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Hao Li Date

Stereocontrolled Synthesis of Ketones bearing Stereogenic Centers by Desulfitative Cross-Coupling of Thiol Esters and Organostannanes

By
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Doctor of Philosophy

Chemistry

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Date

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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

Stereocontrolled Synthesis of Ketones bearing Stereogenic Centers by Desulfitative Cross-Coupling of Thiol Esters and Organostannanes

By Hao Li

An efficient synthesis of high enantiopurity *N*-protected α-amino ketones is described. Complementing other studies using boronic acids and thiol esters, this palladium-catalyzed, Cu(I) diphenylphosphinate-mediated coupling of α-amino thiol esters with aryl, heteroaryl, allyl and vinyl organostannanes gives *N*-protected α-amino ketones in high yields with high enantiopurity (in almost all cases) under mild and pH-neutral reaction conditions. Advantages of this new reaction compared to the related boronic acid system are the use of only 1.1 equiv of the organostannane reactant to complete the coupling reaction, and the viability of π–deficient heteroarylstannanes, which are superior to the corresponding boronic acids in overall coupling reactivity.

A stereocontrolled synthesis of α,α′-aminoalkoxy ketones is described. As a new approach to enantioenriched α-alkoxy ketones, this pH-neutral copper(I) thiophene-2-carboxylate-catalyzed cross-coupling of amino acid thiol esters and chiral α-(thiocarbamoyl)alkylstannanes gives α,α′-aminoalkoxy ketones in good to excellent yields with complete retention of configuration at the α-stannyl- and α-alkoxy-substituted stereocenters.

Thiol esters derived from 4-nitrothiophenol were coupled with chiral α-alkoxyalkylstannanes in the presence of stoichiometric Cu(I) thiophene-2-carboxylate to give α-sulfenylated ketones in moderate to good yields through a stereocontrolled O-S rearrangement. Compared with the α,α′-aminoalkoxy ketone synthesis using catalytic amounts of CuTC, this stoichiometric CuTC-mediated thiol ester–α-alkoxyalkylstannane cross-coupling/O-S rearrangement provided an efficient method for the construction of enantioenriched α-sulfenylated ketones. Using only CuTC in this alkylstannane coupling suggests a non-oxidative addition pathway.

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List of Abbreviations

app	apparent
Ar	aryl
Arg	arginine
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
ºC	degrees Celsius
calcd	calculated
cat.	catalytic
Cbz	benzyloxycarbonyl
COD	1,5-cyclooctadiene
CuDPP	copper (I) diphenylphosphinate
CuMeSal	copper(I) 3-methylsalicylate
CuTC	copper(I) thiophene-2-carboxylate
cm^{-1}	wavenumber unit
δ	chemical shift (in ppm for NMR)
d	doublet
dba	dibenzylideneacetone
DCC	1,3-dicyclohexylcarbodiimide
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether

DMF	dimethylformamide
DMAP	*N*,*N*-dimethylaminopyridine
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
Gln	glutamine
Glu	glutamic acid
Het	heteroaryl
His	histidine
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
hr	hour
HRMS	high-resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
LDA	lithium diisopropylamide
Leu	leucine

Lys	lysine
m	multiplet (for NMR)
m	medium (for IR)
M	molar
Me	methyl
MeCN	acetonitrile
Met	methionine
mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimole
mol	mole
mol %	mole percent
Mp	melting point
Ms	mesyl
N	normal
OAc	acetate
OTf	trifluoromethanesulfonate
Ph	phenyl
Phe	phenylalanine
p-NO_2	*para*-nitro
ppm	parts per million
Pro	proline
PTC	pyrrolidinylthionocarbamoyl
pyphos	6-diphenylphosphino-2-pyridonate
q	quartet

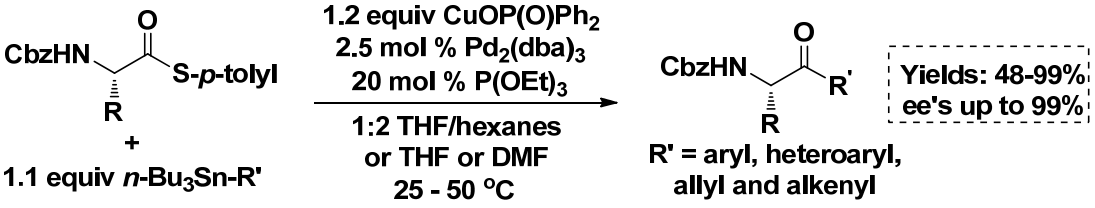
R_f	R_f value
s	singlet (for NMR)
s	strong (for IR)
Ser	serine
stoich.	stoichiometric
t	triplet
T	temperature
TBS	*t*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tolyl	toluene
t_R	retention time
Trp	tryptophan
Tyr	tyrosine
UV	ultraviolet
vs	very strong
w	weak
Z	benzyloxycarbonyl

Chapter 1

Synthesis of High Enantiopurity *N*-Protected α-Amino Ketones by Thiol Ester–Organostannane Cross-Coupling using pH-Neutral Conditions

Abstract：*An efficient synthesis of high enantiopurity N-protected α-amino ketones is described. Complementing other studies using boronic acids and thiol esters, this palladium-catalyzed, Cu(I) diphenylphosphinate (CuDPP)-mediated coupling of α-amino thiol esters with aryl, heteroaryl, allyl and vinyl organostannanes gives N-protected α-amino ketones in high yields with high enantiopurity (in almost all cases) under mild and pH-neutral reaction conditions. Advantages of this new reaction compared to the related boronic acid system are the use of only 1.1 equiv of the organostannane reactant to complete the coupling reaction, and the viability of π–deficient heteroarylstannanes, which are superior to the corresponding boronic acids in overall coupling reactivity* (**Scheme 1.1**).

Scheme 1.1 Peptidyl Ketones from Thiol Esters and Organostannanes



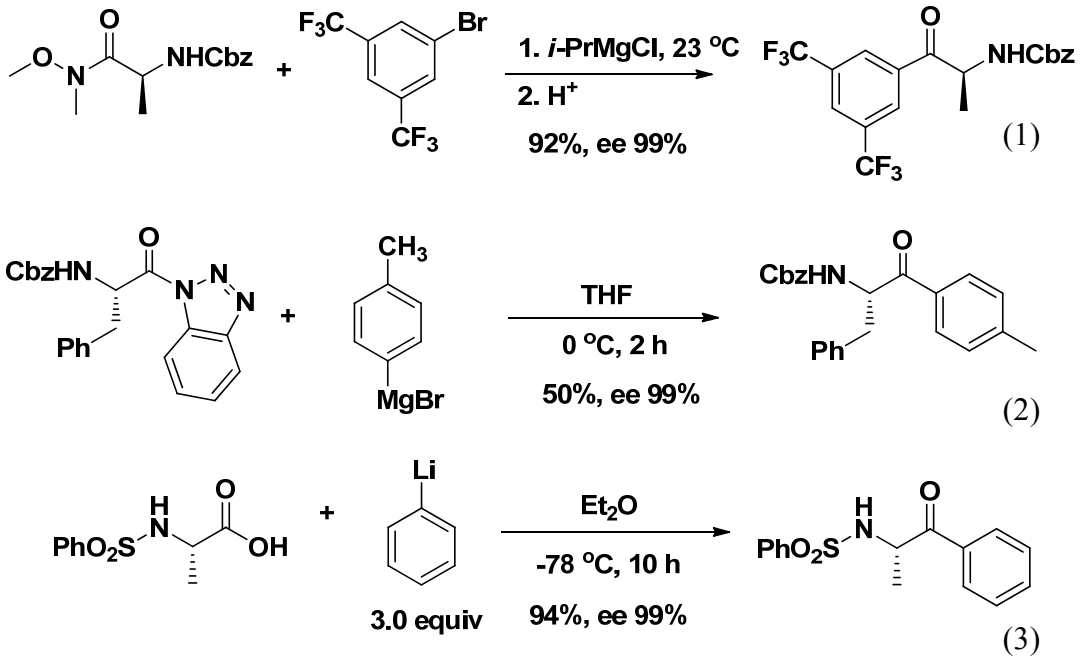
1.1 Introduction and Background

Peptidic ketones and their derived α-ketoheterocycles represent significant functionalities for the development of molecular therapeutics.[1] Potent enzyme inhibitors based on the peptidic α-ketoheterocycle motif have been found for a large number of enzymes.[1b]

Many different approaches for the synthesis of α-amino ketones and aldehydes are known, with recent studies focusing on the construction of enantiopure α-amino ketones starting from naturally occurring amino acids.[2] Most of the current methods for the synthesis of enantiopure α-amino ketones are based on Weinreb amides.

Conrad and co-workers found that *N*-Cbz-alanine-*N*-methoxy-*N*-methylamide could react with Grignard reagents to give enantiopure α-amino ketones (**Scheme 1.2**, **equation 1**).[21] Similarly, Katritzky and co-workers described an enantiocontrolled synthesis of α-amino ketones in moderate yields using *N*-acylbenzotriazoles derived from *N*-protected amino acids in which the enantioselectivity is questionable (**Scheme 1.2**, **equation 2**).[2k] Rapoport and co-workers published a direct α-amino ketone synthesis from *N*-benzenesulfonylalanine and phenyllithium. Although this method provided good yields and excellent enantioselectivities when *N*-benzenesulfonyl amino acids were used as the substrates, synthetically more useful *N*-carbamoyl amino acids led to complete racemization of the α-amino carbon (**Scheme 1.2**, **equation 3**).[3]

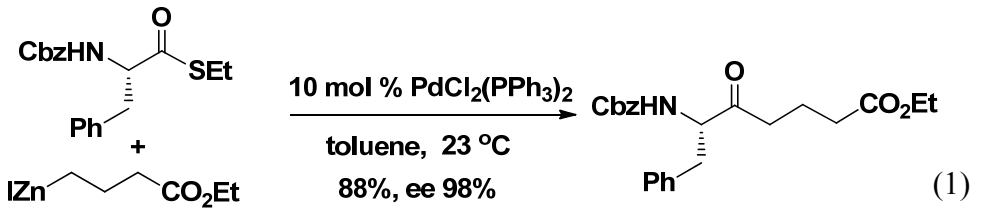
Scheme 1.2 Known Methods for the Synthesis of α-Amino Ketones



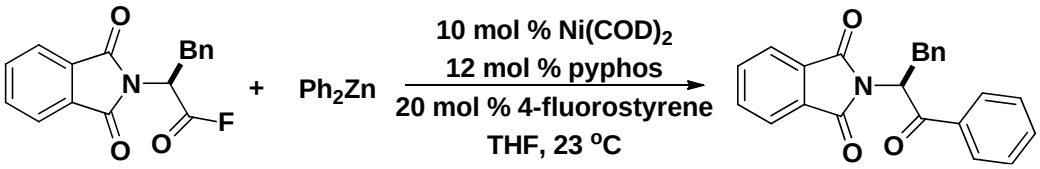
Notably, the use of organozinc reagents by Fukuyama/Tokuyama and Rovis provides improved functional group compatibility relative to basic and nucleophilic organomagnesium and organolithium reagents. Fukuyama and co-workers developed a palladium-catalyzed cross-coupling of *N*-protected amino acid thiol esters and

alkylzinc reagents to generate a few examples of α-amino ketones with high enantiopurity (**Scheme 1.3**, **equation 1**).[2c] Recently, Rovis published a nickel-catalyzed cross-coupling of *N*-protected amino acid fluorides and aryl- or alkylzinc reagents to produce the corresponding α-amino ketones without epimerization (**Scheme 1.3**, **equation 2**).[2p] However, none of the known reactions takes place under non-basic conditions, nor are they adequately functional group selective to be broadly general.

Scheme 1.3 Ketone Synthesis Using Organozinc Reagents



(1)



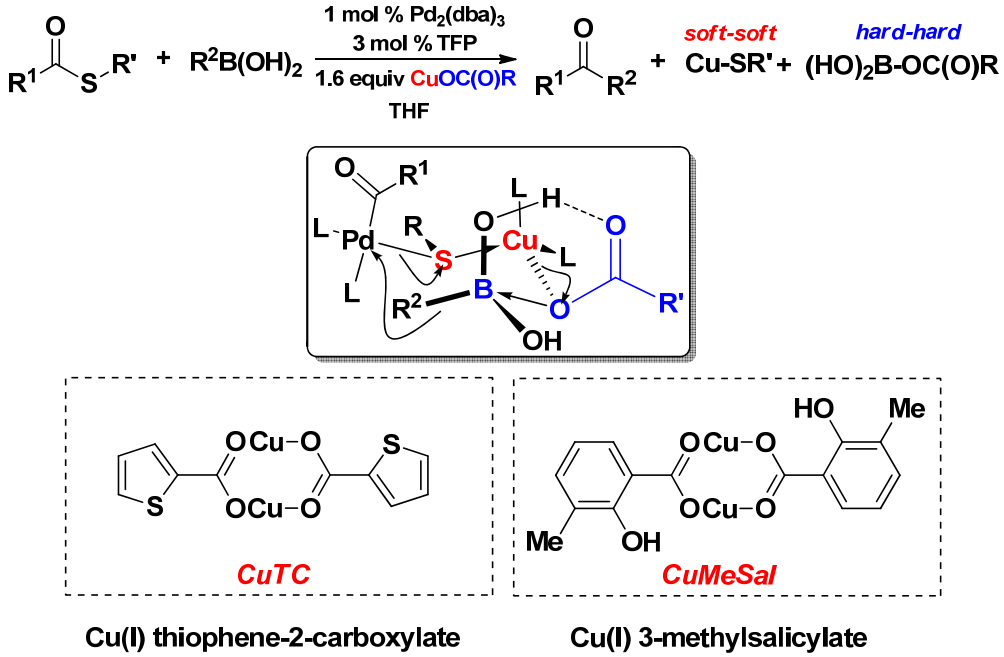
(2)

In contrast to the use of RLi, RMgX and RZnX-based protocols, the metal-catalyzed reaction of COOH-equivalent functionalities with boronic acids offers the potential for a fully general and functional group compatible approach to peptidic ketone synthesis. However, known constructions of ketones by the reaction of boronic acids with various acid equivalents such as anhydrides,[4] esters,[5] acid fluorides,[2p] and acid chlorides[6] are not suitable for use with functionally complex molecules because the carboxyl equivalent functional groups are either too reactive, or the reactions take place under conditions that are inappropriate for racemization sensitive substrates or products.

To address this issue, Liebeskind and Srogl discovered a mild, pH-neutral palladium-catalyzed copper(I)-mediated desulfitative cross-coupling of thiol esters and boronic acids (**Scheme 1.4**).[7] This reaction proceeds at ambient temperature

with broad substrate scope and improved functional group compatibility. The first step of the reaction is oxidative addition of Pd^0 into the C-S bond of the thiol ester. It was assumed that Cu^I was coordinated to sulfur to weaken the strong Pd-S bond, while the carboxylate counterion was coordinated to boron to activate the boronic acid toward transmetallation. After reductive elimination, the ketone products were formed accompanied by thermodynamically stable copper(I) thiolates and boronic esters.

