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Matthew G. Lindale Date

Desulfitative Coupling Reactions for the Mild Construction of Carbon-Carbon, Carbon-Nitrogen, and Carbon-Oxygen Bonds

By

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Doctor of Philosophy

Chemistry

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Desulfitative Coupling Reactions for the Mild Construction of Carbon-Carbon, Carbon-Nitrogen, and Carbon-Oxygen Bonds

By

Matthew G. Lindale

B.S., Davidson College, 2009

Advisor: Lanny S. Liebeskind, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Chemistry
2015

Abstract

Desulfitative Coupling Reactions for the Mild Construction of Carbon-Carbon, Carbon-Nitrogen, and Carbon-Oxygen Bonds

By: Matthew G. Lindale

A novel cross-coupling of thiol esters bearing an *ortho*-directing group and organostannanes is explored using stoichiometric copper carboxylate to mediate the coupling, generating ketones. When the imine is carefully selected, it is possible to couple boronic acids/esters as well as organostannanes. The coordination of copper to the *ortho*-imine directing group as well as the thiol ester activates the system, allowing the reaction to occur under mild conditions (50 °C). The reaction is the first reported base-free coupling on thiol esters and boronic esters.

The second generation Liebeskind-Srogl reaction, an aerobic cross-coupling of *S*-acylthiosalicyamides and boronic acids, is a mild, base-free reaction that has been utilized to generate a variety of diverse ketones. Unfortunately, the reaction generates a stoichiometric amount of an undesired thioether byproduct. An investigation to prevent thioether formation was undertaken by altering the core structure of the *S*-acylthiosalicylamide as well as the ligand environment of the copper catalyst. Optimization of the reaction conditions provided a mild reaction for ketoconjugation, eliminating the undesired thioether byproduct in favor of the generation of benzoisothiazolone (BIT). The BIT byproduct could be recycled back to *S*-acythiosalicylamide by gentle reaction with triethylphosphite and carboxylic acid. This discovery allowed for the one-pot ketoconjugation of carboxylic acids and boronic acids.

A variety of benzoisothiazolones (BITs) were tested as oxidation-reduction condensation catalysts for the formation of amide bonds from carboxylic acids and amines. It was found that a number of BITs proved effective as organocatalysts for the reaction, however, 4-pyridyl-*N*-isopropylbenzisothiazolone proved the most effective, providing high yields of the desired amides in 24 hours at 50 °C. The rate of oxidative closure of the reduced BIT was studied, and disulfide was found to form as an intermediate before closure to BIT occurred.

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I would be remiss to leave out the friends who have helped to keep me grounded over the last six years, both in and out of the laboratory. I have had the pleasure of working with some of the greatest lab mates who were always willing to take time to explain chemistry, equipment, etc. Dr. Hao Li, Dr. Wenting Wu, Dr. Ethel Garnier, Dr. Angus Lamar, Dr. Pavan Kumar Gangireddy have all been instrumental in my time at Emory. Thanks also to Greg Goschy, John Wiseman, Edo Mwenda, Biruk Forsido, Leighann Lam, and Stephen Wilson for their help in the Liebeskind lab. Outside of the laboratory, Andrew Carlson, Lauren Cunningham, Katie Busch, Emily and Matt Mosby, Chelsea Henderson, and Nick Kahler always provided an opportunity to set work aside and relax with the best friends that anyone could imagine.

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Appendix A

List of Abbreviations

Ar	aryl
BIT	benzisothiazolone
Bn	benzyl
Boc	*t*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl

ºC	degrees Celsius
calcd	calculated
cat.	catalytic
Cbz	benzyloxycarbonyl
CuMeSal	copper(I) 3-methylsalicylate
CuTC	copper(I) thiophene-2-carboxylate
cm^{-1}	wavenumber unit
δ	chemical shift (in ppm for NMR)
d	doublet
DMF	dimethylformamide
DMAP	*N*,*N*-dimethylaminopyridine
DMSO	dimethylsulfoxide
dr	*diastereo*meric *ratio*
ee	*enantiomeric excess*
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
Het	heteroaryl
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
hr	hour
HRMS	high-resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
IR	infrared spectroscopy

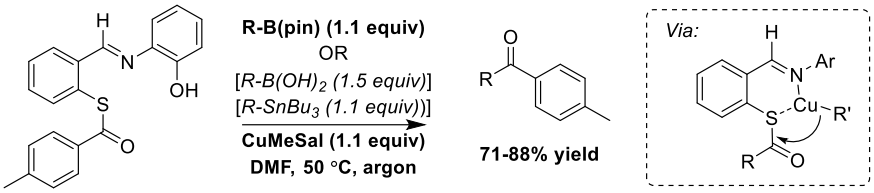
J	coupling constant
m	multiplet (for NMR)
m	medium (for IR)
M	molar
Me	methyl
MeCN	acetonitrile
mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimole
mol	mole
mol %	mole percent
Mp	melting point
N	normal
OAc	acetate
ORC	oxidation-reduction condensation
OTf	trifluoromethanesulfonate
Ph	phenyl
Phe	phenylalanine
p-NO_2	*para*-nitro
ppm	parts per million
q	quartet
R*f*	R*f* value
s	singlet (for NMR)
s	strong (for IR)
stoich.	stoichiometric

t	triplet
T	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tolyl	toluene
t_R	retention time
UV	ultraviolet
vs	very strong
w	weak
Z	benzyloxycarbonyl

Chapter 1

Mild, Copper-Templated Cross-Coupling of Thiol Esters with Boronic Acids and Esters

Abstract: Stoichiometric copper carboxylate is utilized for the first base-free cross-coupling of boronic esters and thiol esters to give ketones. Based on previous results that utilized oximes as ortho-*directing groups, a series of* ortho-*imine thiol esters were synthesized and tested for efficacy in desulfitative cross-coupling to form ketones. These thiol esters are also suitable partners for cross-coupling with boronic acids or organostannanes (**Scheme 1.1**).*

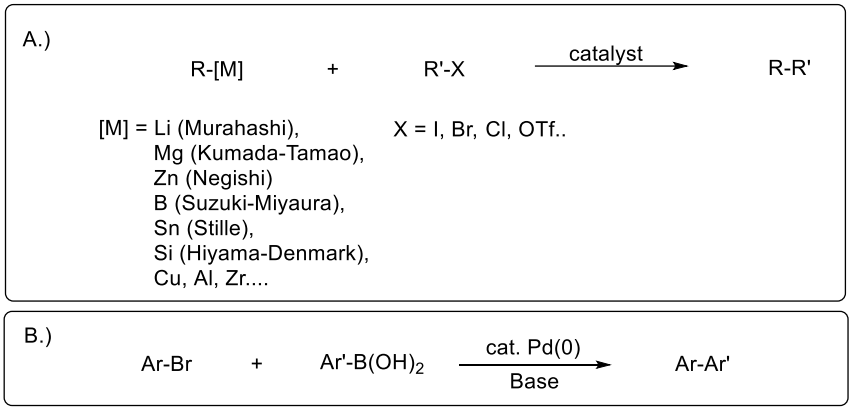


Scheme 1.1 Desulfitative Cross-Coupling of Thiol Esters and Boronic Esters Through a Templated Approach

1.1 Introduction

Over the previous sixty years, the chemical literature has exploded with examples of transition metal catalyzed carbon-carbon and carbon-heteroatom bond forming reactions.[1-3] In general, these reactions utilize an electrophilic organic halide or pseudohalide (i.e. triflates) as well as a nucleophilic organometallic reagent. A variety of organometallics have been applied including lithium,[4-5] magnesium,[6-7] zinc,[8] boron,[9-11] tin,[12-13] and silicon[14-16] among others (Scheme 1.2A). For example, the Suzuki-Miyaura cross-coupling reaction generates C-C bonds from aryl, alkenyl, or alkyl (pseudo)halides and organoboron reagents (Scheme 1.2B). These reactions provide a reliable method for

the formation of carbon-carbon and carbon-heteroatom bonds and have been used extensively in the literature for the construction of pharmaceuticals and natural products.

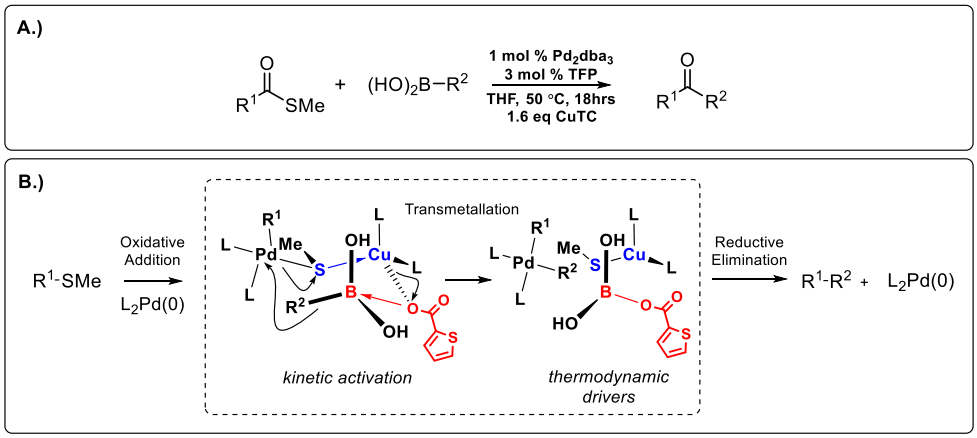


Scheme 1.2 A.) General Transition-Metal Catalyzed Cross-Coupling of Organometallic Reagents with Organic Halides. B.) Suzuki-Miyaura Cross-Coupling of Organoboron Reagents with Aryl Halides.

Several of the organometallic reagents previously listed, however, suffer from drawbacks that limit their usefulness. For example, organolithium and organomagnesium reagents are strongly basic and sensitive to air, limiting not only their functional group compatibility, but also their shelf stability. Organostannanes show varying levels of toxicity, with the triorganostannane byproduct of cross-coupling reactions being the most toxic of the organostannanes.[17] Organosilicon reagents are stable and non-toxic, but require the addition of strong bases for activation- again limiting applicability. Because of the limitations of these organometallic reagents, boron-based reagents have emerged as the preferred reactants for cross-coupling reactions. Boronic acids are generally shelf-stable, nontoxic, free-flowing solids that are easily handled and stored. Although they have gained popularity for their stability and ease-of-use, boronic acids still require basic reaction conditions to function reliably as cross-coupling partners. Activation through its

empty valence renders the boron-organometallic more nucleophilic, facilitating transmetalation to the catalyst.[18]

For nearly twenty years, the Liebeskind group has been interested in the reactivity of thioorganics as substrates for base-free carbon-carbon bond formation. The group's initial publication of the cross-coupling of thiol esters with boronic acids opened the door for pH neutral desulfitative catalysis (Scheme 1.3A).[19] Interestingly, the group found that besides catalytic amounts of palladium, stoichiometric quantities of a copper(I) carboxylate were essential for a productive reaction. The working model used to explain the requirement of the copper carboxylate is pictured in Scheme 1.3B. The group proposed that the copper carboxylate played a dual role in the reaction by both polarizing the palladium-sulfur bond as well as activating the boronic acid *via* coordination. It was also suggested that the copper carboxylate balances the thermodynamics of the reaction with the strength of the copper-sulfur and boron-oxygen bonds driving the reaction to completion.



Scheme 1.3 The Liebeskind-Srogl Reaction A.) Overall Reaction B.) Proposed Working Model for Reaction Mechanism.

In 2009, a computational study[20] performed by Dr. Djamaladdin Musaev provided further insight into the Liebeskind-Srogl reaction mechanism uncovering a non-innocent role for the carboxylate anion. The computational data indicated that the carboxylate counter-anion actively influences the reactivity at the Pd atom by displacing a phosphine ligand from palladium (Figure 1.1). The ligand displacement increases the electrophilicity of the palladium intermediate and decreases steric hindrance lowering electronic and steric barriers to transmetalation. The study also supported the group's initial hypothesis that copper helps to polarize the palladium-sulfur bond while the carboxylate coordinates with boron, thereby activating the organometallic reagent for transmetalation.

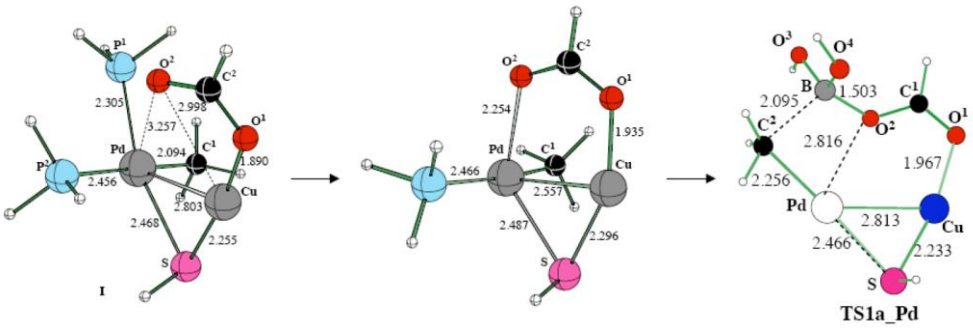
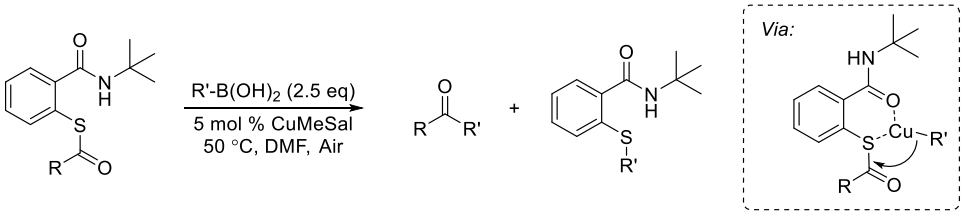


Figure 1.1 Computational Study of the Mechanism of the Liebeskind-Srogl Reaction.[21]

Since the initial publication in 2000, the Liebeskind-Srogl reaction has been used extensively in academic research as well as industrial applications.[22-39] While the initial reaction employed boronic acids and thiol esters to form ketones, the reaction scope has been expanded to include heteroarylation[40], cyanation[29], amidination[41], as well as

alkynylation[42]. Desulfitative catalysis proved to be a mild, reliable reaction that provided orthogonal reactivity to alternatives such as Suzuki and Stille cross-coupling reactions.[43]

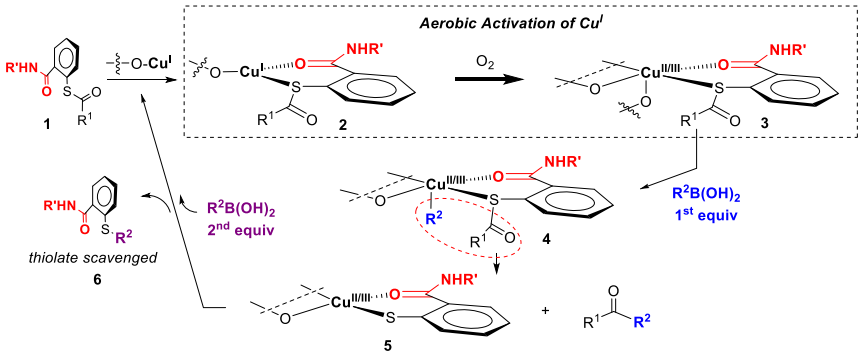
Despite its generality, the Liebeskind-Srogl reaction suffers from the required use of a stoichiometric copper(I) carboxylate additive. To avoid this limitation, a second-generation reaction was developed that regenerated the copper catalyst through an aerobic recycle.[44] The second generation Liebeskind-Srogl reaction (Scheme 1.4) employs a specific class of thiol ester – S-acylthiosalicylamide derivatives – that allow the templated delivery of an organometallic reagent (generated by transmetalation from B to Cu) into close proximity with the electrophilic thiol ester. The ketone products are generated in good yields, with reasonable reaction rates occurring between room temperature and 50 °C. The mild reaction conditions have been used for the generation of enantiomerically pure peptidyl ketones.[45] Unfortunately, as shown in Scheme 1.5, below, the aerobic, Cu-catalyzed reaction suffers from the formation of stoichiometric quantities of an undesired, but mechanistically required, thioether byproduct. This limits the utility of the Cu-catalyzed reaction when the boron partner is expensive and/or precious.



Scheme 1.4 Second Generation Liebeskind-Srogl Reaction

The second generation reaction mechanism is assumed to begin with coordination of copper to the thiol ester S-atom and to the *ortho* coordinating amide group of the thiosalicylamide, yielding intermediate **2** (Scheme 1.5). Under the aerobic

conditions, the copper (I) catalyst is rapidly oxidized to give copper intermediate **3**. This higher oxidation state at Cu favors rapid transmetalation from the boronic acid, which yields organometallic intermediate **4**. The proximity of the organocopper intermediate with the electrophilic thiol ester allows for nucleophilic attack, producing the desired ketone and a copper thiolate intermediate (**5**). Because the copper retains its high oxidation state (II/III), a second equivalent of boronic acid undergoes transmetalation, followed by reductive elimination to regenerate the copper (I) catalyst and an undesired thioether side-product (**6**).

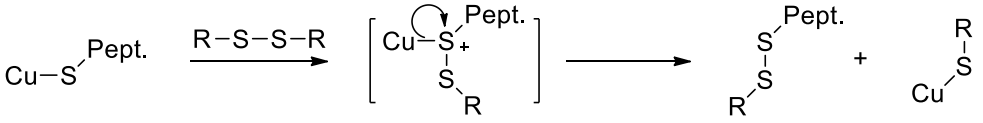


Scheme 1.5 Proposed Mechanism for the Aerobic Cross-Coupling of S-Acylthiosalicylamides and Boronic acids.

While the first and second generation reaction mechanisms are different on the surface, a careful comparison of the two generations of desulfitative cross-coupling leads to the understanding that two common requirements must be met in order to drive the chemistry forward: 1) the thiolate must be fully captured/scavenged. In the first generation cross-coupling, the thiolate was trapped stoichiometrically as the copper thiolate, freeing palladium to reenter the catalytic cycle. In the second generation, the thiolate (attached to Cu) is trapped *via* its aerobic reaction with an extra equivalent of the boronic acid to form the thioether with concomitant regeneration of the copper catalyst.

2) The $-B(OH)_2$ moiety of the boronic acid requires a stoichiometric amount of a strongly bonding oxygenate partner to occupy its third valence (available after transmetalation of the boronic acid "R" group). The first generation Liebeskind-Srogl reaction uses carboxylate to satisfy this requirement, while the second generation reaction utilizes ½ O_2 derived from the atmosphere to fulfill boron's requirements.

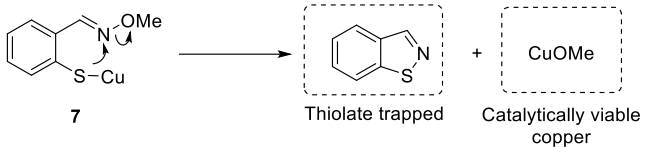
Desiring a catalytic reaction in which copper could be released from thiolate without sacrificing an equivalent of the boronic acid, the Liebeskind lab looked to Nature to help solve the problem of the liberation of metals from strongly binding thiolates. Metallothioneins (MTs) are a class of proteins that are capable of binding metal cations including zinc and copper among others.[46] While the metals are strongly bound to the protein through multiple cysteine residues, the metal ions can be released when the protein is introduced to exogenous disulfide,[47] NO,[48-49] or related reagents.[50-51] Scheme 1.6 depicts the release of copper from a cysteinate thiolate through exchange with an exogenous disulfide. Through the disulfide exchange, the protein's cysteine residues are effectively trapped while releasing the newly generated metal thiolate, Cu-S-R, into the surrounding environment (Scheme 1.6).



Scheme 1.6 Release of Metal Ions From Metallothioneins.

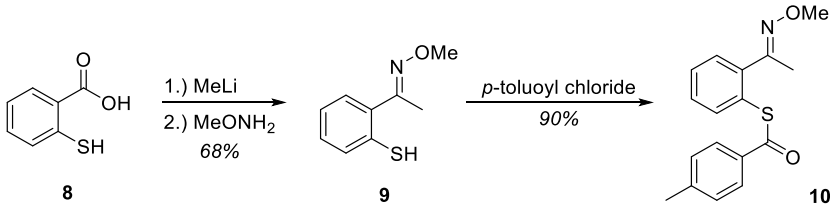
A parallel can be drawn between the trapping of cysteine thiolate with concurrent copper release and the mechanism of Cu-catalyzed desulfitative coupling. The group reasoned that a similar thiolate trapping mechanism might prove effective in the Liebeskind-Srogl reaction. In order to provide a catalytic cross-coupling reaction without

a sacrificial second equivalent of the boronic acid, the group designed a small molecule structure intended to mimic MTs. The oxime derivative **7** shown in Scheme 1.7 was developed with the intention that the copper thiolate generated from cross-coupling would undergo an S-centered oxidation. The internal trapping of the thiolate would not only release copper from the strongly binding thiolate, but also eliminate methoxide as a suitable oxygenate for eventual reaction with the boronic acid –$B(OH)_2$ moiety.



Scheme 1.7 Proposed Mechanism for the Release of Catalytically Viable Copper.

Synthesis of the required thiol esters was performed from the *O*-methyl oxime of 2-mercaptoacetophenone (**9**), which was prepared in a straightforward manner from 2-mercaptoacetic acid (**8**). The *O*-methyl oxime 9 was stable and easily storable and, when reacted with *p*-toluoyl chloride, provided the desired thiol ester (**10**) in good yield (Scheme 1.8).[52]

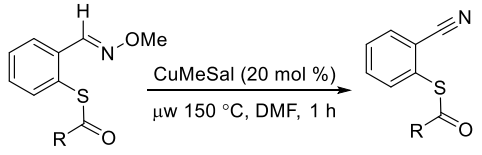


Scheme 1.8 Preparation of MT-mimic Thiol Ester.

Dr. Zhihui Zhang[53] prepared and tested a number of alternative oxime pendants under the cross-coupling conditions, of which the *O*-methyl oxime proved the most effective. The *O*-acyl and *O*-phenyl oxime derivatives provided little to no ketone, presumably because of reaction of copper(I) with the N-O bond of the oxime. Precedent

exists for the oxidative addition of copper (I) species to the N-O bond of oximes and hydroxamic acids.[54] Apparently, the *O*-methyl oxime provides a strong enough N—O bond to prevent side reactions with the copper catalyst, while at the same time the oxime remains electrophilic enough to allow nucleophilic attack by the copper thiolate to form benzoisothiazole.

Oximes derived from 2-mercaptoacetophenone form both *E* and *Z* stereoisomers. While the majority of the oxime exists as the *E* isomer, approximately 14% exits as the *Z* isomer as determined by ^{1}H NMR. Table 1.1 shows that at lower temperatures the *E* isomer is reactive in the formation of benzoisothiazole, since only the *Z* isomer can be recovered from the reaction mixture. At higher temperature, however, the interconversion between the *E* and *Z* isomers is fast enough so as not to limit the reaction yield. Although the reaction outcome at higher temperatures is not disturbed by the presence of stereoisomers, Dr. Zhang also prepared the aldoxime derivative **13** that exists solely as the *E* isomer. Unfortunately, upon exposure to the Cu-catalyzed reaction conditions, rapid elimination of methanol from oxime **13** took place to form the corresponding nitrile (Scheme 1.9).[53]



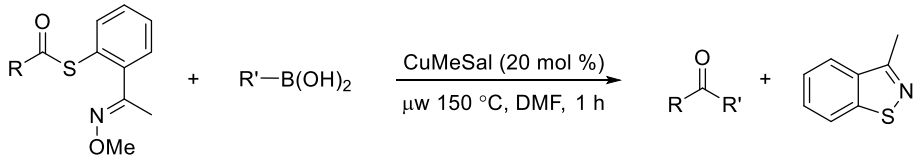
13 **14**

Scheme 1.9. Reaction of Benzaldehyde Oxime to Give Nitriles.

Dr. Zhang explored the scope of the reaction, showing that a variety of functional groups are compatible with the reaction conditions (Table 1.2). Boronic acids bearing halogen, ester, ketone, alcohol, and aldehyde functionality were well tolerated (entries 1-

7). Heteroaromatic boronic acids were also well tolerated under the reaction conditions (entry 10). The use of vinylic boronic acids, however, led to decreased yields of product (entry 8). Aromatic, vinylic, and alkyl thiol esters were efficient partners in the cross-coupling reaction (entries 8-12).[53]

Table 1.1 Scope of Copper-Catalyzed Desulfitative Coupling Using MT-Mimics.



Entry	R	R'	Ketone %[a]
1	*p*-tolyl	4-chlorophenyl	91
2	*p*-tolyl	4-cyanophenyl	88
3	*p*-tolyl	4-(methoxylcarbonyl)phenyl	86
4	*p*-tolyl	3-acetylphenyl	71
5	*p*-tolyl	3-formylphenyl	69
6	*p*-tolyl	3-hydroxyphenyl	70
7	*p*-tolyl	2,5-dimethoxylphenyl	68
8	*p*-tolyl	trans-2-(4-chlorophenyl)vinyl	52
9	*n*-propyl	4-(methoxylcarbonyl)phenyl	82
10	acetoxylmethyl	3-furyl	73
11	acetoxylmethyl	4-(methoxylcarbonyl)phenyl	78
12	(*E*)-1-propenyl	4-methoxyphenyl	80

a. Isolated yield

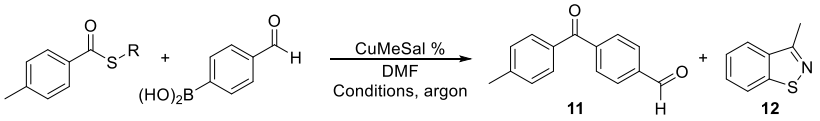
1.2 Results

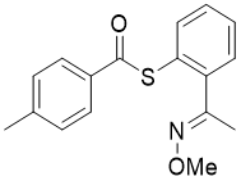
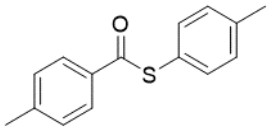
1.2.1 Oxime-Templated Anaerobic Coupling of Thiol Esters and Boronic Acids

A number of important control reactions helped elucidate the mechanism of the MT-mimic system. Initial reaction between thiol ester **10,** copper(I) methyl salicylate (CuMeSal),[42] and a boronic acid under anaerobic conditions provided low yields of ketone when carried out at 60 ºC in DMF (Table 1.1). In fact, the anticipated ketone product was formed in proportion to the amount of copper used. At 60 ºC it appeared

that, while the oxime moiety was sufficient to direct copper and facilitate cross-coupling, the subsequent closure of copper thiolate to benzoisothiazole with release of CuOMe was unsuccessful. This theory was born out when stoichiometric amounts of CuMeSal were added to the reaction and a near quantitative yield of ketone was obtained along with low yields of 3-methylbenzoisothiazole. Heating the reaction possessing 20 mol % CuMeSal to 100 ºC rendered the reaction catalytic in Cu providing moderate yields of ketone and 3-methylbenzoisothiazole in nearly a one-to-one ratio. Running the reaction under microwave irradiation increased reaction rate, decreasing the reaction time from twelve hours to only two hours. Finally, increasing the temperature to 150 ºC under microwave irradiation provided the desired ketone and 3-methylbenzoisothiazole in good yield. As expected, control reactions removing copper or boronic acid from the reaction mixture prevented the generation of ketone or 3-methylbenzoisothiazole.

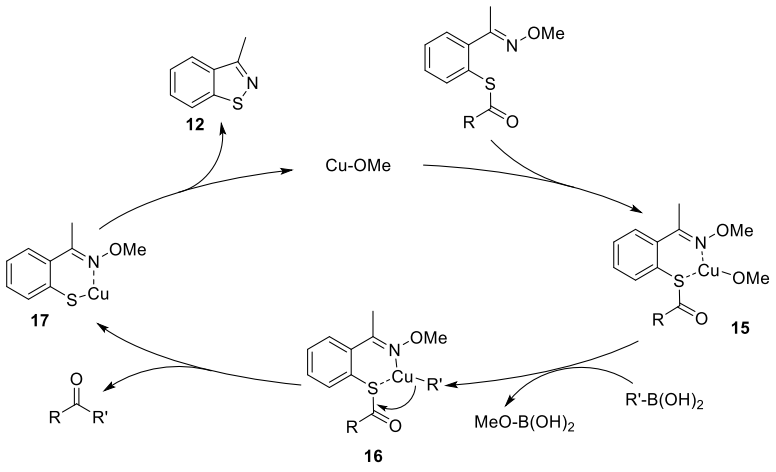
Table 1.2 Control Reactions of MT-Mimic.



Entry	Thiol Ester	CuMeSal %	Conditions	Ketone %	S-N trap %
1		20	60 °C, 24 h	16	0[a]
2		120	60 °C, 12 h	85[b]	44
3		20	100 °C, 12 h	76	60
4		20	µw, 100 °C, 2h	72	65
5		20	µw, 150 °C, 1h	80	78
6		0	µw, 150 °C, 1h	0	trace
7		20	µw, 150 °C, 1h	N/A	trace
8		20	µw, 150 °C, 1h	0	N/A

[a] Benzoisothiazole is not formed in this reaction. Rather, 20% of the S-arylation product (4-[2-(1- methoxyimino-ethyl)-phenylsulfanyl]-benzaldehyde) is formed. However, when the reaction was quenched under argon prior to the work up, neither the thioether nor the benzoisothiazole was generated. [b] The Z-oxime stereoisomer of the thiol ester was recovered.

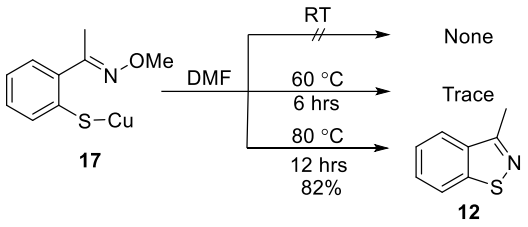
The mechanism of the MT mimic cross-coupling reaction is presumed to begin in a fashion similar to that of the second generation, aerobic Liebeskind-Srogl reaction.[52] Initial coordination of a low-valent copper to the oxime pendent provides intermediate **15** (Scheme 1.10). Coordination provides not only a templated copper positioned for both transmetalation and concurrent reaction with the adjacent thiol ester, but also helps to further activate the thiol ester through coordination with the sulfur. Following coordination, transmetalation from the boronic acid to the copper provides intermediate **16** in which the organocopper's proximity to the thiol ester allows for nucleophilic attack and release of the desired ketone. It is here that the catalytic cycle would falter at low reaction temperatures. As seen in the control experiments presented above, at 60 °C little to no 3-methylbenzoisothiazole is formed under the reaction conditions. At elevated temperature, copper thiolate **17** reacts with the internal oxime to generate the benzoisothiazole **12** and to liberate the catalytically viable copper methoxide.



Scheme 1.10 Mechanism of the Copper-Catalyzed Anaerobic Cross-Coupling.

It is not until higher temperatures are reached that we see catalytic turnover of the copper. Further experimentation was conducted in which the copper thiolate was

generated from 2-mercaptoacetophenone oxime. When the thiolate was placed in DMF at room temperature, no reaction was observed after 4 h. Upon heating to 60 °C, a trace of 3-methylbenzoisothiazole was observed, but it was not until the reaction was heated to 80 °C that the copper thiolate efficiently closed to the 3-methylbenzoisothiazole (Scheme 1.11).

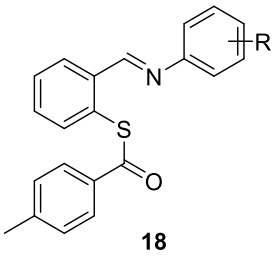


Scheme 1.11 Reaction of Copper Thiolate to Form Benzoisothiazole.

1.2.2 Aldimine Templated Cross-Coupling with Stoichiometric Copper

While Dr. Zhang's study of the oxime moiety showed a variety of advantages as a thiol ester pendant, such as the pre-association of reactants *via* a copper-templated mechanism, activation of the electrophilic thioester, and regeneration of a catalytic copper species through S→N closure, there were still several limitations. The first drawback is the formation of stereoisomeric oximes based on the 2-mercaptoacetophenone - stereoisomers are formed in a 6:1 (*E*:*Z*) ratio. Although the oxime is able to isomerize at high temperature, the *Z* isomer does not react at lower temperature. The second drawback is the use of high temperatures required to render the reaction catalytic in copper. Microwave conditions have the additional problem of limited scalability. To overcome these limitations, modifications were sought that allowed the reaction to proceed under milder conditions using a stoichiometric amount of an inexpensive copper source.

In order to perform a mild, room temperature reaction it was necessary to find a thioester reactant bearing a directing group similar to the oxime moiety that would pre-associate the co-reactants. This functional group would need to be easily prepared and stable in order to be practical. By designing the reaction around the use of a stoichiometric copper carboxylate, the need for an S→N trap became unnecessary. In this case, as in the first generation desulfitative coupling reaction, the stoichiometric carboxylate anion would function to fill the third valence of boron, while the stoichiometric copper would remain bound to the thiolate. With these requirements in mind a variety of aryl aldimines of type **18** were chosen for study (Figure 1.2). Due to the nature of the aldimine structure, only the desired *E*-isomer would result from condensation with the various aniline derivatives.

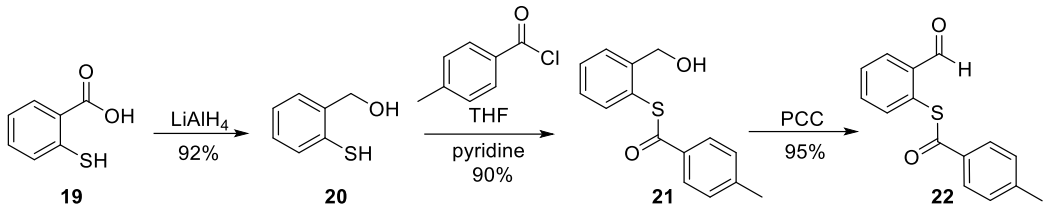


18

Figure 1.2 Aldimine Substrates Designed for Stoichiometric Copper Cross-Coupling.

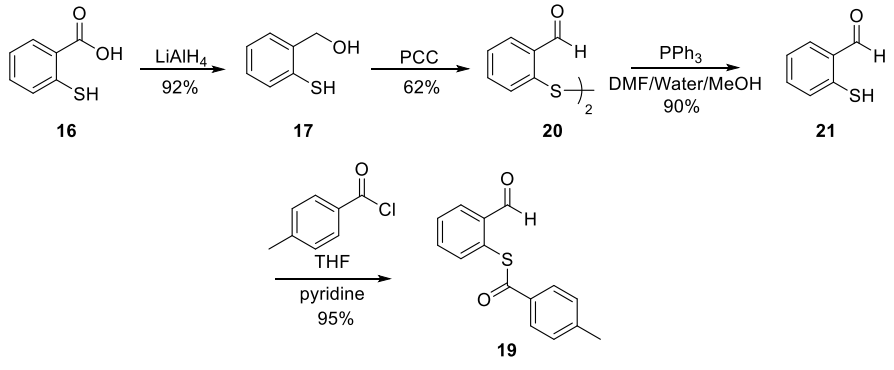
In order to obtain the 2-mercaptobenzaldehyde precursor to these imines, a synthetic route was devised beginning from the commercially available thiosalicylic acid (Scheme 1.12). Thiosalicylic acid was reduced using $LiAlH_4$ to provide alcohol **20**. The o-mercaptobenzylic alcohol was reacted with *p*-toluoyl chloride in the presence of pyridine, providing only the desired thioester **21** with no trace of the benzylic ester in the reaction mixture. Oxidation of the alcohol using pyridinium chlorochromate (PCC) led to the aldehyde **22**. All steps in the synthesis provided excellent yields, culminating in a

75% overall yield of the desired aldehyde. The reactions also proved scalable; each reaction was easily performed on a multigram scale.



Scheme 1.12. Preparation of Aldehyde Starting Materials.

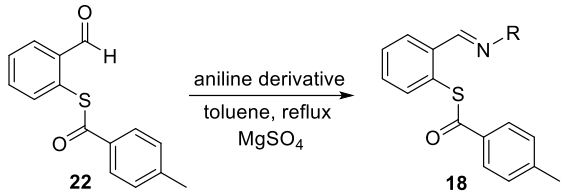
A second route to thiolester **22** was formulated based on literature precedent[55] with the intention that the thioester could be introduced at a later stage, allowing for more versatility (Scheme 1.13). Thiosalicylic acid was again reduced with $LiAlH_4$ to produce 2-mercaptobenzylic alcohol in good yield. Alcohol **20** was then oxidized at both OH and SH using PCC to form the 2,2'-dithiobenzaldehyde. Selective reduction of the disulfide moiety using triphenylphosphine in a mixture of DMF/MeOH/water led to 2-mercaptobenzaldehyde **23**. Reaction of **23** with *p*-toluoyl chloride gave the desired aldehyde starting material. This route was also quite scalable, having been performed on a 5 gram scale.



Scheme 1.13 Preparation of Aldehyde Starting Materials

Finally, the desired imine starting materials were obtained by reacting compound **22** with various aniline derivatives. While the imines were stable solids, purification *via* silica gel provided low yields of the desired aldimine, even when the silica gel column was deactivated with triethyl amine. Rather than using chromatography, recrystallization of the crude imines from ethanol provided the aldimines in good yields. Table 1.3 shows the yields obtained of the various aniline derivatives.

Table 1.3. Reaction of Aniline Derivatives with Aldehyde **22**.

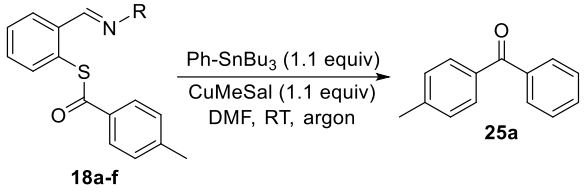


Compound	R	Yield (%)
18a	phenyl	85
18b	benzyl	67
18c	*p*-methoxy	83
18d	*p*-hydroxy	77
18e	*p*-nitro	66
18f	*o*-hydroxy	74
18g	*o*-methoxy	81
18h	*m*-nitro	70

With the imine starting materials in hand, each was tested to determine if the basicity of the imine would affect the reaction. Because previous reactions within the Liebeskind laboratory and in the literature[19] have indicated that the use of stoichiometric quantities of copper carboxylate can lead to problems with copper-mediated protodeborylation, tributylphenylstannane was chosen as the initial coupling partner. Table 1.4 shows the results of these reactions. Electron donating substituents on the imine

provide high yields of ketone in approximately 18-24 hours (Table 1.4, Entries 3,4, 6, and 7). Electron withdrawing substituents such as *p*-nitro (Table 1.4, Entry 5) produced excellent yields after three days of reaction. These results indicate that electron donating groups on the imine speed reaction *via* increased electron donation to the copper. These results can be rationalized either by stronger coordination with copper through electron rich imines or increased nucleophilicity of the organocopper intermediate that is generated following transmetalation.

Table 1.4. Reaction of Imines with Tributylphenyl Tin.



Compound	R	Yield (%)	Time
18a	phenyl	84	2 days
18b	benzyl	71	3 days
18c	*p*-methoxy	90	18 hrs
18d	*p*-hydroxy	86	24 hrs
18e	*p*-nitro	98	3 days
18f	*o*-hydroxy	84	24 hrs
18g	*o*-methoxy	87	18 hrs

Furthermore, a screening of copper sources including CuMeSal, CuTC, CuDPP, CuCl, and CuBr found that a majority of copper(I) salts worked for the coupling of tributylphenyl tin and the *p*-methoxy imine-derived thioester; however, none worked as quickly or as efficiently as copper 3-methyl salicylate (CuMeSal). In addition to a survey of copper sources, a variety of solvents were screened including DCM, THF, toluene, dioxane, and DMF. DMF proved to be the only solvent that could effectively promote the

desired reaction with THF and dioxane providing 53% and 66% of the desired ketone, respectively. DCM and toluene completely shut down the reaction.

These data led to the conclusion that imine **18c**, based on *p*-methoxyaniline, would be an ideal candidate for further study. Because the reaction takes place at a modest rate when conducted at room temperature, the reaction mixture was heated to 50 °C to ensure a reasonably fast reaction. As depicted in Figure 1.3 a variety of stannanes were assayed and showed that the reaction tolerates both aryl and heteroaryl coupling partners as well as vinyl and allyl tin species. While never isolated from the reaction, the presumed side-product of the reaction is a stoichiometric amount of copper (I) thiolate.

