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Wenting Wu Date

Mild Amide and Peptide Constructions by the Condensation of *O*-Silylthionoesters with Amines and Metal Mediated Cross-Coupling Reactions for Carbon-Carbon Bond Formation

By

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Doctor of Philosophy

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B.S., Tianjin University, Tianjin, China, 2006

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An abstract of
A dissertation submitted to the Faculty of the
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Abstract

Mild Amide and Peptide Constructions by the Condensation of *O*-Silylthionoesters with Amines and Metal Mediated Cross-Coupling Reactions for Carbon-Carbon Bond Formation

By

Wenting Wu

A novel, pH-neutral method for in situ activation of thiol acids for room-temperature amide and peptide bonds construction is described. The unique carboxyl activation relies upon the known spontaneous formation of *O*-silylthionoesters from their *S*-silylthiol ester by a tautomerization of the triorganosilicon group from sulfur to oxygen. *O*-silylthionoesters were in situ generated from a trimethylsilylation protocol using bistrimethylsilylacetamide (BSA) and thiol acids. The efficient reaction of *O*-silylthionoesters with amines to generate amide rather than thioamide linkages and peptides with stereoretention is unknown.

The syntheses and characterization of the new dicopper(I) 2,6-dihydroxybenzoate complexes are reported. The reactivity of copper(I) 2,6-dihydroxybenzoate (CuDHB) showed mild improvement over CuTC, CuMeSal and CuDPP in cross-coupling reactions. CuDHB mediated Suzuki cross-coupling reaction under pH-neutral and mild condition has been explored. This CuDHB mediated coupling of vinyliodides with vinylboronic acids and arylboronic acids with *ortho* coordination groups gives 1,3-dienes and aryl-alkenes in moderate to good yields.

A novel system modeled from a biochemical process of metallothioneins (MT-mimic) was developed for the construction of C-C bonds through Pd-catalyzed desulfitative cross-coupling reaction. Peptidyl thiol esters bearing MT-mimic pendant reacted with a variety of boronic acids to produce peptidyl ketones in good to excellent yields with complete retention of configuration under palladium catalyzed desulfitative conditions. The application of the desulfitative reaction was also extended to thiol ethers. Thiol ethers with *O*-acetyl oxime pendant coupled with boronic acids to generate heteroaryls and biaryls under Pd-catalyzed cross-coupling condition.

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List of Abbreviations

app	apparent
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
br	broad
Bu	butyl
^{o}C	degrees Celsius
calcd	calculated
cm^{-1}	wavenumber unit
δ	chemical shift (in ppm for NMR)
Cbz	benzyloxycarbonyl
CuTC	copper(I) thiophene-2-carboxylate
CuMeSal	copper(I) 3-methylsalicylate
d	double
dba	dibenzylideneacetone
DCC	1,3-dicyclohexylcarbodiimide
DIPEA	diisopropylethylamine
DMF	dimethylformamide
DMAP	*N*,*N*-dimethylaminopyridine
DMSO	dimethylsulfoxide
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate
Fmoc	9-fluorenylmethoxycarbonyl
g	gram(s)
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
IR	infrared spectroscopy
HRMS	high-resolution mass spectrometry
OAc	acetate
Ph	phenyl
THF	tetrahydrofuran
Bz	benzoyl
Cat.	catalytic
Cbz	benzyloxycarbonyl
COD	1,5-cyclooctadiene
CuDPP	copper(I) diphenylphosphinate
ee	enantiomeric excess
Glu	glutamic aci
Gln	glutamine
hr	hours
Hz	hertz

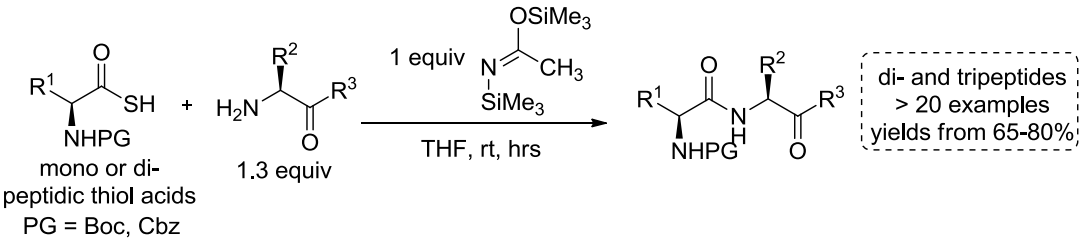
i-Pr	isopropyl
J	coupling constant
Leu	leucine
M	molar
m	medium (for IR)
Met	methionine
Mg	milligram
mL	milliliter
mmol	millimol
Mp	melting point
Phe	phenylalanine
p-NO_2	para-nitro
Pro	proline
Ser	serine
TFA	trifluoroacetic acid
TFP	tri(2-furyl)phosphine
TMS	trimethylsilyl
Tolyl	toluene
Trp	tryptophan
Tyr	tyrosine
Z	benzyloxycarbonyl
Val	valine
Aib	isobutyric acid
Ala	alanine
Gly	glycine
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
vs	very strong

Chapter 1

In Situ Carboxyl Activation Using a Silatropic Switch: A New Approach to Amide and Peptide Constructions

*Abstract: The novel reactivity of O-silylthionoesters with amine nucleophiles to generate oxoamides (rather than thioamides) is described. A straightforward trimethylsilylation protocol using bistrimethylsilylacetamide (BSA) combined with the unique reactivity of the O-silylthionoesters toward 1^o and 2^o amines to generate oxoamides provides the simplest means of activating a thiol acid for peptide bond formation at neutral pH. Excellent stereoretention is observed (**Scheme 1.1**).*

Scheme 1.1 Peptide Synthesis via Silylative Activation of Thiol Acids



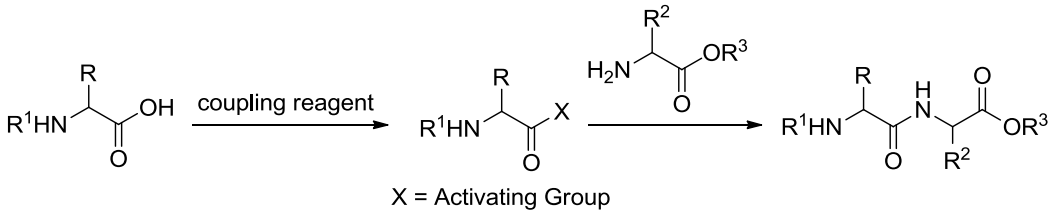
1.1 Introduction and Background

1.1.1 Brief History of Peptides Synthesis

The development of methods for reliable, chemoselective formation of amide bonds, in particular from the context of racemization-free peptide ligations, remains a focus of much modern research activity.[1] In fact, the development of new amide-forming reactions tops a recent priority list of process improvements desired by the pharmaceutical industry.[2] Numerous strategies and reagents have been developed for the synthesis of amide-peptide bonds.

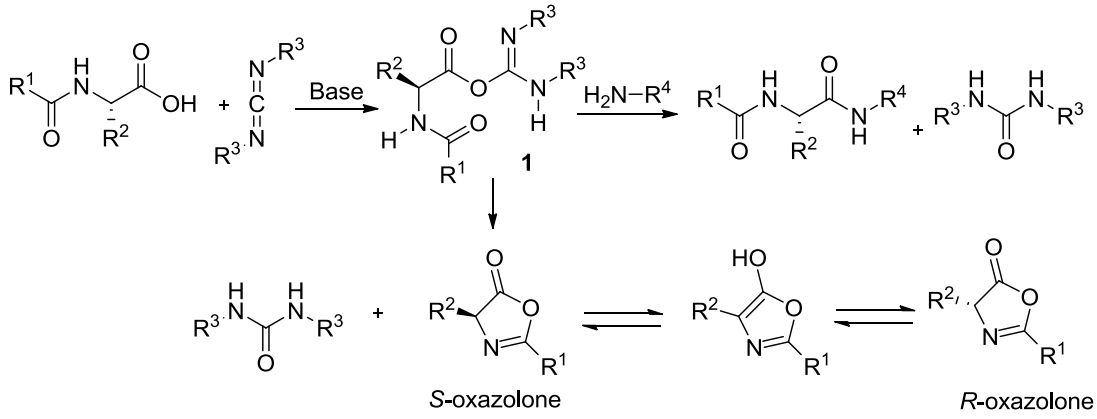
Amide bonds are typically synthesized from carboxylic acids and amines; however, the combining of these two functional groups does not occur spontaneously at ambient temperature, with the elimination of water only taking place at high temperatures (>200 ^oC).[3] For this reason, it is usually necessary to first activate the carboxylic acids, a process that usually takes place by converting the OH of the acid into a good leaving group. In order to activate carboxylic acids, one can use coupling reagents to generate compounds such as acid chlorides, anhydrides, carbonic anhydrides or active esters (**Scheme 1.2**).

Scheme 1.2 Principle of the Activation Process for Amide Bond Formation



Carbodiimides including dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) are the most commonly used coupling reagents.[4] Dicyclohexylcarbodiimide has been used for coupling since 1955.[4a] The reaction between carboxylic acids and carbodiimides forms the highly reactive *O*-acylurea intermediates **1**, which can lead to the formation of the corresponding oxazolone through an intramolecular cyclization. With an acidic proton, oxazolone rapidly undergoes racemization via a aromatic intermediate (**Scheme 1.3**).[5]

Scheme 1.3 Amides/Peptides Formation with Carbodiimides



In order to reduce the epimerization level, 1*H*-hydroxybenzotriazole (HOBt) and 1-hydroxy-7-azabenzotriazole (HOAt) are introduced as additives into the coupling reaction.[6] HOAt is believed to work by initially reacting with *O*-acylurea **1** to give a less reactive OAt active ester **2**, which enhances the reactivity of the ester by encouraging/stabilizing the approach of the amine via hydrogen bonding (**Scheme 1.4**).[6c] Even though HOBt derivatives are efficient in minimizing epimerization, they are potentially explosive, so shipment by air or sea is heavily restricted and

they have been removed from many chemical vendor catalogues. For this reason, reagents based on 1*H*-benzotriazoles, including uronium/aminium[7] and phosphonium salts[8] have been developed (**Figure 1.1**). However, the cost of these reagents prohibits their large scale application and they are often used as last resorts.

Scheme 1.4 Mechanism of Using HOBt as Additive with Carbodiimides

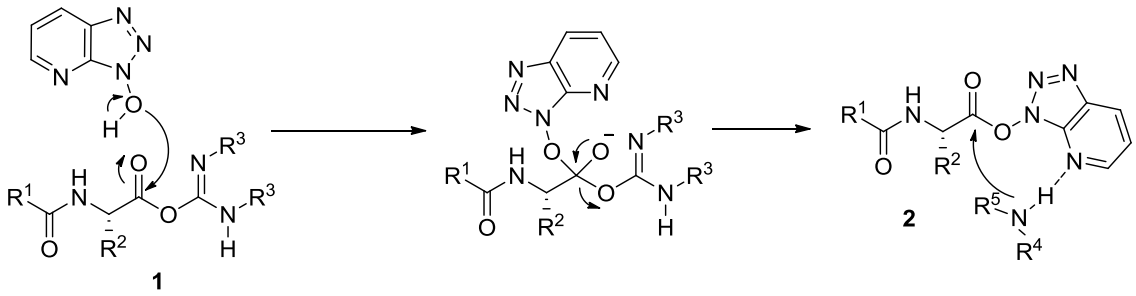
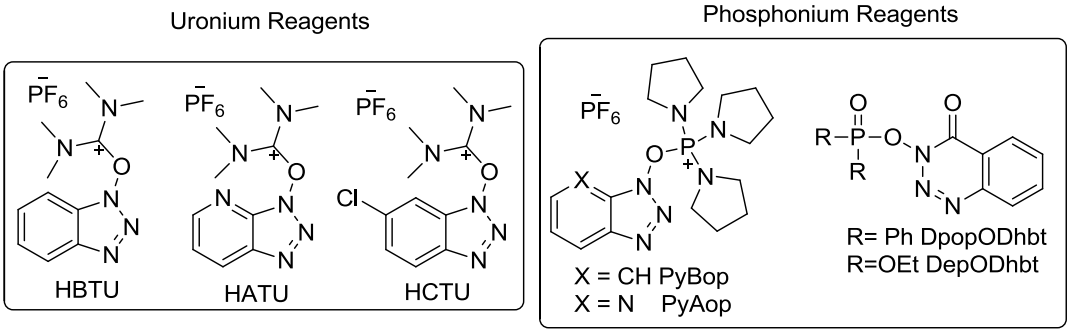


Figure 1.1 Coupling Reagents

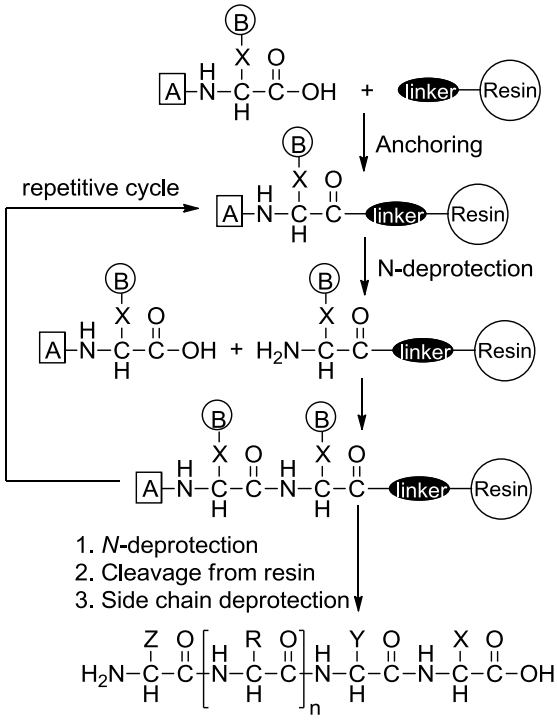


One major breakthrough in peptide chemistry was solid-phase peptide synthesis (SPPS).[9] In contrast to the solution-phase methodology, where after each reaction the product has to be purified before the next step, the growing peptide in the solid-phase approach is linked to an insoluble support and therefore, after each reaction step, the byproducts are simply removed by filtration and washing (**Scheme 1.5**). Furthermore, the repetitive nature of SPPS and the use of an insoluble support allow for the automation of the processes and the synthesis of peptides and small proteins with sizes up to 50 amino acid residues. However, the average length of a protein is approximately 250 amino acids. In order to overcome the limitation of solid-phase

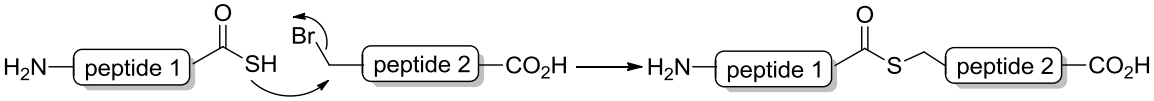
methodology for the preparation of longer proteins, chemical ligation for the coupling of unprotected peptide fragments in aqueous solution has been developed.

Schnölzer and Kent first introduced a novel strategy for the coupling of unprotected peptide fragments in aqueous solution in 1992.[10] The chemistry was used for a nucleophilic substitution reaction between an SH group of a thiol acid attached to the C-terminus of one peptide, and an alkyl bromide attached to the N-terminus of the other fragment, leading to the formation of a thiol ester at the ligation site (**Scheme 1.6**).

Scheme 1.5 Principles of Solid-phase Peptide Synthesis



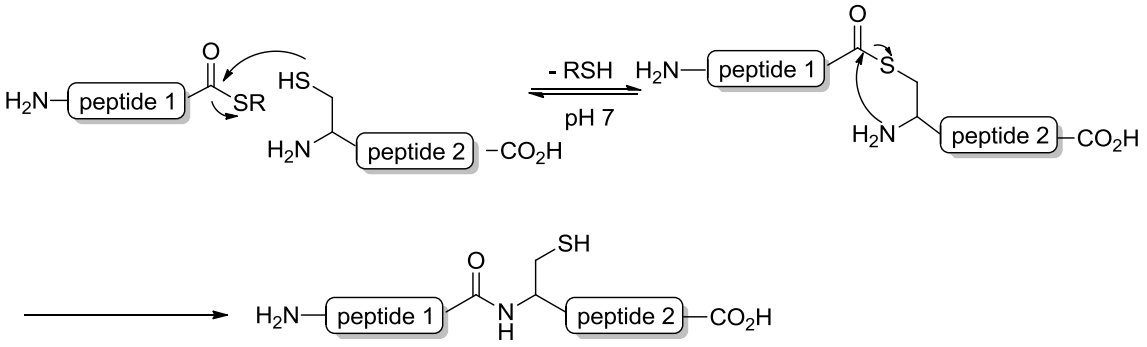
Scheme 1.6 Strategy of Chemical Ligation



The major disadvantage of the initial chemical ligation was that the reaction needed an unnatural structure at the ligation site, which leads to the formation of a non-native peptide. A second generation of ligation chemistry was introduced in 1994 by Dawson *et al.* referred to as "native chemical ligation (NCL)".[11] The unnatural alkyl bromide was replaced by a cysteine

residue from N-terminus, allowing the trans thiol esterification with a C-terminal thiol ester in aqueous solution, with the formation of a native amide bond at the ligation site. The NCL strategy overcomes the limitations of the traditional convergent approach for the synthesis of peptides or proteins (i.e., poor solubility and difficulty in purifying the fully protected peptide fragments) and is demonstrated as a reliable and practical methodology for the synthesis of small-to-medium size peptides with no epimerization (**Scheme 1.7**).

Scheme 1.7 Native Chemical Ligation of Unprotected Peptides



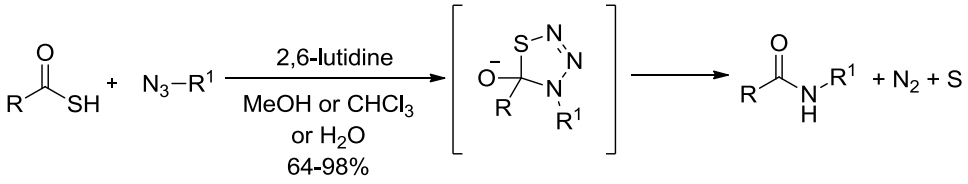
1.1.2 Amide and Peptide Generation from Thiol Acids

Although the native chemical ligation has proven very useful, it has some limitations, because of the fact that naturally occurring proteins do not always contain a cysteine residue in the right position of their sequences, making them difficult to synthesize using this methodology. Other methodologies have also been effectively utilized in the direct peptide bond formation. Recently, thiol acids mediated amide bond coupling reactions have been gaining more and more attention due to their unique reactivity and selectivity compared to those of carboxylic acids. The application range of thiol acids in amide bond formation reactions extends from fragment coupling to enzyme-mediated condensation, synthesis of proteins with backbone-engineered or non-native architectures, peptide dendrimers and cyclic peptides.[12]

In 2003 Williams and co-workers developed a coupling strategy of thiol acids and organic azides.[13] This method does not need active esters and amines as precursors for amide synthesis

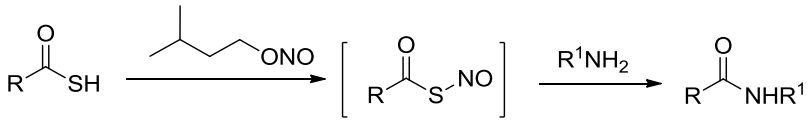
and has been applied to the preparation of several classes of complex amides in nonpolar and polar solvents including water (**Scheme 1.8**). However, this methodology requires the synthesis of different azides and restricts to the formation of secondary amides.

Scheme 1.8 Reactions of Thiol Acids and Azides to Form Amides



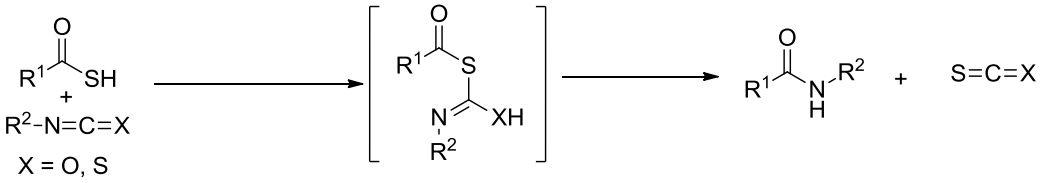
Xian and co-workers have found that thiol acids could react with RONO to generate the corresponding *S*-nitrosothioacids. In such a way, thiol acids can be activated to react with nucleophiles like amines to form amide bonds (**Scheme 1.9**).[14] An excess of amyl nitrite was required for the reaction to proceed in good yields.

Scheme 1.9 Facile Amide Formation via *S*-Nitrosothioacids



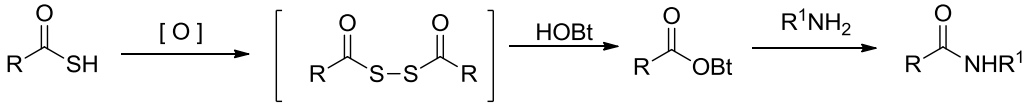
Crich and Sasaki have also developed a new methodology based on the reaction of thiol acids with more widely available isocyanates and isothiocyanates at room temperature to generate amide bonds in good to excellent yield.[15] Even though this methodology is potentially applicable for combinatorial and parallel synthesis, it requires extra steps to synthesize isocyanates and isothiocyanates in advance (**Scheme 1.10**).

Scheme 1.10 Reactions of Thiol Acids with Isocyanates and Isothiocyanates



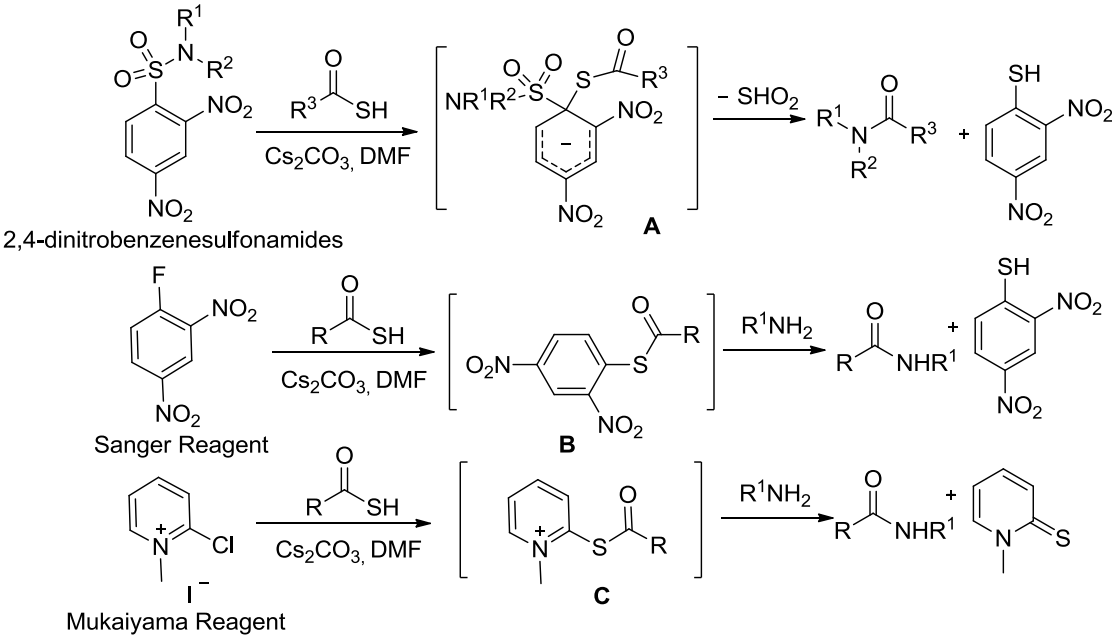
Diacyl disulfides are also facile acylation reagents toward amines. Danishefsky and co-workers have demonstrated that diacyl disulfides formed upon oxidation of thiol acids can react with HOBt followed by amines to construct amide bonds. The method works well in the contexts of macrolactamization, glycopeptide-peptide and glycopeptides-glycopeptide constructions (**Scheme 1.11**).[16] The usage of excess HOBt limited the application of this method.

Scheme 1.11 HOBt Mediated Peptide Coupling



The high nucleophilicity of thiocarboxylates enables their preferential reaction with electron-deficient aromatics by nucleophilic substitution. This method allows for the activation of thiol acids towards amines with 2,4-dinitrobenzenesulfonamides,[17] or Sanger Reagent and Mukaiyama Reagent[18] through different intermediates **A**, **B** and **C** (**Scheme 1.12**).

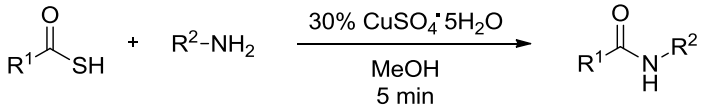
Scheme 1.12 Activation of Thiol Acids by Electron-deficient Aromatics



A copper salt mediated novel, ultrafast, mild and scalable amide bond formation strategy in methanol using thiol acids and amines was described by Gopi.[19] The mechanism suggests that the

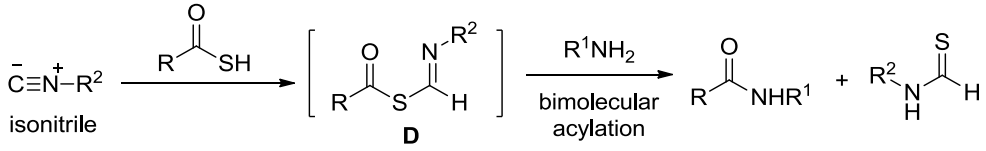
coupling reactions are initially mediated by $CuSO_4 \cdot 5H_2O$ and subsequently catalyzed by in situ generated copper sulfide (**Scheme 1.13**).

Scheme 1.13 Copper(II) Mediated Facile Peptide Synthesis in Methanol



Danishefsky's laboratory reported the reaction of thiol acids with *tert*-butylisonitrile to afford thio formimidate carboxylate mixed anhydride **D** as a potential bimolecular acylating agent. In the presence of nucleophilic amines, intermolecular acyl transfer to amines took place instead of 1,3-S→N intramolecular acylation. The chemistry is easily executed under neutral conditions at room temperature in dichloromethane with application to biologic-level molecules (**Scheme 1.14**).[20] Extra equivalents of amines and *tert*-butylisonitrile were required to achieve efficient reactions.

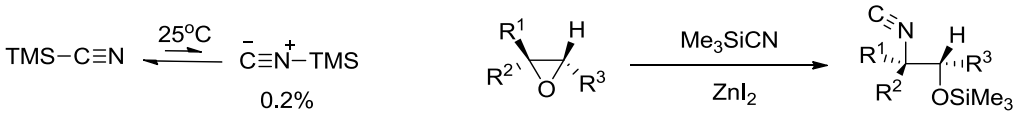
Scheme 1.14 Thiol Acids as Strong Acyl Donors for the Formation of Amide Bonds



Despite its effectiveness in activating thiol acid, the reaction requires excess amine nucleophiles and the unpleasant odor of *tert*-butylisonitrile may preclude its wide application.[21] Based on the proposed mechanism by Danishefsky (**Scheme 1.14**),[20] any *tert*-butylisonitrile equivalent should activate thiol acid in a similar way. Isocyanotrimethylsilane has been known to be in equilibrium with trimethylsilyl cyanide. Even though isocyanotrimethylsilane is not the major form, Lewis acids such as zinc iodide can catalyze the opening of epoxides by trimethylsilyl cyanide to produce *β*–hydroxy isonitriles (**Scheme 1.15**).[22] Our initial attempt was

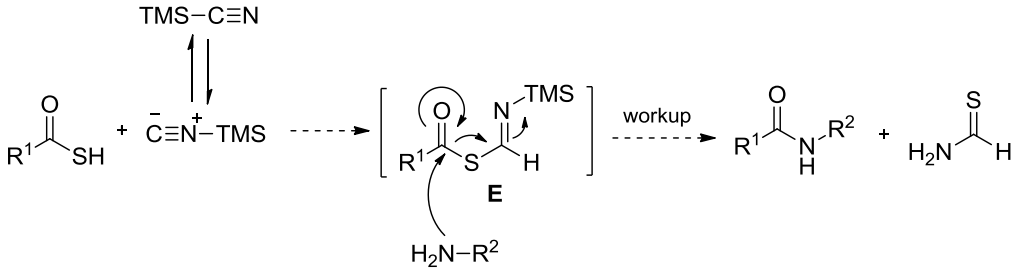
to explore whether TMSCN could act as a surrogate for *tert*-butylisonitrile to activate thiol acid through a isonitrile mechanism.

Scheme 1.15 Equilibrium and Reaction of Trimethylsilyl Cyanide



We hypothesized that isocyanotrimethylsilane in equilibrium with TMSCN could react with thiol acids to generate intermediate **E** analogous to the Danishefsky intermediate **D** (shown in **Scheme 1.14**). Intermediate **E** is postulated to react with external amine nucleophiles to generate amides (**Scheme 1.16**).

Scheme 1.16 Proposed Amide Bond Formation by Thiol Acid and TMSCN



With the initial goal of investigating TMSCN-mediated amide bonds formation between thiol acids and amines, we discovered an unexpected, novel, pH-neutral method for in situ activation of the carboxyl functional group. We used this discovery for a surprisingly simple system for room temperature amide and peptide bond construction.[23]

1.2 Results and Discussion

1.2.1 Preliminary Study

The preliminary results from the former group member Dr. Zhihui Zhang showed that TMSCN indeed could mediate amide bond formation between thioacetic acid with aniline (**Scheme**

1.17).[24] Based on this promising result, an investigation into the generality and scope of the TMSCN-mediated reaction between thiol acids and amines was undertaken (**Table 1.1**).

Scheme 1.17 Carboxyl Activation Using a Silicon Switch

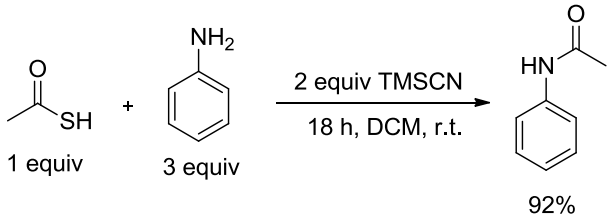
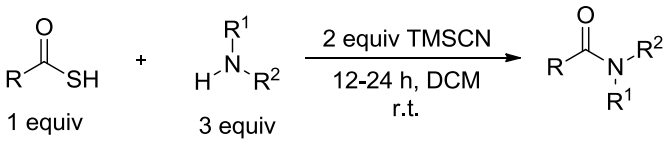
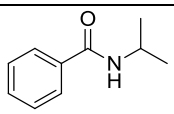
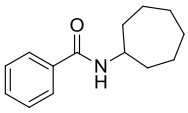
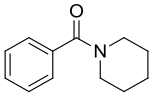
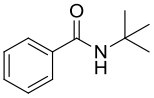
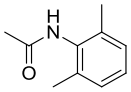
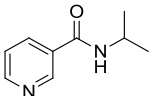
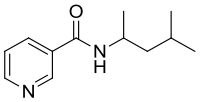
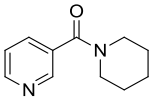


Table 1.1 TMSCN Mediated Amide Bond Formation



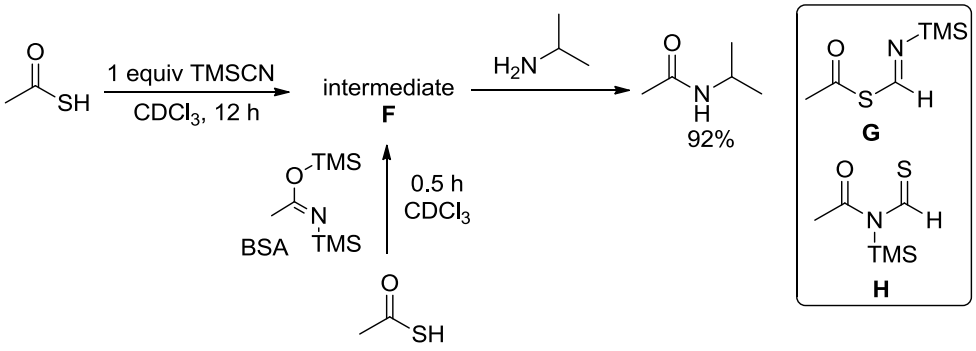
entry	R	R^1	R^2	Product	yields (%)[b]
1	Ph	Isopropyl	H		78
2	Ph	Cycloheptyl	H		80
3	Ph	$CH_2CH_2CH_2CH_2CH_2$			89
4	Ph	*t*Bu	H		28
5[c]	CH_3	2,6-di-CH_3-Ph	H		10
6	3-pyridyl	Propyl	H		72
7	3-pyridyl	2-(4-methylpentanyl)	H		91
8	3-pyridyl	$CH_2CH_2CH_2CH_2CH_2$			94

[a] General procedure: Thiol acid (1 equiv), amine (3 equiv) and TMSCN (2 equiv) were mixed together in dichloromethane and stirred at room temperature for 12 to 24 hours. [b] Isolated yields. [c] Determined by crude ^{1}H NMR with 4,4'-di-*tert*-butyl-1,1'-biphenyl as internal standard.

Thiobenzoic acid, thioacetic acid and thionicotinic acid could react with a series of amines using TMSCN as the activator. As shown in **Table 1.1**, primary and secondary amines reacted smoothly with these thiol acids. However, amines with steric hindrance were not as efficient (entries 4 and 5).

To probe whether amide bonds were formed via Danishefsky's intermediate, 1:1 thioacetic acid and TMSCN were combined. The reaction between thioacetic acid and TMSCN indeed generated an intermediate **F** which could further react with isopropyl amine cleanly (**Scheme 1.18**). However we were unable to observe the formyl proton in the crude ^{1}H NMR of intermediate **F**. This suggested that intermediate **F** was neither Danishefsky's intermediate **G** (generated through a two-component coupling reaction between trimethylsilyl isonitrile and thioacetic acid) nor thioformylacetamide intermediate **H (**formed via a 1,3-S→N acylation transfer reaction from **G**). To our surprise, bistrimethylsilylacetamide (BSA) also reacted with thioacetic acid to produce the same intermediate **F,** which confirmed that TMSCN is not activating thioacetic acid through an isonitrile pathway but rather the trimethylsilyl group was involved in the reaction mechanism somehow.

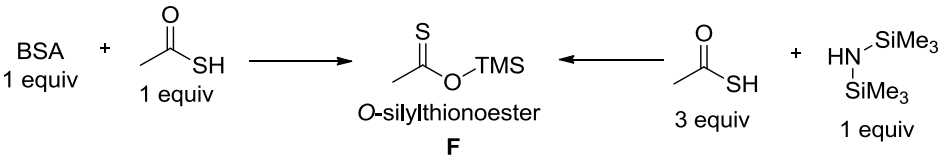
Scheme 1.18 Thiol Acid Activation of TMSCN and BSA



Intermediate **F** does not possess an infrared spectrum with a typical carbonyl absorption. The characteristic IR peaks appeared at 1275 cm^{-1}, 1249 cm^{-1} and 1214 cm^{-1}. The proton and carbon NMR matched with thionoacyloxysilane generated by the reaction between

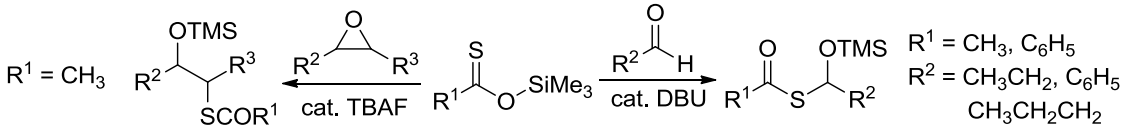
bis(trimethylsilyl)amine and thioacetic acid,[25a] which suggested that the actual active intermediate in the reaction is *O*-silylthionoester **F** instead of **G** or **H** (**Scheme 1.19**).

Scheme 1.19 Generation of *O*-Silylthionoester by Thiol Acid and BSA



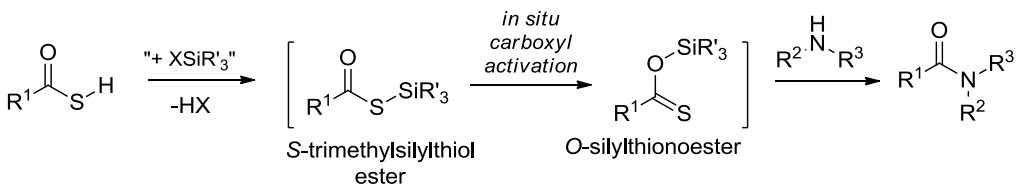
Thionoacetoxytrimethylsilane is not stable and can be hydrolyzed back to thioacetic acid by water, ethanol or acetic acid.[25b] Also, it can act as a nucleophile to open epoxides or add to aldehydes.[26] But the reaction of a thionoacetoxytrimethylsilane with amines to produce amides instead of thioamides has never been reported.

Scheme 1.20 Reaction of Thionoacetoxytrimethylsilane



This unique carboxyl activation relies upon the known spontaneous formation of *O*-silylthionoesters from their *S*-silylthiol ester isomers by a thermodynamically driven tautomerization of the triorganosilicon group from sulfur to oxygen.[27] The silylation of thiol acids occurs kinetically at sulfur to generate the *S*-trimethylsilylthiol ester, but a rapid silatropic equilibration to the more stable *O*-silylthionoester ensues. Since thionoesters are significantly more reactive toward nucleophiles than their oxoester counterparts (thiol esters are of lesser electrophilicity), the *S*-to-*O* silatropy and the attendant formation of oxoamides serves as a novel and mild in situ activation of the carboxyl function for nucleophilic addition (**Scheme 1.21**).

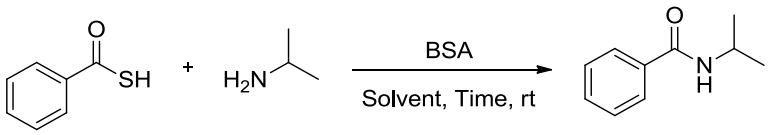
Scheme 1.21 In Situ Carboxyl Activation Using a Silicon Switch



1.2.2 BSA Mediated Simple Amide Formation

With this background in hand, we sought to optimize the reaction conditions by using thiobenzoic acid and *i*-PrNH_2 as a template reaction (**Table 1.2**). Compared with TMSCN, BSA is a more efficient trimethylsilylating reagent (**Scheme 1.18**). Protic solvent like methanol were not good for the reaction, which probably lead to the hydrolysis of thionoester (entry 1). Among all the solvents we tried, THF proved to be the best solvent for the reaction. Lowering the amine loading to 1.3 equivalents and increasing the reaction time to 3 hours, the best yield of 70% was achieved (entry 14).

Table 1.2 Reaction Conditions Optimization



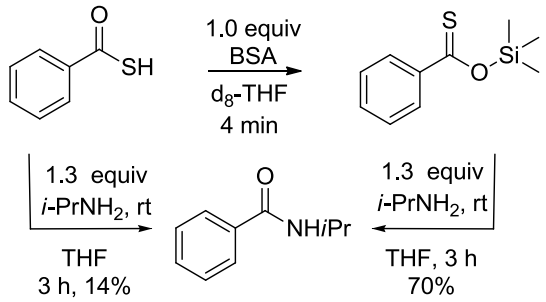
entry	solvent	thiol acid (equiv)	amine (equiv)	BAS (equiv)	time (h)	yield (%)[a]
1	Methanol	1	2	1	2	17
2	DMF	1	2	1	2	25
3	Acetone	1	2	1	2	30
4	Toluene	1	2	1	2	43
5	EtOAc	1	2	1	2	46
6	$CHCl_3$	1	2	1	2	51
7	Ether	1	2	1	2	54
8	Acetonitrile	1	2	1	2	62
9	DCM	1	2	1	2	69
10	THF	1	2	1	2	71
11	THF	1.5	1	1.5	2	50
12	THF	1	1.5	1	2	66
13	THF	1	1.3	1	2	62
14	THF	1	1.3	1	3	70

[a] Isolated yields.

With thiobenzoic acid serving as a model, in situ silylation with bistrimethylsilylacetamide (BSA) generated the *O*-trimethylsilylthionoester within 4 min at room temperature. Upon addition of isopropylamine, a reaction ensued at room temperature to provide the corresponding

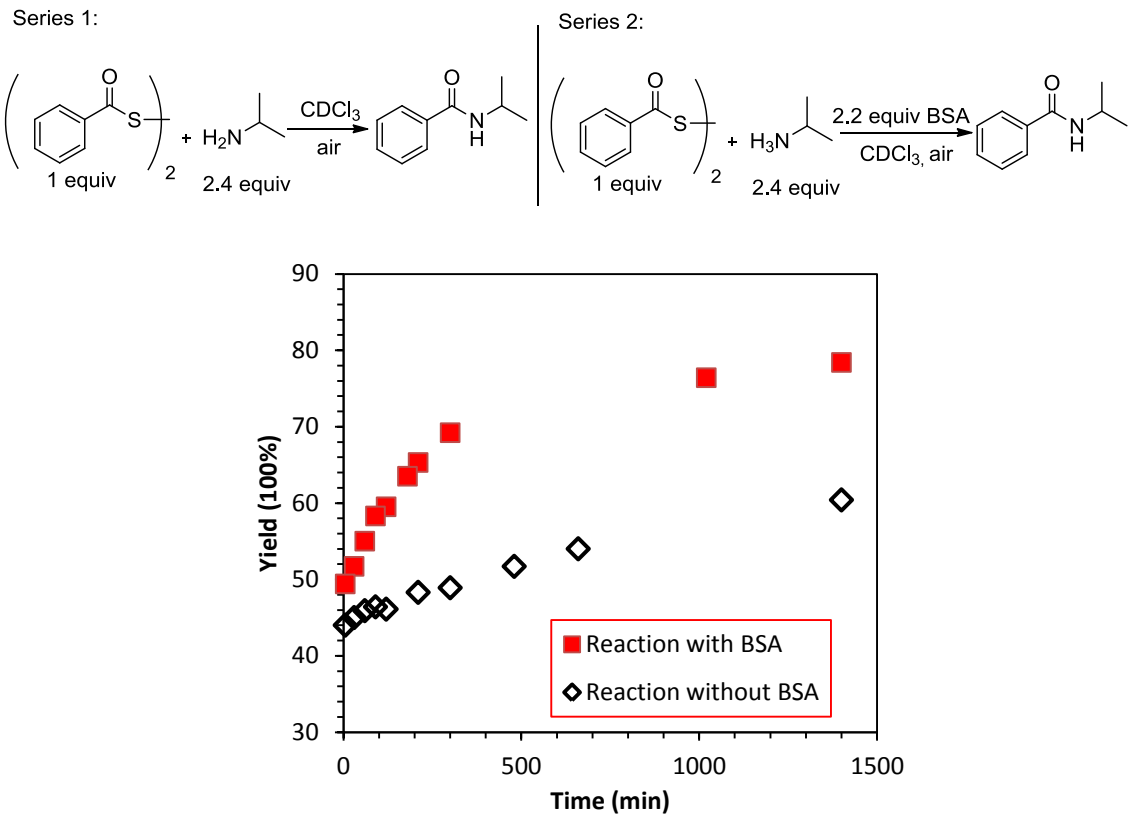
amide in 70% yield after 3 hours. In this process, no additional base was needed. The free thiol acid itself was poorly reactive with *i*-PrNH$_2$, giving only 14% of corresponding amide in the same time frame (**Scheme 1.22**). These experiments demonstrate the activation of thiol acids towards amine nucleophiles via *O*-silylthionoester intermediates.

Scheme 1.22 Exploratory Reactions Using Thiobenzoic Acid



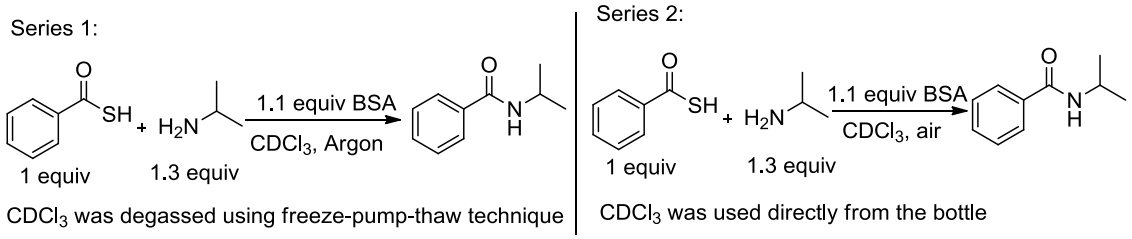
A previous report by Orgel *et al.* suggested that thiol acids do not directly react with amines to form amides; rather, diacyldisulfides are formed upon oxidation of thiol acids and these serve as facile acyl donors.[28] The reactivity of bisbenzoyldisulfide with *i*-PrNH$_2$ was therefore investigated. An authentic sample of bisbenzoyldisulfide alone does react rapidly with *i*-PrNH$_2$. In the presence of BSA, however, the reaction is slower (**Chart 1.1**).

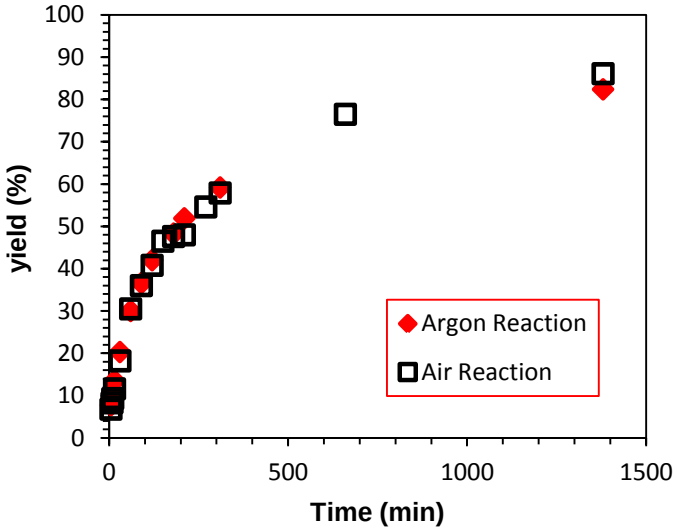
Chart 1.1 Amide Bond Formation from Bisbenzoyldisulfide



Almost identical isolated yields of the amide resulted from a silylative activation reaction run under an argon atmosphere (64%) and one conducted open to air (70%). The amide yields observed from the silylative activation protocol open to air are a function of the reactivity of the *O*-silylthionoester and are not caused by oxidation of the thiol acid to its corresponding diacyldisulfide, which then reacts with the amine. A variety of observations support this analysis: (1) a $CDCl_3$ solution of thiobenzoic acid (1.0 equiv), BSA (1.1 equiv), and Et_3N (1.3 equiv) exposed to air showed no evidence of formation of the dibenzoyldisulfide after 2 days at room temperature, and (2) reaction rates are essentially identical for experiments run under argon after freeze-thaw degassing or open to air (1.0 equiv thiobenzoic acid, 1.3 equiv *i*-$PrNH_2$, 1.0 equiv BSA in $CDCl_3$) (**Chart 1.2**).

Chart 1.2 Reaction Rate with Argon and Under Air





1.2.3 BSA Mediated Peptides Formation

With the optimized conditions in hand, a study of the BSA activation of thiol acids for amide and peptide bond formation was undertaken. The thiol acids were either commercially available or were prepared from the corresponding 9-fluorenylmethyl thiol esters via a standard piperidine deprotection/acidification process following Crich's protocol[17] and were used without further purification (**Scheme 1.23**). **Figure 1.2** shows the peptidyl 9-fluorenylmethyl (Fm) thiol esters generated for the exploration of amides and peptides. 9-Fluorenmethyl thiol was prepared following Crich's protocol from 9-fluorenmethanol.

Scheme 1.23 Protocol for the Synthesis of Thiol Acids

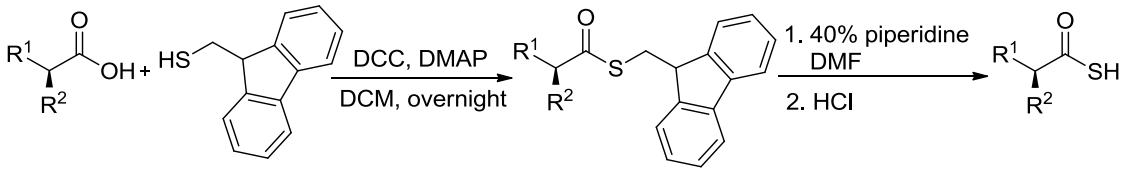
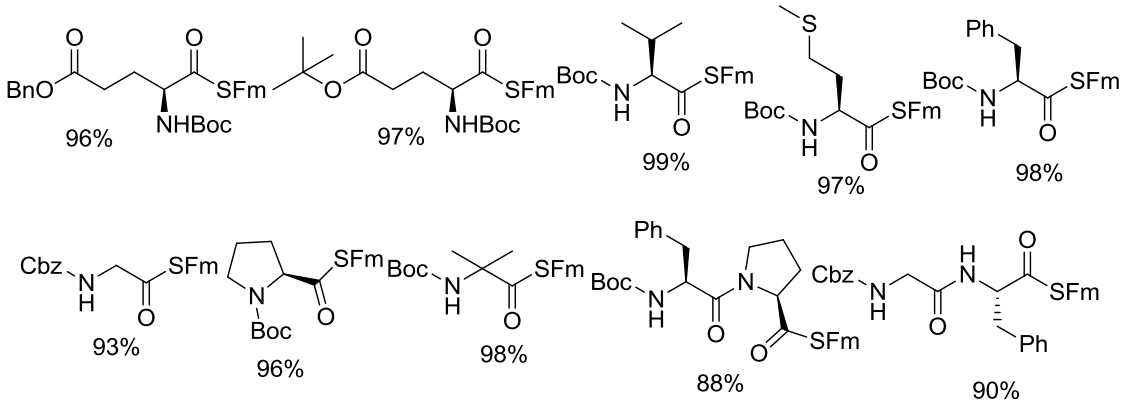
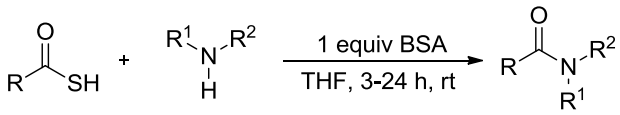


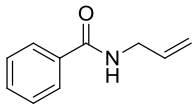
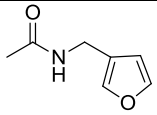
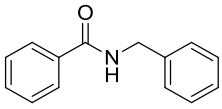
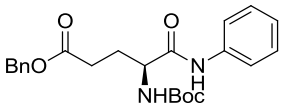
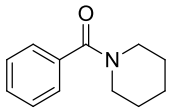
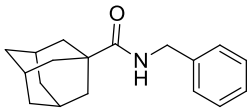
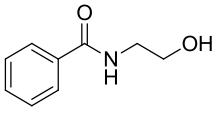
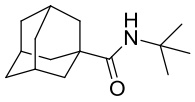
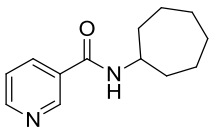
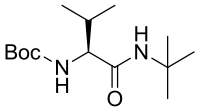
Figure 1.2 Peptidyl Thiol Esters Synthesized



Results for amide formation are gathered in **Table 1.3**. When the silylation of the thiol acids was carried out at room temperature in the presence of a primary or secondary amines, amide linkages were generated in very good yields within a matter of hours. Both aromatic thiol acids (entries 1-5) and aliphatic thiol acids (entries 6-10) reacted effectively with primary and secondary amines to produce secondary and tertiary amides, respectively. The hydroxyl group was well tolerated under the reaction conditions, which also demonstrates the selectivity of amine over hydroxyl functionality (entry 4). Even aniline, which has low nucleophilicity, reacted smoothly with *N*-Boc-L-Glu thiol acid to produce the corresponding anilide (entry 7). Sterically hindered thiol acids and amines also reacted to provide the sterically congested amides in quite good yields (entries 8-10). Remarkably, doubly hindered amides were also obtained in good yields (entries 9-10), although longer reaction times were required at room temperature. No racemization was observed for entries 7 and 10 by chiral HPLC.

Table 1.3 *S* to *O* Silylative Switch Induced Amide Formation



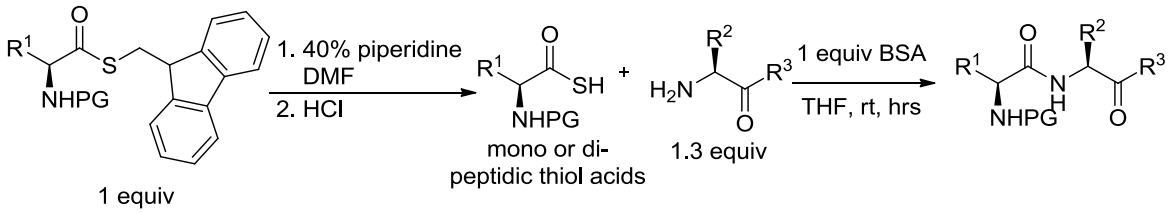
entry	amide	time (hrs) yld (%)[b]	entry	Amide	time (hrs) yld (%)[b]
1		3 91	6		3 82
2		3 89	7[c]		24 69
3		3 76	8		5 65
4		5 74	9		23 81
5		24 62	10[c]		24 71

[a] General procedure: 1 equiv of thiol acid, 1.3 equiv of amine, and 1 equiv of BSA were stirred at room temperature in THF. Isolated yields are shown. [b] Isolated yields. [c] No racemization was observed by chiral HPLC.

Peptide bond formation was also easily accomplished using the silylative activation of *N*-protected *α*-amino thiol acids (**Table 1.4**). As shown in **Table 1.4**, Gly, Met, Phe, Glu, and Pro thiol acid residues reacted smoothly to give the corresponding dipeptides (entries 1-12). It is noteworthy that sterically hindered *α*-amino thiol acids like Val (entries 10 and 11) and even 2-aminoisobutyric thiol acid (entry 12) were effectively coupled using this method, although longer reaction times were required to achieve acceptable yields. The amino acids, Phe, Tyr, Val, Ala, Gly, Met, Trp and Pro were all equally effective as *N*-terminal coupling partners (entries 1-13).

The formation of Cbz-Gly-L-Tyr-OMe indicates that phenolic residues do not interfere with the coupling reaction (entry 2).

Table 1.4 Activation of Thiol Acids for Peptide Synthesis via the "Silylative Switch"



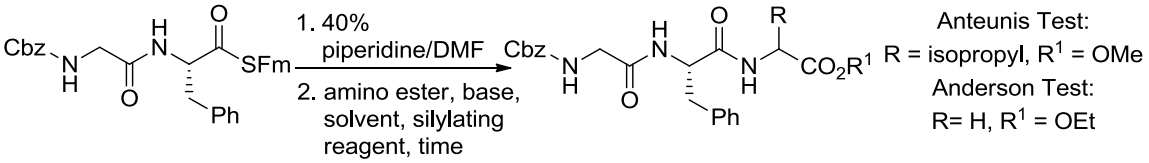
entry	amino thiol acid	amino ester	di or tripeptide	time (hr)	yld[b] (%)	epimerization[c]
1	Cbz-Gly-SH	L-Phe-OMe	Cbz-Gly- L-Phe-OMe	10	78	L/D = 100 : 0
				10	71[d]	
2	Cbz-Gly-SH	L-Tyr-OMe	Cbz-Gly-L-Tyr-OMe	10	69	
3	Boc- L-Met-SH	L-Val-OEt	Boc-L-Met-L-Val-OEt	10	83	LL/DL > 99 : 1
4	Boc-L-Phe-SH	L-Ala-OEt	Boc-L-Phe-L-Ala-OEt	12	72	LL/DL > 99 : 1
5	Boc-L-Glu(O*t*Bu)-SH	L-Val-OMe	Boc-L-Glu(O*t*Bu)-L-Val-OMe	10	71	LL/DL > 99 : 1
6	Boc-L-Glu(OBn)-SH	Gly-OEt	Boc-L-Glu(OBn)-Gly-OEt	8	76	
7	Boc-L-Glu(OBn)-SH	L-Met-OMe	Boc-L-Glu(OBn)-L-Met-OMe	10	68	
8	Boc-L-Glu(OBn)-SH	L-Trp-OMe	Boc-L-Glu(OBn)-L-Trp-OMe	8	74	
9	Boc-L-Pro-SH	L-Val-OMe	Boc-L-Pro-L-Val-OMe	10	65	
10	Boc-L-Val-SH	L-Pro-OMe	Boc-L-Val-L-Pro-OMe	48	70	
11	Boc-L-Val-SH	L-Phe-OMe	Boc-L-Val-L-Phe-OMe	63	67	
12	Boc-Aib-SH	L-Trp-OMe	Boc-Aib-L-Trp-OMe	54	74	
13	Boc-L-Phe-L-Pro-SH	L-Ala-OEt	Boc-L-Phe-L-Pro-L-Ala-OEt	8	65	LLL/LDL > 99 : 1

[a] General procedure: A solution of 1 equiv of the *N*-protected *α*-amino thiol acid (generated from the corresponding 9-fluorenylmethyl thiol esters via piperidine deprotection-HCl acidification) and 1 equiv of BSA in THF was added to a solution of 1.3 equiv of the amino acid hydrochloride salt and 1.3 equiv of triethylamine in THF. The mixture was then stirred at room temperature for 8-63 h. [b] Isolated yield. [c] the epimerization ratio was determined by HPLC. [d] A solution of 1 equiv of Cbz-Gly-SH and 1 equiv of BSA in THF was added to a solution of 1 equiv of Cbz-L-Arg-OH, 1.3 equiv of L-Phe-OMe·HCl and 1.3 equiv of triethylamine. The reaction mixture was stirred at room temperature for 10 h.

Cbz-Gly-L-Phe-OMe, which is formed as a single dipeptide in 78% yield from Cbz-Gly-SH and L-Phe-OMe under the general coupling conditions (**Table 1.4**, entry 1), is generated in almost an identical isolated yield (71%) when an equimolar amount of Cbz-L-Arg-OH is added to the reaction mixture. This simple experiment confirms the compatibility of this method with both carboxylic acid and guanidine functionalities. One important aspect of peptide synthesis is the epimerization test. The absence of epimerization at both coupling partners was verified by HPLC analysis for the dipeptides shown in entries 1 and 3-5 of **Table 1.4** and for the tripeptide Boc-L-Phe-L-Pro-L-Ala-OEt in entry 13.

Furthermore, both the Anteunis (entries 1-8)[29a] and Anderson (entries 9-11)[29b] tests were conducted to evaluate epimerization-prone linkages during the peptide formation process (**Table 1.5**). The standard reaction condition using BSA as the trimethylsilylation reagent and THF as the solvent led to greater than 13% epimerization for the Anteunis test (entry 1). After screening solvents, acetonitrile proved to be the best solvent to minimize epimerization (entries 1-3). Sterically hindered amine bases *N*-methylmorpholine (NMM) and *N*,*N*-diisopropylethylamine (DIEA) could further reduce epimerization (entries 4 and 5). Of significance for future systematic studies of the influence of the silylating agent, $PhSiH_2Cl$ gave lower levels of epimerization than BSA in the few cases preliminarily investigated, probably due to slightly faster amide bond forming step (entries 7 and 8). In the Anteunis test, this latter method gave less than 4% epimerization, which is superior to results using *N*,*N*'-dicyclohexylcarbodiimide (18.8% DL) and PyBop (6.6% DL) to facilitate the coupling between *Z*-Gly-L-Phe-OH and L-Val-OMe·HCl, as reported in the literature.[29a] In the Anderson test, the same method gave around 3% epimerization (entries 10 and 11). Even prior to any extensive studies of the influence of electronic and steric effects of the silicon reagent, epimerization of sensitive stereocenters using the pH-neutral "silylative switch" protocol for peptide coupling was found to be competitive with or better than existing technologies.

Table 1.5 Epimerization Studies for Anteunis and Aderson Tests

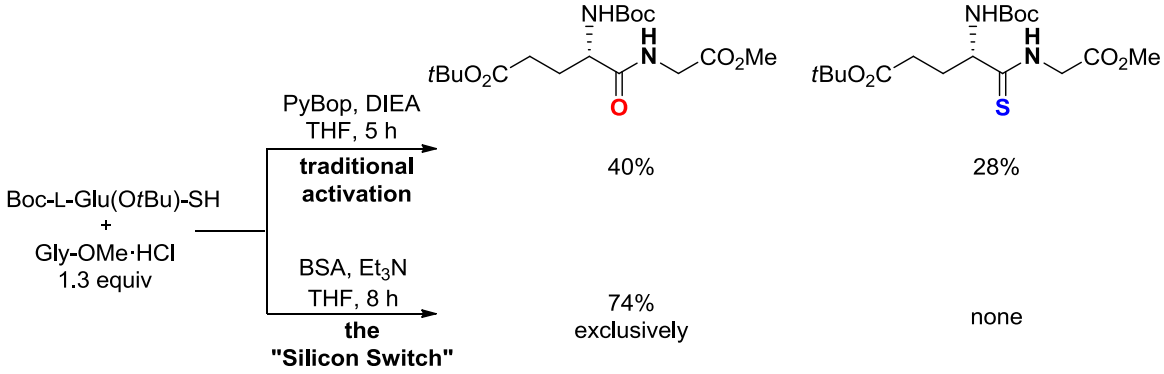


entry	amine	silylating reagent	Solvent	base	time (h)	yield (%)[b]	LL/DL ratio[c]
1	L-Val-OMe	BSA	THF	NEt_3	3	50	87.5:12.5
2	L-Val-OMe	BSA	DCM	NEt_3	3	46	91.3:8.7
3	L-Val-OMe	BSA	CH_3CN	NEt_3	3	48	93.3:6.7
4	L-Val-OMe	BSA	CH_3CN	NMM	3	44	95.0:5.0
5	L-Val-OMe	BSA	CH_3CN	DIEA	3	46	95.7:4.3
6	L-Val-OMe	BSA	CH_3CN	DIEA	15	74	95.6:4.4
7[d]	L-Val-OMe	1.1 equiv $PhSiH_2Cl$	CH_3CN	DIEA	15	50	96.2:3.8
8[e]	L-Val-OMe	1.1 equiv $PhSiH_2Cl$	CH_3CN	DIEA	15	55	97.0:3.0
9	Gly-OEt	BSA	CH_3CN	DIEA	18	81	95.8:4.2
10[d]	Gly-OEt	1.1 equiv $PhSiH_2Cl$	CH_3CN	DIEA	15	60	96.8:3.2
11[e]	Gly-OEt	1.1 equiv $PhSiH_2Cl$	CH_3CN	DIEA	15	73	97.0:3.0

[a] General procedure: A solution of 1 equiv of the *N*-protected α-amino thiol acid (from the corresponding 9-fluorenylmethyl thiol esters via piperidine deprotection-HCl acidification) and 1 equiv of BSA in THF was added to a solution of 1.3 equiv of the amino acid hydrochloride salt and 1.3 equiv of triethylamine or diisopropylethylamine (DIEA) in THF. The mixture was then stirred at room temperature for 3 or 15 h. [b] Isolated yield; [c] the epimerization ratio was determined by chiral HPLC. [d] To a THF solution of 1 equiv dipeptidic thiol acid, 1.1 equiv $PhSiH_2Cl$, 1.3 equiv amino ester hydrochloride salt was added 2.3 equiv DIEA stirred at room temperature for 15 h. [e] To a THF solution of 1 equiv of dipeptidic thiol acid, 1.1 equiv $PhSiH_2Cl$, 2 equiv amino acid ester hydrochloride salt was added 3.0 equiv DIEA stirred at room temperature for 15 h.

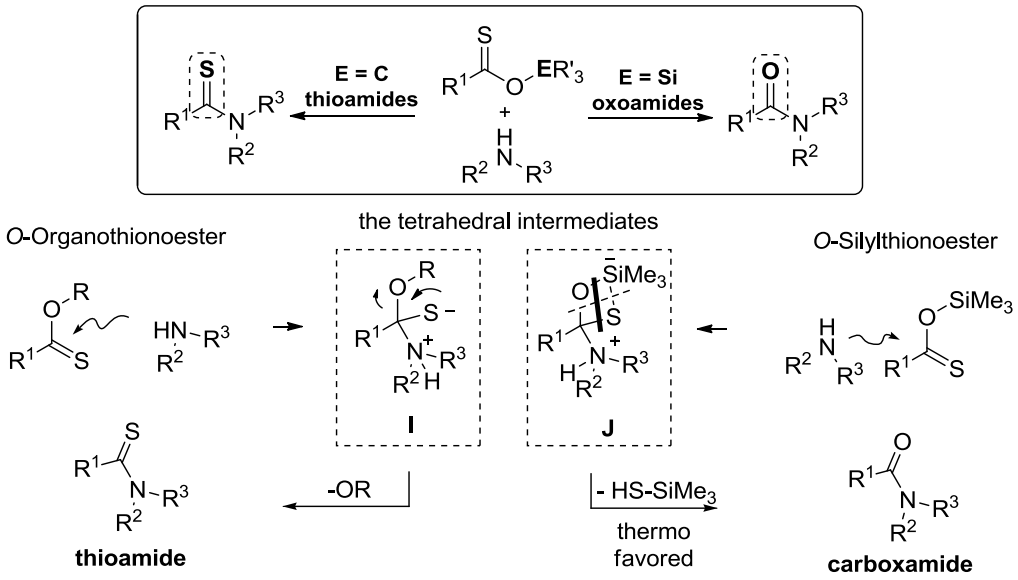
A comparison of the reaction of Boc-L-Glu(O-*t*Bu)-SH and Gly-OMe using a traditional peptide-coupling protocol with the new silylative activation is both illustrative and compelling, demonstrating the unique reactivity of the *O*-silylthionoester approach to peptide construction. A 1:1.3 mixture of Boc-L-Glu(O-*t*Bu)-SH and Gly-OMe·HCl was first exposed to Et_3N to liberate the amine and then to 1 equiv of BSA in THF at room temperature to produce the peptide in 74% yield within 8 h. In contrast, traditional activation of the thiol acid with PyBop and diisopropylethylamine (DIEA) gave a mixture of the desired peptide (40%) and the thioamide (28%), as depicted in **Scheme 1.24**.