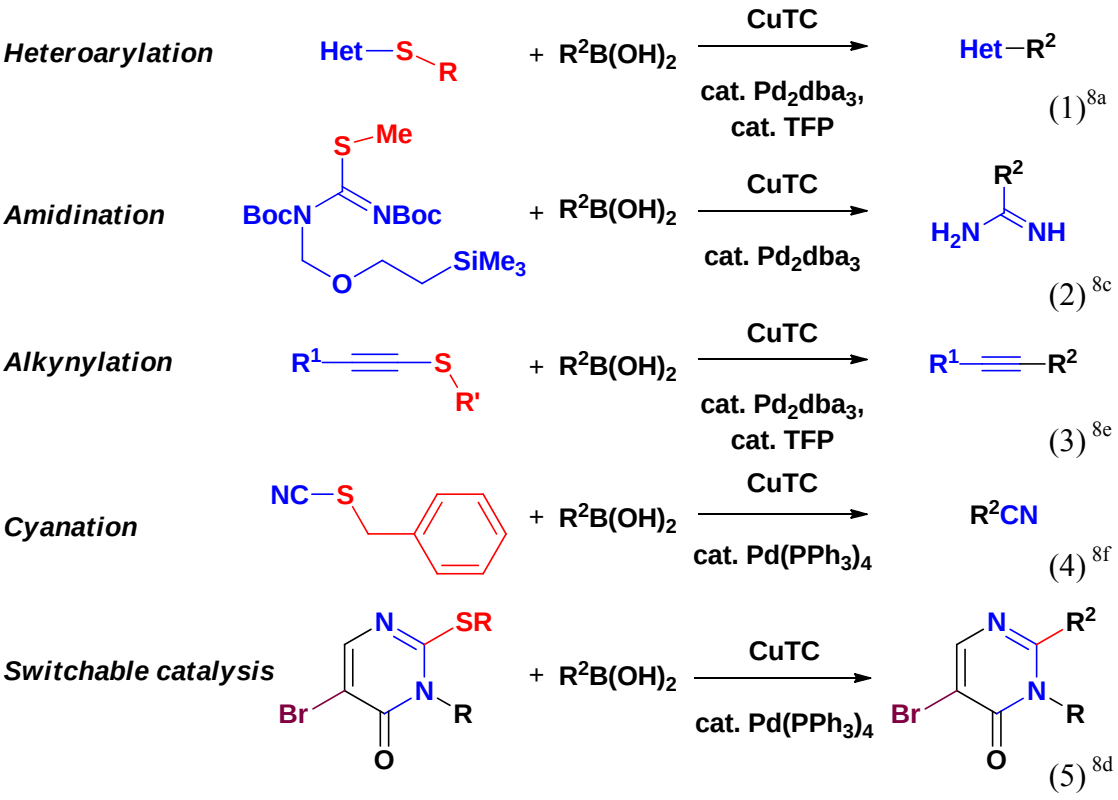
Scheme 1.4 Liebeskind-Srogl Cross-Coupling



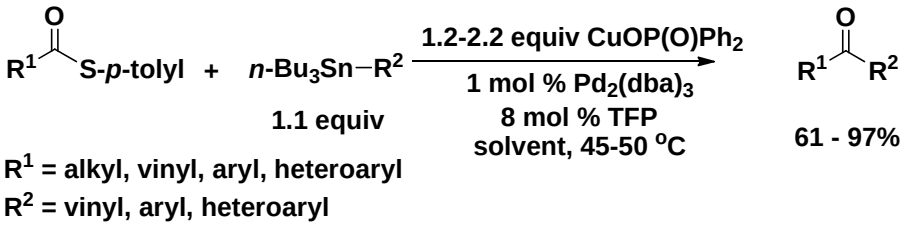
In addition to the construction of ketones from thiol esters and boronic acids, a full family of desulfitative cross-couplings has been developed by Liebeskind's laboratory in last decade (**Scheme 1.5**).[8] All these reactions take place selectively under mild, neutral conditions. Importantly, the switchable catalysis showed that the desulfitative coupling is orthogonal to traditional Suzuki reaction since C-S bond of the heterocyclic thioether is selectively cleaved to form a C-C bond with the presence of a C-Br bond (**Scheme 1.5**, **equation 5**).[8d] In addition to boronic acids, this general cross-coupling reaction has been extended to organostannanes (**Scheme 1.6**).[9]

sp^2-Hybridized vinyl, aryl and heteroaryl stannanes was coupled well with a variety of thiol esters to give functionalized ketones in good to excellent yields. The advantage of organostannanes over boronic acids is that only 1.1 equivalent of the organometallic reagents is required for an efficient coupling.

Scheme 1.5 A Family of Desulfitative Cross-Couplings

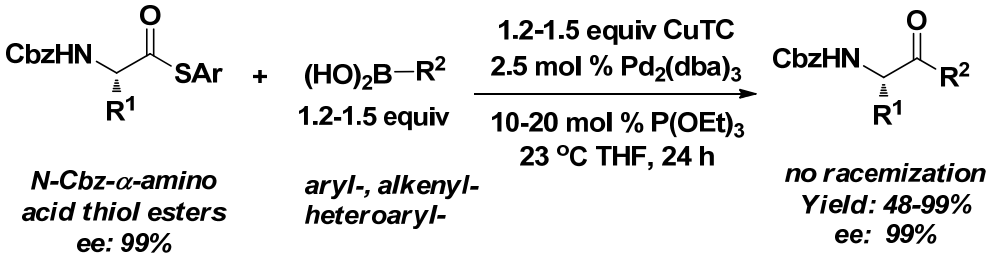


Scheme 1.6 Thiol Ester–Organostannane Cross-Coupling



The Liebeskind-Srogl cross-coupling was also probed for the coupling of base-sensitive peptidyl thiol esters with boronic acids (**Scheme 1.7**).[10] The reaction occurs at or near ambient temperature and has proven valuable for the synthesis of racemization-sensitive peptidyl ketones.

Scheme 1.7 *N*-Protected α-Amino Thiol Esters and Boronic Acids Coupling



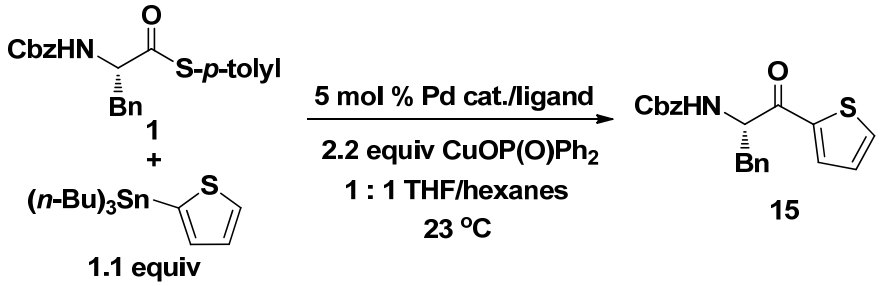
As a follow-up to the first study, a variant of that chemistry was undertaken in which organostannanes rather than boronic acids are the reaction partners (**Scheme 1.1**). Since α-amino ketone synthesis using thiol esters and organostannanes as reaction partners has not been previously disclosed, a study of the scope and limitations of this new α-amino ketone synthesis will be discussed in this chapter.

1.2 Results and Discussion

1.2.1 Preliminary Study

This new reaction was initially probed by exposure of the prototypical substrates L-*Z*-Phe-S-*p*-tolyl and 2-thienyl-tri-*n*-butylstannane to 2.2 equiv of the Cu(I) cofactor, copper(I) diphenylphosphinate (CuDPP), in the presence of various palladium catalysts and supporting ligands (**Table 1.1**). The use of CuDPP was dictated by earlier published studies comparing copper(I) thiophene-2-carboxylate (CuTC) with CuDPP in the desulfitative coupling of thiol esters with organostannanes.[9] A control experiment (**Table 1.1**, **entry 7**) showed that CuDPP is required for the cross-coupling. This brief study revealed that optimum yields of L-*Z*-Phe-2-thienyl were obtained using 2.5 mol % $Pd_2(dba)_3$ with 20 mol % of freshly distilled $P(OEt)_3$ as the supporting ligand. (**Table 1.1**, **entry 4**)

Table 1.1 Palladium Catalysts and Supporting Ligands Screening

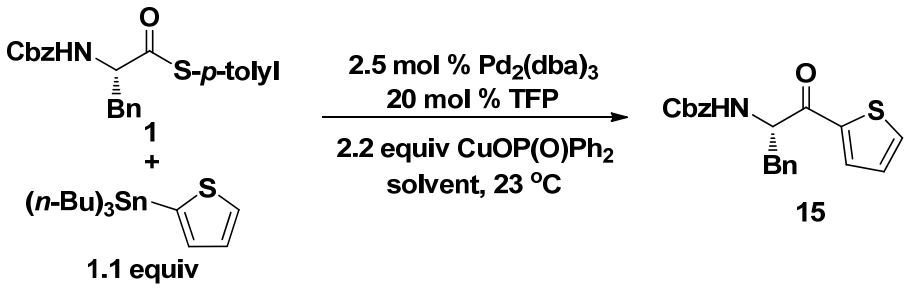


entry	Pd cat./ligand	yield[a] (%)
1	$Pd[P(t\text{-}Bu)_3]_2$	30
2	$PdCl(PPh_3)_2Bn$	55
3	1 : 8 $Pd_2(dba)_3$/TFP	82
4	1 : 8 $Pd_2(dba)_3$/$P(OEt)_3$	98
5	20 mol% $P(OEt)_3$, no $Pd_2(dba)_3$	0
6	$Pd_2(dba)_3$, no $P(OEt)_3$	0
7	No CuDPP	0

[a] Isolated yield.

The reactions proceeded well using THF or a THF/hexanes mixture as the reaction solvent; 1 : 2 THF/hexanes provided the best yield of the desired ketone product (**Table 1.2**, **entry 3**). A THF/hexanes mixture was previously demonstrated to prevent undesired Cu-catalyzed side reactions like protiodestannylation and oxidative homocoupling by minimizing the effective concentration of copper(I) carboxylate in solution.[9]

Table 1.2 Solvent Effect



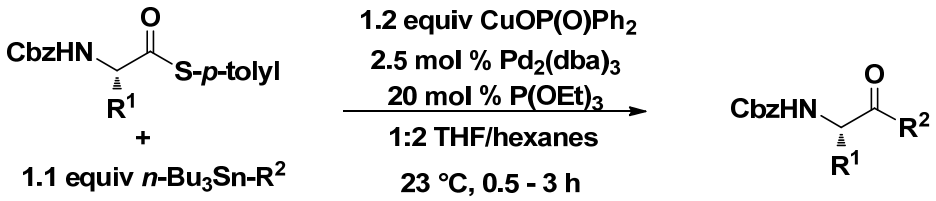
entry	solvent	yield[a] (%)
1	THF	72
2	1 : 1 THF/hexanes	79
3	1 : 2 THF/hexanes	82
4	1 : 3 THF/hexanes	75

[a] Isolated yield.

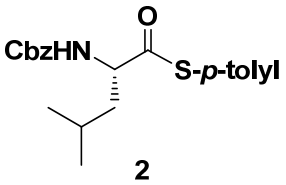
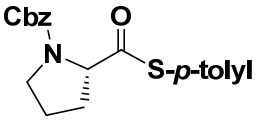
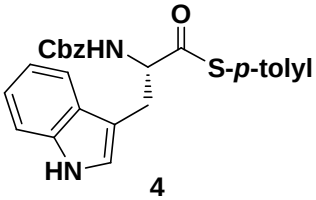
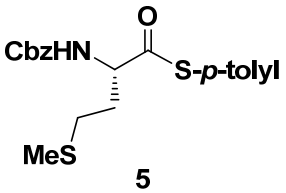
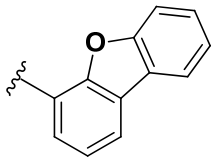
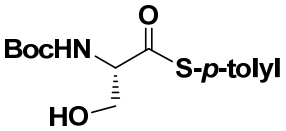
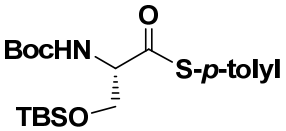
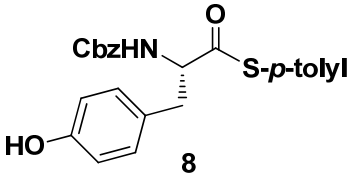
1.2.2 Scope and Limitations of Peptidic Thiol Ester–Organostannane Cross-Coupling

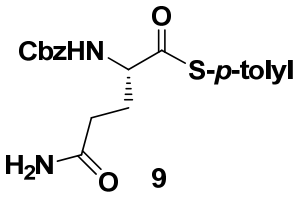
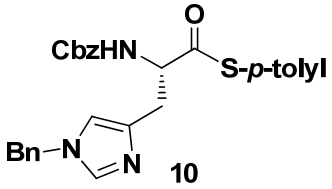
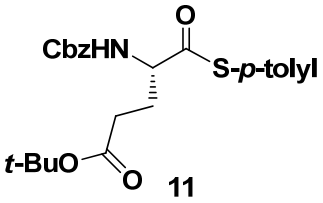
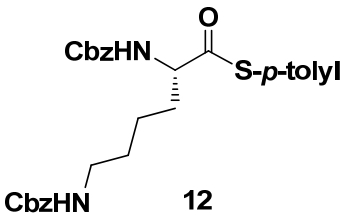
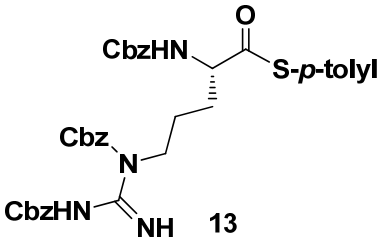
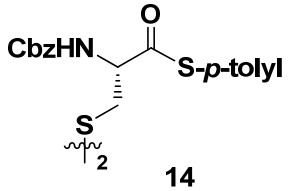
The scope and limitations of the desulfitative coupling of peptidic thiol esters and organostannanes were explored. Results are depicted in **Table 1.3**. Freshly distilled $P(OEt)_3$ is essential for an efficient coupling. A near stoichiometric quantity of CuDPP (1.2 equiv) is sufficient for most reactions, although 2.2 equiv of CuDPP delivered incrementally higher yields in some cases (**Table 1.3**, **entry 1**: 98% *vs* 93%; **entry 17**: 80% *vs* 70%; **entry 20**: 92% *vs* 86%; **entry 27**: 84% *vs* 80%). Electron-rich heteroarylstannanes reacted efficiently in 1:2 THF/hexanes at or slightly above room temperature (**Table 1.3**, **entries 1-4**, **15**, **17-20**, **22**, **24-30**). Allyl (**Table 1.3**, **entry 6**), vinyl (**Table 1.3**, **entry 7**), and *Z*-1-propenyl (**Table 1.3**, **entry 14**) stannanes reacted to give acceptable to good yields of corresponding peptidyl ketone products, the latter stannane with complete retention of the double bond stereochemistry. A variety of arylstannanes (**Table 1.3**, **entries 7-10**, **13**, **21**) reacted well in the cross-coupling, although a solvent switch to DMF at 50 °C was required for acceptable reaction rates and product yields in these cases.

Table 1.3 Peptidyl Ketones from Thiol Esters and Organostannanes



entry	thiol ester	R^2	yield[a] (%)	ee[b] (%)
1	**1**	2-thienyl	93	99
2	**1**	2-furyl	97	--
3	**1**	2-*N*-methylpyrolyl	76	--
4	**1**	2-*N*-methylindolyl	95	--
5	**1**	ethenyl	52	--
6[c]	**1**	2-propen-1-yl	62	99
7[d]	**1**	phenyl	95	99

8[d]	**1**	*p*-tolyl	83	--
9[d]	**1**	*p*-methoxyphenyl	82	--
10[d]	**1**	*p*-chlorophenyl	98	--
11[c]	**1**	2-pyridyl	72	37
12[e]	**1**	3-pyridyl	89	94
13[d]	**1**	1-naphthyl	91	99
14	**1**	*Z*-1-propenyl	81	95
15	 **2**	2-thienyl	91	99
16[f]	**2**	2-thiazolyl	48	0
17	 **3**	2-thienyl	70	99
18	 **4**	2-thienyl	97	99
19	**4**	*N*-methyl-2-indolyl	93	99
20	 **5**	2-thienyl	86	99
21	**5**		79	99
22	 **6**	2-thienyl	79	96
23[d]	 **7**	2-methoxy-3-pyridyl	83	99
24	 **8**	2-thienyl	68	99

25[g]		2-thienyl	81	99
26[g]		2-thienyl	78	--
27		2-thienyl	80	99
28		2-thienyl	99	99
29		2-thienyl	65	--
30[h]		2-thienyl	73	--

[a] Isolated yield. [b] ee determined by HPLC chiral OD, OJ or AS reversed phase column using racemic mixtures as standards. [c] 35 °C, 1:2 THF/hexanes, 2 h. [d] 50 °C, DMF, 1 h. [e] 50 °C, THF, 1 h. [f] 50 °C, 1:2 THF/hexanes, 2 h. [g] 23 °C, THF, 1 h. [h] 2-thienyl-tri-*n*-butylstannane (2.2 equiv), $CuOP(O)Ph_2$ (2.4 equiv), $Pd_2(dba)_3$ (5 mol %), $P(OEt)_3$ (40 mol %), 23 °C, THF, 3 h.