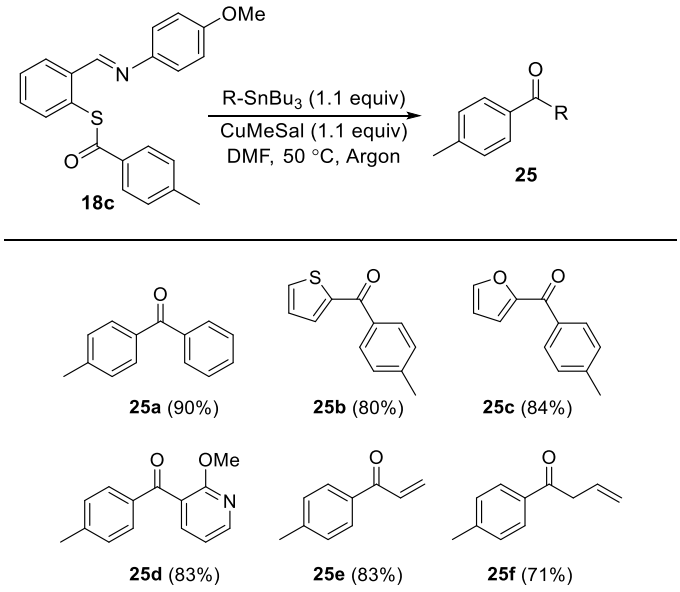
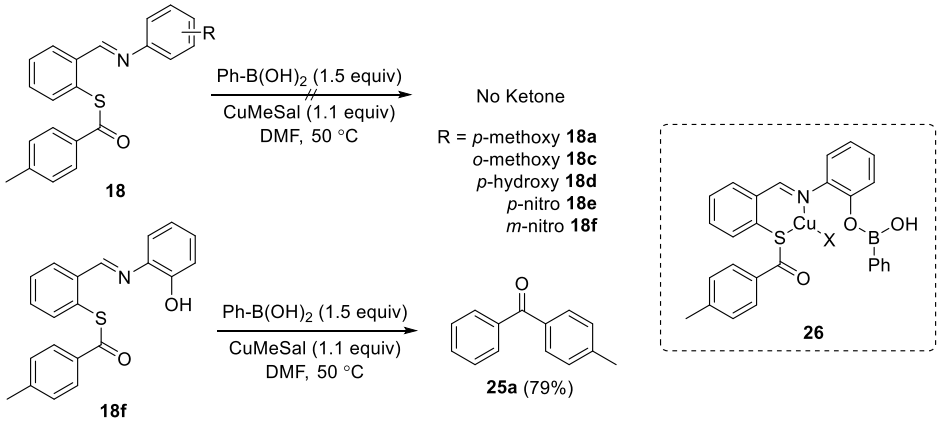


Figure 1.3. Reaction of Organotributyltin Derivatives with Imine **18c**.

Unfortunately, when imine **18c** was used to couple with boronic acids, no reaction occurred, even over long periods of time. Previous examples within the group indicate that copper-mediated protodeborylation can be a fast side-reaction with the use of stoichiometric copper carboxylate.[19, 52] In this case, it is possible that protodeborylation

may outcompetes cross-coupling, but control experiments to observe the protodeborylation pathway were not carried out.

In order to address this problem the imine structure was varied seeking a suitable partner for boronic acid cross-couplings. Of the imines tested, only thioester **18f** was successful at coupling boronic acids when carried out in the presence of stoichiometric CuMeSal (Scheme 1.14). This phenomenon can be rationalized by assuming that the phenolic oxygen of **18f** exchanges with an oxygen on the boronic acid, bringing it into position for coupling and increasing reactivity though proximity (Scheme 1.14, **26**). This hypothesis is supported by the fact that thioesters derived from *p*-hydroxyphenylimine are incapable of supporting the coupling reaction, although the two imines should have similar electronic properties.



Scheme 1.14 Reaction of Thiol Esters with Phenylboronic Acid

Using this rationale, a boronic ester was also tested as a coupling partner. The literature shows that boronic esters usually require the addition of a strong base to fill the fourth valence of boron and activate the boronate ester for transmetalation. Because the phenolic oxygen of the ortho-hydroxyphenylimine-based thiol ester was presumed to activate the boronic acid during the ketone-forming coupling reaction, it was thought that

the same activity might occur for boronic esters. This would be the first example of a base-free cross-coupling of boronic esters that had previously proven inefficient in desulfitative cross-coupling. Boronic esters possess a number of characteristics that improve upon the already desirable boronic acids such as the fact that boronic esters are less polar than boronic acids and can be easily chromatographed for purification. Furthermore, boronic esters do not form anhydrides (boroxines)[56] which can limit the efficiency of reactions, occasionally requiring the use of 1.5 – 2 equivalents of the boron reagent. Figure 1.4 shows the results of the desulfitative coupling of a variety of boronic esters using stoichiometric CuMeSal and thiol ester **33**. The reaction was carried out at 50 °C in DMF under argon. Again a wide variety of aryl and heteroaryl substrates were tolerated. As with boronic acids, we postulate that the phenolic oxygen is capable of activating the boronic ester to facilitate transmetalation.

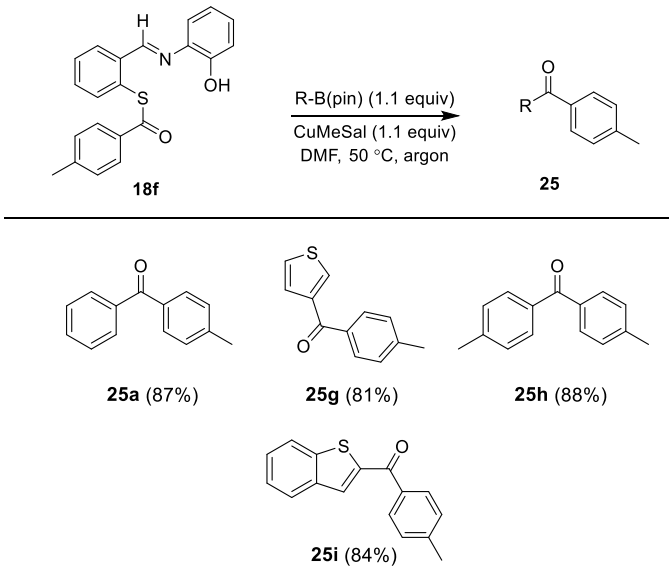


Figure 1.4. Reaction of Boronic Esters with *o*-Hydroxy Imine.

1.3 Conclusion

The use of a stoichiometric copper(I) carboxylate for the templated cross-coupling of thiol esters and boronic esters represents the first base-free cross coupling of boronic esters to date. The procedure can also be used to couple boronic acids and organotin derivatives. While a variety of imine directing group can be used for the cross-coupling of organostannanes, the boronic acid/esters require the use of the *ortho*-hydorxy imine **18f**. This requirement can be explained by proximity induced transmetalation/activation as the imine *ortho*-hydroxyl group is capable of coordinating boronic acids and estsers. Without this activation, it is presumed that copper-mediated protodeborylation predominates the reaction.

1.4 Experimental

1.4.1 General Procedure

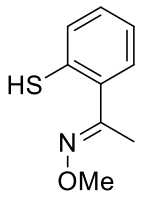
All reactions were performed under an atmosphere of dry argon in flame-dried glassware unless otherwise stated. Solvents used as reaction media were purchased in > 99% purity and were purged for several minutes with argon then dried and stored over 4Å molecular sieves (water content below 10 ppm). Ethyl acetate (EtOAc), hexanes, and ethyl ether (Et_2O) were obtained from Sigma-Aldrich and used as purchased. 'Brine' refers to a saturated solution of sodium chloride in water. Flash chromatography was performed using Whatman 60Å 230-400 mesh silica, using compressed air as a source of positive pressure. Analytical thin-layer chromatography was performed using Merck Kieselgel $60F_{254}$ plates with UV or PMA (phosphomolybdic acid) for visualization.

^{1}H NMR and ^{13}C NMR were performed using a Varian Inova 400 MHz NMR spectrometer at room temperature. Samples were dissolved in $CDCl_3$ and referenced at 7.26 ppm and 77.23 ppm, respectively. Signals are reported as follows: chemical shifts are reported (δ), multiplicities are indicated (s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet)), coupling constants are indicated (Hz), and integrations are given. Infrared spectra were recorded using Nicolet 510 FT-IT. Peaks are given as s (strong), m (medium), w(weak), or br (broad).

All organostannanes and boronic acids were used as generously provided by Dr. Gary Allred at Synthonix.

1.4.2 Preparation of Oxime Starting Materials

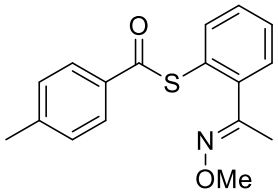
1-(2-Mercapto-phenyl)ethanone O-methyloxime (9)[52]



2'-Mercaptoacetophenone (3.04 g, 20 mmol) and O-methylhydroxylamine hydrochloride (2.51 g, 30 mmol) were dissolved in 60 mL MeOH. Pyridine (2.77 g, 35 mmol) was slowly added via syringe and the reaction mixture was stirred at room temperature for 18 hours. The solvent was evaporated and the residue was dissolved in diethyl ether (20 mL). The organic phase was washed with 1 M HCl (2×10 mL), water (10 mL) and brine (5 mL). After drying over anhydrous $MgSO_4$ and filtering, the solvent was evaporated. Purification by flash chromatography (silica gel, 20:1 hexanes:EtOAc) afforded the title compound as a yellow oil (6:1 mixture of E/Z isomers, 3.11 g, 86%). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.16-7.14 (m, 2H), 4.01 (s, 3H), 3.97 (s,

1H), 2.22 (s, 3H); characteristic signals for minor isomer: ^{1}H NMR δ 2.16 (s, 3H), 3.84 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 135.8, 131.2, 129.2, 128.9, 125.7, 62.2, 15.3; IR (neat, cm^{-1}): 3061 (m), 2937 (s), 2548 (m), 1613 (m); HRMS (FAB) Calcd. for $C_9H_{12}ONS$ (M+H): 182.0634. Found: 182.0632.

_S_-2-(1-(Methoxyimino)ethyl)phenyl 4-methylbenzothioate (10)[52]

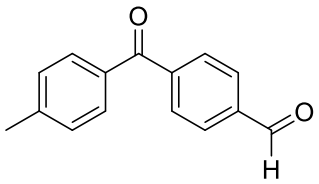


1-(2-Mercaptophenyl)ethanone O-methyloxime (181 mg, 1.0 mmol) and p-toluoyl chloride (162 mg, 1.05 mmol) were dissolved in 20 mL THF. Pyridine (87 mg, 1.1 mmol) was added slowly via syringe and after stirring at room temperature for 4 h a white precipitate was removed by filtration. The filtrate was washed with water (10 mL) and brine (5 mL) and then dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated to give a yellow oil. Purification by flash chromatography (silica gel, 10:1 hexanes:EtOAc) afforded the title compound as a clear oil (6:1 mixture of E/Z isomers, 293 mg, 98%). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 2H), 7.57-7.54 (m, 1H), 7.46-7.40 (m, 3H), 7.28 (d, J = 8.0 Hz, 2H), 3.92 (s, 3H), 2.42 (s, 3H), 2.12 (s, 3H); characteristic signals for minor isomer: ^{1}H NMR δ 3.76 (s, 3H), 2.42 (s, 3H), 2.10 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 156.6, 144.9, 142.6, 137.7, 134.1, 130.1, 129.6, 129.4, 127.8, 126.3, 62.1, 21.9, 16.6; IR (neat, cm^{-1}): 3065 (m), 1695 (s), 1671 (s); HRMS (FAB) Calcd for $C_{17}H_{18}O_2NS$ (M+H): 300.1052. Found: 300.1051.

1.4.3 General Procedure for Microwave Irradiation Experiments.

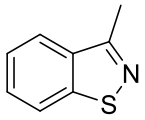
Microwave irradiation experiments were carried out using a Discover microwave reactor from CEM. All experiments were performed in sealed tubes (capacity 10 mL) under argon atmosphere utilizing microwave irradiation of 300 W. The temperature was ramped from room temperature to 150 °C in 1 minute. Once this temperature was reached, the reaction temperature was held at 150 °C for 60 minutes. In the control experiments, the couplings of thiol esters with 4-formylphenylboronic acid were conducted by the following general experimental procedure. A Schlenk tube (entry 1-3) or microwave tube (entry 4-8) was charged with a stir bar. To the tube was added the thiol ester (0.1 mmol), CuMeSal (0.02 mmol) and boronic acid (0.12 mmol). After flushing with argon, anhydrous and degassed DMF (1 mL) was added. The reaction mixture was stirred under the indicated reaction conditions. After cooling, ethyl ether (10 mL) was added to the mixture. The reaction mixture was washed with water, brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative plate silica chromatography using hexanes/EtOAc as the eluent.

4-(4-Methyl-benzoyl)-benzaldehyde (11)[57]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid. Mp = 86-87 °C. [Lit[58] 84-86 °C]. ^{1}H NMR (400 MHz, CDCl3) δ 10.13 (s, 1 H), 8.0 (d, J = 7.8 Hz, 2 H), 7.90 (d, J = 8.2 Hz, 2 H), 7.72 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 2.42 (s, 3 H); IR (neat, cm^{-1}) 1700 (s), 1640 (s).

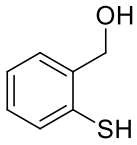
3-Methyl-1,2-benzisothiazole (12)[59]



Isolated along with the ketone product as a yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 7.93-7.89 (m, 2H), 7.52-7.48 (m, 1H), 7.43-7.39 (m, 1H), 2.74 (s, 3 H); IR (neat, cm^{-1}): 3065 (m), 1733 (s), 1633 (s).

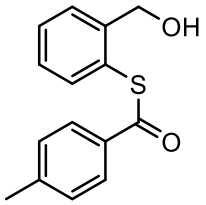
1.4.4 Preparation of Imine Starting Materials

2-Mercaptobenzyl alcohol (20)[55]



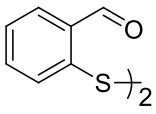
Lithium aluminum hydride (2.46 g, 64.8 mmol) was taken up in THF (50 mL). At room temperature, 2-mercaptobenzoic acid (5.00 g, 32.4 mmol) in THF (25 mL) was added dropwise over one hour. The reaction was stirred for 24 hours before dropwise addition of EtOAc (8 mL) followed by 10% aqueous H_2SO_4 (24 mL). The reaction was filtered and washed with brine (2 x 60 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to provide the title compound (4.28 g, 94%) as a yellow solid. No further purification was carried out, and the crude mixture was used as obtained in the following reactions. TLC (R*f* = 0.25, silica gel, 25% ethyl acetate in hexanes). Mp = 41 °C [Lit[55] 36 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2 H), 7.17-7.15 (m, 2 H), 4.66 (s, 2 H), 3.67 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 131.5, 130.5, 128.9, 128.6, 126.5, 64.4. IR (neat, cm^{-1}) 3295 (br s), 1464 (s), 1440 (s), 1067 (s), 1043 (vs), 1032 (vs), 989 (s), 746 (s).

_S_-(2-(Hydroxymethyl)phenyl)-4-methylbenzothioate (21)



2-Mercaptobenzyl alcohol **20** (2.2 g, 15.5 mmol) was taken up in THF (25 mL) and 4-methylbenzoyl chloride (2.25 mL, 17.0 mmol) was added to the mixture. The solution was stirred at room temperature and pyridine (1.38 mL, 17.0 mmol) was added slowly. After one hour, the solution was filtered and concentrated *in vacuo*. The crude mixture was purified *via* flash chromatography (25% EtOAc : hexanes) to provide pure **21** as a white solid (90%, 3.6 g). TLC (R*f* = 0.32, silica gel, 25% ethyl acetate in hexanes). Mp = 74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 2 H, *J* = 8.8 Hz), 7.64 (dd, *J* = 6.4, 2.0 Hz, 1 H), 7.52-7.48 (m, 1H), 7.36 (dt, *J* = 7.6, 1.6Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2 H), 4.72 (d, *J* = 4 Hz, 2 H), 2.43 (s, 3H), 2.23 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.58, 145.02, 144.77, 136.56, 133.73, 130.75, 129.64, 129.47, 128.53, 127.80, 125.70, 63.89, 21.77. IR (neat, cm^{-1}) 3289 (br), 1670 (s), 1607 (w), 1442 (w), 1209 (m), 1178 (m), 1033 (m), 1004 (m), 904 (m), 746 (m). HRMS (FAB) Calcd for $C_{15}H_{14}O_2S$ ($[M+H]^+$): 259.0787. Found: 258.0785.

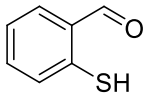
2, 2'-Dithiobenzaldehyde (23)[55]



Pyridinium chlorochromate (3.84 g, 17.8 mmol) was taken up in DCM (25 mL). To this mixture was added **(20)** (1.00 g, 7.1 mmol) slowly over 5 minutes. The reaction was stirred for 5 hours at room temperature and the supernatant from the reaction mixture was

passed through a plug of silica gel. The remaining tar-like residue from the reaction was washed with DCM (3 x 25mL) and ether (2 x 20mL) until becoming granular, with these organic layers also passed through the silica plug. Finally, excess ether was used to wash the silica to provide **23** (704 mg, 72%) as a white solid after concentration *in vacuo*. TLC (R*f* = 0.25, silica gel, 25% ethyl acetate in hexanes). Mp = 140 °C [Lit[55] 45 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 2 H), 7.86 (dd, *J* = 7.6, 1.6 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H), 7.48 (dt, *J* = 7.2, 1.6 Hz, 2 H), 7.38 (dt, *J* = 7.2, 0.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 140.2, 135.0, 134.5, 134.0, 126.8, 126.5. IR (neat, cm^{-1}) 1665 (vs), 1556 (s), 1196 (vs), 839 (s), 765 (vs), 750 (vs), 670 (s), 653 (vs).

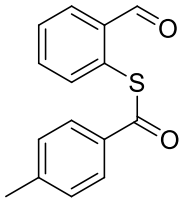
2-Mercaptobenzaldehyde (24)[55]



To a solution of 2,2'-dithiobenzaldehyde **23** (1.7 g, 6.2 mmol) in degassed DMF (54 mL), were added degassed MeOH (54 mL) and water (30 mL). Triphenylphosphine (2.42 g, 9.2 mmol) was added by portions and the reaction was stirred for 30 minutes at room temperature. The reaction was cooled to 0 °C and continued to stir for 30 minutes. The reaction mixture was combined with cold ether (0 °C) and washed with water. The aqueous layer was further washed with cold ether (2 x 50 mL). The organic layers were combined, washed with brine (2 x 70 mL) and dried over $MgSO_4$. The organic layer was concentrated *in vacuo* to provide crude **24**. The crude mixture was purified by flash chromatography (100% ether) to provide pure 24 as a yellow liquid (1.6 g, 96%). TLC (R*f* = 0.31, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1

(s, 1 H), 7.74 (d, *J* = 1.2 Hz, 1 H), 7.39 (d, *J* = 7.2 Hz, 1 H), 7.32-7.28 (m, 2 H), 5.53 (s, 1H). IR (neat, cm^{-1}) 1667 (s), 746 (s).

_S_-(2-Formylphenyl) 4-methylbenzothioate (22)



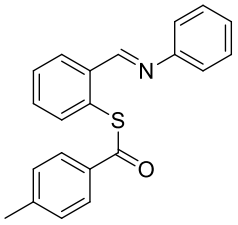
Aldehyde **24** (500 mg, 3.6 mmol) was taken up in THF (10 mL) and 4-methylbenzoyl chloride (0.52 mL, 3.96 mmol) was added to the mixture. The solution was stirred at room temperature and pyridine (0.32 mL, 3.96 mmol) was added slowly. After one hour, the solution was filtered and concentrated *in vacuo*. The crude mixture was purified *via* flash chromatography (25% EtOAc : hexanes) to provide pure **22** as a white solid (90%, 827 mg). TLC (R*f* = 0.44, silica gel, 25% ethyl acetate in hexanes). Mp = 74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1 H), 8.20 (dd, *J* = 7.4, 1.6 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 7.68-7.58 (m, 3 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 2.45 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 188.5, 145.6, 137.7, 137.2, 134.4, 133.5, 131.2, 130.6, 129.8, 129.2, 128.1, 22.0. IR (neat, cm^{-1}) 1692 (s), 1667(s), 1603 (m), 1583 (m), 1198 (s), 1176 (m), 895 (m). HRMS (FAB) Calcd for $C_{15}H_{14}O_2S$ ($[M+H]^+$): 257.0631. Found: 257.0632.

1.4.5 General Procedure for the Production of Imines

Aniline derivative (1.0 equiv) and *S*-(2-formylphenyl) 4-methylbenzothioate (1.0 equiv) were mixed in toluene (0.5 M). Anhydrous magnesium sulfate was added to the reaction and the mixture was stirred at 100 °C for 4 hours. The mixture was filtered, concentrated

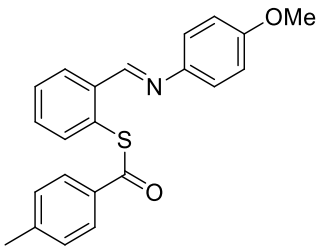
in vacuo, and purified by recrystallization from ethanol to provide the desired imine product.

_S_-(2-((Phenylimino)methyl)phenyl) 4-methylbenzothioate (18a)



Following the general procedure, aniline (73 mg, 0.78 mmol) and *S*-(2-formylphenyl) 4-methylbenzothioate (200 mg, 0.78 mmol) were mixed in toluene (5 mL). Recrystallization afforded pure **18a** (219 mg, 85%). TLC (R*f* = 0.36, silica gel, 25% ethyl acetate in hexanes). Mp = 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1 H), 7.96 (d, *J* = 6.8 Hz, 2 H), 7.61-7.51 (m, 3 H), 7.34 (t, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.22-7.17 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 158.7, 152.3, 145.3, 139.0, 137.2, 133.9, 131.7, 130.6, 129.8, 129.4, 129.3, 128.5, 128.0, 126.3, 121.3, 22.0. IR (neat, cm^{-1}) 1665 (s), 1615 (m), 1606(m), 1579(m),1209 (s), 1175 (s), 899 (s), 763 (s), 756 (s). HRMS (FAB) Calcd for ($[M+H]^+$): 331.1103. Found: 331.1100.

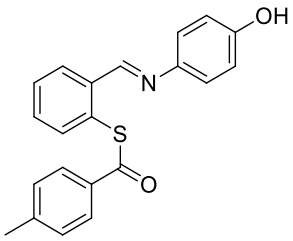
_S_-(2-(((4-Methoxyphenyl)imino)methyl)phenyl) 4-methylbenzothioate (18c)



Following the general procedure, the desired compound was obtained in 83% yield (233 mg). TLC (R*f* = 0.34, silica gel, 25% ethyl acetate in hexanes). Mp = 101°C. ^{1}H NMR

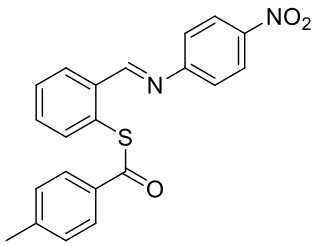
(400 MHz, $CDCl_3$) δ 8.35 (s, 1 H), 8.39 (d, *J* = 8.4 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 2 H), 7.60-7.44 (m, 3 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 9.2 Hz, 2 H), 3.78 (s, 3 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 158.6, 156.6, 145.2, 139.3, 137.1, 133.9, 131.4, 130.6, 129.7, 129.1, 128.3, 128.0, 122.6, 114.5, 55.7, 22.0. IR (neat, cm^{-1}) 1664 (s), 1603(s), 1504 (s), 1173 (s), 897 (s), 819 (s), 7.66 (s). HRMS (FAB) Calcd for ($[M+H]^+$):362.1209. Found: 362.1205.

_S_-(2-(((4-Hydroxyphenyl)imino)methyl)phenyl) 4-methylbenzothioate (18d)



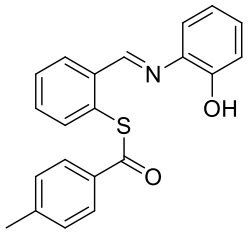
Following the general procedure, the desired compound was obtained in 77% yield (220 mg). TLC (R*f* = 0.31, silica gel, 25% ethyl acetate in hexanes). Mp = 162°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.76 (d, 8.4 Hz, 2 H), 7.59-7.50 (m, 3 H), 7.27 (d, *J* = 8.4 Hz, 3 H), 6.86-6.78 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 158.0, 155.2, 143.2, 139.0, 137.1, 133.6, 131.4, 130.6, 128.7, 128.1, 128.3, 127.1, 121.8, 114.5, 22.0. IR (neat, cm^{-1}). 3270(br), 1663(s), 1618 (m), 1604 (m), 1506 (m), 1206 (m), 1174 (m), 901 (s), HRMS (FAB) Calcd for ($[M+H]^+$):348.1053. Found: 348.1050.

_S_-(2-(((4-Nitrophenyl)imino)methyl)phenyl) 4-methylbenzothioate (18e)



Following the general procedure, the desired compound was obtained in 66% yield (192 mg). TLC (R*f* = 0.29, silica gel, 25% ethyl acetate in hexanes). Mp = 145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1 H), 8.45 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 7.61-7.51 (m, 3 H), 7.29 (d, *J* = 8.0 Hz, 3 H), 6.97-6.90 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 159.6, 152.6, 145.1, 139.1, 137.1, 133.9, 131.6, 130.5, 129.7, 129.6, 129.3, 128.7, 127.3, 121.2, 111.7, 22.0. IR (neat, cm^{-1}) 1650 (s), 1598 (s), 1481 (s), 1308 (s), 761 (s). HRMS (FAB) Calcd for ($[M+H]^+$): 377.0954. Found: 377.0952.

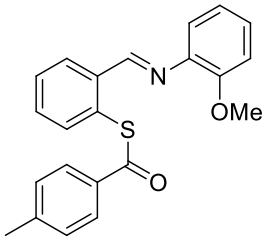
_S_-(2-(((2-Hydroxyphenyl)imino)methyl)phenyl) 4-methylbenzothioate (18f)



Following the general procedure, the desired compound was obtained in 74% yield (199 mg). TLC (R*f* = 0.37, silica gel, 25% ethyl acetate in hexanes). Mp = 151°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1 H), 8.40 (d, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 8.4 Hz, 2 H), 7.61-7.53 (m, 3 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.23 (s, 1 H), 7.18 (t, *J* = 8.0 Hz, 2 H), 7.00 (dd, *J* = 8.4, 1.2 Hz, 1 H), 6.84 (dt, *J* = 7.6, 1.2 Hz, 1 H), 2.45 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 155.4, 152.7, 145.4, 138.7, 137.4, 135.8, 133.8, 131.9, 130.6,

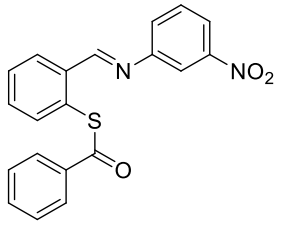
129.8, 129.6, 129.5, 128.4, 128.1, 120.3, 116.4, 115.3, 22.0. IR (neat, cm^{-1}) 3486 (br), 1668 (s), 1605 (m), 1484 (m), 1208 (s), 1174 (s), 898 (s), 756 (s), 741 (m). HRMS (FAB) Calcd for ($[M+H]^+$): 348.1053. Found: 348.1050.

_S_-(2-(((2-Methoxyphenyl)imino)methyl)phenyl) 4-methylbenzothioate (18g)



Following the general procedure, the desired compound was obtained in 81% yield (226 mg). TLC (R*f* = 0.37, silica gel, 25% ethyl acetate in hexanes). Mp = 105°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1 H), 8.46 (d, *J* = 8.4 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.60-7.50 (m, 3 H), 7.29 (d, *J* = 8.4 Hz, 3 H), 6.96-6.80 (m, 3 H), 3.5 (s, 3 H), 2.44 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 159.6, 152.6, 145.1, 139.1, 137.1, 133.9, 131.6, 130.5, 129.7, 129.6, 129.3, 128.7, 127.3, 123.9, 121.4, 121.2, 111.7, 56.1, 22.0. IR (neat, cm^{-1}) 1667 (m), 1247 (m), 1173 (m), 898 (s), 767 (s), 743 (s), 623 (m). HRMS (FAB) Calcd for ($[M+H]^+$): 362.1209. Found: 362.1205.

_S_-(2-(((3-Nitrophenyl)imino)methyl)phenyl) 4-methylbenzothioate (18h)



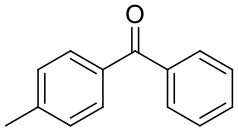
Following the general procedure, the desired compound was obtained in 70% yield (208 mg). TLC (R*f* = 0.33, silica gel, 25% ethyl acetate in hexanes). Mp = 132 °C. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.79 (s, 1 H), 8.42 (d, *J* = 7.2 Hz, 1 H), 8.04 (dt, *J* = 8.0, 1.2 Hz, 1 H), 7.98-7.96 (m, 3 H), 7.62-7.59 (m, 3 H), 7.53-7.43 (m, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 2.44 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 161.1, 153.5, 145.5, 138.2, 137.1, 133.7, 132.4, 130.7, 130.0, 129.8, 128.7, 128.1, 127.8, 120.7, 115.9, 22.0. IR (neat, cm^{-1}) 1663 (s), 1605 (s), 1520 (s), 1348 (s), 1174 (s), 895 (s), 818 (s), 770 (s). HRMS (FAB) Calcd for ($[M+H]^+$): 377.0954. Found: 377.0952.

1.4.6 General Procedure for Desulfitative Coupling

Copper 3-methylsalicylate (1.1 equiv) and the imine (1.0 equiv) were mixed in a flame dried test tube. DMF (0.05 M) was added to the test tube, followed by the organostannane, boronic acid, or boronic ester (1.1 equiv). The reaction was stirred at 50 °C until the reaction was complete (monitored by TLC). The reaction was taken up in diethyl ether (10 mL) and washed with brine (6 mL x 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude mixture was purified *via* flash chromatography (hexanes :EtOAc 4:1) to provide the desired ketone.

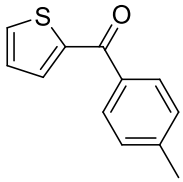
Phenyl(*p*-tolyl)methanone (25a)[60]



Following the general procedure, compound **18f** (20 mg, 0.055 mmol) was combined with CuMeSal (13.1 mg, 0.061 mmol). DMF (2.0 mL) was added to the reaction, followed by tributylphenyltin (or phenyl boronic ester) (22.4 mg, 0.061 mmol). The reaction was allowed to stir at 50 °C until completion (monitored by TLC). The title compound was isolated as a white solid (9.8 mg, 90% from the organostannane; 9.8 mg,

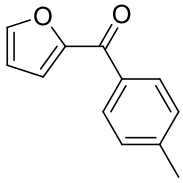
87% from the phenyl boronic ester). TLC (R*f* = 0.66, silica gel, 25% ethyl acetate in hexanes). Mp = 57 °C [Lit[60] 56.5-57 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 7.2 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 143.5, 138.2, 135.1, 132.4, 130.5, 130.2, 129.2, 128.4, 21.8. IR (neat, cm^{-1}) 1656 (s).

Thiophen-2-yl(*p*-tolyl)methanone (25b)[61]



Following the general procedure, the desired compound was obtained as a white solid (80%, 8.9 mg from the organostannane). TLC (R*f* = 0.60, silica gel, 25% ethyl acetate in hexanes). Mp = 72 °C [Lit[61] 74-75 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2 H), 7.59-7.52 (m, 2 H), 7.18 (d, *J* = 7.8, 2 H), 7.30-7.05 (m, 1 H), 2.42 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 143.3, 142.7, 135.0, 134.1, 133.6, 129.0, 128.8, 127.5, 21.2. IR (neat, cm^{-1}) 1632 (s).

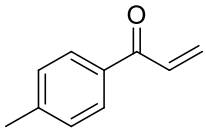
Furan-2-yl(*p*-tolyl)methanone (25c)[62]



Following the general procedure, the desired compound was obtained as a white solid (84%, 8.6 mg from the organostannane). TLC (R*f* = 0.58), silica gel, 25% ethyl acetate in hexanes). Mp = 72-73 °C [Lit[63] 70 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4, 2

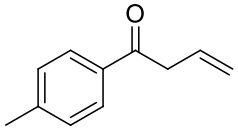
H), 7.62-7.63 (m, 1 H), 7.15-7.24 (m, 3 H), 6.51-6.52 (m, 1 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 152.2, 146.8, 143.4, 134.3, 129.3, 129.0, 120.3, 112.0, 21.5. IR (neat, cm^{-1}) 1643 (s).

1-(*p*-Tolyl)prop-2-en-1-one (25e)[61]



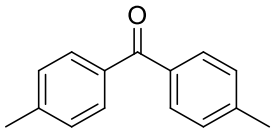
Following the general procedure, the desired compound was obtained as a yellow oil (83 %, 6.8 mg from the organostannane). TLC (R*f* = 0.59, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 6.49-6.25 (m, 2 H), 5.8 (d, *J* = 16.0 Hz, 1 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 143.5, 134.5, 132.2, 129.3, 129.1, 128.5, 21.5. IR (neat, cm^{-1}) 1660 (s).

1-(*p*-Tolyl)but-3-en-1-one (25f)[64]



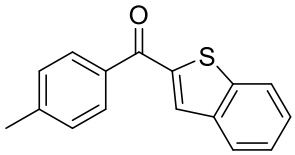
Following the general procedure, the desired compound was obtained as a yellow oil (71%, 8.8 mg). TLC (R*f* = 0.55, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 6.28-6.02 (m, 1H), 5.23-5.16 (m, 2 H), 3.71 (d, *J* = 4.8 Hz, 2 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 129.7, 129.5, 128.6, 128.0, 43.6, 28.0, 27.1, 13.8. IR (neat, cm^{-1}) 1672 (s).

Di-*p*-tolylmethanone (25h)[62]



Following the general procedure, the desired compound was obtained as a white solid (88 %, 10.7 mg from boronic ester; 85%, 10.3 mg from the boronic acid). TLC (R*f* = 0.62, silica gel, 25% ethyl acetate in hexanes). Mp = 92 °C [Lit.[62] 92-93 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.2 Hz, 4 H), 7.26 (d, *J* = 7.2 Hz, 4 H), 2.42 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 142.5, 134.7, 129.7, 128.5, 21.1. IR (neat, cm^{-1}) 1653 (s), 1603 (s).

Benzo[*b*]thiophen-2-yl(*p*-tolyl)methanone (25i).



Following the general procedure, the desired compound was obtained as a yellow oil (84 %, 12.2 mg from boronic ester; 80%, 11.6 mg from the boronic acid). TLC (R*f* = 0.61, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.83 (m, 4 H), 7.58 (s, 1 H), 7.28 (d, *J* = 8.0 Hz, 3 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 134.4, 133.8, 129.8, 128.3, 127.6, 126.5, 125.7, 124.9, 124.4, 124.1, 122.7, 120.7, 22.0. IR (neat, cm^{-1}) 1657.

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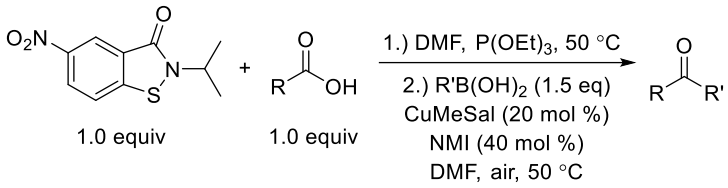
Chapter 2

Recyclable Reagent for the Keto-Conjugation of Carboxylic Acids with Boronic Acids

Abstract: The Liebeskind-Srogl reaction allows for the mild, base-free construction of carbon-carbon bonds through desulfitative cross-coupling. The reaction has been developed over the past fifteen years, with three published "generations" having emerged. The "second-generation" reaction has now been modified through the use of ligands on the copper catalyst to eliminate unnecessary byproducts (Scheme 2.1). Furthermore, the reaction proceeds in one pot, beginning with carboxylic acids, which, when reacted with benzisothiazolinones and triethylphosphite, produce thiol esters in situ*. S-acylthiosalicylamides then react under aerobic conditions with boronic acids/stannanes and catalytic copper to generate ketones in good yield. The chemistry can be conducted in a catalytic fashion with between two and three turnovers of the organocatalyst.*



Scheme 2.1 One-Pot Desulfitative Cross-Coupling of Carboxylic Acids and Boronic Acids

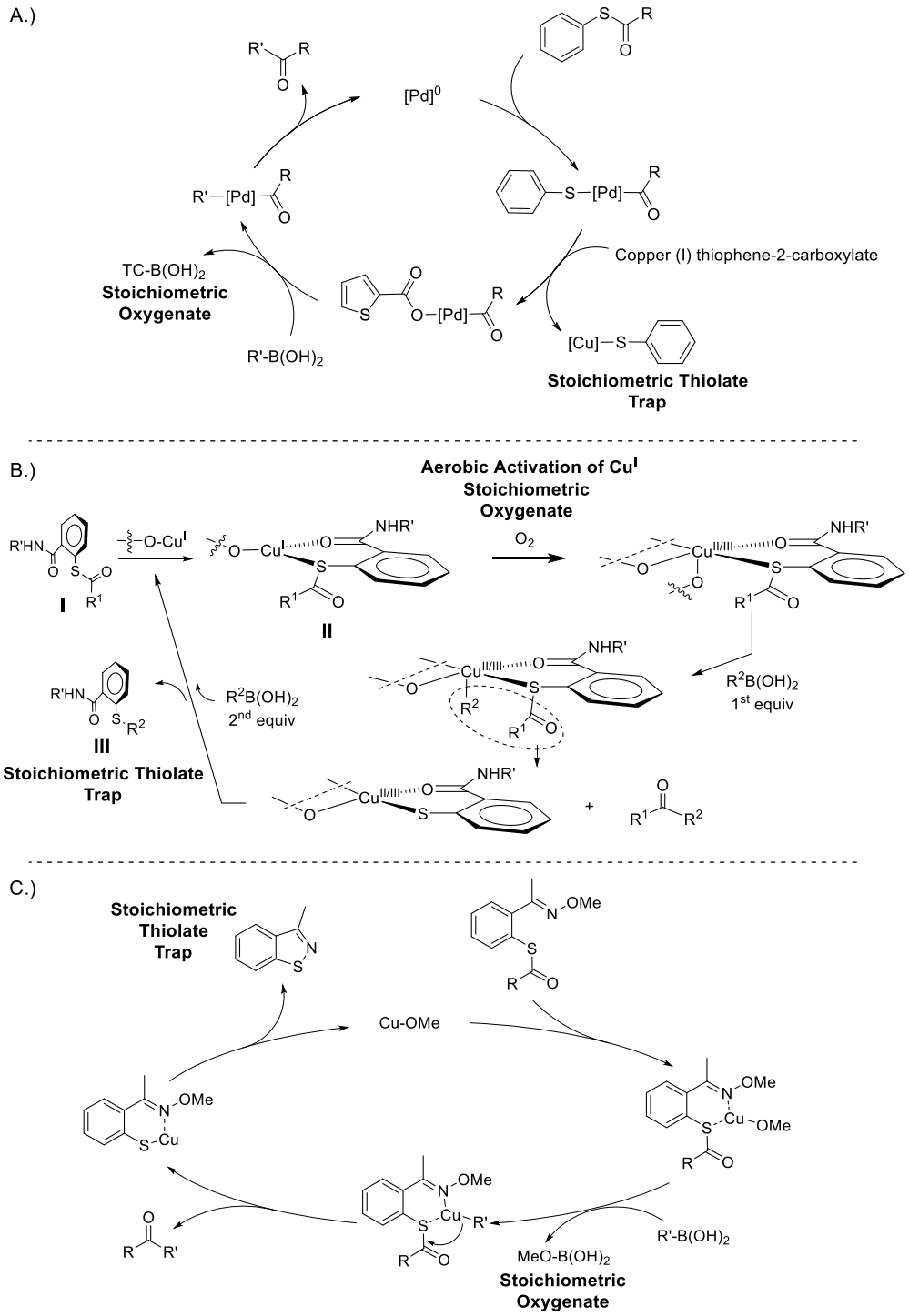
2.1 Introduction

For the past two decades, the Liebeskind laboratory has been interested in the pH neutral desulfitative cross-coupling of thioorganics with boronic acids for the generation of C-C bonds.[1-8] As noted in Chapter 1 of this Thesis, the original Liebeskind-Srogl reaction coupled thiol esters and boronic acids in the presence of catalytic palladium and stoichiometric copper carboxylate cofactor under anaerobic conditions to provide ketones

(Scheme 2.2A). While the reaction is both mild and versatile, the requirement of a stoichiometric equivalent of a copper carboxylate can be viewed as drawback.[9]

The second generation of the Liebeskind-Srogl reaction utilized an *ortho*-ligating group to position copper in close proximity to an electrophilic thiol ester **II** (Scheme 2.2B).[6-7, 10] This directing group effect allowed copper to be used in the absence of the palladium catalyst that was required in the original 1st generation cross-coupling reaction. Furthermore, the aerobic conditions of the 2nd generation coupling system allowed the copper catalyst to turn over in the presence of excess boronic acid. After transmetalation of the boronic acid, reductive elimination from the aryl copper thiolate gives thioether **III** effectively releasing copper from the tightly binding thiolate and allowing the copper to participate in further reaction.

