4-dione (I-21):   Purified with 10% ether/hexanes,

yielding 93 mg (77%) of **I-21** as a colorless oil. R_f = 0.50 (40/60

ether/hexanes); IR (film) 3054, 2986, 1681, 1598 cm^{-1}; ^{1}H NMR (500 MHz,

CDCl$_3$) δ 8.06-7.98 (m, 4H); 7.58-7.54 (m, 1H); 7.49-7.39 (m, 6H); 7.37-7.32 (m, 2H); 7.26-

7.22 (m, 1H); 5.34 (dd, J = 10.1, 3.5 Hz, 1H); 4.23 (dd, J = 17.9, 10.1 Hz, 1H); 3.32 (dd, J =

17.9, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.0, 198.2, 138.8, 136.6, 133.5, 133.1,

129.4, 129.1, 128.8, 128.7, 128.4, 128.4, 127.6, 48.9, 44.2; LRMS (electrospray): Mass

calculated for C$_{22}$H$_{18}$O$_2$Na [M+Na]$^+$, 337.1. Found 337.0.   All spectral data are similar to

Henrick and coworkers.[96]
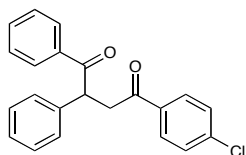
4-(4-chlorophenyl)-1-2-diphenylbutane-1-4-dione (I-27): Purified with 10% ether/hexanes yielding 77 mg (82%) of **I-27** as a clear oil. R_f = 0.44 (40/60 ether/hexanes); IR (film): 3060, 2932, 1679, 1590, 1492 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.15-8.13 (m, 4H), 7.74-7.41 (m, 10H), 5.42 (dd, J=9.8, 3.3 Hz, 1H), 4.20 (dd, J = 18.1, 4.0 Hz, 1H), 3.47 (dd, J = 18.0, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.0, 197.2, 139.9, 138.7, 136.6, 135.1, 133.2, 129.8, 129.5, 129.2, 128.8, 128.5, 127.7, 49.0, 44.1; Mass calculated for C$_{22}$H$_{17}$ClO$_2$Na [M+Na]$^+$, 371.1. Found 371.0.
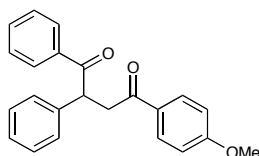
4-(4-methoxyphenyl)-1,2-diphenylbutane-1-4-dione (I-28): Purified with 15 ether/hexanes yielding 75 mg (79%) of **I-28** as yellow crystals. R_f = 0.35 (40/60 ether/hexanes); IR (film): 3061, 2917, 1680, 1588, 1570 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.18-8.12 (m, 4H), 7.70-7.41 (m, 8H), 6.99 (d, J = 8.7, 2H), 5.44 (dd, J = 9.9, 3.67, 1H), 4.33 (dd, J = 18.1, 9.9, 1H), 3.90 (s, 3H), 3.39 (dd, J = 17.9, 3.7, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.4, 198.5, 159.1, 136.8, 133.5, 133.1, 130.8, 129.6, 129.2, 128.8, 128.7, 128.4, 117.1, 55.5, 48.1, 44.2. All spectral data match those reported by Horspool and Khalaf.[97]
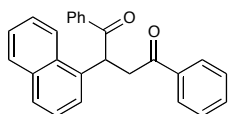
2-(Naphthalene-4-yl)-1,4-diphenylbutane-1,4-dione (I-29): Purified with 10% ether/hexanes yielding 101 mg (72%) of **I-29** as a white solid. R_f = 0.40 (40/60 ether/hexanes); IR (film): 3059, 1681, 1598 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.34-8.33 (m, 1H); 8.00-7.92 (m, 5H); 7.78-7.76 (m, 1H); 7.67-7.64 (m, 1H); 7.59-7.54 (m, 2H); 7.46-7.41 (m, 3H); 7.37-7.28 (m, 4H); 6.12 (dd, J = 10.4, 2.0 Hz, 1H); 4.30 (dd, J = 18.1, 10.6 Hz, 1H);

3.28 (dd, J = 18.1, 2.3 Hz, 1H); ^{13}C NMR (125 MHz CDCl$_3$) δ 199.4, 198.4, 136.7, 136.5, 135.3, 134.7, 133.5, 133.1, 130.8, 129.6, 129.0, 128.8, 128.7, 128.5, 128.3, 127.3, 126.3, 126.0, 122.7, 44.5, 43.0; LRMS (electrospray): Mass calculated for C$_{26}$H$_{20}$O$_2$Na [M+Na]$^+$, 387.2. Found 387.0.
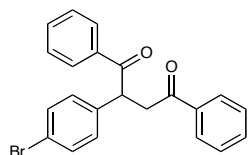
2-(4-Bromophenyl)-1,4-diphenylbutane-1,4-dione (I-30): Purified with 10% ether/hexanes, yielding 100 mg (66%) of **I-30** as a colorless oil. R$_f$ = 0.50 (40/60 ether/hexanes); IR (film) 3060, 2922, 1681, 1596 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.02-7.97 (m, 4H); 7.58-7.50 (m, 2H); 7.47-7.40 (m, 4H); 7.32-7.27 (m, 4H); 5.32 (dd, J = 9.7, 4.0 Hz, 1H); 4.17 (dd, J = 18.1, 9.7 Hz, 1H); 3.31 (dd, J = 18,1, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ198.9, 198.0, 137.3, 136.5, 136.4, 133.6, 133.6, 133.4, 129.8, 129.6, 129.1, 128.9, 128.8, 128.4, 48.2, 43.9. LRMS (electrospray): Mass calculated for C$_{22}$H$_{17}$BrO$_2$Na [M+Na]$^+$, 415.0. Found 416.8.
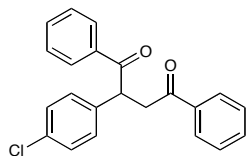
2-(4-Chlorophenyl)-1,4-diphenylbutane-1,4-dione (I-31): Purified with 10% ether/hexanes yielding 99 mg (74%) of **I-31** as a white solid. R$_f$ = 0.50 (40/60 ether/hexanes); IR (film): 3054, 2986, 1682, 1597 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04-7.97 (m, 4H), 7.58-7.55 (m, 1H), 7.53-7.50 (m, 1H), 7.47-7.40 (m, 4H), 7.32-7.27 (m, 4H), 5.32 (dd, J = 9.9, 3.8 Hz, 1H), 4.17 (dd, J = 17.9, 9.9 Hz, 1H), 3.31 (dd, J = 17.9, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.8, 197.9, 137.3, 136.5, 136.4, 133.6, 133.5, 133.3, 129.8, 129.6, 129.1, 128.8, 128.4, 48.2, 44.0; LRMS (electrospray): Mass calculated for C$_{22}$H$_{17}$ClO$_2$Na [M+Na]$^+$, 371.1. Found 371.0.
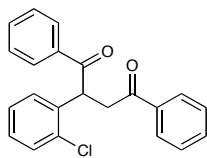
2-(2-Chlorophenyl)-1,4-diphenylbutane-1,4-dione (I-32): Purified with 10% ether/hexanes yielding 66 mg (68%) of **I-32** as a colorless oil. R = 0.48 (40/60 ether/hexanes); IR (film) 3054, 1681, 1597 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.02-8.00 (m, 4H), 7.59-7.39 (m, 7H), 7.22-7.16 (m, 3H), 5.79 (dd, J = 10.9, 4.0 Hz, 1H), 4.10 (dd, J = 17.7, 10 Hz, 1H), 3.23 (dd, J = 17.7, 3.7 Hz, 1H) ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.8, 197.8, 136.6, 136.3, 133.5, 133.4, 130.5, 129.3, 129.1, 128.9, 128.8, 128.8, 128.4, 127.8, 45.1, 42.5; LRMS (electrospray): Mass calculated for C$_{22}$H$_{17}$ClO$_2$Na [M+Na]$^+$ 371.1. Found 372.0.
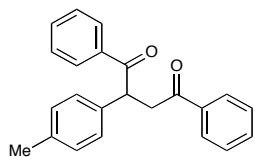
(2-(4-Methylphenyl)-1,4-diphenylbutane-1-4-dione (I-33): Purified with 10% ether/ hexanes yielding 118 mg (84%) of **I-33** as a white solid. R$_f$= 0.47 (40/60 ether hexanes); IR (film) 3054, 1681, 1597 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05-7.99 (m, 4H), 7.56 –7.27 (m, 8H), 7.14-7.12 (m, 2H), 5.32 (dd, J = 10.1, 3.5 Hz, 1H), 4.24 (dd, J = 18.0, 3.6) 3.31 (dd, J = 18.0, 3.5 Hz), 2.30 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.3, 198.4, 137.3, 136.7, 135.8, 133.5, 133.1, 130.5, 129.2, 128.8, 128.7, 128.4, 128.3, 48.5, 44.1, 21.3; LRMS (electrospray): Mass calculated for C$_{23}$H$_{20}$O$_2$Na [M+Na]$^+$ 351.1. Found 351.0. All spectral data match those reported by Nagarajan and Shechter.[98]
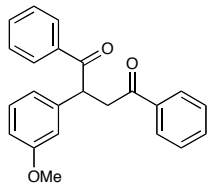
2-(3-Methoxyphenyl)-1,4-diphenylbutane-1,4-dione (I-34): Purified with 15% ether/hexanes yielding 99 mg (75%) of **I-34** as a yellow oil. R$_f$ = 0.38 (40/60 ether/hexanes); IR (film) 2922, 1680, 1597, 1485 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.41-8.35 (m, 4H), 7.92-7.31 (m, 8H), 7.15 (m, 1H), 7.13 (m, 1H), 5.66 (dd, J = 10.3, 3.1 Hz, 1H), 4.57 (dd, J = 17.9, 9.5 Hz, 1H), 4.14 (s, 3H), 3.66 (dd, J = 17.9, 3.7 Hz, 1H);

^{13}C NMR (125 MHz, CDCl$_3$) δ 198.9, 198.3, 160.3, 140.4, 136.7, 133.5, 130.5, 129.2, 128.8, 128.7, 126.4, 114.1, 112.9, 55.5, 48.9, 44.1; LRMS (electrospray): Mass calculated for C$_{23}$H$_{20}$O$_3$Na [M+Na]$^+$ 367.1. Found 367.0.
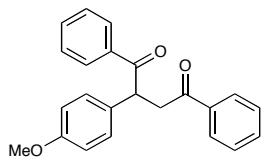
2-(4-Methoxyphenyl)-1,4-diphenylbutane-1,4-dione (I-35): Purified with 15% ether hexanes yielding 102 mg (77%) of **I-35** as a yellow solid. R$_f$ = 0.35 (40/60 ether/hexanes); IR (film) 1678, 1596 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.01-7.99 (m, 4H), 7.53-7.35 (m, 8H), 7.24 (m, 2H), 5.27 (dd, J = 10.0, 4.0 Hz, 1H), 4.17 (dd, J = 18.0, 9.7 Hz, 1H), 3.72 (s, 3H), 3.25 (dd, J = 18.3, 3.6, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.4, 198.5, 159.1, 136.8, 133.5, 133.1, 130.8, 129.6, 129.2, 128.8, 128.4, 127.8, 114.9, 55.5, 48.1, 44.1; LRMS (electrospray): Mass calculated for C$_{23}$H$_{20}$O$_3$Na [M+Na]$^+$ 367.1. Found 367.0. All other spectral data match those reported by Nagarajan and Shechter.[98]
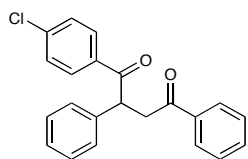
1-(4-chlorophenyl)-2-4-diphenylbutane-1,4-dione (I-37): Purified with 10% ether/hexanes yielding 67 mg (82%) of **I-37** as a clear oil. R$_f$ = 0.48 (40/60 ether/hexanes); IR (film): 3061, 2930, 1680, 1588 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97-7.93 (m, 4H), 7.55 (m, 2H), 7.47-7.25 (m, 8H), 5.25(dd, J = 10.4, 3.7 Hz, 1H), 4.23 (dd, J = 18.3, 10.4 Hz, 1H), 3.30 (dd, J = 17.7, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.3, 198.0, 139.6, 138.5, 136.5, 135.0, 133.6, 130.6, 129.6, 129.1, 128.9, 128.4, 127.8, 49.0, 44.1; LRMS (electrospray): Mass calculated for C$_{22}$H$_{17}$ClO$_2$Na [M+Na]$^+$, 371.1. Found 371.0. All spectral data match those reported by Stetter and Schreckenberg.[99]
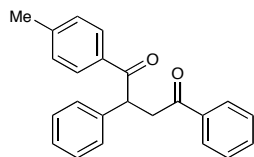
2,4-diphenyl-1-*p*-tolylbutane-1,4-dione (I-38): Purified with 10% ether/hexanes yielding 84 mg (70 %) of **I-38** as a white solid. R_f = 0.42 (40/60 ether/hexanes); IR (film): 2927, 1678, 1596, 1511 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.15-8.08 (m, 4H), 7.66-7.22 (m, 10H), 5.41 (dd, J = 9.9, 3.6 Hz, 1H), 4.29 (dd, J = 17.9, 9.9 Hz, 1H), 3.39 (dd, J = 17.9, 3.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.3, 198.4, 137.4, 136.7, 135.8, 133.5, 133.1, 130.2, 129.2, 128.8, 128.7, 128.4, 128.3, 48.6, 44.2, 21.3; All spectral data match those reported by Zdrojweski and Jonczyk.[100]
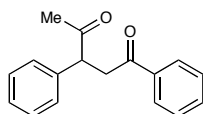
1,3-Diphenylpentane-1,4-dione (I-39): Purified with 10% ether/hexanes yielding 49 mg (70%) of **I-39** as a pale yellow oil. R_f = 0.42 (40/60 ether/hexanes); IR (film): 3060, 3028, 2918, 1716, 1684 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97-7.95 (m, 2H); 7.58-7.52 (m, 1H); 7.55-7.42 (m, 2H); 7.37-7.34 (m, 2H); 7.30-7.29 (m, 3H); 4.45-4.42 (dd, J = 10.1, 3.7 Hz, 1H); 4.05-3.99 (dd, J = 17.9, 10.1 Hz, 1H); 3.16-3.12 (dd, J = 17.9, 3.7 Hz, 1H); 2.22 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 207.47, 198.4, 138.2, 136.7, 133.5, 129.4, 128.8, 128.6, 128.3, 127.9, 54.1, 42.5, 29.4; LRMS (electrospray): Mass calculated for C$_{17}$H$_{16}$O$_2$Na [M+Na]$^+$, 272.3. Found 275.0. All spectral data match those reported by Hegedus and Perry.[101]
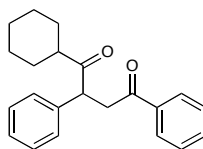
1-Cyclohexyl-2-4-diphenyl-1-4-dione (I-40): Purified with 10% ether/hexanes yielding 40 mg (63 %) of **I-40** as a clear oil. R_f = 0.48 (40/60 ether/hexanes); IR (film): 3059, 2929, 1721, 1664, 1605, 1576 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06-7.97 (m, 4H), 7.68-7.29 (m, 6H), 4.60 (dd, J = 10.1, 2.9 Hz, 1H), 4.01 (dd, J = 19.8, 10.4 Hz, 1H), 3.09 (dd, J = 17.9, 3.11 Hz, 1H), 2.53 (m, 1H), 2.15 (m, 1H), 1.81 –

1.09 (m, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 212.5, 198.5, 138.5, 133.4, 130.8, 129.3, 129.2, 128.9, 128.4, 127.6, 52.0, 50.8, 43.0, 29.7, 28.6, 26.2, 26.1;   All spectral data match those reported by Yus and coworkers.[102]
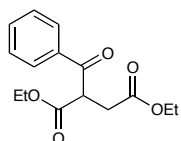
Diethyl 2-benzoylsuccinate (I-41): Purified with 10% ether/hexanes yielding 50 mg (65%) of **I-41** as a pale yellow oil. R_f = 0.35 (40/60 ether/hexanes); IR (film) 3057, 2985, 1735, 1688, 1598 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.07-8.06 (m, 2H), 7.64-7.61 (m, 1H), 7.53-7.50 (m, 2H); 4.89 (dd, J = 7.3, 7.3 Hz, 1H), 4.16 (m, J = 7.0 Hz, 4H), 3.12 (dd, J = 17.4, 7.7 Hz, 1H), 3.04 (dd, J = 17.4, 6.6 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.5, 171.5, 169.0, 136.2, 133.9, 129.1, 129.0, 62.1, 61.3, 49.9, 33.5, 14.3, 14.2; LRMS (electrospray): Mass calculated for C$_{15}$H$_{18}$O$_5$Na [M+Na]$^+$ 301.1. Found 301.0. All spectral data match those reported by Saigo and coworkers.[103]
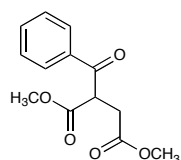
Dimethyl 2-benzoylsuccinate (I-42): Purified with 15% ethyl acetate/ hexanes yielding 50 mg (72%) of **I-42** as a clear oil. R_f = 0.35 (50/50 ethyl acetate/hexanes); IR (film): 3002, 2945, 1738, 1684, 1596, 1581 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04 (d, J = 7.7 Hz, 2H), 7.62-7.52 (m, 3H), 4.91(dd, J = 7.3, 7.3 Hz, 1H), 3.69 (s, 6H), 3.12 (dd, J = 8.8, 7.7 Hz, 1H), 3.10 (dd, J = 8.8, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.3, 171.9, 169.4, 136.1, 134.0, 129.2, 129.0, 53.1, 52.4, 49.5, 33.3; LRMS (electrospray): Mass calculated for C$_{13}$H$_{14}$O$_5$Na [M+Na]$^+$, 273.1. Found 272.9. All spectral data match those reported by Kawenoki and co-workers.[104]
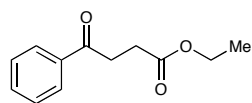
Ethyl 4-oxo-4-phenylbutanoate (I-43): Purified with 10% ethyl acetate/hexanes yielding 40 mg (72%) of **I-43** as a clear oil. R_f =0.32; IR: 2951, 1732, 1595, 1447 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.00-7.98 (m, 2H), 7.58-7.45 (m, 3H), 4.14 (q, J = 6.7, 2H), 3.33 (t, J = 6.7, 2H), 2.75 (t, J = 6.1, 2H), 1.27 (t, J = 6.7, 3H); ^{13}C (125 MHz, CDCl$_3$) δ 198.4, 172.5, 135.3, 133.0, 128.9, 128.0, 61.5, 33.3, 28.1, 13.8. All spectral data match those reported by Rieke and coworkers.[105]
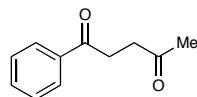
1-Phenylpentane-1,4-dione (I-44): Purified with 15% ethyl acetate/hexanes yielding 36 mg (75%) of **I-44** as a yellow oil. R_f = 0.35 (50/50 ethyl acetate/hexanes); IR (film) 2975, 2931, 1716, 1685; 1H (500 MHz, CDCl3) δ 8.00 (d, J = 7.3, 2H), 7.50-7.47 (m, 3H), 3.31 (t, J = 6.6, 2H), 2.92 (t, J = 6.4, 2H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 207.6, 198.8, 136.9, 133.4, 128.8, 128.3, 37.3, 32.7, 30.4; All spectral data match those reported by Shibata and coworkers.[106]
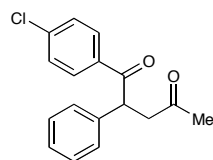
1-(4-chlorophenyl)-2-phenylpentane-1,4-dione (I-45): Purified using a gradient starting with 5% ether/hexanes yielding 55 mg (40%) of **I-45** as a yellow oil. R_f = 0.27 (40% ether/hexanes); IR (film) 3062, 2920, 1715, 1588 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93-7.92 (m, 2H), 7.38-7.25 (m, 7H), 5.07 (dd, J = 9.8, 3.7 Hz, 1H), 3.60 (dd, J = 18.3, 9.8 Hz, 1H), 2.75 (dd, J = 18.3, 3.7 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 207.0, 198.3, 139.6, 138.4, 134.8, 130.6, 129.6, 129.1, 128.5, 128.3, 128.0, 127.7, 49.05, 48.3, 30.2. All spectral data match that of Stetter and Schreckenberg.[99]

1.8.2.3   Investigation of Alcohol Additive

An authentic sample of 3-trimethylsilyloxy-octane was prepared by combining 3-octanol (1 mL, 6.29 mmol), trimethylsilyl chloride (2.4 mL, 18.9 mmol), and triethylamine (2.6 mL, 18.9 mmol) in CH_2Cl_2 (16 mL) and stirring at room temperature for 24 hours. Upon completion, the reaction mixture was diluted with pentane, washed with water (30 mL) and saturated $CuSO_4$ (3 x 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. A retention time (3.95 min) was collected on an Agilent Technologies 6890N gas chromatograph (equipped with Agilent 19091J-413 HP-5 5% phenylmethylsiloxane capillary column- 30.0 m x 320 μm x 0.25 μm nominal) using the following conditions: 70 °C for 1 min then a ramp of 25 °C/min to 285 °C with 3 minute hold.

A screw-capped test tube was charged with 3-benzyl-4,5-dimethylthiazolium bromide (51 mg, 0.183 mmol) in a nitrogen filled glove box. The test tube was removed from box and put under a positive pressure of nitrogen. Benzoyltrimethylsilane (50 mg, 0.274 mmol) in THF (0.25 mL) was added by syringe to the test tube followed by the addition of DBU (27 μL, 0.183 mmol). The reaction mixture was heated to 70 °C after which the chalcone (0.183 mmol) in THF (0.25 mL) was added by syringe followed by the addition of 3-octanol (50 μL, 0.314 mmol). The reaction was allowed to stir at 70 °C for 4 hours. At this time an aliquot was filtered through glass wool and analyzed by GC (see above for details). The following retention times were observed: 3.25 min (3-octanol), 3.95 min (3-trimethylsilyloxy-octane), 4.99 min (benzoyltrimethylsilane), 8.37 min (chalcone), 10.89 min (1,2,4-triphenylbutane-1,4-dione).

1.8.3   NHC-Catalyzed Acysilane Additions to N-Phosphinoyl Imines

N-Phosphinoyl imines were prepared according to the previously published procedure of Jennings and Lovely.[82]   A screw-capped tube was charged with the thiazolium salt (20 mg, 0.08 mmol) in a nitrogen-filled dry box. The tube was removed from the box and placed under a positive pressure of nitrogen. Benzoyltrimethylsilane (84 mg, 0.47 mmol) in $CHCl_3$ (0.25 mL) was added by syringe followed by the addition of DBU (12 μL, 0.08 mmol).   The reaction mixture was heated to 60 °C after which the phosphinoyl imine (0.26 mmol) in $CHCl_3$ (0.25 mL) was added by syringe followed by the addition of isopropanol (80 μL, 1.05 mmol). The reaction was allowed to stir at 60 °C for 24 hours. Upon completion by HPLC the reaction was cooled to room temperature, diluted with methylene chloride (20 mL) and washed with water (20 mL). The aqueous layer was washed with methylene chloride (3x30 mL) and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*.   The resulting residue was purified by flash column chromatography on silica gel.

1.8.3.1   Characterization of α-Amino Ketones
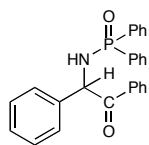
2-(Diphenylphosphinamide)-1,2-diphenylethanone (I-51): Purified   with   1% methanol/ethyl acetate, yielding 100 mg (93%) of **I-51** as a white foam. $R_f = 0.69$ (100% ethyl acetate); Mp: 135.5-136 °C; IR (film) 3184, 3057, 1682, 1200 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86-7.81 (m, 4H); 7.69-7.65 (m, 2H); 7.47-7.39 (m, 4H); 7.33-7.30 (M, 4H); 7.15 (bs, 5H); 5.96 (dd, *J* = 8.9, 8.9 Hz, 1H); 4.96 (dd, *J* = 7.9, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 138.9, 134.4, 133.8, 133.5, 132.7, 132.7, 132.5, 132.2, 131.9, 131.8, 131.7, 129.4, 129.2, 128.9, 128.8, 128.8, 128.4, 128.3, 128.2, 128.2, 59.4; LRMS (MALDI-TOF): Mass calculated for $C_{26}H_{23}NO_2P$ $[M+H]^+$, 412.1. Found 412.2.
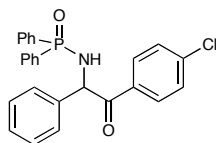
1-(4-Chlorophenyl)-2-(diphenylphosphinamide)-2-phenylethanone (I-52):

Purified with 1% methanol/ethyl acetate, yielding 105 mg (90%) of **I-52** as a

white foam. R_f = 0.74 (100% ethyl acetate); Mp: 150-151 °C; IR (film) 3170,

3057, 1685, 1200 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84-7.82 (m, 3H); 7.80-7.65 (m, 2H);

7.48-7.40 (m, 3H); 7.39-7.29 (m, 3H); 7.16-7.14 (m, 4H); 5.91 (dd, J = 8.6, 8.6 Hz, 1H); 4.91

(dd, J = 8.1, 8.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.6, 140.3, 138.7, 138.5, 132.8,

132.7, 132.7, 132.5, 132.3, 131.9, 131.8, 131.6, 130.7, 129.3, 129.2, 128.9, 128.8, 128.5, 128.4,

128.3, 128.2, 59.4; LRMS (MALDI-TOF): Mass calculated for C$_{26}$H$_{22}$ClNO$_2$P [M+H]$^+$, 446.1.

Found 447.4.
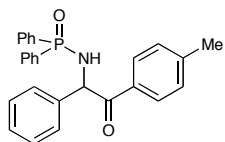
2-(Diphenylphosphinamide)-2-phenyl-1-*p*-tolylethanone (I-53): Purified

with 1% methanol/ethyl acetate, yielding 90 mg (81%) of **I-53** as a white

foam. R_f = 0.74 (100% ethyl acetate); Mp: 138-138.5 °C; IR (film) 3177,

3057, 1680, 1202 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ (7.85-7.81, 2H); 7.77-7.75 (m, 2H); 7.69-

7.65 (m, 2H), 7.48-7.28 (m, 4H); 7.15-7.11 (m, 6H); 5.94 (dd, J = 10.1, 8.2 Hz, 1H); 4.99 (dd, J

= 8.2, 8.2 Hz, 1H); 2.31 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.2, 144.9, 139.3, 132..7,

132.7, 132.2, 131.9, 131.8, 129.5, 129.1, 128.9, 128.8, 128.4, 128.3, 128.2, 128.1, 59.2, 21.9;

LRMS (MALDI-TOF): Mass calculated for C$_{27}$H$_{25}$NO$_2$P [M+H]$^+$, 426.2. Found 427.8.
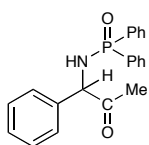
1-(Diphenylphosphinamide)-1-phenylpropan-2-one (I-54): Purified with 1%

methanol/ethyl acetate, yielding 80 mg (87%) of **I-54** as a white foam. R_f = 0.46

(100% ethyl acetate); Mp: 99-100 °C; IR (film) 3168, 3057, 1717, 1196 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84-7.80 (m, 2H); 7.61-7.57 (m, 2H); 7.49-7.41 (m, 3H); 7.34-7.32 (m, 1H); 7.21-7.17 (m, 4H); 7.07-7.06 (m, 2H); 5.05 (dd, J = 11.1, 6.7 Hz, 1H); 4.84 (dd, J = 6.2, 6.2 Hz, 1H); 2.02 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 204.0, 138.3, 132.7, 132.7, 132.4, 132.3, 131.8, 131.8, 129.1, 128.9, 128.8, 128.4, 128.3, 128.2, 128.1, 64.0, 27.1; LRMS (MALDI-TOF): Mass calculated for C$_{21}$H$_{21}$NO$_2$PNa [M+H+Na]$^+$, 372.1. Found 372.4.
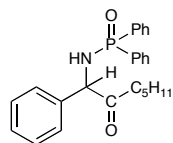
1-(Diphenylphosphinamide)-1-phenylheptane-2-one: Purified with 1% methanol/ethyl acetate, yielding 73 mg (71%) as a white foam. R$_f$ = 0.75 (100% ethyl acetate); Mp: 100-101 °C; IR (film) 3178, 3057, 2953, 1717, 1194 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84-7.78 (m, 2H); 7.61-7.56 (m, 2H); 7.49-7.31 (m, 5H); 7.21-7.18 (m, 5H); 7.17-7.04 (m, 2H); 5.02 (dd, J = 11.0, 6.7 Hz, 1H); 4.84 (dd, J = 6.6, 6.6 Hz, 1H); 2.30-2.25 (m, 2H); 1,46-1.40 (m, 2H); 1.15-1.03 (m, 4H); 0.77 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 206.6, 138.4, 132.7, 132.6, 132.5, 132.2, 131.8, 131.7, 129.0, 128.8, 128.7, 128.3, 128.3, 128.2, 128.1, 63.4, 39.7, 31.3, 23.7, 22.5, 14.1; LRMS (MALDI-TOF): Mass calculated for C$_{25}$H$_{30}$NO$_2$P [M+H]$^+$, 406.2. Found 406.7.
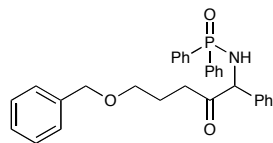
5-(Benzyloxy)-1-(diphenylphosphinamide)-1-phenylpentan-2-one (I-55): Purified with 1% methanol/ethyl acetate, yielding 40 mg (63%) of **I-55** as an orange oil. R$_f$ = 0.70 (100% ethyl acetate); IR (film) 3175, 3059, 2928, 1718, 1198 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83-7.79 (m, 2H); 7.62-7.58 (m, 2H); 7.50-7.21 (m, 16H); 7.06 (m, 2H); 5.03 (dd, J = 10.4, 7.0 Hz, 1H); 4.84 (m, 1H); 4.33 (q, J = 12.2 Hz, 2H); 3.30 (m, 2H); 2.43 (m, 2H); 1.78 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 210.7,

138.4, 132.7, 132.6, 132.3, 131.9, 131.8, 129.1, 128.9, 128.8, 128.6, 128.4, 128.3, 128.3, 128.2, 127.8, 127.8, 69.0, 63.5, 36.4, 24.1; LRMS (MALDI-TOF): Mass calculated for $C_{30}H_{31}NO_3PNa$ [M+H+Na]$^+$, 507.2. Found 507.2.
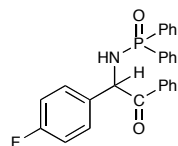
2-(Diphenylphosphinamide)-2-(4-fluorophenyl)-1-phenylethanone   (I-56): Purified with 1% methanol/ethyl acetate, yielding 101 mg (89%) of **I-56** as a white foam. R_f = 0.69 (100% ethyl acetate); Mp: 169-170 °C; IR (film) 3156, 3057, 1686, 1200 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83-7.80 (m, 4H); 7.66-7.64 (m, 2H); 7.46-7.28 (m, 8H); 7.10 (m, 2H); 6.83-6.80 (m, 2H); 5.97 (dd, J = 8.5, 8.5 Hz, 1H); 4.96 (dd, J = 7.3, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.5, 163.5, 161.5, 134.9, 134.2, 134.0, 132.7, 132.6, 132.3, 131.9, 131.9, 131.8, 131.7, 130.0, 130.0, 129.3, 128.9, 128.8, 128.5, 128.4, 116.2, 116.0, 58.58; LRMS (MALDI-TOF): Mass calculated for $C_{26}H_{22}FNO_2PNa$ [M+H+Na]$^+$, 453.1. Found 453.5.
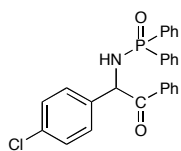
2-(4-Chlorophenyl)-2-(diphenylphosphinamide)-1-phenylethanone   (I-57): Purified with 1% methanol/ethyl acetate, yielding 100 mg (85%) of **I-57** as a white foam. R_f = 0.69 (100% ethyl acetate); Mp: 152-152.5 °C; IR (film) 3171, 3057, 1685, 1197 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82-7.81 (m, 4H); 7.67-7.63 (m, 2H); 7.48-7.28 (m, 8H); 7.11-7.05 (M, 4H); 5.94 (dd, J = 8.5, 8.5 Hz, 1H); 4.96 (dd, J = 7.9, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.3, 137.6, 134.2, 134.1, 134.1, 132.7, 132.6, 132.3, 131.9, 131.9, 131.8, 129.6, 129.3, 128.9, 128.8, 128.5, 128.4, 58.7; LRMS (MALDI-TOF): Mass calculated for $C_{26}H_{22}ClNO_2PNa$ [M+H+Na]$^+$, 469.1. Found 469.3.