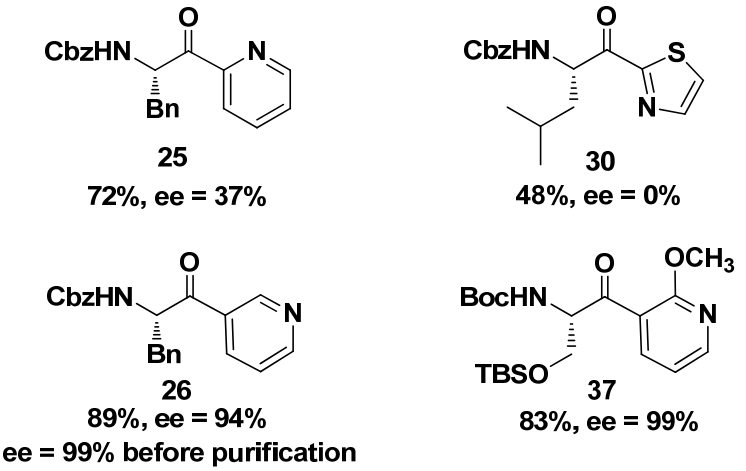
The results in **Table 1.3** demonstrate that a diverse range of amino acid thiol esters can couple efficiently with organostannanes. Those reactants derived from nonpolar *N*-protected amino acids included Phe, Leu, Pro, Trp and Met (**Table 1.3**, **entries 1-21**). Polar *N*-protected amino acids studied included Ser, Tyr, Gln, His, Glu, Lys

and Arg (**Table 1.3**, **entries 22-29**). Unprotected indole (**Table 1.3**, **entries 18-19**), thioether (**Table 1.3**, **entries 20-21**), alcohol (**Table 1.3**, **entry 22**), phenol (**Table 1.3**, **entry 24**) and amide (**Table 1.3**, **entry 25**) functional groups were well-tolerated using this pH-neutral reaction. In addition, protected imidazole, carboxylic acid, amine and guanidine functional groups did not interfere in the transformation (**Table 1.3**, **entries 26-29**). Although disulfides are known to be cleaved by CuI and couple with boronic acids to produce thioethers,[11] the bisthiol ester derived from *N*-protected cystine reacted with 2-thienyl-tri-*n*-butylstannane to cleanly give the bisketonic product without cleaving the disulfide bond (**Table 1.3**, **entry 30**). Given the chemical sensitivity of the disulfide linkage this example shows the high chemoselectivity of the cross-coupling toward the C-S bond of thiol esters.

The enantiopurity of the *N*-protected α-amino ketones was determined in a number of cases. No racemization was found in most of the cases investigated. Serine, however, is known to easily racemize during peptide coupling,[12] and the serine-derived coupling system did show slight racemization in the preparation of Cbz protected serine thiol ester. Using Boc protected L-serine (in place of Cbz protection used for the other amino acids), the high enantiopurity thiol ester reactant L-Boc-Ser-*S*-*p*-tolyl can be obtained in high enantiopurity after recrystallization from CH_2Cl_2/hexanes (ee > 99%). However, when was coupled with 2-thienyl-tri-*n*-butylstannane, a 3% ee loss was observed during silica gel chromatographic purification (**Table 1.3**, **entry 22**). The slight racemization can be prevented by using the *O*-protected variant *O*-TBS-L-Boc-Ser-*S*-*p*-tolyl; upon coupling with 2-methoxy-3-(tri-*n*-butylstannyl)pyridine the enantiopure α-amino ketone was delivered in excellent yield after the silica gel column purification (**Table 1.3**, **entry 23**).

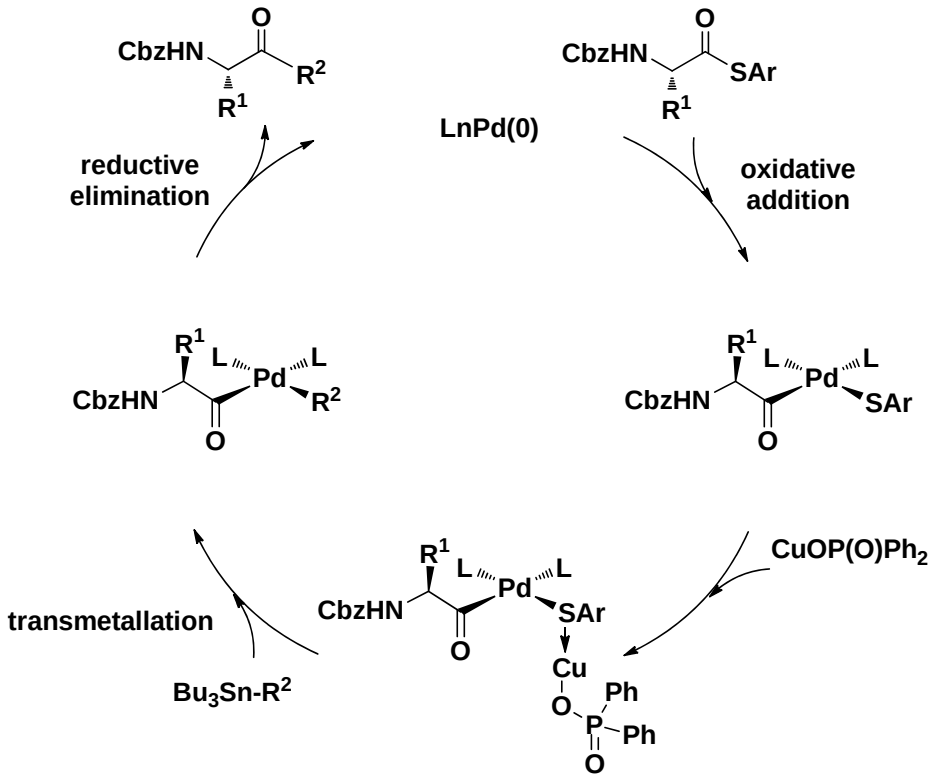
For the other examples assayed for enantiopurity, only those reaction systems using π-deficient heteroarylstannanes as coupling partners showed any tendency towards racemization. Relevant examples from **Table 1.3** are gathered for comparison in **Figure 1.1**. The peptidyl ketone products from reactions using 2-(tri-*n*-butylstannyl)thiazole and 2-(tri-*n*-butylstannyl)pyridine were obtained with significant to complete racemization. However, the racemization is not a function of the reaction conditions used; rather, it appears to be inherent to the structure of the products. A purified sample of the 2-pyridyl α-amino ketone L-Z-Phe-2-pyridyl racemized slowly in solution (24 h, ee from 37% to 31%) even in the absence of CuDPP. Not surprisingly, those π-deficient heteroaryl peptidyl ketones that possess functionality similar to 1,2-diketones (2-pyridyl, 2-thiazolyl) are inherently prone to racemization, presumably *via* facile enol-keto equilibration. Note, in contrast, that the isomeric 3-pyridyl peptidyl ketones L-Cbz-Phe-3-pyridyl and L-Z-Phe-2-methoxy-3-pyridyl were significantly less prone to racemization: 3-(tri-*n*-butylstannyl)pyridine gave the desired α-amino ketone in 94% ee (crude 99% ee), while 3-(tri-*n*-butylstannyl)-2-methoxypyridine provided the peptidyl ketone in 99% ee.

Figure 1.1 Structural Features Influencing Racemization



The reaction mechanism for the palladium-catalyzed, copper-mediated cross-coupling of amino acid thiol esters and organostannanes is proposed in **Figure 1.2**. Similar to the related thiol ester–organostannane cross-coupling,[9] oxidative addition of Pd^0 into C-S bond of an amino acid thiol ester would afford the acylpalladium(II) thiolate. Transmetallation from tin to palladium, which was facilitated by thiophilic activation with CuDPP, followed by reductive elimination would give the desired α-amino ketone and release Pd^0 catalyst back to the catalytic cycle.

Figure 1.2 Proposed Mechanism



1.3 Conclusion

In summary, a synthesis of high enantiopurity *N*-protected α-amino ketones has been developed using thiol esters derived from 13 amino acids and a variety of organostannanes. Structurally diverse *N*-protected α-amino ketones were prepared in

good yields with high ee. Advantages of this new reaction compared to the related system that uses boronic acids as coupling partners are the use of only 1.1 equiv of the organostannane reactant to complete the coupling reaction, and the viability of π–deficient heteroarylstannanes, which are far superior to the corresponding boronic acids in overall coupling reactivity. Racemization was problematic only when some electron-deficient heteroarylstannanes were used. This mild, pH-neutral method possesses high functional group compatibility and could be very useful for constructing more complex molecular systems.

1.4 Experimental Section

1.4.1 General Experimental

^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 600 MHz, 400 MHz spectrometers and VNMRS 400 MHz spectrometer in deuteriochloroform ($CDCl_3$) with the solvent residual peak ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.23 ppm) as internal reference unless otherwise stated. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broad), 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 510 FT-IT or ASI ReactIR 1000 spectrometer. Peaks are reported (cm^{-1}) with the following relative intensities: vs (very strong), s (strong), m (medium), w (weak), and br (broad). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. 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 Merck silica gel glass plates with F-254 indicator. Visualization was accomplished by UV light, or with solutions of $K_2CO_3/KMnO_4$ in water, phosphomolybdic acid in ethanol, or *p*-anisaldehyde in ethanol. Solvents for chromatography were reagent grade and used as received. Flash column chromatography was performed by the method of Still[13] with 32-63 μm silica gel 60 (Woelm). HPLC analyses were carried out using an Agilent 1100 system with a quarternary pump. Separations were achieved on a Zorbax Eclipse XDB C8 4.6 x 150 mm column or DAICEL chiral AD, AS, OD, OJ reversed phase columns. Solvents used as reaction media were purchased in > 99% purity purged for several minutes with argon then dried and stored over 4Å molecular sieves (water content below 10 ppm). All reactions requiring inert atmospheres were carried out under dry argon in oven-dried glassware. Bulb-to-bulb ("Kugelrohr") distillations were done on a Büchi GKR-50 Kugelrohr and boiling points (bp) correspond to uncorrected air bath temperatures. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of NH_4Cl, $NaHCO_3$ refer to saturated solutions.

1.4.2 Starting Materials

Copper (I) diphenylphosphinate (CuDPP), 1-methyl-2-(tri-*n*-butylstannyl)-1*H*-pyrrole, 1-methyl-2-(tri-*n*-butylstannyl)-1*H*-indole, 2-(tri-*n*-butylstannyl)pyridine, 3-(tri-*n*-butylstannyl)pyridine, 2-methoxy-3-(tri-*n*-butylstannyl)pyridine, 2-(tri-*n*-butylstannyl)thiazole were obtained from Synthonix. All the *N*-Protected α-amino acids, *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) ($PdCl(PPh_3)_2CH_2Ph$), *N,N*'-dicyclohexylcarbodiimide (DCC), 4-methylbenzenethiol, *tert*-butyldimethylsilyl chloride, 4-(*N,N*'-dimethylamino)pyridine, triethylamine, *N*-methyl morpholine, tri-*n*-butyl(thiophen-2-yl)stannane, tri-*n*-butyl(furan-2-yl)stannane, tri-*n*-butyl(vinyl)-

stannane, allyltri-*n*-butylstannane, tri-*n*-butyl(phenyl)stannane, and solvents were purchased from Sigma-Aldrich. Tri-Cbz-L-Arginine was purchased from TCI. Tri-*n*-butyl(4-methoxyphenyl)stannane was purchased from Texas Biochemicals Product List. (*Z*)-Tri-*n*-butyl(prop-1-enyl)stannane was purchased from Alfa Aesar. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), 1-hydroxybenzotriazole (HOBt), and triethylphosphite ($P(OEt)_3$) were purchased from Acros. Bis(tri-*t*-butylphosphine)palladium (0) ($Pd[P(t\text{-}Bu)_3]_2$) and tri(2-furyl)phosphine were purchased from Strem Chemicals, Inc. Triethylphosphite was purified by distillation at 1 atm (157 °C).[14]

N-Protected α-amino thiol esters of high enantiopurity were prepared using the method of Steglich (DCC/DMAP/EtSH).[15] Tri-*n*-butyl(*p*-tolyl)stannane,[16] tri-*n*-butyl(4-chlorophenyl)stannane,[17] tri-*n*-butyl(naphthalen-1-yl)stannane,[18] and tri-*n*-butyl(4-dibenzofuranyl)stannane[19] were prepared according to literature procedures.

1.4.3 Experimental

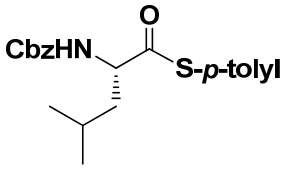
General Procedure for the Preparation of Thiol Esters Derived from *N*-Protected Amino Acids

4-Methylbenzenethiol (1.05 equiv) and 1-hydroxybenzotriazole (1.50 equiv) were added to a solution of *N*-protected amino acid in dry ethyl acetate (2 mL/mmol) at 0 °C followed by *N,N*′-dicyclohexylcarbodiimide (1.0 equiv). The mixture was stirred for 24 h at room temperature. At the end of the reaction a few drops of 50 % acetic acid in ethyl acetate were added. The mixture was filtered through Celite™ and the organic phase was washed with $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, ethyl acetate in hexanes) affording the desired product.

(-)-*N*-Cbz-L-Phenylalanine *p*-tolylthiol ester, 1

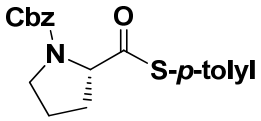
Following the general procedure, 4-methylbenzenethiol (1.302 g, 10.5 mmol) and 1-hydroxy-benzotriazole (2.025 g, 15.0 mmol) was added to a solution of *N*-Cbz-L-phenylalanine (2.990 g, 10 mmol) in dry ethyl acetate (2 mL/mmol) at 0 °C followed by *N,N'*-dicyclohexylcarbodiimide (2.060 g, 10.0 mmol). The mixture was stirred for 24 h at room temperature. At the end of the reaction a few drops of 50 % acetic acid in ethyl acetate were added. The mixture was filtered through Celite™ and the organic phase was washed with $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 25% ethyl acetate in hexanes) affording the title compound as a white solid. Yield: 3.767 g (93%). TLC (R_f = 0.49, silica gel, 25% ethyl acetate in hexanes). Mp = 116-117 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 16.4 min, D-isomer t_R = 15.4 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 12H), 7.18-7.16 (m, 2H), 5.22 (d, *J* = 8.8 Hz, 1H), 5.16 (AB q, *J* = 12.8 Hz, 1H), 5.10 (AB q, *J* = 12.8 Hz, 1H), 4.86-4.81 (m, 1H), 3.17-3.15 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 155.8, 140.1, 136.2, 135.4, 134.7, 130.3, 129.6, 128.9, 128.7, 128.4, 128.3, 127.5, 123.5, 67.4, 61.4, 38.6, 21.5. IR (neat, cm^{-1}) 3320 (m), 1695 (vs), 1498 (s). HRMS (FAB) Calcd for $C_{24}H_{24}NO_3S$ ($[M+H]^+$): 406.1471. Found: 406.1480. $[\alpha]_D^{20}$ -66.0 (*c* 1.20, $CHCl_3$)

(-)-*N*-Cbz-L-Leucine *p*-tolylthiol ester, 2



Following the general procedure, the title compound was prepared as a white solid. Yield: 326 mg (88%). TLC (R_f= 0.45, silica gel, 20% ethyl acetate in hexanes). Mp = 59.5-60.5 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 13.4 min, D-isomer t_R = 15.8 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.26 (m, 7H), 7.23-7.20 (m, 2H), 5.16-5.11 (m, 3H), 4.60-4.54 (m, 1H), 2.37 (s, 3H), 1.75-1.72 (m, 2H), 1.56-1.52 (m, 1H), 0.96-0.94 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 156.0, 139.7, 136.2, 134.6, 130.0, 128.5, 128.2, 128.1, 123.6, 67.2, 59.5, 41.5, 24.7, 23.1, 21.5, 21.3. IR (neat, cm^{-1}) 3316 (w), 1698 (vs), 1525 (s). HRMS (FAB) Calcd for $C_{21}H_{26}NO_3S$ ($[M+H]^+$): 372.1627. Found: 372.1636. $[\alpha]_D^{20}$ -38.5 (*c* 1.15, $CHCl_3$).