Scheme 1.24 Silylative versus Traditional Activation of a Thiol Acid



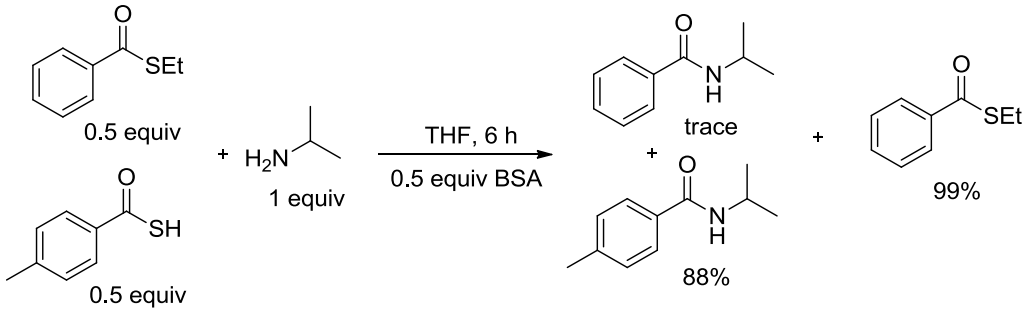
The origin of the different reactivities of *O*-alkylthionoesters and *O*-silylthionoesters toward amines is suggested in **Scheme 1.25**. The mechanism of the known reaction of *O*-alkylthionoesters with amines to give thioamides is straightforward.[30] Attack by the nucleophilic amine at the C=S bond of the thionoester generates tetrahedral intermediate **I**, which can only collapse to create a thioamide or revert back to starting materials. Without cleavage of the strong R-O bond of **I** in **Scheme 1.25**, an oxoamide cannot be formed from the tetrahedral intermediate generated from the *O*-alkylthionoesters. In contrast, however, the tetrahedral intermediate formed by attack of an amine on an *O*-silylthionoester can participate in a tautomeric migration of silicon from oxygen to sulfur, possibly via the pentavalent Si intermediate **J**.

Scheme 1.25 S- to *O*-Silylative Switch Amidation Mechanism



In other control studies, PhCOSEt was fully intact after treatment with *i*-$PrNH_2$ in THF for 24 h at room temperature, both in the presence and in the absence of BSA, reaction conditions under which the *O*-silylthionoester is converted completely to the amide. Furthermore, treating 0.5 equiv of PhCOSEt and 0.5 equiv of 4-$CH_3C_6H_4COSH$ with 0.5 equiv of BSA and 1 equiv of *i*-$PrNH_2$ in THF at room temperature provided the "unscrambled" reaction product (4-$CH_3C_6H_4CONH$*i*-Pr) in 88% isolated yield with recovery of PhCOSEt in 99% yield, further supporting the mechanistic framework suggested herein (**Scheme 1.26**).

Scheme 1.26 Compared Reactivity between *O*-Thionoester and Thiol Ester



1.3 Conclusion

In conclusion, *O*-silylthionoesters, generated *in situ* from thiol acids via a straightforward and simple sequence of *S*-silylation followed by *S*-to-*O* silatropy were shown to react with 1° and 2° amines in a mild, ambient temperature construction of amides and mono-, di-, and tripeptides. Both unhindered and highly hindered substrates participated in room temperature amide and peptide bond formation, although longer reaction times were required for the sterically encumbered entities. Stereocenter epimerization was absent for most substrates, and very low in substrates known to be problematic in traditional peptide coupling protocols. Although a thorough study of the influence of the nature of the silane on the reaction rate and epimerization level of the amide/peptide coupling has yet to be undertaken, a single example probing variation of the silane structure suggests that unwanted epimerization can be positively influenced by the nature of the silylating agent. At present, this straightforward first-generation trimethylsilylation protocol combined with the unique reactivity of the *O*-silylthionoesters toward 1° and 2° amines to generate oxoamides provides the simplest means of activating a thiol acid for peptide bond formation at neutral pH.[23] The tolerance of hydroxylic and phenolic groups to the reaction conditions holds promise for extension of the silylative protocol to glycopeptide synthesis.

1.4 Experimental

1.4.1 General Experimental

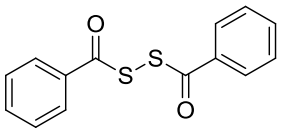
^{1}H and ^{13}C NMR spectra were recorded on Inova 400 MHz spectrometers in deuteriochloroform ($CDCl_3$) with the solvent residual peak as internal reference unless otherwise stated ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported (Hz); integration is provided. Infrared spectra were recorded on a Nicolet 380 FT-IR spectrometer with a diamond plate. Peaks

are reported (cm^{-1}) with the following relative intensities: vs (very strong), s (strong), m (medium), w (weak), and br (broad). Optical rotation values were measured at 20 ˚C on a Perkin Elmer Model 341 polarimeter with chloroform ($CHCl_3$) as solvent. Uncalibrated melting points were taken on a *Thomas-Hoover* melting point apparatus in open capillary tubes. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator. Visualization was accomplished by UV light, or with solutions of ninhydrin in ethanol or *p*-anisaldehyde in ethanol. Purification by chromatography was performed using Whatman 60Å 230-400 mesh SiO_2 with compressed air as a source of positive pressure. HPLC analyses were carried out using an Agilent 1100 system with a quaternary pump. Separations were achieved on DAICEL Chiralpak AS-RH or Chiralcel OD-RH, OJ-RH column. Solvents for reactions and chromatography were reagent grade and used as received. "Brine" refers to a saturated aqueous solution of NaCl. Solutions of NH_4Cl, $NaHCO_3$ refer to saturated aqueous solutions. Solvents used as reaction media were purchased in > 99% purity without further purification, unless otherwise specified.

1.4.2 Starting Materials

All protected amino acids, thiobenzoic acid, thioacetic acid, primary and secondary amines, 9-fluorenemethanol, *N*,*N*-dimethylaminopyridine (DMAP), *N*-phenyltriazolinedione, 1-admantanecarboxylic acid, *N*,*O*-bis(trimethylsilyl)acetamide (BSA), *N*,*N'*-dicyclohexylcarbodiimide (DCC), *N*,*N*-diisopropylethylamine (DIEA), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), chlorophenylsilane, 4-toluenesulfonyl chloride, pyridine, diisobutylaluminium hydride (1.0 M in hexane), potassium thioacetate were purchased from Sigma-Aldrich and used without further purification. Thionicotinic acid was purchased from TCI.

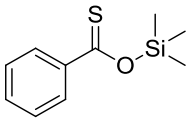
Benzoyldisulfide[31]



The disulfide was prepared from thiobenzoic acid (0.32g, 2.28 mmol) using Elemes's method.[31] Crystallization of the reaction mixture using 1 : 3 ethyl acetate/hexanes to afford the desired product as a white solid (376 mg, 60% yield). Mp 128-130 ^{o}C [Lit.[31] 132 ^{o}C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 1.2 Hz, 8.0 Hz, 2H), 7.66 (tt, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.53 (dt, *J* = 1.6 Hz, 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 135.5, 134.6, 129.2, 128.4; IR (cm^{-1}): 3368(w), 3063(w), 1699(m), 1679(vs), 1579(m), 1444(s), 1203(vs), 881(vs), 769(m), 673(m).

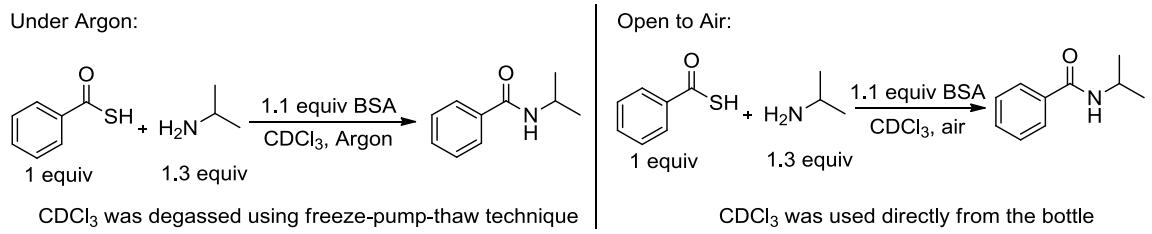
Control Experiments

***S*-(Trimethylsilyl)benzothioate**[32]



N,*O*-bis(trimethylsilyl)acetamide (BSA, 0.1 mL, 0.42 mmol) was added to a 10 mL flask containing thiobenzoic acid (0.045 mL, 0.38 mmol) in $CDCl_3$ (0.8 mL). The solution was allowed to stir at room temperature for 5 minutes and monitored by ^{1}H NMR. The proton NMR showed the disappearance of thiobenzoic acid resonances and the appearance of *S*-(trimethylsilyl) benzothioate resonances. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 2H), 0.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 139.6, 133.0, 128.9, 128.1, 0.3.

$CDCl_3$ Reactions, Degassed *vs.* Open to Air

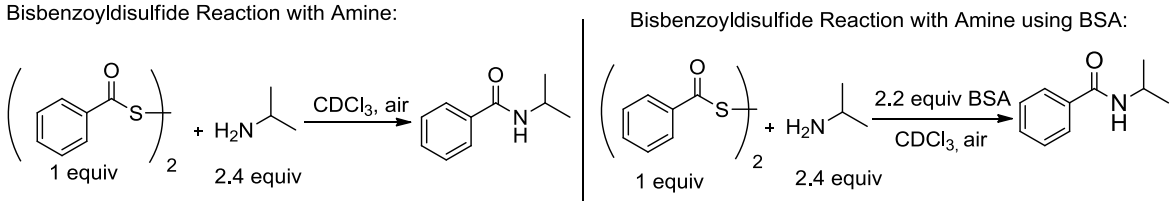


$CDCl_3$ degassed reaction under argon: A sealed 10 mL flask was filled with argon. In between the addition of reagents, it was flushed several times with argon. Thiobenzoic acid (0.10 mL, 0.87 mmol), 4,4'-di-*tert*-butyl-1,1'-biphenyl (internal standard, 26 mg, 0.096 mmol), $CDCl_3$ (1.8 mL) degassed by freeze-pump-thaw technique, BSA (0.23 mL, 0.95 mmol) and isopropyl amine (0.092 mL, 1.13 mmol) were added to the flask sequentially. Then, 0.6 mL of the reaction mixture was transferred to a sealed NMR tube filled with argon. Proton NMR spectra were taken at different time points and the yield of the formed amide was determined based on the ratio to the internal standard (amide *ortho* protons chemical shift at 7.74 ppm; internal standard 9 CH_3 chemical shift at 1.36 ppm).

$CDCl_3$ reaction open to air: To a stirred solution of thiobenzoic acid (0.11 mL, 0.93 mmol), 4,4'-di-*tert*-butyl-1,1'-biphenyl (internal standard, 28 mg, 0.10 mmol) in $CDCl_3$ (1.9 mL) were added BSA (0.25 mL, 1.02 mmol) and isopropyl amine (0.098 mL, 1.20 mmol) sequentially at room temperature. Proton NMR spectra of the reaction mixture were taken at different time points and the yield of the formed amide was determined based on the ratio to the internal standard (amide *ortho* protons chemical shift at 7.74 ppm; internal standard 9 CH_3 chemical shift at 1.36 ppm).

The rates of the two reactions are depicted in **Chart 1.1**.

Bisbenzoyldisulfide Control Experiments

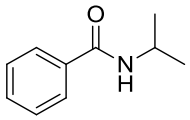


$CDCl_3$ Reaction of Bisbenzoyldisulfide without BSA: To a stirred solution of bisbenzoyldisulfide (80 mg, 0.29 mmol), 4,4'-di-*tert*-butyl-1,1'-biphenyl (internal standard, 18 mg, 0.065 mmol) in $CDCl_3$ (0.6 mL) was added isopropyl amine (0.061 mL, 0.70 mmol) at room temperature. Proton NMR spectra of the reaction mixture were taken at different time points and the yield of the formed amide was determined based on the ratio to the internal standard (amide *ortho* protons chemical shift at 7.74 ppm; internal standard 9 CH_3 chemical shift at 1.36 ppm).

$CDCl_3$ Reaction of Bisbenzoyldisulfide with BSA: To a stirred solution of bisbenzoyldisulfide (85 mg, 0.31 mmol), 4,4'-di-*tert*-butyl-1,1'-biphenyl (internal standard, 17 mg, 0.069 mmol) in $CDCl_3$ (0.6 mL) were added BSA (0.084 mL, 0.34 mmol) and isopropyl amine (0.058 mL, 0.75 mmol) sequentially at room temperature. Proton NMR spectra of the reaction mixture were taken at different time points and the yield of the formed amide was determined based on the ratio to the internal standard (amide *ortho* protons chemical shift at 7.74 ppm; internal standard 9 CH_3 chemical shift at 1.36 ppm).

The rate of the two reactions was shown in **Chart 1.2**.

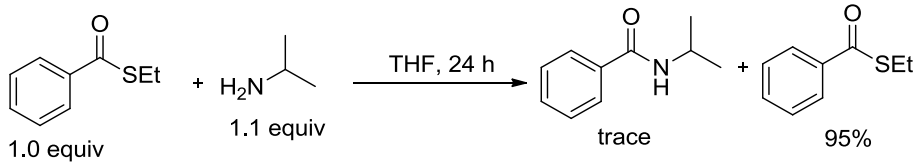
***N*-Isopropylbenzamide**[33]



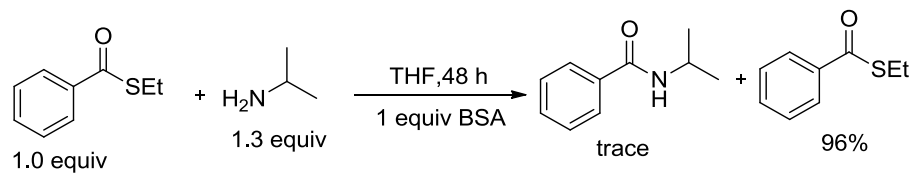
Reaction with BSA: To a stirred solution of thiobenzoic acid (0.077 mL, 0.65 mmol) in THF (1.3 mL) were added BSA (0.16 mL, 0.65 mmol) and isopropyl amine (0.069 mL, 0.85 mmol) sequentially. After 3 h, the reaction was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, it was purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired product as a white solid 74.0 mg (70% yield). R_f = 0.31, 25% EtOAc/hexanes. Mp 100-102 ^oC [Lit.[33] 101 ^oC]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 1.6 Hz, 6.8 Hz, 2H), 7.47 (tt, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.42 (dt,

J = 1.6 Hz, 7.2 Hz, 2H), 5.99 (br s, 1H), 4.28 (septet, *J* = 6.8 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 135.1, 131.4, 128.7, 127.0, 42.0, 23.0; IR (neat, cm^{-1}): 3291(m), 2970(w), 2931(w), 1630(s), 1531(s), 1346(m), 1288(m), 692(vs).

Control Reaction without BSA: To a solution of thiobenzoic acid (0.11 mL, 0.98 mmol) in THF (2 mL) was added isopropyl amine (0.10 mL, 1.27 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, the crude mixture was purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired product as a white solid 22.0 mg (14% yield).

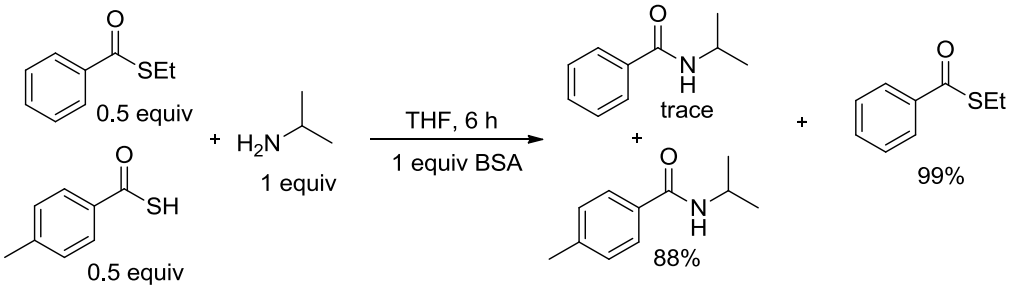


Reaction between Thiol Ester and Amine without BSA: To a solution of thiobenzoic ethyl ester PhCOSEt (0.80 mmol) in THF (1.6 mL) was added isopropyl amine (0.085 mL, 1.04 mmol) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, ^{1}H NMR of the crude mixture showed trace formation of *N*-isopropylbenzamide. After purification by chromatography (silica gel, 19:1 hexanes: EtOAc), PhCOSEt was recovered as a colorless oil (126 mg, 95% yield).



Reaction between Thiol Ester and Amine with BSA: To a solution of thiobenzoic ethyl ester PhCOSEt (0.78 mmol) in THF (1.6 mL) was added BSA (0.19 mL, 0.78 mmol) and isopropyl

amine (0.083 mL, 1.01 mmol). Then the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, ^{1}H NMR of the crude mixture showed trace formation of *N*-isopropylbenzamide. After purification by chromatography (silica gel, 19:1 hexanes: EtOAc), PhCOSEt was recovered as a colorless oil (125 mg, 96% yield).

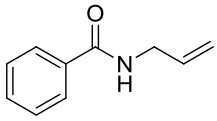


Competitive Reaction between Thiol Acid and Thiol Ester: To a solution of thiobenzoic ethyl ester PhCOSEt (0.24 mmol) and 4-methylthiobenzoic acid 4-MePhCOSH (0.24 mmol) in THF (0.6 mL) was added BSA (0.060 mL, 0.24 mmol) and isopropyl amine (0.040 mL, 0.48 mmol). Then the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, ^{1}H NMR of the crude mixture showed trace formation of *N*-isopropylbenzamide. After purification by chromatography (silica gel, 19:1 hexanes: EtOAc, followed by 3:1 hexanes: EtOAc), PhCOSEt was recovered as a colorless oil 39.5 mg (99%) and *N*-isopropyl-4-methylbenzamide as a white solid 37.4 mg (88% yield). R_f = 0.30, 25% EtOAc/hexanes. Mp 134 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.01 (br s, 1H), 4.26 (septet, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 141.8, 132.3, 129.3, 127.0, 42.0, 23.1, 21.6; IR (neat, cm^{-1}): 3303(m), 2972(w), 2931(w), 1628 (s), 1532(s), 1346(m), 1285(m), 1172(w).

General Procedure for the Synthesis of Simple Amides

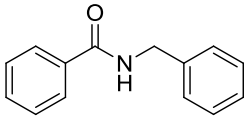
To a stirred solution of thiol acid (0.5 mmol), and BSA (0.5 mmol) in THF (1 mL) was added the amine (0.65 mmol). The reaction mixture was stirred for 3-24 h at room temperature then diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, the reaction residue was purified by chromatography to afford the desired amide.

***N*-Allylbenzamide**[34]



Prepared according to the general procedure from thiobenzoic acid (83 mg, 0.60 mmol), stirred at room temperature for 3 h and purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired product as a colorless oil 89 mg (91% yield). R_f = 0.26, 25% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 1.6 Hz, 7.6 Hz, 2H), 7.48- 7.44 (m, 1H), 7.37 (dt, *J* = 1.2 Hz, 7.2 Hz, 2H), 6.72 (br s, 1H), 5.94-5.84 (m, 1H), 5.21 (dd, *J* = 17.2 Hz, 1.2 Hz, 1H), 5.13 (ddd, *J* = 10.0 Hz, 1.2 Hz, 1.2 Hz, 1H), 4.05-4.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 134.7, 134.4, 131.7, 128.7, 127.2, 116.7, 42.6; IR (cm^{-1}): 3305(br), 3066(w), 1634(s), 1532(vs), 1488(m), 1291(m), 692(vs).

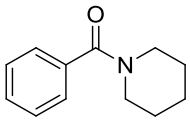
***N*-Benzylbenzamide**[35]



Prepared according to the general procedure from thiobenzoic acid (83 mg, 0.60 mmol), stirred at room temperature for 3 h and purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired product as a white solid 114 mg (89% yield). R_f = 0.36, 25% EtOAc/hexanes. Mp 96-97 °C [Lit.[33] 98-104 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 0.8 Hz, 7.6 Hz, 2H), 7.46-7.42 (m, 1H), 7.36 -7.24 (m, 7H), 7.03 (br s, 1H), 4.54 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100

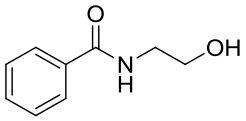
MHz, $CDCl_3$) δ 167.8, 138.6, 134.6, 131.7, 128.9, 128.7, 128.0, 127.7, 127.3, 44.2; IR (cm^{-1}): 3337(m), 2901(s), 2847(m), 1630(s), 1531(vs), 1450(s), 1283(s), 1001(m), 716(vs).

***N*-Benzoylpiperidine**[36]



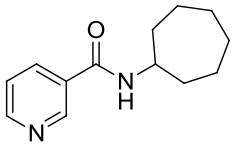
Prepared according to the general procedure from thiobenzoic acid (83 mg, 0.60 mmol), stirred at room temperature for 5 h and purified by chromatography (silica gel, 2:1 hexanes: EtOAc) to afford the desired product as a colorless oil 84 mg (74% yield). R_f = 0.40, 50% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (br s, 5H), 3.67 (br s, 2H), 3.30 (br s, 2H), 1.64-1.47 (br m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 25.8, 26.7, 43.3, 48.9, 127.0, 128.6, 129.5, 136.7, 170.5; IR (cm^{-1}): 2934(m), 2852(m), 1625(vs), 1428(s), 1273(s), 1109(m),707(s).

***N*-(2-Hydroxyethyl)benzamide**[37]



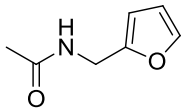
Prepared according to the general procedure from thiobenzoic acid (81 mg, 0.59 mmol), stirred at room temperature for 5 h and purified by chromatography (silica gel, 12:1 DCM: methanol) to afford the desired product as a white solid 74 mg (76% yield). R_f = 0.44, 10% MeOH/dichloromethane. Mp 58-59 °C [Lit.[37] 54-55 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.8 Hz, 1.6 Hz, 2H), 7.47-7.43 (m, 1H), 7.35 (dt, *J* = 1.6 Hz, 7.6 Hz, 2H), 7.07 (br s, 1H), 3.76-3.74 (m, 2H), 3.67 (br s, 1H), 3.57-3.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 134.3, 131.9, 128.8, 127.2, 62.1, 43.0; IR (cm^{-1}): 3302(br), 2938(w), 2876(w), 1635(s), 1537(vs), 1325(s), 1291(s), 1055(m), 1036(vs), 692(s).

***N*-Cycloheptylnicotinamide**



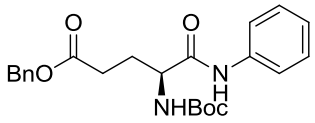
Prepared according to the general procedure from pyridine-3-carbothioic *S*-acid (102 mg, 0.73 mmol), stirred at room temperature for 24 h and purified by chromatography (silica gel, 4:3 hexanes: EtOAc) to afford the desired product as a white solid 112 mg (70% yield). R_f = 0.20, 75% EtOAc/hexanes. Mp 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.66-8.63 (m, 1H), 8.06 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.33 (dd, *J* = 4.8 Hz, 8.0 Hz, 1H), 6.32 (br s, 1H), 4.14-4.12 (m, 1H), 2.04-1.99 (m, 2H), 1.68-1.51 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 152.1, 148.1, 135.3, 130.9, 123.6, 51.4, 35.3, 28.2, 24.3; IR (cm^{-1}): 3317(m), 2930(s), 2859(m), 1630(vs), 1532(vs), 1322(m), 1026(m), 828(m), 709(vs), 672(s); HRMS (APCI$^+$) Calcd for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1492. Found: 219.1495.

***N*-(Furan-2-ylmethyl)acetamide**[38]



Prepared according to the general procedure from thioacetic acid (76 mg, 1.0 mmol), stirred at room temperature for 3 h and purified by chromatography (silica gel, 1:1 hexanes: EtOAc) to afford the desired product as a yellow oil 114 mg (82% yield). R_f = 0.25, 75% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.26 (m, 1H), 6.79 (br s, 1H), 6.24-6.23 (m, 1H), 6.14-6.12 (m, 1H), 4.31 (d, *J* = 5.6 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 151.6, 142.2, 110.6, 107.5, 36.6, 23.1; IR (cm^{-1}): 3271(br), 3079(w), 1649(vs), 1545(vs), 1286(s), 1147(m), 1017(m), 734(s).

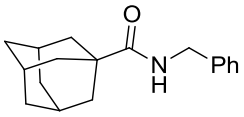
***N*-Phenyl-*N*-α-*tert*-butoxycarbonyl-γ-*tert*-benzyl ester L-glutamide**



Prepared according to the general procedure from (*S*)-5-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)pentanethioic *S*-acid (104 mg, 0.30 mmol), stirred at room temperature for 24 h and purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired product as a white solid 85 mg (69% yield, HPLC of the crude reaction mixture showed no detectable epimerization). R_f = 0.38, 25% EtOAc/hexanes. Mp 101-104 °C; $[\alpha]^{20}_{D}$ -19.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.37-7.32 (m, 5H), 7.26 (t, *J* = 7.2 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 5.63 (d, *J* = 2.8 Hz, 1H), 5.11 (AB quartet, *J* = 12.4 Hz, 2H), 4.40 (br s, 1H), 2.65-2.49 (m, 2H), 2.23 (app sextet, *J* = 6.8 Hz, 1H), 2.06 (app sextet, *J* = 7.2 Hz, 1H), 1.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 170.3, 156.4, 137.9, 135.8, 129.1, 128.8, 128.6, 128.5, 124.6, 120.2, 80.6, 66.9, 54.6, 30.8, 28.5, 27.9; IR (cm^{-1}): 3315(m), 3313(m), 2977(w), 2928(w), 1723(s), 1686(m), 1666(vs), 1516(vs), 1445(s), 1157(vs), 1072(m), 754(s); HRMS (ESI^+) Calcd for $C_{23}H_{28}N_2O_5$ $[M+Na]^+$: 435.1890. Found: 435.1895.

HPLC OJ-RH column: 50% acetonitrile in water over 20 min with a flow rate of 0.75 mL/min and 254 nm UV detection, retention time = 8.03 min (Boc-DL-Glu(OBn)-NH-Ph with retention times of 8.39 min and 10.51 min).

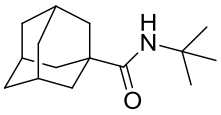
***N*-Benzyladamantane-1-carboxamide**[39]



Prepared according to the general procedure from adamantane-1-carbothioic *S*-acid (94 mg, 0.48 mmol), stirred at room temperature for 5 h and purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired product as a white solid 84 mg (65% yield). R_f = 0.40, 25% EtOAc/hexanes. Mp 168-170 °C [Lit.[39] 172-173 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.29-7.24 (m, 3H), 5.89 (br s, 1H), 4.43 (d, *J* = 5.2 Hz, 2H), 2.04 (br m, 3H), 1.92-1.83 (m, 6H), 1.76-1.68 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 138.9, 128.9, 127.9, 127.6, 43.5,

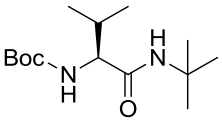
40.9, 39.5, 36.7, 28.3; IR (cm^{-1}): 3336(m), 2901(s), 2847(s), 1631(s), 1530(vs), 1450(s), 1283(s), 1001(m), 716(s), 659(s).

***N*-(*tert*-Butyl)adamantane-1-carboxamide**[40]



Prepared according to the general procedure from adamantane-1-carbothioic *S*-acid (80 mg, 0.41 mmol), stirred at room temperature for 23 h and purified by chromatography (silica gel, 7:1 hexanes: EtOAc) to afford the desired product as a white solid 78 mg (81% yield). R_f = 0.64, 25% EtOAc/hexanes. Mp 175-178 °C [Lit.[40] 188-189 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (br s, 1H), 2.01 (br s, 3H), 1.81-1.78 (m, 6H), 1.73-1.64 (m, 6H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 50.7, 41.1, 39.6, 36.7, 29.0, 28.4; IR (cm^{-1}): 3328(m), 2899(vs), 2849(s), 1635(vs), 1533(vs), 1446(s), 1286(s), 1229(m), 637(m).

***N*-*tert*-Butoxycarbonyl-L-valyl-*tert*-butamide**[41]



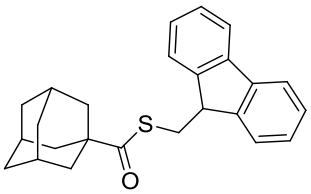
Prepared according to the general procedure Boc-L-Val-SH (70 mg, 0.30 mmol), stirred at room temperature for 24 h and purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired product as a white solid 58 mg (71% yield, HPLC of the crude reaction mixture showed no detectable epimerization). R_f = 0.54, 33% EtOAc/hexanes. Mp 118-120 °C [Lit.[41] 120-121 °C]; $[\alpha]^{20}_D$ -18.9 (*c* 1.0, MeOH) [Lit. $[\alpha]^{25}_D$ -19.0 (*c* 1.0, MeOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (br s, 1H), 5.07 (d, *J* = 6.8 Hz, 1H), 3.70 (dd, *J* = 6.8 Hz, 8.4 Hz, 1H), 2.08-2.00 (m, 1H), 1.43 (s, 9H), 1.33 (s, 9H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 156.2, 79.9, 60.7, 51.6, 31.3, 28.9, 28.5, 19.5, 18.2; IR (cm^{-1}): 3297(br), 2968(w), 2931(w), 1683(m), 1650(vs), 1530(s), 1363(m), 1251(m), 1171(s), 1019(m).

HPLC AS-RH column: 25% acetonitrile in water over 20 min with a flow rate of 0.75 mL/min and 210 nm UV detection, retention time = 12.54 min (Boc-DL-Val-NH-C(CH_3)$_3$ with retention times of 12.21 min and 14.42 min).

General Procedure for the Synthesis of 9-Fluorenylmethyl Thioesters of Amino Acids

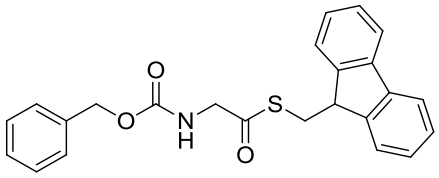
To the 2.0 M solution of 1-adamantanecarboxylic acid (1 equiv) or *N*-*tert*-butoxycarbonyl-α-amino acid (1 equiv), 9-fluorenylmethylthiol (1.2 equiv) and DMAP (0.1 equiv) in dichloromethane, was added a 2.0 M solution of DCC (1.1 equiv) in dichloromethane at 0 °C. The suspension was allowed to stir at 0 °C for one hour and then overnight at room temperature. The white solid was removed by filtration and washed with dichloromethane. The filtrate was concentrated under vacuum and purified by chromatography to afford the corresponding 9-fluorenylmethyl thioesters.

Adamantane 9-fluorenylmethyl thioester.



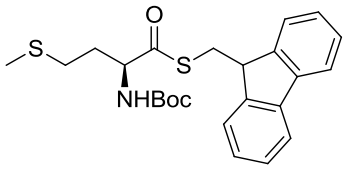
Prepared according to the general procedure from adamantane-1-carboxylic acid (108 mg, 0.6 mmol) and purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired product as a colorless foam 202 mg (90% yield). R_f = 0.71, 16% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.30 (dt, *J* = 1.2 Hz, 7.4 Hz, 2H), 4.12 (t, *J* = 6.0 Hz, 1H), 3.44 (d, *J* = 6.0 Hz, 2H), 2.02 (br m, 3H), 1.85-1.84 (m, 6H), 1.74-1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 146.0, 141.3, 127.8, 127.2, 125.0, 120.0, 48.7, 47.3, 39.4, 36.6, 31.7, 28.4; IR (cm^{-1}): 2902(s), 2848(m), 1671(s), 1449(s), 1139(w), 987(w), 737(vs); HRMS (ESI^+) Calcd for $C_{25}H_{27}OS$ $[M+H]^+$: 375.1777. Found: 375.1779.

***N*-Benzyloxycarbonyl-glycine 9-fluorenylmethyl thioester**.



Prepared according to the general procedure from Cbz-Gly-OH (172 mg, 0.82 mmol) and purified by chromatography (silica gel, 7:1 hexanes: EtOAc) to afford the desired product as colorless foam 309 mg (93% yield). R_f = 0.22, 16% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.42-7.30 (m, 9H), 5.32 (t, *J* = 6.0 Hz, 1H), 5.13 (s, 2H), 4.17 (t, *J* = 5.8 Hz, 1H), 4.05 (d, *J* = 6.0 Hz, 2H), 3.55 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 156.3, 145.4, 141.3, 136.3, 128.8, 128.5, 128.4, 128.0, 127.4, 124.9, 120.2, 67.5, 50.9, 46.8, 32.3; IR (cm^{-1}): 3325(br), 3034(w), 2927(w), 1688(vs), 1509(m), 1448(m), 1235(s), 1156(m), 960(m), 736(vs), 696(m); HRMS (ESI^+) Calcd for $C_{24}H_{21}NO_3S$ $[M+Na]^+$: 426.1134. Found: 426.1143.

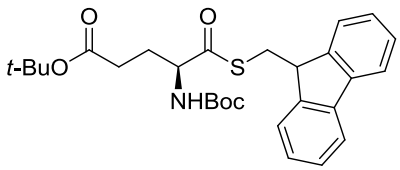
***N*-*tert*-Butoxycarbonyl-L-methioine 9-fluorenylmethyl thioester**.



Prepared according to the general procedure Boc-L-Met-OH (189 mg, 0.75 mmol) and purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired product as a white solid 323 mg (97% yield). R_f = 0.37, 16% EtOAc/hexanes. Mp 88-90 °C; $[\alpha]^{20}_D$ -35.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (ddt, *J* = 1.2 Hz, 2.4 Hz, 7.6 Hz, 2H), 5.06 (d, *J* = 8.8 Hz, 1H), 4.37 (app dt, *J* = 5.2 Hz, 8.0 Hz, 1H), 4.19 (t, *J* = 5.4 Hz, 1H), 3.60 (dd, *J* = 5.6 Hz, 14.0 Hz, 1H), 3.54 (dd, *J* = 5.8 Hz, 13.4 Hz, 1H), 2.35-2.32 (m, 2H), 2.03 (s, 3H), 1.94-1.86 (m, 1H), 1.72-1.63 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 155.2, 145.3, 141.4, 128.0, 127.3, 124.9, 120.1, 80.6, 60.1, 46.9, 32.2, 32.1, 29.9, 28.5, 15.6; IR (cm^{-1}): 3350(w), 2971(w), 2918(w), 1675(vs),

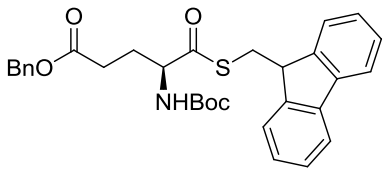
1504(s), 1446(m), 1364(m), 1250(m), 1159(m), 860(w), 734(vs); HRMS (ESI^+) Calcd for $C_{24}H_{29}NO_3S_2$ $[M+Na]^+$: 466.1481. Found: 466.1490.

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-butyl ester L-glutamine 9-fluorenylmethyl thioester**.



Prepared according to the general procedure from Boc-Glu(O*t*Bu)-OH (203 mg, 0.65 mmol) and purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired product as a white solid 314 mg (97% yield). R_f = 0.45, 16% EtOAc/hexanes. Mp 94-96 °C; $[\alpha]^{23}_D$ -32.4 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.29 (ddt, *J* = 1.2 Hz, 2.4 Hz, 7.6 Hz, 2H), 5.20 (d, *J* = 8.0 Hz, 1H), 4.26 (dt, *J* = 4.8 Hz, 8.4 Hz, 1H), 4.16 (t, *J* = 5.8 Hz, 1H), 3.54 (dd, *J* = 5.6 Hz, 13.6 Hz, 1H), 3.48 (dd, *J* = 6.0 Hz, 13.2 Hz, 1H), 2.21-2.16 (m, 2H), 1.98-1.89 (m, 1H), 1.78-1.69 (m, 1H), 1.45 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 172.4, 155.4, 145.5, 141.4, 127.9, 127.3, 125.0, 120.1, 81.1, 80.4, 60.6, 46.9, 32.2, 31.7, 28.5, 28.3, 27.5; IR (cm^{-1}): 3303(br), 2976(w), 2930(w), 1719(vs), 1693(vs), 1524(m), 1448(m), 1366(m), 1248(s), 1147(vs), 1022(m), 736(vs); HRMS (ESI^+) Calcd for $C_{28}H_{35}NO_5S$ $[M+Na]^+$: 520.2128. Found: 520.2134.

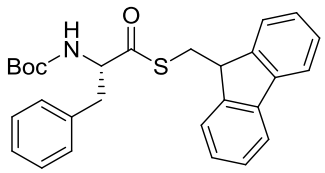
***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-benzyl ester L-glutamine 9-fluorenylmethyl thioester**.



Prepared according to the general procedure from Boc-Glu(OBn)-OH (294 mg, 0.85 mmol) and purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired product as a white solid 419 mg (96% yield). R_f = 0.39, 16% EtOAc/hexanes. Mp 108-110 °C; $[\alpha]^{20}_D$ -24.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.36-7.26 (m, 9H), 5.11 (s, 2H), 5.09 (br s, 1H), 4.28 (dd, *J* = 8.0 Hz, 13.2 Hz, 1H), 4.17 (t, *J* =

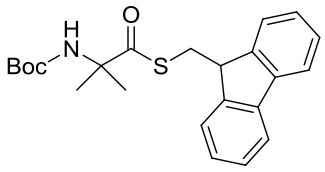
5.2 Hz, 1H), 3.57 (dd, *J* = 5.0 Hz, 13.4 Hz, 1H), 3.52 (dd, *J* = 6.4 Hz, 14.4 Hz, 1H), 2.34-2.21 (m, 2H), 2.03-1.94 (m, 1H), 1.80-1.71 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 172.8, 155.3, 145.3, 141.4, 135.9, 128.8, 128.6, 128.5, 128.0, 127.3, 124.9, 120.1, 80.6, 66.8, 60.2, 46.9, 32.1, 30.3, 28.5, 27.7; IR (cm^{-1}): 3348(br), 2930(w), 1718(s), 1678(vs), 1499(s), 1447(m), 1250(m), 1164(s), 1148(s), 1080(m), 734(vs), 698(s), 622; HRMS (ESI^+) Calcd for $C_{31}H_{33}NO_5S$ $[M+Na]^+$: 554.1972. Found: 554.1978.

***N*-*tert*-Butoxycarbonyl-L-phenylalanine 9-fluorenylmethyl thioester**.



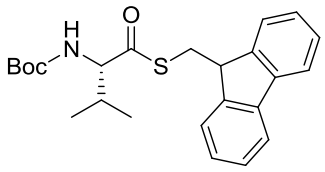
To a stirred solution of *N*-(tert-butoxycarbonyl)-L-phenylalanine (133 mg, 0.50 mmol), 9-fluorenyl-methylthiol (127 mg, 0.60 mmol) in DMF (5 mL) were added (benzotriazol-1-yloxy)tripyrrolidino phosphonium hexafluorophosphate (PyBop, 390 mg, 0.75 mmol) and diisopropylethylamine (DIEA, 162 mg, 1.25 mmol) at 0 ^oC sequentially. The reaction mixture was stirred at 0 °C for 30 min and warmed up to room temperature and stirred for 2.5 h. The reaction solution was washed with water and brine, dried with anhydrous Na_2SO_4, filtrated and then concentrated under reduced pressure. Purification by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired product as a colorless foam 225 mg (98% yield). R_f = 0.45, 16% EtOAc/hexanes. $[\alpha]^{20}_D$ -35.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.27-7.23 (m, 3H), 7.07 (d, *J* = 6.4 Hz, 2H), 4.82 (d, *J* = 8.4 Hz, 1H), 4.58 (app dt, *J* = 6.0 Hz, 8.0 Hz, 1H), 4.17 (t, *J* = 5.8 Hz, 1H), 3.51 (d, *J* = 6.0 Hz, 2H), 3.00 (dd, *J* = 5.2 Hz, 14.4 Hz, 1H), 2.87 (dd, *J* = 7.8 Hz, 14.4 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 155.2, 145.6, 145.5, 141.3, 135.9, 129.5, 128.9, 127.9, 127.3, 125.1, 120.1, 80.6, 61.3, 46.8, 38.4, 32.6, 28.5; IR (cm^{-1}): 3338(w), 2976(w), 2928(w), 1681(s), 1494(m), 1449(m), 1365(m), 1247(m), 1160(s), 738(vs), 697(m); HRMS (ESI^+) Calcd for $C_{28}H_{29}NO_3S$ $[M+Na]^+$: 482.1760. Found: 482.1774.

***N-tert*-Butoxycarbonyl-α-aminoisobutyryl 9-fluorenylmethyl thioester**[17]



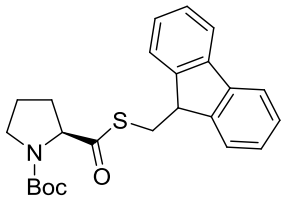
Prepared according to the general procedure from Boc-Aib-OH (102 mg, 0.50 mmol) and purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired product as a colorless foam 195 mg (98% yield). R_f = 0.46, 16% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.30 (app dt, *J* = 0.8 Hz, 7.6 Hz, 2H), 4.93 (s, 1H), 4.18 (t, *J* = 5.6 Hz, 1H), 3.50 (d, *J* = 5.6 Hz, 2H), 1.42 (s, 9H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 154.2, 145.8, 141.4, 127.8, 127.2, 125.1, 120.0, 80.3, 62.3, 47.2, 32.4, 28.6, 25.7; IR (cm^{-1}): 3351(br), 2977(w), 2929(w), 1690(vs), 1493(m), 1449(s), 1250(s), 1156(vs), 1077(s), 982(s), 739(vs).

***N-tert*-Butoxycarbonyl-L-valine 9-fluorenylmethyl thioester**[17]



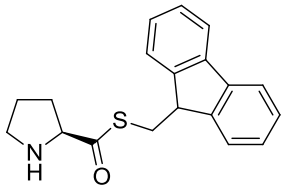
Prepared according to the general procedure from Boc-L-Val-OH (145 mg, 0.65 mmol) and purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired product as a colorless foam 265 mg (99% yield). R_f = 0.49, 16% EtOAc/hexanes. $[\alpha]^{20}_D$ -36.8 (*c* 1.0, $CHCl_3$) [Lit.[17] $[\alpha]^{23}_D$ -37.6 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.32-7.28 (m, 2H), 4.91 (d, *J* = 8.8 Hz, 1H), 4.21 (dd, *J* = 4.6 Hz, 9.2 Hz, 1H), 4.17 (t, *J* = 5.8 Hz, 1H), 3.59-3.51 (m, 2H), 2.15-2.05 (m, 1H), 1.45 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 155.7, 145.5, 141.4, 127.9, 127.3, 124.9, 120.1, 80.4, 65.6, 46.9, 32.1, 31.2, 28.5, 19.6, 16.9; IR (cm^{-1}): 3341(br), 2967(w), 2929(w), 1681(vs), 1492(s), 1448(s), 1365(s), 1249(m), 1160(vs), 999(m), 738(vs).

***N-tert*-Butoxycarbonyl-L-proline 9-fluorenylmethyl thioester**[17]



Prepared according to the general procedure from Boc-L-Pro-OH (133 mg, 0.62 mmol) and purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired product as a white solid 244 mg (96% yield, with a 5 : 9 ratio of two rotamers). R_f = 0.34, 16% EtOAc/hexanes. Mp 92-94 °C; $[\alpha]^{20}_D$ -92.3 (*c* 1.0, $CHCl_3$) [Lit.[17] $[\alpha]^{20}_D$ -72.9 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.65-7.60 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.31-7.28 (m, 2H), 4.39 (dd, *J* = 2.0 Hz, 8.4 Hz, 0.36H), 4.27-4.25 (dd, *J* = 2.8 Hz, 9.2 Hz, 0.64H), 4.17 (t, *J* = 5.6 Hz, 1H), 3.64-3.27 (m, 4H), 2.07-1.97 (m, 1H), 1.76-1.60 (m, 3H), 1.47 (s, 3.21H), 1.33 (s, 5.79H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 201.9, 154.7, 154.1, 145.8, 145.6, 145.5, 145.4, 141.5, 141.4, 127.9, 127.8, 127.3, 127.2, 127.1, 125.2, 125.1, 124.9, 124.8, 120.0, 119.9, 80.6, 80.4, 66.4, 66.1, 47.1, 47.0, 46.7, 31.9, 31.7, 31.6, 30.8, 28.7, 28.5, 24.1, 23.3; IR (cm^{-1}): 3037(w), 2975(w), 2926(w), 1689(vs), 1670(vs), 1446(m), 1386(s), 1363(s), 1162(m), 1099(m), 863(m), 751(m), 736(m).

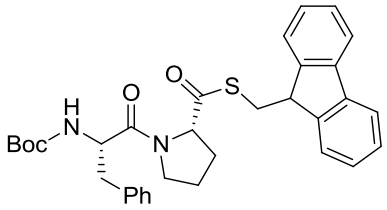
NH-L-Proline 9-fluorenylmethyl thioester.



N-tert-butoxycarbonyl-L-proline 9-fluorenylmethyl thioester (123 mg, 0.30 mmol) was dissolved in 40% TFA in dichloromethane (7 mL) and stirred at room temperature for 10 min. Dichloromethane was removed under vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 20% aqueous sodium carbonate solution and brine. After drying

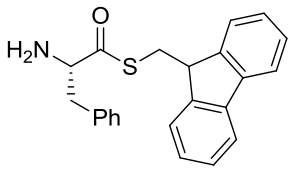
with anhydrous Na_2SO_4, the organic layer was filtrated and concentrated under reduced pressure to afford the free amine, which was applied immediately in the next step.

***N*-*tert*-Butoxycarbonyl-L-phenylalanyl-L-proline 9-fluorenylmethyl thioester**.



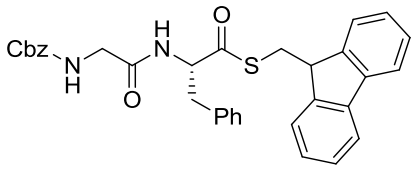
To a stirred solution of Boc-L-Phe-OH (103 mg, 0.39 mmol), freshly prepared NH-L-Pro-SFm (0.3 mmol) in DMF (3 mL) was added PyBop (234 mg, 0.45 mmol) and DIEA (0.12 mL, 0.75 mmol) at 0 ^{o}C sequentially. The reaction mixture was stirred at 0 °C for 30 min and warmed up to room temperature and stirred for 2.5 h. The reaction solution was washed with water and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under reduced pressure. Purification by chromatography (silica gel, 3:2 hexanes: EtOAc) to afford the desired product as a colorless foam 147 mg (88% yield, with a 3 : 1 ratio of rotamer). R_f = 0.46, 33% EtOAc/hexanes. $[\alpha]^{20}_{D}$ -80.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.68 (m, 2H), 7.60-7.53 (m, 2H), 7.39-7.17 (m, 9H), 5.27 (d, *J* = 8.0 Hz, 0.74H), 4.98 (d, *J* = 7.8 Hz, 0.26H), 4.64-4.57 (m, 2H), 4.20 (t, *J* = 5.4 Hz, 0.74H), 4.10 (t, *J* = 5.4 Hz, 0.26H), 3.62-3.55 (m, 2H), 3.44-3.18 (m, 2H), 3.10-2.94 (m, 1H), 2.86-2.76 (m, 1H), 1.99-1.89 (m, 1H), 1.83-1.74 (m, 1H), 1.70-1.54 (m, 2H), 1.41 (s, 2.37H), 1.34 (s, 6.63H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 171.6, 155.5, 145.4, 141.5, 136.6, 129.8, 129.7, 129.6, 129.5, 129.4, 128.8, 128.7, 128.6, 127.9, 127.8, 127.3, 127.2, 127.1, 127.0, 125.0, 124.8, 120.0, 79.9, 66.1, 54.4, 53.3, 47.3, 47.2, 47.0, 38.9, 32.2, 31.8, 29.7, 28.5, 24.5; IR (cm^{-1}): 3305(br), 2975(w), 1785(w), 1694(vs), 1644(vs), 1496(m), 1447(s), 1248(m), 1163(vs), 1017(m), 742(vs), 699(s); HRMS (ESI^+) Calcd for $C_{33}H_{36}N_2O_4S$ $[M+Na]^+$: 579.2288. Found: 579.2293.

NH_2-L-Phenylalanine 9-fluorenylmethyl thioester.



Prepared according to the same procedure as NH-L-proline 9-fluorenylmethyl thioester. After drying with anhydrous Na_2SO_4 and filtration, the organic layer was concentrated under reduced pressure to afford the free amine, which was applied immediately in the next step.

***N*-Benzyloxycarbonyl-glycine-L-phenylalanine 9-fluorenylmethyl thioester**.



Prepared according to the same procedure as Boc-L-Phe-L-Pro-SFm from Cbz-Gly-L-Phe-OH (178 mg, 0.5 mmol) and purified by chromatography (silica gel, 3:2 hexanes: EtOAc) to afford the desired product as a colorless foam 248 mg (90% yield). R_f = 0.58, 50% EtOAc/hexanes. $[\alpha]^{20}_{D}$ -30.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 6.2 Hz, 2H), 7.41-7.20 (m, 12H), 7.00 (br s, 2H), 6.30 (d, *J* = 7.6 Hz, 1H), 5.27 (br m, 1H), 5.10 (s, 2H), 4.87 (app q, *J* = 7.2 Hz, 1H), 4.15 (t, *J* = 6.0 Hz, 1H), 3.82 (dd, *J* = 5.6 Hz, 17.2 Hz, 1H), 3.76 (dd, *J* = 6.0 Hz, 16.8 Hz, 1H), 3.52 (d, *J* = 5.6 Hz, 2H), 3.00 (dd, *J* = 5.2 Hz, 14.0 Hz, 1H), 2.88 (dd, *J* = 7.2 Hz, 14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 168.8, 145.4, 141.4, 135.3, 129.4, 128.9, 128.8, 128.5, 128.3, 128.0, 127.5, 127.4, 127.3, 124.9, 124.8, 120.1, 67.5, 59.8, 46.8, 44.8, 38.4, 32.5; IR (cm^{-1}): 3292(br), 3032(w), 2927(w), 2160(w), 1666(vs), 1497(s), 1449(m), 1229(s), 1047(m), 737(s), 696(s); HRMS (ESI^+) Calcd for $C_{33}H_{30}N_2O_4S$ $[M+Na]^+$: 573.1819. Found: 573.1830.

General Procedure for the Synthesis of Amino Thiol acids

A solution of amino acid 9-fluorenylmethyl thioester in 40% piperidine in DMF (0.1 M solution) was stirred for 1 hour at room temperature. Then the reaction was diluted with ethyl acetate and neutralized by a 1 M HCl solution as indicated by pH paper. The organic layer was

washed by water and brine, then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, the crude thiol acid was used without further purification.

General Procedure for the Synthesis of di- and tri Peptides

Method A: To a stirred solution of amino acid hydrochloride salt (0.33 mmol) with triethylamine (0.33 mmol) in THF (0.2 mL) was added the solution of amino thiol acid (0.25 mmol) and BSA (0.25 mmol) in THF (0.3 mL). The reaction was stirred for 8-63 h at room temperature and then diluted with ethyl acetate and quenched with a 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated on vacuum. Chromatographic purification afforded the desired peptides.

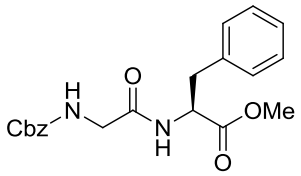
Method B: To a stirred solution of amino acid hydrochloride salt (0.33 mmol) with DIEA (0.33 mmol) in CH_3CN (0.2 mL) was added the solution of amino thiol acid (0.25 mmol) and BSA (0.25 mmol) in CH_3CN (0.3 mL). The reaction was stirred for 8-10 h at room temperature then diluted with ethyl acetate and quenched with a 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under vacuum. Purification by chromatography afforded the desired peptides.

Method C: To a stirred solution of amino thiol acid (0.25 mmol), $PhSiH_2Cl$ (0.28 mmol), amino acid hydrochloride salt (0.33 mmol) in CH_3CN (0.5 mL) was added DIEA (0.33 mmol) slowly. The reaction was stirred for 15 h at room temperature then diluted with ethyl acetate and quenched by a 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under vacuum. Purification by chromatography afforded the desired peptides.

Method D: To a stirred solution of amino thiol acid (0.25 mmol), $PhSiH_2Cl$ (0.28 mmol), amino acid hydrochloride salt (0.50 mmol) in CH_3CN (0.5 mL) was added DIEA (0.75 mmol) slowly. The reaction was stirred for 15 h at room temperature then diluted with ethyl acetate and quenched by 1M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution

and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under vacuum. Purification by chromatography afforded the desired peptides.

***N*-Benzyloxycarbonyl-glycyl-L-phenylalanine methyl ester**[42]



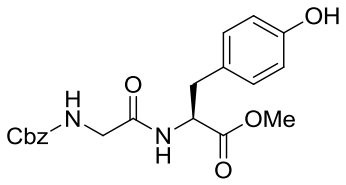
Path 1: Prepared according to **Method A** from Cbz-Gly-SFm (122 mg, 0.3 mmol), stirred at room temperature for 10 h and purified by chromatography (silica gel, 1:1 hexanes: EtOAc) to afford the desired product as a colorless oil 87 mg (78% yield, HPLC of the crude reaction mixture showed no detectable epimerization). R_f = 0.49, 66% EtOAc/hexanes. $[\alpha]^{20}_D$ +3.2 (*c* 1.0, DMF) [Lit.[43] $[\alpha]^{25}_D$ +2.7 (*c* 1.0, DMF)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 8H), 7.07 (d, *J* = 6.4 Hz, 2H), 6.54 (br s, 1H), 5.46 (br s, 1H), 5.11 (s, 2H), 4.87 (app dt, *J* = 6.0 Hz, 8.0 Hz, 1H), 3.87 (dd, *J* = 6.2 Hz, 17.6 Hz, 1H), 3.81 (dd, *J* = 6.0 Hz, 17.6 Hz, 1H), 3.71 (s, 3H), 3.13 (dd, *J* = 6.2 Hz, 14.2 Hz, 1H), 3.07 (dd, *J* = 6.2 Hz, 13.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 168.8, 156.7, 136.3, 135.8, 129.5, 128.8, 128.7, 128.5, 128.3, 127.4, 67.4, 53.3, 52.6, 44.6, 38.0; IR (cm^{-1}): 3306(br), 3030(w), 2951(w), 1722(vs), 1662(vs), 1516(vs), 1454(s), 1212(vs), 1176(s), 1047(s), 986(m), 739(s), 697(vs).

HPLC AS-RH column: 40% acetonitrile in water over 15 min with a flow rate of 0.7 mL/min and 210 nm UV detection, retention time = 9.70 min (Z-Gly-DL-Phe-OMe with retention times of 9.44 min and 12.07 min).

Path 2: To a stirred solution of L-phenylalanine methyl ester hydrochloride (84 mg, 0.39 mmol), Z-L-Arg-OH (92 mg, 0.30 mmol) with triethylamine (0.054 mL, 0.39 mmol) in THF (0.6 mL) were added freshly prepared Z-Gly-SH (68 mg, 0.30 mmol) and BSA (0.073 mL, 0.30 mmol) sequentially at room temperature. The reaction was stirred for 10 h at room temperature and then diluted with ethyl acetate and quenched with a 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, then filtrated and

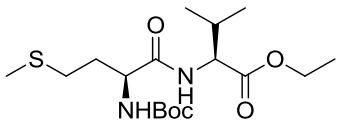
concentrated on vacuum. Purification by chromatography afforded the product Z-Gly-L-Phe-OMe 78 mg (71% yield).

***N*-Benzyloxycarbonyl-glycyl-L-tyrosine methyl ester**



Prepared according to **Method A** from Cbz-Gly-SFm (114 mg, 0.28 mmol), stirred at room temperature for 10 h and purified by chromatography (silica gel, 1:1 hexanes: EtOAc) to afford the desired product as a colorless oil 75 mg (69% yield). R_f = 0.27, 66% EtOAc/hexanes. $[\alpha]^{20}_D$ +44.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 5H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 2H), 6.59 (br s, 1H), 5.51 (br s, 1H), 5.11 (s, 2H), 4.83 (app dd, *J* = 5.8 Hz, 13.4 Hz, 1H), 3.87-3.77 (m, 2H), 3.73 (s, 3H), 3.05 (dd, *J* = 5.2 Hz, 14.4 Hz, 1H), 2.97 (dd, *J* = 6.4 Hz, 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 169.4, 157.0, 155.7, 136.2, 130.5, 128.8, 128.5, 128.3, 127.0, 115.9, 67.6, 53.5, 52.8, 44.5, 37.2; IR (cm^{-1}): 3306(br), 3014(w), 2952(w), 1706(s), 1660(vs), 1514(vs), 1442(s), 1216(vs), 1173(s), 1048(m), 750(s); HRMS ($APCI^+$) Calcd for $C_{20}H_{23}N_2O_6$ $[M+H]^+$: 387.1551. Found: 387.1557.

***N*-*tert*-Butoxycarbonyl-L-methionyl-L-valine ethyl ester**

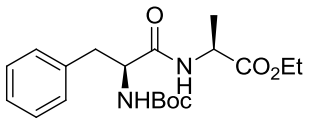


Prepared according to **Method B** from Boc-L-Met-SFm (111 mg, 0.25 mmol), stirred at room temperature for 10 h and purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired product as a white solid 78 mg (83% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/DL = 99.4 : 0.6). R_f = 0.42, 33% EtOAc/hexanes. Mp 98-101 °C; $[\alpha]^{20}_D$ +4.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 7.6 Hz, 1H), 5.25 (d, *J* = 8.4 Hz, 1H), 4.48 (dd, *J* = 4.6 Hz, 8.6 Hz, 1H), 4.31 (app q, *J* = 6.8 Hz, 1H), 4.22-4.13 (m,

2H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.22-2.14 (m, 1H), 2.01 (s, 3H), 2.08-2.01 (m, 1H), 1.98-1.89 (m, 1H), 1.42 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.6, 155.7, 80.3, 61.5, 57.4, 53.4, 31.5, 31.3, 30.3, 28.5, 19.2, 17.8, 15.3, 14.4; IR (cm^{-1}): 3303(br), 2970(m), 2932(w), 2160(w), 1743(vs), 1679(s), 1649(vs), 1531(s), 1366(s), 1293(m), 1203(s), 1148(s), 1050(m), 1025(m), 867(m); HRMS (ESI^+) Calcd for $C_{17}H_{32}N_2O_5S$ $[M+Na]^+$: 397.1924. Found: 399.1929.

HPLC AS-RH column: 30% acetonitrile in water over 25 min with a flow rate of 0.75 mL/min and 210 nm UV detection, retention time = 17.74 min (99.4%) and 24.73 (0.6%) (Boc-DL-Met-L-Val-OEt with retention times of 17.57 min and 24.50 min).

***N*-*tert*-Butoxycarbonyl-L-phenylalanyl-L-alanine ethyl ester**

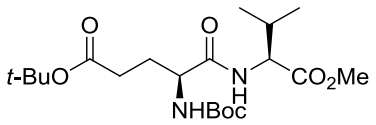


Prepared according to **Method B** from Boc-L-Phe-SFm (115 mg, 0.25 mmol), stirred at room temperature for 12 h and purified by chromatography (silica gel, 2:1 hexanes: EtOAc) to afford the desired product as a white solid 66 mg (72% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/LD = 99.5 : 0.5). R_f = 0.31, 33% EtOAc/hexanes. Mp 94-97 °C; $[\alpha]^{20}_D$ +3.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H), 6.51 (d, *J* = 5.2 Hz, 1H), 5.04 (d, *J* = 5.6 Hz, 1H), 4.48 (app quintet, *J* = 7.0 Hz, 1H), 4.39-4.35 (m, 1H), 4.21-4.10 (m, 2H), 3.06 (d, *J* = 6.4 Hz, 2H), 1.39 (s, 9H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 170.9, 155.6, 136.7, 129.6, 128.8, 127.1, 80.4, 61.7, 55.8, 48.4, 38.6, 28.4, 18.6, 14.3; IR (cm^{-1}): 3290(br), 2979(w), 2933(w), 2160(w), 1741(m), 1655(vs), 1530(s), 1366(m), 1159(vs), 1048(m), 1021(m), 698(m); HRMS (ESI^+) Calcd for $C_{19}H_{28}N_2O_5$ $[M+Na]^+$: 387.1890. Found: 387.1895.

HPLC AS-RH column: 30% acetonitrile in water over 15 min, 30-40% acetonitrile over 5 min, 40-50% acetonitrile over 5 min with a flow rate of 0.70 mL/min and 210 nm UV detection,

retention time = 16.73 min (99.5%) and 23.58 (0.5%) (Boc-DL-Phe-L-Ala-OEt with retention times of 16.84 min and 23.88 min).

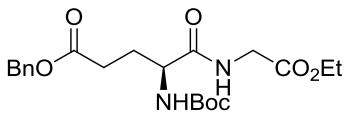
***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-butyl ester L-glutamyl-L-valine methyl ester**



Prepared according to **Method A** from Boc-L-Glu(O*t*Bu)-SFm (114 mg, 0.23 mmol), stirred at room temperature for 10 h and purified by chromatography (silica gel, 2:1 hexanes: EtOAc) to afford the desired product as a colorless oil 68 mg (71% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/LD = 99.5 : 0.5). R_f = 0.39, 33% EtOAc/hexanes. $[\alpha]^{20}_D$ -10.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 8.0 Hz, 1H), 5.31 (d, *J* = 7.6 Hz, 1H), 4.48 (dd, *J* = 4.8 Hz, 8.8 Hz, 1H), 4.15 (app dd, *J* = 7.6 Hz, 13.2 Hz, 1H), 3.71 (s, 3H), 2.45-2.30 (m, 2H), 2.22-2.12 (m, 1H), 2.08-2.00 (m, 1H), 1.94-1.85 (m, 1H), 1.43 (s, 9H), 1.41 (s, 9H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.3, 171.9, 155.9, 81.1, 80.2, 57.4, 54.1, 52.3, 32.0, 31.2, 28.5, 28.3, 27.7, 19.2, 17.8; IR (cm^{-1}): 3309(br), 2974(w), 1727(s), 1659(s), 1520(m), 1366(s), 1250(m), 1148(vs), 1026(m); HRMS (ESI^+) Calcd for $C_{20}H_{36}N_2O_7$ $[M+Na]^+$: 439.2415. Found: 439.2422.

HPLC AS-RH column: 30% acetonitrile in water over 25 min then 40-100% acetonitrile over 4 min with a flow rate of 0.75 mL/min and 210 nm UV detection, retention time = 20.17 min (99.5%) and 24.65 (0.5%) (Boc-DL-Glu(O*t*Bu)-L-Val-OMe with retention times of 19.91 min and 24.22 min).

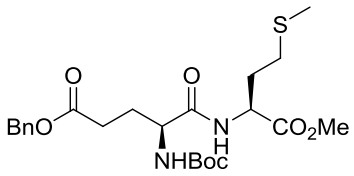
***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-benzyl ester L-glutamyl-glycine ethyl ester**



Prepared according to **Method A** from Boc-L-Glu(OBn)-SFm (132 mg, 0.25 mmol), stirred at room temperature for 8 h and purified by chromatography (silica gel, 3:2 hexanes: EtOAc) to

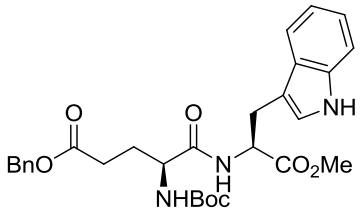
afford the desired product as a white solid 80 mg (76% yield). R_f = 0.51, 50% EtOAc/hexanes. Mp 80-82 °C; $[\alpha]^{20}_D$ -3.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 6.93 (br s, 1H), 5.42 (d, *J* = 5.6 Hz, 1H), 5.11 (s, 2H), 4.27 (app dd, *J* = 7.8 Hz, 13.4 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.03 (dd, *J* = 5.4 Hz, 18.2 Hz, 1H), 3.95 (dd, *J* = 5.4 Hz, 18.2 Hz, 1H), 2.59-2.44 (m, 2H), 2.21-2.12 (m, 1H), 1.99-1.91 (m, 1H), 1.41 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 172.1, 169.8, 155.9, 135.9, 128.8, 128.5, 128.4, 80.3, 66.7, 61.7, 53.7, 41.5, 30.6, 28.5, 28.2, 14.3; IR (cm^{-1}): 3285(br), 2979(w), 1735(s), 1668(s), 1649(s), 1518(s), 1367(s), 1202(s), 1159(vs), 1022(m), 746(m), 698(m); HRMS (ESI^+) Calcd for $C_{21}H_{30}N_2O_7$ $[M+Na]^+$: 445.1945. Found: 445.1949.