2-(4-Bromophenyl)-2-(diphenylphosphinamide)-1-phenylethanone (I-58): Purified with 1% methanol/ethyl acetate, yielding 105 mg (82%) of **I-58** as a white foam. R_f = 0.69 (100% ethyl acetate); Mp: 143-144 °C; IR (film) 3165, 3056, 1685, 1197 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84-7.81 (m, 4H); 7.68-7.64 (m, 2H); 7.50-7.42 (m, 4H); 7.36-7.26 (m, 5H); 7.02-7.01 (m, 2H); 5.94 (dd, J = 8.8, 8.8 Hz, 1H); 4.97 (dd, J = 8.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.2, 138.1, 134.1, 132.7, 132.6, 132.4, 132.3, 132.0, 131.9, 131.8, 129.9, 129.3, 128.9, 128.9, 128.5, 128.4, 122.4, 58.8; LRMS (MALDI-TOF): Mass calculated for C$_{26}$H$_{21}$BrNO$_2$P [M]$^+$, 513.1. Found 513.9.
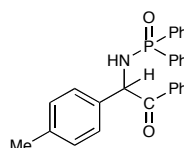
2-(Diphenylphosphinamide)-1-phenyl-2-*p*-tolylethanone (I-59): Purified with 1% methanol/ethyl acetate, yielding 104 mg (94%) of **I-59** as a white foam. R_f = 0.69 (100% ethyl acetate); Mp: 151-152 °C; IR (film) 3179, 3056, 2976, 2918, 1684, 1437, 1199 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.86-7.82 (m, 4H); 7.72-7.68 (m, 2H); 7.48-7.41 (m, 4H); 7.33-7.27 (m, 4H) 7.04-7.03 (m, 2H); 6.98-6.96 (m, 2H); 5.92 (dd, J = 9.2, 9.2 Hz, 1H); 4.91 (dd, J = 8.2, 8.2 Hz, 1H); 2.23 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.8, 138.0, 136.0, 134.5, 133.8, 133.5, 132.8, 132.7, 132.5, 132.2, 132.0, 131.9, 131.8, 129.9, 129.3, 128.9, 128.8, 128.4, 128.3, 128.1, 59.2, 21.3; MALDI: Mass (m/e) calculated for C$_{27}$H$_{25}$NO$_2$PNa [M+H+Na]$^+$, 449.2: Found 449.4.
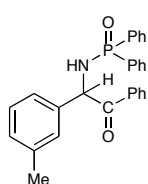
2-(Diphenylphosphinamide)-1-phenyl-2-*m*-tolylethanone (I-60): Purified with 1% methanol/ethyl acetate, yielding 92 mg (83%) of **I-60** as a white foam. R_f = 0.69 (100% ethyl acetate); Mp: 111.5-113 °C; IR (film) 3179, 3056, 2976, 1684, 1199 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87-7.81 (m, 4H), 7.71-7.67 (m, 2H); 7.48-7.41 (m,

4H); 7.39-7.28 (m, 4H); 7.07-7.04 (m, 1H); 6.95-6.91 (m, 3H); 5.92 (dd, J = 9.1, 9.1 Hz, 1H); 4.92 (dd, J = 8.0, 8.0 Hz, 1H); 2.17 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.7, 138.9, 138.8, 134.4, 133.8, 133.6, 132.8, 132.7, 132.6, 132.2, 131.9, 131.8, 129.4, 129.1, 129.0, 128.9, 128.8, 128.3, 128.2, 125.2, 59.4, 21.5; LRMS (MALDI-TOF): Mass calculated for C$_{27}$H$_{25}$NO$_2$P [M+H]$^+$, 426.2. Found 427.9.
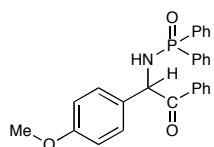
2-(Diphenylphosphinamide)-2-(4-methoxyphenyl)-1-phenylethanone   (I-61): Purified with 1% methanol/ethyl acetate, yielding 100 mg (86%) of **I-61** as a white foam. R$_f$ = 0.58 (100% ethyl acetate); Mp: 157-158 °C; IR (film) 3179, 3055, 2957, 1684, 1198 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85-7.81 (m, 4H); 7.71-7.67 (m, 2H); 7.47-7.41 (m, 4H); 7.33-7.29 (m, 4H); 7.06-7.05 (m, 2H); 6.69-6.67 (m, 2H); 5.92 (dd, J = 8.9, 8.9 Hz, 1H); 4.91 (dd, J = 7.8, 7.8 Hz, 1H); 3.69 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.7, 159.5, 134.5, 133.7, 132.8, 132.7, 132.2, 131.9, 131.9, 131.1, 129.5, 129.3, 128.9, 128.8, 128.4, 128.3, 114.6, 58.8, 55.4; LRMS (MALDI-TOF): Mass calculated for C$_{27}$H$_{25}$NO$_3$PNa [M+H+Na]$^+$, 465.2. Found 465.8.
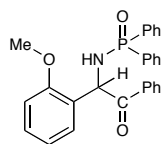
2-(Diphenylphosphinamide)-2-(2-methoxyphenyl)-1-phenylethanone: Purified with 1% methanol/ethyl acetate, yielding 81 mg (70%) as a white foam. R$_f$ = 0.50 (100% ethyl acetate); Mp: 80-80.5 °C; IR (film) 3175, 3057, 1686, 1204 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.91-7.82 (m, 4H); 7.68-7.64 (m, 2H); 7.47-7.39 (m, 4H); 7.37-7.22 (m, 4H); 7.14-7.10 (m, 2H); 6.82-6.79 (m, 1H); 6.60-6.58 (m, 1H); 6.36 (dd, J = 10.2, 8.1 Hz, 1H); 5.02 (dd, J = 7.6, 7.6 Hz, 1H); 3.47 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.9, 156.0, 134.5, 133.9, 133.6, 133.0, 132.9, 132.0, 131.8, 131.7, 131.5, 129.7, 129.1, 128.9, 128.8, 128.7,

128.6, 128.1, 128.0, 128.0, 121.3, 111.2, 55.4, 53.0; LRMS (MALDI-TOF): Mass calculated for $C_{27}H_{24}NO_3PNa$ [M+Na]$^+$, 464.2. Found 464.9.
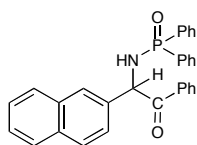
2-(Diphenylphosphinamide)-2-(napthalen-2-yl)-1-phenylethanone (I-62): Purified with 1% methanol/ethyl acetate, yielding 97 mg (80%) of **I-62** as a white foam. R_f = 0.69 (100% ethyl acetate); Mp: 134-135 °C; IR (film) 3173, 3056, 1685, 1200 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92-7.84 (m, 4H); 7.73-7.62 (m, 4H); 7.54-7.41(m, 6H); 7.32-7.25 (m, 4H); 7.15-7.13 (m, 2H); 6.15 (dd, J = 9.2, 9.2 Hz, 1H); 5.06 (dd, J = 8.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.6, 136.3, 134.4, 133.9, 133.5, 133.0, 132.7, 132.6, 132.5, 132.5, 131.9, 131.9, 131.8, 131.6, 129.4, 129.3, 128.9, 128.8, 128.3, 128.2, 127.9, 127.8, 126.6, 126.5, 125.4, 59.6; LRMS (MALDI-TOF): Mass calculated for $C_{30}H_{25}NO_2PNa$ [M+H+Na]$^+$, 485.2. Found 485.1.
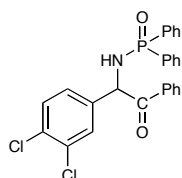
2-(3,4-Dichlorophenyl)-2-(diphenylphosphinamide)-1-phenylethanone (I-63): Purified with 1% methanol/ethyl acetate, yielding 85 mg (67%) of **I-63** as a white foam. R_f = 0.69 (100% ethyl acetate); Mp: 111-112 °C; IR (film) 3157, 3057, 1686, 1189 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84-7.81 (m, 4H); 7.68-7.64 (m, 2H); 7.50-7.30 (m, 7H); 7.20-7.17 (m, 2H); 7.00-6.98 (m, 1H); 5.95 (dd, J = 8.5, 8.5 Hz, 1H); 5.02 (dd, J = 8.06, 8.06 Hz, 1H); ^{13}C NMR (500 MHz, CDCl$_3$) δ 195.7, 195.7, 139.1, 134.3, 133.9, 133.1, 132.6, 132.5, 132.5, 132.1, 131.9, 131.8, 131.4, 131.1, 130.2, 29.3, 129.1, 129.0, 128.9. 128.5, 128.4, 127.6, 58.3; LRMS (MALDI-TOF): Mass calculated for $C_{26}H_{21}Cl_2NO_2PNa$ [M+H+Na]$^+$, 503.1. Found 503.1.
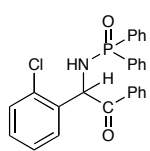
2-(2-Chlorophenyl)-2-(diphenylphosphinamide)-1-phenylethanone **(I-64)**:

Purified with 1% methanol/ethyl acetate, yielding 90 mg (77%) of **I-64** as a white

foam. R_f = 0.69 (100% ethyl acetate); Mp: 158-158.5 °C; IR (film) 3149, 3058,

1685, 1197 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90-7.83 (m, 4H); 7.70-7.67 (m, 2H); 7.47-7.38

(m, 7H); 7.37-7.31 (m, 3H); 7.25-7.06 (m, 3H); 6.35 (dd, J = 10.2, 7.5 Hz, 1H); 5.09 (dd, J =

7.2, 7.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.3, 136.9, 134.2, 134.0, 133.6, 132.9,

132.8, 132.5, 132.2, 131.8, 131.7, 131.5, 130.3, 129.8, 129.6, 129.1, 128.9, 128.8, 128.3, 128.2,

127.7, 56.4; LRMS (MALDI-TOF): Mass calculated for C$_{26}$H$_{22}$ClNO$_2$PNa [M+H+Na]$^+$, 469.1.

Found 469.6.
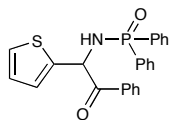
2-(Diphenylphosphinamide)-1-phenyl-2-(thiophen-2-yl)ethanone **(I-65):**

Purified with 1% methanol/ethyl acetate, yielding 87 mg (80%) of **I-65** as a

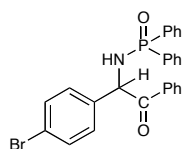white foam. R_f = 0.61 (100% ethyl acetate); IR (film) 3187, 2058, 1685, 1199

cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92-7.80 (m, 5H); 7.51-7.36 (m, 8H); 7.16-7.15 (m, 1H);

6.77 (s, 2H); 6.24 (dd, J = 9.3, 9.3 Hz, 1H); 4.89 (dd, J = 8.4, 8.4 Hz, 1H); ^{13}C NMR (125

MHz, CDCl$_3$) δ 195.6, 141.9, 134.1, 133.2, 132.7, 132.6, 132.4, 132.1, 132.0, 131.9, 131.6,

129.4, 128.9, 128.8, 128.6, 128.5, 127.3, 127..2, 126.5, 54.1; LRMS (MALDI-TOF): Mass

calculated for C$_{24}$H$_{21}$NO$_2$PSNa [M+H+Na]$^+$, 441.1. Found 440.7.

1.8.3.2 *Investigation of Alcohol Additive*

Determination of Silyl Acceptor: An authentic sample of 3-trimethylsilyloxy-octane was

prepared by combining 3-octanol (1 mL, 6.29 mmol), trimethylsilyl chloride (2.4 mL, 18.9

mmol), and triethylamine (2.6 mL, 18.9 mmol) in CH$_2$Cl$_2$ (16 mL) and stirring at room

temperature for 24 hours. Upon completion, the reaction mixture was diluted with pentane, washed with water (30 mL) and saturated aqueous CuSO$_4$ (3 x 30 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. A retention time (4.720 min) was collected on an Agilent Technologies 6890N gas chromatograph (equipped with Agilent 19091J-413 HP-5 5% phenylmethylsiloxane capillary column- 30.0 m x 320 μm x 0.25 μm nominal) using the following conditions: 70 °C for 1 min then a ramp of 25 °C/min to 285 °C with 3 minute hold.

In the experiment, a screw-capped tube was charged with 3,4,5-trimethylthiazolium iodide (**I-20c**, 10 mg, 0.04 mmol) in a nitrogen filled glove box. The tube was removed from box and put under a positive pressure of nitrogen. Benzoyltrimethylsilane (41 mg, 0.23 mmol) in CHCl$_3$ (0.25 mL) was added by syringe to the tube followed by the addition of DBU (12 μL, 0.04 mmol). The reaction mixture was heated to 60 °C after which imine **I-50a** (0.13 mmol) in CHCl$_3$ (0.25 mL) was added by syringe followed by the addition of 3-octanol (83 μL, 0.52 mmol). The reaction was allowed to stir at 60 °C for 4 hours. At this time an aliquot was filtered through glass wool and analyzed by GC (see above for details). The following retention times were observed: 3.89 min (3-octanol), 4.71 min (3-trimethylsilyloxy-octane), 5.96 min (benzoyltrimethylsilane), 15.00 min (imine). The α-amino ketone product (**I-51**) was not observed.
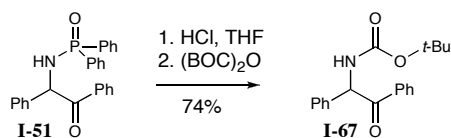
1.8.3.3 Boc Protection

A flame-dried 10 mL round bottom flask was charged with α-amino ketone **I-51** (50 mg, 0.122 mmol) and THF (0.6 mL). The resulting solution was cooled to 0 °C and concentrated HCl (0.6 mL) was added. The reaction was allowed to warm to room temperature and stirred for 3 hours. After this time, the reaction was complete as judged by thin layer chromatography (8:1 methylene chloride:methanol). The reaction was diluted with 5 mL H_2O and 5 mL THF and then neutralized with solid $NaHCO_3$. The reaction mixture was then cooled to 0 °C, (Boc)$_2$O (40 mg, 0.18 mmol) was added, and allowed to attain room temperature then stirred overnight. Analysis by thin layer chromatography (100% ethyl acetate) indicated that the reaction was complete. The solution was diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and then concentrated *in vacuo*. The unpurified residue (60 mg) was then purified by flash column chromatography (SiO$_2$, 10% ethyl acetate/hexanes) to afford 28 mg (74%) of **I-67** as a white solid. R_f = 0.44 (20% ethyl acetate/hexanes); Mp = 104-106 °C; IR (film) 3424, 3379, 3061, 22977, 1709, 1684 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97-7.96 (m, 2H); 7.52-7.50 (m, 1H); 7.41-7.31 (m, 3H); 7.29-7.23 (m, 2H); 6.28 (dd, J = 7.5 Hz, 1H), 6.03 (dd, J = 6.2 Hz, 1H); 1.44 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.4, 155.2, 137.8, 134.8, 133.8, 129.4, 129.3, 128.9, 128.5, 128.3, 80.2, 60.0, 28.6; LRMS (MALDI-TOF): Mass calculated for $C_{19}H_{22}NO_3Na$ [M+H+Na]$^+$, 335.2. Found 335.3.
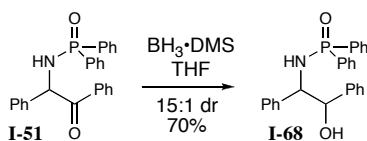
1.8.3.4 Reduction of α-Amino Ketone I-51 and Determination of Relative Stereochemistry

To a solution of α-amino ketone **I-51** (100mg, 0.24 mmol) in THF (2.4 mL) was added DMS-borane (24 μL, 0.25 mmol). After 24 hours at room temperature, the reaction was *carefully* quenched with saturated aqueous NH_4Cl. The reaction was diluted with ethyl acetate and then washed with water. The aqueous layer was extracted two times with ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and then concentrated *in vacuo*. The resulting white solid was purified by flash column chromatography (SiO_2, 1-4% methanol/ethyl acetate), yielding 35 mg (70%) of **I-68** as a white solid.[107] R_f = 0.69 (100% ethyl acetate); Mp: 229-229.5 °C; IR (KBr) 3337, 1162 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ;7.89-7.82 (m, 3H); 7.54-7.40 (m, 5H); 7.32-7.27 (m, 6H); 7.17-7.16 (m, 3H); 7.05-7.03 (m, 2H); 6.92-6.90 (m, 2H); 5.1 (d, J = 2.0 Hz, 1H); 4.74 (dd, J = 11.7, 9.9 Hz, 1H); 3.21 (dd, J = 11.9, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 132.2, 132.1, 132.0, 131.9, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 127.3, 127.1, 126.9, 77.8, 61.8; LRMS (MALDI-TOF): Mass calculated for $C_{26}H_{24}NO_2PNa$ $[M+Na]^+$, 436.2. Found 436.5.
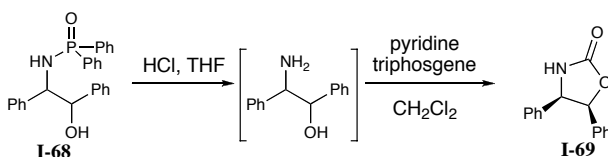
A flame-dried 10 mL round bottom flask was charged with **I-68** (73 mg) and THF (0.8 mL), then cooled to 0 °C at which time concentrated HCl (0.8 mL) was added. Reaction was allowed to

warm to room temperature and stirred overnight. Upon completion of the reaction (as judged

by thin layer chromatography) solid K_2CO_3 was added to adjust the pH to 10. The reaction was

then extracted 3 times with CH_2Cl_2. The combined organic layers were dried over anhydrous

Na_2SO_4, filtered and concentrated *in vacuo* to ~2 mL. This solution was then cooled to −78 °C

and pyridine (20 μL, 0.25 mmol) was added by syringe, followed by triphosgene (35 mg, 0.12

mmol). The cold reaction mixture was stirred for 4 hours, after which time it was quenched with

saturated aqueous $NaHCO_3$. The biphasic mixture was diluted with ethyl acetate, the layers were

separated, and the organic layer was washed with 1M HCl, followed by saturated aqueous

$NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in

vacuo*. The resulting residue (28 mg) was purified by flash column chromatography (30-50%

ethyl acetate/hexanes) yielding 10 mg (24%) of **I-69** as a white solid. R_f = 0.40 (50% ethyl

acetate/hexanes); IR (KBr) 3277, 3171, 3034, 1712 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12(s,

6H), 6.97 (s, 4H); 5.96 (d, *J* = 8.1 Hz, 1H); 5.75 (s, 1H); 5.2 (d, *J* = 8.1 Hz; 1H); ^{13}C NMR (500

MHz, $CDCl_3$) δ 147.0, 136.2, 134.6, 128.5, 128.3, 128.2, 127.2, 126.4, 82.6, 61.7; LRMS

(MALDI-TOF): Mass calculated for $C_{15}H_{13}NO_2Na$ $[M+Na]^+$, 262.3. Found 262.5. The relative

stereochemistry of the two phenyl substituents of the 2-oxazolidinone product was determined to

be cis by 1D NOE experiments.
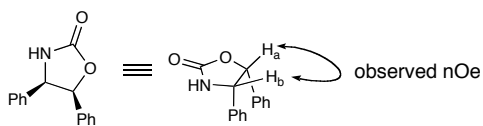
	I-69	Cis[108]	Trans[109]
H_a	5.96ppm	5.95ppm	5.24ppm
H_b	5.20ppm	5.15ppm	4.76ppm

1.8.4 Preparation of Thiazolium Carbinol I-VI
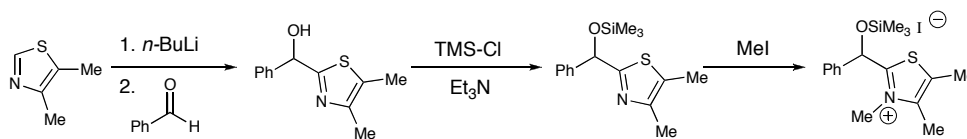
Synthesis of Carbinol:

A flame-dried round bottom flask under N_2 was charged with 4,5-dimethylthiazole (1 mL, 9.45 mmol). THF (45 mL) was added and the solution was cooled to −78 °C. *n*-Butyl lithium (1.9M, 6 mL, 11.3 mmol) was added dropwise to the cold reaction mixture. The resulting dark red solution was stirred for 45 min at −78 °C. The aldehyde (28.4 mmol) was then added, causing the solution to turn yellow, and the reaction was stirred for 1h at −78 °C. The reaction was warmed to room temperature and stirred for 2h. At this time, water (50 mL) was added to quench the reaction. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (200 mL). The aqueous layer was extracted two additional times with ethyl acetate (100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by recrystallization (ethyl acetate/hexanes).

(4,5-Dimethylthiazol-2-yl)(phenyl)methanol: Purified by recrystallization (ethyl acetate/hexanes), yielding 1.94 g (84%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ7.46 (m, 2H); 7.38 (m, 3H); 5.95 (s, 3H); 2.30 (s, 3H); 2.29 (s, 3H)

Protection and Alkylation of Carbinols:

To a flame-dried round bottom flask under N_2 was added the carbinol (7.3 mmol) followed by dichloromethane (75 mL). Next, trimethylcholorosilane (22 mmol) was added followed by triethylamine (8.0 mmol). The resulting suspension was then stirred overnight at

room temperature. The reaction mixture was diluted with dichloromethane (100 mL) and washed three times with brine (200 mL). The combined aqueous layers were washed with dichloromethane. The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo.* The pale yellow oil was used in the next step without further purification. To the protected carbinol in a flame-dried round bottom flask was added iodomethane (10 equiv) and the reaction was heated at reflux at 80 °C. After 12 h the reaction was cooled to room temperature and concentrated *in vacuo.* Diethyl ether was then added to the yellow residue and the product precipitated. The solid was collected by vacuum filtration, washed with diethyl ether and dried under vacuum. The resulting product was used with further purification.
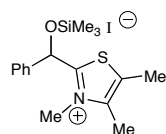
I-VI was isolated as a pale yellow solid in a 85% yield over the two steps. IR (film) 2955, 1601, 1447, 1255, 1070, 852 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.57-7.56 (m, 2H); 7.44-7.43 (m, 3H); 6.92 (s, 1H); 3.97 (s, 3H); 2.49 (s, 3H); 2.44 (s, 3H); 0.16 (s, 9H); ^{13}C NMR (500 MHz, CDCl$_3$) 176.4, 143.7, 136.8, 130.5, 130.1, 129.5, 128.2, 72.9, 40.3, 13.2, 12.8, 0.50 δ; LRMS (MALDI-TOF): Mass calculated for [M-I]$^+$ 306.1, 306.7 Found.

Chapter 2

Thiazolium Carbinols as Acyl Anion Precursors

Chapter 2 Thiazolium Carbinols as Acyl Anion Precursors

2.1 Stoichiometric Acyl Anion Addition Methods as Synthetic Tools

New carbon-carbon bond-forming strategies that operate with the inversion of normal reactivity patterns, or *Umpolung*, are valuable processes in organic synthesis. The polarity reversal of carbonyl groups affords acyl anions, one useful class of *Umpolung* intermediates. Although catalytic methods to access acyl anion reactivity have been known since the mid-1800's, their overall role in target-oriented synthesis is considerably underdeveloped when compared to stoichiometric acyl anion approaches. The two most standard methods to accomplish acyl anion addition reactions in natural product synthesis involve the use of dithianes and protected cyanohydrins.

2.1.1 Dithianes as Acyl Anion Precursors

Pioneering work reported by Corey and Seebach in 1965 revealed that 1,3-dithianes can operate as acyl anion equivalents (Scheme 2-1).[1] The deprotonation of a 1,3-dithiane with a strong base generates the corresponding anion, which is stabilized by the adjacent α-sulfur atoms. The subsequent addition of this species to an electrophile followed by hydrolysis of the dithioketal affords the desired carbonyl compound. The unmasking of the carbonyl functionality is often difficult and can require the use of toxic heavy metals, like cadmium or mercury. The hydrolysis of dithioketals remains challenging and is case specific.