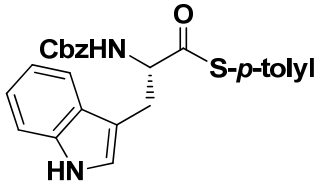
(-)-*N*-Cbz-L-Proline *p*-tolylthiol ester, 3



Following the general procedure, the title compound was prepared as a white solid. Yield: 114 mg (64%). TLC (R_f= 0.72, silica gel, 50% ethyl acetate in hexanes). Mp = 61-62 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 19.6 min, D-isomer t_R = 18.5 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) two rotamers δ 7.42-7.10 (m, 9H), 5.31-5.09 (m,

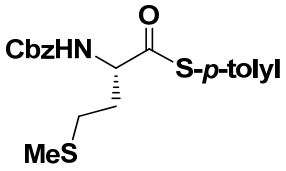
2H), 4.64 (dd, *J* = 8.4, 3.2 Hz, 0.4H), 4.54 (dd, *J* = 8.8, 3.2 Hz, 0.6H), 3.75-3.51 (m, 2H), 2.38 (s, 3H), 2.32-1.92 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 200.8, 200.3, 155.3, 154.6, 139.8, 139.7, 136.7, 136.5, 134.8, 134.7, 130.2, 128.6, 128.2, 128.1, 123.9, 123.7, 67.4, 66.5, 66.1, 47.4, 47.0, 31.8, 30.9, 24.2, 23.5, 21.5. IR (neat, cm^{-1}) 1710 (vs), 1409 (s). HRMS (FAB) Calcd for $C_{20}H_{22}NO_3S$ ($[M+H]^+$): 356.1314. Found: 356.1322. $[\alpha]_D^{20}$ -112.9 (*c* 0.78, $CHCl_3$).

(-)-*N*-Cbz-L-Tryptophan *p*-tolylthiol ester, 4



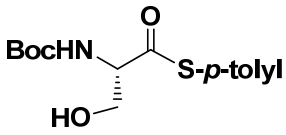
Following the general procedure, the title compound was prepared as a pale yellow solid. Yield: 410 mg (92%). TLC (R_f = 0.51, silica gel, 40% ethyl acetate in hexanes). Mp = 51-52.5 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.6 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 20 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 5 min, L-isomer t_R = 29.7 min, D-isomer t_R = 28.8 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.37-7.32 (m, 6H), 7.24-7.10 (m, 6H), 7.00 (d, *J* = 2.0 Hz, 1H), 5.36 (d, *J* = 8.8 Hz, 1H), 5.14 (s, 2H), 4.90-4.88 (m, 1H), 3.42 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.32 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 156.0, 139.9, 136.3, 136.2, 134.7, 130.2, 128.6, 128.3, 128.2, 127.5, 123.6, 123.4, 122.4, 119.9, 118.9, 111.5, 109.2, 67.3, 61.1, 28.3, 21.4. IR (neat, cm^{-1}) 3405 (s), 1695 (vs), 1499 (s). HRMS (FAB) Calcd for $C_{26}H_{25}N_2O_3S$ ($[M+H]^+$): 445.1580. Found: 445.1590. $[\alpha]_D^{20}$ -79.6 (*c* 1.25, $CHCl_3$).

(-)-*N*-Cbz-L-Methionine *p*-tolylthiol ester, 5



Following the general procedure, the title compound was prepared as a white solid. Yield: 335 mg (86%). TLC (R_f = 0.46, silica gel, 25% ethyl acetate in hexanes). Mp = 143-144 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 13.3 min, D-isomer t_R = 14.9 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.26 (m, 7H), 7.23-7.21 (m, 2H), 5.46 (d, *J* = 8.8 Hz, 1H), 5.17 (s, 2H), 4.73-4.70 (m, 1H), 2.63-2.55 (m, 2H), 2.37 (s, 3H), 2.25-2.21 (m, 1H), 2.10 (s, 3H), 2.01-1.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 155.9, 139.8, 136.0, 134.5, 130.1, 128.5, 128.2, 128.1, 123.2, 67.3, 60.0, 31.8, 29.9, 21.3, 15.3. IR (neat, cm^{-1}) 3312 (m), 1695 (vs), 1521 (s). HRMS (FAB) Calcd for $C_{20}H_{24}NO_3S_2$ ($[M+H]^+$): 390.1192. Found: 390.1201. $[\alpha]_D^{20}$ -34.9 (*c* 1.20, $CHCl_3$).

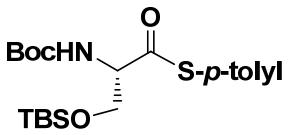
(-)-*N*-Boc-L-Serine *p*-tolylthiol ester, 6



Following the general procedure, the title compound was prepared as a white solid. Yield: 217 mg (70%). TLC (R_f = 0.44, silica gel, 50% ethyl acetate in hexanes). Mp = 121-122 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 4.5 min, D-isomer t_R = 3.7 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H),

5.59 (d, J = 8.4 Hz, 1H), 4.55 (t, J = 4.0 Hz, 1H), 4.14 (dd, J = 11.2, 2.8 Hz, 1H), 3.83 (dd, J = 11.2, 4.0 Hz, 1H), 2.37 (s, 3H), 2.17 (br s, 1H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 155.6, 140.1, 134.7, 130.3, 123.5, 80.9, 63.4, 61.9, 28.5, 21.5. IR (neat, cm^{-1}) 3439 (m), 3377 (m), 1695 (vs), 1494 (s). HRMS (FAB) Calcd for $C_{15}H_{22}NO_4S$ ($[M+H]^+$): 312.1264. Found: 312.1264. $[\alpha]_D^{20}$ -77.9 (*c* 1.51, $CHCl_3$).

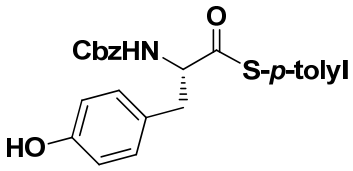
(-)-*O-tert*-Butyldimethylsilyloxy-*N*-Boc-L-serine *p*-tolylthiol ester, 7



To a solution of *N*-Boc-L-Ser-S-*p*-tolyl (30 mg, 0.1 mmol), TBSCl (150 mg, 1.0 mmol) and DMAP (3 mg, 0.02 mmol) in DMF (1.5 mL) was added *N*-methyl morpholine (10 mg, 0.1 mmol) at 0 ºC. The resulting reaction solution was stirred for 30 min at room temperature. The reaction crude was then diluted with ethyl acetate and washed with 0.1 M aq HCl, $NaHCO_3$, and brine. The combined organic layer was concentrated *in vacuum* to produce the title compound as a white solid. Yield: 113 mg (89%). TLC (R_f = 0.82, silica gel, 50% ethyl acetate in hexanes). Mp = 92-93.5 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 7 min, L-isomer t_R = 11.5 min, D-isomer t_R = 10.5 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 5.51 (d, J = 8.8 Hz, 1H), 4.47-4.43 (m, 1H), 4.16 (dd, J = 10.4, 2.4 Hz, 1H), 3.78 (dd, J = 10.0, 3.2 Hz, 1H), 2.36 (s, 3H), 1.51 (s, 9H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 155.5, 139.8, 134.7, 130.2, 124.2, 80.6, 63.7, 61.9, 28.5, 25.9, 21.5, 18.4, -5.3. IR (neat, cm^{-1}) 1722 (vs), 1702 (vs), 1490 (s). HRMS (FAB) Calcd for $C_{21}H_{36}NO_4SSi$ ($[M+H]^+$): 426.2128. Found: 426.2130. $[\alpha]_D^{20}$ -53.8

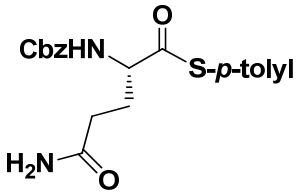
(*c* 0.88, $CHCl_3$).

(-)-*N*-Cbz-L-Tyrosine *p*-tolylthiol ester, 8



Following the general procedure, the title compound was prepared as a white solid. Yield: 355 mg (84%). TLC (R_f = 0.70, silica gel, 50% ethyl acetate in hexanes). Mp = 143.5-144 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 12.5 min, D-isomer t_R = 11.8 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 5H), 7.24-7.20 (m, 4H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 5.47 (br s, 1H), 5.26 (d, *J* = 8.8 Hz, 1H), 5.16- 5.08 (m, 2H), 4.81-4.76 (m, 1H), 3.13-3.04 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 155.9, 155.1, 140.1, 136.1, 134.7, 130.8, 130.3, 128.7, 128.5, 128.3, 127.2, 123.4, 115.8, 67.5, 61.6, 37.8, 21.5. IR (neat, cm^{-1}) 3335 (m), 1695 (vs), 1517 (s). HRMS (FAB) Calcd for $C_{24}H_{24}NO_4S$ ($[M+H]^+$): 422.1420. Found: 422.1430. $[\alpha]_D^{20}$ -72.8 (*c* 0.89, $CHCl_3$).

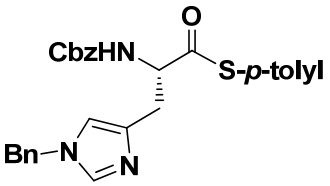
(-)-*N*-Cbz-L-Glutamine *p*-tolylthiol ester, 9



Following the general procedure, the title compound was prepared as a white solid. Yield: 221 mg (57%). TLC (R_f = 0.40, silica gel, ethyl acetate). Mp = 121-123 °C.

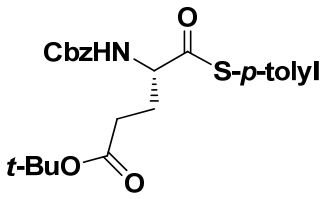
HPLC Chiral AS-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 10 min, hold for 5 min, L-isomer t_R = 12.0 min, D-isomer t_R = 11.1 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 7H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.93 (d, *J* = 8.4 Hz, 1H), 5.65 (br s, 1H), 5.36 (br s, 1H), 5.15 (s, 2H), 4.56-4.51 (m, 1H), 2.41-2.25 (m, 6H), 2.12-2.05 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 174.7, 156.4, 140.1, 136.3, 134.7, 130.3, 128.7, 128.4, 128.3, 123.4, 67.4, 60.7, 31.7, 28.0, 21.5. IR (neat, cm^{-1}) 3385 (m), 3316 (s), 1695 (vs), 1656 (s), 1532 (s). HRMS (FAB) Calcd for $C_{20}H_{23}N_2O_4S$ ($[M+H]^+$): 387.1373. Found: 387.1382. $[\alpha]_D^{20}$ -33.3 (*c* 1.00, $CHCl_3$).

(-)-*N*α-Cbz-*N*(im)-Benzyl-L-histidine *p*-tolylthiol ester, 10



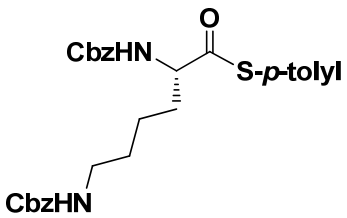
Following the general procedure, the title compound was prepared as a pale yellow oil. Yield: 444 mg (92%). TLC (R_f = 0.56, silica gel, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.43-7.30 (m, 7H), 7.14-7.04 (m, 7H), 6.66 (s, 1H), 5.23 (AB q, *J* = 12.4 Hz, 1H), 5.17 (AB q, *J* = 12.4 Hz, 1H), 5.08 (AB q, *J* = 15.6 Hz, 1H), 5.00 (AB q, *J* = 15.6 Hz, 1H), 4.74 (m, 1H), 3.19 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.00 (dd, *J* = 14.8, 4.4 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 156.3, 139.5, 137.5, 137.4, 136.6, 136.1, 134.6, 130.0, 129.2, 128.6, 128.4, 128.3, 128.2, 127.3, 124.3, 117.5, 67.2, 60.9, 50.9, 30.1, 21.4. IR (neat, cm^{-1}) 3316 (w), 1718 (vs), 1498 (s). HRMS (FAB) Calcd for $C_{28}H_{28}N_3O_3S$ ($[M+H]^+$): 486.1845. Found: 486.1855. $[\alpha]_D^{20}$ -51.9 (*c* 1.57, $CHCl_3$).

(-)-*N*-Cbz-L-Glutamic acid 5-*tert*-butyl 1-*p*-tolylthiol ester, 11



Following the general procedure, the title compound was prepared as a white solid. Yield: 405 mg (91%). TLC (R_f= 0.47, silica gel, 25% ethyl acetate in hexanes). Mp = 82-82.5 °C. HPLC Chiral AS-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 16.0 min, D-isomer t_R = 14.0 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 7H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.62 (d, *J* = 8.4 Hz, 1H), 5.16 (s, 2H), 4.58-4.52 (m, 1H), 2.43-2.32 (m, 5H), 2.26-2.18 (m, 1H), 2.04-1.94 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 172.4, 156.1, 140.1, 136.2, 134.7, 130.3, 128.7, 128.4, 128.3, 123.4, 81.3, 67.4, 60.7, 31.6, 28.2, 27.7, 21.5. IR (neat, cm^{-1}) 3327 (w), 1702 (vs), 1525 (s). HRMS (FAB) Calcd for $C_{24}H_{30}NO_5S$ ($[M+H]^+$): 444.1839. Found: 444.1839. $[\alpha]_D^{20}$ -37.8 (*c* 1.24, $CHCl_3$).

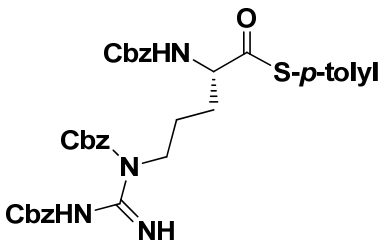
(-)-*N,N'*-Di-Cbz-L-Lysine *p*-tolylthiol ester, 12



Following the general procedure, the title compound was prepared as a white solid. Yield: 479 mg (92%). TLC (R_f= 0.42, silica gel, 33% ethyl acetate in hexanes). Mp = 100.5-102 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.6 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 20 min, 75% CH_3CN to 100

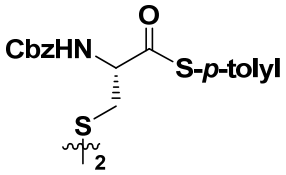
% CH_3CN in 15 min, hold for 5 min, L-isomer t_R = 30.6 min, D-isomer t_R = 32.6 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 12H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.48 (d, *J* = 8.4 Hz, 1H), 5.23-5.01 (m, 4H), 4.79 (s, 1H), 4.53-4.50 (m, 1H), 3.24-3.13 (m, 2H), 2.37 (s, 3H), 2.00-1.66 (m, 2H), 1.56-1.43 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 156.8, 156.2, 140.0, 136.6, 136.2, 134.7, 130.3, 128.8, 128.5, 128.4, 128.3, 123.4, 67.4, 66.9, 60.8, 40.3, 32.2, 29.6, 22.2, 21.5. IR (neat, cm^{-1}) 3320 (m), 1695 (vs), 1529 (s). HRMS (FAB) Calcd for $C_{29}H_{33}N_2O_5S$ ($[M+H]^+$): 521.2104. Found: 521.2117. $[\alpha]_D^{20}$ -31.3 (*c* 1.03, $CHCl_3$).

(-)-*N,N′,N″*-Tri-Cbz-L-Arginine *p*-tolylthiol ester, 13

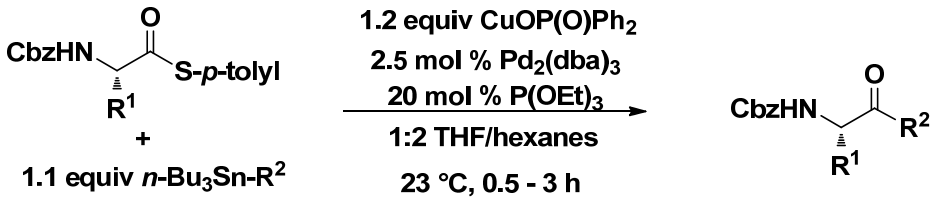


Following the general procedure, the title compound was prepared as a white solid. Yield: 151 mg (44%). TLC (R_f = 0.51, silica gel, 33% ethyl acetate in hexanes). Mp = 132-134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (br s, 1H), 9.27 (br s, 1H), 7.35-7.18 (m, 19H), 6.01 (d, *J* = 8.8 Hz, 1H), 5.22 (s, 2H), 5.17-5.05 (m, 4H), 4.54-4.51 (m, 1H), 4.06-3.88 (m, 2H), 2.36 (s, 3H), 1.89-1.85 (m, 1H), 1.78-1.66 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 163.9, 160.7, 156.3, 155.9, 139.9, 137.0, 136.4, 130.2, 129.1, 129.0, 128.7, 128.5, 128.3, 128.2, 128.1, 127.9, 123.8, 69.2, 67.3, 67.1, 61.1, 44.3, 28.6, 25.1, 21.5. IR (neat, cm^{-1}) 3389 (w), 1718 (vs), 1610 (s), 1509 (s), 1254 (vs). HRMS (FAB) Calcd for $C_{37}H_{39}N_4O_7S$ ($[M+H]^+$): 683.2534. Found: 683.2547. $[\alpha]_D^{20}$ -8.3 (*c* 0.47, $CHCl_3$).