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-benzyl ester L-glutamyl-L-methionine methyl ester**



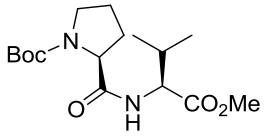
Prepared according to **Method A** from Boc-L-Glu(OBn)-SFm (117 mg, 0.22 mmol), stirred at room temperature for 10 h and purified by chromatography (silica gel, 3:2 hexanes: EtOAc) to afford the desired product as a colorless oil 72 mg (68% yield). R_f = 0.24, 33% EtOAc/hexanes. $[\alpha]^{20}_D$ +6.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 6.94 (d, *J* = 7.6 Hz, 1H), 5.32 (d, *J* = 7.6 Hz, 1H), 5.12 (s, 2H), 4.67 (app dt, *J* = 5.0 Hz, 7.8 Hz, 1H), 4.20 (app dd, *J* = 7.2 Hz, 13.6 Hz, 1H), 3.72 (s, 3H), 2.57-2.47 (m, 4H), 2.19-2.10 (m, 2H), 2.07 (s, 3H), 2.02-1.89 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 172.2, 171.7, 155.8, 135.9, 128.8, 128.5, 128.4, 80.4, 66.8, 53.8, 52.7, 51.7, 31.6, 30.6, 30.1, 28.5, 28.1, 15.6; IR (cm^{-1}): 3306(br), 2917(w), 1725(s), 1661(vs), 1516(s), 1444(m), 1366(s), 1213(s), 1162(vs), 1052(m), 697(m); HRMS (ESI^+) Calcd for $C_{23}H_{34}N_2O_7S$ $[M+Na]^+$: 505.1979. Found: 505.1985.

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-benzyl ester L-glutamyl-L-tryptophan methyl ester**



Prepared according to **Method A** Boc-L-Glu(OBn)-SFm (132 mg, 0.25 mmol), stirred at room temperature for 8 h and purified by chromatography (silica gel, 3:2 hexanes: EtOAc) to afford the desired product as a sticky oil 99 mg (74% yield). R_f = 0.40, 50% EtOAc/hexanes. $[\alpha]^{20}_D$ +26.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.37-7.26 (m, 6H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 6.84 (br s, 1H), 5.34 (d, *J* = 6.4 Hz, 1H), 5.13-5.03 (m, 2H), 4.90 (dd, *J* = 6.4 Hz, 12.6 Hz, 1H), 4.22-4.17 (m, 1H), 3.64 (s, 3H), 3.33-3.23 (m, 2H), 2.46-2.32 (m, 1H), 2.25-2.17 (m, 1H), 2.05-1.78 (m, 1H), 1.87-1.78 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 172.4, 171.3, 155.9, 136.3, 136.0, 128.8, 128.6, 128.5, 127.5, 123.3, 122.4, 119.8, 118.6, 111.5, 109.8, 80.3, 66.7, 53.8, 52.9, 52.7, 30.4, 28.5, 28.1, 27.9; IR (cm^{-1}): 3325(br), 2931(w), 1712(vs), 1659(vs), 1501(s), 1454(m), 1365(m), 1248(s), 1160(vs), 1050(m), 740(s); HRMS (ESI^+) Calcd for $C_{29}H_{35}N_3O_7$ $[M+Na]^+$: 560.2367. Found: 560.2374.

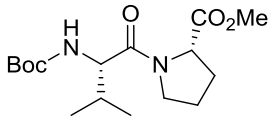
***N*-*tert*-Butoxycarbonyl-L-prolyl-L-valine methyl ester**[44]



Prepared according to **Method A** from Boc-L-Pro-SFm (94 mg, 0.23 mmol), stirred at room temperature for 10 h and purified by chromatography (silica gel, 2:1 hexanes: EtOAc) to afford the desired product as a colorless oil 49 mg (65% yield, with a 7 : 5 ratio of two rotamers). R_f = 0.30, 33% EtOAc/hexanes. $[\alpha]^{20}_D$ -88.0 (*c* 0.25, $CHCl_3$) [Lit.[16] $[\alpha]^{22}_D$ -88.4 (*c* 0.25, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (br s, 0.58H), 6.51 (br s, 0.42H), 4.49-4.44 (m, 1H), 4.32-4.24 (m, 1H), 3.69 (s, 3H), 3.45-3.30 (m, 2H), 2.18-2.19 (m, 2H), 1.91-1.83 (m, 3H); ^{13}C NMR (100

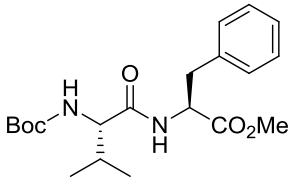
MHz, $CDCl_3$) δ 172.4, 156.1, 154.9, 80.5, 61.4, 59.8, 57.4, 52.2, 47.2, 31.5, 31.3, 28.5, 27.7, 24.9, 23.9, 19.2, 17.8; IR (cm^{-1}): 3305(w), 2968(w), 2876(w), 1742(m), 1692(vs), 1662(vs), 1547(m), 1397(s), 1364(m), 1158(s), 1118(m), 1011(w), 773(w); HRMS (ESI^+) Calcd for $C_{16}H_{28}N_2O_5$ $[M+Na]^+$: 351.1890. Found: 351.1894.

***N*-*tert*-Butoxycarbonyl-L-valyl-L-proline methyl ester**[45]



Prepared according to **Method A** from Boc-L-Val-SFm (98 mg, 0.24 mmol), stirred at room temperature for 48 h and purified by chromatography (silica gel, 3:2 hexanes: EtOAc) to afford the desired product as a colorless oil 55 mg (70% yield, with a 7 : 1 ratio of two rotamers). R_f = 0.20, 33% EtOAc/hexanes. $[\alpha]^{20}_D$ -73.7 (*c* 1.0, $CHCl_3$) [Lit.[17] $[\alpha]^{25}_D$ -73.8 (*c* 1.51, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (d, *J* = 8.8 Hz, 1H), 4.50 (dd, *J* = 4.8 Hz, 8.4 Hz, 0.88H), 4.40 (dd, *J* = 3.4 Hz, 8.2 Hz, 0.12H), 4.30 (dd, *J* = 6.2 Hz, 9.4 Hz, 0.12H), 4.26 (dd, *J* = 6.2 Hz, 9.4 Hz, 0.88H), 3.79 -3.73 (m, 1H), 3.70 (s, 3H), 3.66-3.06 (m, 1H), 2.23-2.17 (m, 1H), 2.06-1.91 (m, 4H), 1.40 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.4, 156.1, 79.6, 58.9, 57.0, 52.4, 47.3, 46.4, 31.6, 31.5, 29.4, 29.2, 28.5, 25.2, 24.9, 19.5, 17.6; IR (cm^{-1}): 3306(br), 2972(w), 1745(s), 1703(s), 1639(vs), 1499(m), 1431(vs), 1365(m), 1164(vs), 1015(s).

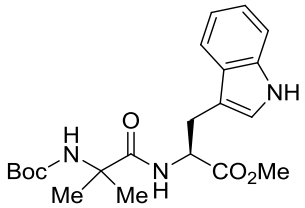
***N*-*tert*-Butoxycarbonyl-L-valyl-L-phenylalanine methyl ester**[46]



Prepared according to **Method A** from Boc-L-Val-SFm (91 mg, 0.22 mmol), stirred at room temperature for 63 h and purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired product as a white solid 56 mg (67% yield). R_f = 0.41, 33% EtOAc/hexanes. Mp 96-

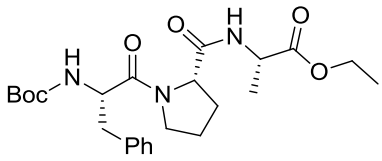
100 °C [Lit.[18] mp 101 °C]; $[\alpha]^{20}_D$ +38.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (m, 3H), 7.09 (dd, *J* = 1.6 Hz, 8.0 Hz, 2H), 6.40 (br s, 1H), 5.05 (d, *J* = 6.0 Hz, 1H), 4.85 (app dd, *J* = 6.0 Hz, 13.6 Hz, 1H), 3.90 (t, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 3.11 (dd, *J* = 5.8 Hz, 13.6 Hz, 1H), 3.06 (dd, *J* = 5.8 Hz, 13.6 Hz, 1H), 2.09-2.02 (m, 1H), 1.42 (s, 9H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 171.5, 155.9, 135.9, 129.4, 128.8, 127.4, 80.0, 60.1, 53.3, 52.5, 38.2, 31.1, 28.5, 19.4, 17.9; IR (cm^{-1}): 3351(br), 3291(br), 2966(w), 2927(w), 1745(s), 1688(vs), 1655(vs), 1503(s), 1163(vs), 1017(s), 880(m), 699(s).

***N*-*tert*-Butoxycarbonyl-*α*-aminoisobutyryl-L-tryptophan methyl ester**[17]



Prepared according to **Method A** from Boc-Aib-SFm (87.9 mg, 0.22 mmol), stirred at room temperature for 54 h and purified by chromatography (silica gel, 3:2 hexanes: EtOAc) to afford the desired product as a colorless oil 66 mg (74% yield). R_f = 0.30, 50% EtOAc/hexanes. $[\alpha]^{20}_D$ +35.7 (*c* 1.0, $CHCl_3$) [Lit.[17] $[\alpha]^{22}_D$ +37.2 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.01 (s, 1H), 6.89 (br s, 1H), 5.00 (s, 1H), 4.88 (app dt, *J* = 5.6 Hz, 7.2 Hz, 1H), 3.62 (s, 3H), 3.33 (dd, *J* = 6.0 Hz, 15.4 Hz, 1H), 3.27 (dd, *J* = 6.0 Hz, 15.4 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 172.7, 154.8, 136.3, 127.8, 123.3, 122.3, 119.6, 118.7, 111.5, 110.0, 56.9, 53.3, 52.5, 28.5, 27.9, 25.8; IR (cm^{-1}): 3324(br), 2979(w), 1693(s), 1659(s), 1503(s), 1438(m), 1364(s), 1250(s), 1159(vs), 1075(s), 741(vs).

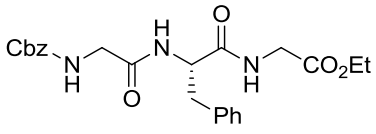
***N*-*tert*-Butoxycarbonyl-L-phenylalanyl-L-prolyl-L-alanine ethyl ester**



Prepared according to **Method C** from Boc-L-Phe-L-Pro-SFm (111 mg, 0.20 mmol), stirred at room temperature for 8 h and purified by chromatography (silica gel, 1:1 hexanes: EtOAc) to afford the desired product as a colorless oil 57 mg (62% yield, with a 3 : 1 ratio of rotamers. HPLC of the crude reaction mixture showed the epimerization ratio LLL/LDL = 99.5 : 0.5). R_f = 0.46, 75% EtOAc/hexanes. $[\alpha]^{20}_D$ -34.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 0.25H), 7.32-7.18 (m, 5.75H), 5.32 (d, *J* = 8.4 Hz, 0.75H), 5.12 (d, *J* = 5.2 Hz, 0.25H), 4.63 (app q, *J* = 7.4 Hz, 0.75H), 4.54 (app d, *J* = 4.8 Hz, 0.75H), 4.47 (app quintet, *J* = 7.2 Hz, 2.50H), 4.39 (app q, *J* = 7.2 Hz, 0.25H), 4.19 (dq, *J* = 2.2 Hz, 7.2 Hz, 1.50H), 4.09 (dq, *J* = 2.0 Hz, 7.2 Hz, 0.50H),3.56-3.41 (m, 2H), 3.03 (app dd, *J* = 7.4 Hz, 13.4 Hz, 1H), 2.92 (app dd, *J* = 6.4 Hz, 12.0 Hz, 1H), 2.31-2.27 (m, 1H), 1.98-1.79 (m, 3H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.38 (s, 9H), 1.27 (dt, *J* = 2.4 Hz, 7.0 Hz, 2.25H), 1.19 (dt, *J* = 2.0 Hz, 7.4 Hz, 0.75H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.0, 171.3, 171.1, 170.4, 155.8, 155.3, 136.4, 135.8, 129.7, 129.6, 129.1, 128.7, 127.7, 127.2, 80.3, 79.9, 77.5, 61.6, 60.8, 60.1, 54.4, 53.5, 48.7, 48.6, 47.5, 46.9, 39.6, 39.1, 30.9, 28.5, 27.3, 25.3, 22.2, 18.3, 17.0, 14.4; IR (cm^{-1}): 3306(br), 2977(w), 1688(s), 1638(vs), 1525(s), 1444(s), 1366(s), 1160(vs), 1019(m), 700(m); HRMS (ESI^+) Calcd for $C_{24}H_{35}N_3O_6$ $[M+Na]^+$: 484.2418. Found: 484.2422.

HPLC AS-RH column: 30% acetonitrile in water over 20 min with a flow rate of 0.70 mL/min and 210 nm UV detection, retention time = 10.98 min (99.5%) and 13.61 (0.5%) (Boc-L-Phe-DL-Pro-L-Ala-OEt with retention times of 10.83 min and 13.52 min).

***N*-Benzyloxycarbonyl-glycyl-L-phenylalanyl-glycine ethyl ester**[47]



Prepared according to **Method D** from Cbz-Gly-L-Phe-SFm (109 mg, 0.20 mmol), stirred at room temperature for 15 h and purified by chromatography (silica gel, 2:3 hexanes: EtOAc) to afford the desired product as a colorless oil 64 mg (73% yield, HPLC of the crude reaction

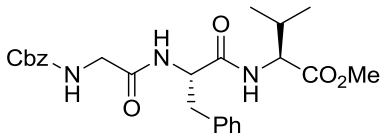
mixture showed the epimerization ratio L/D = 97 : 3). R_f = 0.16, 66% EtOAc/hexanes. $[\alpha]^{20}_D$ -13.5 (*c* 2.0, EtOH) [Lit.[48] $[\alpha]^{25}_D$ -12.4 (*c* 2.0, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.15 (m, 11H), 7.03 (br s, 1H), 5.79 (br m, 1H), 5.07 (s, 2H), 4.82 (app q, *J* = 6.8 Hz, 1H), 4.12 (q, *J* = 6.8 Hz, 2H), 3.96 (dd, *J* = 5.2 Hz, 18.0 Hz, 1H), 3.86-3.76 (m, 3H), 3.10 (dd, *J* = 6.4 Hz, 13.6 Hz, 1H), 3.00 (dd, *J* = 7.6 Hz, 13.2 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 169.8, 169.6, 156.9, 136.6, 136.4, 129.5, 128.7, 128.4, 128.3, 127.2, 67.4, 61.7, 54.4, 44.6, 41.5, 38.4, 14.3; IR (cm^{-1}): 3292(br), 3065(w), 2935(w), 1723(s), 1649(vs), 1525(s), 1201(s), 1027(s), 739(m), 697(s); HRMS (ESI^+) Calcd for $C_{23}H_{27}N_3O_6$ $[M+Na]^+$: 464.1792. Found: 464.1798.

HPLC OD-RH column: 30% acetonitrile in water over 15 min, 30-40% acetonitrile over 5 min, then 40-50% acetonitrile over 5 min with a flow rate of 0.70 mL/min and 210 nm UV detection, retention time = 25.01 min (3%) and 26.47 min (97%) (Z-Gly-DL-Phe-Gly-OEt with retention times of 24.87 min and 26.39 min).

Path 2: Prepared according to **Method B** from Cbz-Gly-L-Phe-SFm (82 mg, 0.15 mmol), stirred at room temperature for 15 h and purified by chromatography (silica gel, 2:3 hexanes: EtOAc) to afford the desired product as a sticky oil 53 mg (80% yield, HPLC of the crude reaction mixture showed the epimerization ratio L/D = 96.2 : 3.8).

Path 3: Prepared according to **Method C** from Cbz-Gly-L-Phe-SFm (114 mg, 0.21 mmol), stirred at room temperature for 15 h and purified by chromatography (silica gel, 2:3 hexanes: EtOAc) to afford the desired product as a sticky oil 55 mg (60% yield, HPLC of the crude reaction mixture showed the epimerization ratio L/D = 96.8 : 3.2).

***N*-Benzyloxycarbonyl-glycyl-L-phenylalanyl-L-valine methyl ester**[49]

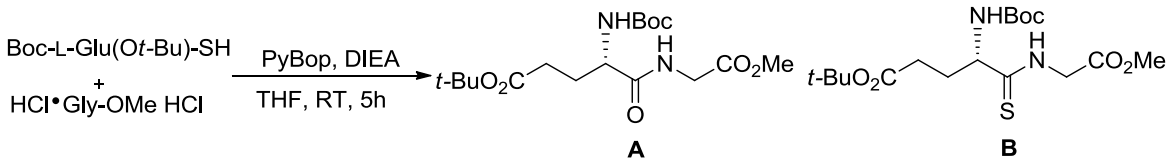


Path 1: Prepared according to **Method D** from Cbz-Gly-L-Phe-SFm (111 mg, 0.20 mmol), stirred at room temperature for 15 h and purified by chromatography (silica gel, 1:1 hexanes: EtOAc) to afford the desired product as a colorless oil 52 mg (55% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/DL = 97 : 3). R_f = 0.33, 66% EtOAc/hexanes. $[\alpha]^{20}_D$ -15.0 (*c* 1.0, EtOH) [Lit.[50] $[\alpha]^{20}_D$ -14.1 (*c* 0.8, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 7.24-7.19 (m, 3H), 7.15 (d, *J* = 7.2 Hz, 2H), 6.98 (br s, 1H), 6.69 (br s, 1H), 5.65 (br s, 1H), 5.09 (s, 2H), 4.79 (app q, *J* = 7.0 Hz, 1H), 4.42 (dd, *J* = 5.6 Hz, 8.8 Hz, 1H), 3.85 (d, *J* = 4.0 Hz, 2H), 3.66 (s, 3H), 3.03 (d, *J* = 6.8 Hz, 2H), 2.09-2.02 (m, 1H), 0.83 (d, *J* = 6.8 Hz, 6H), 0.80 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.9, 169.2, 156.8, 136.5, 136.4, 129.5, 128.8, 128.7, 128.4, 128.3, 127.2, 67.4, 57.6, 54.7, 52.3, 44.6, 38.6, 31.3, 19.0, 18.0; IR (cm^{-1}): 3290(br), 3065(w), 2962(w), 1724(s), 1645(vs), 1520(s), 1212(s), 1148(m), 739(m), 697(m); HRMS (ESI^+) Calcd for $C_{25}H_{31}N_3O_6$ $[M+Na]^+$: 492.2105. Found: 492.2116.

HPLC AS-RH column: 30% acetonitrile in water over 15 min, 30-40% acetonitrile over 5 min, 40-50% acetonitrile over 5 min then 50-100% acetonitrile over 4 min with a flow rate of 0.70 mL/min and 210 nm UV detection, retention time = 19.08 min (97%) and 25.13 (3%) (Z-Gly-DL-Phe-L-Val-OMe with retention times of 18.99 min and 25.05 min).

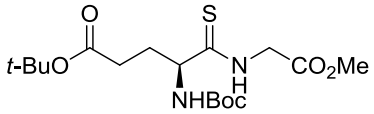
Path 2: Prepared according to **Method B** from Cbz-Gly-L-Phe-SFm (76 mg, 0.14 mmol), stirred at room temperature for 15 h and purified by chromatography (silica gel, 1:1 hexanes: EtOAc) to afford the desired product as a colorless oil 48 mg (74% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/DL = 95.6 : 4.4).

Path 3: Prepared according to **Method C** from Cbz-Gly-L-Phe-SFm (131 mg, 0.24 mmol), stirred at room temperature for 15 h and purified by chromatography (silica gel, 1:1 hexanes: EtOAc) to afford the desired product as a colorless oil 56 mg (50% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/DL = 96.2 : 3.8).



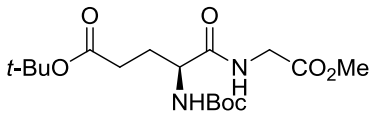
To a stirred solution of Boc-L-Glu(O*t*-Bu)-SH (83 mg, 0.26 mmol), glycine methyl ester hydrochloride salt (25 mg, 0.20 mmol) in THF (2 mL) was added PyBop (156 mg, 0.30 mmol) and DIEA (0.083 mL, 0.50 mmol) at 0 °C sequentially. The reaction mixture was stirred at 0 °C for 30 min and warmed up to room temperature and then stirred for 4.5 h. The reaction mixture was washed with water and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under reduced pressure. Purification by column chromatography (silica gel, 30% ethyl acetate in hexane) afforded compound **A** 30 mg (40% yield) as a colorless oil (R_f = 0.25, 50% EtOAc/hexanes) and compound **B** 23 mg (28% yield) as a colorless oil (R_f = 0.50, 50% EtOAc/hexanes).

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-butyl ester L-glutamyl-thioxo-glycine methyl ester**.



$[\alpha]^{20}_{D}$ -10.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 5.62 (d, *J* = 8.0 Hz, 1H), 4.54-4.50 (m, 2H), 4.34 (dd, *J* = 4.4 Hz, 18.4 Hz, 1H), 3.78 (s, 3H), 2.45-2.30 (m, 2H), 2.20-2.12 (m, 1H), 2.06-1.97 (m, 1H), 1.45 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 173.2, 168.9, 155.7, 81.3, 80.5, 60.3, 52.8, 47.0, 32.0, 31.0, 28.5, 28.3; IR (cm^{-1}): 3276(br), 2977(w), 1689(vs), 1499(m), 1444(m), 1366(vs), 1247(s), 1211(m), 1151(vs); HRMS (ESI^+) Calcd for $C_{17}H_{30}N_2O_6S$ $[M+Na]^+$: 413.1717. Found: 413.1722.

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-butyl ester L-glutamyl-glycine methyl ester**.



$[\alpha]^{20}_{D}$ -8.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (br s, 1H), 5.38 (d, *J* = 7.6 Hz, 1H), 4.19 (app dd, *J* = 7.4 Hz, 13.2 Hz, 1H), 4.05 (dd, *J* = 5.4 Hz, 18.0 Hz, 1H), 4.0 (dd, *J* = 5.4 Hz, 18.0 Hz, 1H), 3.73 (s, 3H), 2.44-2.29 (m, 2H), 2.13-2.04 (m, 1H), 1.95-1.86 (m, 1H), 1.43 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.3, 170.2, 155.9, 81.1, 80.3, 54.0, 52.5, 41.4, 31.9, 28.5, 28.3, 27.9; IR (cm^{-1}): 3307(br), 2977(w), 1720(s), 1664(s), 1515(m), 1366(s), 1208(m), 1149(vs), 1048(w), 1026(w); HRMS ($APCI^+$) Calcd for $C_{17}H_{31}N_2O_7$ $[M+H]^+$: 375.2126. Found: 375.2132.

Boc-L-Glu(O*t*-Bu)-Gly-OMe could also be prepared according to **Method A**, stirred at room temperature for 8 h and purified by chromatography (silica gel, 2:1 hexanes: EtOAc) to afford compound **A** as an only product 64 mg (74% yield).

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Chapter 2

Structural Characterization of Dicopper(I) 2,6-dihydroxybenzoate (CuDHB) Complexes and CuDHB-Mediated Suzuki Cross-Coupling Reaction

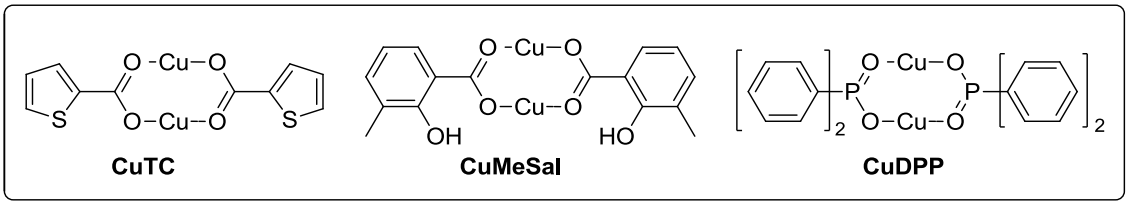
Abstract: The syntheses, characterization, and behavior of the new dicopper(I) 2,6-dihydroxybenzoate complexes are reported. The complexes are stable at room temperature in solid form and they can be handled in air for some time. The reactivity of copper(I) 2,6-dihydroxybenzoate (CuDHB) was compared with copper(I) 3-methylsalicylate (CuMeSal) and copper(I) thiophene-2-carboxylate (CuTC). CuDHB mediated Suzuki cross-coupling under mild reaction condition (free of bases, low temperature) was studied. Vinyliodides and aryliodides with ortho coordinating group could couple in the presence of CuDHB with vinyl- and aryl-boronic acids to give 1,3-diene and aryl-alkene compounds in good yields.

2.1 Introduction and Background

2.1.1 Copper Carboxylate Mediated Stille Cross-Coupling Reaction

For the last few years, the Liebeskind laboratory has focused on uncovering new C-C bond forming transformations through the cross-coupling of the thioorganics with mild organometallic reagents including organoboron reagents and organostannanes.[1] In most of the reactions, copper carboxylates play a crucial role. New copper carboxylates including copper(I) thiophene-2-carboxylate (CuTC),[2] copper(I) 3-methylsalicylate (CuMeSal)[3] and copper(I) diphenylphosphinate (CuDPP)[4] developed in the Liebeskind Laboratory have been widely used as catalysts or mediators in cross-coupling reactions or click chemistry (**Figure 2.1**).[5]

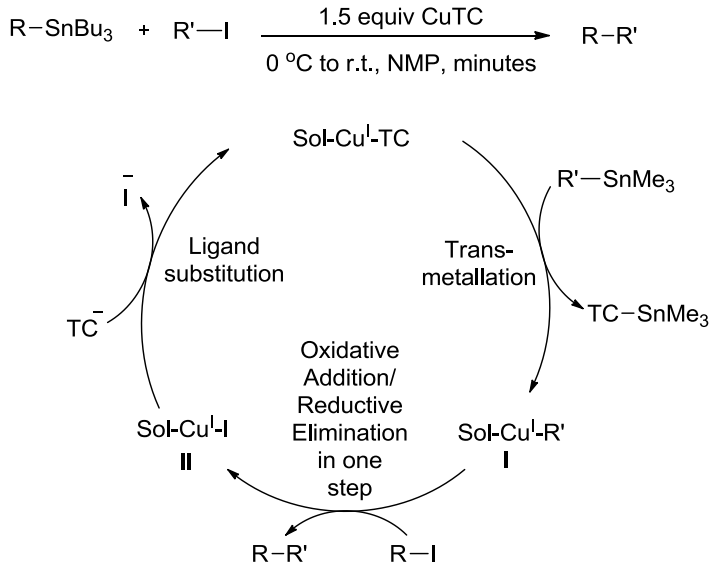
Figure 2.1 Copper(I) Carboxylate Developed in the Liebeskind Laboratory



More than 15 years ago, the Liebeskind laboratory developed CuTC as an efficient mediator for Stille cross-coupling reaction between aryl-, heteroaryl-, and alkenylstannanes and alkenyl iodides at or below room temperature (**Scheme 2.1**).[6] Computational results suggest that the

reaction occurs through (1) transmetallation between Cu carboxylate and vinyl stannane to give the organocopper intermediate **I** followed by (2) a one-step process involving oxidative addition of vinyl iodide to **II** and reductive elimination to generate the cross-coupling product.[7] Calculations also shows that regeneration of the active species CuTC via a ligand substitution is favorable when a stoichiometric amount of free TC ligand is provided. This suggests that the cross-coupling reaction could be promoted either by forming a stable organostannane carboxylate byproduct due to the strong Sn-O interaction so that it does not participate in back reaction, or by using an excess of copper carboxylate to drive an unfavorable transmetallation from tin to copper (**Scheme 2.1**).

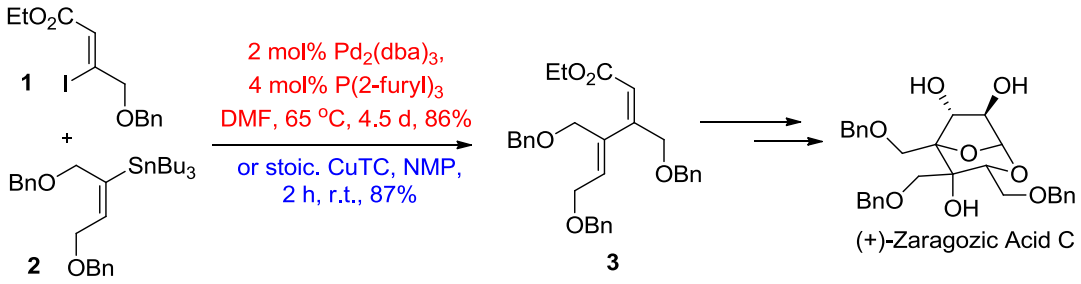
Scheme 2.1 Copper Mediated Stille Cross-Coupling Reaction



This powerful method shows several advantages over palladium catalyzed Suzuki cross-coupling reactions for the synthesis of functionalized unsymmetrical 1,3-dienes, and has been widely applied to the total synthesis of different natural products. Armstrong utilized this method for the synthesis of Zaragozic Acid C (**Scheme 2.2**).[8] Palladium-catalyzed cross-coupling between iodide **1** and stannane **2** was found to proceed smoothly in 86% yield, however, the

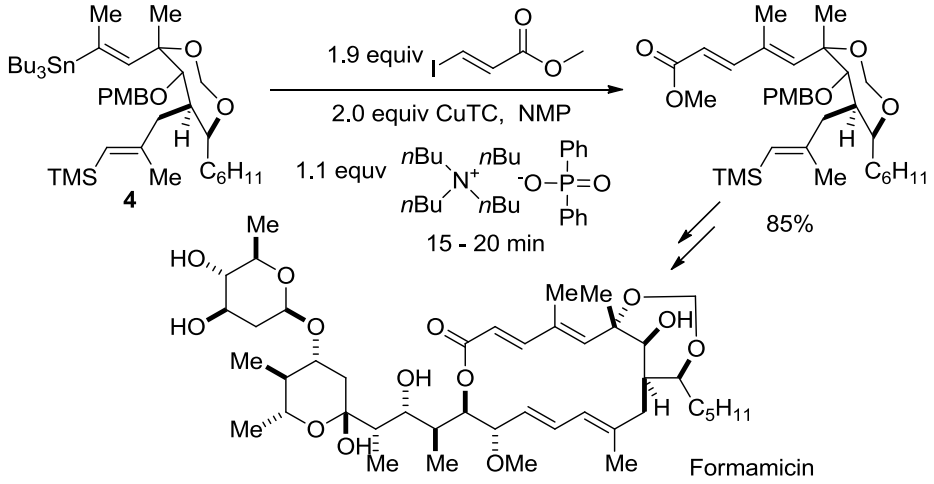
reaction required elevated temperature and took 4.5 days. A facile Stille cross-coupling reaction could be accomplished using stoichiometric CuTC at room temperature in only 2 hours.

Scheme 2.2 Comparison of Copper-mediated and Palladium-catalyzed 1,3-Diene Formation



Roush also showcased the advantage of copper-mediated Stille cross-coupling reactions (**Scheme 2.3**).[9] During a total synthesis of Formamicin, initial attempts to achieve an efficient cross-coupling under a variety of Pd(0)-catalyzed conditions proved unsuccessful. However, CuTC proved effective when a solution of the vinyl iodide was slowly added into a mixture of vinyl stannane and CuTC in order to avoid homocoupling of the vinyl iodide.

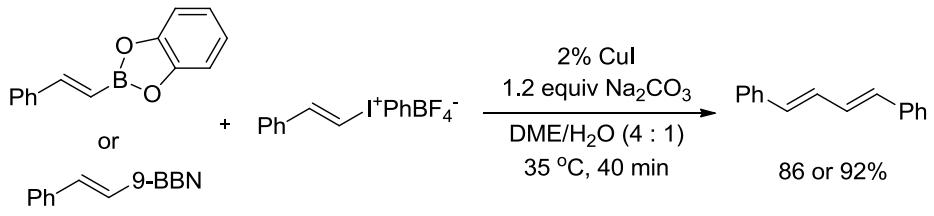
Scheme 2.3 Copper Mediated Stille Cross-Coupling in Total Synthesis of Formamicin



Advantages of the copper-mediated Stille cross-coupling include: (1) rapid and efficient cross-coupling in good to excellent yields at or below room temperature; (2) rapid increase in molecular complexity; (3) CuTC is cheap and easy to prepare which mitigates the fact that it is used

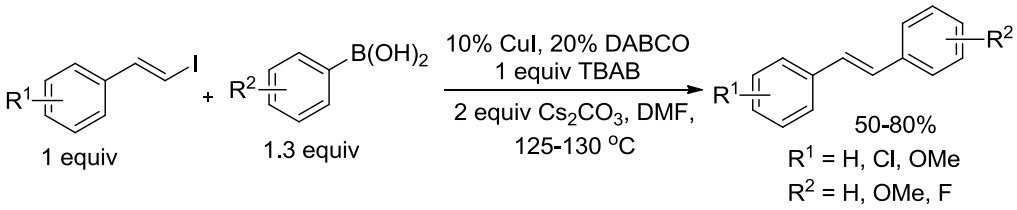
stoichiometrically. Despite these advantages, there are some drawbacks assosciated with this method. Organotin reagents are notorious for their toxicity in causing irritation, loss of memory, and insomnia as well as other symptoms including death.[10] Also, the byproducts of organotins are often difficult to remove using standard purification processes. In order to overcome the disadvantages while retaining the positive aspects of the overall Stille cross-coupling reaction, we sought to use boronic acids (benign, easily removable) as coupling reagents instead of organostannanes in the copper carboxylate mediated Suzuki cross-coupling reaction to synthesize 1,3-dienes and aryl-alkenes. The copper-catalyzed Suzuki-Miyaura reaction is capable of coupling a range of organoboron reagents with organohalides and pseudohalides to construct carbon-carbon bonds.[11] However, the copper-catalyzed Suzuki-type reaction between alkenyl boronic acids and alkenyl halides is rare in the literature. Kang and co-workers described an example of copper-catalyzed cross-coupling reaction between highly reactive alkenyliodonium tetrafluoroborates and vinyl boronates or alkenyl-9-BBN in water with stoichiometric Na_2CO_3 to promote boron to copper transmetallation (**Scheme 2.4**).[12]

Scheme 2.4 Copper Catalyzed 1,3-Dienes Formation



An efficient CuI/DABCO catalyzed cross-coupling system has also been developed for the ene-aryl bond formation. Li and co-workers reported that use of a full equivalent of TBAB (n-Bu_4NBr) and 20 mol% of DABCO as an additional ligand copper could catalyze an efficient cross-coupling between aryl/vinyl halides and arylboronic acids above 100 ^oC (**Scheme 2.5**).[13]

Scheme 2.5 Copper Catalyzed Aryl-Alkenes Formation



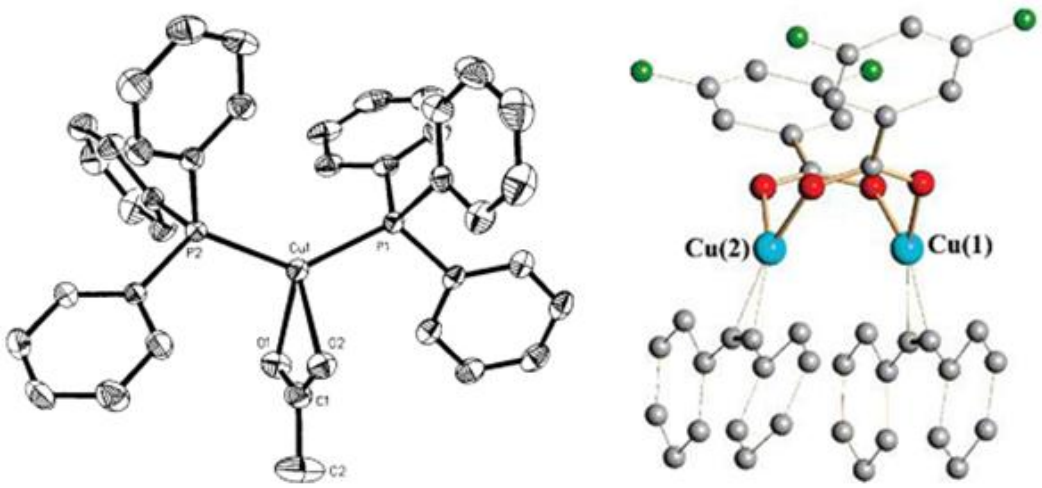
As stated previously (**Scheme 2.4** and **2.5**), copper catalyzed Suzuki cross-coupling reactions to synthesize unsymmetric 1,3-dienes and aryl-alkenes usually require prolonged reaction time or hash conditions at elevated temperature or the addition of bases/additives. Thus, copper-mediated Suzuki cross-coupling reactions under mild condition, fast reaction rates and high tolerance to functionality is of particular interest to the organic chemistry community in the context of synthesis of highly functionalized complex molecules with sensitive 1,3-diene motifs.

2.1.2 Structure of Copper Carboxylate Complexes

Despite their widespread application, the structures of the copper carboxylates developed in the Liebeskind's laboratory have not been reported. A handful of copper(I) carboxylate complexes have been crystallographically characterized to date, showing polymeric or tetrameric structures in the solid state.[14] Even though copper(I) carboxylate complexes attract special attention due to their rich catalytic and photoluminescence properties,[15] they have not been studied as extensively as their analogous Cu(II) species, due to their air and moisture sensitivity.[16] The Cu(I) complexes increase in stability when olefins, amines, phosphites or phosphines are introduced to the coordination sphere.[17] Cu(I) carboxylate complexes with phosphines have been most intensively studied. The monomeric $[Cu(OOCR)(PPh_3)_2]$, where R = H, CH_3, $C_6H_5CONHCH_2$ *etc.*, exhibited a distorted tetrahedral geometry of Cu(I), with varying degrees of asymmetry and bidentately linked carboxylates. An X-ray structure is shown in **Figure 2.2**, left, illustrating the chelating monoacetate in a complex with triphenylphosphine.[18]

The structure of copper(I)—π-alkyne complexes are also depicted in the literature. To date, only a few copper(I) carboxylate complexes with alkyne ligands have been reported, including $[Cu_2(O_2CC_6H_5)_2(C_{14}H_{10})_2]$, $[Cu_4(O_2CCH_3)_4(C_8H_{18}Si_2)_2]$, $[Cu_4(O_2CCF_3)_4(C_6H_{10})_2]$, $[Cu_2(O_2C(3,4\text{-}F)_2C_6H_3)_2\ (C_{14}H_{10})_2]$, and $[Cu_2(O_2C(3,5\text{-}F)_2C_6H_3)_2(C_{24}H_{18})]_2$.[19] The structure of $[Cu_2(O_2C(3,4\text{-}F)_2C_6H_3)_2(C_{14}H_{10})_2]$ consists of a dicopper(I,I) unit which is cis-bridged by two 3,5-difluorobenzoates. Each copper(I) center coordinates one diphenylacetylene molecule through two alkyne C atoms, involved in an η^2 interaction with the triple bond of an alkyne ligand (**Figure 2.2**, right).

Figure 2.2 Structures of Copper Carboxylate Triphenylphosphine and Alkyne Complexes



We chose to characterize some of the copper carboxylates developed in our laboratory. In addition, we reported the synthesis of a new copper carboxylate and investigated the reactivity of this new copper species in Suzuki cross-coupling reaction to synthesize 1,3-dienes and aryl-alkenes.

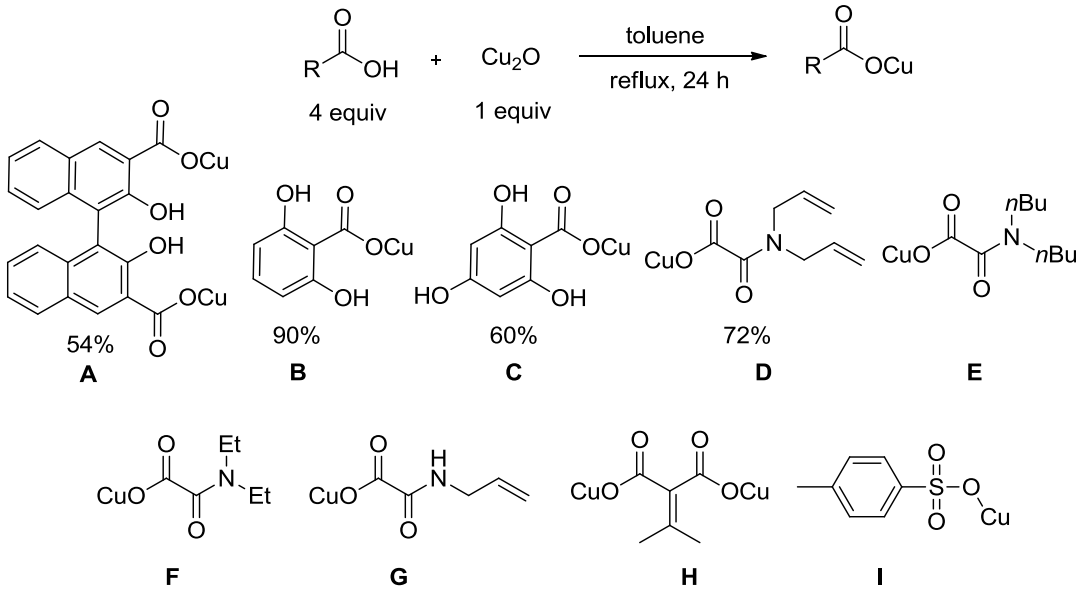
2.2 Results and Discussion

2.2.1 Synthesis of CuDHB and Structure of CuDHB Complexes

The initial attempts to form complexes of CuTC, CuMeSal and CuDPP were not successful. Those three copper species failed to react with styrene, 1,2-diphenylethyne, 1,2-

bis(trimethylsilyl)ethyne) or triphenylphosphine to form stable Cu(I) carboxylate complexes. In order to form a stable copper carboxylate complex, we started to explore the synthesis of new copper carboxylates. Considering that the parent acids of CuTC and CuMeSal are aromatic and contain heteroatoms, it is reasonable to begin investigating copper(I) carboxylates whose parent acids are similar to that of 2-thiophene carboxylic acid and 3-methylsalicylic acid. Copper(I) carboxylates **A**-**D** can be synthesized in the same manner as CuTC through the reaction between the corresponding carboxylic acids and copper(I) oxide in refluxing toluene with the azeotropic removal of water (**Scheme 2.6**). Copper(I) 2,6-dihydroxybenzoate **B** (CuDHB) is a beige white solid which can be stored under air at room temperature for a long period of time. It gradually decomposes to a dark gray solid above 200 ^{o}C. CuDHB has good solubility in polar solvents such as DMF, water, acetone, acetonitrile and THF. Compared to CuDHB, the copper carboxylates **A**, **C** and **D** have poor solubility even in DMF and DMSO. The stability and solubility of CuDHB can be explained by the intramolecular hydrogen bonding between the hydroxyl group and carboxylic acid moiety (**Scheme 2.7**).

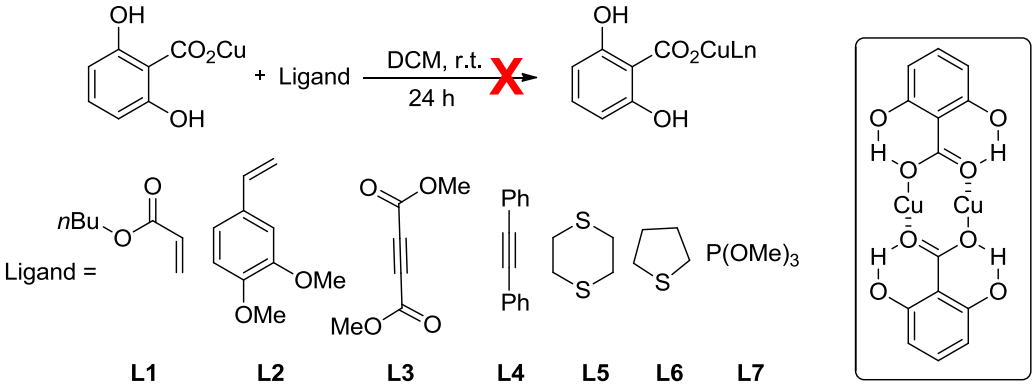
Scheme 2.6 Synthesis of Copper(I) Caroxylates



Attempts to form copper(I) carboxylates **E-G** only resulted the formation of brown oil which became green upon exposure to air indicating the presence of copper(II). It has been reported that long chain (>8 carbons) aliphatic Cu(I) carboxylates can be prepared, which are soluble in hydrocarbon solvents. These Cu(I) carboxylates are typically oils which readily disproportionate in air.[20] Cuprous carboxylates **H-I** could not be obtained possibly due to the poor solubility of the corresponding carboxylic acids in toluene.

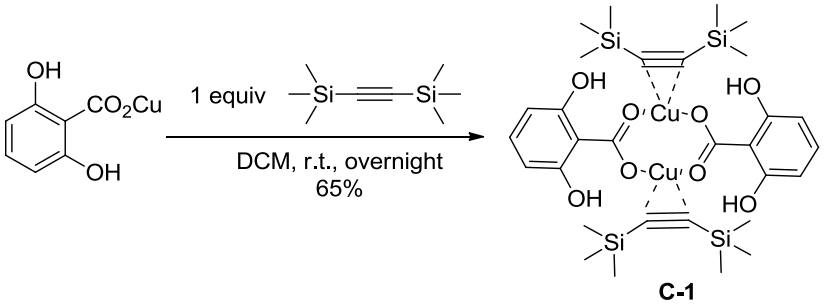
Due to the stability and solubility of CuDHB, it was chosen for further exploration, and was exposed to different alkenes, alkynes, phosphites and organosulfur ligands. Alkenyl and alkynyl ligands with different electronic properties (**L1-L4**), alkyl sulfides (**L5** and **L6**) and trimethylphosphite (**L7**) all failed to react with CuDHB to produce a stable copper carboxylate complex (**Scheme 2.7**).

Scheme 2.7 Ligands Failed to Generate CuDHB Complexes

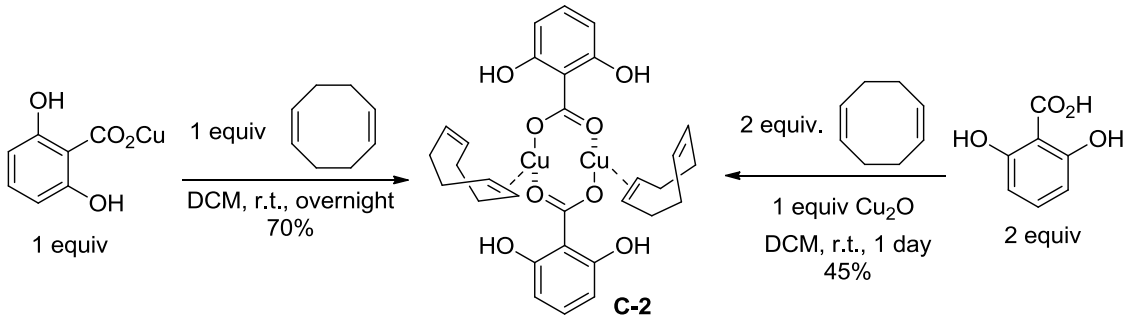


However, the alkyne ligand 1,2-bis(trimethylsilyl) ethyne did react with CuDHB in dichloromethane. After the filtration of a red precipitate presumed to be elemental copper, the leftover dichloromethane was layered with hexanes and stored in the refrigerator to form a white crystal **C-1** (**Scheme 2.8**). Also, another white crystal **C-2** could be generated between the reaction of CuDHB and alkene ligand 1,5-cyclooctadiene (COD). Copper oxide could directly react with 2,6-dihydroxylbenzoic acid and 1,5-cyclooctadiene to produce complex **C-2** (**Scheme 2.9**). Both **C-1** and **C-2** have a general formula $[Cu_2(O_2C(2,6\text{-}OH)_2C_6H_3)_2(ligand)_2]$.

Scheme 2.8 Generation of CuDHB·$Me_3SiC{\equiv}CSiMe_3$ Complex C-1

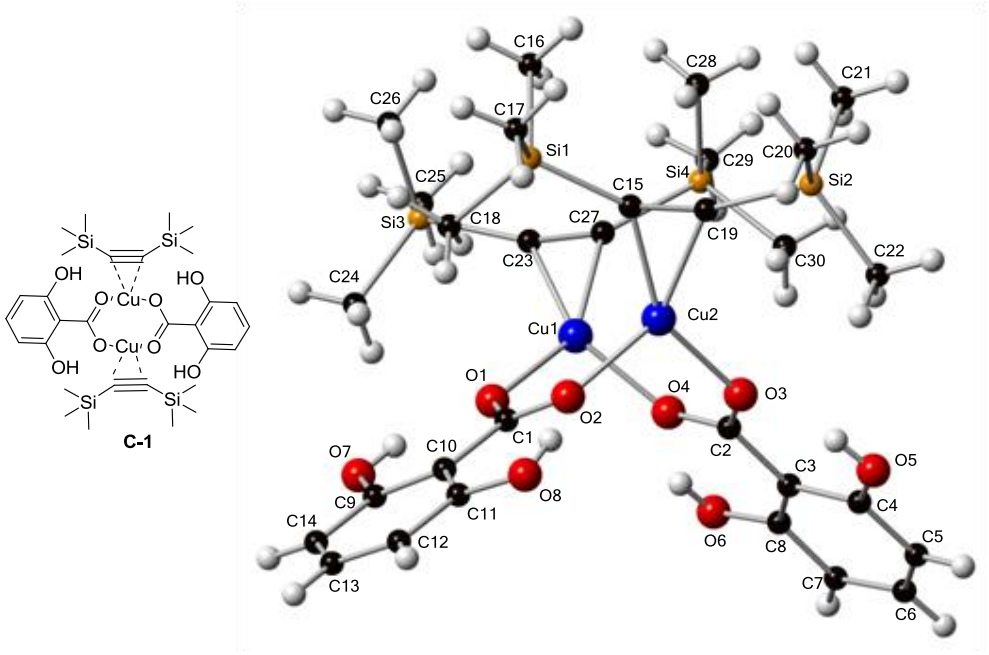


Scheme 2.9 Generation of CuDHB·COD Complex C-2



The structure of complex **C-1** is shown in **Figure 2.3**. Complex **C-1** has a dinuclear copper(I) core which is cis-bridged by two 2,6-dihydroxylbenzoates, similar to that of the previously reported $[Cu_2(O_2C(3,5\text{-}F)_2C_6H_3)_2(C_{14}H_{10})_2]$ (**Figure 2.3**).[19d] Each copper(I) center coordinates one 1,2-bis(trimethylsilyl)ethyne molecule through two alkyne carbon atoms at averaged distance of 2.001(0) Å, in the same range as that generally observed for other copper(I)-π-alkyne complexes (1.95-2.01 Å).[19d] The coordination geometry at each Cu center is considered to be distorted square planar with the inclusion of two carboxylate oxygens and a triple C≡C bond. Complex **C-1** reveals an elongation of the copper-copper distance 3.110(1) Å, compared to 2.782(9) Å in $[Cu_2(O_2C(3,5\text{-}F)_2C_6H_3)_2(C_{14}H_{10})_2]$, indicating a nonbonding interaction.[16]

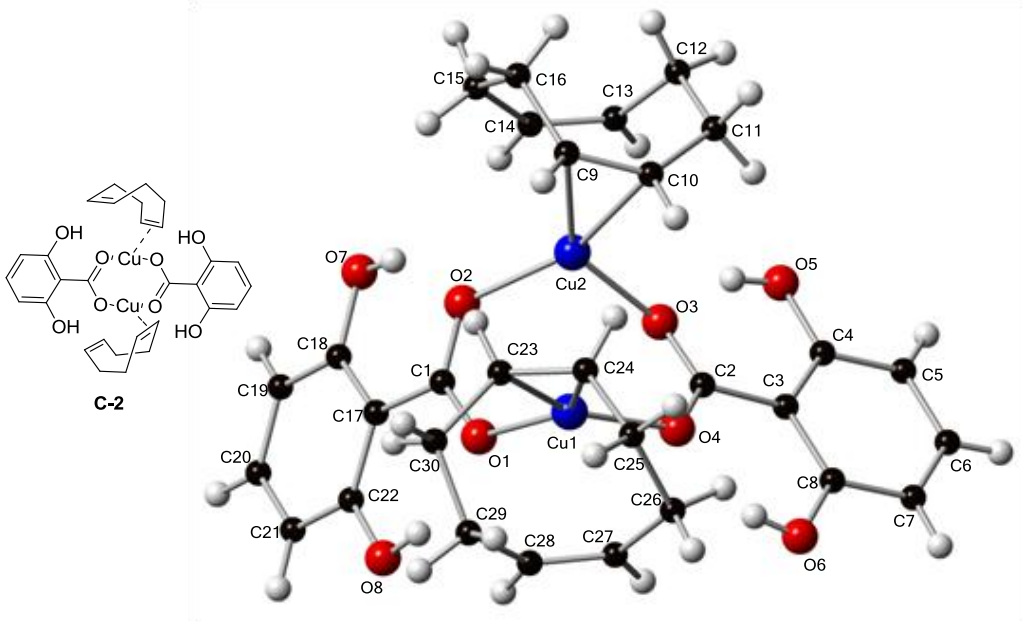
Figure 2.3 X-ray Structure of $[Cu_2(O_2C(2,6\text{-}OH)_2C_6H_3)_2(C_8H_{18}Si_2)_2]$



Blue: Cu; Red: Oxygen; Black: C; White: H; Orange: Si.

Complex **C-2** also has a dinuclear copper(I) core. Each copper(I) center coordinates one 1,5-cyclooctadiene (COD) adopting an η^2 coordination mode (**Figure 2.4**). The distances between Cu1 and the olefinic carbon atoms C23 and C24 are 2.039(1) Å and 2.090(7) Å respectively, thus similar to those of $[Cu_2(CF_3COO)_2(COD)]$ between 2.011(3) and 2.054(3) Å.[21] The distance of Cu1 and C28 of a second double bond from COD is 2.567(2) Å, longer than what is usually reported for copper olefinic carbon bonds of $[Cu_2(CF_3COO)_2(COD)]$ between 2.011(3) and 2.054(3) Å or $[Cu(COD)_2]NTf_2$ between 2.227(6) and 2.329(5) Å.[22] The distance between the Cu1 and Cu2 of **C-2** is 2.90 Å. The structure of **C-2** is slightly different from that reported for $[Cu(CF_3COO)(COD)_{0.5}]$, which shows a 1:0.5 metal to ligand molar ratio and has infinite chains built up through bidentate COD ligand.[21]

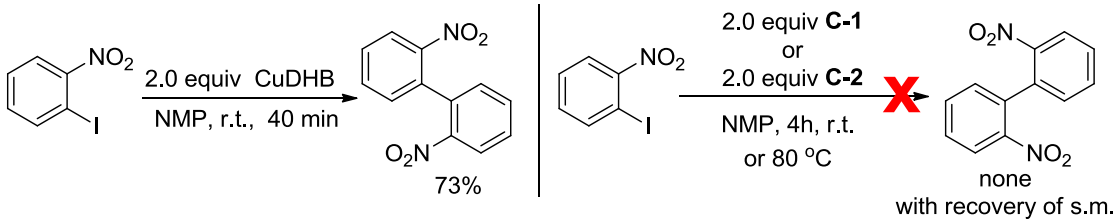
Figure 2.4 X-ray Structure of $[Cu_2(O_2C(2,6\text{-}OH)_2C_6H_3)_2(C_8H_{12})_2]$



Blue: Cu; Red: Oxygen; Black: C; White: C.

The reactivity of **C-1**/**C-2** was tested under Ullmann reductive coupling reactions, see **Scheme 2.10**. Copper(I) carboxylates are capable of inducing reductive coupling of substituted aromatic iodides and bromides efficiently at room temperature.[23] CuDHB mediated the reductive coupling of 1-iodo-2-nitrobenzene to generate 2,2'-dinitro-1,1'-biphenyl in good yield at room temperature. However, CuDHB complexes **C-1** or **C-2** were reluctant to mediate an Ullmann reductive coupling of 1-iodo-2-nitrobenzene even at elevated temperature with near quantitative recovery of starting material (**Scheme 2.10**).

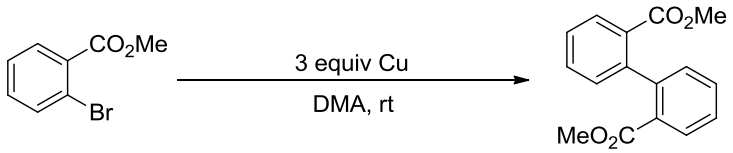
Scheme 2.10 Reactivity of CuDHB and C-1/C-2 in Ullmann Reductive Coupling



2.2.2 The Reactivity of CuDHB and CuDHB Mediated Suzuki Cross-Coupling Reaction

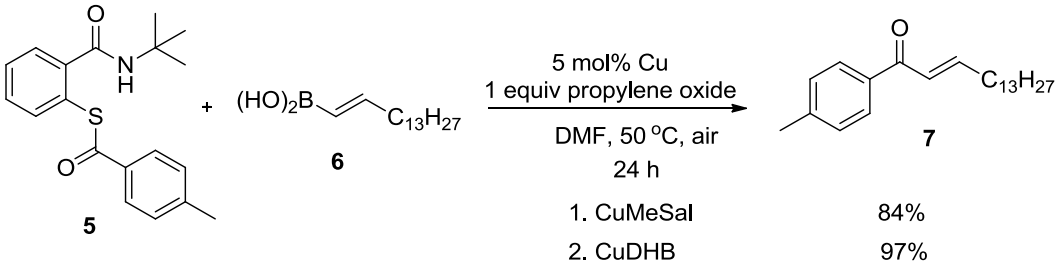
Since CuDHB is a relatively new copper caboxylate,[24] its reactivity was compared with the well known CuMeSal and CuTC (**Figure 2.1**). The reactivity of CuDHB and CuMeSal was first compared in the Ullmann reductive coupling of methyl 2-bromobenzoate (**Scheme 2.11**). Complete consumption of methyl 2-bromobenzoate was observed within 40 minutes using CuDHB, a dramatic increase in the rate of the reaction as compared with CuMeSal.

Scheme 2.11 Comparison of CuDHB and CuMeSal in Ullmann Reductive Coupling



The reactivity of CuDHB and CuMeSal was also tested in the Cu-catalyzed desulfitative cross-coupling reaction of thiol esters and boronic acids.[25] For the reaction of thiol ester **5** and vinyl boronic acid **6** to generate ketone **7**, CuDHB provided better yield than CuMeSal (**Scheme 2.12**). Propylene oxide was added as a mild acid scavenger to minimize proto-deborylation.

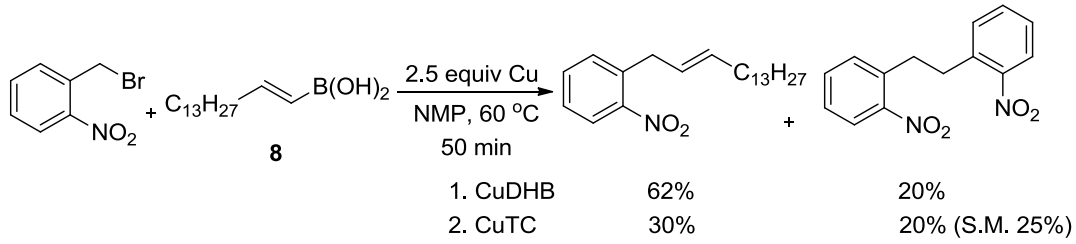
Scheme 2.12 Comparison of CuDHB and CuMeSal in Desulfitative Cross-Coupling Reaction



CuDHB also showed an improvement over CuTC in mediating Suzuki cross-coupling reactions, see **Scheme 2.13**. CuDHB can mediate the reaction between 2-nitro benzyl bromide and vinyl boronic acid **8** to produce the desired cross-coupling product in 62% yield. 1,2-Bis(2-

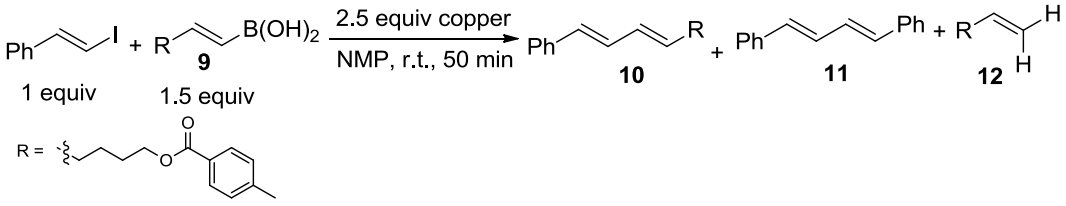
nitrophenyl)ethane was generated as the byproduct from homo-coupling of benzyl bromide. In contrast, CuTC led to only 30% of cross-coupling product together with the recovery of the starting benzyl bromide under the same reaction condition (**Scheme 2.13**).

Scheme 2.13 Reactivity Comparison between CuDHB and CuTC



The increased reactivity of CuDHB in comparison to CuMeSal and CuTC might be a result of the increased solubility and stability of CuDHB in the solvent. Cohen and co-workers have observed enhanced reactivity of Ullmann reductive reaction when using aqueous ammonia to solubilize copper(I) species.[26] Therefore, the promising results of soluble and air-stable CuDHB prompted us to study the Suzuki cross-coupling reaction between (*E*)-(2-iodovinyl)benzene and vinyl boronic acid **9** (**Table 2.1**).

Table 2.1 Copper Mediated Suzuki Cross-Coupling Reaction to Form 1,3-Dienes



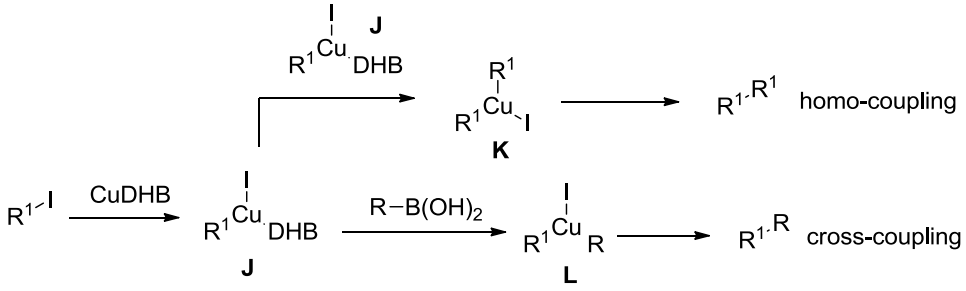
entry	copper source	yield of **10** (%)[a]	yield of **11** (%)[a]	yield of **12** (%)[a]	recovery of S.M. (%)[a]
1	CuDHB	62	22	40	0
2	CuTC	55	25	46	0
3	CuMeSal	43	31	35	0
4	CuDPP	Trace	trace	50	82

[a] Isolated yield. [b] General procedure: Under argon protection, degassed and dried NMP was added to a flask containing vinyliodide (1 equiv), vinylboronic acid (1 equiv) and copper carboxylate (2.5 equiv). The mixture was stirred at room temperature for 50 minutes.

Polar solvents like NMP, DMF and DMI proved to be superior to DCM, toluene and ethyl acetate for this reaction. Among the polar solvents, NMP proved to be the best. Using CuDHB as the mediator, the desired 1,3-diene product **10** was generated in 62% yield, together with vinyl iodide homo-coupling product **11** and proto-deborylation product **12** (**Table 2.1**, entry 1). CuDHB produced a slightly better yield of the desired product when compared to CuTC and CuMeSal (**Table 2.1**, entries 1-3). CuDPP was less effective in the cross-coupling reaction generating only a trace of **10**, most likely due to the poor solubility of CuDPP in NMP (**Table 2.1**, entry 4).

The presumed mechanism of copper mediated Suzuki cross-coupling is shown in **Scheme 2.14**. Compared to copper(I), copper(II) and copper(III) species are known to be more effective at transmetallation with boronic acids.[25] Combined with the fact that homo-coupling product of vinyliodide was obtained as a major byproduct (**Table 2.1**), oxidative addition of copper to the C-I bond instead of transmetallation was proposed as the first step. The Cu(III) specie **J** would be formed as an activated intermediate after oxidative addition. Disproportionation between two molecules of intermediate **J** could produce a new Cu(III) specie **K**. Followed by a reductive elimination, the Ullmann product would then be produced. Following a second path, **J** could initially transmetalate with the boronic acid to give intermediate **L**, followed by reductive elimination to produce the Suzuki cross-coupling product. The similar oxidative addition, transmetallation and reductive elimination process were proposed for CuI/DABCO catalyzed Suzuki cross-coupling reaction.[13a] The rates of the disproportionation and transmetallation steps influence the ratio of homo-coupling and cross-coupling products.

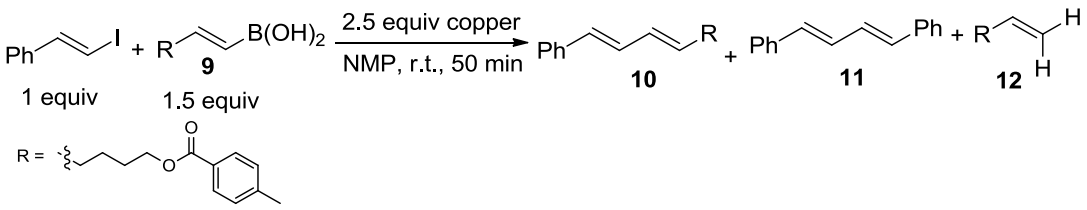
Scheme 2.14 Copper Mediated Suzuki Cross-Coupling Reaction Mechanism

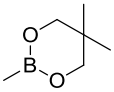
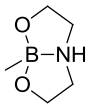
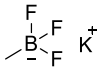


Based on the proposed mechanism, the undesired homo-coupling product could be minimized by lowering the concentration of intermediate **J** or by increasing the rate of transmetallation. Based on this proposal, CuDHB was added to the reaction mixture of (*E*)-*β*-iodostyrene and vinylboronic acid **9** portionwise to reduce the concentration of Cu(III) intermediate **J**. Indeed, the undesired homo-coupling product **11** could be minimized by following this procedure (**Table 2.2**, entries 1 and 2). Adding vinyliodide into the reaction mixture of CuDHB and vinylboronic acid could also reduce the formation of homo-coupling product **11** with a lower yield of the desired cross-coupling product **10** and an increase of proto-deborylation product **12** (entries 2 and 3).