The 3rd generation of desulfitative cross-coupling to be published by the group utilized an internal trap to eliminate the need for a sacrificial equivalent of boronic acid (Scheme 2.2C). The *ortho*-oxime functions as a directing group, again placing copper in close proximity to, and activating, the thiol ester. However, in the third generation coupling reaction, the copper thiolate formed in the course of reaction undergoes an internal S→N trapping to release a copper (I) oxygenate back for further reaction in the catalytic cycle.

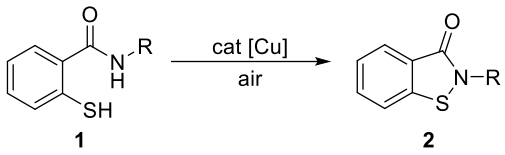


Scheme 2.2 Three Generations of the Liebeskind-Srogl Reaction.

All three generations of Liebeskind-Srogl cross-coupling (LSCC) have benefits and disadvantages. While the first generation is both mild and general, it requires the use

of a stoichiometric copper(I) carboxylate. The second generation introduces the use of catalytic amounts of copper and eliminates Pd, while maintaining mild reaction conditions. However, the added mechanistic requirement of excess boronic acid limits the reaction when the boronic acid is precious. The third generation removes the requirement of excess boronic acid, however, reaction temperatures in excess of 80-100 °C are required for efficient turnover of the copper catalyst.

The thiosalicylamides utilized in the second generation cross-coupling provide an interesting opportunity to modify reaction conditions to improve the overall efficiency of the reaction. Results obtained by the Liebeskind group[10], as well as the published work of Kanai[11] indicated that thiosalicylamides of type **1**, possess the ability to oxidatively close to form benzoisothiazolones of type **2** when exposed to catalytic copper and air (Figure 2.1).

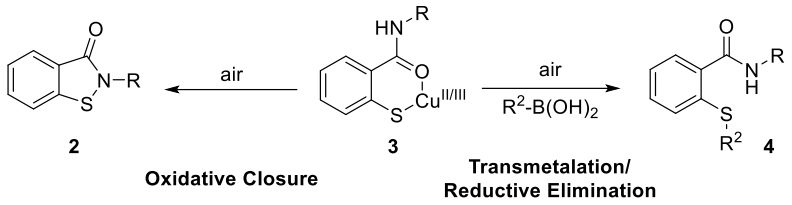


1 **2**

Figure 2.1 Oxidative Closure of Thiosalicylamides to Benzoisothiazolones.

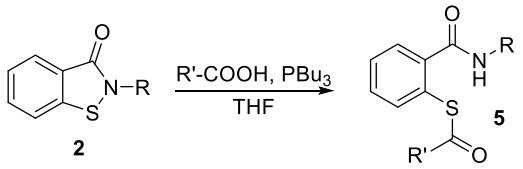
The aerobic oxidative closure of thiosalicylamides to benzoisothiazlones catalyzed by copper salts indicates that an alternate, more desirable pathway may be accessed in the second generation Liebeskind-Srogl reaction under certain conditions. This pathway would invoke the oxidative closure of the copper thiosalicylamide to the benzoisothiazolone at a rate faster than transmetalation with a second equivalent of boronic acid. Scheme 2.3 suggests that if transmetalation could be avoided, an extra

equivalent of boronic acid would be unnecessary, and the undesired thioether byproduct **4** would be eliminated.



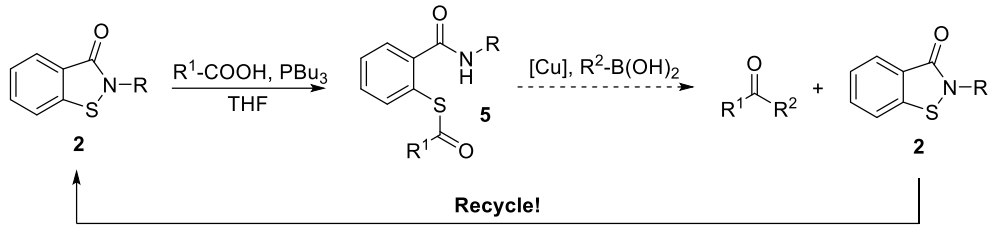
Scheme 2.3 Oxidative Closure of Copper Thiolate versus Transmetalation/Reductive Elimination.

Oxidative trapping of the copper thiosalicylamide as a benzoisothiazolone would provide an additional benefit when viewed in the context of sustainable chemistry. Initial reports from the Liebeskind laboratory,[10] which were later expanded by Srogl,[12] indicated that benzoisothiazolones are easily converted into thiol esters in the presence of tri-*n*-butylphosphine and carboxylic acids. This reaction provides thiosalicylamide derivatives in good yields (Scheme 2.4, 63-95%).



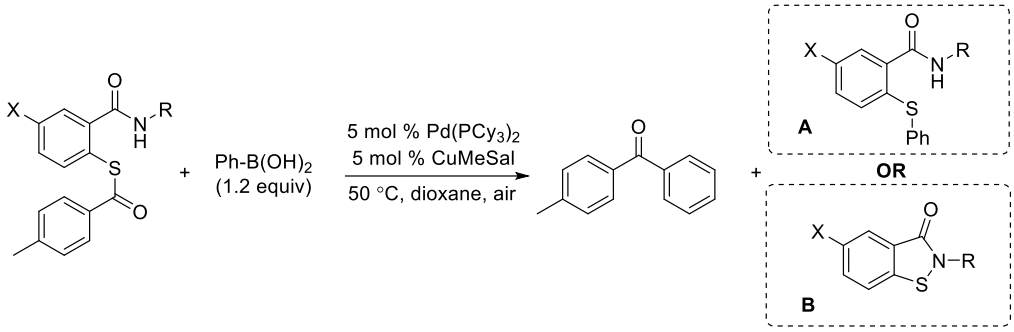
Scheme 2.4 Conversion of Benzoisothiazolones into S-Acylthiosalicylamide Derivatives

The conversion of benzoisothiazolones into thiosalicylamide derivatives, which are utilized in the second-generation Liebeskind-Srogl reaction, would provide a method for the recycling of benzoisothiazolones (Scheme 2.5). As long as the second generation LSCC could be modified to produce benzoisothiazolones as the sole byproduct, the reaction's atom economy could be greatly increased by removing the need for excess boronic acid, eliminating the unnecessary thioether byproduct, and allowing the benzoisothiazolone to be recycled into a usable starting material.



Scheme 2.5 Benzoisothiazolone Recycle

Unfortunately, under the published aerobic cross-coupling conditions utilizing catalytic copper carboxylate and S-acylthiosalicylamides in DMF[6, 13-14] no benzoisothiazalone is obtained. Previous attempts in the Liebeskind Laboratory to drive the reaction towards benzoisothiazolone have proven somewhat successful, however, conditions have not been discovered that provide high yields of ketone and benzoisothiazolone as the sole byproduct. Dr. Janette Villalobos focused attention on this reaction, initially using catalytic amounts of palladium and copper under aerobic conditions to mediate the cross-coupling.[10] Despite altering the thiosalicylamide core in various ways as listed in Scheme 2.6, only moderate yields of ketone and benzoisothiazolone were recovered (Scheme 2.6). Although yields of ketone remained low, the trends indicated that electron deficient thiosalicylamides favored oxidative closure to the benzoisothiazolone (entries 2 versus 3). Furthermore, it was seen that the nature of N-substituent of the coordinating amide played a role in both ketone production and closure (entries 1 versus 2).



Entry	R	X	% Ketone	A:B
1	*i*Pr	H	50%	A
2	*t*Bu	H	35%	mix
3	*t*Bu	NO_2	34%	B

Scheme 2.6 Previous Attempts to Form Benzoisothiazolone during LSCC

These results suggest that altering the electronic and steric properties of the thiosalicylamide will alter the relative rates of oxidative closure of the copper thiolate versus transmetalation/reductive elimination. However, an alternative source of modification is the ligand environment around copper itself. Copper-dioxygen species and their surrounding ligand environment have been thoroughly studied in the previous twenty years.[15-22] Depending on the coordinating properties of the ligands themselves, copper has been found to coordinate oxygen in three different forms, each form distinct in reactivity (Figure 2.2). For example, {Cu-(μ-O)$_2$-Cu} complexes show a high level of electrophilicity, and are known to oxidize aliphatic and aromatic C-H bonds, whereas complexes bearing the {Cu-(μ-η^2:η^2-O_2)-Cu} motif are known to be nucleophilic and basic.[23] Finally, {Cu-(μ-η^1:η^1-O_2)-Cu} exhibit enhanced electrophilic character of the bound dioxygen species. With the different reactivities dependent on the coordination sphere, it was determined that a variety of ligands should be tested in the second-generation LSCC reaction for the purpose of driving the reaction toward benzoisothiazolone formation.

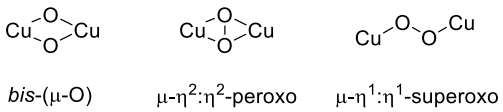
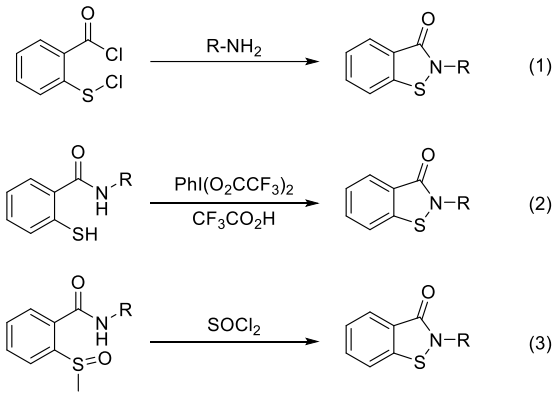


Figure 2.2 Copper-Dioxygen Coordination Motifs

2.2 Results

2.2.1 Synthesis of Starting Materials

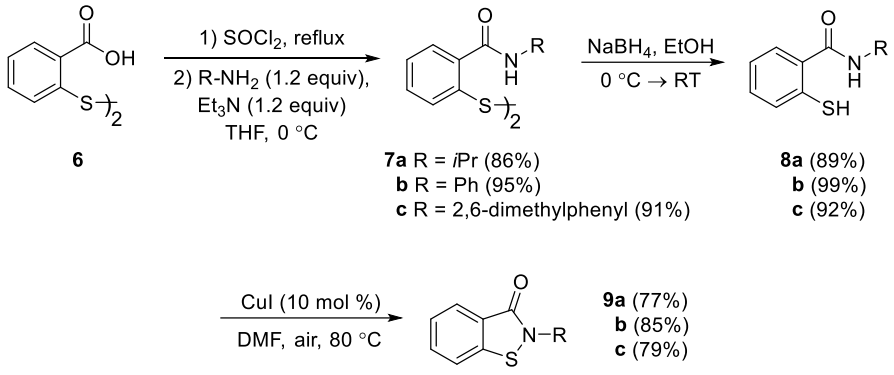
A number of routes to synthesize benzoisothiazolones have been developed over the previous forty years due to their antifungal and antibacterial characteristics.[24-25] Scheme 2.7 depicts some of the most popular methods for BIT construction. The classical method condenses 2-(chlorocarbonyl)phenyl hypochlorothioite and an appropriate amine (Eq. 1).[26-27] A second method employs hypervalent iodine, phenyliodine(III) bistrifluoroacetate, as an oxidant to close 2-mercapto-*N*-alkyl/arylbenzamides (Eq. 2).[28] Similarly, oxidation of thioethers to sulfoxides and activation with sulfonyl chloride produce the desire benzoisothiazolones in good yield (Eq. 3).[29]



Scheme 2.7 Common Synthetic Routes to Benzoisothiazolones

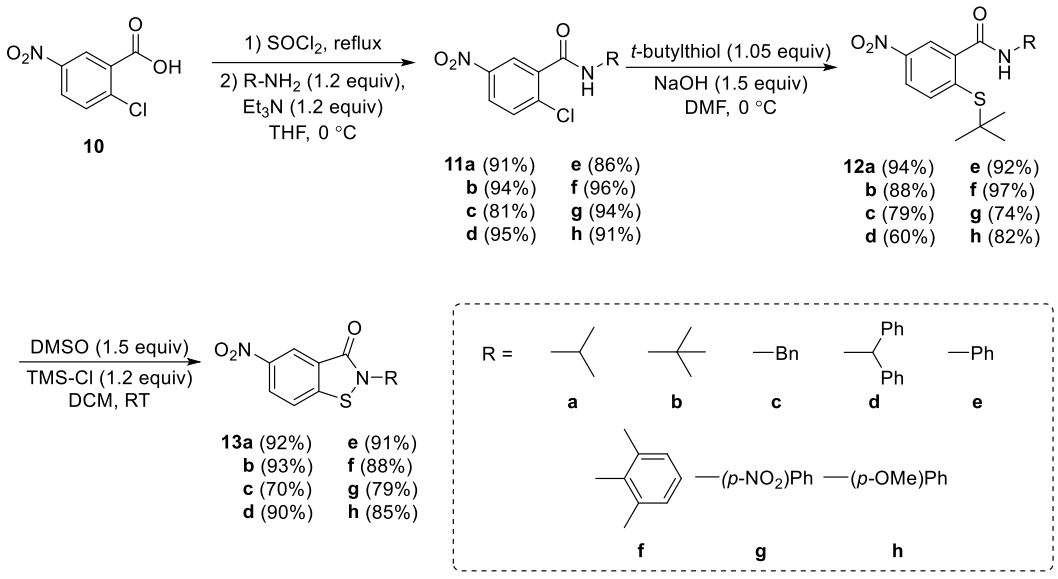
In 2013 Kanai reported the use of catalytic copper (I) iodide and oxygen to oxidatively close 2-mercaptobenzamides in DMF at 70 °C.[11] This method was used to synthesize the BITs **9a-c** (Scheme 2.8). Beginning with 2,2'-dithiosalicylic acid,

conversion to the acid chloride *via* refluxing thionyl chloride, followed by reaction with the desired amines provided 2,2'-dithiosalicylamides **7a-c**. Selective reduction with sodium borohydride provided the desired thiols in good yield. Finally, following Kanai's procedure, the thiols were oxidized to BITs **9a-c**.



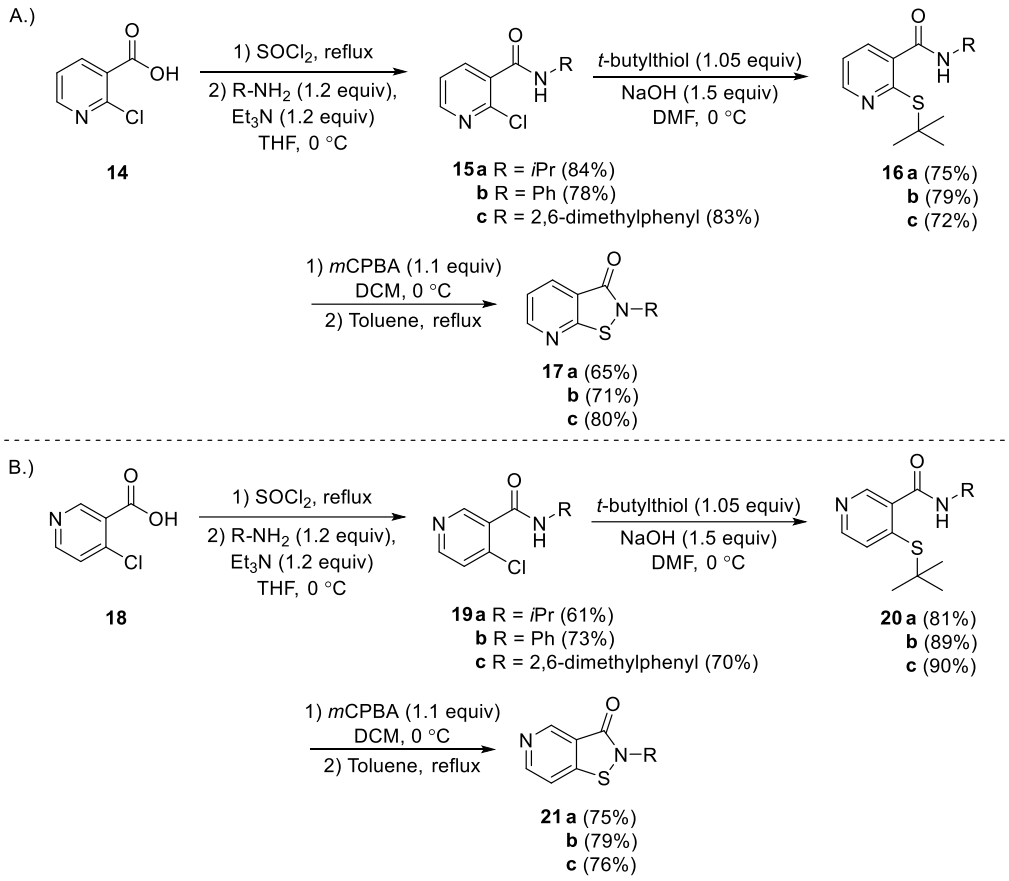
Scheme 2.8 Synthesis of BITs **9a-c**

Because previous work in the lab indicated that electron deficient thiosalicylamides provided higher yields of benzoisothiazolone when reacted in the LSCC, a number of 4-nitro BITs (**13)** were also constructed. [10] Following the previously reported procedure developed in the Liebeskind laboratory[10] and later used by Srogl[12], synthesis began with amidation of 2-chloro-5-nitrobenzoic acid, followed by nucleophilic aromatic substitution to give the *t*-butylthioether. Oxidation and closure of the thioether mediated by DMSO/TMSCl provide the desired BITs in excellent yield. Furthermore, purification of all intermediates and products *via* recrystallization prevents the need for column chromatography. Using this methodology, 4-nitrobenzoisothiazolones **13a-h** were synthesized in good yield (Scheme 2.9). Each of the BITs were synthesized on at least a 4 g scale, with **13a** constructed on a 15 g scale. All intermediates were easily purified by recrystallization from ethanol or a mixture of ethanol/water.



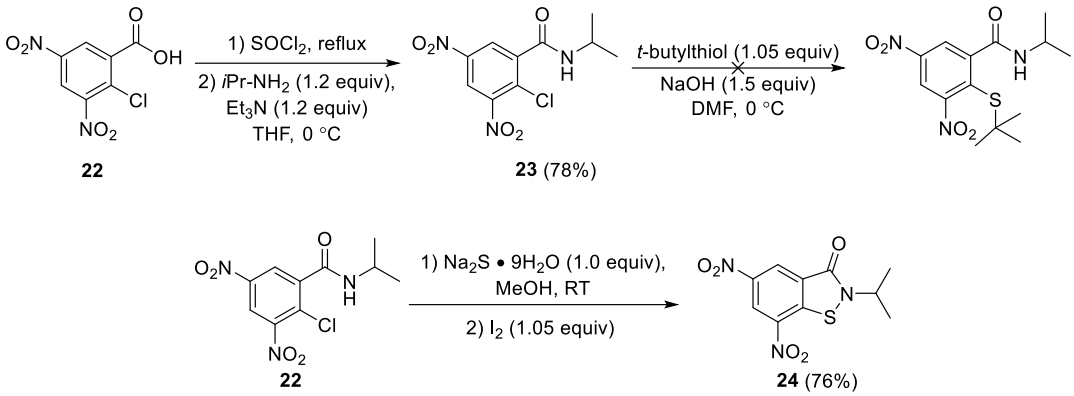
Scheme 2.9 Synthesis of BITs **13a-h**

Unfortunately, the DMSO/TMS-Cl mediated oxidative closure of *t*-butylthioethers was ineffective in generating the pyridine ring-derived BITs. However, following the literature precedent[30] used by Dr. Janette Villalobos,[10] BITs **17a-c** and **21a-c** were synthesized *via* mCPBA oxidation of the thioethers **16a-c** and **20a-c** to their corresponding sulfoxides with subsequent closure to the benzisothiazolinone upon refluxing in toluene. This method proved useful for a variety of pyridine ring-derived BITs, whose synthesis is shown in Scheme 2.10A and 2.10B.



Scheme 2.10 Synthesis of Pyridine BITs **17a-c** and **21a-c**

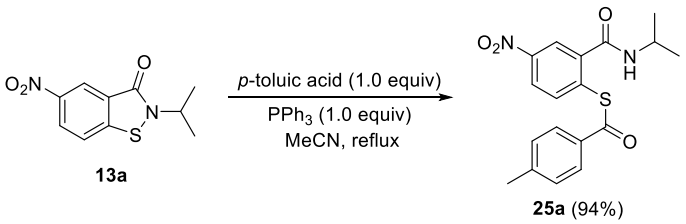
A third procedure was used for the synthesis of the 3,5-dinitrobenzoisothiazolone **24** (Scheme 2.11). After synthesis of the isopropyl amide **23** substitution with *t*-butylthiol to give the desired thioether proved ineffective. However, following the known procedure,[31] amide **23** was treated with sodium sulfide followed by iodine mediated oxidation to yield the desired BIT **25**.



Scheme 2.11 Synthesis of BIT **24**

2.2.2 Thiol Ester Formation

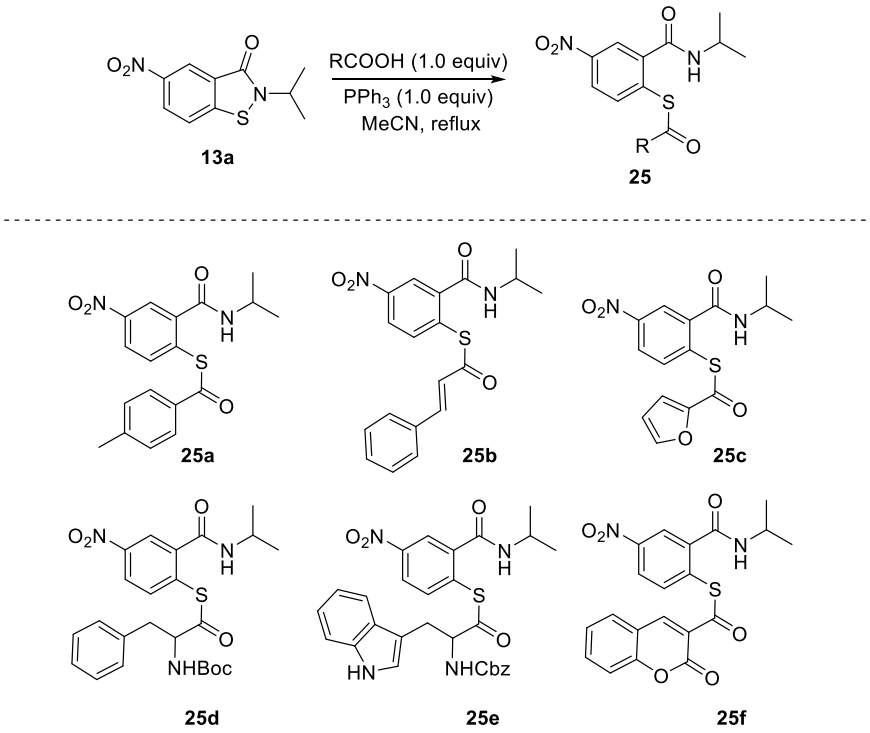
With the structurally diverse BITs in hand, the efficacy of their redox condensation with carboxylic acids to generate S-acylthiosalicylamides was tested. While Srogl reported the reaction of benzoisothiazolones with carboxylic acids in the presence of tri-*n*-butylphosphine, we sought to use the less reactive, more easily handled triphenylphosphine. Mukaiyama reported that disulfides react efficiently with carboxylic acids in refluxing acetonitrile in the presence of triphenylphosphine to provide thiol esters.[32] Identical conditions afforded the desired S-acylthiosalicylamide from BITs as well (Scheme 2.12).



Scheme 2.12 Synthesis of Thiol Ester **25a** from BIT **13a**

Following the same procedure, a variety of thiol esters were synthesized in order to test the efficacy of the redox condensation between BITs and carboxylic acids. As seen

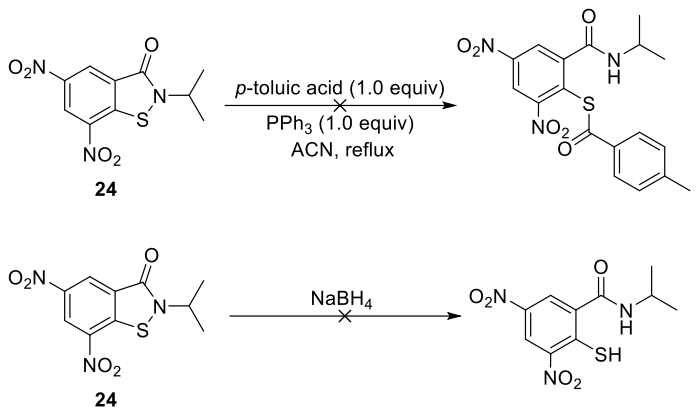
in Scheme 2.13, a number of thiol esters were synthesized from BIT **13a** in good yield, including those derived from aromatic, heteroaromatic, alkenyl, and alkyl carboxylic acids. Furthermore, several structurally diverse BITs were tested for their efficacy of producing thiol esters when treated with triphenylphosphine and carboxylic acids. While the majority of these BITs proved effective in the condensation reaction with carboxylic acids, dinitro BIT **24** was not able to react under any of the attempted conditions. Steric hindrance from the *ortho*-nitro group was assumed to prohibit reaction with triphenylphosphine. Even simple reduction of **24** with sodium borohydride failed to provide the desired thiol (Scheme 2.14).



Scheme 2.13 Condensation Reaction of BIT **13a** with Carboxylic Acids to Form Thiol Esters

While the majority of these BITs proved effective in the condensation reaction with carboxylic acids, dinitro BIT **24** was not able to react under any of the attempted

conditions. Steric hindrance from the *ortho*-nitro group was assumed to prohibit reaction with triphenylphosphine. Even simple reduction of **24** with sodium borohydride failed to provide the desired thiol (Scheme 2.14).



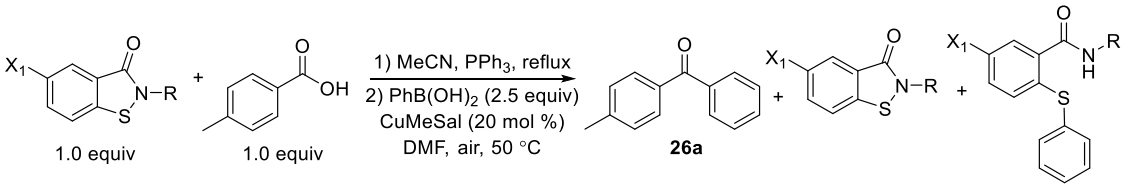
Scheme 2.14 Attempted Reactions of 3,5-Dinitrobenzisothiazolone

2.2.3 Ketone Formation

With a general method established for the production of a wide variety of *S*-acylthiosalicylamides, a number of variables were tested to optimize the aerobic oxidative closure of the resulting copper thiolate to the benzoisothiazolone during the second generation LSCC in a one-pot reaction. To begin, the steric and electronic nature of the BIT were varied to determine the effect these structural changes would have on oxidative closure. As shown in Table 2.1, when the BITs **9a-c** were utilized as the starting materials, no oxidative closure was observed under the reaction conditions. Rather, the undesired *S*-arylation byproduct was obtained in a one-to-one ratio with ketone, consistent with previous reports.[4, 6-7, 14] When the starting benzoisothiazolone structure was modified to include an electron withdrawing nitro group *para* to sulfur, the BIT was observed as a byproduct of the reaction (57% yield) with a slightly higher isolated yield than that of undesired thioether (35% yield). Modification of the –R group

attached to the amide nitrogen provided an increase in oxidative closure in the case of R = *t*-butyl (**13b**) and when R = an aromatic substituent (**13e-h**). However, these substrates also showed an overall decrease in the yield of ketone.

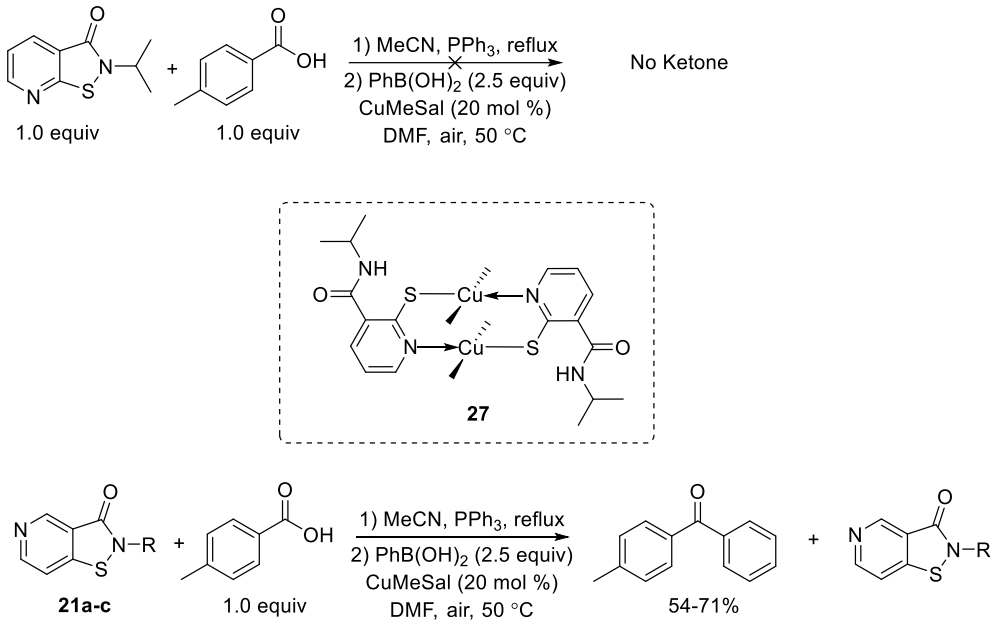
Table 2.1 Optimization of One-Pot Aerobic Cross-Coupling of Thiosalicylamides



BIT	R	X_1	Ketone	S-N closure	S-Arylation
9a	*i*-Pr	H	87%	0%	85%
9b	Ph	H	57%	0%	61%
9c	2,6-xylyl	H	43%	0%	41%
13a	*i*-Pr	NO_2	85%	57%	35%
13b	*t*-butyl	NO_2	75%	69%	11%
13c	Bn	NO_2	80%	71%	10%
13d	$CHBn_2$	NO_2	77%	73%	8%
13e	Ph	NO_2	62%	57%	7%
13f	2,6-xylyl	NO_2	47%	43%	0%
13g	(*p*-NO_2)Ph	NO_2	41%	40%	0%
13h	(*p*-MeO)Ph	NO_2	67%	61%	10%

When the 2-pyridine derived BIT **17a** was used as a substrate for reaction, no ketone was formed. This result corresponds with previous experiments in the Liebeskind Laboratory in which 2-pyridine derived S-acylthiosalicylamides are not effective coupling partners in the second generation Liebeskind-Srogl cross coupling reaction.[10] It was assumed that the 2-pyridine thiolate formed **27,** coordinated too strongly to copper and prohibiting catalysis (Scheme 2.15). While 2-pyridine derived BITs proved

ineffective in the reaction, 4-pyridine derived BITs **21a-c** were successful substrates for cross-coupling (Scheme 2.15).

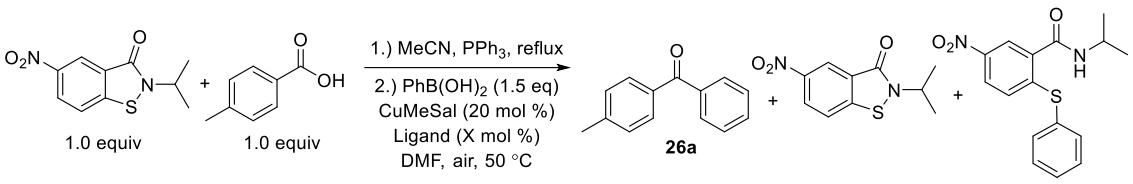


Scheme 2.15 Reaction of 2-Pyridine BIT **17a** in Liebeskind-Srogl Cross-Coupling

Although it did not produce the highest ratio of BIT/S-arylation, BIT **13a** was chosen for further study because of its high yield of ketone produced as well its ease of synthesis. With the BIT structure decided, a variety of nitrogen-based ligands in combination with 20% CuMeSal as the copper source were tested to determine their ability to affect the BIT/S-arylation ratio. Table 2.1 shows the results of these experiments. *N*-Methylmorpholine proved an effective ligand for increasing the ratio of oxidative closure to thioetherification when used in a 4:1 ratio with the copper catalyst (entry 2). TMEDA provided 14% of the desired S-N closure, however, aromatic bidentate ligands such as bipyridine and phenanthroline eliminated ketone formation (entries 4 & 5). The most successful ligands discovered for the regeneration of the benzoisothiazolone under aerobic reaction conditions were N-methylimidazole and DABCO. Interestingly,

both ligands were capable of suppressing the production of the undesired thioetherification byproduct, while still affording high yields of ketone (entries 9 & 11). Lastly, phosphine ligands such as triphenylphosphine and dppe completely shut down the generation of ketone (entries 13 and 14).

Table 2.2 Optimization of Copper Ligands (*molecular sieves were used)

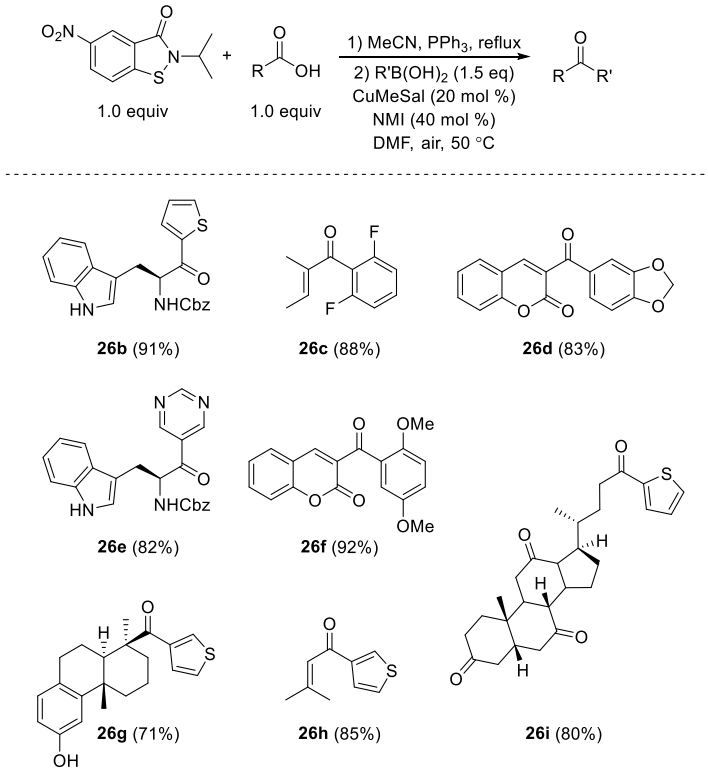


Entry	Ligand	Ketone	S-N closure	S-Arylation	RSM
1	20% NMM	71%	35%	39%	19%
2	40% NMM	82%	72%	15%	8%
3	20% TMEDA	53%	14%	41%	43%
4	20% 1,10-Phen	Trace	Trace	Trace	90%
5	20% Bipyridine	Trace	Trace	Trace	89%
6	40% Pyridine	79%	55%	26%	13%
7	40% 2-Picoline	81%	71%	15%	0%
8	40% 2,6-Lutidine	82%	60%	29%	7%
9	40% DABCO*	83%	90%	0%	0%
10	20% DABCO*	86%	71%	12%	0%
11	40% N-methylimidazole*	85%	91%	0%	0%
12	40% DMAP*	54%	91%	0%	0%
13	40% PPh_3	0%	0%	0%	91%
14	20% dppe	0%	0%	0%	88%

2.2.4 Benzoisothiazolone Mediated, One-Pot Cross-Coupling

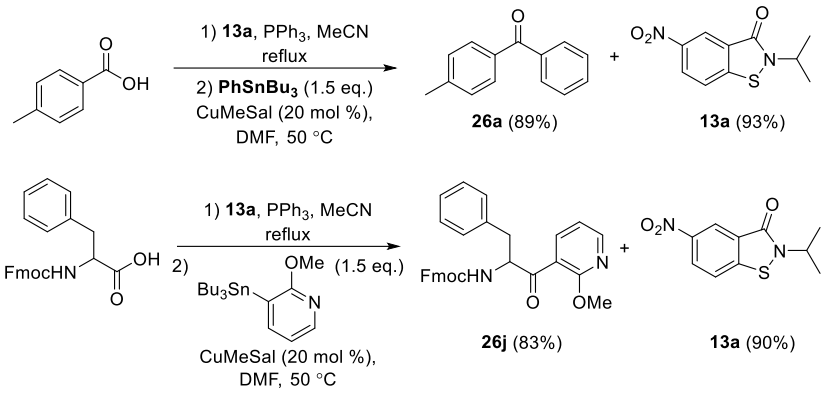
Having determined reaction conditions that maximized the formation of benzisothiazolinone and minimized S-arylation in a one-pot cross-coupling, we began to explore the substrate scope of this reaction. A number of carboxylic acids were tested

including alkyl, alkenyl, and aromatic, all of which produced high yields of the desired ketones (Scheme 2.16). Furthermore, peptidyl ketone **26b** showed no epimerization when measured by HPLC against the racemic ketone. In all cases, BIT **13a** was recovered in greater than 80% yield.



Scheme 2.16 Benzoisothiazolone Mediated, One-Pot Liebeskind-Srogl Cross-Coupling

Finally, the single-pot reaction was tested with organostannanes in place of boronic acid. Interestingly, it was found that no ligand was necessary when organostannanes were used as the organometallic reagent and BIT **13a** as the chosen benzoisothiazolone (Scheme 2.17).



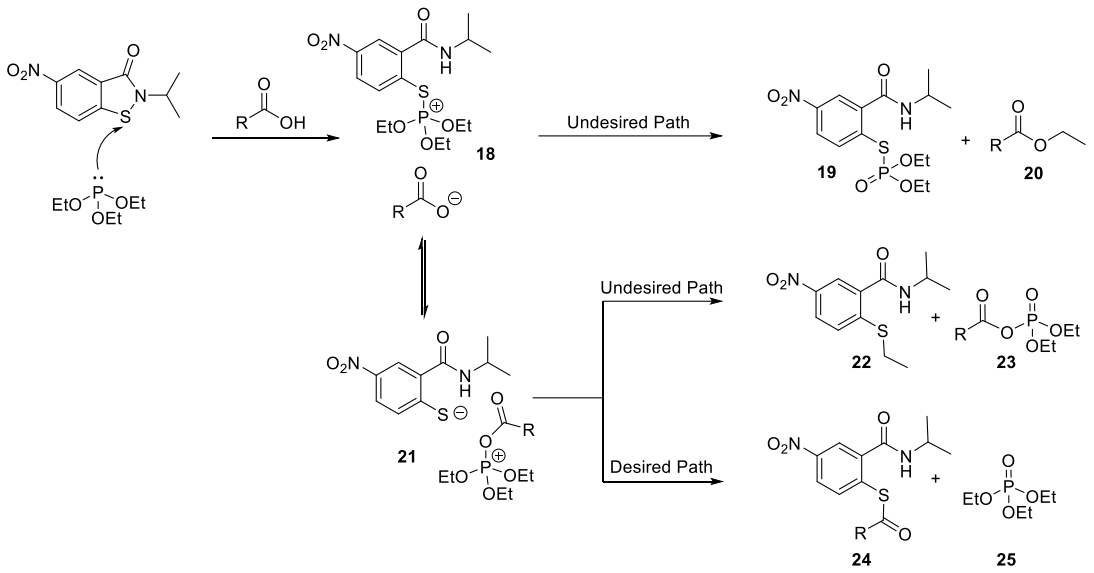
Scheme 2.17 BIT Mediated, One-Pot Cross-Coupling with Organostannanes

2.2.5 Triethylphosphite as a Reducing Agent

The one-pot generation of ketones from carboxylic acids described above provides a more atom efficient method to construct ketones when compared to the original second generation aerobic Liebeskind-Srogl cross-coupling. However, the atom economy can be increased further if the reducing agent used to generate the S-acylthiosalicylamide from the BIT and the carboxylic acid were modified from triphenylphosphine to triethylphosphite. Besides having a lower molecular weight than triphenylphosphine, triethylphosphite has the additional benefit that the oxidized byproduct is water soluble and easily removed from reaction mixtures by aqueous workup. Conversely, triphenylphosphine oxide, the stoichiometric byproduct of the cross-coupling, is notoriously difficult to separate from reaction mixtures.