(-)-*N,N'*-Di-Cbz-L-Cystine *bis*-*p*-tolylthiol ester, 14



Following the general procedure, the title compound was prepared as a white solid. Yield: 373 mg (72%). TLC (R_f= 0.65, silica gel, 33% ethyl acetate in hexanes). Mp = 151-152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 14H), 7.20 (d, *J* = 8.4 Hz, 4H), 5.74 (d, *J* = 9.2 Hz, 2H), 5.20-5.13 (m, 4H), 4.86-4.81 (m, 2H), 3.23-3.13 (m, 4H), 2.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 156.0, 140.2, 136.1, 134.7, 130.4, 128.7, 128.5, 128.4, 123.1, 67.7, 60.2, 41.2, 21.5. IR (neat, cm^{-1}) 3331 (s), 1691 (vs), 1517 (s). HRMS (FAB) Calcd for $C_{36}H_{37}N_2O_6S$ ($[M+H]^+$): 721.1529. Found: 721.1549. $[\alpha]_D^{20}$ -25.0 (*c* 1.02, $CHCl_3$).

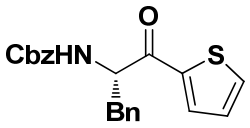


General Procedure for Thiol Ester and Organostannane Cross-Coupling

N-Protected amino acid thiol ester (0.10 mmol, 1.0 equiv), $CuOP(O)Ph_2$ (34 mg, 0.12 mmol, 1.2 equiv) and $Pd_2(dba)_3$ (2 mg, 2.5 μmol, 0.025 equiv) were placed under an argon atmosphere. Then 1:2 THF/hexanes (1.5 mL, degassed and dried over 4Å molecular sieves) and $P(OEt)_3$ (3.4 μl, 20 μmol, 0.2 equiv) were added followed by dropwisely adding organostannane (0.11 mmol, 1.1 equiv) dropwisely *via* syringe at room temperature. The reaction mixture was stirred for 0.5-3 h and then evaporated. The residue was suspended in CH_2Cl_2 (10 mL) and the suspension was filtered through a plug of Celite™. The organic layer was evaporated and purified by SiO_2

column chromatography to give the desired product.

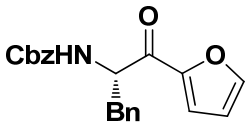
(+)-(*S*)-Benzyl 1-oxo-3-phenyl-1-(thiophen-2-yl)propan-2-yl carbamate, 15



N-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv), $CuOP(O)Ph_2$ (34 mg, 0.12 mmol, 1.2 equiv) and $Pd_2(dba)_3$ (2 mg, 2.5 μmol, 0.025 equiv) were placed under an argon atmosphere. Then 1:2 THF/hexanes (1.5 mL, degassed and dried over 4Å molecular sieves) and $P(OEt)_3$ (3.4 μl, 20 μmol, 0.2 equiv) were added followed by dropwisely adding tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) *via* syringe at room temperature. The reaction mixture was stirred for 2 h and then evaporated. The residue was diluted with CH_2Cl_2 (10 mL) and the suspension was filtered through a plug of Celite™. The organic layer was evaporated and purified by SiO_2 column chromatography (25% ethyl acetate in hexanes) to give the title compound as a colorless oil. Yield: 34 mg (93%). TLC (R_f = 0.37, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.65 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN for 35 min, 50% CH_3CN to 100 % CH_3CN in 10 min, L-isomer t_R = 35.6 min, D-isomer t_R = 36.6 min, ee = 99%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73-7.70 (m, 2H), 7.36-7.32 (m, 5H), 7.24-7.20 (m, 3H), 7.14-7.11 (m, 1H), 7.06 (dd, *J* = 7.2, 2.0 Hz, 2H), 5.60 (d, *J* = 8.4 Hz, 1H), 5.42-5.37 (m, 1H), 5.13 (AB q, 12.0 Hz, 1H), 5.07 (AB q, 12.0 Hz, 1H), 3.26 (dd, *J* = 13.6, 6.0 Hz, 1H), 3.09 (dd, *J* = 14.0, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 155.7, 141.7, 136.4, 135.7, 135.2, 133.4, 129.6, 128.7, 128.6, 128.3, 128.2, 127.2, 67.1, 57.7, 40.0. IR (neat, cm^{-1}) 3331 (w), 1718 (vs), 1664 (vs), 1502 (s). HRMS (FAB) Calcd for $C_{21}H_{20}NO_3S$ ($[M+H]^+$): 366.1158. Found: 366.1154. $[\alpha]_D^{20}$

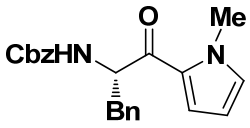
+70.4 (*c* 1.00, $CHCl_3$).

(+)-(*S*)-Benzyl 1-(furan-2-yl)-1-oxo-3-phenylpropan-2-yl carbamate, 16



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(furan-2-yl)stannane (41 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a colorless oil.[20] Yield: 34 mg (97%). TLC (R_f= 0.30, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.35-7.31 (m, 5H), 7.24-7.19 (m, 4H), 7.06-7.04 (m, 2H), 6.54 (t, *J* = 2.0 Hz, 1H), 5.54 (d, *J* = 8.4 Hz, 1H), 5.38-5.33 (m, 1H), 5.11 (AB q, *J* = 12.4 Hz, 1H), 5.05 (AB q, *J* = 12.4 Hz, 1H), 3.23 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.06 (dd, *J* = 14.0, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 155.8, 151.1, 147.5, 136.5, 135.7, 129.6, 128.7, 128.5, 128.3, 128.2, 127.1, 119.3, 112.8, 67.1, 57.1, 39.2. IR (neat, cm^{-1}) 3335 (w), 1718 (s), 1675 (vs), 1502 (s). HRMS (FAB) Calcd for $C_{21}H_{20}NO_4$ ($[M+H]^+$): 350.1386. Found: 350.1383. $[\alpha]_D^{20}$ +68.4 (*c* 0.50, $CHCl_3$).

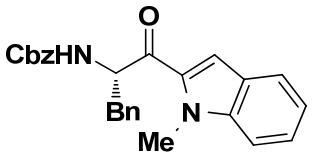
(+)-(*S*)-Benzyl 1-(1-methyl-1*H*-pyrrol-2-yl)-1-oxo-3-phenyl propan-2-yl carbamate, 17



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with 1-methyl-2-(tri-*n*-butylstannyl)-1*H*-pyrrole (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a pale yellow oil. Yield: 28 mg (76%). TLC (R_f= 0.34, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$)

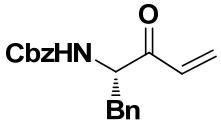
δ 7.37-7.30 (m, 5H), 7.24-7.18 (m, 3H), 7.03 (d, *J* = 5.6 Hz, 3H), 6.86 (s, 1H), 6.14 (dd, *J* = 4.0, 2.4 Hz, 1H), 5.61 (d, *J* = 8.0 Hz, 1H), 5.31-5.26 (m, 1H), 5.10 (AB q, *J* = 12.0 Hz, 1H), 5.04 (AB q, *J* = 12.0 Hz, 1H), 3.88 (s, 3H), 3.23 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.02 (dd, *J* = 14.0, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 155.8, 136.7, 136.4, 132.4, 129.6, 128.6, 128.4, 128.2, 128.1, 126.9, 120.6, 108.9, 66.9, 56.9, 40.6, 37.8. IR (neat, cm^{-1}) 3335 (w), 1718 (vs), 1648 (vs), 1525 (s). HRMS (FAB) Calcd for $C_{22}H_{23}N_2O_3$ ([M+H]$^+$): 363.1703. Found: 363.1699. $[\alpha]_D^{20}$ +54.6 (*c* 1.94, $CHCl_3$).

(+)-(*S*)-Benzyl 1-(1-methyl-1*H*-indol-2-yl)-1-oxo-3-phenyl propan-2-ylcarbamate, 18



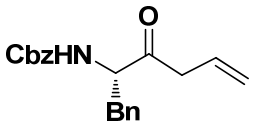
Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with 1-methyl-2-(tri-*n*-butylstannyl)-1*H*-indole (49 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a pale yellow oil. Yield: 39 mg (95%). TLC (R_f = 0.53, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 1H), 7.44-7.31 (m, 8H), 7.25-7.17 (m, 4H), 7.07-7.05 (m, 2H), 5.72 (d, *J* = 8.4 Hz, 1H), 5.54 (dd, *J* = 14.0, 6.0 Hz, 1H), 5.15 (AB q, *J* = 12.4 Hz, 1H), 5.09 (AB q, *J* = 12.4 Hz, 1H), 4.00 (s, 3H), 3.34 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.13 (dd, *J* = 13.6, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 155.8, 140.7, 136.5, 136.0, 132.8, 129.6, 128.6, 128.5, 128.3, 128.2, 128.1, 127.1, 126.7, 126.0, 123.5, 121.2, 112.7, 110.5, 67.0, 57.6, 40.4, 32.3. IR (neat, cm^{-1}) 1714 (s), 1660 (vs), 1509 (s). HRMS (FAB) Calcd for $C_{26}H_{25}N_2O_3$ ([M+H]$^+$): 413.1859. Found: 413.1859. $[\alpha]_D^{20}$ +38.7 (*c* 0.61, $CHCl_3$).

(+)-(*S*)-Benzyl 3-oxo-1-phenylpent-4-en-2-ylcarbamate, 19



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(vinyl)stannane (36 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a colorless oil.[21] Yield: 16 mg (52%). TLC (R_f = 0.35, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 7.27-7.21 (m, 3H), 7.07-7.05 (m, 2H), 6.44 (dd, *J* = 17.6, 10.0 Hz, 1H), 6.35 (dd, *J* = 17.6, 2.0 Hz, 1H), 5.87 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.48 (d, *J* = 7.6 Hz, 1H), 5.12 (AB q, *J* = 12.4 Hz, 1H), 5.06 (AB q, *J* = 12.4 Hz, 1H), 4.93 (dd, *J* = 13.6, 6.0 Hz, 1H), 3.17 (dd, *J* = 14.4, 6.8 Hz, 1H), 3.03 (dd, *J* = 13.6, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 155.8, 136.5, 136.0, 135.6, 133.3, 130.7, 129.6, 128.7, 128.4, 128.2, 128.1, 127.2, 67.1, 58.8, 38.2. IR (neat, cm^{-1}) 1798 (vs), 1498 (s). HRMS (FAB) Calcd for $C_{19}H_{20}NO_3$ ($[M+H]^+$): 310.1437. Found: 310.1439. $[\alpha]_D^{20}$ +19.7 (*c* 0.62, $CHCl_3$).

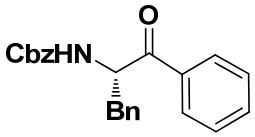
(+)-(*S*)-Benzyl 3-oxo-1-phenylhex-5-en-2-ylcarbamate, 20



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with allyltri-*n*-butylstannane (38 mg, 0.11 mmol, 1.1 equiv) at 35 ^{o}C to give the title compound as a colorless oil. Yield: 20 mg (62%). TLC (R_f = 0.46, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in

10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 9.6 min, D-isomer t_R = 8.1 min, ee = 99%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 8H), 7.11 (d, *J* = 6.4 Hz, 2H), 5.88-5.79 (m, 1H), 5.36 (d, *J* = 7.6 Hz, 1H), 5.19-5.04 (m, 4H), 4.66 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.17-2.98 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 155.8, 141.7, 136.3, 135.8, 129.6, 129.4, 128.9, 128.7, 128.4, 128.2, 127.4, 119.7, 67.1, 60.2, 45.7, 37.9. IR (neat, cm^{-1}) 1710 (vs), 1498 (m). HRMS (FAB) Calcd for $C_{20}H_{22}NO_3$ ($[M+H]^+$): 324.1594. Found: 324.1599. $[\alpha]_D^{20}$ +48.2 (*c* 0.67, $CHCl_3$).

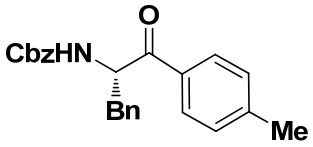
(+)-(*S*)-Benzyl 1-oxo-1,3-diphenylpropan-2-ylcarbamate, 21



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(phenyl)stannane (42 mg, 0.11 mmol, 1.1 equiv) in DMF (1.5 mL) at 50 °C to give the title compound as a colorless oil. Yield: 34 mg (95%). TLC (R_f = 0.46, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral AS-RH, λ = 254 nm, Method: Flow: 0.65 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN for 45 min, L-isomer t_R = 17.2 min, D-isomer t_R = 16.3 min, ee = 99%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.38-7.31 (m, 5H), 7.22-7.18 (m, 3H), 6.97-6.95 (m, 2H), 5.67 (d, *J* = 8.4 Hz, 1H), 5.63-5.58 (m, 1H), 5.14 (AB q, *J* = 12.4 Hz, 1H), 5.08 (AB q, *J* = 12.4 Hz, 1H), 3.26 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.01 (dd, *J* = 14.0, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 155.8, 136.5, 135.6, 134.8, 134.0, 129.7, 129.1, 128.9, 128.7, 128.5, 128.3, 128.2, 127.1, 67.0, 56.6, 39.2. IR (neat, cm^{-1}) 1718 (s), 1683 (vs), 1498 (m). HRMS (FAB) Calcd for $C_{23}H_{22}NO_3$ ($[M+H]^+$): 360.1594. Found: 360.1591.

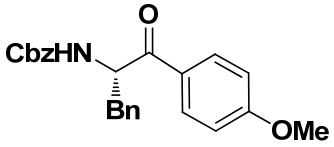
$[\alpha]_D^{20}$ +41.4 (*c* 0.87, $CHCl_3$) [Lit.[22] $[\alpha]_D^{20}$ -13.3 (*c* 0.55, $CHCl_3$)].

(+)-(*S*)-Benzyl 1-oxo-3-phenyl-1-*p*-tolylpropan-2-ylcarbamate, 22



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(p-tolyl)stannane (44 mg, 0.11 mmol, 1.1 equiv) in THF (1.5 mL) at 50 ^oC to give the title compound as a colorless oil. Yield: 31 mg (83%). TLC (R_f= 0.50, silica gel, 25% ethyl acetate in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.36-7.26 (m, 7H), 7.20-7.18 (m, 3H), 6.98-6.96 (m, 2H), 5.72 (d, *J* = 8.0 Hz, 1H), 5.62-5.57 (m, 1H), 5.14 (AB q, *J* = 12.4 Hz, 1H), 5.08 (AB q, *J* = 12.4 Hz, 1H), 3.28 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.01 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 155.8, 145.0, 136.6, 135.7, 132.2, 134.0, 129.8, 129.7, 129.1, 128.9, 128.6, 128.4, 128.2, 128.1, 127.0, 66.9, 56.4, 39.3, 21.9. IR (neat, cm^{-1}) 1722 (s), 1679 (vs), 1498 (s). HRMS (FAB) Calcd for $C_{24}H_{24}NO_3$ ($[M+H]^+$): 374.1750. Found: 360.1746. $[\alpha]_D^{20}$ +58.1 (*c* 0.47, $CHCl_3$) [Lit.[23] $[\alpha]_D^{20}$ +10.0 (*c* 1.0, $CHCl_3$)].

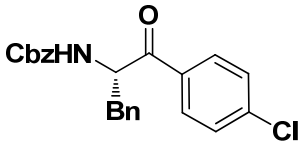
(+)-(*S*)-Benzyl 1-(4-methoxyphenyl)-1-oxo-3-phenylpropan-2-yl carbamate, 23



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(4-methoxyphenyl)stannane (46 mg, 0.11 mmol, 1.1 equiv) in THF (1.5 mL) at 50 ^oC to give the title compound as a colorless oil.

