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Janette Villalobos

Aerobic, Metal Mediated Ketone Synthesis from Thiol Esters and Boronic Acids

By

Janette M. Villalobos

B.S. University of Florida

Advisor: Dr. Lanny S. Liebeskind

Department of Chemistry

Approved for the Department

_____

Dr. Lanny S. Liebeskind, Advisor

_____

Dr. Albert Padwa, Committee member

_____

Dr. Simon Blakey, Committee member

Accepted:

_____

Lisa A. Tedesco, Ph.D.

Dean of Graduate School

_____

Date

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An Abstract of

A dissertation submitted to the Faculty of the

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Abstract

Thiol esters derived from *N*-substituted and aryl substituted thiosalicylamides were synthesized. Their aerobic coupling with one equivalent of aryl boronic acids to give ketones was investigated in the presence of catalytic palladium(0) bis(tricyclohexylphosphine) and copper(I) methyl salicylate. The byproducts of the reaction were found to be mixtures *S*-arylation of the thiosalicylamide pendant and ring closure of the thiosalicylamide to form a benzoisothiazolinone.

A novel, aerobic ketone synthesis from simple and complex thiol esters and commercially available boronic acids catalyzed by copper (I) methyl salicylate (CuMeSal) is reported. The reaction is highly chemoselective for thiol esters containing an *N*-*tert*-butyl or *N*-*iso*-propyl -2-mercaptobenzamide pendant. The reaction occurs under very mild reaction conditions (ambient temperature, aerobic, neutral conditions, and in the presence of a broad range of functional groups). The application of this chemistry may prove useful for selective carbon-carbon bond forming reactions on complex biomolecules. Thiol esters bearing *ortho*-chelating groups that did not react with copper alone were found to undergo cross-coupling with catalytic amounts of added $Pd(PCy_3)_2$.

A new ketone synthesis from simple thiol esters and organic halides using copper (I) carboxylates is reported. The reaction requires the use of thiol esters containing an N-isopropyl -2-mercaptobenzamide pendant. The reaction occurs under mild reaction conditions (ambient temperature, neutral conditions, under argon). A preliminary study of the reaction is presented.

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Dedicated to my mother Deanna, my aunt Liz, and my grandmother Martha - my heroines.

And to my father, Miguel and my little brother, Mig.

With their love, support and humor, I can do anything.

LISTING OF ABBREVIATIONS

app	apparent
Ar	aryl
Bpy	2,2'-bipyridine
Bn	benzyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoate
^{o}C	degrees Celsius
CuMeSal	copper(I) methyl salicylate
CuTC	copper(I) thiophene carboxylate
calcd	calculated
cm^{-1}	wavenumber unit
Cy	cyclohexyl
δ	chemical shilft (in ppm for NMR)
d	doublet
dba	dibenzylideneacetone
DMF	dimethylformamide
DMA	dimethylacetamide
DMAP	dimethylaminopyridine
DMSO	dimethylsulfoxide
equiv.	equivalents
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
Hex	hexane
HPLC	high pressure liquid chromatography
hrs	hour(s)
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
L	liter
M	molar
Me	methyl
mg	milligram
MHz	megahertz
ml	milliliter
mmol	millimole
mol %	mole percent
mol	mole

M.p.	melting point
N	normal
NMP	*N*-methyl pyrrolidinone
OAc	acetate
Ph	phenyl
ppm	parts per million
py	pyridine
q	quartet
s	singlet
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	toluene
UV	ultraviolet
w	weak

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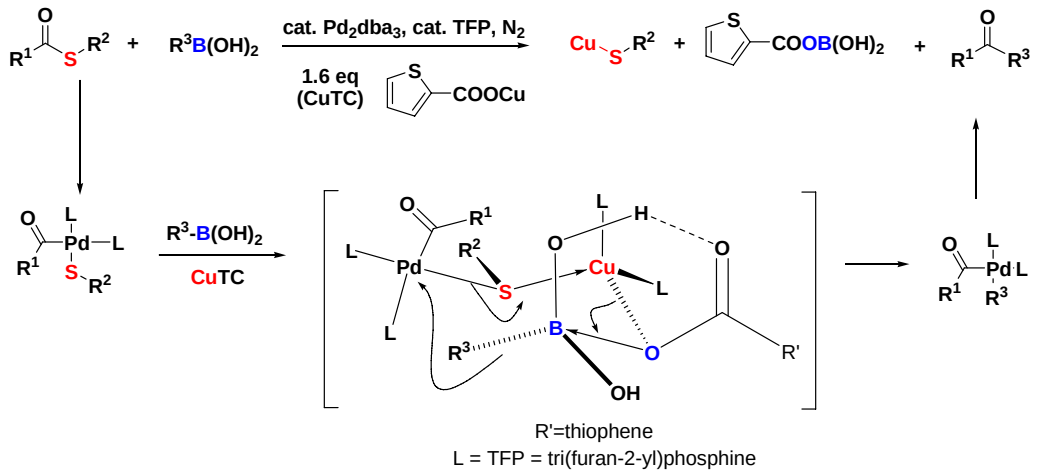
Chapter 1

Aerobic Palladium and Copper Catalyzed Coupling of Boronic Acids and Thiol Esters Derived from Thiosalicylamide: Benzoisothiazolinone Formation *versus* *S*-Arylation

Abstract: Thiol esters derived from N-substituted and aryl substituted thiosalicylamides were synthesized. Their coupling with one equivalent of aryl boronic acids to give ketones was investigated in the presence of catalytic palladium(0) bis(tricyclohexylphosphine) and copper(I) methyl salicylate and open to air. The byproducts of the reaction were found to be mixtures S-arylation of the thiosalicylamide pendant and ring closure of the thiosalicylamide to form a benzoisothiazolinone.

1.1 Introduction and Background

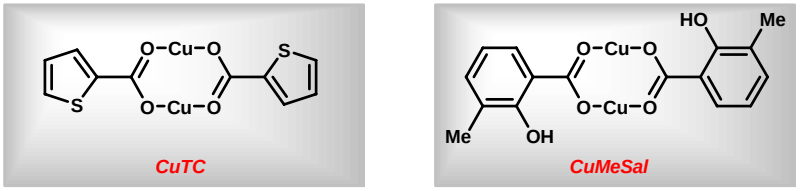
In 2000, Liebeskind and Srogl published a palladium-catalyzed coupling of thiol esters with boronic acids to give ketones (Scheme 1.1).[1] The reaction proceeds in the presence of Cu (I) thiophene-2-carboxylate (CuTC) under non-basic conditions unlike the traditional Suzuki-Miyaura cross-coupling of boronic acid and organic halides, where base is required to activate transmetallation.[2]



Scheme 1.1 Ketone Synthesis Catalyzed by Palladium with a Copper CoFactor

The Liebeskind-Srogl reaction is mediated by a stoichiometric amount of copper(I)thiophene-2-carboxylate (CuTC) (Figure 1.1).[3] CuTC and the more recently

used copper(I)methylsalicylate (CuMeSal)[4] are air stable copper carboxylates and are easily prepared on large scale.

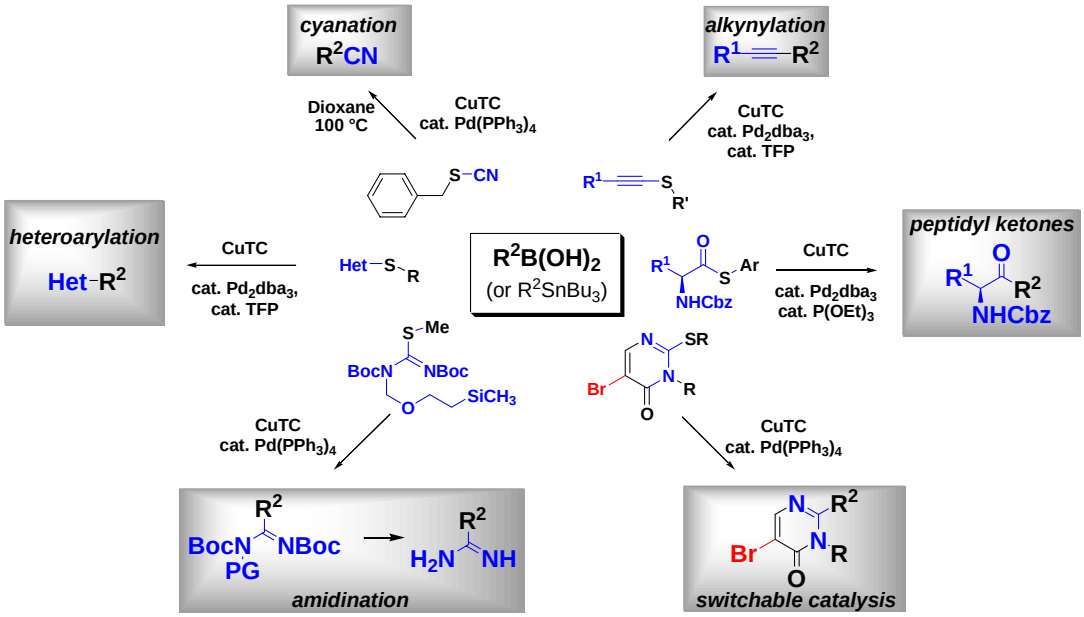


Cu(I) thiophene-2-carboxylate Cu(I) 3-methylsalicylate

Figure 1.1 Structures of CuTC and CuMeSal

Scheme 1.1 represents the transmetallation as proceeding through a six membered ring mechanism facilitated by the additive copper carboxylate. The requirement for a full equivalent of Cu(I) carboxylate is two-fold: While the Cu(I) ion kinetically labilizes the Pd–SR bond of the catalytic intermediate increasing its electrophilicity, it also ends up paired with the thiolate in a thermodynamically strong Cu-SR bond (Scheme 1.1). At the same time, a full equivalent of the borophilic carboxylate counter-ion is required to fully balance the equation and drive the $–B(OH)_2$ moiety to a $RC(O)O-B(OH)_2$ thermodynamic sink.

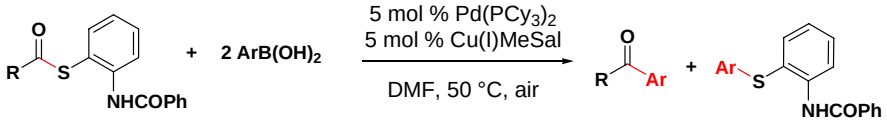
This reaction has been extended to a number of substrates (alkynes[4], α-amino ketones[5], heteroaromatics[6], aryl and heteroaryl amidines[7], functionalized pyrimidinones[8], and cyanates[9] (Scheme 1.2).



Scheme 1.2 Extensions of Liebeskind-Srogl Reaction

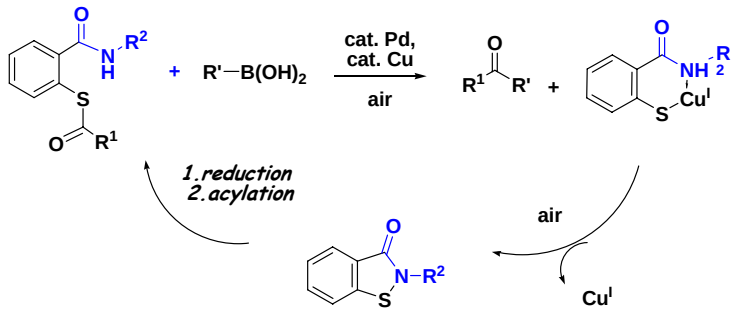
In a complete catalytic system, the inactive copper thiolate, Cu-SR, produced in the reaction must be reactivated to a copper oxygenate, Cu-OC(O)R or Cu-OR. Therefore, for copper to be recycled, sulfur must be scavenged and converted into a weaker ligand for copper while an oxygenate counter-ion is regenerated for pairing with boron to fully balance the equation.

Dr. Jiri Srogl discovered that the incorporation of an *o*-amidophenyl thiolate led to catalysis by palladium *and* copper (Scheme 1.3). In the overall process, catalysis was achieved by arylating the thiolate with excess boronic acid and an oxygenate counter ion for boron was generated by opening the reaction to air. However, the reaction required at least two equivalents of the aryl boronic acid to complete the reaction, one equivalent for the ketone and one equivalent for *S*-arylation.



Scheme 1.3 Aerobic Ketone Synthesis

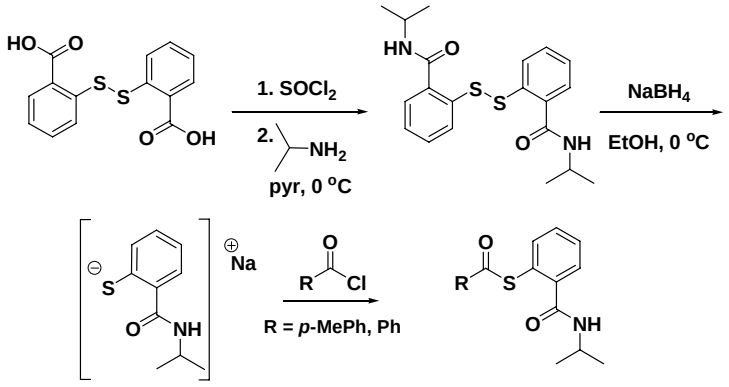
Thiol esters derived from thiosalicylamide were chosen in an attempt to spare the excess boronic acid (Scheme 1.4). The copper thiolate generated was designed to incorporate an *N*-alkyl or *N*-aryl amide at the 2 position of the aryl thiolate. After oxidation in air, the copper thiolate could undergo a ring closure via the formation of a sulfur-nitrogen bond. The idea was to release copper by forming a benzoisothiazolinone which after isolation could easily be converted back to the thiol ester starting material. This would represent a complete catalytic system that would abide by the principles of atom economy.



Scheme 1.4 Scavenging Sulfur with Thiosalicylamide Pendant

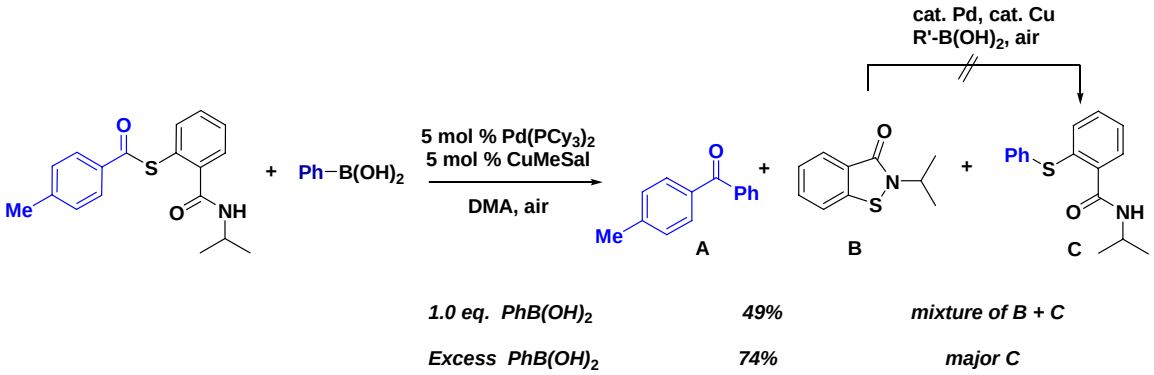
1.2 Results and Discussion

The thiosalicylamide thiol esters were synthesized starting with the disulfide (Scheme 1.5). Commercially available 2,2'-dithiobenzoic acid was treated with thionyl chloride. The resulting acid chloride was treated with isopropyl amine in pyridine at 0°C. The product, 2,2'-bis *N*-isopropyl dithiobenzamide, was then reduced with sodium borohydride in ethanol. The sodium thiolate salt was quenched *in situ* with the aryl acid chloride to give the thiol ester in good yield.



Scheme 1.5 Thiol Ester Synthesis from Disulfide

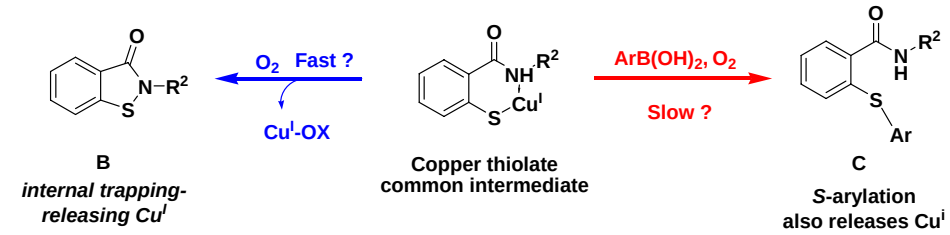
S-2-(Isopropylcarbamoyl)phenyl 4-methylbenzothioate was treated with catalytic amounts of palladium(0) bis(tricyclohexylphosphine) and copper(I) methyl salicylate in DMA and open to air (Scheme 1.6). Optimal conditions required 2 equivalents of boronic acid for high yields of ketone. A mixture of isothiazolinone B and *S*-arylation C was observed when 1 equivalent of boronic acid was used. *S*-arylation C was the major byproduct when 2 equivalents of boronic acid were used.



Scheme 1.6 Reactivity of Thiosalicylamide Thiol Esters under Catalytic, Aerobic Conditions

In the Liebeskind-Srogl reaction, a full equivalent of copper thiolate is formed (Scheme 1.1). Similarly, a copper N-isopropyl-2-benzamidothiolate could be formed in the catalytic reaction (Scheme 1.7). This copper thiolate could be a common

intermediate for both products B and C. The copper thiolate could be oxidized by air, then undergo a ring closure to give B. The copper thiolate could also be oxidized by air followed by transmellation with a second equivalent of boronic acid to give S-arylation product C. Because a control experiment showed that isothiazolinone B could not be transformed into S-arylated product C under the reaction conditions, a competition reaction must exist between both oxidative closure and oxidative S-arylation.



Scheme 1.7 Rationale for S-Arylation *versus* Benzoisothiazolinone Formation

The following experiments were devised as ways to circumvent pendant *S*-arylation. Tuning steric and electronic properties of the R group on nitrogen or the aromatic ring may favor benzoisothiazolinone formation (Figure 1.2). Substituting R^1 with an electron-withdrawing substituent should make the aromatic ring more electron poor. The nucleophilicity of sulfur should be decreased favoring isothiazolinone formation. Increasing the steric bulk of R^2 could shield the copper from transmetallation with boron, thereby preventing unwanted *S*-arylation and favoring internal ring closure (isothiazolinone formation).

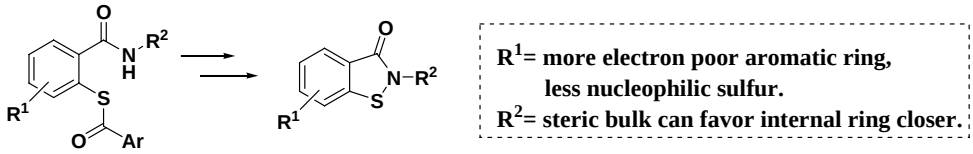
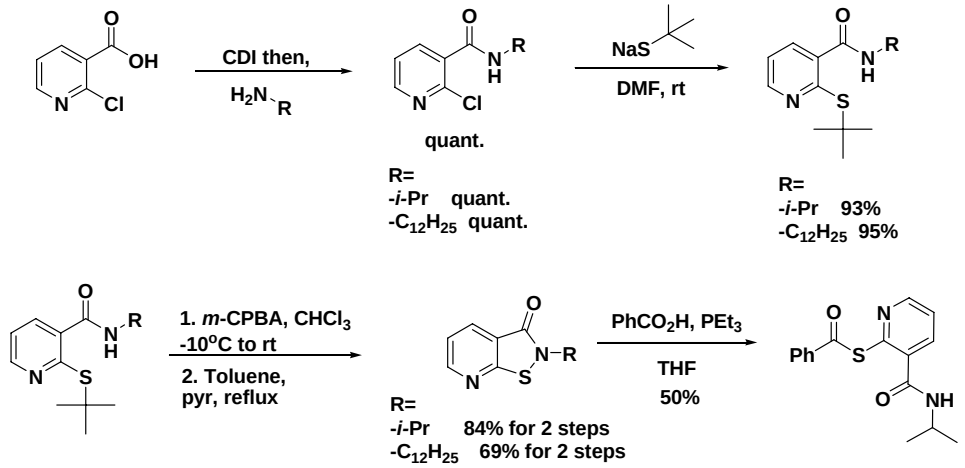


Figure 1.2 Tuning Steric and Electronic Properties of Pendent

1.2.1 Pyridyl Thiol Esters and Their Reactivity

It was hypothesized that the pyridine ring in thiol ester derivatives of 2-mercaptonicotinamide would draw electron density from S making it more vulnerable to nucleophilic attack by N thereby favoring isothiazolinone formation and circumventing the need for 2 equivalents of boronic acid.

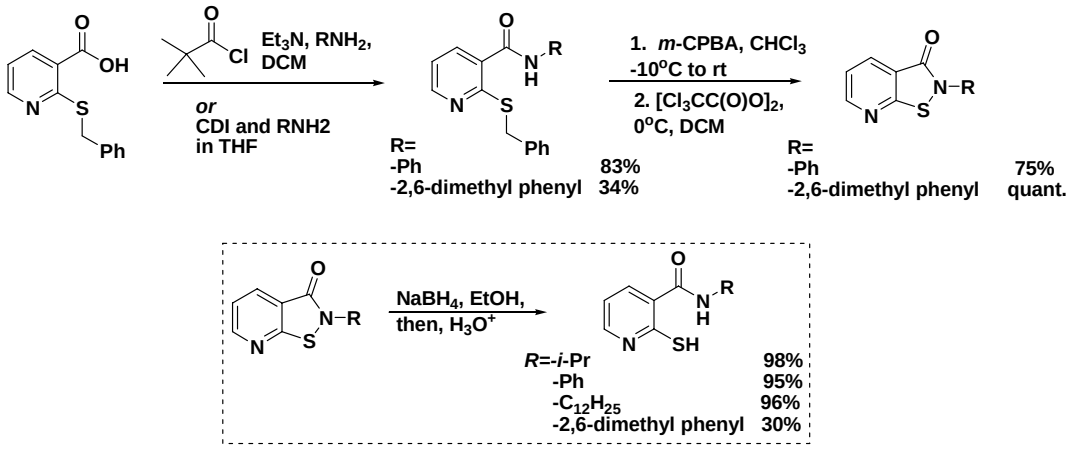
In the literature, 2-mercaptonicotinamides are described as disulfide and pyridoisothiazolone derivatives having medicinal properties such as antibacterial activity against *Mycobacterium* species and inhibition of cytokine Interleukin-1 related to cartilage erosion in arthritis.[10, 11] Based on known syntheses, the following two procedures were developed (Scheme 1.8 and 1.9). Commercially available 2-chloronicotinic acid was reacted with 1,1'-carbonyldiimidazole (CDI) in THF or DMF with the appropriate amine to give the amide in quantitative yield. Next, *t*-butyl sodium thiolate was added to the 2-chloronicotinamide in DMF at room temperature to afford the protected thioether in high yield. The thioether was then oxidized to the sulfoxide using 3-chloroperoxybenzoic acid (*m*-CPBA). In refluxing toluene and pyridine, the crude sulfoxide undergoes an ene-type rearrangement followed by ring closure to give the pyridoisothiazolinone product in high yield.



Scheme 1.8 Sythesis of Thiol Ester Derived from 2-Mecaptonicotinamide

In the literature, disulfides have been converted to thiol esters in one step by using trialkyl, -aryl, or -methoxy phosphine with the corresponding alkyl or aryl carboxylic acid.[12] Pyridoisothiazolinones contain adjacent heteroatoms *S*-*N*. The lone pairs on each heteroatom create a vicinal dipole effect making its bond weak and easily reducible. By this logic, the S-N bond can be considered a disulfide equivalent. Accordingly, the pyridothiol ester was produced in one step from the pyridoisothiazolinone using one equivalent of triethylphosphine and benzoic acid in THF. Unfortunately, yields above 50% were not obtained and reduction by sodium borohydride followed by quenching with an aryl acid chloride only gave the thiol, not the thiol ester.

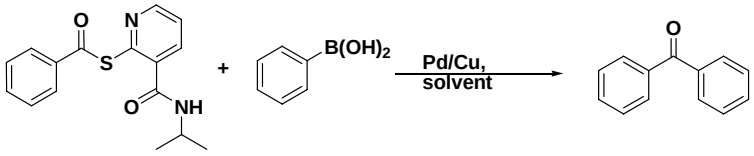
An alternative route to that described in Scheme 1.8 starts by using the benzyl protected thioether which is synthesized from commercially available 2-mercaptonicotinic acid, triethylamine, and benzyl chloride (Scheme 1.9). The advantage of this route is synthetic variety. While both procedures work well, this method is preferred for more hindered amides with R groups such as 2,6-dimethylphenyl. The *S*-benzyl protected nicotinic acid was reacted with triethylamine and trimethylacetyl chloride, followed by the slow addition of the appropriate amine to give the amide in moderate to high yield. CDI also gave the amide in high yield. Oxidation with *m*-CPBA followed and the resulting sulfoxide was treated with trichloroacetic anhydride at 0^{o}C to give the interrupted Pummerer product. The pyridoisothiazolinones were then reduced by sodium borohydride in ethanol with an acid work-up to give the corresponding thiols.



Scheme 1.9 Alternate Synthesis of Thiol Ester Derived from 2-Mecaptonicotinamide

Once the thiol esters were in hand, they were exposed to Liebeskind-Srogl cross-coupling conditions. By HPLC, the starting material was rapidly decomposing. Only one example gave moderate yields of ketone when *stoichiometric palladium and copper* were used (Table 1.1). Two questions needed to be answered: Was the starting material stable under cross-coupling conditions? Because stoichiometric Pd seemed to be needed for ketone synthesis, was the Pd catalyst being poisoned in the other coupling examples?

Table 1.1 Nicotinamide Thiol Ester Cross-Coupling Optimization



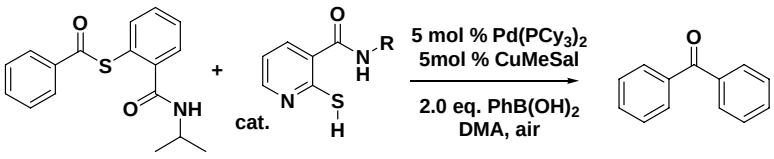
Pd	Cu	Solvent	Yield (%)
10% $Pd(PCy_3)_2$	10% CuMeSal	DMA	4
10% $Pd(PPh_3)_4$	1.0 eq. CuMeSal	DMA	20
1.0 eq $Pd(PPh_3)_4$	1.0 eq CuMeSal	DMA	49 (63 HPLC)

Under catalytic conditions in air but in the absence of boronic acid, the thiol ester decomposed to its thiol, and disulfide together with benzoic acid as shown by ^{1}H NMR.

Even protecting the reaction using dry air made no difference in yields and decomposition of starting material was still observed.

In order to probe the activity of the Pd catalyst, the following control experiments were done (Table 1.2). Catalytic amounts of 2-mercaptonicotinamide derivatives were added to the two working cross-coupling reactions. Ketone inhibition was observed no matter the nature of the R group on the amide of the thiol. Therefore, the 2-mercaptopyridine moiety appeared to be binding tightly to Pd and therefore poisoning it as a catalyst.

Table 1.2 Ketone Inhibition by 2-Mercaptonicotinamides



R=	**Ketone (HPLC)**
No Thiol	85%
*i*Pr	0%
Ph	trace
$C_{12}H_{25}$	0%
2,6-dimethyl phenyl	0%

In the literature, 2-mercapto pyridine is an excellent ligand for metals such as Fe, Ag, Pd, or Cu with many possible coordination modes [can be neutral (thione) ligand or anionic (thiolate) ligand].[13] When 2-mercapto-*N*-isopropyl-nicotinamide was reacted with Pd(II) acetate in dioxane, a very stable Pd complex was formed. The ^{1}H NMR showed the aromatic and isopropyl peaks clearly. Elemental analysis showed that the complex exits as a [Pd_nL_{n+2}] complex. While many modes of coordination are possible, in the absence of a crystal structure a proposed complex is shown in Figure 1.1.[14]

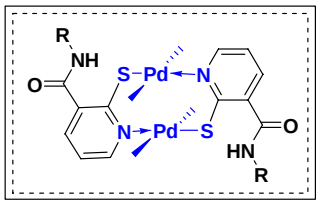
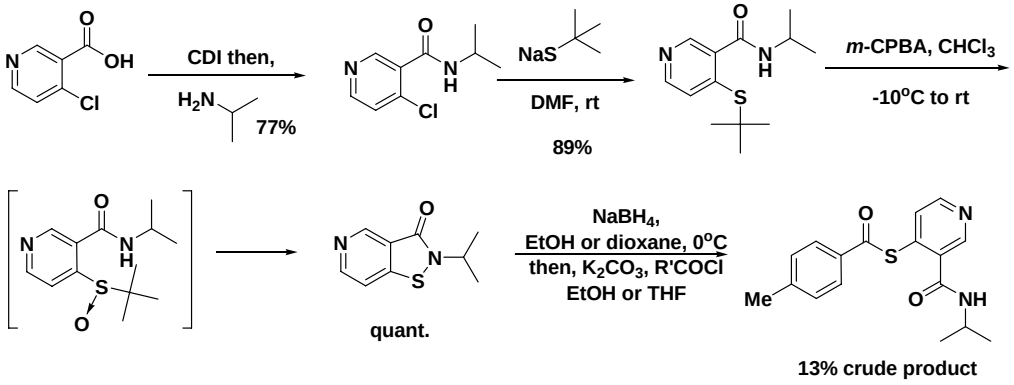


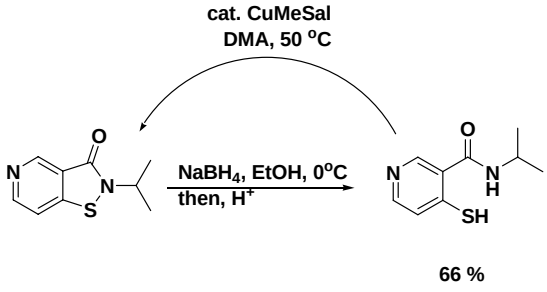
Figure 1.3 Proposed Structure for Pd_nL_{n+2}

It was anticipated the pyridine isomer, 4-mercaptonicotinamide, would prevent the formation of the proposed stable palladium species. Scheme 1.10 illustrates the synthetic strategy for its thiol ester analog. Commercially available 2-chloro-4-nicotinic acid treated in the same way smoothly converted to 4-chloro-*N*-isopropyl nicotinamide. The amide was treated with *t*-butyl sodium thiolate in DMF. Surprisingly, oxidation with *m*-CPBA of the resulting protected thioether gave the 4-pyridoisothiazolinone isomer directly in quantitative yield.



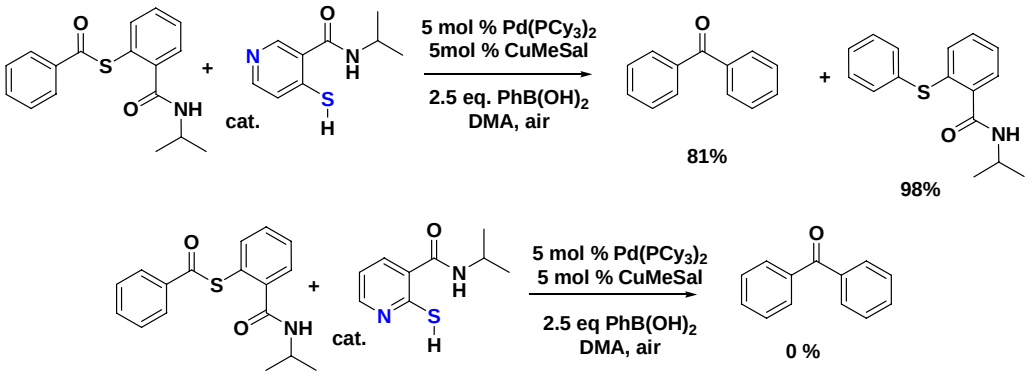
Scheme 1.10 Synthesis of Thiol Ester Derived from 4-Mecaptonicotinamide

Using two different solvent systems, reduction of the 4-pyrido isothiazolinone with sodium borohydride followed by quenching with benzoyl chloride failed to give the clean thiol ester in high yield presumably due to the difficulty of acylation on the tautomeric *N*-isopropyl-4-mercapto-nicotinamide anion and the expected instability of the resulting thiol ester. Nevertheless, the thiol was generated in the usual way. It could be oxidized back to the ring closed product by catalytic CuMeSal in DMA open to air (Scheme 1.11).



Scheme 1.11 Reduction and Oxidation of N-isopropyl-4-mercapto-nicotinamide

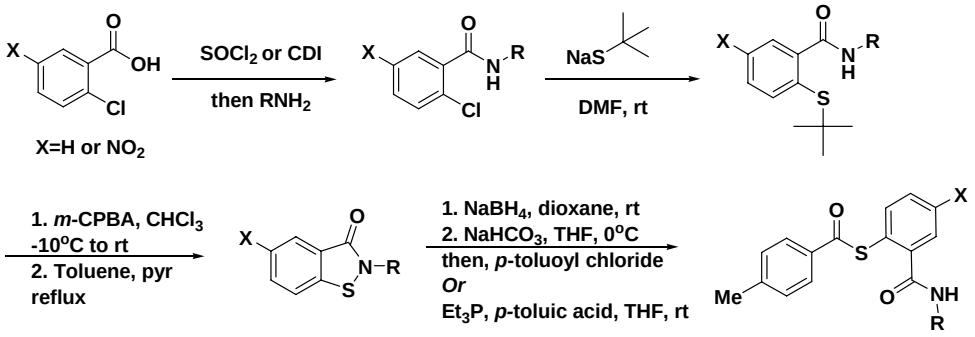
As a proof of principle, the thiol isomer was added to the cross coupling reaction and, as expected, did not inhibit ketone formation. This result supported the conclusion that the 2-mercapto pyridine moiety strongly chelates to the catalyst shutting down ketone production (Scheme 1.12).



Scheme 1.12 Probing Ketone Inhibition with N-isopropyl-4-mercapto-nicotinamide

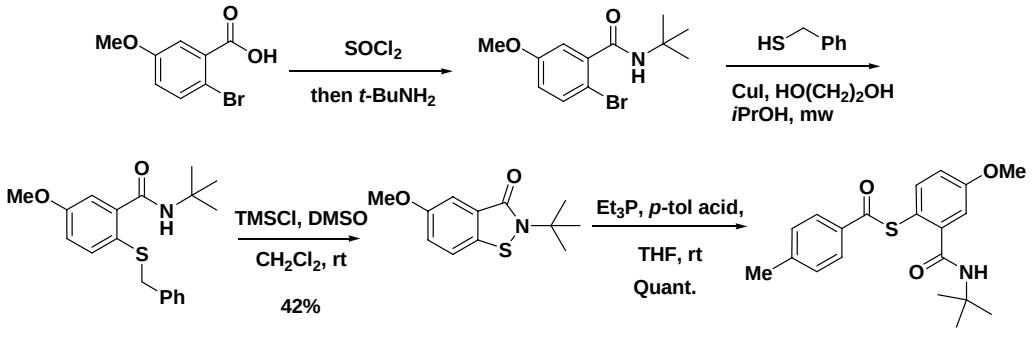
1.2.2 Extending the Thiol Ester Library

A library of thiol esters derived from thiosalicylamide was prepared. The general synthetic route is analogous to that of the pyridine series. (Scheme 1.13). Starting from commercially available 2-chlorobenzoic acid or 2-chloro-5-nitrobenzoic acid, the amide was generated using two different procedures. Thionyl chloride and the corresponding amine generated the amide with more hindered R^2 groups. CDI and the corresponding amine generated the amide in one pot for less hindered R^2 groups. The sulfur atom was introduced by nucleophilic aromatic substitution of aryl chloride by *t*-butyl sodium thiolate. After oxidation with *m*-CPBA and thermolysis of the resulting sulfoxide, the benzoisothiazolinone was obtained in good yield. The thiol esters were generated in a one pot reaction with $NaBH_4$ reduction, followed by quenching the sulfur anion with *p*-toluoyl chloride. An alternative synthesis was treatment with one equivalent of triethylphosphine and toluic acid in THF. The latter reaction condition is preferred because of the easy, non-aqueous work up.



Scheme 1.13 General Synthesis for Thiol Ester Library

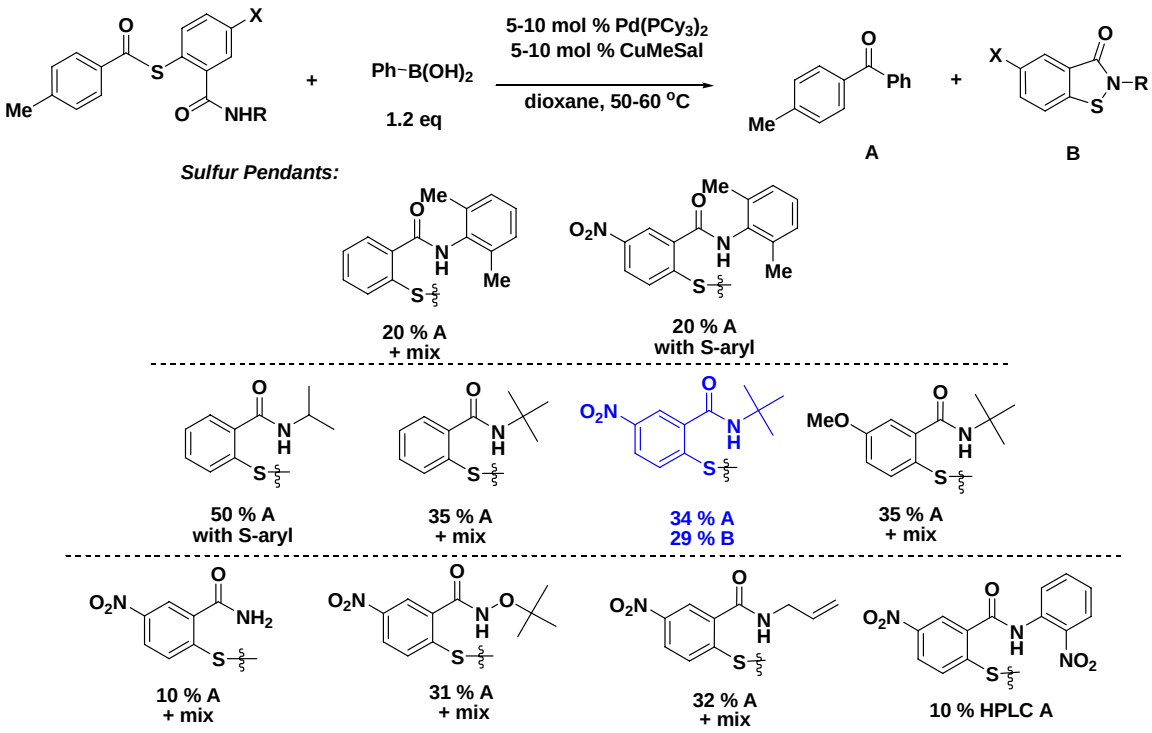
A new approach was needed for the preparation of the unactivated *p*-methoxy thiol ester. Starting from commercially available 2-bromo-5-methoxybenzoic acid, the amide was generated in the usual way (Scheme 1.14). To introduce the sulfur group, nucleophilic aromatic substitution was not an option and lithium halogen exchange followed by treatment with dimethyldisulfide only yielded starting material. Using Buchwald chemistry[15], the aryl bromide was treated with catalytic CuI, phenyl-methanethiol, ethylene glycol, and K_2CO_3 in isopropanol. However, the reaction did not go to completion despite using a microwave at high temperature and pressure. The *S*-benzyl thioether was obtained in 42 % yield and taken to the next step. Ring closure using TMSCl and DMSO gave quantitative yield of the 5-methoxybenzoisothiazolinone. Finally, treatment with triethylphosphine and toluic acid gave the thiol ester in one step.



Scheme 1.14 Synthesis of Electron Rich Thiol Ester

1.2.3 Ketone Synthesis

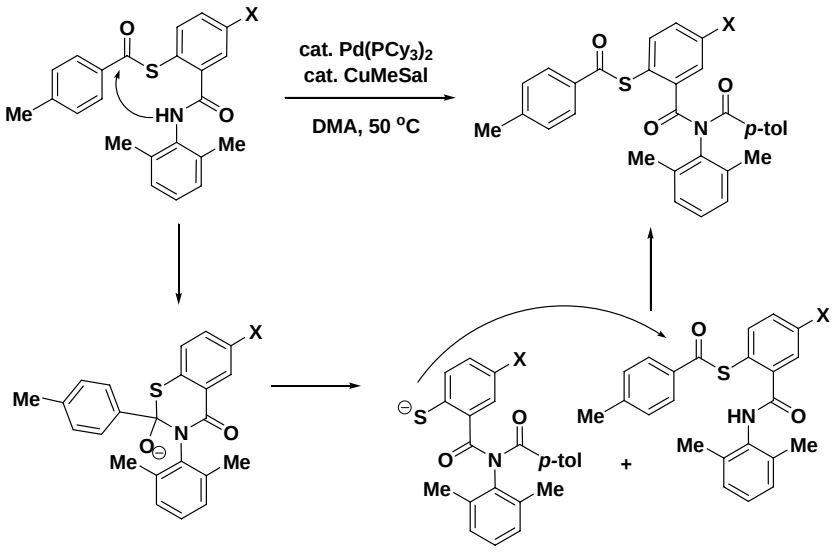
The thiol ester was treated under the standard reaction conditions: catalytic $Pd(PCy_3)_2$, catalytic CuMeSal with 1.2 equivalents of phenylboronic acid in dioxane at 50-60 ^oC open to air with vigorous stirring (Scheme 1.15). The reactions were monitored by HPLC with an internal standard. Most of the benzamide pendants gave similar ketone yields (20-30 % **A**), but failed to produce the analogous SN (**B**) product instead generating mixtures of *S*-aryl and other byproducts.