However, despite their easy removal from reaction mixtures, trialkylphosphites incorporate additional complications in the form of an Arbuzov reaction between phosphonium intermediates and nucleophiles. Scheme 2.18 show two possible pathways which the phosphonium intermediate postulated to form between the BIT and triethylphosphite could follow an undesired pathway, resulting in diminished yields and/or byproducts. In the first pathway, the carboxylate anion acts as a nucleophile in an

Arbuzov reaction producing thiophosphate **19** and the ethyl ester of the carboxylic acid **20**. In the second undesired pathway thiolate acts as a nucleophile to produce the ethyl thioether byproduct **22**.



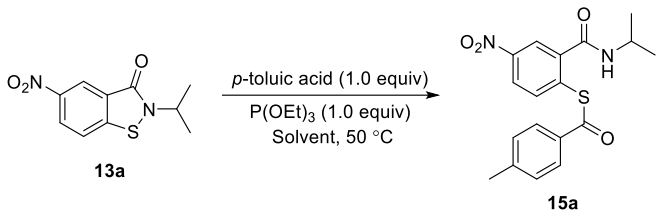
Scheme 2.18 Possible Byproducts of Triethylphosphite Reduction of BIT

Despite the possible side reactions of activated alkylphosphites in redox condensations, one report uses triisopropylphosphite to replace triphenylphosphine in the Mitsunobu reaction.[33] While triethylphosphite underwent dealkylative side reactions in the Mitsunobu reaction, the more sterically hindered triisopropylphosphite could be effectively substituted for phosphine. With this precedent set, we began to explore the option of introducing triethylphosphite into the condensation reaction.

Triethylphosphite proved to be a reliable reducing agent for the redox condensation of benzoisothiazolones and carboxylic acids in a variety of solvents. For example, thiol ester **25a** was produced in 90% yield when equimolar amounts of carboxylic acid, **13a**, and triethylphosphite were combined in acetonitrile at 50 °C.

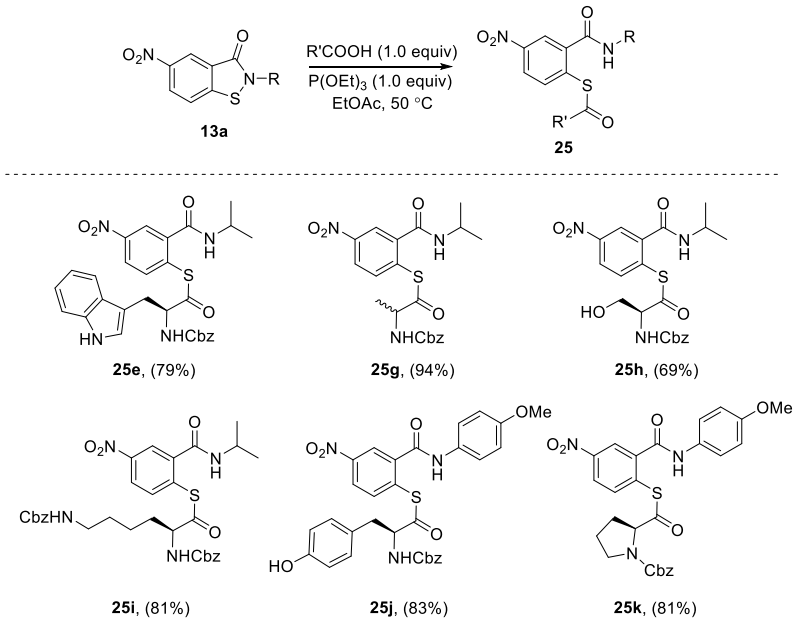
Similarly, DMF, ethyl acetate, THF, and toluene could all be used effectively as solvents with the results shown in Table 2.3.

Table 2.3 Solvent Screen of Triethylphosphite as Reducing Agent



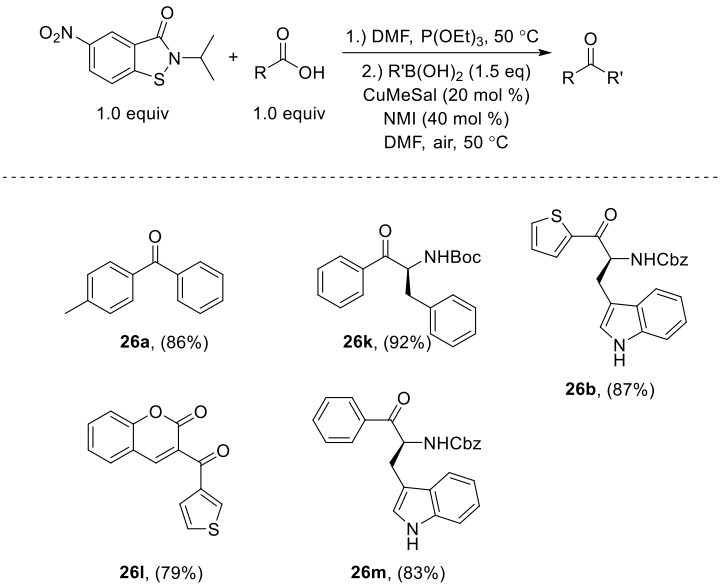
Entry	Solvent	Time	Yield
1	acetonitrile	2 hrs	90%
2	DMF	1 hr	84%
3	EtOAC	3 hrs	91%
4	toluene	8 hrs	88%
5	THF	3 hrs	87%

The reaction scope was explored to ensure the generality of the triethylphosphite mediated condensation reaction (Scheme 2.19). The reaction proved reliable for producing high yields of thiol ester when a variety of carboxylic acids were reacted with triethylphosphite and BIT **13a**. Reaction workup proved efficient with simple removal of solvents and trituration with chloroform/hexanes providing pure (solid) products in good yields.



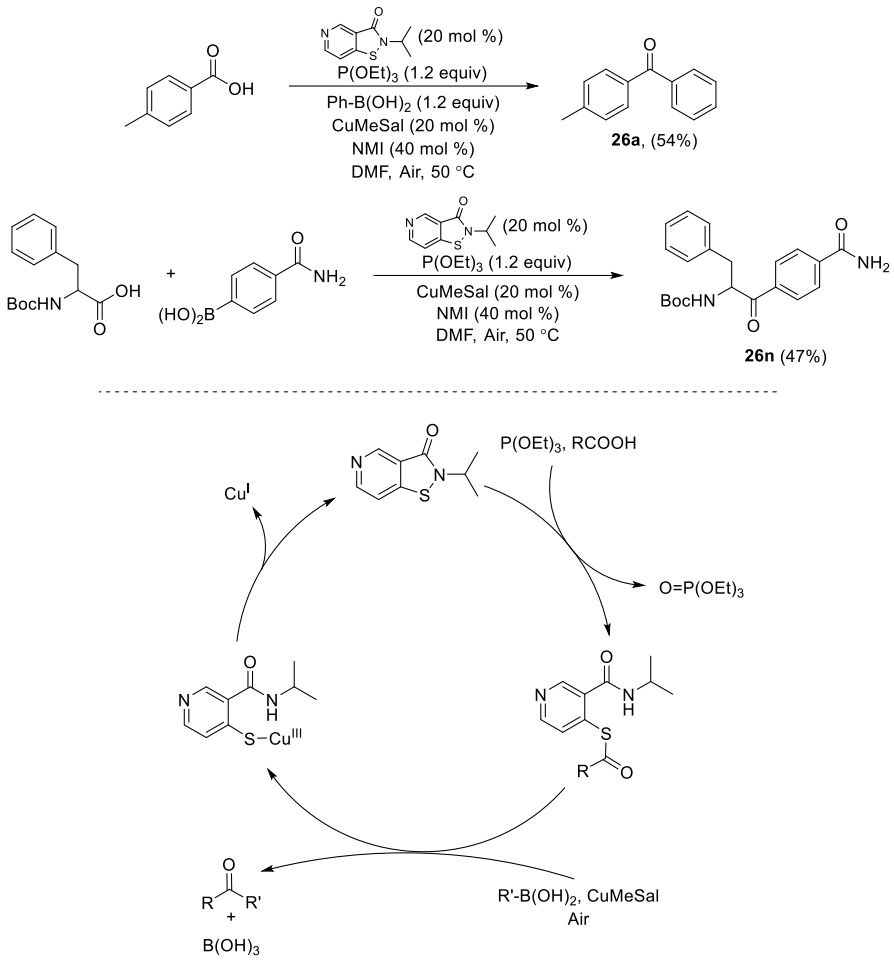
Scheme 2.19 Scope of Triethylphosphite-Mediated Condensation Reaction

With triethylphosphite proven to successfully mediate the redox condensation of BIT **13a** and carboxylic acids, triethylphosphite was tested to replace triphenylphosphine in the one-pot ketone forming reaction. As previously mentioned, the use of triethylphosphite provides a number of benefits when compared to triphenylphosphine, including increased atom economy as well as increased ease of byproduct purification. Scheme 2.20 shows the results of the reaction of these triethylphosphite mediated ketoconjugations. Again aromatic and alkyl carboxylic acids coupled efficiently with aromatic boronic acids in good yields. Importantly, peptidyl ketone **26k** was coupled with complete retention of stereochemistry.



Scheme 2.20 Triethylphosphite-Mediated Ketoconjugation

It should also be noted that the reaction can theoretically be carried out in a single step using catalytic amounts of benzoisothiazolone. Scheme 2.21 shows how BIT can be used in a fully catalytic cycle for the direct ketoconjugation of carboxylic acids and boronic acids. It was possible to carry out the reaction catalytically, however low yields of ketone were obtained. Having obtained 54% of the desired ketone as seen in Scheme 2.21, it appears that the BIT has completed between two and three turnovers before the reaction ends.



Scheme 2.21 Organocatalytic Ketoconjugation of Carboxylic Acids and Boronic Acids

2.3 Conclusion

Using nitrogen ligands to influence reactivity at copper, a modification of the aerobic second generation Liebeskind-Srogl cross-coupling reaction has been developed which prevents the generation of the undesired thioetherification byproduct, thereby eliminating the wasteful use of an additional equivalent of boronic acid. The new reaction conditions generate benzoisothiazolone as the sole reaction byproduct through an efficient aerobic oxidative closure of the copper thiolate intermediate. The benzoisothiazolone can be easily isolated and recycled to in order to make the requisite S-

acylthiosalicylamide starting materials. Beginning with a carboxylic acid and benzoisothiazolone, the reaction can be conveniently carried out in a single pot. Besides boronic acids, organostannanes are capable partners in cross coupling and do not require the use of additional modulating ligands for copper. Two early examples show that the reaction can be rendered catalytic in benzoisothiazolone, although further studies need to be conducted to determine optimal conditions for catalytic ketone formation.

2.4 Experimental

2.4.1 General Experimental

All reactions were performed under an atmosphere of dry argon in flame-dried glassware unless otherwise stated. Solvents used as reaction media were purchased in >99% purity, purged for several minutes with argon, then dried and stored over 4Å molecular sieves (water content below 20 ppm). Ethyl acetate (EtOAc), hexanes, and ethyl ether (Et_2O) were obtained from Sigma-Aldrich and used as purchased. 'Brine' refers to a saturated solution of sodium chloride in water. Flash chromatography was performed using Whatman 60Å 230-400 mesh silica, using compressed air as a source of positive pressure. Analytical thin-layer chromatography was performed using Merck Kieselgel $60F_{254}$ plates with UV or PMA (phosphomolybdic acid solution) for visualization.

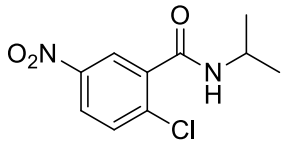
^{1}H NMR and ^{13}C NMR were performed using a Varian Inova 400 MHz NMR spectrometer at room temperature. Samples were dissolved in $CDCl_3$ and referenced at 7.26 ppm and 77.23 ppm, respectively. Signals are reported as follows: chemical shifts are reported (δ), multiplicities are indicated (s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet)), coupling constants are provided (Hz), and integrations are

given. Infrared spectra were recorded using Nicolet 510 FT-IT spectrometer. Peaks are given as s (strong), m (medium), w (weak), or br (broad).

2.4.2 General Procedure for the Synthesis of Amides 11a-i

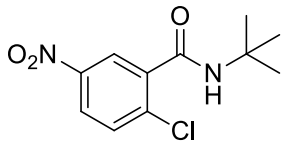
In a flame-dried round bottom flask, 2-chloro-5-nitrobenzoic acid (22.3 mmol) was added to 15 mL of thionyl chloride. The reaction was heated to reflux for one hour and cooled to room temperature. Excess thionyl chloride was removed *in vacuo*. The resulting white solid was taken up in 15 mL of dry THF and added dropwise to a solution of appropriate amine (26.8 mmol) and triethylamine (26.8 mmol) in 50 mL of THF at 0 °C. After completion of the reaction as monitored by TLC (by reacting a small portion of the reaction mixture with methanol), the reaction was concentrated to dryness. The product was mixed with 1:1 water/EtOH and refluxed. The crystallized product was collected by filtration.

2-Chloro-*N*-isopropyl-5-nitrobenzamide (11a)[12]



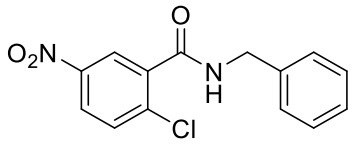
Prepared according to the general procedure from 2-chloro-5-nitrobenzoic acid (4.5 g, 22.3 mmol), isopropyl amine (2.2 mL, 26.8 mmol), and triethylamine (3.7 mL, 26.8 mmol) in 50 mL of THF at 0 °C, **11a** was obtained as a white solid (4.9 g, 91% yield). Mp = 184-185 °C (Lit.[12] 186-186.5 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 7.8 Hz, 1H), 8.23 (dd, J = 8.8, 2.8 Hz, 1H), 8.16 (d, J = 2.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 4.01 (m, 1H), 1.13 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.7, 151.4, 143.6, 142.5, 136.7, 130.5, 128.8, 46.7, 27.5. IR (neat, cm^{-1}): 3268 (m), 2972 (m), 1647

***N*-(*tert*-Butyl)-2-chloro-5-nitrobenzamide (11b)**[34]



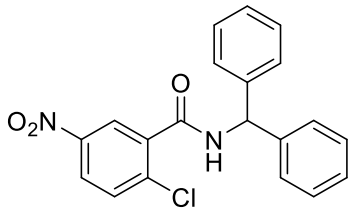
Prepared according to the general procedure from 2-chloro-5-nitrobenzoic acid (3.0 g, 14.9 mmol), *t*-butyl amine (2.0 mL, 17.9 mmol), and triethylamine (2.5 mL,17.9 mmol) in 50 mL of THF at 0 °C, **11b** was obtained as a white solid (3.6 g, 94% yield). Mp = 109-111 °C (Lit.[34] 113.0-113.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 2.8 Hz, 1H), 8.15 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 5.91 (s, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 146.7, 138.0, 137.6, 131.4, 125.4, 124.9, 53.0, 28.9. IR (neat, cm^{-1}): 3388 (m), 2964 (w), 1669 (s).

***N*-Benzyl-2-chloro-5-nitrobenzamide (11c)**[35]



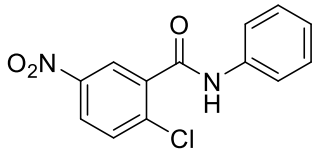
Prepared according to the general procedure from 2-chloro-5-nitrobenzoic acid (3.0 g, 14.9 mmol), benzyl amine (1.95 mL, 17.9 mmol), and triethylamine (2.5 mL,17.9 mmol) in 50 mL of THF at 0 °C, **11c** was obtained as a white solid (3.50 g, 81% yield). Mp = 193-194 °C (Lit.[35] 195 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (t, *J* = 5.6 Hz), 8.27-8.24 (m, 2H), 7.80 (dt, *J* = 8.8, 1.6 Hz, 1H) 7.36-7.31 (m, 4H), 7.26-7.25(m, 1H), 4.46 (d, *J* = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 146.4, 139.1, 138.1, 137.6, 131.8, 128.8, 127.8, 127.4, 125.9, 124.1, 43.1. IR (neat, cm^{-1}): 3291 (w), 1646 (m).

_N_-Benzhydryl-2-chloro-5-nitrobenzamide (11d)



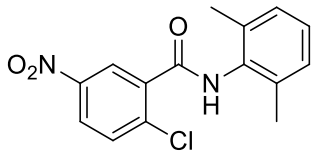
Prepared according to the general procedure from 2-chloro-5-nitrobenzoic acid (3.0 g, 14.9 mmol), benzyl amine (3.1 mL, 17.9 mmol), and triethylamine (2.5 mL,17.9 mmol) in 50 mL of THF at 0 °C, **11d** was obtained as a white solid (5.19 g, 95% yield). Mp = 178-179°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (d, *J* = 8.4 Hz, 1H), 8.26 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.19 (d, J = 2.8Hz, 1H), 7.79, (d, *J* = 8.8 Hz, 1H), 7.36-7.31 (m, 8H), 7.27-7.23 (m, 2H), 6.30 (d, *J* = 8.4Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 140.5, 131.5, 129.1, 128.9, 128.5, 128.4, 127.8, 127.4, 125.8, 125.6, 58.2. IR (neat, cm^{-1}): 1646. HRMS (ESI) Calcd for $C_{20}H_{16}N_2O_3Cl$ ($M+H^+$): 367.0844. Found: 367.0847.

2-Chloro-5-nitro-*N*-phenylbenzamide (11e)[12]



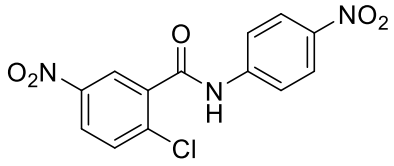
Prepared according to the general procedure from 2-chloro-5-nitrobenzoic acid (4.0 g, 19.8 mmol), aniline (2.2 mL, 23.8 mmol), and triethylamine (3.0 mL, 23.8 mmol) in 50 mL of THF at 0 °C, **11e** was obtained as a white solid (4.71 g, 86% yield). Mp = 157-158 °C (Lit.[12] 158 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (d, *J* = 2.7 Hz, 1H), 8.26 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.86 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.3, 146.8, 137.7, 137.0, 136.6, 131.7, 129.4, 126.1, 125.7, 125.5, 120.5. IR (neat, cm^{-1}): 3268, 1660.

2-Chloro-*N*-(2,6-dimethylphenyl)-5-nitrobenzamide (11f)[12]



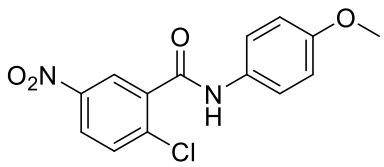
Prepared according to the general procedure from 2-chloro-5-nitrobenzoic acid (4.0 g, 19.8 mmol), 2,6-dimethylaniline (2.9 mL, 23.8 mmol), and triethylamine (3.0 mL, 23.8 mmol) in 50 mL of THF at 0 °C, **11f** was obtained as a white solid (5.8 g, 96% yield). Mp = 191-193 °C (Lit.[12] 193-194.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.7 Hz, 1H), 8.25 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.47 (s, 1H), 7.21 – 7.06 (m, 3H), 2.33 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 146.8, 137.7, 136.8, 135.8, 132.8, 131.8, 128.7, 128.4, 126.1, 125.6, 19.0. IR (neat, cm^{-1}): 3256 (w), 1667 (s).

2-Chloro-5-nitro-*N*-(4-nitrophenyl)benzamide (11g)[36]



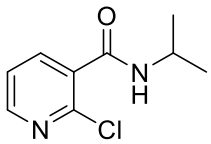
Prepared according to the general procedure from 2-chloro-5-nitrobenzoic acid (3.0 g, 14.9 mmol), 4-nitroaniline (2.5 g, 17.9 mmol), and triethylamine (2.5 mL,17.9 mmol) in 50 mL of THF at 0 °C, **11g** was obtained as a light yellow solid (4.51 g, 94% yield). Mp = 212-214°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (s, 1H), 8.55 (d, *J* = 2.4Hz, 1H), 8.34 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.27 (d, *J* = 8.8 Hz, 2H), 7.88-7.93 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 146.6, 144.9, 143.4, 137.5, 137.4, 131.9, 126.6, 125.5, 124.5, 120.1. IR (neat, cm^{-1}): 3354 (m), 1695 (s).

2-Chloro-*N*-(4-methoxyphenyl)-5-nitrobenzamide (11h)[37]



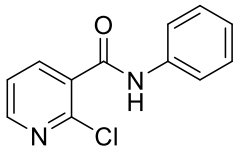
Prepared according to the general procedure from 2-chloro-5-nitrobenzoic acid (3.0 g, 14.9 mmol), 4-methoxyaniline (2.2 g, 17.9 mmol), and triethylamine (2.5 mL,17.9 mmol) in 50 mL of THF at 0 °C, **11g** was obtained as a white solid (4.16 g, 91% yield). Mp = 155-157 °C (Lit.[37] 151-153°C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.7 Hz, 1H), 8.24 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.82 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.2, 157.4, 146.7, 137.7, 136.8, 131.7, 130.0, 126.0, 125.5, 122.4, 114.5, 55.7. IR (neat, cm^{-1}): 3258, 1657.

2-Chloro-*N*-isopropylnicotinamide (15a)[10]



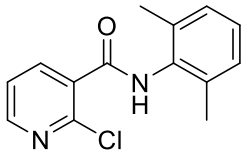
Prepared according to the general procedure from 2-chloronicotinic acid (4.0 g, 25.4 mmol), isopropyl amine (2.62 mL, 30.5 mmol), and triethylamine (4.25 mL, 30.5 mmol) in 50 mL of THF at 0 °C, **15a** was obtained as a white solid (4.24 g, 84% yield). Mp = 82-83 °C (Lit.[10] 82-84°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, J = 4.8, 2.0 Hz, 1H), 8.10 (dd, J = 7.6, 2.0 Hz, 1H), 7.35 (dd, J = 7.6, 4.8 Hz, 1H), 6.20 (bs, 1H), 4.35-4.25 (m, 1H), 1.31 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 150.6, 147.3, 139.5, 132.2, 123.0, 42.6, 22.6. IR (neat, cm^{-1}): 3262 (m), 1641 (s).

2-Chloro-*N*-phenylnicotinamide (15b)[38]



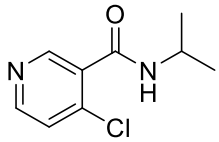
Prepared according to the general procedure from 2-chloronicotinic acid (4.0 g, 25.4 mmol), aniline (2.78 mL, 30.5 mmol), and triethylamine (4.25 mL, 30.5 mmol) in 50 mL of THF at 0 °C, **15b** was obtained as a white solid (4.61 g, 78% yield). Mp = 122-124°C (Lit.[38] 122-124°C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.50 (dd, J = 4.8, 1.9 Hz, 1H), 8.05 (dd, J = 7.5, 1.9 Hz, 1H), 7.74 – 7.63 (m, 2H), 7.53 (dd, J = 7.5, 4.8 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.10 (td, J = 7.3, 1.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 150.9, 146.9, 139.1, 138.6, 133.6, 129.3, 124.5, 123.6, 120.0. IR (neat, cm^{-1}): 3262 (m), 1656 (s).

2-Chloro-*N*-(2,6-dimethylphenyl)nicotinamide (15c)



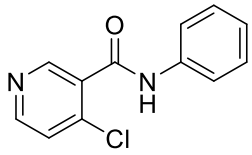
Prepared according to the general procedure from 2-chloronicotinic acid (4.0 g, 25.4 mmol), 2,6-dimethylaniline (3.75 mL, 30.5 mmol), and triethylamine (4.25 mL, 30.5 mmol) in 50 mL of THF at 0 °C, **15c** was obtained as a white solid (5.50 g, 83% yield). Mp = 148-149 °C. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 8.46 (dd, J = 4.8, 2.4 Hz, 1H), 8.12 (dd, J = 8.0, 2.4 Hz, 1H), 7.84 (bs, 1H), 7.35 (dd, J = 8.0, 4.8 Hz, 1H), 7.08-7.16 (m, 3), 2.29 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 151.1, 147.0, 139.9, 135.6, 132.9, 131.4, 128.4, 127.9, 122.9, 18.7. IR (neat, cm^{-1}): 3262 (m), 1658 (s). HRMS (ESI) Calcd for $C_{14}H_{13}N_2OCl$ ($M+H^+$): 261.0789. Found: 261.0791.

4-Chloro-N-isopropylnicotinamide (19a)[10]



Prepared according to the general procedure from 4-chloronicotinic acid (4.0 g, 25.4 mmol), isopropyl amine (2.62 mL, 30.5 mmol), and triethylamine (4.25 mL, 30.5 mmol) in 50 mL of THF at 0 °C, **19a** was obtained as an oil (3.0 g, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 8.64 (d, *J* = 0.5 Hz, 1H), 8.40 (d, *J* = 5.3 Hz, 1H), 7.26 (dd, *J* = 5.4, 0.5 Hz, 1H), 6.40 (bs, 1H), 4.22 (dp, *J* = 8.0, 6.6 Hz, 1H), 1.22 (dd, *J* = 6.5, 0.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 151.2, 150.2, 140.8, 131.5, 124.8, 42.4, 22.5. IR (neat, cm^{-1}): 3262 (m), 1645 (s).

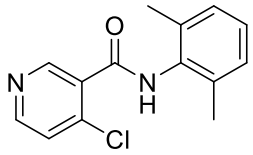
4-Chloro-*N*-phenylnicotinamide (19b)



Prepared according to the general procedure from 4-chloronicotinic acid (4.0 g, 25.4 mmol), aniline (2.78 mL, 30.5 mmol), and triethylamine (4.25 mL, 30.5 mmol) in 50 mL of THF at 0 °C, **19b** was obtained as a white solid (4.31 g, 73% yield). Mp = 51-53°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, *J* = 1.1 Hz, 1H), 8.55 (dd, *J* = 5.4, 1.1 Hz, 1H), 8.16 (s, 1H), 7.68 – 7.59 (m, 2H), 7.44 – 7.33 (m, 4H), 7.23 – 7.14 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 152.3, 150.9, 139.2, 130.0, 129.0, 124.9, 123.0, 121.3, 114.3.

IR (neat, cm^{-1}): 3251 (m), 1655 (s). HRMS (ESI) Calcd for $C_{12}H_9N_2OCl$ ($M+H^+$): 233.0476. Found: 233.0475.

4-Chloro-*N*-(2,6-dimethylphenyl)nicotinamide (19c)

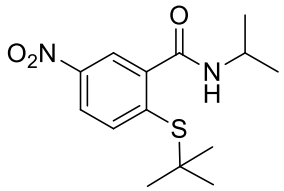


Prepared according to the general procedure from 4-chloronicotinic acid (4.0 g, 25.4 mmol), 2,6-dimethylaniline (3.75 mL, 30.5 mmol), and triethylamine (4.25 mL, 30.5 mmol) in 50 mL of THF at 0 °C, **19c** was obtained as a white solid (4.63 g, 70% yield). Mp = 83-85 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.97 (d, *J* = 1.1 Hz, 1H), 8.59 (d, *J* = 5.4 Hz, 1H), 7.59 (bs, 1H), 7.45 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.19 – 7.10 (m, 3H), 2.33 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 155.0, 149.2, 142.1, 139.7, 129.8, 128.9, 128.1, 125.4, 121.1. IR (neat, cm^{-1}): 3254 (m), 1656 (s). HRMS (ESI) Calcd for $C_{14}H_{13}N_2OCl$ ($M+H^+$): 261.0789. Found: 261.0788.

2.4.3 General Procedure for the Synthesis of Thioethers 12a-h

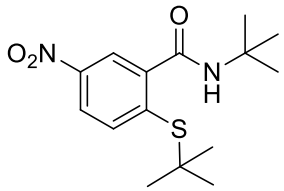
In a flame-dried flask flushed with argon, *t*-butyl thiol (2.7 mL, 24.2 mmol) was combined with sodium hydroxide (900 mg, 22.2 mmol). The mixture was taken up in 15 mL of DMF and cooled to zero degrees. To this mixture was added **11a-i** (20.2 mmol). The reaction was stirred at 0 ºC for 6 hours. The reaction mixture was poured into 150 mL of a 5% HCl solution resulting in an immediate precipitate. The solid was collected and recrystallized from a refluxing mixture of ethanol and water (1:1) to provide **12a-i** as a solid.

2-(*tert*-Butylthio)-*N*-isopropyl-5-nitrobenzamide (12a)[12]



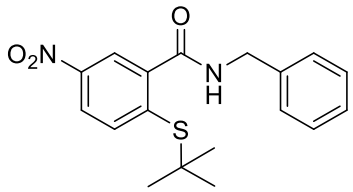
Prepared according to the general procedure from *t*-butyl thiol (2.7 mL, 24.2 mmol), sodium hydroxide (900 mg, 22.2 mmol), and **11a** (4.9 g, 20.2 mmol), **12a** was obtained as a light yellow solid (5.6 g, 94% yield). Mp = 148-150 °C (Lit.[12] 151-151.5 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 7.8 Hz, 1H), 8.18 (dd, J = 8.6, 2.6 Hz, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.81 (d, J = 8.7, 1H), 4.10 – 3.86 (m, 1H), 1.28 (s, 9H), 1.12 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.5, 151.7, 149.5, 145.2, 142.4, 128.5, 127.5, 53.4, 46.5, 36.5, 27.6. IR (neat, cm^{-1}): 3264 (m), 2973 (w), 1642 (s).

***N*-(*tert*-Butyl)-2-(*tert*-butylthio)-5-nitrobenzamide (12b)**[10]



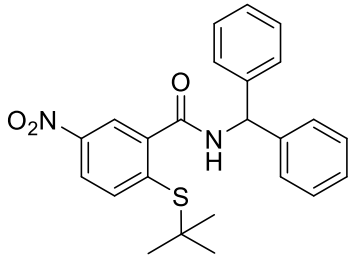
Prepared according to the general procedure from *t*-butyl thiol (1.6 mL, 14.0 mmol), sodium hydroxide (514 mg, 12.9 mmol), and **11b** (3.0 g, 11.7 mmol), **12b** was obtained as a yellow solid (3.2 g, 88% yield). Mp = 146-147 °C (Lit.[13] 145-147 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 2.7 Hz, 1H), 8.14 (dd, J = 8.5, 2.7 Hz, 1H), 7.71 (d, J = 8.6, 1H), 7.29 (s, 1H), 1.47 (s, 9H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 148.2, 143.4, 139.9, 137.7, 125.3, 123.8, 52.6, 50.2, 31.3, 28.9. IR (neat, cm^{-1}): 3289 (w), 2963 (w), 1646 (s).

***N*-Benzyl-2-(*tert*-butylthio)-5-nitrobenzamide (12c)**



Prepared according to the general procedure from *t*-butyl thiol (1.6 mL, 14.0 mmol), sodium hydroxide (514 mg, 12.9 mmol), and **11c** (3.4 g, 11.7 mmol), **12c** was obtained as a yellow solid (3.18 g, 79% yield). Mp = 108-110°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (t, *J* = 6.4 Hz, 1H), 8.20 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.12 (d, *J* = 2.8 Hz, 1H), 8.83 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 3H), 7.23 (t, *J* = 7.2 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 146.7, 144.1, 140.4, 139.4, 137.2, 128.6, 128.0, 127.9, 127.3, 123.8, 122.6, 48.5, 43.1, 31.4. IR (neat, cm^{-1}): 3259 (w), 1641 (s). HRMS (ESI) Calcd for $C_{18}H_{21}N_2O_3S$ ($M+H^+$): 345.1267. Found: 345.1269.

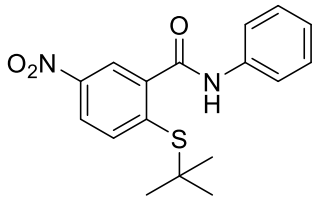
***N*-Benzhydryl-2-(*tert*-butylthio)-5-nitrobenzamide (12d)**



Prepared according to the general procedure from *t*-butyl thiol (0.8 mL, 7.0 mmol), sodium hydroxide (257 mg, 6.5 mmol), and **11d** (2.0 g, 5.7 mmol), **12c** was obtained as a yellow solid (1.44 g, 60% yield). Mp = 152-153°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (d, *J* = 8.4 Hz, 1H), 8.20 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.08 (d, *J* = 2.8 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.39-7.21 (m, 10H), 6.30 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz,

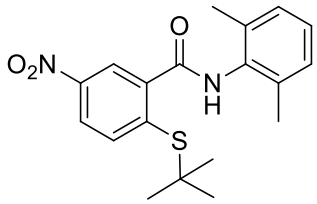
DMSO-d_6) δ 165.9, 146.8, 144.1, 142.4, 140.3, 137.6, 128.7, 128.0, 127.5, 123.8, 122.8, 57.1, 48.5, 31.4. IR (neat, cm^{-1}): 3266 (w), 1635 (m). HRMS (ESI) Calcd for $C_{24}H_{25}N_2O_3S$ ($M+H^+$): 421.1580. Found: 421.1582.

2-(*tert*-Butylthio)-5-nitro-*N*-phenylbenzamide (12e)[12]



Prepared according to the general procedure from *t*-butyl thiol (2.3 mL, 20.2 mmol), sodium hydroxide (740 mg, 18.5 mmol), and **11e** (4.65 g, 16.8 mmol), **12e** was obtained as a yellow solid (5.1 g, 92% yield). Mp = 142-143 °C (Lit.[12] 143-145 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.99 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.1, 148.6, 141.6, 140.7, 137.6, 137.3, 129.4, 126.3, 125.1, 124.6, 120.3, 51.0, 31.0. IR (neat, cm^{-1}): 3235 (m), 1655 (s).

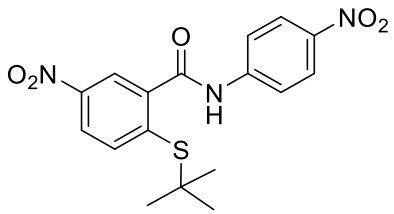
2-(*tert*-Butylthio)-*N*-(2,6-dimethylphenyl)-5-nitrobenzamide (12f)[12]



Prepared according to the general procedure from *t*-butyl thiol (2.3 mL, 20.2 mmol), sodium hydroxide (740 mg, 18.5 mmol), and **11f** (5.13 g, 16.8 mmol), **12f** was obtained as a yellow solid (5.9 g, 97% yield). Mp = 191-192 °C (Lit.[12] 192-194 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.6 Hz, 1H), 8.60 (s, 1H), 8.22 (dd, *J* = 8.5, 2.6, 1H), 7.81 (d,

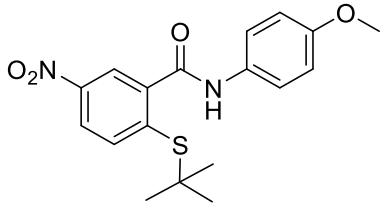
J = 8.5, 1H), 7.18 – 7.04 (m, 3H), 2.33 (s, 6H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 148.0, 142.3, 139.1, 138.8, 135.6, 133.6, 128.6, 127.8, 125.3, 124.3, 50.6, 31.5, 19.3. IR (neat, cm^{-1}): 3238 (w), 1648 (s).

2-(*tert*-Butylthio)-5-nitro-*N*-(4-nitrophenyl)benzamide (12g)



Prepared according to the general procedure from *t*-butyl thiol (1.6 mL, 14.0 mmol), sodium hydroxide (448 mg, 11.2 mmol), and **11g** (3.0 g, 9.3 mmol), **12g** was obtained as a yellow solid (2.6 g, 74% yield). Mp = 167-169°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.98 (d, *J* = 1.6, 1H), 8.27-8.25 (m, 3H), 7.87-7.82 (m, 3H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 148.8, 144.2, 143.4, 141.0, 140.6, 137.4, 126.6, 125.5, 125.3, 119.8, 51.6, 31.1. IR (neat, cm^{-1}): 3258 (w), 1666 (m). HRMS (ESI) Calcd for $C_{17}H_{17}N_3O_5S$ ($M+H^+$): 376.0962. Found: 376.0960.

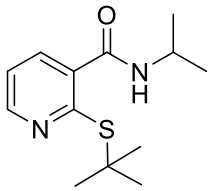
2-(*tert*-Butylthio)-*N*-(4-methoxyphenyl)-5-nitrobenzamide (12h)



Prepared according to the general procedure from *t*-butyl thiol (1.66 mL, 14.7 mmol), sodium hydroxide (470 mg, 11.8 mmol), and **11h** (3.0 g, 9.8 mmol), **12h** was obtained as a yellow solid (2.90 g, 82% yield). Mp = 139-140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.96 (s, 1H), 8.23 (dt, *J* = 8.7, 2.2 Hz, 1H), 7.82 – 7.77 (m, 1H), 7.59 (t, *J* = 8.6

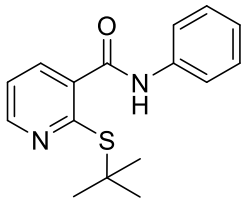
Hz, 2H), 6.93 (t, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 156.9, 148.54, 141.8, 140.6, 137.3, 130.7, 126.2, 124.4, 121.9, 114.5, 55.6, 50.9, 31.1. IR (neat, cm^{-1}): 3233 (m), 1655 (s). HRMS (ESI) Calcd for $C_{18}H_{21}N_2O_4S$ ($M+H^+$): 361.1222. Found: 361.1218.

2-(*tert*-Butylthio)-*N*-isopropylnicotinamide (16a)[10]



Prepared according to the general procedure from *t*-butyl thiol (2.04 mL, 18.1 mmol), sodium hydroxide (906 mg, 22.7 mmol), and **15a** (3.0 g, 15.1 mmol), **16a** was obtained as a solid (2.86 g, 75% yield). Mp = 125-126°C (Lit.[10] 128-129 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, J= 4.8, 1.9 Hz, 1 H), 8.00 (dd, J= 7.9, 1.9 Hz, 1 H), 7.15 (dd, J= 7.9, 4.8 Hz, 1 H), 6.88 (s, br, 1 H), 4.30 (m, 1 H), 1.54, (s, 9H), 1.30 (d, J= 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 155.8, 150.0, 137.2, 133.3, 120.4, 49.5, 42.4, 30.9, 22.7. IR (neat, cm^{-1}): 3273 (s), 1645 (s).

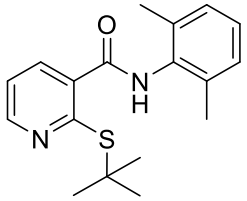
2-(*tert*-Butylthio)-*N*-phenylnicotinamide (16b)



Prepared according to the general procedure from *t*-butyl thiol (1.74 mL, 15.5 mmol), sodium hydroxide (774 mg, 19.3 mmol), and **15b** (3.0 g, 12.9 mmol), **16b** was obtained as a yellow solid (2.92 g, 79% yield). Mp = 135-136°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ

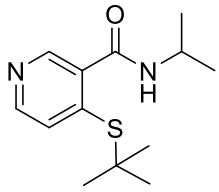
9.25 (s, 1H), 8.56 (dd, *J* = 4.7, 2.0 Hz, 1H), 8.19 – 8.08 (m, 1H), 7.64 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.35 (td, *J* = 8.6, 8.1, 2.1 Hz, 2H), 7.21 – 7.10 (m, 2H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 155.3, 150.4, 137.9, 137.7, 132.9, 129.1, 124.8, 120.8, 120.1, 77.4, 77.0, 76.7, 50.1, 30.9. IR (neat, cm^{-1}): 3251 (m), 1653 (s). HRMS (ESI) Calcd for $C_{16}H_{19}N_2OS$ ($M+H^+$): 287.1213. Found: 287.1214.

2-(*tert*-Butylthio)-*N*-(2,6-dimethylphenyl)nicotinamide (16c)



Prepared according to the general procedure from *t*-butyl thiol (1.56 mL, 13.8 mmol), sodium hydroxide (690 mg, 17.3 mmol), and **15c** (3.0 g, 11.5 mmol), **16c** was obtained as a yellow solid (2.61 g, 72% yield). Mp = 155-156°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.61 – 8.57 (m, 1H), 8.43 (s, 1H), 7.52 (d, *J* = 5.1 Hz, 1H), 7.10-7.15 (m, 3H), 2.34 (s, 6H), 1.43 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 161.2, 147.1, 137.4, 134.1, 130.9, 127.9, 127.1, 126.5, 120.8, 50.5, 30.5, 19.3. IR (neat, cm^{-1}): 3251 (m), 1655 (s). HRMS (ESI) Calcd for $C_{18}H_{22}N_2OS$ ($M+H^+$): 315.1526. Found: 315.1527.