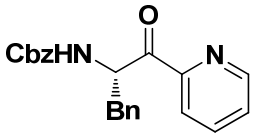
Yield: 32 mg (82%). TLC (R_f = 0.49, silica gel, 33% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H), 7.36-7.31 (m, 5H), 7.20-7.18 (m, 3H), 6.99-6.94 (m, 4H), 5.74 (d, *J* = 8.0 Hz, 1H), 5.59-5.54 (m, 1H), 5.13 (AB q, *J* = 12.4 Hz, 1H), 5.07 (AB q, *J* = 12.4 Hz, 1H), 3.88 (s, 3H), 3.26 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.01 (dd, *J* = 14.0, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 164.2, 155.8, 136.6, 135.9, 131.2, 129.7, 128.6, 128.4, 128.2, 128.1, 127.6, 127.0, 66.9, 56.1, 55.7, 39.5. IR (neat, cm^{-1}) 1714 (s), 1675 (vs), 1602 (vs). HRMS (FAB) Calcd for $C_{24}H_{24}NO_4$ ([M+H]$^+$): 390.1699. Found: 390.1695. $[\alpha]_D^{20}$ +40.8 (*c* 0.37, $CHCl_3$).

(+)-(*S*)-Benzyl 1-(4-chlorophenyl)-1-oxo-3-phenylpropan-2-yl carbamate, 24



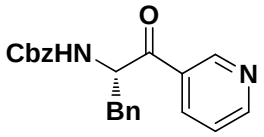
Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(4-chlorophenyl)stannane (47 mg, 0.11 mmol, 1.1 equiv) in DMF (1.5 mL) at 50 °C to give the title compound as a colorless oil. Yield: 39 mg (98%). TLC (R_f = 0.52, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.85 (m, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.36-7.32 (m, 5H), 7.20-7.18 (m, 3H), 6.97-6.94 (m, 2H), 5.62 (d, *J* = 7.6 Hz, 1H), 5.56-5.52 (m, 1H), 5.13 (AB q, *J* = 12.4 Hz, 1H), 5.07 (AB q, *J* = 12.4 Hz, 1H), 3.22 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.00 (dd, *J* = 14.0, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 155.8, 140.5, 136.4, 135.4, 133.2, 130.2, 129.6, 129.4, 128.7, 128.6, 128.4, 128.2, 127.3, 67.1, 56.5, 39.2. IR (neat, cm^{-1}) 1722 (s), 1687 (vs), 1498 (s). HRMS (FAB) Calcd for $C_{23}H_{21}NO_3Cl$ ([M+H]$^+$): 394.1204. Found: 394.1209. $[\alpha]_D^{20}$ +30.4 (*c* 0.25, $CHCl_3$).

(*S*)-Benzyl 1-oxo-3-phenyl-1-(pyridin-2-yl)propan-2-yl carbamate, 25



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with 2-(tri-*n*-butylstannyl)pyridine (48 mg, 0.11 mmol, 1.1 equiv) at 35 ^{o}C to give the title compound as a colorless oil. Yield: 26 mg (72%). TLC (R_f= 0.37, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 10.6 min, D-isomer t_R = 7.9 min, ee = 37%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.8 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.89-7.85 (m, 1H), 7.53-7.50 (m, 1H), 7.35-7.29 (m, 5H), 7.24-7.18 (m, 3H), 7.02-7.00 (m, 2H), 6.10-6.05 (m, 1H), 5.63 (d, *J* = 8.0 Hz, 1H), 5.12 (AB q, *J* = 12.4 Hz, 1H), 5.06 (AB q, *J* = 12.4 Hz, 1H), 3.41 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.09 (dd, *J* = 14.0, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 155.8, 151.7, 149.4, 137.3, 136.6, 136.4, 129.6, 128.5, 128.2, 127.8, 126.9, 123.0, 66.9, 56.9, 38.7. IR (neat, cm^{-1}) 1698 (vs), 1498 (s). HRMS (FAB) Calcd for $C_{22}H_{21}N_2O_3$ ($[M+H]^+$): 361.1546. Found: 361.1545.

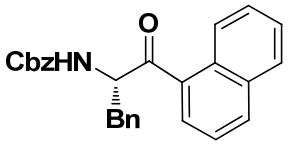
(+)-(*S*)-Benzyl 1-oxo-3-phenyl-1-(pyridin-3-yl)propan-2-yl carbamate, 26



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with 3-(tri-*n*-butylstannyl)pyridine (48 mg, 0.11 mmol, 1.1 equiv) in THF (1.5 mL) at 50 ^{o}C to give the title compound as a colorless oil. Yield: 32 mg (89%). TLC (R_f= 0.46, silica gel, 67% ethyl acetate in hexanes). HPLC Chiral OJ-RH,

λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 5.5 min, D-isomer t_R = 4.0 min, ee = 94% (crude ee = 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.79 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.41-7.30 (m, 6H), 7.21-7.18 (m, 3H), 7.00-6.97 (m, 2H), 5.67 (d, *J* = 7.6 Hz, 1H), 5.56-5.53 (m, 1H), 5.13 (AB q, *J* = 12.0 Hz, 1H), 5.07 (AB q, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 13.6, 6.0 Hz, 1H), 3.04 (dd, *J* = 14.0, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 155.8, 154.1, 150.1, 136.3, 136.1, 135.2, 129.5, 128.7, 128.4, 128.2, 127.4, 123.9, 67.2, 57.0, 39.1. IR (neat, cm^{-1}) 1718 (s), 1691 (vs), 1498 (m). HRMS (FAB) Calcd for $C_{22}H_{21}N_2O_3$ ($[M+H]^+$): 361.1546. Found: 361.1544. $[\alpha]_D^{20}$ +17.6 (*c* 0.21, $CHCl_3$).

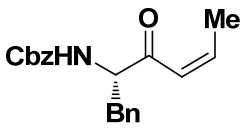
(+)-(*S*)-Benzyl 1-(naphthalen-1-yl)-1-oxo-3-phenylpropan-2-yl carbamate, 27



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(naphthalen-1-yl)stannane (46 mg, 0.11 mmol, 1.1 equiv) in DMF (1.5 mL) at 50 °C to give the title compound as a white solid. Yield: 37 mg (91%). TLC (R_f = 0.46, silica gel, 25% ethyl acetate in hexanes). Mp = 92.5-93 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 18.0 min, D-isomer t_R = 13.2 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.0 Hz, 1H), 8.05-8.01 (m, 2H), 7.92-7.89 (m, 1H), 7.61-7.50 (m, 3H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.38-7.32 (m, 5H), 7.16-7.12 (m, 3H), 6.96-6.94 (m, 2H), 5.83 (d, *J* = 8.0 Hz, 1H), 5.71-5.66 (m, 1H), 5.19 (AB q, *J* = 12.0 Hz, 1H), 5.13 (AB q, *J* = 12.0 Hz, 1H), 3.24 (dd, *J* = 14.0, 6.0

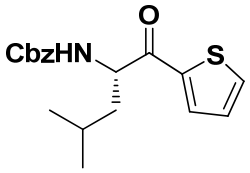
Hz, 1H), 3.00 (dd, *J* = 14.0, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 156.0, 136.5, 135.7, 134.2, 133.8, 133.2, 130.6, 129.6, 128.7, 128.6, 128.5, 128.3, 128.2, 127.0, 126.8, 125.8, 124.5, 67.0, 58.8, 38.7. IR (neat, cm^{-1}) 1718 (s), 1687 (vs), 1498 (s). HRMS (FAB) Calcd for $C_{27}H_{24}NO_3$ ($[M+H]^+$): 410.1750. Found: 410.1753. $[\alpha]_D^{20}$ +18.4 (*c* 0.58, $CHCl_3$).

(+)-(*S*,*Z*)-Benzyl 3-oxo-1-phenylhex-4-en-2-ylcarbamate, 28



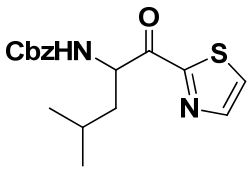
Following the general procedure, *N*-Cbz-L-Phe-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with (*Z*)-tri-*n*-butyl(prop-1-enyl)stannane (40 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a colorless oil. Yield: 26 mg (81%). TLC (R_f= 0.50, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 9.2 min, D-isomer t_R = 8.2 min, ee = 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 7.24-7.21 (m, 3H), 7.07-7.05 (m, 2H), 6.41-6.32 (m, 1H), 6.22 (dd, *J* = 11.2, 1.6 Hz, 1H), 5.53 (d, *J* = 6.8 Hz, 1H), 5.13 (AB q, *J* = 12.0 Hz, 1H), 5.07 (AB q, *J* = 12.0 Hz, 1H), 4.71-4.66 (m, 1H), 3.18 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.02 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.12 (dd, *J* = 7.2, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 155.8, 146.8, 136.6, 135.9, 129.6, 128.6, 128.2, 127.1, 125.2, 66.9, 61.0, 37.8, 16.5. IR (neat, cm^{-1}) 1722 (s), 1691 (vs), 1498 (s). HRMS (FAB) Calcd for $C_{20}H_{22}NO_3$ ($[M+H]^+$): 324.1594. Found: 324.1591. $[\alpha]_D^{20}$ +56.0 (*c* 0.20, $CHCl_3$).

(+)-(*S*)-Benzyl 4-methyl-1-oxo-1-(thiophen-2-yl)pentan-2-yl carbamate, 29



Following the general procedure, *N*-Cbz-L-Leu-S-*p*-tolyl (37 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a colorless oil. Yield: 30 mg (91%). TLC (R_f= 0.39, silica gel, 20% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, L-isomer t_R = 15.4 min, D-isomer t_R = 17.5 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 3.2 Hz, 1H), 7.70 (d, *J* = 5.2 Hz, 1H), 7.36-7.30 (m, 5H), 7.17 (t, *J* = 4.4 Hz, 1H), 5.52 (d, *J* = 9.2 Hz, 1H), 5.24-5.19 (m, 1H), 5.13-5.07 (m, 2H), 1.82-1.77 (m, 1H), 1.70-1.63 (m, 1H), 1.58-1.51 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 156.2, 141.6, 136.4, 135.0, 133.1, 128.7, 128.6, 128.3, 128.2, 67.1, 55.1, 43.4, 25.1, 23.5, 21.9. IR (neat, cm^{-1}) 1714 (s), 1664 (vs), 1513 (s). HRMS (FAB) Calcd for $C_{18}H_{22}NO_3S$ ($[M+H]^+$): 332.1314. Found: 332.1316. $[\alpha]_D^{20}$ +28.7 (*c* 0.47, $CHCl_3$).

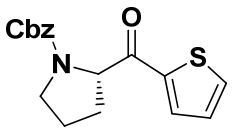
(±)-Benzyl 4-methyl-1-oxo-1-(thiazol-2-yl)pentan-2-yl carbamate, 30



Following the general procedure, *N*-Cbz-L-Leu-S-*p*-tolyl (37 mg, 0.10 mmol, 1.0 equiv) was coupled with 2-(tri-*n*-butylstannyl)thiazole (44 mg, 0.11 mmol, 1.1 equiv) at 50 °C to give the title compound as a colorless oil. Yield: 16 mg (48%). TLC (R_f=

0.38, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, isomer-1 t_R = 7.2 min, isomer-2 t_R = 8.2 min, ee = 0%.[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 2.8 Hz, 1H), 7.70 (d, *J* = 2.8 Hz, 1H), 7.36-7.31 (m, 5H), 5.53 (br s, 2H), 5.10 (s, 2H), 1.81-1.79 (m, 2H), 1.56-1.52 (m, 1H), 1.06 (d, *J* = 6.0 Hz, 3H), 0.93 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 164.7, 156.2, 145.3, 136.4, 128.7, 128.3, 126.9, 67.2, 55.9, 42.3, 25.3, 23.5, 21.7. IR (neat, cm^{-1}) 1718 (s), 1695 (vs), 1521 (s). HRMS (FAB) Calcd for $C_{17}H_{21}N_2O_3S$ ($[M+H]^+$): 333.1267. Found: 333.1269.

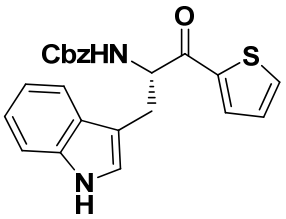
(-)-(*S*)-Benzyl 2-(thiophene-5-carbonyl)pyrrolidine-1- carboxylate, 31



Following the general procedure, *N*-Cbz-L-Pro-S-*p*-tolyl (41 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a pale yellow oil. Yield: 22 mg (70%). TLC (R_f= 0.60, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, L-isomer t_R = 11.1 min, D-isomer t_R = 10.6 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) two rotamers δ 7.82-7.81 (m, 0.5H), 7.71-7.69 (m, 0.5H), 7.66-7.64 (m, 1H), 7.38-7.30 (m, 3H), 7.19-7.09 (m, 3H), 5.19-5.02 (m, 3H), 3.75-3.55 (m, 2H), 2.38-2.29 (m, 1H), 2.06-1.91 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 191.8, 191.5, 155.0, 154.4, 141.6, 141.2, 136.9, 136.5, 134.2, 132.6, 132.4, 128.6,

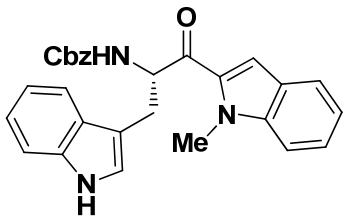
128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 67.2, 62.7, 62.6, 47.5, 46.9, 31.7, 30.6, 24.5, 23.8. IR (neat, cm^{-1}) 1702 (s), 1671 (vs), 1413 (s). HRMS (FAB) Calcd for $C_{17}H_{18}NO_3S$ ($[M+H]^+$): 316.1001. Found: 316.1004. $[\alpha]_D^{20}$ -33.4 (*c* 0.61, $CHCl_3$).

(+)-(*S*)-Benzyl 3-(1*H*-indol-3-yl)-1-oxo-1-(thiophen-2-yl) propan-2-ylcarbamate, 32



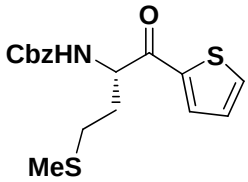
Following the general procedure, *N*-Cbz-L-Trp-S-*p*-tolyl (43 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a pale yellow oil. Yield: 39 mg (97%). TLC (R_f= 0.66, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.7 mL/min; T = 30 °C; Gradient: 50 % H_2O in CH_3CN for 35 min, during 45 min to 100 % CH_3CN hold for 5 min, L-isomer t_R = 36.7 min, D-isomer t_R = 39.5 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.66 (app t, *J* = 5.2 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.38-7.29 (m, 6H), 7.17 (t, *J* = 8.0, 7.2 Hz, 1H), 7.10-7.04 (m, 2H), 6.83 (d, *J* = 2.0 Hz, 1H), 5.73 (d, *J* = 8.4 Hz, 1H), 5.48 (m, 1H), 5.15 (AB q, *J* = 12.0 Hz, 1H), 5.09 (AB q, *J* = 12.0 Hz, 1H), 3.45 (dd, *J* = 6.0, 14.4 Hz, 1H), 3.31 (dd, *J* = 5.6, 14.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 191.4, 155.9, 141.9, 136.5, 136.2, 135.0, 133.3, 128.7, 128.5, 128.3, 128.2, 127.7, 123.2, 122.3, 119.8, 118.8, 111.4, 109.9, 67.1, 57.2, 29.9. IR (neat, cm-1) 1702 (s), 1660(s), 1505 (s). HRMS (FAB) Calcd for $C_{23}H_{21}N_2O_3S$ ($[M+H]^+$): 405.1267. Found: 405.1261. $[\alpha]_D^{20}$ +111.5 (*c* 1.20, $CHCl_3$) [Lit.[10] $[\alpha]_D^{20}$ +112.6 (*c* 1.25, $CHCl_3$)].

(+)-(*S*)-Benzyl 3-(1*H*-indol-3-yl)-1-(1-methyl-1*H*-indol-2-yl)-1-oxopropan-2-yl carbamate, 33



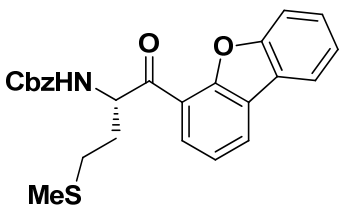
Following the general procedure, *N*-Cbz-L-Trp-S-*p*-tolyl (44 mg, 0.10 mmol, 1.0 equiv) was coupled with 1-methyl-2-(tri-*n*-butylstannyl)-1*H*-indole (49 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a pale yellow solid. Yield: 42 mg (93%). TLC (R_f = 0.45, silica gel, 40% ethyl acetate in hexanes). Mp = 68-69.5 °C. HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.8 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 25 min, 75% CH_3CN to 100 % CH_3CN in 10 min, hold for 10 min, L-isomer t_R = 27.8 min, D-isomer t_R = 27.1 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.44-7.27 (m, 9H), 7.21-7.17 (m, 2H), 7.14 (t, *J* = 8.0, 7.6 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 5.84 (d, *J* = 8.0 Hz, 1H), 5.62-5.57 (m, 1H), 5.18 (AB q, *J* = 12.0 Hz, 1H), 5.12 (AB q, *J* = 12.0 Hz, 1H), 3.82 (s, 3H), 3.50 (dd, *J* = 6.0, 14.8 Hz, 1H), 3.31 (dd, *J* = 5.6, 14.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 191.4, 155.9, 140.6, 136.6, 136.1, 132.9, 128.6, 128.2, 127.6, 126.6, 126.0, 123.4, 123.0, 122.1, 121.1, 119.6, 118.7, 112.5, 111.3, 110.5, 110.0, 67.0, 57.2, 32.1, 30.3. IR (neat, cm^{-1}) 1706 (s), 1660(vs), 1509 (s). HRMS (FAB) Calcd for $C_{28}H_{26}N_3O_3$ ($[M+H]^+$): 452.1968. Found: 452.1972. $[\alpha]_D^{20}$ +40.5 (*c* 0.44, $CHCl_3$).