Scheme 1.15 Screening Pendants under Aerobic, Catalytic Conditions

Dioxane was the solvent of choice at higher temperatures. The thiol esters containing a 2,6-dimethyl phenyl group on the amide were found to decompose in DMA (Scheme 1.16). Under catalytic conditions, in the absence of phenylboronic acid, the starting material converted to a new compound. This compound was fully characterized and found to be an imide presumably resulting from an S to N acyl migration following a

six membered-transition state mechanism. The anion can react with the thiol ester of a neighboring molecule to produce the final product. This side reaction was controlled by keeping the temperature below 60 ^{o}C and using a less polar, but higher boiling point solvent (dioxane). The reaction was not observed for the bulkier *N*-*t*-butyl amide group.

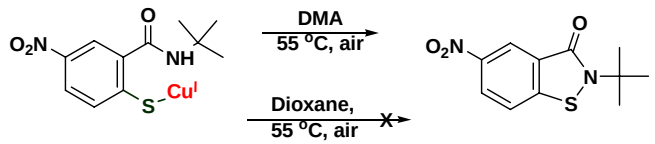


Scheme 1.16 Starting Material Decomposition

The best results gave 34 % 4-methyl benzophenone and 29 % *N*-*t*-butyl-5-nitro-benzoisothiazolinone isolated yield using the *N*-*tert*-butyl-2-mercapto-5-nitro-benzamide pendant highlighted in Scheme 1.15. However, the reaction could not be driven to completion with 2.0 equivalents $PhB(OH)_2$ and SN/S-aryl mixtures were observed. 30 % CuMeSal improved the yield but led to SN/*S*-arylation mixture. Finally, S-N formation does not poison the catalysts. These observations led to speculation that ring closure to form the benzoisothiazolinone might be slow.

Thus far, the thiol ester was designed to slow down *S*-arylation using steric effects (Scheme 1.17). The effect on SN formation was probed in a control experiment. The copper thiolate was synthesized from refluxing thiol in Cu_2O in toluene with azeotropic removal of water. In dioxane, the copper thiolate was completely insoluble and no SN

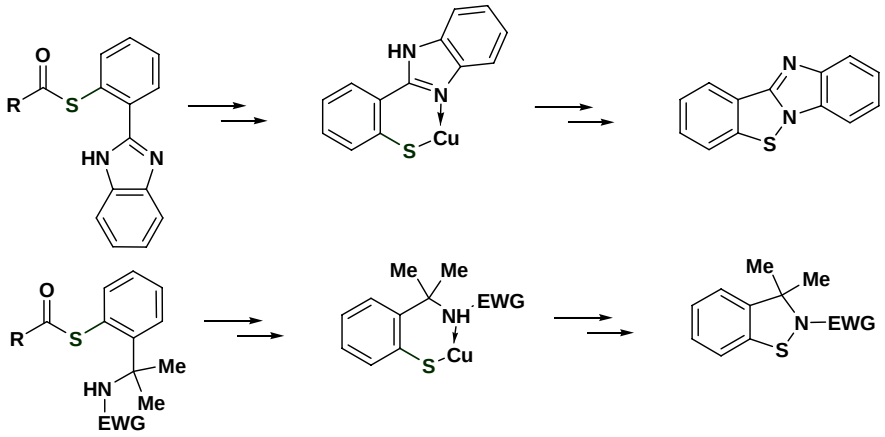
product was isolated. In DMA, the reaction was homogenous and SN compound was the major product. Unfortunately, using DMA in the cross-coupling led to poor results; many byproducts were observed.



Scheme 1.17 Reactivity of Copper Thiolate

1.2.4 Imidazol and Thiazol Derived Thiol Esters

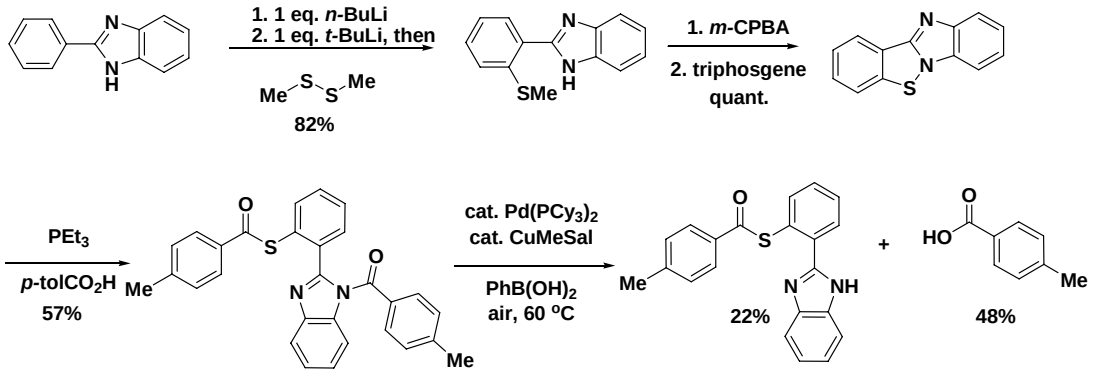
Imidazole and thiazole derived thiol esters were investigated to force chelation through nitrogen and hopefully influence the rate of ring closure (Scheme 1.18).



Scheme 1.18 Thiol Esters with Imidazole and gem-Dimethyl Thiazole Pendants

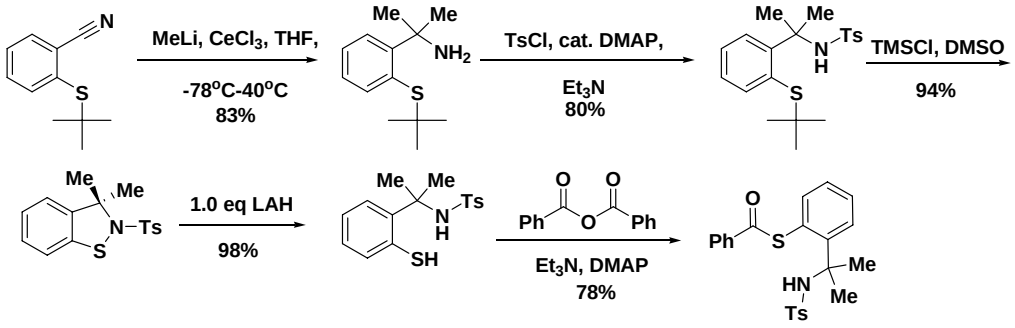
The synthesis of the imidazole derived thiol ester is described in Scheme 1.19. Treating commercially available 2-phenylbenzimidazole with one equivalent *n*-BuLi, then one equivalent of *t*-BuLi gave the dianion that was quenched with dimethyldisulfide giving 82 % yield of the methyl protected thioether. Oxidation with *m*-CPBA gave the sulfoxide, which was treated directly with triphosgene in a dehydration reaction to give the SN product. When the SN product was treated with triethyl phosphine and toluic acid, the thiol ester was obtained in 57 % yield. However, ^{1}H NMR showed the

benzimidazole group was also acylated. Although efforts to prevent double acylation were not successful, the thiol ester was treated under standard coupling conditions. The singlely acylated thiol ester was isolated in 22 % yield along with 48% of toluic acid.



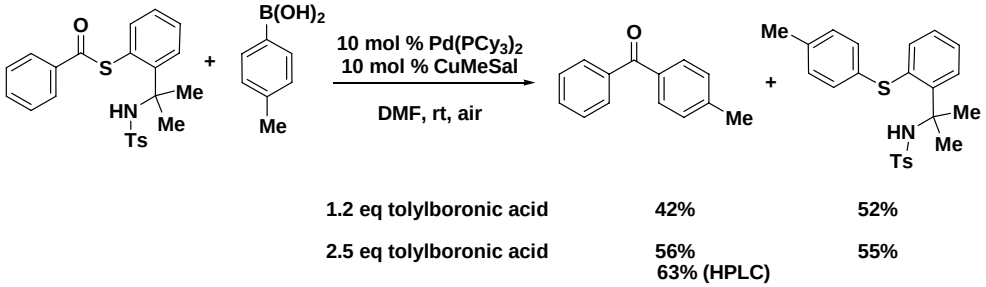
Scheme 1.19 Synthesis and Coupling of Thiol Ester with Benzimidazole Pendant

In a 2005 review, Jung and Piizzi state the *gem*-dialkyl effect is the name given to the acceleration of a cyclization due to the replacement of hydrogen atoms with alkyl groups on the carbons tethering the two reacting centers.[16] The two reacting centers in the case of the *gem*-dimethyl amine pendant are -*N*Ts and *S*. The hope was to accelerate the S-N ring closure pathway *via* copper chelation through nitrogen and the *gem*-dimethyl effect. The synthetic preparation of the thiol ester bearing the *gem*-dimethyl amine pendant begins by treating the nitrile with 2 equivalents of $MeCeCl_2$ generated *in situ* (Scheme 1.20). The resulting *gem*-dimethyl amine was protected with tosyl chloride followed by treatment with TMSCl and DMSO to give the thiazole in 98 % yield. Reduction by LAH and acylation with benzoic anhydride gave the thiol ester in 78% yield.



Scheme 1.20 Synthesis of Thiol Ester with gem-Dimethyl Thiazole Pendant

Unfortunately, treatment of the thiol ester prepared in Scheme 1.20 under standard reaction conditions (10 mol % $Pd(Cy_3)_2$, 10 mol % CuMeSal, DMF, air) led exclusively to formation of the *S*-arylation product (Scheme 1.21). No trace of the SN product was observed.

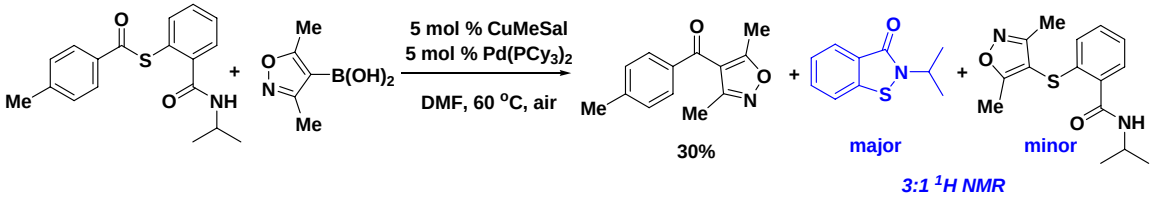


1.2 eq tolylboronic acid	42%	52%
2.5 eq tolylboronic acid	56% 63% (HPLC)	55%

Scheme 1.21 Coupling of Thiol Ester with gem-Dimethyl Thiazole Pendant

1.2.5 Sterically Hindered Boronic Acids

Treatment of *S*-2-(isopropylcarbamoyl)phenyl 4-methylbenzothioate with 3,5-dimethylisoxazol-4-yl-4-boronic acid produced 30 % of the ketone along with a mixture of *N*-isopropyl benzoisothiazolinone and *S*-arylation in a 3:1 ratio by ^{1}H NMR (Scheme 1.22). It is only when *S*-arylation is severely impeded by the steric nature of the boronic acid that ring closure becomes the major product.



Scheme 1.22 Reactivity of a Sterrically Hindered Boronic Acid

1.3 Conclusion

The aim of this project was to create an aerobic ketone synthesis catalytic in *both* palladium and copper. Liberation of copper through arylation of S with a second equivalent of boronic acid and not through S-N bond formation was the favored pathway. Strongly coordinating groups such as replacing phenyl with 2-pyridyl on the aryl ring of the thiol pendant kills catalysis most likely *via* N/S coordination. Thiol ester decomposition through acyl migration was also revealed. The features that promote stability included alkyl groups on the nitrogen of the amide and electron neutral or rich aromatic groups on thiol esters.

1.4 References

1. Liebeskind, L. S.; Srogl, J. Thiol Ester-Boronic Acid Coupling. A Mechanistically Unprecedented and General Ketone Synthesis. *J. Amer. Chem. Soc.* **2000**, *122*, 11260-11261.

2. Kotha, S.; Lahiri, K.; Kashinath, D. Recent Applications of the Suzuki-Miyaura Cross-Coupling Reaction in Organic Synthesis. *Tetrahedron* **2002**, *58*, 9633-9695.

3. Zhang, S.; Zhang, D.; Liebeskind, L. S. Ambient Temperature, Ullmann-like Reductive Coupling of Aryl, Heteroaryl, and Alkenyl Halides. *J. Org. Chem.* **1997**, *62*, 2312-2313.

4. Savarin, C.; Srogl, J.; Liebeskind, L. S. Substituted Alkyne Synthesis under Nonbasic Conditions: Copper Carboxylate-Mediated, Palladium-Catalyzed Thioalkyne-Boronic Acid Cross-Coupling. . *Org. Lett.* **2001**, *3*, 91-93.

5. Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. Ambient Temperature Synthesis of High Enantiopurity *N*-Protected Peptidyl Ketones by Peptidyl Thiol Ester-Boronic Acid Cross-Coupling. *Journal of the American Chemical Society* **2007**, *129*, 1132-1140.

6. Liebeskind, L. S.; Srogl, J. Heteroaromatic Thioether-Boronic Acid Cross-Coupling under Neutral Reaction Conditions. *Org. Lett.* **2002**, *4*, 979-981.

7. Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. A New Catalytic Cross-Coupling Approach for the Synthesis of Protected Aryl and Heteroaryl Amidines. *Org. Lett.* **2002**, *4*, 983-985.

8. Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. Switchable Catalysis: Modular Synthesis of Functionalized Pyrimidinones *via* Selective Sulfide and Halide Cross-Coupling Chemistry. *Org. Lett.* **2003**, *5*, 4349-4352.

9. Zhang, Z.; Liebeskind, L. S. Palladium-Catalyzed, Copper(I)-Mediated Coupling of Boronic Acids and Benzylthiocyanate. A Cyanide-Free Cyanation of Boronic Acids. *Org. Lett.* **2006**, *8*, 4331-4333.

10. Wright, S. W.; Abelman, M. M.; Bostrom, L. L.; Corbett, R. L. Benzyl and *tert*-Butyl Sulfoxides as Sulfenyl Halide Equivalents: a Convenient Preparation of Benzisothiazolones. *Tetrahedron Lett.* **1992**, *33*, 153-156.

11. Wright, S. W.; Petraitis, J. J.; Abelman, M. M.; Batt, D. G.; Bostrom, L. L.; Corbett, R. L.; Decicco, C. P.; Di Meo, S. V.; Freimark, B.; Giannaras, J. V. Heteroaryl-Fused 2-Phenylisothiazolone Inhibitors of Cartilage Breakdown. *J. Med. Chem.* **1994**, *37*, 3071-3078.

12. Endo, T.; Kobayashi, T.; Mukaiyama, T. Preparation of Thiols Susceptible to Oxidation. Effect of Nitrogen on the Susceptibility to Oxidation-Reduction in Sulfur of Divalent Sulfur Compounds. *Tetrahedron Lett.* **1970**, 1493-1496.

13. Umakoshi, K.; Ichimura, A.; Kinoshita, I.; Ooi, S. The Dinuclear Palladium(II) Complex of Pyridine-2-thiol. Synthesis, Structure, and Electrochemistry. *Inorg. Chem.* **1990**, *29*, 4005-4010.

14. Gupta, M.; Cramer, R. E.; Ho, K.; Pettersen, C.; Mishina, S.; Belli, J.; Jensen, C. M. Trans Influence of Phosphines on Dimer-Monomer Interconversion of 2-Pyridinethiolate Complexes: Structures of $[Pd(\mu\text{-}\eta^2\text{-py}S\text{-}N,S)Cl(L)]_2$ (L = PMe_2Ph, $PMePh_2$) and $Pd(\eta^2\text{-py}S)Cl(PPh_3)$. *Inorg. Chem.* **1995**, *34*, 60-65.

15. Kwong, F. Y.; Buchwald, S. L. A General, Efficient, and Inexpensive Catalyst System for the Coupling of Aryl Iodides and Thiols. *Org. Lett.* **2002**, *4*, 3517-3520.

16. Jung, M. E.; Piizzi, G. *gem*-Disubstituent Effect: Theoretical Basis and Synthetic Applications. *Chem. Rev.* **2005**, *105*, 1735-1766.

17. Guiu, E.; Claver, C.; Castillon, S. Ir(I) Complexes with Oxazoline-Thioether Ligands: Nucleophilic Attack of Pyridine on Coordinated 1,5-Cyclooctadiene and Application as Catalysts in Imine Hydrogenation. *J. Organomet. Chem.* **2004**, *689*, 1911-1918.

1.5 Experimental:

General Methods:

Starting material preparations were preformed under an atmosphere of dry N_2 or Ar in over-dried glassware unless otherwise noted. Solvents (DMA, DMF, DMSO, EtOH, dioxane, isoproanol, ethylene glycol, $CHCl_3$, Et_3N, pyridine) for reaction media were ACS reagent grade and purchased from Aldrich. They were dried over 4 Å molecular sieves, purged with dry N_2 or Ar, and titrated for water level with a Karl Fisher Coulomatic K-F titrator. Solvents (THF, toluene, CH_2Cl_2) were purified and dried using a Seca Solvent System purchased from GlassContour. Hexane (hex), ethyl acetate (EtOAc), and diethyl ether (Et_2O) used for extraction, recrystallization, or chromatography were obtained from EM Science and used as purchased. Solution of $NaHCO_3$, NaOH, or HCl refers to aqueous solution. Brine is a saturated solution of sodium chloride in water. Analytical thin-layer chromatography (TLC) was carried out using Merk Kieselgel 0.25 mm 60 F_{254} plates with visualization by UV, $KMnO_4$, or iodine crystals in silica gel.

^{1}H NMR spectra were recorded on a Varian Inova 400 or 600 MHz NMR spectrometer at room temperature in $CDCl_3$ or *d*-DMSO and were internally referenced to either, (7.27 ppm and 2.5 ppm, respectively). ^{13}C NMR spectra were recorded on a Varian Inova 150 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported in Hz; integration is provided. Infrared (IR) spectroscopy was preformed on an ASi Applied

Systems ReactIR 1000 Electronics Module. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100 %), m (medium, 40-67 %), w (weak, 20-40 %), and br (broad). Uncalibrated melting points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes. Elemental analyses were preformed by Atlantic Microlab, Inc., Norcross, Georgia. HPLC analysis was carried out on an Aligent 1100 Series HPLC using an Eclipse XDB-C8 (5 μm, 4.6 x 150 mm) column.

All boronic acids were purchased from Frontier Scientific, Inc. Palladium catalysts, CuI, Cu_2O, and $CeCl_3$ were purchased from Strem Chemicals. CuTC [1] and CuMeSal[2] were prepared according to the literature procedure. Regents $SOCl_2$, CDI, all amines and anilines, trimethyl acetyl chloride, *tert*-butyl sodium thiolate, phenyl sodium thiolate, *m*-CPBA, trimethylsilane, dimethyl sulfide, trichloroacetic anhydride, 4.4'-di-*tert*-butylbiphenyl, sodiumborohydride ($NaBH_4$), triethylphosphine, benzoic acid, benzoic anhydride, benzoyl choride, *para*-tolouyl chloride, dimethyl disulfide, *n*-butyl lithium, *tert*-butyl lithium, acetic acid, potassium carbonate, tosylchloride, and dimethyl aminopyridine were purchased from Aldrich. Starting materials 2-chlorobenzoic acid, 2-chloro-5-nitrobenzoic acid, 2-bromo-5-methoxybenzoic acid, 2-chloronicotinic acid, 4-chloronicotinic acid, and 2-benzimidazole were purchased from Aldrich or Matrix.

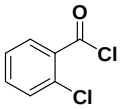
Starting Material Synthesis:

General Procedure for Acid Chloride:

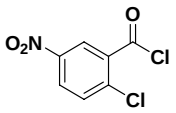
[1] Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312-2313.

[2] Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91-93.

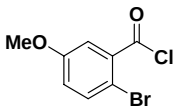
Commercially available 2-chloro or 2-bromobenzoic acid (1.0 equiv.) was suspended in neat $SOCl_2$ (50 equiv.). The reaction was refluxed for one hour as the acid dissolved. $SOCl_2$ was then removed via vacuum and the residual oil was treated with cycles of dry toluene and vacuum until no traces of $SOCl_2$ remained. The crude product was directly in subsequent steps.



2-Chloro-benzoyl chloride: From commercially available 2-Chlorobenzoic acid (5.00 g, 29 mmol) in 194 ml $SOCl_2$ was obtained 2-chlorobenzoyl chloride with matching known spectra. Yield: Quantitative. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 7.57-7.51 (m, 2H), 7.45-7.41 (m, 1H). IR (neat, cm^{-1}): 1783 (s).



2-Chloro-5-nitro-benzoyl chloride: From commercially available 2-Chloro-5-nitrobenzoic acid (20 g, 100 mmol) in 600 ml $SOCl_2$ was obtained 22 g of 2-chloro-5-nitrobenzoyl chloride with matching known spectra. Yield: 99 %. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.92 (d, *J*= 2.4 Hz, 1H), 8.39 (dd, *J*=8.6, 2.6 Hz, 1H), 7.74 (d, *J*= 8.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 146.4, 140.3, 134.3, 133.0, 128.6, 128.1. IR (neat, cm^{-1}): 1787 (s), 1760 (s), 1529 (s), 1347 (s).



2-Bromo-5-methoxy-benzoyl chloride: From commercially available 2-Bromo-5-methoxybenzoic acid (5.06 g, 22 mmol) in 132 ml $SOCl_2$ was obtained 2-bromo-5-

methoxybenzoyl chloride with matching known spectra. Yield: Quantitative. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J*= 8.9 Hz, 1H), 7.57 (d, *J*= 2.9 Hz, 1H), 7.00 (dd, *J*= 8.9, 3.1 Hz, 1H), 3.87 (s, 3H).

General Procedure for Amide Synthesis:

Method A via CDI Coupling Reagent

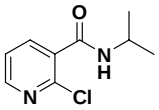
To the carboxylic acid (1.0 equiv.) was added dry THF or DMF under nitrogen. 1,1'-Carbodiimidazole or CDI (1.06 equiv.) was added slowly at room temperature. After 1 hour, disappearance of bubbles was observed. At 0 ^oC and in THF (0.15 M), the corresponding amine (1.06 equiv.) was added slowly. The reaction was allowed to stir overnight. The reaction was quenched with H_2O. Pure product was obtained by extracting the aqueous phase with $CHCl_3$ three times, drying with $MgSO_4$, and condensed. If necessary, the residue was passed through a short silica column.

Method B via Mixed Anhydride

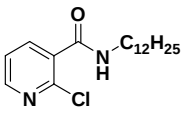
The carboxylic acid (1.0 equiv.) was suspended in 400 ml of CH_2Cl_2 (0.11 M) and treated with Et_3N (1.1 equiv.). After the acid dissolved, the mixture was stirred for 5 minutes before being treated with trimethylacetyl chloride (0.9 equiv.). The mixture was stirred at 45 ^oC for 1 hour and then cooled to 25 ^oC and treated with the corresponding aniline (0.9 equiv.) and allowed to stir at 25 ^oC for 24 hours. The reaction was quenched with 1 M NaOH and the mixture was partitioned between brine and $CHCl_3$. The layers were separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried, and concentrated. Pure product was obtained from recrystallization from hexane and EtOAc or column chromatography.

Method C via Acid Chloride

To the crude acid chloride was added dry dichloromethane (3.4 M) and dry pyridine (2.0 M) at 0 ^{o}C under argon with stirring. The corresponding amine (1.1 equiv.) was added slowly *via* syringe and the reaction was allowed to stir overnight while coming to room temperature. The mixture was quenched with 5 % HCl and ice. The resulting solid was filtered and dried. If product did not precipitate, the aqueous layer was extracted with dichloromethane and then washed with 1 M NaOH to remove any remaining acid. The organic layer was then dried with $MgSO_4$, filtered and condensed giving the final product.

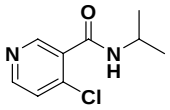


2-Chloro-*N*-isopropyl-nicotinamide: *Method A:* From commercially available 2-chloronicotinic acid (23 g, 0.15 mol) in 200 ml dry THF, CDI (26 g, 0.16 mol), and isopropylamine (14 ml, 0.16 mol) in 10 ml of THF was obtained 30 g of pure product. Yield: 99 %. Light yellow solid, M.p. 82-84 ^{o}C. TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.28). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, *J*= 4.8, 1.9 Hz, 1 H), 8.09 (dd, *J*= 3.6, 1.9 Hz, 1 H), 7.35 (dd, *J*= 7.6, 4.8 Hz, 1 H), 6.24 (s, br, 1 H), 4.34-4.28 (m, 1 H), 1.29 (d, *J*= 6.7 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 150.7, 147.3, 139.3, 132.1, 122.8, 42.6, 22.6. IR (neat, cm^{-1}): 3262 (s), 1640 (s). HRMS (FAB) Calcd for $C_9H_{12}ClN_2O$ ($M+H^+$): 198.0638. Found: 199.0638.

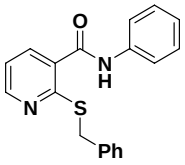


2-Chloro-*N*-dodecyl-nicotinamide: *Method A:* From commercially available 2-chloronicotinic acid (5.03 g, 32 mmol) in 150 ml dry THF, CDI (5.70 g, 35 mmol), and

dodecylamine (6.80 g, 35 mmol) in 10 ml of THF was obtained 10.7 g of pure product. Yield: 99 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J*= 4.8, 1.9 Hz, 1 H), 8.12 (dd, *J*= 7.6, 1.9 Hz, 1H), 7.37 (dd, *J*= 7.9, 4.8 Hz, 1H), 6.47 (bs, 1 H), 3.48 (m, 2H), 1.64 (m, 2H), 1.27 (m, 18H), 0.88 (m, 3H).



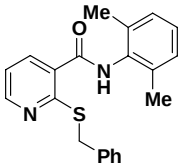
4-Chloro-N-isopropyl-nicotinamide: *Method A:* From commercially available 4-chloronicotinic acid (2.00 g, 13 mmol) in 30 ml dry DMF, CDI (2.36 g, 14 mmol) and isopropyl amine (1.2 ml, 14 mmol,) was obtained 1.94 g of pure product after the crude was passed through a short silica column with 1:1 Et_2O:EtOAc. Yield: 77 %. Light orange crystals, M.p. 106-109 ^oC. TLC (silica gel, 1:1 Et_2O:EtOAc, R_f= 0.50). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.54 (d, *J*= 5.7 Hz, 1H), 7.37 (d, *J*= 5.2 Hz, 1H), 5.98 (bs, 1H), 4.39-4.28 (m, 1H), 1.30 (d, J=6.2, 1H). IR (neat, cm^{-1}): 3258 (m), 1640 (s), 1579 (s), 1556 (s).



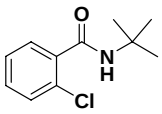
2-Benzylsulfanyl-*N*-phenyl-nicotinamid[3]: *Method B:* From 2-Benzylsulfanyl-nicotinic acid[13] (11.3 g, 46 mmol) in 400 ml of CH_2Cl_2, Et_3N (7.1 ml, 51 mmol), trimethylacetyl chloride (6.4 ml, 51 mmol), and aniline (4.7 ml, 51 mmol) was obtained 12.0 g of pure

[3] Wright, S. W.; Petraitis, J. J.; Abelman, M. M.; Batt, D. G.; Bostrom, L. L.; Corbett, R. L.; Decicco, C. P.; Di Meo, S. V.; Freimark, B.; Giannaras, J. V. *J. Med. Chem.* **1994**, *37*, 3071-3078.

product after recrystallization from hexane and EtOAc. Yield: 81 %. Light orange crystals, M.p. 160-162°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (dd, *J*= 4.6, 1.5 Hz, 1 H), 8.03 (bs, 1H), 7.96 (d, *J*= 7.6 Hz, 1H), 7.60 (d, *J*= 7.6 Hz, 2 H), 7.42 (d, *J*= 7.6 Hz, 2H), 7.37 (t, *J*= 7.6 Hz, 2H), 7.30 (t, *J*= 6.9 Hz, 2H), 7.25 (m, 2H), 4.54 (s, 2H). IR (neat, cm^{-1}): 3300 (m), 1648 (s). HRMS (FAB) Calcd for $C_{19}H_{16}LiN_2OS$ ($M+Li^+$): 327.1143. Found: 327.1143.



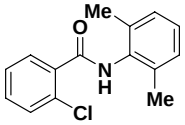
2-Benzylsulfanyl-*N*-(2,6-dimethyl-phenyl)-nicotinamide[6]: *Method B:* From 2-Benzylsulfanyl-nicotinic acid[6] (2.12 g, 8.7 mmol) in 70 ml of CH_2Cl_2, Et_3N (1.2 ml, 0.9 mmol), trimethylacetyl chloride (1.1 ml, 9.0 mmol), and 2,6-dimethyl aniline (1.1 ml, 9.0 mmol) was obtained 1.03 g of pure product after recrystallization from hexane and EtOAc. Yield: 34 %. Light gray crystals, M.p. 92-95 °C. TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.57). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J*= 4.8, 1.9 Hz, 1 H), 8.05 (dd, *J*= 7.6, 1.9 Hz, 1H), 7.66 (bs, 1H), 7.43 (m, 2H), 7.30 (m, 2H), 7.24 (m, 1H), 7.17 (t, *J*= 7.6 Hz, 1H), 7.12 (m, 3H), 4.56 (s, 2H), 2.31 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ. IR (neat, cm^{-1}): 3227 (bs), 1652 (s).



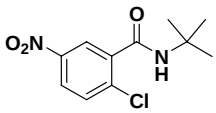
***N*-*tert*-Butyl-2-chloro-benzamid[4]:** *Method C:* From 2-chloro-benzoyl chloride (5.59 g, 32 mmol), *tert*-butyl amine (3.7 ml, 34 mmol), and 16 ml of dry pyridine with no added

[4] Fong, C. W.; Hameister, C. R. *Org. Mass Spectrom.* **1978**, *13*, 711-714.

dichloromethane, was obtained 3.20 g of pure product after filtration. Yield: 47 %. Beige solid, M.p. 99-100 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (dd, *J*= 7.1, 1.9 Hz, 1H), 7.38 (dd, *J*= 7.6, 1.9 Hz, 1H), 7.34-7.29 (m, 2H), 5.90 (bs, 1H), 1.49 (s, 9H). IR (neat, cm^{-1}): 3258 (m), 1637 (s), 1552 (m). HRMS (FAB) Calcd for $C_{11}H_{14}ClNO$ ($M+Li^+$): 218.0924. Found: 218.0924.



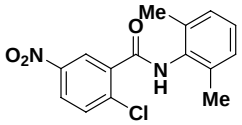
2-Chloro-*N*-(2,6-dimethyl-phenyl)-benzamide [5] : *Method B:* From commercially available 2-chlorobenzoic acid (3.00 g, 19 mmol) in 25 ml of CH_2Cl_2, Et_3N (2.7 ml, 19 mmol), trimethylacetyl chloride (2.3 ml, 19 mmol), and 2,6-dimethylaniline (2.3 ml, 19 mmol) was obtained 2.70 g of pure product after chromatography on silica gel (Hex:EtOAc 2:1). Yield: 55 %. White crystals, M.p. 149-150 °C. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.30). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, *J*= 7.1, 2.4 Hz, 1 H), 7.49 (dd, *J*= 7.6, 1.6 Hz, 1 H), 7.46-7.38 (m, 2 H), 7.19-7.13 (m, 3 H), 2.37 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 135.7, 135.3, 133.4, 131.7, 131.5, 131.2, 130.7, 130.3, 128.4, 127.8, 18.9. IR (neat, cm^{-1}): 3223 (m), 3026 (m), 2976 (m), 2926 (m), 1806 (m), 1648 (s), 1594 (m). HRMS (APCI) Calcd for $C_{15}H_{15}ClNO$ ($M+H^+$): 260.0842. Found: 260.0832.



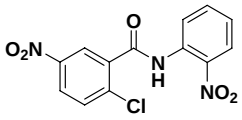
***N-tert*-Butyl-2-chloro-5-nitro-benzamide:** *Method C:* From 2-chloro-5-nitrobenzoyl chloride (3.87 g, 017 mmol), 5 ml of dry dichloromethane, 9 ml of pyridine, and *tert*-

[5] Wright, S.W.; Petraitis, J. J.; Ableman, M. M.; Bostrom, L. L.; Corbett, R. L.; Green, A. M.; Kindt, R. M.; Sherk, S. R.; Magolda, R. L. *Bioorg. & Med. Chem. Lett.* **1993**, *3*, 2875-2878.

*b*utyl amine (2.0 ml, 19 mmol) was obtained 3.39 g of pure product after extraction. Yield: 75 %. Light yellow solid, M.p. 173-176 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J*= 2.8 Hz, 1H), 8.19 (dd, *J*= 8.9, 2.8 Hz, 1H), 7.58 (d, *J*= 8.9 Hz, 1H), 5.87 (bs, 1H), 1.51 (s, 9H). IR (neat, cm^{-1}): 3281 (m), 1648 (s), 1529 (s), 1347 (s). HRMS (FAB) Calcd for $C_{11}H_{13}ClN_2O_3$ ($M+H^+$): 257.0615. Found: 257.0693.



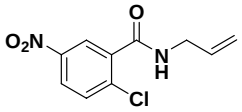
2-Chloro-*N*-(2,6-dimethyl-phenyl)-5-nitro-benzamide[6]: *Method C:* From 2-chloro-5-nitrobenzoyl chloride (4.98 g, 23 mmol), 9 ml of dry dichloromethane, 11 ml of pyridine, and 2,6-dimethyl aniline (3.1 ml, 25 mmol) was obtained 6.00 g of pure product after extraction. Yield: 86 %. Light yellow solid, M.p. 141-145 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J*= 2.8 Hz, 1H), 8.29 (dd, *J*= 8.9, 2.8 Hz, 1H), 7.69 (d, *J*= 8.9 Hz, 1H), 7.42 (bs, 1H), 7.23-7.16 (m, 3H), 2.38 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 146.9, 137.7, 136.8, 135.7, 132.9, 131.7, 128.7, 128.3, 126.1, 125.5, 18.9. IR (neat, cm^{-1}): 3258 (m), 1664 (s), 1529 (s), 1347 (s). HRMS (APCI) Calcd for $C_{15}H_{14}ClN_2O_3$ ($M+H^+$): 305.0693. Found: 305.0688.



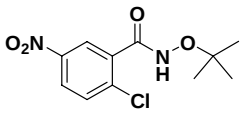
2-Chloro-5-nitro-*N*-(2-nitro-phenyl)-benzamide: *Method C:* From 2-chloro-5-nitrobenzoyl chloride (5.08 g, 23 mmol), 10 ml of dry dichloromethane, 11 ml of pyridine, and *o*-nitroaniline (3.47 g, 25 mmol) was obtained 7.46 g of pure product after filtration. Yield: Quantitative. Bright yellow solid, M.p. 177-180 ^{o}C. ^{1}H NMR (600

[6] Yale, H. L. *J. Heterocycl. Chem.* **1971**, *8*, 193-204.

MHz, $CDCl_3$) δ 10.99 (bs, 1H), 8.94 (d, *J*= 8.6 Hz, 1H), 8.61 (d, *J*= 2.4 Hz, 1H), 8.33 (dd, *J*= 9.0, 2.8 Hz, 1H), 8.31 (dd, *J*= 8.1, 1.4 Hz, 1H), 7.78 (app t, *J*= 8.6 Hz, 1H), 7.71 (d, *J*= 8.6 Hz, 1H), 7.33 (app t, *J*= 7.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2, 146.9, 137.9, 137.2, 136.5, 136.4, 134.0, 132.2, 126.7, 126.2, 125.5, 124.8, 122.8. IR (neat, cm^{-1}): 1691 (s), 1606 (s), 1529 (s), 1502 (s), 1343 (s). HRMS (APCI) Calcd for $C_{13}H_9ClN_3O_5$ ($M+H^+$): 322.0231. Found: 322.0219.



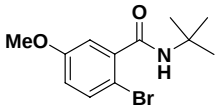
***N*-Allyl-2-chloro-5-nitro-benzamide** [7] **:** *Method C:* From 2-chloro-5-nitrobenzoyl chloride (5.00 g, 23 mmol), 12 ml of pyridine with no added dichloromethane, and allyl amine (1.9 ml, 25 mmol) was obtained 4.63 g of pure product after extraction. Yield: 84 %. Light yellow crystals, M.p. 142-143 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J*= 2.8 Hz, 1H), 8.21 (dd, *J*= 8.6, 2.4 Hz, 1H), 7.60 (d, *J*= 9.0 Hz, 1H), 6.40 (bs, 1H), 5.97-5.91 (m, 1H), 5.32 (d, *J*= 17.1 Hz, 1H), 5.23 (d, *J*= 10.0 Hz, 1H), 4.11 (t, *J*= 5.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 146.7, 137.7, 136.6, 133.2, 131.6, 125.9, 125.4, 117.6, 42.9. IR (neat, cm^{-1}): 3269 (s), 1652 (s), 1540 (s), 1355 (s). HRMS (APCI) Calcd for $C_{10}H_{10}ClN_2O_3$ ($M+H^+$): 241.0380. Found: 241.0371.



***N-tert*-Butoxy-2-chloro-5-nitro-benzamide:** *Method A:* From 2-chloro-5-nitrobenzoyl chloride (1.50 g, 7.00 mmol), 3 ml of pyridine with no added dichloromethane, and *O-tert*-butyl-hydroxylamine·HCl (0.94 g, 7.50 mmol) was obtained 1.64 g of pure product

[7] Siegrist, U.; Baumeister, P.; Blaser, H.-U.; Studer, M. *Chem. Ind.* **1998**, *75*, 207-219.

after filtration. Yield: 88 %. White crystals, M.p. 149-150 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.26 (dd, *J*= 8.5, 1.9 Hz, 1H), 8.15 (s, 1H), 7.64 (d, *J*= 8.5 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.6, 146.7, 138.3, 134.7, 131.7, 126.4, 125.5, 83.8, 26.6. IR (neat, cm^{-1}): 3184 (m), 2984 (m), 1660 (s), 1529 (s), 1351 (s). HRMS (APCI) Calcd for $C_{11}H_{14}ClN_2O_4$ ($M+H^+$): 273.0642. Found: 273.0637.

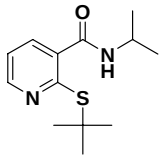


2-Bromo-*N*-*tert*-butyl-5-methoxy-benzamide: *Method A:* From 2-bromo-5-methoxybenzoyl chloride (5.38 g, 22 mmol), 11 ml of pyridine with no added dichloromethane, and *tert*-butyl amine (2.5 ml, 24 mmol) was obtained 3.70 g of pure product after filtration. Yield: 60 %. Light brown crystals, M.p. 92-94 ^{o}C. TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.50). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J*= 8.5 Hz, 1H), 7.08 (d, *J*= 3.1 Hz, 1H), 6.82 (dd, *J*= 8.7, 3.1 Hz, 1H), 5.79 (bs, 1H), 3.81 (s, 3H), 1.49 (s, 9H). IR (neat, cm^{-1}): 3385 (m), 2968 (m), 1648 (s), 1540 (s), 1463 (s). HRMS (APCI) Calcd for $C_{12}H_{17}BrNO_2$ ($M+H^+$): 286.0443. Found: 286.0434.

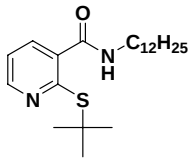
General Procedure for Alkyl or Aryl Thioether Synthesis:

The corresponding 2-chloro benzamide (1.0 equiv) was placed in a round bottom flask equipped with a stir bar under argon and 0.2 M DMF, occasionally with ethylene glycol (1.1 equiv), was added. *tert*-Butyl sodium thiolate or phenyl sodium thiolate (1.1 equiv) was added at room temperature. If the starting material was an unactivated aryl chloride, the reaction was heated. When the reaction was complete as monitored by TLC, iced water was added and the precipitate collected. If no product precipitated, the

water layer was washed with Et_2O or CH_2Cl_2, dried with $MgSO_4$, filtered, condensed, and the products were separated over silica if needed to give the pure thioether.

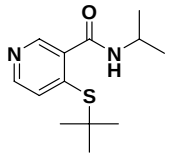


2-*tert*-Butylsulfanyl-*N*-isopropyl-nicotinamide: From 2-chloro-*N*-isopropyl-nicotinamide (30 g, 15 mmol) and sodium *tert*-butyl thiolate (18.7 g, 16 mmol) in 500 ml dry DMF was obtained 36 g of pure product after the reaction was quenched with excess iced water and collecting the solid. Yield: 93 %. White needles, M.p. 128-129 ^oC. TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.48). ^1H 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 (150 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), 1633 (s). HRMS (FAB) Calcd for $C_{13}H_{21}N_2OS$ ($M+H^+$): 253.1375. Found: 253.1375.