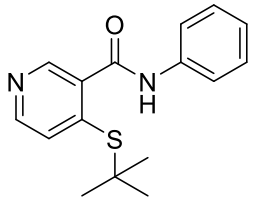
4-(*tert*-Butylthio)-*N*-isopropylnicotinamide (20a)[10]



Prepared according to the general procedure from *t*-butyl thiol (2.04 mL, 18.1 mmol), sodium hydroxide (906 mg, 22.7 mmol), and **19a** (3.0 g, 15.1 mmol), **20a** was obtained

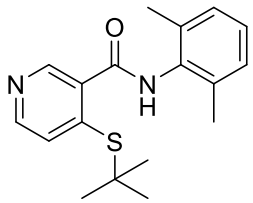
as a yellow oil (3.09 g, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (d, *J* = 0.6 Hz, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 7.42 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.24 (s, 1H), 4.40 – 4.20 (m, 1H), 1.35 (d, *J* = 0.8 Hz, 9H), 1.28 (dd, *J* = 6.6, 0.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 151.0, 150.1, 140.4, 135.1, 131.1, 49.4, 42.2, 31.0, 22.6. IR (neat, cm^{-1}): 3250 (m), 1640 (s).

4-(*tert*-Butylthio)-*N*-phenylnicotinamide (20b)



Prepared according to the general procedure from *t*-butyl thiol (1.74 mL, 15.5 mmol), sodium hydroxide (774 mg, 19.3 mmol), and **19b** (3.0 g, 12.9 mmol), **20b** was obtained as a yellow solid (3.29 g, 89% yield). Mp = 110-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 9.18 (s, 1H), 8.57 (d, *J* = 5.1 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.45 (d, *J* = 5.1 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.18 – 7.10 (m, 1H), 1.33 (d, *J* = 0.6 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 151.9, 150.9, 140.0, 137.6, 134.4, 131.8, 129.2, 124.8, 120.1, 50.2, 31.0. IR (neat, cm^{-1}): 3254 (w), 1655 (m). HRMS (ESI) Calcd for $C_{16}H_{19}N_2OS$ ($M+H^+$): 287.1213. Found: 287.1211.

4-(*tert*-Butylthio)-*N*-(2,6-dimethylphenyl)nicotinamide (20c)

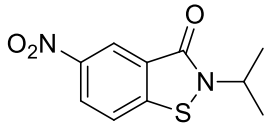


Prepared according to the general procedure from *t*-butyl thiol (1.56 mL, 13.8 mmol), sodium hydroxide (690 mg, 17.3 mmol), and **19c** (3.0 g, 11.5 mmol), **20c** was obtained as a yellow solid (3.26 g, 90% yield). Mp = 131-133°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.67 – 8.54 (m, 1H), 8.43 (s, 1H), 7.52 (d, *J* = 5.1 Hz, 1H), 7.12 (q, *J* = 5.1 Hz, 3H), 2.34 (s, 6H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 154.1, 151.5, 145.0, 134.7, 130.8, 127.4, 126.8, 126.1, 120.0, 49.9, 30.7, 19.2. IR (neat, cm^{-1}): 3260 (w), 1659 (m). HRMS (ESI) Calcd for $C_{18}H_{22}N_2OS$ ($M+H^+$): 315.1526. Found: 315.1524.

2.4.4 General Procedure for the Synthesis of Benzoisothiazolones (BITs) 13a-h

In a flamed-dried round bottom flask filled with argon, *t*-butylthioethers **12a-h** (18.9 mmol) and DMSO (2.0 mL, 28.3 mmol) were combined and taken up in 50 mL of DCM. TMSCl (3.1 mL, 24.6 mmol) was slowly added to this mixture and the reaction stirred for 8 hours. Upon completion of the reaction as judged by TLC on silica gel plates (EtOAc:hexanes), 100 mL of hexanes was added to the reaction and the product precipitated. The solid was collected and recrystallized from ethanol to provide the products **13a-h**.

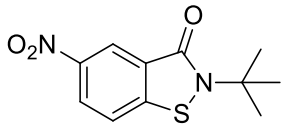
2-Isopropyl-5-nitrobenzo[*d*]isothiazol-3(*2H*)-one (13a)[12]



Prepared according to the general procedure from 1**2a** (5.6 g, 18.9 mmol), DMSO (2.0 mL, 28.3 mmol), and TMSCl (3.1 mL, 24.6 mmol), 1**3a** was obtained as yellow needles (4.15 g, 92% yield). Mp = 168-169 °C (Lit.[12] 164-165 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 – 8.33 (m, 2H), 8.22 (d, *J* = 8.8 Hz, 1H), 4.72 (sep, *J* = 6.6 Hz, 1H), 1.33 (d, *J*

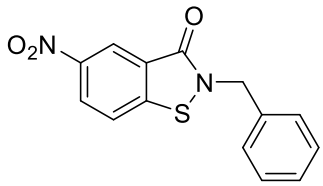
= 6.6 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.00, 152.20, 150.81, 130.99, 130.83, 129.10, 126.01, 51.48, 27.18. IR (neat, cm^{-1}): 1652 (s).

2-(*tert*-Butyl)-5-nitrobenzo[*d*]isothiazol-3(2*H*)-one (13b)[13]



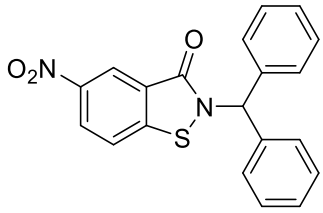
Prepared according to the general procedure from **12b** (3.0 g, 9.7 mmol), DMSO (1.0 mL, 14.5 mmol), and TMSCl (1.6 mL, 12.6 mmol), **13b** was obtained as yellow crystals (2.2 g, 93% yield). Mp = 215-216 °C (Lit.[13] 205-210). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 2.2 Hz, 1H), 8.39 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 1.70 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.26, 145.74, 127.60, 125.90, 122.44, 121.05, 59.89, 28.57. IR (neat, cm^{-1}): 1634 (s).

2-Benzyl-5-nitrobenzo[*d*]isothiazol-3(2*H*)-one (13c)[39]



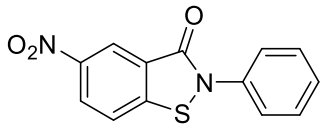
Prepared according to the general procedure from **12c** (3.0 g, 8.7 mmol), DMSO (0.93 mL, 13.1 mmol), and TMSCl (1.3 mL, 10.5mmol), **13c** was obtained as orange solid (1.74 g, 70%). Mp = 179-180°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, *J* = 2.4 Hz, 1H), 8.43 (dd, *J* = 9.2, 2.4 Hz), 8.20 (d, *J* = 9.2 Hz, 1H), 7.37-7.28 (m, 5H), 5.04 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 147.7, 145.9, 136.9, 129.2, 128.6, 128.5, 126.4, 125.1, 124.3, 121.4, 47.1. IR (neat, cm^{-1}): 1651. HRMS (ESI) Calcd for $C_{14}H_{11}N_2O_3S$ ($M+H^+$): 287.0485. Found: 287.0485.

2-Benzhydryl-5-nitrobenzo[*d*]isothiazol-3(2*H*)-one (13d)



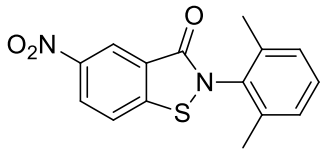
Prepared according to the general procedure from **12d** (3.5g, 8.3 mmol), DMSO (0.89 mL, 12.5 mmol), and TMSCl (1.27 mL, 10.0 mmol), **13d** was obtained as a yellow solid (2.71g, 90%). Mp = 211-212°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 2.0, 1H), 8.44 (d, J = 8.8, 2.0 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.41-7.32 (m, 6H), 7.21 (d, J = 8.4 Hz, 4H), 6.92 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 147.8, 146.0, 139.3, 129.3, 128.7, 126.4, 125.4, 1214.4, 121.4, 61.0. IR (neat, cm^{-1}): 1638. HRMS (ESI) Calcd for $C_{20}H_{15}N_2O_3S$ (M+H$^+$): 363.0798. Found: 363.0798.

5-Nitro-2-phenylbenzo[*d*]isothiazol-3(2*H*)-one (13e)[40]



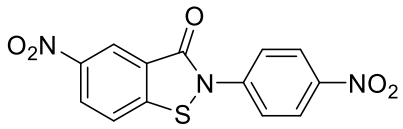
Prepared according to the general procedure from **12c** (2.5g, 7.6 mmol), DMSO (0.81 mL, 11.3 mmol), and TMSCl (1.15 mL, 9.1 mmol), **13c** was obtained as a yellow solid (1.87 g, 91%). Mp = 219-221°C (Lit. **[40]** 221-223°C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.54 (d, J = 2.4 Hz, 1H), 8.50 (dd, J = 9.6, 2.4 Hz, 1H), 8.31 (d, J = 9.6 Hz, 1H), 7.67 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.8 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.8, 147.5, 146.5, 137.1, 130.3, 128.3, 127.1, 125.7, 125.4, 124.5, 121.9. IR (neat, cm^{-1}): 1645. HRMS (ESI) Calcd for $C_{13}H_9N_2O_3S$ (M+H$^+$): 273.0328. Found: 273.0329.

2-(2,6-Dimethylphenyl)-5-nitrobenzo[*d*]isothiazol-3(2*H*)-one (13f)[12]



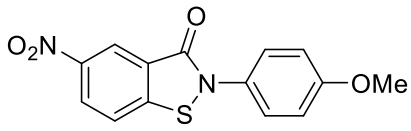
Prepared according to the general procedure from **12f** (5.1 g, 14.2 mmol), DMSO (1.5 mL, 21.3 mmol), and TMSCl (2.4 mL, 18.5 mmol), **13f** was obtained as yellow crystals (3.2 g, 88% yield). Mp = 234-236 (Lit.[12] 241-242 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 2.2 Hz, 1H), 8.50 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 147.7, 146.4, 138.2, 132.7, 130.5, 129.1, 126.7, 125.0, 123.4, 121.8, 18.2. IR (neat, cm^{-1}): 1656 (s).

5-Nitro-2-(4-nitrophenyl)benzo[d]isothiazol-3(2H)-one (13g)



Prepared according to the general procedure from **12g** (2.5g, 6.66 mmol), DMSO (0.71 mL, 9.99 mmol), and TMSCl (1.0 mL, 7.99 mmol), **13g** was obtained as a yellow solid (1.67g, 79%). Mp = >300°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.58 (d, *J* = 1.8 Hz, 1H), 8.55 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.38 (dt, *J* = 9.0, 2.4 Hz, 2H), 8.35 (d, *J* = 9.0 Hz, 1H), 8.07 (dt, *J* = 9.0, 2.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ. 162.9, 147.0, 143.0, 140.9, 127.6, 125.6, 124.5, 124.0, 122.0. IR (neat, cm^{-1}): 1692. HRMS (ESI) Calcd for $C_{13}H_8N_3O_5S$ ($M+H^+$):318.0179. Found: 318.0180.

2-(4-Methoxyphenyl)-5-nitrobenzo[d]isothiazol-3(2H)-one (13h)[39]

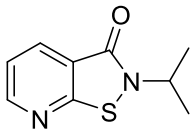


Prepared according to the general procedure from **12h** (2.5 g, 6.94 mmol), DMSO (0.74 mL, 10.4 mmol), and TMSCl (1.0 mL, 8.3 mmol), **13h** was obtained as a yellow solid (1.78 g, 85% yield). Mp = 237-238 °C (Lit[39] 236-238°C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.57 (d, *J* = 2.3 Hz, 1H), 8.53 (dd, *J* = 8.9, 2.3 Hz, 1H), 8.32 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 8.9 Hz, 2H), 7.10 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.2, 158.6, 146.9, 145.8, 128.8, 127.0, 126.3, 124.9, 123.8, 121.2, 114.7, 55.5. IR (neat, cm^{-1}): 1665. HRMS (ESI) Calcd. for $C_{14}H_{11}N_2O_4S$ ($M+H^+$): 303.0440. Found: 303.0436.

2.4.5 General Procedure for the Synthesis of Benzoisothiazolones (BITs) 17a-c and 21a-c

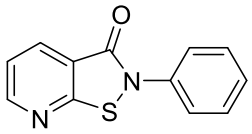
In a flame-dried flask, t-butylthioethers **16a-c** and **20a-c** (5 mmol) was taken up in 50 mL of DCM. The mixture was cooled to 0 °C, and mCPBA (5.5 mmol) was added in portions. The mixture was stirred at 0 °C. Upon completion by TLC (EtOAc:hexanes), the mixture was allowed to warm to room temperature and quenched with sodium bicarbonate and brine. The layers were separated and the aqueous layer extracted with DCM (50 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The residue of the crude sulfoxide was dissolved in toluene (100 mL) and pyridine (10 mL) and heated to reflux with azeotropic removal of water. After 3 hours, the reaction was cooled to room temperature and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc:hexanes) when necessary.

Isopropylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (17a)[10]



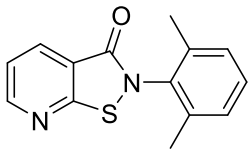
Prepared according to the general procedure from **16a** (3.0 grams, 11.9 mmol) and mCPBA (2.93 g, 13.1 mmol), **17a** was obtained as a yellow solid (1.5 g, 65% yield). Mp = 53-54°C (Lit.[10] 56-59°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, J= 4.8, 1.6 Hz, 1 H), 8.29 (dd, J= 3.9, 1.9 Hz, 1 H), 7.37 (dd, J= 7.9, 4.8 Hz, 1 H), 5.06 (m, 1 H), 1.46 (d, J= 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 162.3, 153.4, 134.6, 120.6, 120.3, 45.6, 22.2. IR (neat, cm^{-1}): 1661 (s).

2-Phenylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (17b)[41]



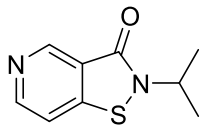
Prepared according to the general procedure from **16b** (3.0 grams, 10.5 mmol) and mCPBA (2.58 g, 11.5 mmol), **17b** was obtained as a yellow solid (1.70 g, 71% yield). Mp = 136-137 °C (Lit.[41] 134-136 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.32 (ddd, *J* = 7.9, 1.7, 0.5 Hz, 1H), 7.74 – 7.63 (m, 2H), 7.51 – 7.43 (m, 2H), 7.38 (ddd, *J* = 7.9, 4.7, 0.5 Hz, 1H), 7.35 – 7.29 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 161.8, 154.0, 136.6, 135.2, 129.4, 127.4, 124.8, 121.0, 119.7. IR (neat, cm^{-1}): 1666 (m).

2-(2,6-Dimethylphenyl)isothiazolo[5,4-*b*]pyridin-3(2*H*)-one (17c)[42]



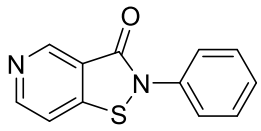
Prepared according to the general procedure from **16c** (3.0 grams, 9.5 mmol) and mCPBA (2.35 g, 10.5 mmol), **17c** was obtained as a yellow solid (1.96 g, 80% yield). Mp = 109-110 °C (Lit.[42] 110-112°C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.73 (d, *J* = 5.6 Hz, 1H), 7.57 (dd, *J* = 5.6, 1.0 Hz, 1H), 7.27 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.20 – 7.13 (m, 2H), 2.18 (d, *J* = 0.7 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 163.2, 147.3, 139.9, 138.2, 134.9, 128.3, 126.8, 124.1, 122.9, 19.2. IR (neat, cm^{-1}): 1667 (m).

2-Isopropylisothiazolo[4,5-*c*]pyridin-3(2*H*)-one (21a)



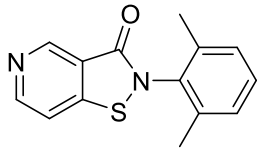
Prepared according to the general procedure from **20a** (3.0 grams, 11.9 mmol) and mCPBA (2.93 g, 13.1 mmol), **20a** was obtained as a yellow solid (1.73 g, 75% yield). Mp = 101-103°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (p, *J* = 1.0 Hz, 1H), 8.61 (dq, *J* = 5.7, 1.0 Hz, 1H), 7.50 (dt, *J* = 5.6, 1.0 Hz, 1H), 5.08 – 4.82 (m, 1H), 1.39 (dd, *J* = 6.7, 2.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 149.5, 148.7, 121.4, 115.2, 77.4, 77.0, 76.7, 46.2, 22.2. IR (neat, cm^{-1}): 1660 (s). HRMS (ESI) Calcd. for $C_9H_{11}N_2OS$ ($M+H^+$): 195.0587. Found: 195.0585.

2-Phenylisothiazolo[4,5-*c*]pyridin-3(2*H*)-one (21b)



Prepared according to the general procedure from **20b** (3.0 grams, 10.5 mmol) and mCPBA (2.58 g, 11.5 mmol), **20b** was obtained as a yellow solid (1.89 g, 79% yield). Mp = 114-115°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, *J* = 1.1 Hz, 1H), 8.72 (dt, *J* = 5.6, 0.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.55 (ddd, *J* = 5.6, 1.0, 0.5 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.39 – 7.30 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 150.4, 149.4, 148.6, 136.3, 129.5, 127.6, 124.8, 120.6, 114.9, 77.4, 77.0, 76.7. IR (neat, cm^{-1}): 1665 (m). HRMS (ESI) Calcd. for $C_{12}H_9N_2OS$ ($M+H^+$): 229.0430. Found: 229.0431.

2-(2,6-Dimethylphenyl)isothiazolo[4,5-*c*]pyridin-3(2*H*)-one (21c)

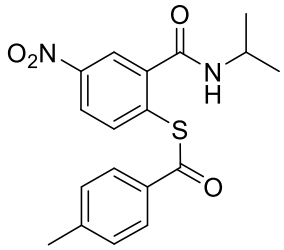


Prepared according to the general procedure from **20c** (3.0 grams, 9.5 mmol) and mCPBA (2.35 g, 10.5 mmol), **20c** was obtained as a yellow solid (1.86 g, 76% yield). Mp = 143-136°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.73 (d, *J* = 5.6 Hz, 1H), 7.57 (dd, *J* = 5.6, 1.0 Hz, 1H), 7.27 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.19 – 7.14 (m, 2H), 2.18 (d, *J* = 0.7 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.3, 152.8, 146.7, 140.8, 139.5, 134.4, 129.8, 129.9, 127.0, 122.3, 19.5. IR (neat, cm^{-1}): 1667 (s). HRMS (ESI) Calcd. for $C_{14}H_{13}N_2OS$ ($M+H^+$): 257.0743. Found: 257.0740.

2.4.4 General Procedure for the Synthesis of Thiol Esters with Triphenylphosphine

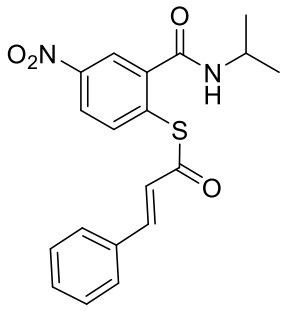
In a flame-dried flask, the desired benzoisothiazolinone (1 equiv) was combined with carboxylic acid (1 equiv) and triphenylphosphine (1 equiv). The mixture was flushed with argon, taken up in acetonitrile, and refluxed until completion by TLC (hexanes/EtOAc). After concentration *in vacuo*, purification by column chromatography on silica gel (hexanes/EtOAc) provided the desired product.

_S_-(2-(Isopropylcarbamoyl)-4-nitrophenyl) 4-methylbenzothioate (25a)



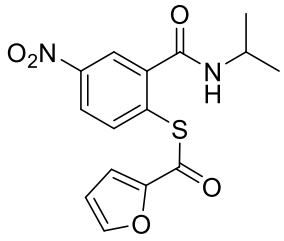
Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), p-toluic acid (43 mg, 0.315 mmol), and triphenylphosphine (83 mg, 0.315 mmol), **25a** was obtained as a white solid (106 mg, 94% yield) after trituration from chloroform/hexane (solvent/antisolvent). Mp = 166-167°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 2.5 Hz, 1H), 8.26 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.3, 1.0 Hz, 2H), 5.98 (d, *J* = 8.3 Hz, 1H), 4.16 (dp, *J* = 8.2, 6.5 Hz, 1H), 2.43 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 6H). δ. ^{13}C NMR (100 MHz, $CDCl_3$) δ. IR (neat, cm^{-1}): 3293 (w) 1671 (m), 1636(m). HRMS (ESI) Calcd. for $C_{18}H_{18}N_2O_4S$ ($M+H^+$): 358.0987. Found: 358.0988.

***S*-(2-(Isopropylcarbamoyl)-4-nitrophenyl) (*E*)-3-phenylprop-2-enethioate (25b)**



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), cinnamic acid (46 mg, 0.315 mmol), and triphenylphosphine (83 mg, 0.315 mmol), **25b** was obtained as a white solid (99 mg, 85% yield) after trituration from chloroform/hexane (solvent/antisolvent). Mp = 159-160°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.4 Hz, 1H), 2.27 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.69-7.76 (m, 2H), 7.57 (d, *J* = 6.8 Hz, 2H), 7.42-7.44 (m, 3H), 6.79 (d, *J* = 15.6 Hz, 1H), 5.97 (d, *J* = 7.6 Hz, 1H), 4.21-4.25 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 165.2, 143.7, 143.5, 137.6, 133.4, 132.7, 131.5, 129.2, 129.0, 128.7, 124.3, 123.2, 123.1, 42.3, 22.5. IR (neat, cm^{-1}): 3281 (w), 1685 (m), 1634 (m). HRMS (ESI) Calcd. for $C_{19}H_{18}N_2O_4S$ ($M+H^+$): 370.0987. Found: 270.0985.

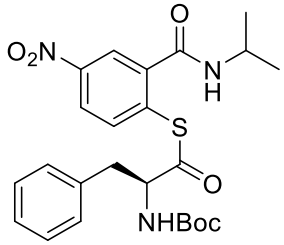
***S*-(2-(Isopropylcarbamoyl)-4-nitrophenyl) furan-2-carbothioate (25c)**



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), furanoic acid (35 mg, 0.315 mmol), and triphenylphosphine (83 mg, 0.315 mmol), **25c** was

obtained as a white solid (85 mg, 82% yield) after trituration from chloroform/hexane (solvent antisolvent). Mp = 171-172°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.32 (d, *J* = 2.8 Hz, 1H), 6.61 (d, *J* = 1.6 Hz, 1H), 5.97 (d, *J* = 7.6 Hz, 1H), 4.16-4.22 (m, 1H), 1.13 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 165.2, 149.5, 148.6, 147.6, 144.0, 138.0, 131.5, 124.3, 123.1, 117.8, 112.8, 50.4, 42.3, 22.4. IR (neat, cm^{-1}): 3273 (w), 1665 (m), 1634(m). HRMS (ESI) Calcd. for $C_{15}H_{14}N_2O_5S$ ($M+H^+$): 334.0623. Found: 334.0624.

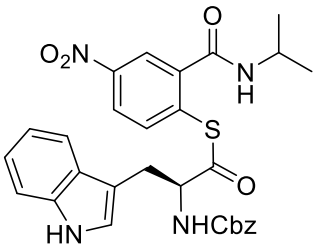
_S_-(2-(Isopropylcarbamoyl)-4-nitrophenyl) (_S_)-2-((_tert_-butoxycarbonyl)amino)-3-phenylpropanethioate (25d)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), Boc-phenylalanine (86 mg, 0.315 mmol), and triphenylphosphine (83 mg, 0.315 mmol), **25d** was obtained as a white solid (137 mg, 85% yield) after trituration from chloroform/hexane (solvent antisolvent). Mp = 180 °C (decomp.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.6 Hz, 1H), 8.23 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.32 (dd, *J* = 8.2, 6.6 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.16 (dd, *J* = 7.0, 1.7 Hz, 2H), 5.85 (d, *J* = 7.9 Hz, 1H), 4.93 (d, *J* = 8.4 Hz, 1H), 4.69 (td, *J* = 8.3, 5.1 Hz, 1H), 4.20 (dp, *J* = 7.9, 6.4 Hz, 1H), 3.18 (dd, *J* = 14.2, 5.1 Hz, 1H), 3.04 (dd, *J* = 14.2, 8.2 Hz, 1H), 1.40 (s, 9H), 1.23 (dd, *J* = 6.6, 5.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 137.6, 136.6, 129.3, 128.7, 128.6, 127.6, 127.4, 126.9, 56.1, 43.4, 38.5, 28.2. IR (neat, cm^{-1}):

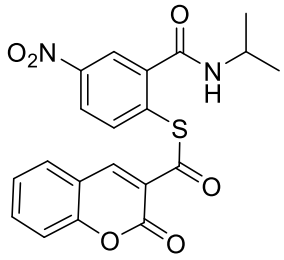
3322 (w), 1712 (w), 1687 (m), 1639 (m). HRMS (ESI) Calcd for $C_{15}H_{14}N_2O_5S$ ($M+H^+$): 487.1777. Found: 487.1779.

_S_-(2-(Isopropylcarbamoyl)-4-nitrophenyl) (_S_)-2-(((benzyloxy)carbonyl)amino)-3-(1_H_-indol-3-yl)propanethioate (25e)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), Cbz-tryptophan (103 mg, 0.315 mmol), and triphenylphosphine (83 mg, 0.315 mmol), **25e** was obtained as an orange solid (157 mg, 89% yield) after trituration from chloroform/hexane (solvent antisolvent). Mp = 76-78 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, *J* = 2.5 Hz, 1H), 8.21 (s, 1H), 8.13 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.28 (m, 4H), 7.24 – 7.17 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 5.83 (d, *J* = 8.0 Hz, 1H), 5.34 (d, *J* = 8.3 Hz, 1H), 5.10 (s, 2H), 4.81 (dt, *J* = 8.3, 6.0 Hz, 1H), 4.23 – 4.13 (m, 1H), 3.39 (dd, *J* = 15.0, 6.2 Hz, 1H), 3.28 (dd, *J* = 14.9, 5.4 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.50, 165.38, 155.96, 148.36, 143.14, 137.78, 136.48, 136.05, 133.08, 128.81, 128.58, 128.34, 127.38, 124.37, 123.67, 123.26, 122.70, 120.14, 118.79, 111.75, 108.86, 67.67, 61.56, 42.77, 28.23, 22.59. IR (neat, cm^{-1}): 3303 (w), 1703 (s), 1642 (s). HRMS (ESI) Calcd for $C_{29}H_{28}N_4O_6S$ ($M+H^+$): 560.1730. Found: 560.1728.

_S_-(2-(Isopropylcarbamoyl)-4-nitrophenyl) 2-oxo-2_H_-chromene-3-carbothioate (25f)



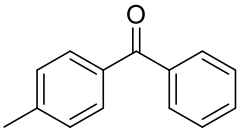
Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), coumarin-3-carboxylic acid (60 mg, 0.315 mmol), and triphenylphosphine (83 mg, 0.315 mmol), **25f** was obtained as a white solid (104 mg, 80% yield) after trituration from chloroform/hexane (solvent antisolvent). Mp = 190-192°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.51 (d, J = 7.8 Hz, 1H), 8.33 (dd, J = 8.5, 2.6 Hz, 1H), 8.22 (d, J = 2.6 Hz, 1H), 8.01 (dd, J = 7.8, 1.6 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.83 – 7.74 (m, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 3.96 (dt, J = 13.6, 6.7 Hz, 1H), 1.09 (d, J = 6.6 Hz, 6H). IR (neat, cm^{-1}): 3252 (w), 1730 (s), 1692 (m), 1650(m). IR (neat, cm^{-1}): 3253 (m), 1730, 1693 (m), 1650 (m). HRMS (ESI) Calcd for (M+H$^+$): 412.0729. Found: 412.0730.

2.4.6 General Procedure for the One-Pot Ketoconjugation (Triphenylphosphine)

In a flame-dried flask, the desired benzoisothiazolinone (1 equiv) was combined with carboxylic acid (1 equiv) and triphenylphosphine (1 equiv). The solids were taken up in acetonitrile and refluxed for three hours. The reaction mixture was allowed to cool to room temperature before the solvent was evaporated *in vacuo*. Following evaporation of solvent, the solid was dissolved in DMF (2 mL) and boronic acid (1.5 equiv), copper(I) 3-methylsalicylate (20 mol %), and N-methylimidazole (40 mol %) were added. The reaction was heated to 50 ºC and allowed to stir open to air. The reaction was monitored

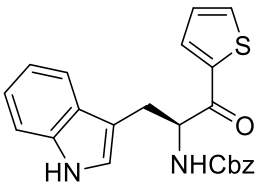
by TLC (hexanes/EtOAc) and, upon completion, the EtOAc (30 mL) was added to the reaction mixture, which was washed with saturated ammonium chloride solution (1 x 20 mL), saturated sodium bicarbonate solutions (1 x 20 mL), water (1 x 20 mL), and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexanes/EtOAc) provided the desired ketone.

Phenyl(p-tolyl)methanone (26a) [43]



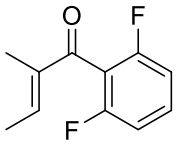
Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), p-toluic acid (43 mg, 0.315 mmol), triphenylphosphine (83 mg, 0.315 mmol), phenyl boronic acid (58 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26a** was obtained as a white solid (53 mg, 86% yield) after column chromatography (hexanes/EtOAc, 5:1). Mp = 57 °C (Lit[43] 56.5-57 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 7.2 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 143.5, 138.2, 135.1, 132.4, 130.5, 130.2, 129.2, 128.4, 21.8. IR (neat, cm^{-1}) 1656 (s).

Benzyl (*S*)-(3-(1*H*-indol-3-yl)-1-oxo-1-(thiophen-2-yl)propan-2-yl)carbamate (26b)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), N-Cbz-phenylalanine (83 mg, 0.315 mmol), triphenylphosphine (83 mg, 0.315 mmol), 2-thiophene boronic acid (61 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26b** was obtained as a yellow oil (116 mg, 91% yield) after column chromatography (hexanes/EtOAc, 3:1). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.7 mL/min; T = 25 °C; Isogradient: 50 % H_2O in CH_3CN for 25 min, 50% CH_3CN to 100 % CH_3CN in 15 min, t_R = 33.6 min and 35.1 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (bs, 1H), 7.65 (d, *J* = 4.8 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.38-7.38 (m, 5H), 7.18-7.13 (m, 2H), 7.07-7.03 (m, 2H), 6.84 (d, *J* = 2.8 Hz, 1H), 5.67 (d, *J* = 8.0 Hz, 1H), 5.48-5.43 (m, 1H), 5.09 (q, *J* = 10Hz, 2H), 3.43 (dd, *J* = 15.6, 6.4 Hz, 1H), 3.30 (dd, *J* = 15.6, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 155.9, 151.1, 147.4, 136.4, 136.2, 128.6, 128.3, 128.2, 127.7, 123.1, 122.2, 119.7, 119.2, 118.6, 112.7, 111.3, 109.8, 67.0, 56.6, 28.9. IR (neat, cm^{-1}): 3408 (m), 3347 (s), 3061 (w), 2953 (w), 1702 (s), 1671 (s). HRMS (ESI) Calcd for $C_{23}H_{20}N_2O_3S$ ($M+H^+$): 405.1267. Found: 405.1268.

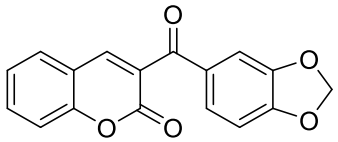
(*E*)-1-(2,6-Difluorophenyl)-2-methylbut-2-en-1-one (26c)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), tiglic acid (32 mg, 0.315 mmol), triphenylphosphine (83 mg, 0.315 mmol), 2,6-difluorophenylboronic acid (75 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26c** was obtained as a clear oil (54 mg, 88% yield) after column chromatography (hexanes/EtOAc, 9:1). ^{1}H NMR

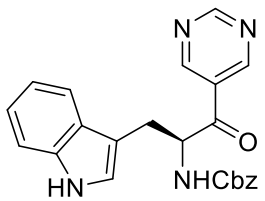
(400 MHz, $CDCl_3$) δ 7.55 (t, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 6.55 (q, *J* = 15Hz, 1H), 2.33-2.35 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 162.1, 143.1, 139.3, 135.6, 111.8, 110.9, 15.8, 12.2. IR (neat, cm^{-1}): 1679 (m). HRMS (ESI) Calcd for $C_{11}H_{10}F_2O$ ($M+H^+$): 196.0700. Found: 196.0701.

3-(Benzo[*d*][1,3]dioxole-5-carbonyl)-2*H*-chromen-2-one (26d)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), coumarin-3-carboxylic acid (60 mg, 0.315 mmol), triphenylphosphine (83 mg, 0.315 mmol), 3,4-(methylenedioxy)boronic acid (78 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26d** was obtained as a clear oil (77 mg, 83% yield) after column chromatography (hexanes/EtOAc, 5:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.86-7.89 (m, 2H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.33-7.41 (m, 3H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.12 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 159.4, 154.4, 153.0, 149.3, 139.5, 129.4, 128.5, 127.9, 127. 7, 125.6, 122.9, 118.9, 116.1, 101.3. IR (neat, cm^{-1}): 1732 (s), 1668 (s). HRMS (ESI) Calcd for $C_{17}H_{10}O_5$ ($M+H^+$): 294.0598. Found: 294.0598.

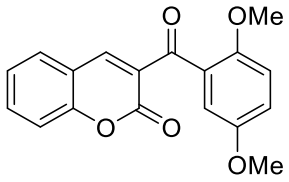
Benzyl (S)-(3-(1H-indol-3-yl)-1-oxo-1-(pyrimidin-5-yl)propan-2-yl)carbamate (26e)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), L-Cbz-tryptophan (106 mg, 0.315 mmol), triphenylphosphine (83 mg, 0.315 mmol), pyrimidine-

5-boronic acid (59 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26e** was obtained as a light yellow oil (103 mg, 82% yield) after column chromatography (hexanes/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 9.31(s, 2H), 7.93 (bs, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.38-7.38 (m, 5H), 7.18-7.13 (m, 2H), 7.07-7.03 (m, 2H), 5.67 (d, *J* = 8.0 Hz, 1H), 5.48-5.43 (m, 1H), 5.09 (q, *J* = 10Hz, 2H), 3.43 (dd, *J* = 15.6, 6.4 Hz, 1H), 3.30 (dd, *J* = 15.6, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 158.2, 158.0, 155.5, 136.8, 136.1, 130.2, 128.9, 127.8, 127.4, 127.1, 123.1, 121.4, 119.8, 118.9, 111.1, 110.5, 68.6, 66.8, 28.6. IR (neat, cm^{-1}): 3280(m), 1701 (m), 1666 (s). HRMS (ESI) Calcd for $C_{23}H_{20}H_4O_3$ ($M+H^+$): 400.1535. Found: 400.1533.

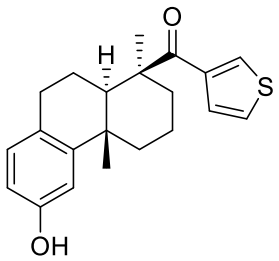
3-(2,5-Dimethoxybenzoyl)-2*H*-chromen-2-one (26f)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), coumarin-3-carboxylic acid (60 mg, 0.315 mmol), triphenylphosphine (83 mg, 0.315 mmol), 2,5-dimethoxyphenylboronic acid (86 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26f** was obtained as a clear oil (90 mg, 92% yield) after column chromatography (hexanes/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.35-7.41 (m, 3H), 7.15 (s, 2H), 3.91 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 159.6, 153.4, 153.0, 150.2, 139.6, 128.5, 127.7, 127.5, 125.2, 122.1,

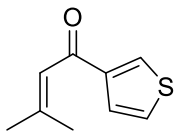
121.0, 118.5, 116.3, 115.9, 106.1, 55.7, 55.1. IR (neat, cm^{-1}): 1736(s), 1661(s). HRMS (ESI) Calcd for $C_{18}H_{14}O_5$ ($M+H^+$): 310.0841. Found: 310.0842.

((1*S*,4a*S*,10a*R*)-6-Hydroxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)(thiophen-3-yl)methanone (26g)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), podocarpic acid (86 mg, 0.315 mmol), triphenylphosphine (83 mg, 0.315 mmol), 3-thienylboronic acid (61 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26g** was obtained as a clear oil (76 mg, 71% yield) after column chromatography (hexanes/EtOAc, 3:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (br s, 1H), 8.31 (d, *J* = 2.4Hz, 1H), 7.81 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.11-7.15 (m, 2H), 6.95 (dd, *J* = 7.6, 2.4 Hz, 1H), 2.81-2.92 (m, 2H), 1.81-1.92 (m, 2H), 1.55-1.71(m, 3H), 1.43-1.54 (m, 4H), 1.35 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.1, 153.8, 149.8, 143.3, 132.8, 129.4, 128.2, 127.9, 127.0, 113.5, 110.9, 56.1, 48.5, 39.9, 38.7, 38. 3, 30.1, 29.7, 25.5, 20.7, 19.9. IR (neat, cm^{-1}): 3380 (br), 1660 (s). HRMS (ESI) Calcd for $C_{21}H_{24}O_2S$ ($M+H^+$): 340.1497. Found: 340.1496.

3-Methyl-1-(thiophen-3-yl)but-2-en-1-one (26h)

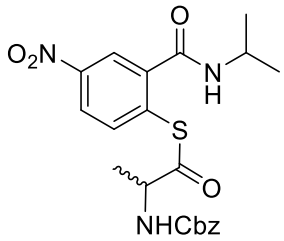


Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), 3,3-dimethylacrylic acid (32 mg, 0.315 mmol), triphenylphosphine (83 mg, 0.315 mmol), 3-thienylboronic acid (61 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26h** was obtained as a clear oil (45mg, 85% yield) after column chromatography (hexanes/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.4Hz, 1H), 7.83 (dd, *J* = 7.6, 2.4Hz, 1H), 7.54 (d, *J* = 7.6Hz, 1H), 5.95 (s, 1H), 2.22 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 160.1, 141.7, 135.6, 127.5, 123.1, 119.5, 25.9, 22.1. IR (neat, cm^{-1}): 1674 (m). HRMS (ESI) Calcd for $C_9H_{10}OS$ ($M+H^+$): 167.0525. Found: 167.0525.

2.4.7 General Procedure for the Generation of Thiol Esters from Triethylphosphite

In a flame-dried flask, the desired benzoisothiazolinone (1 equiv) was combined with carboxylic acid (1 equiv) and triethylphosphite (1 equiv). The mixture was flushed with argon, taken up in ethyl acetate, and refluxed until completion by TLC (hexanes/EtOAc). After concentration *in vacuo*, purification by column chromatography on silica gel (hexanes/EtOAc) provided the desired product.

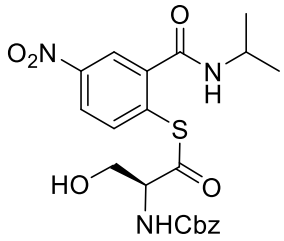
_S_-(2-(Isopropylcarbamoyl)-4-nitrophenyl) 2-((benzyloxy)carbonyl)amino) propanethioate (25g)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), N-Cbz-DL-alanine (70 mg, 0.315 mmol), and triethylphosphite (54 µL, 0.315 mmol), **25g** was

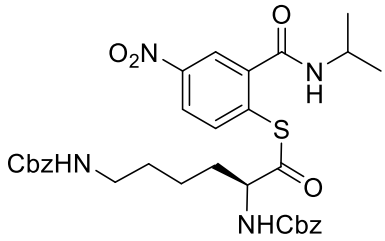
obtained as a white solid (132 mg, 94% yield) after trituration from chloroform/hexane (solvent antisolvent). Mp = 182-183°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.46 (d, J = 7.8 Hz, 1H), 8.28 (t, J = 6.6 Hz, 2H), 8.15 (d, J = 2.4 Hz, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.30-7.36 (m, 5H), 5.06 (s, 2H), 4.27 (p, J = 7.2 Hz, 1H), 3.94-3.97 (m, 1H), 1.28 (d, J = 7.2 Hz, 3H), 1.10-1.11 (m, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 195.4, 165.4, 156.0, 143.2, 141.2, 137.6, 136.5, 130.5, 128.9, 127.8, 127.1, 126.5, 122.6, 67.2, 45.1, 24.5, 19.4. IR (neat, cm-1): 3304(w), 1707 (m), 1688 (s), 1629 (m). HRMS (ESI) Calcd for $C_{21}H_{23}N_3O_6S$ ($M+H^+$): 445.1308. Found: 445.1309.