The proto-deborylation reaction is still problematic. Vinylboronic acids are inherently unstable during benchtop storage and under cross-coupling reaction conditions.[27] Adding boronic acid last into the reaction failed to eliminate proto-deborylation product but gave a rise to homo-coupling product (entry 4). Other boronic acid surrogates including boronic esters and trifluoroborate salt known to be more stable under cross-coupling conditions were less reactive (**Table 2.2**, entries 5-7). Those results suggest that without activation *via* a base or the use of an aqueous solution, boronic esters and trifluoroborate salt were less prone to transmetallation.

Table 2.2 Optimization of the Cross-Coupling Reaction

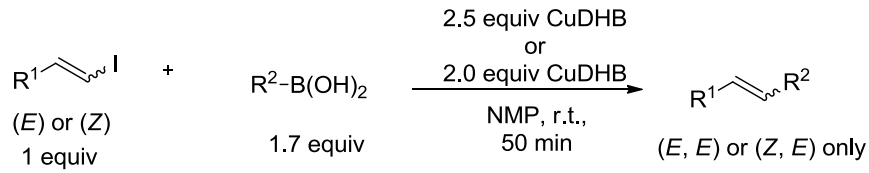


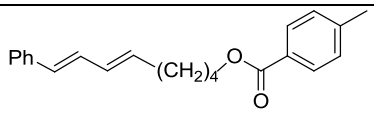
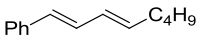
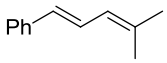
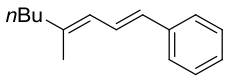
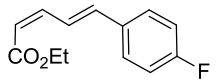
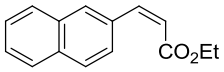
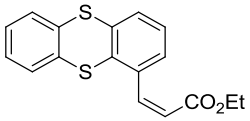
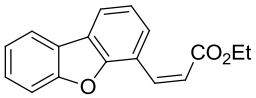
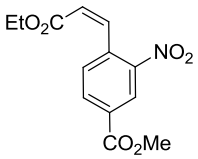
entry	"B"	yield of **10** (%)[b]	yield of **11** (%)[b]	yield of **12** (%)[b]	recovery of s.m. (%)[b]
1[c]	—$B(OH)_2$	62	22	40	0
2	—$B(OH)_2$	70	trace	30	0
3[d]	—$B(OH)_2$	56	0	45	30
4[e]	—$B(OH)_2$	58	30	50	0
5		56	30	47	10
6		12	19	70	62
7		none	35	none	60

[a] General procedure: Under argon protection, 2.5 equivalent of CuDHB was added to the solution of vinyliodide (1.0 equiv) and vinylboronic acid (1.5 equiv) in degassed NMP (1 M) portionwise (0.5 equivalent every 5 min). The reaction mixture was stirred at room temperature for 50 min. [b] Isolated yields. [c] Degassed NMP (1 M) was added to the flask containing CuDHB (2.5 equiv), vinyliodide (1.0 equiv) and vinylboronic acid (1.5 equiv) at once. [d] Vinyliodide (1.0 equiv) was added to the reaction mixture of vinylboronic acid (1.5 equiv) and CuDHB (2.5 equiv) in degassed NMP dropwise during 10 min. [e] Boronic acid (1.5 equiv) was added to the reaction mixture of vinyliodide (1.5 equiv) and CuDHB (2.5 equiv) in degassed NMP portionwise (0.5 equivalent every 5 min).

Using mixed solvent systems such as NMP/hexanes, NMP/toluene and NMP/DCM to dissolve the copper salt slowly, the proto-deborylation product still could not be minimized. However, a good reaction was achieved by using an excess of the boronic acid (1.7 equivalent) (**Table 2.3**). Cis and trans vinyl iodide were found to react with vinyl boronic acid to produce the desired 1,3-dienes (**Table 2.3**, entries 1-5). Vinyl boronic acid and vinyl iodide with steric hindrance were not as reactive leading to the incomplete consumption of starting materials (**Table 2.3**, entries 3 and 4).

Table 2.3 Suzuki Cross-Coupling from Vinyl Iodides and Boronic Acids



entry	R^1	R^2	product	yield (%)[e]
1	(*E*)-*β*-iodostyrene	(*E*)-(6-((4-methylbenzoyl)oxy)hex-1-en-1-yl)		78
2	(*E*)-*β*-iodostyrene	(*E*)-hex-1-en-1-yl		72
3[b]	(*E*)-*β*-iodostyrene	(2-methylprop-1-en-1-yl)		35
4[c]	(*E*)-1-iodo-2-methylhex-1-ene	(*E*)-styryl		40
5	Ethyl (*Z*)-*β*-iodoacrylate	(*E*)-(4-fluorostyryl)		71
6[d]	Ethyl (*Z*)-*β*-iodoacrylate	naphthalen-2-yl		47
7[d]	Ethyl (*Z*)-*β*-iodoacrylate	thianthren-1-yl		69
8[d]	Ethyl (*Z*)-*β*-iodoacrylate	dibenzo[b,d]furan-4-yl		64
9[d]	Ethyl (*Z*)-*β*-iodoacrylate	(4-(methoxycarbonyl)-2-nitrophenyl)		70

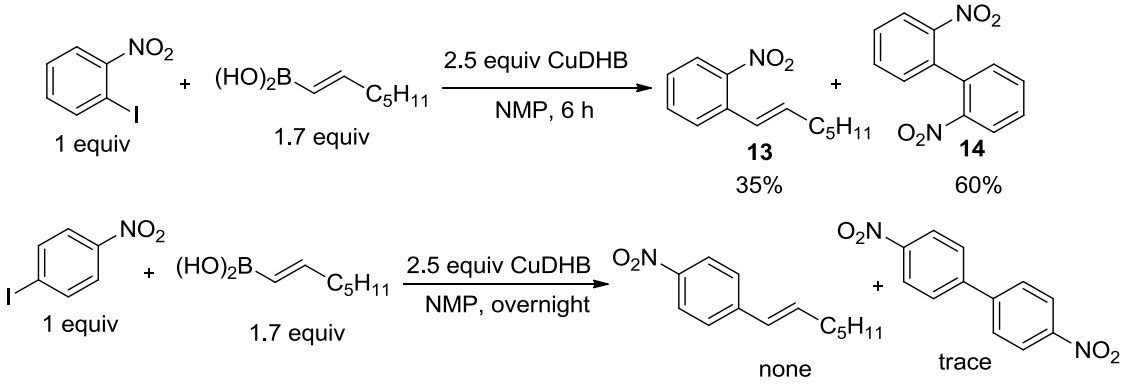
[a] General procedure: Under argon protection, 2.5 equiv of CuDHB was added into the solution of 1 equiv of vinyl iodide and 1.7 equiv of boronic acids in the solution of NMP (1M) portionwise (0.5 equiv of CuDHB every 5 minutes). The reaction was quenched after another 30 minutes of stirring at room temperature. [b] with the recovery of vinyliodide starting material 53%. [c] with the recovery of vinyliodide starting material 50%. [d] reaction heated at 60 °C. [e] Isolated yield.

In addition to vinyl boronic acids, aryl boronic acids could also be applied in the transformation at higher temperature (60 °C) to generate aryl-alkenes (**Table 2.3**, entries 6-9).

Interestingly, arylboronic acids with *ortho* directing groups (S, O) reacted more efficiently to produce Suzuki cross-coupling products in better yields (**Table 2.3**, entries 7-9).

Unfortunately, attempts to expand the scope from vinyl iodides to aryl iodides proved unsatisfactory (**Scheme 2.15**). The rate of generating the Ullmann homo-coupling product **14** occurs more quickly than the formation of the cross-coupling product **13**, yielding biaryl compound **14** as the major product. Interestingly 1-iodo-4-nitrobenzene failed to react with vinyl boronic acid at all, suggesting the requirement of precoordination of the substrate to copper prior to oxidative addition to C-I bond.

Scheme 2.15 Suzuki Cross-Coupling from Aryl Iodides and Boronic Acids



2.3 Conclusion

In summary, a new copper(I) carboxylate CuDHB was synthesized. The X-ray structures of CuDHB complexes $[Cu_2(O_2C(2,6\text{-}OH)_2C_6H_3)_2(C_8H_{18}Si_2)_2]$ and $[Cu_2(O_2C(2,6\text{-}OH)_2C_6H_3)_2(C_8H_{12})_2]$ proved to be dinuclear copper(I) complexes. CuDHB is air-stable and has good solubility in most polar solvents. CuDHB showed some modest improvement over CuTC, CuMeSal and CuDPP in the Ullmann reductive reaction as well as various cross-coupling reactions. A CuDHB mediated Suzuki cross-coupling reaction was developed for the synthesis of 1,3-dienes between vinyl iodides and vinyl boronic acids under mild reaction condition. Aryl boronic acids with *ortho*-coordination groups could also act as effective coupling partners with vinyl iodides in the Suzuki cross-coupling reaction to synthesize aryl-alkenes. Aryl iodide with *ortho*-ligation group

undergoes Ullmann reductive coupling reactions faster than Suzuki cross-coupling. An example of CuDHB mediated Suzuki cross-coupling between 1-(bromomethyl)-2-nitrobenzene and vinyl boronic acid was also reported.

2.4 Experimental

2.4.1 General Experimental

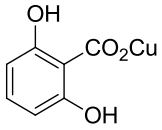
^{1}H and ^{13}C NMR spectra were recorded on Inova 400 MHz spectrometers in deuteriochloroform ($CDCl_3$) with the solvent residual peak as internal reference unless otherwise stated ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported (Hz); integration is provided. Infrared spectra were recorded on a Nicolet 380 FT-IR spectrometer with a diamond plate. Peaks are reported (cm^{-1}) with the following relative intensities: vs (very strong), s (strong), m (medium), w (weak), and br (broad). Uncalibrated melting points were taken on a *Thomas-Hoover* melting point apparatus in open capillary tubes. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator. Visualization was accomplished by UV light, or with solutions of ninhydrin in ethanol or *p*-anisaldehyde in ethanol. Purification by chromatography was performed using Whatman 60Å 230-400 mesh SiO_2 with compressed air as a source of positive pressure. Solvents for reactions and chromatography were reagent grade and used as received. "Brine" refers to a saturated aqueous solution of NaCl. Solutions of NH_4Cl, $NaHCO_3$ refer to saturated aqueous solutions. Solvents used as reaction media were purchased in > 99% purity without further purification, unless otherwise specified.

2.4.2 Starting Material

(*E*)-(2-Iodovinyl)benzene, Cu_2O, 2,6-dihydroxybenzoic acid, butyl acrylate, 1,2-dimethoxy-4-vinylbenzene, dimethyl but-2-ynedioate, 1,2-diphenylethyne, 1,4-dithiane, tetrahydrothiophene,

trimethyl phosphite, (1*Z*,5*Z*)-cycloocta-1,5-diene, 1,2-bis(trimethylsilyl)-ethyne, 2,2-dimethylpropane-1,3-diol, (*Z*)-ethyl 3-iodoacrylate, 1-iodo-2-nitrobenzene, 1-iodo-4-nitrobenzene, 1-(bromo methyl)-2-nitrobenzene, and 1-(bromomethyl)-4-nitrobenzene were purchased from Sigma-Aldrich and used without further purification. All the boronic acids except for (*E*)-(6-((4-methylbenzoyl)oxy)hex-1-en-1-yl)boronic acid and (*E*)-hex-1-en-1-ylboronic acid were from Synthonix and used without further purification. CuTC, CuMeSal and CuDPP were synthesized by others in the Liebeskind laboratory.[6]

((2,6-Dihydroxybenzoyl)oxy)copper



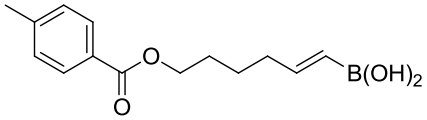
Prepared according to the literature procedure for the preparation of CuTC.[6] A 250 mL round bottomed flask was charged with 2,6-dihydroxybenzoic acid (8 g, 51.9 mmol, 4 equiv), Cu_2O (1.86 g, 13.0 mmol, 1 equiv) and tolene (25 mL). The flask was connected to a Dean-Stark trap and condenser. The mixture refluxed for one day with azeotropic removal of water. The light yellow suspension was cooled to room temperature, then filtrated with a fine pore fritted glass funnel. Under a stream of nitrogen with an inverted funnel, the filter cake was washed with methanol (20 mL) to remove excess acid, and then with ether until the eluant was colorless, and then with a small amount of hexanes. The product was dried under a flow of nitrogen, then transferred to a flask and dried further under vacuum. The product was obtained as a white powder (2.5 g, 90%); IR (neat, cm^{-1}): 3027 (br), 1648 (s), 1586 (s), 1558 (vs), 1449 (s), 1395 (vs), 1330 (s), 1288 (s), 1210 (vs), 1150 (s), 1022 (s), 809 (s), 687 (s). Anal. Calcd for $C_7H_5O_4Cu$: C, 38.81; H, 2.33. Found: C, 38.49; H, 2.28.

Preparation of Vinylboronic Acids

To the solution of alkyne (1 equiv) in dichloromethane (1 M) was added dibromoborane dimethyl sulfide (1 equiv) at 0 ^oC. The reaction mixture was stirred at room temperature

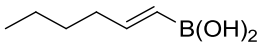
overnight. Diethyl ether and cold water were added into the reaction mixture and stirred for 1 hour. The reaction mixture was washed with $NaHCO_3$ and then extracted into ethyl acetate. The combined organic layers were dried with anhydrous Na_2SO_4, then filtrated and concentrated on vacuum. Chromatographic purification afforded the desired vinylboronic acids.

(*E*)-(6-((4-Methylbenzoyl)oxy)hex-1-en-1-yl)boronic acid[28]



Prepared according to general procedure from hex-5-yn-1-yl 4-methylbenzoate (0.85 g, 3.94 mmol) and purified by column chromatography (silica gel, 3:1 hexanes: EtOAc) to give the product as a white solid 0.93 g (90%, with a 0.9 : 1 ratio of boroxin and boronic acid); Mp 70-74 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 3.8H), 7.22 (d, *J* = 7.8 Hz, 3.8H), 6.96 (dt, *J* = 6.6 Hz, 18.0 Hz, 0.9H, boroxin), 6.53 (dt, *J* = 6.6 Hz, 18.0 Hz, 1H, boronic acid), 5.56 (d, *J* = 18.0 Hz, 0.9H, boroxin), 5.44 (d, *J* = 18.0 Hz, 1H), 4.85 (brs, 1.8H), 4.32-4.29 (m, 3.8H), 2.40 (s, 5.4H), 2.29 (q, *J* = 6.6 Hz, 1.8H, boroxin), 2.23 (q, *J* = 6.6 Hz, 2H, boronic acid), 1.82-1.75 (m, 3.8H), 1.65-1.54 (m, 3.8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 167.1, 157.1, 152.1, 143.8, 143.7, 129.8, 129.3, 127.8, 127.7, 64.9, 35.4, 35.3, 28.5, 28.4, 24.9, 24.8, 21.9; IR (neat, cm^{-1}): 3351 (br), 2934 (w), 1688 (s), 1634 (w), 1374 (s), 1280 (vs), 1094 (s), 954 (m), 751 (s).

(*E*)-Hex-1-en-1-ylboronic acid[29]

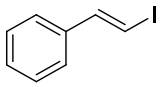


Prepared according to general procedure from hex-1-yne (0.60 g, 7.34 mmol) and purified by column chromatography (silica gel, 3:1 hexanes: EtOAc) to give the product as a white solid 0.80 g (85%, with a 1 : 0.6 ratio of boroxin and boronic acid); Mp 86-90 ^oC [Lit[28] 90-93 ^oC]; ^1H NMR (600 MHz, $CDCl_3$) δ 6.96 (dt, *J* = 6.6 Hz, 18.0 Hz, 1H, boroxin), 6.51 (dt, *J* = 6.6 Hz, 18.0 Hz, 0.6H, boronic acid), 5.54 (d, *J* = 18.0 Hz, 1H, boroxin), 5.40 (d, *J* = 18.0 Hz, 0.6H, boronic acid), 4.34 (brs, 1.2H), 2.23-2.14 (m, 3.2H), 1.46-1.25 (m, 6.4H), 0.92-0.88 (m, 4.8H); ^{13}C NMR (150

MHz, $CDCl_3$) δ 158.1, 153.3, 35.6, 35.5, 30.7, 30.6, 22.5, 22.4, 14.2; IR (neat, cm^{-1}): 3198 (br), 2926 (m), 1635 (s), 1354 (vs), 1263 (m), 1160 (s), 993 (s), 825 (m), 594 (w).

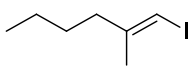
Preparation of Vinyliodide

(*E*)-(2-Iodovinyl)benzene[30]



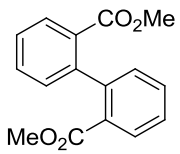
Prepared from benzaldehyde (1.0g, 9.41 mmol) according to Cook's protocol[30] and purified by column chromatography (silica gel, hexanes) to give the product as a yellow oil (1.71 g,79%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 15.0 Hz, 1H), 7.34-7.29 (m, 5H), 6.83 (d, *J* = 15.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.2, 137.9, 128.9, 128.6, 126.2, 79.6; IR (neat, cm^{-1}): 3056 (w), 1595 (m), 1493 (M), 1168 (s), 943 (vs), 723 (vs), 686 (vs), 549 (s).

(*E*)-1-Iodo-2-methylhex-1-ene.[31a]



Prepared from hex-1-yne (0.55 g, 6.69 mmol) according to Wipf's protocol[31b] and purified by column chromatography (silica gel, hexanes) to give the product as a light yellow oil (0.75 g, 50%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 2.18 (t, *J* = 7.6 Hz, 2H), 1.80 (s, 3H), 1.43-1.35 (m, 2H), 1.27 (quintet, *J* = 7.2 Hz, 2H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 74.5, 39.7, 30.0, 24.2, 22.2, 13.9; IR (neat, cm^{-1}): 3056 (w), 2955 (vs), 2927 (vs), 2870 (m), 2858 (m), 1616 (w), 1456 (m), 1266 (vs), 1142 (s), 762 (s), 666 (s).

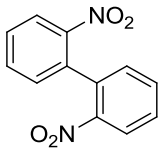
Dimethyl [1,1'-biphenyl]-2,2'-dicarboxylate[23]



Methyl 2-bromobenzoate (43 mg, 0.2 mmol) was added to a slurry of CuDHB (130 mg, 0.6 mmol) in NMP (1.5 mL). The mixture was stirred for 40 min and then diluted with Et_2O (10 mL). The resulting slurry was filtered through a plug of SiO_2 using Et_2O and the solution was washed

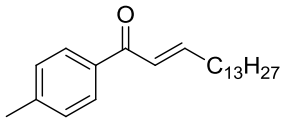
with saturated NH_4Cl solution (30 mL). The aqueous layer was extracted with Et_2O (30 mL) and the combined Et_2O layers were dried with Na_2SO_4 and filtered. After removing the solvent, the residue was purified by column chromatography (silica gel, 19:1 hexnanes: EtOAc) to give the product as a white solid 36 mg (67%); Mp 70-72 ^oC [Lit[22] 69-71 ^oC]. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, *J* =7.5, 1.2 Hz, 2H), 7.52 (dt, *J* = 7.5, 1.5 Hz, 2H), 7.41 (dt, *J* = 7.5, 1.2 Hz, 2H), 7.20 (dd, *J* = 7.5, 1.2 Hz, 2H), 3.60 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.1, 143.0, 131.2, 130.0, 129.6, 129.1, 126.9, 51.5.

2,2'-Dinitro-1,1'-biphenyl[32]



1-Iodo-2-nitrobenzene (50 mg, 0.2 mmol) was added to a slurry of CuDHB (87 mg, 0.4 mmol) in NMP (1.5 mL). The mixture was stirred for 30 min and then diluted with Et_2O (10 mL). The resulting slurry was filtered through a plug of SiO_2 using Et_2O and the solution was washed with saturated NH_4Cl solution (30 mL). The aqueous layer was extracted with Et_2O (30 mL) and the combined Et_2O layers were dried with Na_2SO_4 and filtered. After removing the solvent, the residue was purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to give the product as a white solid 36 mg (73%); Mp 123-125 ^oC [Lit[31] 124-126 ^oC]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 134.5, 133.6, 131.1, 128.4, 125.0. IR (neat, cm^{-1}): 3172 (w), 1625 (w), 1363 (s), 1048 (w).

(*E*)-1-(*p*-Tolyl)hexadec-2-en-1-one[25]



S-(2-(*tert*-Butylcarbamoyl)phenyl) 4-methylbenzothioate (65 mg, 0.2 mmol) was placed in a 10 mL test tube with a magnetic stir bar. CuDHB (2.2 mg, 0.01 mmol) was added followed by (*E*)-

pentadec-1-en-1-ylboronic acid (127 mg, 0.5 mmol) and propylene oxide (0.015 mL, 0.22 mmol). Then 1.6 mL of dry dimethylformamide (DMF) was added and the reaction was allowed to sir in air at 50 ^{o}C for 24 hours. The reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted three times with 15 mL diethyl ether. After removing the solvent, the residue was purified by column chromatography (silica gel, 9:1 hexanes: EtOAc) to give the product as a white solid 64 mg (97%). Mp 42-43 ^{o}C [Lit[25] 40 ^{o}C]; ^{1}H 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 (100 MHz, $CDCl_3$) δ 190.6, 149.8, 143.5, 135.6, 129.4, 128.8, 125.9, 33.0, 31.2, 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), 1664 (s), 1618 (s).

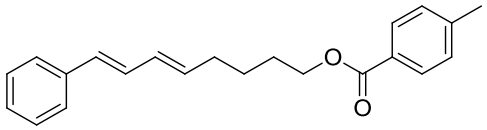
General Procedure for Copper Carboxylate Mediated Cross-Coupling Reaction

Method A: A 10 mL Schlenk flask was charged with vinyliodide (1.0 equiv) and vinylboronic acid (1.7 equiv). Under argon protection, degassed dry NMP (1M) was added into the flask and the suspension was stirred at room temperature. ((2,6-Dihydroxybenzoyl)oxy)copper (2.5 equiv) was added into the solution five times during 20 minutes (0.5 equiv per 5 minutes interval). The reaction mixture was stirred for another 30 minutes and then diluted with ether. The organic layer was washed with saturated ammonium chloride solution and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated on vacuum. Chromatographic purification afforded the desired products.

Method B: A 10 mL Schlenk flask was charged with vinyliodide (1.0 equiv) and arylboronic acid (1.7 equiv). Under argon protection, degassed dry NMP (1M) was added into the flask and the suspension was stirred at 60 ^{o}C. ((2,6-Dihydroxybenzoyl)oxy)copper (2.0 equiv) was added into the solution five times during 20 minutes (0.4 equiv per 5 minutes interval). The reaction mixture was stirred for another 30 minutes and then diluted with ether. The organic layer was

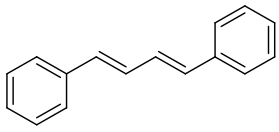
washed with saturated ammonium chloride solution and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated on vacuum. Chromatographic purification afforded the desired products.

(5*E*,7*E*)-8-Phenylocta-5,7-dien-1-yl 4-methylbenzoate



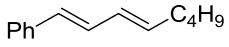
Prepared according to **Method A** from (*E*)-(2-iodovinyl)benzene (35 mg, 0.15 mmol) and (*E*)-(6-((4-methylbenzoyl)oxy)hex-1-en-1-yl)boronic acid (67 mg, 0.26 mmol), then purified by column chromatography (silica gel, 49:1 hexanes: EtOAc) gave the product as a colorless oil 34 mg (70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.75 (dd, *J* = 10.8 Hz, 15.6 Hz, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 6.23 (dd, *J* = 10.8 Hz, 15.0 Hz, 1H), 5.83 (dt, *J* = 7.2 Hz, 15.0 Hz, 1H), 4.32 (t, *J* = 6.6 Hz, 2H), 2.41 (s, 3H), 2.23 (q, *J* = 7.2 Hz, 2H), 1.81 (quintet, *J* = 6.6 Hz, 2H), 1.59 (quintet, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 143.7, 137.7, 137.4, 135.2, 131.3, 130.6, 129.8, 129.4, 129.3, 128.8, 127.4, 126.4, 65.0, 32.6, 28.5, 25.9, 21.9; IR (neat, cm^{-1}): 3021 (w), 2932 (w), 1710 (vs), 1611 (m), 1447 (w), 1269 (vs), 1176 (s), 1106 (s), 986 (m), 751 (m), 689 (m). HRMS (EI) Calcd for $C_{22}H_{25}O_2$ (M+H) 321.1855, found: 321.1859.

(1*E*,3*E*)-1,4-Diphenylbuta-1,3-diene[32]



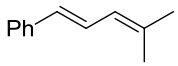
Generated as a white solid byproduct from the reaction preparing (5*E*,7*E*)-8-phenylocta-5,7-dien-1-yl 4-methylbenzoate. Mp 152-154 ^{o}C [Lit[31] 150-152 ^{o}C]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, J = 7.2 Hz, 4H), 7.34 (t, J = 7.2 Hz, 4H), 7.24 (t, J = 7.2 Hz, 2H), 6.99-6.94 (m, 2H), 6.71-6.66 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.6, 133.0, 129.5, 128.9, 127.8, 126.6; IR (neat, cm^{-1}): 3054 (w), 3015 (m), 1489 (s), 1443 (s), 1259 (s), 983 (vs), 736 (vs), 687 (vs).

(1*E*,3*E*)-Octa-1,3-dien-1-ylbenzene[33]



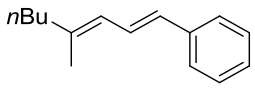
Prepared according to **Method A** from (*E*)-*β*-iodostyrene (30 mg, 0.13 mmol) and hex-1-en-1-ylboronic acid (28 mg, 0.22 mmol), then purified by column chromatography (silica gel, 49:1 hexanes: EtOAc) to give the product as a colorless oil 17 mg (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 6.75 (dd, *J* = 10.8, 15.6 Hz, 1H), 6.42 (d, *J* = 15.6 Hz, 1H), 6.19 (dd, *J* = 10.8, 15.6 Hz, 1H), 5.82 (dt, *J* = 7.2, 15.0 Hz, 1H), 2.16-2.13 (m, 2H), 1.35-1.32 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.3, 130.5, 130.0, 129.6, 128.8, 127.3, 126.5, 32.6, 31.4, 22.4, 14.0. IR (neat, cm^{-1}): 3048 (w), 3001 (m), 1492 (s), 1462 (s), 745 (vs).

(*E*)-(4-Methylpenta-1,3-dien-1-yl)benzene[34]



Prepared according to **Method A** from (*E*)-*β*-iodostyrene (31 mg, 0.13 mmol) and (2-methylprop-1-en-1-yl)boronic acid (22 mg, 0.22 mmol), then purified by column chromatography (silica gel, 49:1 hexanes: EtOAc) to give the product as a colorless oil 7.2 mg (35%) with the recovery of (*E*)-*β*-iodostyrene 16 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 3H), 7.15 (t, *J* = 6.8 Hz, 2H), 6.92 (dd, *J* = 10.8, 15.6 Hz, 1H), 6.35 (d, *J* = 16.2 Hz, 1H), 6.01 (d, *J* = 10.4 Hz, 1H), 1.86, 1.84 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 136.7, 129.6, 128.5, 126.9, 126.3, 125.9, 125.6, 26.4, 18.3. IR (neat, cm^{-1}): 3054 (w), 1684 (m), 1640 (s), 1598 (vs), 989 (s).

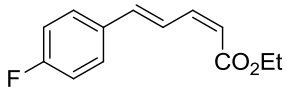
((1*E*,3*E*)-4-Methylocta-1,3-dien-1-yl)benzene[35]



Prepared according to **Method A** from (*E*)-*β*-iodostyrene (29 mg, 0.12 mmol) and (*E*)-styrylboronic acid (30 mg, 0.20 mmol), then purified by column chromatography (silica gel, 49:1 hexanes: EtOAc) to give the product as a colorless oil 9.6 mg (40%) with the recovery of (*E*)-*β*-iodostyrene 15 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.44 (m, 2H), 7.39-7.23 (m, 3H),

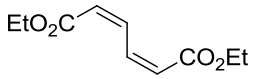
7.02 (d, *J* = 15.2 Hz, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 6.07 (d, *J* = 10.8 Hz, 1H), 2.24 (t, *J* = 7.2 Hz, 2H), 1.89 (s, 3H), 1.45-1.30 (m, 4H), 0.95 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 138.3, 129.7, 128.6, 126.6, 126.1, 125.5, 124.8, 39.5, 32.7, 30.3, 22.6, 14.1. IR (neat, cm^{-1}): 3035 (w), 2957 (w), 1641 (m), 1589 (s), 962 (s), 764 (m).

(2*Z*,4*E*)-Ethyl 5-(4-fluorophenyl)penta-2,4-dienoate



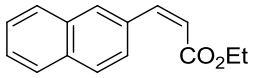
Prepared according to **Method A** from (*Z*)-ethyl 3-iodoacrylate (25 mg, 0.11 mmol) and (E)-(4-fluorostyryl)boronic acid (31 mg, 0.19 mmol), then purified by column chromatography (silica gel, 19:1 hexanes: EtOAc) to give the product as a colorless oil 17 mg (71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 11.4 Hz, 15.6 Hz, 1H), 7.50-7.48 (m, 2H), 7.03 (dt, *J* = 2.4 Hz, 7.8 Hz, 2H), 6.77 (d, *J* = 15.6 Hz, 1H), 6.72 (t, *J* = 11.4 Hz, 1H), 5.72 (d, *J* = 11.4 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 164.2, 162.5, 144.8, 139.9, 132.8, 129.3, 124.9, 117.7, 116.1, 115.9, 60.3, 14.6; IR (neat, cm^{-1}): 2982 (w), 1708 (s), 1623 (m), 1569 (s), 1507 (s), 1227 (s), 1178 (vs), 1156 (vs), 1027 (m), 817 (s). HRMS (EI) Calcd for $C_{13}H_{14}FO_2$ (M+H) 221.0978, found: 221.0977.

(2*Z*,4*Z*)-Diethyl hexa-2,4-dienedioate[36]



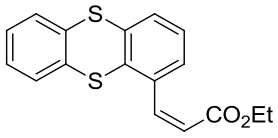
Generated as a byproduct from the reaction preparing (2*Z*,4*E*)-Ethyl 5-(4-fluorophenyl)penta-2,4-dienoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.84 (m, 2H), 5.99-5.91 (m, 2H), 4.19 (q, *J* = 7.2 Hz, 4H), 1.29 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 138.2, 124.4, 61.3, 14.6; IR (neat, cm^{-1}): 2985 (w), 2967 (w), 2904 (w), 1712 (vs), 1589 (s), 1369 (vs), 1217 (s), 1160 (vs), 1026 (vs), 830 (s), 749 (m).

(*Z*)-Ethyl 3-(naphthalen-2-yl)acrylate[37]



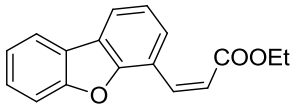
Prepared according to **Method B** (heating at 80 °C) from (*Z*)-ethyl 3-iodoacrylate (36 mg, 0.16 mmol) and naphthalen-2-ylboronic acid (47 mg, 0.27 mmol), then purified by column chromatography (silica gel, 19:1 hexanes: EtOAc) to give the product as a colorless oil 17 mg (47%).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.84-7.79 (m, 3H), 7.72 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 7.52-7.45 (m, 2H), 7.10 (d, *J* = 12.6 Hz, 1H), 6.02 (d, *J* = 12.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 143.2, 133.7, 133.1, 132.7, 130.1, 128.7, 127.8, 127.6, 127.2, 126.9, 126.4, 120.3, 60.6, 14.4; IR (neat, cm^{-1}): 2979 (w), 1713 (vs), 1623 (m), 1369 (m), 1156 (vs), 1027 (s), 860 (s), 828 (s), 741 (s).

(*Z*)-Ethyl 3-(thianthren-1-yl)acrylate



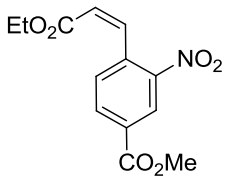
Prepared according to **Method B** from (*Z*)-ethyl 3-iodoacrylate (16 mg, 0.07 mmol) and thianthren-1-ylboronic acid (31 mg, 0.12 mmol), then purified by column chromatography (silica gel, 19:1 hexanes: EtOAc) to give the product as a white solid 13 mg (69%). Mp 88-90 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49-7.46 (m, 3H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 12.0 Hz, 1H), 7.26-7.21 (m, 3H), 6.11 (d, *J* = 12.0 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 141.1, 136.2, 135.7, 135.5, 135.2, 129.09, 129.05, 128.98, 128.92, 128.2, 127.9, 126.9, 122.7, 60.6, 14.2; IR (neat, cm^{-1}): 3047 (w), 2967 (w), 2924 (w), 1724 (vs), 1631 (s), 1446 (s), 1382 (s), 1224 (s), 1182 (s), 1036 (m), 808 (s), 722 (s), 692 (m). HRMS (EI) Calcd for $C_{17}H_{15}O_2S_2$ (M+H) 315.0514, found: 315.0517.

(*Z*)-Ethyl 3-(dibenzo[b,d]furan-4-yl)acrylate[37]



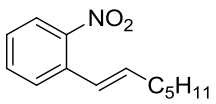
Prepared according to **Method B** from (*Z*)-ethyl 3-iodoacrylate (20 mg, 0.09 mmol) and dibenzo[b,d]furan-4-ylboronic acid (32 mg, 0.15 mmol), then purified by column chromatography (silica gel, 19:1 hexanes: EtOAc) to give the product as a white solid 16 mg (64%). Mp 54-56 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, J = 7.6 Hz, 2H), 7.82 (d, J = 6.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 12.8 Hz, 1H), 7.38-7.32 (m, 2H), 7.20 (d, *J* = 12.8 Hz, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 1.15 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 156.1, 154.2, 135.9, 128.1, 127.5, 124.3, 124.3, 123.1, 122.6, 122.3, 121.7, 120.9, 120.1, 111.9, 60.7, 14.2; IR (neat, cm^{-1}): 3063 (w), 2973 (m), 1727 (vs), 1637 (m), 1451 (s), 1412 (s), 1175 (vs), 1031 (s), 739 (vs).

(*Z*)-Methyl 4-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-nitrobenzoate



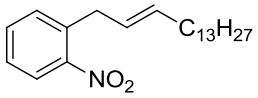
Prepared according to **Method B** from (*Z*)-ethyl 3-iodoacrylate (18 mg, 0.08 mmol) and (4-(methoxycarbonyl)-2-nitrophenyl)boronic acid (31 mg, 0.14 mmol), then purified by column chromatography (silica gel, 9:1 hexanes: EtOAc) to give the product as a yellow solid 15 mg (70%). Mp 78-79 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (d, J = 1.8 Hz, 1H), 8.24 (dd, J = 1.8 Hz, 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 12.0 Hz, 1H), 6.15 (d, *J* = 12.0 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 165.0, 147.2, 140.6, 137.0, 133.7, 131.7, 131.3, 125.8, 122.4, 60.8, 53.0, 14.1; IR (neat, cm^{-1}): 3096 (w), 2992 (w), 1716 (vs), 1616 (m), 1527 (s), 1415 (m), 1343 (m), 1298 (s), 1198 (vs), 1025 (s), 807 (m). HRMS (EI) Calcd for $C_{13}H_{14}NO_6$ (M+H) 280.0816, found: 280.0811.

(*E*)-1-(Hept-1-en-1-yl)-2-nitrobenzene



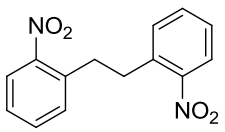
Prepared according to **Method B** from 1-iodo-2-nitrobenzene (49 mg, 0.20 mmol) and (*E*)-hept-1-en-1-ylboronic acid (48 mg, 0.34 mmol), then purified by column chromatography (silica gel, 2.5% ethyl acetate in hexanes) to give the product as a yellow oil 15 mg (35%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.33 (dt, *J* = 1.2 Hz, 7.8 Hz, 1H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.24 (dt, *J* = 7.2 Hz, 15.6 Hz, 1H), 2.28-2.24 (m, 2H), 1.50 (quintet, *J* = 7.2 Hz, 2H), 1.36-1.31 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.9, 137.2, 133.6, 133.0, 128.6, 127.5, 125.1, 124.6, 33.4, 31.6, 28.9, 22.7, 14.3; IR (neat, cm^{-1}): 2956 (m), 2926 (s), 2855 (m), 1606 (w), 1520 (vs), 1343 (vs), 961 (s), 736 (s). HRMS (EI) Calcd for $C_{13}H_{18}NO_2$ (M+H) 220.1332, found: 220.1330.

(*E*)-1-(Hexadec-2-en-1-yl)-2-nitrobenzene



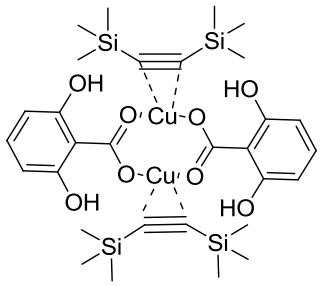
Prepared according to **Method B** from 1-(bromomethyl)-2-nitrobenzene (25 mg, 0.11 mmol) and (*E*)-pentadec-1-en-1-ylboronic acid (48 mg, 0.19 mmol), then purified by column chromatography (silica gel, 19:1 hexanes: EtOAc) to give the product as a yellow oil 24 mg (62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 1.2 Hz, 8.4 Hz, 1H), 7.51 (dt, *J* = 1.2 Hz, 7.8 Hz, 1H), 7.34-7.33 (m, 2H), 5.57-5.49 (m, 2H), 3.64-3.59 (m, 2H), 2.02-1.99 (m, 2H), 1.35-1.25 (m, 22H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.6, 136.2, 134.0, 133.1, 131.9, 127.3, 126.4, 124.8, 36.0, 32.7, 32.2, 29.9 (brs), 29.8, 29.7, 29.6, 29.5, 29.4; IR (neat, cm^{-1}): 2921 (vs), 2851 (s), 1727 (w), 1525 (vs), 1444 (m), 1348 (s), 969 (m), 740 (m). HRMS (EI) Calcd for $C_{22}H_{35}NO_2Na$ (M+Na) 368.2560, found: 368.2556.

1,2-Bis(2-nitrophenyl)ethane[38]



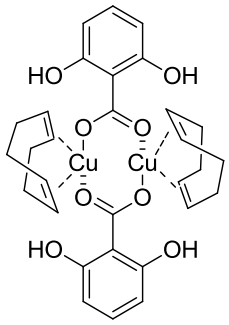
Generated as a white solid byproduct from the reaction preparing ((*E*)-1-(hexadec-2-en-1-yl)-2-nitrobenzene. Mp 118-120 ^{o}C [Lit.[39] 118-121 ^{o}C]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 1.2 Hz, 7.8 Hz, 2H), 7.54 (dt, *J* = 1.2 Hz, 7.8 Hz, 2H), 7.43 (dd, *J* = 1.2 Hz, 7.8 Hz, 2H), 7.39 (dt, *J* = 1.2 Hz, 7.8 Hz, 2H), 3.25 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 136.3, 133.6, 132.7, 127.8, 125.1, 34.7; IR (neat, cm^{-1}): 2954 (w), 2922 (w), 1606 (m), 1575 (m), 1517 (vs), 1450 (s), 1338 (vs), 1260 (s), 1020 (s), 860 (s), 785 (vs), 743 (vs).

CuDHB trimethylsilylacetylene complex C-1: $[Cu_2(O_2C(2,6\text{-}OH)_2C_6H_3)_2(C_8H_{18}Si_2)_2]$



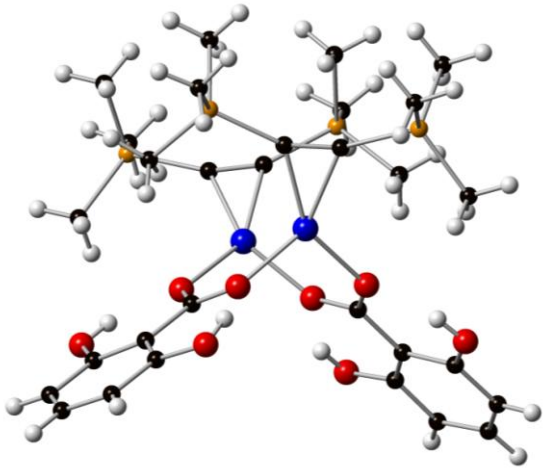
A 100 mL Schlenk flask was charged with ((2,6-dihydroxybenzoyl)oxy)copper (1.12 g, 5.17 mmol, 1.0 equiv) and trimethylsilyacetylene (0.88 g, 5.17 mmol, 1.0 equiv). Under argon protection, 20 mL dichloromethane was added into the flask and the suspension was stirred at room temperature overnight. Filtration with a fine pore fritted glass funnel was conducted under a stream of nitrogen with an inverted funnel, and the filter cake was washed with 10 mL dichloromethane. The filtrate was condensed under vacuum to generate a light yellow solid 1.30 g (65%). Colorless crystals can be formed in dichloromethane solution layered by hexane. Gradually decomposition above 120 ^{0}C to a dark brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (s, 2H), 7.23 (t, *J* = 8.4 Hz, 1H), 6.41 (d, *J* = 8.4 Hz, 2H), 0.25 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 162.1, 135.7, 117.1, 107.5, 103.1, 0.2; IR (neat, cm^{-1}): 3119 (w), 2958 (w), 2922 (w), 1926 (m), 1636 (m), 1577 (s), 1394 (vs), 1194 (s), 834 (vs), 699 (m). Anal. Calcd for $C_7H_5O_4Cu$: C, 46.55; H, 5.99. Found: C, 46.37; H, 5.77. X-ray data is attached below.

Copper carboxylate COD complex C-2: $[Cu_2(O_2C(2,6\text{-}OH)_2C_6H_3)_2(C_8H_{12})_2]$



A 100 mL Schlenk flask was charged with ((2,6-dihydroxybenzoyl)oxy)copper (1.12 g, 5.17 mmol, 1.0 equiv) and 1,5-cyclooctadiene (0.64 mL, 1.0 equiv). Under argon protection, 20 mL dichloromethane was added into the flask and the suspension was stirred at room temperature overnight. Filtration with a fine pore fritted glass funnel was conducted under a stream of nitrogen with an inverted funnel, and the filter cake was washed with 10 mL dichloromethane. The filtrate was condensed under vacuum to generate a white solid 1.19 g (70%). Colorless crystals can be formed in dichloromethane solution layered by hexane. Gradually decomposition above 160 ^{0}C to a dark brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.3 (s, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.38 (d, *J* = 8.0 Hz, 2H), 5.66 (brs, 4H), 2.43 (brs, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 161.7, 135.4, 116.9, 107.6, 28.3; IR (neat, cm^{-1}): 2980 (m), 2921 (m), 1640 (s), 1586 (vs), 1443 (s), 1395 (vs), 1221 (vs), 1029 (m), 818 (s), 701 (m). Anal. Calcd for $C_7H_5O_4Cu$: C, 55.46; H, 5.27. Found: C, 55.36; H, 5.32. X-ray data is attached below.

X-Ray Diffraction Study of C-1



The crystals grew as very fine, thin long needles. The largest crystals were only about 50 µm thick. A crystal was mounted onto a nylon fibre with paratone oil and placed under a cold stream at 173K. Single crystal X-ray data were collected on a Bruker APEX2 diffractometer with 1.5 kW graphite monochromated Cu radiation. The detector to crystal distance was 5.1 cm. Variable exposure times of (30s - 90s per frame) and scan widths of 0.5º were used throughout the data collection. The crystals diffracted to a maximum angle of 55º in θ. The data collection was performed using a combination of 11 sets of ω scans and φ scans with different φ values yielding data in the θ range 3.41 to 57.92° and with an average completeness of 96.4% to 55°. The frames were integrated with the SAINT v7.68a (Bruker, 2009). The distances of the faces from the center of the crystal were measured for a numerical absorption correction. A combination of a numerical and a multi-scan absorption correction was carried out using the program SADABS V2008-1 (Bruker, 2008). The structure was solved and refined with Olex2 and SHELX (Sheldrick, 2008). The hydrogen atoms were located from difference electron density maps but were refined with constraints. In the final cycles of refinement all non-hydrogen atoms were refined anisotropically.

Table 1. Crystal data and structure refinement for C-1.

Identification code	**C-1**
Empirical formula	C31 H48 Cl2 Cu2 O8 Si4
Formula weight	859.03
Temperature	173(2) K

Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 14.5042(11) Å □= 90°.
	b = 13.6562(11) Å □= 101.107(6)°.
	c = 21.1878(14) Å □ = 90°.
Volume	4118.1(5) $Å^3$
Z	4
Density (calculated)	1.386 Mg/m^3
Absorption coefficient	3.939 mm^{-1}
F(000)	1784
Crystal size	0.46 x 0.15 x 0.06 mm^3
Theta range for data collection	3.41 to 57.92°.
Index ranges	-14<=h<=15, -13<=k<=14, -19<=l<=22
Reflections collected	14962
Independent reflections	5283 [R(int) = 0.0789]
Completeness to theta = 55.00°	96.4 %
Absorption correction	Numerical
Max. and min. transmission	0.8096 and 0.2668
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5283 / 0 / 436
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0741, wR2 = 0.1845
R indices (all data)	R1 = 0.1217, wR2 = 0.2081
Largest diff. peak and hole	0.640 and -0.636 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for C-1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cu(1)	6477(1)	1496(1)	5165(1)	34(1)
Cu(2)	6104(1)	3519(1)	4487(1)	33(1)
Si(1)	7586(2)	5560(2)	4593(1)	37(1)
Si(2)	7355(2)	2715(2)	3333(1)	49(1)
Si(3)	8667(2)	2325(2)	5961(1)	40(1)
Si(4)	7744(2)	-530(2)	4768(1)	43(1)
O(1)	5861(4)	2380(5)	5693(3)	36(2)
O(2)	5724(4)	3924(4)	5308(3)	32(2)
O(3)	5061(4)	2611(4)	4158(3)	36(2)
O(4)	5332(4)	1082(4)	4529(3)	33(2)
O(5)	4219(4)	-292(5)	4088(3)	40(2)
O(6)	3588(4)	3012(5)	3300(3)	45(2)
O(7)	5202(4)	5291(4)	5980(3)	34(2)
O(8)	5360(5)	1959(5)	6757(3)	47(3)
C(1)	5644(6)	3288(7)	5736(4)	34(3)
C(2)	4830(6)	1707(7)	4163(4)	30(3)
C(3)	3982(6)	1383(7)	3727(4)	30(3)
C(4)	3710(6)	393(7)	3690(4)	33(3)
C(5)	2938(7)	76(8)	3266(4)	41(3)
C(6)	2392(7)	727(9)	2874(5)	48(4)
C(7)	2619(7)	1719(8)	2888(4)	43(4)
C(8)	3411(6)	2053(7)	3303(4)	32(3)
C(9)	5121(6)	4594(7)	6425(4)	29(3)
C(10)	5320(6)	3612(7)	6324(4)	30(3)
C(11)	5214(6)	2923(7)	6821(4)	36(3)
C(12)	4927(7)	3251(8)	7364(4)	41(3)
C(13)	4759(7)	4212(7)	7447(4)	41(4)
C(14)	4840(6)	4902(8)	6987(4)	42(4)
C(15)	7165(6)	4306(8)	4293(5)	42(4)
C(16)	8822(7)	5430(8)	4998(5)	50(4)

C(17)	6852(7)	6070(8)	5132(5)	47(4)
C(18)	7497(7)	6311(7)	3863(4)	43(3)
C(19)	7077(7)	3573(7)	3938(4)	40(3)
C(20)	6514(9)	1665(9)	3215(6)	71(5)
C(21)	8545(9)	2267(10)	3657(6)	73(5)
C(22)	7336(10)	3405(9)	2583(5)	73(5)
C(23)	7869(7)	1457(8)	5445(5)	38(3)
C(24)	9256(8)	1682(9)	6689(5)	66(5)
C(25)	9554(7)	2692(9)	5493(5)	58(4)
C(26)	7998(7)	3399(8)	6151(5)	49(4)
C(27)	7639(6)	706(8)	5104(5)	40(3)
C(28)	8376(8)	-1273(9)	5454(5)	64(4)
C(29)	8472(9)	-430(8)	4143(6)	64(5)
C(30)	6576(8)	-1055(8)	4462(6)	63(4)
Cl(1)	1345(3)	3993(3)	3236(2)	93(1)
Cl(2)	-373(2)	5075(3)	3240(2)	82(1)
C(31)	452(8)	4736(10)	2789(5)	67(5)

Table 3. Bond lengths [Å] and angles [°] for C-1.

Cu(1)-O(1)	1.973(7)
Cu(1)-O(4)	2.008(6)
Cu(1)-C(23)	1.993(10)
Cu(1)-C(27)	2.027(10)
Cu(1)-O(5)#1	2.616(7)
Cu(2)-O(2)	2.001(6)
Cu(2)-O(3)	1.976(6)
Cu(2)-C(15)	1.984(10)
Cu(2)-C(19)	1.996(10)
Cu(2)-O(7)#2	2.547(6)
Cl(1)-C(31)	1.769(13)
Cl(2)-C(31)	1.732(12)
Si(1)-C(15)	1.887(11)
Si(1)-C(18)	1.840(9)
Si(1)-C(16)	1.841(11)
Si(1)-C(17)	1.841(11)

Si(2)-C(19)	1.838(10)
Si(2)-C(22)	1.843(11)
Si(2)-C(20)	1.868(13)
Si(2)-C(21)	1.835(14)
Si(3)-C(25)	1.840(11)
Si(3)-C(26)	1.845(11)
Si(3)-C(23)	1.858(11)
Si(3)-C(24)	1.836(11)
Si(4)-C(27)	1.849(11)
Si(4)-C(30)	1.839(12)
Si(4)-C(28)	1.862(11)
Si(4)-C(29)	1.851(13)
O(1)-C(1)	1.287(12)
O(2)-C(1)	1.277(11)
O(3)-C(2)	1.280(11)
O(4)-C(2)	1.282(11)
O(5)-C(4)	1.375(11)
O(6)-C(8)	1.335(12)
O(7)-C(9)	1.361(11)
O(8)-C(11)	1.344(12)
O(5)-H(5)	0.8400
O(6)-H(6)	0.8400
O(7)-H(7)	0.8400
O(8)-H(8)	0.8400
C(1)-C(10)	1.481(12)
C(2)-C(3)	1.458(12)
C(3)-C(8)	1.430(13)
C(3)-C(4)	1.406(13)
C(4)-C(5)	1.364(13)
C(5)-C(6)	1.362(15)
C(6)-C(7)	1.393(16)
C(7)-C(8)	1.383(13)
C(9)-C(14)	1.396(12)
C(9)-C(10)	1.397(13)
C(10)-C(11)	1.442(13)
C(11)-C(12)	1.372(12)

C(12)-C(13)	1.352(14)
C(13)-C(14)	1.377(13)
C(15)-C(19)	1.244(14)
C(23)-C(27)	1.262(15)
C(5)-H(5A)	0.9500
C(6)-H(6A)	0.9500
C(7)-H(7A)	0.9500
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
C(14)-H(14)	0.9500
C(16)-H(16B)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17A)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18C)	0.9800
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20A)	0.9800
C(20)-H(20C)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21A)	0.9800
C(21)-H(21C)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(22)-H(22A)	0.9800
C(24)-H(24C)	0.9800
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(25)-H(25C)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26A)	0.9800

C(26)-H(26C)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28A)	0.9800
C(28)-H(28C)	0.9800
C(29)-H(29B)	0.9800
C(29)-H(29C)	0.9800
C(29)-H(29A)	0.9800
C(30)-H(30C)	0.9800
C(30)-H(30A)	0.9800
C(30)-H(30B)	0.9800
C(31)-H(31A)	0.9900
C(31)-H(31B)	0.9900

O(1)-Cu(1)-O(4)	98.4(2)
O(1)-Cu(1)-C(23)	113.0(4)
O(1)-Cu(1)-C(27)	146.6(3)
O(1)-Cu(1)-O(5)#1	76.8(2)
O(4)-Cu(1)-C(23)	148.4(4)
O(4)-Cu(1)-C(27)	113.4(3)
O(4)-Cu(1)-O(5)#1	82.1(2)
C(23)-Cu(1)-C(27)	36.6(4)
O(5)#1-Cu(1)-C(23)	106.8(3)
O(5)#1-Cu(1)-C(27)	97.3(3)
O(2)-Cu(2)-O(3)	99.2(2)
O(2)-Cu(2)-C(15)	112.6(4)
O(2)-Cu(2)-C(19)	147.2(3)
O(2)-Cu(2)-O(7)#2	81.5(2)
O(3)-Cu(2)-C(15)	147.0(4)
O(3)-Cu(2)-C(19)	113.4(3)
O(3)-Cu(2)-O(7)#2	78.6(2)
C(15)-Cu(2)-C(19)	36.4(4)
O(7)#2-Cu(2)-C(15)	97.0(3)
O(7)#2-Cu(2)-C(19)	107.8(3)
C(15)-Si(1)-C(16)	107.0(5)
C(15)-Si(1)-C(17)	111.4(5)
C(15)-Si(1)-C(18)	104.9(4)

C(16)-Si(1)-C(17)	112.0(5)
C(16)-Si(1)-C(18)	110.5(5)
C(17)-Si(1)-C(18)	110.8(5)
C(19)-Si(2)-C(20)	110.9(5)
C(19)-Si(2)-C(21)	105.6(5)
C(19)-Si(2)-C(22)	107.9(5)
C(20)-Si(2)-C(21)	109.7(6)
C(20)-Si(2)-C(22)	112.1(6)
C(21)-Si(2)-C(22)	110.5(6)
C(23)-Si(3)-C(24)	109.0(5)
C(23)-Si(3)-C(25)	106.1(5)
C(23)-Si(3)-C(26)	110.0(5)
C(24)-Si(3)-C(25)	108.8(5)
C(24)-Si(3)-C(26)	112.1(5)
C(25)-Si(3)-C(26)	110.7(5)
C(27)-Si(4)-C(28)	105.2(5)
C(27)-Si(4)-C(29)	108.0(5)
C(27)-Si(4)-C(30)	110.7(5)
C(28)-Si(4)-C(29)	109.6(5)
C(28)-Si(4)-C(30)	110.2(5)
C(29)-Si(4)-C(30)	113.0(6)
Cu(1)-O(1)-C(1)	140.7(6)
Cu(2)-O(2)-C(1)	120.5(5)
Cu(2)-O(3)-C(2)	141.8(6)
Cu(1)-O(4)-C(2)	121.2(5)
Cu(1)#1-O(5)-C(4)	125.1(5)
Cu(2)#2-O(7)-C(9)	124.0(5)
C(4)-O(5)-H(5)	110.00
Cu(1)#1-O(5)-H(5)	106.00
C(8)-O(6)-H(6)	110.00
Cu(2)#2-O(7)-H(7)	111.00
C(9)-O(7)-H(7)	109.00
C(11)-O(8)-H(8)	110.00
O(2)-C(1)-C(10)	118.8(8)
O(1)-C(1)-C(10)	118.0(8)
O(1)-C(1)-O(2)	123.2(8)

O(3)-C(2)-O(4)	121.9(8)
O(3)-C(2)-C(3)	118.6(8)
O(4)-C(2)-C(3)	119.5(8)
C(2)-C(3)-C(4)	121.4(8)
C(2)-C(3)-C(8)	121.3(8)
C(4)-C(3)-C(8)	117.3(8)
O(5)-C(4)-C(5)	117.6(9)
O(5)-C(4)-C(3)	120.5(8)
C(3)-C(4)-C(5)	121.9(9)
C(4)-C(5)-C(6)	120.1(10)
C(5)-C(6)-C(7)	121.0(10)
C(6)-C(7)-C(8)	119.9(9)
O(6)-C(8)-C(7)	117.2(8)
C(3)-C(8)-C(7)	119.9(9)
O(6)-C(8)-C(3)	122.8(8)
O(7)-C(9)-C(14)	117.3(8)
O(7)-C(9)-C(10)	121.2(7)
C(10)-C(9)-C(14)	121.5(8)
C(1)-C(10)-C(11)	121.0(8)
C(1)-C(10)-C(9)	121.6(8)
C(9)-C(10)-C(11)	117.4(8)
C(10)-C(11)-C(12)	119.4(9)
O(8)-C(11)-C(10)	121.6(8)
O(8)-C(11)-C(12)	118.9(8)
C(11)-C(12)-C(13)	121.2(9)
C(12)-C(13)-C(14)	122.0(9)
C(9)-C(14)-C(13)	118.5(9)
Si(1)-C(15)-C(19)	157.4(9)
Cu(2)-C(15)-Si(1)	129.4(5)
Cu(2)-C(15)-C(19)	72.3(7)
Cu(2)-C(19)-C(15)	71.3(6)
Cu(2)-C(19)-Si(2)	131.1(5)
Si(2)-C(19)-C(15)	157.5(9)
Cu(1)-C(23)-C(27)	73.2(6)
Cu(1)-C(23)-Si(3)	129.7(6)
Si(3)-C(23)-C(27)	157.2(9)

Si(4)-C(27)-C(23)	158.4(9)
Cu(1)-C(27)-Si(4)	129.9(5)
Cu(1)-C(27)-C(23)	70.3(7)
C(4)-C(5)-H(5A)	120.00
C(6)-C(5)-H(5A)	120.00
C(5)-C(6)-H(6A)	119.00
C(7)-C(6)-H(6A)	120.00
C(6)-C(7)-H(7A)	120.00
C(8)-C(7)-H(7A)	120.00
C(11)-C(12)-H(12)	119.00
C(13)-C(12)-H(12)	119.00
C(12)-C(13)-H(13)	119.00
C(14)-C(13)-H(13)	119.00
C(9)-C(14)-H(14)	121.00
C(13)-C(14)-H(14)	121.00
Si(1)-C(16)-H(16A)	109.00
Si(1)-C(16)-H(16B)	109.00
Si(1)-C(16)-H(16C)	109.00
H(16A)-C(16)-H(16B)	109.00
H(16A)-C(16)-H(16C)	109.00
H(16B)-C(16)-H(16C)	109.00
Si(1)-C(17)-H(17A)	109.00
Si(1)-C(17)-H(17B)	109.00
Si(1)-C(17)-H(17C)	109.00
H(17A)-C(17)-H(17B)	109.00
H(17A)-C(17)-H(17C)	110.00
H(17B)-C(17)-H(17C)	110.00
Si(1)-C(18)-H(18A)	109.00
Si(1)-C(18)-H(18B)	110.00
Si(1)-C(18)-H(18C)	109.00
H(18A)-C(18)-H(18B)	109.00
H(18A)-C(18)-H(18C)	110.00
H(18B)-C(18)-H(18C)	109.00
Si(2)-C(20)-H(20A)	109.00
Si(2)-C(20)-H(20B)	110.00
Si(2)-C(20)-H(20C)	110.00

H(20A)-C(20)-H(20B)	109.00
H(20A)-C(20)-H(20C)	109.00
H(20B)-C(20)-H(20C)	109.00
Si(2)-C(21)-H(21A)	109.00
Si(2)-C(21)-H(21B)	109.00
Si(2)-C(21)-H(21C)	110.00
H(21A)-C(21)-H(21B)	109.00
H(21A)-C(21)-H(21C)	109.00
H(21B)-C(21)-H(21C)	109.00
Si(2)-C(22)-H(22A)	109.00
Si(2)-C(22)-H(22B)	109.00
Si(2)-C(22)-H(22C)	109.00
H(22A)-C(22)-H(22B)	110.00
H(22A)-C(22)-H(22C)	109.00
H(22B)-C(22)-H(22C)	110.00
Si(3)-C(24)-H(24A)	110.00
Si(3)-C(24)-H(24B)	109.00
Si(3)-C(24)-H(24C)	109.00
H(24A)-C(24)-H(24B)	109.00
H(24A)-C(24)-H(24C)	109.00
H(24B)-C(24)-H(24C)	109.00
Si(3)-C(25)-H(25A)	109.00
Si(3)-C(25)-H(25B)	110.00
Si(3)-C(25)-H(25C)	109.00
H(25A)-C(25)-H(25B)	110.00
H(25A)-C(25)-H(25C)	109.00
H(25B)-C(25)-H(25C)	110.00
Si(3)-C(26)-H(26A)	110.00
Si(3)-C(26)-H(26B)	109.00
Si(3)-C(26)-H(26C)	110.00
H(26A)-C(26)-H(26B)	110.00
H(26A)-C(26)-H(26C)	109.00
H(26B)-C(26)-H(26C)	109.00
Si(4)-C(28)-H(28A)	109.00
Si(4)-C(28)-H(28B)	109.00
Si(4)-C(28)-H(28C)	109.00

H(28A)-C(28)-H(28B)	109.00
H(28A)-C(28)-H(28C)	109.00
H(28B)-C(28)-H(28C)	109.00
Si(4)-C(29)-H(29A)	109.00
Si(4)-C(29)-H(29B)	109.00
Si(4)-C(29)-H(29C)	109.00
H(29A)-C(29)-H(29B)	110.00
H(29A)-C(29)-H(29C)	110.00
H(29B)-C(29)-H(29C)	110.00
Si(4)-C(30)-H(30A)	109.00
Si(4)-C(30)-H(30B)	109.00
Si(4)-C(30)-H(30C)	110.00
H(30A)-C(30)-H(30B)	109.00
H(30A)-C(30)-H(30C)	109.00
H(30B)-C(30)-H(30C)	109.00
Cl(1)-C(31)-Cl(2)	111.7(6)
Cl(1)-C(31)-H(31A)	109.00
Cl(1)-C(31)-H(31B)	109.00
Cl(2)-C(31)-H(31A)	109.00
Cl(2)-C(31)-H(31B)	109.00
H(31A)-C(31)-H(31B)	108.00

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z+1 #2 -x+1,-y+1,-z+1

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C-1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cu(1)	36(1)	32(1)	35(1)	-4(1)	8(1)	0(1)
Cu(2)	40(1)	31(1)	30(1)	-2(1)	12(1)	-2(1)
Si(1)	39(2)	34(2)	40(2)	-1(1)	11(1)	-4(1)
Si(2)	65(2)	49(2)	40(2)	-8(1)	26(1)	-4(2)
Si(3)	42(2)	39(2)	37(2)	-1(1)	4(1)	-5(1)
Si(4)	49(2)	35(2)	47(2)	-8(1)	14(1)	5(1)
O(1)	47(4)	30(4)	33(3)	3(3)	14(3)	3(3)

O(2)	42(4)	31(4)	25(3)	5(3)	9(3)	-5(3)
O(3)	43(4)	23(4)	39(4)	-2(3)	2(3)	1(3)
O(4)	40(4)	27(4)	33(3)	-1(3)	8(3)	4(3)
O(5)	38(4)	35(4)	46(4)	-5(3)	4(3)	-4(3)
O(6)	46(4)	37(4)	46(4)	11(3)	-6(3)	-2(3)
O(7)	52(4)	29(4)	23(3)	2(3)	14(3)	6(3)
O(8)	73(5)	28(4)	41(4)	6(3)	17(3)	6(4)
C(1)	33(5)	32(6)	38(6)	-5(5)	10(4)	-4(5)
C(2)	27(5)	34(6)	29(5)	-6(4)	9(4)	-2(5)
C(3)	31(5)	29(6)	28(5)	0(4)	4(4)	6(4)
C(4)	37(5)	26(6)	38(5)	-2(5)	10(4)	10(5)
C(5)	45(6)	38(6)	38(6)	-3(5)	2(5)	-9(5)
C(6)	36(6)	65(8)	39(6)	-11(6)	-6(5)	0(6)
C(7)	51(6)	41(7)	37(6)	9(5)	6(5)	8(5)
C(8)	40(6)	27(6)	29(5)	-6(4)	7(4)	-3(5)
C(9)	31(5)	27(6)	29(5)	0(4)	8(4)	-4(4)
C(10)	35(5)	29(6)	27(5)	3(4)	11(4)	-1(4)
C(11)	43(6)	34(6)	35(5)	6(5)	17(5)	-4(5)
C(12)	56(6)	40(7)	30(5)	7(5)	14(5)	2(5)
C(13)	66(7)	39(7)	23(5)	3(5)	22(5)	5(5)
C(14)	46(6)	43(7)	38(6)	-4(5)	14(5)	3(5)
C(15)	37(6)	48(7)	45(6)	10(6)	20(5)	6(5)
C(16)	43(6)	59(8)	51(6)	6(6)	20(5)	-8(5)
C(17)	63(7)	34(6)	44(6)	-9(5)	12(5)	-1(5)
C(18)	58(7)	36(6)	37(5)	4(5)	15(5)	-4(5)
C(19)	56(6)	33(6)	33(5)	-7(5)	13(5)	-4(5)
C(20)	86(9)	66(9)	71(8)	-22(7)	39(7)	-12(7)
C(21)	90(9)	72(9)	70(8)	-3(7)	46(7)	2(7)
C(22)	99(10)	72(9)	46(7)	-7(7)	13(7)	-5(8)
C(23)	41(6)	35(6)	42(6)	9(5)	22(5)	2(5)
C(24)	68(8)	67(9)	57(7)	15(6)	-1(6)	-13(7)
C(25)	50(7)	61(8)	62(7)	-16(6)	9(6)	-7(6)
C(26)	41(6)	51(7)	53(6)	-20(6)	2(5)	-9(5)
C(27)	33(5)	43(7)	45(6)	14(5)	11(5)	8(5)
C(28)	70(8)	59(8)	62(7)	4(6)	7(6)	16(6)
C(29)	85(9)	41(7)	70(8)	-4(6)	29(7)	10(6)

C(30)	60(7)	42(7)	89(9)	-20(7)	20(7)	-1(6)
Cl(1)	115(3)	79(2)	73(2)	-25(2)	-13(2)	36(2)
Cl(2)	72(2)	111(3)	63(2)	-8(2)	17(2)	4(2)
C(31)	76(8)	68(9)	54(7)	-15(7)	3(6)	3(7)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for C-1.

	x	y	z	U(eq)
H(5)	4678	-19	4325	60
H(5A)	2780	-600	3245	50
H(6)	4137	3120	3500	68
H(6A)	1848	501	2587	58
H(7)	5442	5042	5687	51
H(7A)	2230	2165	2613	52
H(8)	5576	1860	6422	69
H(12)	4845	2795	7688	50
H(13)	4580	4418	7835	49
H(14)	4707	5572	7050	50
H(16A)	8860	5005	5375	74
H(16B)	9080	6076	5135	74
H(16C)	9184	5140	4700	74
H(17A)	6197	6102	4904	70
H(17B)	7072	6730	5266	70
H(17C)	6896	5649	5511	70
H(18A)	7849	5997	3567	64
H(18B)	7760	6962	3979	64
H(18C)	6836	6374	3654	64
H(20A)	6529	1333	3628	106
H(20B)	6693	1202	2907	106
H(20C)	5877	1908	3050	106
H(21A)	8997	2801	3658	110
H(21B)	8697	1729	3388	110
H(21C)	8577	2032	4097	110

H(22A)	6691	3432	2337	108
H(22B)	7740	3078	2327	108
H(22C)	7566	4071	2687	108
H(24A)	9507	1058	6569	98
H(24B)	8804	1558	6969	98
H(24C)	9771	2087	6918	98
H(25A)	9246	3036	5103	87
H(25B)	9875	2109	5374	87
H(25C)	10013	3129	5753	87
H(26A)	8434	3894	6371	74
H(26B)	7567	3199	6430	74
H(26C)	7638	3676	5752	74
H(28A)	8030	-1252	5808	96
H(28B)	9008	-1006	5600	96
H(28C)	8422	-1953	5315	96
H(29A)	8508	-1071	3941	95
H(29B)	9105	-212	4342	95
H(29C)	8188	45	3817	95
H(30A)	6646	-1692	4263	94
H(30B)	6218	-613	4141	94
H(30C)	6241	-1140	4818	94
H(31A)	739	5331	2643	81
H(31B)	136	4374	2403	81

Table 6. Torsion angles [°] for C-1.