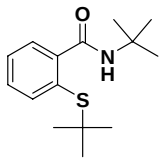


2-*tert*-Butylsulfanyl-*N*-dodecyl-nicotinamide: From 2-chloro-*N*-dodecyl-nicotinamide (10.8 g, 33 mmol) in 100 ml of DMF and *tert*-butyl sodium thiolate (4.06 g, 36 mmol) was obtained 12.6 g of pure product after quenching with excess iced water and collecting the solid. Yield: 95 %. Light yellow solid, M.p. 48-50 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, *J*= 4.4, 1.6 Hz, 1 H), 8.02 (m, 1H), 7.15 (dd, *J*= 7.6, 4.4 Hz, 1H), 7.05 (bs, 1 H), 3.47 (dd, *J*= 12.7, 6.4 Hz, 2H), 1.64 (m, 2H), 1.55 (s, 9H), 1.27 (m,

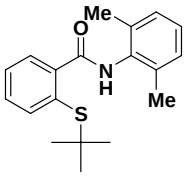
18H), 0.89 (t, *J*= 6.4 Hz, 3H). IR (neat, cm^{-1}): 3260 (w), 2915 (s), 2849 (w), 1635 (s), 1533 (m).



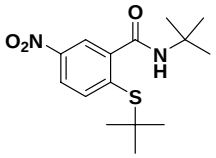
4-*tert*-Butylsulfanyl-*N*-isopropyl-nicotinamide: From 4-chloro-*N*-isopropyl-nicotiniamide (1.09 g, 5.5 mmol) in 20 ml non-dried DMF, and *tert*-butyl sodium thiolate (0.68 g, 6.0 mmol) was obtained 1.17 g of pure product after quenching the reaction with water, extracting with CH_2Cl_2, drying with $MgSO_4$, and condensing. 89 %. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.54 (d, *J*= 5.2 Hz, 1H), 7.50 (d, *J*= 4.7 Hz, 1H), 7.20 (bs, 1H), 4.34-4.28 (m, 1H), 1.41 (s, 9H), 1.31 (d, J=6.2, 1H).



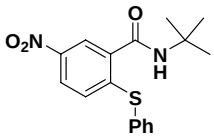
***N*-*tert*-Butyl-2-*tert*-butylsulfanyl-benzamide:** From *N*-*tert*-butyl-2-chloro-benzamide (3.00 g, 14 mmol) and *tert*-butyl sodium thiolate (1.80 g, 16 mmol) in 60 ml DMF at 70 ^{o}C with overnight stirring was obtained 2.77 g of pure product after quenching with iced water and collecting the solid. Yield: 74 %. White crystals, M.p. 60-61 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (dd, *J*= 7.6, 1.4 Hz, 1H), 7.62 (bs, 1H), 7.55 (d, *J*= 7.6 Hz, 1H), 7.45 (t, *J*= 7.6 Hz, 1H), 7.36 (dt, *J*= 7.6, 1.6 Hz, 1H), 1.48 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 142.2, 140.1, 130.7, 129.9, 129.7, 128.7, 52.0, 48.5, 31.1, 29.0. IR (neat, cm^{-1}): 3293 (m), 2964 (m), 1656 (s), 1536 (s), 1455 (s), 1363 (s).



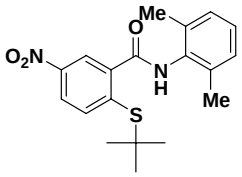
2-*tert*-Butylsulfanyl-*N*-(2,6-dimethyl-phenyl)-benzamide: From 2-chloro-*N*-(2,6-dimethyl-phenyl)-benzamide (2.20 g, 8.6 mmol) and *tert*-butyl sodium thiolate (1.06 g, 9.4 mmol) in 7 ml of dry DMF at 80 ^{o}C with overnight stirring was obtained 2.40 g of pure product after quenching with water, washing with Et_2O, drying with $MgSO_4$, and condensing. Yield: 91 %. White solid, M.p. 72-75 ^{o}C**.** TLC (silica gel, 2:1 hex:EtoAc, R_f= 0.41). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (br s, 1 H), 8.12 (dd, *J*= 7.9, 1.9 Hz, 1 H), 7.66 (dd, *J*= 7.3, 0.9 Hz, 1 H), 7.55-7.44 (m, 2 H), 7.16-7.14 (m, 3 H), 2.38 (s, 6 H), 1.36 (s, 9 H). IR (neat, cm^{-1}): 3239 (s), 2964 (m), 1648 (s), 1505 (s), 1475 (s). HRMS (APCI) Calcd for $C_{19}H_{24}NOS$ ($M+H^+$): 314.1579. Found: 314.1573.



***N*-*tert*-Butyl-2-tert-butylsulfanyl-5-nitro-benzamide:** From *N*-*tert*-butyl-2-chloro-5-nitro-benzamide (3.38 g, 13 mmol) and *tert*-butyl sodium thiolate (1.56 g, 14 mmol) in 60 ml dry DMF at room temperature with overnight stirring was obtained 3.69 g of pure product after quenching with iced water and collecting the crystals. Yield: 90 %. Light yellow crystals, M.p. 145-147 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (d, *J*= 2.8 Hz, 1H), 8.17 (dd, *J*= 8.6, 2.8 Hz, 1H), 7.74 (d, *J*= 8.6 Hz, 1H), 7.28 (bs, 1H), 1.50 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 148.3, 143.5, 139.8, 137.7, 125.2, 123.752.6, 50.2, 31.3, 29.0. IR (neat, cm^{-1}): 3296 (m), 2968 (m), 1648 (s), 1525 (s), 1347 (s). HRMS (APCI) Calcd for $C_{15}H_{23}N_2O_3S$ ($M+H^+$): 311.1429. Found: 311.1424.

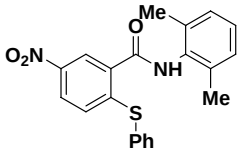


***N*-*tert*-Butyl-5-nitro-2-phenylsulfanyl-benzamide:** From *N*-*tert*-butyl-2-chloro-5-nitro-benzamide (300 mg, 1.2 mmol) and phenyl sodium thiolate (168 mg, 1.3 mmol) in 5 ml DMF at room temperature with overnight stirring was obtained 287 mg of pure product after quenching with iced water and collecting the crystals. Yield: 80 %. White crystals, M.p. 163-164 ^{o}C. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.75). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J*= 2.5 Hz, 1H), 7.96 (dd, *J*= 8.8, 2.5 Hz, 1H), 7.54-7.52 (m, 2H), 7.47-7.45 (m, 3H), 6.91 (d, *J*= 8.8 Hz, 1H), 5.93 (bs, 1H), 1.31 (s, 9H). IR (neat, cm^{-1}): 3246 (m), 1648 (s), 1513 (s), 1339 (s). HRMS (APCI) Calcd for $C_{17}H_{19}N_2O_3S$ ($M+H^+$): 331.1116. Found: 311.1111.

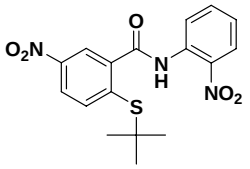


2-*tert*-Butylsulfanyl-*N*-(2,6-dimethyl-phenyl)-5-nitro-benzamide: From 2-chloro-*N*-*tert*-(2,6-dimethyl-phenyl)-5-nitro-benzamide (7.85 g, 26 mmol) and *tert*-butyl sodium thiolate (3.18 g, 28 mmol) in 100 ml DMF at room temperature with overnight stirring was obtained pure product after quenching with iced water and collecting the crystals. Yield: Quantitative. Light yellow crystals, M.p. 188-189 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J*= 2.5 Hz, 1 H), 8.57 (bs, 1H), 8.27 (dd, *J*= 8.5, 2.5 Hz, 1H), 7.85 (d, *J*= 8.6 Hz, 1H), 7.17 (m, 3H), 2.38 (s, 6H), 1.43 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 148.1, 142.3, 139.1, 138.0, 135.6, 133.7, 128.6, 127.8, 125.4, 124.2, 50.6, 31.4,

19.3. IR (neat, cm^{-1}): 3239 (m), 1652 (s), 1521 (s). HRMS (FAB) Calcd for $C_{19}H_{23}N_2O_3S$ ($M+H^+$): 359.1429. Found: 359.1417.

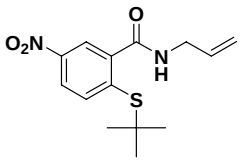


***N*-(2,6-Dimethyl-phenyl)-5-nitro-2-phenylsulfanyl-benzamide:** From 2-chloro-*N*-*tert*-(2,6-dimethyl-phenyl)-5-nitro-benzamide (166 mg, 0.50 mmol) and phenyl sodium thiolate (89 mg, 0.70 mmol) in 4 ml DMA at room temperature with overnight stirring was obtained 190 mg of pure product after quenching with iced water and collecting the crystals. Yield: 93 %. White crystals, M.p. 229-230 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J*= 2.4 Hz, 1H), 8.04 (dd, *J*= 9.0, 2.4 Hz, 1H), 7.60-7.58 (m, 2H), 7.52-7.49 (m, 4H), 7.21-7.15 (m, 3H), 6.99 (d, *J*= 9.0 Hz, 1H), 2.39 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 148.8, 144.9, 135.7, 135.6, 133.9, 133.2, 130.5, 130.4, 130.3, 128.7, 128.3, 128.2, 125.4, 123.3, 19.0. IR (neat, cm^{-1}): 3246 (m), 1648 (s), 1513 (s), 1339 (s). HRMS (FAB) Calcd for $C_{21}H_{18}N_2O_3SLi$ ($M+Li^+$): 385.1180. Found: 385.1198.

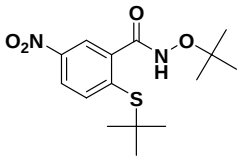


2-*tert*-Butylsulfanyl-5-nitro-*N*-(2-nitro-phenyl)-benzamide: From 2-chloro-5-nitro-*N*-(2-nitro-phenyl)-benzamide (5.08 g, 16 mmol) and *tert*-butyl sodium thiolate (2.04 g, 18 mmol) in 70 ml DMF at room temperature with overnight stirring was obtained pure product after quenching with iced water and collecting the solid. Yield: 96 %. Light orange solid, M.p. 118-119 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 11.0 (bs, 1H), 8.87 (dd, *J*= 8.6, 1.3 Hz, 1H), 8.62 (d, *J*= 2.5 Hz, 1H), 8.30 (dd, *J*= 8.6, 2.8 Hz, 1H), 8.27 (dd, *J*=

8.6, 1.3 Hz, 1H), 7.86 (d, *J*= 8.7 Hz, 1H), 7.76 (dt, *J*= 8.6, 1.6 Hz, 1H), 7.30 (dt, *J*= 8.6, 1.3 Hz, 1H), 1.37 (s, 9H). IR (neat, cm^{-1}): 3343 (m), 2964 (m), 1687 (s), 1606 (s), 1498 (s), 1339 (s), 1278 (s). HRMS (APCI) Calcd for $C_{17}H_{18}N_3O_5S$ ($M+H^+$): 376.0967. Found: 376.0962.



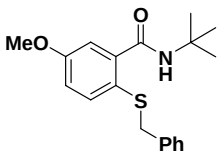
***N*-Allyl-2-*tert*-butylsulfanyl-5-nitro-benzamide:** From *N*-allyl-2-chloro-5-nitro-benzamide (2.74 g, 11 mmol) and *tert*-butyl sodium thiolate (1.40 g, 13 mmol) in 50 ml DMF at room temperature with overnight stirring was obtained 2.93 g of pure product after quenching with iced water and collecting the solid. Yield: 87 %. Light yellow solid, M.p. 100-101 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J*= 2.4 Hz, 1H), 8.21 (dd, *J*= 8.6, 2.8 Hz, 1H), 7.77 (d, *J*= 8.6 Hz, 1H), 7.70 (bs, 1H), 6.07-5.95 (m, 1H), 5.36 (dd, *J*= 17.1, 1.4 Hz, 1H), 5.24 (dd, *J*= 10.5, 1.4 Hz, 1H), 4.13 (tt, *J*= 5.7, 1.4 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 148.3, 141.9, 140.0, 137.9, 133.6, 125.7, 124.2, 117.6, 50.6, 42.9, 31.2. IR (neat, cm^{-1}): 3281 (m), 1644 (s), 1521 (s), 1347 (s). HRMS (APCI) Calcd for $C_{14}H_{19}N_2O_3S$ ($M+H^+$): 295.1116. Found: 295.1110.



***N*-*tert*-Butoxy-2-*tert*-butylsulfanyl-5-nitro-benzamide:** From *N*-*tert*-butoxy-2-chloro-5-nitro-benzamide (1.64 g, 6.0 mmol) and *tert*-butyl sodium thiolate (0.78 g, 7.0 mmol) in 26 ml DMF with ethylene glycol (0.4 ml, 7.0 mmol) at room temperature with over night stirring was obtained 1.60 g of pure product after quenching with iced water and the

collecting solid. Yield: 82 %. White powder, M.p.191-192 ^{o}C. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.50). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.77 (s, 1H), 8.24 (dd, *J*= 8.6, 2.8 Hz, 1H), 7.79 (d, *J*= 8.6 Hz, 1H), 1.38 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 148.4, 140.7, 139.8, 137.9, 125.9, 124.6, 82.9, 50.9, 31.2, 26.7. IR (neat, cm^{-1}): 3192 (s), 2980 (s), 1652 (s), 1521 (s), 1347 (s). HRMS (APCI) Calcd for $C_{15}H_{23}N_2O_4S$ ($M+H^+$): 327.1379. Found: 327.1373.

***p*-Methoxy Substituted Thioether:**



2-Benzylsulfanyl-*N*-*tert*-butyl-5-methoxy-benzamide: To 2-bromo-*N*-*tert*-butyl-5-methoxy-benzamide (0.908 g, 3.2 mmol) was added anhydrous potassium carbonate (0.881 g, 6.4 mmol), and CuI (0.044 g, 0.2 mmol) with a stir bar in a microwave reactor pressurized tube. The tube was sealed and run through three cycles of vacuum evacuation with argon replacement. Ethylene glycol (0.4 ml, 7.2 mmol) and benzyl thiol (0.6 ml, 5.0 mmol) in 8 ml of isopropanol were then added. The reaction was place in a CEM Discover Microwave reactor and run through ten 60 minute cycles (P= 300 watts, Pressure= 200 psi, Temp= 80 ^{o}C). After cooling the reaction, diethyl ether was added and the mixture was filtered through silica. The filtrate was washed with saturated ammonium chloride and brine, then dried with $MgSO_4$, filtered and condensed. Column chromatography with 5:1 hex:EtOAc gave 0.547 g of pure 2-benzylsulfanyl-*N*-*tert*-butyl-5-methoxy-benzamide with recovered starting material. Yield: 47 %. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J*= 2.8 Hz, 1H), 7.04-6.97

(m, 4H), 6.88-6.86 (m, 2H), 6.70 (bs, 1H), 6.58 (dd, *J*= 8.6, 2.8 Hz, 1H, 3.75 (s, 2H), 3.59 (s, 3H), 1.22 (s, 9H). IR (neat, cm^{-1}): 3282 (w), 2967 (m), 1646 (s), 1225 (s).

General Methods for Oxidative Ring Closure:

Method D via m-CPBA, Thermolysis

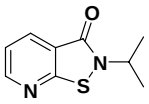
The protected thioether (1.0 equiv.) was dissolved in 25 ml of CH_2Cl_2 and cooled to 0 ^oC. 3-Chloroperbenzoic acid or *m*-CPBA (77 %, Aldrich, 1.1 equiv.) was added in parts, and the mixture was monitored by TLC. The reaction was allowed to come to room temperature and quenched with saturated $NaHCO_3$ and brine. If solid precipitated, it was collected by filtration. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was combined with the collected precipitate to give the crude sulfoxide which was taken directly to the next step.

Unless otherwise noted, the crude sulfoxide was dissolved in dry degassed toluene (0.3 M) and dry pyridine (0.8 M). The solution was refluxed with an azeotropic removal of water (for small scale, dry, crushed 4 Å molecular sieves were added). After one hour, the reaction was cooled, filtered if necessary, and concentrated to dryness to give pure product.

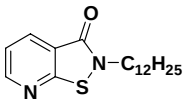
Method E via TMSCl, DMSO

The protected thioether (1.0 equiv.) was dissolved in dry 0.3 M CH_2Cl_2 under argon with stirring. At room temperature, dry DMSO (2.2 equiv.) were added followed by TMSCl (2.2 equiv.). The reaction was monitored by TLC. If starting material remained after 12 hours, DMSO and TMSCl was added in 1.0 equiv. increments until no

starting material remained. The reaction was concentrated to dryness and the resulting solid was washed with DI water to remove excess reagents to give pure benzoisothiazolinone.

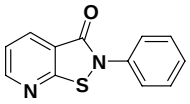


2-Isopropyl-isothiazolo[5,4-*b*]pyridin-3-one: *Method D:* From 2-*tert*-butylsulfanyl-*N*-isopropyl-nicotinamide (28.6 g, 113 mmol) in 400 ml of $CHCl_3$ and *m*-CPBA (25 g, 150 mmol) was obtained 26 g of the crude sulfoxide after addition of 20 ml of Me_2S to destroy any remaining peracid and extracting with 1 M $NaHCO_3$, washing with water and brine. The concentrated green oil was used directly in the next step without further purification. From the crude sulfoxide in 400 ml of dry Toluene and 130 ml of dry pyridine was obtained 17 g of pure product. Yield: 92 % for two steps. Light yellow solid, M.p. 56-59 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J*= 4.8, 1.6 Hz, 1 H), 8.28 (dd, *J*= 3.9, 1.9 Hz, 1 H), 7.36 (dd, *J*= 7.9, 4.8 Hz, 1 H), 5.05 (m, 1 H), 1.45 (d, *J*= 6.7 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2, 162.3, 153.4, 134.6, 120.6, 120.3, 45.6, 22.2. IR (neat, cm^{-1}): 1660 (s). HRMS (FAB) Calcd for $C_9H_{11}N_2OS$ ($M+H^+$): 195.0592. Found: 195.0592.



2-Dodecyl-isothiazolo[5,4-*b*]pyridin-3-one: *Method D:* From 2-*tert*-butylsulfanyl-*N*-dodecyl-nicotinamide **(**11.9 g, 31 mmol) in 115 ml of $CHCl_3$ and *m*-CPBA (7.74 g, 35 mmol) was obtained 11.0 g of the crude sulfoxide after addition of 20 ml of Me_2S to destroy any remaining peracid and extracting with 1 M $NaHCO_3$, washing with water and brine. The concentrated solid was used directly in the next step without further

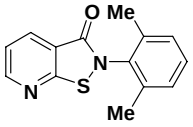
purification. From the crude sulfoxide in 110 ml of dry Toluene and 4 ml of dry pyridine was obtained 3.73 g of pure product after solvent was removed under vacuum. Yield: 37 % for two steps. Light yellow solid, M.p. 58-60 ^{o}C. TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.43). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J*= 4.8, 1.6 Hz, 1 H), 8.28 (dd, *J*= 7.9, 1.9 Hz, 1H), 7.36 (dd, *J*= 7.6, 4.8 Hz, 1H), 3.93 (t, *J*= 7.3 Hz, 2H), 1.79 (dt, *J*= 14.0, 7.3 Hz, 2H), 1.26 (m, 18H), 0.88 (t, *J*= 6.7 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 162.3, 153.6, 134.9, 120.8, 119.8, 44.1, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 26.7, 22.8, 14.3. IR (neat, cm^{-1}): 2914 (s), 2849 (s), 1656 (s). HRMS (FAB) Calcd for $C_{18}H_{29}N_2OS$ ($M+H^+$): 327.2082. Found: 327.2082.



2-Phenyl-isothiazolo[5,4-*b*]pyridin-3-one [8] : *Method D:* From 2-benzylsulfanyl-*N*-phenyl-nicotinamide (12.0 g, 37 mmol) in 300 ml of CH_2Cl_2 and *m*-CPBA (8.40 g, 50 mmol) was obtained 14.1 g the crude sulfoxide after the reaction was quenched with 2 % NaOH, filtered, the precipitate was collect, and the organic phase was dried and concentrated and combined with the precipitate. This was used directly in the next step without further purification. The crude sulfoxide was dissolved in 250 ml of CH_2Cl_2 was cooled to 0 ^{o}C and treated with trichloroacetic anhydride (8.4 ml, 46.0 mmol). The mixture became homogenous in 15 min, and was stirred overnight while warming to 25 ^{o}C. After quenching with 2 M NaOH, extracting the aqueous phase with $CHCl_3$, the combined organic phases were dried and concentrated. The residue was recrystallized

[8] Monge, A.; Martinez-Merino, V.; Fernandez-Alvarez, E. *J. Heterocycl. Chem.* **1985**, *22*, 1353-1356.

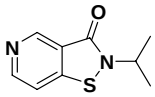
from hex:EtOAc to give 6.50 g of pure product. Yield: 75 % in two steps (1.2 g, 34 % for two steps using toluene/Et_3N thermolysis). Beige crystals, M.p. 122-124 ^oC. TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.42). ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J*= 4.8, 1.9 Hz, 1 H), 8.34 (dd, *J*= 7.9, 1.6 Hz, 1H), 7.71 (m, 2H), 7.51 (m, 2 H), 7.43 (dd, *J*= 7.4, 4.4 Hz, 1H), 7.34 (tt, *J*= 7.6, 0.95 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6, 162.0, 154.2, 136.7, 135.5, 129.7, 127.7, 125.0, 121.2, 120.0. IR (neat, cm^{-1}): 3065 (m), 1660 (s), 1563 (s). HRMS (FAB) Calcd for $C_{12}H_9N_2OS$ ($M+H^+$): 229.0436. Found: 229.0436.



2-(2,6-Dimethyl-phenyl)-isothiazolo[5,4-*b*]pyridin-3-one [9] : *Method D:* From 2-benzylsulfanyl-*N*-2,6-dimethylphenyl-nicotinamide (1.03 g, 3.0 mmol) in 15 ml of CH_2Cl_2 and *m*-CPBA (0.730 g, 3.2 mmol) was obtained 1.03 g the crude sulfoxide after the reaction was quenched with 2 % NaOH, filtered, the precipitate was collect, and the organic phase was dried and concentrated and combined with the precipitate. This was used directly in the next step without further purification. From the crude sulfoxide in 2 ml of CH_2Cl_2 with trichloroacetic anhydride (0.6 ml, 3.1 mmol), was obtained 1.04 g of pure product after quenching with 2 M NaOH, extracting the aqueous phase with $CHCl_3$, and drying the combined organic phases. Yield: Quantitative for two steps (1.2 g, 34 % for two steps using toluene/Et_3N thermolysis). TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.57). ^1H NMR (600 MHz, $CDCl_3$) δ 9.01 (d, *J*= 1.9 Hz, 1 H), 8.55 (dd, *J*= 9.1, 2.4 Hz,

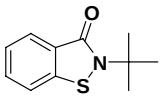
[9] Monge, A.; Martinez-Merino, V.; Fernandez-Alvarez, E. *J. Heterocycl. Chem.* **1988**, *25*, 23-28.

1H), 7.79 (d, *J*= 8.6 Hz, 1H), 7.32 (t, *J*= 8.1 Hz, 1H), 7.21 (d, *J*= 7.6 Hz, 2H), 2.21 (s, 6H).

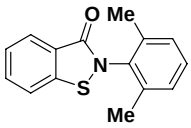


2-Isopropyl-isothiazolo[4,5-*c*]pyridin-3-one: *Method D:* From 4-*tert*-butylsulfanyl-*N*-isopropyl-nicotinamide (1.17 g, 4.6 mmol) in 15 ml of dry chloroform and *m*-CPBA (1.07 g, 77 % from Aldrich) was obtained 0.700 g of pure 2-isopropyl-isothiazolo[*4,5-c*]pyridin-3-one after the reaction was quenched with 1 M $NaHCO_3$ and brine, the aqueous was extracted with dichloromethane and the combined organic layers were dried with $MgSO_4$, filtered and condensed. The resulting residue was passed through a silica column with 1:1 EtOAc:Et_2O to give the pure product in one step. Yield: 77 % (Quantitative on smaller scale). Clear yellow oil. TLC (silica gel, 1:1 EtOAc:Et_2O, R_f= 0.30). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.67 (d, *J*= 5.2 Hz, 1H), 7.54 (d, *J*= 5.6 Hz, 1H), 5.03-4.96 (m, 1H), 1.44 (d, *J*= 6.7 Hz, 1H). IR (neat, cm^{-1}): 2972 (w), 1644 (s), 1583 (s).

From the Thiol: To *N*-isopropyl-4-mercapto-nicotinamide (51 mg, 0.26 mmol) in 2 ml of dry DMA was added catalytic CuMeSal (5.8 mg, 10 mol %, 0.027 mmol) and 4,4'-di-*tert*-butylbiphenyl (65 mg, 0.24 mmol) internal standard. The reaction was placed in a 50 ^oC oil bath and monitored by HPLC. When no starting material remained, the reaction was quenched with DI water and extracted with chloroform. The organic layer was dried with $MgSO_4$, filtered and condensed. The residue was run on a prep silica plate with 2:1 hex:EtOAc to give 22 mg of 2-isopropyl-isothiazolo[*4,5-c*]pyridin-3-one with spectral data matching authentic sample. Yield: 43 %. Light yellow oil.



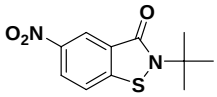
2-*tert*-Butyl-benzo[*d*]isothiazol-3-one [10] : *Method D:* From *N*-*tert*-Butyl-2-*tert*-butylsulfanyl-benzamide (2.70 g, 10 mmol) and *m*-CPBA (2.20 g, 13 mmol) in 30 ml CH_2Cl_2 was obtained 99 % sulfoxide after workup. From the sulfoxide, 34 ml of dry, degassed toluene and 12 ml of dry pyridine with molecular sieves was obtained product. Yield: Quantitative. Colorless crystals, M.p. 51-53 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J*= 8.1 Hz, 1H), 7.57 (t, *J*= 8.6 Hz, 1H), 7.51 (d, *J*= 7.6 Hz, 1H), 7.37 (t, *J*= 7.1 Hz, 1H), 1.72 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 139.6, 131.5, 127.1, 126.3, 125.3, 119.9, 58.8, 28.6. IR (neat, cm^{-1}): 2972 (s), 1640 (s), 1594 (s). HRMS (FAB) Calcd for $C_{11}H_{13}NOS$ (M^+): 207.0718. Found: 207.0714.



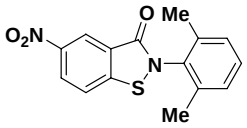
2-(2,6-Dimethyl-phenyl)-benzo[*d*]isothiazol-3-one: *Method D:* From 2-*tert*-butylsulfanyl-*N*-(2,6-dimethyl-phenyl)-benzamide (3.07 g, 9.8 mmol) and *m*-CPBA (1.77 g, 10.3 mmol) in 25 ml CH_2Cl_2 was obtained 2.23 g of the sulfoxide after workup. From the sulfoxide (2.23 g, 6.8 mmol), 23 ml of dry degassed toluene and 8 ml of dry pyridine with molecular sieves was obtain 1.70 g of pure product after recrystallization from hexanes. Yield: 68 % for two steps. TLC (silica gel, 2:1 hex:EtoAc, R_f= 0.33). ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J*= 7.6 Hz, 1 H), 7.69 (dt, *J*= 7.0, 1.3 Hz, 1 H), 7.62 (d, *J*=

[10] (a) Sano, T.; Takagi, T.; Gama, Y.; Shibuya, I.; Shimizu, M. *Synthesis* **2004**, 1585-1588. (b) Kamigata, N.; Hashimoto, S.; Kobayashi, M. *Org. Prep. Proced. Int.* **1983**, *15*, 315-319.

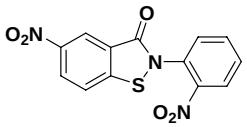
7.9 Hz, 1 H), 7.47 (dt, *J*= 7.9, 0.6 Hz, 1 H), 7.27 (d, *J*= 7.0 Hz, 1 H), 7.18 (d, *J*= 7.6 Hz, 2 H), 2.21 (s, 6 H).



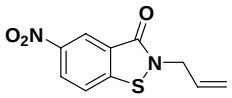
2-*tert*-Butyl-5-nitro-benzo[*d*]isothiazol-3-one: *Method E:* From *N-tert*-butyl-2-tert-butylsulfanyl-5-nitro-benzamide (8.11 g, 26 mmol), 7 ml TMSCl, and 4 ml DMSO in 80 ml dry CH_2Cl_2 with overnight stirring was obtained pure product. Yield: Quantitative. Clear Crystals. M.p. 205-210 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 8.81 (d, *J*= 1.9 Hz, 1H), 8.42 (dd, *J*= 8.6, 2.4 Hz, 1H), 7.66 (d, *J*= 8.6 Hz, 1H), 1.73 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 146.1, 145.7, 127.7, 125.9, 122.5, 120.9, 59.9, 28.6. IR (neat, cm^{-1}): 1637 (s), 1521 (s), 1366 (m). HRMS (ESI) Calcd for $C_{11}H_{13}N_2O_3S$ ($M+H^+$): 253.0647. Found: 253.0642.



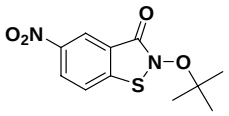
2-(2,6-Dimethyl-phenyl)-5-nitro-benzo[*d*]isothiazol-3-one: *Method D:* From *2-tert*-butylsulfanyl-*N*-(2,6-dimethyl-phenyl)-5-nitro-benzamide (1.17 g, 4.0 mmol) and *m*-CPBA (0.84 g, 5.0 mmol) in 13 ml CH_2Cl_2 was obtained pure sulfoxide. From the sulfoxide, 13 ml of dry, degassed toluene and 4 ml of dry pyridine with molecular sieves was obtained 0.92 mg of pure product. Yield: 81 %. Yellow crystals, M.p. 240-242 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, *J*= 2.2 Hz, 1H), 8.55 (dd, *J*= 8.9, 2.2 Hz, 1H), 7.79 (d, *J*= 8.8 Hz, 1H), 7.32 (t, *J*= 7.9 Hz, 1H), 7.21 (d, *J*= 7.6 Hz, 2 H), 2.21 (s, 6H). IR (neat, cm^{-1}): 1652 (s), 1602 (s), 1521 (s), 1339 (s), 1293 (s). HRMS (FAB) Calcd for $C_{15}H_{13}N_2O_3S$ ($M+H^+$): 301.0649. Found: 301.0647.



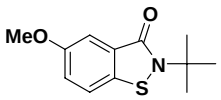
5-Nitro-2-(2-nitro-phenyl)-benzo[*d*]isothiazol-3-one: *Method E:* From pure 2-*tert*-butylsulfanyl-5-nitro-*N*-(2-nitro-phenyl)-benzamide (1.52 g, 4.0 mmol), 1 ml TMSCl, and 0.6 ml DMSO in 10 ml CH_2Cl_2 with overnight stirring was obtained pure 5-nitro-2-(2-nitro-phenyl)-benzo[*d*]isothiazol-3-one. Yield: Quantitative. Yellow crystals, M.p. 250-251 ^oC. ^1H NMR (400 MHz, DMSO) δ 8.60-8.58 (m, 2H), 8.41 (dd, *J*= 8.6, 1.3 Hz, 1H), 8.20 (dd, *J*= 8.3, 1.3 Hz, 1H), 7.96 (dt, *J*= 7.9, 1.3 Hz, 1H), 7.84 (dd, *J*= 7.9, 1.3 Hz, 1H), 7.78 (dt, *J*= 7.3, 1.3 Hz, 1H). IR (neat, cm^{-1}): 1671 (s), 1502 (s), 1339 (s), 1285 (s). HRMS (APCI) Calcd for $C_{13}H_8N_3O_5S$ ($M+H^+$): 318.0185. Found: 318.0179.



2-Allyl-5-nitro-benzo[*d*]isothiazol-3-one: *Method E:* From pure *N*-allyl-2-*tert*-butylsulfanyl-5-nitro-benzamide (1.06 g, 4.0 mmol), 1.0 ml TMSCl, and 0.6 ml DMSO in 10 ml CH_2Cl_2 with overnight stirring was obtained 0.81 g of pure 2-allyl-5-nitro-benzo[*d*]isothiazol-3-one. Yield: 96 %. Yellow crystals, M.p. 118-120 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.44 (d, *J*= 7.6 Hz, 1H), 7.72 (d, *J*= 8.6 Hz, 1H), 5.97-5.90 (m, 1H), 5.37 (m, 2H), 4.53 (dd, *J*= 6.2, 0.95 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.8, 146.6, 146.2, 131.8, 126.3, 125.5, 122.8, 121.6, 120.6, 46.7. IR (neat, cm^{-1}): 3096 (m), 1640 (s), 1513 (s), 1339 (s). HRMS (APCI) Calcd for $C_{10}H_9N_2O_3S$ ($M+H^+$): 237.0334. Found: 237.0329.



2-*tert*-Butoxy-5-nitro-benzo[*d*]isothiazol-3-one: *Method E:* From pure *N*-*tert*-butoxy-2-*tert*-butylsulfanyl-5-nitro-benzamide (0.506 g, 1.5 mmol), 0.4 ml TMSCl, and 0.3 ml DMSO in 5 ml CH_2Cl_2 with overnight stirring was obtained 0.321 g of pure 2-*tert*-butoxy-5-nitro-benzo[*d*]isothiazol-3-one. Yield: 80 %. ^{1}H NMR (600 MHz, DMSO) δ 8.53-8.51 (m, 2H), 8.20 (d, *J*= 9.1 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 146.1, 146.0, 127.2, 123.1, 121.5, 87.4, 27.0. IR (neat, cm^{-1}): 3096 (w), 2984 (w), 1671 (s), 1517 (s), 1339 (s).



2-*tert*-Butyl-5-methoxy-benzo[*d*]isothiazol-3-one: *Method E:* From 2-benzylsulfanyl-*N*-*tert*-butyl-5-methoxy-benzamide (0.547 g, 1.7 mmol), 0.5 ml TMSCl, and 0.3 ml DMSO in 5 ml CH_2Cl_2 with overnight stirring was obtained 0.381 g of 2-*tert*-butyl-5-methoxy-benzo[*d*]isothiazol-3-one. Yield: 96 %. White crystals, M.p. 95-96 ^{o}C. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.25). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J*= 2.8 Hz, 1H), 7.36 (d, *J*= 9.1 Hz, 1H), 7.19 (dd, *J*= 9.1, 2.8 Hz, 1H), 3.85 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 158.3, 131.6, 128.0, 122.3, 120.9, 107.1, 58.9, 55.8, 28.5. IR (neat, cm^{-1}): 1637 (s), 1475 (s).

General Thiol Ester Synthesis:

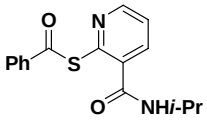
Method F via $NaBH_4$ Reduction and Acid Chloride Quench

The appropriate benzoisothiazolinone was placed in 0.2 M EtOH or dioxane in a round bottom flask under nitrogen or argon with stirring. Sodiumborohydride ($NaBH_4$) (1.1 equiv.) was added at 0 ^{o}C and the reaction immediately began to bubble turning

bright yellow. After allowing the reaction to warm to room temperature for 30 minutes, the bubbles ceased. If dioxane was used, the reaction was concentrated to dryness and dry 0.2 M THF was added. If the pH was below 7, it was made basic by adding anhydrous K_2CO_3 (1.0 equiv.). 4-Methyl benzoyl chloride or benzoic anhydride (1.1-1.2 equiv) was then added at 0 ^oC and allowed to warm to room temperature overnight. The reaction was then quenched with H_2O unless otherwise noted. The product was collected by filtration or aqueous workup using EtOAc. The extracted organic layers were combined, dried with $MgSO_4$, filtered, and condensed to give pure thiol ester.

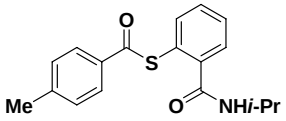
Method G via PEt_3 and Arylcarboxylic Acid

The appropriate benzoisothiazolinone and toluic acid were placed in a dry round bottom flask under argon with stirring. 1 M Triethyl phosphine (PEt_3) (1.1 equiv.) was added at room temperature. The reaction went from light yellow to bright yellow instantly. The reaction was stirred at room temperature overnight at which time it was quenched with H_2O. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered, and condensed. The resulting oil was filtered through a short silica column to give pure thiol.

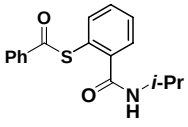


***S*-3-(Isopropylcarbamoyl)pyridin-2-yl benzothioate:** *Method G:* From 2-Isopropyl-isothiazolo[5,4-*b*]pyridin-3-one (1.00 g, 5.1 mmol), benzoic acid (0.692 g, 5.6 mmol) in 25 ml of dry THF and PEt_3 (5.7 ml, 5.6 mmol) was obtained 1.80 g of pure thiol ester after recrystallization from EtOAc and hexane. Yield: 50 %. Light yellow crystals, M.p. 84-86 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J*= 4.8, 1.9 Hz, 1 H), 8.02 (dd, *J*= 8.6,

1.3 Hz, 2 H), 7.99 (dd, *J*= 7.6, 1.6 Hz, 1H), 7.66 (tt, *J*= 7.3, 1.3 Hz, 1 H), 7.52 (t, *J*= 7.9 Hz, 2H), 7.48 (dd, *J*= 7.6, 4.8 Hz, 1H), 6.18 (br d, *J*= 7.6 Hz, 1 H), 4.18 (m, 1H), 1.08 (d, *J*= 6.4 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.6, 166.1, 151.4, 146.6, 140.4, 137.1, 136.1, 134.6, 129.2, 127. 9, 124.6, 42.1, 22.5. IR (neat, cm^{-1}): 3273 (m), 1679 (s), 1579 (s). HRMS (FAB) Calcd for $C_{16}H_{16}LiN_2O_2S$ ($M+Li^+$): 307.1093. Found: 307.1093.

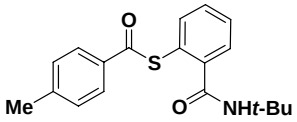


***S*-2-(Isopropylcarbamoyl)phenyl 4-methylbenzothioate:** *Method F:* From 2,2'-dithio-bis(*N*-isopropyl)benzamide[11] (2.00 g, 5.2 mmol), $NaBH_4$ (0.457 g, 12 mmol), *p*-toluoyl chloride (1.6 ml, 12 mmol), and K_2CO_3 (4.50 g, 32 mmol) in 12 ml of EtOH was obtained 2.30 g of pure thiol ester after quenching with saturated $NaHCO_3$, extracting the aqueous layer with Et_2O three times, then drying the organic layer with $MgSO_4$, filtering and condensing. Yield: 71 %. White solid, M.p. 99-102 ^oC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (dd, *J*= 8.2, 0.95 Hz, 2H), 7.67-7.60 (m, 2H), 7.56-7.46 (m, 5H), 6.00 (br d, *J*= 7.9 Hz, 1H), 4.22-4.14 (m, 1H), 1.07 (d, *J*= 6.3 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.5, 167.8, 143.7, 137.2, 136.3, 134.4, 130.8, 129.1, 128.7, 127.9, 123.8, 41.9, 22.7. IR (neat, cm^{-1}) 3281 (w), 2972 (m), 1637 (s), 1532 (s). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68; S, 10.71. Found: C, 68.37; H, 5.70; N, 4.72; S, 10.75.

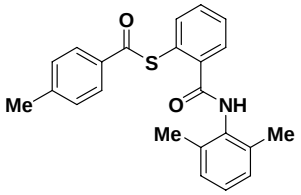


[11] (a) Prepared by modifying known literature procedure: Shinkai, H.; Maeda, K.; Yamasaki, T.; Okamoto, H.; Uchida, I.. *J. Med. Chem.* **2000,** 43, 3566-3572. (b) Known compound: Gialdi, F.; Ponci, R.; Baruffini, A. *Farmaco, Edizione Scientifica* **1959,** 14, 648-665.

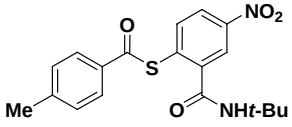
***S*-2-(Isopropylcarbamoyl)phenyl benzothioate:** *Method F:* From 2,2'-dithio-bis(*N*-isopropyl)benzamide[11] (0.250 g, 0.64 mmol), $NaBH_4$ (0.061 g, 1.61 mmol), and benzoic anhydride (0.336 g, 1.48 mmol) in 1.5 ml of EtOH was obtained 0.230 g of pure thiol ester after quenching with saturated $NaHCO_3$. Yield: 60 %. Beige solid, M.p. 104-106 ^oC. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (dd, *J*= 8.2, 0.95 Hz, 2H), 7.67-7.60 (m, 2H), 7.56-7.46 (m, 5H), 6.00 (br d, *J*= 7.9 Hz, 1H), 4.22-4.14 (m, 1H), 1.07 (d, *J*= 6.3 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.5, 167.8, 143.7, 137.2, 136.3, 134.4, 130.8, 129.1, 128.7, 127.9, 123.8, 41.9, 22.7. IR (neat, cm^{-1}) 3281 (w), 2972 (m), 1637 (s), 1532 (s). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68; S, 10.71. Found: C, 68.37; H, 5.70; N, 4.72; S, 10.75.