_S_-(2-(isopropylcarbamoyl)-4-nitrophenyl) (_S_)-2-(((benzyloxy)carbonyl)amino)-3-hydroxypropanethioate (25h)[44]



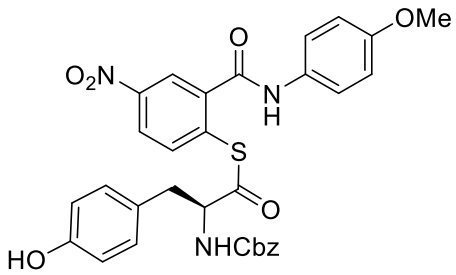
Prepared according to the general procedure from **13a** (100 mg, 0.42 mmol), N-Cbz-L-serine (100 mg, 0.42 mmol), and triethylphosphite (72 μL, 0.42 mmol), **25h** was obtained as a yellow solid (134 mg, 69% yield) after trituration from chloroform/hexane (solvent antisolvent). Mp = 141-142 °C (Lit.[44] 141-143 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.18 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.34 (s, 6H), 6.29 (s, 2H), 5.14 (s, 2H), 4.47 – 4.41 (m, 1H), 4.20 – 4.07 (m, 2H), 3.77 (d, J = 10.4 Hz, 1H), 1.24 (d, J = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 166.2, 156.2, 148.2, 141.1, 138.0, 136.0, 134.6, 128.7, 128.4, 128.2, 124.9, 122.9, 67.5, 63.4, 63.2, 42.9, 22.6, 22.5. IR (neat, cm^{-1}): 3271 (br), 3077 (m), 1683(s), 1635(m).

_S_-(2-(isopropylcarbamoyl)-4-nitrophenyl) (_S_)-2,6-bis(((benzyloxy)carbonyl)amino) hexanethioate (25i)[44]



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), N-Cbz-L-lysine (130 mg, 0.315 mmol), and triethylphosphite (54 μL, 0.315 mmol), **25i** was obtained as a yellow solid (162 mg, 81% yield) after trituration from chloroform/hexane (solvent antisolvent). Mp = 161-162 °C (Lit.[44] 160 ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 7.6Hz, 1H), 8.34 – 8.26 (m, 2H), 8.18 (d, J = 2.6 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.43 – 7.22 (m, 12H), 5.10 (s, 2H), 4.99 (s, 2H), 4.23 – 4.13 (m, 1H), 4.00 (d, J = 6.8 Hz, 1H), 2.97 (s, 1H), 1.69 (s, 2H), 1.38 (s, 4H), 1.13 (dd, J = 6.6, 2.6 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 198.3, 164.3, 156.2, 156.1, 147.2, 142.5, 137.4, 137.3, 136.7, 134.2, 128.4, 128.34, 128.0, 127.8, 127.7, 123.9, 122.3, 66.0, 65.1, 61.6, 41.2, 30.7, 30.5, 28.9, 22.5, 22.1. IR (neat, cm^{-1}): 3321 (br), 3282 (w), 2952 (w), 1738 (m), 1703 (m), 1683 (s), 1634 (m).

_S_-(2-((4-methoxyphenyl)carbamoyl)-4-nitrophenyl) (_S_)-2-(((benzyloxy)carbonyl) amino)-3-(4-hydroxyphenyl)propanethioate (25j)[44]



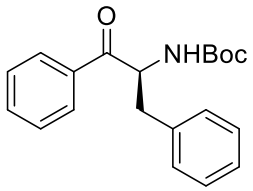
Prepared according to the general procedure from **13h** (95 mg, 0.315 mmol), N-Cbz-L-tyrosine (100 mg, 0.315 mmol), and triethylphosphite (54 μL, 0.315 mmol), **25j** was obtained as a yellow solid (157 mg, 83% yield) after trituration from chloroform/hexane (solvent antisolvent). Mp = 173-175 °C (Lit. 173-175 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.26 (s, 1H), 8.43 (s, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.62 (d, *J* = 8.9 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 8.3 Hz, 2H), 4.98 (s, 2H), 4.37 (s, 1H), 3.73 (s, 3H), 2.98 – 2.93 (m, 1H), 2.79 – 2.72 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 197.5, 163.3, 156.1, 156.0, 155.9, 147.3, 142.1, 137.5, 136.7, 134.6, 131.8, 130.1, 128.4, 127.8, 127.4, 126.8, 124.3, 122.8, 121.5, 115.1, 113.9, 65.7, 63.5, 55.2, 35.6. IR (neat, cm-1): 3456 (br), 3292 (w), 1690 (m), 1649 (m).

2.4.8 General Procedure for the One-Pot Ketoconjugation (Triethylphosphite)

In a flame-dried flask, the desired benzoisothiazolinone (1 equiv) was combined with carboxylic acid (1 equiv) and triethylphosphite (1 equiv). The solids were taken up in ethyl acetate and heated at 50 ºC three hours. The reaction mixture was allowed to cool to room temperature before the solvent was evaporated *in vacuo*. Following evaporation of solvent, the solid was dissolved in DMF (2 mL) and boronic acid (1.5 equiv), copper(I) 3-methylsalicylate (20 mol %), and NMI (40 mol %) were added. The reaction was heated to 50 ºC and allowed to stir open to air. The reaction was monitored by TLC (hexanes/EtOAc) and, upon completion, the EtOAc (30 mL) was added to the reaction mixture, which was washed with saturated ammonium chloride solution (1 x 20 mL), saturated sodium bicarbonate solutions (1 x 20 mL), water (1 x 20 mL), and brine (1 x 20

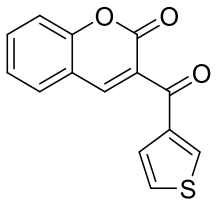
mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexanes/EtOAc) provided the desired ketone.

***tert*-Butyl (1-oxo-1,3-diphenylpropan-2-yl)carbamate (26k)[45]**



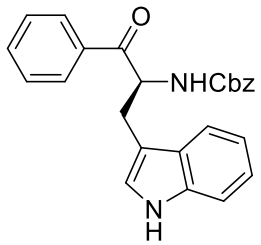
Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), L-*N*-Boc-phenylalanine (86 mg, 0.315 mmol), triethylphosphite (54 µL, 0.315 mmol), phenyl boronic acid (58 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and *N*-methylimidazole (10 µL, 0.126 mmol), **26k** was obtained as a white solid (94 mg, 92% yield) after column chromatography (hexanes/EtOAc, 4:1). Mp = 101-102 °C. HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.7 mL/min; T = 25 °C; Isogradient: 50 % H_2O in CH_3CN for 25 min, 50% CH_3CN to 100 % CH_3CN in 15 min, t_R = 36.9 min and 38.8 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) 7.93 (d, *J* = 6.8Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.17-7.23 (m, 3H), 7.00 (d, *J* = 6.4 Hz, 1H), 5.51-5.55 (m, 1H), 5.39 (d, *J* = 7.6Hz, 1H), 3.23 (dd, *J* = 13.6, 6 Hz, 1H), 2.95 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 155.1, 135.9, 134.9, 133.6, 129.5, 128.8, 128.6, 128.3, 126.8, 79.7, 55.9, 39.1, 28.3. IR (neat, cm^{-1}): 3321 (w), 1679 (s).

3-(Thiophene-3-carbonyl)-2H-chromen-2-one (26l)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), coumarin-3-carboxylic acid (60 mg, 0.315 mmol), triethylphosphite (54 µL, 0.315 mmol), 3-thienylboronic acid (61 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26l** was obtained as a clear oil (64 mg, 79% yield) after column chromatography (hexanes/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.31 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.74-7.81 (m, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.35-7.41 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 159.6, 153.2, 143.4, 139.8, 136.2, 128.6, 128.1, 127.9, 127.5, 125.5, 125.1, 118.9, 116.3. IR (neat, cm^{-1}): 1729 (m), 1662(s). HRMS (ESI) Calcd for $C_{14}H_8O_3S$ ($M+H^+$): 257.0267. Found: 257.0269.

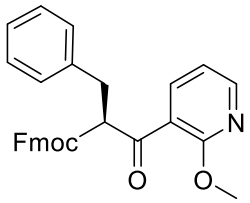
Benzyl (3-(1H-indol-3-yl)-1-oxo-1-phenylpropan-2-yl)carbamate (26m)



Prepared according to the general procedure from **13a** (75 mg, 0.315 mmol), L-Boc-phenylalanine (83 mg, 0.315 mmol), triethylphosphite (54 µL, 0.315 mmol), phenylboronic acid (57 mg, 0.473 mmol), copper (I) 3-methylsalicylate (14 mg, 0.063 mmol), and N-methylimidazole (10 µL, 0.126 mmol), **26m** was obtained as a light yellow oil (104 mg, 83% yield) after column chromatography (hexanes/EtOAc, 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.55-7.60 (m, 3H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.28 (m, 4H), 7.24 – 7.17 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 5.34 (d, *J* = 8.3 Hz, 1H), 5.10 (s, 2H), 4.81 (dt, *J* = 8.3, 6.0 Hz, 1H), 3.39 (dd, *J* = 15.0, 6.2 Hz, 1H), 3.28 (dd, *J* = 14.9, 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 193.4, 156.1, 136.7, 136.4, 133.7, 128.9, 128.7, 128.3, 127.7, 121.1, 120.0, 69.5, 65.2, 31.1. IR (neat, cm^{-1}): 3320 (w), 1675 (m). HRMS (ESI) Calcd for $C_{25}H_{22}O_3N_2$ ($M+H^+$): 399.1703. Found: 399.1705.

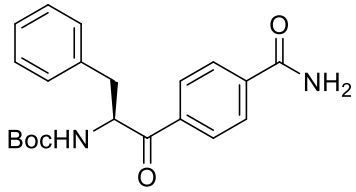
(9H-Fluoren-9-yl)methyl 2-benzyl-3-(2-methoxypyridin-3-yl)-3-oxopropanoate (26j)



In a flame-dried flask, the **13a** (75 mg, 0.315 mmol) was combined with L-Fmoc-phenylalanine (122 mg, 0.315 mmol) and triphenylphosphine (83 mg, 0.315 mmol). The solids were taken up in acetonitrile and refluxed for three hours. The reaction mixture was allowed to cool to room temperature before the solvent was evaporated *in vacuo*. Following evaporation of solvent, the solid was dissolved in DMF (2 mL) and 2-methoxy-3-(tri-n-butylstannyl)pyridine (188 mg, 0.473 mmol) and copper(I) 3-methylsalicylate (14 mg, 0.063 mmol) were added. The reaction was heated to 50 ºC and allowed to stir open to air. The reaction was monitored by TLC (hexanes/EtOAc, 3:1) and, upon completion, the EtOAc (30 mL) was added to the reaction mixture, which was washed with saturated ammonium chloride solution (1 x 20 mL), saturated sodium bicarbonate solutions (1 x 20 mL), water (1 x 20 mL), and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexanes/EtOAc, 3:1) provided the desired ketone as an oil (125 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.61-7.65 (m, 3H), 7.38-7.41 (m, 2H), 7.21-7.31 (m, 7H), 6.98 (t, *J* = 7.2 Hz, 1H),

5.26 (d, *J* = 7.2 Hz, 2H), 5.51-5.55 (m, 1H), 5.39 (s, 1H), 4.18-4.25 (m, 4H), 3.22 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.96 (dd, *J* = 14.0, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 163.5, 155.5, 147.1, 146.5, 143.1, 142.7, 137.9, 137.0, 128.6, 128.0, 126.9, 126.2, 126.0, 125.7, 124.9, 122.5, 114.1, 67.5, 57.1, 54.1, 47.1, 39.1. IR (neat, cm^{-1}): 3347 (w), 1667 (m). HRMS (ESI) Calcd for $C_{30}H_{26}O_4N_2$ ($M+H^+$): 479.1965. Found: 479.1964.

***tert*-Butyl (*S*)-(1-(4-carbamoylphenyl)-1-oxo-3-phenylpropan-2-yl)carbamate (26n)**



In a flame-dried test tube, L-Boc-phenylalanine (50 mg, 0.188 mmol), (4-carbamoylphenyl)boronic acid (46.6 mg, 0.282 mmol), **21a** (8 mg, 0.037 mmol), and CuMeSal (8 mg, 0.037 mmol) were combined in 2 mL of dry DMF. To this mixture, NMI (10 µL, 0.075 mmol) and triethylphosphite (49 µL, 0.282 mmol) were added sequentially. The reaction mixture was heated to 50 °C and stirred under dry air for 24 hours. The reaction mixture was quenched with sat. NH_4Cl solution. Ethyl acetate (20 mL) was added and washed with 1M HCl (25 mL), saturated sodium bicarbonate (25 mL), and brine (25 mL). The organic layer was dried over MgSO4 and concentrated. The crude product was purified by column chromatography (EtOAc:hexanes) to provide **26n** as a clear liquid (32 mg, 47 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) 8.11 (d, *J* = 7.2 Hz, 2H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.26-7.39 (m, 5H), 6.64 (bs, 1H), 6.12 (bs, 2H), 5.51-5.55 (m, 1H), 3.23 (dd, *J* = 13.6, 6 Hz, 1H), 2.95 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 168.1, 155.1, 136.5, 135.9, 134.9, 133.6, 129.5, 128.6,

128.3, 126.8, 79.7, 55.9, 39.1, 28.3. IR (neat, cm^{-1}): 3356 (w), 3221 (m), 1693 (s), 1675 (s). HRMS (ESI) Calcd for $C_{21}H_{25}O_4N_2$ ($M+H^+$): 369.1809. Found: 369.1807.

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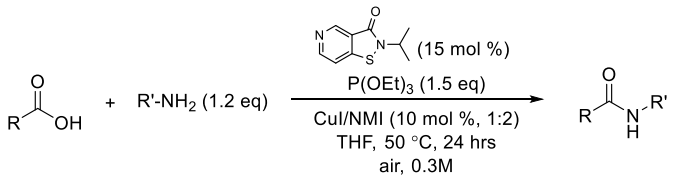
Chapter 3

Organocatalytic Oxidation-Reduction Condensation for Amide and Ester Formation

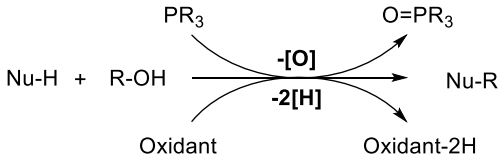
Abstract: Since their introduction over fifty years ago, oxidation-reduction condensation reactions have become popular because of their mildness and generality. Unfortunately, the use of stoichiometric amounts of oxidant and reductant that drive the reaction under such mild conditions are also one of the greatest drawbacks. The wasted materials are of concern not only because of the atom ineconomy, but also because these byproducts can be difficult to separate away from the desired products. Herein we report the use of an organocatalytic oxidant for the acylative oxidation-reduction condensation of carboxylic acids and amines to yield amides. Dioxygen derived from air plays the role of the terminal oxidant. A variety of amides were synthesized in good yields from alkyl and aryl carboxylic acids and primary and secondary amines (Scheme 3.1).



Scheme 1.1 Organocatalytic Oxidation-Reduction Condensation Reaction

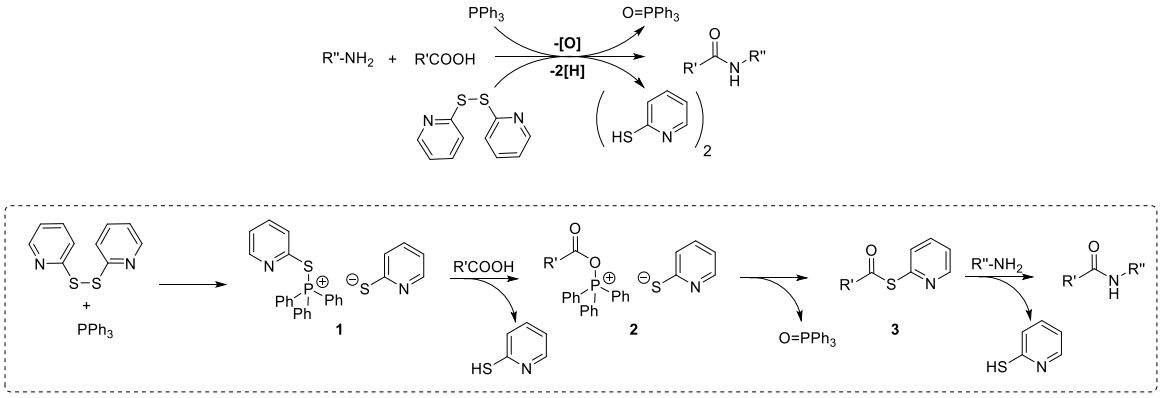
3.1 Introduction

In 1963 Mukaiyama reported the first example of an oxidation-reduction condensation (ORC) reaction.[1] The subsequent fifty years saw the rapid development of this class of chemistry into a mild, robust method utilized by researchers in academia and industry for the construction of C-O, C-N, C-S, and even C-C bonds.[2] Generally speaking, ORC reactions utilize a stoichiometric weak oxidant and reductant to condense two molecules by removing water as 2[H] and [O] (Scheme 3.2).



Scheme 3.2 General Representation of Oxidation-Reduction Condensation

Mukaiyama's seminal report described the self-condensation of carboxylic acids to form anhydrides *via* diphenyl or bis(*p*-methoxyphenyl)mercury as a hydrogen acceptor and tri-*n*-butyphosphine as the oxygen acceptor.[1] While the use of a stoichiometric organomercury reagent makes the chemistry far from practical by today's standards, the concept was laid out for further development. In 1970, Mukaiyama reported the condensation of amino acids to form dipeptides in good yield and enantiopurity.[3] Rather than stoichiometric diphenyl mercury as a hydrogen acceptor, this reaction employed 2,2'-dipyridyldisulfide as the oxidant. Depicted in Scheme 3.3, reaction between the 2,2'-dipyridyldisulfide and triphenylphosphine generates an activated phosphonium intermediate **1** that further reacts with the carboxylic acid. The activated phosphonium intermediate **2** can either react directly with amine to generate an amide or with thiolate to generate thiol ester **3**. Importantly, the thiol ester generated from the reaction also reacts smoothly with amines to yield amides.



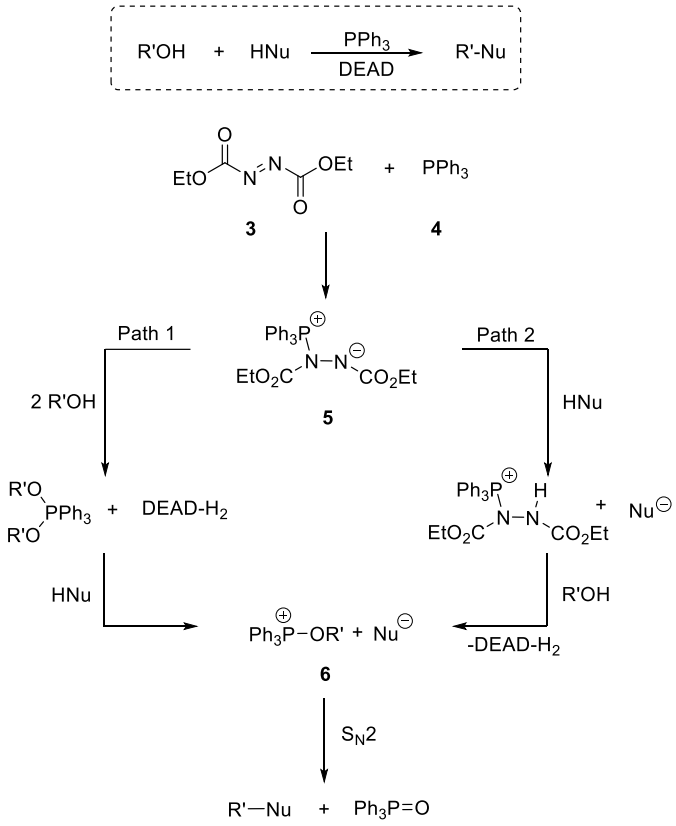
Scheme 3.3 Mukaiyama Redox Dehydration of Carboxylic Acids and Amines

The generality of the oxidation-reduction-condensation reaction was demonstrated by Corey who developed a method for the generation of macrolactones from 2,2'-diphenyldisulfide, a hydroxycarboxylic acid, and triphenylphosphine.[4] Corey then utilized the reaction in the total synthesis of important macrocyclic compounds such as erythronolide B,[5] vermiculine,[6] and enterobactin.[7]

While 2,2'-dipyridyldisulfide performs well as a stoichiometric oxidant in the amidation of carboxylic acids and in macrolactonization reactions, a number of other reagents have also been effectively utilized as oxidants in ORC reactions. For example, quinones[8-9], diazodicarboxylates[10-12], and sulfenamides[13-14] have all been used as reagents for redox condensation. Arguably the most famous of these are the diazodicarboxylates used in the Mitsunobu reaction.

The Mitsunobu reaction, reported initially in 1967 by Oyo Mitsunobu, is an ORC reaction that couples an alcohol and pronucleophile (such as a carboxylic acid), mediated by the reaction of a trialkyl- or triarylphosphine and a diazodicarboxylate, commonly diethylazodicarboxylate (DEAD).[10-12] Scheme 3.4 shows the mechanism of the Mitsunobu reaction, which works in a similar fashion to the Mukaiyama redox dehydration. Initial reaction between triphenylphosphine and DEAD produces the betaine intermediate **5**, which can then proceed through two differing pathways. Path 1 depicted in Scheme 3.3 shows reaction of betaine **5** with two molecules of alcohol, yielding the reduced hydrazine byproduct from DEAD. Further reaction with the pronucleophile generates alkoxyphosphonium intermediate **6**. The second path illustrates deprotonation of the pronucleophile by the betaine intermediate **5**, followed by reaction of the alcohol and phosphonium intermediate to produce the alkoxyphosphonium intermediate **6**.

Finally, reaction of the nucleophile with the alkoxyphosphonium gives the dehydrated product and triphenylphosphine oxide.[11]



Scheme 3.4 Mechanism of the Mitsunobu Reaction

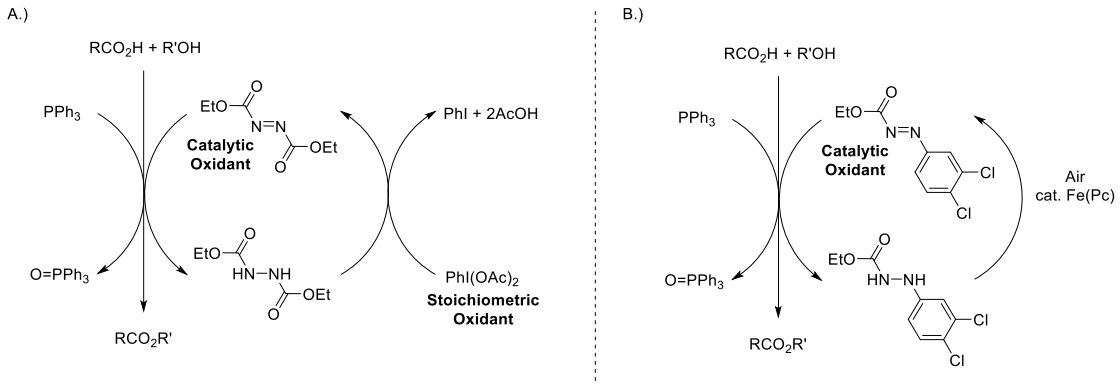
The Mitsunobu reaction has gained popularity because of its reliability, mildness, and stereospecificity. While erosion of enantiopurity is noticed in certain cases, the reaction reliably delivers the Walden inversion product from the starting alcohol.[11] However, despite these advantages, the Mitsunobu reaction suffers from two major drawbacks: the range of pronucleophiles that effectively participate in Mitsunobu reaction as well as the use of stoichiometric oxidant and reductant to drive the condensation.

The first drawback is explained by an inspection of the reaction mechanism depicted in Scheme 3.4, which shows that pronucleophiles introduced into the reaction must be deprotonated to efficiently take part in the Mitsunobu reaction. In general, only reagents with a pKa of less than 14-15 function as pronucleophiles.[12] Reagents with higher pKa's cannot be sufficiently deprotonated at equilibrium by the betaine intermediate to form an active nucleophile. The second major drawback of the Mitsunobu reaction is the stoichiometric quantities of the oxidant and reductant that are required to mediate the reaction. These reagents can also be toxic (e.g. DEAD), and their byproducts are notoriously difficult to separate from the desired products (e.g. triphenylphosphine oxide, DEAD-H_2).[10]

A number of attempts have been made to overcome the requirement of stoichiometric reagents used in the Mitsunobu reaction by employing either a catalytic organic oxidant or reducing agent in combination with a separate terminal oxidant or reductant. For example, in 2006 Toy introduced a modified Mitsunobu reaction in which DEAD functioned catalytically, and iodosobenzene diacetate acted as a terminal oxidant (Scheme 3.5A).[15] The reaction functioned nearly as well as reactions stoichiometric in DEAD, with the added benefit that the stoichiometric byproducts (iodobenzene and acetate) are easily removed from the reaction.

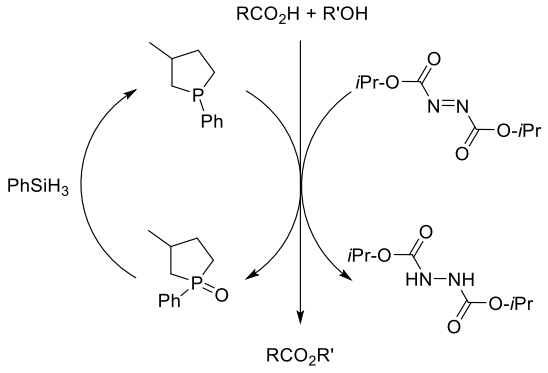
Taniguchi also reported a reaction catalytic in ethyl 2-phenylazocarboxylate as an oxidant for the Mitsunobu reaction (Scheme 3.5B).[16] In this case, O_2 in air was the terminal oxidant as the hydrazine byproduct formed from ethyl 2-phenyazocarboxylate was reoxidized by an iron (II) phthalocyanine catalyst exposed to air. Because DEAD was not oxidized effectively by the iron catalyst, a number of 2-arylhydrazine-

carboxylates were tested for efficacy as catalysts in the reaction with the 3,4-dichlorophenylhydrazine being most efficient and providing the best ratio of inversion product.



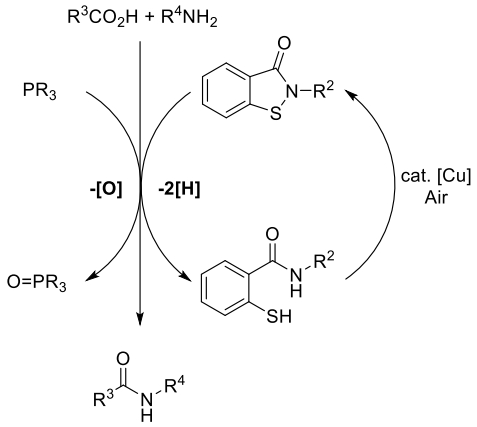
Scheme 3.5 Mitsunobu Reactions Catalytic in Azodicarboxylate

Conversely, *in situ* reduction of triorganophosphine oxide to triorganophosphine for catalytic use in the Mitsunobu reaction has only a single example listed in the literature.[17] In a patent application mainly devoted to the development of a Wittig reaction catalytic in triorganophosphine,[17] O'Brien provides one example in which the process was extended from the Wittig reaction to a Mitsunobu reaction. The reaction requires a stoichiometric amount of a silane as the terminal reductant (Scheme 3.6).



Scheme 3.6 Mitsunobu Reaction Catalytic in Triorganophosphine

While working with benzoisothiazolones (BITs), the Liebeskind laboratory envisioned the use of these organic molecules as organocatalytic oxidants in ORC reactions. BITs possess several characteristics that make them ideal candidates for ORC catalysts. For example, in the presence of tri-*n*-butylphosphine BITs react readily with carboxylic acids to form thiol esters.[18-19] Furthermore, thiol esters can be used for the generation of amides and esters (*vide supra*).[3-7] Lastly, the thiosalicylamides generated in the reaction can be gently reoxidized to the starting BIT in the presence of catalytic copper and air.[19-20] The proposed reaction sequence is depicted in Scheme 3.7.



Scheme 3.7 Proposed ORC of Carboxylic Acids and Amines Facilitated by Catalytic BIT

3.2 Results

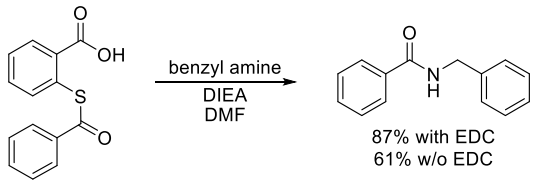
3.2.1 Stoichiometric Amidation

BIT catalysts **7a-c**, **8a-c**, **9a-c**, and **10a-c** (Figure 3.1) were constructed according to the reaction conditions reported in Chapter 2. Following their synthesis, the desired BITs were then used for the construction of a number of S-acylthiosalicylamides from carboxylic acids and triethylphosphite. While tributylphosphine has been used for the ORC of BITs and carboxylic acids,[18-19] triethylphosphite has not previously been used in this reaction.

Figure 3.1 Potential Benzisothiazolinone Organocatalysts for ORC

As discussed in Chapter 2, the use of triethylphosphite in place of triorganophosphines provides the dual benefits of increased atom economy, as well as simplified purification of byproducts. Triphenylphosphine oxide, the oxidized byproduct of the dehydrative condensation, can prove problematic during purification. On the other hand, triethylphosphate, the oxidized byproduct of triethylphosphite, can be easily removed *via* aqueous workup.[21]

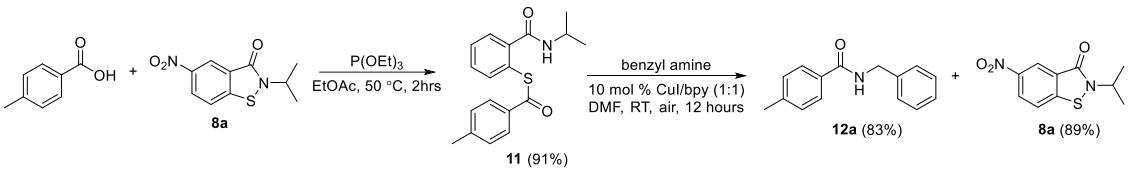
As was described in Chapter 2 of this Thesis, S-acylthiosalicylamides are generated in good yield from the condensation of various BITs and carboxylic acids mediated by triethylphosphite. With this simple route to *S*-acylthiosalicylamides, their reactivity in amide formation was tested. One reference to the reactivity of *S*-acylthiosalicylic acid derivatives with amines shows that this family of thiol esters may be uniquely suited to amidation (Scheme 3.8).[22] It was hoped that the *S*-acylthiosalicylamides would participate in a similar manner.



Scheme 3.8 Reaction of 2-(Benzoylthio)benzoic Acid with Benzyl Amine

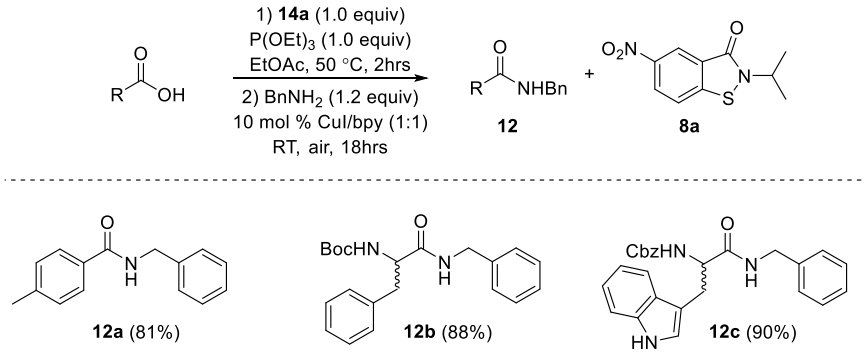
Initial reaction of a stoichiometric amount of BIT **8a**, *p*-toluic acid, and triethylphosphite produced thiol ester **23** in 91% isolated yield. Reaction of thiol ester **23**

with benzyl amine in the presence of 10 mol % copper (I) iodide/2,2'-bipyridine (1:1) and open to air successfully produced the desired amide in 83% yield and returned starting BIT **8a** in 89% yield (Scheme 3.9).



Scheme 3.9 Stoichiometric Amidation from *S*-Acylthiosalicylamide **11** with BIT Recovery

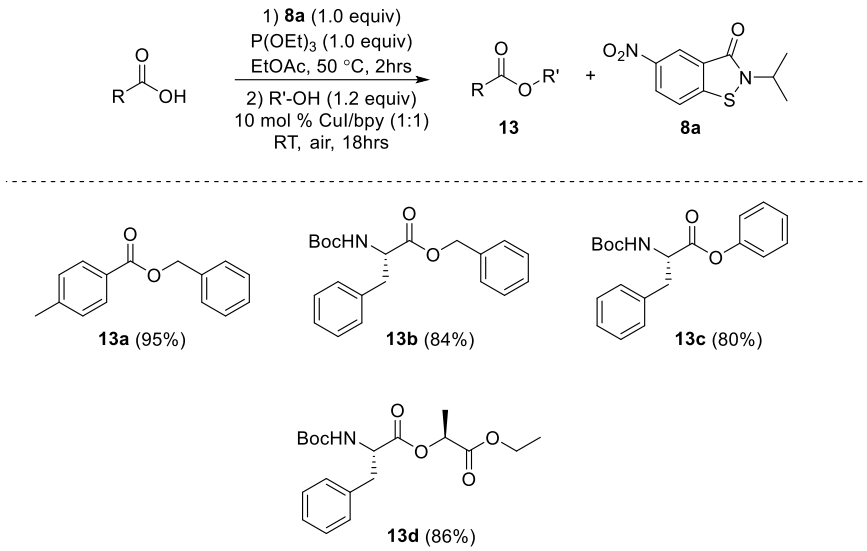
This stoichiometric amidation could also be performed without isolation of the thiol ester intermediate in a one-pot reaction. An initial triethylphosphite-based ORC reaction of BIT **8a** with the appropriate carboxylic acid in ethyl acetate for 2 hours before addition of benzyl amine and copper catalyst (Scheme 3.10) provided benzylamides **12a-c** in good yields.



Scheme 3.10 One-Pot ORC of Carboxylic Acids and Benzyl Amine

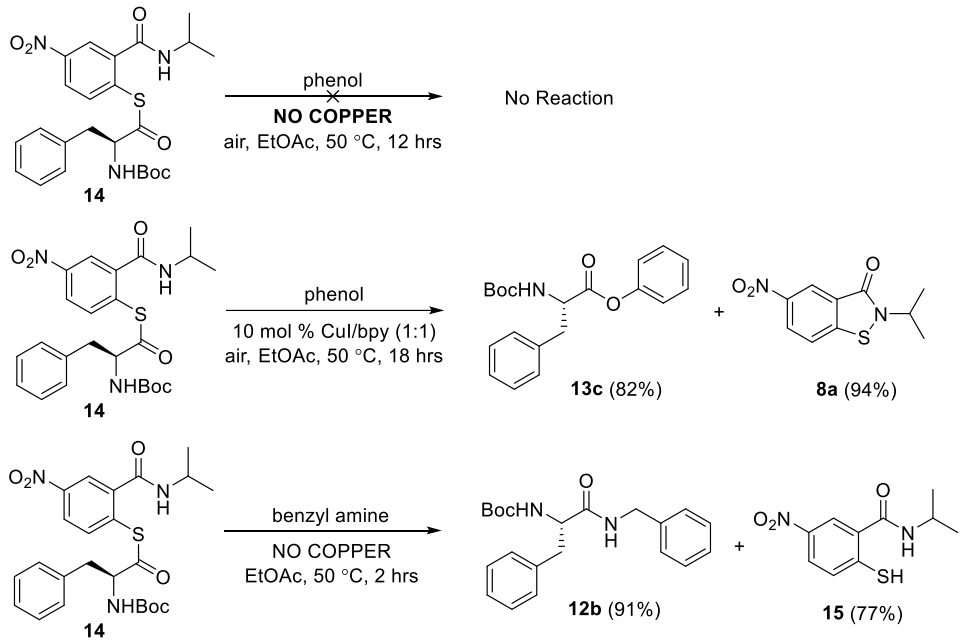
Interestingly, the one-pot stoichiometric amidation procedure could be extended to esterification. Again, ORC reaction of a carboxylic acid and BIT **8a** provided *in situ* generation of the corresponding S-acylthiosalicylamide, which in the presence of 10 mol % CuI/bpy reacted efficiently with alcohols to produce the corresponding carboxylic acid

ester. The four examples chosen show that not only can aliphatic alcohols react, but phenols can participate effectively as well (Scheme 3.11).



Scheme 3.11 Stoichiometric ORC of Carboxylic Acids and Alcohols

It is important to note that in the case of phenol as reactant, the presence of copper is necessary for esterification to occur at an acceptable rate. A test reaction in which thiol ester **14** and phenol were submitted to the reaction conditions (ethyl acetate, 50 °C) in the absence of copper showed no reaction over a 12 hour period (Scheme 3.12).



Scheme 3.12 Requirement of Copper in Stoichiometric Esterification

However, copper is not required for reaction with amines, which react quickly with thiol ester **13b** to form amide in the presence or absence of copper catalyst (Scheme 3.12, note thiol **15** is formed in the amidation reaction under the copper-free, non-oxidative conditions). It is likely that coordination of copper plays an important role in the activation of the thiol ester for reaction with phenols (Figure 3.2). Computational data has shown that the coordination of copper to *S*-acylthiosalicylamides can increase the electrophilicity of the thiol ester.[23]

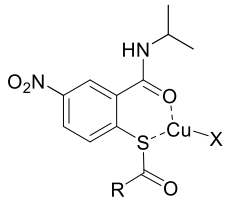
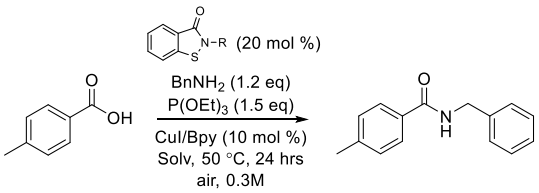


Figure 3.2 Proposed Activation of S-Acylthiosalicylamides for Stoichiometric Esterification

3.2.2 Catalytic Amidation and Esterification

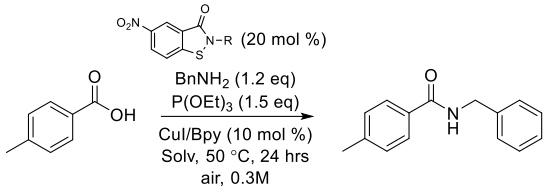
Having proven that *S*-acylthiosalicylamides react with amines and alcohols to give the corresponding amides and esters, respectively, we began testing the ability of various BITs to function as ORC catalysts (Table 3.1). Beginning with **7a-c** (Figure 3.1), 20 mol % of benzoisothiazole was combined with carboxylic acid, triethylphosphite, amine, and copper catalyst. Toluene, DMF, and ethyl acetate were each tested as solvents for each individual BIT. BIT **7a** showed little activity of catalysis in any solvent with 10 mol % copper (I) iodide/2,2'-bipyridine present to facilitate the aerobic oxidation of thiol to BIT. BIT **7b** showed slightly higher activity in each of the solvents under identical reaction conditions when compared to **7a**, but still gave only a moderate yield of the desired amide. By moving to the more electron deficient 4-nitrobenzoisothiazolones **8a-c** (Figure 3.1) amide yields were improved. In fact, when used at 20 mol % loading, BIT **8c** provided an 85% yield of amide when run in toluene at 50 °C.

Table 3.1 Catalytic Amidation Optimization: BIT



Solvent	**7a** R = *i*-Pr	**7b** R = Phenyl	**7c** R = 2,6-dimethylphenyl
toluene	None	47%	65%
DMF	41%	73%	71%
EtOAc	33%	67%	77%

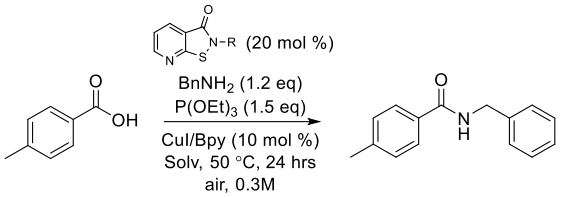
Table 3.2 Catalytic Amidation Optimization: BIT



	8a	**8b**	**8c**
Solvent	R = *i*-Pr	R = Phenyl	R = 2,6-dimethylphenyl
Toluene	72%	77%	85%
DMF	78%	74%	76%
EtOAc	71%	72%	81%

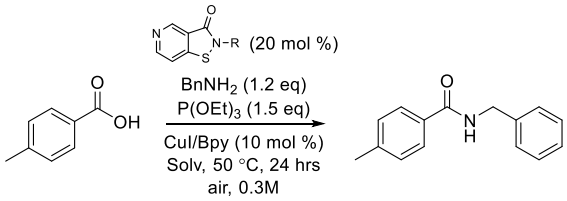
While BIT **8c** showed promise as an ORC catalyst, 2-pyridyl BITs **9a-c** and 4-pyridyl BITs **10a-c** (Figure 3.1) were tested in order to determine the effect of the heteroaromatic core on the activity of BIT. With these BITs as catalysts, the yields of the desired amide ranged from good to moderate at 50 ºC, again using 10 mol % of copper (I) iodide/2,2'-bipyridine to facilitate the reoxidation of BIT under aerobic conditions. Of the pyridine derived BITs, 4-pyridyl BIT **10a** (R = *i*Pr) showed the most aptitude as an oxidation-reduction condensation catalyst. Although the overall difference in yield of **10a** and **8c** were insignificant, **10a** was taken forward for further testing because of its simple extractive removal during acidic aqueous workup.