O(4)-Cu(1)-O(1)-C(1)	-92.2(9)
C(23)-Cu(1)-O(1)-C(1)	85.1(10)
C(27)-Cu(1)-O(1)-C(1)	104.9(10)
O(5)#1-Cu(1)-O(1)-C(1)	-172.0(9)
O(1)-Cu(1)-O(4)-C(2)	61.3(7)
C(23)-Cu(1)-O(4)-C(2)	-113.9(8)
C(27)-Cu(1)-O(4)-C(2)	-128.9(7)
O(5)#1-Cu(1)-O(4)-C(2)	136.6(6)
O(1)-Cu(1)-C(23)-Si(3)	-17.6(8)
O(1)-Cu(1)-C(23)-C(27)	161.8(6)

O(4)-Cu(1)-C(23)-Si(3)	157.2(5)
O(4)-Cu(1)-C(23)-C(27)	-23.4(11)
C(27)-Cu(1)-C(23)-Si(3)	-179.3(12)
O(5)#1-Cu(1)-C(23)-Si(3)	-100.1(7)
O(5)#1-Cu(1)-C(23)-C(27)	79.3(7)
O(1)-Cu(1)-C(27)-Si(4)	139.4(6)
O(1)-Cu(1)-C(27)-C(23)	-31.6(10)
O(4)-Cu(1)-C(27)-Si(4)	-22.1(8)
O(4)-Cu(1)-C(27)-C(23)	166.9(6)
C(23)-Cu(1)-C(27)-Si(4)	171.0(12)
O(5)#1-Cu(1)-C(27)-Si(4)	62.4(7)
O(5)#1-Cu(1)-C(27)-C(23)	-108.6(7)
O(1)-Cu(1)-O(5)#1-C(4)#1	-124.2(7)
O(4)-Cu(1)-O(5)#1-C(4)#1	135.2(7)
C(23)-Cu(1)-O(5)#1-C(4)#1	-13.8(7)
C(27)-Cu(1)-O(5)#1-C(4)#1	22.4(7)
O(3)-Cu(2)-O(2)-C(1)	60.0(7)
C(15)-Cu(2)-O(2)-C(1)	-129.0(7)
C(19)-Cu(2)-O(2)-C(1)	-113.2(8)
O(7)#2-Cu(2)-O(2)-C(1)	136.9(6)
O(2)-Cu(2)-O(3)-C(2)	-91.6(9)
C(15)-Cu(2)-O(3)-C(2)	103.8(11)
C(19)-Cu(2)-O(3)-C(2)	84.4(10)
O(7)#2-Cu(2)-O(3)-C(2)	-171.0(9)
O(2)-Cu(2)-C(15)-Si(1)	-21.5(8)
O(2)-Cu(2)-C(15)-C(19)	165.6(6)
O(3)-Cu(2)-C(15)-Si(1)	142.0(5)
O(3)-Cu(2)-C(15)-C(19)	-30.9(10)
C(19)-Cu(2)-C(15)-Si(1)	172.9(11)
O(7)#2-Cu(2)-C(15)-Si(1)	62.2(7)
O(7)#2-Cu(2)-C(15)-C(19)	-110.7(6)
O(2)-Cu(2)-C(19)-Si(2)	153.1(5)
O(2)-Cu(2)-C(19)-C(15)	-25.0(10)
O(3)-Cu(2)-C(19)-Si(2)	-19.7(8)
O(3)-Cu(2)-C(19)-C(15)	162.3(6)
C(15)-Cu(2)-C(19)-Si(2)	178.1(11)

O(7)#2-Cu(2)-C(19)-Si(2)	-104.6(6)
O(7)#2-Cu(2)-C(19)-C(15)	77.3(6)
O(2)-Cu(2)-O(7)#2-C(9)#2	133.6(6)
O(3)-Cu(2)-O(7)#2-C(9)#2	-125.1(6)
C(15)-Cu(2)-O(7)#2-C(9)#2	21.7(7)
C(19)-Cu(2)-O(7)#2-C(9)#2	-14.0(7)
C(16)-Si(1)-C(15)-Cu(2)	121.9(7)
C(16)-Si(1)-C(15)-C(19)	-76(2)
C(17)-Si(1)-C(15)-Cu(2)	-0.9(9)
C(17)-Si(1)-C(15)-C(19)	161(2)
C(18)-Si(1)-C(15)-Cu(2)	-120.8(7)
C(18)-Si(1)-C(15)-C(19)	41(2)
C(20)-Si(2)-C(19)-Cu(2)	3.2(8)
C(20)-Si(2)-C(19)-C(15)	179(2)
C(21)-Si(2)-C(19)-Cu(2)	-115.5(7)
C(21)-Si(2)-C(19)-C(15)	60(2)
C(22)-Si(2)-C(19)-Cu(2)	126.4(7)
C(22)-Si(2)-C(19)-C(15)	-58(2)
C(24)-Si(3)-C(23)-Cu(1)	117.5(7)
C(24)-Si(3)-C(23)-C(27)	-61(2)
C(25)-Si(3)-C(23)-Cu(1)	-125.5(7)
C(25)-Si(3)-C(23)-C(27)	56(2)
C(26)-Si(3)-C(23)-Cu(1)	-5.8(9)
C(26)-Si(3)-C(23)-C(27)	176(2)
C(28)-Si(4)-C(27)-Cu(1)	-119.4(7)
C(28)-Si(4)-C(27)-C(23)	37(3)
C(29)-Si(4)-C(27)-Cu(1)	123.7(7)
C(29)-Si(4)-C(27)-C(23)	-80(2)
C(30)-Si(4)-C(27)-Cu(1)	-0.4(9)
C(30)-Si(4)-C(27)-C(23)	156(2)
Cu(1)-O(1)-C(1)-O(2)	9.1(15)
Cu(1)-O(1)-C(1)-C(10)	-168.5(6)
Cu(2)-O(2)-C(1)-O(1)	5.1(11)
Cu(2)-O(2)-C(1)-C(10)	-177.3(6)
Cu(2)-O(3)-C(2)-O(4)	9.2(15)
Cu(2)-O(3)-C(2)-C(3)	-169.4(6)

Cu(1)-O(4)-C(2)-O(3)	4.1(11)
Cu(1)-O(4)-C(2)-C(3)	-177.4(6)
Cu(1)#1-O(5)-C(4)-C(3)	126.1(7)
Cu(1)#1-O(5)-C(4)-C(5)	-53.6(10)
Cu(2)#2-O(7)-C(9)-C(10)	126.7(7)
Cu(2)#2-O(7)-C(9)-C(14)	-53.9(10)
O(1)-C(1)-C(10)-C(9)	176.4(8)
O(1)-C(1)-C(10)-C(11)	-2.5(13)
O(2)-C(1)-C(10)-C(9)	-1.4(13)
O(2)-C(1)-C(10)-C(11)	179.8(8)
O(3)-C(2)-C(3)-C(4)	177.4(8)
O(3)-C(2)-C(3)-C(8)	-0.4(13)
O(4)-C(2)-C(3)-C(4)	-1.2(13)
O(4)-C(2)-C(3)-C(8)	-178.9(8)
C(2)-C(3)-C(4)-O(5)	2.9(13)
C(2)-C(3)-C(4)-C(5)	-177.4(8)
C(8)-C(3)-C(4)-O(5)	-179.3(8)
C(8)-C(3)-C(4)-C(5)	0.4(13)
C(2)-C(3)-C(8)-O(6)	-3.3(13)
C(2)-C(3)-C(8)-C(7)	179.0(8)
C(4)-C(3)-C(8)-O(6)	178.9(8)
C(4)-C(3)-C(8)-C(7)	1.1(13)
O(5)-C(4)-C(5)-C(6)	178.0(8)
C(3)-C(4)-C(5)-C(6)	-1.7(14)
C(4)-C(5)-C(6)-C(7)	1.3(15)
C(5)-C(6)-C(7)-C(8)	0.2(15)
C(6)-C(7)-C(8)-O(6)	-179.3(8)
C(6)-C(7)-C(8)-C(3)	-1.5(14)
O(7)-C(9)-C(10)-C(1)	1.2(13)
O(7)-C(9)-C(10)-C(11)	-179.9(8)
C(14)-C(9)-C(10)-C(1)	-178.3(8)
C(14)-C(9)-C(10)-C(11)	0.7(13)
O(7)-C(9)-C(14)-C(13)	-179.6(8)
C(10)-C(9)-C(14)-C(13)	-0.1(13)
C(1)-C(10)-C(11)-O(8)	-3.3(13)
C(1)-C(10)-C(11)-C(12)	179.0(8)

C(9)-C(10)-C(11)-O(8)	177.8(8)
C(9)-C(10)-C(11)-C(12)	0.0(13)
O(8)-C(11)-C(12)-C(13)	-179.1(9)
C(10)-C(11)-C(12)-C(13)	-1.3(14)
C(11)-C(12)-C(13)-C(14)	1.9(15)
C(12)-C(13)-C(14)-C(9)	-1.2(14)
Cu(2)-C(15)-C(19)-Si(2)	-176(2)
Si(1)-C(15)-C(19)-Cu(2)	-166(2)
Si(1)-C(15)-C(19)-Si(2)	18(4)
Cu(1)-C(23)-C(27)-Si(4)	-161(2)
Si(3)-C(23)-C(27)-Cu(1)	179(2)
Si(3)-C(23)-C(27)-Si(4)	18(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z+1 #2 -x+1,-y+1,-z+1

Table 7. Hydrogen bonds for C-1 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5)-H(5)...O(4)	0.8400	1.7900	2.534(9)	147.00
O(6)-H(6)...O(3)	0.8400	1.8700	2.583(9)	142.00
O(6)-H(6)...O(7)#2	0.8400	2.5400	3.122(9)	128.00
O(7)-H(7)...O(2)	0.8400	1.8100	2.550(8)	146.00
O(8)-H(8)...O(1)	0.8400	1.8200	2.564(9)	147.00
O(8)-H(8)...O(5)#1	0.8400	2.4400	3.030(9)	128.00
C(31)-H(31B)...O(8)#3	0.9900	2.3400	3.169(14)	141.00

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z+1 #2 -x+1,-y+1,-z+1 #3 x-3/2,-y-1/2,z-3/2

X-Ray Diffraction Study of C-2

The crystals grew as long needles. A crystal with well defined faces was cut into a suitable size for the analysis. The crystal was mounted onto a nylon fibre with paratone oil and placed under a

cold stream at 110K. Single crystal X-ray data were collected on a Bruker APEX2 diffractometer with 1.6 kW graphite monochromated Mo radiation. The detector to crystal distance was 5.1 cm. Exposure times of 30 s per frame and scan widths of 0.5º were used throughout the data collection. The data collection was performed using three ω scans and a φ –scan with different φ values yielding data in the θ range 1.85 to 27.48° with an average completeness of 99.9%. The frames were integrated with the SAINT v7.45a (Bruker, 2005). A multi-scan absorption correction was carried out using the program SADABS V2008-1 (Bruker, 2008). The structure was solved and refined with X-SEED, a graphical interface to SHELX (Sheldrick, 2008). The hydrogen atoms were located from difference electron density maps but were refined with constraints. In the final cycles of refinement all non-hydrogen atoms were refined anisotropically.

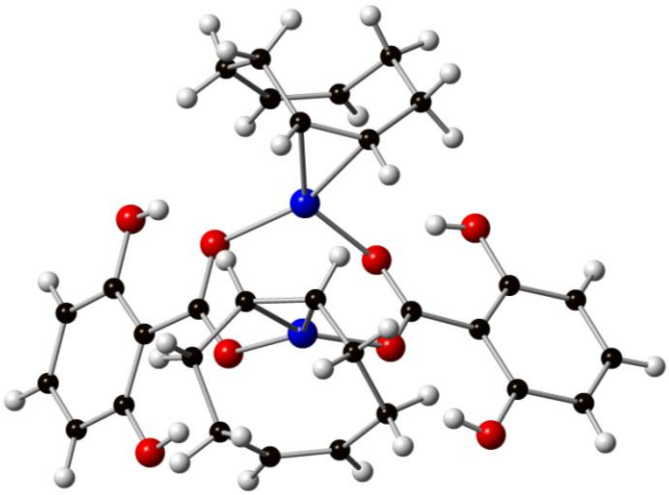


Table 1. Crystal data and structure refinement for C-2.

Identification code	**C-2**	
Empirical formula	C30.50 H35 Cl Cu2 O8	
Formula weight	692.11	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 27.564(4) Å	□= 90°.

	b = 12.7517(19) Å	□= 128.389(2)°.
	c = 21.216(3) Å	□ = 90°.
Volume	5845.0(15) Å^3	
Z	8	
Density (calculated)	1.573 Mg/m^3	
Absorption coefficient	1.597 mm^{-1}	
F(000)	2856	
Crystal size	0.32 x 0.22 x 0.19 mm^3	
Theta range for data collection	1.85 to 27.48°.	
Index ranges	-35<=h<=35, -15<=k<=16, -27<=l<=27	
Reflections collected	34996	
Independent reflections	6697 [R(int) = 0.0303]	
Completeness to theta = 27.48°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7459 and 0.6322	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6697 / 6 / 431	
Goodness-of-fit on F^2	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0261, wR2 = 0.0656	
R indices (all data)	R1 = 0.0316, wR2 = 0.0686	
Largest diff. peak and hole	0.595 and -0.682 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for C-2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cu(1)	2209(1)	8910(1)	7084(1)	17(1)
Cu(2)	3442(1)	9139(1)	7550(1)	16(1)
O(1)	2713(1)	8312(1)	8191(1)	20(1)
O(2)	3609(1)	8156(1)	8406(1)	19(1)
O(3)	3051(1)	8206(1)	6604(1)	20(1)
O(4)	2213(1)	7728(1)	6464(1)	22(1)
O(5)	1565(1)	6162(1)	5591(1)	28(1)
O(6)	3459(1)	7056(1)	6036(1)	29(1)
O(7)	4585(1)	7644(1)	9788(1)	23(1)
O(8)	2594(1)	7536(1)	9200(1)	23(1)

C(1)	3279(1)	8058(1)	8630(1)	15(1)
C(2)	2595(1)	7598(1)	6327(1)	18(1)
C(3)	2516(1)	6682(1)	5847(1)	18(1)
C(4)	2013(1)	5987(1)	5520(1)	21(1)
C(5)	1962(1)	5088(1)	5113(1)	25(1)
C(6)	2408(1)	4875(1)	5024(1)	27(1)
C(7)	2903(1)	5537(1)	5328(1)	26(1)
C(8)	2960(1)	6437(1)	5737(1)	21(1)
C(9)	3549(1)	10705(1)	7406(1)	19(1)
C(10)	3754(1)	10514(1)	8173(1)	19(1)
C(11)	4410(1)	10396(1)	8942(1)	21(1)
C(12)	4904(1)	10049(1)	8863(1)	22(1)
C(13)	4733(1)	9064(1)	8381(1)	23(1)
C(14)	4418(1)	9004(1)	7591(1)	24(1)
C(15)	4154(1)	9867(2)	6982(1)	28(1)
C(16)	3947(1)	10870(1)	7149(1)	26(1)
C(17)	3572(1)	7650(1)	9446(1)	14(1)
C(18)	4218(1)	7491(1)	9998(1)	17(1)
C(19)	4497(1)	7168(1)	10782(1)	23(1)
C(20)	4134(1)	6995(1)	11013(1)	26(1)
C(21)	3499(1)	7121(1)	10488(1)	23(1)
C(22)	3218(1)	7438(1)	9704(1)	17(1)
C(23)	1918(1)	10462(1)	6962(1)	21(1)
C(24)	1768(1)	10085(1)	6255(1)	21(1)
C(25)	1148(1)	9680(1)	5531(1)	26(1)
C(26)	717(1)	9209(1)	5683(1)	26(1)
C(27)	1028(1)	8426(1)	6361(1)	23(1)
C(28)	1314(1)	8613(1)	7137(1)	23(1)
C(29)	1426(1)	9647(1)	7549(1)	26(1)
C(30)	1481(1)	10603(1)	7156(1)	24(1)
Cl(1C)	4818(1)	5144(2)	6961(2)	50(1)
Cl(2C)	5042(1)	6150(2)	8368(2)	50(1)
C(1S)	4980(7)	6278(4)	7509(5)	56(1)
Cl(1D)	4833(2)	5309(3)	6776(2)	53(1)
Cl(2D)	5127(2)	5800(3)	8341(2)	53(1)

C(1SD)	4893(2)	6238(3)	7417(2)	56(1)

Table 3. Bond lengths [Å] and angles [°] for C-2.

Cu(1)-O(1)	1.9948(11)
Cu(1)-O(4)	2.0043(13)
Cu(1)-C(23)	2.0907(17)
Cu(1)-C(24)	2.0391(16)
Cu(1)-C(28)	2.567(2)
Cu(2)-O(2)	2.0094(12)
Cu(2)-O(3)	1.9801(11)
Cu(2)-C(9)	2.0694(16)
Cu(2)-C(10)	2.0373(16)
Cl(1C)-C(1S)	1.731(7)
Cl(2C)-C(1S)	1.728(14)
Cl(1D)-C(1SD)	1.732(5)
Cl(2D)-C(1SD)	1.732(5)
O(1)-C(1)	1.265(2)
O(2)-C(1)	1.268(2)
O(3)-C(2)	1.270(2)
O(4)-C(2)	1.267(3)
O(5)-C(4)	1.352(3)
O(6)-C(8)	1.354(2)
O(7)-C(18)	1.351(2)
O(8)-C(22)	1.353(2)
O(5)-H(5)	0.8400
O(6)-H(6)	0.8400
O(7)-H(7)	0.8400
O(8)-H(8)	0.8400
C(1)-C(17)	1.4788(19)
C(2)-C(3)	1.475(2)
C(3)-C(4)	1.412(3)
C(3)-C(8)	1.414(3)
C(4)-C(5)	1.390(2)
C(5)-C(6)	1.381(3)
C(6)-C(7)	1.378(3)

C(7)-C(8)	1.388(2)
C(9)-C(16)	1.514(3)
C(9)-C(10)	1.374(2)
C(10)-C(11)	1.512(2)
C(11)-C(12)	1.536(3)
C(12)-C(13)	1.498(2)
C(13)-C(14)	1.328(2)
C(14)-C(15)	1.498(3)
C(15)-C(16)	1.529(3)
C(17)-C(18)	1.411(2)
C(17)-C(22)	1.411(3)
C(18)-C(19)	1.392(2)
C(19)-C(20)	1.377(3)
C(20)-C(21)	1.381(3)
C(21)-C(22)	1.389(2)
C(23)-C(24)	1.373(2)
C(23)-C(30)	1.506(3)
C(24)-C(25)	1.511(2)
C(25)-C(26)	1.535(3)
C(26)-C(27)	1.506(2)
C(27)-C(28)	1.333(2)
C(28)-C(29)	1.504(2)
C(29)-C(30)	1.537(3)
C(5)-H(5A)	0.9400
C(6)-H(6A)	0.9600
C(7)-H(7A)	0.9300
C(9)-H(9)	0.9200
C(10)-H(10)	0.9400
C(11)-H(11B)	0.9800
C(11)-H(11A)	0.9400
C(12)-H(12B)	0.9500
C(12)-H(12A)	0.9200
C(13)-H(13)	0.9300
C(14)-H(14)	0.9700
C(15)-H(15B)	0.9400
C(15)-H(15A)	0.9300

C(16)-H(16A)	0.9600
C(16)-H(16B)	0.9100
C(19)-H(19)	0.9200
C(20)-H(20)	0.8900
C(21)-H(21)	0.9000
C(23)-H(23)	0.9400
C(24)-H(24)	0.9300
C(25)-H(25A)	0.9400
C(25)-H(25B)	0.9900
C(26)-H(26A)	0.9600
C(26)-H(26B)	0.9700
C(27)-H(27)	0.9500
C(28)-H(28)	0.9500
C(29)-H(29B)	0.9400
C(29)-H(29A)	0.9900
C(30)-H(30B)	0.9100
C(30)-H(30A)	0.9500
C(1S)-H(1SC)	0.9900
C(1S)-H(1SD)	0.9900
C(1SD)-H(1SA)	0.9900
C(1SD)-H(1SB)	0.9900

O(1)-Cu(1)-O(4)	101.63(5)
O(1)-Cu(1)-C(23)	116.14(5)
O(1)-Cu(1)-C(24)	154.54(6)
O(1)-Cu(1)-C(28)	82.90(5)
O(4)-Cu(1)-C(23)	142.10(5)
O(4)-Cu(1)-C(24)	103.31(6)
O(4)-Cu(1)-C(28)	108.29(6)
C(23)-Cu(1)-C(24)	38.80(6)
C(23)-Cu(1)-C(28)	80.73(7)
C(24)-Cu(1)-C(28)	94.09(7)
O(2)-Cu(2)-O(3)	102.52(5)
O(2)-Cu(2)-C(9)	139.64(5)
O(2)-Cu(2)-C(10)	100.58(5)
O(3)-Cu(2)-C(9)	117.83(6)

O(3)-Cu(2)-C(10)	156.85(6)
C(9)-Cu(2)-C(10)	39.08(6)
Cu(1)-O(1)-C(1)	127.01(11)
Cu(2)-O(2)-C(1)	125.78(10)
Cu(2)-O(3)-C(2)	126.48(12)
Cu(1)-O(4)-C(2)	126.34(11)
C(4)-O(5)-H(5)	110.00
C(8)-O(6)-H(6)	109.00
C(18)-O(7)-H(7)	109.00
C(22)-O(8)-H(8)	109.00
O(2)-C(1)-C(17)	118.45(15)
O(1)-C(1)-C(17)	118.61(16)
O(1)-C(1)-O(2)	122.93(13)
O(3)-C(2)-O(4)	122.72(15)
O(3)-C(2)-C(3)	118.84(19)
O(4)-C(2)-C(3)	118.41(16)
C(2)-C(3)-C(8)	121.09(17)
C(2)-C(3)-C(4)	120.93(19)
C(4)-C(3)-C(8)	117.88(15)
O(5)-C(4)-C(5)	117.22(17)
C(3)-C(4)-C(5)	120.9(2)
O(5)-C(4)-C(3)	121.93(15)
C(4)-C(5)-C(6)	119.39(19)
C(5)-C(6)-C(7)	121.55(17)
C(6)-C(7)-C(8)	119.6(2)
C(3)-C(8)-C(7)	120.75(18)
O(6)-C(8)-C(3)	121.68(15)
O(6)-C(8)-C(7)	117.56(19)
Cu(2)-C(9)-C(16)	112.97(12)
Cu(2)-C(9)-C(10)	69.20(9)
C(10)-C(9)-C(16)	126.50(17)
Cu(2)-C(10)-C(11)	110.78(11)
Cu(2)-C(10)-C(9)	71.72(9)
C(9)-C(10)-C(11)	129.23(19)
C(10)-C(11)-C(12)	117.26(13)
C(11)-C(12)-C(13)	113.07(17)

C(12)-C(13)-C(14)	126.30(15)
C(13)-C(14)-C(15)	129.31(16)
C(14)-C(15)-C(16)	117.77(15)
C(9)-C(16)-C(15)	115.14(16)
C(1)-C(17)-C(18)	120.88(17)
C(18)-C(17)-C(22)	118.08(13)
C(1)-C(17)-C(22)	121.01(15)
O(7)-C(18)-C(19)	117.75(16)
C(17)-C(18)-C(19)	120.71(18)
O(7)-C(18)-C(17)	121.54(13)
C(18)-C(19)-C(20)	119.20(17)
C(19)-C(20)-C(21)	121.99(15)
C(20)-C(21)-C(22)	119.10(19)
O(8)-C(22)-C(17)	121.44(13)
O(8)-C(22)-C(21)	117.68(17)
C(17)-C(22)-C(21)	120.88(16)
Cu(1)-C(23)-C(30)	112.97(12)
C(24)-C(23)-C(30)	126.25(17)
Cu(1)-C(23)-C(24)	68.57(10)
C(23)-C(24)-C(25)	127.9(2)
Cu(1)-C(24)-C(25)	108.57(11)
Cu(1)-C(24)-C(23)	72.64(9)
C(24)-C(25)-C(26)	116.99(14)
C(25)-C(26)-C(27)	113.87(17)
C(26)-C(27)-C(28)	127.56(16)
Cu(1)-C(28)-C(27)	79.59(14)
Cu(1)-C(28)-C(29)	92.33(13)
C(27)-C(28)-C(29)	128.74(15)
C(28)-C(29)-C(30)	115.70(15)
C(23)-C(30)-C(29)	114.73(15)
C(4)-C(5)-H(5A)	118.00
C(6)-C(5)-H(5A)	123.00
C(5)-C(6)-H(6A)	118.00
C(7)-C(6)-H(6A)	120.00
C(8)-C(7)-H(7A)	118.00
C(6)-C(7)-H(7A)	122.00

Cu(2)-C(9)-H(9)	101.00
C(10)-C(9)-H(9)	115.00
C(16)-C(9)-H(9)	116.00
C(11)-C(10)-H(10)	114.00
Cu(2)-C(10)-H(10)	97.00
C(9)-C(10)-H(10)	116.00
C(10)-C(11)-H(11B)	108.00
C(10)-C(11)-H(11A)	108.00
H(11A)-C(11)-H(11B)	105.00
C(12)-C(11)-H(11A)	108.00
C(12)-C(11)-H(11B)	110.00
C(13)-C(12)-H(12B)	108.00
C(13)-C(12)-H(12A)	110.00
C(11)-C(12)-H(12A)	112.00
H(12A)-C(12)-H(12B)	105.00
C(11)-C(12)-H(12B)	108.00
C(14)-C(13)-H(13)	118.00
C(12)-C(13)-H(13)	116.00
C(15)-C(14)-H(14)	116.00
C(13)-C(14)-H(14)	115.00
H(15A)-C(15)-H(15B)	108.00
C(16)-C(15)-H(15B)	108.00
C(14)-C(15)-H(15A)	108.00
C(14)-C(15)-H(15B)	107.00
C(16)-C(15)-H(15A)	109.00
C(9)-C(16)-H(16A)	109.00
C(9)-C(16)-H(16B)	105.00
C(15)-C(16)-H(16A)	109.00
C(15)-C(16)-H(16B)	110.00
H(16A)-C(16)-H(16B)	108.00
C(20)-C(19)-H(19)	121.00
C(18)-C(19)-H(19)	119.00
C(19)-C(20)-H(20)	119.00
C(21)-C(20)-H(20)	119.00
C(20)-C(21)-H(21)	123.00
C(22)-C(21)-H(21)	118.00

C(30)-C(23)-H(23)	115.00
Cu(1)-C(23)-H(23)	102.00
C(24)-C(23)-H(23)	117.00
Cu(1)-C(24)-H(24)	102.00
C(23)-C(24)-H(24)	118.00
C(25)-C(24)-H(24)	113.00
C(26)-C(25)-H(25B)	107.00
C(24)-C(25)-H(25A)	108.00
C(24)-C(25)-H(25B)	109.00
H(25A)-C(25)-H(25B)	107.00
C(26)-C(25)-H(25A)	109.00
C(25)-C(26)-H(26B)	107.00
C(27)-C(26)-H(26A)	110.00
C(25)-C(26)-H(26A)	111.00
C(27)-C(26)-H(26B)	109.00
H(26A)-C(26)-H(26B)	105.00
C(26)-C(27)-H(27)	115.00
C(28)-C(27)-H(27)	117.00
Cu(1)-C(28)-H(28)	100.00
C(29)-C(28)-H(28)	116.00
C(27)-C(28)-H(28)	115.00
C(28)-C(29)-H(29A)	108.00
C(28)-C(29)-H(29B)	110.00
C(30)-C(29)-H(29A)	108.00
H(29A)-C(29)-H(29B)	108.00
C(30)-C(29)-H(29B)	107.00
C(23)-C(30)-H(30B)	107.00
C(29)-C(30)-H(30A)	111.00
C(23)-C(30)-H(30A)	110.00
H(30A)-C(30)-H(30B)	106.00
C(29)-C(30)-H(30B)	108.00
Cl(1C)-C(1S)-Cl(2C)	116.4(5)
Cl(1C)-C(1S)-H(1SD)	108.00
Cl(2C)-C(1S)-H(1SC)	108.00
Cl(2C)-C(1S)-H(1SD)	108.00
H(1SC)-C(1S)-H(1SD)	107.00

Cl(1C)-C(1S)-H(1SC)	108.00
Cl(1D)-C(1SD)-Cl(2D)	117.1(3)
Cl(1D)-C(1SD)-H(1SA)	108.00
Cl(1D)-C(1SD)-H(1SB)	108.00
Cl(2D)-C(1SD)-H(1SA)	108.00
Cl(2D)-C(1SD)-H(1SB)	108.00
H(1SA)-C(1SD)-H(1SB)	107.00

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for C-2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cu(1)	17(1)	16(1)	16(1)	1(1)	9(1)	3(1)
Cu(2)	18(1)	14(1)	16(1)	0(1)	12(1)	-2(1)
O(1)	15(1)	24(1)	18(1)	4(1)	10(1)	5(1)
O(2)	19(1)	20(1)	21(1)	5(1)	14(1)	2(1)
O(3)	25(1)	18(1)	20(1)	-3(1)	15(1)	-3(1)
O(4)	24(1)	20(1)	25(1)	-5(1)	17(1)	-1(1)
O(5)	32(1)	27(1)	33(1)	-8(1)	25(1)	-9(1)
O(6)	28(1)	30(1)	34(1)	-9(1)	23(1)	-4(1)
O(7)	14(1)	32(1)	23(1)	7(1)	12(1)	3(1)
O(8)	16(1)	32(1)	23(1)	3(1)	13(1)	0(1)
C(1)	17(1)	11(1)	18(1)	-1(1)	11(1)	-1(1)
C(2)	22(1)	16(1)	14(1)	3(1)	10(1)	2(1)
C(3)	24(1)	16(1)	14(1)	1(1)	12(1)	1(1)
C(4)	28(1)	19(1)	16(1)	2(1)	13(1)	0(1)
C(5)	33(1)	19(1)	18(1)	-2(1)	13(1)	-4(1)
C(6)	38(1)	22(1)	16(1)	-3(1)	14(1)	4(1)
C(7)	32(1)	30(1)	20(1)	-2(1)	18(1)	5(1)
C(8)	26(1)	22(1)	17(1)	2(1)	13(1)	2(1)
C(9)	18(1)	13(1)	23(1)	1(1)	11(1)	-1(1)
C(10)	19(1)	14(1)	24(1)	-5(1)	14(1)	-2(1)
C(11)	21(1)	23(1)	18(1)	-4(1)	12(1)	-2(1)
C(12)	18(1)	29(1)	18(1)	1(1)	10(1)	-1(1)
C(13)	21(1)	26(1)	26(1)	4(1)	17(1)	4(1)
C(14)	21(1)	30(1)	28(1)	-5(1)	19(1)	-1(1)

C(15)	20(1)	50(1)	18(1)	2(1)	13(1)	0(1)
C(16)	21(1)	31(1)	21(1)	9(1)	11(1)	-3(1)
C(17)	16(1)	12(1)	17(1)	-1(1)	10(1)	0(1)
C(18)	17(1)	14(1)	21(1)	0(1)	12(1)	-1(1)
C(19)	17(1)	27(1)	18(1)	2(1)	8(1)	0(1)
C(20)	27(1)	32(1)	14(1)	2(1)	11(1)	-1(1)
C(21)	25(1)	28(1)	22(1)	-2(1)	18(1)	-3(1)
C(22)	17(1)	16(1)	20(1)	-3(1)	12(1)	-2(1)
C(23)	19(1)	11(1)	22(1)	1(1)	8(1)	-1(1)
C(24)	22(1)	15(1)	20(1)	4(1)	10(1)	-1(1)
C(25)	25(1)	21(1)	17(1)	1(1)	6(1)	0(1)
C(26)	17(1)	22(1)	22(1)	-2(1)	4(1)	-1(1)
C(27)	14(1)	17(1)	31(1)	0(1)	10(1)	-3(1)
C(28)	15(1)	22(1)	30(1)	6(1)	14(1)	1(1)
C(29)	23(1)	29(1)	29(1)	1(1)	18(1)	5(1)
C(30)	23(1)	19(1)	23(1)	-4(1)	10(1)	3(1)
Cl(1C)	38(1)	36(1)	67(1)	-11(1)	27(1)	-5(1)
Cl(2C)	38(1)	36(1)	67(1)	-11(1)	27(1)	-5(1)
Cl(1D)	36(1)	30(2)	70(1)	-11(1)	22(1)	-3(1)
Cl(2D)	36(1)	30(2)	70(1)	-11(1)	22(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C-2.

	x	y	z	U(eq)
H(5)	1642	6719	5850	60(8)
H(5A)	1617	4648	4907	25(5)
H(6)	3437	7590	6250	41(6)
H(6A)	2361	4259	4733	31(5)
H(7)	4367	7818	9301	47(7)
H(7A)	3209	5393	5281	30(5)
H(8)	2480	7812	8768	41(6)
H(9)	3141	10913	7044	24(5)
H(10)	3457	10566	8257	18(4)
H(11A)	4536	11043	9217	19(4)

H(11B)	4401	9906	9293	20(4)
H(12A)	4997	10566	8653	24(5)
H(12B)	5279	9927	9386	30(5)
H(13)	4867	8439	8673	34(5)
H(14)	4344	8297	7381	40(6)
H(15A)	4447	10043	6914	45(6)
H(15B)	3807	9586	6490	40(6)
H(16A)	4304	11272	7550	26(5)
H(16B)	3709	11266	6694	30(5)
H(19)	4918	7075	11133	32(5)
H(20)	4319	6810	11523	32(5)
H(21)	3253	6985	10621	27(5)
H(23)	2297	10824	7307	25(5)
H(24)	2041	10214	6148	26(5)
H(25A)	1223	9170	5279	30(5)
H(25B)	921	10260	5139	26(5)
H(26A)	521	9744	5770	21(5)
H(26B)	384	8863	5194	32(5)
H(27)	1010	7720	6207	27(5)
H(28)	1460	8012	7470	11(4)
H(29A)	1815	9588	8109	25(5)
H(29B)	1104	9783	7575	43(6)
H(30A)	1084	10820	6690	23(5)
H(30B)	1629	11148	7509	29(5)
H(1SC)	5374	6570	7666	84
H(1SD)	4651	6796	7153	84
H(1SA)	5189	6783	7515	84
H(1SB)	4484	6581	7136	84

Table 6. Torsion angles [°] for C-2.

O(4)-Cu(1)-O(1)-C(1)	64.45(13)
C(23)-Cu(1)-O(1)-C(1)	-112.26(13)
C(24)-Cu(1)-O(1)-C(1)	-103.7(2)
C(28)-Cu(1)-O(1)-C(1)	171.74(13)
O(1)-Cu(1)-O(4)-C(2)	-92.31(12)

C(23)-Cu(1)-O(4)-C(2)	82.87(16)
C(24)-Cu(1)-O(4)-C(2)	82.48(13)
C(28)-Cu(1)-O(4)-C(2)	-178.58(11)
O(1)-Cu(1)-C(23)-C(24)	174.14(12)
O(1)-Cu(1)-C(23)-C(30)	-64.29(13)
O(4)-Cu(1)-C(23)-C(24)	-0.61(19)
O(4)-Cu(1)-C(23)-C(30)	120.96(12)
C(24)-Cu(1)-C(23)-C(30)	121.57(18)
C(28)-Cu(1)-C(23)-C(24)	-108.55(13)
C(28)-Cu(1)-C(23)-C(30)	13.02(10)
O(1)-Cu(1)-C(24)-C(23)	-12.3(2)
O(1)-Cu(1)-C(24)-C(25)	-137.31(14)
O(4)-Cu(1)-C(24)-C(23)	179.62(12)
O(4)-Cu(1)-C(24)-C(25)	54.63(15)
C(23)-Cu(1)-C(24)-C(25)	-125.0(2)
C(28)-Cu(1)-C(24)-C(23)	69.73(13)
C(28)-Cu(1)-C(24)-C(25)	-55.27(14)
O(1)-Cu(1)-C(28)-C(27)	-145.98(11)
O(1)-Cu(1)-C(28)-C(29)	85.02(9)
O(4)-Cu(1)-C(28)-C(27)	-46.04(11)
O(4)-Cu(1)-C(28)-C(29)	-175.03(9)
C(23)-Cu(1)-C(28)-C(27)	95.98(11)
C(23)-Cu(1)-C(28)-C(29)	-33.02(10)
C(24)-Cu(1)-C(28)-C(27)	59.43(11)
C(24)-Cu(1)-C(28)-C(29)	-69.57(10)
O(3)-Cu(2)-O(2)-C(1)	-99.46(12)
C(9)-Cu(2)-O(2)-C(1)	79.76(16)
C(10)-Cu(2)-O(2)-C(1)	78.92(13)
O(2)-Cu(2)-O(3)-C(2)	51.67(14)
C(9)-Cu(2)-O(3)-C(2)	-127.76(14)
C(10)-Cu(2)-O(3)-C(2)	-124.28(19)
O(2)-Cu(2)-C(9)-C(10)	-1.31(18)
O(2)-Cu(2)-C(9)-C(16)	120.70(12)
O(3)-Cu(2)-C(9)-C(10)	177.83(11)
O(3)-Cu(2)-C(9)-C(16)	-60.16(13)
C(10)-Cu(2)-C(9)-C(16)	122.01(18)

O(2)-Cu(2)-C(10)-C(9)	179.14(12)
O(2)-Cu(2)-C(10)-C(11)	53.20(14)
O(3)-Cu(2)-C(10)-C(9)	-4.9(3)
O(3)-Cu(2)-C(10)-C(11)	-130.84(17)
C(9)-Cu(2)-C(10)-C(11)	-125.9(2)
Cu(1)-O(1)-C(1)-O(2)	-0.2(2)
Cu(1)-O(1)-C(1)-C(17)	178.49(9)
Cu(2)-O(2)-C(1)-O(1)	22.8(2)
Cu(2)-O(2)-C(1)-C(17)	-155.89(10)
Cu(2)-O(3)-C(2)-O(4)	22.0(2)
Cu(2)-O(3)-C(2)-C(3)	-156.05(10)
Cu(1)-O(4)-C(2)-O(3)	2.8(2)
Cu(1)-O(4)-C(2)-C(3)	-179.13(9)
O(1)-C(1)-C(17)-C(18)	-171.24(14)
O(1)-C(1)-C(17)-C(22)	6.8(2)
O(2)-C(1)-C(17)-C(18)	7.5(2)
O(2)-C(1)-C(17)-C(22)	-174.45(13)
O(3)-C(2)-C(3)-C(4)	-179.44(13)
O(3)-C(2)-C(3)-C(8)	4.2(2)
O(4)-C(2)-C(3)-C(4)	2.5(2)
O(4)-C(2)-C(3)-C(8)	-173.88(13)
C(2)-C(3)-C(4)-O(5)	4.0(2)
C(2)-C(3)-C(4)-C(5)	-175.72(13)
C(8)-C(3)-C(4)-O(5)	-179.59(13)
C(8)-C(3)-C(4)-C(5)	0.7(2)
C(2)-C(3)-C(8)-O(6)	-3.1(2)
C(2)-C(3)-C(8)-C(7)	175.86(14)
C(4)-C(3)-C(8)-O(6)	-179.49(13)
C(4)-C(3)-C(8)-C(7)	-0.6(2)
O(5)-C(4)-C(5)-C(6)	179.97(15)
C(3)-C(4)-C(5)-C(6)	-0.3(2)
C(4)-C(5)-C(6)-C(7)	-0.3(2)
C(5)-C(6)-C(7)-C(8)	0.4(2)
C(6)-C(7)-C(8)-O(6)	178.98(14)
C(6)-C(7)-C(8)-C(3)	0.0(2)
Cu(2)-C(9)-C(10)-C(11)	102.29(17)

C(16)-C(9)-C(10)-Cu(2)	-103.78(16)
C(16)-C(9)-C(10)-C(11)	-1.5(3)
Cu(2)-C(9)-C(16)-C(15)	4.44(17)
C(10)-C(9)-C(16)-C(15)	84.9(2)
Cu(2)-C(10)-C(11)-C(12)	58.46(18)
C(9)-C(10)-C(11)-C(12)	-24.5(2)
C(10)-C(11)-C(12)-C(13)	-53.20(19)
C(11)-C(12)-C(13)-C(14)	89.4(3)
C(12)-C(13)-C(14)-C(15)	0.1(4)
C(13)-C(14)-C(15)-C(16)	-30.5(3)
C(14)-C(15)-C(16)-C(9)	-47.7(2)
C(1)-C(17)-C(18)-O(7)	-4.1(2)
C(1)-C(17)-C(18)-C(19)	175.99(14)
C(22)-C(17)-C(18)-O(7)	177.81(14)
C(22)-C(17)-C(18)-C(19)	-2.1(2)
C(1)-C(17)-C(22)-O(8)	4.3(2)
C(1)-C(17)-C(22)-C(21)	-175.71(14)
C(18)-C(17)-C(22)-O(8)	-177.65(14)
C(18)-C(17)-C(22)-C(21)	2.4(2)
O(7)-C(18)-C(19)-C(20)	-179.33(15)
C(17)-C(18)-C(19)-C(20)	0.6(2)
C(18)-C(19)-C(20)-C(21)	0.7(3)
C(19)-C(20)-C(21)-C(22)	-0.5(3)
C(20)-C(21)-C(22)-O(8)	178.90(15)
C(20)-C(21)-C(22)-C(17)	-1.1(2)
Cu(1)-C(23)-C(24)-C(25)	100.34(17)
C(30)-C(23)-C(24)-Cu(1)	-103.42(16)
C(30)-C(23)-C(24)-C(25)	-3.1(3)
Cu(1)-C(23)-C(30)-C(29)	10.69(17)
C(24)-C(23)-C(30)-C(29)	90.25(19)
Cu(1)-C(24)-C(25)-C(26)	54.67(19)
C(23)-C(24)-C(25)-C(26)	-27.4(3)
C(24)-C(25)-C(26)-C(27)	-48.3(2)
C(25)-C(26)-C(27)-C(28)	90.2(3)
C(26)-C(27)-C(28)-Cu(1)	-87.3(2)
C(26)-C(27)-C(28)-C(29)	-2.7(4)

Cu(1)-C(28)-C(29)-C(30)	49.95(17)
C(27)-C(28)-C(29)-C(30)	-28.6(3)
C(28)-C(29)-C(30)-C(23)	-49.2(2)

Table 7. Hydrogen bonds for C-2 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5)-H(5)...O(4)	0.8400	1.8100	2.5487(17)	146.00
O(6)-H(6)...O(3)	0.8400	1.8200	2.558(2)	146.00
O(7)-H(7)...O(2)	0.8400	1.8000	2.5431(16)	147.00
O(8)-H(8)...O(1)	0.8400	1.8100	2.5566(18)	147.00
C(10)-H(10)...O(5)#1	0.9400	2.6000	3.346(2)	137.00

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,-z+1

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Chapter 3

Palladium-Catalyzed Desulfitative Cross-Coupling Reactions of Peptidyl Thiol Esters and Thiol Ethers with Boronic Acids

Abstract: A novel MT-mimic catalyst system has been developed for the construction of C-C bonds through a Pd-catalyzed desulfitative reaction, modeled after the biochemical process of metallothioneins (MT), in which Cu(I) and other metals are rapidly released from a strongly binding thiolate by exposure to an exogenous disulfide ligand. An efficient Pd-catalyzed cross-coupling of peptidyl thiol esters containing an O-acetyl oxime pendant with a wide range of boronic acids has been developed for the synthesis of high enantiopurity N-protected α-amino ketones. The reaction proceeds under mild reaction conditions and demonstrates a high tolerance for different functional groups. The "metallothionein mimic" concept has been further exploited for the cross-coupling of aromatic and heteroaromatic thiol ethers and boronic acids. The O-mercaptoacetophenone O-acetyl oxime pendant activates aryl C-S bonds under catalytic palladium and copper conditions towards transmetallation with boronic acids. The application of this "metallothionein mimic" concept may prove useful for selective carbon-carbon bond formation in more complex molecules.

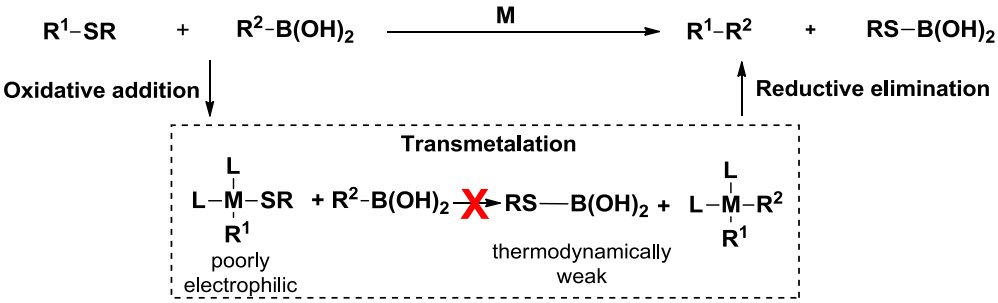
3.1 Introduction and Background

3.1.1 History of Desulfitative Cross-Coupling Reaction

During the past decade, metal-mediated cross-coupling reactions have become one of the most versatile tools to construct carbon-carbon and carbon-heteroatom bonds.[1] These methodologies have been widely applied in the area of organic synthesis and material science because of their tolerance to many functional groups.[2] Most of these reactions utilize a variety of nucleophilic organometallic reagents (including organozinc, Grignard or organolithium reagents) reacting with organic halides[3a-c] or triflates.[3d-f] The introduction of a new class of readily available reaction partners to these cross-coupling protocols would significantly extend the impact of these powerful processes. The more polarizable C-S bond compared to C-halogen and C-O bonds may provide opportunities for unique chemoselectivity and functional group compatability. Recently, organosulfur compounds have shown increasing importance as coupling partners.[4] The

Liebeskind laboratory is interested in the exploration of the cross-coupling reactions of thioorganics with mild organometallic reagents such as organoboron or organotin compounds under pH-neutral conditions (**Scheme 3.1**).

Scheme 3.1 Thioorganic-Boronic Acid Cross-Croupling Reaction



Scheme 3.1 displays a representative disulfitative cross-coupling between thioorganics and boronic acids. A transition metal catalyst selectively cleaves the C-S bond to generate an R^1-M-SR intermediate as the first step of the transformation. Low-valent complexes of transition metals such as palladium,[5] nickel,[6] platinum,[7] ruthenium,[8] and rhodium,[9] *etc.* have been extensively studied for C-S oxidative addition reactions in order to gain a better understanding of the heterogeneous catalysis hydrosulfurization in the petroleum industry.[10] Usually the oxidative addition of C-S substrates to low-valent transition metals is reversible.

Although the oxidative addition of organosulfur compounds to a low-valent transition metal species has been well established for various C-S bonds, the key to catalytic cross-coupling reactions with organosulfur compounds is the activation of the very stable sulfur-metal bond that is assumed to be thermodynamically strong. Additionally, the generated S-B bond, a soft-hard interaction, is not thermodynamically favored (**Scheme 3.1**).

To address these challenges, Liebeskind and Srogl reported the first examples of palladium-catalyzed, copper-mediated cross-cooupling between thiol esters and boronic acids under base-free condition in 2000.[11] The crucial requirement of this protocol is the inclusion of a

stoichiometric amount of a copper(I) carboxylate such as copper(I) thiophene-2-carboxylate (CuTC) as a reaction mediator (**Scheme 3.2**).

Scheme 3.2 Palladium-catalyzed, Copper Carboxylate Mediated Desulfitative Couplings

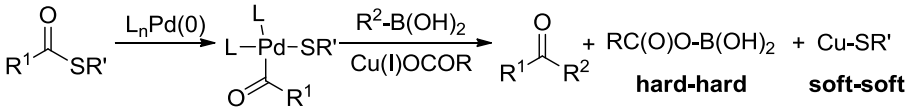
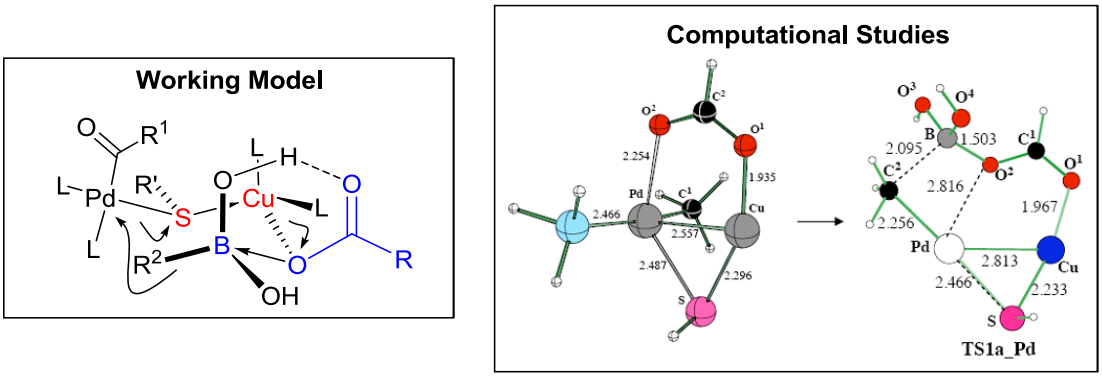


Figure 3.1 Working Model and Computational Studies of the Mechanism

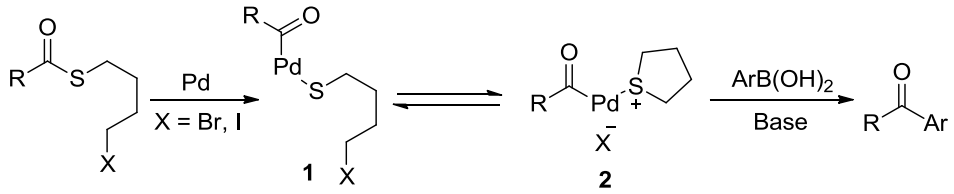


The working model for cross-coupling is proposed in **Figure 3.1** left, which depicts a chair like transition state during transmetallation. In contrast to the hypothetical model, the computational model developed by Dr. Jamal Musaev demonstrated the multiple roles of the Cu(I) carboxylate in this transformation.[12] As shown in **Figure 3.1** right, the carboxylate on Cu not only facilitates phosphine dissociation from the palladium center to form a more electrophilic and less hindered Pd monophosphine intermediate, but also coordinates to the trivalent boron center to activate the boronic acid and bring it into proximity with the Pd-complex. The stoichiometry of the Cu(I) carboxylate was used to completely scavenge the thiolate by forming CuSR (a soft-soft interaction), and to thermodynamically balance the reaction by providing a full equivalent of a carboxylate counterion to pair with the $-B(OH)_2$ moiety (a hard-hard interaction).

The anaerobic Liebeskind-Srogl cross-coupling has exhibited its versatility in carbon-carbon bond formation as demonstrated by different groups,[13] however, the use of at least a stoichiometric quantity of copper(I) carboxylate is not economical. Based on the understanding of

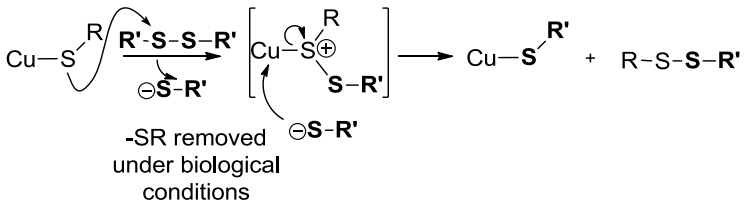
the first generation desulfitative coupling reaction, we know that it is essential to liberate Pd(0) from the strong Pd-thiolate bond in order to realize a full catalytic desulfitative cross-coupling reaction. Another feasible tactic is to use alkylative activation of the palladium thiolate intermediate (**Scheme 3.3**).[14] During this transformation, the stable Pd-thiolate bond (intermediate **1**) is converted to a labile Pd-thioether bond (intermediate **2**), so that the thiolate is internally scavenged by alkylation. However, this reaction requires high temperature (90 ^{o}C) and an external oxygenate base to activate the poorly nucleophilic boronic acids.

Scheme 3.3 Pd-Catalyzed Thiol Ester Cross-Coupling using Alkylative Activation



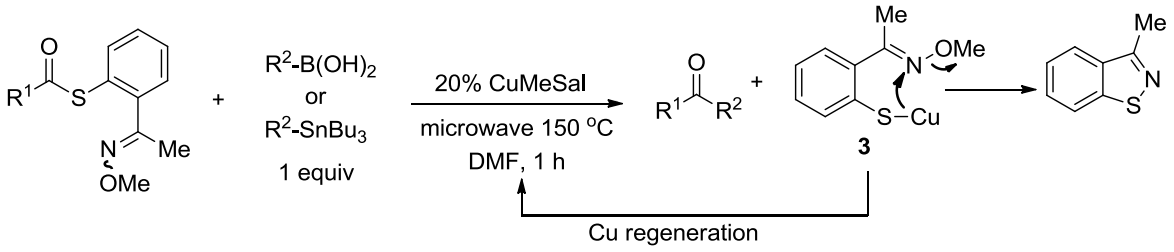
On the way to developing a mild Pd-catalyzed desulfitative cross-coupling reaction, the metallothionein (MT) mimic Cu(I) catalyzed cross-coupling drew our attention.[15] The MT-mimic catalyst system was inspired from the function of biological metallothioneins.[16] Metallothioneins are relatively small proteins comprised of roughly 30% cysteine residues which can bind up to 7 equivalents of divalent metals such as Zn and Cu. When exposed to an exogenous disulfide, the strongly bound metal thiolate of metallothioneins is converted to a weakly binding disulfide through a disulfide exchange mechanism, and the released Cu is rebounded to a new thiolate (Cu-SR', **Scheme 3.4**).[17]

Scheme 3.4 Liberating Cu from the Thiolate Ligand by Oxidative Trap of Thiolate



In order to effectively couple boronic acids, it is necessary to generate a catalytically viable Cu-oxygenate after copper is liberated from the thiolate. Thus, a "metallothionein mimic" thiol ester was designed, which possesses an *ortho* oxime functional group as the disulfide equivalent to trap the Cu-thiolate (**Scheme 3.5**).[15] In the MT mimic system, the *ortho* oxime functional group acts as an internal oxidant to trap the copper thiolate **3** in the form of 3-methyl-1,2-benzisothiazole, while at the same time regenerating a copper(I)-oxygenate. The internal oxime pendant also provides a stoichiometric oxygenate counterion (-OMe) to pair with -$B(OH)_2$ or -$SnBu_3$ moieties.

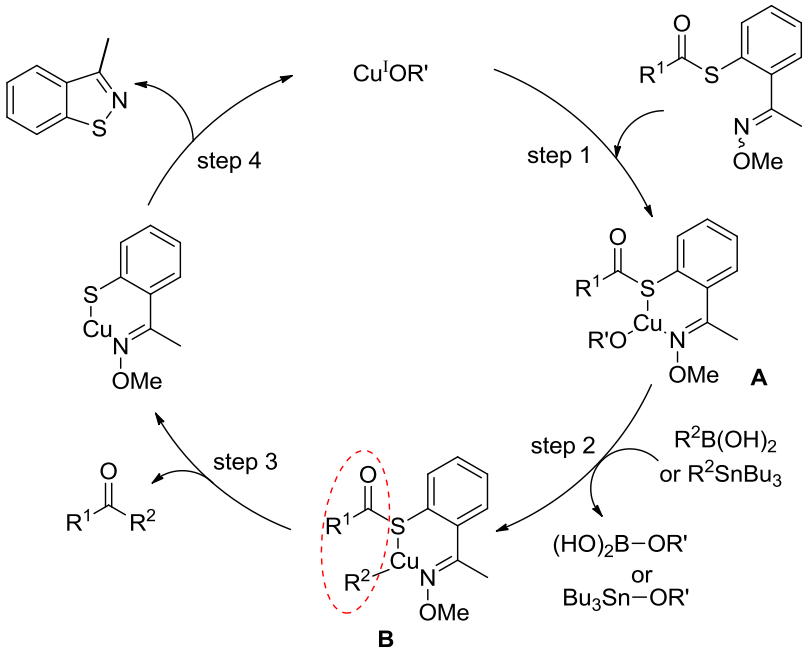
Scheme 3.5 Cu-catalyzed MT-mimic Desulfitative Cross-Coupling Reaction



The proposed catalytic cycle for the Cu-catalyzed MT-mimic reaction is shown in **Scheme 3.6**. It was assumed that the coupling begins with coordination of Cu(I) to the thiol ester and the pendant oxime nitrogen (step 1). Subsequent transmetallation would afford the organocopper intermediate **B** (step 2). In intermediate **B**, R^2 is brought into close proximity with the thiol ester through Cu S,N-chelation. After nucleophilic substitution, the desired ketone product is produced (step 3). At the same time, the active copper catalyst is regenerated via S-N closure by the reaction of the copper thiolate with the internal oxime functionality (step 4). This allows the oxime pendant to oxidatively scavenge the thiolate through a 'metallothionein mimic' mechanism. Since B→Cu transmetallation (step 2) and the template C-C formation (step 3) can take place at 60 °C,[18] the S→N closure/catalyst regeneration (step 4) is the rate-determining step requiring hight temperature (above 100 °C) in the catalytic cycle (when methoxide used as the leaving group).[15] This new Cu catalysis follows a mechanism different from the traditional metal-

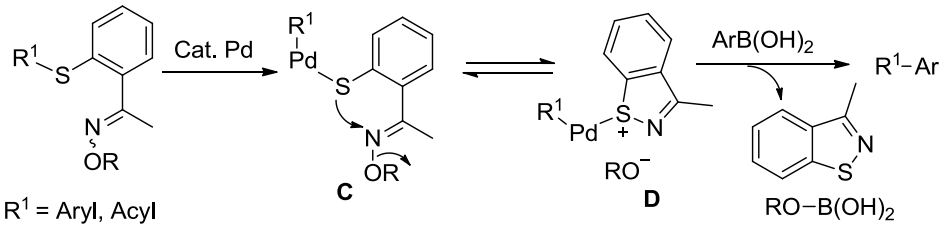
mediated cross-coupling mechanism (oxidative addition-transmetallation-reductive elimination) and has a good substrate scope and fuctional group tolerance in the synthesis of ketones.

Scheme 3.6 Proposed Mechanism for Copper Catalyzed MT-mimic Desulfitative Cross-Coupling Reaction



The MT-mimic cross-coupling reaction described above would provide another feasible pathway to activate a Pd-thiolate (**Scheme 3.7**) for reactions that are catalytic in Pd-only. For example, the palladium thiolate formed after selective C-S oxidative addition could be activated via in situ formation of a sulfonium salt like intermediate **D** (similar to intermediate **2**, **Scheme 3.3**). Then, transmetallation followed by reductive elimination would afford the desired cross-coupling product (**Scheme 3.7**). The overall reaction is thermodynamically balanced by both full scavenging of the thiolate by S-N closure and by providing a stoichiometric quantity of an oxygenate cofactor for the boronic acid. Based on the proposed mechanism, a palladium catalyzed, MT-mimic desulfitative cross-coupling reaction could be realized without the addition of external bases to activate the boronic acid. Additionally, with the mechanism of oxidative addition, transmetallation and elimination, this Pd-based method might offer potential application to a broad range of thioorganic reactants other than the Cu-catalyzed reaction of thiol esters.

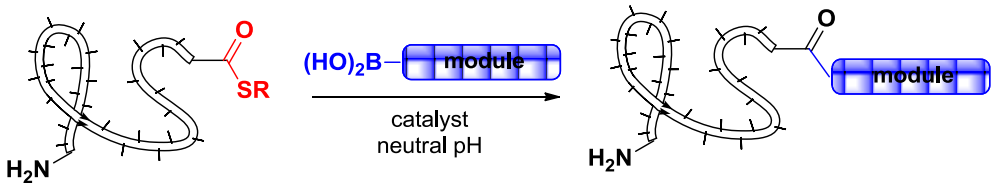
Scheme 3.7 Pd-catalyzed Desulfitativ Cross-Coupling Using MT-mimic System



3.1.2 Synthesis of High Enantiopurity *N*-Protected α-Amino Ketones

The potential of a Pd-catalyzed desulfitative cross-coupling of thiol esters and boronic acids may allow its application in more complicated systems. **Scheme 3.8** demonstrates a desulfitative cross-coupling reaction in joining a boron functionalized module with a biomolecule. From the context of a pH-neutral ketoconjugation, such a desulfitative cross-coupling reaction could be used to generate a C-C bond that is hydrolysis/proteolysis stable compared with the C-N bond of amides.

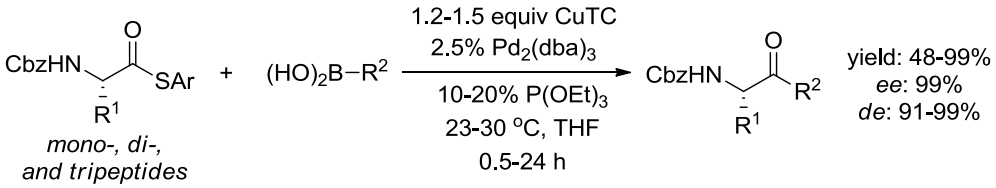
Scheme 3.8 Application of Desulfitative Cross-Coupling in Complicated System



Many different approaches to transform *α*-amino acids and small peptides to the corresponding C-terminal ketones are reported in the literature, with the focus on the construction of enantiopure *α*-amino ketones.[19] Most of the methodologies are based on the reaction of basic and nucleophilic organometallic reagents with *N*-protected *α*-amino acids derivatives such as acid halides,[20] Weinreb amides[21] and thiol esters.[22] Traditionally, these methods have been restricted to the use of strongly basic/nucleophilic organometallic reagents such as Grignard, organolithium and organozinc reagents which limits their application in the synthesis of more complex molecules containing base-sensitive stereogenic centers and nucleophile incompatible functional groups.

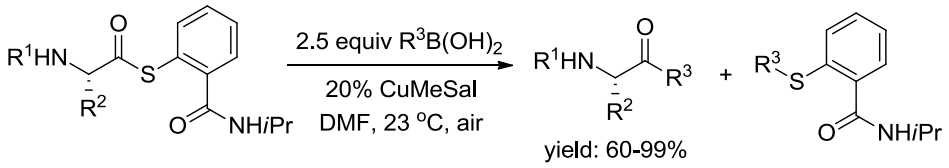
To address this issue, a new, non-basic desulfitative cross-coupling of thiol esters and boronic acids to prepare *N*-protected *α*-amino ketones was recently developed by the Liebeskind laboratory based on the first generation Liebeskind-Srogl reaction (**Scheme 3.9**).[13c] Since boronic acids are non-basic and non-nucleophilic in contrast to organolithium, magnesium and zinc reagents, the desulfitative thiol ester-boronic acid cross-coupling reaction conditions are mild and non-basic allowing the retention of stereocenters of functionally-rich and epimerization-sensitive peptidyl thiol esters. In the presence of stoichiometric Cu(I) thiophene-2-carboxylate and catalytic $Pd_2(dba)_3$/triethylphosphite, *N*-protected *α*-amino ketones were produced in good-to-excellent yields without racemization. However, the use of stoichiometric copper carboxylate will serverely limit the application of the first generation Liebeskind-Srogl reaction in the more complex biological system (**Scheme 3.9**).