***S*-(2-*tert*-Butylcarbamoyl-phenyl) ester**: *Method F:* From 2-*tert*-butyl-benzo[*d*]isothiazol-3-one (2.00 g, 10 mmol), $NaBH_4$ (0.43 g, 11 mmol), *p*-toluoyl chloride (2.2 ml, 17 mmol) in 50 ml of dioxane/THF was obtained thiol ester. After recrystallization from dry toluene, 0.950 g of pure product was obtained. Yield: 29 %. Light yellow crystals, M.p. 106-107 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 7.95-7.39 (m, 1H), 7.61-7.44 (m, 3H), 7.32-7.26 (m, 4H), 6.01 (bs, 1H), 2.45 (s, 3H), 1.29 (s, 9H). IR (neat, cm^{-1}): 2968 (m), 1668 (s), 1525 (s). Anal. Calcd for $C_{19}H_{21}NO_5S$ (MW=327.44): C, 69.69; H, 6.46; N, 4.28; O, 9.77; S, 9.79. Found: C, 69.48; H, 6.50; N, 4.34; S, 9.70.

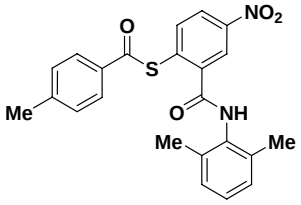


***S*-2-(2,6-Dimethylphenylcarbamoyl)phenyl 4-methylbenzothioate:** *Method F:* From 2-(2,6-Dimethyl-phenyl)-benzo[*d*]isothiazol-3-one (1.70 g, 7.0 mmol), $NaBH_4$ (0.28 g, 8.0 mmol), anhydrous K_2CO_3 (2.00 g, 14 mmol), *p*-toluoylchloride (1.0 ml, 8.0 mmol), in 25 ml of EtOH was obtained 2.10 g (94 %) crude thiol ester. Recrystallization from toluene/Hex gave 1.50 g of clean thiol ester. Yield: 60 %. White solid, M.p.159-160 ^{o}C. TLC (silica gel, 2:1 hex:EtoAc, R_f= 0.33). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J*= 6.3, 1.6 Hz, 2 H), 7.8 (dd, *J*= 7.6, 1.3 Hz, 1 H), 7.64-7.53 (m, 3 H), 7.43 (br s, 1 H), 7.29 (d, *J*= 7.9 Hz, 2 H), 7.13-7.04 (m, 3 H), 2.45 (s, 3 H), 2.25 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 167.0, 145.5, 143.3, 137.6, 135.9, 133.7, 133.7, 130.8, 130.65, 129.7, 129.0, 128.4, 128.0, 127.7, 124.4, 22.0, 18.9. IR (neat, cm^{-1}): 3254 (br, s), 2964 (s), 2926 (s), 1671 (s), 1606 (m), 1509 (s), 1475 (m), 903 (s). HRMS (APCI) Calcd for $C_{23}H_{22}NO_2S$ ($M+H^+$): 376.1317. Found: 376.1366.

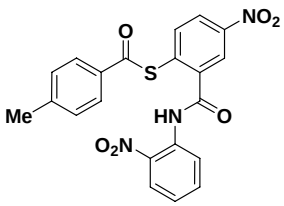


***S*-2-(*tert*-Butylcarbamoyl)-4-nitrophenyl 4-methylbenzothioate:** *Method G:* From of 2-*tert*-butyl-5-nitro-benzo[*d*]isothiazol-3-one (0.502 g, 2.0 mmol), *p*-toluic acid (0.298 g, 2.2 mmol), and PEt_3 (2.2 ml, 2.2 mmol) in 10 ml THF was obtained 0.441 g of pure thiol ester after column filtration with 2:1 hex:EtOAc. Yield: 60 %. Yellow solid, M.p. 130-135 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J*= 2.2 Hz, 1H), 8.28 (dd, *J*= 8.6, 2.5 Hz, 1H), 7.92 (d, *J*= 8.3 Hz, 2H), 7.75 (d, *J*= 8.6 Hz, 1H), 7.33 (d, *J*= 8.0 Hz, 2H), 5.95 (bs, 1H), 2.47 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.7, 165.6, 148.7, 146.1, 144.9, 138.1, 133.2, 132.4, 129.9, 127.9, 124.2, 123.3, 52.4, 28.6, 22.0. IR (neat, cm^{-1}): 3296 (w), 2972 (w), 1671 (s), 1648 (s), 1525 (s), 1347 (s). Anal. Calcd for

$C_{19}H_{20}N_2O_4S$ (MW=372.44): C, 61.27; H, 5.41; N, 7.52; O, 17.18; S, 8.61. Found: C, 61.43; H, 5.55; N, 7.27; S, 8.41.

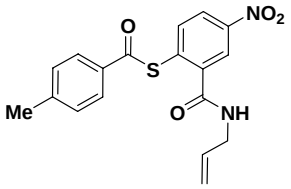


***S*-2-(2,6-Dimethylphenylcarbamoyl)-4-nitrophenyl 4-methylbenzothioate:** *Method F:* From 2-(2,6-dimethyl-phenyl)-5-nitro-benzo[*d*]isothiazol-3-one (3.03 g, 10 mmol), $NaBH_4$ (0.419 g, 11 mmol), $NaHCO_3$ (0.815 g, 10 mmol), and *p*-toluoyl chloride (1.4 ml, 11 mmol) in 50 ml of dioxane/THF was obtained 2.14 g of pure 4-methyl-thiobenzoic acid 2-(2,6-dimethyl-phenylcarbamoyl)-4-nitro-phenyl ester after filtering reaction through celite (25 g) and precipitating by adding hexane. Yield: 51 %. Yellow solid, M.p. 192 ^oC decomposed. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.40). ^1H NMR (600 MHz, $CDCl_3$) δ 8.61 (d, *J*= 2.4 Hz, 1H), 8.38 (dd, *J*= 8.6, 2.4 Hz, 1H), 7.91 (d, *J*= 8.6 Hz, 1H), 7.87 (d, *J*= 8.6 Hz, 2H), 7.41 (bs, 1H), 7.31 (d, *J*= 8.1 Hz, 1H), 7.15-7.07 (m, 3H), 2.46 (s, 3H), 2.27 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.2, 164.8, 148.7, 146.2, 143.9, 138.7, 135.7, 133.3, 133.2, 133.0, 129.9, 128.6, 128.2, 128.1, 128.0, 124.9, 123.6, 22.0, 18.9. IR (neat, cm^{-1}): 3227 (m), 1671 (s), 1652 (s), 1521 (s), 1347 (s). HRMS (APCI) Calcd for $C_{23}H_{21}N_2O_4S$ ($M+H^+$): 421.1222. Found: 421.1221.



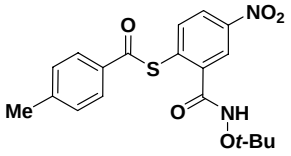
***S*-2-(2-Nitrophenylcarbamoyl)-4-nitrophenyl 4-methylbenzothioate:** *Method F:* From 5-nitro-2-(2-nitro-phenyl)-benzo[*d*]isothiazol-3-one (0.713 g, 2.2 mmol), $NaBH_4$

(0.105 g, 2.8 mmol), $NaHCO_3$ (0.203 g, 2.4 mmol), and *p*-toluoyl chloride (0.33 ml, 2.5 mmol) in 10 ml of dioxane/THF was obtained 0.494 g of pure 4-methyl-thiobenzoic acid *S*-[4-nitro-2-(2-nitro-phenylcarbamoyl)-phenyl] ester after filtering reaction through celite (25 g) and precipitating by adding hexane. Yield: 50 %. Bright yellow solid, M.p. 148-150 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.8 (bs, 1H), 8.80 (d, *J*= 8.9 Hz, 1H), 8.64 (d, *J*= 2.2 Hz, 1H), 8.42 (dd, *J*= 8.6, 2.5 Hz, 1H), 8.22 (dd, *J*= 8.6, 1.6 Hz, 2H), 7.94-7.86 (m, 4H), 7.70 (t, *J*= 8.6 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.9, 183.4, 164.8, 148.4, 145.9, 141.8, 138.5, 137.3, 136.2, 134.6, 134.0, 133.2, 129.9, 128.1, 126.1, 125.5, 124.5, 123.6, 122.8, 22.0. IR (neat, cm^{-1}): 3339 (w), 2254 (m), 1695 (m), 1606 (m), 1525 (m), 1502 (s), 1343 (s). HRMS (APCI) Calcd for $C_{21}H_{16}N_3O_6S$ ($M+H^+$): 438.0760. Found: 438.0758.

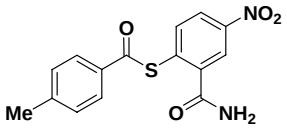


***S*-2-(Allylcarbamoyl)-4-nitrophenyl 4-methylbenzothioate:** *Method F:* From 2-allyl-5-nitro-benzo[*d*]isothiazol-3-one (0.377 g, 1.6 mmol), $NaBH_4$ (0.069 mg, 1.8 mmol), $NaHCO_3$ (0.156 g, 1.8 mmol), and *p*-toluoyl chloride (0.22 ml, 1.7 mmol) in 8 ml of dioxane/THF was obtained 0.127 g of pure 4-methyl-thiobenzoic acid *S*-(2-allylcarbamoyl-4-nitro-phenyl) ester after filtering reaction through celite (25 g) and precipitating by adding hexane. Yield: 22 %. Bright yellow solid, M.p. 145-148 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (t, *J*= 1.9 Hz, 1H), 8.30 (dt, *J*= 6.7, 1.4 Hz, 1H), 7.90 (d, *J*= 7.6 Hz, 2H), 7.79 (dd, *J*= 8.1, 0.95 Hz, 1H), 7.30 (d, *J*= 8.1 Hz, 2H), 6.29 (bs, 1H), 5.80-5.73 (m, 1H), 5.19 (dt, *J*= 17.1, 0.95 Hz, 1H), 5.04 (dt, *J*= 10.5, 1.4 Hz, 1H), 3.99 (t,

J= 5.7 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.1, 166.2, 148.5, 146.1, 143.5, 138.3, 133.3, 133.2, 129.9, 129.4, 128.1, 126.9, 124.7, 123.4, 117.6, 42.7, 22.0. IR (neat, cm^{-1}): 3269 (m), 1671 (s), 1640 (s), 1521 (s), 1347 (s). HRMS (APCI) Calcd for $C_{18}H_{17}N_2O_4S$ ($M+H^+$): 357.0909. Found: 357.0904.

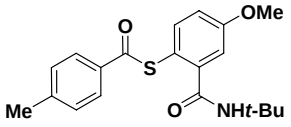


***S*-2-(*tert*-Butoxycarbamoyl)-4-nitrophenyl 4-methylbenzothioate:** *Method G:* From 2-*tert*-butoxy-5-nitro-benzo[*d*]isothiazol-3-one (0.102 g, 0.40 mmol), *p*-toluic acid (0.056 g, 0.40 mmol), and PEt_3 (0.45 ml, 4.4 mmol) in 2 ml THF was obtained 0.101 g of pure thiol ester after quenching with 1 M $NaHCO_3$, extracting with diethyl ether, drying organic layer with anhydrous Na_2SO_4, filtering, and condensing. Yield: 68 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.34 (app dd, *J*= 8.5, 2.3 Hz, 1H), 8.18 (s, 1H), 7.91 (dd, *J*= 8.1, 1.4 Hz, 2H), 7.81 (d, *J*= 8.5 Hz, 1H), 7.31 (app d, *J*= 7.6 Hz, 2H), 2.46 (s, 3H), 1.28 (s, 9H).



***S*-2-Carbamoyl-4-nitrophenyl 4-methylbenzothioate:** *Method F:* From 2-*tert*-butoxy-5-nitro-benzo[*d*]isothiazol-3-one (0.308 g, 1.1 mmol), $NaBH_4$ (0.049 g, 1.3 mmol), $NaHCO_3$ (0.112 g, 1.3 mmol), and *p*-toluoyl chloride (0.2 ml, 1.3 mmol) in 5 ml of dioxane/THF was obtained 0.195 g of pure thiol ester after filtering reaction through celite (25 g), aqueous workup with EtOAc and 1 M $NaHCO_3$, and filtering through a short silica column with 5:1 hex:EtOAc to 2:1 hex:EtOAc. Yield: 54 %. White solid,

M.p.146-149 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J*= 2.4 Hz, 1H), 8.23 (dd, *J*= 8.6, 2.4 Hz, 1H), 7.91 (d, *J*= 8.6 Hz, 2H), 7.81 (d, *J*= 8.6 Hz, 1H), 7.32 (d, *J*= 8.1 Hz, 2H), 6.29 (bs, 1H), 6.22 (bs, 1H), 2.55 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.6, 168.3, 148.5, 146.5, 142.3, 138.4, 133.5, 133.2, 130.3, 129.9, 129.3, 128.2, 125.0, 123.6, 22.0. IR (neat, cm^{-1}): 3366 (m), 3181 (m), 1691 (s), 1652 (s), 1347 (s). HRMS (APCI) Calcd for $C_{15}H_{13}N_2O_4S$ ($M+H^+$): 317.0596. Found: 317.0591.

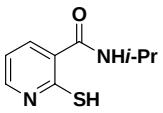


***S*-2-(*tert*-Butylcarbamoyl)-4-methoxyphenyl 4-methylbenzothioate:** *Method G:* From 2-*tert*-butyl-5-methoxy-benzo[*d*]isothiazol-3-one (0.373 g, 1.6 mmol), *p*-toluic acid (0.235 g, 1.7 mmol), and PEt_3 (1.7 ml, 1.8 mmol) in 8 ml THF was obtained 0.272 g of pure thiol ester after quenching with 1 M $NaHCO_3$, extracting with diethyl ether, drying organic layer with anhydrous $MgSO_4$, filtering, and condensing. Yield: 49 %. White crystals, M.p.124-127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*= 8.3 Hz, 2H), 7.39 (d, *J*= 8.6 Hz, 1H), 7.30 (d, *J*= 7.9 Hz, 2H), 7.14 (d, *J*= 2.8 Hz, 1H), 6.97 (dd, *J*= 8.6, 2.8 Hz, 1H), 6.10 (bs, 1H), 3.88 (s, 3H), 2.45 (s, 3H), 1.29 (s, 9H). IR (neat, cm^{-1}): 2968 (w), 1668 (s), 1525 (s), 1220 (s). HRMS (APCI) Calcd for $C_{20}H_{24}NO_3S$ ($M+H^+$): 358.1277. Found: 358.1272.

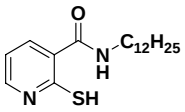
General Procedure for Thiol Synthesis:

The corresponding benzoisothiazolinone (1.0 equiv.) was placed in a round bottom flask equipped with a stir bar under argon. 0.3 M EtOH was added and the reaction mixture was place in a 0 °C ice bath. $NaBH_4$ (1.1 equiv.) was added and bubbles

were immediately observed. The reaction was allowed to stir to room temperature. After 30 minutes to one hour, no more bubbles were observed. The reaction was complete as monitored by TLC. Unless otherwise noted, work up included quenching with 1 M HCl and ice. The resulting solid was filtered to give the pure thiol in high yield.

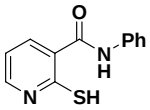


2-Mercapto-*N*-isopropyl-nicotinamide: From 2-isopropyl-isothiazolo[5,4-*b*]pyridin-3-one (1.00 g, 5.2 mmol) in 10 ml of EtOH and $NaBH_4$ (0.214 g, 5.7 mmol) was obtained 0.998 g of 2-mercapto-*N*-isopropyl-nicotinamide. Yield: 98 %. Bright yellow crystals, M.p. 178-179 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 10.62 (bs, 1 H), 8.84 (dd, *J*= 7.3, 1.6 Hz, 1H), 7.67 (d, *J*= 4.4 Hz, 1H), 6.96 (dd, *J*= 7.6, 6.4 Hz, 1 H), 4.25 (m, 1H), 1.32 (d, *J*= 6.7 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.4, 163.0, 143.7, 139.4, 133.7, 114.3, 42.7, 22.8. IR (neat, cm^{-1}): 2972 (s), 2362 (s), 1637 (s), 1559 (s). HRMS (FAB) Calcd for $C_9H_{13}N_2OS$ ($M+H^+$): 197.0749. Found: 197.0749.

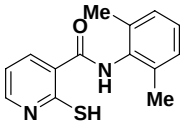


***N*-Dodecyl-2-mercapto-nicotinamide:** From 2-dodecyl-isothiazolo[5,4-*b*]pyridin-3-one (1.02 g, 3.2 mmol) in 20 ml of EtOH and $NaBH_4$ (0.152 g, 4.0 mmol) was obtained 0.981 g. Yield: 96 %. Yellow solid, M.p. 95-98 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 10.64 (bs, 1H), 8.85 (dd, *J*= 7.6, 1.9 Hz, 1 H), 7.67 (m, 1H), 6.97 (m, 1H), 3.50 (dd, *J*= 12.4, 6.7 Hz, 2H), 1.67 (dt, *J*= 14.9, 7.3 Hz, 2H), 1.26 (m, 18H), 0.88 (t, *J*= 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 163.6, 143.8 139.2, 134.2, 114.4, 40.4, 32.1, 29.8, 29.7, 29.6,

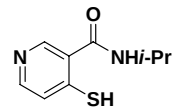
29.5, 29.3, 27.4, 22.9, 14.3. IR (neat, cm^{-1}): 2926 (s), 1637 (s), 1571 (m). HRMS (FAB) Calcd for $C_{18}H_{31}N_2OS$ ($M+H^+$): 323.2157. Found: 323.2157.



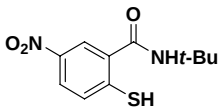
2-Mercapto-*N*-phenyl-nicotinamide[8]: From 2-phenyl-isothiazolo[5,4-*b*]pyridin-3-one (1.00 g, 4.4 mmol) in 10 ml of EtOH and $NaBH_4$ (0.180 g, 4.8 mmol) was obtained 0.965 g. Yield: 95 %. Bright yellow solid, M.p. 178-180 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 11.15 (bs, 1 H), 8.91 (dd, *J*= 7.1, 1.4 Hz, 1H), 7.79 (d, *J*= 8.1 Hz, 2H), 7.70 (m, 1 H), 7.38 (t, *J*= 8.6 Hz, 2H), 7.16 (t, *J*= 7.6 Hz, 1H), 7.00 (t, *J*= 7.6 Hz, 1H). IR (neat, cm^{-1}): 1652 (s), 1559 (s). HRMS (FAB) Calcd for $C_{12}H_{10}LiN_2OS$ ($M+Li^+$): 237.0674. Found: 237.0674.



***N*-(2,6-Dimethyl-phenyl)-2-mercapto-nicotinamide[9]:** From 2-(2,6-dimethylphenyl)-isothiazolo[5,4-*b*]pyridin-3-one (0.760 g, 3.0 mmol) in 10 ml of EtOH and $NaBH_4$ (0.167 g, 4.4 mmol) was obtained 0.228 g. Yield: 30 %. Yellow crystals, M.p. 225 ^oC decomposed. TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.57). ^1H NMR (400 MHz, $CDCl_3$) δ 11.20 (bs, 1H), 8.93 (dd, *J*= 7.6, 1.9 Hz, 1 H), 7.64 (bs, 1H), 7.13 (s, 3H), 6.98 (t, *J*= 6.0 Hz, 1H), 2.32 (s, 6H). IR (neat, cm^{-1}): 2926 (m), 1644 (s). HRMS (FAB) Calcd for $C_{14}H_{15}N_2OS$ ($M+H^+$): 259.0905. Found: 259.0905.

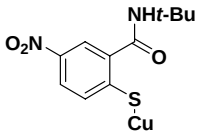


***N*-Isopropyl-4-mercapto-nicotinamide:** From 2-isopropyl-isothiazolo[*4,5-c*]pyridin-3-one (0.69 g, 3.6 mmol) in 10 ml of EtOH and $NaBH_4$ (0.154 g, 4.1 mmol) was obtained 0.469 g of pure *N*-isopropyl-4-mercapto-nicotinamide. Yield: 66 %. Yellow solid, M.p. 161-164 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.43 (bs, 1H), 12.16 (d, *J*= 6.4 Hz, 1H), 8.77 (s, 1H), 7.70 (d, *J*= 6.9 Hz, 1H), 7.30 (d, *J*= 6.9 Hz, 1H), 4.20-4.14 (m, 1H), 1.36 (d, *J*= 6.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.1, 164.8, 139.5, 135.4, 129.8, 129.5, 43.0, 22.7. IR (neat, cm^{-1}): 3385 (b), 1637 (s), 1559 (m).



***N-tert*-Butyl-2-mercapto-5-nitrobenzamide:** From 2-*tert*-butyl-5-nitro-benzo[*d*]isothiazol-3-one (2.012 g, 8.0 mmol) and 0.332 g (9.0 mmol) $NaBH_4$ in 40 ml EtOH was obtained 1.721 g pure thiol. Yield: 86 %. Yellow solid, M.p. 235-238 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J*= 2.5 Hz, 1H), 8.06 (dd, *J*= 8.9, 2.5 Hz, 1H), 7.43 (d, *J*= 8.6 Hz, 1H), 5.96 (bs, 1H), 5.13 (bs, 1H), 1.51 (s, 9H). IR (neat, cm^{-1}): 3296 (m), 2972 (m), 2555 (w), 1640 (s), 1521 (s), 1343 (s). HRMS (APCI) Calcd for $C_{11}H_{15}N_2O_3S$ ($M+H^+$): 255.0803. Found: 255.0797.

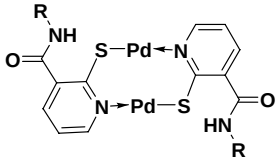
Synthesis Copper Thiolate (Scheme 1.17):



***N-tert*-Butyl-5-nitrobenzamide copper thiolate:** *N*-tert-butyl-2-mercapto-5-nitrobenzamide (100 mg, 0.39 mmol) and Cu_2O (27 mg, 0.18 mmol) in 1 ml of EtOH was placed in a pressure sealed microwave tube equipped with a stir bar. The reaction was

run in a CEM Discover microwave reactor using 50 watts, 20 psi, for 15 minutes at 100 ^{o}C for 3 cycles. Solution turned from red to yellow. The solution was place in a round bottom flask, the solvent removed, the solid washed with Et_2O, and dried under vacuum to obtain 100 mg of the copper thiolate. Yield: 80 %. Bright yellow powder. IR (neat, cm^{-1}): 2922 (w), 1602 (m), 1513 (m), 1339 (s). *N*-tert-butyl-5-nitrobenzamide copper thiolate was place in a 10 ml vial equipped with a stir bar and 2 ml of DMA was added. The reaction was allowed to stir at 55 ^{o}C open to air for 5 hrs. The reaction was quenched with Et_2O and saturated NH_4Cl. The organic layer was separated, dried with MgSO4, filtered and the volatiles were reduced under vacuum to give quantitative yield of 2-*tert*-butyl-5-nitro-benzo[*d*]isothiazol-3-one by ^{1}H NMR.

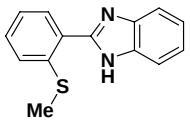
Synthesis of Palladium Thiolate (Figure 1.3):



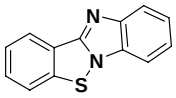
$Pd(OAc)_2$ (0.224 g, 0.51 mmol) and 2-mercapto-*N*-isopropyl-nicotinamide (0.200 g, 1.0 mmol) in 5 ml of dry dioxane was placed in a pressure sealed microwave tube equipped with a stir bar. A brown solid initially precipitated, which then dissolved to give a red solution. The reaction was run in a CEM Discover microwave reactor using 50 watts, 150 psi, for 30 minutes at 120 ^{o}C for 3 cycles. An orange solid precipitated and was filtered then washed with dioxane and ethanol and dried under vacuum to obtain 140.5 mg of a light orange solid. Elemental analysis showed the compound to be $[Pd_2L_{n+2}]$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, *J*= 8.2, 1.9 Hz, 1 H), 7.70 (dd, *J*= 5.4, 1.6 Hz, 1 H), 7.41 (br d, *J*= 6.9 Hz, 1 H), 6.88 (dd, *J*= 7.9, 5.3 Hz, 1 H), 4.34-4.25 (m, 1

H), 1.34 (d, *J*= 6.7 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ. IR (neat, cm^{-1}): 3296 (w), 1633 (s), 1532 (s). Anal. Calcd for $C_{36}H_{44}N_8O_4Pd_2S_4$ (MW=993.89): C, 43.50; H, 4.46; N, 11.27; S, 12.90. Found: C, 43.40; H, 4.49; N, 11.04; S, 12.77.

Procedures for Benzimidazole Compounds:



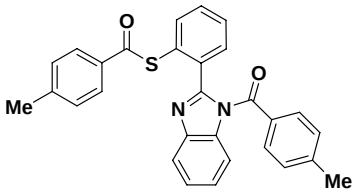
2-(2-(Methylthio)phenyl)-1H-benzo[*d*]imidazole: 2-Benzimidazole (5.00 mg, 25 mmol) was dissolved in 50 ml of dry THF under argon then cooled to 0 ^{o}C. The solution was treated with *n*-BuLi (2.5 M in Hexane, 10 ml, 28 mmol) and stirred for 1 hour. The reaction was then treated with *tert*-BuLi (1.7 M in Et_2O, 16 ml, 28 mmol) and allowed to stir for 8 hours while coming to room temperature. Dimethyldisulfide (2.5 ml, 28 mmol) was added at 0 ^{o}C and the reaction was allowed to come to room temperature over night. The reaction was quenched with a pH 7 phosphate buffer, extracted with EtOAc three times, the organic phases dried with $MgSO_4$ and condensed to give 4.34 mg of pure product. Yield: 70 %. Clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.93 (bs, 1H), 8.37 (dd, *J*= 7.1, 2.4 Hz, 1H), 7.87-7.85 (m, 1H), 7.54 (dd, *J*= 7.6, 1.9 Hz, 2H), 7.44-7.39 (m, 2H), 7.32-7.30 (m, 2H), 2.49 (s, 3H).



2-(1H-Benzo[*d*]imidazol-2-yl)benzoisothiazole [12] : 2-(2-(methylthio)phenyl)-1H-benzo[*d*]imidazole (2.65 g, 11 mmol) was dissolved in 30 ml CH_2Cl_2 was cooled to 0 ^{o}C

[12] Bossio, R.; Marcaccini, S.; Parrini, V.; Pepino, R. *Heterocycles* **1985**, *23*, 2705-2708.

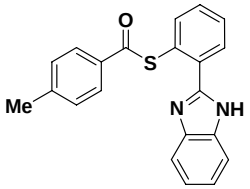
and treated with *m*-CPBA (1.90 g, 11 mmol) in three parts following each addition by TLC to prevent over oxidation. The reaction was quenched at 0 ^{o}C with saturated $NaHCO_3$ and brine. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The crude sulfoxide (0.720 g, 2.8 mmol) was dissolved in 6 ml of CH_2Cl_2 and treated with triphosgene (0.833 g, 2.8 mmol) at room temperature. The reaction was stirred for 4 hours and the resulting solid was filtered to give 0.730 g of the HCl salt of 2-(1H-benzo[*d*]imidazol-2-yl)benzoisothiazole. Yield: 25 %. For the free base: White solid., M.p. 230-232^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J*= 7.8 Hz, 1H), 7.95 (d, *J*= 7.3 Hz, 1H), 7.75 (d, *J*= 7.8 Hz, 1H), 7.64 (dt, *J*= 7.3, 1.4 Hz, 1H), 7.60-7.54 (m, 2H), 7.44-7.33 (m, 2H). IR (neat, cm^{-1}): 3381 (br), 1656 (w), 1536 (w), 1436 (s).



_S_-2-[(1H-Benzo[*d*]imidazol-2-yl)(*p*-tolyl)methanone]-4-methylbenzothioate:

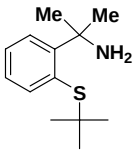
Followed Method G for general thiol ester preparation: From 2-(1H-benzo[*d*]imidazol-2-yl)benzoisothiazole (0.119 g, 0.50 mmol) in 2.5 ml dry THF, *p*-toluic acid (0.079 g, 0.55 mmol), and Et_3P (1 M in THF, 0.6 ml, 0.60 mmol) was obtained 0.133 g of the thiol ester. Yield: 57 %. M.p. 142 ^{o}C liquescent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J*= 7.6, 1.5 Hz, 1H), 8.01 (d, *J*= 7.9 Hz, 2H), 7.94 (d, *J*= 8.2 Hz, 2H), 7.67-7.62 (m, 3H), 7.58-7.54 (m, 2H), 7.31-7.25 (m, 6H), 2.45 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 171.5, 150.8, 145.6, 144.3, 138.3, 137.8, 135.4, 133.6, 132.2, 130.7, 130.6, 130.3, 129.7, 129.3, 128.1, 127.4, 125.9, 123.2, 115.6, 21.96, 21.92. IR (neat, cm^{-}

[1]): 3389 (br), 1695 (s), 1671 (s). HRMS (APCI) Calcd for $C_{29}H_{23}N_2O_2S$ ($M+H^+$): 463.1480. Found: 463.1476.

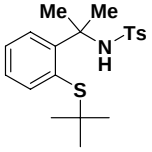


S-2-(1H-Benzo[d]imidazol-2-yl)-4-methylbenzothioate: *S*-2-[(1H-benzo[*d*]imidazol-2-yl)(*p*-tolyl)methanone]-4-methylbenzothioate (52 mg, 0.11 mmol) was placed in a side armed test tube with a v-shaped magnetic stir bar and 2 ml of dry dioxane in air. Catalytic amounts of bis(tricyclohexylphosphine) palladium(0) (8 mg, 0.011 mmol) and copper methylsalicylate (3 mg, 0.013 mmol) were added followed by phenyl boronic acid (17 mg, 0.14 mmol) along with 2,2'-di-*tert*-butylbiphenyl as the internal standard (17 mg, 0.06 mmol). The reaction was monitored for 24 hours by GC-MS. Toluic acid was identified in the mixture. The reaction was quenched with water, extracted with Et_2O, and dried with $MgSO_4$. After condensing the crude under vacuum, products were separated on Silica G prep TLC plates (2000 μm) using a solvent gradient 2:1 Hex:Et_2O to 1:1 Hex:Et_2O to give 8 mg of the mono-acylated thiol ester. Yield: 22 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J*= 7.0 Hz, 2H), 8.01 (d, *J*= 8.2 Hz, 2H), 7.78 (br, 1H), 7.63-7.59 (m, 2H), 7.52 (t, *J*= 7.3 Hz, 2H), 7.45-7.43 (m, 1H), 7.29-7.24 (m, 3H), 2.44 (s, 3H). IR (neat, cm^{-1}): 2934 (br), 1679 (s), 1351 (s).

Procedures for gem-Dimethyl Compounds:

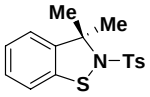


2-(2-(*tert*-Butylthio)phenyl)propan-2-amine: Anhydrous $CeCl_3$ (4.74 g, 19 mmol) was placed in a flame-dried round bottom flask and 40 ml of dry THF was added at 0 ^oC. The heterogeneous mixture was stirred overnight while coming to room temperature. At -78 ^oC, MeLi (1.6 M in Et_2O, 11.3 ml, 18.0 mmol) was added drop wise and the reaction was stirred for 1 and a half hours at which time 2-(*tert*-butylthio)benzonitrile[17] (1.15 g, 6.0 mmol) was added via syringe in 5 ml of dry THF. The reaction was allowed to stir at -78 ^oC for 3 and a half hours at which time TLC showed starting material consumption. At -78 ^oC, 0.52 M (11 ml) of concentrated NH_4OH was added, the flask was warmed to room temperature, and the mixture filtered through celite. Water was added and the aqueous layer was extracted with CH_2Cl_2 three times, dried with $MgSO_4$ and concentrated to give 1.11 g of pure product. Yield: 83 %. Clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J*= 7.6, 1.6 Hz, 1H), 7.50 (dd, *J*= 7.9, 1.6 Hz, 1H), 7.23 (dt, *J*= 7.6, 1.6 Hz, 1H), 7.15 (dt, *J*= 1.6, 1.6 Hz, 1H), 2.41 (br, 2H), 1.60 (s, 6H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 138.5, 132.6, 128.1, 126.2, 126.1, 54.3, 48.4, 32.6, 32.2, 31.3, 30.5. IR (neat, cm^{-1}): 3362 (br), 2964 (s), 1459 (s). HRMS (ESI) Calcd for $C_{13}H_{22}NS$ ($M+H^+$): 224.1473. Found: 224.1464.

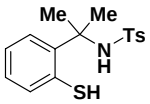


2-(2-(*tert*-Butylthio)phenyl)-*N*-tosylpropan-2-amine: 2-(2-(*tert*-butylthio)phenyl)propan-2-amine (0.500 g, 2.2 mmol) was dissolved in 5 ml of dry CH_2Cl_2 under argon, then Et_3N (0.64 ml, 4.5 mmol) was added followed by tosyl chloride (0.520 g, 2.7 mmol) and a few small crystals of DMAP. When the reaction was completed by TLC, the reaction was quenched with 5 % HCl and the aqueous phase was

extracted with CH_2Cl_2 three times, dried with $MgSO_4$ to give 0.673 g of pure product. 81 %. White solid, M.p. ($CHCl_3$) 117-119 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J*= 8.2 Hz, 2H), 7.41 (dd, *J*= 7.3 Hz, 1.9 Hz, 1H), 7.28-7.27 (m, 1H), 7.24 (br, 1H), 7.18-7.09 (m, 3H), 2.41 (br, 2H), 2.35 (s, 3H), 1.70 (s, 6H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 142.6, 139.6, 137.6, 132.4, 129.3, 128.1, 127.3, 126.9, 126.5, 59.1, 49.7, 32.2, 30.1, 21.6. IR (neat, cm^{-1}): 3385 (br), 2968 (m), 1602 (w), 1324 (s).

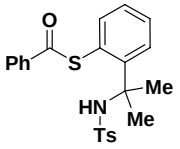


2,3-Dihydro-3,3-dimethyl-2-tosylbenzo[*d*]isothiazole: To 2-(2-(*tert*-butylthio)phenyl)-*N*-tosylpropan-2-amine (0.454 g, 1.2 mmol) in 4 ml of dry CH_2Cl_2 was added TMSCl (0.75 ml, 6.0 mmol) and dry DMSO (0.62 ml, 8.7 mmol) and the reaction was allowed to stir at room temperature for 24 hours. The reaction was quenched with water, the aqueous layer extracted with CH_2Cl_2 twice, EtOAc once, and the combined organic layers dried with $MgSO_4$ and condensed to give 0.384 mg of pure product. Yield: 96 %. White crystals, M.p.195-197 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J*= 8.1 Hz, 2H), 7.81 (d, *J*= 7.6 Hz, 1H), 7.59 (t, *J*= 7.6 Hz, 1H), 7.52 (d, *J*= 7.6 Hz, 1H), 7.31 (d, *J*= 8.5 Hz, 2H), 7.26 (d, *J*= 7.6 Hz, 2H), 2.41 (s, 3H), 1.72 (s, 3H), 1.66 (s, 3H). IR (neat, cm^{-1}): 2926 (m), 1668 (s), 1343 (s).



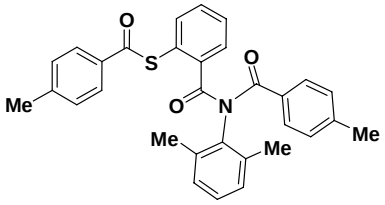
2-(2-(Tosylamino)propan-2-yl)benzenethiol: To 2,3-dihydro-3,3-dimethyl-2-tosylbenzo[*d*]isothiazole (0.366 g, 1.2 mmol) in 7 ml of dry THF was added drop wise LAH (1.0 M in Et_2O, 1.15 ml, 1.2 mmol) at 0 ^oC. The reaction was allowed to come to room temperature over 2 hours and quenched with 5 % HCl. The aqueous layer was

extracted with EtOAc three times, the organic layers combined, dried with $MgSO_4$, and condensed to give 0.369 g of pure thiol. Yield: 98 %. White solid, M.p. 185-187 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J*= 8.2 Hz, 2H), 7.29 (d, *J*= 8.2 Hz, 2H), 7.08-7.00 (m, 4H), 5.64 (bs, 1H), 3.48 (s, 1H), 2.35 (s, 3H), 1.78 (s, 6H). IR (neat, cm^{-1}): 3277 (w), 2926 (m), 2563 (m), 1598 (w), 1324 (s).

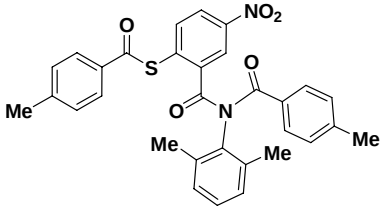


***S*-2-(2-(Tosylamino)propan-2-yl)phenyl benzothioate:** To 2-(2-(tosylamino)propan-2-yl)benzenethiol (0.361 g, 1.1 mmol) in 4 ml of dry CH_2Cl_2 was added benzoic anhydride (0.304 g, 1.3 mmol), Et_3N (0.31 ml, 2.2 mmol), and a few crystals of DMAP at 0 ^oC. The reaction was allowed to come to room temperature over night and then quenched with 5 % HCl. The organic layer was separated and washed with saturated $NaHCO_3$. The organic layer was then dried with $MgSO_4$ and condensed to give 0.222 g of pure thiol ester. Yield: 45 %. White crystals, M.p. 138-140 ^oC. TLC (silica gel, 2:1 hex:EtoAc, R_f= 0.35). ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J*= 8.1 Hz, 2H), 7.61 (t, *J*= 7.6 Hz, 1H), 7.49-7.44 (m, 5H), 7.33 (dd, *J*= 7.6 Hz, 1H), 7.24 (t, *J*= 6.7 Hz, 1H), 7.20 (d, *J*= 7.6 Hz, 1H), 6.99 (d, *J*= 8.1 Hz, 2H), 5.62 (bs, 1H), 2.28 (s, 3H), 1.74 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 147.1, 142.7, 140.4, 138.9, 136.6, 134.1, 130.1, 129.3, 129.0, 128.2, 127.8, 127.5, 127.3, 125.6, 59.0, 29.8, 21.6. IR (neat, cm^{-1}): 3277 (w), 2926 (m), 2563 (m), 1598 (w), 1324 (s).

Thiol Ester Decomposition (Scheme 1.16):



4-Methyl-thiobenzoic acid-2-(2,6-dimethyl-phenyl)-(4-methyl-benzoyl)-aminocarbonyl) - phenyl ester: The thiol ester (94 mg, 0.30 mmol) was placed in a side armed test tube with a v-shaped magnetic stir bar and 2 ml of DMA in air. Catalytic amounts of bis(tricyclohexylphosphine) palladium(0) and copper methylsalicylate (5 mol %, 0.013 mmol) were added. The reaction was allowed to run for 48 hours and monitored by HPLC using an internal standard, 4,4'-di-*tert*-butyl biphenyl (0.50 mmol). The reaction was then quenched with acid and extracted with diethyl ether, dried with $MgSO_4$, and condensed under vacuum. Products were separated on Silica G prep TLC plates (2000 μm) using a solvent gradient 2:1 hex:Et_2O to 1:1 hex:Et_2O. White crystals, M.p. 160-161 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J*= 8.2 Hz, 2H), 7.65 (dd, *J*= 7.9 Hz, 1.3, 1H), 7.62 (dd, *J*= 7.5, 0.98 Hz, 1H), 7.49 (d, *J*= 8.2 Hz, 2H), 7.44 (dt, *J*= 7.5, 1.3 Hz, 1H), 7.37 (dt, *J*= 7.5, 1.3 Hz, 1H), 7.28 (d, *J*= 6.7 Hz, 2H), 7.14 (t, *J*= 7.5 Hz, 1H), 7.06 (d, *J*= 7.5 Hz, 2H), 6.98 (d, *J*= 8.2 Hz, 2H), 2.43 (s, 3H), 2.34 (s, 6H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 172.2, 170.5, 144.8, 143.2, 141.0, 138.0, 137.9, 136.2, 134.2, 131.9, 130.5, 129.6, 129.3, 129.3, 129.0, 128.9, 127.9, 127.8, 29.9, 21.9, 21.7, 19.2. IR (neat, cm^{-1}): 1691 (s), 1606 (s), 1262 (s). HRMS (FAB) Calcd for $C_{31}H_{27}LiNO_3S$ ($M+Li^+$): 500.1872. Found: 500.1876.



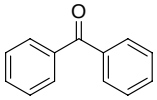
4-Methyl-thiobenzoic acid 2-(2,6-dimethyl-phenyl)-(4-methyl-benzoyl)-aminocarbonyl)-4-nitro-phenyl ester: Isolated from the exact procedure for the preparation of *S*-2-(2,6-dimethylphenylcarbamoyl)-4-nitrophenyl 4-methylbenzothioate in EtOH. Yellow solid, M.p. 192-195 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J*= 2.5 Hz, 1H), 8.29 (dd, *J*= 8.6, 2.2 Hz, 1H), 7.88 (t, *J*= 8.6 Hz, 3H), 7.43 (d, *J*= 8.3 Hz, 2H), 7.29 (d, *J*= 8.3 Hz, 2H), 7.18-7.14 (m, 1H), 7.08 (d, *J*= 7.3 Hz, 2H), 7.00 (d, *J*= 7.9 Hz, 2H), 2.45 (s, 3H), 2.34 (s, 6H), 2.28 (s, 3H). IR (neat, cm^{-1}): 1695 (s), 1525 (s), 1347 (s), 1262 (s). HRMS (APCI) Calcd for $C_{31}H_{27}N_2O_5S$ ($M+H^+$): 539.6215. Found: 539.1637.