Scheme 2-1. Dithianes as acyl anion precursors
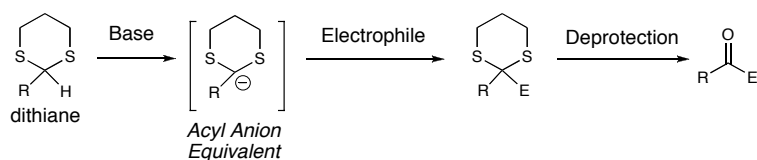
Since its discovery, the acyl anion reactivity of dithianes has become a valuable tool in organic synthesis.[2-4] A key feature adding to the synthetic utility of metallated dithianes is their ability to add to a wide range of electrophiles, including alkyl halides, aldehydes, ketones, epoxides and aziridines. For this reason, many investigators have found dithianes to be useful synthons in the synthesis of natural products (Figure 2-1). For example, Seebach and coworkers were able employ the dithiane approach in the synthesis of natural products like (–)-pyrenophorin, norphyrenophorin and (+)-gloeosporane.[3,5] The Nicolaou group synthesized the cytotoxic marine natural product swinholide A using a dithiane to accomplish a key coupling step.[6] Smith and coworkers have been able to further demonstrate the synthetic value of dithianes in the syntheses of complex, bioactive natural products like the spongistatins, potent tumor inhibitors, and the antifungal agent mycoticin A.[4] In their syntheses of the spongistatins, the AB and CD spiroketal fragments were prepared using a multicomponent linchpin strategy in which two larger fragments are brought together with one dithiane.
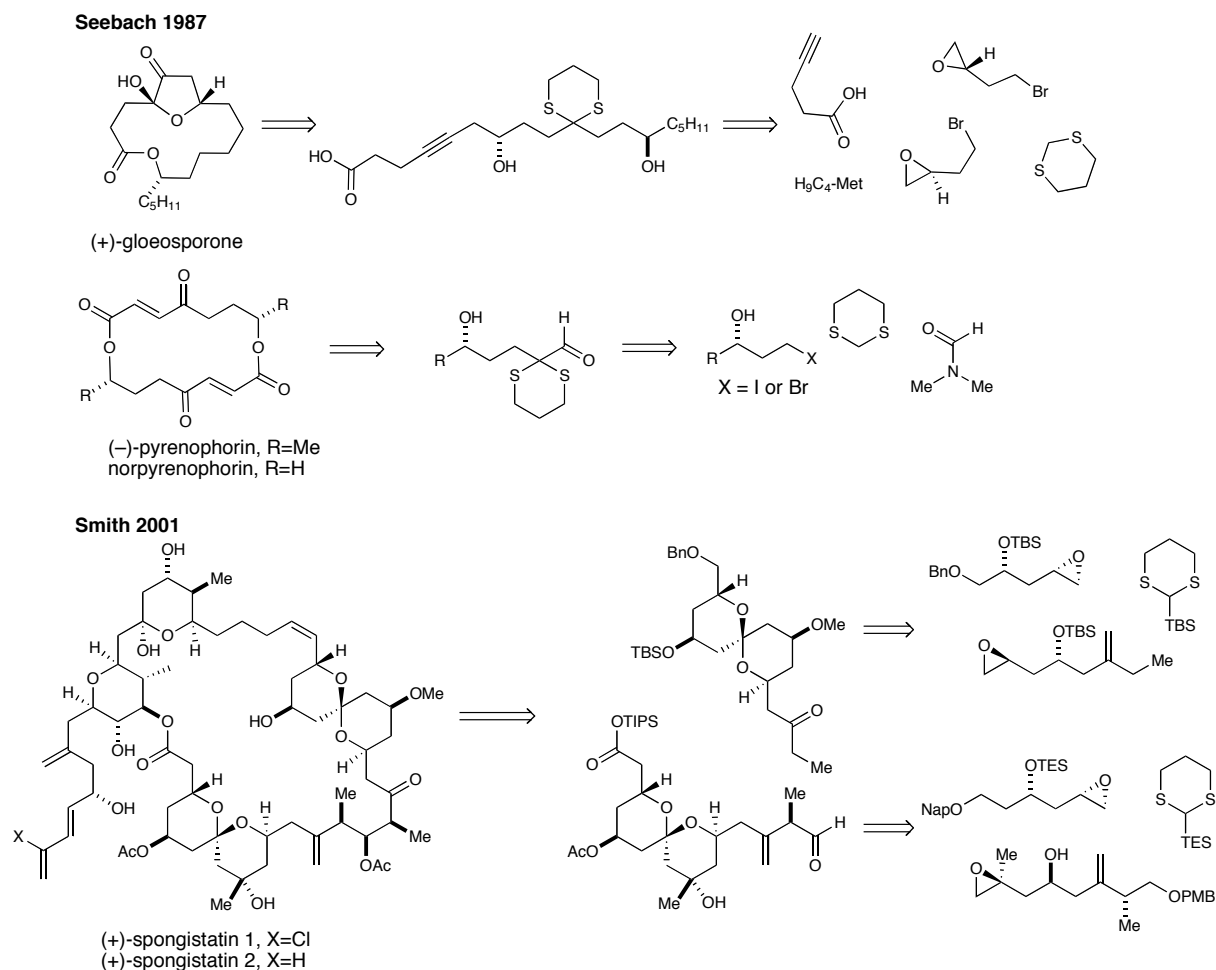
Figure 2-1. Examples of natural products synthesized with dithianes

2.1.2 Cyanohydrins as Acyl Anion Precursors

In 1971, Stork and Maldonado disclosed conditions in which protected cyanohydrins can be employed as acyl anion equivalents (Scheme 2-2).[7] Much like dithianes, cyanohydrins can be deprotonated with a strong base which produces an anion that is partially stabilized by the proximal nitrile. The addition of this anion to an electrophile that is present in the reaction system followed by a final deprotection step affords the desired acylated product. One limitation of this strategy is the toxicity of cyanide.

Scheme 2-2. Cyanohydrins as acyl anion precursors
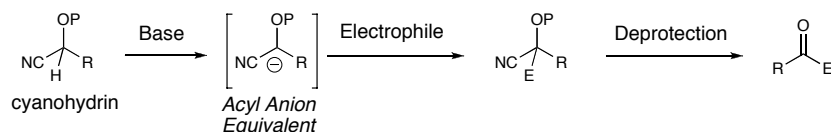
The total synthesis of biologically relevant natural products has been accomplished when protected cyanohydrins are employed in key bond-forming steps (Figure 2-2). For example, Stork and coworkers employed an intramolecular alkylation of a cyanohydrin in their early synthesis of prostaglandin $F_{2\alpha}$.[8] More recently, dermostatin A, a potent antifungal and potential HIV treatment, was constructed by Sinz and Rychnovsky.[9] In this synthesis, cyanohydrin acetonides were used in key intermolecular alkylation reactions.

Stork 1978
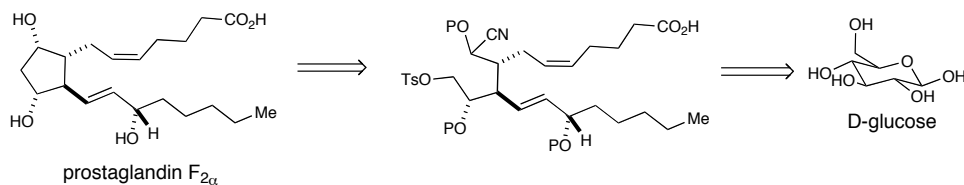
Rychnovsky 2001
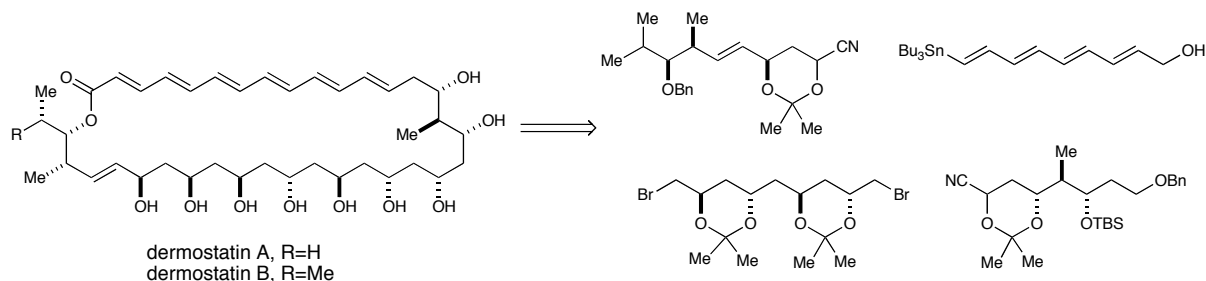
Figure 2-2. Protected cyanohydrins in natural product synthesis

2.1.3   N,N-Dialkylhydrazones as Acyl Anion Equivalents

While dithiane and cyanohydrin approaches towards acyl anion reactivity have found wide applicability in organic synthesis, the strongly basic reaction conditions that are often required can significantly limit the value of these transformations when sensitive substrates are employed as electrophiles. *N,N*-Dimethylhydrazones constitute a class of stoichiometric acyl anion equivalents that can operate under more mild reaction conditions.[10] These substrates can be regarded as azaenamines and when treated with an appropriate electrophile an addition reaction will occur at the hydrazone carbon (Scheme 2-3). Early reports from Brehme et al. revealed *N,N*-dialkylhydrazones undergo nucleophilic additions to strong electrophiles such as sulfonylisocyanates[11] and Mannich salts.[12] Hojo and coworkers later reported these hydrazones also add to trifluoroacetic anhydrides.[13,14] More recent advances from Lassaletta and coworkers have demonstrated that under the appropriate reaction conditions formaldehyde *N,N*-dialkylhydrazones can be suitable acylating reagents for nitroalkenes, enones, α,β-unsaturated lactones, aldehydes, and activated ketones.[10] While there are definite advantages associated with the mild reaction conditions required for this transformation, the method is limited in substrate scope and, similar to both the dithianes and cyanohydrins, additional processing is required to access the carbonyl functionality.

Scheme 2-3. Formyl *N,N*-dialkyhydrazones as stoichiometric acyl anion equivalents
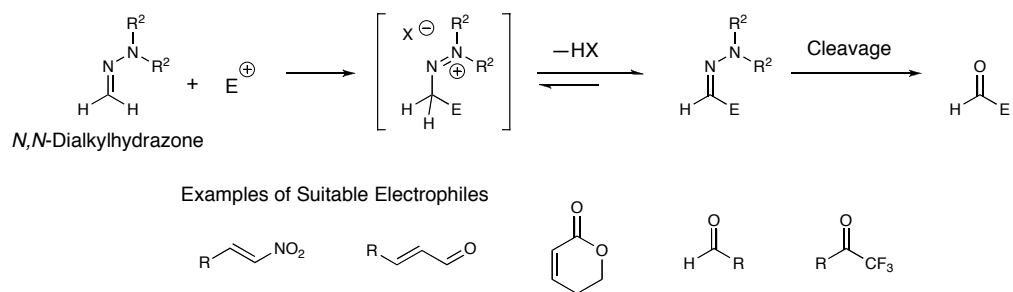
As part of our studies involving the development of new acyl anion addition strategies, we sought to develop a method in which the direct nucleophilic acylation of electrophiles could be accomplished under mild reaction conditions. During our investigations of NHC-catalyzed acylsilane addition reactions, we discovered that *O*-silyl thiazolium carbinols like **II-1** are operative acyl anion precursors for the direct installation of carbonyl groups (Scheme 2-4).[15,16] One particularly intriguing aspect of the carbinol addition reactions that was observed during our studies was the acylation event proceeds at 23 °C in the presence of an amine base. Since these conditions are milder than the reflux temperatures required for the acylsilane addition reactions, we reasoned they may be more compatible with sensitive substrates. Furthermore, these unique acyl anion precursors are stable, convenient to store and easy to handle making them excellent reagents to employ in new reaction manifolds. We envisioned utilizing these thiazolium carbinols in the development of novel acyl anion addition reactions.

Scheme 2-4. A thiazolium carbinol as a stoichiometric acylating reagent
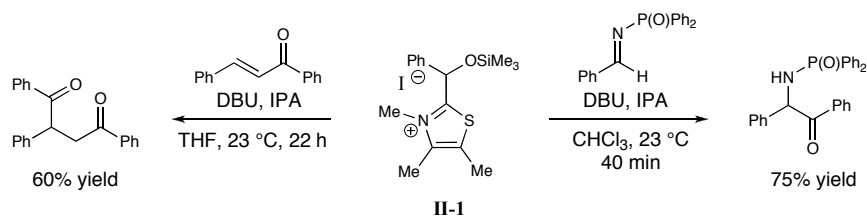
2.2 Synthesis of Thiazolium Carbinols

One attribute that makes *O*-silyl thiazolium carbinols especially useful as acyl anion precursors is the ease with which they can be prepared from commercial, non-toxic starting materials. A majority of these carbinols can be synthesized in three experimentally simple steps that require no column chromatography (Scheme 2-5). In addition, the final products are typically stable solids that are easy to handle and convenient to store.

Scheme 2-5. Synthesis of thiazolium carbinols
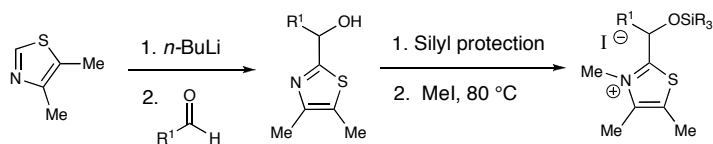
The deprotonation of 4,5-dimethylthiazole followed by the addition of the resulting anion to an aldehyde affords the corresponding carbinol in excellent yield (> 90%).[17]   Simple recrystallization of the carbinols at this point is often the only necessary purification.   Silyl protection under standard conditions is followed by an alkylation in neat iodomethane.   The precipitation of the iodide salt occurs after addition of diethyl ether and the resulting solid that is isolated by filtration is >95% pure as judged by ^{1}H NMR spectroscopy.   The overall yields for the three-step sequence are up to 77% depending on the silyl protecting group used.   Alkyl, aryl and α,β-unsaturated carbinols have been accessed via this method (Figure 2-3).   The carbinols derived from alkyl aldehydes are prepared in lower yields than those derived from aryl aldehydes and this is most likely due to side reactions associated with the acidic α-protons when the thiazole is added to the aldehyde (**II-1f** through **II-1h**).
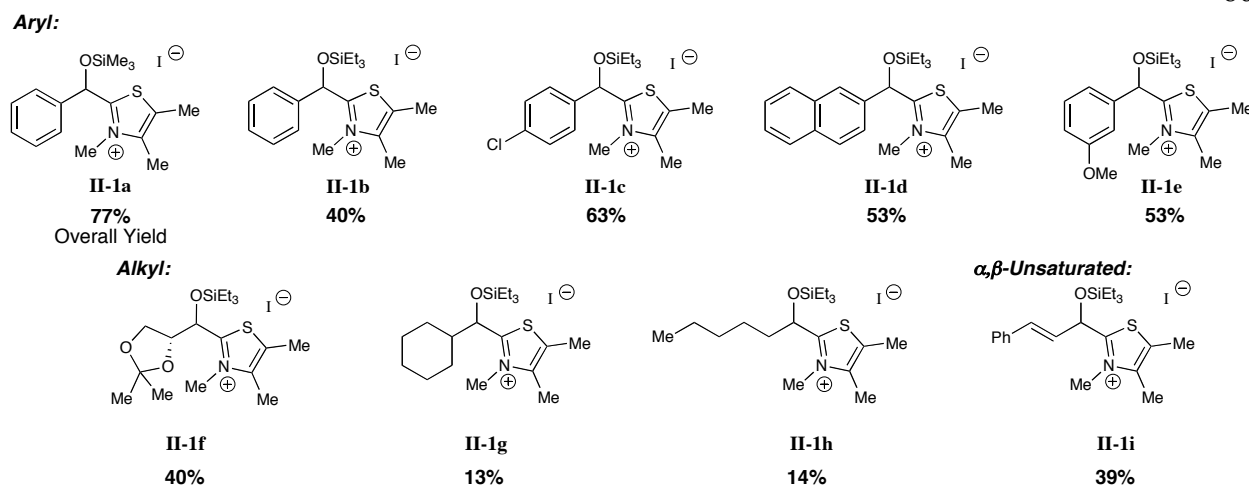
Figure 2-3. Examples of *O*-silyl thiazolium carbinols that have been synthesized

Certain electron-rich thiazolium carbinols are more difficult to prepare using this procedure (Figure 2-4). Initially, we were surprised to find the carbinol derived from *p*-anisaldehyde could not be prepared when the analogous carbinol derived from *m*-anisaldehyde was readily prepared in good yield. After a comparison of the two structures, we came to realize that all of the substrates that have been problematic have electron-donating groups that are electronically linked to the silyloxy group and we reasoned a possible elimination of this group occurs during the alkylation step. Further evidence to support this hypothesis was obtained from the ^{1}H NMR spectrum of the unpurified reaction mixture of the final alkylation step. There were no silyloxy peaks present indicating that this group was no longer attached to the carbinol. In an attempt to remedy this problem more reactive alkylating agents, such as methyl triflate, were employed so the alkylation event might be accomplished at lower temperatures. Unfortunately, alternate conditions did not improve the results and further work is necessary to access these substrates.
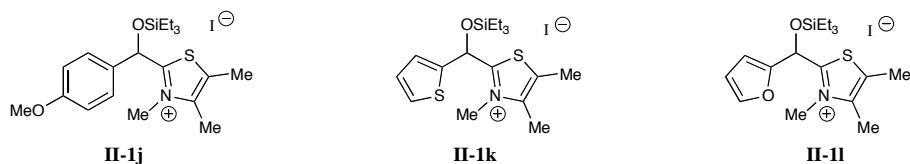
Figure 2-4. Electron-rich carbinols that cannot be prepared according to the standard procedure

2.3 Direct Nucleophilic Acylations of Nitroalkenes

One class of substrates we were particularly interested in employing as electrophiles in our acyl anion addition reactions was nitroalkenes. In general, conjugate additions to nitroalkenes afford highly useful compounds because the nitro group can be easily manipulated into various functionalities, including amines, aldehydes and acids.[18,19] At the beginning of our investigation, the direct nucleophilic acylation of nitroalkenes had not been previously reported.

We began by surveying catalytic methods that installed carbonyl groups using aldehydes or acylsilanes as nucleophilic precursors and *N*-heterocyclic carbenes (NHCs) as catalysts (Scheme 2-6). Unfortunately, our attempts with these approaches met with little success and only low levels of the desired β-nitroketone products were observed. The heteroazolium-derived catalysts generated in situ for these processes typically require basic conditions and elevated temperatures. Presumably the nitroalkenes were sensitive to the basic conditions required and the low yields were a result of decomposition that occurred under these reaction conditions. Prompted by the paucity of efficient means to directly add carbonyl anions to this sensitive electrophile class, we hypothesized that accessing carbonyl anion reactivity under more mild conditions might afford a synthetically useful reaction.

Scheme 2-6. Attempted nucleophilic acylations of nitroalkenes using aldehydes or acylsilanes and NHCs as catalysts
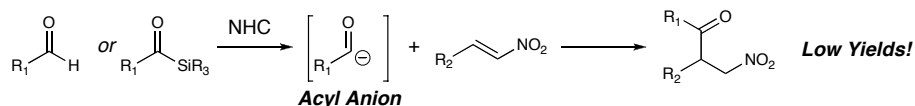
2.3.1 *Additions of Thiazolium Carbinols to Nitroalkenes*

In an attempt to overcome the problems associated with the catalytic method above, we focused our attention on developing a method to add *O*-silyl thiazolium carbinols (**II-1**) to nitroalkenes. We speculated that the lower reaction temperatures required for these acylating reagents may reduce any decomposition and side reactions to enable the carbonyl anion to add efficiently to the nitroalkene. To investigate the potential of carbinol additions to nitroalkenes, a survey of reaction conditions was conducted. Solvents, temperatures and bases were varied and the best combination found (DBU and $CHCl_3$) afforded a 57% yield of the β-nitro ketone product (Scheme 2-7). While these results were an improvement over the catalytic attempts, the yields remained moderate at best. There was still a substantial amount of decomposition observed in the ^{1}H NMR spectra of the unpurified reaction mixtures and we continued to believe the basic reaction conditions were the cause of the low yields. Two control experiments provided evidence that both the carbinol (**II-1**) and the nitroalkene (**II-2**) undergo rapid decomposition (full consumption in < 1 h at room temperature observed by ^{1}H NMR spectroscopy and thin layer chromatography) in the presence of DBU.

Scheme 2-7. Thiazolium carbinol additions to nitroalkenes promoted by DBU
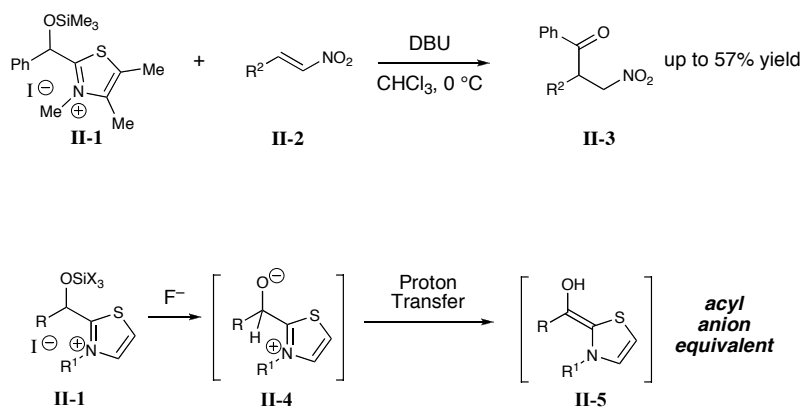
Figure 2-5. Fluoride promoted generation of a carbonyl anion from a thiazolium carbinol

After considering potential pathways through which the acyl anion equivalent can be generated from the carbinol, we became curious if fluoride would be able to promote the addition of thiazolium carbinols to nitroalkenes (Figure 2-5). In this process, fluoride would desilylate thiazolium carbinol **II-1** to afford the corresponding alkoxide **II-4**. This alkoxide could then undergo an intermolecular proton transfer to generate **II-5**, an intermediate described by Breslow in the benzoin reaction. Alternatively, alkoxide **II-4** could also collapse to eject the thiazolium zwitterion and thus, not undergo the desired addition reaction. Importantly, generating intermediate alkoxide **II-4** via addition of a deprotonated thiazolium salt to an aldehyde is untenable due to competing pathways, such as dimerization of the resulting thiazolium zwitterion. Thus, accessing a pathway to produce nucleophile **II-5** cleanly *in the presence* of the nitroalkene is clearly a key requirement for success. To assess this approach, we began by examining the addition of thiazolium carbinols (**II-1**) to nitroalkene **II-2a** (Table 2-1).

Table 2-1. Fluoride-promoted carbonyl anion additions to nitroalkenes

entry	R	X	fluoride source	additive	yield (%)
1	Ph	Me	Bu$_4$N•Ph$_3$SiF$_2$	none	33
2	Ph	Me	Bu$_4$N•Ph$_3$SiF$_2$	**II-9**	66
3	Ph	Me	Me$_4$N•F	**II-9**	53
4	Ph	Et	Me$_4$N•F	**II-9**	59
5	4-Cl-Ph	Et	Me$_4$N•F	**II-9**	78
6	4-Cl-Ph	Et	Me$_4$N•F	**II-8**	75

Thiourea activation of
a nitroalkene

Our initial investigations demonstrated that β-nitroketone **II-6** could be isolated, using tetrabutylammonium triphenyl-difluorosilicate[20] to generate the carbonyl anion equivalent in situ at −40 °C (entry 1). Encouraged by the direct installation of a carbonyl unit at low temperature via this new process, we continued to survey conditions to obtain improved yields. It is known that thioureas are able to activate nitroalkenes through hydrogen-bonding and we speculated there might be an increase in yield with a thiourea additive.[21,22] Gratifyingly, this unique fluoride/thiourea combination afforded an improved 66% yield of **II-6** (entry 2). Tetramethylammonium fluoride (Me$_4$N·F)[23,24] was superior in terms of reaction times and simplicity of purification, but the yields remained unsatisfactory. To improve the process, silyl protecting groups were evaluated. Triethylsilyl (TES) protected carbinols afforded increased yields of **II-6** compared to trimethylsilyl (TMS) variants, while more robust *t*-butyldimethyl (TBS) analogs prevented the nitroalkene from being completely consumed. With the optimal fluoride source and protecting group in hand, placement of an electron-withdrawing group on the

thiazolium carbinol increased the yield to 78% (entry 5). Finally, commercial thiocarbanilide

(**II-8)** was a convenient additive and provided good yields of **II-7** (75%, entry 6).

It was apparent that the thiourea additive was necessary to obtain high yields of product

and we became interested in exploring this component of the reaction in more detail (Scheme 2-

8). A survey was conducted in order to identify how the thiourea catalyst loading affects the

outcome of the reaction. With 100 mol % **II-9**, the highest yield of β-nitroketone was obtained

(79%). Reducing the catalyst loading to 30 mol % resulted in slower reaction times as well as a

decreased yield of acylated product (60%). From this study it is clear the best results are

obtained when stoichiometric amounts of thiourea are employed in our reaction system.

Scheme 2-8. Investigation of thiourea catalyst loading affects on yield
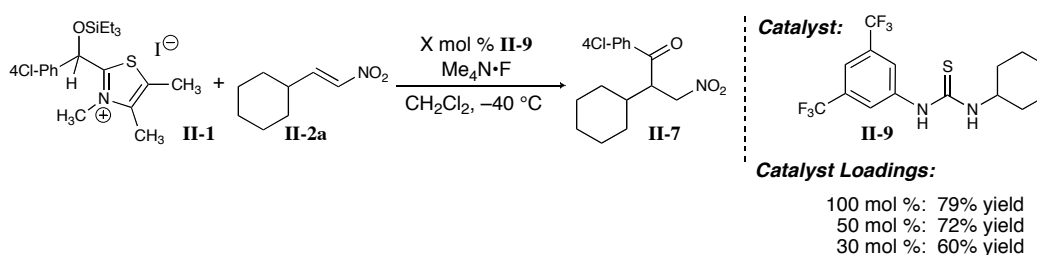
2.3.2   *Reaction Scope of the Nucleophilic Acylation of Nitroalkenes*

An investigation into the reaction scope was carried out with the optimal combination of

fluoride source (Me$_4$N·F) and thiourea **II-8** (Table 2-2). The nitroalkenes were prepared from

the corresponding aldehyde and nitroalkane in a two-step addition-elimination sequence.[25]

Various nitroalkenes are competent substrates in the addition reaction, including branched and

straight chain variants (entries 1-4). The nucleophilic acylation of a cyclic nitroalkene occurs

smoothly with excellent diastereoselectivity to yield trans product **II-13** (20:1 dr, entry 5).

Remarkably, formation of a quaternary center is possible by addition of the carbonyl anion

equivalent to a β,β-disubstituted nitroalkene (entry 6).   All attempts to acylate aryl
nitroalkenes, such as β-nitrostyrene, resulted in low yields of the desired product.

Table 2-2. Nucleophilic acylations of nitroalkenes

entry	nitroalkene	product		Yield (%)
1			**II-7**	78%
2			**II-10**	65%
3			**II-11**	73%
4			**II-12** (1:1 dr)	63%
5			**II-13** (20:1 dr)	80%
6			**II-14**	56%

Various thiazolium carbinols were also examined (Table 2-3).   The 2-napthyl derived
carbinol was successfully added to nitroalkene **II-2a** (entry 2).   In addition to electron-
withdrawing groups the reaction is also tolerant of an electron-donating substituent on the phenyl
ring (entry 3).   Currently, thiazolium carbinols derived from saturated aldehydes provide poor
yields of desired product (<30%), underscoring the delicate balance between hydrogen transfer
and unproductive reaction pathways.

Table 2-3. Survey of thiazolium carbinols in the nucleophilic acylation of nitroalkenes

entry	R	product	yield (%)
1	Ph (**II-1b**)	**II-6**	59
2	2-napthyl (**II-1d**)	**II-15**	82
3	3-MeO-Ph (**II-1e**)	**II-16**	60
4	4-Br-Ph (**II-1m**)	**II-17**	81

2.3.3   *Asymmetric Nucleophilic Acylations of Nitroalkenes*

Once the new bond-forming process had been optimized, we directed our attention towards the development of an asymmetric variant.   Racemization of the newly formed stereogenic center is always a concern in the development of asymmetric direct acylation reactions; however, our conditions are relatively neutral and can operate under low reaction temperatures.   We believed that these novel reaction conditions might provide the ideal environment to foster a highly enantioselective direct acylation.   Furthermore, recent progress in the area of non-covalent catalysis has shown that chiral thioureas can catalyze asymmetric nucleophilic addition reactions through hydrogen-bonding.[21,22]   The addition of a chiral thiourea additive in our new reaction might hydrogen-bond to the nitroalkene and render the process asymmetric.

Our investigation into the asymmetric nucleophilic acylation of nitroalkenes began by employing a chiral thiourea derived from quinine. This catalyst has been previously reported by Soós and coworkers to effect the enantioselective addition of nitromethane to chalcone and is readily accessible from quinine in just two steps.[26] Furthermore, the cinchona alkaloid, quinine, is a good starting material because it is commercially available. We were pleased to find that

incorporation of thiourea **II-18** under the previously described optimal reaction conditions afforded a 72% yield of product with moderate enantioselectivity (62% ee, Scheme 2-9).

Scheme 2-9. Initial results obtained from employing a chiral thiourea in the nucleophilic acylation of nitroalkenes
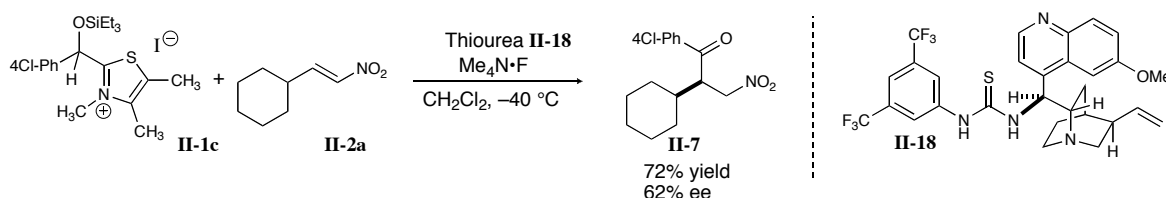
Encouraged by our initial success, we continued our investigation with an examination of the thiourea structure. Additional thiourea additives were synthesized to evaluate the effect the aromatic substituent has on the enantioselectivity. It is clear the bis-trifluoromethyl phenyl component is a key feature of the catalyst structure since the naphthyl (**II-19**) and adamantly (**II-20**) analogs prepared resulted in reduced yields and poor enantioselectivity (Scheme 2-10). Previous studies have found similar results and it has been hypothesized that the electron-withdrawing group is able to enhance the hydrogen-bonding ability of the thiourea by increasing the acidity of the hydrogens.

Further exploration revealed that lowering the reaction to −78 °C resulted in improved enantioselectivity (74% ee) when the quinine-derived thiourea was employed. To complete the brief catalyst survey, potential thiourea catalysts were prepared from the remaining three cinchona alkaloids (Scheme 2-11, **II-18**, **II-21** through **II-23**). Generally, the cinchona alkaloid-derived thioureas afford the β-nitroketone product in moderate yield with good enantioselectivity. Importantly, the β-nitroketones can be recrystallized to > 99% ee. Chiral

thioureas prepared from (R)-(+)-BINAM[27] (**II-24**) and (R)-α-methyl benzylamine (**II-25**) provided high yields of product (61% and 78% respectively); however, there was no selectivity observed. X-ray crystallography was used to determine the configuration of the newly formed stereogenic center of the major enantiomer (purified by recrystallization) of **II-17** that was produced in the asymmetric reaction (Scheme 2-12, Figure 2-6).

Scheme 2-10. Investigation of thiourea structure.