Scheme 3.9 Peptidyl Ketones from Peptidyl Thiol Esters and Boronic Acids



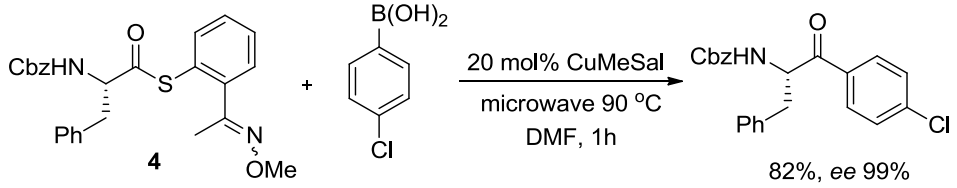
The second generation Cu-only, catalyzed aerobic cross-coupling reaction was used to synthesize high enantiopurity *N*-Cbz protected di-, and tripeptidyl ketones (**Scheme 3.10**).[23] This new reaction takes place at room temperature in DMF or DMF/H_2O open to air and requires only a catalytic amount of a copper(I) carboxylate. The conversion of the in situ generated Cu–SR to a catalytically viable Cu–oxygenate and the trapping of the thiolate (–SR) as a weakly binding thioether are essential for the completion the catalytic cycle.[24] Unfortunately, a second equivalent of boronic acid is required to release the active copper catalyst back into the catalytic cycle by forming an *S*-arylation product. This wasted equivalent of boronic acid is not economical, especially if the boronic acid is precious or integrated in the coupling partner for the thiol ester.

Scheme 3.10 Peptidyl Ketones from *S*-Acylthiosalicylamides and Boronic Acids



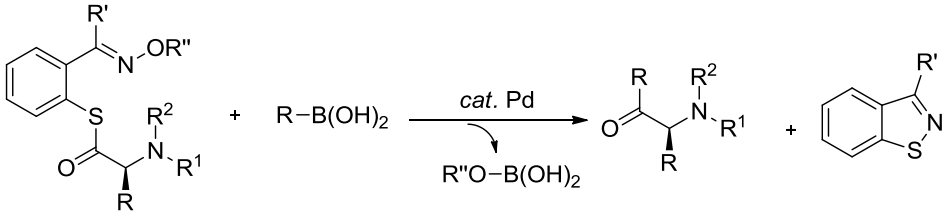
The copper catalyzed MT-mimic cross-coupling under anaerobic conditions was effectively extended to peptidyl ketone synthesis. A boronic acid coupled with the high enantiopurity phenylalanine derived MT-mimic thiol ester **4** at 90 °C and afforded the corresponding peptidly ketones in good yields without racemization (**Scheme 3.11**).[15] However, this cross-coupling takes place at elevated temperature, which precludes its utilization in more complicated or sensitive system.

Scheme 3.11 Cu-Catalyzed Desulfitative Cross-Coupling of Peptidyl Thiol Esters



To overcome the limitations of the reported desulfitative peptidyl ketone syntehsis, a study of the palladium-catalyzed MT-mimic desulfitative cross-coupling of peptidyl thiol esters and boronic acids under mild and pH-neutral conditions was undertaken (**Scheme 3.12**). This cross-coupling has the potential to be applied to a broad range of thioorganic reactants.

Scheme 3.12 Pd-Catalyzed MT-mimic Cross-Coupling of Peptidyl Thiol Esters

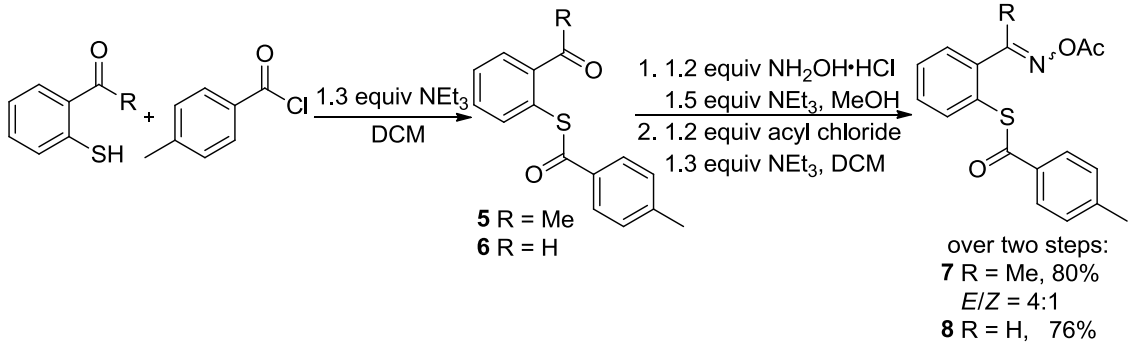


3.2 Results and Discussion

3.2.1 Pd-Catalyzed MT-mimic Cross-Coupling of Peptidyl Thiol Esters with Boronic Acids

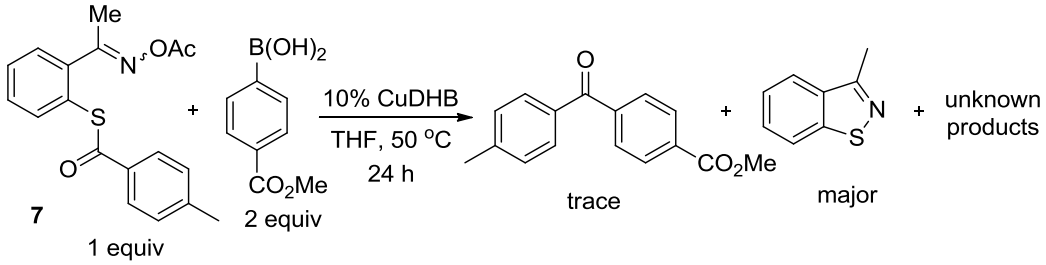
As demonstrated previously, Cu-catalyzed MT-mimic cross-coupling requires elevated temperature (**Scheme 3.6**). In order to render a milder MT-mimic desulfitative cross-coupling reaction, a better oxygenate leaving group (OAc) on the oxime (=N-OR) was installed in order to weaken the N-O bond and facilitate its cleavage. Ketoxime thiol ester **7** and aldoxime thiol ester **8** containing an *O*-acyl oxime pendant were prepared from thiol esters **5** and **6** following the procedures depicted in **Scheme 3.13**. Ketoxime thiol ester **7** was isolated as a mixture of the *E*/*Z* isomers with a ratio of 4:1, while aldoxime thiol ester **8** exsits as a single *E* isomer.

Scheme 3.13 Preparation of Simple Ketoxime and Aldoxime Thiol Esters



When ketoxime thiol ester **7** was subjected to the catalytic Cu cross-coupling conditions (**Scheme 3.14)**, only a trace amount of the desired ketone product was observed in the crude ^{1}H NMR along with 3-methyl-1,2-benzisothiazole and some unidentified byproducts. Although ketone was produced only in low yield, the starting thiol ester **7** was not recovered indicating that side-reactions took place over the desired cross-coupling at C-S bond of the thiol ester. Copper(I) can efficiently mediate the cleavage of an N-O bond (=N-OAc) to construct C-N bonds,[25] thus the precedented N-O bond cleavage chemistry could possibly interfere with the desired thiol ester cross-coupling.

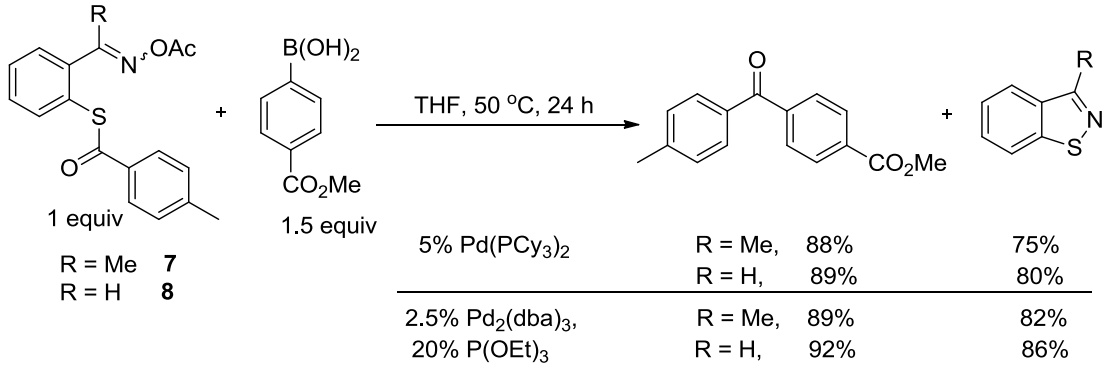
Scheme 3.14 Copper Catalyzed Desulfitative MT-mimic Ketone Formation



Switching to palladium in order to develop a milder MT-mimic desulfitative cross-coupling reaction for ketone synthesis, we still face the challenge that low-valent Pd sources can react with oxime derivatives bearing a good leaving group. For example, the oxidative addition of Pd(0) into the N-O bond of oxime esters has been reported to generate alkylideneaminopalladium(II) species at room temperature.[26] However, palladium is not as efficient as copper in mediating C-N bond formation through N-O bond cleavage of oxime derivatives.[25] On the other hand, palladium can participate in C-S bond oxidative addition at ambient temperatures.[5,27] The differing reactivity of palladium and copper may provide a solution to suppress side-reactions at the N-O bond.

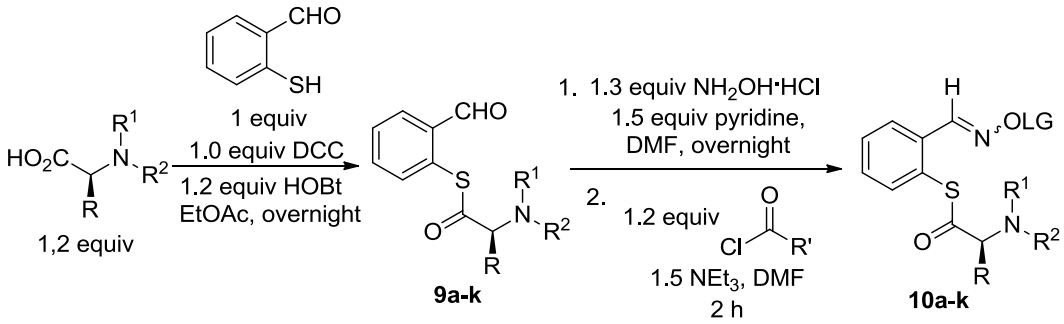
In order to explore the Pd-catalyzed MT-mimic ketone formation, thiol esters **7** and **8** were treated with (4-(methoxycarbonyl)phenyl)boronic acid and 5% palladium catalyst ($Pd(PCy_3)_2$ or $Pd_2(dba)_3/P(OEt)_3$) at 50 ^oC. Thiol esters **7** and **8** reacted smoothly under the cross-coupling reaction conditions to generate the desired ketone product and benzo[d]isothiazole as the expected byproduct, both in high yields (**Scheme 3.15**). At room temperature, the cross-coupling between **7** and the boronic acid produced less than 10% of the desired ketone with 88% recovery of thiol ester **7** after 24 hours. These results show the superiority of palladium over copper in catalyzing desulfitative MT-mimic cross-coupling reactions.

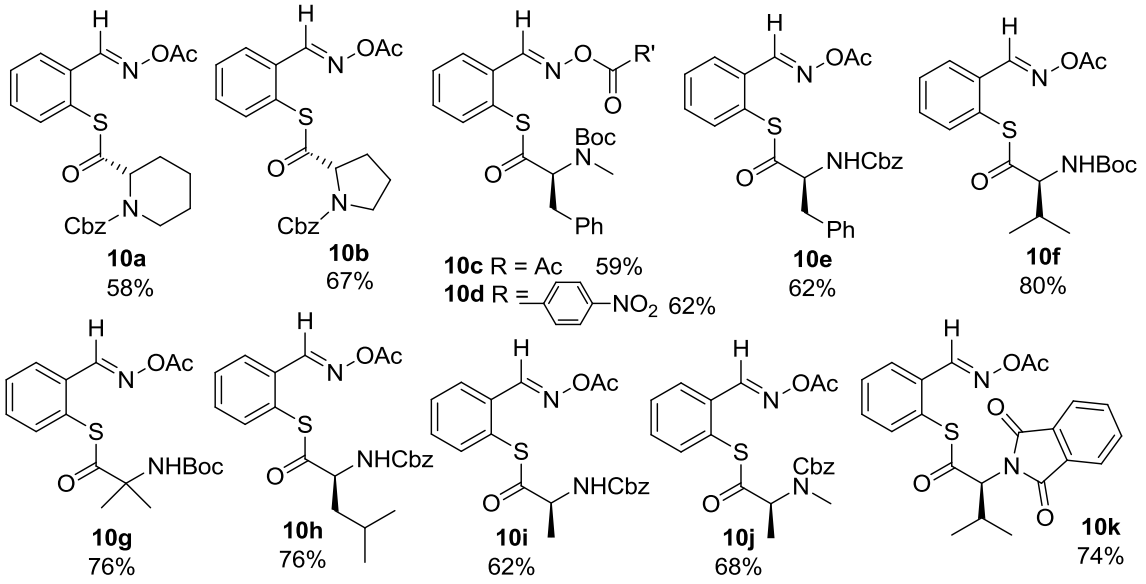
Scheme 3.15 Pd-catalyzed Desulfitative MT-mimic Simple Ketone Formation



The Pd-catalyzed MT-mimic desulfitative cross-coupling reaction was extended to the synthesis of high enantiopurity peptidyl ketones. *O*-acyl aldoxime was chosen as the preferred pendant instead of ketoxime due to its ability to form a single *E* stereoisomer. Amino acid thiol esters **9a-k** were synthesized by standard DCC coupling reactions. Followed by an oxime formation and reaction with an acid chloride in DMF, a series of peptidyl thioesters **10a-k** with aldoxime MT-mimic pendant were synthesized (**Scheme 3.16**).

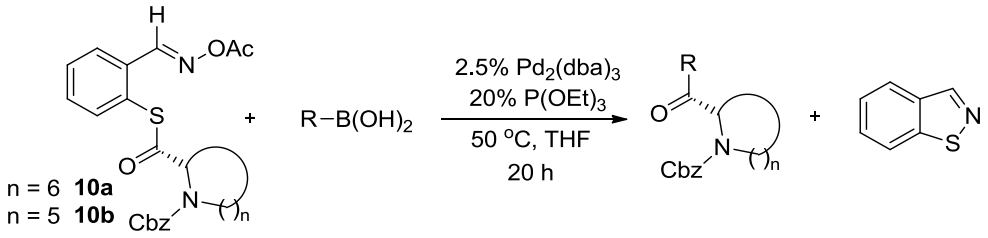
Scheme 3.16 Preparation of Peptidyl Thioesters with MT-mimic Pendant

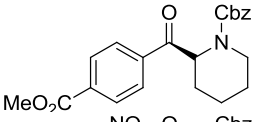
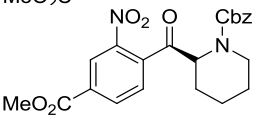
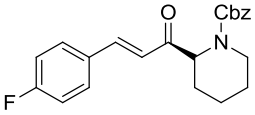
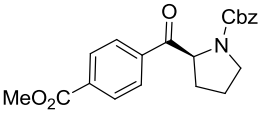
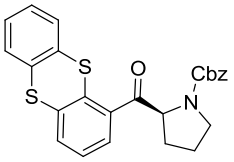
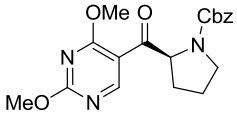
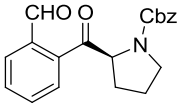
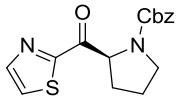




For prolinyl and piperidyl thiol esters **10a** and **10b**, a standard cross coupling was conducted in the presence of 2.5% $Pd_2(dba)_3$ and 20% $P(OEt)_3$ under an argon atmosphere for 20 hours. Aryl, vinyl and heteroaryl boronic acids could react with **10a/b** producing the desired peptidyl ketones in good yields (**Table 3.1**, entries 1-7). 2-(Tri-n-butylstannyl)thiazole cross-coupled with **10b** efficiently without significant destannylation (entry 8). No racemization was observed for entries 1 and 3 by chiral HPLC. Benzo[d]isothiazole was generated as the byproduct of the transformation.

Table 3.1 Prolinyl and Piperidyl Thiol Esters MT-mimic Cross-Coupling Reaction



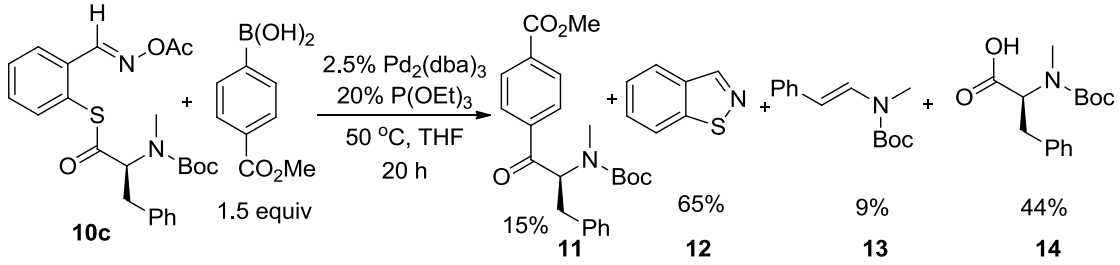
entry	substates	R	product	yield (%)[a]
1[b]	**10a**	4-(methoxycarbonyl)phenyl		74
2	**10a**	2-nitro-(4-methoxycarbonyl)phenyl		87
3[b]	**10a**	trans-2-(4-fluorophenyl)vinyl		83
4	**10b**	4-(methoxycarbonyl)phenyl		75
5	**10b**	2-thianthrenyl		84
6[c]	**10b**	5-(2,4-dimethoxypyrimidyl)		52
7[c]	**10b**	2-formylphenyl		75
8[d]	**10b**	2-thiazolyl		70

[a] Isolated yield. [b] No racemization was observed by HPLC chiral column using racemic mixtures. [c] 5% CuDHB was added into the reaction mixture. [d] Reaction with 2-(tributylstannyl)thiazole.

In contrast to the high yields of peptidyl ketones typically produced from peptidyl thiol esters **10a/b**, Boc protected *N*-methyl phenylalanine thiol ester **10c** (**Scheme 3.17**) failed to react efficiently under the standard reaction condition, only producing 15% of the desired peptidyl

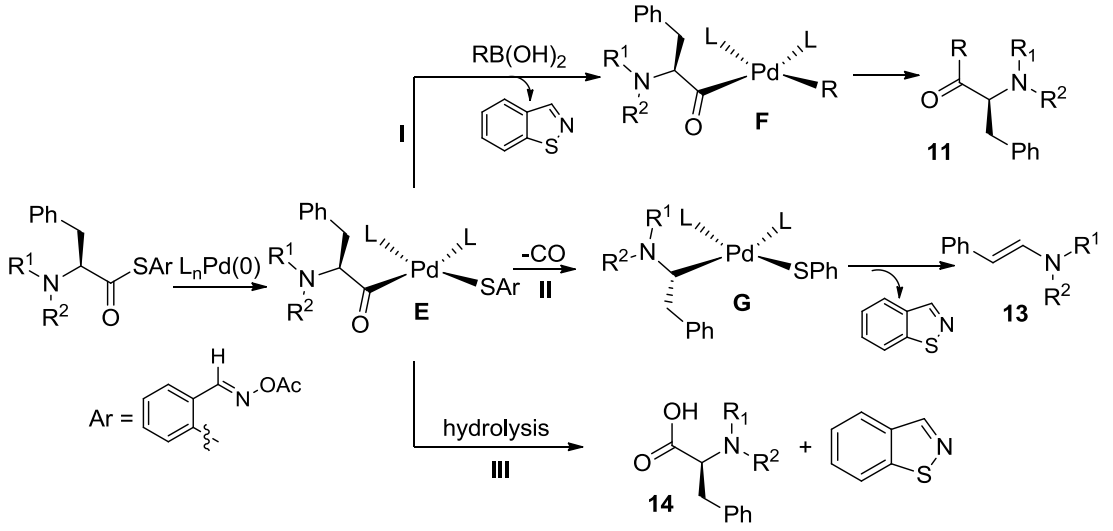
ketone **11** (**Scheme 3.17**). Two byproducts were isolated from the reaction: the enimide side product **13** and the hydrolyzed amino acid **14** from thiol ester.

Scheme 3.17 Doubly *N*-protected Phenylalanine Thiol Ester-Boronic Acid Cross-Coupling



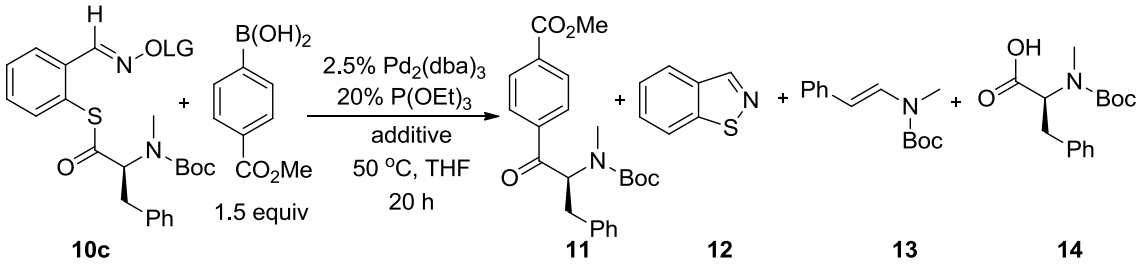
Guided by the formation of enimide **13** and amino acid **14**, a putative understanding of this reaction mechanism is necessary to develop a more efficient cross-coupling protocol (**Scheme 3.18**). In the first stage, the acylpalladium(II) intermediate **E** ($RCOPdL_2SAr$) would be formed by oxidative addition of the thiol ester to $L_nPd(0)$. Proceeding through the desired route **I** of **Scheme 3.18** requires S→N closure to trap the palladium thiolate followed by transmetallation from the boronic acid to the acylpalladium(II) intermediate. However, if the S→N closure and transmetallation step are slow, the enimide side product **13** could be generated following a Pd-catalyzed decarbonylation-*β*-hydride elimination sequence (Route **II**).[28] If there is water present in the reaction system and the hydrolysis of palladium thiolate **E** occurs at a reasonable rate, then the amino acid can be produced by the reaction sequence depicted in the Route **III**, **Scheme 3.18**.

Scheme 3.18 Proposed Mechanism Pathways for Pd-catalyzed MT-mimic Cross-Coupling



The reaction outcome should be influenced by the rates of transmetallation, decarbonylation and hydrolysis. Therefore, to achieve a more selective cross-coupling reaction one must either increase the rate of transmetallation from boron to palladium or decrease the rate of hydrolysis and decarbonylation. As described for the first generation Liebeskind-Srogl reaction, copper(I) carboxylate enhances the transmetallation step by generating a Pd monophosphine intermediate as well as by acting as a reactive transmetallation center for the boronic acid.[11,12] It might be possible to develop a successful cross-coupling by adding co-catalytic copper carboxylate into the reaction.

Table 3.2 Optimization of the Peptidyl Ketone Formation



entry	LG	additive	**11** (%)[a]	**12** (%)[a]	**13** (%)[a]	**14** (%)[a]
1	Ac	none	15	65	9	44
2	Ac	5% CuDHB	55	70	20	10
3	Ac	5% CuTC	40	90	10	30
4	Ac	5% CuMeSal	20	94	trace	68
5[b]	Ac	5% CuDHB	66 (47[c])	93 (90[c])	22 (45[c])	none
6[b]	4-nitrobenzoyl	5% CuDHB	20	80	10	none

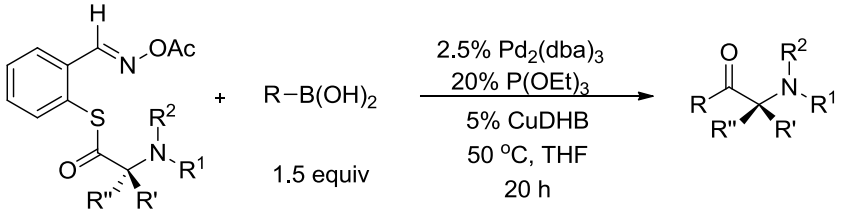
[a] Isolated yield. [b] with the addition of 4Å molecular sieve. [c] heated at 60 °C.

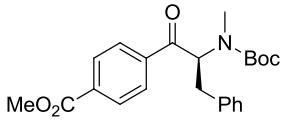
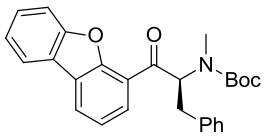
With the addition of a 5% CuDHB to assist transmetallation, a better cross-coupling reaction was achieved (**Table 3.2**, entry 2). CuDHB was the best copper carboxylate tested for the cross-coupling reaction (**Table 3.2**, entries 2-4). The hydrolyzed amino acid **14** could be totally eliminated with the application of 4Å molecular sieve (entry 5). Increasing the reaction temperature resulted in an increase in the decarbonylation side reaction (entry 5). Changing to a more reactive 4-nitrobenzoate leaving group did not improve the outcome of the reaction (entry

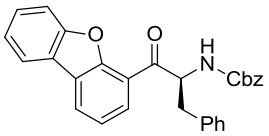
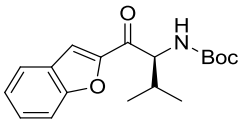
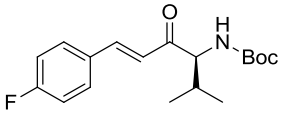
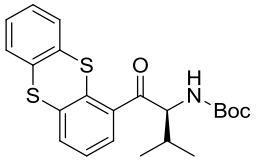
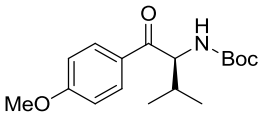
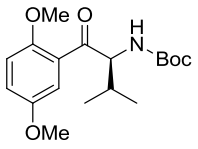
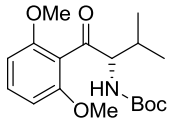
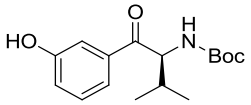
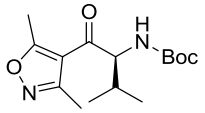
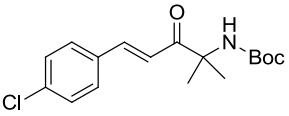
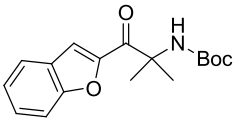
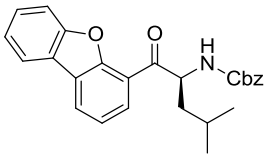
6). Various palladium/ligand systems ($Pd(PCy_3)_2$, $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, $Pd_2(dba)_3/P(OPh)_3$, $Pd_2(dba)_3/P(OMe)_3$) were inefficient in catalyzing the cross-coupling reaction. Among all the palladium/ligand system tried, $Pd_2(dba)_3/P(OEt)_3$ (1:4 ratio) gave the best ratio of ketone to enimide (3:1, entry 5).

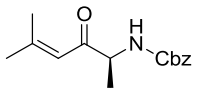
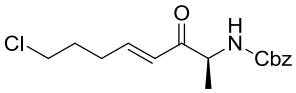
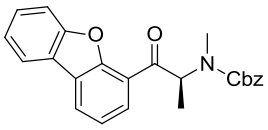
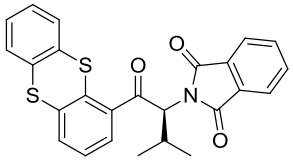
Aldoxime thiol esters **10c-k** (**Scheme 3.16**) were subjected to the cross-coupling condition using $Pd_2(dba)_3/P(OEt)_3$–CuDHB catalyst system with various of boronic acids. A variety of aryl (electron-rich, electron-deficient), heteroaryl (dibenzofuryl, thianthrenyl) and vinyl boronic acids were efficiently coupled with thiol esters of *N*-Cbz, *N*-Boc and *N*-phthaloyl protected *α*-amino acids as well as *N*-methyl *α*-amino acids (**Table 3.3**). Unfortunately, sterically hindered boronic acids were not effective and gave only low yields of peptidyl ketone products (entries 9 and 11). No racemization was detected by HPLC during the cross-coupling process reinforcing the mild and non-basic nature of the palladium catalyzed couplings of thioorganics and boronic acids. Moreover, even valine and 2-methylalanine derived thiol esters were excellent cross-coupling substrates highlighting the compatibility of somewhat hindered thiol ester substrates in this chemistry (entries 4-13).

Table 3.3 Synthesis of Amino Ketones in High Enantiomeric Purity



entry	subtrates	R	product	yield (%)[a]	ee (%)[b]
1	**10c**	4-(methoxycarbonyl)phenyl		60	
2	**10c**	4-dibenzo[b,d]furyl		79	

3	**10e**	4-dibenzo[b,d]furyl		63	
4	**10f**	2-benzofuranyl		83	
5	**10f**	trans-2-(4-fluorophenyl)vinyl		82	> 99
6	**10f**	2-thianthrenyl		73	
7	**10f**	4-methoxyphenyl		58	
8	**10f**	2,5-dimethoxyphenyl		67	
9	**10f**	2,6-dimethoxyphenyl		20	
10	**10f**	3-hydroxyphenyl		64	
11	**10f**	4-(3,5-dimethylisoxazolyl)		43	> 99
12	**10g**	trans-2-(4-chlorophenyl)vinyl		70	
13	**10g**	2-benzofuranyl		72	
14	**10h**	4-dibenzo[b,d]furyl		78	> 99

15	**10i**	1-(2-methylpropenyl)		75	> 99
16	**10i**	1-(5-chloropentenyl)		91	> 99
17	**10j**	4-dibenzo[b,d]furyl		82	
18	**10k**	2-thianthrenyl		64	

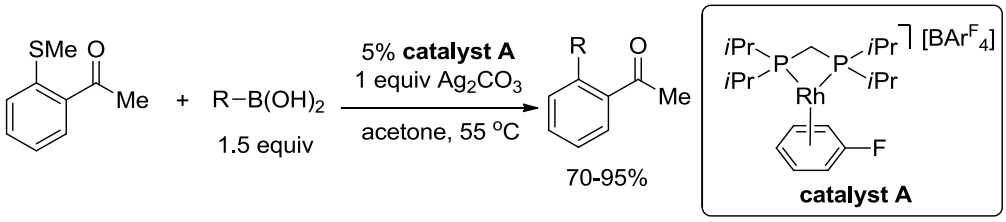
[a] Isolated yield. [b] *ee* was determined by HPLC chiral AD, OD, AS and OJ column using racemic mixtures.

3.2.2 Pd-Catalyzed MT-mimic Desulfitative Cross-Coupling of Heteroaromatic Thiol Ethers

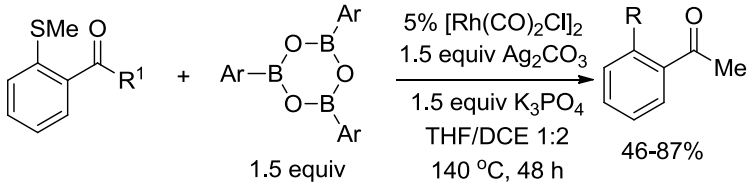
Due to their unique chemoselectivities and the mild reaction conditions, the metallothionein mimic Pd-catalyzed desulfitative couplings would be useful if they can be applied to a broader range of thioorganic reactants. The original palladium-catalyzed, copper-mediated Liebeskind-Srogl reaction has been successfully applied to the coupling of heteroaromatic thioethers with boronic acids.[27,29] However, simple aryl thiol ethers showed limited reactivity under the first generation Liebeskind-Srogl cross-coupling system, presumably due to a sluggish oxidative addition to palladium by the relatively electron-rich aryl thiol ether (in constrast to the more electron-deficient heteroaryl thiol ethers).[29] Aryl thiolethers are more stable toward the transition-metal catalyzed system because of their higher bond dissociation enthalpies as well as their better σ-donor ability relative to heteroaryl thiol ethers.[13r] In general, the transition-metal-catalyzed reaction initiated by oxidative cleavage of inert C-S bonds is challenging and is scarcely reported. Until recently, two examples of rhodium-catalyzed cross-coupling of aryl methyl sulfides with organoboron reagents to construct carbon-carbon bonds were reported. Willis and co-workers

discovered that rhodium catalyst **A** could catalyze the coupling of simple aryl methyl sulfides with a carbonyl directing group and boronic acids (**Scheme 3.19**).[30] The use of a thiophilic inorganic additive such as Ag_2CO_3 was necessary for efficient catalytic turnover in this transformation. Concurrently, Shi's laboratory reported a similar Rh(I)-catalyzed cross-coupling with aryl boroxines using a carbonyl directing strategy to cleave the strong aryl-S bond in aryl methyl sulfide (**Scheme 3.20**).[31] Similarly, thiophilic salts, such as Ag_2CO_3 was essential for this transformation.

Scheme 3.19 Rh-Catalyzed Aryl Methyl Sulfides Cross-Coupling with Boronic Acids



Scheme 3.20 Rh-Catalyzed Aryl Methyl Sulfides Cross-Coupling with Boroxins

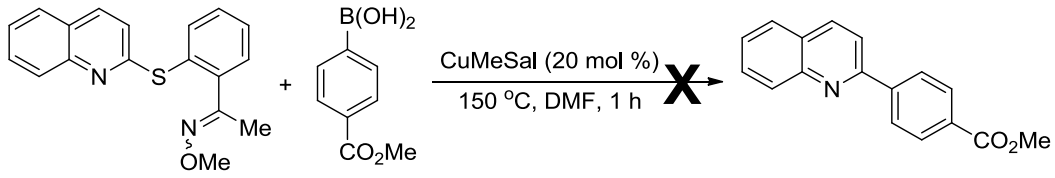


In our continued efforts to understand the transition metal catalyzed activation of C-S bonds, we are interested in applying the MT-mimic concept towards the cross-coupling of thiol ethers and boronic acids. Our initial goal is not to establish a useful synthetic application for biaryl synthesis, but rather to understand the conditions under which the MT-mimic system can activate less reactive C-S bonds toward cross-coupling with boronic acids.

An early attempt to extend the Cu-catalyzed MT-mimic S→N closure/catalyst regeneration concept to thioorganic reactants other than thiol esters was unsuccessful. The preliminary results from the former group member Dr. Zhihui Zhang showed that 2-quinoline thioether failed to react

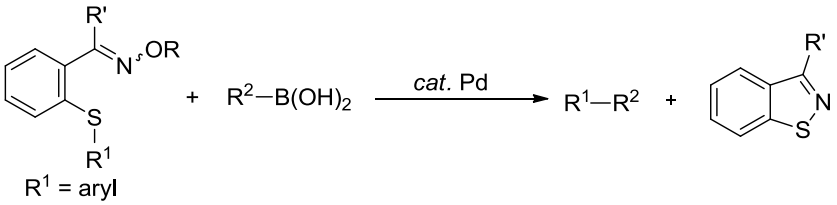
with a boronic acid to produce any cross-coupling product under standard MT-mimic conditions (**Scheme 3.21**).[32]

Scheme 3.21 Cu-catalyzed MT-mimic Cross-Coupling of Heteroaromatic Thiol Ether



The reactivity difference between thiol ethers and thiol esters in the Cu-catalyzed chemistry can be simply explained by the native electrophilicity of thiol esters when compared with thiol ethers. The thiol ester with a proper *S*-pendant can directly couple with boronic acids under Cu only conditions (through a in situ generated organocopper species), while the thiol ether is not reactive enough toward nucleophilic substitution. However, these less reactive thioorganics can be activated through oxidative addition using a low valent Pd species. Unlike copper, palladium can oxidatively insert into the C-S bond thus forming a potential electrophile R^1-Pd-SR'.[5] In the MT-mimic system, the resulting Pd-thiolate intermediate (R^1-Pd-SR') can be further activated by a S→N closure process to allow transmetallation from B to Pd (**Scheme 3.22**). Stoichiometric thiophilic salts would not be required for the transformation.

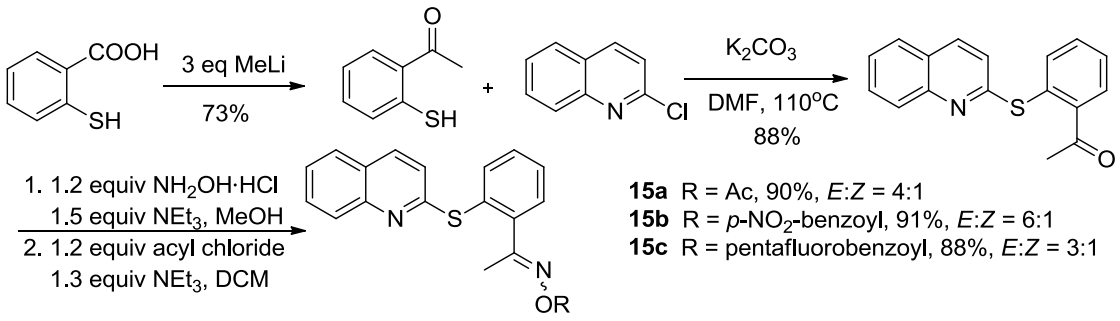
Scheme 3.22 Pd-Catalyzed MT-mimic Desulfitative Cross-Coupling of Thiol Ethers



In order to explore the feasibility of the palladium-catalyzed desulfitative MT-mimic cross-coupling of thiol ethers, we started with more reactive heteroaromatic thiol ether **15**. Quinoline thiol ethers **15a-c** containing an *O*-acyl oxime pendant were prepared from 2'-mercaptoacetophenone as depicted in **Scheme 3.23**. Thiol ethers **15a-c** bearing different leaving

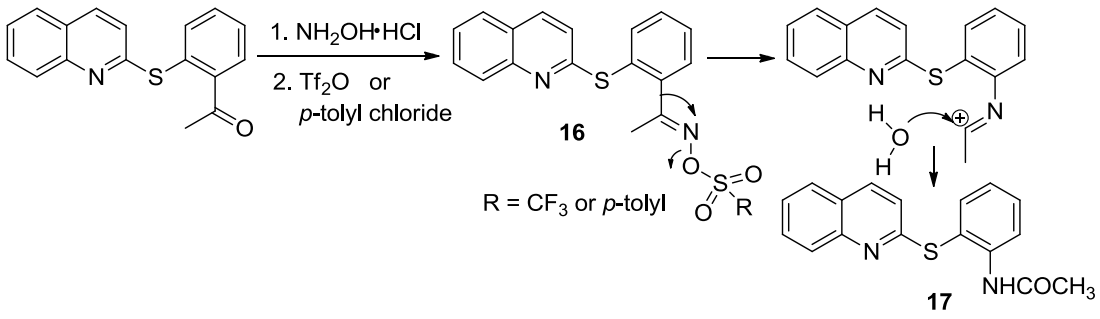
groups exist as two geometric stereoisomers of oxime, an *E* isomer and a *Z* isomer, in different ratios (**Scheme 3.23**).

Scheme 3.23 Synthesis of Heteroaromatic Thiol Ethers with MT-mimic Pendant



The attempt to synthesize compound **16** bearing a sulphonate as the leaving group failed. Under the reaction conditions, compound **16** quickly proceeded through a Beckmann rearrangement to produce the corresponding thiol ether amide **17** (**Scheme 3.24**).

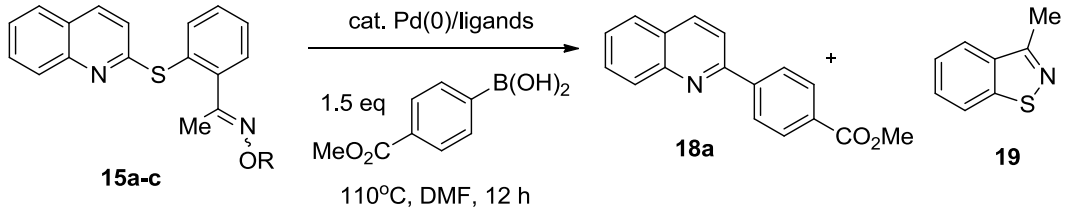
Scheme 3.24 Beckmann Rearrangement of Oxime



Thiol ether **15** was reacted with (4-(methoxycarbonyl)phenyl)boronic acid in the presence of 5% $Pd_2(dba)_3$ and tri-2-furylphosphine (TFP) as the ligand at 110 ^oC (**Table 3.4**). The desired biaryl compound **18a** was isolated in a yield of 26% together with 3-methyl-1,2-benzisothiazole **19** in 78% yield. Since the nature of the Pd complexes can greatly affect cross-coupling efficiency, the reaction between **15a** and (4-(methoxycarbonyl)phenyl)boronic acid was used as a template to study the influence of Pd complexes with different steric and electronic properties. As shown in **Table 3.4**, electron-deficient phosphine ligands were not as efficient as electron-rich ligands (entries 1-3, 5 and 6), possibly due to a less favorable oxidative addition. Although bulky

phosphine ligands can facilitate reductive elimination, they didn't improve the yield of the cross-coupling product (entries 4 and 6). Tricyclohexylphosphine with 2:1 ratio to palladium(0) proved to be the best combination of ligand and catalyst system (entries 6-8). It was assumed that a better oxygenate leaving group on the oxime (=N-OR) could facilitate the overall transformation. However, thiol ethers bearing *p*-NO_2-benzoyl and pentafluorobenzoyl group investigated did not result in better isolated yields of **18a** (entries 10-14).

Table 3.4 Optimization of Palladium Catalyst system



entry	R	temp (°C)	Pd(0) (5 mol%)	yield **18a** (%)[a]	ratio[b] **18a : 19**
1	Ac	110	$Pd_2(dba)_3$/TFP (1 : 4)	26	1 : 3
2	Ac	110	$Pd(PPh_3)_4$	78	1 : 1.2
3	Ac	110	$Pd_2(dba)_3$/P(4-Cl-Ph)$_3$ (1 :	60	1 : 0.5
4	Ac	110	Pd(P*t*-Bu_3)$_2$	28	1 : 1.2
5	Ac	110	$Pd_2(dba)_3$/P(OC_2H_5)$_3$ (1 : 4)	20	1 : 5
6	Ac	110	$Pd_2(dba)_3$/PCy_3 (1 : 4)	80	1 : 1.1
7	Ac	110	$Pd_2(dba)_3$/PCy_3 (1 : 2)	60	1 : 1
8	Ac	110	$Pd_2(dba)_3$/PCy_3 (1 : 8)	45	1 : 1.7
9[c]	Ac	80	$Pd_2(dba)_3$/PCy_3 (1 : 4)	58	1 : 1.6
10[d]	Ac	90	$Pd_2(dba)_3$/PCy_3 (1 : 4)	31	1 : 2.1
11[e]	*p*-NO_2-benzoyl	90	$Pd_2(dba)_3$/PCy_3 (1 : 4)	51	1 : 1.5
12	*p*-NO_2-benzoyl	110	$Pd_2(dba)_3$/PCy_3 (1 : 4)	73	1 : 1.1
13[f]	pentafluorobenzoyl	85	$Pd_2(dba)_3$/PCy_3 (1 : 4)	27	1 : 4
14	pentafluorobenzoyl	110	$Pd_2(dba)_3$/PCy_3 (1 : 4)	41	1 : 1.4

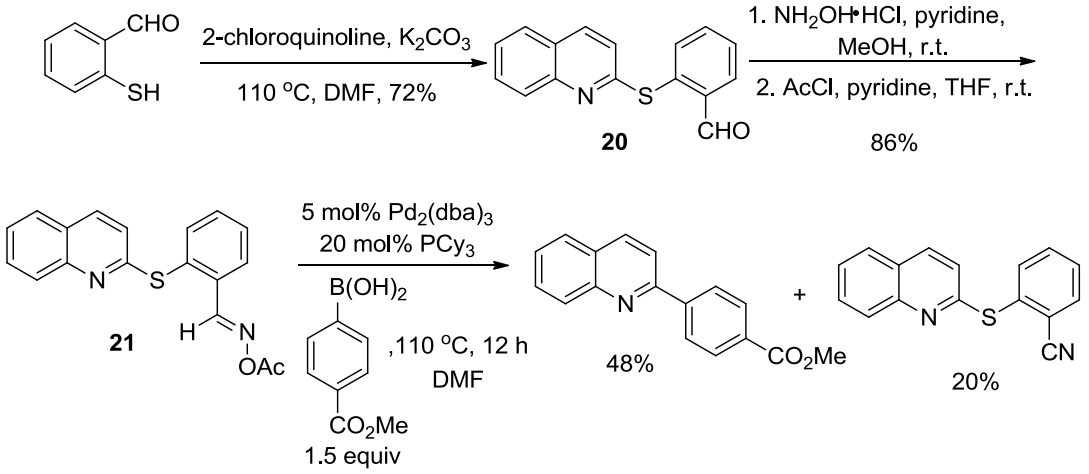
[a] Isolated yields. [b] Crude ^{1}HNMR ratio to **18a**. [c] Microwave irradiation at 80 °C for 1h. Only *Z*-oxime stereoisomer of **15a** was recovered in the yield of 18%. [d] 50% **15a** recovered. [e] 31% **15a** recovered. [f] 30% **15a** recovered

At temperature below 100 °C a low yield of biaryl compound was obtained and recovery of starting material was noted (**Table 3.4**, entry 10). Desulfitative coupling performed at 80 °C using microwave irradiation was facile for the *E*-oxime stereoisomer with the *Z*-oxime stereoisomer untouched (**Table 3.4**, entry 9). Although the *O*-acetyl oximes exist as mixtures of *E* and *Z*

stereoisomers, the stereoisomerism was not problematic at the higher reaction temperatures explored, because the oxime stereoisomers are easily interconverted under the reaction conditions[33] allowing both isomers to participate in the coupling. At 110 ^{o}C, the starting material **15a** with *E*/*Z* isomers in 4:1 ratio was totally consumed to give the cross-coupling product **18a** in 80% isolated yield (**Table 3.4**, entry 6).

The corresponding 2-mercaptobenzaldehyde oxime **21** prepared from 2-mercaptobenzaldehyde was also investigated under desulfitative cross-coupling condition (**Scheme 3.25**). Although aldoxime **21** exists exclusively in the *E*-configuration, it was an ineffective substrate for cross-coupling reactions carried out at higher reaction temperatures because of its tendency to eliminate AcOH under metal catalyzed conditions generating the corresponding nitriles.

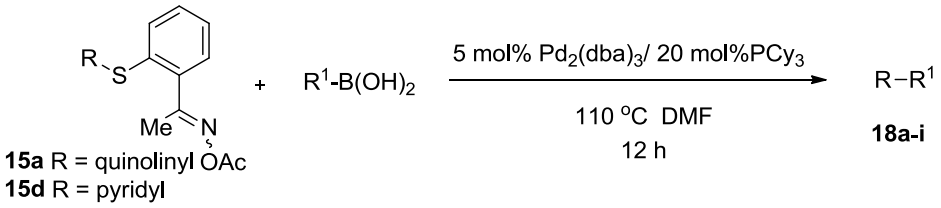
Scheme 3.25 Pd-Catalyzed MT-mimic Cross-Coupling Reaction of Aldoxime Thiol Ethers



Upon completing the optimization of this new desulfitative coupling, the scope of the reaction was explored. Both 2-quinolinyl and 2-pyridyl thiol ethers containing an *O*-acetyl oxime pendant were treated with 5 mol% $Pd_2(dba)_3$/20 mol% PCy_3 in the presence of 1.5 equiv of boronic acids or organostannes (**Table 3.5**). Electron-deficient (entries 1-5) and electron-rich (entry 6) aryl boronic acids gave the desired biaryls in moderate to good yields. Alkenyl boronic acids (entry 7) could also participate in the cross-coupling reaction. Tributyl(phenyl)stannane also effectively coupled with **15a** (entry 8). These results showed that a modest range of organoborons and

organostannanes can be potential reaction partners in this Pd only desulfitative cross-coupling reaction.

Table 3.5 Pd-catalyzed MT-mimic Cross-Coupling of Heteroaromatic Thioethers with Boronic Acids



15a R = quinolinyl OAc
15d R = pyridyl

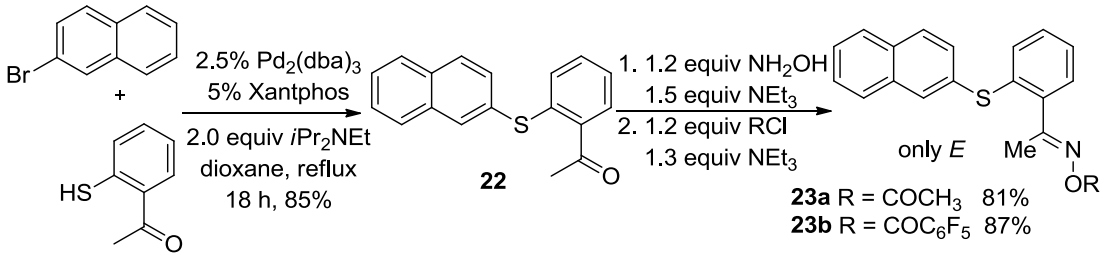
entry	R	R^1	$R\text{-}R^1$	yield (%)[a]
1	2-quinolinyl	4-(methoxycarbonyl)phenyl	**18a**	80
2	2-quinolinyl	4-formylphenyl	**18b**	58
3	2-quinolinyl	4-acetylphenyl	**18c**	63
4	2-quinolinyl	3-cyanophenyl	**18d**	60
5	2-quinolinyl	3-nitrophenyl	**18e**	42
6	2-quinolinyl	3-methoxyphenyl	**18f**	73
7	2-quinolinyl	*trans*-2-(4-trifluoromethyl)vinyl	**18g**	48
8[b]	2-quinolinyl	phenyl	**18h**	64
9	2-pyridyl	4-(methoxycarbonyl)phenyl	**18i**	68

[a] Isolated yield. [b] phenyl tributyltin was used instead of boronic acid.

3.2.3 Pd-Catalyzed MT-mimic Desulfitative Cross-Coupling of Simple Aromatic Thiol Ethers

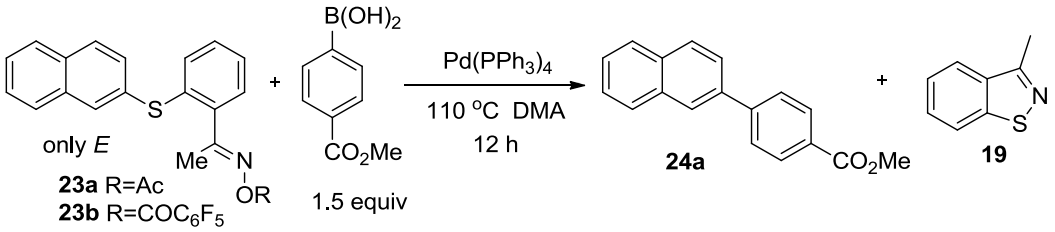
The generation of 3-methyl-1,2-benzisothiazole proves that the MT-mimic oxime pendant works as an internal thiolate trap for palladium and the formation of heteroaromatic biaryls shows that the palladium-catalyzed MT-mimic desulfitative concept can be applied to heteroaromatic thiol ethers and boronic acids cross-coupling. We took a step further to explore the reactivity of more challenging aromatic thiol ether substrates. 1-(2-(Naphthalen-2-ylthio)phenyl)ethanone *O*-acetyl oxime **23** was prepared from 2-bromonaphthalene and 1-(2-mercaptophenyl)ethanone following the procedure shown in **Scheme 3.26**. The *E* isomers of simple thiol ethers **23** with *O*-acyl oxime pendant were obtained by column chromatography.

Scheme 3.26 Preparation of Simple Aromatic Thioether with MT-Mimic Pendant



When **23a** was subjected to standard cross-coupling reaction conditions with 5% $Pd(PPh_3)_4$, only 10% of the desired product **24a** was observed with the recovery of starting material (**Table 3.6**, entry 1). Upon the addition of 10% copper(I) 2,6-dihydroxybenzoate (CuDHB) the yield of **24a** improved to 44% (entry 2). Increasing the palladium catalyst loading to 8% helped to promote the reaction further (entry 3). Thiol ether **23b** with pentafluoroacetate leaving group also participated in the coupling reaction (entries 4 and 5). From the comparison, a catalytic amount of copper carboxylate can help to achieve a better reaction outcome (entries 1 and 2, 3 and 4).

Table 3.6 Preliminary Studies of Simple Thioether Desulfitative MT-mimic Cross-Coupling



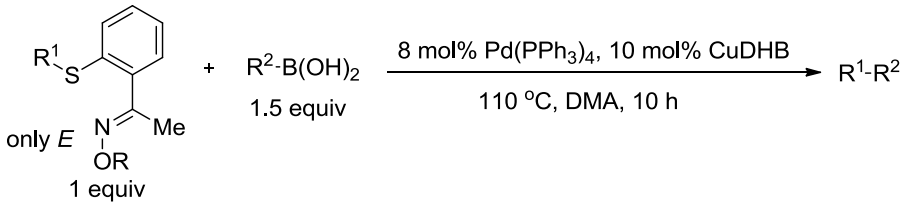
entry	Pd (mol%)	R	additive	**24a** (%)[a]	**19** (%)[a]
1	5	$COCH_3$	None	~ 10	8
2	5	$COCH_3$	10% CuDHB	44	20
3	8	$COCH_3$	10% CuDHB	85	57
4	8	COC_6F_5	10% CuDHB	89	60
5	8	COC_6F_5	none	50	30

[a] Isolated yields.

The generality of this method was explored for different thiol ethers with an *O*-acyl pendant (**Table 3.7**). Naphthalene and phenanthrene thiol ethers reacted with different electron-rich,

electron-poor, and vinyl boronic acids to generate biaryls and aryl-alkenes in good yields (entries 1-5). Also, unprotected alcohols were tolerated under the reaction conditions (entry 5). Phenyl thiol ethers bearing an meta/para electron withdrawing group also reacted smoothly (entries 7-10). However, a relatively electron-rich phenyl thiol ether reacted poorly to produce less than 15% of the desired biaryl compound (entry 11).

Table 3.7 Pd-Catalyzed MT-mimic Defulfitative Cross-Coupling of Simple Thioethers



entry	R^1	R^2	R	yield (%)[a]
1	2-naphthyl	2-nitro-(4-methoxycarbonyl)phenyl	COC_6F_5	85
2	2-naphthyl	3,4-methylenedioxyphenyl	COC_6F_5	61
3	2-naphthyl	4-(methoxycarbonyl)phenyl	COC_6F_5	89
4	2-naphthyl	*trans*-2-(4-fluorophenyl)vinyl	COC_6F_5	80
5	9-phenanthrenyl	3-hydroxylphenyl	COC_6F_5	68
6	4-nitrophenyl	4-dibenzo[b,d]furyl	COC_6F_5	60
7	4-nitrophenyl	4-(methoxycarbonyl)phenyl	COC_6F_5	78
8	4-nitrophenyl	4-(methylsulfide)phenyl	COC_6F_5	74
9	4-nitrophenyl	4-(methoxycarbonyl)phenyl	$COCH_3$	71
10	3-nitrophenyl	4-(methoxycarbonyl)phenyl	$COCH_3$	50
11[b]	4-methylphenyl	4-(methoxycarbonyl)phenyl	$COCH_3$	15

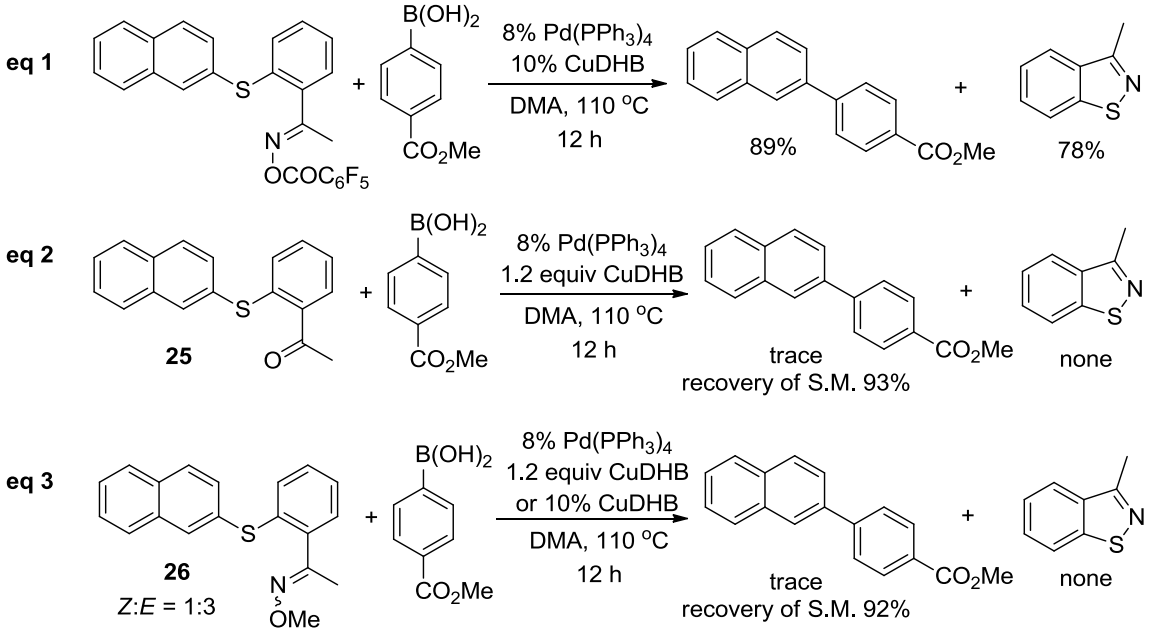
[a] Isolated yields. [b] Determined by crude NMR.

3.2.4 Control Experiments and Mechanistic Hypothesis for Thiol Ether Cross-Coupling

The control experiments in **Scheme 3.27** suggest the importance of the MT-mimic pendant in activating less reactive C-S bonds of aryl thiol ethers for cross coupling chemistry. Naphthalene thiol ether **25** failed to react with boronic acid under the first generation Liebeskind Srogl reaction conditions most likely because of an unfavorable oxidative addition of palladium to the aryl C-S bond (**Scheme 3.27**, **eq 2**).[29] With OMe installed as the oxime "leaving group", thiol ether **25** was

reluctant to react with boronic acid, indicating the importance of a good leaving group of the oxime pendant (**Scheme 3.27**, **eq 3**). These control experiments demonstrate that the incorporated 2-mercaptoacetophenone *O*-acyl oxime pendant is crucial for the catalysis not only as an internal thiolate trap for palladium but also an activator toward oxidative addition for the less reactive aryl-S bond.

Scheme 3.27 Control Experiments

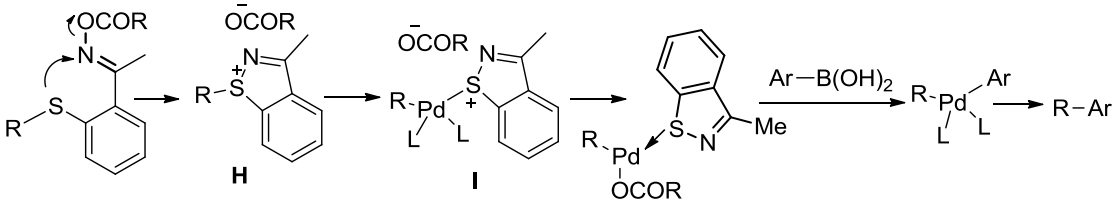


Different mechanistic pathways can be proposed for this palladium-catalyzed MT-mimic desulfitative cross-coupling of thiol ethers.

2-(Alkylthio)phenyl ketoxime derivatives are known to be converted to 1,2-benzisothiazole through a thermal S-N closure mechanism.[34] It is possible that at the reaction temperature used in the chemistry above, azasulfonium salt **H** could be formed as the first step of the reaction (**Scheme 3.28**). In this way, the C-S bond is activated toward palladium oxidative addition to generate intermediate **I**. Then, transmetallation from boron to palladium and reductive elimination would produce the observed biaryl compounds. This process is similar to the alkylative activation of the palladium thiolate intermediate reported previously from the Liebeskind lab (**Scheme 3.3**).[14] Although this looks like a plausible pathway, the experimental

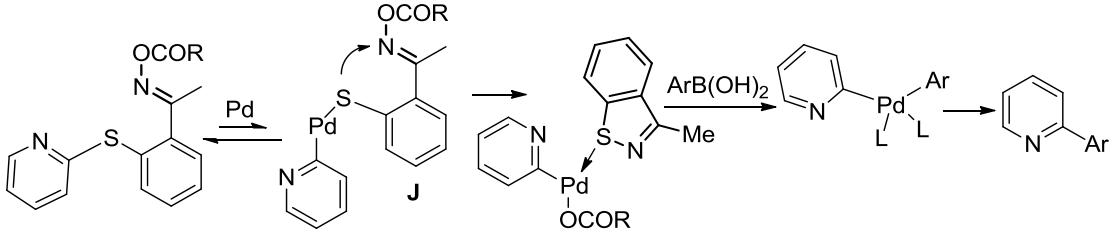
evidence suggests otherwise. Comparing the results of entry 9 and 11 from **Table 3.7**, the electron-poor thiol ether bearing a 4-nitrophenyl substituent produced a better yield of product than the electron-rich thiol ether bearing a 4-methylphenyl substituent, even though the electron-rich thioether is a better substrate for the sulfonium salt formation. Therefore, it is unlikely that the MT mimic thiol ether forms an azasulfonium salt as the first step.

Scheme 3.28 Sulfonium Salt Formation as the First Step



Since Pd can oxidatively add into C-S bonds of thiol ethers,[5] the first step of the reaction might be the oxidative addition of palladium to the C-S bond. For heteroaromatic thiol ethers, palladium can selectively insert to the more reactive C-S bond to form palladium thiolates **J**.[28,30] Followed by S→N closure on the palladium thiolate to scavenge the thiolate, transmetallation and reductive elimination would generate the desired heteroaromatic biaryls (**Scheme 3.29**).

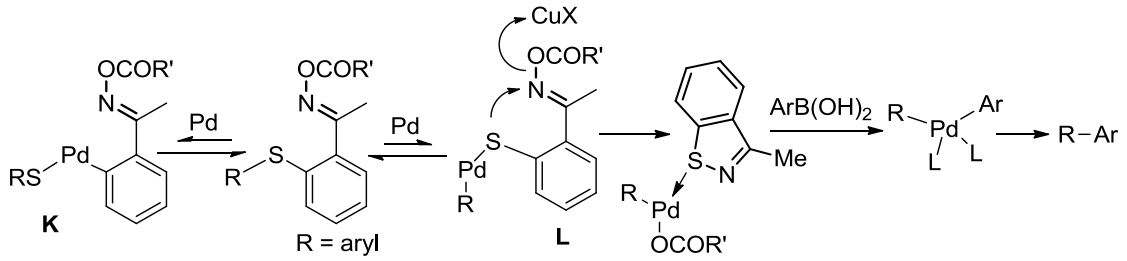
Scheme 3.29 Pd-catalyzed MT-mimic Heteroaromatic Thiol Ether Cross-Coupling



For a simple aryl thiol ether, the oxidative addition of palladium to the aryl C-S bond can produce palladium thiolates **K** or **L** (**Scheme 3.30**). Without a stoichiometric thiophilic reagent to weaken the strong Pd-S bond, intermediate **K** is probably unable to react with boronic acids to complete the catalytic cycle, but would revert back to the starting materials. In contrast, the S–N closure of intermediate **L** could drive an unfavorable reversible oxidative addition by generation of 3-methyl-1,2-benzisothiazole. Transmetallation and reductive elimination would complete the

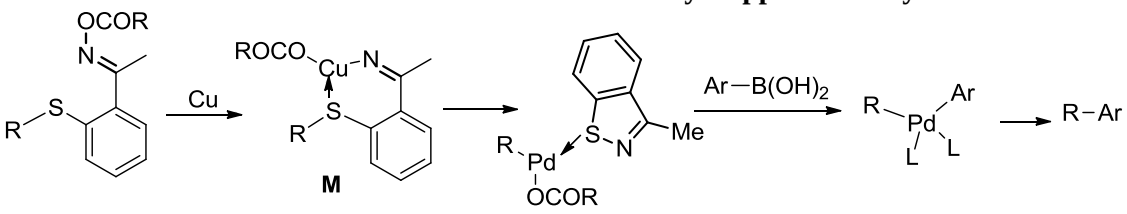
catalytic process (**Scheme 3.30**). In this scenario, the copper carboxylate could act as a Lewis acid to weaken the N-O bond (=N-OCOR'). In this way, the copper carboxylate can assist the cross-coupling reaction by promoting the S–N closure of intermediate **L** to scavenge the thiolate.

Scheme 3.30 Oxidative Addition of Palladium to C-S bond as the First Step



A third mechanistic option that cannot be ruled out is depicted in **Scheme 3.31**. Copper slats are known to insert into =N-OR bonds when the OR is a good leaving group.[26] As a first step, copper could oxidatively insert into the N-O bond generating intermediate **M**. Then, with the coordination of the thiol ether S to copper, the C-S bond of less reactive simple thiol ethers **15** would become activated toward oxidative addition to the palladium catalyst, as described in the first generation Liebeskind-Srogl reaction mechanism. Followed by an S-N closure, transmetallation and reductive elimination, the catalytic cycle could be accomplished. This mechanism demonstrates the activation of the relatively "inert" C-S bond via Cu→S coordination.