General Procedure for Pd and Cu Catalyzed Ketone Inhibition (Table 1.2 and Scheme 1.12):

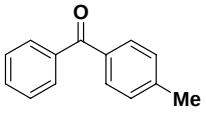
The thiol ester (1.0 equiv., 0.25 mmol) was placed in a side armed test tube with a v-shaped magnetic stir bar and 2 ml of dry dimethylacetamide (DMA) in air. Catalytic amounts of bis(tricyclohexylphosphine) palladium(0) (5 mol %, 0.0125 mmol) and copper methylsalicylate (5 mol %, 0.0125 mmol) were added followed by phenyl boronic acid (1.0 equiv., 0.25 mmol). The 2- or 4-mercapto nicotinamide was then added (15 mol %, 0.04 mmol). The reaction was monitored for 48 hours by HPLC using an internal standard, 4,4'-di-*tert*-butyl-biphenyl (2.0 equiv., 0.50 mmol). If product was observed, the reaction was quenched with dilute HCl, extracted with Et_2O, and dried with $MgSO_4$. After condensing the crude under vacuum, products were separated on Silica G prep TLC plates (2000 μm) using a solvent gradient 2:1 hex:Et_2O to 1:1 hex:Et_2O.

General Procedure for Pd and Cu Catalyzed Ketone Synthesis:

The thiol ester (1.0 equiv., 0.25 mmol) was placed in a side armed test tube with a v-shaped magnetic stir bar. Catalytic amounts of bis(tricyclohexylphosphine) palladium(0) or tetrakistriphenylphosphine palladium(0) (5 mol %, 0.0125 mmol) and copper methylsalicylate (5 mol %, 0.0125 mmol) were added followed by the corresponding boronic acid (unless otherwise noted, 1.0 equiv., 0.25 mmol) and 2 ml of dry dimethylacetamide (DMA) or dry dioxane. The reactions were allowed to run for 48 hrs, then quenched with Et_2O and saturated NH_4Cl. The organic layer was separated, and the aqueous was extract again with Et_2O. The combined organic layers were dried with $MgSO_4$, filtered and the volatiles were reduced under vacuum. If the reaction was monitored by HPLC, the internal standard, 4,4'-di-*tert*-butyl biphenyl (2.0 equiv., 0.50 mmol) was used. Products were separated via column chromatography using a solvent gradient 10:1 hex:Et_2O to 5:1 hex:Et_2O.

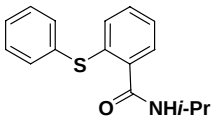


Benzophenone: For yields, refer to Table 1.2 and Scheme 1.12. Colorless oil matching known spectra. TLC (silica gel, 10:1 hex:EtoAc, R_f= 0.35). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (app d, *J*= 6.7 Hz, 4H), 7.60 (t, *J*= 7.6 Hz, 2H), 7.49 (t, *J*= 7.6 Hz, 4H). IR (neat, cm^{-1}): 1658 (s), 1276 (s).

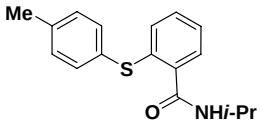


4-Methylbenzophenone: For yields, refer to Schemes 1.6, 1.15, 1.21. Colorless oil matching known spectra. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.64). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8 (d, *J*= 7.1 Hz, 2 H), 7.74 (d, *J*= 8.1 Hz, 2 H), 7.58 (t, *J*= 7.1 Hz, 1

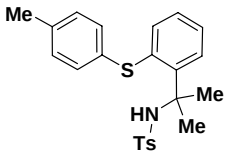
H), 7.48 (t, *J*= 7.1 Hz, 2 H), 7.30 (d, *J*= 8.1 Hz, 2 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 143.8, 138.5, 135.4, 132.7, 130.8, 130.6, 129.5, 128.7, 22.2. IR (neat, cm^{-1}): 2922 (s), 1656 (s), 1606 (s), 1447 (m), 1278 (s), 1316 (m).



***N*-Isopropyl-2-(phenylthio)benzamide:** For yields, refer to Scheme 1.6 and Table 1.2. Beige solid, M.p. 100-101 °C. TLC (silica gel, 10:1 hex:EtoAc, R_f= 0.11). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 1 H), 7.33 -7.28 (m, 7 H), 7.22-7.20 (m, 1 H), 6.20 (bs, 1 H), 4.27-4.19 (m, 1H), 1.18 (d, *J*= 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 137.4, 135.0, 133.7, 132.5, 131.3, 130.8, 129.7, 129.2, 127.7, 127.5, 42.2, 22.8. IR (neat, cm^{-1}): 2926 (m), 1679 (s), 1648 (s), 1571 (s).

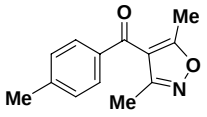


2-(*p*-Tolylthio)-*N*-isopropylbenzamide: Yellow solid, M.p. 122-123 °C. TLC (silica gel, 2:1 hex:EtoAc, R_f=0.37). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 1 H), 7.29-7.22 (m, 3 H), 7.16 (d, *J*= 7.9 Hz, 2 H), 7.11-7.09 (m, 1H), 6.17 (bs, 1 H), 4.31-4.22 (m, 1H), 2.36 (s, 3H), 1.22 (d, *J*= 6.3 Hz, 6H). IR (neat, cm^{-1}): 3302 (m), 2967 (w), 1629 (s), 1529 (s).



2-(2-(*p*-Tolylthio)phenyl)-*N*-tosylpropan-2-amine: From *S*-2-(2-(tosylamino)propan-2-yl)phenyl benzothioate (52 mg, 0.12 mmol), *p*-tolylboronic acid (46 mg, 0.34 mmol),

$Pd(PCy_3)_2$ (6 mg, 0.009 mmol), and CuMeSal (2 mg, 0.009 mmol) in 2 mL of DMF was obtained 28 mg of the pure ketone after column purification with a 2:1 hex:EtOAc gradient. Yield: 55 %. Light beige crystals, ($CHCl_3$) M.p.139-141 ^oC. TLC (silica gel, 2:1 hex:EtoAc, R_f= 0.56). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J*= 8.1 Hz, 2H), 7.33 (d, *J*= 8.1 Hz, 1H), 7.13-7.10 (m, 4H), 7.01-7.00 (m, 4H), 6.40 (bs, 1H), 2.33 (s, 3H), 2.32 (s, 1H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 142.7, 138.9, 137.3, 135.4, 133.7, 132.7, 130.8, 130.2, 129.2, 127.9, 127.4, 126.9, 115.3, 59.0, 29.7, 21.6, 21.3. IR (neat, cm^{-1}): 3282 (m), 1320 (m), 1143 (s).



(3,5-Dimethylisoxazol-4-yl)(p-tolyl)methanone [13] : From *S*-2-(isopropylcarbamoyl) phenyl 4-methylbenzothioate (52 mg, 0.16 mmol), naphthalen3,5-dimethylisoxazol-4-yl-4-boronic acid (56 mg, 0.40 mmol), $Pd(PCy_3)_2$ (5 mg, 0.008 mmol), and CuMeSal (3 mg, 0.008 mmol) in 2 mL of DMF was obtained 11 mg of the pure ketone after column purification with a 10:1 hex:EtOAc gradient. Yield: 30 %, Clear oil. TLC (silica gel, 10:1 hex:EtoAc, R_f= 0.47). ^1H NMR d (600 MHz, $CDCl_3$) δ 7.64 (d, *J*= 8.1 Hz, 2H), 7.30 (d, *J*= 8.1 Hz, 2H), 2.45 (s, 3H), 2.34 (s, 3H), 2.31 (s, 3H). IR (neat, cm^{-1}): 1649 (s), 1604 (s), 1420 (m).

[13] (a) Nagamine, M.; Hiraga, K.; Sakai, A.; Uchida, M. 87-110180 253370, 19870714., 1988. (b) Sokolov, S. D.; Savochkina, L. P.; Kochetkov, N. K. *Russ. J. Gen. Chem.* **1964**, *34*, 2207-2209.

CHAPTER 2

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Chapter 2

An Aerobic, Chemoselective, *Copper*-Templated Coupling of Thiol Esters with Boronic Acid

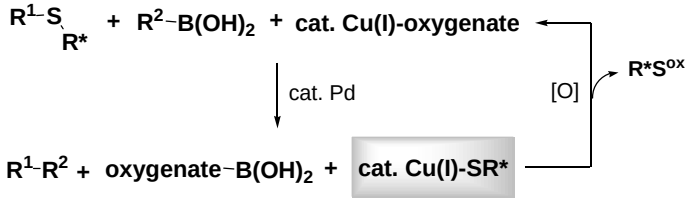
Abstract: A novel, aerobic ketone synthesis from simple and complex thiol esters and commercially available boronic acids catalyzed by copper (I) methyl salicylate (CuMeSal) is reported. The reaction is highly chemoselective for thiol esters containing an N-tert-butyl or N-isopropyl -2-mercaptobenzamide pendant. The reaction occurs under very mild reaction conditions (ambient temperature, aerobic, neutral conditions, and in the presence of a broad range of functional groups). The application of this chemistry may prove useful for selective carbon-carbon bond forming reactions on complex biomolecules.

2.1 Introduction

To a synthetic chemist, selectivity in complex chemical systems is the absolute goal for method development. There are few examples of selective chemical reactions that occur under mild enough conditions for the site-selective modification of large, complex molecules such as proteins.[1-5] However Nature is able to achieve selectivity using enzymatic control and exploit the inherent chemical reactivity differences associated with thioorganics versus that of other common *O*- and *N*-containing functional groups.[6, 7]

Efforts in our laboratory have focused on the discovery of novel, selective C-C bond forming reactions of Nature's acylating agents, thiol esters, under biologically relevant conditions (protic solvents, neutral pH, ambient temperature, aerobic conditions, and broad functional group tolerance). In 2000, our laboratory published a palladium-catalyzed ketone synthesis of thiol esters with boronic acids.[8] The reaction is mediated by a stoichiometric amount of copper(I)thiophene-2-carboxylate (CuTC) under strictly non-basic conditions. CuTC and the more recently used copper(I)methylsalicylate (CuMeSal) are air stable copper carboxylates and are easily synthesized on a large scale.

This reaction has been extended to a number of substrates (α-amino ketones, heteroaromatics[9], aryl and heteroaryl amidines[10], thioalkynes[11], functionalized pyrimidinones[12], and thiocyanates[13]). Drawing inspiration from biologically relevant processes for liberation of a metal from a thiolate ligand (e.g. zinc and copper release in metallothioneins[14, 15]), our group sought to develop a completely catalytic ketone synthesis (Scheme 2.1).



Scheme 2.1 Regenerating an Active Cu-OC(O)R Catalyst for a Completely Catalytic Ketone Synthesis

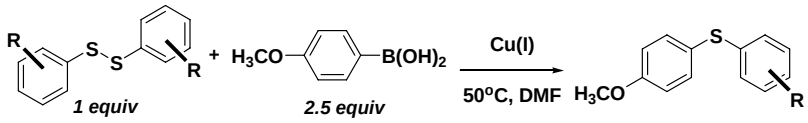
The requirement for a full equivalent of Cu(I) carboxylate is critical in understanding the criteria for achieving catalysis: While the Cu(I) ion kinetically labilizes the Pd–SR bond of the catalytic intermediate, it also ends up paired with the thiolate in a thermodynamically strong Cu-SR bond. At the same time, a full equivalent of the borophilic carboxylate counter ion is required to fully balance the equation and drive the $–B(OH)_2$ moiety to a $RC(O)OB(OH)_2$ thermodynamic sink.

The catalytically inactive copper thiolate, Cu-SR, produced in the reaction must be activated and transformed to an active catalyst, Cu-OC(O)R. Therefore, for copper to be recycled, sulfur must be scavenged and converted into a weak ligand for copper while an oxygenate counter-ion is regenerated for pairing with boron to again fully balance the equation.

2.2 Results and Discussion

As a first-level pursuit to develop reactions supported by only catalytic quantities of Cu, we chose to study the copper-catalyzed reaction of disulfides with boronic acids under both anaerobic and aerobic conditions (Table 2.1).

Table 2.1 Probing Copper Catalysis with Disulfides



Entry	R	*Yield (%)*	
		Under N_2, 1.2 eq Cu(I)MeSal	***Open to air, 5% Cu(I)MeSal***
1	H	77	trace
2	*para*-NHCOPh	64	0
3	*ortho*-NHCOPh	66	99

Treatment of the disulfide under ***anaerobic*** conditions with ***stoichiometric*** CuMeSal and 2.2 equivalents of *para*-methoxyphenyl boronic acid gave high yields of the corresponding aryl thioether (Table 2.1, entries 1-3). The yield is based on a 50 % maximum conversion because only half of the disulfide is transformed to an aryl thioether and the second half presumably forms a stable Cu(I) thiolate that does not react further without an oxidant such as oxygen. The reaction was also effective regardless of the nature and position of the aryl substituent. However, treatment of diphenyl disulfide (R = H, Table 2.1, entry 1) under ***aerobic*** conditions with ***catalytic*** CuMeSal yielded a trace amount of the phenyl thioether. When 2,2'-dithio-bis-*N*,*N'*-phenylbenzamide[16] containing a ligating *ortho* pendant was used, catalytic quantities of CuMeSal were enough to induce the efficient reaction of both halves of the disulfide (R = *ortho*-

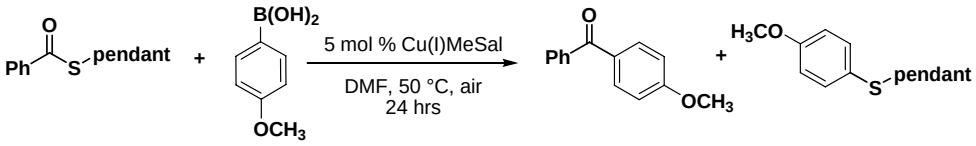
NHCOPh, Table 2.1, entry 3). In this process, the aerobic conversion of the thiolate ligand to an aryl thioether ligand constitutes a formal oxidation of the sulfur ligand.

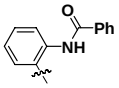
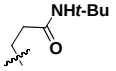
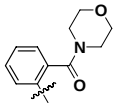
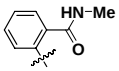
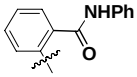
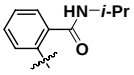
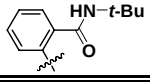
The ability of the *ortho*-NHCOPh but not the isoelectronic *para*-NHCOPh disulfide to participate in aerobic *S*-arylation catalysis by copper is *not* related to the redox property of the disulfide or thiolate derivatives (Table 2.1, compare entries 2 and 3). Therefore, the key to the catalysis is the structural requirement imposed upon the disulfide: the presence of a suitably positioned ligating functional group.

2.2.1 Reaction Optimization

In accord with the above observations, a ketone synthesis was thought to be feasible with *copper only* through the design of an appropriate *S*-pendant ligand system on the thiol ester. A subset of thiol esters coupled efficiently with boronic acids under aerobic conditions in the presence of catalytic Cu alone (Table 2.2). *!No palladium was necessary!* Appropriate control experiments with new glassware and stirring bars were carried out to ensure no contamination by Pd. After surveying the scope and limitations of the copper-only chemistry, the reaction appears to be most efficient with *S*-pendant thiol esters that are able to form 6-membered ring chelates (Table 2.2, entries 2 and 7-8), but even within this class of substrate there are differences (Table 2.2, entries 3-6).

Table 2.2 A Survey of Pendants for the Aerobic, Cu-Templated Cross-Coupling



		Yield (%)		
Entry	Pendant	Ketone	*S*-Aryl	Ar-Ar
1		trace	trace	57
2		6	trace	37
3		trace	trace	31
4		30	28 [a]	54
5		32	32[a]	trace
6		34	28 [a]	8
7		77	84	7
8		81	75	4

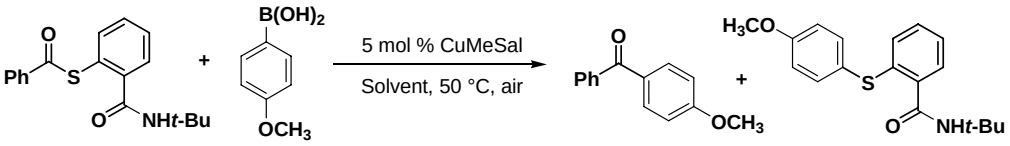
a: NMR yield with 4,4'-di-*tert*-butylbiphenyl.

The best pendants were found to be the *N*-*iso*-propyl and *N*-*tert*-butyl benzamides, (Table 2.2, entries 6 and 7) and the mechanistic implications will be discussed in section 2.2.3. The *N*-*tert*-butyl benzamide pendant was used for further optimization studies.

A survey of solvents revealed DMF to be ideal for this reaction (Table 2.3). Protic solvents such as ethanol (Table 2.3, entry 2) and polar non-coordinating solvents such as THF and dioxane (Table 2.3, entry 1 and 4) led to little or no product. Toluene (Table 2.3, entry 3) gave no reaction. Surprisingly, when acetonitrile (Table 2.3, entry 7) was used no reaction was observed. Oxidation of copper must be fast in order to achieve efficient yields. Perhaps acetonitrile is a strong ligand for copper and backbonding

prevents copper oxidation by air. Finally, entry 6 demonstrates that the reaction can be carried out in a mixture of DMF and water (2:1). The only limitation is the insolubility of the thiol ester in water.

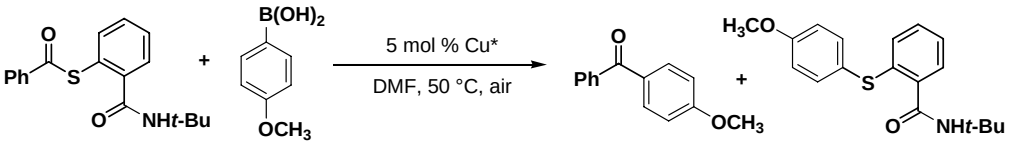
Table 2.3 Solvent Optimization

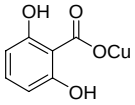
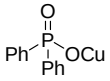


		Yield (%)	
Entry	**Solvent**	**% ketone**	**% *S*-arylation**
1	THF	>10	>10
2	EtOH	>10	>10
3	Toluene	N.R.	N.R.
4	Dioxane	trace	trace
5	DMF	81	75
6	DMF:H_20 (2:1)	60	mix
7	CH_3CN	N.R.	N.R.

A survey of copper salts led to important conclusions (Table 2.4). All copper(I) salts gave high ketone yields regardless of the counter-ions (Table 2.4, entries 1-5). When copper(II) salts were used, an oxygenate counter-ion was necessary (Table 2.4, entries 6 and 7). If copper(II) chloride was used (Table 2.4, entry 8), no reaction was observed. Surprisingly, very little homocoupling product is isolated in these reactions considering it is a very fast and quantitative reaction in the absence of the thiol ester. Copper(II) salts can by reduced by boronic acid to copper(I) *via* homocoupling; however, this process may be slow with chloride. In Suzuki cross-coupling chemistry, an oxygenate counterion is required to facilitate boron to palladium transmetallation.[17] These observations collectively imply that it is necessary to start with copper (I). Oxidation by air leads to a copper(III) active catalyst.

Table 2.4 Optimization of Copper Catalysis



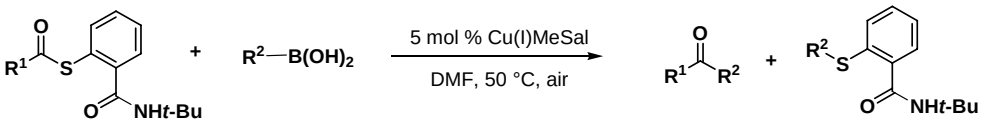
Entry	Cu*	% ketone	% *S*-arylation	% Ar-Ar
1	CuCl	72	79	39
2	CuMeSal	81	75	4
3		73	88	10
4	CuTC	70	79 [a]	10
5		82	84	10
6	$Cu(OAc)_2$	56	66[a]	trace
7	$Cu(OTf)_2$	65	64	trace
8	$CuCl_2$	N.R.	N.R.	N.R.

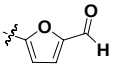
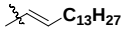
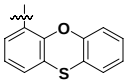
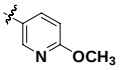
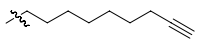
a: estimated NMR yield.

2.2.2 Cross-Coupling Examples

After the best *S*-pendant was identified (Table 2.2, *N*-*tert*-butyl, entry 7), a variety of thiol esters were treated with boronic acids (Table 2.5). Electron rich and poor aromatics as well as heteroaromatics were well tolerated (Table 2.5, entries 1-4, 7, 9-10). Alkenyl boronic acids also reacted well (Table 2.5, entries 5 and 6). The heterocyclic phenoxathiine boronic acid (entry 8) gave low yield of ketone and the major product isolated from the reaction was deborylation. The simple aliphatic boronic acid, cyclohexyl boronic acid, gave only starting material. Finally, alkynyl and α,β-unsaturated thiol esters were well tolerated in the reaction (entries 10-11).

Table 2.5 Coupling Examples

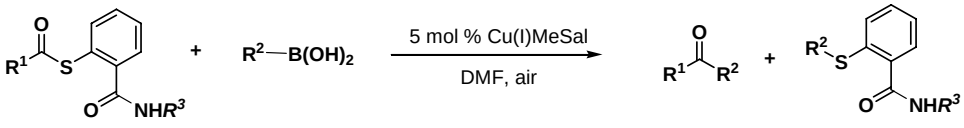


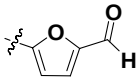
Entry	R^1	R^2	Yield (%) Ketone	Yield (%) *S*-Aryl
1	**-Ph**	**-*p*-OMePh**	81	75
2	**-Ph**		91	78
3	**-*p*-Tol**		86	83
4	**-*p*-Tol**		83	92
5	**-*p*-Tol**		87	83
6 [a,b,c]	**-*p*-Tol**		97	74
7	**-CH_3**		75	71
8	**-CH_3**		18	18
9 [c]			68	61
10			50	51
11 [c]			74	81

a: propylene oxide added, b: copper 2,6-dihydroxycarboxylate, c: based on recovered sm.

The cross-coupling reaction could also be carried out at room temperature by changing the pendant from *N-tert*-butyl to *N-iso*-propyl (Table 2.6). Although reaction times are longer (up to 24 hours), the product yields are comparable under milder conditions (lower temperature).

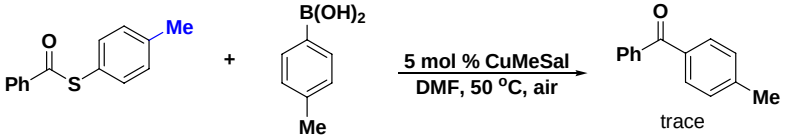
Table 2. 6 Coupling at Room Temperature



			Yield (%)			
			R^3 = *i*-Pr, r.t.		R^3 = *t*-Bu, 50°C	
Entry	**R^1**	**R^2**	**Ketone**	***S*-Aryl**	**Ketone**	***S*-Aryl**
1	-Ph	-*p*-OMePh	82	77	81	75
2	-Ph		78	60	91	78
3	-*p*-Tol		77	quant	86	83

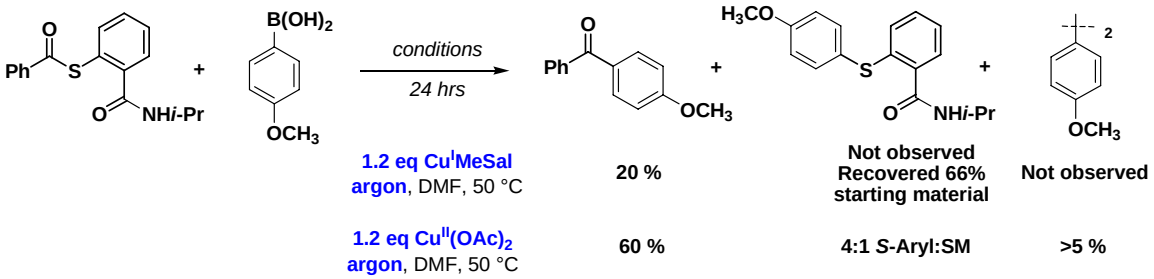
2.2.3 Mechanism

The control experiment in Scheme 2.2 demonstrated the critical importance of the *ortho S*-pendant ligand. If the pendant is left out, trace ketone is observed.



Scheme 2.2 Control Experiment with No Pendant

Control experiments demonstrated when *S*-2-(isopropylcarbamoyl)phenyl benzothioate was treated with a stoichiometric amount of CuMeSal and *p*-tolylboronic acid *under argon*, only 20 % ketone was isolated along with most of the starting material, illustrating the necessity for an oxidant (Scheme 2.3). This also suggests that an oxidative addition mechanism is not a viable pathway. In fact there is no precedent in the literature for copper(I) undergoing oxidative addition to thiol esters. However, a higher oxidation state of copper might be responsible for the observed reactivity. When stoichiometric $Cu(OAc)_2$ was used, 60 % ketone was isolated.



Scheme 2.3 Control Experiments

Given that a mechanism involving oxidative addition was unlikely, a novel, higher oxidation state, metal-templated, mechanism is depicted in Figure 2.1. The Cu(I)-X catalyst bound to the thiol ester through the oxygen of the amide and sulfur could be oxidized by ambient air to a Cu(III)-oxo dimmer. Upon transmetallation with the first equilavent of Ar-$B(OH)_2$, complex I would be formed. Metal templating would provide simultaneous Lewis acid activation of the thiol ester along with coincident delivery of an adjacent nucleophilic organometallic moiety (Ar in Figure 2.1) to produce the ketone. In this redox neutral step, a copper thiolate is also produce (complex II, Figure 2.1).

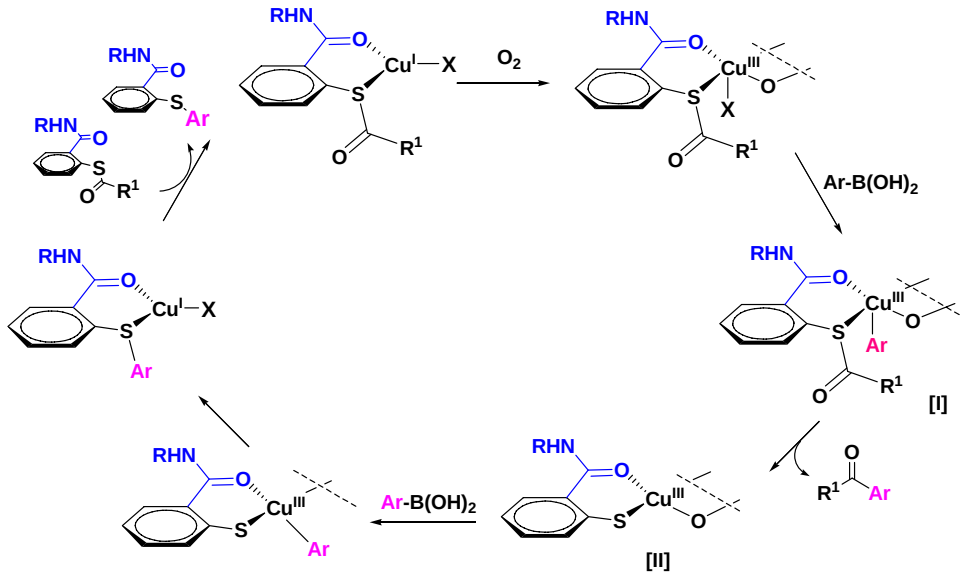


Figure 2.1 Possible Mechanism of *Aerobic, Cu-Templated* Cross-Coupling

A subsequent *S*-arylation of the Cu thiolate (complex II) *via* a transmetallation-reductive elimination sequence would remove the thiolate ligand from the catalytic cycle by forming a weakly coordinating thioether. The overall process is fully catalytic in Cu because each turn of the Cu catalytic cycle uses oxygen to generate an effective "oxygenate" counter-ion for pairing with the $-B(OH)_2$ residue. There are extensive literature studies on dioxygen-Cu reactions relevant to biological systems.[18] These studies give strong evidence for the generation of $[Cu_2(\mu\text{-}O_2]^{2+}$ cores upon activation of Cu(I) by oxygen. In addition, the low-energy interconversion between $[Cu_2(\mu\text{-}O_2]^{2+}$ and $[Cu_2(\mu\text{-}\eta2\text{:}\eta2\text{-}O_2]^{2+}$ suggesting an aerobic copper-catalyzed mechanism that proceeds through either a Cu^{II} or Cu^{III} entity can be confidently proposed.[19]

Copper-templating was most efficient with *N*-*iso*-propyl and *N*-*tert*-butyl pendants. The different performance of the various *S*-pendants can be attributed to a planar chelate geometry to copper (Figure 2.2). The better performing bulkier 2^o thiosalicylamide pendants likely favor the requisite planar chelate geometry with the amide bonding to copper through the carbonyl oxygen. The apparently preferred planar chelate geometry would be disfavored in 3^o salicylamide pendants. An *N*-methyl amide chelated to copper through nitrogen or an alkyl or 5-membered ring pendant cannot reinforce the thiol ester and copper chelation through resonance.

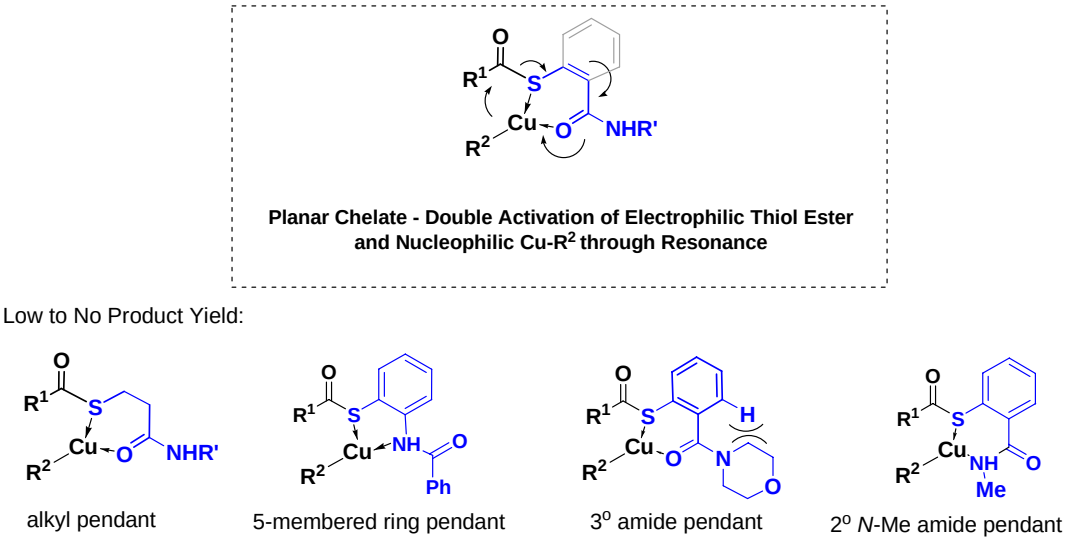


Figure 2.2 Planar Chelate

2.3 Conclusion

In conclusion, a new aerobic cross-coupling of thiol esters and boronic acids was described. A novel, higher oxidation state, metal-templated, mechanism involving generation of a $[Cu_2(\mu\text{-}O_2]^{2+}$ core was speculated. Copper-templating was most efficient with *N-iso*-propyl and *N-tert*-butyl pendants perhaps due to the geometrical requirements induced by copper. Palladium can also form oxo-bridged cores upon oxidation of palladium(0) with oxygen.[20-24] As described in the next chapter, pendants inactive in the aerobic copper catalyzed ketone synthesis can be activated with added amounts of catalytic palladium(0).

The copper-catalyzed chemistry described within may prove uniquely useful in the selective modification of proteins through C-C coupling transformations at *C*-terminal thiol esters. It would be an alternative to introducing unnatural functional groups or labeled fusion proteins.[25-27] In addition, for such activities the equivalent amounts of boronic acids will be unimportant, as might be the formation of the *S*-aryl thioether side-

product. Nevertheless, tactics to overcome the boronic acid stoichiometry are currently being explored in our laboratory.

2.4 References

1. Antos, J. M.; Francis, M. B. Transition Metal Catalyzed Methods for Site-Selective Protein Modification. *Curr. Opin. Chem. Biol.* **2006**, *10*, 253-262.

2. Beatty, K. E.; Xie, F.; Wang, Q.; Tirrell, D. A. Selective Dye-Labeling of Newly Synthesized Proteins in Bacterial Cells. *J. Am. Chem. Soc.* **2005**, *127*, 14150-14151.

3. Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. Bioconjugation by Copper(I)-Catalyzed Azide-Alkyne [3 + 2] Cycloaddition. *J. Am. Chem. Soc.* **2003**, *125*, 3192-3193.

4. Link, A. J.; Tirrell, D. A. Cell Surface Labeling of Escherichia coli via Copper(I)-Catalyzed [3+2] Cycloaddition. *J. Am. Chem. Soc.* **2003**, *125*, 11164-11165.

5. Saxon, E., Bertozzi, Carolyn R. Cell Surface Engineering by a Modified Staudinger Reaction. *Science* **2000**, *287*, 2007-2010.

6. Jacob, C.; Giles, G. I.; Giles, N. M.; Sies, H. Sulfur and Selenium: The Role of Oxidation State in Protein Structure and Function. *Angew. Chem. Int. Ed.* **2003**, *42*, 4742-4758.

7. Giles Niroshini, M.; Giles Gregory, I.; Jacob, C. Multiple Roles of Cysteine in Biocatalysis. *Biochem. Biophys. Res. Commun.* **2003**, *300*, 1-4.

8. Liebeskind, L. S.; Srogl, J. Thiol Ester-Boronic Acid Coupling. A Mechanistically Unprecedented and General Ketone Synthesis. *J. Amer. Chem. Soc.* **2000**, *122*, 11260-11261.

9. Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. Ambient Temperature Synthesis of High Enantiopurity *N*-Protected Peptidyl Ketones by Peptidyl Thiol Ester-Boronic Acid Cross-Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 1132-1140.

10. Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. A New Catalytic Cross-Coupling Approach for the Synthesis of Protected Aryl and Heteroaryl Amidines. *Org. Lett.* **2002**, *4*, 983-985.

11. Savarin, C.; Srogl, J.; Liebeskind, L. S. Substituted Alkyne Synthesis under Nonbasic Conditions: Copper Carboxylate-Mediated, Palladium-Catalyzed Thioalkyne-Boronic Acid Cross-Coupling. *Org. Lett.* **2001**, *3*, 91-93.

12. Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. Switchable Catalysis: Modular Synthesis of Functionalized Pyrimidinones *via* Selective Sulfide and Halide Cross-Coupling Chemistry. *Org. Lett.* **2003**, *5*, 4349-4352.

13. Zhang, Z.; Liebeskind, L. S. Palladium-Catalyzed, Copper(I)-Mediated Coupling of Boronic Acids and Benzylthiocyanate. A Cyanide-Free Cyanation of Boronic Acids. *Org. Lett.* **2006**, *8*, 4331-4333.

14. Calderone, V.; Dolderer, B.; Hartmann, H.-J.; Echner, H.; Luchinat, C.; Del Bianco, C.; Mangani, S.; Weser, U. The Crystal Structure of Yeast Copper Thionein: The Solution of a Long-Lasting Enigma. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 51-56.

15. Maret, W. Oxidative Metal Release from Metallothionein *via* Zinc-Thiol/Disulfide Interchange. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 237-241.

16. Shinkai, H.; Maeda, K.; Yamasaki, T.; Okamoto, H.; Uchida, I. Bis[2-(Acylamino)phenyl] Disulfides, 2-(Acylamino)benzenethiols, and *S*-[2-

(Acylamino)phenyl] Alkanethioates as Novel Inhibitors of Cholesteryl Ester Transfer Protein. *J. Med. Chem.* **2000**, *43*, 3566-3572.

17. Kotha, S.; Lahiri, K.; Kashinath, D. Recent Applications of the Suzuki-Miyaura Cross-Coupling Reaction in Organic Synthesis. *Tetrahedron* **2002**, *58*, 9633-9695.

18. Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. Structure and Spectroscopy of Copper-Dioxygen Complexes. *Chem. Rev.* **2004**, *104*, 1013-1046.

19. Mahadevan, V.; Henson, M. J.; Solomon, E. I.; Stack, T. D. P. Differential Reactivity between Interconvertible Side-On Peroxo and Bis-m-oxodicopper Isomers Using Peralkylated Diamine Ligands. *J. Am. Chem. Soc.* **2000**, *122*, 10249-10250.

20. Popp, B. V.; Wendlandt, J. E.; Landis, C. R.; Stahl, S. S. Reaction of Molecular Oxygen with an NHC-Coordinated Pd^0 Complex: Computational Insights and Experimental Implications. *Angew. Chem. Int. Ed.* **2007**, *46*, 601-604.

21. Popp, B. V.; Stahl, S. S. "Oxidatively Induced" Reductive Elimination of Dioxygen from an η2-Peroxopalladium(II) Complex Promoted by Electron-Deficient Alkenes. *J. Am. Chem. Soc.* **2006**, *128*, 2804-2805.

22. Landis, C. R.; Morales, C. M.; Stahl, S. S. Insights into the Spin-Forbidden Reaction between L_2Pd^0 and Molecular Oxygen. *J. Am. Chem. Soc.* **2004**, *126*, 16302-16303.

23. Konnick, M. M.; Guzei, I. A.; Stahl, S. S. Characterization of Peroxo and Hydroperoxo Intermediates in the Aerobic Oxidation of *N*-Heterocyclic-Carbene-Coordinated Palladium(0). *J. Am. Chem. Soc.* **2004**, *126*, 10212-10213.

24. Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. Oxygenation of Nitrogen-Coordinated Palladium(0): Synthetic, Structural, and Mechanistic Studies and Implications for Aerobic Oxidation Catalysis. *J. Am. Chem. Soc.* **2001**, *123*, 7188-7189.

25. Walsh, D. P.; Chang, Y. T. Chemical Genetics. *Chem. Rev.* **2006**, *106*, 2476-2530.

26. Marks, K. M.; Nolan, G. P. Chemical Labeling Strategies for Cell Biology. *Nature Methods* **2006**, *3*, 591-596.

27. Giepmans, B. N. G.; Adams, S. R.; Ellisman, M. H.; Tsien, R. Y. The Fluorescent Toolbox for Assessing Protein Location and Function. *Science* **2006**, *312*, 217-224.

2.5 Experimental

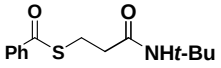
All reactions were preformed under an atmosphere of dry N_2 or Ar in flame-dried glassware unless otherwise noted. Solvents (THF, DMA, DMF, dioxane, toluene, DCM, $CHCl_3$, Et_3N, pyridine) for reaction media were ACS reagent grade and purchased from Aldrich. They were dried over 4 Å molecular sieves and titrated for water level with a Karl Fisher Coulomatic K-F titrator. All solvents were purged with dry N_2 or Ar before using unless otherwise noted. Hexane (hex), ethyl acetate (EtOAc), and diethyl ether (Et_2O) used for extraction, recrystallization, or chromatography were obtained from EM Science and used as purchased. Solution of $NaHCO_3$, NaOH, or HCl refers to aqueous solution. Brine is a saturated solution of sodium chloride in water. Analytical thin-layer chromatography (TLC) was carried out using Merk Kieselgel 0.25 mm 60 F_{254} plates with visualization by UV, $KMnO_4$, or iodine crystals in silica gel.

^{1}H NMR spectra were recorded on a Varian Inova 400 or 600 MHz NMR spectrometer at room temperature in $CDCl_3$ or *d*-DMSO and were internally referenced to either, (7.27 ppm and 2.50 ppm, respectively). ^{13}C NMR spectra were recorded on a Varian Inova 100 or 150 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated (b (broadened), s (singlet), t (triplet), q (quartet), d (doublet), m (multiplet), app (apparent); coupling constants, *J*, are reported in Hz; integration is provided. Infrared (IR) spectroscopy was preformed on an ASi Applied Systems ReactIR 1000 Electronics Module or a Thermo Corporation Nicolet 380 FTIR. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100%), m (medium, 40-67%), w (weak, 20-40%), and br (broad). Uncalibrated melting

points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes. Elemental analyses were preformed by Atlantic Microlab, Inc., Norcross, Georgia. HPLC analysis was carried out on an Aligent 1100 series with an Eclipse XDB-C_8 capillary column. (4.6 x 150 mm id, 5 μm).

Boronic acids were purchased from Frontier Scientific, Inc. Copper catalysts were purchased from Strem Chemicals or Aldrich. CuTC[1], CuMeSal[2], and CuDPP[3] were prepared according to the literature procedure. Diphenyl disulfide, *N*-*tert*-butylacrlamide, *N*,*N*-dimethylbenzylamine, *tert*-butyl lithium, *n*-butyl lithium, sublimed sulfur, benzoic anhydride, sodium borohydride, benzoyl, chloride, toluoyl chloride, acetic anhydride, butyric anhydride, triethyl phosphine, undec-10-ynoic acid, crotonyl chloride, and propylene oxide were purchased from Aldrich. Disulfide or equivalents were prepared according to referenced literature procedures.