II-18
72% yield
62% ee

II-19
54% yield
12% ee

II-20
53% yield
6% ee
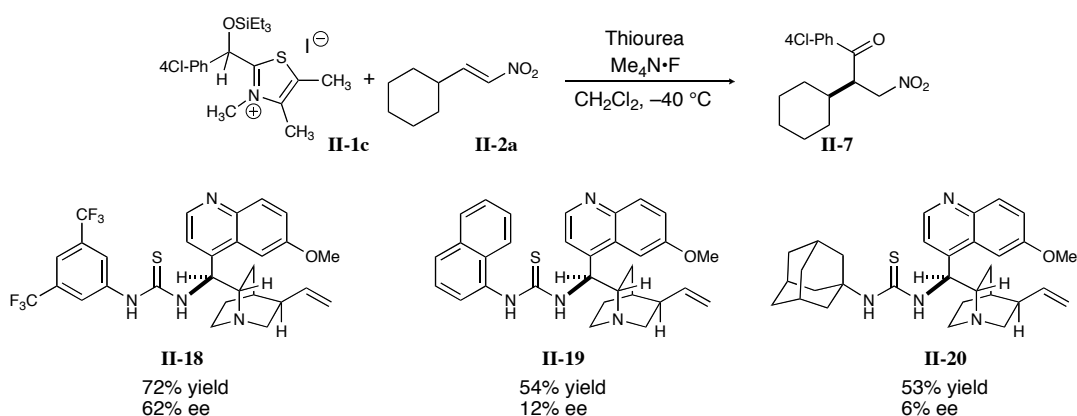
Scheme 2-11. Comparison of the cinchona-alkaloid derived thiourea additives.

Quinine-derived
64% yield
74% ee

Cinchonidine-derived
68% yield
65% ee

Quinidine-derived
72% yield
– 76% ee

Cinchonine-derived
66% yield
– 61% ee

II-18   **II-21**   **II-22**   **II-23**

II-24
61% yield
Racemic

II-25
78% yield
Racemic
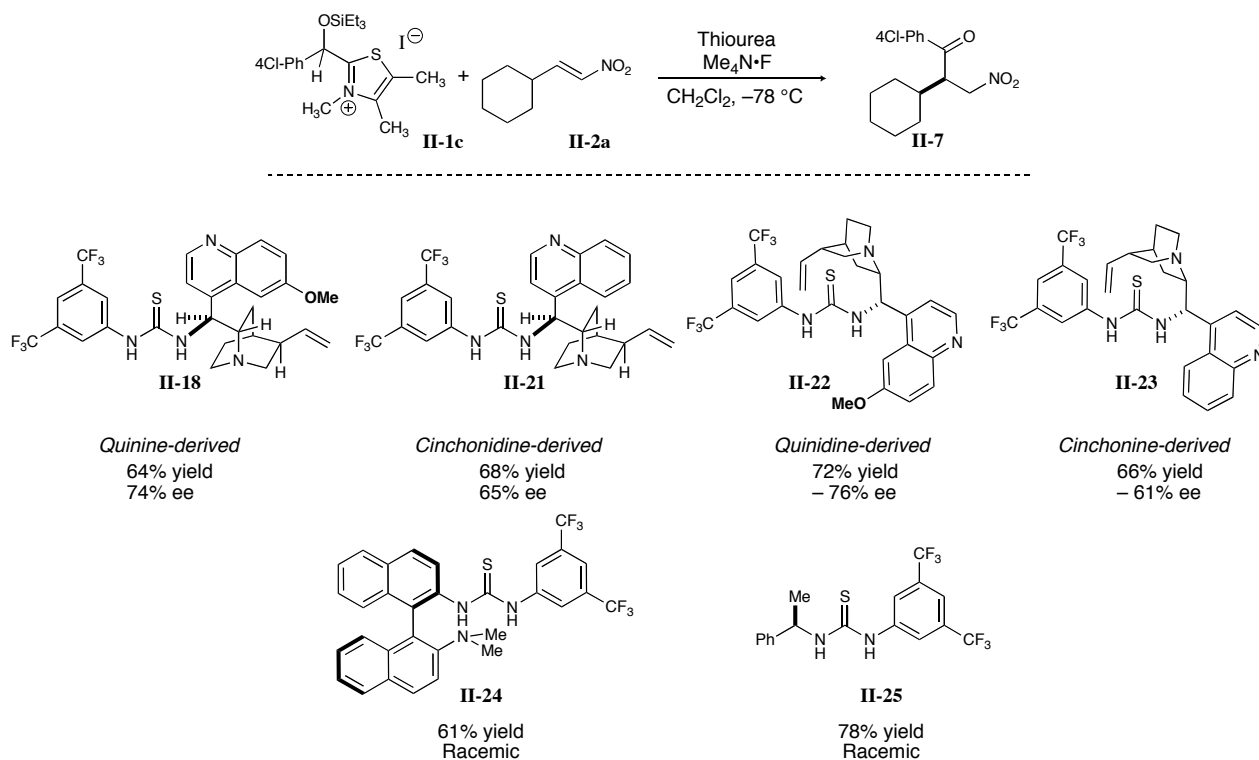
Scheme 2-12. Enantioselective preparation of **II-17**.
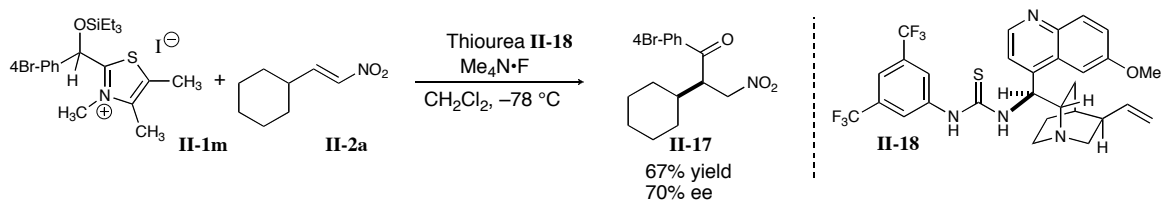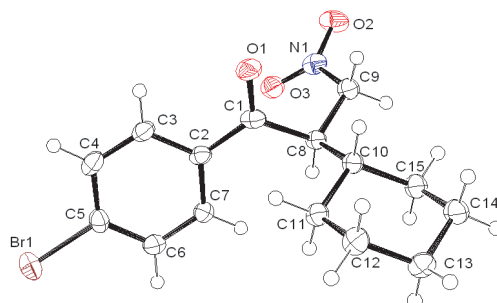
II-17
67% yield
70% ee

Figure 2-6. Crystal structure of **II-17**

Additional nitroalkene and thiazolium carbinol substrates were examined in the acylation reactions using the chiral thiourea additive derived from quinine **II-18** and the results are listed in Scheme 2-13. The enantioselectivities were moderate in most cases and the yields ranged from good to high. In the preparation of **II-12**, the diastereoselectivity was increased from 1:1 to 6:1 when the quinine-derived thiourea (**II-18**) was employed as the additive. Notably, no racemization of the newly formed stereogenic centers were observed over the course of the reaction (ee did not change with reaction times of 2 h or 24 h).

Scheme 2-13. Results from nitroalkene substrates evaluated in acylation reaction with quinine-derived thiourea
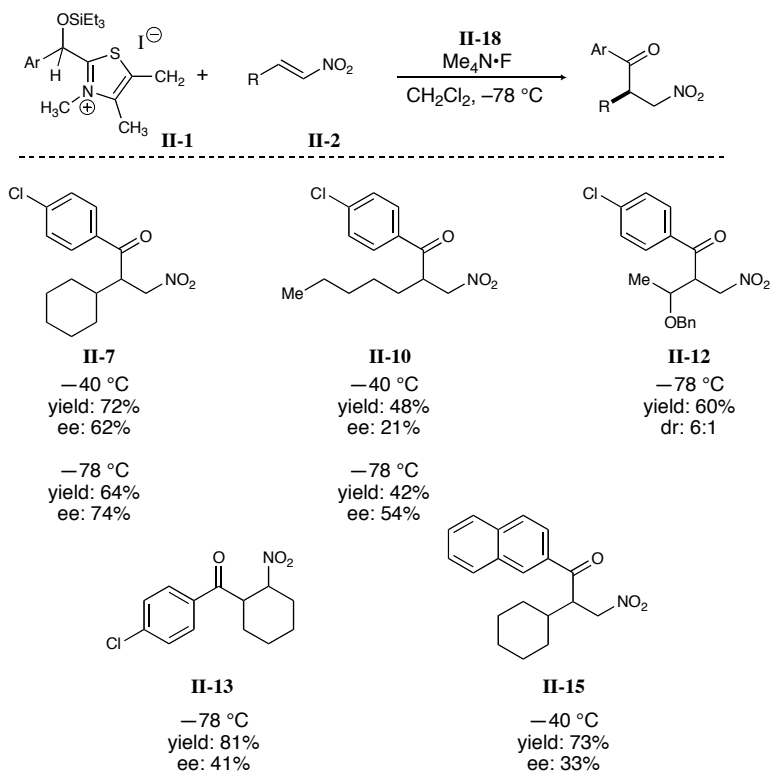
To our knowledge, this is the first reaction system to accomplish the asymmetric, direct nucleophilic acylation of a nitroalkene. This discovery is important because it demonstrates the generation of an acyl anion equivalent from a thiazolium carbinol using a fluoride anion and thiourea combination. These are mild reaction conditions that enable the acylation event to occur in an enantioselective fashion with no racemization of the new stereocenter.

2.3.4 *Attempted Addition of Thiazolium Carbinols to Additional Electrophiles Using a Fluoride Anion and Thiourea Combination*

Once we had discovered mild reaction conditions to access acyl anion reactivity and were able to accomplish asymmetric nucleophilic acylation reactions, we sought to utilize the unique fluoride anion/thiourea combination in additional systems. α,β-Unsaturated imides and alkylidene malonates were two substrate classes of particular interest since they have two point binding capabilities and could potentially work well with a thiourea additive. Takemoto and coworkers had reported catalyzing the enantioselective addition of malonates to α,β-unsaturated imides using chiral thioureas.[28] For this reason, our investigation into extending the utility of our newly developed fluoride anion and thiourea system first focused on adding acyl anions to α,β-unsaturated imides (Scheme 2-14). Unfortunately, when the optimal conditions that had been established for the nitroalkene acylation were applied with various imides (**II-26**) there was only decomposition of the thiazolium carbinol and recovery of the starting imide. All modifications made to the reaction systems afforded similar results and no product was ever identified in the unpurified reaction mixtures. From these results it was concluded that even if the imide is being activated by the thiourea, the acyl anion generated from the carbinol is not nucleophilic enough to undergo the addition reaction.

Scheme 2-14. Attempts to acylate α,β-unsaturated imides using thiourea additives
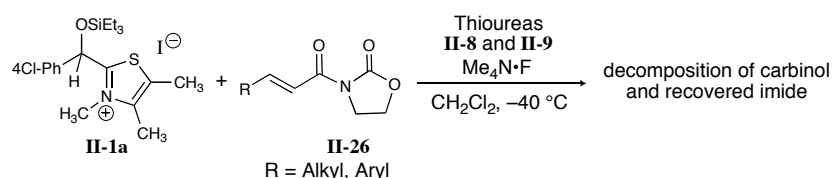
Since it seemed likely a more active electrophile was necessary, we decided to apply

our acyl anion addition strategy to alkylidene malonates (**II-27**, Scheme 2-15). We reasoned that

the two esters in combination with the thiourea would generate a suitably active electrophile to

enable the acylation event. Unfortunately, all attempts failed to produce any desired product and

only starting alkylidene malonate was recovered. In an effort to enhance the reactivity of the

alkylidene malonate, Lewis acids were investigated including; Ti(Oi-Pr)$_4$, Cu(OTf)$_2$ and ZnCl$_2$.

Only the starting alkylidene malonate was recovered in these processes. It was concluded that

the carbinols are not compatible with any Lewis acids examined up to this point. At this time it

is not clear how the carbinol is decomposing under these reaction conditions.

Scheme 2-15. Attempts to acylate alkylidene malonates using thiourea additives
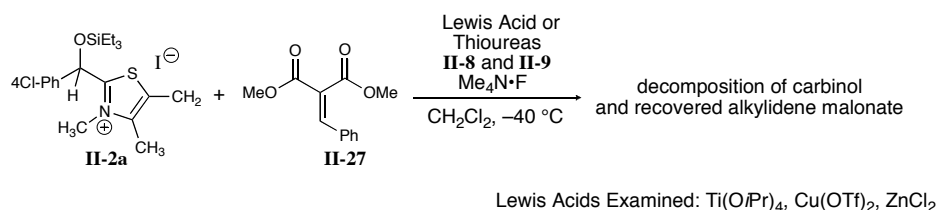
Additional electrophiles that have been examined in nucleophilc acylation reactions with

thiazolium carbinols are listed in Figure 2-7. Fluoride was always employed to promote the acyl

anion formation and surveying was performed with and without the thiourea additive.

Unfortunately, no desired product was observed in any of the reactions and typically the carbinol

was consumed and the starting material was recovered.
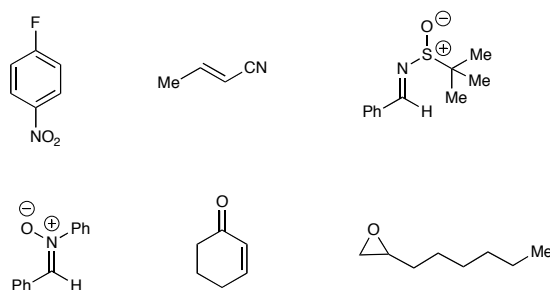
Figure 2-7. Electrophiles screened for reactivity with thiazolium carbinols

The lack of reactivity with respect to the thiazolium carbinol and various electrophiles was somewhat surprising. After considering the potential problems with this system, one explanation is that there has to be a specific balance of reactivity between the carbinol and the electrophile. After desilylation of the carbinol, one pathway the resulting alkoxide can follow is an intermolecuclar proton transfer to render the carbon nucleophilic (Path A, Figure 2-8). This species can then add to an appropriate electrophile to afford the desired acylated product. Alternatively, the alkoxide can collapse to generate an aldehyde and the thiazolium zwitterion (Path B). In order for the acylation reaction to be productive the electrophile has to be suitably reactive to enable the acyl anion equivalent addition while simultaneously avoiding aldehyde formation. The development of more nucleophilic thiazolium carbinols that are less prone decompose would be a definite advantage with many electrophiles. This may be possible by making appropriate modifications to the azolium component of the carbinol.
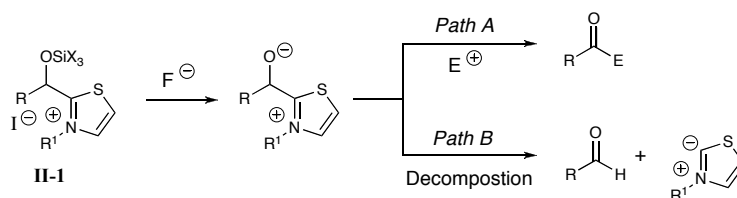
Figure 2-8. Two potential competing reaction pathways of the thiazolium carbinol

2.4 Direct Nucleophilic Acylations of Quinone Methides

During the development of our new strategy to form acyl anion equivalents from a fluoride anion and a thiazolium carbinol, we sought electrophiles that could also be generated from fluoride, such as *O*-silylated phenols (such as **II-28**) that produce *o*-quinone methides[29,30] when exposed to fluoride. Rokita and coworkers were the first to employ fluoride to generate quinone methides in their studies of DNA alkylation.[31-33] There have been a limited number of additional publications in this area, including a report from Barrero et al. utilizing fluoride-generated quinone methides in the synthesis of puupehedione analogs[34] and the stereoselective total synthesis of thielocine Alβ described by Young and coworkers from the Merck research laboratories.[35]

Given our interest in the development of new *Umpolung* strategies, we identified *o*-quinone methides as potential electrophiles in our acyl anion addition reactions. The product of this acylation reaction would be an α-aryl ketone and the preparation of α-aryl ketones is a challenging goal in organic synthesis. The majority of recent progress has focused on the development of transition metal-catalyzed couplings of enolates and aryl halides.[36-38] We envisioned developing an *Umpolung* approach by combining compounds with the general structures of **II-1** and **II-28** with an appropriate fluoride source to simultaneously generate the corresponding carbonyl anion and *o*-quinone methide species (Figure 2-9). The subsequent combination of the nucleophilic carbonyl anion and electrophilic *o*-quinone methide should provide an α-aryl ketone (**II-29**) in a single operation. The main challenge with this approach is that two highly reactive intermediates are presumably generated in the same flask and potential dimerization and/or decomposition could prevent the desired carbon-carbon bond-forming reaction.
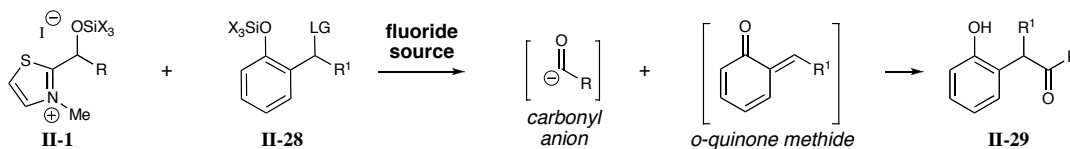
Figure 2-9. Nucleophilic acylation of quinone methides.

Our investigations of this new coupling strategy focused on the addition of thiazolium carbinol **II-1c** to *o*-quinone methide precursor **II-28a** in the presence of tetramethylammonium fluoride (Table 2-4). The exposure of **II-1c** and **II-28a** to this fluoride source at –50 °C afforded an encouraging 43% yield of the desired α-aryl ketone **II-29** (entry 1). Further optimization of the reaction conditions revealed that lower temperatures (–78 °C) provide improved yields of **II-29** (60%, entry 2). Given the bimolecular nature of this process, an important factor affecting the yield is concentration: the optimal value of 0.1 M affords 72% of **II-29** (entries 2-4). Although bromide leaving groups on the *o*-quinone methide precursor give the highest yields, the corresponding benzylic chloride is also a suitable reaction partner (entry 3 vs. entry 5), albeit in reduced yield (53%). Additional leaving groups were examined, such as acetates and amines, however no desired product was observed in these systems.

Table 2-4. Optimization of carbonyl anion additions to *o*-quinone methides

entry	temp. (°C)	X	concentration	yield
1	–50 to 23	Br	0.1 M	43%
2	–78	Br	0.3 M	23%
3	–78	Br	0.1 M	**72%**
4	–78	Br	0.05 M	45%
5	–78	Cl	0.1 M	53%

2.3.2   Evidence for an o-Quinone Methide Intermediate

The potential reaction pathway is one aspect of the new process that warrants further discussion.   A plausible route to the α-aryl ketone products involves the fluoride-promoted generation of an *o*-quinone methide intermediate. However, direct alkylation via an S_N2 process with a separate deprotection step would also afford the same α-aryl ketone products. To probe the viability of the direct alkylation pathway, benzyl bromide was employed as the electrophile under standard reaction conditions (Scheme 2-16). The corresponding aryl ketone was isolated in 26% yield suggesting that direct alkylation of the acyl anion equivalent can be accomplished under the standard reaction protocol.   This result prompted us to carry out a competition experiment between **II-28a** and *o*-methoxy benzyl bromide. The substrates **II-28a** and **II-31** were selected because they have very similar electronic properties, however, only **II-28a** would be able to form a quinone methide upon silyl cleavage. In this study we found that the α-aryl ketone **II-29** was isolated in 44% yield. There was no recovery of **II-28a**. The ^{1}H NMR spectrum of the unpurified reaction mixture of the competition experiment contains mainly **II-29** and **II-31** with no sign of the methoxy α-aryl ketone **II-32** when compared to an authentic sample of **II-32** (Figure 2-10). The recovery of **II-31** was low at 30%; however, this compound is volatile and it is likely the yield was substantially reduced during isolation.   This evidence strongly suggests that under standard reaction conditions the quinone methide pathway predominates.

Scheme 2-16. Investigation into quinone methide reaction pathway

II-1c

II-30

26% yield

1 equiv   1 equiv   1 equiv

II-1c   II-28a   II-31

44% yield

II-29

not observed in the
^{1}H NMR of the unpurified
reaction mixture
II-32
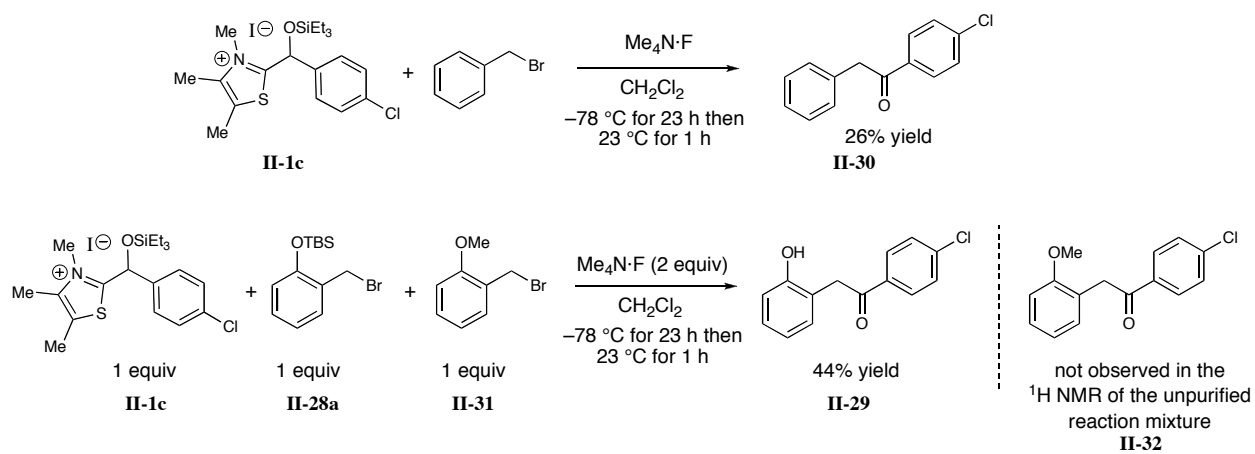
Figure 2-10. ^{1}H NMR spectrum of unpurified competition experiment
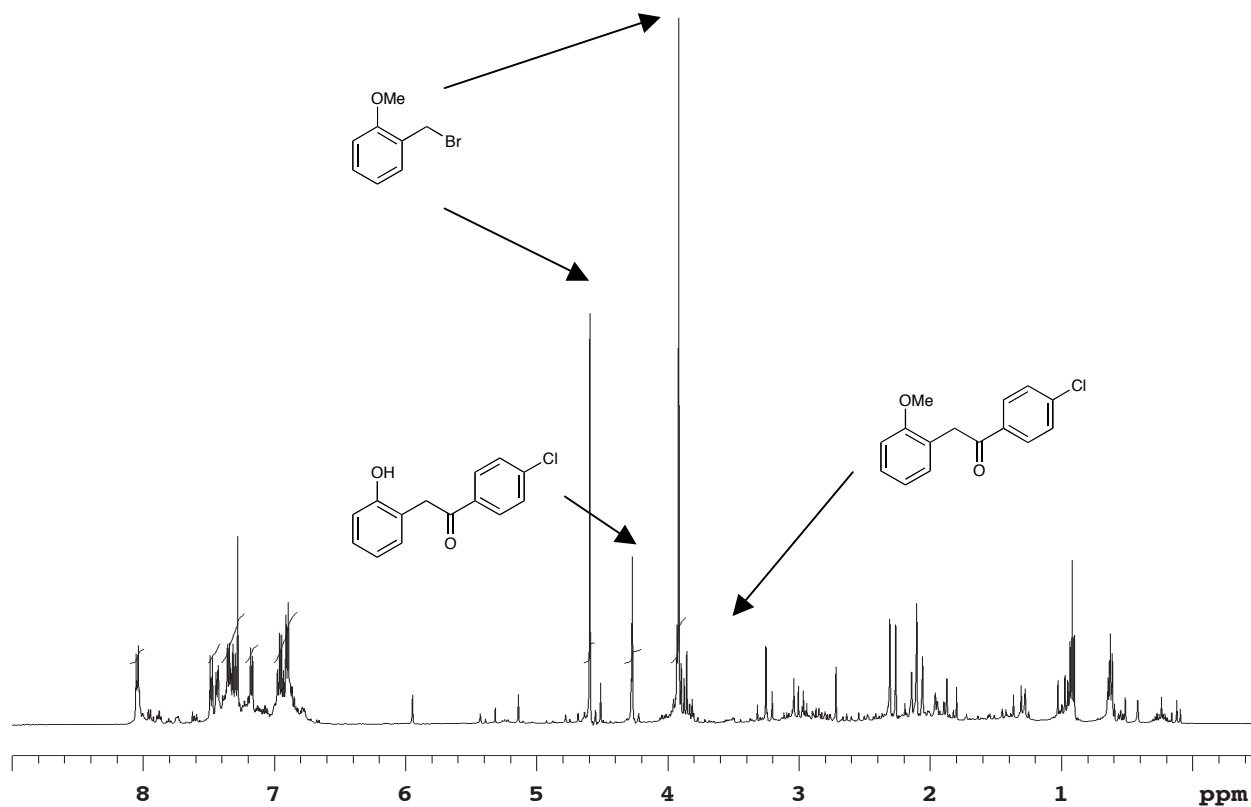
Authentic Sample
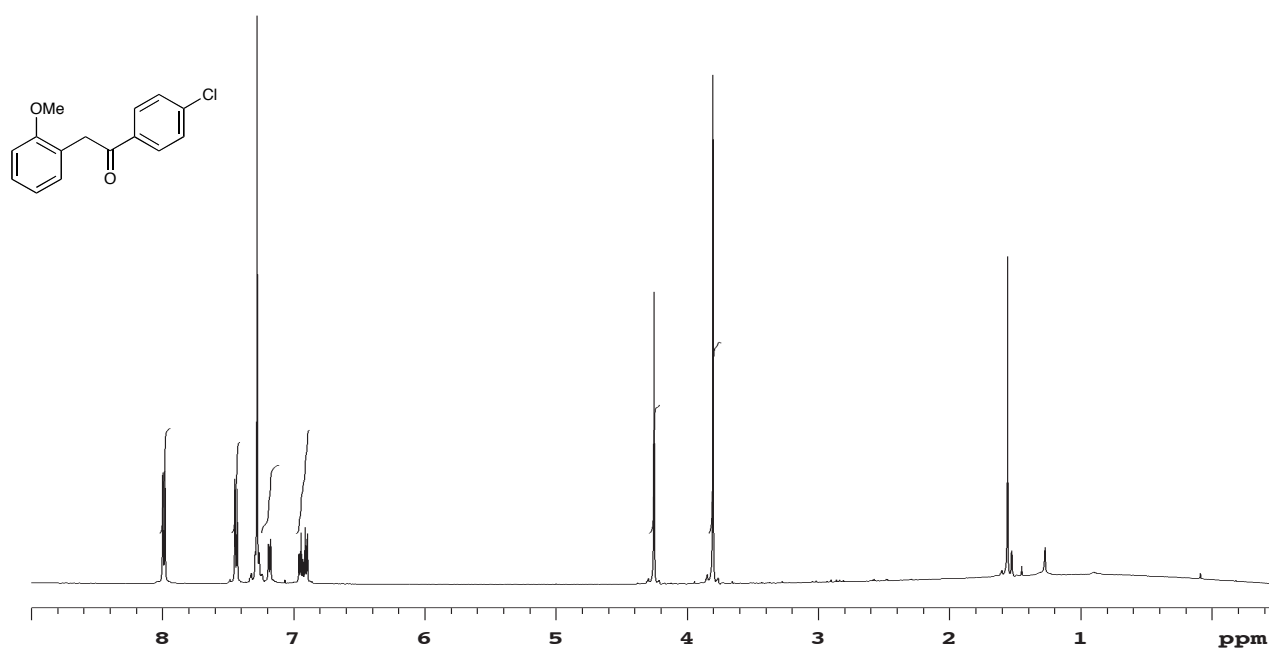
Additional experiments were conducted to evaluate the importance of the temperature profile (Scheme 2-17). Stirring **II-1c** and **II-28a** for just one hour at − 78 °C then warming to room temperature resulted in a reduced yield (45%) compared to the optimized reaction conditions of 23 hours at –78 °C. If the reaction is carried out at –25 °C for 23 hours then warmed to 23 °C for one hour, only a 25% yield of the desired α-aryl ketone is isolated. These results indicate the reaction temperature significantly affects to the outcome of the reaction.

Scheme 2-17. Investigation of reaction temperature on the nucleophilic acylation of quinone methides
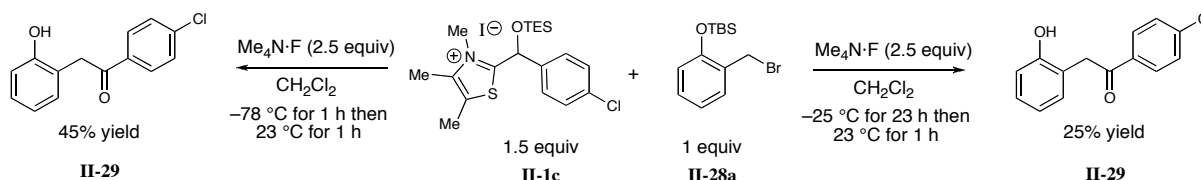
2.3.3 Reaction Scope of the Nucleophilic Acylation of Quinone Methides

With the optimal parameters established for this *Umpolung* reaction, we turned our attention to investigating the scope of the process (Table 2-5). A brief survey of thiazolium carbinols reveals the reaction accommodates additional aromatic substituents (entries 1-3). When carbinols derived from alkyl and α,β-unsaturated aldehydes are employed as the acyl anion precursor, the desired α-aryl ketones are formed in moderate yields (40-53%). For example, the carbinol prepared from cinnamaldehyde affords a 53% yield of the corresponding α-aryl ketone **II-35** (entry 4). Further work to accommodate these particular substrates is necessary.