Table 3.3 Catalytic Amidation Optimization: BIT



	9a	**9b**	**9c**
Solvent	R = *i*-Pr	R = Phenyl	R = 2,6-dimethylphenyl
Toluene	80%	72%	79%
DMF	71%	57%	68%
EtOAc	77%	64%	73%

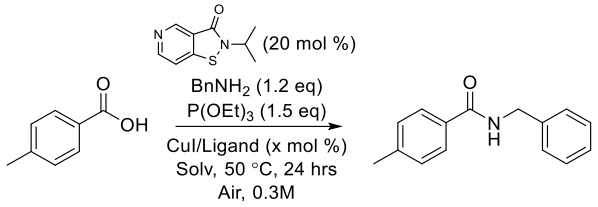
Table 3.4 Catalytic Amidation Optimization: BIT



	10a	**10b**	**10c**
Solvent	R = *i*-Pr	R = Phenyl	R = 2,6-dimethylphenyl
Toluene	86%	75%	77%
DMF	83%	60%	61%
EtOAc	79%	68%	72%

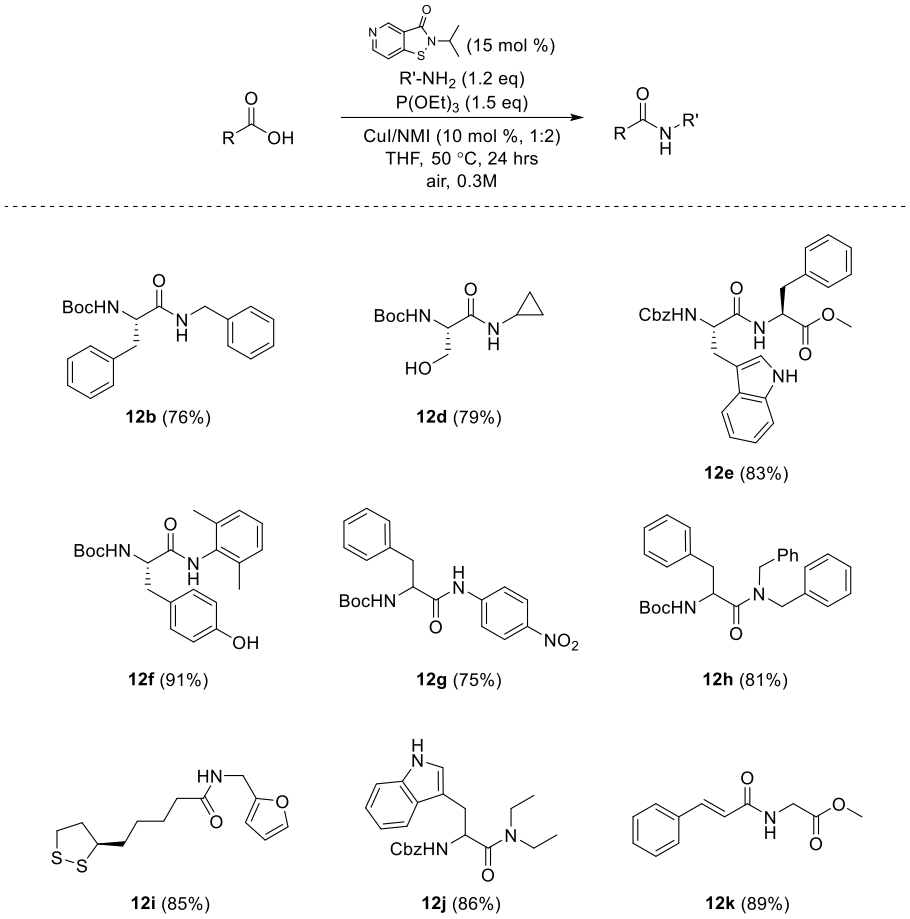
With BIT **10a** chosen for further testing, stoichiometries of BIT and copper were varied as were the solvents as well as the ligands used on copper (Table 3.5). Ideal loadings of BIT were found to be 15 mol %. Decreasing the quantity of copper catalyst in the reaction below 10 mol % was found to be detrimental to the reaction. A brief exploration of ligands showed that NMI was superior to 2,2'-bipyridine, whereas phenanthroline was considerably worse than other ligands explored, an interesting observation considering that 2,2'-bipyridine functions well. All solvents tested provided good yields of amide, however, THF provided the highest yield.

Table 3.5 Catalytic Amidation Optimization: Copper Catalyst and Solvent



Solvent	mol % BIT	mol % [Cu]	Ligand	% Yield Amide
DMF	20%	10% CuI	10% Bpy	83%
DMF	15%	10% CuI	10% Bpy	80%
DMF	10%	10% CuI	10% Bpy	76%
DMF	15%	5% CuI	5% Bpy	74%
DMF	15%	10% CuI	10% Phen	45%
DMF	15%	10% CuI	20% DABCO	73%
DMF	15%	10% CuI	20% NMI	89%
EtOAc	15%	10% CuI	20% NMI	84%
acetonitrile	15%	10% CuI	20% NMI	81%
THF	15%	10% CuI	20% NMI	91%
toluene	15%	10% CuI	20% NMI	86%

With appropriate conditions determined for catalytic ORC, a number of structurally interesting carboxylic acids and amines were used to explore the reaction scope (Scheme 3.13). Both primary and secondary amines coupled well under the reaction conditions. Aniline derivatives were successfully coupled in good yields; even electron-deficient *p*-nitroaniline was able to efficiently participate under the given reaction conditions.

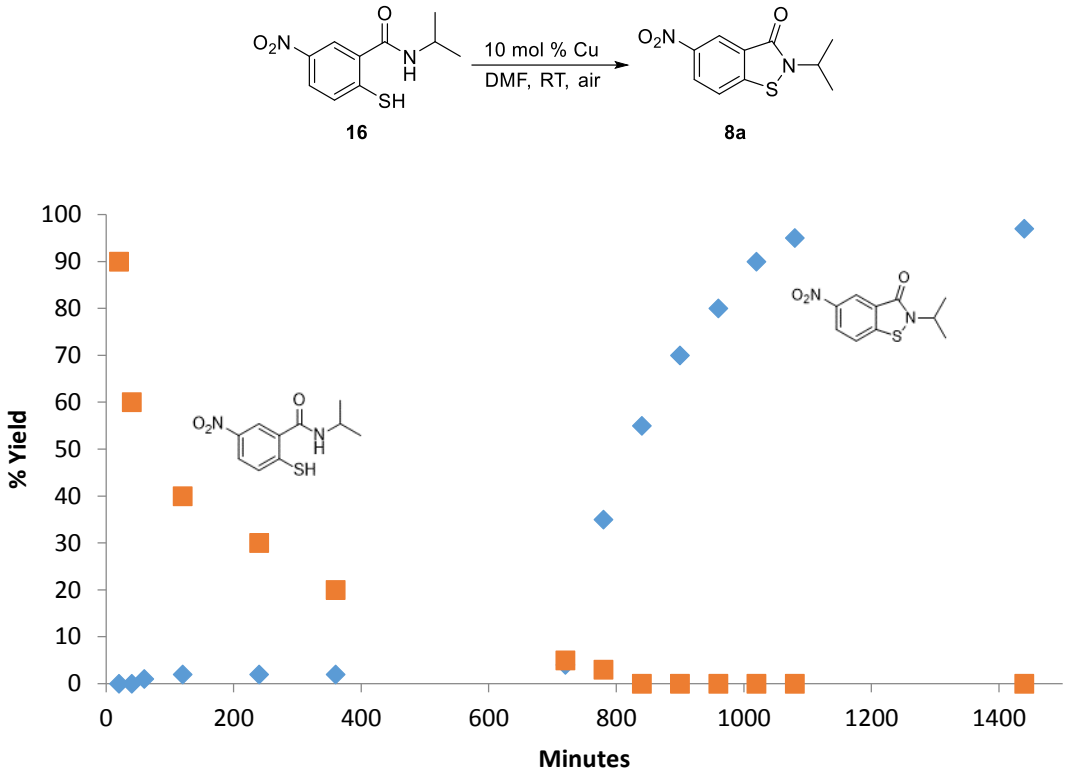


Scheme 3.13 Organocatalytic ORC Reaction Scope

3.2.3 Mechanistic Considerations: Aerobic Oxidation of Thiosalicylamide

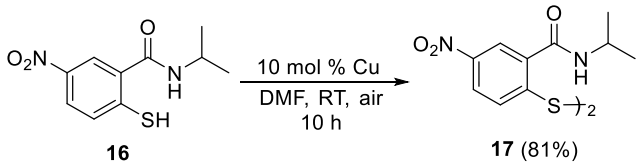
Not much is known in the literature about the mechanism of the oxidation of thiosalicylamides to benzisothiazolinones. In an attempt to understand how molecular structure affects the rate of oxidative closure of thiosalicylamides to BITs, the aerobic oxidation of thiol **16** to form **8a** was studied by HPLC. Initial studies provided an unexpected result, as the disappearance of thiol was observed over a 12-hour period, without concurrent production of the desired BIT (Scheme 3.14). It is not until the amount of thiol reaches less than ten percent of its original concentration that appearance

of BIT **8a** occurs. Over the subsequent twelve hours, a near quantitative generation of the desired BIT is observed (Scheme 3.14).



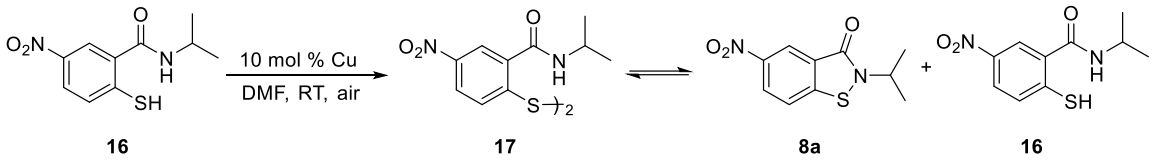
Scheme 3.14 HPLC Rate Study of Thiosalicylamide **21** Oxidation to BIT **8a**

Although not visible in the HPLC trace, it was believed that an intermediate must be forming as thiol disappeared, but before the concentration of BIT **8a** began to build. It is currently believed that the intermediate being formed during the course of the oxidation reaction is the disulfide. Gentle oxidation of thiols to disulfides has been seen utilizing a number of reagents including copper catalysts open to air.[24] Furthermore, quenching the reaction at 10 hours led to the isolation of 81% of disulfide **17** (Scheme 3.15).



Scheme 3.15 Isolation of Intermediate of Oxidation

It is interesting that less than 10% of BIT formation is seen in the study until nearly all thiol has been converted to disulfide. This observation can be explained by the fact that BIT **8a** and thiol readily react to form one molecule of disulfide.[25-26] Therefore, as disulfide reacts to generate a molecule of BIT and a molecule of thiol (Scheme 3.16), BIT reacts with excess thiol present in the system to revert back to disulfide. The concentration of BIT, therefore, cannot increase appreciably until nearly all of the thiol has been converted to disulfide.



Scheme 3.16 Equilibrium Reactions of BIT **8a** and Thiosalicylamide

Studies into the thiolate/disulfide interconversion of dinuclear copper complexes show that intricate equilibria are involved in the process.[27] The oxidation is easily affected by the ligands present, concentration, and solvents as well as the structure of the thiolate itself. Copper (II) thiolates are intimately linked with the generation of copper (I) disulfide complexes through valence electron tautomerization (Figure 3.3).

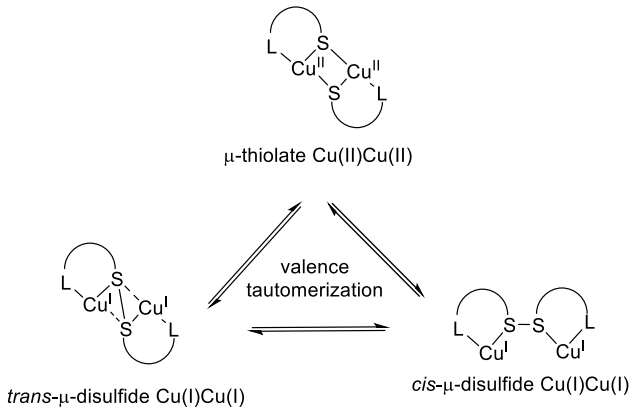


Figure 3.3 Valence Electron Tautomerization Between Copper (II) Thiolates and Copper (I) Disulfides

3.3 Conclusion

Over the past fifty years, oxidation-reduction condensation reactions have become a popular source of C-C, C-N, C-O, and C-S bonds because of the mild reaction conditions as well as reaction reliability. Despite the generality of ORC, the requirement for the use of a stoichiometric amount of oxidant and reductant to drive the reaction provides serious concerns about the overall atom economy. We have developed a novel aerobic organocatalyst that facilitates ORC of carboxylic acids and amines using air as the terminal oxidant. The benzoisothiazolone derived organocatalyst provides good yields of amides and carboxylic esters in a batch recycle, and has been shown to produce a wide variety of amides in a fully catalytic reaction.

3.4 Experimental

3.4.1 General Experimental

All reactions were performed under an atmosphere of dry air in flame-dried glassware unless otherwise stated. Solvents used as reaction media were purchased in >99% purity, dried and stored over 4Å molecular sieves (water content below 20 ppm). Ethyl acetate

(EtOAc), hexanes, and ethyl ether (Et_2O) were obtained from Sigma-Aldrich and used as purchased. 'Brine' refers to a saturated solution of sodium chloride in water. Flash chromatography was performed using Whatman 60Å 230-400 mesh silica, using compressed air as a source of positive pressure. Analytical thin-layer chromatography was performed using Merck Kieselgel $60F_{254}$ plates with UV or PMA (phosphomolybdic acid solution) for visualization.

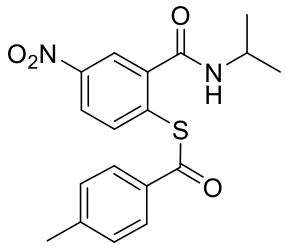
^{1}H NMR and ^{13}C NMR were performed using a Varian Inova 400 MHz NMR spectrometer at room temperature. Samples were dissolved in $CDCl_3$ and referenced at 7.26 ppm and 77.23 ppm, respectively. Signals are reported as follows: chemical shifts are reported (δ), multiplicities are indicated (s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet)), coupling constants are provided (Hz), and integrations are given. Infrared spectra were recorded using Nicolet 510 FT-IT spectrometer. Peaks are given as s (strong), m (medium), w (weak), or br (broad).

Benzisothiazolinone (BIT) derivatives were synthesized according to the experimental method reported in Chapter 2. Characterization data for each of the BITs can be found in Chapter 2, section IV.

3.4.2 General Method for the Synthesis of S-Acylthiosalicylamides

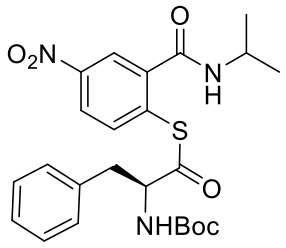
In a flame-dried flask, the desired benzisothiazolinone (1 equiv) was combined with carboxylic acid (1 equiv). The mixture was flushed with argon, taken up in 2 mL of ethyl acetate, and triethylphosphite (1 equiv) was added along with activated 4Å molecular sieves. The reaction mixture was heated at 50 ºC until completion as monitored by TLC (ethyl acetate/hexanes). After concentration *in vacuo*, purification by trituration from chloroform/hexanes (solvent/antisolvent) provided the desired thiol ester.

_S_-(2-(isopropylcarbamoyl)-4-nitrophenyl) 4-methylbenzothioate (11)



Following the general procedure, **8a** (75 mg, 0.315 mmol) was reacted with *p*-toluic acid (43 mg, 0.315 mmol) and triethylphosphite (54 µL, 0.315 mmol) to provide **11** as a white solid (102 mg, 94% yield). Mp = 173-174 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 2.5 Hz, 1H), 8.26 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 2H), 5.96 (d, *J* = 8.2 Hz, 1H), 4.23 – 4.10 (m, 1H), 2.43 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.69, 165.55, 148.74, 146.14, 144.37, 138.27, 133.23, 132.77, 129.99, 128.07, 124.52, 123.42, 42.39, 22.66, 22.06. IR (neat, cm^{-1}): 3300 (w), 1667 (m), 1634 (s). HRMS (ESI) Calcd for $C_{18}H_{18}N_2O_4S$ ($M+H^+$) ($M+H^+$): 359.1060. Found: 359.1057.

_S_-(2-(isopropylcarbamoyl)-4-nitrophenyl) (S)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanethioate (14)



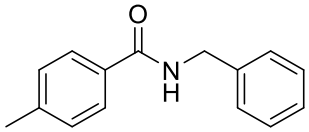
Following the general procedure, **8a** (75 mg, 0.315 mmol) was reacted with L-*N*-Boc-phenylalanine (83 mg, 0.315 mmol) and triethylphosphite (54 µL, 0.315 mmol) to provide **14** as a white solid (130 mg, 85% yield). Mp = 180°C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.4Hz, 1H), 8.24 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.54 (d, *J* = 8.4

Hz, 1H), 7.33 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.84 (d, *J* = 6.8 Hz, 1H), 4.93 (d, *J* = 8.4Hz, 1H), 4.69 (m, 1H), 4.20 (m, 1H), 3.18 (dd, *J* = 14.0, 5.2Hz, 1H), 3.04 (dd, *J* = 14.0, 8.4 Hz, 1H), 1.34 (s, 9H), 1.23 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 137.6, 136.6, 129.3, 128.7, 128.6, 127.6, 127.4, 126.9, 56.1, 43.4, 38.5, 28.2. IR (neat, cm^{-1}): 3322 (w), 1712 (w), 1687 (m), 1639 (m). HRMS (ESI) Calcd for $C_{15}H_{14}N_2O_5S$ ($M+H^+$) ($M+H^+$): 487.1777. Found: 487.1779.

3.4.3 General Procedure for the Stoichiometric Synthesis of Amides

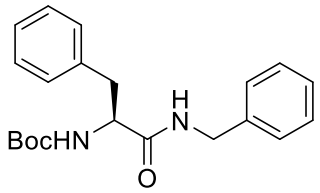
In a flame-dried flask, the desired BIT (1 equiv) was combined with carboxylic acid (1.0 equiv), and ethyl acetate was added. After the addition of triethylphosphite (1.0 equiv), 4Å molecular sieves were added and the reaction stirred at 50 ºC. Upon disappearance of BIT by TLC on silica gel (EtOAc/hexanes), the reaction mixture was cooled to room temperature and the desired amine (1.2 equiv) was added to the reaction, as well as copper (I) iodide (10 mol %) and 2,2'-bipyridine (10 mol %). Upon addition of amine an immediate color change to deep red is usually observed. The reaction was monitored by TLC for the disappearance of the intermediate thiol ester. Upon completion, the reaction mixture develops a green color. Additional ethyl acetate is added, and the mixture washed with 1M HCl, sodium bicarbonate, water, and brine. The organic layer is dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography (hexanes/ethyl acetate) provided the desired amide.

_N_-Benzyl-4-methylbenzamide (12a)[28]



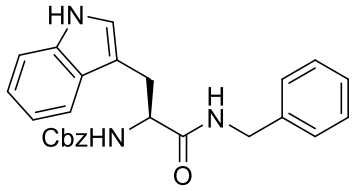
Following the general procedure, **8a** (75 mg, 0.315 mmol) was reacted with *p*-toluic acid (43 mg, 0.315 mmol) and triethylphosphite (54 µL, 0.315 mmol) in ethyl acetate for 3 hours, before cooling to room temperature and addition of benzylamine (42 µL, 0.378 mmol), copper (I) iodide (6 mg, 0.032 mmol), and 2,2'-bipyridine (5 mg, 0.032 mmol). Purification yielded **12a** as white crystalline solid (57 mg, 81% yield). Mp = 135-136°C (Lit.[28] 133-134.5°C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.33 (d, *J* = 4.8 Hz, 4H), 7.30 (m, 1H), 7.20 (d, *J* = 7.8Hz, 2H), 6.37 (s, 1H), 4.63 (d, *J* = 6Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.22, 141.94, 138.30, 131.52, 129.21, 128.74, 127.88, 127.55, 126.93, 44.06, 21.39. IR (neat, cm^{-1}): 3304 (w), 1640 (m).

***tert*-Butyl (*S*)-(1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate (12b)[29]**



Following the general procedure, **8a** (75 mg, 0.315 mmol) was reacted with L-Boc-phenylalanine (84 mg, 0.315 mmol) and triethylphosphite (54 µL, 0.315 mmol) in ethyl acetate for 3 hours, before cooling to room temperature and addition of benzylamine (42 µL, 0.378 mmol), copper (I) iodide (6 mg, 0.032 mmol), and 2,2'-bipyridine (5 mg, 0.032 mmol). Purification yielded **12a** as white crystalline solid (98 mg, 88% yield). Mp = 135-136 °C (Lit.[29] 136-137 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 8H), 7.09 (bs, 2H), 6.13 (bs, 1H), 5.07 (bs, 1H), 4.33 (d, *J* = 5.6Hz, 3H), 3.06 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 137.6, 136.6, 129.3, 128.7, 128.6, 127.6, 127.4, 126.9, 56.1, 43.4, 38.5, 28.2. IR (neat, cm^{-1}): 3328 (m),3292 (m), 1680(m), 1656 (s).

Benzyl (1-(benzylamino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (12c)[30]



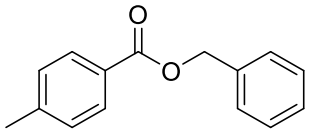
Following the general procedure, **8a** (75 mg, 0.315 mmol) was reacted with L-Cbz-tryptophan (106 mg, 0.315 mmol) and triethylphosphite (54 µL, 0.315 mmol) in ethyl acetate for 3 hours, before cooling to room temperature and addition of benzylamine (42 µL, 0.378 mmol), copper (I) iodide (6 mg, 0.032 mmol), and 2,2'-bipyridine (5 mg, 0.032 mmol). Purification yielded **12a** as white crystalline solid (121 mg, 90% yield) Mp = 151-153°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.68 (br s, 1H), 6.90-7.35 (m, 14H), 5.84 (br s, 1H), 5.48 (br s, 1H), 5.08 (s, 2H), 4.49 (br s, 1H), 4.23-4.31 (m, 2H), 3.35-3.38 (m, 1H), 3.14 (dd, *J* = 14.0, 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 156.1, 137.7, 137.6, 136.2, 136.1, 128.5, 128.2, 128.1, 127.7, 127.4, 123.2, 122.4, 120.0, 118.9, 111.2, 67.0, 55.7, 43.5 28.7. IR (neat, cm^{-1}): 3360 (w), 1651 (s).

3.4.4 General Procedure for the Stoichiometric Synthesis of Esters

In a flame-dried flask, the desired BIT (1 equiv) was combined with carboxylic acid (1.0 equiv), and ethyl acetate was added. After the addition of triethylphosphite (1.0 equiv), 4Å molecular sieves were added and the reaction stirred at 50 ºC. Upon disappearance of BIT by TLC (EtOAc/hexanes), the reaction mixture was cooled to room temperature and the desired alcohol (1.2 equiv) was added to the reaction, as well as copper (I) iodide (10 mol %) and 2,2'-bipyridine (10 mol %). Upon addition of alcohol an immediate color change to deep red is usually observed. The reaction is monitored by TLC for the disappearance of the intermediate thiol ester. Upon completion, the reaction mixture

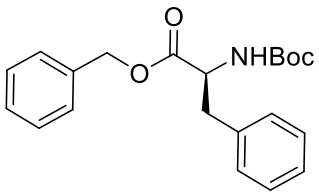
develops a green color. Additional ethyl acetate is added, and the mixture washed with sodium bicarbonate, water, and brine. The organic layer is dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexanes/ethyl acetate) provided the desired ester.

Benzyl 4-methylbenzoate (13a)[31]



Following the general procedure, BIT 8a (75 mg, 0.315 mmol) was reacted with *p*-toluic acid (43 mg, 0.315 mmol), and triethylphosphite (54 µL, 0.315 mmol). After 3 hours, benzyl alcohol (40 µL, 0.378 mmol) was added along with copper (I) iodide (6 mg, 0.032 mmol), and 2,2'-bipyridine (5 mg, 0.032 mmol). Purification by column chromatography (4:1 hexanes/EtOAc) provided **13a** as a white solid (68 mg, 95% yield). Mp = 42-43°C (Lit.[31] 45-46°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.45-7.27 (m, 7H), 5.36 (s, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 143.1, 136.8, 129.9, 128.5, 127.8, 127.1, 66.1, 22.1. IR (neat, cm^{-1}): 1719(s).

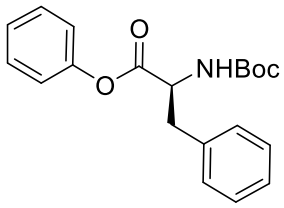
Benzyl (*S*)-(*tert*-butoxycarbonyl)phenylalaninate (13b)[32]



Following the general procedure, BIT **8a** (75 mg, 0.315 mmol) was reacted with L-Boc-phenylalanine (83 mg, 0.315 mmol), and triethylphosphite (54 µL, 0.315 mmol). After 3 hours, benzyl alcohol (40 µL, 0.378 mmol) was added along with copper (I) iodide (6

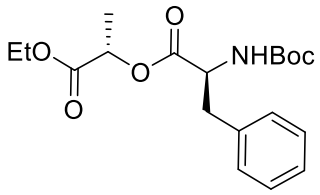
mg, 0.032 mmol), and 2,2'-bipyridine (5 mg, 0.032 mmol). Purification by column chromatography (4:1 hexanes/EtOAc) provided **13b** as a white solid (94 mg, 84% yield). Mp = 62-63°C (Lit.[32] 65°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.36 (m, 8H), 7.02-7.04 (m, 2H), 5.12, (q, *J* = 13.6 Hz, 2H), 4.96 (d, *J* = 8.4 Hz, 1H), 4.61 (q, *J* = 8.0 Hz, 1H), 3.07 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 155.0, 135.8, 135.2, 129.3, 128.5, 128.5, 128.4, 126.9, 79.9, 67.1, 54.4, 38.3, 28.3. IR (neat, cm^{-1}): 3367 (m), 1740(s), 1691(s).

Phenyl (*S*)-(*tert*-butoxycarbonyl)phenylalaninate (13c)[33]



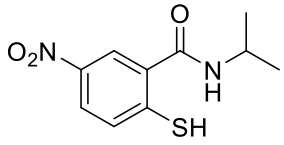
Following the general procedure, BIT **8a** (75 mg, 0.315 mmol) was reacted with L-Boc-phenylalanine (83 mg, 0.315 mmol), and triethylphosphite (54 µL, 0.315 mmol). After 3 hours, phenol (36 mg, 0.378 mmol) was added along with copper (I) iodide (6 mg, 0.032 mmol), and 2,2'-bipyridine (5 mg, 0.032 mmol). Purification by column chromatography (4:1 hexanes/EtOAc) provided **13c** as a colorless oil (86 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.40 (m 8H), 7.10 (d, *J* = 7.6 Hz, 2H), 5.05 (d, *J* = 6.4 Hz, 1H), 4.69 (m, 1H), 3.18 (dd, *J* = 14.0, 5.2Hz, 1H), 3.04 (dd, *J* = 14.0, 8.4 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 156.0, 151.2, 137.1, 129.6, 128.7, 127.5, 125.9, 125.5, 121.4, 79.2, 57.9, 36.4, 28.3. IR (neat, cm^{-1}): 3360(m), 1734(s), 1694(s).

(*S*)-1-ethoxy-1-oxopropan-2-yl (*tert*-butoxycarbonyl)-*L*-phenylalaninate (13d)



Following the general procedure, BIT **8a** (75 mg, 0.315 mmol) was reacted with L-Boc-phenylalanine (83 mg, 0.315 mmol), and triethylphosphite (54 µL, 0.315 mmol). After 3 hours, ethyl lactate (43 µL, 0.378 mmol) was added along with copper (I) iodide (6 mg, 0.032 mmol), and 2,2'-bipyridine (5 mg, 0.032 mmol). Purification by column chromatography (4:1 hexanes/EtOAc) provided **13d** as a colorless oil (99 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.12 (q, *J* = 7.2 Hz, 1H), 4.87 (d, *J* = 8.0 Hz, 1H), 4.60 (q, *J* = 5.2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.27 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.99 (dd, *J* = 14.0, 7.6Hz, 1H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.36 (s, 9H), 1.26 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 169.5, 155.9, 137.1, 128.9, 128.1,126.0, 79.8, 70.1, 61.2, 58.5, 37.1, 28.9, 17.3, 16.5. IR (neat, cm^{-1}): 3362 (w), 1731 (s). HRMS (ESI) Calcd for $C_{19}H_{27}NO_6$ ($M+H^+$): 365.1838. Found: 365.1839.

***N*-isopropyl-2-mercapto-5-nitrobenzamide (15)[34]**

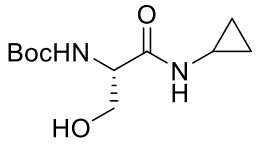


Obtained under non-oxidative conditions. Mp = 253-256 °C (Lit.[34] 252-254°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 2.4 Hz, 1H), 8.08 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 5.91 (s, 1H), 5.51 (s, 1H), 4.27 (s, 7.6 Hz, 1H), 1.30 (d, *J* = 6.4Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.11, 144.71, 132.81, 131.27, 125.03, 122.80, 42.87, 22.86. IR (neat, cm^{-1}): 3279 (m), 2971 (w), 2360 (w), 1634 (s).

3.4.5 General Procedure for Organocatalytic Amidation

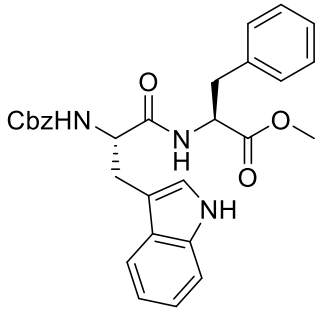
In a flame-dried test tube filled with dry air, carboxylic acid (1.0 equiv), BIT (15 mol %), and copper(I) iodide (10 mol %) were taken up in 2 mL of dry THF. Activated 4Å molecular sieves were added to the solution, followed by N-methylimidazole (20 mol %), triethylphosphite (1.5 equiv), and amine (1.2 equiv). The reaction was heated at 50 °C overnight with vigorous stirring under an atmosphere of dry air. Upon completion, the reaction was diluted with EtOAc (20 mL), and washed with 1M HCl (1 x 15 mL), sodium bicarbonate (1 x 15 mL), water (1 x 15 mL), and brine (1 x 15 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuo to yield the crude amide. Further purification by column chromatography on silica gel (EtOAc/hexanes) provided pure product.

***tert*-Butyl (*S*)-(1-(cyclopropylamino)-3-hydroxy-1-oxopropan-2-yl)carbamate (12d)**



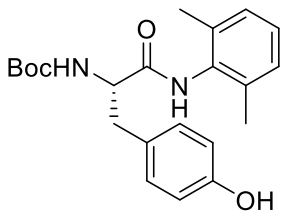
Following the general procedure, **10a** (9 mg, 0.047 mmol) was reacted with L-*N*-Boc-serine (65 mg, 0.315 mmol), triethylphosphite (81 µL, 0.473 mmol), cyclopropyl amine (27 µL, 0.378), CuI (6 mg, 0.032 mmol), and NMI (5 µL) to provide **12d** as a clear oil (61 mg, 79% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (s, 1H), 5.60 (d, *J* = 7.6 Hz, 1H), 3.88-4.21 (m, 1H), 3.46-3.72 (m, 1H), 2.68 (dq, *J* = 7.2, 3.6 Hz, 1H), 1.41 (s, 9H), 0.74 (dd, *J* = 7.1, 2.0 Hz, 2H), 0.48 (td, *J* = 3.8, 1.4Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 155.9, 79.1, 62.3, 61.7, 28.5, 25.1, 6.9. IR (neat, cm^{-1}): 3250 (br), 1675 (s). HRMS (ESI) Calcd for $C_{11}H_{20}N_2O_4$ ($M+H^+$): 245.1496. Found: 245.1494.

Methyl ((benzyloxy)carbonyl)-*L*-tryptophyl-*L*-phenylalaninate (12e)[35]



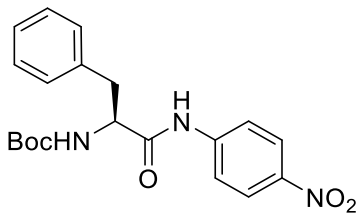
Following the general procedure, **10a** (9 mg, 0.047 mmol) was reacted with L-*N*-Cbz-tryptophan (106 mg, 0.315 mmol), triethylphosphite (81 µL, 0.473 mmol), L-phenylalanine methyl ester (82 mg, 0.378 mmol), *N*,*N*-diisopropylethylamine (82 µL, 0.473 mmol), CuI (6 mg, 0.032 mmol), and NMI (5 µL) to provide **12e** as a white solid (131 mg, 83% yield). Mp = 129-131 °C (Lit.[35] 129-131 °C) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.3 (br s, 1H), 7.63 (d, *J* = 7.7Hz, 1H), 7.27-7.38 (m, 6H), 7.06-7.19 (m, 5H), 6.93 (s, 1H), 6.81 (d, *J* = 7.3 Hz, 2H), 6.22-6.30 (m, 1H), 5.46-5.57 (m, 1H), 5.01-5.14 (m, 2H), 4.71 (dt, *J* = 7.6, 5.9 Hz, 1H), 4.51 (d, *J* = 6.2 Hz, 1H), 3.58 (s, 3H), 3.25-3.36 (m, 1H), 3.12 (dd, *J* = 14.6, 7.4 Hz, 1H), 2.91 (td, *J* = 15.3, 13. 7, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.8, 156.0, 136.1, 135.4, 129.1, 128.6, 128.5, 128.5, 128.2, 128.1, 127.4, 127.0, 123.3, 122.4, 119.9, 118.8, 111.2, 110.3, 67.0, 55.4, 53.3, 52.3, 37.7, 28.4. IR (neat, cm^{-1}): 3321 (w), 1705 (m), 1661 (s).

***tert*-Butyl (*S*)-(1-((2,6-dimethylphenyl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (12f)**



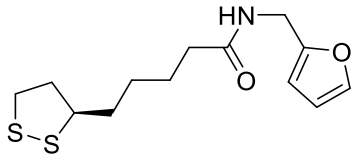
Following the general procedure, **10a** (9 mg, 0.047 mmol) was reacted with *N*-Boc-tyrosine (89 mg, 0.315 mmol), triethylphosphite (81 µL, 0.473 mmol), 2,6-dimethylaniline (47 µL, 0.378 mmol), CuI (6 mg, 0.032 mmol), and NMI (5 µL) to provide **12f** as a clear oil (110 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 7.15-7.22 (m, 3H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 7.6 Hz, 2H), 5.51 (bs, 1H), 5.08-5.11 (m, 1H), 3.41 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.16 (dd, *J* = 14.0, 7.6Hz, 1H), 2.43 (s, 6H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 155.9, 155.4, 137.4, 130.9, 130.5, 129.6, 127.9, 126.3, 117.1, 79.3, 58.6, 37.1, 28.5, 21.3. IR (neat, cm^{-1}): 3276 (br), 1659 (s). HRMS (ESI) Calcd for $C_{20}H_{28}N_2O_4$ ($M+H^+$): 385.2122. Found: 385.2120.

***tert*-Butyl (1-((4-nitrophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (12g)[36]**



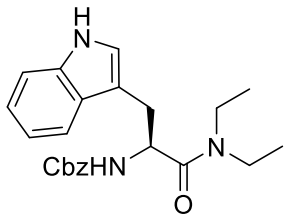
Following the general procedure, **10a** (9 mg, 0.047 mmol) was reacted with L-*N*-Boc-phenylalanine (83 mg, 0.315 mmol), triethylphosphite (81 µL, 0.473 mmol), 4-nitroaniline (52 mg, 0.378 mmol), CuI (6 mg, 0.032 mmol), and NMI (5 µL) to provide **12f** as a yellow solid (91 mg, 75% yield). Mp = 157-158 °C (Lit.[36] 158-160 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.07 (d, *J* = 8.7 Hz, 2H), 7.41-7.58 (m, 2H), 7.11-7.39 (m, 5H), 5.24 (d, *J* = 7.7 Hz, 1H), 4.55 (s, 1H), 2.92-3.34 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 160.1, 144.4, 143.1, 136.8, 128.5, 127.2, 125.7, 124.8, 120.3, 79.4, 58.9, 37.5, 28.2. IR (neat, cm^{-1}): 3286 (w), 1690 (s), 1515 (m).

(*R*)-5-(1,2-Dithiolan-3-yl)-*N*-(furan-2-ylmethyl)pentanamide (12i)[37]



Following the general procedure, **10a** (9 mg, 0.047 mmol) was reacted with *R*-lipoic acid (65 mg, 0.315 mmol), triethylphosphite (81 µL, 0.473 mmol), furfuryl amine (33 µL, 0.378 mmol), CuI (6 mg, 0.032 mmol), and NMI (5 µL) to provide **12f** as a clear oil (76 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 1.2 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.2 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 5.73, (br s, 1H), 4.42 (d, *J* = 5.6 Hz, 2H), 3.55 (p, *J* = 6.0 Hz, 1H), 3.06-3.19 (m, 2H), 2.39-2.47 (m, 1H), 2.19 (t, *J* = 8.0 Hz, 2H), 1.84-1.92 (m, 1H), 1.61-1.69 (m, 4H), 1.37-1.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 152.5, 142.2, 110.4, 107.4, 56.3, 40.2, 38.4, 36.4, 36.3, 34.6, 28.8, 25.2. IR (neat, cm^{-1}): 1660 (m).

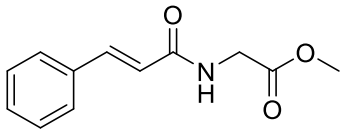
Benzyl (1-(diethylamino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (12j)[38]



Following the general procedure, **10a** (9 mg, 0.047 mmol) was reacted with L-*N*-Cbz-tryptophan (106 mg, 0.315 mmol), triethylphosphite (81 µL, 0.473 mmol), diethylamine (39 µL, 0.378 mmol), CuI (6 mg, 0.032 mmol), and NMI (5 µL) to provide **12j** as a clear light yellow oil (107 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.1 (s, 1H), 7.65 (d, *J* = 7.7 Hz, 1H),. 7.41-7.27 (m, 5H), 7.05-7.20 (m, 2H), 6.98 (d, *J* = 2.4 Hz, 1H), 5.69 (d,

J = 8.8 Hz, 1H), 5.18-5.01(m, 2H), 4.91 (dt, *J* = 9.0,7.0 Hz, 1H), 3.41 (dd, *J* =13.6, 7.0Hz, 1H), 3.22-2.96 (m, 4H), 2.86 (dd, *J* = 14.9, 7.3 Hz, 1H), 1.32 (td, *J* = 7.1, 1.0 Hz, 2H), 0.96 (t, *J* = 7.1Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 156.1, 136.3, 135.8, 129.1, 127.9, 127.5, 123.4, 121.8, 119.9, 118.5, 111.2, 110.6, 66.7, 57.5, 44.1, 29.7, 18.1. IR (neat, cm^{-1}): 3265 (w), 1671 (m).

Methyl cinnamoylglycinate (12k)[39]



Following the general procedure, **10a** (9 mg, 0.047 mmol) was reacted with cinnamic acid (47 mg, 0.315 mmol), triethylphosphite (81 µL, 0.473 mmol), glycine methyl ester (47 mg, 0.378 mmol), *N*,*N*-diisopropylethylamine (82 µL, 0.473 mmol), CuI (6 mg, 0.032 mmol), and NMI (5 µL) to provide **12k** as a clear oil (62 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0Hz, 2H), 7.29-7.35 (m, 4H), 6.51 (br s, 1H), 6.31 (d, *J* = 15.2 Hz, 1H), 3.89 (s, 2H), 3.67(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 167.5, 141.5, 134.2, 128.9, 128.5, 127.5, 120.1, 53.1, 42.7. IR (neat, cm^{-1}): 3345 (w), 1729 (s), 1661 (s).

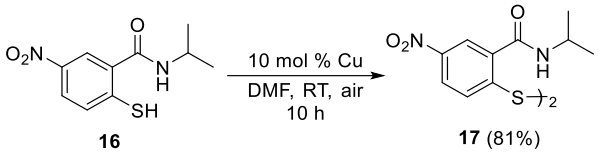
3.4.6 Procedure for Monitoring Thiol Oxidation by HPLC

16 **8a**

Thiol **16** (100 mg, 0.417 mmol) was taken up in 3 mL of DMF and CuMeSal (11.2 mg, 0.042 mmol) was added to the mixture. The reaction was stirred at room temperature.