Scheme 3.31 Activation of =N-OR Bond by Copper Carboxylate



At this point, we cannot pin down a precise mechanism for the palladium catalyzed MT-mimic desulfitative cross-coupling reaction. However, by the installment of the MT-mimic pendant with a good leaving group, the C-S bonds of aryl thiol ethers can be activated toward cross-coupling with boronic acids in the presence of co-catalytic palladium and copper. This palladium-catalyzed

MT-mimic desufitative cross-coupling is different from the reported Rh-catalyzed aryl thiol ether cross-croupling which requires an ortho carbonyl coordination group. Additionally, by incorporating an *O*-acyl oxime pendant, the palladium catalysis does not require an external thiolate scavenger.

3.3 Conclusion

In summary, a palladium catalyzed metallothionein-mimic system has been developed for the construction of new C-C bonds through a desulfitative reaction. An *O*-acetyl oxime pendant functions as a scavenger of the thiolate and it simultaneously provids a stoichiometric oxygenate for pairing with the boronic acid residues in an efficient Pd-catalyzed cross-coupling of thiol esters with organoboron and organotin reagents. A mild, efficient and general method for the synthesis of high enantiopurity *N*-protected α-amino ketones was developed from the corresponding thiol esters with an MT-mimic pendant and aryl, heteroaryl, or alkenyl boronic acids in moderate to excellent yields. The cross-coupling utilized only co-catalytic palladium and copper carboxylate. Under these mild and neutral reaction conditions, no racemization was detected throughout the cross-coupling process and the configuration of the stereogenic centers was completely conserved. This protocol has also been studied for the cross-coupling of heteroaromatic and simple aryl thiol ethers. Fused aromatic and electron-deficient thiol ethers bearing an MT-mimic pendant are efficient coupling partners for boronic acids under the palladium catalyzed cross-coupling conditions. Copper carboxylate (CuDHB) was used as a co-catalyst in the cross-coupling reaction and is assumed to facilitate breaking of the N-O bond of oxime and to assist in the oxidative addition of palladium to the C-S bond.

3.4 Experimental

3.4.1 General Experimental

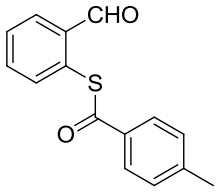
^{1}H and ^{13}C NMR spectra were recorded on Inova 400 MHz spectrometers in deuteriochloroform ($CDCl_3$) with the solvent residual peak as internal reference unless otherwise stated ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported (Hz); integration is provided. Infrared spectra were recorded on a Nicolet 380 FT-IR spectrometer with a diamond plate. Peaks are reported (cm^{-1}) with the following relative intensities: vs (very strong), s (strong), m (medium), w (weak), and br (broad). Optical rotation values were measured at 20 ˚C on a Perkin Elmer Model 341 polarimeter with chloroform ($CHCl_3$) as solvent. Uncalibrated melting points were taken on a *Thomas-Hoover* melting point apparatus in open capillary tubes. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator. Visualization was accomplished by UV light, or with solutions of ninhydrin in ethanol or *p*-anisaldehyde in ethanol. Purification by chromatography was performed using Whatman 60Å 230-400 mesh SiO_2 with compressed air as a source of positive pressure. HPLC analyses were carried out using an Agilent 1100 system with a quaternary pump. Separations were achieved on DAICEL Chiralpak AS-RH or Chiralcel OD-RH, OJ-RH column. Solvents for reactions and chromatography were reagent grade and used as received. "Brine" refers to a saturated aqueous solution of NaCl. Solutions of NH_4Cl, $NaHCO_3$ refer to saturated aqueous solutions. Solvents used as reaction media were purchased in > 99% purity without further purification, unless otherwise specified.

3.4.2 Starting Materials

2-Mercaptobenzoic acid, 2-chloroquinoline, hydroxylamine hydrochloride, acyl chloride, bis(dibenzylideneacetone)palladium(0) ($Pd_2(dba)_3$), tetrakis(triphenylphosphine)palladium(0)

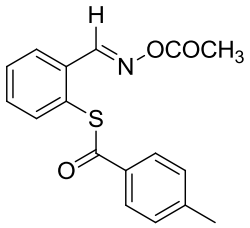
($Pd(PPh_3)_4$), bis(tricyclohexylphosphine)palladium(0) ($Pd(PCy_3)_2$), 4-bromoisoquinoline, phosphine ligands, 9-bromophenanthrene, pyridinium chlorochromate, 1-iodo-4-nitrobenzene, *p*-nitro-benzoyl chloride, pentafluorobenzoyl chloride, 2-chloropyridine, 2-bromonaphthalene, *O*-methylhydroxylamine hydrochloride, 4-methylbenzoyl chloride, methyl lithium, *N*,*N'*-dicyclohexylcarbodiimide (DCC), triethylamine, 1-hydroxybenzotriazole (HOBt), methyl iodide, pyridine and all the amino acids were purchased from Sigma Aldrich. All the boronic acids were provided by Dr. Gary Allred of Synthonix.

_S_-(2-Formylphenyl) 4-methylbenzothioate



2-Mercaptobenzaldehyde (138 mg, 1.0 mmol) and *p*-toluoyl chloride (170 mg, 0.15 mL, 1.1 mmol) were dissolved in 20 mL dichloromethane. NEt_3 (121 mg, 0.87 mL, 1.2 mmol) was added slowly via syringe at 0 ^oC. The solution was warmed to room temperature and stirred for 3 hours. The reaction mixture was washed with 10 mL saturated $NaHCO_3$ solution, 10 mL saturated NH_4Cl solution and 10 mL brine solution sequentially. After drying over $MgSO_4$, the solvent was evaporated and purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a white solid 256 mg (90% yield). Mp 78-80 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 10.30 (s), 8.10 (dd, *J* = 2 Hz, 7.2 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.69-7.59 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.2, 188.6, 145.6, 137.7, 137.2, 134.4, 133.5, 131.2, 130.6, 129.8, 129.2, 128.1, 22.0; IR (neat, cm^{-1}): 3029 (w), 1692 (vs), 1666 (vs), 1603 (s), 1403 (m), 1202 (vs), 1174 (vs), 895 (vs); HRMS (EI) Calcd for $C_{15}H_{13}O_2S$ ($M+H^+$): 257.0636, found 257.0636.

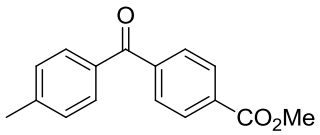
(_E_)-S-(2-((Acetylimino)methyl)phenyl) 4-methylbenzothioate



S-(2-Formylphenyl) 4-methylbenzothioate (192 mg, 0.75 mmol) and hydroxylamine hydrochloride (63 mg, 0.9 mmol) were dissloved in 10 mL DMF. Pyridine (0.09 mL, 1.13 mmol) was added to the solution and stirred at room temperature overnight. Saturated NH_4Cl (10 mL) was added to the solution and extraced with 10 mL ether twice. The combained organic layer was washed twice with 10 mL saturated brine and dried over $MgSO_4$. The solvent was evaporated to give a yellow oil.

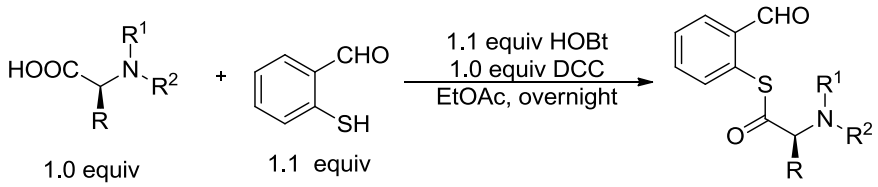
The yellow oil from the first step and acetyl chloride (0.064 mL, 0.9 mmol) were dissolved in 8 mL dichloromethane. Triethylamine (0.21 mL, 1.5 mmol) was added to the solution dropwide at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was washed with 10 mL saturated $NaHCO_3$ solution, 10 mL saturated NH_4Cl solution and 10 mL brine solution sequentially. After drying over $MgSO_4$, the solvent was evaporated and purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a white solid 181 mg (87% yield). Mp 99-100 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.25-8.20 (m, 1H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.57-7.52 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.3, 168.9, 154.3, 145.5, 137.3, 134.1, 133.6, 132.2, 130.7, 129.8, 128.9, 128.3, 128.1, 22.0, 19.8; IR (neat, cm^{-1}): 2933 (w), 1778 (s), 1667 (s), 1604 (m), 1173 (vs), 1038 (m), 895 (vs), 766 (m); HRMS (EI) Calcd for $C_{17}H_{16}O_3NS$ ($M+H^+$): 314.0851, found 314.0845.

Methyl 4-(4-methylbenzoyl)benzoate[17]



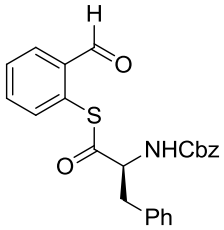
(*E*)-S-(2-((Acetylimino)methyl)phenyl) 4-methylbenzothioate (50 mg, 0.17 mmol), $Pd(PCy_3)_2$ (5.7 mg, 0.0085 mmol) and (4-(methoxycarbonyl)phenyl)boronic acid (47 mg, 0.26 mmol) were placed in a microwave tube and sealed. The tube was vaccumed and filled with argon three times. After 2.4 mL degassed THF was added via syring under argon, the reaction mixture was stirred at 50 ^{o}C for 20 hours. The solvent was evaporated and purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a white solid 38 mg (88% yield). Mp 120-122 ^{o}C [Lit.[18] 119-120 ^{o}C]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 3.96 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 166.6, 144.1, 141.9, 134.4, 133.2, 130.6, 129.9, 129.7, 129.4, 52.7, 21.9; IR (neat, cm^{-1}): 2958 (w), 1718 (vs), 1644 (s), 1432 (s), 1278 (vs), 1184 (m), 1105 (vs).

***N*-protected amino thioester were generated from 2-mercaptobenzaldehyde and amnio acids by the following general procedure.**



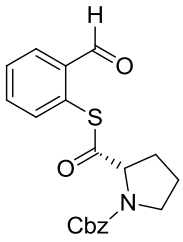
2-Mercaptobenzaldehyde (152 mg, 1.1 mmol), amino acid (1.0 mmol) and HOBt (149 mg, 1.1 mmol) were stirred in 10 mL ethyl acetate at 0 ^{o}C followed by the addition of 1,3-dicyclohexylcarbodiimide (DCC) (206 mg, 1.0 mmol) slowly in small portions. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was filtered and washed with 10 mL saturated $NaHCO_3$ solution followed by concentration *in vacuo*. The residue was purified by chromatography to afford the desired compound.

(*S*)-*S*-(2-Formylphenyl) 2-(((benzyloxy)carbonyl)amino)-3-phenylpropanethioate



Prepared according to the general procedure from Cbz-L-Phe-OH (186 mg, 0.62 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 204 mg (78% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.63-7.58 (m, 2H), 7.42-7.30 (m, 9H), 7.17-7.15 (m, 2H), 5.23 (d, *J* = 9.2 Hz, 1H), 5.15 (AB, *J* = 12.0 Hz, 2H), 4.85 (q, *J* = 8.4 Hz, 1H), 3.21-3.12 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4, 190.9, 155.9, 137.3, 136.8, 136.1, 135.1, 134.5, 130.8, 129.6, 129.4, 129.2, 128.8, 128.6, 128.5, 127.8, 67.8, 61.9, 38.3; IR (neat, cm^{-1}): 3303 (m), 3030 (w), 1691 (vs), 1585 (m), 1496 (s), 1240 (s), 1050 (s), 742 (s); HRMS (EI) Calcd for $C_{24}H_{21}O_4NNaS$ ($M+Na^+$): 442.1089, found 442.1084; $[\alpha]^{20}_D$ -23.8 (*c* 2.01, $CHCl_3$).

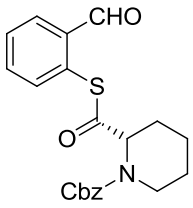
(*S*)-Benzyl 2-(((2-formylphenyl)thio)carbonyl)pyrrolidine-1-carboxylate



Prepared according to the general procedure from Cbz-L-Pro-OH (216 mg, 0.87 mmol), purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 320 mg (84% yield, with a 4:5 ratio of rotamer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 0.44H), 9.99 (s, 0.56H), 8.05-8.00 (m, 1H), 7.61-7.23 (m, 8H), 5.30-5.12 (m, 2H), 4.66 (dd, *J* = 2.8 Hz, 8.4 Hz, 0.44H), 4.59 (dd, *J* = 2.8 Hz, 8.4 Hz, 0.56H), 3.76-3.53 (m, 2H), 2.34-2.23 (m, 1H), 2.18-1.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 199.1, 191.1, 190.6, 155.5, 154.7, 137.3, 137.2, 136.9, 136.8, 136.6, 136.3, 134.4, 131.0, 130.8, 130.6, 130.5, 129.5, 129.4, 128.8, 128.7, 128.5, 128.4, 128.2, 67.8, 67.7, 66.8, 66.4, 47.6, 47.2, 31.9, 30.8, 24.6, 23.7; IR (neat, cm^{-}

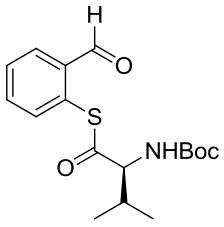
[1]):2953 (w), 2878 (w), 1692 (vs), 1585 (m), 1403 (s), 1114 (s), 759 (s); HRMS (EI) Calcd for $C_{20}H_{20}O_4NS$ ($M+H^+$): 370.1113, found 370.1107; $[\alpha]^{20}_D$ -91.4 (*c* 0.97, $CHCl_3$).

(*S*)-Benzyl 2-(((2-formylphenyl)thio)carbonyl)piperidine-1-carboxylate



Prepared according to the general procedure from (*S*)-1-((benzyloxy)carbonyl)piperidine-2-carboxylic acid (258 mg, 0.98 mmol), purified by chromatography (silica gel 3:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 296 mg (79% yield, with a 6:5 ratio of rotamer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 0.55H), 9.56 (s, 0.45H), 7.51 (app d, *J* = 6.8 Hz, 1H), 7.09-7.03 (m, 2H), 6.95 (app d, *J* = 7.2 Hz, 1H), 6.86-6.73 (m, 5H), 4.79-4.52 (m, 3H), 3.77 (d, *J* = 12.4 Hz, 0.45H), 3.67 (d, *J* = 13.6 Hz, 0.55H), 2.66-2.53 (m, 1H), 1.86-1.78 (m, 1H), 1.20-1.12 (m, 3H), 0.94 (br t, *J* = 13.6 Hz, 1H), 0.83 (br t, *J* = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 197.6, 190.4, 190.2, 155.9, 155.1, 136.8, 136.5, 136.02, 135.9, 135.8, 134.0, 133.9, 130.5, 130.4, 130.3, 130.2, 129.1, 128.3, 127.9, 127.7, 67.6, 61.8, 61.5, 42.3, 41.9, 26.3, 26.0, 24.3, 24.1, 20.1; IR (neat, cm^{-1}): 2941(w), 1692 (vs), 1585 (m), 1410 (s), 1252 (m), 1168 (m), 760 (s); HRMS (EI) Calcd for $C_{21}H_{22}ON_4S$ ($M+H^+$): 384.1270, found 384.1264; $[\alpha]^{20}_D$ -84.6 (*c* 2.43, $CHCl_3$).

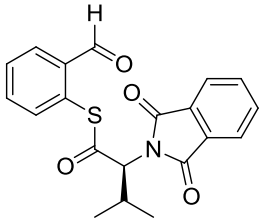
(*S*)-*S*-(2-Formylphenyl) 2-((*tert*-butoxycarbonyl)amino)-3-methylbutanethioate



Prepared according to the general procedure from Boc-L-Val-OH (217 mg, 1.0 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a white

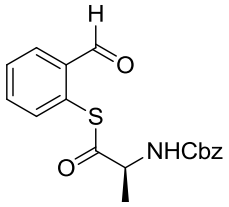
solid 352 mg (87% yield). Mp 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.05 (dd, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.65-7.56 (m, 2H), 7.47 (d, *J* = 7.2 Hz, 1H), 5.06 (d, *J* = 9.2 Hz, 1H), 4.41 (dd, *J* = 4.8 Hz, 9.2 Hz, 1H), 2.37-2.29 (m, 1H), 1.50 (s, 9H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 190.7, 155.5, 137.2, 136.6, 134.2, 130.9, 130.4, 129.1, 80.7, 65.7, 30.8, 28.3, 19.4, 17.2; IR (neat, cm^{-1}): 3335 (m), 2973 (w), 1694 (vs), 1502 (vs), 1316 (m), 1255 (s), 1156 (s), 1016 (m); HRMS (EI) Calcd for $C_{17}H_{27}O_4N_2S$ ($M+NH_4^+$): 355.1692, found 355.1686; $[\alpha]^{20}_D$ -59.1 (*c* 2.01, $CHCl_3$).

(*S*)-*S*-(2-Formylphenyl) 2-(1,3-dioxoisoindolin-2-yl)-3-methylbutanethioate



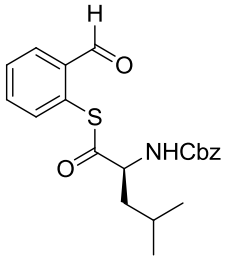
Prepared according to the general procedure from (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-methylbutanoic acid (158 mg, 0.64 mmol), purified by chromatography (silica gel, 2:1 hexanes: EtOAc) to afford the desired compound as a white solid 234 mg (87% yield). Mp 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.02 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.95-7.93 (m, 2H), 7.82-7.78 (m, 2H), 7.60-7.53 (m, 2H), 7.42 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 4.75 (d, *J* = 9.2 Hz, 1H), 2.88-2.79 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 190.8, 167.5, 137.2, 136.6, 134.7, 134.2, 131.5, 130.5, 130.1, 129.1, 123.9, 64.7, 28.3, 20.9, 19.4; IR (neat, cm^{-1}): 2885 (w), 1781 (m), 1766 (m), 1711 (vs), 1693 (vs), 1585 (m), 1466 (m), 1378 (s), 1337 (m), 1198 (m), 1014 (m); HRMS (EI) Calcd for $C_{20}H_{21}O_4N_2S$ ($M+NH_4^+$): 385.1222, found 385.1217; $[\alpha]^{20}_D$ -6.5 (*c* 1.18, $CHCl_3$).

(*S*)-*S*-(2-Formylphenyl) 2-(((benzyloxy)carbonyl)amino)propanethioate



Prepared according to the general procedure from Cbz-L-Ala-OH (223 mg, 1.0 mmol), purified by chromatography (silica gel 4:1 hexanes: EtOAc) to afford the desired compound as a white solid 213 mg (87% yield). Mp 114-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.03 (dd, *J* = 1.6 Hz, 6.8 Hz, 1H), 7.63-7.55 (m, 2H), 7.46 (d, 7.2 Hz, 1H), 7.37-7.30 (m, 5H), 5.27 (d, *J* = 7.2 Hz, 1H), 5.16 (s, 2H), 4.59 (quintet, *J* = 7.2 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 190.6, 155.5, 137.1, 136.7, 135.9, 134.2, 130.5, 130.3, 129.4, 128.6, 128.4, 128.2, 67.4, 56.9, 18.5; IR (neat, cm^{-1}): 3318 (m), 1708 (s), 1690 (vs), 1582 (w), 1518 (s), 1450 (m), 1270 (s), 1249 (vs), 1190 (m), 1048 (s); HRMS (EI) Calcd for $C_{18}H_{18}O_4NS$ ($M+H^+$): 344.0957, found 344.0951; $[\alpha]^{20}_D$ -29.8 (*c* 1.96, $CHCl_3$).

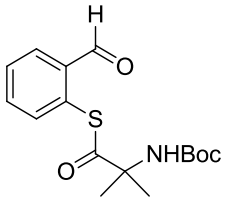
(*S*)-*S*-(2-Formylphenyl) 2-(((benzyloxy)carbonyl)amino)-4-methylpentanethioate



Prepared according to the general procedure by Cbz-L-Leu-OH (109 mg, 0.41 mmol), purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 136 mg (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.61-7.53 (m, 2H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.38-7.29 (m, 5H), 5.29-5.13 (m, 3H), 4.56 (dt, *J* = 3.6 Hz, 9.0 Hz, 1H), 1.76-1.68 (m, 2H), 1.62-1.53 (m, 1H), 0.95 (d, *J* = 3.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 190.7, 155.9, 137.1, 136.7, 135.9, 134.2, 130.6, 130.4, 129.2, 128.6, 128.4, 128.2, 67.5, 59.9, 41.3, 24.8, 23.0, 21.5; IR (neat, cm^{-1}): 3320 (w), 2957 (w), 1691 (vs),

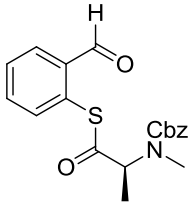
1586 (w), 1517 (s), 1454 (m), 1243 (s), 1198 (m), 1052 (m); HRMS (EI) Calcd for $C_{21}H_{27}O_4N_2S$ ($M+NH_4^+$): 403.1692, found 403.1693; $[\alpha]^{20}_D$ -37.1 (*c* 2.96, $CHCl_3$).

_S_-(2-Formylphenyl) 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanethioate



Prepared according to the general procedure from Boc-Aib-OH (205 mg, 1.01 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 253 mg (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.03 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.60-7.52 (m, 2H), 7.45 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H), 5.07 (s, 1H), 1.53 (s, 6H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 191.5, 154.2, 137.7, 136.8, 134.0, 131.9, 130.1, 128.8, 80.6, 62.5, 28.4, 25.4; IR (neat, cm^{-1}): 3365 (w), 2979 (w), 1689 (vs), 1585 (m), 1501 (m), 1365 (m), 1251 (s), 1155 (vs), 1079 (m), 970 (m); HRMS (EI) Calcd for $C_{16}H_{22}O_4NS$ ($M+H^+$): 324.1270, found 324.1264.

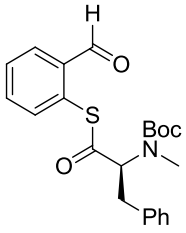
(_S_)-_S_-(2-Formylphenyl) 2-(((benzyloxy)carbonyl)(methyl)amino)propanethioate



Prepared according to the general procedure from Cbz-*N*-Me-L-Ala-OH (130 mg, 0.55 mmol), purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 177 mg (90% yield, with a 3:2 ratio of rotamer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.2 (s, 0.6H), 10.1 (s, 0.4H), 8.02 (d, J = 6.8 Hz, 1H), 7.61-7.54 (m, 2H), 7.46-7.30 (m, 6H), 5.29-5.15 (m, 2H), 5.08 (q, *J* = 6.8 Hz, 0.6H), 4.86 (quartet, *J* = 7.2 Hz, 0.4H), 3.02, 2.98 (s, 3H), 1.45, 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 197.7, 190.7, 190.4, 156.9, 155.7, 137.1, 136.7, 136.3, 134.2, 130.4, 130.3, 129.3, 128.6, 128.2, 127.9, 67.9, 61.8, 61.7, 31.6, 31.5, 14.9, 14.2; IR

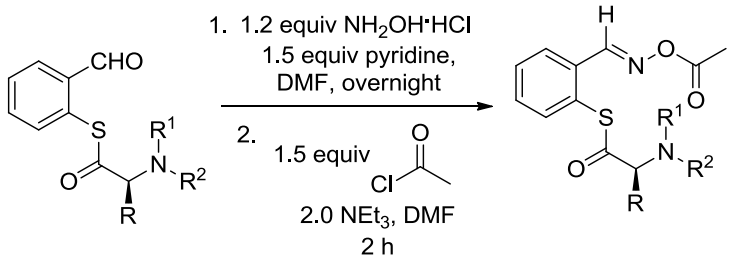
(neat, cm^{-1}): 2941 (w), 1692 (vs), 1585 (w), 1453 (m), 1395 (m), 1304 (s), 1154 (s), 1007 (m), 753 (s); HRMS (EI) Calcd for $C_{19}H_{23}O_4N_2S$ ($M+NH_4^+$): 375.1379, found 375.1373; $[\alpha]^{20}_D$ -44.3 (*c* 0.68, $CHCl_3$).

(*S*)-*S*-(2-Formylphenyl) 2-((tert-butoxycarbonyl)(methyl)amino)-3-phenylpropanethioate



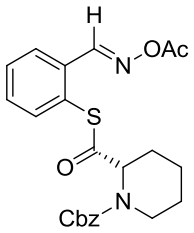
Prepared according to the general procedure Boc-*N*-Me-L-Phe-OH (232 mg, 0.83 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 265 mg (80% yield, with a 1:1 ratio of rotamer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.06 (dt, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.65-7.56 (m, 2H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.33-7.16 (m, 5H), 4.97 (dd, *J* = 5.2 Hz, 10.4 Hz, 0.5H), 4.83 (brs, 0.5H), 3.39-3.32 (m, 1H), 3.10-2.99 (m, 1H), 2.85 (s, 1.5H), 2.77 (s, 1.5H), 1.45 (s, 4.5H), 1.42 (s, 4.5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.2, 196.9, 155.8, 154.9, 137.5, 137.3, 137.1, 137.0, 136.9, 136.8, 134.5, 134.4, 131.3, 131.2, 130.7, 130.5, 129.6, 129.3, 129.2, 129.1, 128.9, 128.8, 127.1, 126.9, 81.6, 81.2, 69.3, 67.9, 34.9, 34.6, 33.6, 28.48, 28.44; IR (neat, cm^{-1}): 2975 (w), 1690 (vs), 1586 (m), 1452 (m), 1385 (m), 1144 (s), 1048 (m), 736 (s); HRMS (EI) Calcd for $C_{22}H_{26}O_4NS$ ($M+H^+$): 400.1583, found 400.1577; $[\alpha]^{20}_D$ -61.3 (*c* 1.47, $CHCl_3$).

***O*-Acetyl oxime thioester were generated by the following general procedure.**



S-(2-Formylphenyl) thioester (1.0 mmol) and hydroxyamine hydrochloride (1.2 mmol) was dissloved in 10 mL DMF. Pyridine (1.5 mmol) was added to the solution. After stirred at room temperature overnight, acetyl chloride (1.5 mmol) was added, then triethylamine (2.0 mmol) was added to the solution dropwide at 0 ^{o}C. Reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was added 20 mL ethyl ether and washed with 10 mL saturated $NaHCO_3$ solution, 10 mL saturated NH_4Cl solution and 10 mL brine solution sequentially. After drying over $MgSO_4$, the solvent was evaporated and purified by chromatography (silica gel) to afford the desired compound.

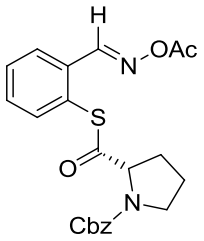
(*S*,*E*)-Benzyl 2-(((2-((acetoxyimino)methyl)phenyl)thio)carbonyl)piperidine-1-carboxylate 10a



Prepared according to the general procedure from (*S*)-benzyl 2-(((2-formylphenyl)thio)carbonyl)piperidine-1-carboxylate (276 mg, 0.72 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 234 mg (74% yield, with a 4:3 ratio of rotamers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (s, 0.57H), 8.52 (s, 0.43H), 8.18 (brs, 1H), 7.51-7.45 (m, 3H), 7.41-7.31 (m, 5H), 5.31-5.17 (m, 2.57H), 5.04 (d, *J* = 4.8 Hz, 0.43H), 4.31 (d, *J* = 12.6 Hz, 0.43H), 4.19 (brd, *J* = 13.2 Hz, 0.57H), 3.15 (t, *J* = 13.2 Hz, 0.57H), 3.08 (t, *J* = 13.2 Hz, 0.43H), 2.36 (d, *J* = 13.8Hz, 0.57H), 2.31 (d, *J* = 13.8 Hz, 0.43H), 2.23 (s, 1.71H), 2.20 (s, 1.29H), 1.73-1.63 (m, 3H), 1.52-1.42 (m, 1H), 1.38-1.31 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.8, 197.7, 168.9, 156.5, 155.5, 154.0, 153.7, 137.0, 136.9, 136.5, 136.4, 133.8, 133.6, 132.2, 130.6, 130.5, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 68.1, 62.2, 61.9, 42.8, 42.4, 26.7, 26.5, 24.8, 24.6, 20.6, 20.5, 19.9; IR (neat, cm^{-1}): 2942 (w),

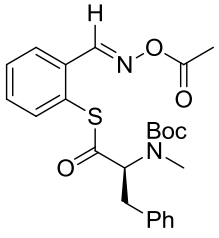
1769 (s), 1695 (vs), 1410 (s), 1335 (m), 1192 (vs), 1000 (s), 902 (s), 759 (s); HRMS (EI) Calcd for $C_{23}H_{25}O_5N_2S$ ($M+H^+$): 441.1484, found 440.1484; $[\alpha]^{20}_D$ -84.9 (*c* 0.87, $CHCl_3$).

(*S*,*E*)-Benzyl 2-(((2-((acetoxyimino)methyl)phenyl)thio)carbonyl)pyrrolidine-1-carboxylate 10b



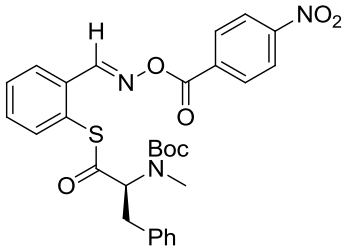
Prepared according to the general procedure from (*S*)-benzyl 2-(((2-formylphenyl)thio) carbonyl)pyrrolidine-1-carboxylate (236 mg, 0.64 mmol), purified by chromatography (silica gel, 2:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 217 mg (80% yield, with a 1:1 ratio of rotamers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (s, 0.5H), 8.48 (s, 0.5H), 8.18-8.14 (m, 1H), 8.49-7.29 (m, 7.5H), 7.26-7.22 (m, 0.5H), 5.28-5.18 (m, 2H), 4.62 (dd, *J* = 3.0 Hz, 8.8 Hz, 0.5H), 4.56 (dd, *J* = 2.8 Hz, 8.8 Hz, 0.5H), 3.76-3.52 (m, 2H), 2.30-2.23 (m, 1H), 2.20 (s, 1.5H), 2.16-2.04 (m, 2H), 2.13 (s, 1.5H), 2.01-1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 198.8, 168.9, 168.7, 155.4, 154.6, 154.3, 153.7, 136.8, 136.7, 136.6, 136.4, 133.9, 133.6, 132.1, 132.0, 130.6, 130.5, 128.8, 128.6, 128.5, 128.44, 128.41, 128.3, 128.2, 67.7, 66.7, 66.3, 47.6, 47.1, 31.9, 30.8, 24.6, 23.7, 19.9, 19.8; IR (neat, cm^{-1}): 2955 (w), 1768 (s), 1697 (vs), 1405 (s), 1348 (s), 1192 (vs), 1115 (s), 1000 (m), 757 (m); HRMS (EI) Calcd for $C_{22}H_{23}O_5N_2S$ ($M+H^+$): 427.1328, found 427.1322; $[\alpha]^{20}_D$ -75.9 (*c* 1.24, $CHCl_3$).

(*S*,*E*)-S-(2-((Acetoxyimino)methyl)phenyl) 2-(((benzyloxy)carbonyl)amino)-3-phenyl propane thioate 10c



Prepared according to the general procedure from (*S*)-*S*-(2-formylphenyl) 2-((*tert*-butoxycarbonyl)(methyl)amino)-3-phenylpropanethioate (176 mg, 0.44 mmol), purified by chromatography (silica gel, 2:1 hexanes: EtOAc) to afford the desired compound as a white solid 149 mg (74% yield, with a 1:1 ratio of rotamers). Mp 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 0.5H), 8.62 (s, 0.5H), 8.20-8.17 (m, 1H), 7.53-7.41 (m, 3H), 7.31-7.16 (m, 5H), 4.78 (dd, *J* = 4.8 Hz, 9.6 Hz, 1H), 3.39-3.31 (m, 1H), 3.14-2.96 (m, 1H), 2.84 (s, 1.5H), 2.75 (s, 1.5H), 1.47 (s, 4.5H), 1.44 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 196.6, 168.9, 168.8, 155.8, 154.9, 154.5, 153.9, 137.3, 137.2, 136.94, 136.90, 136.8, 134.1, 133.7, 132.2, 132.1, 130.7, 130.6, 129.2, 129.1, 128.96, 128.92, 128.8, 128.5, 128.3, 127.1, 126.9, 81.6, 81.1, 68.6, 34.9, 34.6, 34.3, 28.5, 28.49, 19.9; IR (neat, cm^{-1}): 2975 (w), 1767 (s), 1691 (vs), 1453 (m), 1366 (s), 1197 (vs), 1147 (vs), 908 (s); HRMS (EI) Calcd for $C_{24}H_{29}O_5N_2S$ ($M+H^+$): 457.1792, found 457.1809; $[\alpha]^{20}_D$ -65.2 (*c* 1.77, $CHCl_3$).

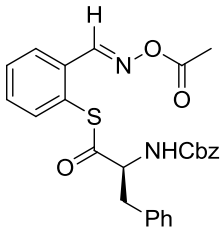
(*S*,*E*)-*S*-(2-((((4-Nitrobenzoyl)oxy)imino)methyl)phenyl) 2-((*tert*-butoxycarbonyl)(methyl) amino)-3-phenyl propanethioate 10d



Prepared according to the general procedure from (*S*)-*S*-(2-formylphenyl) 2-((*tert*-butoxycarbonyl)(methyl)amino)-3-phenylpropanethioate (124 mg, 0.31 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 135 mg (77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 0.66H), 9.06 (s, 0.34H), 8.60-8.46 (m, 4H), 7.79-7.69 (m, 3H), 7.54-7.40 (m, 6H), 5.06 (brs, 0.34H), 4.81-4.77 (m, 0.66H), 3.61-3.55 (m, 1H), 3.44-3.38 (m, 0.66H), 3.26-3.21 (m, 0.33H), 3.08 (s, 0.99H), 2.96 (s, 2.01H), 1.70 (s, 5.94H), 1.65 (s, 3.06H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.8, 196.4, 162.3, 162.2, 156.5, 155.8, 155.6,

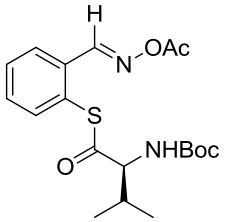
154.8, 151.0, 150.9, 137.4, 137.1, 136.8, 134.4, 134.1, 133.9, 133.3, 133.2, 132.6, 132.5, 131.3, 131.1, 130.8, 130.6, 129.3, 129.2, 129.0, 128.8, 128.5, 127.2, 127.0, 123.9, 123.8, 81.5, 81.0, 69.7, 35.4, 34.9, 34.6, 28.5, 28.4; IR (neat, cm^{-1}): 2975 (w), 1752 (s), 1691 (vs), 1606 (w), 1526 (s), 1453 (m), 1347 (m), 1249 (vs), 1147 (vs), 1072 (vs), 852 (m); HRMS (EI) Calcd for $C_{29}H_{29}O_7N_3NaS$ ($M+Na^+$): 588.1624, found 586.1618; $[\alpha]^{20}_D$ -60.5 (*c* 1.38, $CHCl_3$).

(*S*,*E*)-*S*-(2-((Acetoxyimino)methyl)phenyl) 2-(((benzyloxy)carbonyl)amino)-3-phenyl propane thioate 10e



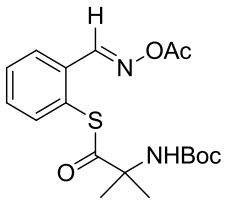
Prepared according to the general procedure from (*S*)-*S*-(2-formylphenyl) 2-(((benzyloxy)carbonyl)amino)-3-phenylpropanethioate (206 mg, 0.49 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 120 mg (52% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.17-8.16 (m, 1H), 7.51-7.50 (m, 2H), 7.39-7.28 (m, 9H), 7.17 (d, *J* = 6.6 Hz, 2H), 5.30 (d, *J* = 8.4 Hz, 1H), 5.14 (AB, *J* = 12.0 Hz, 2H), 4.81 (q, *J* = 8.4 Hz, 1H), 3.20-3.11 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.1, 168.8, 155.9, 154.1, 136.9, 136.1, 135.3, 133.8, 132.2, 130.8, 129.6, 129.2, 128.8, 128.8, 128.6, 128.5, 128.4, 127.7, 67.7, 61.8, 38.2, 19.9; IR (neat, cm^{-1}): 3306 (m), 3031 (w), 1764 (s), 1694 (vs), 1687 (vs), 1516 (s), 1454 (m), 1247 (m), 1197 (vs), 1003 (m); HRMS (EI) Calcd for $C_{21}H_{22}ON_4S$ ($M+H^+$): 477.1484, found 477.1482; $[\alpha]^{20}_D$ -44.4 (*c* 3.68, $CHCl_3$).

(*S*,*E*)-*S*-(2-((Acetoxyimino)methyl)phenyl) 2-((*tert*-butoxycarbonyl)amino)-3-methylbutane thioate 10f



Prepared according to the general procedure (415 mg, 1.23 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a white solid 389 mg (80% yield). Mp 110-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.19-8.17 (m, 1H), 7.51-7.49 (m, 2H), 7.44-7.42 (m, 1H), 5.05 (d, *J* = 8.8 Hz, 1H), 4.37 (dd, *J* = 4.8 Hz, 9.2 Hz, 1H), 2.38-2.29 (m, 1H), 2.22 (s, 3H), 1.51 (s, 9H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.2, 168.5, 155.6, 153.9, 136.6, 133.6, 131.8, 130.4, 128.6, 128.1, 80.6, 65.7, 30.8, 28.3, 19.6, 19.4, 17.2; IR (neat, cm^{-1}): 2930 (w), 1765 (m), 1715 (vs), 1379 (s), 1467 (w), 1365 (s), 1221 (s), 946 (s); HRMS (EI) Calcd for $C_{19}H_{30}O_5N_3S$ ($M+NH_4^+$): 412.1906, found 412.1901; $[\alpha]^{20}_D$ -58.5 (*c* 1.0, $CHCl_3$).

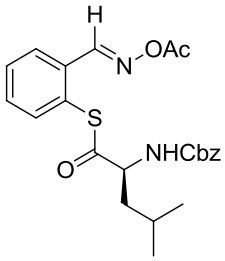
(*E*)-*S*-(2-((Acetoxyimino)methyl)phenyl) 2-((*tert*-butoxycarbonyl)amino)-2-methylpropane thioate 10g



Prepared according to the general procedure *S*-(2-formylphenyl) 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanethioate (272 mg, 0.84 mmol), purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired compound as a white solid 257 mg (80% yield). Mp 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.19-8.16 (m, 1H), 7.49-7.42 (m, 3H), 5.09 (s, 1H), 2.21 (s, 3H), 1.54 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.8, 168.6, 154.8, 154.3, 136.8, 134.4, 131.8, 130.2, 129.2, 127.9, 80.6, 62.3, 28.4, 25.4, 19.6; IR (neat, cm^{-1}): 3405 (w), 1768 (s), 1709 (vs), 1492 (m), 1364 (m), 1201

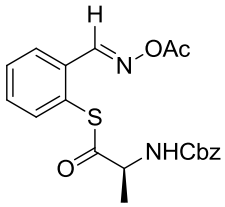
(vs), 1154 (vs), 972 (m); HRMS (EI) Calcd for $C_{18}H_{28}O_5N_3S$ ($M+NH_4^+$): 398.1750, found 398.1744.

(*S*,*E*)-*S*-(2-((Acetoxyimino)methyl)phenyl) 2-(((benzyloxy)carbonyl)amino)-4-methylpentane thioate 10h



Prepared according to the general procedure from (*S*)-*S*-(2-formylphenyl) 2-(((benzyloxy)carbonyl)amino)-4-methylpentanethioate (208 mg, 0.54 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 198 mg (83% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.17-8.15 (m, 1H), 7.51-7.49 (m, 2H), 7.45-7.44 (m, 1H), 7.40-7.31 (m, 5H), 5.23-5.18 (m, 3H), 4.57 (dt, *J* = 4.2 Hz, 9.0 Hz, 1H), 2.22 (s, 3H), 1.78-1.72 (m, 2H), 1.61-1.58 (m, 1H), 0.97 (t, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5, 168.6, 155.9, 153.9, 136.7, 135.9, 133.6, 131.9, 130.4, 128.6, 128.35, 128.30, 128.25, 128.1, 67.4, 59.8, 41.2, 24.8, 22.9, 21.5, 19.6; IR (neat, cm^{-1}): 3317 (w), 2957 (w), 1764 (w), 1697 (vs), 1518 (m), 1243 (s), 1204 (s), 1041 (m); HRMS (EI) Calcd for $C_{23}H_{30}O_5N_3S$ ($M+NH_4^+$): 460.1906, found 460.1901; $[\alpha]^{20}_D$ -20.1 (*c* 2.23, $CHCl_3$).

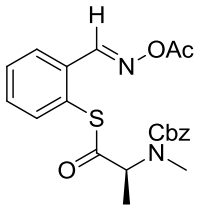
(*S*,*E*)-*S*-(2-((Acetoxyimino)methyl)phenyl) 2-(((benzyloxy)carbonyl)amino)propanethioate 10i



Prepared according to the general procedure from (*S*)-*S*-(2-formylphenyl) 2-(((benzyloxy)carbonyl)amino)propanethioate (316 mg, 0.92 mmol), purified by chromatography

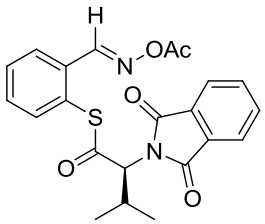
(silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 255 mg (69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.14-8.12 (m, 1H), 7.51-7.30 (m, 8H), 5.31-5.28 (m, 1H), 5.17 (s, 2H), 4.61-4.55 (m, 1H), 2.20 (s, 3H), 1.47 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 168.7, 155.7, 153.9, 136.7, 135.9, 133.6, 131.9, 130.5, 128.6, 128.4, 128.3, 128.2, 128.0, 67.4, 56.9, 19.6, 18.3; IR (neat, cm^{-1}): 3317 (w), 1701 (vs), 1520 (m), 1453 (m), 1239 (s), 1210 (s), 1065 (m), 755 (m); HRMS (EI) Calcd for $C_{20}H_{24}O_5N_3S$ ($M+NH_4^+$): 418.1437, found 418.1431; $[\alpha]^{20}_D$ -14.9 (*c* 1.59, $CHCl_3$).

(*S*,*E*)-*S*-(2-((Acetoxyimino)methyl)phenyl) 2-(((benzyloxy)carbonyl)(methyl)amino)propane thioate 10j



Prepared according to the general procedure from (*S*)-*S*-(2-formylphenyl) 2-(((benzyloxy)carbonyl)(methyl)amino)propanethioate (186 mg, 0.52 mmol), purified by chromatography (silica gel, 3:1 hexanes:EtOAc) to afford the desired compound as a sticky oil 146 mg (68% yield, with a 3:2 ratio of rotamer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 0.6H), 8.51 (s, 0.4H), 8.16-8.14 (m, 1H), 7.50-7.30 (m, 8H), 5.30-5.18 (m, 2H), 5.03 (q, *J* = 7.2 Hz, 0.6H), 4.83 (q, *J* = 7.2 Hz, 0.4H), 3.02, 2.97 (s, 3H), 2.20, 2.17 (s, 3H), 1.45, 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.43, 197.41, 168.64, 168.63, 156.6, 155.7, 153.8, 153.5, 136.7, 136.3, 133.6, 133.4, 131.9, 130.4, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 67.9, 61.85, 61.80, 31.6, 31.0, 19.6, 14.8, 14.1; IR (neat, cm^{-1}): 2940 (w), 1768 (s), 1696 (VS), 1452(m), 1303 (m), 1195 (vs), 1157 (s), 1002 (s), 908 (s); HRMS (EI) Calcd for $C_{21}H_{26}O_5N_3S$ ($M+NH_4^+$): 432.1593, found 432.1588; $[\alpha]^{20}_D$ -62.3 (*c* 1.53, $CHCl_3$).

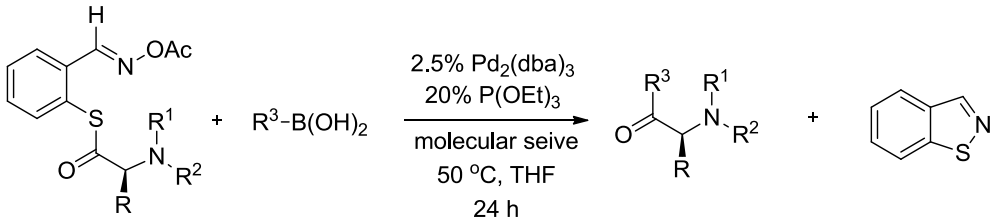
(*S*,*E*)-*S*-(2-((Acetoxyimino)methyl)phenyl) 2-(1,3-dioxoisoindolin-2-yl)-3-methylbutane thioate 10k



Prepared according to the general procedure from (*S*)-*S*-(2-formylphenyl) 2-(1,3-dioxoisoindolin-2-yl)-3-methylbutanethioate (187 mg, 0.51 mmol), purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired compound as a white solid 189 mg (87% yield). Mp 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.18-8.15 (m, 1H), 7.99-7.95 (m, 2H), 7.84-7.80 (m, 2H), 7.51-7.46 (m, 2H), 7.44-7.41 (m, 1H), 4.76 (d, *J* = 8.8 Hz, 1H), 2.89-2.79 (m, 1H), 2.26 (s, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 168.7, 167.5, 153.9, 136.7, 134.7, 133.7, 131.9, 131.5, 130.5, 128.1, 127.7, 123.9, 64.6, 28.4, 20.9, 19.7, 19.4; IR (neat, cm^{-1}): 3336 (m), 2977 (w), 1785 (s), 1765 (m), 1706 (s), 1683 (vs), 1502 (vs), 1365 (m), 1189 (vs), 1158 (vs), 904 (s); HRMS (EI) Calcd for $C_{22}H_{24}O_5N_3S$ ($M+NH_4^+$): 442.1437, found 442.1431; $[\alpha]^{20}_D$ -14.3 (*c* 1.0, $CHCl_3$).

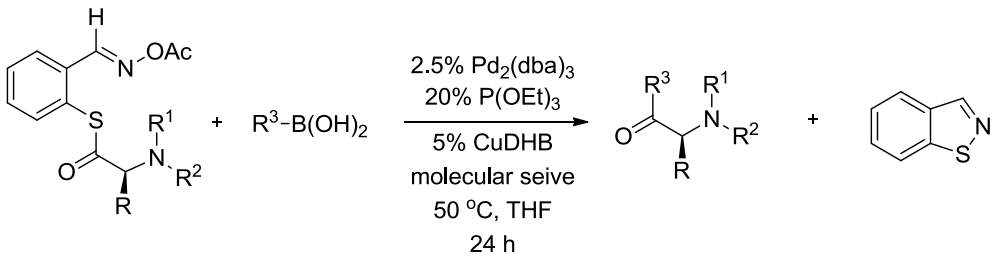
Peptidyl ketones were generated from the thiol ester by the following general procedure.

Method E:



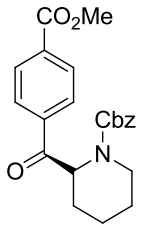
O-acetyl oxime thioester (0.07 mmol), boronic acid (0.105 mmol) and $Pd_2(dba)_3$ (0.00175 mmol) were placed in a microwave tube with 4Å molecular seive and sealed. The tube was vaccumed and filled with argon three times. Triethyl phosphite (0.014 mmol) was added via syring under argon followed by 1 mL THF. The reaction mixture was stirred at 50 °C for 20 hours. The solvent was evaporated and purified by chromatography (silica gel) to afford the desired compound.

Method F:



O-acetyl oxime thioester (0.07 mmol), boronic acid (0.105 mmol), ((2,6-dihydroxybenzoyl)oxy) copper (CuDHB, 0.0035 mmol) and $Pd_2(dba)_3$ (0.0035 mmol) and was placed in a microwave tube with 4Å molecular seive and sealed. The tube was vaccumed and filled with argon three times. Triethyl phosphite (0.014 mmol) was added via syring under argon followed by 1 mL THF. The reaction mixture was stirred at 50 °C for 20 hours. The solvent was evaporated and purified by chromatography (silica gel) to afford the desired compound.

(*R*)-Benzyl 2-(4-(methoxycarbonyl)benzoyl)piperidine-1-carboxylate

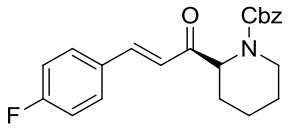


Prepared according to **Method E** from **10a** (24 mg, 0.06 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 16 mg (74% yield, with a 4:1 ratio of rotamers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1.33H), 8.02 (d, *J* = 7.8 Hz, 0.67H), 7.96 (d, *J* = 8.4 Hz, 1.33H), 7.81 (d, *J* = 7.8 Hz, 0.67H), 7.37-7.23 (m, 5H), 5.69 (d, *J* = 5.4 Hz, 0.67H), 5.57 (brd, *J* = 4.8 Hz, 0.33H), 5.16-5.08 (m, 2H), 4.10 (brd, *J* = 13.2 Hz, 0.33H), 4.01 (brd, *J* = 13.2, 0.67H), 3.95 (s, 3H), 3.18 (app q, *J* = 12.6 Hz, 1H), 2.13 (brd, *J* = 13.8 Hz, 0.67H), 2.04 (brd, *J* = 13.2 Hz, 0.33H), 1.86-1.79 (m, 1H), 1.74-1.71 (brd, *J* = 13.2 Hz, 0.33H), 1.67-1.61 (m, 1.67H), 1.48-1.37 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.6, 166.4, 156.6, 155.8, 139.4, 139.3, 136.8, 136.5, 133.9, 130.0, 128.7, 128.3, 128.2, 128.1, 127.9, 67.7,

57.3, 52.7, 42.7, 42.6, 26.4, 26.1, 25.1, 24.8, 20.1, 19.8; IR (neat, cm^{-1}): 2947 (m), 1722 (s), 1685 (vs), 1404 (s), 1341 (m), 1273 (vs), 1106 (s), 1015 (m); HRMS (EI) Calcd for $C_{22}H_{23}O_5N_2S$ ($M+H^+$): 382.1654, found 382.1649; $[\alpha]^{20}_D$ -29.7 (*c* 0.58, $CHCl_3$).

HPLC AS-RH column: 50-75% acetonitrile in water over 10 min, 75-100% acetonitrile over 8 min, then 10% acetonitrile over 7 min with a flow rate of 1.0 mL/min and 210 nm UV detection, retention time = 6.592 min (0.3%) and 9.730 min (99.7%) (DL peptidyl ketone with retention times of 6.604 min and 9.782 min).

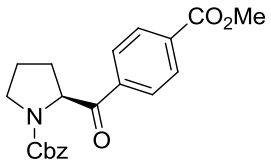
(*R*,*E*)-Benzyl 2-(3-(4-fluorophenyl)acryloyl)piperidine-1-carboxylate



Prepared according to **Method E** from **10a** (26 mg, 0.06 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 18 mg (83% yield, with a 2:3 ratio of rotamers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (m, 1H), 7.47-7.31 (brm, 6H), 7.05 (brt, *J* = 7.8 Hz, 2H), 6.80 (d, *J* = 16.2 Hz, 0.6H), 6.73 (d, *J* = 15.0 Hz, 0.4H), 5.26-5.07 (m, 2.6H), 4.92 (brs, 0.4H), 4.19 (brd, *J* = 10.8 Hz, 0.4H), 4.10 (brd, *J* = 12.0 Hz, 0.6H), 3.03 (brt, *J* = 10.8 Hz, 0.6H), 2.92 (brt, *J* = 11.4 Hz, 0.4H), 2.30-2.27 (brm, 1H), 1.68-1.62 (brm, 4H), 1.46-1.38 (brm, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.58, 198.57, 165.1, 163.5, 156.7, 155.9, 142.9, 142.6, 130.7, 130.6, 128.8, 128.3, 128.1, 121.8, 121.1, 116.3, 116.2, 67.6, 60.5, 60.0, 42.9, 42.7, 25.6, 25.4, 25.3, 25.0, 20.5; IR (neat, cm^{-1}): 2940 (w), 1685 (vs), 1610 (s), 1597 (s), 1507 (s), 1414 (s), 1340 (m), 1232 (vs), 1158 (s), 1070 (m); HRMS (EI) Calcd for $C_{22}H_{23}O_3NF$ ($M+H^+$): 368.1662, found 368.1657; $[\alpha]^{20}_D$ -135.3 (*c* 0.6, $CHCl_3$).

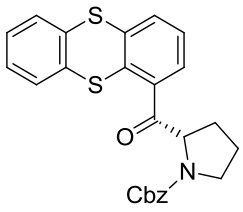
HPLC AS-RH column: 50-75% acetonitrile in water over 18 min, 75-100% acetonitrile over 2 min, then 100% acetonitrile over 5 min with a flow rate of 0.8 mL/min and 210 nm UV detection, retention time = 9.987 min (100%) (DL peptidyl ketone with retention times of 8.488 min and 9.977 min).

(*S*)-Benzyl 2-(4-(methoxycarbonyl)benzoyl)pyrrolidine-1-carboxylate



Prepared according to **Method E** from **10b** (28 mg, 0.07 mmol), purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 18 mg (75% yield, with a 6:5 ratio of rotamers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.8 Hz, 1.10H), 8.07 (d, *J* = 7.8 Hz, 0.90H), 8.04 (d, *J* = 1.10H), 7.90 (d, *J* = 7.8 Hz, 0.90H), 7.38-7.30 (m, 3H), 7.19-7.16 (m, 1.10H), 7.10-7.09 (m, 0.90H), 5.37 (dd, *J* = 3.0 Hz, 9.0 Hz, 0.55H), 5.27 (dd, *J* = 2.4 Hz, 8.4 Hz, 0.45H), 5.14 (AB, *J* = 12.6 Hz, 1.1Hz, 1H), 5.01 (AB, *J* = 12.6 Hz, 0.90H), 3.96, 3.95 (2s, 6H), 3.78-3.71 (m, 0.90H), 3.65-3.56 (m, 1.10H), 2.39-2.30 (0.90H), 2.00-1.92 (m, 3.10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 198.0, 166.4, 155.1, 154.3, 138.5, 138.4, 136.9, 136.5, 134.3, 130.1, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 67.3, 62.0, 61.6, 52.8, 52.7, 47.4, 46.9, 30.9, 29.9, 24.5, 23.6; IR (neat, cm^{-1}): 2952 (w), 1690 (vs), 1409 (s), 1352 (m), 1276 (vs), 1106 (s), 717 (m); HRMS (EI) Calcd for $C_{21}H_{22}O_5N$ ($M+H^+$): 368.1498, found 368.1493; $[\alpha]^{20}_D$ -22.6 (*c* 0.73, $CHCl_3$).

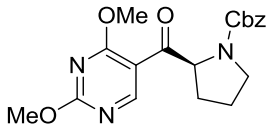
(*S*)-Benzyl 2-(thianthrene-1-carbonyl)pyrrolidine-1-carboxylate



Prepared according to **Method E** from **10b** (23 mg, 0.05 mmol), purified by chromatography (silica gel, 2:1 hexanes: EtOAc) to afford the desired compound as a yellow sticky oil 20 mg (84% yield, with a 1:1 ratio of rotamers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.2 Hz, 0.5H), 7.59 (d, *J* = 7.2 Hz, 0.5H), 7.54 (d, *J*= 7.6 Hz, 0.5H), 7.45-7.41 (m, 1.5H), 7.38-7.17 (m, 8.5H), 7.08 (t, *J* = 8.0Hz, 0.5H), 5.20-5.06 (m, 2.5H), 4.97 (d, *J* = 11.6 Hz, 0.5H), 3.83-3.74 (m, 1H), 3.63-3.51

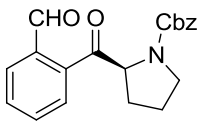
(m, 1H), 2.16-2.04 (m, 1H), 1.97-1.89 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.6, 200.3, 155.2, 154.4, 138.3, 137.8, 137.6, 137.4, 136.9, 136.7, 136.4, 136.3, 136.1, 135.7, 135.5, 132.0, 131.9, 129.03, 129.02, 128.8, 128.7, 128.6, 128.4, 128.3, 128.26128.19, 128.05, 128.02, 127.98, 127.7, 127.1, 126.9, 126.6, 67.6, 67.3, 63.8, 63.3, 47.5, 47.0, 29.9, 28.8, 24.4, 23.5; IR (neat, cm^{-1}): 2952 (w), 1691 (vs), 1449 (m), 1411 (s), 1397 (s), 1348 (s), 1234 (m), 1186 (m), 1115 (s), 1013 (m), 722 (vs); HRMS (EI) Calcd for $C_{25}H_{22}O_3NS_2$ ($M+H^+$): 448.1041, found 448.1036; $[\alpha]^{20}_D$ -233.6 (*c* 1.07, $CHCl_3$).

(*S*)-Benzyl 2-(2,4-dimethoxypyrimidine-5-carbonyl)pyrrolidine-1-carboxylate



Prepared according to **Method F** from **10b** (36 mg, 0.08 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 16 mg (52% yield, with a 5:4 ratio of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 0.56H), 8.74 (s, 0.44H), 7.36-7.21 (m, 5H), 7.15-7.13 (m, 1H), 5.28-4.97 (m, 3H), 4.08, 4.05, 4.04, 4.02 (4s, 6H), 3.73-3.65 (m, 1H), 3.58-3.47 (m, 1H), 2.31-2.21 (m, 1H), 1.93-1.85 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.9, 195.4, 169.5, 169.3, 167.3, 167.2, 164.1, 163.7, 155.1, 154.5, 137.1, 136.8, 128.7, 128.5, 128.1, 128.06, 128.02, 127.9, 111.7, 111.6, 67.2, 67.1, 65.0, 64.3, 55.8, 54.8, 47.6, 47.0, 30.3, 29.2, 23.9, 23.1; IR (neat, cm^{-1}): 2954 (w), 1702 (s), 1679 (s), 1580 (vs), 1465 (m), 1388 (s), 1318 (s), 1203 (m), 1004 (m); HRMS (EI) Calcd for $C_{19}H_{22}O_5N_3$ ($M+H^+$): 372.1559, found 372.1554; $[\alpha]^{20}_D$ -19.6 (*c* 0.54, $CHCl_3$).

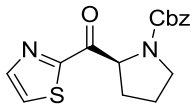
(*S*)-Benzyl 2-(2-formylbenzoyl)pyrrolidine-1-carboxylate



Prepared according to **Method F** from **10b** (29 mg, 0.07 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 17 mg (75% yield,

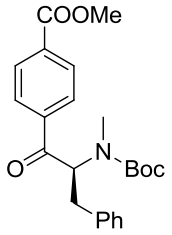
with a 5:4 ratio of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 0.56H), 9.89 (s, 0.44H), 7.93-7.7.82 (m, 1H), 7.66-7.55 (m, 1H), 7.49-7.28 (m, 4H), 7.24-7.15 (m, 3H), 5.19-4.96 (m, 3H), 3.74-3.53 (m, 2H), 2.27-1.92 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 191.2, 191.1, 151.14, 151.13, 139.8, 139.1, 136.5, 136.1, 132.9, 132.8, 131.7, 131.6, 129.6, 129.4, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 125.4, 122.3, 67.5, 67.2, 63.7, 63.5, 47.3, 46.8, 29.7, 29.4, 24.3, 24.0; IR (neat, cm^{-1}): 2924 (w), 1695 (vs), 1415 (s), 1353 (m), 1203 (m), 1120 (m), 981 (w); HRMS (EI) Calcd for $C_{20}H_{20}O_4N$ ($M+H^+$): 338.1387, found 338.1398; $[\alpha]^{20}_D$ -23.5 (*c* 0.63, $CHCl_3$).

(*S*)-Benzyl 2-(thiazole-2-carbonyl)pyrrolidine-1-carboxylate



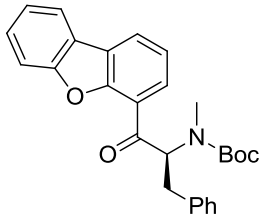
Prepared according to **Method E** from **10b** (32 mg, 0.08 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 17 mg (70% yield, with a 1:1 ratio of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.8 Hz, 0.5H), 7.97 (d, *J* = 2.8 Hz, 0.5H), 7.68 (d, *J* = 2.8 Hz, 0.5H), 7.67 (d, *J* = 2.8 Hz, 0.5H), 7.36-7.24 (m, 3H), 7.18-7.16 (m, 1H), 7.15-7.08 (m, 1H), 5.58 (dd, *J* = 4.0 Hz, 9.2 Hz, 0.5H), 5.53 (dd, *J* = 4.0 Hz, 9.2 Hz, 0.5H), 5.08 (AB, *J* = 12.4 Hz, 28.0 Hz, 1H), 5.01 (AB, *J* = 12.8 Hz, 19.2 Hz, 1H), 3.75-3.53 (m, 2H), 2.48-2.37 (m, 1H), 2.09-1.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 191.3, 165.0, 164.9, 154.8, 154.1, 144.9, 136.7, 136.4, 128.4, 128.2, 127.9, 127.8, 127.6, 127.4, 126.6, 126.5, 67.0, 66.9, 62.0, 61.6, 47.3, 46.8, 30.9, 29.9, 24.3, 23.5; IR (neat, cm^{-1}): 2954 (w), 2137 (w), 1694 (vs), 1413 (s), 1388 (m), 1353 (m), 1238 (w), 1116 (m); HRMS (EI) Calcd for $C_{16}H_{17}O_3N_2S$ ($M+H^+$): 317.0954, found 317.0961; $[\alpha]^{20}_D$ -57.3 (*c* 0.775, $CHCl_3$).

(*S*)-Methyl 4-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropanoyl)benzoate



Prepared according to **Method F** from **10c** (26 mg, 0.06 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 14 mg (60% yield, with a 1:1 ratio of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.29-7.20 (m, 5H), 5.79 (dd, J = 6.0 Hz, 8.8 Hz, 0.5H), 5.37 (dd, *J* = 5.2 Hz, 10.0 Hz, 0.5H), 3.95 (s, 1.5H), 3.94 (s, 1.5H), 3.32-3.21 (m, 1H), 3.07-2.99 (m, 1H), 2.64 (s, 1.5H), 2.59 (s, 1.5H), 1.30 (s, 4.5H), 1.28 (s, 1.5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5, 198.0, 167.1, 167.0, 155.5, 154.4, 139.2, 138.1, 134.1, 130.4, 130.0, 129.9, 129.8, 129.2, 128.8, 128.6, 128.4, 127.5, 126.9, 126.8, 126.7, 81.1, 81.0, 60.8, 52.73, 52.69, 52.5, 34.2, 33.9, 28.34, 28.29; IR (neat, cm^{-1}): 2955 (w), 1721 (s), 1689 (vs), 1433 (m), 1276 (vs), 1107 (m), 729 (m); HRMS (EI) Calcd for $C_{23}H_{27}O_5NNa$ ($M+Na^+$): 420.1787, found 420.1781; $[\alpha]^{20}_D$ -62.8 (*c* 0.42, $CHCl_3$).

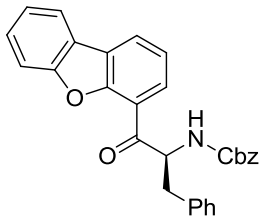
(*S*)-*tert*-Butyl (1-(dibenzo[b,d]furan-4-yl)-1-oxo-3-phenylpropan-2-yl)(methyl)carbamate



Prepared according to **Method F** from **10c** (29 mg, 0.06 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 21 mg (79% yield, with a 4:3 ratio of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.09 (m, 1H), 8.03 (d, *J* = 7.6 Hz, 0.44H), 7.95 (t, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 0.56H), 7.64 (d, *J* = 8.4 Hz, 0.44H), 7.60 (d, *J* = 8.4 Hz, 0.56H), 7.51-7.46 (m, 1H), 7.42-7.28 (m, 7H), 7.24-7.20 (m, 1H), 5.91 (dd, *J* = 4.8 Hz, 9.6 Hz, 0.44H), 5.65 (dd, *J* = 8.4 Hz, 9.6 Hz, 0.56H), 3.49-3.38 (m, 1H), 3.14-3.07 (m, 1H),

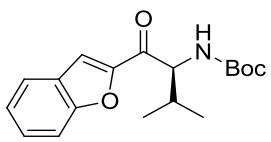
2.74 (s, 1.68H), 2.68 (s, 1.32H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 196.9, 156.1, 155.9, 155.6, 154.8, 153.8, 153.6, 138.2, 138.1, 129.32, 129.31, 128.6, 128.38, 128.37, 127.9, 127.7, 126.6, 126.4, 125.6, 125.4, 125.16, 125.15, 123.5, 123.3, 123.2, 122.8, 121.8, 121.7, 120.8, 120.6, 112.1, 111.7, 80.5, 79.9, 66.6, 64.6, 34.6, 34.1, 33.4, 32.5, 28.1; IR (neat, cm^{-1}): 2974 (w), 1686 (vs), 1597 (w), 1451 (m), 1364 (m), 1183 (s), 1146 (m), 751 (vs); HRMS (EI) Calcd for $C_{27}H_{28}O_4N$ ($M+H^+$): 430.2018, found 430.2013; $[\alpha]^{20}_D$ +7.7 (*c* 1.23, $CHCl_3$).