An examination of the *o*-quinone methide component of the reaction indicates that variously substituted protected phenols are competent electrophile progenitors. In addition to the

unsubstituted methides (e.g. derived from **II-28**), alkyl and aryl substitution at R^1 provides

good yields of the corresponding acylated products (60% and 68%, entry 5).   Substitution on the

phenyl ring is also well tolerated. The quinone methide precursor derived from *o*-vanillin was

able to produce the desired α-aryl ketone in 68% yield (entry 6). A high yield of product was

also observed when the quinone methide precursor **II-28e** was subjected to the reaction

conditions (75%, entry 7). For certain structures, the benzylic bromide reactants are unstable and

could not be easily isolated. For these cases, the corresponding benzylic chlorides (**II-28b**, **II-28c** and **II-28e**) can be successfully employed in the reaction (entries 5 and 7).

Table 2-5. α-Aryl ketones prepared from thiazolium carbinols (**II-1**) and silylated phenols (**II-28**)

This fluoride-induced *Umpolung* strategy can be extended beyond *o*-quinone methides.

For example, α-indoyl ketone compounds such as **II-41** can be accessed in good yield (70%)

from the combination of a silyl protected gramine derivative **II-40** and thiazolium carbinol

II-1c in the presence of 2.5 equivalents of Me$_4$N•F (Scheme 2-18).[39]

Scheme 2-18. Nucleophilic acylation of silyl protected gramine derivative **II-40**
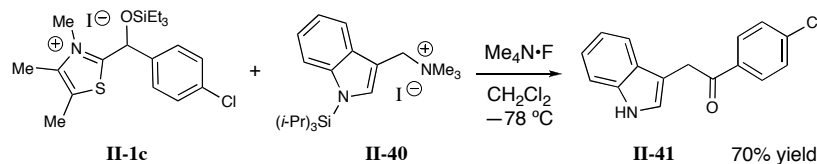
The addition of the thiazolium carbinol **II-1c** to the *p*-quinone methide derived from **II-42** was accomplished in low yield (14%, Scheme 2-19). The decrease in yield as compared to the *o*-quinone methide reaction may result from the more difficult generation of the *p*-quinone methide. No further attempts were made to improve the yield of this alkylation.

Scheme 2-19. Nucleophilic acylation of *p*-quinone methide
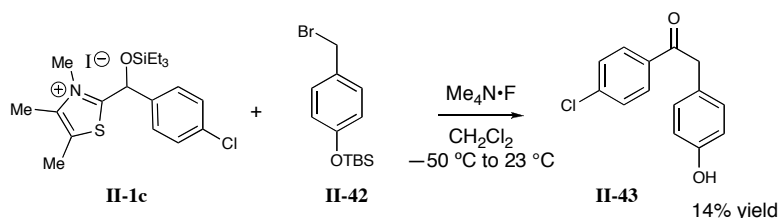
To demonstrate the synthetic utility of our new bond-forming process, we utilized it in the total synthesis of the naturally occurring aromatase inhibitor, demethylmoracin I (**II-44**, Figure 2-11).[40] Demethylmoracin I is an electron rich benzofuran that we envisioned would be accessible from α-aryl ketone **II-46** using an acid catalyzed cyclization. Key to our synthesis would be the preparation of the α-aryl ketone employing the newly developed strategy to couple thiazolium carbinol **II-47** with the quinone methide generated from **II-28e** using Me$_4$N·F. The

thiazolium carbinol and quinone methide precursor could be prepared from commercially available aldehydes.
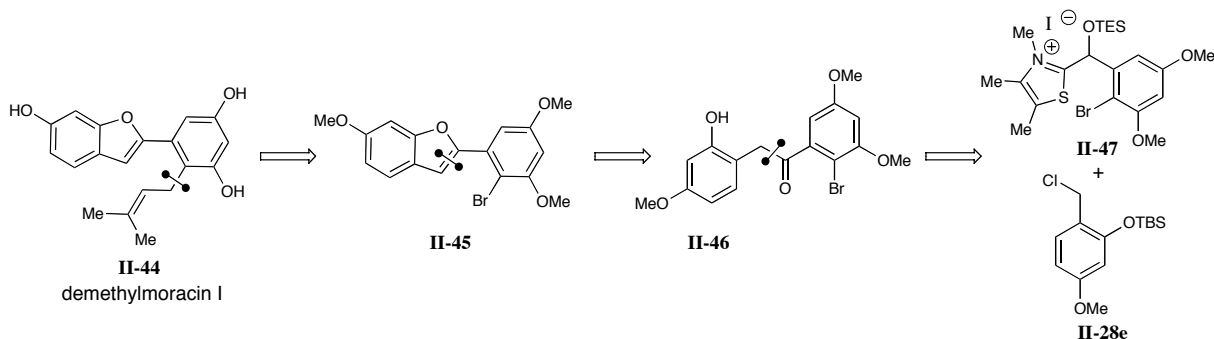
Figure 2-11. Retrosynthetic analysis of demethylmoracin I

Initially, it was not clear whether the highly substituted carbinol could be easily prepared or would operate as a successful acyl anion equivalent in our reaction since simpler carbinols had been tested to this point. The carbinol **II-47** was synthesized in four steps from commercially available 3,5-dimethoxybenzaldehyde (Scheme 2-20). The mono-brominated aldehyde was isolated in good yield according to a known procedure using bromine and acetic acid.[41] The addition of lithiated 4,5-dimethylthiazole to aldehyde **II-48** was accomplished to afford the carbinol in excellent yield. This resulting alcohol was protected with a TES group under standard conditions and alkylated with neat iodomethane at 80 °C to afford the desired thiazolium carbinol as an off-white solid. Notably, this highly substituted carbinol was readily prepared in a 49% overall yield.

Scheme 2-20. Synthesis of thiazolium carbinol **II-47**
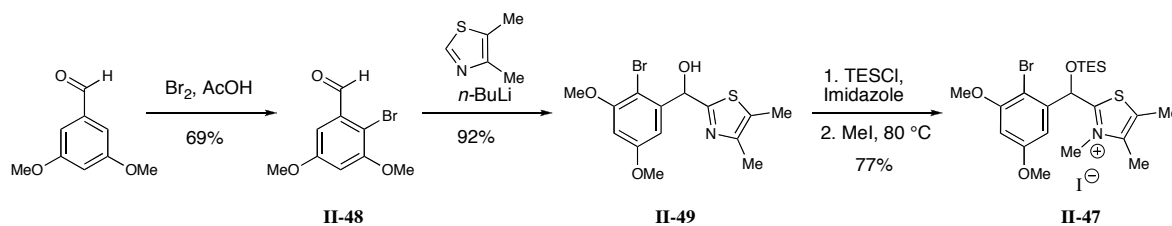
The preparation of the quinone methide precursor **II-28e** began with the mono-alkylation

of 2,4-dihydroxybenzaldehyde at the least sterically hindered position (Scheme 2-21). This

reaction is regiospecific due to hydrogen-bonding between the aldehyde and the phenol at the

ortho position. However, dialkylation was problematic resulting in the moderate yield in this

step. The silyl protection of **II-50** was accomplished using TBS-Cl and imidazole to yield the

protected aldehyde **II-51**. Due to the lability of the silyl group, all attempts to improve the yields

in this step were ineffective. Sodium borohydride was used to reduce **II-51** to the corresponding

benzylic alcohol in good yield. After exposure of **II-52** to freshly distilled thionyl chloride, the

benzyl chloride was isolated in 22% overall yield.

Scheme 2-21. Synthesis of quinone methide precursor **II-28e**
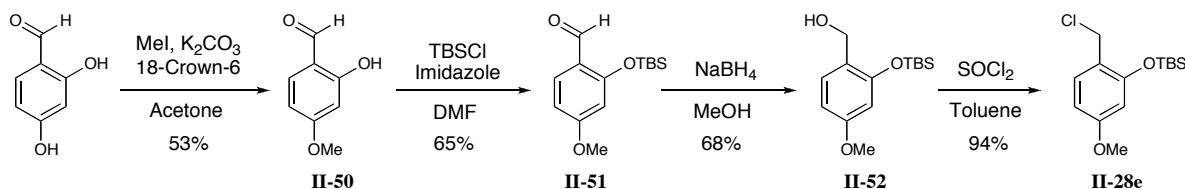
With the two fragments in hand, we focused on completing the synthetic sequence

(Scheme 2-22). In the key step, highly substituted α-aryl ketone **II-46** was prepared in 62%

yield from thiazolium carbinol **II-47** and **II-28e**. The acid-catalyzed cyclization to the corresponding benzofuran **II-45** was accomplished in 79% yield with Amberlyst 15 resin. The prenyl group was installed using a Stille cross coupling reaction[42,43] and global demethylation with lithium diphenylphosphanide[44] in refluxing THF afforded demethylmoracin I. The ^{1}H and ^{13}C NMR spectra matched the values reported in the literature.[40]

Scheme 2-22. Synthesis of demethylmoracin I
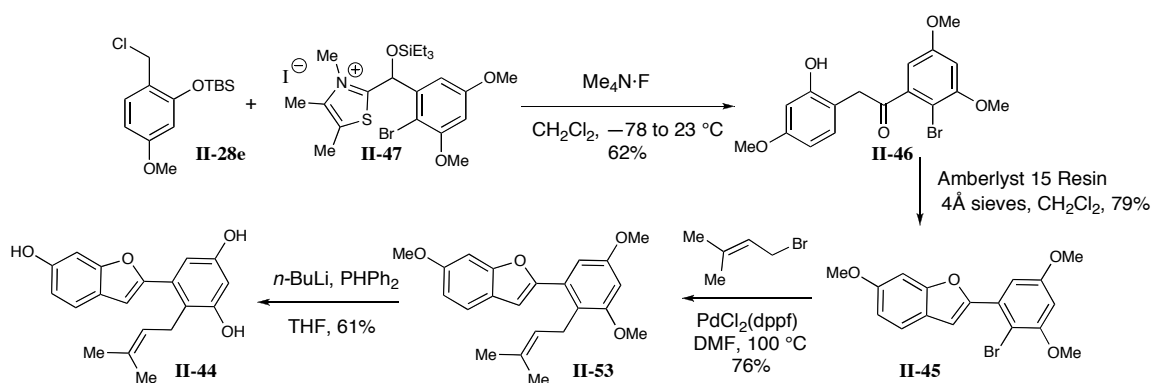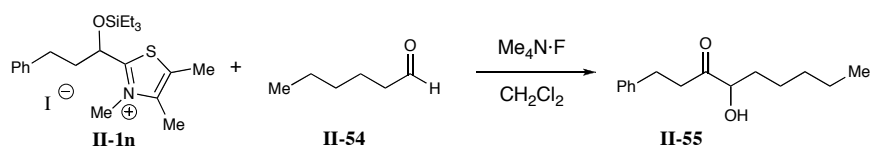
2.5   *Thiazolium Carbinol Additions to Aldehydes*

During the course of our studies into acyl anion addition reactions, it became clear that the development of a direct, crossed acyloin reaction for the synthesis of α-hydroxy ketones remains a difficult task. There are several aspects of acyloin reactions that make them particularly challenging. For example, under standard reaction conditions four possible acyloin products can be formed and competing aldol processes can lead to undesired side products. Typical approaches to synthesize acyloin products employ aldehydes as acyl anion precursors.[45] These methods can be especially problematic because acyl anion equivalent generated in situ can can undergo addition reactions with the acyl anion precursor and generally the formation of more

than one product cannot be avoided. Johnson et al. managed to control the outcome of the crossed benzoin reaction using acylsilanes as acyl anion precursors.[46,47] However, their method has not been suitable for the formation of crossed acyloin products. To date there is not a general method to directly prepare these compounds using an acyl anion strategy. We hypothesized that the addition of thiazolium carbinols to aldehydes may offer a synthetically useful route to access α-hydroxy ketones.

Our investigation into the development of this new method began with the addition of hydrocinnamaldehyde-derived thiazolium carbinol **II-1n** to hexanal. Initially, we subjected the carbinol and 2 equivalents of aldehyde to tetramethylammonium fluoride at −78 °C in CH_2Cl_2 (Table 2-6). The desired α-hydroxy ketone **II-54** was isolated in 34% yield along with a moderate amount of the hexanal homodimer. Because the homodimer of the aldehyde electrophile was isolated, we reasoned the carbene that is generated during the course of the reaction may be catalyzing an additional, undesired self-condensation reaction of the hexanal. In an attempt to reduce this unwanted dimer formation, hexafluoroisopropanol was added with the hope that the amounts of free carbene in solution would be limited and thus the undesired side reaction would be eliminated. While the dimer formation was drastically reduced with the addition of an alcohol, the yield was also reduced to only 25%. The decrease in yield may come as a result of the direct protonation of the carbonyl anion that is generated in situ in the presence of the acidic alcohol. Finally, a moderate yield of 61% was observed when the amount of aldehyde was increased to 4 equivalents with no alcohol additive present.

Table 2-6. Thiazolium carbinol additions to aldehydes

entry	Temp. (°C)	Equiv II-54	Equiv Me₄N·F	Additive	yield
1	−78	2	1.5	none	34%
2	−78	2	0.38	none	0%
3	0 to 23	2	0.38	none	38%
4	0 to 23	2	1.5	(CF₃)CHOH	25%
5	0 to 23	4	1.5	none	61%

These preliminary results demonstrate an exciting advance in the synthesis of crossed acyloin products. *O*-silyl thiazolium carbinols undergo nucleophilic additions to aldehyde electrophiles to yield the corresponding α-hydroxy ketones. At this time, the investigations into this promising new acylation reaction are ongoing.

2.6   Summary

O-Silyl thiazolium carbinols operate as stoichiometric acyl anion precursors under mild reaction conditions. We have found that fluoride can promote the nucleophilic addition of a thiazolium carbinol to nitroalkenes, *o*-quinone methides and aldehydes. The value of these carbinols as acylating agents is further enhanced because they are readily prepared, stable, easy to handle and convenient to store.

The direct nucleophilic acylation of nitroalkenes has been accomplished in good yield using the *O*-silyl carbinols with a fluoride anion and thiourea combination. Thiazolium carbinols derived from both electron rich and electron poor aldehydes operate as suitable acyl anion precursors and the corresponding β-nitro ketones have been isolated in high yield. Additionally,

many alkyl nitroalkenes are competent electrophiles in the newly developed reaction system. This process can be rendered asymmetric when a chiral thiourea is employed as an additive.

The synthesis of α-aryl ketones has been accomplished by the direct nucleophilic acylation of *o*-quinone methide electrophiles. In this transformation, two reactive intermediates, carbonyl anions and *o*-quinone methides, are generated in one flask upon the addition of fluoride. These intermediates then undergo productive addition reactions to afford the desired α-aryl ketone adducts. This new strategy has been applied to a short synthesis of the natural product demethylmoracin I, a naturally occurring aromatase inhibitor.

Finally, promising results indicate that thiazolium carbinols undergo productive additions to aldehydes for the synthesis of crossed acyloin products. Direct access to unsymmetrical α-hydroxy ketones is a challenging goal and research toward developing this method into a useful synthetic transformation is currently underway.

2.7 *Experimental Section*

General Information. All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. THF, Et$_2$O, CH$_2$Cl$_2$, DMF and toluene were purified by passage through a bed of activated alumina.[48] CHCl$_3$ was purified by passage through a pad of alumina prior to use. Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[49] Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and anisaldehyde, ceric ammonium nitrate stain, potassium

permangenate, or phosphomolybic acid followed by heating. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bio-Rad Win FT-IR Pro spectrometer. ^{1}H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) or Mercury 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 7.26 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 Varian Inova 500 (125 MHz) or Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 77.0 ppm). Laser desorption mass spectra were obtained with PE BioSystems time-of-flight MALDI mass spectrometer with 2,5-dihydroxybenzoic acid as matrix. Electrospray ionization mass spectra were obtained on a Thermo Finnigan lcms ion trap mass spectrometer.

Tetrabutylammonium triphenyldifluorosilicate (TBAT) and tetramethylammonium fluoride (TMAF) were purchased from Aldrich and used without further purification. Nitroalkenes (**2**) were prepared according to the procedure of Feringa et al.[25] 1-Nitrocyclohexene was purchased from Aldrich and used with further purification. Thiocarbanilide was used as received from Aldrich. Thiourea **II-18** was prepared according to the procedure of Soós and coworkers.[26]

2.7.1 General Procedure for the Preparation of Protected Thiazolium Carbinols
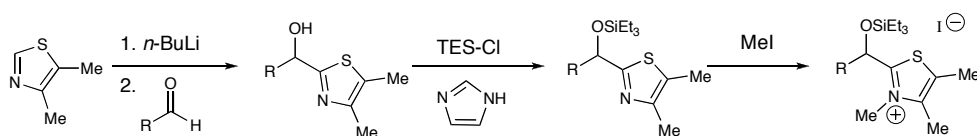
Synthesis of Carbinols:

A flame-dried round bottom flask under N_2 was charged with 4,5-dimethylthiazole (1 mL, 9.45 mmol). THF (45 mL) was added and the solution was cooled to -78 °C. *n*-Butyllithium (1.9M, 6 mL, 11.3 mmol) was added dropwise to the cold reaction mixture. The resulting dark red solution was stirred for 45 min at 78 °C. The aldehyde (28.4 mmol) was then added, causing the solution to turn yellow, and the reaction was stirred for 1 h at -78 °C. The reaction was warmed to room temperature and stirred for 2 h. At this time, water (50 mL) was added to quench the reaction. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (200 mL). The aqueous layer was extracted two additional times with ethyl acetate (100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by recrystallization (ethyl acetate/hexanes).

Partial Characterization of Carbinols:
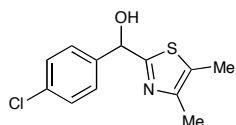
(4-Chlorophenyl)(4,5-dimethylthiazol-2-yl)methanol: Purified by recrystallization (ethyl acetate/hexanes), yielding 79% as a yellow solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ7.42 (m, 2H); 7.35 (m, 2H); 5.93 (s, 3H); 4.46 (s, 1H); 2.30 (s, 3H); 2.28 (s, 3H)
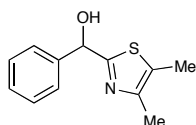
(4,5-Dimethylthiazol-2-yl)(phenyl)methanol: Purified by recrystallization (ethyl acetate/hexanes), yielding 1.94 g (84%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ7.46 (m, 2H); 7.38 (m, 3H); 5.95 (s, 3H); 2.30 (s, 3H); 2.29 (s, 3H)
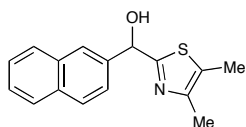
(4,5-Dimethylthiazol-2-yl)(naphthalen-3-yl)methanol: Purified by recrystallization (ethyl acetate/hexanes), yielding 1.99 g (78%) as an off white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ7.98 (m, 1H); 7.87 (m, 1H); 7.86 (m, 1H); 7.86 (m, 1H); 7.59 (m, 1H); 7.57 (m, 1H); 7.51 (m, 1H); 6.14 (s, 1H); 2.32 (s, 3H); 2.30 (s, 3H)
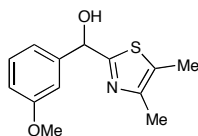
(3-Methoxyphenyl)(4,5-dimethylthiazol-2-yl)methanol: Purified by recrystallization (ethyl acetate/hexanes), yielding 2.18 g (93%) as a yellow solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ7.30 (m, 1H); 7.06 (m, 2H); 6.88 (m, 1H); 5.93 (s, 1H); 3.82 (s, 3H); 2.30 (s, 3H); 2.28 (s, 3H)
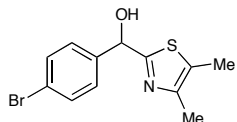
(4-Bromophenyl)(4,5-dimethylthiazol-2-yl)methanol: Purified by recrystallization (ethyl acetate/hexanes), yielding 1.87 g (70%) as a yellow solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ7.51-7.50 (m, 2H); 7.37-7.35 (m, 2H); 5.90 (s, 3H); 2.31 (s, 3H); 2.30 (s, 3H)

Typical Protection and Alkylation of Carbinols:

To a flame-dried round bottom flask under N$_2$ was added the carbinol (7.3 mmol) followed by dichloromethane (75 mL). Next, triethylsilylchloride (22 mmol) was added followed by imidazole (8.0 mmol). The resulting suspension was then stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane (100 mL) and washed three times with brine (200 mL). The combined aqueous layers were washed with dichloromethane.

The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo.*

The pale yellow oil was used in the next step without further purification.

To the protected carbinol in a flame-dried round bottom flask was added iodomethane (10 eq) and the reaction was heated to 80 °C. After 12 h the reaction was cooled to room temperature and concentrated *in vacuo.* Diethyl ether was then added to the yellow residue and the product precipitated. The solid was collected by vacuum filtration, washed with diethyl ether and dried under vacuum. The resulting product was used with further purification.
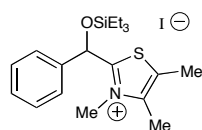
II-1b was isolated as a pale yellow solid in a 40% yield over the three steps. R_f = 0.50 (20% methanol/chloroform); Mp: 150-151°C; IR (film) 2953, 2875, 1604, 1455, 1073, 1008, 808, 735 cm^{-1} ; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.56 (m, 2H); 7.44 (m, 3H); 6.86 (s, 1H); 3.95 (s, 3H); 2.51 (s, 3H); 2.43 (s, 3H); 0.87 (t, *J* =7.6 Hz, 9H); 0.65 (m, 6H) ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.0, 143.9, 137.0, 130.6, 129.7, 128.5, 73.4, 40.6, 13.5, 13.1, 6.9, 5.1; LRMS (MALDI-TOF): Mass calculated for C$_{19}$H$_{30}$NO$_2$SSi [M-I]$^+$, 348.2. Found 348.80.
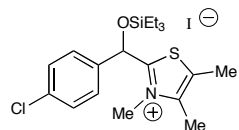
II-1c was isolated as a pale yellow solid in a 63% yield over the three steps. R_f = 0.49 (20% methanol/chloroform); Mp: 152-154°C; IR (film) 2951, 2876, 1600, 1242, 1083, 1101, 806, 735 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.62 (m, 2H); 7.42 (m, 2H); 7.05 (s, 1H); 4.01 (s, 3H); 2.52 (s, 3H); 2.44 (s, 3H); 0.89 (t, *J* =8.0 Hz, 9H); 0.69 (m, 6H) ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.0, 144.0, 136.4, 135.8, 130.7, 130.0, 72.4, 40.9, 13.3,

12.9, 7.0, 5.1; LRMS (MALDI-TOF): Mass calculated for $C_{19}H_{29}NO_2SSi$ $[M-I]^+$, 382.1.

Found 382.75.
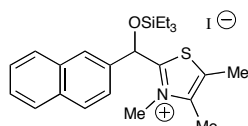
II-1d was isolated as a yellow solid in a 53% yield over the three steps. R_f = 0.55 (20% methanol/chloroform); Mp: 160-161 °C; IR (film) 2951, 2874, 1600, 1456, 1085, 1009, 807, 745 cm^{-1} ; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.21 (s, 1H); 7.96 (m, 1H); 7.90 (m, 1H); 7.87 (m, 1H); 7.59 (m, 1H); 7.57 (m, 1H); 7.52 (m, 1H); 3.97 (s, 3H); 2.53 (s, 3H); 2.42 (s, 3H); 0.87 (t, J =8.0 Hz, 9H); 0.68 (m, 6H) ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.0, 144.0, 134.1,133.9, 133.2, 130.7, 130.0, 128.7, 128.6, 128.1, 127.7, 127.3, 124.6, 73.6, 40.7, 13.4, 13.1, 6.9, 5.1; LRMS (MALDI-TOF): Mass calculated for $C_{23}H_{32}NOSSi$ $[M-I]^+$, 398.2. Found 398.7.
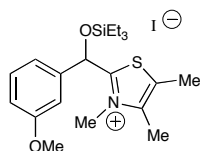
II-1e was isolated as a yellow solid in a 53% yield over the three steps. R_f = 0.55 (20% methanol/chloroform); Mp: 118-120 °C; IR (film) 2951, 2875, 1597, 1456, 1261, 1078, 1008, 806, 745 cm^{-1} ; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (m, IH); 7.12 (s, 1H); 7.10 (s, IH); 6.94 (m, IH); 6.79 (s, IH); 3.95 (s, 3H); 3.84 (s, 3H); 2.45 (s, 3H); 2.43 (s, 3H); 0.87 (t, J =8.0 Hz, 9H); 0.65 (m, 6H) ; ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.2, 160.4, 143.9, 138.5, 130.8, 130.5, 120.6, 115.9, 114.0, 73.3, 56.0, 40.7, 13.4, 12.9, 6.9, 5.1; LRMS (MALDI-TOF): Mass calculated for $C_{20}H_{34}NOSSi$ $[M-I]^+$, 378.2. Found 378.9.
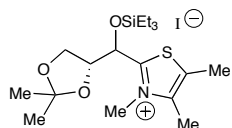
II-1f was isolated as a yellow solid in a 40% yield over the three steps as a mixture of diastereomers (1:1 dr). IR (film) 2951, 2878, 1603, 1454, 1377, 1258, 1216, 1142, 1070, 1009 cm^{-1} ; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.95 (d, J = 3.7 Hz, 1H);

5.34 (d, *J* = 5.8 Hz, 1H); 4.49 (q, *J* = 2.8 Hz, 1H); 4.22 (s, 3H); 4.18 (s, 3H); 4.13, (q, J = 4.6

Hz, 1H), 4.03 (m, 2H); 3.96 (m, 2H); 2.53 (s, 3H); 2.49 (s, 3H); 2.48 (S, 3H); 2.47 (s, 3H); 1.39

(s, 3H); 1.20 (s, 3H); 1.18 (s, 3H); 1.12 (s, 3H); 0.89-0.81 (m, 18H); 0.67-0.60 (m, 12H);

^{13}C NMR (100 MHz, CDCl$_3$) δ 173.0, 172.9, 143.6, 142.8, 130.9, 130.7, 110.4, 110.1, 79.0,

76.2, 70.9, 69.9, 66.1, 64.4, 41.4, 25.7, 25.3, 24.3, 24.1, 13.3, 13.1, 12.8, 12.7, 6.2, 4.3, 4.2;

LRMS (MALDI-TOF): Mass calculated for C$_{18}$H$_{34}$NO$_3$SSi [M-I]$^+$ 372.2, . 373.1 Found.
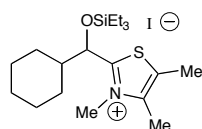
II-1g was isolated as a white solid in a 13% yield over the three steps. IR (film) 2928, 2870, 1605, 1450, 1110, 1008 cm^{-1} ; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.25 (d, *J* = 3.7 Hz, 1H); 4.28 (s, 3H); 2.63 (s, 3H); 2.50 (s, 3H); 1.88-1.01 (m, 11H); 0.97 (t, *J* =7.9 Hz, 9H); 0.70 (q, *J* = 7.9 Hz, 6H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 176.4, 144.1, 130.3, 75.0,

43.8, 41.5, 30.1, 26.1, 25.9, 25.7, 14.0, 13.1, 7.1, 5.0; LRMS (MALDI-TOF): Mass calculated

for C$_{19}$H$_{36}$NOSSi [M-I]$^+$ 354.2, 354.9 Found.
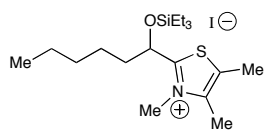
II-1h was isolated as a pale yellow solid in a 14% yield over the three steps. IR (film) 2951, 1606, 1458, 1241, 1092, 1009 cm^{-1} ; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.55 (t, *J* = 5.5 Hz, 1H); 4.25 (s, 3H); 2.60 (s, 3H); 2.50

(s, 3H); 1.96-1.87 (m, 2H); 1.51-1.50 (m, 2H); 1.30-1.26 (m, 4H); 0.97 (t, *J* =7.6 Hz, 9H); 0.88

(m, 3H); 0.72 (q, *J* = 7.6 Hz, 6H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 177.3, 143.9, 130.2, 70.8,

41.1, 37.1, 31.4, 23.8, 22.6, 14.1, 13.8, 13.1, 6.9, 4.9; LRMS (MALDI-TOF): Mass calculated

for C$_{18}$H$_{36}$NOSSi [M-I]$^+$, 342.2. Found 342.7.
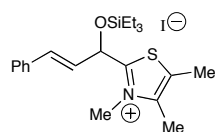
II-1i was isolated as a white solid in a 39% yield over the three steps. IR (film) 2951, 2876, 1602, 1446, 1092, 1006, 975 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.49-7.48 (m, 2H); 7.38-7.32 (m, 3H); 7.24 (d, J = 16 Hz, 1H); 6.38 (d, J = 7.9 Hz, 1H); 6.19 (dd, J = 8.2 Hz, 16 Hz, 1H); 4.20 (s, 3H); 2.50 (s, 3H); 2.49 (s, 3H); 0.99 (t, J = 7.9 Hz, 9H); 0.77 (q, J = 7.9 Hz, 6H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.7, 144.0, 137.5, 134.8, 130.7, 129.4, 129.0, 127.5, 123.9, 72.1, 40.7, 13.5, 13.0, 7.0, 5.2; LRMS (MALDI-TOF): Mass calculated for C$_{21}$H$_{32}$NOSSi [M-I]$^+$ 374.2, 375.0 Found.
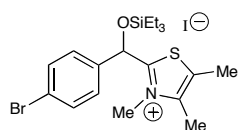
II-1m was isolated as a yellow solid in a 31% yield over the three steps. R$_f$ = 0.55 (20% methanol/chloroform); Mp: 170-172 °C; IR (film) 2955, 2876, 1597, 1486, 1242, 1080, 1010, 806, 731 cm^{-1} ; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.56(m, 4H); 7.04 (s, IH); 4.00 (s, 3H); 2.52 (s, 3H); 2.44 (s, 3H); 0.87 (t, J = 7.9 Hz, 9H); 0.65 (m, 6H) ; ^{13}C NMR (125 MHz, CDCl$_3$) δ 176.2, 144.1, 136.2, 132.9, 130.8, 130.2, 124.6, 72.5, 40.8, 13.4, 13.0, 7.0, 5.1; LRMS (MALDI-TOF): Mass calculated for C$_{20}$H$_{34}$NOSSi [M-I]$^+$, 426.1. Found 426.9.