Thiol ester synthesis:



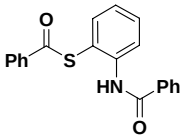
***S*-2-(*tert*-Butylcarbamoyl)ethyl benzothioate:** Dry dichloromethane (4 ml) were added to *N*-*tert*-butyl acrylamide (7.86 mmol, 1g) to solubilize the solid. Thiobenzoic acid (7.86 mmol, 0.925 ml) was then added at 0 ^{o}C. The reaction was stirred overnight. The

[1] Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312-2313.

[2] Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91-93.

[3] Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132-1140.

reaction was quenched with 100 ml of saturated $NaHCO_3$ and extracted three times with 25 ml of dichloromethane. The organic layer was dried with $MgSO_4$, filtered, and concentrated to give 1.909 g of the pure thiol ester. Yield: 92 %. White solid, M.p. 99-100 ^oC. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96 (m, 2H), 7.59 (tt, *J*= 8.6, 1.2 Hz, 1H), 7.46 (m, 2H), 5.35 (bs, 1H), 3.33 (t, *J*= 7.0 Hz, 2H), 2.51 (t, J= 6.6 Hz, 2H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.4, 170.1, 137.1, 133.7, 128.8, 127.3, 51.6, 37.4, 28.9, 25.1. IR (neat, cm^{-1}) 3312 (m), 2695 (w), 1658 (s), 1637 (s), 1545 (s); HRMS (ESI) Calcd for $C_{14}H_{20}NO_2S$ ($M+H^+$): 266.1215. Found: 266.1209.

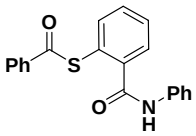


***S*-2-(Benzamido)phenyl benzothioate:** *Method F*[4]*:* From 2,2'-dithio-bis-*N,N'*-phenylbenzamide[5] (2.0 g, 4.40 mmol) in 90 ml of EtOH, $NaBH_4$ (0.43 g, 11.3 mmol), and benzoyl chloride (13.2 mmol) was obtained the pure thiol ester after hydrolyzing with 5 ml of 1M solution of HCl and 300 ml of water and collecting the resulting solid. NOTE: After no more gas evolved from $NaBH_4$ addition, a pH = 7 phospate buffer solution was added followed before the addition of benzyl chloride. Yield: 96 %. White solid, M.p. 153-154 ºC (toluene). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.65 (bs, 1H), 8.55 (dd, *J*= 8.3, 0.9 Hz, 1H), 8.09-8.07 (m, 2H), 7.82-7.80 (m, 2H), 7.69-7.65 (m, 1H), 7.60-7.48 (m, 5H), 7.43-7.41 (m, 2H), 7.23 (dt, *J*= 7.6, 1.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.2, 165.2, 140.4, 136.4, 135.9, 134.7, 134.3, 131.9, 131.7, 129.0, 128.9, 127.8,

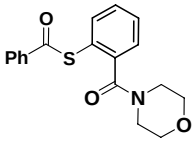
[4] *Method F* refers to General Thiol Ester Synthesis, *Method F*, section 1.5 Experimental.

[5] Shinkai, H.; Maeda, K.; Yamasaki, T.; Okamoto, H.; Uchida, I. *J. Med. Chem.* **2000**, *43*, 3566-3572.

127.0, 124.9, 122.4, 116.9. IR (neat, cm^{-1}) 3393 (m), 1683 (s). HMRS (FAB+) Calcd for $C_{20}H_{16}NO_2S$ (M+H): 334.0918. Found: 334.0902. Anal. Calcd for $C_{20}H_{15}NO_2S$: C, 72.05; H, 4.53; N, 4.20; S, 9.86. Found: C, 72.17; H, 4.64; N, 4.20; S, 9.49.



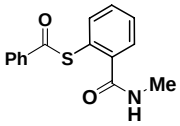
***S*-2-(Phenylcarbamoyl)phenyl benzothioate:** *Method F:* From 2,2'-dithio-bis(phenyl)benzamide (162 mg, 0.35 mmol) in 1 mL of EtOH, $NaBH_4$ (40 mg, 1.0 mmol), and benzoic anhydride (259 mg, 1.0 mmol) was obtained 205 mg of pure thiol ester after quenching with saturated $NaHCO_3$ (100 mL) and filtering the solid. Yield: 85 %. White solid, M.p. 133-134 ^oC. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (bs, 1H), 8.02 (app d, *J*= 6.3 Hz, 2H), 7.75 (d, *J*= 7.8 Hz, 1H), 7.64-7.46 (m, 8H), 7.28 (app t, *J*= 7.4 Hz, 2H), 7.08 (t, *J*= 7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.9, 166.5, 134.4, 137.9, 137.3, 136.2, 134.5, 130.9, 129.2, 129.1 (2), 127.9, 124.6, 123.8, 119.8. IR (neat, cm^{-1}) 3274 (w), 1678 (s), 1656 (s). HMRS ESI (M+H) Calcd for $C_{20}H_{16}NO_2S$ (M+H): 334.0918. Found: 334.0893.



***S*-2-(Morpholinylcarbamoyl)phenyl benzothioate:** *Method F:* From 2,2'-dithio-bis(morpholino)benzamide[6] (1.04 g, 2.3 mmol) in 12 ml of dioxane and 2 ml of EtOH, $NaBH_4$ (195 mg, 5.1 mmol), and benzoic anhydride (1.35 g, 5.1 mmol) was obtained 1.15

[6] Domagala, J. M.; Bader, J. P.; Gogliotti, R. D.; Sanchez, J. P.; Stier, M. A.; Song, Y.; Prasad, J. V. N. V.; Tummino, P. J.; Scholten, J.; et al. *Bioorg. Med. Chem.* **1997,** 5, 569-579.

g of pure thiol ester after quenching with saturated $NaHCO_3$ (100 ml), extracting with EtOAc, and purifying *via* column chromatography (2:1 to 1:1 hex:EtOAc gradient). Yield: 77 %. Beige solid, M.p. 92-93 ^oC. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.10). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.0 (m, 2H), 7.62-7.56 (m, 2H), 7.52-7.42 (m, 4H), 7.33 (m, 1H), 3.52 (s, 2H), 2.23 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.1, 168.2, 141.6, 137.8, 136.2, 134.3, 130.3, 130.0, 129.1, 127.8, 127.1, 124.7, 67.0, 66.9, 47.6, 42.1. IR (neat, cm^{-1}) 1679 (s), 1637 (s), 1432 (s); HRMS (ESI) Calcd for $C_{18}H_{18}NO_3S$ (M+H): 328.1007. Found: 328.1000.



***S*-2-(Methylcarbamoyl)phenyl benzothioate:** *Method F:* From 197 mg, 0.60 mmol, of 2,2'-dithio-bis(*N*-methyl)benzamide[7] with 55 mg, 1.32 mmol, of $NaBH_4$ and 361 mg, 1.32 mmol, of benzoic anhydride in 2 ml of EtOH was obtained 248 mg of pure thiol ester after column chromatography (1:1 hex:EtOAc to 100% EtOAc gradient). Yield: 77 %. White solid, M.p. 140-141 ^oC (CH_2Cl_2) TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.11). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (dd, *J*= 8.1, 0.96 Hz, 2H), 7.65-7.59 (m, 2H), 7.55 (dd, *J*= 5.9 1.4 Hz, 1H), 7.52-7.47 (m, 4H), 6.16 (bs, 1H), 2.88 (d, *J*= 4.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.8, 169.4, 142.9, 137.2, 136.4, 134.3, 130.5, 130.3, 129.0, 128.6, 127.8, 124.3, 26.8, ; IR (neat, cm^{-1}) 3290 (m), 1669 (s), 1635 (s). HRMS (ESI) Calcd for $C_{15}H_{14}NO_2S$ (M+H): 272.0745. Found: 272.0740.

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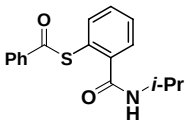
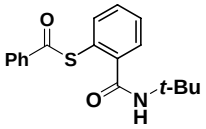
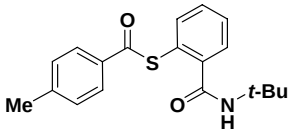
[7] Nagy, P.; Csampai, A.; Szabo, D.; Varga, J.; Harmat, V.; Ruff, F.; Kucsman, *J. Chem. Soc., Perkin Trans. 2* **2001**, 3, 339-349.



S-2-(Isopropylcarbamoyl)phenyl benzothioate[8]



S-2-(*tert*-Butylcarbamoyl)phenyl benzothioate: *Method F:* From 221 mg, 0.53 mmol, of 2,2'-dithio-bis(*N*-*t*-butyl)benzamide[4] with 50 mg, 1.32 mmol, of $NaBH_4$ and 290mg, 1.1 mmol, of benzoic anhydride in 1.1 ml of EtOH was obtained 210 mg of pure thiol ester after filtering over Celite followed by column chromatography with 2:1 to 1:1 hex:EtOAc gradient. Yield: 60 %. Light yellow solid, M.p. 95-96 ^{o}C. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.47). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, *J*= 7.0 Hz, 2H), 7.65 (t, *J*= 7.4, 1H), 7.61-7.59 (m, 1H), 7.54-7.44 (m, 5H), 5.98 (bs, 1H), 1.30 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.4, 167.9, 144.4, 137.1, 136.3, 130.7, 130.2, 129.1, 128.6, 127.8, 123.5, 51.9, 28.7. IR (neat, cm^{-1}) 3305 (w), 2966 (w), 1667 (s), 1522 (m). HRMS (ESI) Calcd for $C_{18}H_{1H}NO_2S$ (M+): 314.1215. Found: 314.1207.

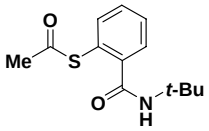


S-2-(*tert*-Butylcarbamoyl)phenyl 4-methylbenzothioate: *Method F:* From 2-*tert*-butyl-benzo[*d*]isothiazol-3-one[9] (748 mg, 3.6 mmol), $NaBH_4$ (168 mg, 4.3 mmol), *p*-

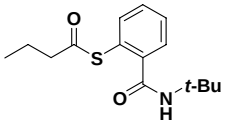
[8] Described in section 1.5 Experimental.

[9] (a) Method derived from the following citation: Wright, S. W.; Abelman, M. M.; Bostrom, L. L.; Corbett, R. L. *Tetrahedron Lett.* **1992,** 33, 153-156. (b) Known procedure: Kamigata, N.; Hashimoto, S.; Kobayashi, M. *Org. Prep. Proced. Int.* **1983,** 15, 315-319.

toluoyl chloride (0.70 ml, 4.9 mmol) in 20 ml of EtOH was obtained 866 mg of the pure thiol ester after column purification with 1:1 hex:EtOAc elutant. Yield: 74 %, White crystals, M.p. 107-108 ^{o}C. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.17). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95-7.39 (m, 1H), 7.61-7.44 (m, 3H), 7.32-7.26 (m, 4H), 6.01 (bs, 1H), 2.45 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.1, 168.0, 145.4, 144.4, 137.2, 133.7, 130.6, 130.1, 129.8, 128.6, 127.8, 123.5, 51.8, 28.7, 21.9. IR (neat, cm^{-1}) 2968 (m), 1668 (s), 1525 (s). Anal. Calcd for $C_{19}H_{21}NO_5S$ (MW=327.44): C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 69.48; H, 6.50; N, 4.34; S, 9.70.

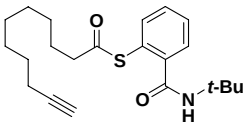


***S*-2-(*tert*-Butylcarbamoyl)phenyl ethanethioate:** *Method F:* From 320 mg, 0.72 mmol, of 2,2'-dithio-bis(*N*-*t*-butyl)benzamide[4] with 74 mg, 1.9 mmol, of $NaBH_4$ and 0.15 ml of acetic anhydride in 5 ml of EtOH was obtained 245 mg of pure thiol ester after a quenching with water and collecting the solid. Yield: 68 %. Beige solid., M.p. 140-141 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54-7.52 (m, 1H), 7.49-7.42 (m, 3H), 5.80 (bs, 1H), 2.54 (s, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.9, 167.9, 143.5, 136.6, 130.5, 130.2, 128.4, 124.3, 52.0, 30.4, 28.9. IR (neat, cm^{-1}) 3289 (m), 2972 (m), 1702 (s), 1656 (s), 1536 (s). HRMS (ESI) Calcd for $C_{13}H_{18}NO_2S$ (M+H): 252.1058. Found: 252.1053.



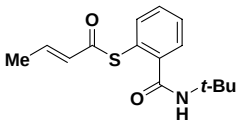
***S*-2-(*tert*-Butylcarbamoyl)phenyl butanethioate:** *Method F:* From 257 mg, 0.60 mmol, of 2,2'-dithio-bis(*N*-*t*-butyl)benzamide[4] with 57 mg, 1.32 mmol, of $NaBH_4$ and

0.25 ml of butyric anhydride in 3 ml of EtOH was obtained 211 mg of pure thiol ester after quenching with saturated $NaHCO_3$. Yield: 63 %. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.49 (m, 1H), 7.45-7.40 (m, 3H), 5.84 (bs, 1H), 2.65 (t, *J*= 7.0 Hz, 2H), 1.73 (dd, *J*= 7.4 Hz, 2H), 1.39 (s, 9H), 0.99 (t, *J*= 7.4Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.1, 167.9, 143.4, 136.6, 130.3, 130.0, 128.3, 124.2, 51.9, 45.7, 28.8, 19.2, 13.8. IR (neat, cm^{-1}) 3305 (w), 2965 (m), 2158 (m), 1697 (s), 1656 (s). HRMS (ESI) Calcd for $C_{15}H_{22}NO_2S$ (M+H): 280.1371. Found: 280.1364.



S-2-(*tert*-Butylcarbamoyl)phenyl dec-9-ynethioate: *Method G*[10]*:* 2-*tert*-butyl-benzo[*d*]isothiazol-3-one[8] (341 mg, 1.6 mmol), and undec-10-ynoic acid (323 mg, 1.8 mmol) were placed in a dry round bottom flask under argon with stirring. 1M Triethyl phosphine (2 ml, 1.1 equiv) was added at room temperature. The volatiles were removed under vacuum and the residue was directly placed on a column and eluted with 10:1 to 1:1 hex:EtOAc gradient to give 530 mg of the pure thiol ester. Yield: 86 %. Light yellow viscous solid. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.57). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.50 (m, 1H), 7.48-7.40 (m, 3H), 5.82 (bs, 1H), 2.67 (t, *J*= 7.0 Hz, 2H), 2.18 (dt, *J*= 7.0, 2.3 Hz, 2H), 1.94 (t, *J*= 2.7 Hz, 1H), 7.40-1.66 (m, 2H), 1.56-1.46 (m, 3H), 1.42-1.26 (m, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.2, 167.9, 143.4, 136.6, 130.3, 130.0, 128.3, 124.2, 84.8, 68.3, 51.9, 43.9, 29.2, 29.1, 29.0, 28.8, 28.7, 28.5, 25.7, 18.4. IR (neat, cm^{-1})[1].3304 (w), 2928 (m), 1694 (s), 1657 (s), 1519 (s). HRMS (ESI) Calcd for $C_{22}H_{32}NO_2S$ (M+H): 374.2154. Found: 374.2146.

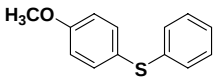
[10] *Method G* refers to General Thiol Ester Synthesis, *Method G*, section 1.5 Experimental.



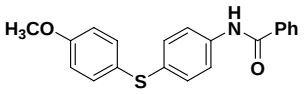
(*E*)-*S*-2-(*tert*-Butylcarbamoyl)phenyl but-2-enethioate: *Method F:* From 2-*tert*-butyl-benzo[*d*]isothiazol-3-one[8] (270 mg, 1.2 mmol), $NaBH_4$ (76 mg, 2.0 mmol), crotonoyl chloride (0.14 ml, 1.4 mmol) in 6 ml of EtOH was obtained 270 mg of the pure thiol ester after quenching with saturated $NaHCO_3$. Yield: 83 %. Yellow solid, M.p. 79-80 ^oC ^1H NMR ($CDCl_3$, 400 MHz): δ 7.56-7.41 (m, 4H), 7.08-7.02 (m, 1H), 6.28 (dd, *J*= 15.2, 1.5 Hz, 1H), 5.95 (bs, 1H), 1.96 (dd, *J*= 6.6, 1.5 Hz, 3H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.1, 167.9, 144.0, 143.3, 136.8, 130.5, 130.0, 129.3, 128.5, 123.6, 51.9, 28.7, 18.4. IR (neat, cm^{-1}) 3369 (w), 2966 (w), 1669 (s), 1635 (s), 1524 (m). HRMS (ESI) Calcd for $C_{15}H_{20}NO_2S$ (M+H): 278.1215. Found: 278.1208.

General Procedure for disulfide coupling with copper and boronic acids:

The corresponding disulfide (1.0 equiv, 0.25 mmol) was placed in 10 ml vial equipped with a small magnetic stir bar. Catalytic amounts of copper methylsalicylate (5 %, 0.0125 mmol) were added followed by the *p*-methoxyphenyl boronic acid (2.5 equiv, 0.625 mmol). Then, 2 ml of dry dimethylformamide (DMF) was added and the reaction was allowed to stir in air until completion via TLC or for 12 hours. The reaction was quenched with 2 % HCl. The aqueous layer was extracted twice with 50 ml diethyl ether. The combined organic layers were was once with 100 ml of water. The organic layer was dried with $MgSO_4$, filtered and the volatiles evaporated. The viscous solid was than subjected to column chromatography (hexane, EtOAc gradient).



(4-Methoxyphenyl)(phenyl)sulfane[11]: From commercially available diphenyldisulfide (29 mg, 0.11 mmol), *p*-methoxyphenyl boronic acid (45 mg, 0.27mmol), and CuMeSal (28 mg, 0.132 mmol) in 2 ml of DMF *under argon* was obtained 22 mg of the pure thioether after column purification with a 10:1 hex:Et_2O elutant. Yield: 77 %. Clear oil. TLC (silica gel, 10:1 hex:EtOAc, R_f= 0.56). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J*=8.6 2H), 7.24 (d, *J*= 7.0 Hz, 2H), 7.19-7.15 (m, 3H), 6.91 (d, *J*= 8.9 Hz, 2H), 3.83 (s, 3H). IR (neat, cm^{-1}) 1591 (m), 1492 (s), 1244 (s).



***N*-(4-(4-Methoxyphenylthio)phenyl)benzamide:** From 4,4'-dithio-bis-*N,N'*-phenylbenzamide[12] (52 mg, 0.11 mmol), *p*-methoxyphenyl boronic acid (47 mg, 0.27mmol), and CuMeSal (31 mg, 0.132 mmol) in 2 ml of DMF *under argon* was obtained 24 mg of the pure thioether after column purification with a 1:1 hex:EtOAc elutant. Yield: 64 %. White solid, M.p. 149-150 ^{o}C. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.62). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (bs, 1H), 7.84 (d, *J*= 7.0 Hz, 2H), 7.56-7.53 (m, 3H), 7.44 (t, *J*= 7.4 Hz, 2H), 7.38 (d, *J*= 8.9 Hz, 2H), 7.22 (d, *J*= 8.9 Hz, 2H), 6.88 (d, *J*= 8.9 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 159.8, 136.4, 134.9,

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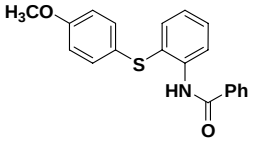
[11] Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. *Synlett* **2004**, 7, 1254-1258.

[12] (a) 2,2'-Dithio-bis-*N,N'*-phenylbenzamide was synthesized by modifying the following literature procedure: Sengar, R. S.; Nemykin, V. N.; Basu, P. *New J. Chem.* **2003,** 27, 1115-1123. (b) Known compound: Baruffini, A.; Gialdi, F. *Farmaco, Edizione Scientifica* **1958,** 13, 911-921.

134.7, 133.7, 132.1, 130.2, 129.0, 127.2, 125.3, 121.0, 115.1, 55.6. IR (neat, cm^{-1}) 3347 (w), 1652 (s). HRMS (ESI) Calcd for $C_{20}H_{18}NO_2S$ (M+H): 336.1058. Found: 336.1052.



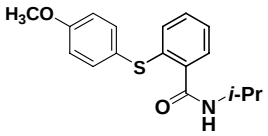
***N*-(2-(4-Methoxyphenylthio)phenyl)benzamide:** From 2,2'-dithio-bis-*N,N'*-phenylbenzamide[4] (52 mg, 0.11 mmol), *p*-methoxyphenyl boronic acid (47 mg, 0.27 mmol), and CuMeSal (30 mg, 0.132 mmol) in 2 ml of DMF *under argon* was obtained 25 mg of the pure thioether after column purification with a 10:1 hex:EtOAc elutant. Yield: 66 %. From 2,2'-dithio-bis-*N,N'*-phenylbenzamide[9] (51 mg, 0.11 mmol), *p*-methoxyphenyl boronic acid (45 mg, 0.27 mmol), and CuMeSal (1.2 mg, 0.055 mmol) in 2 ml of DMF *open to air* was obtained 73 mg of the pure thioether after aqueous work-up (no column purification). Yield: 99 %. Light beige solid, M.p. 72-73 ^{o}C. TLC (silica gel, , 5:1 hex:EtOAc, R_f= 0.48). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (bs, 1H), 8.63 (dd, *J*= 8.2, 1.2 Hz, 1H), 7.75 (d, *J*= 6.26. 2H), 7.58 (dd, *J*= 7.8, 1.5 Hz, 1H) 7.54 (t, *J*= 7.4 Hz, 1H), 7.45 (t, *J*= 7.4 Hz, 3H), 7.16-7.11 (m, 3H), 6.81 (d, *J*= 8.6 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 159.1, 139.5, 135.7, 135, 132.1, 130.6, 130.5, 128.9, 127.2, 125.6, 124.6, 122.6, 120.8, 115.3, 55.6. IR (neat, cm^{-1}): 3356 (w), 1667 (s). HRMS (ESI) Calcd for $C_{20}H_{18}NO_2S$ (M+H): 336.1058. Found: 336.1051.

General Procedure for aerobic Copper catalyzed ketone synthesis (Tables 2.2-2.6):

The corresponding thiol ester (1.0 equiv, 0.25 mmol) was placed in 10 ml vial equipped with a small magnetic stir bar. Catalytic amounts of copper catalyst (5%, 0.0125 mmol) were added followed by the boronic acid (2.5 equiv, 0.625 mmol). Then,

2 ml of dry dimethylformamide (DMF) or other solvent was added and the reaction was allowed to stir in air at 50 ^{o}C until completion via TLC. The reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted three times with 20 ml diethyl ether. The combined organic layers were was once with 100 ml of water. The organic layer was dried with $MgSO_4$, filtered and the volatiles evaporated. The viscous solid was than subjected to column chromatography (hexane, EtOAc gradient).

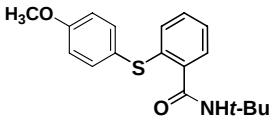
4-Methoxy benzophenone: From *S*-2-(isopropylcarbamoyl)phenyl benzothioate (74 mg, 0.25 mmol), *p*-methoxyphenyl boronic acid (98 mg, 0.64 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 42 mg of the pure ketone after column purification with a 5:1 to 2:1 hex:EtOAc gradient. Yield: 77 %, White crystals, M.p. 59-60 ^{o}C [Lit. 60-63 ^{o}C Aldrich]. The ketone matched known spectra from commercially available material. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.87). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J*= 8.8, 2H), 7.76 (m, 2H), 7.57 (dt, *J*= 7.3, 2.2, 1H), 7.50-7.46 (m, 2H), 3.90 (s, 3H). IR (neat, cm^{-1}): 1694 (s), 1595 (s), 1253 (s).



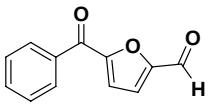
2-(4-Methoxyphenylthio)-*N*-isopropylbenzamide: From *S*-2-(isopropylcarbamoyl)phenyl benzothioate (74 mg, 0.25 mmol), *p*-methoxyphenyl boronic acid (98 mg, 0.64 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 42 mg of the pure thioether after column purification with a 5:1 to 2:1 Hex:EtOAc gradient. Yield: 84 %. White crystals, M.p. 129-131 ^{o}C. TLC (silica gel, R_f= 0.25, 2:1 Hex:EtoAc). M.p. 129-131 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J*= 8.8, 2H), 7.76 (m, 2H), 7.57 (dt, *J*= 7.3, 2.2, 1H), 7.50-7.46 (m, 2H), 3.90 (s, 3H). ^{13}C NMR

(150 MHz, $CDCl_3$) δ 167.3, 160.2, 137.4, 135.9, 135.0, 130.5, 129.1, 128.5, 127.7, 125.7, 123.5, 115.3, 55.5, 42.2, 22.9. IR (neat, cm^{-1}): 3282 (m), 1633 (s), 1493 (s). HRMS (ESI) Calcd for $C_{17}H_{20}NO_2S$ (M+H): 302.1215. Found: 302.1210.

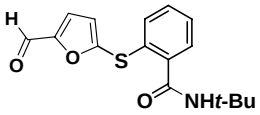
4-Methoxy benzophenone: From *S*-2-(*tert*-butylcarbamoyl)phenyl benzothioate (76.3 mg, 0.24 mmol), *p*-methoxyphenyl boronic acid (102 mg, 0.66 mmol), and CuMeSal (4 mg, 0.018 mmol) in 2 ml of DMF was obtained 42 mg of the pure ketone after column purification with a 5:1 to 2:1 hex:EtOAc gradient. Yield: 81 %.



2-(4-Methoxyphenylthio)-*N*-*tert*-butylbenzamide: From *S*-2-(*tert*-butylcarbamoyl)phenyl benzothioate (76 mg, 0.24 mmol), *p*-methoxyphenyl boronic acid (102 mg, 0.66 mmol), and CuMeSal (4 mg, 0.018 mmol) in 2 ml of DMF was obtained 58 mg of the pure thioether after column purification with a 5:1 to 2:1 hex:EtOAc gradient. Yield: 75 %. Light yellow crystals. M.p. 115-116 ^oC. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.11). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J*= 7.4, 1.5 Hz, 1H), 7.39 (d, *J*= 8.9 Hz, 2H), 7.22-7.13 (m, 2H), 6.94-6.91 (m, 3H), 6.11 (bs, 1H), 1.45 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 160.2, 136.8, 136.2, 135.6, 130.4, 129.4, 128.5, 125.8, 123.7, 115.3, 55.5, 52.1, 28.9. IR (neat, cm^{-1}): 3305 (w), 2965 (m), 1650 (s), 1492 (s). HRMS (ESI) Calcd for $C_{18}H_{22}NO_2S$ (M+H): 316.1371. Found: 316.1366.



5-Methylfuran-2-carboxaldehyde[13]: From *S*-2-(*tert*-butylcarbamoyl)phenyl benzothioate (79 mg, 0.25 mmol), 5-formylfuran-2-yl-2-boronic acid (88 mg, 0.63 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 46 mg of the pure ketone after column purification with a 1:1 hex:EtOAc elutant. Yield: 91 %. Yellow solid, M.p. 93-95 ^{o}C [Lit. 94-95 ^{o}C[14]]. TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.47). ^{1}H NMR (400 MHz, CDCl3) δ 9.89 (s, 1H), 8.08 (d, *J*= 6.3 Hz, 2H), 7.66 (t, *J*= 7.4 Hz, 1H), 7.53 (t, *J*= 7.8 Hz, 3H), 7.37 (dd, *J*= 6.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.7, 179.4, 154.8, 154.0, 136.2, 133.7, 129.9, 128.9, 120.4, 119.4. IR (neat, cm^{-1}): 1683 (s), 1646 (s).



2-(5-Formylfuran-2-ylthio)-*N*-*tert*-butylbenzamide: From *S*-2-(*tert*-butylcarbamoyl)phenyl benzothioate (79 mg, 0.25 mmol), 5-formylfuran-2-yl-2-boronic acid (88 mg, 0.63 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 60 mg of the pure thioether after column purification with a 1:1 hex:EtOAc elutant. Yield; 91 %. Orange crystals, M.p. 79-80 ^{o}C. TLC (silica gel, 1:1 hex:EtOAc, R_f= 0.41). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.45 (dd, *J*= 6.6, 2.3 Hz, 1H), 7.28-7.22 (m, 4H), 7.08 (dd, *J*= 6.3, 1.9 Hz, 1H), 6.75 (d, *J*=3.5 Hz, 1H), 5.99 (bs, 1H), 1.43 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.3, 167.4, 154.9, 153.1, 137.9, 131.9, 131.1, 130.8, 128.1, 127.7, 122.5, 119.3, 52.4, 50.9, 28.9. IR (neat, cm^{-1}): 3305 (w), 2968 (w), 1675 (s), 1652 (s), 1452 (s). HRMS (ESI) Calcd for $C_{16}H_{18}NO_3S$ (M+H): 304.1007. Found: 304.1004.

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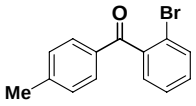
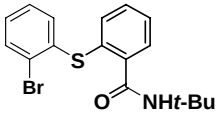
[13] Carpenter, Andrew J.; Chadwick, Derek J. *Tetrahedron* **1985**, *41*, 3803-3812.



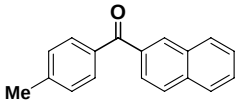
(2-Bromophenyl)(*p*-tolyl)methanone[14]: From *S*-2-(*tert*-butylcarbamoyl)phenyl 4-methylbenzothioate (83 mg, 0.25 mmol), 2-bromophenyl boronic acid (124 mg, 0.62 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 60 mg of the pure ketone after column purification with a 5:1 hex:EtOAc elutant. Yield: 86 %. Light Yellow oil. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.62). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J*= 8.2 Hz, 2H), 7.64 (d, *J*= 8.2 Hz, 1H), 7.42 (t, *J*= 7.4 Hz, 1H), 7.37-7.32 (m, 2H), 7.27 (d, *J*= 7.8 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.7, 145.0, 141.0, 133.7, 133.3, 131.1, 130.5, 129.6, 129.0, 127.3, 119.6, 22.0. IR (neat, cm^{-1}) 1666 (s), 1603 (m), 1287 (s).



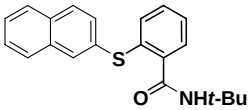
2-(2-Bromophenylthio)-*N*-*tert*-butylbenzamide: From *S*-2-(*tert*-butylcarbamoyl)phenyl 4-methylbenzothioate (83 mg, 0.25 mmol), 2-bromophenyl boronic acid (124 mg, 0.62 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 77 mg of the pure thioether after column purification with a 5:1 hex:EtOAc elutant. Yield: 83 %. Light yellow oil. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J*= 7.8 Hz, 1H), 7.57 (d, *J*= 8.6 Hz, 1H), 7.46-7.37 (m, 3H), 7.18 (t, *J*= 7.4 Hz, 1H), 7.06 (dt, *J*= 7.8, 1.5 Hz, 1H), 6.89 (dd, *J*= 7.8, 1.5 Hz, 1H), 6.48 (bs, 1H), 1.27 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 140.2, 137.9, 135.1, 133.3, 131.1, 130.3, 129.4, 129.4, 129.3, 128.4, 127.8, 122.8, 51.9, 28.6. IR (neat,

[14] Karagoz, S.; Astley, D. K.; Astley, S. T. *Appl. Organomet. Chem.* **2000,** 14, 341-344.

cm^{-1}): 3307 (m), 2966 (m), 1651 (s), 1446 (s). HRMS (ESI) Calcd for $C_{17}H_{19}BrNOS$ (M+H): 364.0371. Found: 354.0364.



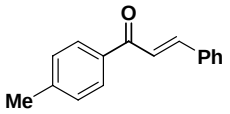
(Naphthalen-3-yl)(*p*-tolyl)methanone[15]: From *S*-2-(*tert*-butylcarbamoyl)phenyl 4-methylbenzothioate (81 mg, 0.25 mmol), naphthalen-2-yl-2-boronic acid (108 mg, 0.62 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 50 mg of the pure ketone after column purification with a 5:1 to 1:1 hex:EtOAc gradient. Yield: 83 %. White solid, M.p. 87-88 ^{o}C [Lit. 87-89 ^{o}C[16]]. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.62). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.92-7.88 (m, 4H), 7.77 (d, *J*= 8.2 Hz, 2H), 7.61-7.51 (m, 2H), 7.30 (d, *J*= 8.2 Hz, 2H) 2.54 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.7, 143.4, 135.3, 132.4, 131.7, 130.5, 129.5, 129.2, 128.4, 128.3, 127.9, 126.9, 126.0, 21.8. IR (neat, cm^{-1}): 1650 (s).



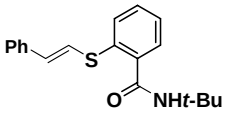
***N*-*tert*-Butyl-2-(naphthalen-3-ylthio)benzamide:** From *S*-2-(*tert*-butylcarbamoyl)phenyl 4-methylbenzothioate (81 mg, 0.25 mmol), naphthalen-2-yl-2-boronic acid (108 mg, 0.62 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 50 mg of the pure thioether after column purification with a 5:1 to 1:1 hex:EtOAc gradient. Yield 92 %. Orange crystals, M.p. 59-60 ^{o}C. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.01). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.78 (m, 3H), 7.75-7.73 (m, 1H), 7.66-7.63 (m, 1H), 7.50-7.47 (m, 2H), 7.39 (dd, *J*= 8.6, 1.9 Hz, 1H), 7.30-7.20 (m,

[15] Utley, J. H. P.; Rozenberg, G. G. *Tetrahedron* **2002,** 58, 5251-5265.

3H), 6.22 (bs, 1H), 1.38 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 138.3, 134.0, 133.5, 132.5, 132.4, 132.3, 130.6, 130.5, 130.3, 129.4, 129.0, 128.7, 127.9, 127.6, 127.4, 126.9, 126.6, 52.1, 28.8. IR (neat, cm^{-1}): 3307 (m), 1650 (s), 1528 (m). HRMS (ESI) Calcd for $C_{21}H_{22}NOS$ (M+H): 336.1422. Found: 336.1414.



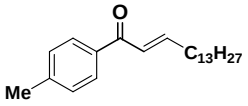
(*E*)-3-Phenyl-1-*p*-tolylprop-2-en-1-one[16]: From *S*-2-(*tert*-butylcarbamoyl)phenyl 4-methylbenzothioate (82 mg, 0.25 mmol), (*E*)-2-phenylvinylboronic acid (95 mg, 0.64 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 48 mg of the pure ketone after column purification with a 10:1 to 2:1 hex:EtOAc gradient. Yield: 87 %. Yellow solid, M.p. 49-50 ^{o}C. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.63). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J*= 8.2 Hz, 2H), 7.82 (d, *J*= 15.6 Hz, 1H), 7.67-7.64 (m, 2H), 7.55 (d, *J*= 15.6 Hz, 1H), 7.43-7.42 (m, 3H), 7.32 (d, *J*= 8.2 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.2, 144.6, 143.8, 135.8, 135.2, 130.6, 129.5, 129.1, 128.8, 128.6, 122.3, 21.9. IR (neat, cm^{-1}): 1656 (s), 1597 (s).



***N*-*tert*-Butyl-2-(styrylthio)benzamide:** From *S*-2-(*tert*-butylcarbamoyl)phenyl 4-methylbenzothioate (82 mg, 0.25 mmol), (*E*)-2-phenylvinylboronic acid (95 mg, 0.64 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 64 mg of the pure thioether after column purification with a 10:1 to 2:1 hex:EtOAc gradient. Yield: 83 %. White crystals, M.p. 103-104 ^{o}C. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.5). ^{1}H

[16] Xia, M.; Chen, Z. *J. Chem. Res., Synop.* **1999**, 6, 400-401.

NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 1H), 7.42 (m, 1H), 7.34-7.24 (m, 8H), 6.78 (d, *J*= 3.9 Hz, 1H), 6.10 (bs, 1H), 1.44 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 137.8, 136.5, 133.8, 133.7, 130.7, 130.6, 128.9, 128.7, 128.0, 127.0, 126.3, 123.0, 52.2, 29.0. IR (neat, cm^{-1}): 3297 (m), 1632 (s), 1531 (s). HRMS (ESI) Calcd for $C_{19}H_{22}NOS$ (M+H): 312.1422. Found: 312.1415.



(*E*)-1-*p*-Tolylhexadec-2-en-1-one: From *S*-2-(*tert*-butylcarbamoyl)phenyl 4-methylbenzothioate (83 mg, 0.25 mmol), (*E*)-pentadec-1-enylboronic acid (161 mg, 0.64 mmol), 2,6-dihydroxycopper(I) benzoate[17] (3 mg, 0.013 mmol), and propylene oxide (0.02 ml, 0.28 mmol) in 2 ml of DMF was obtained 59 mg of the pure ketone after column purification with a 10:1 hex:EtOAc elutant. Yield: 97 % based on recovered starting material. White crystals, M.p. 39-40 °C. TLC (silica gel, 10:1 hex:EtOAc, R_f= 0.5). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J*= 8.2 Hz, 2H), 7.26 (d, *J*= 7.8 Hz, 2H), 7.06 (dt, *J*= 15.2, 7.0, Hz, 1H), 6.87 (d, *J*= 15.2 Hz, 1H), 2.42 (s, 3H), 2.31 (dd, *J*= 13.8, 7.0 Hz, 2H), 1.52 (m, 2H), 1.40-1.26 (m, 28H), 0.88 (t, *J*= 6.4 Hz, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.6, 149.8, 143.5, 135.6, 129.4, 128.8, 125.9, 33.0, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 28.4, 22.8, 21.8, 14.3. IR (neat, cm^{-1}): 2914 (s), 2848 (s), 1665 (s), 1618 (s). HRMS (ESI) Calcd for $C_{23}H_{37}O$ (M+H): 329.2844. Found: 329.2840.

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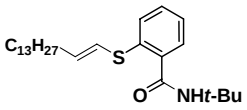
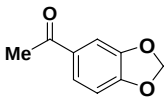
[17] Prepared by modifying the following literature procedure using 2,6-dihydroxybenzoic acid: Zhang S.; Zhang, D.; Liebeskind, L. S.; *J. Org. Chem.,* **1997,** *62*, 2312. IR (neat, cm^{-1}): 3028 (br, m), 1648 (m), 1558 (s). Anal. Calcd for $C_7H_5CuO_4$ (MW=216.66) C, 38.81; H, 2.33. Found: C, 38.63; H, 2.28.

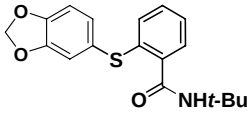


2-((*E*)-Pentadec-1-enylthio)-*N*-*tert*-butylbenzamide: From *S*-2-(*tert*-butylcarbamoyl)phenyl 4-methylbenzothioate (83 mg, 0.25 mmol), (*E*)-pentadec-1-enylboronic acid (161 mg, 0.64 mmol), 2,6-dihydroxycopper(I) benzoate (3 mg, 0.013 mmol), and propylene oxide (0.02 ml, 0.28 mmol) in 2 ml of DMF was obtained 57 mg of the pure thioether after column purification with a 10:1 hex:EtOAc elutant. Yield: 74 % based on recovered starting material. White crystals, M.p.48-50 ^{o}C. TLC (silica gel, 10:1 hex:EtOAc, R_f= 0.08). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J*= 7.0 Hz, 1H), 7.34-7.32 (m, 2H), 7.23-7.19 (m, 1H), 6.08 (bs, 1H), 6.05-6.02 (m, 2H), 2.38 (m, 2H), 1.47 (s, 9H), 1.47-1.26 (m, 31H), 0.88 (t, *J*= 6.4 Hz, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 139.4, 136.8, 134.9, 130.3, 129.4, 128.6, 126.2, 120.5, 52.1, 33.3, 32.1, 29.85, 29.80, 29.6, 29.5, 29.3, 29.1, 28.9, 22.8, 14.3. IR (neat, cm^{-1}): 3257 (w), 2916 (s), 2849 (s), 1631 (s), 1586 (s). HRMS (ESI) Calcd for $C_{26}H_{44}NOS$ (M+H): 418.3344. Found: 418.3134.

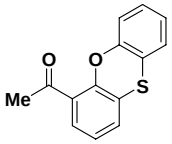


1-(Benzo[*d*][1,3]dioxol-5-yl)ethanone: From *S*-2-(*tert*-butylcarbamoyl)phenyl ethanethioate (63 mg, 0.25 mmol), benzo[*d*][1,3]dioxol-5-yl-5-boronic acid (104 mg, 0.63 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 31 mg of the pure ketone after column purification with a 10:1 to 5:1 hex:EtOAc gradient. Yield: 75 %. Spectra matched that of commercially available compound. Brown crystals, M.p. 77-79 ^{o}C. TLC (silica gel, 5:1 Hex:EtOAc, R_f= 0.28). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J*= 8.2, 1.5 Hz, 1H), 7.43 (d, *J*= 1.5, 1H), 6.85 (d, *J*= 8.2 Hz, 1H), 6.04 (s, 2H),

2.54. (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.5, 151. 9, 148.3, 132.2, 124.9, 108.3, 108.1, 108.0, 102.0, 26.6. IR (neat, cm^{-1}): 1660 (s), 1602 (m). HRMS (ESI) Calcd for $C_9H_9O_3$ (M+H): 165.0546. Found: 165.0552.