Aliquots of the reaction mixture (0.1 mL) were removed at regular intervals and filtered through 100 mg plug of Celite with 2 mL of acetonitrile. HPLC analysis revealed ratios of thiol **16** and BIT **8a**. HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.7 mL/min; T = 25 °C; Isogradient: 50 % H_2O in CH_3CN for 25 min, t_R thiol **16**= 8.25 min; t_R BIT **8a** = 15.1 min.

3.4.7 Isolation of Oxidation Intermediate



16 **17** (81%)

Thiol **16** (100 mg, 0.417 mmol) was taken up in 3 mL of DMF and CuMeSal (11.2 mg, 0.042 mmol) was added to the mixture. The reaction was stirred at room temperature for 10 hours and poured into 15 mL of water. The solid precipitate was filtered to provide **17** as a light yellow solid (81 mg, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (d, J = 7.6 Hz, 1H), 8.56 (d, J = 2.5 Hz, 1H), 8.27 (dd, J = 8.9, 2.5 Hz, 1H), 7.79 (d, J = 8.9 Hz, 1H), 4.26 – 3.96 (m, 1H), 1.19 (d, J = 6.6 Hz, 6H).. ^{13}C NMR (100 MHz, DMSO-d_6) δ . IR (neat, cm^{-1}):166.7, 144.1, 137.2, 135.1, 128.6, 126.6, 126.3. HRMS (ESI) Calcd for $C_{20}H_{22}N_4O_6S_2$ ($M+H^+$): 479.1054. Found: 479.1055.

3.5 References

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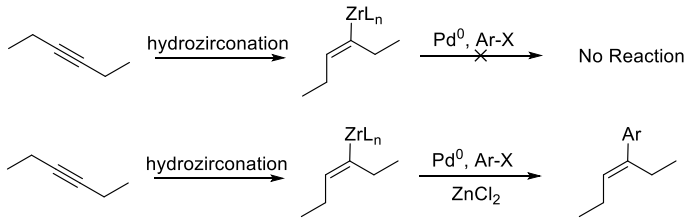
Appendix A

Zinc Thiocarboxylate-Mediated Cross-Coupling of Esters and Boronic Acids

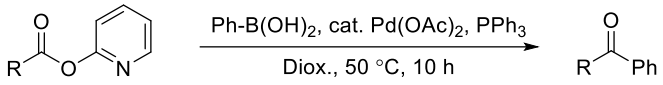
A.1 Introduction

A number of cross-coupling reactions exist in the literature that utilize Lewis acids as activating agents in the construction of carbon-carbon bonds. For example, the product of hydrozirconation of internal alkynes does not efficiently couple with aryl halides and catalytic palladium (Scheme A.1). However, upon addition of a Lewis acid ($ZnCl_2$), the transmetalation functions smoothly.[1]



Scheme A.1 Influence of Lewis Acids on Transmetalation of Zirconium to Palladium

Despite the rapid growth in the field of transition metal-mediated cross-coupling, there exist a number of substrates that do not easily undergo cross-coupling. In an attempt to expand the synthetic toolbox, we began looking into the use of Lewis acids to help mediate some of these difficult cross-couplings. One class of substrates that does not easily undergo cross-coupling is carboxylic esters. While other acyl derivatives undergo cross-coupling (acid chlorides, thiol esters, anhydrides), to date very few examples exist of carboxylic ester couplings. One notable exception is the palladium catalyzed cross-coupling of 2-pyridyl esters described by Chatani in 2004 (Scheme A.2).[2] In this particular case, the 2-pyridyl ester acts as both a directing group to aid in oxidative insertion, but also as an activated ester due to the increased leaving-group ability of the 2-hydroxypyridine.

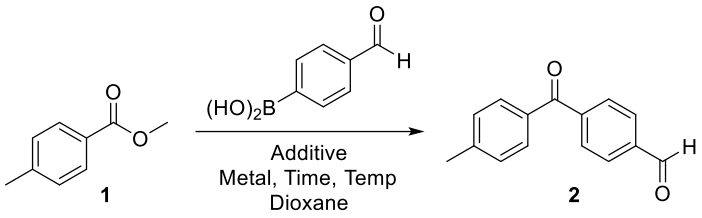


Scheme A.2 Cross-Coupling of 2-Pyridyl Esters and Boronic Acids

A.2 Results

In an attempt to activate the less reactive methyl esters, we began exploring several Lewis acids. While initial attempts to activate *p*-toluic acid methyl ester with zinc acetate proved unsuccessful, switching to zinc thioacetate provided promising results. The use of a stoichiometric amount of zinc thioacetate, when combined with *p*-toluic acid methyl ester, phenyl boronic acid, and 5 mol % of palladium tetrakistriphenylphosphine in dioxane at fifty degrees provided the desired ketone in 52% yield (Entry 1, Table A.1).

Table A.1 Optimization of *p*-Toluic Methyl Ester Cross-Coupling



Entry	Metal	Additive	Temp	Time	% Yield **2**
1	5 mol % $Pd(PPh_3)_4$	1.1 $Zn(OAc)_2$	80 °C	24 h	0%
2	5 mol % $Pd(PPh_3)_4$	1.1 $Zn(SAc)_2$	80 °C	24 h	52%
3	None	1.1 $Zn(SAc)_2$	80 °C	24 h	0%
4	5 mol % $Pd(PPh_3)_4$	None	80 °C	24 h	0%
5	5 mol % $Pd(PPh_3)_4$	1.1 $Zn(SAc)_2$	80 °C	72 h	49%
6	5 mol % $Pd(PPh_3)_4$	1.1 $Zn(SAc)_2$	100 °C	24 h	54%
7	5 mol % $Pd(PPh_3)_4$	0.5 $Zn(SAc)_2$	80 °C	24 h	14%
8	5 mol % $Pd(PPh_3)_4$	2.1 $Zn(SAc)_2$	80 °C	24 h	56%
9	5 mol % $NiCl_2$	1.1 $Zn(SAc)_2$	80 °C	24 h	0%

As shown in Table A.1, despite the attempts to optimize conditions, yields never exceeded 56%. In an attempt to understand why the reaction was not going to completion, the reaction was monitored by HPLC. As shown in Figure A.1, the reaction proceeded steadily for approximately 12 hours before levelling out near twenty hours.

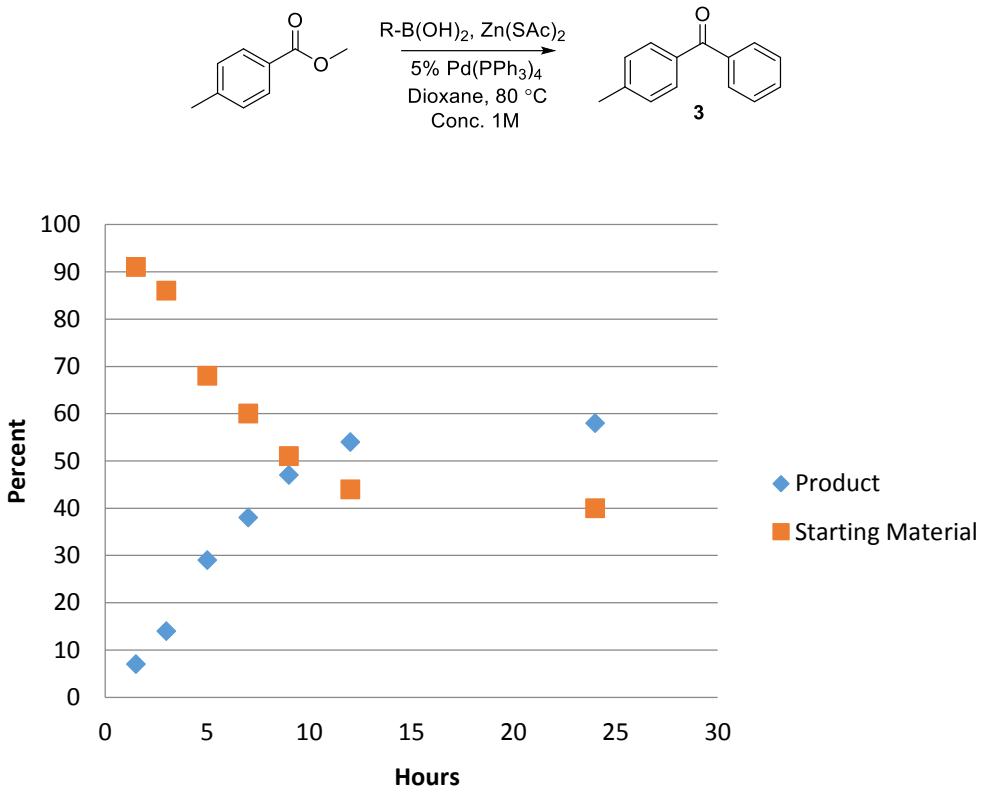


Figure A.1 Rate Study of Zinc Thioacetate Mediate Cross-Coupling

In order to understand what was limiting the progress of the reaction, several control experiments were run. To begin, the concentration of the reaction was varied from 1M to 3M in order to observe any change in rates that might occur. Unfortunately, increasing the concentration did not increase the yield of ketone or significantly increase the rate of the reaction (Figure A.2).

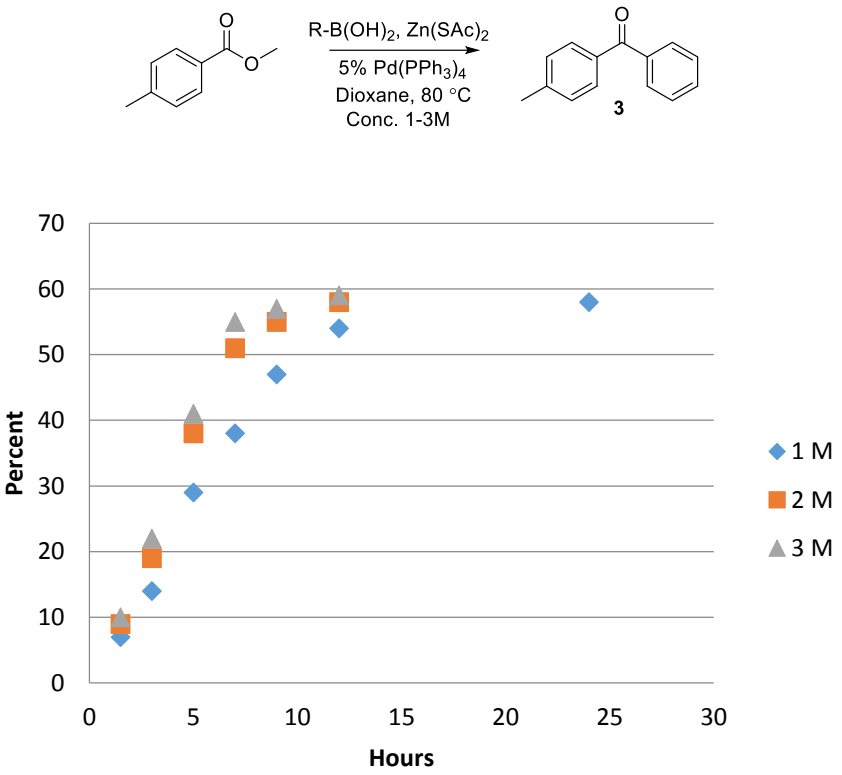


Figure A.2 Effect of Concentration on Reaction Rate

Following the variation in concentration, the stoichiometry of palladium was varied in order to observe if poisoning of the palladium catalyst was causing the decreased yield of ketone. Interestingly, when the concentration of palladium was increased from 5 mol % to 10 mol % there was, again, no appreciable change in reaction yield or reaction rate (Figure A.3).

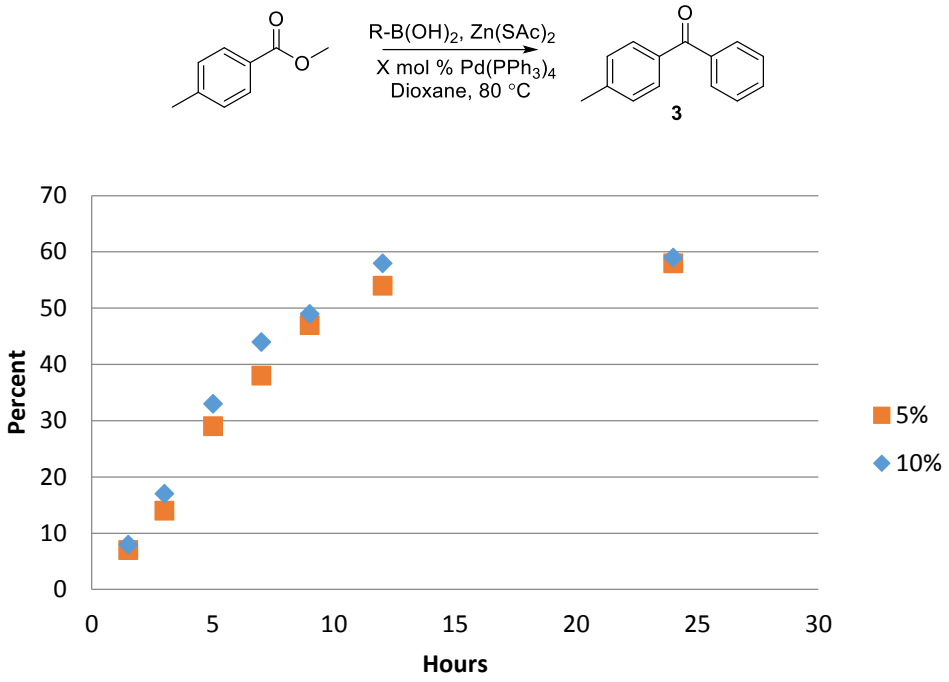


Figure A.3 Effect of Palladium Loading on Reaction Rate

Operating under the belief that the reaction was inhibited by the buildup of a product of the reaction, we began to explore exactly which of the products might be preventing the reaction. The first product to consider was the ketone itself. As the reaction proceeds, the buildup of ketone could inhibit the reaction if the coordination of zinc thioacetate to ketone was preferable to coordination with *p*-toluic acid methyl ester. In order to test if ketone could inhibit the reaction, the cross-coupling was run under normal conditions until, at 5 hours, the reaction was doped with 1 equivalent of ketone. Figure A.4 shows how the reaction rate decreases in comparison to the control reaction.

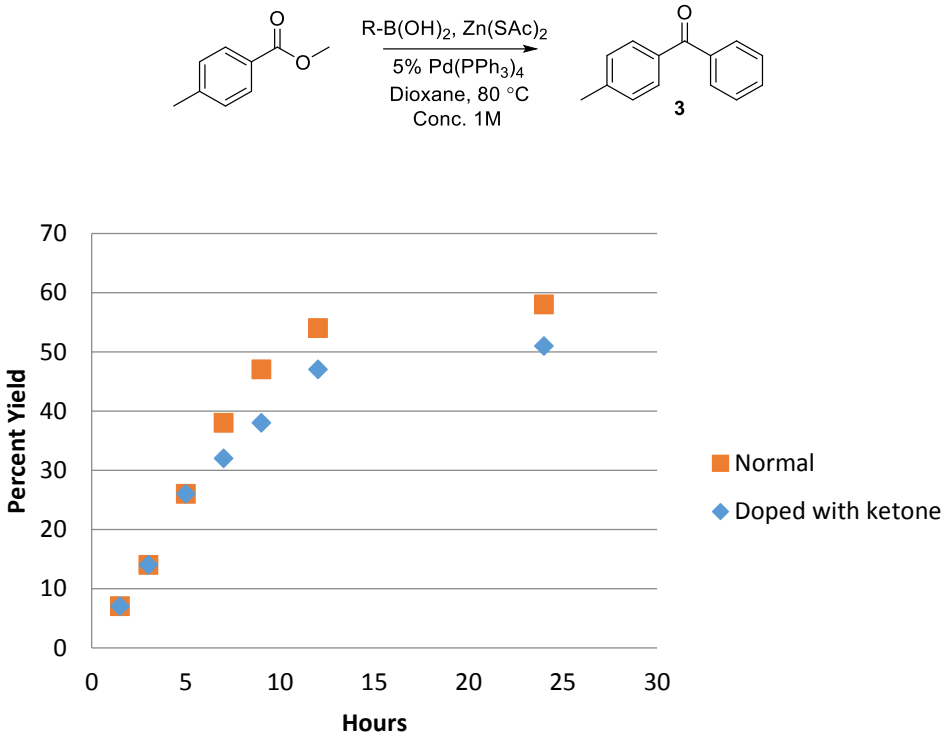


Figure A.4 Reaction Inhibition Upon Addition of Ketone

Although the reaction rate does appear to decrease slightly upon the addition of ketone, there are additional products that might also inhibit the reaction. For example, as the reaction proceeds, the possibility of the buildup of zinc methoxide could affect the ability of the zinc to act as a Lewis acid. In fact, this hypothesis is confirmed when the reaction is doped with one equivalent of zinc methoxide after five hours (Figure A.5). A dramatic decrease in reaction rate is observed and, in this particular case, the reaction yield does not exceed 35% (as compared to 54% under non-doped conditions.

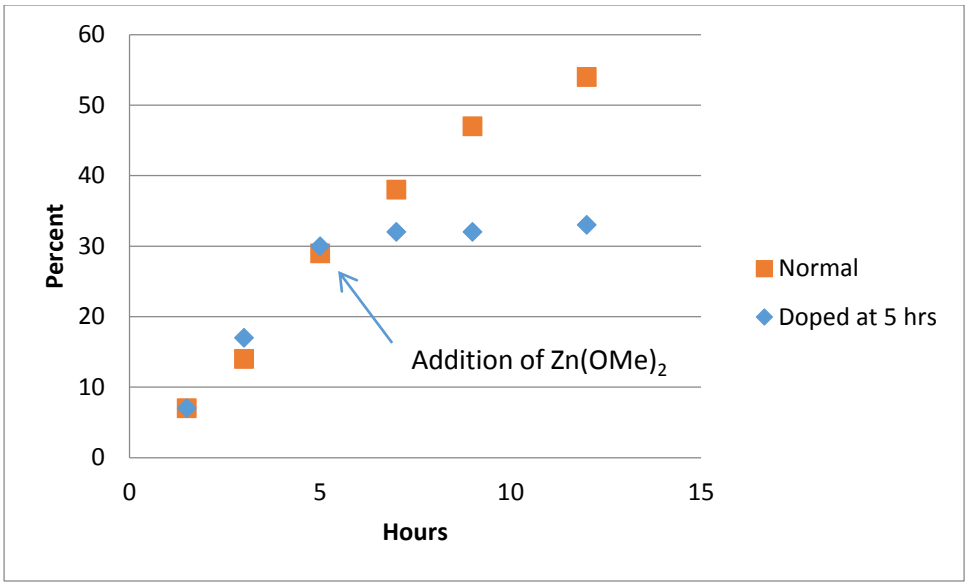


Figure A.5 Effect of Zinc Methoxide on Reaction Rate.

Despite the interesting mode of activation observed in the zinc thiocarboxylate mediated cross-coupling of esters, no attempt to increase the yield of the desired ketone ever resulted in yields above 70%. This project was not pursued further.

A.3 Conclusion

A mechanistically interesting, but synthetically limited reaction was developed using zinc thioacetate to activate typically non-reactive methyl esters. Although the initial rate of reaction was promising, build-up of zinc methoxide and ketone appear to inhibit the reaction, limiting yields to approximately 60%.

A.4 Experimental

A.4.1 General Experimental

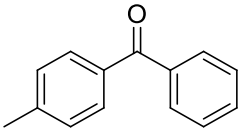
All reactions were performed under an atmosphere of dry argon in flame-dried glassware unless otherwise stated. Solvents used as reaction media were purchased in >99% purity, purged for several minutes with argon, then dried and stored over 4Å molecular sieves

(water content below 20 ppm). Ethyl acetate (EtOAc), hexanes, and ethyl ether (Et_2O) were obtained from Sigma-Aldrich and used as purchased. 'Brine' refers to a saturated solution of sodium chloride in water. Flash chromatography was performed using Whatman 60Å 230-400 mesh silica, using compressed air as a source of positive pressure. Analytical thin-layer chromatography was performed using Merck Kieselgel $60F_{254}$ plates with UV or PMA (phosphomolybdic acid solution) for visualization.

^{1}H NMR and ^{13}C NMR were performed using a Varian Inova 400 MHz NMR spectrometer at room temperature. Samples were dissolved in $CDCl_3$ and referenced at 7.26 ppm and 77.23 ppm, respectively. Signals are reported as follows: chemical shifts are reported (δ), multiplicities are indicated (s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet)), coupling constants are provided (Hz), and integrations are given. Infrared spectra were recorded using Nicolet 510 FT-IT spectrometer. Peaks are given as s (strong), m (medium), w (weak), or br (broad).

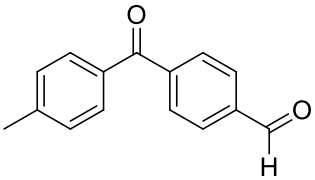
A.4.2 General Procedure for the Coupling of Carboxylic Esters with Boronic Acids: In a flame-dried test tube purged with argon, carboxylic ester (0.2 mmol, 1 equiv) was combined with zinc thioacetate (0.22 mmol, 1.1 equiv), palladium tetrakistriphenylphosphine (0.01 mmol, 0.05 equiv) and boronic acid (or organotributylstannane) (0.3 mmol, 1.5 equiv). The mixture was purged with argon and combined with 2 mL of degassed dioxane. The reaction mixtures were heated at the indicated temperature and stirred for 24 hours. The reaction mixture was concentrated and taken up in ethyl acetate (10 mL), washed with water (2 x 5 mL), and brine (1 x 5 mL), dried over magnesium sulfate, and concentrated i*n vaccuo*. Purification by flash chromatography provided the pure compounds in the indicated yields.

Phenyl(*p*-tolyl)methanone (**2**)[3]



Following the general procedure, compound *p*-toluic acid methyl ester (30 mg, 0.2 mmol) was combined with zinc thioacetate (47.4 mg, 0.22 mmol, 1.1 equiv), palladium tetrakistriphenylphosphine (11 mg, 0.01 mmol, 0.05 equiv), and pheny boronic acid (36 mg, 0.3 mmol, 1.5 equiv). The mixture was purged with argon and filled with degassed dioxane (2 mL). The reaction mixture was heated to 80 °C in a preheated oil bath and stirred for 24 hours. After work-up, purification by flash chromatography (10:1 hexanes to ethyl ether) yielded compound **4** as a white solid (22 mg, 54% yield). Mp = 57-58 °C (Lit.[3] 56.5-57 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 143.5, 138.2, 135.1, 132.4, 130.5, 130.2, 129.2, 128.4, 21.8. IR (neat, cm^{-1}) 1656 (s).

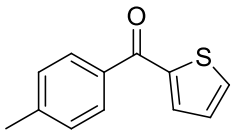
4-(4-Methylbenzoyl)benzaldehyde (**3**)[4]



Following the general procedure, compound *p*-toluic acid methyl ester (30 mg, 0.2 mmol) was combined with zinc thioacetate (47.4 mg, 0.22 mmol, 1.1 equiv), palladium tetrakistriphenylphosphine (11 mg, 0.01 mmol, 0.05 equiv), and 4-formyl boronic acid (45 mg, 0.3 mmol, 1.5 equiv). Purification by flash chromatography (10:1 hexanes to ethyl ether) yielded compound **6** as a white solid (23.3 mg, 52% yield). Mp = 87-89 °C

(Lit.[4] 87-89 °C). ^{1}H NMR (400 MHz, CDCl3) δ 10.13 (s, 1H), 8.0 (d, *J* = 7.8 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 195.5, 191.6, 144.1, 143.0, 138.3, 134.1, 130.3, 130.2, 129.5, 129.2, 21.7. IR (neat, cm^{-1}) 1700 (s), 1640(s).

Thiophene-2-yl(*p*-tolyl)methanone (**4**)[5]



Following the general procedure, compound *p*-toluic acid methyl ester (30 mg, 0.2 mmol) was combined with zinc thioacetate (47.4 mg, 0.22 mmol, 1.1 equiv), palladium tetrakistriphenylphosphine (11 mg, 0.01 mmol, 0.05 equiv), and 2-thiophene boronic acid (38 mg, 0.3 mmol, 1.5 equiv). Purification by flash chromatography (10:1 hexanes to ethyl ether) yielded compound **5** as a white solid (19.4 mg, 48% yield). Mp = 71-72 °C (Lit.[5] 74-75 °C). ^{1}H NMR (400 MHz, CDCl3) δ 7.68(d, *J* = 8.4 Hz, 2H), 7.59-7.52 (m, 2H), 7.18 (d, *J* = 7.8, 2H), 7.10-7.05 (m, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 187.7, 143.3, 142.7, 135.0, 134.1, 133.6, 129.0, 128.8, 127.5, 21.2. IR (neat, cm^{-1}) 1632 (s).

A.5 References

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Appendix B

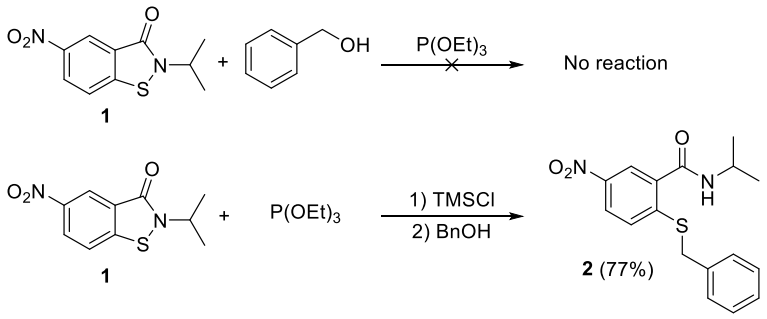
Alkylative Oxidation-Reduction Dehydration

B.1 Introduction

Chapter 2 introduced the concept of an organocatalytic oxidation-reduction condensation reaction. While the focus of Chapter 2 was on acylative transformations (amide and ester synthesis), the concept can be extended to alkylative reactions. In the interest of expanding the chemistry to cover a larger reaction scope, a number of preliminary alkylative test reactions were conducted.

B.2 Results

Unfortunately, simple mixing of benzyl alcohol with 2-isopropyl-5-nitrobenzo[*d*]isothiazol-3(*2H*)-one (BIT) **1** in the presence of triethylphosphite yielded no reaction. The absence of reaction is not surprising considering that reaction between **1** and triethylphosphite does not occur in the absence of carboxylic acid, as discovered in the acylative reaction discussed in Chapter 2 (Scheme B.1). Understanding that a proton source is necessary for acylative redox dehydration, BIT **1** and triethylphosphite were mixed in the presence of TMSCl, which could act as a proton surrogate. Fortunately, the addition of TMSCl did lead to reaction between BIT, triethylphosphite, and benzyl alcohol in DMF at 50 ºC (Scheme B.1) resulting in the synthesis of **2** in 77% yield.



Scheme B.1 Reaction of BIT **1** with Benzyl Alcohol

Triethylphosphite worked well for the ORC of benzyl alcohol and BIT **1**, however, when the benzyl alcohol was replaced by the secondary alcohol, α-methylbenzyl alcohol, a competitive thioetherification was observed (Scheme B.2). In this case it was necessary to use the more sterically hindered triisopropylphosphite as the reducing agent. The increased steric bulk of the isopropyl groups helps to reduce the undesired S-ethyl thioether product formed from nucleophilic attack on the activated phosphorous intermediate **3** (Figure B.1).

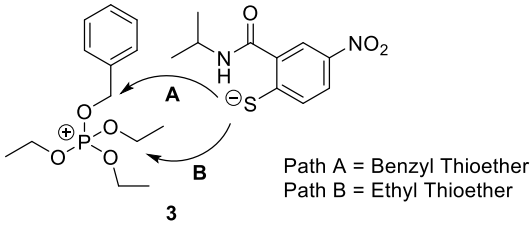
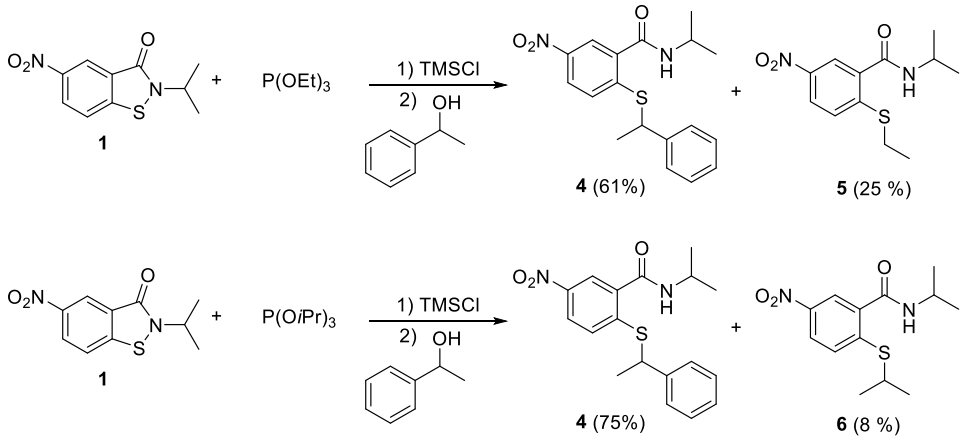


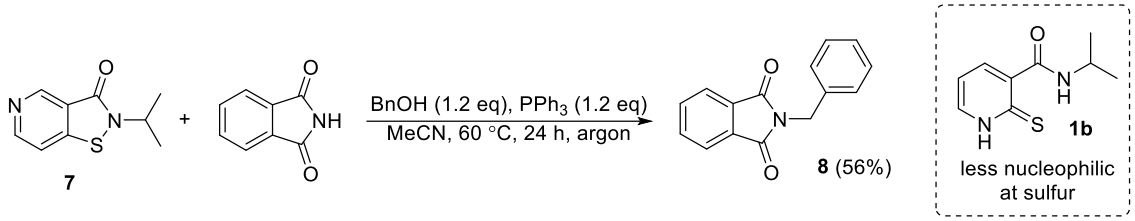
Figure B.1 Paths to Benzyl and Ethyl Thioether Products



Scheme B.2 Oxidation-Reduction Condensation of Secondary Alcohols

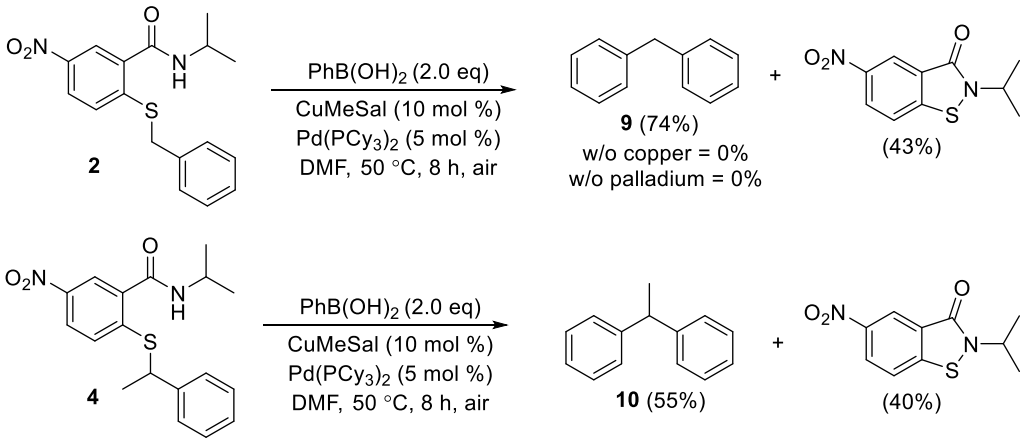
Furthermore, by altering the structure of the BIT, it proved possible to move from thioether formation to a more traditional Mitsunobu reaction. For example, Scheme B.3

shows the use of 2-pyridyl BIT **7** (which remains in the less nucleophilic thione tautomer aftter its reduction) as an oxidant for the Mitsunobu reaciton.



Scheme B.3 Mitsunobu Reaction Using BIT as Oxidant

Lastly, the benzylic products formed from oxidation-reduction condensation can be further reacted in desulfitative catalysis in the presence of co-catalytic copper(I) 3-methylsalicylate and bis(tricyclohexylphosphine)palladium(0) under aerobic conditions. This reaction is mechanistically interesting as it appears to proceed through an oxidative addition to palladium(0), even under the aerobic conditions. Control experiments show that both the copper and palladium play a crucial role in the reaction, as the absence of either catalyst from the reaction mixture results in the absence of reaction (Scheme B.4).



Scheme B.4 Aerobic Cross-Coupling of Boronic Acids and *S*-Benzyl Thiosalicylamides

B.3 Conclusion

Preliminary test reactions into the use of BITs as substrates for alkylative ORC reactions has proven successful. The condensation of BIT **1** with benzylic alcohols provides the desired thioether in good yield. When secondary alcohols are used for condensation, switching to triisopropyl phosphite is beneficial to reduce the undesired S-ethel etherification product derived from the activated phosphorous intermediate. By altering the structure of the BIT, it is possible to decrease the nucleophilicity of the thiolate so that pronucleophiles can be introduced into the system in a similar fashion to the Mitsunobu reaction. Finally, the benzylic thioethers created from alkylative ORC prove to be reasonable substrates for cross coupling with boronic acids in the presence of co-catalytic copper(I) and palladium(0).

B.4 Experimental

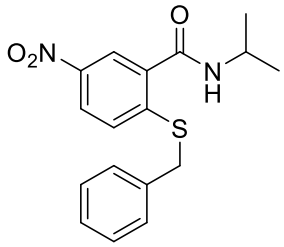
B.4.1 General Experimental

All reactions were performed under an atmosphere of dry argon in flame-dried glassware unless otherwise stated. Solvents used as reaction media were purchased in >99% purity, purged for several minutes with argon, then dried and stored over 4Å molecular sieves (water content below 20 ppm). Ethyl acetate (EtOAc), hexanes, and ethyl ether (Et_2O) were obtained from Sigma-Aldrich and used as purchased. ‘Brine’ refers to a saturated solution of sodium chloride in water. Flash chromatography was performed using Whatman 60Å 230-400 mesh silica, using compressed air as a source of positive pressure. Analytical thin-layer chromatography was performed using Merck Kieselgel $60F_{254}$ plates with UV or PMA (phosphomolybdic acid solution) for visualization.

^{1}H NMR and ^{13}C NMR were performed using a Varian Inova 400 MHz NMR spectrometer at room temperature. Samples were dissolved in $CDCl_3$ and referenced at 7.26 ppm and 77.23 ppm, respectively. Signals are reported as follows: chemical shifts are reported (δ), multiplicities are indicated (s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet)), coupling constants are provided (Hz), and integrations are given. Infrared spectra were recorded using Nicolet 510 FT-IT spectrometer. Peaks are given as s (strong), m (medium), w (weak), or br (broad).

B.4.2 Procedures

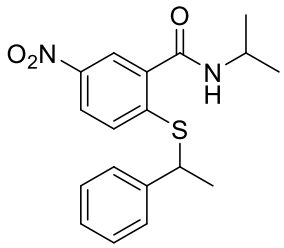
2-(benzylthio)-N-isopropyl-5-nitrobenzamide (2)



In a flame dried flask filled with argon, BIT **1** (75 mg, 0.315mmol) was dissolved in THF (2 mL), and TMS-Cl (46 µL, 0.315 mmol) as well as triethylphosphite (65 µL, 0.378 mmol) were added at room temperature. The reaction was stirred for five minutes at room temperature before the addition of benzyl alcohol (39 µL, 0.378 mmol). The reaction was stirred overnight at 50 °C. After diluting the reaction mixture with EtOAc (20 mL), the organic layer was washed with satd. sodium bicarbonate solution (2 x 15 mL) and brine (1 x 15 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to provide the crude product. The crude material was purified by column chromatography (EtOAc/hexanes, 1:4) to yield **2** as a light yellow solid (80 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.40 (d, J =

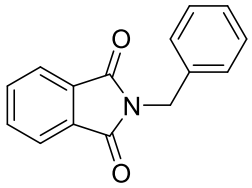
8.8 Hz, 1H), 7.24-7.34 (m, 5H), 5. 91 (br s, 1H), 4.20-4.30 (m, 1H), 4.19 (s, 2H), 1.25 (d, *J* = 6.4 Hz, 6H). IR (neat, cm^{-1}) 1652.

N-isopropyl-5-nitro-2-((1-phenylethyl)thio)benzamide (4)



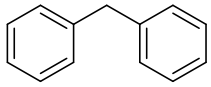
In a flame dried flask filled with argon, BIT **1** (75 mg, 0.315mmol) was dissolved in THF (2 mL), and TMS-Cl (46 µL, 0.315 mmol) as well as triethylphosphite (65 µL, 0.378 mmol) were added slowly at room temperature. The reaction was stirred for five minutes at room temperature before the addition of *sec*-phenethyl alcohol (39 µL, 0.378 mmol). The reaction was stirred overnight at 50 °C. After diluting the reaction mixture with EtOAc (20 mL), the organic layer was washed with satd. sodium bicarbonate solution (2 x 15 mL) and brine (1 x 15 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to provide a crude product. The crude material was purified by column chromatography (EtOAc/hexanes, 1:5) to yield **2** as a light yellow solid (82 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.24-7.34 (m, 5H), 5. 85 (br s, 1H), 4.20-4.31 (m, 1H), 4.33 (q, *J* = 7.6 Hz, 1H), 1.36 (d, *J* = 7.6 Hz, 3H), 1.25 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 146.2, 144.1, 137.8, 135.6, 134.9, 128.9, 128.0, 127.5, 126.3, 121.2, 44.7, 42.1, 35.2, 24.6. IR (neat, cm^{-1}) 1645.

2-Benzylisoindoline-1,3-dione (8)[1]



In a flame-dried flask filled with argon, BIT **1b** was combined with triphenylphosphine (99 mg, 0.378 mmol), phthalimide (46 mg, 0.315 mmol), and benzyl alcohol ((39 µL, 0.378 mmol). The mixture was dissolved in acetonitrile (2 mL) and stirred at 60 °C for 24 hours. After completion, the mixture was diluted with ethyl acetate (20 mL) and washed with water (3 x 15 mL) and brine (1 x 15 mL). The solvent was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude reaction mixture was purified by column chromatography (3:1 EtOAc/hexanes) to provide **8** as a white solid. Mp = 117-118 °C (Lit.[1] 119-121 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.83 (m, 2H), 7.66-7.69 (m, 2H), 7.41 (d, *J*= 7.6 Hz, 2H), 7.24-7.3 (m, 3H), 4.82 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 136.4, 133.9, 132.1, 128.6, 128.6, 127.8, 123.3, 41.6.

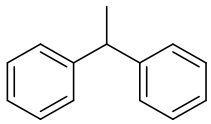
Diphenylmethane (9)[2]



In a flame-dried flask open to air, thioether **2** (105 mg, 0.315 mmol) was combined with phenyl boronic acid (56 mg, 0.378 mmol), CuMeSal (6.7 mg, 0.032 mmol), and $Pd(PCy_3)_2$ (10.5 mg, 0.015 mmol) in DMF (2 mL). The solution was heated at 50 °C overnight under an atmosphere of dry air. Upon completion, the mixture was diluted with EtOAc (20 mL), washed with satd. sodium bicarbonate (1 x 15 mL), water (2 x 15 mL), and brine (1 x 15 mL). The organic layer was dried over magnesium sulfate, filtered and

concentrated *in vacuo*. The crude product was purified by column chromatography (hexanes) to provide **9** as an oil (41 mg, 77% yield), with BIT recoverd in 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.37 (m, 2H), 7.26-7.30 (m, 3H), 3.91 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 129.2, 128.3, 126.4, 41.5.

Ethane-1,1-diyldibenzene (10)[3]



In a flame-dried flask open to air, thioether **3** (108 mg, 0.315 mmol) was combined with phenyl boronic acid (56 mg, 0.378 mmol), CuMeSal (6.7 mg, 0.032 mmol), and $Pd(PCy_3)_2$ (10.5 mg, 0.015 mmol) in DMF (2 mL). The solution was heated at 50 °C overnight under an atmosphere of dry air. Upon completion, the mixture was diluted with EtOAc (20 mL), washed with satd. sodium bicarbonate (1 x 15 mL), water (2 x 15 mL), and brine (1 x 15 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (hexanes) to provide **9** as a colorless oil (31 mg, 55% yield), with BIT recovered in 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.40 (m, 4H), 7.25-7.31 (m, 6H), 4.22 (q, J = 7.6 Hz, 1H), 1.35 (d, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 129.0, 127.9, 126.4, 45.0, 22.1.

B.5 References

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