2.7.2   Typical Procedure for the Nucleophilic Acylation of Nitroalkenes

A dry screw-capped tube containing a magnetic stir bar was charged with thiourea **II-8** (76 mg, 0.335 mmol) in a nitrogen-filled glove box. Also in the box the protected thiazolium carbinol (260 mg, 0.510 mmol) and tetramethylammonium fluoride (48 mg, 0.510 mmol) were weighed into two separate dram vials. All items were removed from box and the tube was put under a positive N$_2$ pressure. The nitroalkene (52 mg, 0.335 mmol) was added to the thiourea in dicholoromethane (1.6 mL). Reaction mixture was cooled to –40 °C. Next, carbinol was added

in dicholormethane (0.5 mL) and the reaction was allowed to stir for 5 min. Last, Me₄N·F

was added in dicholormethane (0.5 mL). Reaction was allowed to stir at –40 °C for 2-24 h until

complete by thin layer chromatography (20% ether/hexanes). Upon completion reaction was

quenched with water and diluted with dicholormethane then allowed to warm to room

temperature. The layers were separated and the aqueous layer was extracted two additional

times with dichloromethane (30 mL). The combined organic extracts were dried over sodium

sulfate, filtered and concentrated *in vacuo*. The resulting orange residue was purified by flash

column chromatography on silica gel.
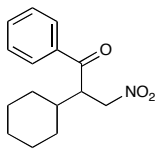
2-Cyclohexyl-3-nitro-1-phenylpropan-1-one (II-6): Purified with 5% ether/hexanes, yielding 59 mg (59%) of **II-6** as a colorless oil. R_f = 0.39 (20% ether/hexanes); IR (film) 2929, 2854, 1679, 1551, 1375 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.00-7.98 (m, 2H); 7.63-7.60 (m, 1H); 7.52-7.49 (m, 2H); 5.09 (dd, J =14.5, 10.4 Hz, 1H); 4.53 (dd, J =14.6, 3.3 Hz, 1H); 4.20-4.16 (m, 1H); 1.72-1.62 (m, 6H); 1.25-1.06 (m, 4H); 0.96-0.91 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ; 199.9, 136.8, 133.8, 129.1, 128.7, 73.9, 49.2, 39.5, 31.7, 29.8, 26.6, 26.4, 26.1; LRMS (ESI): Mass calculated for C₁₅H₁₉NO₃Na [M+Na]⁺, 284.13. Found 284.2.
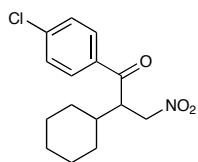
1-(4-Chlorophenyl)-2-cylcohexyl-3-nirtropropan-1-one (II-7): Purified with 5% ether/hexanes, yielding 78 mg (78%) of **II-7** as a white solid. R_f = 0.39 (20% ether/hexanes); Mp: 69.5-70.5 °C; IR (film) 2929, 1680, 1554, 1375 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.94-7.92 (m, 2H); 7.49-7.47 (m, 2H); 5.07 (dd, J =14.7, 10.4 Hz, 1H); 4.53 (dd, J =15.0, 3.4 Hz, 1H); 4.13-4.09 (m, 1H); 1.73-1.61 (m, 6H); 1.20-1.05 (m, 4H);

0.95-0.88 (m, 1H) ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.9, 140.4, 135.2, 130.1, 129.5, 73.9, 49.1, 39.5, 31.9, 29.9, 26.6, 26.4, 26.0; LRMS (ESI): Mass calculated for C$_{15}$H$_{18}$ClNO$_3$Na [M+Na]$^+$, 318.1. Found 319.1.

1-(4-Chlorophenyl)-2-(nitromethyl)heptan-1-one (II-10): Purified with 5% ether/hexanes, yielding 65 mg (65%) of **II-10** as a colorless oil. R$_f$ = 0.42 (20% ether/hexanes); IR (film) 2931, 2862, 1683, 1555, 1378 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94-7.92 (m, 2H); 7.50-7.48 (m, 2H); 5.01 (dd, J =14.6, 9.5 Hz, 1H); 4.49 (dd, J =14.6, 4.2 Hz, 1H); 4.21-4.20 (m, 1H); 1.72-1.66 (m, 1H); 1.55-1.50 (m, 1H); 1.29-1.24 (m, 6H); 0.84-0.82 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.9, 140.6, 134.4, 130.2, 129.6, 75.2, 44.0, 31.8, 30.3, 26.6, 22.5, 14.1; LRMS (ESI): Mass calculated for C$_{14}$H$_{18}$ClO [M-NO$_2$]$^+$, 237.1. Found 236.3.
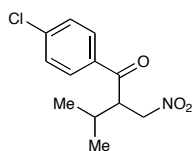
1-(4-Chlorophenyl)-3-methyl-2-(nitromethyl)butan-1-one (II-11): Purified with 5% ether/hexanes, yielding 73 mg (73%) of **II-11** as a colorless oil. R$_f$ = 0.32 (20% ether/hexanes); IR (film) 2967, 2932, 1681, 1550, 1375 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94-7.93 (m, 2H); 7.50-7.48 (m, 2H); 5.09 (dd, J =10.5, 4.0 Hz, 1H); 4.54 (dd, J =11, 3.5 Hz, 1H); 4.14-4.11 (m, 1H); 2.14-2.11 (m, 1H); 1.04 (d, J =7.0 Hz, 3H); 0.88 (d, J =7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.8, 140.4, 135.0, 130.1, 129.5, 73.3, 49.5, 29.5, 21.2, 19.1;

3-(Benzyloxy)-1-(4-chlorophenyl)-2-(nitromethyl)butan-1-one (II-12):
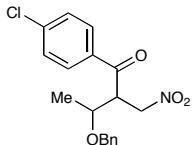
Purified using a gradient from 5% to 40% ether/hexanes, yielding 80 mg (80%) of **II-12**, a non-separable mixture of diastereomors, as a colorless oil. R_f = 0.20 (20% ether/hexanes); IR (film) 2978, 2919, 2872, 1555, 1378 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.95-7.93 (m, 2H); 7.82-7.81 (m, 2H); 7.50-7.48 (m, 2H); 7.44-7.42 (m, 2H); 7.39-7.31 (m, 6H); 7.29-7.27 (m, 2H); 7.24-7.23 (m, 2H); 5.16 (dd, J =14.7, 10.2 Hz, 1H); 5.70 (dd, J =15.0, 9.7 Hz,, 1H); 4.80 (dd, J =15.0, 3.5 Hz, 1H); 4.71 (dd, J =14.8, 2.8 Hz, 1H); 4.66 (d, J =12.1 Hz, 1H), 4.58 (d, J =11.7 Hz, 1H); 4.54 (m, 1H); 4.47 (d, J =11.9 Hz, 1H); 4.37 (m, 1H); 4.34 (d, J =11.7 Hz, 1H); 3.94 (m, 1H); 3.82 (m, 1H); 1.23 (d, J =6.2 Hz, 3H); 1.13 (d, J =6.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.5, 196.7, 140.6, 140.6, 137.6, 137.4, 135.0, 134.5, 130.3, 130.2, 129.5, 129.4, 128.9, 128.8, 128.4, 128.3, 128.1, 128.0, 73.7, 73.6, 72.8, 71.6, 71.4, 71.1, 50.3, 49.6, 18.2, 16.4; LRMS (ESI): Mass calculated for C$_{36}$H$_{36}$Cl$_2$N$_2$O$_8$ [2M]$^+$, 694.2. Found 696.2.

(4-Chlorophenyl)(2-nitrocyclohexyl)methanone (II-13): Purified with 5% ether/hexanes, yielding 80 mg (80%) of **II-13**, the trans diastereomer, as a white solid. R_f = 0.29 (20% ether/hexanes); Mp: 78-79 °C; IR (film) 2943, 2864, 1680, 1546, 1379 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.95-7.93 (m, 2H); 7.51-7.49 (m, 2H); 4.98 (ddd, J =11.9, 11.9, 3.3 Hz, 1H); 3.96 (ddd. J =11.9, 11.9, 2.9 Hz, 1H); 2.65-2.63 (m, 1H); 2.17-2.14 (m, 1H); 2.04-2.02 (m, 1H); 1.90-1.80 (m, 2H); 1.55-1.33 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.9, 140.4, 133.7, 130.1, 129.4, 95.0, 84.9, 48.0, 31.8, 29.4, 25.0, 24.9 LRMS (ESI): Mass calculated for C$_{26}$H$_{28}$Cl$_2$N$_2$O$_6$Na [2M+Na]$^+$, 557.1. Found 557.0. Diastereomer ratio was determined by 500MHz ^{1}H NMR spectrum.
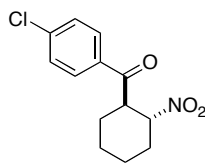
Determination of Conformation of β-Nitroketone II-13:
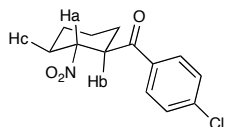
Proton decoupling experiments were preformed in order to determine the conformation of **II-13**.

Decoupled Proton	J - Values
H$_a$	J H$_b$ = 12.3, 2.9 Hz
H$_b$	J H$_a$ = 11.9, 3.3 Hz
H$_c$	J H$_a$ = 11.5, 11.5 Hz

4-
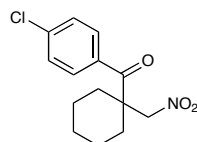
Chlorophenyl)(1-(nitromethyl)cyclohexyl)methanone (II-14): Purified with 5% ether/hexanes, yielding 56 mg (56%) of **II-14** as a colorless oil. R$_f$ = 0.29 (20% ether/hexanes); IR (film) 2936, 2862, 1682, 1551, 13378 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.51-7.49 (m, 2H); 7.41-7.39 (m, 2H); 4.96 (s, 2H); 1.76-1.74 (m, 2H); 1.60-1.58 (m, 3H); 1.50-1.43 (m, 2H); 1.36-1.33 (m, 1H); ^{13}C NMR (500 MHz, CDCl$_3$) δ 206.3, 137.5, 126.9, 128.8, 79.6, 51.8, 32.1, 25.4, 22.0; LRMS (ESI): Mass calculated for C$_{14}$H$_{16}$ClO [M-NO$_2$]$^+$, 235.1. Found 236.4.
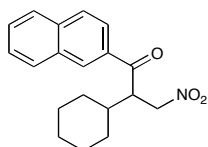
2-Cylcohexyl-1-(napthalen-3-yl)-3-nitropropane-1-one (II-15): Purified with 5% ether/hexanes, yielding 80 mg (80%) of **II-15** as a colorless oil. R$_f$ = 0.28 (20% ether/hexanes); IR (film) 2928, 2854, 1674, 1551, 1375 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.52 (s, 1H); 8.05-8.00 (m, 2H); 7.94-7.89 (m, 2H); 7.64-7.56 (m, 2H); 5.15 (dd, J =14.5, 10.2 Hz, 1H); 4.59 (dd, J =14.6, 3.1 Hz, 1H); 4.35 (m, 1H); 1.81-1.61 (m, 6H); 1.21-0.96 (m, 5H); ^{13}C NMR (500 MHz, CDCl$_3$) δ 200.0, 136.0, 134.3, 132.8, 130.5, 130.0, 129.1, 129.0, 128.1, 127.2, 124.3, 74.1, 49.2, 39.7, 31.7, 30.0, 26.6, 26.5, 26.1; LRMS (ESI): Mass calculated for C$_{19}$H$_{22}$NO$_2$ [M+H]$^+$, 312.2. Found 312.4.
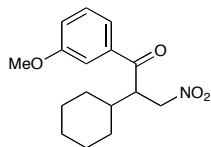
2-Cyclohexyl-1-(3-methoxyphenyl)-3-nitropropan-1-one (II-16): Purified with 5%-40% ether/hexanes, yielding 60 mg (60%) of **II-16** as a colorless oil. $R_f = 0.38$ (20% ether/hexanes); IR (film) 2930, 2854, 1680, 1554, 1266 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.59-7.58 (m, 1H); 7.52 (s, 1H); 7.45-7.42 (m, 1H); 7.18-7.16 (m, 1H); 5.09 (dd, J =14.5, 10.4 Hz, 1H); 4.55 (dd, J =14.5, 2.9 Hz, 1H); 4.2 (m, 1H); 3.89 (s, 3H); 1.73-1.63 (m, 6H); 1.23-1.08 (m, 4H); 0.98-0.93 (m, 1H); ^{13}C NMR (500 MHz, CDCl$_3$) δ 199.7, 160.2, 138.2, 130.1, 121.3, 120.2, 113.1, 73.9, 55.7, 49.3, 39.5, 31.7, 29.8, 26.6, 26.4, 26.1; LRMS (ESI): Mass calculated for C$_{16}$H$_{22}$NO$_4$Na [M+Na+H]$^+$, 315.1. Found 315.5.
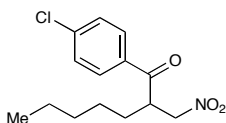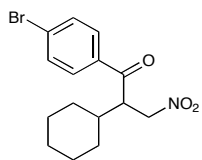
1-(4-Bromophenyl)-2-cyclohexyl-3-nitropropan-1-one (II-17): Purified with 2-6% ether/hexanes, yielding 81 mg (81%) of **II-17** as a colorless oil. $R_f = 0.29$ (20% ether/hexanes); Mp = 95.5-97 °C; IR (film) 2929, 2854, 1680, 1554, 1375, 1250 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87-7.86 (m, 2H); 7.67-7.65 (m, 2H); 5.09 (dd, J =15.0, 10.7Hz, 1H); 4.55 (dd, J =15.0, 3.4 Hz, 1H); 4.13-4.10 (m, 1H); 1.74-1.62 (m, 6H); 1.26-1.06 (m, 4H); 0.97-0.89 (m, 1H); ^{13}C NMR (500 MHz, CDCl$_3$) δ 199.1, 135.6, 132.4, 130.2, 129.1, 73.9, 55.7, 49.1, 39.5, 31.7, 29.9, 26.6, 26.4, 26.0; LRMS (ESI): Mass calculated for C$_{18}$H$_{18}$BrNO$_2$Na [M+Na]$^+$, 362.0. Found 363.5.

2.7.3 *Asymmetric Nucleophilic Acylation of Nitroalkenes*

A dry screw-capped tube containing a magnetic stir bar was charged with thiourea **II-18** (200 mg, 0.335 mmol) in a nitrogen-filled glove box. Also in the box the protected thiazolium carbinol **II-1c** (260 mg, 0.510 mmol) and tetramethylammonium fluoride (Me$_4$N·F, 48 mg, 0.510

mmol) were weighed into two separate dram vials. All items were removed from box and the tube was put under a positive N_2 pressure. The nitroalkene (52 mg, 0.335 mmol) was added to the thiourea in dicholoromethane (1.6 mL). Reaction mixture was cooled to −78 °C. Next, carbinol was added in dicholormethane (0.5 mL) and the reaction was allowed to stir for 5 min. Last, $Me_4N·F$ was added in dicholormethane (0.5 mL). Reaction was allowed to stir at −78 °C for 2-24h until complete by thin layer chromatography (20% ether/hexanes). Upon completion reaction was quenched with water and diluted with dicholormethane then warmed to room temperature. The layers were separated and the aqueous layer was extracted two additional times with dichloromethane (30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting orange residue was purified by flash column chromatography on silica gel.

Enantiomeric excess determined by HPLC on a Chiralcel OD-H column. 10% IPA/Hexanes, 1mL/min.

Determination of Stereochemistry:

The absolute stereochemistry was determined by X-ray crystallography of **II-17** (see Appendix 1). The asymmetric nucleophilic acylation was carried out using the 4-Br-Ph thiazolium carbinol (**II-1m**) and nitroalkene **II-2a** to yield **II-17** with an enantiomeric excess of 70%. Enantiomeric excess determined by HPLC on a Chiralcel OD-H column. 10% IPA/Hexanes, 1mL/min. Recrystallized from ether/hexanes.

HPLC trace of racemic II-7:

Data File C:\HPCHEM\2\DATA\ACHAN\AM000000.D

pCl, racemic

```
=======================================================================
Injection Date  : 6/2/2005 10:30:18 AM
Sample Name     :                            Location : Vial 1
Acq. Operator   : Anita
                                             Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\2\METHODS\ANITA.M
Last changed    : 3/7/2005 7:51:16 PM by Dave
Analysis Method : C:\HPCHEM\2\METHODS\ANITA.M
Last changed    : 9/15/2005 3:48:24 PM by Anita
                  (modified after loading)
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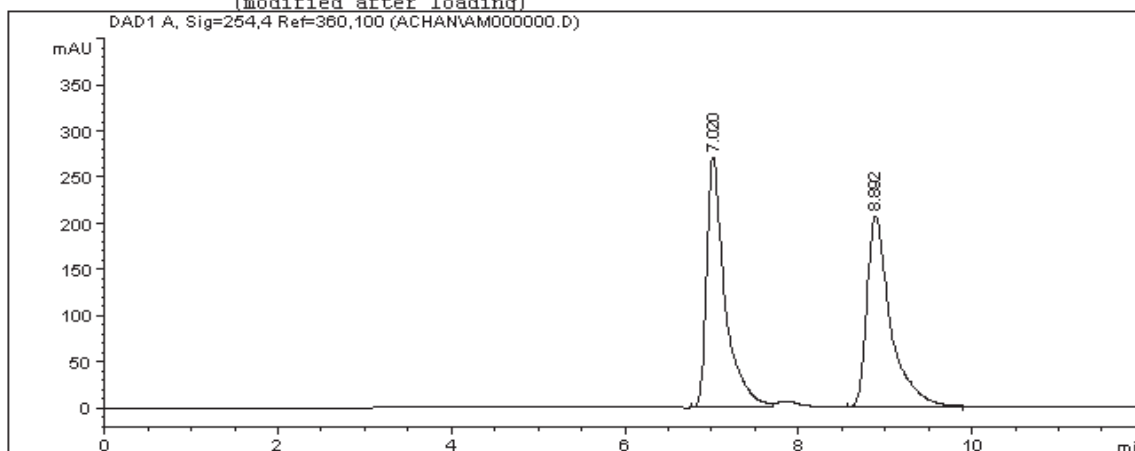

DAD1 A, Sig=254,4 Ref=360,100 (ACHAN\AM000000.D)

```
=======================================================================
                     Area Percent Report
=======================================================================

Sorted By          :      Signal
Multiplier         :      1.0000
Dilution           :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area        Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   7.020 PV   0.2135 3976.90063  270.50851  50.5609
  2   8.892 PB   0.2765 3888.66284  205.71507  49.4391

Totals :                7865.56348  476.22359

 Results obtained with enhanced integrator!
=======================================================================
                     *** End of Report ***
```

HPLC trace of enantioenriched II-7:

```
=====================================================================
Injection Date  : 7/29/2005 11:56:33 AM
Sample Name     : 50-4                           Location : Vial 3
Acq. Operator   : Anita
Acq. Instrument : Instrument 1              Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\AM1.M
Last changed    : 7/29/2005 11:55:55 AM by Anita
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\AM1.M
Last changed    : 9/15/2005 3:56:44 PM by Anita
                  (modified after loading)
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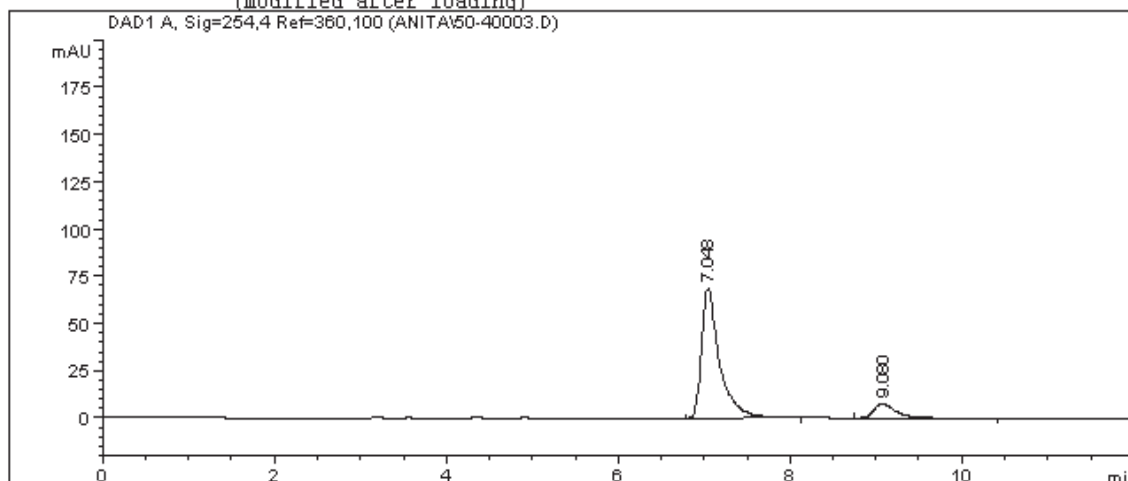


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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By           :      Signal
Multiplier          :      1.0000
Dilution            :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
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  1   7.048 PB   0.2124 1002.51740  68.62119  87.0595
  2   9.080 PP   0.2730  149.01405   8.01220  12.9405

Totals :                1151.53145  76.63338

 Results obtained with enhanced integrator!
=====================================================================
                      *** End of Report ***
```

HPLC trace of enantioenriched II-17:

Data File C:\HPCHEM\1\DATA\ANITA\70-40000.D

pBr with quinine thiourea

```
=====================================================================
Injection Date  : 9/2/2005 1:56:56 PM
Sample Name     :                              Location : Vial 31
Acq. Operator   : Anita
Acq. Instrument : Instrument 1                 Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\AM1.M
Last changed    : 9/2/2005 9:52:57 AM by Anita
                  (modified after loading)
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Last changed    : 9/23/2005 4:24:03 PM by Anita
                  (modified after loading)
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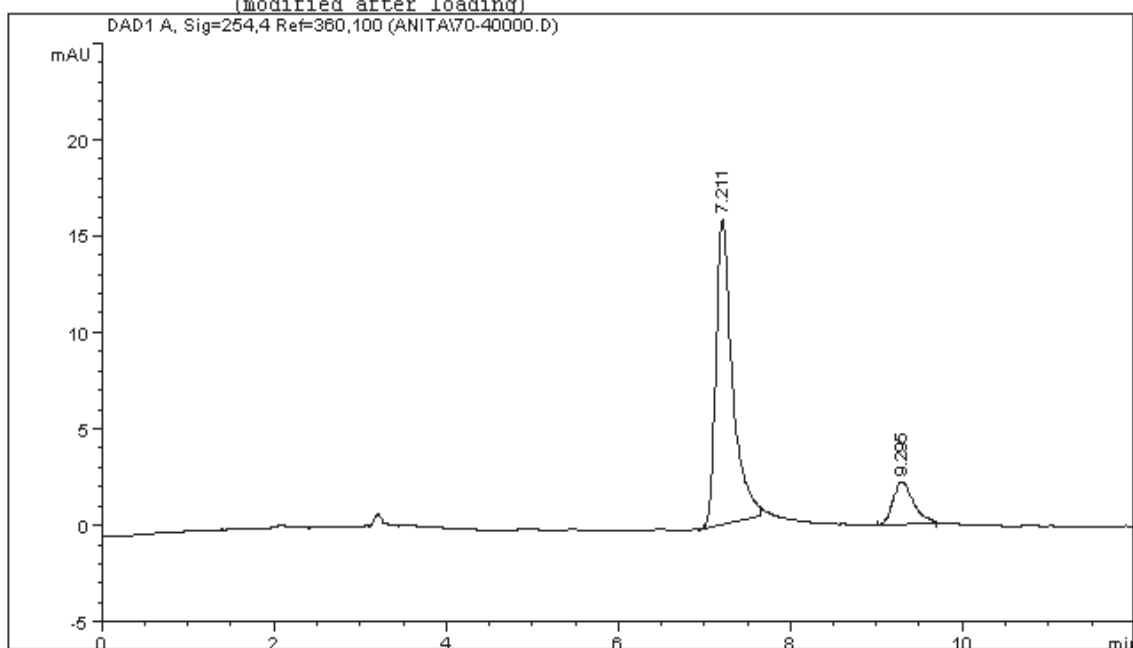


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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By           :      Signal
Multiplier          :      1.0000
Dilution            :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|-------|
  1   7.211 PB   0.1976  210.09106   15.75636  85.1250
  2   9.295 PB   0.2471   36.71182    2.21782  14.8750

Totals :                 246.80289   17.97418

 Results obtained with enhanced integrator!
=====================================================================
                      *** End of Report ***
```

HPLC trace of crystals from II-17 used in X-ray crystallography:

```
Data File C:\HPCHEM\1\DATA\ANITA\PBR00000.D

    pBr crystal

    ====================================================================
    Injection Date  : 9/23/2005 2:59:07 PM
    Sample Name     :                              Location : Vial 31
    Acq. Operator   : Anita
    Acq. Instrument : Instrument 1                 Inj Volume : 5 µl
    Acq. Method     : C:\HPCHEM\1\METHODS\AM1.M
    Last changed    : 9/20/2005 4:00:11 PM by Rob
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    Last changed    : 9/23/2005 3:23:23 PM by Anita
                         (modified after loading)
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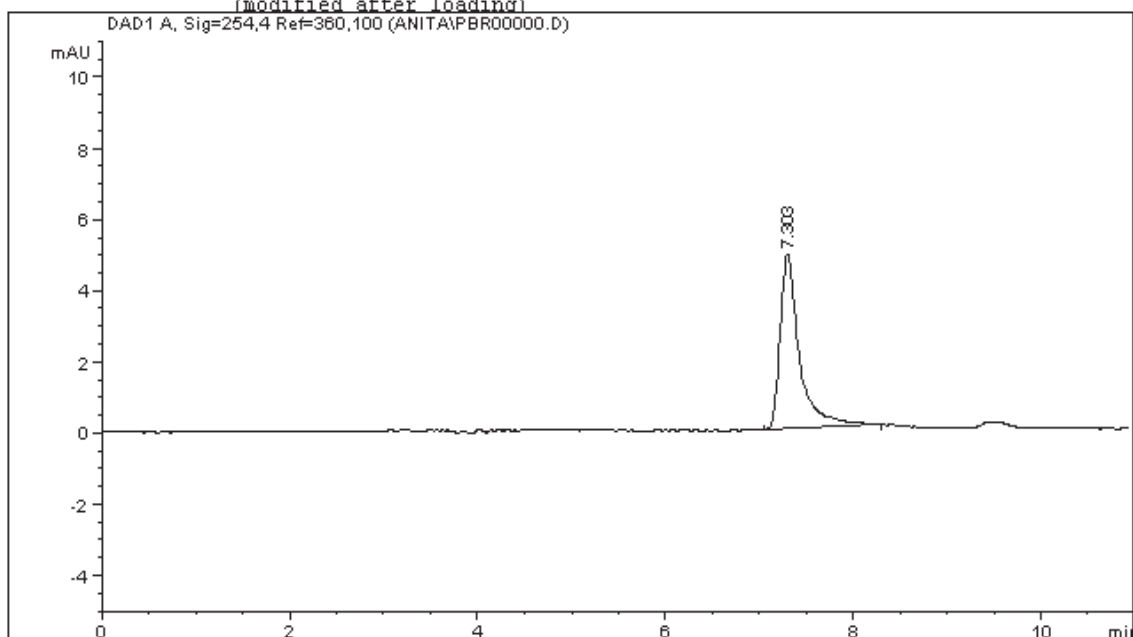


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    ====================================================================
                        Area Percent Report
    ====================================================================

    Sorted By            :      Signal
    Multiplier           :      1.0000
    Dilution             :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
     #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1   7.303 PB   0.2108   70.76501   4.89014 100.0000