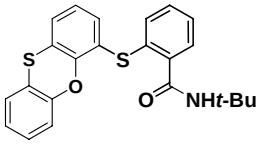


***N*-*tert*-Butyl-2-(benzo[*d*][1,3]dioxol-5-ylthio)benzamide:** From *S*-2-(*tert*-butylcarbamoyl)phenyl ethanethioate (63 mg, 0.25 mmol), benzo[*d*][1,3]dioxol-5-yl-5-boronic acid (104 mg, 0.63 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 58 mg of the pure thioether after column purification with a 10:1 to 5:1 hex:EtOAc gradient. Yield: 71 %. Light brown crystals, M.p. 102-103 ^{o}C. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J*= 7.4, 1.5 Hz, 1H), 7.23 (dt, *J*= 7.4, 1.5 Hz, 1H), 7.18 (dt, *J*= 7.4, 1.5 Hz, 1H), 7.02 (dd, *J*= 7.4, 1.5 Hz, 1H), 6.97 (dd, *J*= 7.8, 1.5 Hz, 1H), 6.89(d, *J*= 1.9 Hz, 1H), 6.81 (d, *J*= 7.8 Hz, 1H), 6.05 (bs, 1H), 5.99 (s, 2H), 1.46 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 148.7, 149.4, 136.6, 136.3, 130.5, 129.8, 128.5, 127.9, 126.2, 125.6, 113.8, 109.4, 101.7, 52.2, 28.9. IR (neat, cm^{-1}): 3339 (m), 1638 (s), 1525 (s). HRMS (ESI) Calcd for $C_{18}H_{20}NOS$ (M+H): 330.1164. Found: 330.1157.

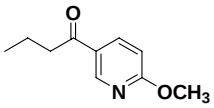


1-(Phenoxathiin-4-yl)ethanone: From *S*-2-(*tert*-butylcarbamoyl)phenyl ethanethioate (62 mg, 0.25 mmol), phenoxathiin-4-yl-4-boronic acid (155 mg, 0.63 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 11 mg of the pure ketone after column purification with a 10:1 to 5:1 hex:EtOAc gradient. Yield: 18 %. Yellow

solid, M.p. 60-61 °C. TLC (silica gel, 5:1 Hex:EtOAc, R_f= 0.46). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J*= 7.8, 1.5 Hz, 1H), 7.29-7.27 (m, 1H), 7.22-7.16 (m, 2H), 7.12-7.06 (m, 3H), 2.79 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.6, 152.0, 151.7, 130.8, 129.3, 128.5, 128.2, 127.2, 125.6, 124.5, 122.3, 120.7, 117.9, 32.2. IR (neat, cm^{-1}): 1608 (s), 1424 (s).

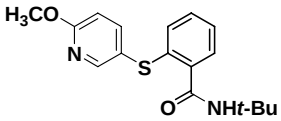


***N-tert*-Butyl-2-(phenoxathiin-4-ylthio)benzamide:** From *S*-2-(*tert*-butylcarbamoyl)phenyl ethanethioate (62 mg, 0.25 mmol), phenoxathiin-4-yl-4-boronic acid (155 mg, 0.63 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 18 mg of the pure thioether after column purification with a 10:1 to 5:1 hex:EtOAc gradient. Yield: 18 %. Orange oil. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.23). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.72 (m, 1H), 7.37-7.33 (m, 1H), 7.29-7.25 (m, 2H), 7.11 (dd, *J*= 7.0, 1.5 Hz, 1H), 7.07-7.01 (m, 3H), 6.95 (d, *J*= 4.7 Hz, 2H), 6.87 (dd, *J*= 8.2, 1.5 Hz, 1H) 6.49 (bs, 1H), 1.35 (s, 9H).^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 151.9, 150.1, 139.2, 133.6, 131.1, 130.8, 129.8, 129.6, 128.3, 128.0, 126.8, 126.1, 125.7, 125.2, 125.1, 122.0, 120.4, 118.1, 52.1, 28.8. IR (neat, cm^{-1}): 3309 (m), 2966 (w), 1654 (s), 1526 (m), 1419 (s). HRMS (ESI) Calcd for $C_{23}H_{22}NO_2S_2$ (M+H): 408.1092. Found: 408.1083.

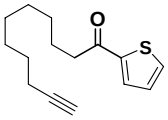


1-(6-Methoxypyridin-3-yl)butan-1-one: From *S*-2-(*tert*-butylcarbamoyl)phenyl butanethioate (43 mg, 0.16 mmol), 6-methoxypyridin-3-yl-3-boronic acid (59 mg, 0.38

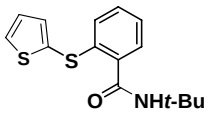
mmol), and CuMeSal (2 mg, 0.009 mmol) in 2 mL of DMF was obtained 19 mg of the pure ketone after column purification with a 5:1 hex:EtOAc elutant. Yield: 68 %. White solid, M.p. 58-59 ^{o}C. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.34). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J*= 2.0 Hz, 1H), 8.15 (dd, *J*= 8.6, 2.3 Hz, 1H), 6.79 (d, *J*= 8.6 Hz, 1H), 4.00 (s, 3H), 2.89 (t, *J*= 7.4 Hz, 2H), 1.79-174 (m, 2H), 1.00 (t, *J*= 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.3, 166.8, 149.1, 138.3, 126.9, 111.3, 54.2, 40.5, 17.9, 14.0. IR (neat, cm^{-1}): 2962 (m), 1682 (s), 1601 (s). HRMS (ESI) Calcd for $C_{10}H_{21}N_2O_2$ (M+H): 180.1024. Found: 180.1015.



2-(6-Methoxypyridin-3-ylthio)-*N*-*tert*-butylbenzamide: From *S*-2-(*tert*-butylcarbamoyl)phenyl butanethioate (43 mg, 0.16 mmol), 6-methoxypyridin-3-yl-3-boronic acid (59 mg, 0.38 mmol), and CuMeSal (2 mg, 0.009 mmol) in 2 mL of DMF was obtained 30 mg of the pure ketone after column purification with a 5:1 hex:EtOAc elutant. Yield: 61 %. White solid, M.p. 111-113 ^{o}C. TLC (silica gel, 5:1 hex:EtOAc, R_f= 0.23). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J*= 2.3 Hz, 1H), 7.65 (dd, *J*= 8.6, 2.3 Hz, 1H), 7.48 (dd, *J*= 7.4, 2.0 Hz, 1H), 7.23-7.14 (m, 2H), 6.90 (dd, *J*= 7.8 1.1 Hz, 1H), 6.77 (d, *J*= 8.6 Hz, 1H), 5.95 (br s, 1H), 3.96 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 164.6, 152.5, 144.8, 136.6, 136.2, 130.6, 128.8, 128.2, 125.9, 121.5, 112.4, 53.9, 52.3. IR (neat, cm^{-1}): 3291 (w), 2970 (w), 1633 (s), 1586 (s), 1535 (s). HRMS (ESI) Calcd for $C_{17}H_{21}N_2O_2S$ (M+H): 317.1324. Found: 317.1315.

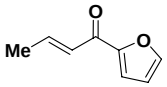


1-(Thiophen-2-yl)dec-9-yn-1-one: From *S*-2-(*tert*-butylcarbamoyl)phenyl dec-9-ynethioate (46 mg, 0.12 mmol), 2-thiophene boronic acid (40 mg, 0.31 mmol), and CuMeSal (1.5 mg, 0.007 mmol) in 2 ml of DMF was obtained 15 mg of the pure ketone after column purification with a 10:1 to 2:1 hex:EtOAc gradient. Yield: 50 %. Light yellow oil. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J*= 3.9, 1.2 Hz, 1H), 7.63 (dd, *J*= 5.0, 1.2 Hz, 1H), 7.13 (dd, *J*= 5.0, 3.9 Hz, 1H), 2.89 (t, *J*= 7.4 Hz, 2H), 2.19 (dt, *J*= 6.6, 2.3 Hz, 2H), 1.94 (t, *J*= 2.7 Hz, 1H), 1.75 (q, *J*= 7.4 Hz, 2H), 1.58-1.49 (m, 3H), 1.45-1.30 (m, 10H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.7, 144.7, 133.5, 131.9, 128.5, 84.9, 68.3, 39.6, 29.5, 29.1, 28.8, 28.6, 24.9, 18.6. IR (neat, cm^{-1}): 3300 (m), 2930 (s), 2856 (m), 2115 (w), 1660 (s). HRMS (APCI) Calcd for $C_{15}H_{21}OS$ (M+H): 249.1313. Found: 249.1304.

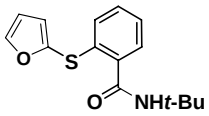


***N*-*tert*-Butyl-2-(thiophen-2-ylthio)benzamide:** From *S*-2-(*tert*-butylcarbamoyl)phenyl dec-9-ynethioate (46 mg, 0.12 mmol), 2-thiophene boronic acid (40 mg, 0.31 mmol), and CuMeSal (1.5 mg, 0.007 mmol) in 2 ml of DMF was obtained 19 mg of the pure thioether after column purification with a 10:1 to 2:1 hex:EtOAc gradient. Yield: 51 %. White crystals, M.p. 102-103 ^{o}C. TLC (silica gel, 2:1 hex:EtOAc, R_f= 0.32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J= 5.5, 1.2 Hz, 1H), 7.44 (dd, *J*= 7.8, 1.5 Hz, 1H), 7.32 (dd, *J*= 3.5, 1.5 Hz, 1H), 7.22 (dt, *J*= 7.8, 1.5 Hz, 1H), 7.16-7.10 (m, 2H), 6.94 (dd, *J*= 8.0, 1.2 Hz, 1H), 5.90 (bs, 1H), 1.51 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 138.4, 137.1, 135.1, 132.0, 130.8, 130.7, 128.4, 127.7, 127.6, 125.6, 52.3, 29.0. IR (neat,

cm^{-1}): 3304 (m), 2930 (m), 1649 (s), 1525 (s). HRMS (ESI) Calcd for $C_{15}H_{18}NOS_2$ (M+H): 292.0830. Found: 292.0822.



(*E*)-1-(Furan-2-yl)but-2-en-1-one[18]: From (*E*)-*S*-2-(*tert*-butylcarbamoyl)phenyl but-2-enethioate (63 mg, 0.25 mmol), 2-furyl boronic acid (71 mg, 0.63 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 17 mg of the pure ketone after column purification with a 10:1 hex:EtOAc elutant. Yield: 74 % based on recovered starting material. Light yellow crystals, M.p. 54-55 ^oC. TLC (silica gel, 10:1 hex:EtOAc, R_f= 0.30). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J*= 1.5 Hz, 1H), 7.23 (d, *J*= 3.5 Hz, 1H), 7.17 (dt, *J*= 15.2, 6.6 Hz, 1H), 6.83 (dd, *J*= 15.2, 1.5 Hz, 1H), 6.56-6.55 (m, 1H), 2.00 (dd, *J*= 6.6, 1.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ178.3, 153.4, 146.7, 144.5, 126.3, 117.7, 112.5, 18.7. IR (neat, cm^{-1}): 2916 (m), 2849 (m), 1660 (s).



***N*-*tert*-Butyl-2-(furan-2-ylthio)benzamide:** From (*E*)-*S*-2-(*tert*-butylcarbamoyl)phenyl but-2-enethioate (63 mg, 0.25 mmol), 2-furyl boronic acid (71 mg, 0.63 mmol), and CuMeSal (3 mg, 0.013 mmol) in 2 ml of DMF was obtained 39 mg of the pure thioether after column purification with a 10:1 hex:EtOAc elutant. Yield: 81 % based on recovered starting material. Yellow solid, M.p. 70 ^oC. TLC (silica gel, 10:1 hex:EtOAc, R_f= 0.22). ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J*= 1.9, 0.8 Hz, 1H), 7.45 (dd, *J*= 7.4, 1.5 Hz, 1H), 7.24 (dt, *J*= 7.4, 1.5 Hz, 1H), 7.16 (dt, *J*= 7.8, 1.5 Hz, 1H), 6.86 (dd, *J*= 7.8, 0.8 Hz, 1H), 6.80 (dd, *J*= 3.2, 0.8 Hz, 1H), 6.50 (dd, *J*= 3.2, 0.8 Hz, 1H), 5.92 (bs, 1H),

[18] Kondo, T.; Mukai, T.; Watanabe, Y. *J. Org. Chem.* **1991,** 56, 487-489.

1.51 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 146.9, 143.1, 136.1, 135.6, 130.7, 128.5, 127.8, 126.1, 120.5, 112.2, 52.3, 29.0. IR (neat, cm^{-1}): 3298 (m), 2972 (m), 1634 (s), 1531 (s). HRMS (ESI) Calcd for $C_{15}H_{18}NO_2S$ (M+H): 276.1056. Found: 276.1051.

General Procedure for Control Experiments under Argon (Scheme 2.3):

S-2-(isopropylcarbamoyl)phenyl benzothioate (1.0 equiv, 0.08 mmol) was placed in dry 10 ml schlenk flask equipped with a small magnetic stir bar. Stoichiometric amounts of copper catalyst (1.2 equiv., 0.10 mmol) were added followed by the boronic acid (2.5 equiv, 0.21 mmol). Then, 2 ml of dry, degassed dimethylformamide (DMF) was added under argon and the reaction was allowed to stir at 50 ^{o}C for 24 hrs. The reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted three times with 20 ml diethyl ether. The combined organic layers were was once with 100 ml of water. The organic layer was dried with $MgSO_4$, filtered and the volatiles evaporated. The viscous solid was than subjected to column chromatography (hexane, EtOAc gradient).

CHAPTER 3

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Chapter 3

An Aerobic, Chemoselective, *Palladium*-Templated Coupling of Thiol Esters with Boronic Acid

Abstract: The Liebeskind-Srogl cross-coupling of thiol esters with boronic acids to form ketones under non-basic conditions mediated by catalytic amounts of Cu(I) and Pd(0) was investigated. Thiol esters bearing ortho-chelating groups were investigated and found to undergo cross-coupling with catalytic amounts of CuMeSal and $Pd(PCy_3)_2$. Their synthesis is also described.

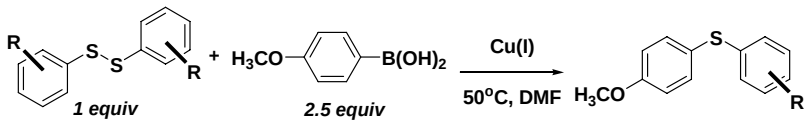
3.1 Introduction and Initial Studies

3.1.1 Probing Catalysis

A new aerobic copper catalyzed cross-coupling of thiol esters and boronic acids was described in Chapter 2. A novel, higher oxidation state, metal-templated mechanism involving the generation of a $[Cu_2(\mu\text{-}O_2]^{2+}$ core was speculated. Copper-templating was most efficient with *N-iso*-propyl and *N-tert*-butyl pendants perhaps due to the geometrical requirements induced by copper. Palladium can also form oxo-bridged cores upon oxidation of palladium(0) with oxygen.[1-5] This chapter describes the reactivity of thiol esters bearing pendants inactive in the aerobic copper catalyzed ketone synthesis but rendered active with added amounts of catalytic palladium(0).

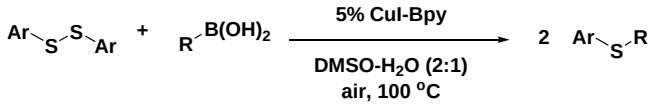
As discussed in Chapter 2, we chose to study the copper-catalyzed reaction of disulfides with boronic acids under both anaerobic and aerobic conditions as a model system (Scheme 3.1). It was found that treatment of diphenyl disulfide under anaerobic or aerobic conditions with CuMeSal, only half of the disulfide was transformed to a thioether; the second half of the disulfide formed a stable Cu(I) thiolate that did not react further with the boronic acid. A *ligating ortho S-pendant* was the key moiety in using catalytic quantities of a Cu(I) carboxylate to induce the efficient reaction of both halves of the disulfide with 2 equiv of a boronic acid *under aerobic conditions*.

Table 3.1 Copper Catalysis with Disulfides



Entry	R	*Yield (%)*	
		Under N_2, 1.2 eq Cu(I)MeSal	***Open to air, 5% Cu(I)MeSal***
1	H	77	trace
2	*para*-NHCOPh	64	0
3	*ortho*-NHCOPh	66	99

Control experiments demonstrated the critical importance of the *ortho*-*S*-pendant ligand. In 2006, Taniguchi reported the aryl- or alkylation of diaryl disulfide with boronic acids catalyzed by CuI-Bpy. The couplings proceeded 100 °C and a DMSO-H_2O mixed solvent system.[6]

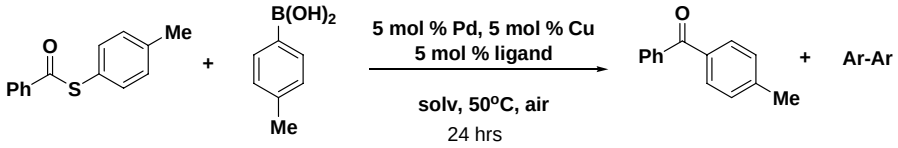


Scheme 3.1 Aryl- or Alkylation of Diaryl Disulfides by Taniguchi

Similar conditions were probed with a thiol ester bearing no pendant, but at milder conditions (i.e. at 50 °C). *S*-*para*-Tolyl benzothioate was treated with 2.5 equivalents of *para*-tolylboronic acid and allowed to stir at 50 °C open to the air. The ketone was obtained in 22 % with 5 mol % $Pd(PCy_3)_2$ and CuMeSal catalysts in DMF (Table 3.2, entry 1). When the catalyst system was changed to 5 mol % $Pd(PCy_3)_2$ and 5 mol % $Cu(OAc)_2$ with 5 mol % Dabco in DMF, 26 % yield of ketone was observed by HPLC (Table 3.2, entry 2). The highest ketone yield was 27 % with 5 mol % $Pd(PCy_3)_2$, 5 mol % CuI, and 5 mol % Bpy (Table 3.2, entry 3). A similar yield was obtained in

DMSO (Table 3.2, entry 4). Without palladium, trace ketone was detected (Table 3.2, entries 5-6). Even if higher temperatures pushed the reaction to completion, it would not be ideal conditions for applying the reaction to complex biomolecule synthesis.

Table 3.2 Probing Catalysis with Simple Thiol Esters

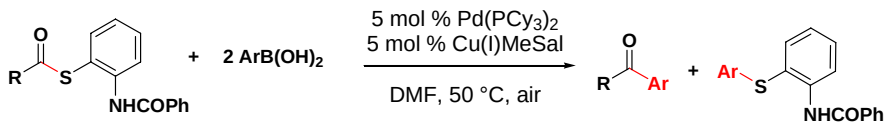


Entry	Pd	Cu	Ligand	Solvent	Ketone (%)	Ar-Ar
1	$Pd(PCy_3)_2$	CuMeSal	--	DMF	22 [a]	observed
2	$Pd(PCy_3)_2$	$Cu(OAc)_2$	Dabco	DMF	26 [a]	trace
3	$Pd(PCy_3)_2$	CuI	Bpy	DMF	27 [a]	observed
4	$Pd(PCy_3)_2$	CuI	Bpy	DMSO	26 [a]	trace
5	--	CuI	Bpy	DMF	trace	100 % conv.
6	--	CuI	Bpy	DMSO	trace	100 % conv.

a: HPLC yield with 4,4'-di-*tert*-butylbiphenyl as internal standard

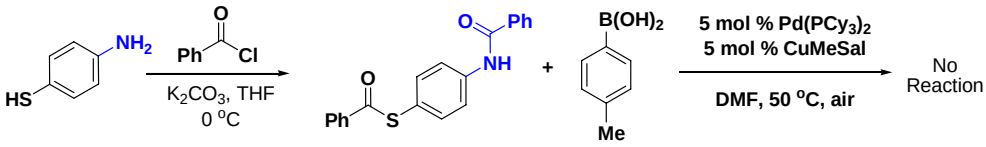
3.1.2 Summary of Work Completed by Dr. Jiri Srogl and Silvia Cabrera (Cabrera, S. Annual Report, Liebeskind Lab, 2003).

The *S-pendant ligand effect* was incorporated into a novel, *aerobic*, Pd- and Cu-catalyzed thiol ester - boronic acid cross-coupling (Scheme 3.2). Similar to the aerobic, copper-catalyzed coupling of disulfides and boronic acids, two equivalents of the boronic acid are also consumed in the aerobic ketone synthesis. The C–S bond of the thiol ester is cleaved and both the C- and S-residues are each arylated by one equivalent of boronic acid.



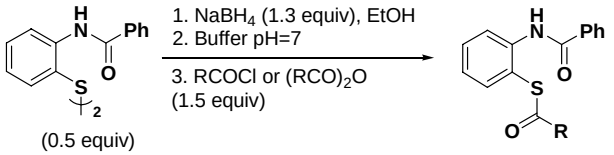
Scheme 3.2 Aerobic Ketone Synthesis

Thiol esters bearing the *S*-2-benzamidophenyl pendant displayed unique behavior for the ketone synthesis. Under these aerobic, catalytic conditions only *S*-2-Benzamidophenyl 4-methylbenzothioate led to a productive ketone synthesis, thus mimicking the effect seen in aerobic reactions of the disulfides. *S*-4-benzamidophenyl 4-methylbenzothioate was synthesized by doubly acylating 4-aminobenzenethiol (Scheme 3.3). This thiol ester, isoelectronic with *S*-2-benzamidophenyl 4-methylbenzothioate, did not yield any ketone.



Scheme 3.3 Synthesis and Coupling of *para*-Substituted Thiol Ester

Having established that the *S*-2-benzamidophenyl moiety provides a structural moiety that permits aerobic catalysis by Cu(I) for reactions of arylboronic acids with both a disulfide and a thiol ester, the efficiency of the process was explored with a small subset of thiol esters varying the boronic acids. A series of *S*-2-benzamidophenyl thiol esters was prepared from commercially available bis[2-(*N*-benzoyl)aminophenyl] disulfide as depicted in Scheme 3.4. The disulfide route to the thiol esters was particularly useful because the thiol derived from bis[2-(*N*-benzoyl)aminophenyl] disulfide is unstable at acidic pH and readily condenses to the corresponding benzothiazoles.

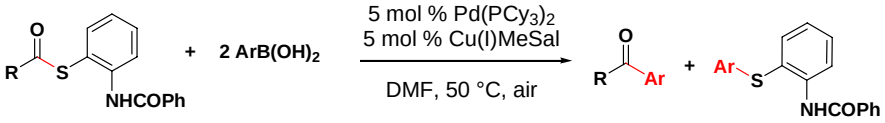


R= Me, 46%
R= Ph, 96%
R= *p*-Tol, 65%
R= *o*-Tol, 78%
R= $C_{11}H_{23}$, 70%

Scheme 3.4 *S*-2-Benzamidophenyl Thiol Ester Synthesis

The thiol esters in turn were exposed to two equivalents of various arylboronic acids in the presence of 5 mol % $Pd(PCy_3)_2$ and 5 mol % Cu(I) 3-methylsalicylate in dimethylformamide at 50 °C (Table 3.3). Under optimized conditions diaryl ketones were isolated in yields between 57 – 81 %. About a 1:1 ratio was observed of ketone to the corresponding diaryl thioether (or *S*-aryl) derived from the arylboronic acid and the *S*-2-benzamidophenyl moiety.

Table 3.3 Substrate Scope



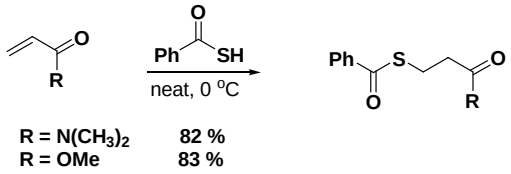
Entry	R =	Ar =	Ketone (%)	*S*-Aryl (%)
1	undecyl	2-formyl-4-methoxyphenyl	62	65
2	undecyl	3-nitrophenyl	57	60
3	phenyl	4-formylphenyl	78	71
4	phenyl	3-acetylphenyl	74	63
5	*p*-tolyl	phenyl	75	63
6	phenyl	3-nitrophenyl	81	76

Traces of product were observed in the absence of air, and no to traces product were formed in the absence of either of the two metallic catalysts. Dimethylformamide (DMF), dimethylacetamide (DMA) and *N*-methylpyrolidone (NMP) were suitable solvents using $Pd(Pcy_3)_2$ and CuMeSal as catalysts. The reaction requires at least 2.0 equivalents of $ArB(OH)_2$. CuMeSal cannot be replaced with non-redox active $Zn(Sal)_2$. Little to no homocoupling arising from the very fast copper-catalyzed dimerization of the boronic acid was observed. The best ratio of Pd and Cu was found to be 1:1.

3.2 Results and Discussion

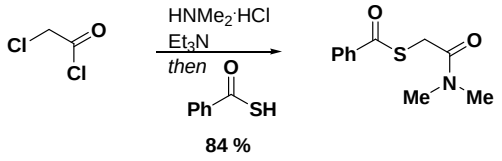
3.2.1 A Thorough Study of Pendants

To understand why the *S*-2-benzamidophenyl pendant displayed unique catalysis in the ketone coupling, a variety of other thiol esters bearing other ligating groups were prepared. Methyl acrylate and *N*,*N*-dimethylacrylamide were converted in good yields to the corresponding thiol ester by treatment in neat thiobenzoic acid at 0 ^{o}C (Scheme 3.6).



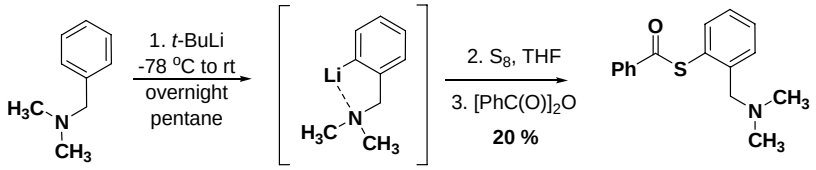
Scheme 3.5 Thiol Ester Synthesis from Methyl Acrylate and *N*,*N*-Dimethylacrylamide

2-Chloroacetyl chloride was treated with 1 equivalent of dimethyl amine hydrochloride and base. Then, thiobenzoic acid was added *in situ* to give *N*-(dimethylcarbamoyl)methyl benzothioate in 84 % yield (Scheme 3.7).



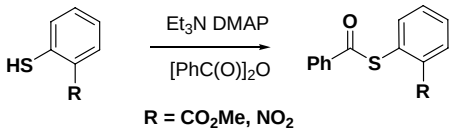
Scheme 3.6 Synthesis of *N*-(Dimethylcarbamoyl)methyl Benzothioate

N,*N*-dimethylbenzyl amine was treated with 1 equivalent of *t*-butyl lithium at -78 ^{o}C in pentane (Scheme 3.8). After warming the reaction to room temperature overnight, sublimed sulfur was added. After 30 minutes, the mercaptolithiate was quenched with benzoic anhydride to give the thiol ester in low, but adequate yield.



Scheme 3.7 Synthesis of *S*-2-((Dimethylamino)methyl) Phenyl Benzothioate

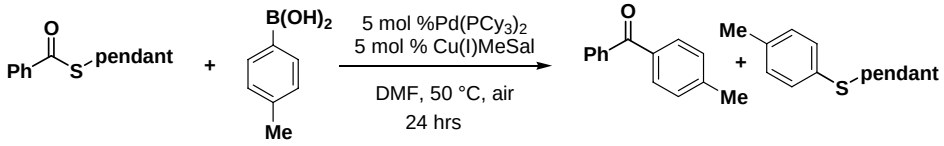
Thiol esters bearing *ortho*-ester and nitro groups were also prepared from their commercially available thiols. Acylation with triethyl amine and catalytic DMAP with benzoic anhydride provided the clean thiol esters in good yields.

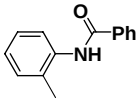
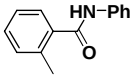
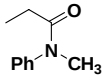
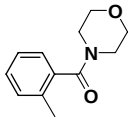
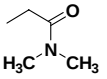
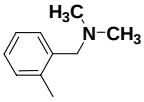
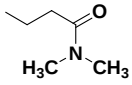
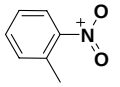
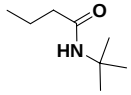
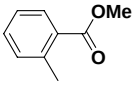
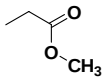
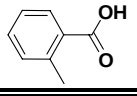
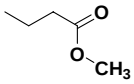


Scheme 3.8 Synthesis of *S*-2-Nitrophenyl Benzothioate and *S*-2-Methylpropanoate Benzothioate

All other pendants had been previously synthesized by different group members or have been described in the literature and are referenced accordingly. The thiol esters were treated under optimized conditions (Table 3.4).

Table 3.4 Probing other Pendants



		Yield (%)					*% Yield*		
Entry	Pendant	time	Ketone	*S*-aryl	Entry	Pendant	time	Ketone	*S*-aryl
1		4h 24h	57 [a] 63 [a] (66 [b])	(52 [b])	8		24h	0	0
2		4h 24h	74 [a] 74 [a] (56 [b])	(68 [b])	9		4h 24h	58 [a] 60 [a] (62 [b])	(63 [b])
3		4h 24h	57 [a] 70 [a] (72 [b])	(84 [b])	10		4h 24h	13 [a] 56 [a]	N.R.
4		24h	trace	trace	11		4h 24h	trace 37 [a]	N.R.
5		4h 24h	18 [a] 36 [a]	N.R.	12		4h 24h	34 [a] 51 [a]	N.R.
6		4h 24h	14 [a] 23 [a]	N.R.	13		4h 24h	23 [a] 25 [a]	N.R.
7		24h	0	0	14		24h	25 [a]	N.R.

a: HPLC yield using 4,4'-di-tert-butylbiphenyl as internal standard. b: isolated yields. N.R.. = not reported

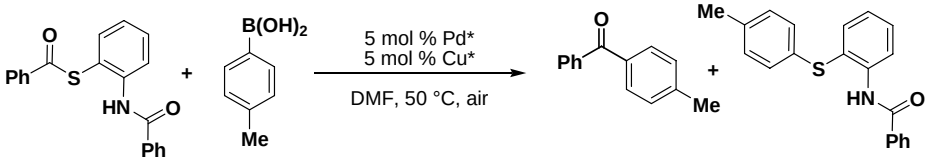
Entries 1 and 2 gave similar yields implying that the observed reactivity is not a result of the electrontric properties of the aryl ring of the thiol ester. The morphinyl pendant (entry 3), gave good yields of the thiol ester. The basic *N*,*N*-dimethylbenzyl pendant (entry 4) gave a trace of ketone. The carboxylate pendant in 2-benzothioate benzoic acid and 2-benzothioate acetic acid was too strongly ligating to copper and thus did not yield any ketone (entries 7-8). Esters were also found not to be effective (entries 6, 13, and 14). Alkyl pendants were also investigated (entries 9-12). The bulkier amides, entries 10-11, react more slowly than the less sterically demanding amide in entry 9. In general,

pendants containing aromatic rings between the sulfur and carbonyl groups gave the best ketone yields. This will be explained in more detail as related to the mechanism.

3.2.3 Mechanistic Insights

Several catalyst systems were investigated. Entries 1-3 demonstrate that when $Pd(PCy_3)_2$ was used, CuMeSal, $CuCl_2$, and $Cu(OAc)_2$ were all effective co-catalyst (Table 3.5). When the phospine ligand was left out, the ketone was obtained in low to trace yield (entries 5-8). Palladium (0) and palladium (II) catalysts were probed with phosphine ligands and both gave high ketone yields (entries 1 and 4). Whether stabilizing or generating the active catalyst, the phosphine ligand plays in key role in the reaction (compare entries 1 and 6).

Table 3.5 Catalyst Screening

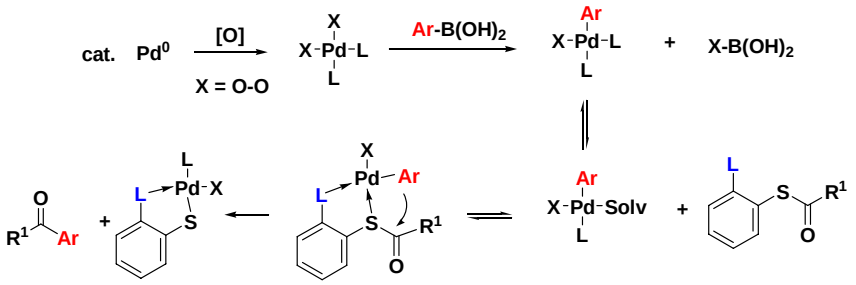


Entry	Pd	Cu	Ketone Yield (%)
1	$Pd(PCy_3)_2$	CuMeSal	66 [a]
2	$Pd(PCy_3)_2$	$CuCl_2$	69
3	$Pd(PCy_3)_2$	$Cu(OAc)_2$	56
4	$Pd(OAc)_2(PCy_3)_2$	CuMeSal	56
5	$Pd(OAc)_2$	CuMeSal	15
6	$PdCl_2$	CuMeSal	trace
7	$Pd(OAc)_2$	$Cu(OAc)_2$	15
8	$PdCl_2$	$CuCl_2$	0
9	--	CuMeSal	6 [a]
10	$Pd(PCy_3)_2$	--	trace

a: isolated yield. all others are HPLC yields with 4,4'-di-*tert*-butylbiphenyl

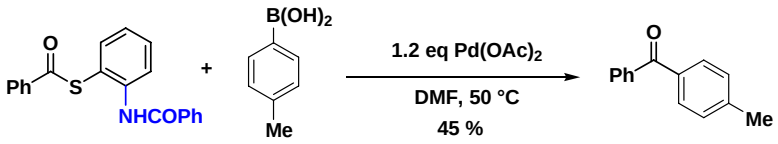
Although oxidative addition to the thiol ester by Pd(0) cannot be ruled out as a first step in the mechanism, it is possible that a palladium-dioxo species is involved in the carbon-carbon bond forming step. This would explain why the most electron rich and,

thus, the most easily oxidized catalyst, $Pd(PCy_3)_2$, gives the best yield. Scheme 3.10 shows a reasonable mechanism for the first half of the aerobic cross-coupling. The aerobic reaction conditions are not easily rationalized through a traditional oxidative cross-coupling sequence of oxidative addition to a low-valent Pd catalyst, followed by transmetallation, and then reductive elimination. Rather, *a novel, higher oxidation state, metal-templated mechanism* is suggested. Just as in the copper catalyzed ketone synthesis in Chapter 2, the metal templating would provide simultaneous Lewis acid activation of the thiol ester along with coincident delivery of an adjacent organometallic moiety (the Ar species in Scheme 3.10). It appears that the palladium-catalyzed metal-templated mechanism has less strict geometric requirements than that of the copper-catalyzed metal-templated ketone synthesis and activates a variety of *S*-pendants. The reactivity may also be attributed to the higher Lewis acidity and/or thiophilicity of palladium *versus* copper under the reaction conditions. In any case, these hypotheses require further study.



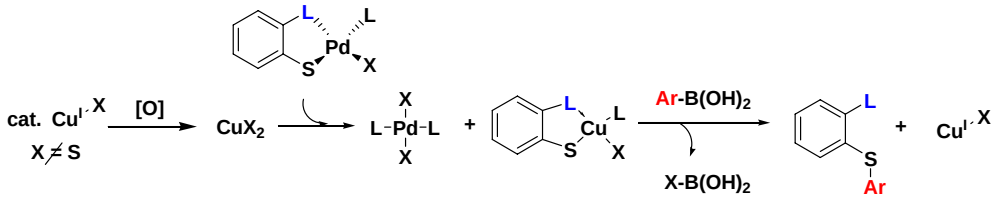
Scheme 3.9 Palladium-Templated Coupling

Moreover, in this mechanism a palladium(II) species is suggested for the carbon-carbon bond forming step. In fact, when the thiol ester containing the *S*-2-benzamidophenyl pendant was treated with stoichiometric $Pd(OAc)_2$ in DMF at 50 ^{o}C under *argon*, 45 % ketone was isolated (Scheme 3.11).



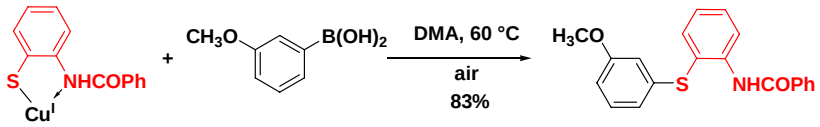
Scheme 3.10 Anaerobic Ketone Synthesis Stoichiometric in Palladium

Given the critical requirement of a Cu co-catalyst in this chemistry, we suggest a thiolate ligand exchange between Pd and an oxidized form of Cu followed by a boron to copper transmetallation and then a reductive elimination to complete the catalytic cycle (Scheme 3.12).



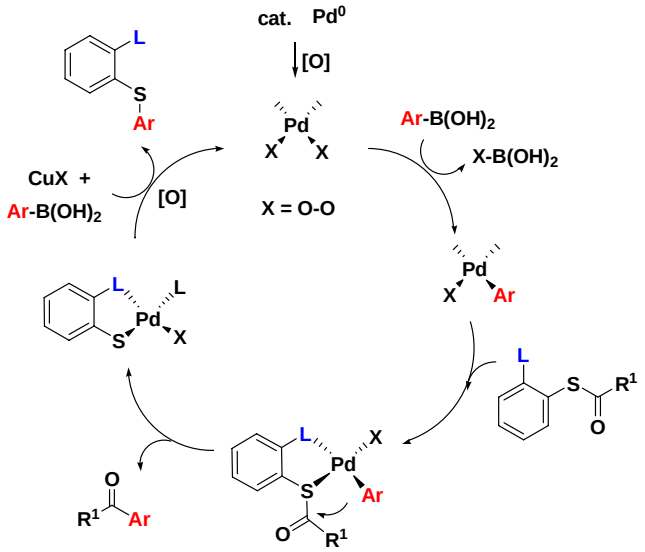
Scheme 3.11 Copper Catalyzed Sulfur Scavenging and Liberation of Palladium

Evidence for the aerobic transformation in Scheme 3.12 was obtained. In unpublished results by Dr. Srogl, stoichiometric Cu(I) 2-(*N*-benzoyl)aminophenylthiolate and 3-methoxyphenylboronic acid were treated in DMA at 60 °C in air to give the diaryl thioether (*S*-aryl product). Thus, the key to catalysis by copper is the conversion of the strong thiolate ligand into a thioether, a weaker ligand for copper, under air in the presence of the boronic acid (Scheme 3.5). In addition, the *S*-arylation product is oxidatively induced – the copper thiolate does not react with the boronic acid under a nitrogen atmosphere.



Scheme 3.12 Oxidatively Induced *S*-Arylation of Preformed Copper Thiolate

In summary, the full catalytic cycle is represented in Scheme 3.6. Palladium is oxidized in air, perhaps to an oxo-bridged core. Then, the resulting complex undergoes transmetallation with the arylboronic acid. The aryl palladium(II) species coordinates to the thiol ester. A palladium-templated carbon-carbon bond formation then occurs producing the ketone and palladium thiolate. Ligand exchange with copper produces a copper thiolate and liberates palladium back into to catalytic system. Finally, copper is liberated by oxidative *S*-arylation with a second equivalent of boronic acid.



Scheme 3.13 Mechanism of Complete Catalytic Cycle

3.3 Conclusion

A new aerobic cross-coupling catalyzed by palladium and copper between thiol esters and boronic acids was described. A ligating pendant on sulfur was needed to achieve catalysis. Many different types of pendants could be used as long as it contained an amide moiety. Just as in the copper-catalyzed ketone synthesis and thioether synthesis from disulfides, two equivalents of boronic acid were required.

3.4 References

1. Popp, B. V.; Wendlandt, J. E.; Landis, C. R.; Stahl, S. S. Reaction of Molecular Oxygen with an NHC-Coordinated Pd^0 Complex: Computational Insights and Experimental Implications. *Angew. Chem. Int. Ed.* **2007**, *46*, 601-604.

2. Popp, B. V.; Stahl, S. S. "Oxidatively Induced" Reductive Elimination of Dioxygen from an η2-Peroxopalladium(II) Complex Promoted by Electron-Deficient Alkenes. *J. Am. Chem. Soc.* **2006**, *128*, 2804-2805.

3. Landis, C. R.; Morales, C. M.; Stahl, S. S. Insights into the Spin-Forbidden Reaction between L_2Pd^0 and Molecular Oxygen. *J. Am. Chem. Soc.* **2004**, *126*, 16302-16303.

4. Konnick, M. M.; Guzei, I. A.; Stahl, S. S. Characterization of Peroxo and Hydroperoxo Intermediates in the Aerobic Oxidation of *N*-Heterocyclic-Carbene-Coordinated Palladium(0). *J. Am. Chem. Soc.* **2004**, *126*, 10212-10213.

5. Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. Oxygenation of Nitrogen-Coordinated Palladium(0): Synthetic, Structural, and Mechanistic Studies and Implications for Aerobic Oxidation Catalysis. *J. Am. Chem. Soc.* **2001**, *123*, 7188-7189.

6. Taniguchi, N. Aryl- or Alkylation of Diaryl Disulfides Using Organoboronic Acids and a Copper Catalyst. *Synlett* **2006**, 1351-1354.

7. Tecilla, P.; Jubian, V.; Hamilton, A. D. Synthetic Hydrogen Bonding Receptors as Models of Transacylase Enzymes. *Tetrahedron* **1995**, *51*, 435-448.