(*S*)-Benzyl (1-(dibenzo[b,d]furan-4-yl)-1-oxo-3-phenylpropan-2-yl)carbamate



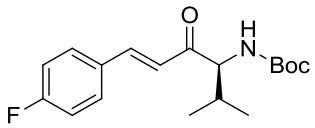
Prepared according to **Method F** from **10e** (33 mg, 0.07 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a white solid 20 mg (63% yield). Mp 160-162 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.8 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.36-7.30 (m, 4H), 7.21-7.16 (m, 4H), 7.07 (d,7.2 Hz, 2H), 6.12 (q, *J* = 6.0 Hz, 1H), 5.75 (d, *J* = 7.2 Hz, 1H), 5.11 (AB, *J* = 12.6 Hz, 33.0 Hz, 2H), 3.42 (dd, *J* = 5.4 Hz, 14.4 Hz, 1H), 2.97 (dd, *J* = 7.2 Hz, 14.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 156.3, 156.0, 154.4, 136.7, 136.1, 129.7, 128.74, 128.72, 128.5, 128.4, 128.3, 128.2, 127.1, 126.6, 126.2, 123.9, 123.5, 123.3, 121.0, 120.2, 112.3, 67.0, 60.3, 38.4; IR (neat, cm^{-1}): 3319 (w), 1738 (vs), 1677 (vs), 1534 (s), 1413 (m), 1348 (s), 1227 (s), 1048 (m); HRMS (EI) Calcd for $C_{29}H_{24}O_4N$ ($M+H^+$): 450.1705, found 450.1699; $[\alpha]^{20}_D$ +42.8 (*c* 2.09, $CHCl_3$).

(*S*)-*tert*-Butyl (1-(benzofuran-2-yl)-3-methyl-1-oxobutan-2-yl)carbamate



Prepared according to **Method F** from **10f** (28 mg, 0.07 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a white solid 18 mg (83% yield). Mp 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 5.34 (d, *J* = 9.2 Hz, 1H), 5.10 (dd, *J* = 4.8 Hz, 9.6 Hz, 1H), 2.31-2.21 (m, 1H), 1.44 (s, 9H), 1.07 (d, *J* = 7.6 Hz, 3H), 0.87 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.6, 156.04, 156.03, 151.5, 128.9, 127.1, 124.3, 123.7, 114.8, 112.8, 80.1, 60.7, 31.8, 28.5, 20.2, 17.2; IR (neat, cm^{-1}): 3384 (w), 1670 (vs), 1506 (vs), 1278 (s), 1144 (s), 1014 (m), 754 (s); HRMS (EI) Calcd for $C_{18}H_{24}O_4N$ ($M+H^+$): 318.1705, found 318.1700; $[\alpha]^{20}_D$ +113.5 (*c* 1.06, $CHCl_3$).

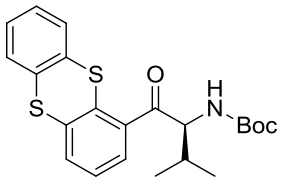
(*S*,*E*)-*tert*-Butyl (6-(4-fluorophenyl)-2-methyl-4-oxohex-5-en-3-yl)carbamate



Prepared according to **Method F** from **10f** (30 mg, 0.07 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a white solid 20 mg (82% yield). Mp 83-84 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 15.6 Hz, 1H), 7.55-7.53 (m, 2H), 7.07 (t, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 15.6 Hz, 1H), 5.27 (d, *J* = 8.4 Hz, 1H), 4.58 (dd, *J* = 4.2 Hz, 8.4 Hz, 1H), 2.20-2.15 (m, 1H), 1.42 (s, 9H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5, 165.3, 163.6, 156.2, 142.9, 130.7, 130.6, 123.3, 116.5, 116.3, 79.9, 62.9, 31.1, 28.5, 20.1, 17.0; IR (neat, cm^{-1}): 3350 (m), 2977 (w), 1696 (s), 1678 (vs), 1615 (m), 1504 (vs), 1331 (w), 1231 (m), 1154 (s), 983 (m); HRMS (EI) Calcd for $C_{18}H_{25}O_3NF$ ($M+H^+$): 322.1818, found 322.1813; $[\alpha]^{20}_D$ +70.4 (*c* 0.93, $CHCl_3$).

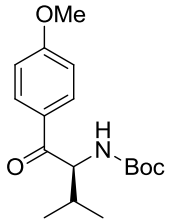
HPLC AD-RH column: 50-75% acetonitrile in water over 18 min, 75-100% acetonitrile over 2 min, then 100% acetonitrile over 5 min with a flow rate of 0.80 mL/min and 210 nm UV detection, retention time = 10.145 min (100%) (DL peptidyl ketone with retention times of 10.252 min and 11.284 min).

(*S*)-*tert*-Butyl (3-methyl-1-oxo-1-(thianthren-1-yl)butan-2-yl)carbamate



Prepared according to **Method F** from **10f** (35 mg, 0.09 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 27 mg (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.2 Hz, 1H), 7.62 (dd, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.45 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H), 7.40 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H), 7.31-7.18 (m, 3H), 5.37 (d, *J* = 8.8 Hz, 1H), 5.06 (dd, *J* = 4.4 Hz, 8.8 Hz, 1H), 2.04-1.96 (m, 1H), 1.45 (s, 9H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.78 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.6, 156.3, 138.2, 138.0, 137.1, 136.6, 135.6, 132.4, 129.1, 128.9, 128.3, 128.1, 127.8, 126.9, 80.1, 62.0, 31.6, 28.6, 20.1, 17.2; IR (neat, cm^{-1}): 2965 (w), 1708 (vs), 1683 (vs), 1495 (s), 1364 (m), 1242 (m), 1164 (vs), 749 (m); HRMS (EI) Calcd for $C_{22}H_{25}O_3NS_2Na$ ($M+Na^+$): 438.1174, found 438.1183; $[\alpha]^{20}_D$ -218.0 (*c* 0.34, $CHCl_3$).

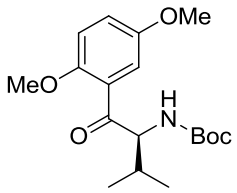
(*S*)-*tert*-Butyl (1-(4-methoxyphenyl)-3-methyl-1-oxobutan-2-yl)carbamate



Prepared according to **Method F** from **10f** (36 mg, 0.09 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a white solid 16 mg (58% yield). Mp 102-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 5.44 (d, *J* = 8.8 Hz, 1H), 5.17 (dd, *J* = 4.0 Hz, 8.8 Hz, 1H), 3.87 (s, 3H), 2.17-2.09 (m, 1H), 1.44 (s, 9H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.75 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.2, 164.1, 156.2, 131.2, 128.4, 114.2, 79.7, 59.3, 55.8, 32.2, 28.6, 20.3, 16.7; IR (neat, cm^{-1}):

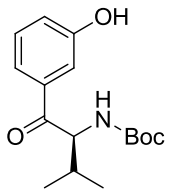
3320 (w), 1696 (vs), 1677 (vs), 1600 (s), 1384 (m), 1252 (s), 1168 (vs), 1011 (m); HRMS (EI) Calcd for $C_{17}H_{26}O_4N$ ($M+H^+$): 308.1862, found 308.1857; $[\alpha]^{20}_D$ +94.3 (*c* 0.58, $CHCl_3$).

(*S*)-*tert*-Butyl (1-(2,5-dimethoxyphenyl)-3-methyl-1-oxobutan-2-yl)carbamate



Prepared according to **Method F** from **10f** (28 mg, 0.07 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a white solid 16 mg (67% yield). Mp 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.8 Hz, 1H), 7.03 (dd, *J* = 2.8 Hz, 8.8 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 5.44-5.36 (m, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 2.16-2.09 (m, 1H), 1.44 (s, 9H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.9, 156.4, 153.8, 153.4, 126.0, 121.1, 114.8, 113.3, 79.5, 63.9, 56.4, 56.0, 30.7, 28.6, 20.7, 15.9; IR (neat, cm^{-1}): 3443 (w), 1714 (vs), 1672 (s), 1494 (vs), 1410 (m), 1223 (m), 1161 (vs), 1048 (m), 1018 (vs); HRMS (EI) Calcd for $C_{18}H_{28}O_5N$ ($M+H^+$): 338.1967, found 338.1965; $[\alpha]^{20}_D$ +60.7 (*c* 0.94, $CHCl_3$).

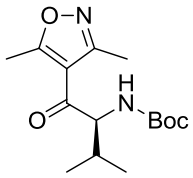
(*S*)-*tert*-Butyl (1-(3-hydroxyphenyl)-3-methyl-1-oxobutan-2-yl)carbamate



Prepared according to **Method F** from **10f** (28 mg, 0.1 mmol), purified by chromatography (silica gel, 3:1 hexanes: EtOAc) to afford the desired compound as a white solid 18 mg (64% yield). Mp 148-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.07 (brs, 1H), 7.05 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 5.45 (d, *J* = 9.6 Hz, 1H), 5.22 (dd, *J* = 4.0 Hz, 8.8 Hz, 1H), 2.18-2.10 (m, 1H), 1.45 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 156.6, 156.4, 136.5, 130.0, 121.0,

120.5, 115.4, 80.2, 59.6, 31.5, 28.3, 19.9, 16.3; IR (neat, cm^{-1}): 3346 (br w), 2967 (w), 1672 (vs), 1584 (m), 1506 (s), 1448 (m), 1366 (s), 1246 (s), 1165 (vs); HRMS (EI) Calcd for $C_{16}H_{24}O_4N$ ($M+H^+$): 294.1705, found 294.1700; $[\alpha]^{20}_D$ +64.8 (*c* 0.64, $CHCl_3$).

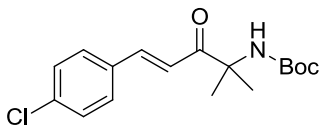
(*S*)-*tert*-Butyl (1-(3,5-dimethylisoxazol-4-yl)-3-methyl-1-oxobutan-2-yl)carbamate



Prepared according to **Method F** from **10f** (47 mg, 0.12 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a white solid 15 mg (43% yield). Mp 95-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (d, *J* = 8.8 Hz, 1H), 4.82 (dd, *J* = 4.0 Hz, 9.6 Hz, 1H), 2.70 (s, 3H), 2.46 (s, 3H), 2.05-1.86 (m, 1H), 1.42 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.4, 174.2, 159.2, 156.0, 115.2, 79.8, 61.8, 31.0, 28.3, 20.1, 16.1, 14.1, 12.2; IR (neat, cm^{-1}): 3363 (w), 2967 (m), 1710 (s), 1673 (vs), 1495 (s), 1418 (s), 1366 (s), 1243 (m), 1165 (vs), 978 (w); HRMS (EI) Calcd for $C_{15}H_{25}O_4N_2$ ($M+H^+$): 297.1814, found 297.1811; $[\alpha]^{20}_D$ +58.0 (*c* 0.24, $CHCl_3$).

HPLC AD-RH column: 40% acetonitrile in water over 12 min, 40-75% acetonitrile over 10 min, then 75-100% acetonitrile over 3 min with a flow rate of 0.80 mL/min and 210 nm UV detection, retention time = 8.677 min (100%) (DL peptidyl ketone with retention times of 8.753 min and 10.448 min).

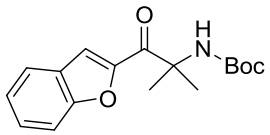
(*E*)-*tert*-Butyl (5-(4-chlorophenyl)-2-methyl-3-oxopent-4-en-2-yl)carbamate



Prepared according to **Method F** from **10g** (27 mg, 0.07 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 16 mg (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 15.6 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4

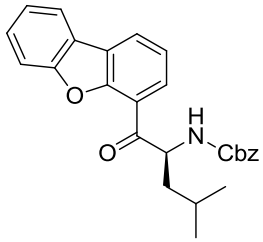
Hz, 2H), 7.12 (d, *J* = 14.4 Hz, 1H), 5.35 (s, 1H), 1.49, 1.41 (2s, 15H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.5, 154.6, 142.8, 136.4, 133.5, 129.7, 129.4, 119.9, 80.0, 60.2, 28.5, 24.2; IR (neat, cm^{-1}): 3329 (m), 2973 (w), 1692 (vs), 1677 (vs), 1614 (vs), 1516 (vs), 1490 (s), 1383 (m), 1285 (vs), 1060 (vs), 988 (m); HRMS (EI) Calcd for $C_{17}H_{23}O_3NCl$ ($M+H^+$): 324.1366, found 324.1363.

***tert*-Butyl (1-(benzofuran-2-yl)-2-methyl-1-oxopropan-2-yl)carbamate**



Prepared according to **Method F** from **10g** (34 mg, 0.09 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a white solid 20 mg (72% yield). Mp 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.44 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 5.39 (s, 1H), 1.62 (s, 6H), 1.25 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.8, 155.3, 154.7, 133.1, 128.2, 127.0, 123.9, 123.3, 114.0, 112.5, 60.2, 28.6, 28.3; IR (neat, cm^{-1}): 2980 (w), 1681 (vs), 1516 (m), 1297 (m), 1164 (s), 1083 (m); HRMS (EI) Calcd for $C_{17}H_{22}O_4N$ ($M+H^+$): 304.1549, found 304.1545.

(*S*)-Benzyl (1-(dibenzo[b,d]furan-4-yl)-4-methyl-1-oxopentan-2-yl)carbamate

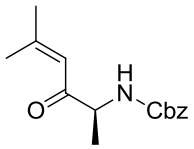


Prepared according to **Method F** from **10h** (31 mg, 0.07 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a white solid 23 mg (78% yield). Mp 121-122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.2 Hz, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.46-7.30 (m, 7H), 5.93 (dt, *J* = 2.4 Hz, 10.0 Hz, 1H), 5.70 (d, *J* = 8.8 Hz, 1H), 5.14 (s, 2H), 1.98-1.89 (m, 1H), 1.70 (dt, 2.4 Hz, 12.0 Hz, 1H), 1.40 (dt, *J* = 2.4 Hz, 12.0 Hz, 1H), 1.24 (d, *J* = 7.8 Hz, 3H), 0.87

(d, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.6, 156.7, 156.2, 154.4, 136.7, 128.8, 128.7, 128.3, 128.2, 126.5, 126.2, 123.8, 123.3, 120.9, 119.8, 112.3, 67.1, 58.3, 42.5, 25.4, 23.9, 21.7; IR (neat, cm^{-1}): 3328 (w), 2953 (w), 1702 (s), 1678 (vs), 1541 (s), 1413 (m), 1274 (m), 1175 (s), 1048 (m); HRMS (EI) Calcd for $C_{26}H_{26}O_4N$ ($M+H^+$): 416.1862, found 416.1856; $[\alpha]^{20}_D$ +51.6 (*c* 1.0, $CHCl_3$).

HPLC OD-RH column: 60-100% acetonitrile in water over 20 min, 100% acetonitrile over 5 min with a flow rate of 0.80 mL/min and 210 nm UV detection, retention time = 14.608 min (100%) (DL peptidyl ketone with retention times of 12.544 min and 14.616 min).

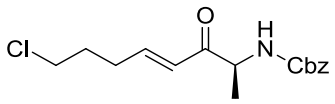
(*S*)-Benzyl (5-methyl-3-oxohex-4-en-2-yl)carbamate



Prepared according to **Method F** from **10i** (34 mg, 0.08 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 17 mg (75% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.28 (m, 5H), 6.07 (s, 1H), 5.71 (d, *J* = 4.8 Hz, 1H), 5.08 (s, 2H), 4.35 (quintet, *J* = 7.2 Hz, 1H), 2.17 (s, 3H), 1.92 (s, 3H), 1.33 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.0, 159.9, 155.9, 136.7, 128.7, 128.3, 128.2, 120.6, 66.9, 55.9, 28.3, 21.5, 18.7; IR (neat, cm^{-1}): 3324 (w), 1682 (vs), 1618 (s), 1497 (s), 1448 (s), 1336 (m), 1212 (s), 1062 (s), 1021 (vs); HRMS (EI) Calcd for $C_{15}H_{20}O_3N$ ($M+H^+$): 262.1443, found 262.1439; $[\alpha]^{20}_D$ +25.2 (*c* 0.86, $CHCl_3$).

HPLC OJ-RH column: 40% acetonitrile in water over 12 min, 40-75% acetonitrile over 10 min, then 75-100% acetonitrile over 3 min with a flow rate of 0.80 mL/min and 210 nm UV detection, retention time = 12.636 min (99.4%) and 13.793 min (0.6%) (DL peptidyl ketone with retention times of 12.675 min and 13.813 min).

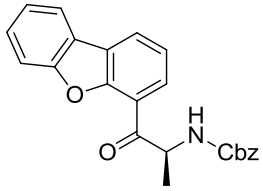
(*S*,*E*)-Benzyl (8-chloro-3-oxooct-4-en-2-yl)carbamate



Prepared according to **Method F** from **10i** (28 mg, 0.07 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a white solid 20 mg (92% yield). Mp 54-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 6.96 (dt, *J* = 7.2 Hz, 15.6 Hz, 1H), 6.25 (d, *J* = 16.0 Hz, 1H), 5.66 (d, *J* = 7.2 Hz, 1H), 5.09 (s, 2H), 4.59 (quintet, *J* = 7.2 Hz, 1H), 3.53 (t, *J* = 8.2 Hz, 2H), 2.41 (q, *J* = 6.8 Hz, 2H), 1.93 (quintet, *J* = 6.8 Hz, 2H), 1.35 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.7, 155.8, 147.9, 136.6, 128.8, 128.4, 128.3, 127.3, 67.0, 54.1, 44.1, 30.8, 29.9, 18.8; IR (neat, cm^{-1}): 3307 (m), 1702 (m), 1678 (vs), 1627 (s), 1526 (vs), 1444 (m), 1346 (s), 1240 (vs), 990 (m); HRMS (EI) Calcd for $C_{16}H_{21}O_3NCl$ ($M+H^+$): 310.1210, found 310.1207; $[\alpha]^{20}_D$ +32.4 (*c* 1.11, $CHCl_3$).

HPLC OJ-RH column: 50-75% acetonitrile in water over 10 min, 70-100% acetonitrile over 8 min, then 100% acetonitrile over 7 min with a flow rate of 1.0 mL/min and 210 nm UV detection, retention time = 4.960 min (100%) (DL peptidyl ketone with retention times of 5.006 min and 5.805 min).

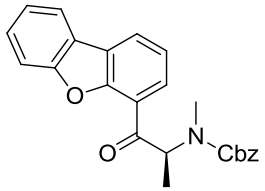
(*S*)-Benzyl (1-(dibenzo[b,d]furan-4-yl)-1-oxopropan-2-yl)carbamate



Prepared according to **Method F** from **10i** (28 mg, 0.07 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a white solid 19 mg (72% yield). Mp 97-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.46-7.30 (m, 7H), 5.98 (d, *J* = 6.8 Hz, 1H), 5.79 (quintet, *J* = 6.8 Hz, 1H), 5.15 (s, 2H), 1.51 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.2, 156.3, 155.9, 154.4, 136.7, 128.8, 128.6, 128.35, 128.32, 126.5,

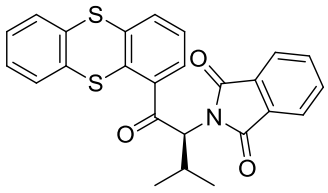
126.2, 123.8, 123.3, 123.2, 120.9, 119.6, 112.4, 67.0, 55.4, 19.4; IR (neat, cm^{-1}): 3312 (w), 1698 (s), 1675 (vs), 1535 (m), 1341 (m), 1256 (s), 1174 (s), 977 (m); HRMS (EI) Calcd for $C_{23}H_{20}O_4N$ ($M+H^+$): 374.1392, found 374.1387; $[\alpha]^{20}_D$ +31.1 (*c* 0.95, $CHCl_3$).

(*S*)-Benzyl (1-(dibenzo[b,d]furan-4-yl)-1-oxopropan-2-yl)(methyl)carbamate



Prepared according to **Method F** from **10j** (30 mg, 0.07 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 23 mg (82% yield, with a 4:3 ratio of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.08 (m, 1H), 8.01 (d, *J* = 8.0 Hz, 0.57H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 0.43H), 7.65 (d, *J* = 8.4 Hz, 0.57H), 7.51-7.46 (m, 1.43H), 7.41-7.36 (m, 1.57H), 7.33-7.21 (m, 5.43H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.2, 156.7, 156.4, 154.2, 153.9, 136.9, 136.5, 128.63, 128.62. 128.4, 128.2, 128.1, 127.9, 127.8, 125.9, 125.8, 125.6, 125.5, 123.7, 123.6, 123.39, 123.38, 123.15, 123.13, 121.5, 121.4, 120.9, 120.8, 112.3, 111.9, 67.7, 67.5, 60.1, 59.6, 32.3, 31.2, 14.2, 13.8; IR (neat, cm^{-1}): 2934 (w), 1686 (vs), 1595 (w), 1472 (m), 1450 (m), 1303 (m), 1183 (s), 973 (m), 751 (vs); HRMS (EI) Calcd for $C_{24}H_{22}O_4N$ ($M+H^+$): 388.1549, found 388.1543; $[\alpha]^{20}_D$ +44.4 (*c* 0.63, $CHCl_3$).

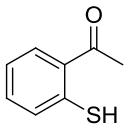
(*S*)-2-(3-Methyl-1-oxo-1-(thianthren-1-yl)butan-2-yl)isoindoline-1,3-dione



Prepared according to **Method F** from **10k** (35 mg, 0.08 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a white solid 24 mg (64% yield). Mp 182-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 2H), 7.64-7.61 (m, 2H), 7.56-7.53 (m, 2H), 7.49 (dd, *J* = 1.2 Hz, 8.0 Hz, 1H), 7.39-7.37 (m, 1H), 7.24-7.19 (m, 2H), 7.16

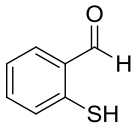
(dt, *J* = 1.2 Hz, 8.0 Hz, 1H), 5.25 (d, *J* = 8.8 Hz, 1H), 3.09-2.99 (m, 1H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.8, 167.8, 137.8, 137.2, 136.3, 135.6, 134.4, 132.0, 131.6, 129.4, 128.6, 128.1, 128.0, 126.9, 126.5, 123.8, 61.4, 27.9, 21.3, 19.6; IR (neat, cm^{-1}): 2961 (w), 1769 (w), 1712 (vs), 1451 (w), 1375 (s), 1357 (m), 1191 (m), 711 (s); HRMS (EI) Calcd for $C_{25}H_{20}O_3NS_2$ ($M+H^+$): 446.0885, found 446.0879; $[\alpha]^{20}_D$ -21.1 (*c* 1.09, $CHCl_3$).

2'-Mercaptoacetophenone[35]



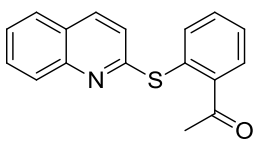
2'-Mercaptoacetophenone was prepared from 2-mercaptobenzoic acid (1.0 g, 6.5 mmol) using the Topolski's method.[35] The residue was purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a yellow oil 0.67 g (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.33-7.31 (m, 2H), 7.23-7.19 (m, 1H), 4.45 (s, 1H), 2.64 (s, 3H); IR (neat, cm^{-1}): 3061 (w), 2536 (m), 1668 (vs).

2-Mercaptobenzaldehyde[36]



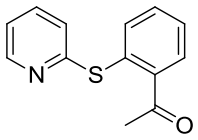
2-Mercaptobenzaldehyde was prepared from 2-mercaptobenzoic acid (1.5 g, 10 mmol) using Kasmai's procedure.[36] The residue was purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a yellow oil 0.72 g (52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1d), 7.36-7.30 (m, 3H), 5.29 (brs, 1H).

1-(2-(Quinolin-2-ylthio)phenyl)ethanone



Under argon protection, 15 mL DMF was added into a 100 mL round bottom flask containing 0.47 g (2.88 mmol) of 2-chloroquinoline, 0.46 g (3.19 mmol) of 2'-mercaptoacetopheone and 0.60 g (4.32 mmol) of potassium carbonate. The suspension was stirred at 110 ^{o}C overnight. The reaction was concentrated *in vacuo*, the resulting residue was diluted with ethyl ether (20 mL), washed with water, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a yellow sticky oil 0.69 g (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.73-7.63 (m, 3H), 7.55-7.52 (m, 1H), 7.48-7.40 (m, 3H), 7.20 (d, *J* = 8.8 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 158.5, 147.5, 140.8, 136.2, 133.7, 131.1, 131.0, 129.5, 128.7, 127.7, 127.4, 127.2, 125.7, 121.26, 121.22, 28.8; IR (neat, cm^{-1}): 3061 (w), 2968 (w), 1695 (vs), 1586 (s). HRMS (EI) Calcd for $C_{17}H_{14}ONS$ ($M+H^{+}$): 280.0790, found 280.0786.

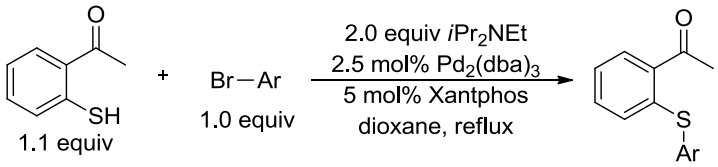
1-(2-(Pyridin-2-ylthio)phenyl)ethanone



Under Argon protection, 25 mL DMF was added into a 100 mL round bottom flask containing 0.60 g (5.31 mmol) of 2-chloropyridine, 0.89 g (5.84 mmol) of 2'-mercaptoacetopheone and 1.10 g (8.00 mmol) of potassium carbonate. The suspension was stirred at 110 ^{o}C overnight. The reaction was concentrated *in vacuo*, the resulting residue was diluted with ethyl ether (20 mL), washed with water, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to yield the desired compound as a yellow sticky oil 1.08 g (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (m, 1H), 7.68 (d, *J* = 6.8 Hz, 1H), 7.58-7.53 (t, *J* = 7.2 Hz, 1H), 7.38-7.34 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.10 (dt, *J* = 1.6 Hz, 7.2 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 158.8, 150.3, 140.9,

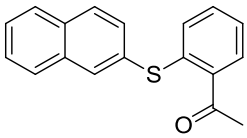
137.3, 133.6, 133.5, 131.9, 129.5, 127.6, 125.4, 121.7, 29.5; IR (neat, cm^{-1}): 1670 (vs), 1572 (s), 1559 (w), 1448 (m); HRMS (FAB) Calcd for $C_{13}H_{12}NOS$ ($M+H^+$): 230.0634, found 230.0633.

Thiol ethers were generated from 2'-mercaptoacetophenone and aryl halide by the following general procedure.



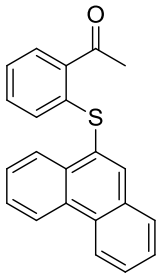
To a 25 mL round bottom flask were added aryl halide (1 mmol), *i*-Pr_2NEt (2 mmol) and 10 mL dry dioxane. The mixture was evacuated and backfilled with nitrogen three times. $Pd_2(dba)_3$ (0.025 mmol), Xantphos (0.05 mmol) and 2'-Mercaptoacetophenone (1.1 mmol) were added and the mixture was degassed twice more. The mixture was heated to reflux overnight. Then the reaction mixture was allowed to cool to room temperature and filtered through a short plug of Celit and washed with 10 mL of ether. The filtrate was concentrated and purified by chromatography (silica gel) to afford the desired thiol ether.

1-(2-(Naphthalen-2-ylthio)phenyl)ethanone



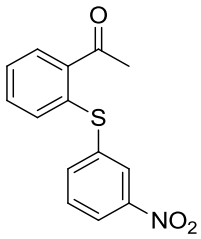
Prepared according to the general procedure from 2-bromonaphthalene (311 mg, 1.5 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a white solid 360 mg (85% yield). Mp 86-88 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.86-7.81 (m, 4H), 7.54-7.49 (m, 3H), 7.21-7.14 (m, 2H), 6.91 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 142.3, 135.0, 134.7, 134.2, 133.4, 132.4, 131.8, 130.9, 130.7, 129.6, 128.6, 128.1, 128.0, 127.3, 126.9, 124.7, 28.4; IR (neat, cm^{-1}): 3054 (w), 1662 (vs), 1586 (m), 1426 (s), 1270 (m), 1246 (vs), 1048 (s), 811 (s), 765 (vs); HRMS (EI) Calcd for $C_{18}H_{15}OS$ ($M+H^+$): 279.0844, found 279.0844.

1-(2-(Phenanthren-9-ylthio)phenyl)ethanone



Prepared according to the general procedure from 9-bromophenanthrene (226 mg, 0.88 mmol), purified by chromatography (silica gel, 5:1 hexanes: EtOAc) to afford the desired compound as a white solid 257 mg (89% yield). Mp 158-160 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (t, J = 8.0 Hz, 2H), 8.34 (dd, *J* = 0.8 Hz, 7.6 Hz, 1H), 8.28 (s, 1H), 7.91 (dt, *J* = 1.6 Hz, 8.4 Hz, 2H), 7.74 (dt, *J* = 1.2 Hz, 8.4 Hz, 1H), 7.71-7.63 (m, 2H), 7.55 (dt, *J* = 1.2 Hz, 7.6 Hz, 1H), 7.12 (dt, *J* = 1.2 Hz, 6.8 Hz, 1H), 7.05 (dt, *J* = 1.6 Hz, 7.2 Hz, 1H), 6.68 (dd, *J* = 1.2 Hz, 8.0 Hz, 1H), 2.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 142.6, 137.6, 133.6, 132.5, 132.3, 131.9, 131.6, 131.4, 129.1, 128.7, 128.2, 127.9, 127.6, 127.4, 127.3, 127.2, 124.2, 123.3, 122.9, 28.3; IR (neat, cm^{-1}): 3053 (w), 1668 (vs), 1583 (m), 1428 (s), 1242 (vs), 1140 (m), 772 (vs). HRMS (EI) Calcd for $C_{22}H_{17}OS$ ($M+H^+$): 329.1000, found 329.1000.

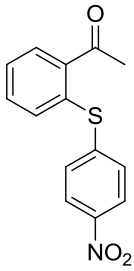
1-(2-((3-Nitrophenyl)thio)phenyl)ethanone



Prepared according to the general procedure from 1-iodo-3-nitrobenzene (374 mg, 1.5 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a yellow solide 315 mg (79% yield). Mp 78-80 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (t, *J* = 1.6 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.27 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H), 6.92

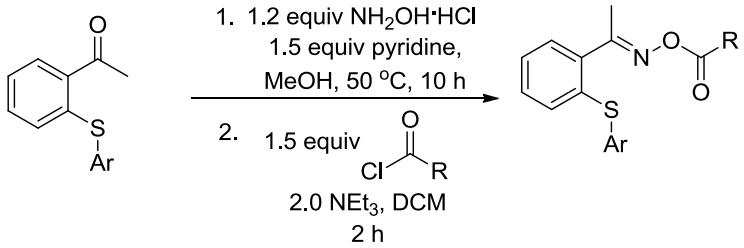
(d, *J* = 8.0 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 149.1, 140.2, 139.2, 137.1, 136.1, 132.7, 130.9, 130.6, 129.3, 128.9, 125.9, 123.6, 28.5; IR (neat, cm^{-1}): 3055 (w), 1663 (s), 1519 (vs), 1434 (m), 1345 (vs), 1252 (s), 1046 (m), 752 (s). HRMS (EI) Calcd for $C_{14}H_{13}O_3NS$ ($M+H^+$): 274.0538, found 274.0529.

1-(2-((2-Nitrophenyl)thio)phenyl)ethanone



Prepared according to the general procedure from 1-iodo-4-nitrobenzene (247 mg, 0.99 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a yellow solid 235 mg (87% yield). Mp 88-90 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.16 (m, 2H), 7.80 (dd, *J* = 2.4 Hz, 6.8 Hz, 1H), 7.51-7.48 (m, 2H), 7.41-7.34 (m, 2H), 7.17 (dd, *J* = 2.4 Hz, 6.8 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 146.9, 144.8, 132.2, 132.06, 132.04, 131.5, 130.1, 127.0, 124.4, 110.0, 28.8; IR (neat, cm^{-1}): 3080 (w), 1666 (vs), 1524 (vs), 1459 (m), 1362 (vs), 1249 (vs), 961 (s), 766 (vs). HRMS (EI) Calcd for $C_{14}H_{11}O_3NNaS$ ($M+Na^+$): 296.0357, found 296.0352.

***O*-Acetyl oxime thioethers were generated by the following general procedure.**

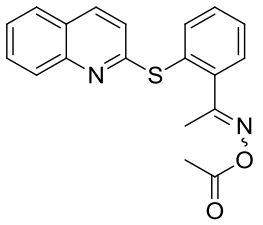


Thiol ether obtained before (1.0 mmol), hydroxyamine hydrochloride (1.2 mmol) and pyridine (1.5 mmol) were dissloved in 10 mL methanol and stirred at 50 ^{o}C for 10 hours. Solvent was

removed and the residue was diluted by 20 mL ether. After washing with 10 mL of saturated NH_4Cl, 10 mL brine, and drying over $MgSO_4$, the solvent was evaporated to give the oxime.

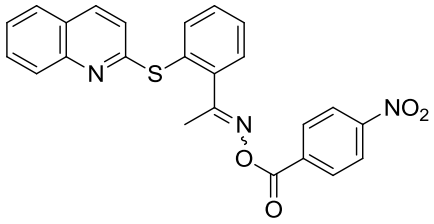
Oxime from the first step and acetyl chloride, 4-nitrobenzoyl chloride or 2,3,4,5,6-pentafluorobenzoyl chloride (1.5 mmol) was dissolved in 8 mL dichloromethane. Triethylamine (2.0 mmol) was added to the solution dropwide at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was washed with 10 mL saturated $NaHCO_3$ solution, 10 mL saturated NH_4Cl solution and 10 mL brine solution sequentially. After drying over $MgSO_4$, the solvent was evaporated and purified by chromatography (silica gel) to afford the desired compound.

1-(2-(Quinolin-2-ylthio)phenyl)ethanone *O*-acetyl oxime 15a



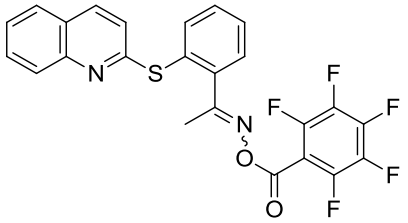
Prepared according to the general procedure from 1-(2-(quinolin-2-ylthio)phenyl)ethanone (0.37 g, 1.32 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as light yellow sticky oil 0.39 g (90% yield, 4:1 mixture of oxime isomers). Major Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.92-7.84 (m, 2H), 7.72-7.63 (m, 3H), 7.52-7.43 (m, 4H), 6.98 (d, J = 8.8 Hz, 1H), 2.34 (s, 3H), 2.10 (s, 3H); Characteristic signals for minor isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 164.5, 160.3, 147.7, 141.0, 137.0, 136.6, 130.3, 129.9, 129.8, 129.7, 128.9, 128.0, 127.5, 125.8, 119.57, 119.53, 19.5, 18.3; IR (neat, cm^{-1}): 3057, 2926, 1768, 1590; HRMS (EI) Calcd for $C_{19}H_{17}O_2N_2S$ ($M+H^+$): 337.1005, found 337.1001.

1-(2-(Quinolin-2-ylthio)phenyl)ethanone *O*-(4-nitrobenzoyl) oxime 15b



Prepared according to the general procedure from 1-(2-(quinolin-2-ylthio)phenyl)ethanone (0.14 g, 2.0 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a yellow oil 0.40 g (89% yield, 6:1 mixture of oxime isomers). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.94-7.87 (m, 2H), 7.79-7.75 (m, 1H), 7.72-7.69 (m, 1H), 7.66-7.54 (4H), 7.46-7.41 (m, 1H), 7.03-7.01 (d, *J* = 8.4 Hz, 1H), 2.51 (s, 3H); Characteristic signals for minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.1, 161.8, 161.6, 160.5, 150.8, 148.2, 141.0, 137.9, 137.6, 137.0, 136.6, 134.7, 131.0, 130.9, 130.6, 130.3, 130.1, 129.8, 129.5, 128.6, 128.5, 127.9, 127.7, 126.9, 126.2, 126.1, 123.9, 123.6, 120.3, 120.0, 22.6, 19.1. IR (neat, cm^{-1}): 1747, 1607, 1586, 1522. HRMS (FAB) Calcd for $C_{24}H_{18}N_3O_4S$ ($M+H^+$): 444.1013, found 444.1011.

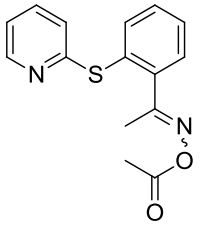
1-(2-(Quinolin-2-ylthio)phenyl)ethanone *O*-perfluorobenzoyl oxime 15c



Prepared according to the general procedure from 1-(2-(quinolin-2-ylthio)phenyl)ethanone (0.28 g, 1.0 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a yellow oil 0.44 g (91% yield, 3:1 mixture of oxime isomers). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.2 Hz, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.74-7.71 (m, 1H), 7.70-7.68 (d, *J* = 8.8 Hz, 1H), 7.64-7.62 (m, 1H), 7.56-7.49 (m, 3H), 7.42 (t, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 2.40 (s, 3H); Characteristic signals for minor isomer: ^{1}H NMR

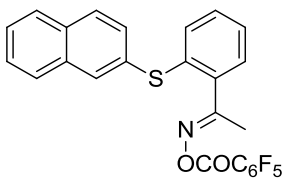
(400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 166.6, 160.3, 159.4, 148.2, 148.1, 140.5, 137.9, 137.6, 137.0, 136.5, 131.1, 130.3, 130.2, 130.1, 130.0, 129.9, 129.6, 128.5, 128.4, 127.9, 127.7, 127.0, 126.3, 126.2, 120.0, 119.9, 22.6, 19.2. Major Isomer: ^{19}F NMR (376 MHz, $CDCl_3$) δ -146.9, -157.8, -170.1; Characteristic signals for minor Isomer: ^{19}F NMR (376 MHz, $CDCl_3$) δ -147.2, -157.9, -170.3; IR (neat, cm^{-1}): 1759, 1651, 1587, 1494; HRMS (FAB) Calcd for $C_{24}H_{14}F_5N_2O_2S$ ($M+H^+$): 489.0691, found 489.0686.

1-(2-(Pyridin-2-ylthio)phenyl)ethanone *O*-acetyl oxime 15d



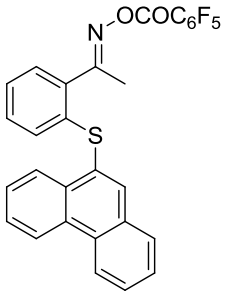
Prepared according to the general procedure from 1-(2-(pyridin-2-ylthio)phenyl)ethanone (1.08 g, 4.7 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired compound as a light yellow sticky oil 1.25 g (93% yield, 3:1 mixture of oxime isomers). Major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (m, 1H), 7.65-7.62 (m, 1H), 7.48-7.43 (m, 4H), 7.28-6.90 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 2.32 (s, 3H), 2.15 (s, 3H); Characteristic signals for minor isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.5, 164.9, 163.7, 160.5, 160.1, 149.9, 149.7, 141.1, 140.4, 137.1, 137.0, 136.9, 136.8, 130.7, 130.1, 129.8, 129.7, 129.6, 127.7, 127.4, 122.1, 122.0, 120.6, 120.5, 22.4, 19.9, 19.6, 18.5; IR (neat, cm^{-1}): 3049, 1764, 1573, 1559; HRMS (FAB) Calcd for $C_{15}H_{15}N_2O_2S$ ($M+H^+$): 287.0849, found 287.0849.

(*E*)-1-(2-(Naphthalen-2-ylthio)phenyl)ethanone *O*-perfluorobenzoyl oxime 23b



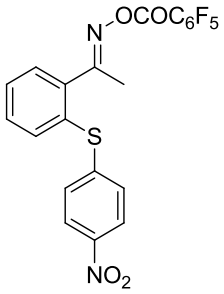
Prepared according to the general procedure from 1-(2-(naphthalen-2-ylthio)phenyl)ethanone (0.19 g, 0.68 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired *E* isomer as a white solid 0.29 g (87% yield). Mp 118-120 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.81-7.80 (m, 1H), 7.77 (d, *J* = 9.6 Hz, 1H), 7.75-7.74 (m, 1H), 7.49-7.44 (m, 3H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.33-7.31 (m, 3H), 2.48 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 156.6, 136.7, 135.5, 133.9, 132.9, 132.6, 132.5, 130.75, 130.72, 129.7, 129.4, 128.9, 127.9, 127.7, 127.5, 126.9, 126.7, 18.7; IR (neat, cm^{-1}): 1769 (vs), 1648 (w), 1491 (vs), 1324 (s), 1184 (vs), 899 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -4.25 (m, 2F), -15.11 (m, 1F), -27.45 (m, 2F); HRMS (EI) Calcd for $C_{25}H_{14}O_2NF_5NaS$ ($M+Na^+$): 510.0563, found 510.0558.

(*E*)-1-(2-(Phenanthren-9-ylthio)phenyl)ethanone *O*-perfluorobenzoyl oxime



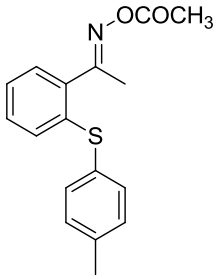
Prepared according to the general procedure from 1-(2-(phenanthren-9-ylthio)phenyl)ethanone (0.24 g, 0.74 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired *E* isomer as a white solid 0.28 g (70% yield). Mp 133 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 8.4 Hz, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.02 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.72-7.67 (m, 2H), 7.63-7.58 (m, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.22 (dt, *J* = 1.2 Hz, 7.6 Hz, 1H), 7.14 (dt, *J* = 1.2 Hz, 7.6 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 136.4, 134.9, 134.8, 131.8, 131.6, 131.3, 130.9, 130.6, 130.3, 129.6, 129.3, 128.8, 127.9, 127.6, 127.5, 127.3, 126.6, 126.5, 123.3, 122.9, 18.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -4.14 (m, 2F), -15.08 (m, 1F), -27.40 (m, 2F); IR (neat, cm^{-1}): 3075 (w), 1757 (vs), 1651 (m), 1495 (vs), 1424 (s), 1324 (vs), 1194 (vs), 999 (m). HRMS (EI) Calcd for $C_{29}H_{16}O_2NF_5NaS$ ($M+Na^+$): 560.0720, found 560.0714.

(*E*)-1-(2-((4-Nitrophenyl)thio)phenyl)ethanone *O*-perfluorobenzoyl oxime



Prepared according to the general procedure from 1-(2-((4-nitrophenyl)thio)phenyl)ethanone (0.13 g, 0.47 mmol), purified by chromatography (silica gel 3:1 hexanes: EtOAc) to afford the desired *E* isomer as an orange stickey oil 0.18 g (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 1.2 Hz, 8.0 Hz, 1H), 8.21-8.17 (m, 2H), 7.99-7.96 (m, 3H), 7.89 (dt, *J* = 1.2 Hz, 8.0 Hz, 1H), 7.66 (dt, *J* = 1.2 Hz, 8.0 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 153.9, 149.0, 147.7, 134.7, 134.1, 131.3, 131.1, 127.8, 125.3, 124.2, 27.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -4.53 (m, 2F), -14.53 (m, 1F), -27.19 (m, 2F); IR (neat, cm^{-1}): 1762 (vs), 1671 (m), 1587 (s), 1478 (s), 1394 (s), 1276 (m), 990 (s); HRMS (EI) Calcd for $C_{21}H_{12}O_4N_2F_5S$ ($M+H^+$): 483.0438, found 483.0433.

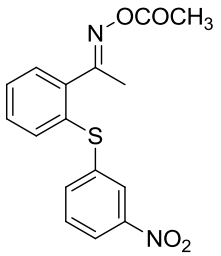
1-(2-(*p*-Tolylthio)phenyl)ethanone *O*-acetyl oxime



Prepared according to general procedure from 1-(2-(p-tolylthio)phenyl)ethanone (0.14 g, 0.59 mmol), purified by chromatography (silica gel 4:1 hexanes: EtOAc) to afford the desired *E* isomer as a stickey oil 0.15 g (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.33 (m, 1H), 7.28-7.21 (m, 4H), 7.17-7.13 (m, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 164.5, 138.1, 136.8, 136.5, 132.6, 131.6, 131.3, 130.4, 130.2, 129.4, 126.8,

21.4, 20.1, 18.2; IR (neat, cm^{-1}): 3020 (w), 2361 (w), 1766 (vs), 1491 (m), 1364 (s), 1194 (vs), 922 (s). HRMS (EI) Calcd for $C_{17}H_{18}O_2NS$ ($M+H^+$): 300.1058, found 300.1048.

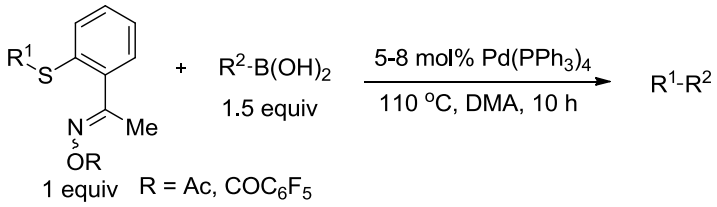
***N*-(1-(2-((3-Nitrophenyl)thio)phenyl)ethylidene)acetamide**



Prepared according to general procedure from 1-(2-((3-nitrophenyl)thio)phenyl)ethanone (0.17 g, 0.64 mmol), purified by chromatography (silica gel, 4:1 hexanes: EtOAc) to afford the desired *E* isomer as a stickey yellow oil 0.17 g (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (t, *J* = 2.0 Hz, 1H), 8.04-8.02 (m, 1H), 7.49 (td, *J* = 1.2 Hz, 8.0 Hz, 1H), 7.46-7.39 (m, 5H), 2.36 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8, 164.0, 148.8, 139.7, 139.6, 135.4, 134.8, 131.7, 130.9, 130.2, 129.3, 124.2, 121.7, 19.9, 18.3; IR (neat, cm^{-1}): 3067 (w), 1766 (vs), 1523 (vs), 1429 (m), 1345 (vs), 1195 (vs), 924 (s). HRMS (EI) Calcd for $C_{16}H_{14}O_3N_2KS$ ($M+K^+$): 353.0362, found 353.0357.

Biaryl compounds were generated by the following procedures.

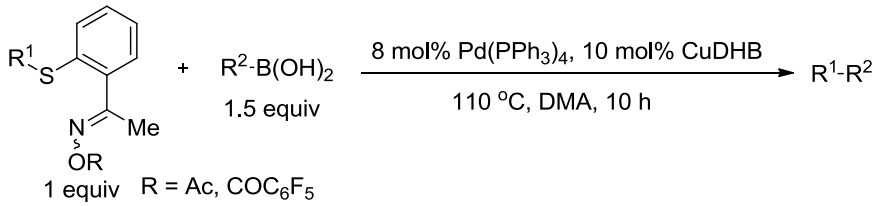
Method C:



Thiol ethers (0.07 mmol), boronic acid (0.105 mmol), and $Pd_2(dba)_3$ (0.0035 or 0.0056 mmol) were placed in a microwave tube and sealed. The tube was vaccumed and filled with argon three times. Degassed DMA (1 mL) was added via syring under argon, the reaction mixture was stirred at 110 ^{o}C for 10 hours. The reaction was quenched by adding 5 mL saturated NH_4Cl and extracted twice with 5 mL diethyl ether. The combined organic solvent was back-washed with

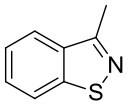
brine, dried over $MgSO_4$ and concentrated. The residue was puridied by chromatography (silica gel) to afford the desired compounds.

Method D:



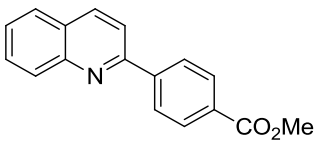
Thiol ethers (0.07 mmol), boronic acid (0.105 mmol), ((2,6-dihydroxybenzoyl)oxy) copper (CuDHB, 0.007 mmol) and $Pd_2(dba)_3$ (0.0056 mmol) were placed in a microwave tube and sealed. The tube was vaccumed and filled with argon three times. Degassed DMA (1 mL) was added via syring under argon, the reaction mixture was stirred at 110 ^oC for 10 hours. The reaction was quenched by adding 5 mL saturated NH_4Cl and extracted twice with 5 mL diethyl ether twice. The combained organic solvent was back washed with brine, dried over $MgSO_4$ and concentrated. The residue was puridied by chromatography (silica gel) to afford the desired compound.

3-Methylbenzo[*d*]isothiazole[37]



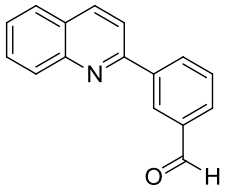
The residue was purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to yield the compound as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93-7.89 (m, 2H), 7.52-7.48 (m, 1H), 7.43-7.39 (m, 1H), 2.74 (s, 3H); IR (neat, cm^{-1}): 3065 (w), 1733 (vs), 1633 (s).

Methyl 4-(quinolin-2-yl)benzoate 18a[38]



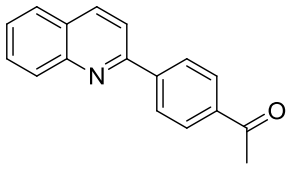
Prepared according to **Method C** from **15a** (33 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as a yellow solid 21 mg (80% yield). Mp 146-148°C [Lit.[38] 151-153 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.18 (m, 4H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.78-7.74 (m, 1H), 7.58-7.54 (m, 1H), 3.96 (s, 3H); IR (neat, cm^{-1}): 2946 (w), 1722 (vs), 1598 (s).

3-(Quinolin-2-yl)benzaldehyde 18b



Prepared according to **Method C** from **15a** (33 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as a light yellow oil 14 mg (58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.69 (t, *J* = 1.6 Hz, 1H), 8.49 (dt, *J* = 1.6 Hz, 7.6 Hz, 1H), 8.29 (d, *J* = 8.8 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.79-7.70 (m, 2H), 7.57 (dt, *J* = 1.6 Hz, 7.6Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 155.9, 148.5, 140.8, 137.4, 137.2, 133.6, 130.4, 130.2, 130.0, 129.8, 129.2, 127.8, 127.6, 127.0, 118.9; IR (neat, cm^{-1}): 3057 (w), 1695 (vs), 1596 (s), 1584 (m). HRMS (FAB) Calcd for $C_{16}H_{12}NO$ ($M+H^+$): 234.0913, found 234.0913.

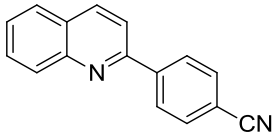
1-(4-(Quinolin-2-yl)phenyl)ethanone 18c



Prepared according to **Method C from 15a** (33 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes:EtOAc) to afford the desired compound as a light yellow solid 16 mg (63% yield). Mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 2H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* =

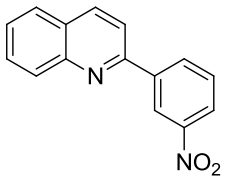
8.0 Hz, 1H), 7.76 (dd, *J* = 8.4 Hz, 6.8 Hz, 1H), 7.57 (dd, *J* = 8.0 Hz, 6.8 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 156.1, 148.5, 144.1, 137.6, 137.3, 130.2, 130.1, 129.1, 127.9, 127.7, 127.6, 127.1, 119.2, 27.1; IR (neat, cm^{-1}): 3004 (w), 1668 (vs), 1617 (s), 1598 (m); HRMS (FAB) Calcd for $C_{17}H_{14}NO$ ($M+H^+$): 248.1070, found 248.1069.

4-(Quinolin-2-yl)benzonitrile 18d



Prepared according to **Method C** from **15a** (33 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as a light yellow solid 14 mg (60% yield). Mp 114-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31-8.28 (m, 3H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.90-7.86 (m, 2H), 7.83-7.80 (m, 2H), 7.80-7.75 (m, 1H), 7.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 148.5, 143.9, 137.5, 132.8, 130.4, 130.1, 128.3, 127.7, 127.4, 119.1, 118.8, 112.9; IR (neat, cm^{-1}): 3043 (w), 2222 (m), 1597 (s), 1496 (m). HRMS (FAB) Calcd for $C_{16}H_{11}N_2$ ($M+H^+$): 231.0917, found 231.0916.

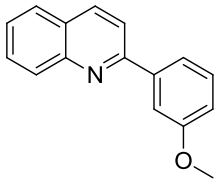
2-(3-Nitrophenyl)quinoline 18e



Prepared according **Method C** from **15a** (33 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as a light yellow solid 11 mg (42% yield). Mp 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (m, 1H), 8.56 (dt, *J* = 7.6 Hz, 1.2 Hz, 1H), 8.33-8.32 (m, 1H), 8.31-8.30 (m, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.80-7.76 (m, 1H), 7.72-7.69 (t, *J* = 8.0 Hz, 1H), 7.61-7.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 148.4, 141.5, 137.6, 133.5, 130.4, 130.1, 130.0, 129.2,

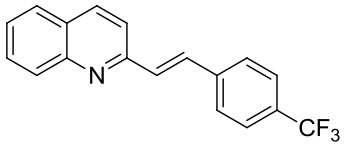
128.6, 127.7, 127.3, 124.1, 122.7, 118.6; IR (neat, cm^{-1}): 3079 (w), 1596 (s), 1520 (m), 1507 (s); HRMS (FAB) Calcd for $C_{15}H_{11}N_2O_2$ ($M+H^+$): 251.0815, found 251.0814.

2-(3-Methoxyphenyl)quinoline 18f[39]



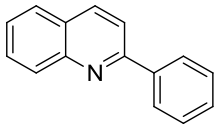
Prepared according to **Method C** from **15a** (33 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as a light yellow solid 17 mg (73% yield). Mp 106-108 °C [Lit.[39] 110 °C]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.77-7.69 (m, 3H), 7.55-7.51 (m, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.03-7.01 (m, 1H), 3.94 (s, 3H); IR (neat, cm^{-1}): 3061 (w), 2957 (w), 1598 (s), 1556 (m).

(*E*)-2-(4-(Trifluoromethyl)styryl)quinoline 18g



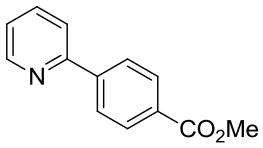
Prepared according to **Method C** from **15a** (33 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as a light yellow oil 14 mg (48% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.8 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.11-8.06 (m, 1H), 8.07-7.98 (m, 2H), 7.91-7.85 (m, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.42-7.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 135.0, 132.9, 131.5, 130.7, 130.5, 130.2, 129.5, 129.2, 128.6, 127.8, 127.7, 127.5, 126.7, 125.9, 125.6, 122.9, 119.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2; IR (neat, cm^{-1}): 3054 (w), 2927 (w), 1650 (s), 1324 (m); HRMS (FAB) Calcd for $C_{18}H_{13}F_3N$ ($M+H^+$): 300.0995, found 300.0994.

2-Phenylquinoline 18h[40]



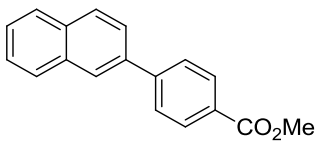
Prepared according to **Method C** from **15a** (33 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as a light yellow solid 13 mg (58% yield). Mp 83-85 °C [Lit.[40] 82-84 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 1H), 8.19-8.16 (m, 3H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.74 (dt, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.56-7.52 (m, 3H), 7.49-7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 148.3, 139.7, 136.6, 129.6, 129.5, 129.3, 128.8, 127.5, 127.3, 127.0, 126.1, 118.9; IR (neat, cm^{-1}): 3033 (w), 1616 (s), 1596 (m), 1553 (s), 1507 (m).

Methyl 4-(pyridin-2-yl)benzoate 18i[41]



Prepared according to **Method C** from **15d** (40 mg, 0.14 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as a light yellow solid 15 mg (52% yield). Mp 96-98 °C [Lit.[41] 99-100 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dt, *J* = 5.2 Hz, 1.2 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.80-7.78 (m, 2H), 7.31-7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 156.5, 150.4, 143.8, 137.5, 133.4, 130.4, 126.9, 123.3, 121.6, 52.3; IR (neat, cm^{-1}): 3070 (w), 1706 (vs), 1606 (s), 1586 (m).

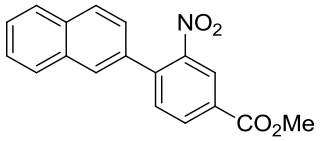
Methyl 4-(naphthalen-2-yl)benzoate[42]



Prepared according to **Method D** from (*E*)-1-(2-(naphthalen-2-ylthio)phenyl)ethanone *O*-perfluorobenzoyl oxime (38 mg, 0.08 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as white solid 18 mg (89% yield). Mp 138-140

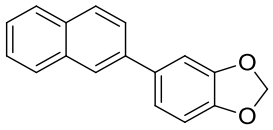
^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 2H), 8.09 (s, 1H), 7.95-7.87 (m, 3H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.54-7.50 (m, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 145.8, 137.5, 133.8, 133.2, 130.4, 129.1, 128.9, 128.6, 127.9, 127.5, 126.8, 126.7, 126.6, 125.5, 52.4; IR (neat, cm^{-1}): 2946 (w), 1709 (vs), 1594 (m), 1435 (m), 1260 (vs), 1109 (vs), 955 (s), 847 (vs).

Methyl 4-(naphthalen-2-yl)-3-nitrobenzoate



Prepared according to **Method D** from (*E*)-1-(2-(naphthalen-2-ylthio)phenyl)ethanone O-perfluorobenzoyl oxime (32 mg, 0.07 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as yellow sticky oil 18 mg (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 1.6 Hz, 1H), 8.30 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.92-7.84 (m, 4H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.57-7.53 (m, 2H), 7.40 (dd, *J* = 1.6 Hz, 8.4 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 149.5, 140.7, 134.1, 133.4, 133.3, 133.2, 132.8, 130.6, 128.9, 128.5, 128.1, 127.4, 127.2, 127.0, 125.7, 125.5, 53.1; IR (neat, cm^{-1}): 2953 (w), 1712 (vs), 1617 (m), 1527 (vs), 1436 (s), 1351 (s), 1286 (s), 1127 (m). HRMS (EI) Calcd for $C_{16}H_{13}O_2N_2$ ($M+Na^+$): 330.0742, found 330.0737.

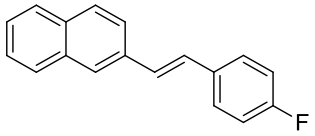
5-(Naphthalen-2-yl)benzo[d][1,3]dioxole[43]



Prepared according to **Method D** from (*E*)-1-(2-(naphthalen-2-ylthio)phenyl)ethanone *O*-perfluorobenzoyl oxime (49 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as white solid 16 mg (yield 61%). Mp 82-84 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.6 Hz, 1H), 7.90-7.84 (m, 3H), 7.67 (dd, *J* = 1.6 Hz, 8.4 Hz, 1H), 7.52-7.45 (m, 2H), 7.21-7.19 (m, 2H), 6.93 (dd, *J* = 0.8 Hz, 7.6 Hz, 1H), 6.03 (s, 2H); ^{13}C

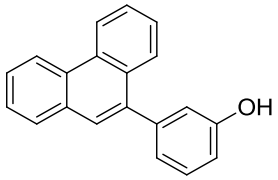
NMR (100 MHz, $CDCl_3$) δ 148.4, 147.3, 138.5, 135.7, 133.9, 132.6, 128.6, 128.3, 127.8, 126.5, 126.0, 125.7, 125.5, 121.2, 108.9, 108.1, 101.4; IR (neat, cm^{-1}): 2897 (w), 1492 (s), 1463 (vs), 1363 (m), 1235 (vs), 1101 (m), 1036 (vs), 800 (vs).

(*E*)-2-(4-Fluorostyryl)naphthalene[44]



Prepared according to **Method D** from (*E*)-1-(2-(naphthalen-2-ylthio)phenyl)ethanone *O*-perfluorobenzoyl oxime (49 mg, 0.1 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as white solid 20 mg (80% yield). Mp 146-148 ^oC [Lit.[44] 148-150 ^oC]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.81 (m, 4H), 7.73 (dd, *J* = 1.2 Hz, 8.4 Hz, 1H), 7.55-7.45 (m, 4H), 7.20 (s, 2H), 7.10-7.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 134.9, 133.9, 133.2, 131.8, 128.8, 128.6, 128.3, 128.2, 128.0, 127.9, 126.8, 126.6, 126.2, 123.6, 115.8; IR (neat, cm^{-1}): 3057 (w), 1594 (s), 1504 (vs), 1411 (m), 1231 (vs), 1156 (m), 964 (s).

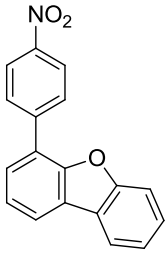
3-(Phenanthren-9-yl)phenol



Prepared according to **Method D** from (*E*)-1-(2-(phenanthren-9-ylthio)phenyl)ethanone *O*-perfluorobenzoyl oxime (48 mg, 0.09 mmol), purified by chromatography (silica gel, 9:1 hexanes: EtOAc) to afford the desired compound as a sticky oil 17 mg (68% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.27-7.18 (m, 3H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.60 (s, 1H), 6.52 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 4.65 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 142.7, 138.5, 131.7, 131.2, 130.8, 130.2, 129.8, 128.9, 127.6, 127.13, 127.11, 126.9, 126.8, 126.76, 126.72, 123.1, 122.9, 122.8, 117.2, 114.5; IR (neat, cm^{-1}):

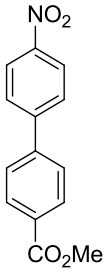
3323 (br), 1579 (s), 1488 (m), 1318 (m), 1186 (s), 724 (vs). HRMS (EI) Calcd for $C_{20}H_{15}O$ ($M+H^+$): 271.1123, found 271.1117.

4-(4-Nitrophenyl)dibenzo[b,d]furan[45]



Prepared according to **Method D** from (*E*)-1-(2-((4-nitrophenyl)thio)phenyl)ethanone *O*-perfluorobenzoyl oxime (61 mg, 0.13 mmol), purified by chromatography (silica gel, 9:1 hexanes: EtOAc) to afford the desired compound as white solid 22 mg (60% yield). Mp 176-178 ^oC [Lit.[45] 174-176 ^oC]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.0 Hz, 2H), 8.02 (t, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 8.8 Hz, 2H), 7.53-7.46 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 153.4, 147.3, 143.2, 129.7, 127.9, 127.0, 125.6, 124.2, 124.0, 123.7, 123.6, 123.4, 121.6, 121.1, 112.1; IR (neat, cm^{-1}): 3081 (w), 1595 (s), 1503 (vs), 1392 (m), 1338 (vs), 1190 (vs), 841 (s).

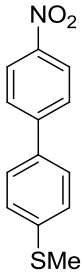
Methyl 4'-nitro-[1,1'-biphenyl]-4-carboxylate[46]



Prepared according to **Method D** from (*E*)-1-(2-((4-nitrophenyl)thio)phenyl)ethanone *O*-perfluorobenzoyl oxime (58 mg, 0.12 mmol), purified by chromatography (silica gel, 9:1 hexanes: EtOAc) to afford the desired compound as white solid 24 mg (78% yield). Mp 185-187 ^oC [Lit.[46] 188-189 ^oC]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

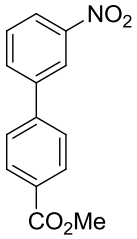
166.8, 147.8, 146.6, 143.2, 130.6, 130.4, 128.3, 127.6, 124.4, 52.5; IR (neat, cm^{-1}): 2956 (w), 1712 (vs), 1594 (s), 1510 (vs), 1426 (m), 1337 (vs), 1274 (vs), 1102 (s), 1013 (m).

Methyl(4'-nitro-[1,1'-biphenyl]-4-yl)sulfane[47]



Prepared according to **Method D** from (*E*)-1-(2-((4-nitrophenyl)thio)phenyl)ethanone *O*-perfluorobenzoyl oxime (41 mg, 0.08 mmol), purified by chromatography (silica gel 9:1 hexanes: EtOAc) to afford the desired compound as yellow solid 15 mg (74% yield). Mp 139-140 ^{o}C [Lit.[47] 138.5-139.5 ^{o}C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 9.2 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 147.1, 140.5, 135.3, 127.9, 127.5, 126.8, 124.4, 15.6; IR (neat, cm^{-1}): 2925 (w), 1592 (s), 1505 (vs), 1391 (m), 1339 (vs), 1098 (s), 813 (vs).

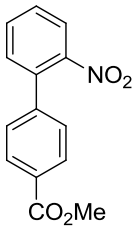
Methyl 4'-nitro-[1,1'-biphenyl]-4-carboxylate[48]



Prepared according to **Method D** from (*E*)-1-(2-((3-nitrophenyl)thio)phenyl)ethanone *O*-acetyl oxime (25 mg, 0.07 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as white solid 14 mg (50% yield). Mp 144-145 ^{o}C [Lit.[48] 144 ^{o}C]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (t, *J* = 1.8 Hz, 1H), 8.26-8.24 (m, 1H), 8.15 (d, 8.4 Hz, 2H), 7.96-7.94 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 148.9, 143.1, 141.9, 133.4, 130.6, 130.4, 130.2, 127.5, 123.1, 122.4, 52.5;

IR (neat, cm^{-1}): 2956 (w), 1714 (vs), 1608 (m), 1525 (s), 1431 (s), 1346 (s), 1279 (vs), 1106 (s), 1015 (m).

Methyl 2'-nitro-[1,1'-biphenyl]-4-carboxylate[49]



Prepared according to **Method D** from (*E*)-1-(2-(p-tolylthio)phenyl)ethanone *O*-acetyl oxime (35 mg, 0.16 mmol), purified by chromatography (silica gel, 19:1 hexanes: EtOAc) to afford the desired compound as white solid 19 mg (71% yield). Mp 80-83 ^{o}C [Lit.[49] 84-85 ^{o}C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 149.1, 142.4, 135.8, 132.8, 132.0, 130.2, 130.1, 129.1, 128.2, 124.6, 52.5; IR (neat, cm^{-1}): 2953 (w), 1711 (vs), 1604 (m), 1518 (vs), 1434 (s), 1279 (vs), 1177 (s), 1110 (vs), 740 (vs).

3.5 Reference

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