    Totals :                   70.76501   4.89014

     Results obtained with enhanced integrator!
    ====================================================================
                        *** End of Report ***
```

2.7.4 Typical Procedure for the Nucleophilic Acylation of o-Quinone Methides

A dry 10 mL round bottom flask was charged with the thiazolium carbinol (0.620 mmol) and fitted with a septa in a nitrogen-filled drybox. Also in the box, a separate vial was charged with tetramethylammonium fluoride (Me$_4$N·F, 96 mg, 1.03 mmol). Both reagents were removed from the box and the carbinol was placed under a positive pressure of nitrogen. The quinone methide precursor (0.413 mmol) dissolved in CH$_2$Cl$_2$ (3 mL) was added to the flask containing the carbinol. The resulting yellow solution was immediately cooled to −78 ºC. Last, the Me$_4$N·F suspended in CH$_2$Cl$_2$ (1.7 mL) was added dropwise to the reaction. Upon Me$_4$N·F addition, the reaction turned dark green or red depending on the substrates. After 24 h at −78 ºC the reaction was allowed to attain room temperature and stirred for an additional hour at 23 ºC. At this time, thin layer chromatography showed all of the quinone methide precusor had been consumed. The reaction was diluted with saturated NaCl and CH$_2$Cl$_2$. The layers were separated and the aqueous layer was extracted two additional times with CH$_2$Cl$_2$. The organic layers were combined, dried over Na$_2$SO$_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel.

2.7.5 Characterization of α-Aryl Ketones
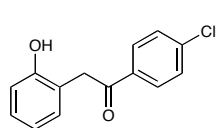
1-(4-chlorophenyl)-2-(2-hydroxyphenyl)ethanone (II-29): Purified with 5 to 40% ether/hexanes, yielding 46 mg (72%) of **II-29** as a white solid. R$_f$ = 0.37 (40/60 ether/hexanes); Mp: 134-135 °C; IR (film) 3418.0; 3028.5, 2959.2, 1673.9, 747.8 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.03-8.01 (m, 2H); 7.48-7.45 (m, 2H); 7.31 (s, 1H); 7.19-7.15 (m, 2H); 6.94-6.86 (m, 2H); 4.25 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.8, 155.5, 140.9, 134.4,

131.2, 130.6, 129.4, 129.4, 121.2, 121.0, 117.8, 41.1; LRMS (electrospray): Mass calculated for $C_{28}H_{22}Cl_2O_4$ [2M]$^+$, 492.1. Found 492.8.
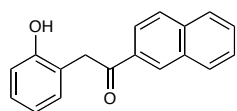
2-(2-hydroxyphenyl)-1-(naphthalen-2-yl)ethanone (II-33): Purified with 4 to 35% ether/hexanes, yielding 66 mg (66%) of **II-33** as a white solid. R_f = 0.28 (40/60 ether/hexanes); Mp: 144-145 °C; IR (film) 3415.6, 3059.3, 2912.7, 1676.1, 1175.9, 747.2 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.69 (s, 1H); 8.13-8.11 (m, 1H); 8.05-8.03 (m, 1H); 7.95-7.90 (m, 2H); 7.86 (s, 1H); 7.68-7.65 (m, 1H); 7.63-7.60 (m, 1H); 7.28 (s, 1H); 7.22-7.19 (m, 1H); 7.01-7.00 (m, 1H), 6.93-6.90 (m, 1H); 4.44 (s, 2H);^{13}C NMR (125 MHz, CDCl$_3$) δ 201.4, 156.0, 136.3, 133.3, 132.7, 131.7, 131.6, 131.3, 130.1, 129.4, 129.1, 128.1, 127.3, 124.4, 121.4, 121.1, 118.1, 41.4; LRMS (electrospray): Mass calculated for $C_{18}H_{14}O_2Na$ [M+Na]$^+$, 285.1. Found 285.3.
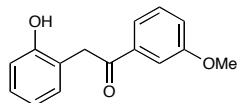
2-(2-hydroxyphenyl)-1-(3-methoxyphenyl)ethanone (II-34): Purified with 4 to 30% ether/hexanes, yielding 70 mg (70%) of **II-34** as a white solid. R_f = 0.24 (40/60 ether/hexanes); Mp: 108-109 °C; IR (film) 3411.6; 3005.3; 2920.4; 1675.2; 1260.2; 753.2 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.74-7.72 (m, 2H); 7.61 (s, 1H); 7.45-7.41 (m, 1H); 7.20-7.17 (m, 3H); 6.97-6.96 (m, 1H); 6.91-6.88 (m, 1H); 4.30 (s, 2H); 3.87 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 201.2, 160.2, 155.7, 137.4, 131.3, 130.1, 129.3, 122.0, 121.3, 121.1, 120.9, 117.8, 113.4, 55.7, 41.3; LRMS (electrospray): Mass calculated for $C_{30}H_{28}O_6$, [2M]$^+$, 484.2. Found 484.4.
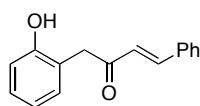
(*E*)-1-(2-hydroxyphenyl)-4-phenylbut-3-en-2-one (II-35): Purified with 4 to 30% ether/hexanes, yielding 17 mg (53%) of **II-35** as a yellow solid. R_f = 0.29 (40/60 ether/hexanes); Mp: 61-63 °C; IR (film) 3357.6, 3029.5, 2924.5, 1681.9, 1600.9, 1454.7, 752.0 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 (s, 1H); 7.79-7.76 (m, 1H); 7.61-7.59 (m, 2H); 7.44-7.43 (m, 3H); 7.22-7.16 (m, 2H); 7.00-6.98 (m, 1H); 6.92-6.86 (m, 2H); 4.01 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 201.1, 156.0, 146.3, 134.2, 131.5, 131.1, 129.4, 129.3, 129.0, 125.4, 121.4, 121.0, 118.1, 44.0; LRMS (electrospray): Mass calculated for C$_{32}$H$_{28}$O$_4$ [2M]$^+$, 476.2. Found 476.5.

1-(4-chlorophenyl)-2-(2-hydroxyphenyl)propan-1-one (II-36): Purified with 4 to 22% ether/hexanes, yielding 41 mg (60%) of **II-36** as a white solid. R_f = 0.40 (40/60 ether/hexanes); Mp: 115-116 °C; IR (film) 3391, 2931.1, 1667.8, 1589, 1453.3, 1093.1, 754.0 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.01-8.00 (m, 2H); 7.41-7.39 (m, 2H); 7.15-7.11 (m, 2H); 6.88-6.85 (m, 2H); 6.83 (s, 1H); 4.95 (q, *J* = 7.0 Hz, 1H); 1.57 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 202.4, 153.8, 140.1, 134.5, 130.5, 129.6, 129.2, 128.9, 126.8, 121.5, 117.3, 43.4, 17.5; LRMS (electrospray): Mass calculated for C$_{30}$H$_{26}$Cl$_2$O$_4$Na [2M+Na]$^+$, 543.1. Found 544.5.
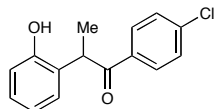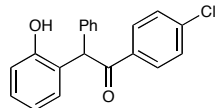
1-(4-chlorophenyl)-2-(2-hydroxyphenyl)-2-phenylethanone (II-37): Purified with 8 to 40% ether/hexanes, yielding 68 mg (68%) of **II-37** as a yellow solid. R_f = 0.28 (40/60 ether/hexanes); Mp: 93.5-95 °C; IR (film) 3407.6, 3030.3, 2925.7, 1673.2, 1587.6, 1455.6, 1093.0, 751.0 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.03-8.01 (m, 2H); 7.43-7.25 (m, 7H); 7.18-716 (m, 1H); 7.05-7.04 (m, 1H); 6.91-6.89 (m, 1H), 6.84-6.82 (m, 1H), 6.28 (s,

1H), 6.23 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.6, 153.9, 140.2, 137.4, 135.2, 130.7, 130.0, 129.3, 129.3, 129.1, 128.8, 127.7, 125.5, 121.2, 116.9, 54.8; LRMS (electrospray): Mass calculated for C$_{40}$H$_{30}$Cl$_2$O$_4$Na [2M +Na]$^+$, 667.1. Found 668.4.
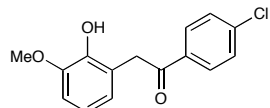
1-(4-chlorophenyl)-2-(2-hydroxy-3-methoxyphenyl)ethanone (II-38): Purified with 4 to 25% ether/hexanes, yielding 67 mg (67%) of **II-38** as a white solid. R$_f$ = 0.23 (40/60 ether/hexanes); Mp: 104-106 °C; IR (film) 3437.8, 2939.6, 2840.9, 1688.0, 1479.8, 1272.7, 1076.3, 762.7 cm^{-1} ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.03-8.02 (m, 2H); 7.44-7.42 (m, 2H); 6.83-6.80 (m, 3H); 5.92 (s, 1H); 4.28 (s, 2H); 3.90 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.0, 146.9, 143.7, 139.7, 135.2, 130.3, 129.1, 123.1, 120.7, 120.0, 109.8, 56.2, 39.6; LRMS (electrospray): Mass calculated for C$_{15}$H$_{13}$ClO$_3$Na [M+Na]$^+$, 299.1. Found 299.8.
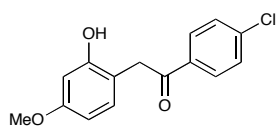
1-(4-chlorophenyl)-2-(2-hydroxy-4-methoxyphenyl)ethanone (II-39): Purified with 5 to 33% ether/hexanes, yielding 54 mg (75%) of **II-39** as a white solid. R$_f$ = 0.23 (40/60 ether/hexanes); Mp: 107.5-109 °C; IR (film) 3419.8, 2956.3, 2836.8, 1675.3, 1619.2, 1589.3, 12079, 1093.9, 819.0 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04-8.03 (m, 2H); 7.62 (s, 1H); 7.49-7.47 (m, 2H); 7.07-7.05 (m, 1H); 6.53 (m, 1H); 6.48-6.45 (m, 1H); 4.20(s, 2H); 3.76 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 200.3, 160.7, 156.7, 140.9, 134.3, 131.6, 130.7, 129.4, 113.0, 107.1, 103.5, 55.6, 40.5; LRMS (electrospray): C$_{15}$H$_{13}$ClO$_3$ [M]$^+$, 276.1. Found 278.4.
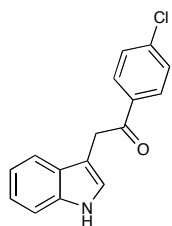
1-(4-chlorophenyl)-2-(1*H*-indol-3-yl)ethanone (II-41): Purified with 4 to 40% ether/hexanes, yielding 49 mg (70%) of **II-41** as a white solid. R_f = 0.25 (40/60 ether/hexanes); Mp: 158.5-159 °C; IR (film) 3352.6, 3080.1, 2917.4, 1681.5, 742.0 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.17 (bs, 1H); 8.01-8.00 (m, 2H); 7.63-7.61 (m, 1H); 7.43-7.41 (m, 2H); 7.37-7.35 (m, 1H); 7.24-7.21 (m, 1H); 7.18-7.15 (m, 1H); 7.08 (s, 1H); 4.39 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.0, 139.7, 163.4, 135.1, 130.3, 129.2, 127.4, 123.5, 122.6, 120.1, 118.9, 111.6, 108.8, 35.9; LRMS (electrospray): C$_{16}$H$_{12}$ClNO [M]$^+$, 269.1. Found 270.4.

2.7.6 Synthesis of Protected Thiazolium Carbinol II-47
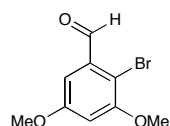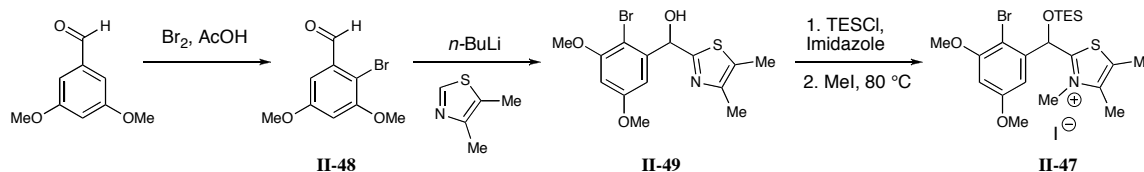
2-bromo-3,5-dimethoxybenzaldehyde (II-48): 2,3-dimethoxybenzaldehyde (1g, 6.02 mmoles) was added to a 25 mL round bottom flask and dissolved in acetic acid (5 mL). The resulting colorless solution was briefly cooled in an ice bath. A solution of bromine (320 μL, 6.25 mmoles) in acetic acid (2 mL) was added dropwise to the cool reaction mixture. Once the addition was complete the ice bath was removed. After approximately 5 min the reaction had solidified and water (10 mL) was added. The solid was collected by vacuum filtration and rinsed with water. The solid was then dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted two additional times with CH_2Cl_2. The combined organic layers were dried with sodium sulfate and then filtered through a plug of silica gel using CH_2Cl_2 as the eluent. The filtrate was concentrated to afford a white solid consisting of both mono and dibrominated aldehydes. A small amount of ethyl acetate was added to the solid. After standing at 5 °C, a white solid (the dibrominated aldehyde) had precipitated. The solid was separated from the liquid by vacuum filitration and the filtrate was concentrated to yield the monobrominated aldehyde (1.02 g, 4.16 mmoles, 69%) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 10.43 (s, 1H); 7.06 (d, 1H, $J =$ 2.7 Hz); 6.73 (d, 1H, $J =$ 2.7 Hz); 3.93 (s, 3H); 3.87 (s, 3H). Spectral data matched the reported data.[41]
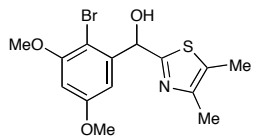
(2-bromo-3,5-dimethoxyphenyl)(4,5-dimethylthiazol-2-yl)methanol (II-49): To a flame-dried 100 mL round bottom flask under positive nitrogen pressure was added 4,5-dimethylthiazole (432 μL, 4.08 mmoles) and THF (20 mL). The resulting solution was cooled to −78 °C. *n*-BuLi (2.1 mL, 4.08 mmoles) was added dropwise to the cold reaction causing it to turn into pink solution that was stirred at −78 °C for 45 min. At this time, the aldehyde (**II-48**, 2 g, 8.16 mmoles) was added in one portion. Upon addition, the reaction turned yellow. After stirring at −78 °C for an hour, the dry ice/acetone bath was removed and the reaction warmed to 23 °C. After 3 h at room temperature the reation was diluted with water and extracted three times with ethyl acetate. The combined organics were dried over sodium sulfate, filtered and concentrated. Recrystallization from ethyl acetate yielded the desired carbinol as a white solid (1.35 g, 3.77 mmoles, 92%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.85 (s, 1H); 6.49 (d, 1H, *J* = 2.7 Hz); 6.38 (d, 1H, *J* = 2.7 Hz); 3.90 (s, 3H); 3.82 (s, 3H); 2.32 (s, 3H); 2.29 (s, 3H)
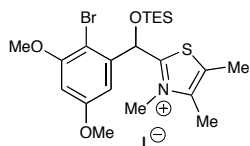
TES-protected thiazolium carbinol (II-47): A dry 100 mL round bottom flask was charged with carbinol **II-49** (1.35 g, 3.77 mmoles) and placed under positive nitrogen pressure. CH$_2$Cl$_2$ (30 mL) was added and the carbinol was completely dissolved. Triethylsilylchloride (1 mL, 5.66 mmoles) was then added followed by imidazole (308 mg, 4.52 mmoles). The resulting suspension was stirred at 23 °C overnight. After 15 h the reaction was diluted with water and CH$_2$Cl$_2$. The layers were separated and the organic layer was washed two additional times with water. The combined aqueous layers were extracted one time with CH$_2$Cl$_2$. The combined organic layers were dried over sodium sulfate, filtered and

concentrated to yield the silyl protected carbinol as a pale yellow oil that was used in the next step without further purification. The TES-protected carbinol was dissolved in iodomethane (5 mL). The resulting pale yellow solution was heated to 80 °C for 20 h. After cooling to room temperature, any remaining iodomethane was removed *in vacuo* to yield a yellow residue. Diethyl ether was added to the residue causing the protected thiazolium carbinol to precipitate as pale yellow solid. The solid was isolated by vacuum filitration and dried under vacuum (1.79 g, 77% over the two steps). ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.82 (s, 1H); 6.63 (s, 1H); 6.54 (s, 1H); 3.91 (s, 3H); 3.86 (s, 6H); 2.54 (s, 6H); 0.92-0.87 (m, 9H); 0.71-0.60 (m, 6H) ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.9, 160.9, 157.3, 144.6, 137.5, 131.1, 107.0, 104.0, 101.3, 73.0, 56.8, 56.5, 40.1, 14.0, 13.2, 6.93, 5.04.

2.7.7 Synthesis of Quinone Methide Precursor II-28e
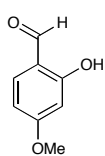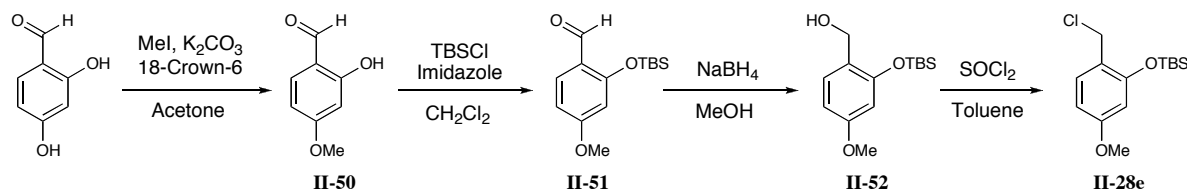
2-hydroxy-4-methoxybenzaldehyde (II-50): K$_2$CO$_3$ (4 g, 28.9 mmoles) and acetone (16 mL) were added to a dry 50 mL round bottom flask under a positive nitrogen pressure. 2,4-Dihydroxybenzaldehyde (2 g, 14.5 mmoles) was added to the reaction mixture to create a light peach suspension. 18-Crown-6 (383 mg, 1.45 mmoles) was added in one portion and last the iodomethane (0.9 mL, 14.5 mmoles) was added dropwise by syringe. The resulting reaction mixture was stirred at 23 °C overnight. After 18 h the reaction

was complete by thin layer chromatorgraphy (40% ether/hexanes). CH_2Cl_2 was added and the organic layer was washed with water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried with sodium sulfate, filtered and concentrated to yield a brown oil. The crude oil was purified by flash column chromatography on silica gel using a 20% to 50% ether/hexanes gradient as eluent. Two spots were isolated. The desired aldehyde was isolated as a white solid (R_f in 40% ether/hexanes = 0.55, 1.17 g, 53%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 11.5 (s, 1H); 9.74 (s, 1H); 7.45 (m, 1H); 6.57-6.55 (m, 1H); 6.45 (m, 1H); 3.89 (s, 3H). Data matched that of commercially available aldehyde. The second compound isolated was the dialkylated aldehyde, also a white solid (R_f in 40% ether/hexanes = 0.32, 383 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 10.3(s, 1H); 7.84 (m, 1H); 6.58-6.55 (m, 1H); 6.45 (m, 1H); 3.92 (s, 3H); 3.89 (s, 3H). Data matched that of commercially available aldehyde.
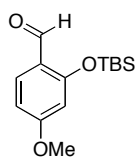
2-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde (II-51): To a dry 50 mL round bottom flask under a positive nitrogen flow containing 2-hydroxy-4-methoxybenzaldehyde (1.17 g, 7.69 mmoles) was added DMF (2.6 mL). Next, *t*-butyldimethylsilylchloride (2.4 g, 15.9 mmoles) was added followed by imidazole (1.3 g, 19.1 mmoles). After stirring at room temperature for 1 h the reaction was complete by thin layer chromatography (40% ether/hexanes). The reaction was diluted with ether and water. The layers were separated and the organic layer was washed two additional times with water. The substrate is acid sensitive so it is important to use neutral conditions during workup. The organic layer was washed with saturated NaCl then dried with magnesium sulfate, filtered and concentrated to a pale yellow oil. The crude oil was purified by bulb to bulb distillation using a Kugelrhor apparatus. At 0.1 torr, the desired product came over between 150-175 °C as a clear,

colorless oil (1.02g, 50%). R$_f$=0.56 (40/60 ether/hexanes); IR (film) 2933.1, 2854.6, 1681.6, 1061.9, 1255.8, 1206.8, 1168.5, 845.9 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 10.3(s, 1H); 7.80 (m, 1H); 6.62-6.60 (m, 1H); 6.36 (m, 1H); 3.86 (s, 3H); 1.04 (s, 9H); 0.30 (s. 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 188.7, 165.9, 151.0, 130.3, 121.6, 108.1, 105.4, 55.8, 25.9, 25.8, 18.6.
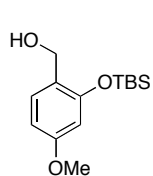
(2-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl)methanol (II-52): To a 50 mL round bottom flask containing **II-51** (1.02 g, 3.82 mmoles) was added methanol (19 mL). The reaction was cooled 0 °C. NaBH$_4$ (178 mg, 4.71 mmoles) was cautiously added to the aldehyde solution. After addition was complete the reaction was allowed to slowly attain room temperature. After 2 h the reaction was complete by thin layer chromatography (40% ether/hexanes). The reaction was quenched with saturated NaCl and concentrated to remove the methanol. The aqueous layer was then extracted three times with ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford a clear, colorless oil (700 mg, 68%) that was pure by ^{1}H NMR. R$_f$=0.38 (40/60 ether/hexanes); IR (film) 3356.5, 2954.3, 2932.1, 2858.5, 1611.3, 1504.6, 1162.7, 844.2 cm^{-1};^{1}H NMR (500 MHz, CDCl$_3$) δ 7.20 (d, 1H, J = 8.2 Hz); 6.51 (dd, 1H, J = 8.4 and 2.0 Hz); 6.40 (d, 1H, J = 2.0 Hz); 4.61 (s, 2H); 3.78 (s, 3H); 1.03 (s, 9H); 0.28 (s, 6H) ^{13}C NMR (125 MHz, CDCl$_3$) δ 160.4, 154.8, 130.1, 124.4, 105.9, 105.8, 61.8, 55.6, 26.0, 25.9, 18.4.
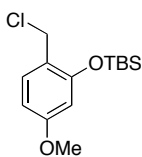
***tert*-butyl(2-(chloromethyl)-5-methoxyphenoxy)dimethylsilane (II-28e):** To a dry 100 mL round bottom flask under nitrogen, containing **II-52** (700 mg, 2.61 mmoles) was added toluene (26 mL). The reaction was cooled to 0 °C then freshly distilled thionyl chloride (552 μL, 7.57 mmoles) was added. Almost immediately, the

reaction turned pink. Allowed to slowly attain room temperature and stirred overnight. After 18 h the reaction was poured into 20% KOH (4 g of KOH in 20 mL of H$_2$O). The layers were separated and the aqueous layer was extracted three times with CH$_2$Cl$_2$. The combined organics were dried with sodium sulfate, filtered and concentrated to yield **II-28e** as a yellow oil (705 mg, 94%) that was pure by ^{1}H NMR. It was used in the next step without further purification. **II-28e** is acid sensitive and decomposes on the SiO$_2$ thin layer chromatography plates. IR (film) 2955.8, 2932.3, 2858.4, 1610.5, 1504.5, 1260.1, 1202.1, 1165.7, 846.6 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26-7.25 (m, 1H); 6.52-6.50 (m, 1H); 6.39 (m, 1H); 4.60 (s, 2H); 3.79 (s, 3H); 1.05 (s, 9H); 0.29 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 161.2, 155.2, 131.8, 121.1, 106.4, 105.6, 55.6, 42.3, 26.0, 25.9, 18.5.
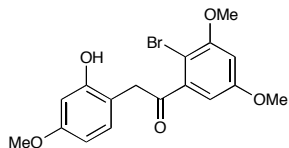