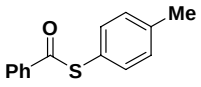
3.5 Experimental

General Methods:

Starting material preparations were preformed under an atmosphere of dry N_2 or Ar in over-dried glassware unless otherwise noted. Solvents (DMA, DMF, $CHCl_3$, Et_3N, pyridine) for reaction media were ACS reagent grade and purchased from Aldrich. They were dried over 4 Å molecular sieves, purged with dry N_2 or Ar, and titrated for water level with a Karl Fisher Coulomatic K-F titrator. Solvents (THF, Tol, CH_2Cl_2) were purified and dried using a Seca Solvent System purchased from GlassContour. Hexane (hex), ethyl acetate (EtOAc), and diethyl ether (Et_2O) used for extraction, recrystallization, or chromatography were obtained from EM Science and used as purchased. Solution of $NaHCO_3$, NaOH, or HCl refers to aqueous solution. Brine is a saturated solution of sodium chloride in water. Analytical thin-layer chromatography (TLC) was carried out using Merk Kieselgel 0.25 mm 60 F_{254} plates with visualization by UV, $KMnO_4$, or iodine crystals in silica gel.

^{1}H NMR spectra were recorded on a Varian Inova 400 or 600 MHz NMR spectrometer at room temperature in $CDCl_3$ or *d*-DMSO and were internally referenced to either, (7.27 ppm and 2.5 ppm, respectively). ^{13}C NMR spectra were recorded on a Varian Inova 150 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported in Hz; integration is provided. Infrared (IR) spectroscopy was preformed on an ASi Applied Systems ReactIR 1000 Electronics Module. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100 %), m (medium, 40-67 %), w (weak, 20-

40 %), and br (broad). Uncalibrated melting points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes. HPLC analysis was carried out on an Aligent 1100 Series HPLC using an Eclipse XDB-C8 (5 μm, 4.6 x 150 mm) column. 4-Methylphenyl boronic acid was purchased from Frontier Scientific, Inc. Palladium catalysts and copper iodide were purchased from Strem Chemicals. CuMeSal[1] was prepared according to the literature procedure. Thiobenzoic acid, *N*,*N*-dimethylacrylamide, methylacrylate, chloroacetyl chloride, *N*,*N*-dimethylbenzylamine, methyl amine·HCl, dimethylamino pyridine (DMAP), benzoic anhydride, *tert*-BuLi, and sublimed sulfur were purchased from Aldrich. The synthesis of thiol esters in Table 3.4, entries 1-4 and 12, have been described in chapter 2. 2-Benzothioate benzoic acid and 2-benzothioate acetic acid were prepared according to the known literature procedure.[2] 2-Aceto-S-benzothioate was prepared by Dr. Jiri Srogl and is described in literature.[3]



***S*-*p*-Tolyl benzothioate[4]:** To 4-methylbenzene thiol (0.750 g, 6.0 mmol) in 2 ml of dry CH_2Cl_2 was added benzoic anhydride (1.64 g, 7.2 mmol), 1.7 ml of Et_3N (12 mmol), and 2 crystals of DMAP at room temperature. The reaction stirred over night and then quenched with 5 % HCl. The aqueous phase was extracted with CH_2Cl_2. The organic layer was washed with 5 % HCl twice then once with saturated $NaHCO_3$. The organic

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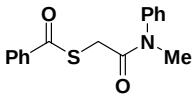
[1] Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91-93.

[2] Tecilla, P.; Jubian, V.; Hamilton, A. D. *Tetrahedron* **1995**, *51*, 435-448.

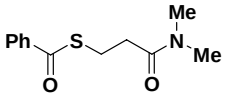
[3] Moore, J. D.; Byrne, R. J.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *Organic Letters* **2003**, *5*, 4241-4244.

[4] Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554-3557.

phase was dried with MgSO4, filtered and condensed to give 0.601 g of pure thiol ester after recrystallization from Tol. Yield: 45 %. White crystals, M.p. 64-67 ^{o}C [Lit. 64-65 ^{o}C[4]]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (app d, *J*= 7.0 Hz, 2H), 7.59 (app t, *J*= 7.4 Hz, 1H), 7.47 (t, *J*= 7.8 Hz, 2H), 7.39 (d, *J*= 7.8 Hz, 2H), 7.26 (d, *J*= 7.8 Hz, 2H), 2.39 (s, 3H). IR (neat, cm^{-1}): 1675 (s).

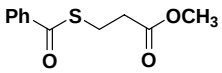


***S*-(*N*-Methyl-*N*-phenylcarbamoyl)methyl benzothioate[5]:** White crystals, M.p. ($CHCl_3$) 83-85 ^{o}C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.94 (d, *J*= 7.3 Hz, 2H), 7.57 (t, *J*= 7.6 Hz, 1H), 7.50-7.40 (m, 5H), 7.34 (d, *J*= 8.2 Hz, 2H), 3.74 (s, 2H), 3.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.9, 167.6, 143.5, 136.5, 133.7, 128.8, 128.5, 127.5, 125.5 (2), 38.1, 33.1. IR (neat, cm^{-1}) 1656 (s), 1211 (m).

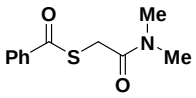


***S*-2-(Dimethylcarbamoyl)ethyl benzothioate:** To commercially available *N*,*N*-dimethylacrylamide (0.96 ml, 10 mmol) at 0 ^{o}C was slowly added thiobenzoic acid (1.2 ml, 10 mmol). The ice bath was then removed and the reaction mixture stirred at room temperature for 15 minutes then quenched with 100 ml of saturated $NaHCO_3$. The aqueous mixture was extracted with Et_2O three times, the organic phases dried with $MgSO_4$, concentrated to give 1.94 g of pure thiol ester. Yield: 82 %. Light pink oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.97 (dd, *J*= 6.2, 1.1 Hz, 2H), 7.56 (dt, *J*= 7.1, 1.6 Hz, 1H), 7.44 (t, *J*= 8.2 Hz, 2H), 3.36 (t, *J*= 7.0 Hz, 2H), 3.00 (s, 3H), 2.98 (s, 3H), 2.74 (t, *J*= 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.5, 170.9, 137.0, 133.5, 128.7, 127.3, 37.1,

35.5, 33.7, 24.6. IR (neat, cm^{-1}) 2933 (w), 1639 (s), 1203 (m). HRMS (ESI) Calcd for $C_{12}H_{15}NO_2S$ (M+H): 238.0902. Found: 238.0894.



***S*-2-(Methylpropanoate)ethyl benzothioate[6]:** To commercially available methylacrylate (0.96 ml, 12 mmol) at 0 ^oC was slowly added thiobenzoic acid (1.4 ml, 12 mmol). The ice bath was then removed and the reaction mixture stirred at room temperature over night then quenched with 100 ml of saturated $NaHCO_3$. The aqueous mixture was extracted with Et_2O three times, the organic phases dried with $MgSO_4$, concentrated to give 2.23 g of pure thiol ester. Yield: 83 %. Light beige, clear oil. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.96 (dd, *J*= 8.5, 0.95 Hz, 2H), 7.58 (t, *J*= 7.1 Hz, 1H), 7.46 (t, *J*= 7.1 Hz, 2H), 3.73 (s, 3H), 3.33 (t, *J*= 7.1 Hz, 2H), 2.75 (t, *J*= 7.1, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.7, 172.4, 136.9, 133.7, 128.8, 127.4, 52.1, 34.4, 24.1. IR (neat, cm^{-1}): 1735 (s), 1658 (s), 1204 (m). HRMS (ESI) Calcd for $C_{11}H_{12}O_3S$ (M+H): 225.0585. Found: 225.0579.



***S*-(Dimethylcarbamoyl)methyl benzothioate[7]:** To a solution of commercially available chloroacetyl chloride (0.62 ml, 0.875 g, 7.7 mmol) at 0 ^oC in 20 ml of CH_2Cl_2 was cannulated (dropwise over 2 hours) a solution of methyl amine·HCl (0.666 g, 7.8 mmol) in 2 equiv of Et_3N (2.2 ml, 15 mmol) in 70 ml of CH_2Cl_2. Then thiobenzoic acid (0.92

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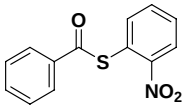
[5] Prepared by Dr. Jiri Srogl.

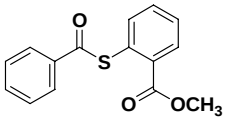
[6] Kreutzkamp, N.; Peschel, H. *Pharmazie* **1970**, *25*, 322-325.

[7] Liebeskind, L. S.; Srogl, J. *J. Amer. Chem. Soc.* **2000**, *122*, 11260-11261.

ml, 7.8 mmol) was added followed by 1 equiv of Et_3N (1.1 ml, 7.5 mmol) at 0 ^oC. The reaction was allowed to come to room temperature as it stirred over night. The reaction was quenched with 150 ml of 5 % HCl and the organic layer was separated and washed twice with 150 ml of saturated $NaHCO_3$. The combined organic layers were dried with $MgSO_4$, filtered and condensed to give 1.446 g of pure thiol ester. Yield: 84%. Light orange crystals, M.p. 65-66 ^oC [Lit. 67-69 ^oC[7]]. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.00 (dd, *J*= 8.3, 0.95 Hz, 2H), 7.59 (t, *J*= 7.6 Hz, 1H), 7.47 (t, *J*= 7.9 Hz, 2H), 4.03 (s, 2H), 3.17 (s, 3H), 3.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.1, 167.7, 136.5, 133.9, 128.8, 127.5, 37.9, 36.2, 32.2. IR (neat, cm^{-1}): 1640 (s).



_S_-2-Nitrophenyl benzothioate[8]: To 2-nitrobenzene thiol (0.264 g, 1.7 mmol) in 5 ml of dry CH_2Cl_2 was added benzoic anhydride (0.577 g, 2.5 mmol), and 0.5 ml of Et_3N (3.4 mmol) at room temperature. The reaction stirred over night and then quenched with 5 % HCl. The aqueous phase was extracted with CH_2Cl_2. The organic layer was washed with 5 % HCl twice then once with saturated $NaHCO_3$. The organic phase was dried with $MgSO_4$, filtered and condensed to give 0.308 g of pure thiol ester. Yield: 70 %. Yellow, orange crystals, M.p. 42-44 ^oC [Lit. 45-47 ^oC[8]]. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.03 (t, *J*= 8.9 Hz, 3H), 7.74 (dt, *J*= 8.8, 1.4 Hz, 1H), 7.67-7.59 (m, 3H), 7.51 (t, *J*= 8.3 Hz, 2H). IR (neat, cm^{-1}) 1638 (s), 1527 (s).



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[8] Barbero, M.; Degani, I.; Dughera, S.; Fochi, R. *Synthesis* **2003**, 1225-1230.

***S*-2-Methylpropanoate benzothioate[5]:** To commercially available methyl 2-mercaptobenzoate (0.500 g, 3.0 mmol) in 8 ml of dry CH_2Cl_2 was added benzoic anhydride (0.830 g, 3.6 mmol), 0.8 ml of Et_3N (5.9 mmol), and 2 crystals of DMAP at room temperature. The reaction stirred over night and then quenched with 5 % HCl. The aqueous phase was extracted with $CHCl_3$. The organic layer was washed with 5 % HCl twice then once with saturated $NaHCO_3$. The organic phase was dried with $MgSO_4$, filtered and condensed to give 0.761 g of pure thiol ester. Yield: 94 %. Yellow viscous oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.05 (d, *J*= 7.0 Hz, 2H), 8.00 (dd, *J*= 7.8, 1.4 Hz, 1H), 7.67-7.47 (m, 6H), 3.87 (s, 3H). IR (neat, cm^{-1}) 1722 (s), 1671 (s).

General Procedure for Probing Catalysis with Simple Thiol Esters (Table 3.2):

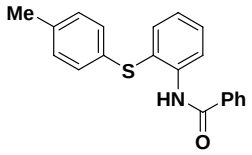
S-*p*-tolyl benzothioate (1.0 equiv., 0.22 mmol) was placed in a 10 ml vial with a magnetic stir bar. Catalytic amounts of the copper catalyst (5 mol %, 0.011 mmol), (if specified in the table) bis(tricyclohexylphosphine) palladium(0) (5 mol %, 0.011 mmol), *p*-tolylboronic acid (2.5 equiv., 0.55 mmol), and (if specified in the table) Dabco or Bpy (5 mol %, 0.011) followed by 2 ml of the specified solvent (DMF or DMSO). The reaction was allowed to stir open to air and monitored for 24 hrs by HPLC with 4,4'-di-*tert*-butylbiphenyl (1.0 equiv., 0.22 mmol) as the internal standard. No work up was done.

General Procedure for Pd and Cu Catalyzed Ketone Synthesis (Table 3.4-3.5):

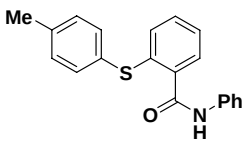
The corresponding thiol ester (1.0 equiv., 0.25 mmol) was placed in a 10 ml vial equipped with magnetic stir bar. Catalytic amounts of bis(tricyclohexylphosphine) palladium(0) (5 mol %, 0.0125 mmol) and copper methylsalicylate (5 mol %, 0.0125

mmol) were added followed by *p*-tolyl boronic acid (1.0 equiv., 0.25 mmol). Once the thiol ester starting material was disappeared or if no change was observed by TLC, the reaction was quenched with aqueous NH_4Cl and extracted with 50 ml Et_2O three times. The combined organic layers were dried over $MgSO_4$ and condensed under vacuum. The viscous solid was than subjected to column chromatography (10:1 to 5:1 hex, EtOAc gradient). In the cases were the reactions were monitored by HPLC with 4,4'-di-*tert*-butylbiphenyl (1.0 equiv., 0.25 mmol) as the internal standard, no work up was done.

4-Methyl benzophenone is described in the experimental section of Chapter 1. In all cases the isolated material matched known spectra. For yields refer to Table 3.4.

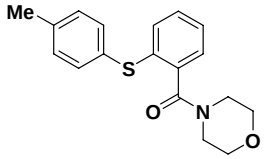


***N*-(2-(*p*-Tolylthio)phenyl)benzamide:** Yield: 52 %. White crystals, M.p. 85-86 ^oC. TLC (silica gel, 5:1 hex:EtoAc, R_f= 0.69). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.11 (bs, 1H), 8.69 (dd, *J*= 8.2, 1.2 Hz, 1H), 7.68 (app d, *J*= 7.0 Hz, 2H), 7.63 (dd, *J*= 7.8, 1.6 Hz, 1H), 7.54-7.48 (m, 2H), 7.42 (t, *J*= 7.8 Hz, 2H), 7.16 (dt, *J*= 7.4, 1.6 Hz, 1H), 7.06 (s, 4H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.4, 140.0, 136.8, 136.5, 134.9, 132.1, 131.9, 131.1, 130.4, 128.9, 127.8, 127.2, 124.6, 121.1, 120.7, 21.1. IR (neat, cm^{-1}): 3247 (m), 1642 (s), 1467 (s). HRMS (ESI) Calcd for $C_{20}H_{18}NOS$ (M+H): 320.1109. Found: 320.1100.

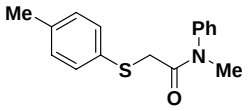


2-(*p*-Tolylthio)-*N*-phenylbenzamide: Yield: 68 %. Yellow solid, M.p. 142-143 ^oC. TLC (silica gel, 2:1 hex:EtoAc, R_f= 0.38). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.24 (bs, 1H),

7.55 (dd, *J*= 7.0, 1.2 Hz, 1H), 7.59 (d, *J*= 7.8 Hz, 2H), 7.37-7.28 (m, 6H), 7.21-7.13 (m, 4H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9, 138.6, 137.9, 135.9, 132.9, 131.5, 131.3, 130.6, 130.2, 129.4, 129.2, 126.9, 124.7, 120.2, 21.4. IR (neat, cm^{-1}): 3347 (m), 1663 (m), 1518 (s), 1432 (s). HRMS (ESI) Calcd for $C_{20}H_{18}NOS$ (M+H): 320.1109. Found: 320.1101.



(2-(*p*-Tolylthio)phenyl)(morpholino)methanone: Yield: 84 %. Yellow oil/solid. TLC (silica gel, 5:1 hex:EtoAc, R_f= 0.11). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 (d, *J*= 8.2 Hz, 2H), 7.20-7.18 (m, 3H), 7.11-7.08 (m, 3H), 3.75-3.74 (m, 4H), 3.57 (bs, 2H), 3.22 (t, *J*= 4.7 Hz, 2H), 2.31 (s, 3H). IR (neat, cm^{-1}): 1636 (s), 1427 (m). HRMS (ESI) Calcd for $C_{18}H_{20}NO_2S$ (M+H): 314.1215. Found: 314.1206.



2-(*p*-Tolylthio)-*N*-methyl-*N*-phenylacetamide: Yield: 63 %. Dark brown oil. TLC (silica gel, 5:1 hex:EtoAc, R_f= 0.27). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, *J*= 7.0 Hz, 1H), 7.39-7.36 (m, 2H), 7.25 (d, *J*= 8.2 Hz, 2H), 7.13 (app d, *J*= 8.6 Hz, 2H), 7.06 (d, *J*= 7.8 Hz, 2H), 3.47 (s, 2H), 3.28 (s, 3H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 137.2, 131.8, 131.2, 130.2, 130.0, 129.8, 128.3, 127.5, 37.9, 33.1, 21.2. IR (neat, cm^{-1}) 1656 (s), 1594 (w), 1494 (m). HRMS (ESI) Calcd for $C_{16}H_{18}NOS$ (M+H): 272.1109. Found: 272.1107.

Control Experiment with Stoichiometric $Pd(OAc)_2$ (Scheme 3.10):

S-2-(Benzamido)phenyl benzothioate (1.0 equiv., 52 mg, 0.16 mmol) was placed in a 10 ml schlenk flask equipped with magnetic stir bar along with $Pd(OAc)_2$ (1.2 equiv., 40 mg, 0.18 mmol). *para*-Tolyl boronic acid (1.2 equiv., 28 mg, 0.20 mmol) in 2 ml of dry, degassed DMF. The reaction was heated to 50 ^{o}C and stirred for 24 hrs. After coming to room temperature, the reaction was filtered through a short silica plug and washed with Et_2O. The volatiles were reduced under vacuum and the viscous solid was then subjected to column chromatography (5:1 hex, EtOAc gradient) to give 13 mg of 4-methylbenzophenone in 45 % yield.

CHAPTER 4

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Chapter 4

The Copper Mediated Coupling of

Thiol Esters with Aryl and Heteroaryl Iodides

Abstract: A new ketone synthesis from simple thiol esters and organo-halides using copper (I) carboxylates is reported. The reaction requires the use of thiol esters containing an N-isopropyl-2-mercaptobenzamide pendant. The reaction occurs under mild reaction conditions (ambient temperature, neutral conditions, under argon). A preliminary study of the reaction is presented.

4.1 Introduction and Background

In chapter 2, a new copper templated, aerobic ketone synthesis was described. The initial catalytic species was suggested to be a copper(III) intermediate formed by a two electron oxidation of copper(I) (Figure 4.1). Transmetallation with an aryl boronic acid leads to an aryl copper(III) intermediate.

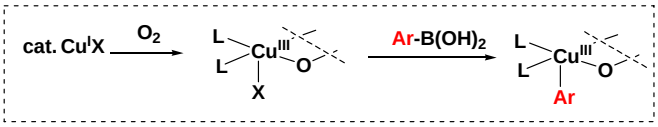
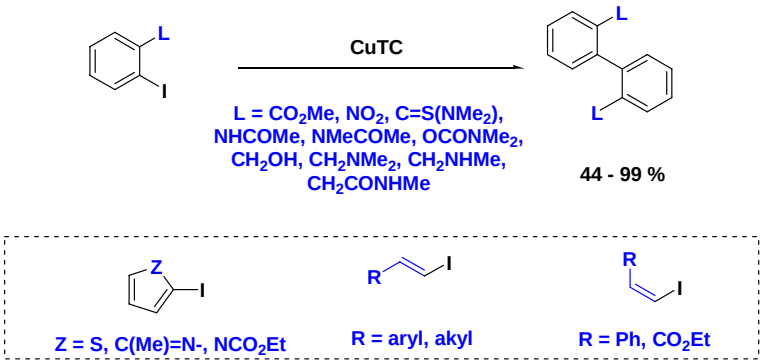


Figure 4.1 Cu^{I}X Oxidation and Transmetallation with ArB(OH)$_2$

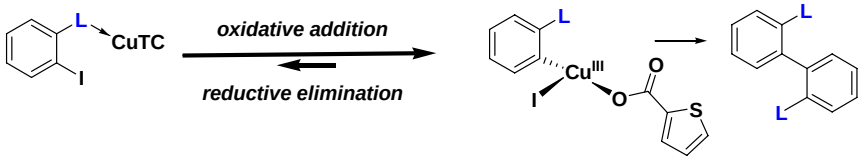
This led to us to think about other ways to generate copper(III) intermediates, such as through oxidative addition to an organo-halide.

In 1997, our laboratory published an Ullmann-like coupling of aryl, heteroaryl, and vinyl halides using copper (I) thiophene carboxylate (CuTC) (Scheme 4.1).[1] Pre-coordination of the substrate to copper prior to oxidative addition was found necessary. The *ortho*-substituent, L, on the aromatic halides, the heteroatom, Z, of the 2-iodoheteroaromatics, and the alkene of the alkenyl substrates all provide the requisite coordination to copper.



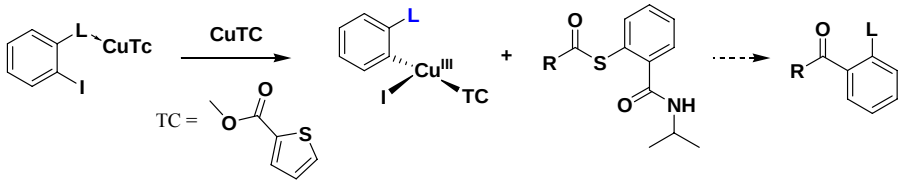
Scheme 4.1 Ullmann-Like Coupling Mediated by CuTC

In the reaction mechanism, a copper(III) intermediate was postulated (Scheme 4.2). It was also suggested that the efficacy of CuTC compared to CuX salts may have been due to an inherent ability of carboxylate to stabilize the oxidative addition product as implied by the equilibrium in equation 4.1.



Scheme 4.2 Oxidative Addition – Reductive Elimination Equilibrium and Disproportionation

If CuTC undergoes oxidative addition to an aryl iodide with an appropriate ligand in the 2 position (Scheme 4.2), the resulting copper(III) aryl intermediate would be analogous to that generated aerobically using boronic acids. The aryl copper(III) intermediate could be generated in the presence of a thiol ester containing the appropriate ligating group in the *ortho*-position. A templated mechanism could give rise to a new ketone.



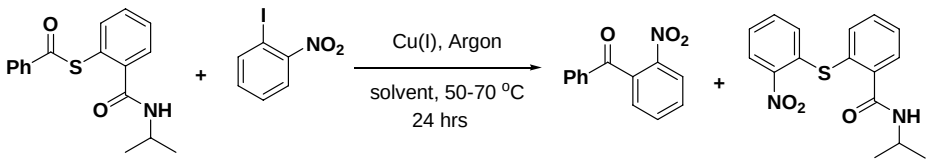
Scheme 4.3 Coupling of Aryl Cu(III) with Thiol Ester – A New Ketone Synthesis

The ketonic product would be formed without using Pd, B, or Sn reagents. The following describes the *preliminary* results designed to investigate this concept.

4.2 Results and Discussion

S-2-(isopropylcarbamoyl)phenyl benzothioate was used to probe the reactivity of different organo-halides. The reactions were carried out at 50-70 ^{o}C under argon and monitored by GC-MS. When 2-iodonitrobenzene was used with 3.0 equivalents of CuTC in DMF, 40 % of 2-nitro benzophenone was obtained (Table 4.1, entry 1). No other products were detected. When the amount of copper was lowered to 1.5 equivalents, the yield was also lower, 23 % (entry 2). Sodium ascorbate was added as a reducing agent. The plan was to observe the effect of an increase in the concentration of Cu(I) as the reaction proceeded. When 1.5 equivalents of CuMeSal and 1.2 equivalents of the aryl iodide were used in the presence of 1.5 equivalents of sodium ascorbate, 57 % of the ketone along with 30 % *S*-arylation was isolated (entry 3). The remaining aryl iodide was also reduced giving 14 % nitrobenzene. Increasing the amount of aryl halide to 2.2 equivalents in the presence of 1.5 equivalents of CuMeSal in THF led to 71 % ketone and 77 % *S*-arylation (Table 4.1, entry 4). No nitrobenzene was isolated.

Table 4.1 Reaction Optimization for Coupling of 2-Iodonitrobenzene and *S*-2-(isopropylcarbamoyl)phenyl Benzothioate

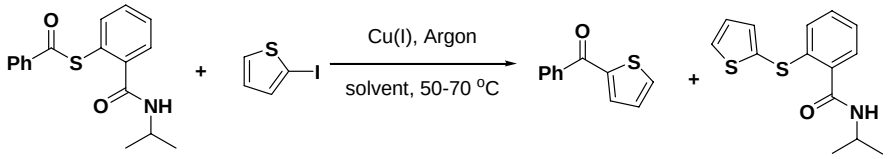


				Yield (%)	
Entry	Cu(I)	Additive	Solv	Ketone	*S*-Aryl
1	3.0 eq CuTC [a]	-	DMF	40	-
2	1.5 eq CuTC [a]	-	DMF	23 (64 con)	-
3	1.5 eq CuMeSal [a]	$AANa^+$	DMF	57	30 (14 NO_2Ph)
4	**1.5 eq CuMeSal [b]**	**$AANa^+$**	**THF**	**71**	**77**

$AANa^+$ = sodium ascorbate; a: 1.2 eq ArI; b: 2.2 eq ArI

Other organic iodides were investigated. When 2-iodothiophene was treated with 3.0 equivalents of CuTC at 50 ^oC in DMF under argon, 33 % of phenyl(thiophen-2-yl)methanone was isolated (Table 4.2, entry 1). No *S*-arylation was observed or isolated. The addition of sodium ascorbate proved helpful with the substrate 2-iodonitrobenzene (Table 4.1, entry 4); however in this reaction only 24 % ketone was isolated along with 39 % *S*-arylation (Table 4.2, entry 2).

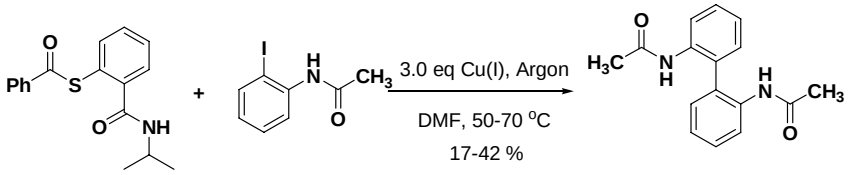
Table 4.2 Coupling of *S*-2-(isopropylcarbamoyl)phenyl benzothioate with 2-Iodothiophene



				Yield (%)	
Entry	Cu(I)	Additive	Solv	Ketone	*S*-Aryl
1	3.0 eq CuTC [a]	-	DMF	33	-
2	1.5 eq CuMeSal [b]	$AANa^+$	THF	24	39

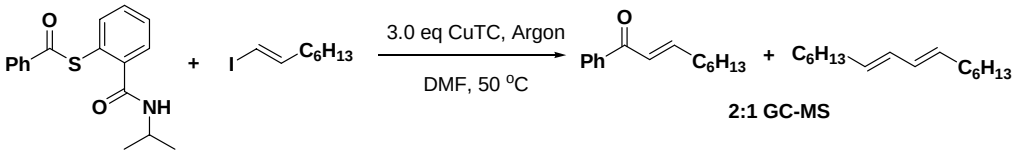
$AANa^+$ = sodium ascorbate; a: 1.2 eq ArI; b: 2.2 eq ArI

N-(2-iodophenyl)acetamide was treated with 3.0 equivalents of CuTC in DMF and *S*-2-(isopropylcarbamoyl)phenyl benzothioate (Scheme 4.2). Only the biaryl Ullman-like coupling was detected and isolated in 17 % yield. Unfortunately, using CuMeSal did not improve results. The biaryl product was isolated in 42 % yield.



Scheme 4.4 Coupling of *S*-2-(isopropylcarbamoyl)phenyl benzothioate with *N*-(2-iodophenyl)benzamide

The alkene (*E*)-1-iodooct-1-ene gave roughly a 2:1 mixture by GC-MS of ketone and Ullmann-like product when treated with 3.0 equivalents of CuTC at 50 °C in DMF under argon (Scheme 4.3). The reaction was very messy and isolation of the products was unsuccessful.



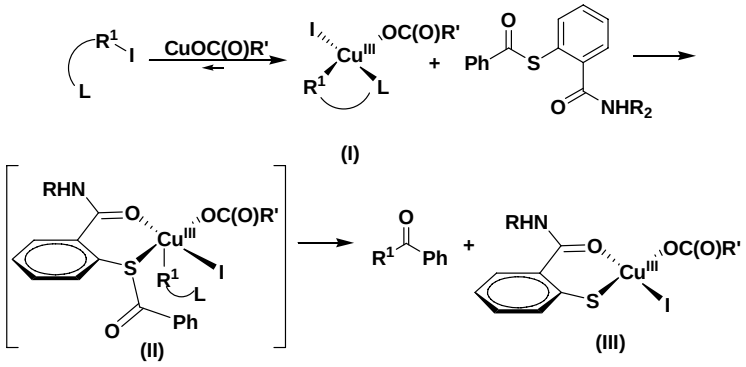
Scheme 4.5 Coupling of *S*-2-(isopropylcarbamoyl)phenyl Benzothioate with (*E*)-1-Iodooct-1-ene

Removing the pendent on the thiol ester or the organo-iodide had detrimental effects on the reaction. When *S*-2-(isopropylcarbamoyl)phenyl benzothioate was replaced with *S*-p-tolyl benzothioate, only starting material was observed. Replacing 2-iodonitrobenzene with 1-iodo-4-methylbenzene did not lead to product.

4.3 Mechanism

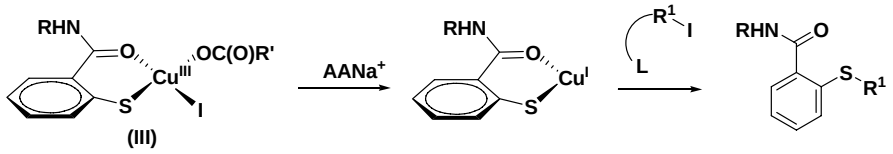
The following mechanism was proposed based on the preliminary data obtained and the mechanism operating in the copper-catalyzed aerobic ketone synthesis (Scheme 4.4). First, copper undergoes oxidative addition with the aryl or heteroaryl iodide containing an internal ligand generating a copper(III) intermediate I. If the internal

ligand is ligated to copper, it must dissociate in order for the thiol ester containing the appropriate pendant to bind to give intermediate II. The key, non-oxidative, carbon-carbon bond forming step then occurs *via* a copper templated mechanism producing the copper thiolate III.



Scheme 4.6 Copper Templated Ketone Synthesis

In the cases where sodium ascorbate was added, the copper(III) thiolate III can be reduced to a copper(I) thiolate which can undergo oxidative addition to a second equivalent of the organo-iodide (Scheme 4.5). Reductive elimination generates the *S*-arylation product.[2]



Scheme 4.7 Mechanism with Added Sodium Ascorbate

This mechanism accounts for several observations. Removing the ligand on the organo-iodide shifts the equilibrium towards reductive elimination significantly slowing the reaction. Removing the pendent on the thiol ester prevents the key coordination needed for the ketone forming step. If the ligand on the organo-iodide is too strong for copper, then the thiol ester cannot bind to the copper(III) intermediate. This may be the

reason why *N*-(2-iodophenyl)benzamide and (*E*)-1-iodooct-1-ene produced biaryl Ullmann-like products in the reaction.

2.4 Conclusion

Although conditions were not general for all organic iodides, the project remains viable. Perhaps other redox active metals such as cobalt could be investigated. Conditions that favor the equilibrium towards oxidative addition of the metal to the halide or pseudo-halide without the use of ligating groups could also be investigated. Replacing halides with boronic acids or organo-tins have its advantages – cost, lower toxicity and availability. Lastly, *anaerobic* coupling could lead to a successful ketone synthesis without *S*-arylation, the byproduct present in the *aerobic* copper- and/or palladium-catalyzed ketone synthesis.

4.5 References

1. Zhang, S.; Zhang, D.; Liebeskind, L. S. Ambient Temperature, Ullmann-like Reductive Coupling of Aryl, Heteroaryl, and Alkenyl Halides. . *J. Org. Chem.* **1997**, *62*, 2312-2313.

2. Kwong, F. Y.; Buchwald, S. L. A General, Efficient, and Inexpensive Catalyst System for the Coupling of Aryl Iodides and Thiols. *Org. Lett.* **2002**, *4*, 3517-3520.

4.6 Experimental

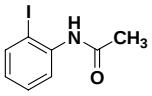
General Methods:

Starting material preparations were preformed under an atmosphere of dry N_2 or Ar in over-dried glassware unless otherwise noted. Solvents (DMF, pyridine) for reaction media were ACS reagent grade and purchased from Aldrich. They were dried over 4 Å molecular sieves, purged with dry N_2 or Ar, and titrated for water level with a Karl Fisher Coulomatic K-F titrator. Solvents (THF) were purified and dried using a Seca Solvent System purchased from GlassContour. Hexanes (Hex), ethyl acetate (EtOAc), and diethyl ether (Et_2O) used for extraction, recrystallization, or chromatography were obtained from EM Science and used as purchased. Solution of $NaHCO_3$ or HCl refers to aqueous solution. Analytical thin-layer chromatography (TLC) was carried out using Merk Kieselgel 0.25 mm 60 F_{254} plates with visualization by UV, $KMnO_4$, or iodine crystals in silica gel.

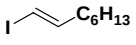
^{1}H NMR spectra were recorded on a Varian Inova 400 or 600 MHz NMR spectrometer at room temperature in $CDCl_3$ or *d*-DMSO and were internally referenced to either, (7.27 ppm and 2.5 ppm, respectively). ^{13}C NMR spectra were recorded on a Varian Inova 150 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported in Hz; integration is provided. Infrared (IR) spectroscopy was preformed on a Thermo Corporation Nicolet 380 FTIR. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100 %), m (medium, 40-67 %), w (weak, 20-40 %), and br (broad). Uncalibrated melting points were taken on a Thomas-Hoover melting point

apparatus in open capillary tubes. GC/MS analysis was carried out on a bonded 5 % diphenylsilozone capillary column (30 m, 0.25 mm id, 0.25 μm df).

(*E*)-Oct-1-enylboronic acid was purchased from Frontier Scientific, Inc. CuTC[1] and CuMeSal[2] were prepared according to the literature procedure. 2-Iodoaniline, 2-iodonitrobenzene, 2-iodothiophene, acetic anhydride, and sodium ascorbate were purchased from Aldrich.



***N*-(2-Iodophenyl)acetamide[3]:** 2-Iodo aniline (0.510 g, 2.3 mmol) was dissolved in 5 ml of dry CH_2Cl_2 at room temperature under argon. Acetic anhydride (0.32 ml, 3.4 mmol) was added follows by pyridine (0.4 ml, 3.6 mmol), and 2 crystals of DMAP. The reaction was stirred over night, then quenched with 5 % HCl. The organic layer was separated and washed again with 5 % HCl. The organic layer was dried with $MgSO_4$, filtered, and condensed to give 0.450 g of the amide. Yield: 75 %. Light beige crystals, M.p. 106-108 ^oC [Lit. 109-111 ^oC[3,4]]. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.22 (d, *J*= 8.2 Hz, 1H), 7.78 (d, *J*= 7.6 Hz, 1H), 7.41 (bs, 1H), 7.35 (t, *J*= 7.6 Hz, 1H), 6.85 (t, *J*= 7.3 Hz, 1H), 2.25 (s, 3H). IR (neat, cm^{-1}) 3271 (w), 1658 (m), 1525 (s).



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[1] Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312-2313.

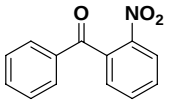
[2] Savarin, C.; Srogl, J.; Liebeskind, L. S. Substituted *Org. Lett.* **2001**, *3*, 91-93.

[3] Larock, R.C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998,** *63,* 7652 – 7662.

(*E*)-1-Iodooct-1-ene[5]: Prepared according to literature procedure. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.16 (ddd, *J*= 14, 7.1 Hz, 1H), 5.97 (d, *J*= 14 Hz, 1H), 2.04 (q, *J*= 8.6 Hz, 2H), 1.39-1.36 (m, 2H), 1.31-1.25 (m, 6H), 0.89 (t, *J*= 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 147.0, 74.5, 36.3, 31.8, 28.8, 28.5, 22.7, 14.3.

General Procedure for coupling with copper and organoiodides:

The corresponding thiol ester (1.0 equiv., 0.25 mmol) was placed in a 10 ml schlenk flask equipped with a small magnetic stir bar and 2 ml of dry dimethacetamide (DMF) under argon. Copper methylsalicylate (1.5 equiv., 0.37 mmol) was added followed by the organic iodide (2.2 equiv., 0.55 mmol) and sodium ascorbate (1.5 equiv., 0.37 mmol). The reaction was monitored *via* TLC. If there was no starting material or no change in the TLC, the reaction was quenched with aqueous NH_4Cl and extracted with 50 ml Et_2O three times. The combined organic layers were dried over $MgSO_4$ and condensed under vacuum. The viscous solid was than subjected to column chromatography (hex, EtOAc gradient).



(2-Nitrophenyl)(phenyl)methanone[6]: Yield: 71 %. Light yellow crystals, M.p. ($CHCl_3$) 104-106 ^{o}C [Lit. 103-104 ^{o}C[5]]. TLC (silica gel, 5:1 hex:EtoAc, R_f= 0.37). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.26 (dd, *J*= 7.3, 0.95 Hz, 1H), 7.8-7.75 (m, 3H), 7.70 (dd,

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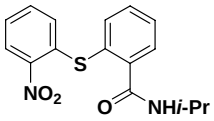
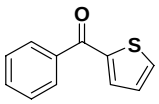
[5] Brown, H. C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N. G. Vinylic organoboranes. 14. *J. Org. Chem.* **1989**, *54*, 6075-6079.

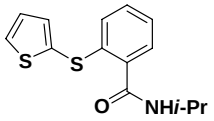
J= 7.3 Hz, 1H), 7.61 (dd, *J*= 7.3 Hz, 1H), 7.52-7.44 (m, 3H). IR (neat, cm^{-1}) 1673 (s), 1527 (s), 1346 (m), 1279 (m).



2-(2-Nitrophenylthio)-*N*-isopropylbenzamide: Yield: 77 %. Yellow crystals, M.p. 83-85 ^{o}C. TLC (silica gel, 5:1 hex:EtoAc, R_f= 0.13). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.23 (dd, *J*= 8.1, 1.4 Hz, 1H), 7.82 (dd, *J*= 7.6, 1.4 Hz, 1H), 7.64 (d, *J*= 6.7 Hz, 1H), 7.58 (t, *J*= 7.1 Hz, 1H), 7.52 (t, *J*= 7.6 Hz, 1H), 7.39 (app t, *J*= 8.1 Hz, 1H), 7.26 (app t, *J*= 6.2 Hz, 1H), 6.90 (dd, *J*= 8.6, 0.95 Hz, 1H), 6.25 (bs, 1H), 4.11-4.08 (m, 1H), 1.04 (d, *J*= 6.7 Hz, 6H). IR (neat, cm^{-1}) 3211 (w), 1622 (m), 1588 (m), 1508 (s).



Phenyl(thiophen-2-yl)methanone[7]: Yield: 23 %. Clear oil. TLC (silica gel, 5:1 hex:EtoAc, R_f= 0.53). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.89 (d, *J*= 7.1 Hz, 2H), 7.73 (d, *J*= 4.8 Hz, 1H), 7.66 (d, *J*= 3.3 Hz, 1H), 7.60 (dd, *J*= 7.1 Hz, 1H), 7.50 (dd, *J*= 7.6 Hz, 2H), 7.17 (dd, *J*= 4.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 188.4, 143.8, 138.3, 135.1, 134.4, 132.4, 129.3, 128.6, 128.1. IR (neat, cm^{-1}) 2926 (w), 1732 (m), 1635 (s), 1446 (s).



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[6] Szmant, H. H.; Harmuth, C. M. *J. Am. Chem. Soc.* **1959**, *81*, 962-966.

[7] Katritzky, A. R.; Le, K. N. B.; Khelashvili, L.; Mohapatra, P. P. *J. Org. Chem.* **2006**, *71*, 9861-9864.

***N*-Isopropyl-2-(thiophen-2-ylthio)benzamide:** Yield: 39 %. White solid, M.p. 117-118 ^{o}C. TLC (silica gel, 5:1 hex:EtoAc, R_f= 0.27). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.52 (d, *J*= 5.7 Hz, 1H), 7.46 (d, *J*= 7.6 Hz, 1H), 7.32 (d, *J*= 3.8 Hz, 1H), 7.24 (dd, *J*= 8.1 Hz, 1H), 7.15 (dd, *J*= 7.6 Hz, 1H), 7.11 (dd, *J*= 5.2, 3.3 Hz, 1H), 6.96 (d, *J*= 8.1 Hz, 1H), 5.91 (br d, *J*= 5.7 Hz, 1H), 4.35-4.29 (m, 1H), 1.30 (d, *J*= 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 167.2, 138.8, 137.2, 134.1, 132.1, 130.9, 130.8, 128.4, 127.8. 127.7, 125.6, 42.3, 23.0. IR (neat, cm^{-1}) 3253 (w), 2967 (w), 1637 (m), 1618 (m), 1544 (s).