(+)-(*S*)-Benzyl 4-(methylthio)-1-oxo-1-(thiophen-2-yl)butan-2-yl carbamate, 34



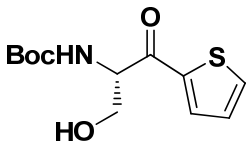
Following the general procedure, *N*-Cbz-L-Met-S-*p*-tolyl (39 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a colorless oil. Yield: 30 mg (86%). TLC (R_f= 0.34, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, L-isomer t_R = 15.5 min, D-isomer t_R = 18.7 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 3.2 Hz, 1H), 7.73-7.71 (m, 1H), 7.35-7.30 (m, 5H), 7.17 (t, *J* = 4.8 Hz, 1H), 5.73 (d, *J* = 8.4 Hz, 1H), 5.37-5.32 (m, 1H), 5.14 (AB q, *J* = 12.4 Hz, 1H), 5.08 (AB q, *J* = 12.4 Hz, 1H), 2.64-2.50 (m, 2H), 2.24-2.16 (m, 1H), 2.05 (s, 3H), 1.97-1.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 156.1, 141.3, 136.3, 135.4, 133.6, 128.7, 128.3, 128.2, 67.2, 55.7, 33.9, 30.3, 15.7. IR (neat, cm^{-1}) 1718 (s), 1664 (vs), 1513 (s). HRMS (FAB) Calcd for $C_{17}H_{20}NO_3S_2$ ($[M+H]^+$): 350.0879. Found: 350.0881. $[\alpha]_D^{20}$ +26.4 (*c* 0.33, $CHCl_3$).

(-)-(*S*)-Benzyl 4-(methylthio)-1-oxo-1-(dibenzofuran-4-yl) butan-2-ylcarbamate, 35



Following the general procedure, *N*-Cbz-L-Met-S-*p*-tolyl (39 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(4-dibenzofuranyl)stannane (53 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a white solid. Yield: 34 mg (79%). TLC (R_f= 0.41, silica gel, 25% ethyl acetate in hexanes). Mp = 144-145 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, L-isomer t_R = 25.3 min, D-isomer t_R = 24.7 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.17 (m, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.48-7.32 (m, 7H), 5.99-5.88 (m, 2H), 5.19-5.16 (m, 2H), 2.79-2.71 (m, 1H), 2.65-2.58 (m, 1H), 2.43-2.34 (m, 1H), 1.97 (s, 3H), 1.91-1.82 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 156.3, 156.2, 154.3, 136.5, 128.7, 128.6, 128.3, 128.2, 126.6, 126.2, 123.8, 123.3, 123.1, 120.9, 119.6, 112.2, 67.2, 59.0, 32.9, 30.6, 15.7. IR (neat, cm^{-1}) 1722 (s), 1683 (vs), 1513 (s). HRMS (FAB) Calcd for $C_{25}H_{24}NO_4S$ ($[M+H]^+$): 434.1420. Found: 434.1422. $[\alpha]_D^{20}$ -1.7 (*c* 0.41, $CHCl_3$).

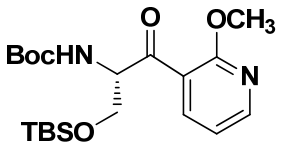
(-)-(*S*)-*tert*-Butyl 3-hydroxy-1-oxo-1-(thiophen-2-yl)propan-2-yl carbamate, 36



Following the general procedure, *N*-Boc-L-Ser -S-*p*-tolyl (31 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a colorless oil. Yield: 21 mg (79%). TLC (R_f= 0.41, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 83 % CH_3CN in 5 min, L-isomer t_R = 4.6 min,

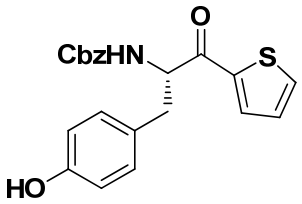
D-isomer t_R = 5.9 min, ee = 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 3.6 Hz, 1H), 7.74-7.73 (m, 1H), 7.19-7.17 (m, 1H), 5.76 (s, 1H), 5.16 (s, 1H), 4.03-3.93 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 156.2, 141.4, 135.5, 133.8, 128.7, 80.7, 65.4, 58.4, 28.5. IR (neat, cm^{-1}) 3412 (br), 1698 (s), 1664 (vs), 1505 (s). HRMS (FAB) Calcd for $C_{12}H_{18}NO_4S$ ($[M+H]^+$): 272.0951. Found: 272.0950. $[\alpha]_D^{20}$ -8.5 (*c* 0.55, $CHCl_3$).

(-)-(*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-1-(2-methoxypyridin-3-yl)-1-oxo-propan-2-ylcarbamate, 37



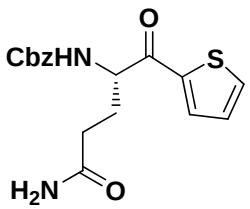
Following the general procedure, *O*-TBS-*N*-Boc-L-serine-S-*p*-tolyl (42 mg, 0.10 mmol, 1.0 equiv) was coupled with 2-methoxy-3-(tri-*n*-butylstannyl)pyridine (46 mg, 0.11 mmol, 1.1 equiv) in DMF (1.5 mL) at 50 ^oC to give the title compound as a colorless oil. Yield: 34 mg (83%). TLC (R_f = 0.50, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 12 min, 75% CH_3CN to 100 % CH_3CN in 12 min, hold for 11 min, L-isomer t_R = 11.2 min, D-isomer t_R = 10.8 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.04 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.00 (dd, *J* = 8.0, 4.4 Hz, 1H), 5.66 (d, *J* = 8.0 Hz, 1H), 5.45-5.41 (m, 1H), 4.04 (s, 3H), 3.93 (d, *J* = 3.2 Hz, 2H), 1.46 (s, 9H), 0.76 (s, 9H), -0.09 (s, 3H), -0.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 161.5, 155.7, 151.2, 140.9, 120.1, 117.4, 79.7, 63.3, 61.4, 54.1, 28.6, 25.8, 18.3, -5.5, -5.6. IR (neat, cm^{-1}) 1718 (s), 1687 (s), 1586 (s). HRMS (FAB) Calcd for $C_{20}H_{35}N_2O_5Si$ ($[M+H]^+$): 411.2309. Found: 411.2309. $[\alpha]_D^{20}$ -10.0 (*c* 0.21, $CHCl_3$).

(+)-(*S*)-Benzyl 3-(4-hydroxyphenyl)-1-oxo-1-(thiophen-2-yl) propan-2-ylcarbamate, 38



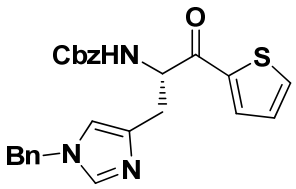
Following the general procedure, *N*-Cbz-L-Tyr-S-*p*-tolyl (42 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a colorless oil. Yield: 26 mg (68%). TLC (R_f= 0.54, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, L-isomer t_R = 15.7 min, D-isomer t_R = 13.2 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.75 (m, 1H), 7.71-7.70 (m, 1H), 7.37-7.30 (m, 5H), 7.14-7.12 (m, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.64-6.61 (m, 2H), 6.03 (s, 1H), 5.67 (d, *J* = 8.0 Hz, 1H), 5.39-5.34 (m, 1H), 5.13 (AB q, *J* = 12.4 Hz, 1H), 5.07 (AB q, *J* = 12.4 Hz, 1H), 3.18 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.99 (dd, *J* = 14.0, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 156.1, 141.3, 136.3, 135.4, 133.6, 128.7, 128.3, 128.2, 67.2, 55.7, 33.9, 30.3, 15.7. IR (neat, cm^{-1}) 3343 (br), 1698 (s), 1660 (vs), 1513 (s). HRMS (FAB) Calcd for $C_{21}H_{20}NO_4S$ ($[M+H]^+$): 382.1107. Found: 382.1109. $[\alpha]_D^{20}$ +63.8 (*c* 0.34, $CHCl_3$).

(+)-(*S*)-Benzyl 5-amino-1,5-dioxo-1-(thiophen-2-yl)pentan-2-yl carbamate, 39



Following the general procedure, *N*-Cbz-L-Gln-S-*p*-tolyl (39 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) in THF (1.5 mL) to give the title compound as a white solid. Yield: 28 mg (81%). TLC (R_f = 0.43, silica gel, 3% methanol in ethyl acetate). Mp = 161-162 °C. HPLC Chiral AS-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 70 % H_2O in CH_3CN to 60% CH_3CN in 10 min, 60% CH_3CN to 100 % CH_3CN in 10 min, hold for 5 min, L-isomer t_R = 13.3 min, D-isomer t_R = 13.9 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 3.6 Hz, 1H), 7.71 (d, *J* = 4.8 Hz, 1H), 7.35-7.29 (m, 5H), 7.16 (t, *J* = 4.4 Hz, 1H), 6.11 (br s, 1H), 6.00 (d, *J* = 8.0 Hz, 1H), 5.64 (br s, 1H), 5.24-5.19 (m, 1H), 5.10 (s, 2H), 2.46-2.29 (m, 3H), 1.86-1.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 174.6, 156.8, 140.9, 136.3, 135.5, 134.2, 128.9, 128.7, 128.4, 128.2, 67.3, 56.0, 31.6, 30.9. IR (neat, cm^{-1}) 1687 (s), 1656 (vs), 1536 (m). HRMS (FAB) Calcd for $C_{17}H_{19}N_2O_4S$ ($[M+H]^+$): 347.1060. Found: 347.1061. $[\alpha]_D^{20}$ +26.4 (*c* 0.33, $CHCl_3$).

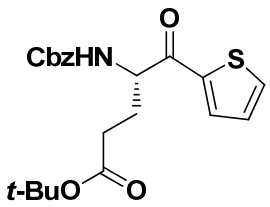
(+)-(*S*)-Benzyl 3-(1-benzyl-1*H*-imidazol-4-yl)-1-oxo- 1-(thiophen-2-yl)propan-2-yl carbamate, 40



Following the general procedure, 1-benzyl-*N*-Cbz-L-His-S-*p*-tolyl (49 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) in THF (1.5 mL) to give the title compound as a pale yellow solid. Yield: 35 mg (78%). TLC (R_f = 0.65, silica gel, 11% methanol in ethyl acetate with 2% triethylamine). Mp = 116-120 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84

(d, *J* = 3.2 Hz, 1H), 7.65-7.64 (m, 1H), 7.41 (d, *J* = 1.2 Hz, 1H), 7.34-7.28 (m, 8H), 7.11-7.09 (m, 1H), 7.04-7.01 (m, 2H), 6.55 (s, 1H), 6.16 (d, *J* = 8.0 Hz, 1H), 5.37-5.33 (m, 1H), 5.07-4.97 (m, 4H), 3.16 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.04 (dd, *J* = 14.8, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 156.0, 141.8, 137.5, 137.4, 136.6, 136.2, 134.7, 133.3, 129.1, 128.6, 128.5, 128.4, 128.3, 128.2, 127.2, 117.4, 67.0, 57.0, 50.9, 32.2. IR (neat, cm^{-1}) 1714 (vs), 1664 (s), 1502 (s). HRMS (FAB) Calcd for $C_{25}H_{24}N_3O_3S$ ($[M+H]^+$): 446.1532. Found: 446.1532. $[\alpha]_D^{20}$ +21.4 (*c* 0.42, $CHCl_3$).

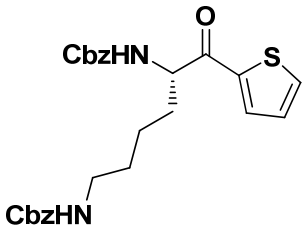
(+)-(*S*)-*tert*-Butyl 4-(benzyloxycarbonyl)-5-oxo-5-(thiophen-2-yl) pentanoate, 41



Following the general procedure, 5-*tert*-butyl-*N*-Cbz-L-Glu-S-*p*-tolyl (45 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a colorless oil. Yield: 32 mg (80%). TLC (R_f = 0.40, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, L-isomer t_R = 17.3 min, D-isomer t_R = 18.5 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 3.6 Hz, 1H), 7.72-7.71 (m, 1H), 7.35-7.30 (m, 5H), 7.18 (t, *J* = 4.4 Hz, 1H), 5.69 (d, *J* = 8.0 Hz, 1H), 5.27-5.22 (m, 1H), 5.13 (AB q, *J* = 12.0 Hz, 1H), 5.07 (AB q, *J* = 12.0 Hz, 1H), 2.45-2.24 (m, 3H), 1.88-1.78 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 172.2, 156.2, 141.3, 136.4, 135.3, 133.9, 128.8, 128.7, 128.3, 128.2, 80.9, 67.2, 55.8, 31.0, 29.5, 28.2. IR (neat, cm^{-1}) 1722 (vs), 1664

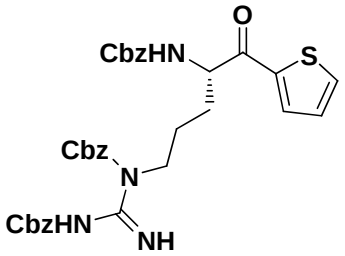
(vs), 1513 (m). HRMS (FAB) Calcd for $C_{21}H_{26}NO_5S$ ($[M+H]^+$): 404.1526. Found: 404.1528. $[\alpha]_D^{20}$ +22.9 (*c* 0.31, $CHCl_3$).

(+)-(*S*)-Benzyl 6-(benzyloxycarbonylamino)-1-oxo- 1-(thiophen-2-yl)hexan-2-yl carbamate, 42



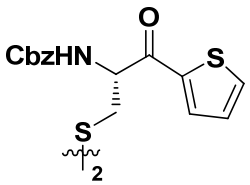
Following the general procedure, *N,N'*-di-Cbz-L-Lys-S-*p*-tolyl (52 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a colorless oil. Yield: 48 mg (99%). TLC (R_f = 0.52, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, L-isomer t_R = 19.7 min, D-isomer t_R = 21.0 min, ee = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 3.6 Hz, 1H), 7.71-7.70 (m, 1H), 7.34-7.29 (m, 10H), 7.16 (t, *J* = 4.8 Hz, 1H), 5.77 (d, *J* = 7.6 Hz, 1H), 5.17-5.06 (m, 5H), 4.89 (br s, 1H), 3.17-3.13 (m, 2H), 1.97-1.92 (m, 1H), 1.72-1.67 (m, 1H), 1.56-1.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 156.6, 156.2, 141.4, 136.7, 136.3, 135.2, 133.2, 128.6, 128.3, 128.2, 67.2, 66.7, 56.3, 40.7, 33.8, 29.5, 22.3. IR (neat, cm^{-1}) 1702 (vs), 1664 (vs), 1517 (s). HRMS (FAB) Calcd for $C_{26}H_{29}N_2O_5S$ ($[M+H]^+$): 481.1791. Found: 481.1793. $[\alpha]_D^{20}$ +23.3 (*c* 0.63, $CHCl_3$).