1-(2-bromo-3,5-dimethoxyphenyl)-2-(2-hydroxy-4-methoxyphenyl)ethanone (II-46): A 25 mL round bottom flask was charged with the protected thiazolium carbinol **II-47** (289 mg, 0.471 mmol) and fitted with a septa in a nitrogen-filled drybox. Also in the box, a separate vial was charged with tetramethylammonium fluoride (Me$_4$N·F, 73 mg, 0.784 mmol). Both reagents were removed from the box and the carbinol was placed under a positive pressure of nitrogen. The quinone methide precursor **II-28e** (90 mg, 0.314 mmol) dissolved in CH$_2$Cl$_2$ (6 mL) was added to the flask containing the carbinol. The resulting yellow solution was immediately cooled to –78 °C. Last, the Me$_4$N·F suspended in CH$_2$Cl$_2$ (1 mL) was added dropwise to the reaction. Upon Me$_4$N·F addition, the reaction turned orange. After 24 h at –78 °C the reaction was allowed to attain room temperature and stirred for an additional hour at 23 °C. The reaction was diluted with saturated NaCl and CH$_2$Cl$_2$. The layers were separated and the aqueous layer was extracted two

additional times with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel. Purified with 50-80% ether/hexanes, yielding 74 mg (62%) of **II-46** as an orange oil. This substrate is sensitive to silica gel so the purification was done quickly using a relatively small amount of silica gel. R_f = 0.19 (60/40 ether/hexanes); IR (film) 3393.3, 3005.3, 2939.7, 1619.4, 736.5 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ7.38 (bs, 1H) 6.99-6.97 (m, 1H); 6.54-6.52 (m, 2H); 6.44-6.45 (m, 2H); 4.17 (s, 2H); 3.89 (s, 3H); 3.76 (s, 3H); 3.75 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 206.7, 160.7, 160.3, 157.1, 156.5, 143.5, 132.1, 113.4, 106.9, 104.5, 103.4, 101.8, 99.3, 56.8, 56.0, 55.6, 45.4; LRMS (electrospray): Mass calculated for $C_{34}H_{34}Br_2O_{10}$ [2M]$^+$, 760.1. Found 762.1.
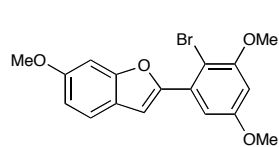
2-(2-bromo-3,5-dimethoxyphenyl)-6-methoxybenzofuran (II-45): To a 10 mL round bottom flask under nitrogen containing **II-46** (71 mg, 0.186 mmoles) was added CH_2Cl_2 (1 mL). Amberlyst 15 resin (260 mg) added and freshly dried, powered 4Å MS (200 mg). Stirred at 0 °C for 10 h then kept in a 4 °C fridge overnight. Thin layer chromatography (60% ether/hexanes) at this time showed the reaction was complete. The reaction was filtered through a plug of silica gel using 5% to 15% ether/hexanes as eluent, yielding 50 mg (74%) of **II-45** as a clear, colorless oil that turned into a white solid upon standing. R_f = 0.61 (60/40 ether/hexanes); Mp: 98-99 °C; IR (film) 3001.3, 2939.2, 1621.6, 1585.1, 824.9 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.56 (s, 1H); 7.52-7.51 (m, 1H); 7.13-7.12 (m, 1H); 7.09 (s, 1H); 6.93-6.91 (m, 1H) 6.52-6.51 (m, 1H); 3.94 (s, 3H); 3.91 (s, 3H); 3.90 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.8; 158.8; 157.5; 155.4; 152.7; 132.9; 122.4; 121.9;

112.5; 107.9; 105.5; 102.0; 99.9; 95.8; 56.8; 56.0; 55.9; LRMS (electrospray): Mass

calculated for $C_{17}H_{15}BrO_4$ $[M]^+$, 362.0. Found 365.2
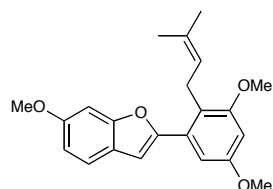
2-(3,5-dimethoxy-2-(3-methylbut-2-enyl)phenyl)-6-

methoxybenzofuran (II-53): To a flame-dried 10 mL round bottom flask

under nitrogen was added benzofuran **II-46** (18 mg, 0.0496 mmoles) and

PdCl$_2$(dppf) (10 mg, 0.0122 mmoles). DMF (0.25 mL) was added to create a red suspension.

Last, prenyl tributyltin (50 μL, 0.148 mmoles) was added in one portion by syringe. The

reaction was heated to 100 °C. TLC (40% ether/hexanes) indicated all of the starting material

had been consumed after 5 h. The reaction was cooled to room temperature and 1 mL of ether

was added along with a spatula tip of KF and the mixture was stirred for 15 min. The mixture

was then purified using a small silica gel column with 5% ether/hexanes as eluent. The product

was isolated as a colorless oil (13 mg, 76%). R_f = 0.76 (60/40 ether/hexanes); IR (film) 2956.6,

2925.9, 2854.8, 1612.4, 1588.4, 1505.4, 1461.4, 1207.8, 1155.8, 1040.4 cm^{-1}; ^{1}H NMR (500

MHz, CDCl$_3$) δ 7.48-7.46 (m, 1H); 7.09 (s, 1H); 6.92-6.88 (m, 2H); 6.80 (s, 1H); 6.54-6.53 (m,

1H); 5.20 (m, 1H); 3.90 (s, 3H); 3.88 (s, 3H); 3.87 (s, 3H); 3.52 (d, 2H, J = 6.1 Hz); 1.73 (s, 6H)

^{13}C NMR (125 MHz, CDCl$_3$) δ 159.2, 158.8, 158.2, 155.8, 154.8, 131.8, 131.7, 123.9, 122.7,

121.5, 121.3, 112.1, 105.5, 104.3, 99.5, 96.0, 56.0, 55.7, 26.2, 26.1, 18.3.
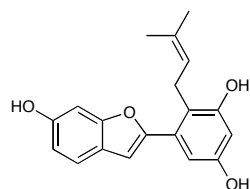
Demethylmoracin I (II-44): To a flame-dried 25 mL round bottom flask

under positive nitrogen pressure was added diphenylphosphine (93 μL,

0.536 mmoles) and THF (1 mL).[44] The solution was cooled to 0 °C. *n-*

BuLi (300 μL, 0.536 mmoles) was added to the cool reaction and immediately a bright orange solution was formed. Stirring was continued for 1 h at 0 °C. In a separate flame-dried 10 mL round bottom flask was prepared a solution of benzofuran **II-53** (21 mg, 0.0596 mmoles) in THF (0.4 mL). This solution was added to the freshly prepared lithium diphenylphosphanide dropwise by cannula. After the addition was complete the reaction was first warmed to room temperature then heated to 70 °C for 20 h. At this time the reaction, now a brown solution, was cooled to room temperature. Ether and 1M NaOH were added and the mixture was stirred until the reaction became homogenous. The reaction was poured into a separatory funnel and acidified to pH 4 with 1M HCl. The layers were separated and the aqueous layer was extracted two additional times with ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford a brown oil. The crude oil was purified by flash column chromatography on silica gel using 5% MeOH/CH_2Cl_2 as eluent to afford 11 mg (61%) of demethylmoracin I as a brown solid that was recrystallized from ether/hexanes to yield white crystals. R_f = 0.45 (8:1 CH_2Cl_2:MeOH); IR (KBr) 3351.0, 2917.6, 1625.1, 1490.0, 1155.9 cm^{-1}; Mp: recrystallized white solid 170-171 °C; ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.0, 157.2, 157.0, 156.7, 156.4, 133.2, 131.5, 125.8, 123.2, 122.0, 119.4, 113.2, 107.8, 105.7, 103.9, 98.5, 26.7, 26.1, 18.2 HREIMS m/z 310.1197, calculated for $C_{19}H_{18}O_4$, 310.1205.

Reported ^{1}H NMR Data for Demethylmoracin I (CD$_3$OD)[6]	Actual ^{1}H NMR Data Found (CD$_3$OD)
1.64 (6H, s)	1.65 (6H, s)
3.42 (2H, d, J = 6.3 Hz)	3.44 (2H, d, J = 6.0 Hz)
5.13 (1H, m)	5.14 (1H, m)
6.33 (1H, d, J = 2.5 Hz)	6.35 (1H, d, J = 2.4 Hz)
6.61 (1H, d, J = 2.5 Hz)	6.62 (1H, d, J = 2.4 Hz)
6.66 (1H, s)	6.68 (1H, s)
6.72 (1H, dd, J = 2.2 and 8.4 Hz)	6.74 (1H, dd, J = 2.0, 8.4 Hz)
6.87 (1H, d, J = 2.1 Hz)	6.88 (1H, d, J = 1.5 Hz)
7.33 (1H, d, J = 8.4 Hz)	7.35 (1H, d, J = 8.4 Hz)

2.7.8 Competition Experiment
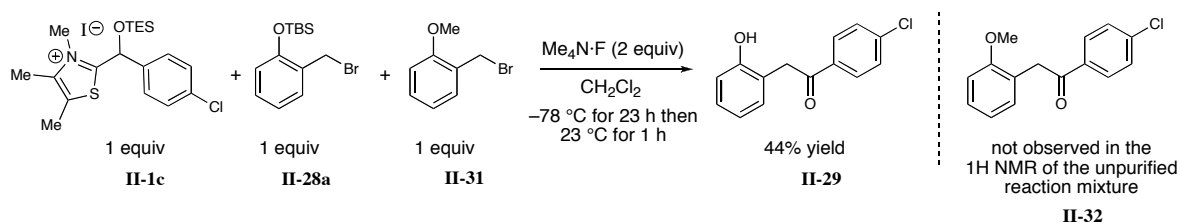
To a flame dried 10 mL round bottom flask was added the protected thiazolium carbinol **II-1c** (100 mg, 0.196 mmoles). The flask was fitted with a septa and put under a positive pressure of nitrogen. CH$_2$Cl$_2$ was added next (0.5 mL) and the reaction was cooled to −78 °C in a dry ice and acetone bath. The methoxybenzyl bromide **II-31** (39 mg, 0.196 mmoles) was added in CH$_2$Cl$_2$ (0.5 mL) then the siloxybenzyl bromide **II-28a** (59 mg, 0.196 mmoles) was added in CH$_2$Cl$_2$ (0.5 mL). Stirred for 5 min to ensure the reaction was cooled to −78 °C. Last, Me$_4$N•F (37 mg, 0.392 mmoles) was added in CH$_2$Cl$_2$ (0.5 mL) and the reaction immediately turned green. Stirred at −78 °C for 6.5 h then kept in a −78 °C freezer overnight. After 23 h total, the reaction was warmed to 23 °C and stirred for an additional hour. The reaction was then diluted with brine and CH$_2$Cl$_2$. The layers were separated and the aqueous layer was extracted two additional times with CH$_2$Cl$_2$. The combined organic layers were dried over sodium sulfate, filtered and concentrated. 108 mg of an unpurified orange residue was isolated. The ^{1}H NMR spectrum of the unpurified reaction mixture showed mainly **II-29** and **II-31** with no sign of the methoxy α-aryl ketone **II-32** when compared to the ^{1}H NMR spectrum of an authentic sample. Purified by flash column chromatography on silica gel using 5% to 35% ether/hexanes as the eluent. The α-aryl ketone **II-29** was isolated (21 mg, 44%).

Preparation of an Authentic Sample of 23
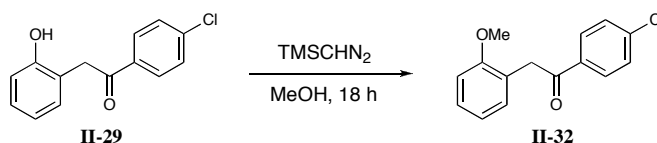
To a reaction vial containing the α-aryl ketone (6 mg, 0.024 mmoles) was added methanol (0.3 mL). Fitted with cap and septa and put under positive nitrogen pressure. Trimethylsilyl diazomethane (0.2 mL, 2M solution in hexanes) was added slowly to the reaction mixture. Stirred at room temperature overnight. At this time the reaction appeared complete by thin layer chromatography and was concentrated. Purified by preparative thin layer chromatography using 40% ether/hexanes as eluent. The product was isolated as a pale yellow oil. ; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.00-7.98 (m, 2H); 7.45-7.43 (m, 2H); 7.19-7.17 (m, 2H); 6.95-6.89 (m, 2H); 4.25 (s, 2H); 3.80 (s, 3H).

2.7.9 Thiazolium Carbinol Additions to Aldehydes

To a dry 10 mL round bottom flask was added the carbinol (0.190 mmoles). Fitted with septa and put under a positive pressure of nitrogen. CH$_2$Cl$_2$ (0.5 mL) added and the resulting orange solution was cooled to 0°C. The aldehyde (0.759 mmoles) was added in one portion by syringe. Last, Me$_4$N·F (0.190 mmoles) was added as a suspension in CH$_2$Cl$_2$ (0.5 mL). Stirred at 0 °C for 2 h then allowed to slowly attain 23 °C. After 5 h total, the reaction was diluted with brine and CH$_2$Cl$_2$ and then poured into a separatory funnel. The layers were separated and the aqueous layer was extracted two additional times with CH$_2$Cl$_2$. The combined organic layers were dried

over sodium sulfate, filtered and concentrated. The resulting yellow residue was purified by

column chromatography on silica gel using 5-25% ether/hexanes as eluent. **II-55** was isolated as

a pale yellow oil. ^{1}H (500 MHz) 7.32-7.20 (m, 5H); 4.17-4.14 (m, 1H); 3.43 (d, J = 6.7 Hz, 1H);

3.01-2.93 (m, 2H); 2.88-2.74 (m, 2H); 1.81-1.76 (m, 2H); 1.53-1.41 (m, 2H); 1.30-1.28 (m, 6H);

0.93-0.88 (t, J = 4.8 Hz, 3H).

2.7.10 Select NMR spectra
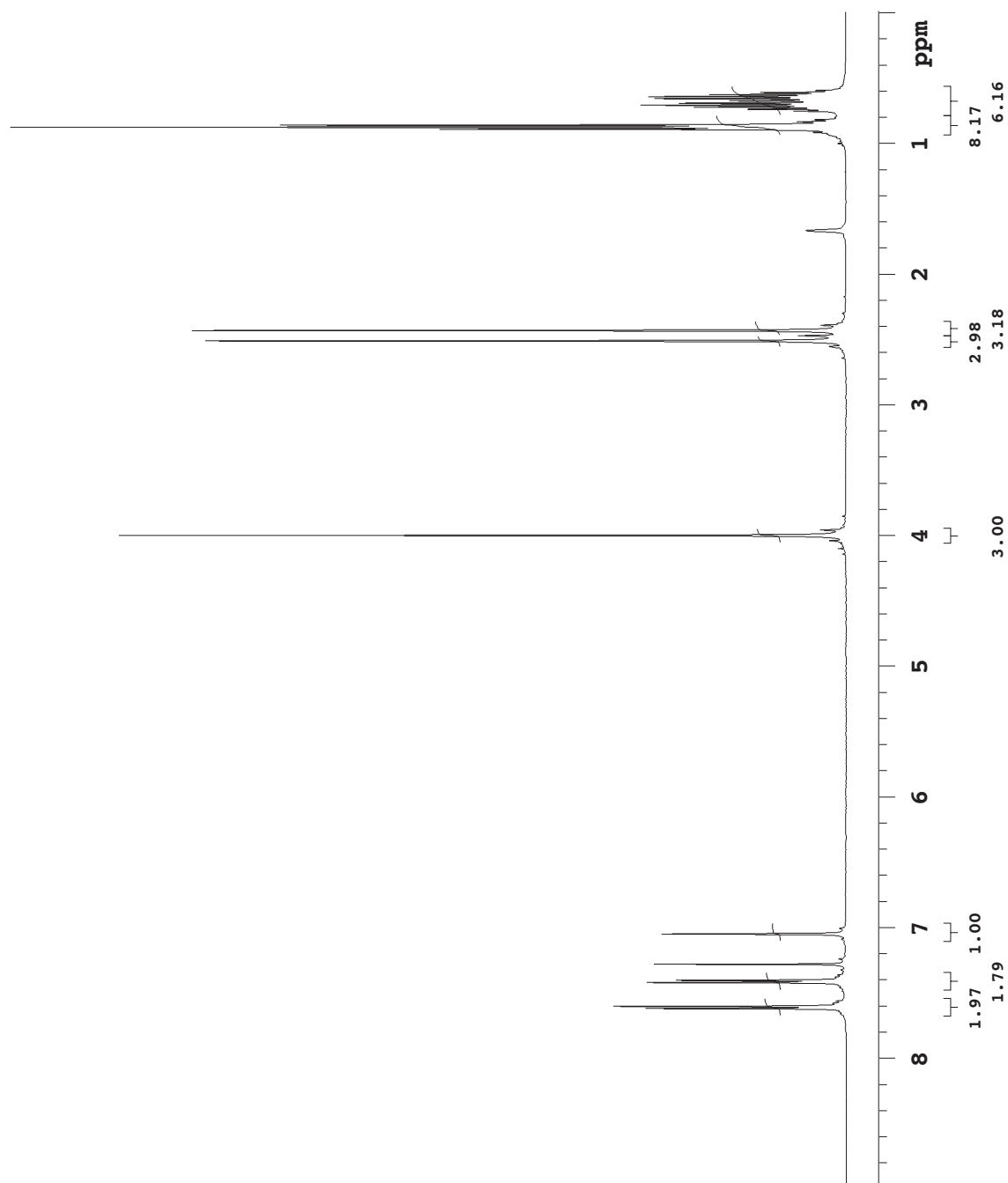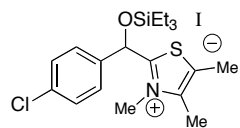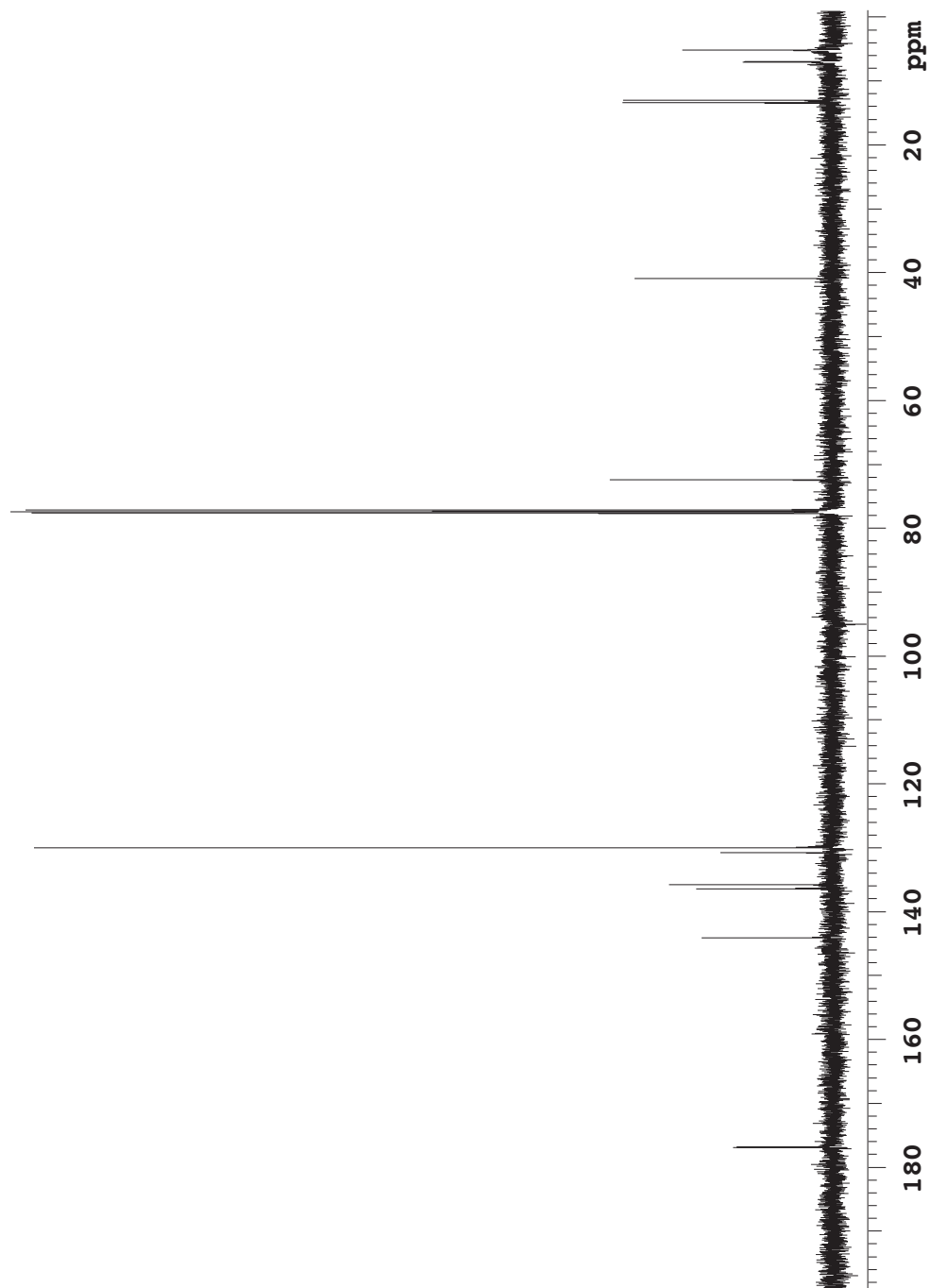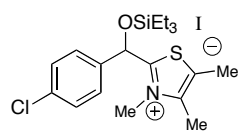
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Appendix 1

Structure Refinement Data, Atomic Coordinates, Bond Lengths and Bond Angle Data for the Crystal Structure of II-17

Crystal structure data provided by Dr. Charlotte Stern (Northwestern University, c-stern@northwestern.edu) and solved by Troy Reynolds (Northwestern University, t-reynolds2@northwestern.edu)

X-Ray Crystal Structure Analysis for II-17
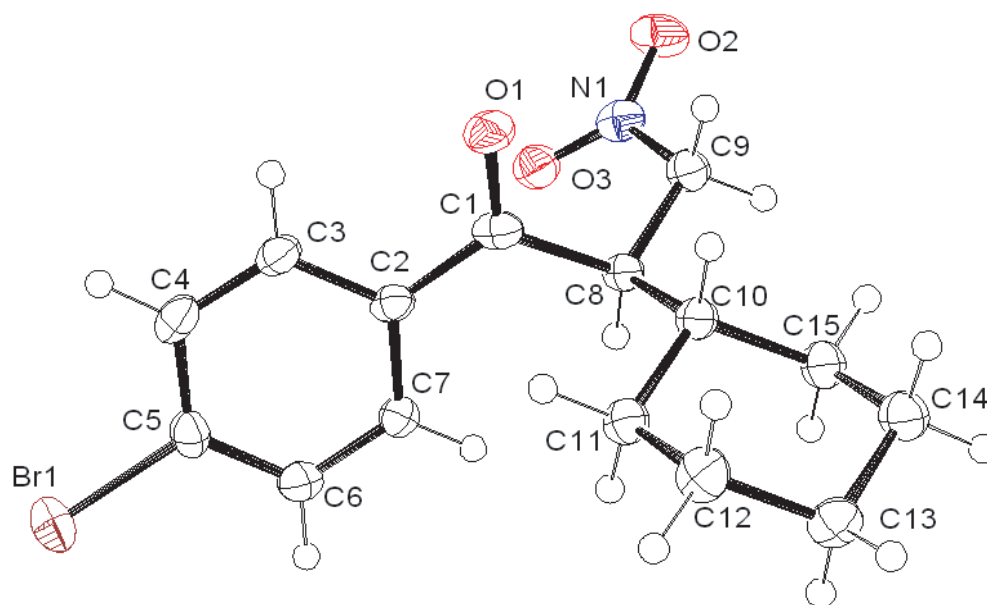
Figure A.1. An ORTEP diagram of the crystal structure of **II-17** showing an atom labeling scheme. Thermal ellipsoids are drawn at 50% probability.

Data Collection: A colorless plate crystal of $C_{15}H_{18}BrNO_3$ having approximate dimensions of 0.401 x 0.320 x 0.024 mm was mounted using oil (Infineum V8512) on a glass fiber. All measurements were made on a CCD area detector with graphite monochromatic radiation.

Cell constants and orientation matrix for data collection corresponded to an Orthorhombic cell with dimensions: a = 5.8906(10) Å, b = 12.736(2) Å, c = 19.540(4) Å, α = 90.00, β = 90.00, γ = 90.00, V = 1466.0(4) Å^3.

For Z = 4 and F.W. = 340.21, the calculated density is 1.541 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be: P2$_1$2$_1$2$_1$.

The data were collected at a temperature of 153(2) K with a theta range for data collection of 1.91 to 28.30°. Data were collected in 0.3° oscillation with 15 second exposures. The crystal-to-detector distance was 50.00 mm with the detector at the 28° swing position.

Data Reduction: Of the 12989 reflections collected, 3349 were unique (Rint = 0.1300). Data were collected using Bruker SMART detector and processed using SAINT-NT from Bruker.[1,2] The linear absorption coefficient, mu, for MoK\a radiation is 0.411^{-1}. An integration absorption correction was applied. Minimum and maximum transmission factors were: 0.3834 and 0.9345, respectively. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement: The structure was solved by direct methods and expanded using Fourier techniques.[3] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in idealized positions, but not refined. The flack parameter refined to - 0.014(9) indicating the correct absolute structure. The final cycle of full-matrix least-squares refinement[4] on F2 was based on 3349 reflections and 181 variable parameters and converged (largest parameter shift was 0.000 times its esd) with unweighted and weighted agreement factors of: R1 = S| |F$_o$|-|F$_c$| |/S|F$_o$| = 0.0350 and wR^2 = $^{1/2}$ = 0.0767. The weighting scheme was calculated from calc w = 1/[s^2(F$_o{}^2$) + (0.0000P)^2 + 0.0000P] where P = (F$_o{}^2$+2F$_c{}^2$)/3. The standard deviation of an observation of unit weight[5] was 0.965. The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. Plots of S w (|F$_o$| - |F$_c$|)^2 versus |F$_o$|, reflection order in data collection, sin θ/λ and various classes of

indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.697 and -0.378 e-/Å3, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[6] Anomalous dispersion effects were included in Fcalc;[7] the values for Df′ and Df′′ were those of Creagh and McAuley.[8] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[9] All calculations were performed using the Bruker SHELXTL crystallographic software package.

Table A.1. Atomic coordinates and equivalent isotropic displacement parameters (A^2 x 10^3) for **II-17**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	-2883(1)	6006(1)	50(1)	37(1)
O(1)	-1060(3)	9075(2)	2844(1)	31(1)
O(2)	4233(3)	10987(2)	2736(1)	37(1)
O(3)	3366(3)	9778(2)	2003(1)	32(1)
N(1)	3699(4)	10081(2)	2589(1)	28(1)
C(1)	273(5)	8456(2)	2577(2)	24(1)
C(2)	-312(5	7889(2)	1944(2)	23(1)
C(3)	-2304(5)	8167(2)	1606(2)	26(1)
C(4)	-3039(5)	7648(2)	1039(2)	29(1)
C(5)	-1781(5)	6801(2)	802(2)	27(1)
C(6)	243(5)	6512(2)	1111(2)	28(1)
C(7)	975(5)	7068(2)	1676(2)	25(1)
C(8)	2535(4)	8264(2)	2948(2)	20(1)
C(9)	3502(5)	9324(2)	3168(2)	26(1)
C(10)	2166(5)	7573(2)	3588(2)	22(1)
C(11)	961(5)	6534(2)	3410(2)	24(1)
C(12)	588(5)	5862(2)	4043(2)	30(1)
C(13)	2827(5)	5630(2)	4408(2)	30(1)
C(14)	4024(5)	6649(2)	4589(2)	29(1)
C(15)	4391(4)	7334(2)	3966(2)	29(1)

Table A.2. Bond lengths (Å) and angles (degrees) for **II-17**.

Br(1)-C(5)	1.899(3	C(9)-H(9A)	0.9900
O(1)-C(1)	1.229(3)	C(9)-H(9B)	0.9900
O(2)-N(1)	1.230(3)	C(10)-C(15)	1.535(4)
O(3)-N(1)	1.224(3)	C(10)-C(11)	1.541(4)

N(1)-C(9)	1.492(4)	C(10)-H(10)	1.0000
C(1)-C(2)	1.474(4)	C(11)-C(12)	1.520(4)
C(1)-C(8)	1.537(4)	C(11)-H(11A)	0.9900
C(2)-C(3)	1.393(4)	C(11)-H(11B)	0.9900
C(2)-C(7)	1.394(4)	C(12)-C(13)	1.528(4)
C(3)-C(4)	1.361(4)	C(12)-H(12A)	0.9900
C(3)-H(3)	0.9500	C(12)-H(12B)	0.9900
C(4)-C(5)	1.388(4)	C(13)-C(14)	1.518(4)
C(4)-H(4)	0.9500	C(13)-H(13A)	0.9900
C(5)-C(6)	1.387(4)	C(13)-H(13B)	0.9900
C(6)-C(7)	1.380(4)	C(14)-C(15)	1.513(4)
C(6)-H(6)	0.9500	C(14)-H(14A)	0.9900
C(7)-H(7)	0.9500	C(14)-H(14B)	0.9900
C(8)-C(9)	1.527(4)	C(15)-H(15A)	0.9900
C(8)-C(10)	1.544(4)	C(15)-H(15B)	0.9900
C(8)-H(8)	1.0000		
O(3)-N(1)-O(2)	123.8(3)	C(15)-C(10)-C(8)	112.5(2)
O(3)-N(1)-C(9)	119.5(2)	C(11)-C(10)-C(8)	111.9(2)
O(2)-N(1)-C(9)	116.6(3)	C(15)-C(10)-H(10)	107.6
O(1)-C(1)-C(2)	121.5(3)	C(11)-C(10)-H(10)	107.6
O(1)-C(1)-C(8)	117.1(3)	C(8)-C(10)-H(10)	107.6
C(2)-C(1)-C(8)	121.4(2)	C(12)-C(11)-C(10)	111.5(3)
C(3)-C(2)-C(7)	118.1(3)	C(12)-C(11)-H(11A)	109.3
C(3)-C(2)-C(1)	118.0(3)	C(12)-C(11)-H(11B)	109.3
C(7)-C(2)-C(1)	123.8(3)	C(10)-C(11)-H(11B)	109.3
C(4)-C(3)-C(2)	122.0(3)	H(11A)-C(11)-H(11B)	108.0
C(4)-C(3)-H(3)	119.0	C(11)-C(12)-C(13)	111.3(2)
C(2)-C(3)-H(3)	119.0	C(11)-C(12)-H(12A)	109.4
C(3)-C(4)-C(5)	118.7(3)	C(13)-C(12)-H(12A)	109.4
C(3)-C(4)-H(4)	120.6	C(11)-C(12)-H(12B)	109.4
C(5)-C(4)-H(4)	120.6	C(13)-C(12)-H(12B)	109.4
C(6)-C(5)-C(4)	121.3(3)	H(12A)-C(12)-H(12B)	108.0
C(6)-C(5)-Br(1)	119.3(2)	C(14)-C(13)-C(12)	110.1(2)
C(4)-C(5)-Br(1)	119.4(2)	C(14)-C(13)-H(13A)	109.6
C(7)-C(6)-C(5)	118.7(3)	C(12)-C(13)-H(13A)	109.6
C(7)-C(6)-H(6)	120.6	C(14)-C(13)-H(13B)	109.6
C(5)-C(6)-H(6)	120.6	C(12)-C(13)-H(13B)	109.6
C(6)-C(7)-C(2)	121.1(3)	H(13A)-C(13)-H(13B)	108.2
C(6)-C(7)-H(7)	119.5	C(15)-C(14)-C(13)	111.9(3)
C(2)-C(7)-H(7)	119.5	C(15)-C(14)-H(14A)	109.2
C(9)-C(8)-C(1)	108.4(2)	C(13)-C(14)-H(14A)	109.2
C(9)-C(8)-C(10)	109.2(2)	C(15)-C(14)-H(14B)	109.2
C(1)-C(8)-C(10)	110.5(2)	C(13)-C(14)-H(14B)	109.2
C(9)-C(8)-H(8)	109.6	H(14A)-C(14)-H(14B)	107.9

C(1)-C(8)-H(8)	109.6	C(14)-C(15)-C(10)	112.3(2)
N(1)-C(9)-C(8)	112.7(2)	C(14)-C(15)-H(15A)	109.1
N(1)-C(9)-H(9A)	109.0	C(10)-C(15)-H(15A)	109.1
N(1)-C(9)-H(9B)	109.0	C(14)-C(15)-H(15B)	109.1
C(8)-C(9)-H(9B)	109.0	C(10)-C(15)-H(15B)	109.1
H(9A)-C(9)-H(9B)	107.8	H(15A)-C(15)-H(15B)	107.9
C(15)-C(10)-C(11)	109.4(2)		

Table A.3.   Anisotropic displacement parameters (A^2 x 10^3) for **II-17**.   The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2a^{*2}U11+…+2$ h k a*b* U12].

	U11	U22	U33	U23	U13	U12
Br(1)	36(1)	43(1)	33(1)	-7(1)	-6(1)	-8(1)
O(1)	23(1)	30(1)	39(1)	-6(1)	0(1)	6(1)
O(2)	36(1)	24(1)	51(2)	-2(1)	6(1)	-9(1)
O(3)	31(1)	31(1)	34(1)	0(1)	0(1)	-1(1)
N(1)	18(1)	27(2)	38(2)	0(1)	4(1)	-1(1)
C(1)	22(2)	19(2)	32(2)	0(1)	6(1)	2(1)
C(2)	20(1)	18(2)	30(2)	1(1)	2(1)	0(1)
C(3)	24(2)	22(2)	33(2)	2(1)	-2(1)	4(1)
C(4)	22(1)	30(2)	34(2)	9(1)	-3(1)	0(1)
C(5)	26(2)	30(2)	25(2)	2(1)	-3(1)	-7(1)
C(6)	28(2)	26(2)	31(2)	-1(1)	-1(1)	3(1)
C(7)	22(2)	24(2)	28(2)	-3(1)	-5(1)	1(1)
C(8)	13(1)	20(2)	27(2)	-2(1)	1(1)	-2(1)
C(9)	23(2)	26(2)	30(2)	-3(1)	-2(1)	-3(1)
C(10)	20(1)	23(1)	24(1)	-2(1)	0(1)	-1(1)
C(11)	19(1)	26(2)	28(2)	0(1)	-1(1)	-2(1)
C(12)	24(1)	33(2)	34(2)	5(2)	0(1)	-6(1)
C(13)	29(2)	27(2)	34(2)	7(1)	3(1)	-2(1)
C(14)	26(2)	31(2)	29(2)	-2(2)	-4(1)	-1(1)
C(15)	22(1)	30(2)	34(2)	-2(1)	-4(1)	-2(1)

Table A.4. Hydrogen coordinates (x10^4) and isotropic displacement parameters (A^2 x 10^3) for **II-17**.

	x	y	z	U(eq)
H(3)	-3177	8737	1777	31
H(4)	-4386	7860	811	34
H(6)	1109	5942	937	34
H(7)	2378	6888	1885	30
H(8)	3623	7910	2631	24
H(9A)	2510	9631	3525	31
H(9B)	5023	9215	3372	31
H(10)	1161	7970	3909	27
H(11A)	-522	6689	3195	29
H(11B)	1890	6138	3076	29
H(12A)	-141	5193	3909	36
H(12B)	-448	6233	4361	36
H(13A)	2527	5224	4831	36
H(13B)	3813	5202	4108	36
H(14A)	3106	7037	4929	34
H(14B)	5511	6486	4800	34
H(15A)	5451	6978	3649	34
H(15B)	5101	8003	4111	

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