(+)-(*S*)-Benzyl 5-(1,3-dibenzyloxycarbonylguanidin-1-yl)- 1-oxo-1-(thiophen-2-yl) pentan-2-ylcarbamate, 43



Following the general procedure, tri-Cbz-L-Arg-S-*p*-tolyl (68 mg, 0.10 mmol, 1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (43 mg, 0.11 mmol, 1.1 equiv) to give the title compound as a pale yellow solid. Yield: 42 mg (65%). TLC (R_f = 0.42, silica gel, 33% ethyl acetate in hexanes). Mp = 136-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (br s, 1H), 9.23 (br s, 1H), 7.75 (d, *J* = 3.2 Hz, 1H), 7.65 (d, *J* = 4.4 Hz, 1H), 7.37-7.26 (m, 15H), 7.07 (t, *J* = 4.4 Hz, 1H), 5.74 (d, *J* = 8.4 Hz, 1H), 5.18-5.04 (m, 7H), 3.98-3.91 (m, 2H), 1.91-1.87 (m, 1H), 1.72-1.64 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 164.0, 160.6, 156.1, 155.9, 141.5, 137.1, 136.4, 135.1, 134.7, 133.3, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 69.1, 67.2, 66.7, 56.4, 44.4, 30.7, 24.8. IR (neat, cm^{-1}) 1718 (vs), 1660 (m), 1610 (s), 1509 (s). HRMS (FAB) Calcd for $C_{34}H_{35}N_4O_7S$ ($[M+H]^+$): 643.2221. Found: 643.2226. $[\alpha]_D^{20}$ +8.1 (*c* 0.27, $CHCl_3$).

(+)-(*R*,*R'*)-3,3'-Dithiobis(2-benzyloxycarbonylamino-1-(thiophen-2-yl)propan-1-one), 44



Following the general procedure, di-Cbz-L-cystine-bis-S-*p*-tolyl (72 mg, 0.10 mmol,

1.0 equiv) was coupled with tri-*n*-butyl(thiophen-2-yl)stannane (86 mg, 0.22 mmol, 2.2 equiv) in THF (1.5 mL) to give the title compound as a colorless oil. Yield: 47 mg (73%). TLC (R_f = 0.48, silica gel, 40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 3.2 Hz, 2H), 7.71 (d, *J* = 4.8 Hz, 2H), 7.32-7.29 (m, 10H), 7.14 (t, *J* = 4.4 Hz, 2H), 5.83 (d, *J* = 8.4 Hz, 2H), 5.44-5.43 (m, 2H), 5.09-5.08 (m, 4H), 3.23 (dd, *J* = 14.4, 5.2 Hz, 2H), 3.07 (dd, *J* = 14.0, 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4, 155.9, 141.5, 136.2, 135.8, 134.0, 133.3, 128.8, 128.7, 128.4, 128.3, 67.4, 55.7, 42.4. IR (neat, cm^{-1}) 1710 (s), 1660 (vs), 1513 (s). HRMS (FAB) Calcd for $C_{30}H_{29}N_2O_6S_4$ ($[M+H]^+$): 641.0903. Found: 641.0898. $[\alpha]_D^{20}$ +44.5 (*c* 0.29, $CHCl_3$).

1.5 References

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characterization data provided for this compound in this paper except for the mass spectrum.

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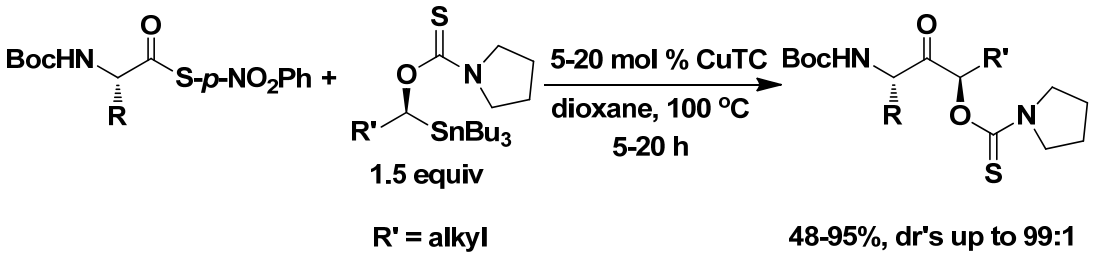
[24] *The ketone product completely racemized due to its 1,2-diketone similar structure.*

Chapter 2

Stereocontrolled α,α′-Aminoalkoxy Ketone Synthesis by Thiol Ester and α-Alkoxyalkylstannanes Cross-Coupling

Abstract: *A stereocontrolled synthesis of α,α'-aminoalkoxy ketones is described. As a new approach to enantioenriched α-alkoxy ketones, this pH-neutral copper(I) thiophene-2-carboxylate (CuTC)-catalyzed cross-coupling of amino acid thiol esters and chiral α-(thiocarbamoyl)alkylstannanes gives α,α'-aminoalkoxy ketones in good to excellent yields with complete retention of configuration at the α-stannyl- and α-alkoxy-substituted stereocenters (***Scheme 2.1***).*

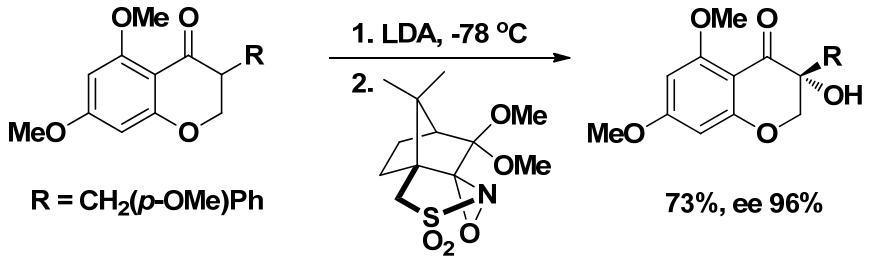
Scheme 2.1 α,α′-Aminoalkoxy Ketones from Thiol Esters and Alkylstannanes



2.1 Introduction and Background

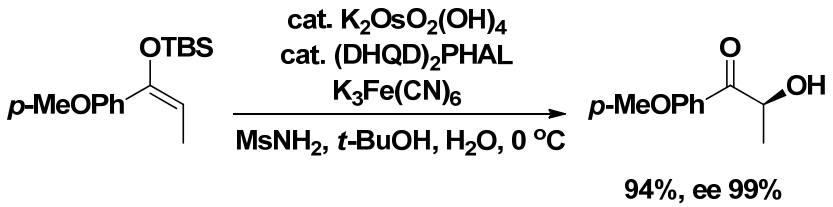
Enantioenriched α-alkoxy ketones are common moieties in natural products and biologically active compounds. They are also useful building blocks in organic synthesis.[1] The most direct method for the construction of enantioenriched α-alkoxy ketones is the asymmetric α-hydroxylation of enolates or silyl enol ethers.[2] Davis and co-workers developed an enantioselective hydroxylation of prochiral enolates with chiral camphorylsulfonyloxaziridines (**Scheme 2.2**).[3] This reaction could provide both enantiomers of the desired α-alkoxy ketone product by choosing the appropriate oxaziridine oxidant.

Scheme 2.2 α-Hydroxylation of Enolates Using Chiral Camphorylsulfonyloxaziridines

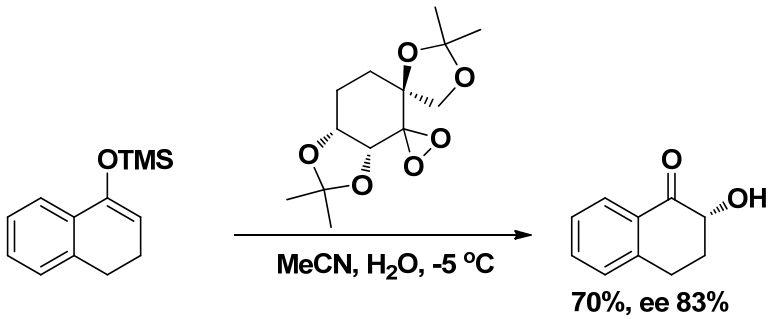


Asymmetric α-hydroxylation of ketone silyl enol ethers was reported by Sharpless and co-workers. Ketone silyl enol ethers were converted to α-alkoxy ketones in good to excellent enantiomeric excess by osmium tetroxide-catalyzed asymmetric dihydroxylation (**Scheme 2.3**, **equation 1**).[4] Another asymmetric α-hydroxylation of ketone silyl enol ethers was based on Shi epoxidation (**Scheme 2.3**, **equation 2**).[5]

Scheme 2.3 Asymmetric α-Hydroxylation of Ketone Silyl Enol Ethers



(1)

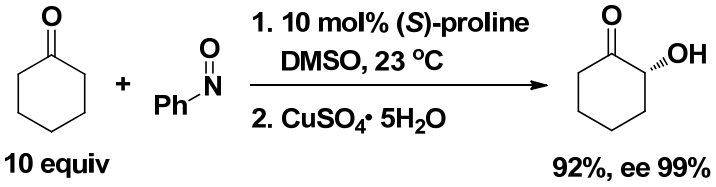


(2)

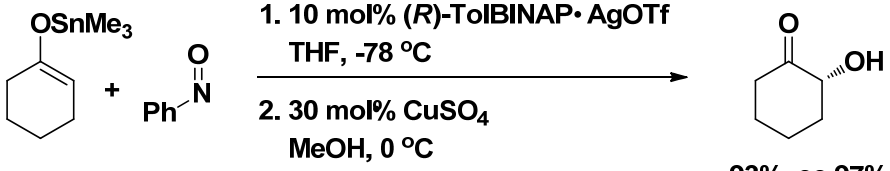
Recent studies[6] for the synthesis of enantioenriched α-alkoxy ketones have focused on asymmetric α-hydroxylation of ketones[7] or tin enolates[8] using chiral catalysts. Córdova and co-workers reported a proline-catalyzed enantioselective α-aminoxylation of ketones to give α-alkoxy ketones after deprotection (**Scheme 2.4**, **equation 1**),[7a] while Hayashi and co-workers published a similar procedure at the same

time.[7c] The synthesis of enantioenriched α-alkoxy ketones was also realized by a catalytic enantioselective α-aminoxylation of tin enolates developed by Yamamoto and co-workers (**Scheme 2.4**, **equation 2**).[8]

Scheme 2.4 Asymmetric α-Hydroxylation Using Chiral Catalysts



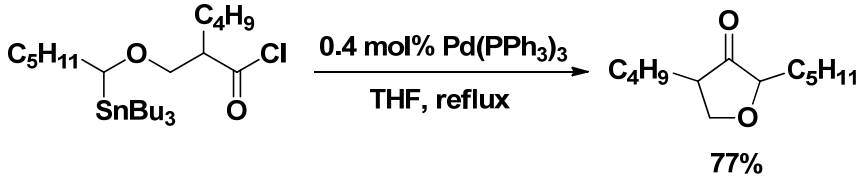
(1)



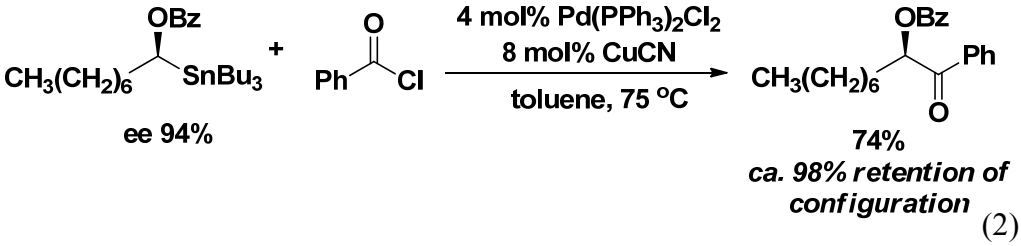
(2)

Complementary synthetic approaches to α-alkoxy ketones *via* Stille-type cross-couplings of acyl chlorides and α-alkoxyalkylstannanes to transfer sp^3-carbon were developed using Pd/Cu cocatalysts.[9] Linderman and co-workers disclosed a palladium-catalyzed intramolecular Stille coupling of acyl chlorides and α-alkoxyalkylstannanes to afford a furanone product (**Scheme 2.5**, **equation 1**).[9d] Falck and co-workers reported a detailed study of the palladium/copper-cocatalyzed cross-coupling of α-alkoxy- and α-aminoalkylstannanes with acyl chlorides (**Scheme 2.5**, **equation 2**).[9a] The authors found that this coupling proceeded with retention of configuration at the α-carbon center of an enantioenriched α-alkoxyalkylstannane.

Scheme 2.5 Palladium-Catalyzed Cross-Couplings of Acyl Chlorides and α-Alkoxyalkylstannanes



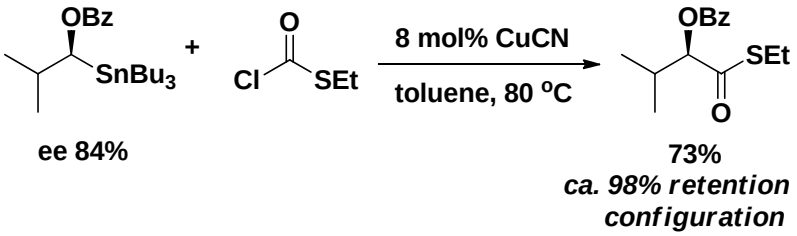
(1)



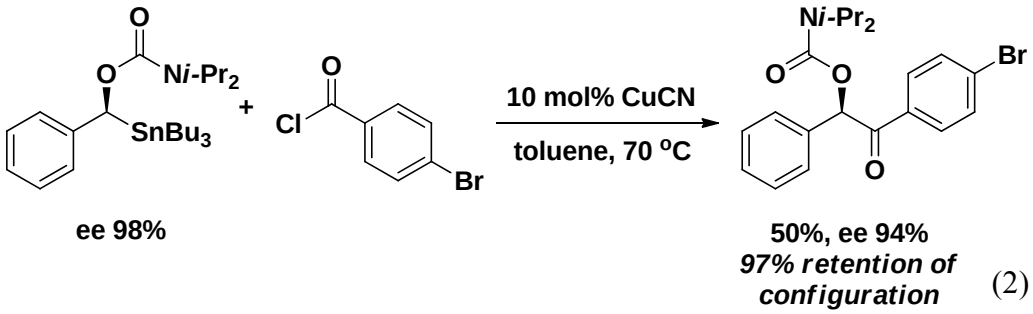
(2)

In the follow-up study by Falck and others,[10] they found that *catalytic amounts of copper salts*, without palladium, were able to mediate the cross-coupling of α-alkoxy- and α-aminoalkylstannanes with acyl chlorides to give α-alkoxy ketones. Importantly, this reaction was proven to proceed with retention of stereochemistry (ca. 98% of retention) at α-carbon center attached to Sn (**Scheme 2.6**, **equation 1**).[10a] Recently, Hoppe and co-workers reported another stereocontrolled α-alkoxy ketone synthesis by enantioenriched α-stannylated benzyl carbamate−acyl chloride cross-coupling with retention of configuration (**Scheme 2.6**, **equation 2**).[10c] Notably, when ethyl chlorothioformate was coupled with (*S*)-2-methyl-1-(tributylstannyl)propyl benzoate (**Scheme 2.6**, **equation 1)**, the C-Cl bond was selectively cleaved, while the C-S bond of ethyl chlorothioformate was untouched. In that regard, the cross-coupling of thiol esters and α-alkoxyalkylstannanes has not been explored.

Scheme 2.6 Copper-Catalyzed Cross-Couplings of Acyl Chlorides and α-Alkoxyalkylstannanes



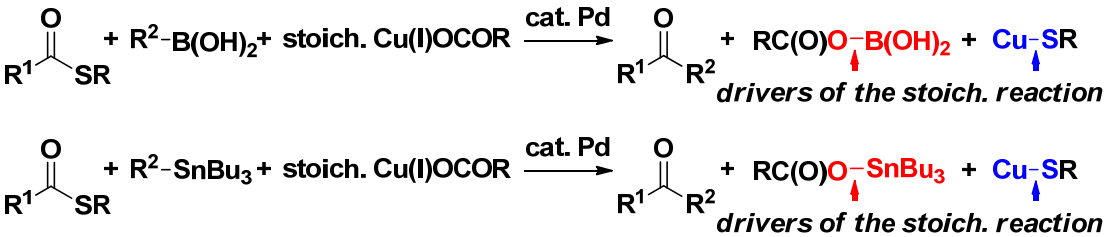
(1)



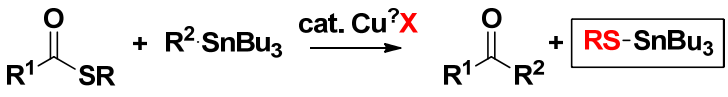
(2)

In our laboratory, a pH-neutral ketone synthesis from thiol esters and boronic acids or organostannanes using palladium catalysts and stoichiometric Cu^{I} carboxylate cofactors was described.[11] This mild reaction has been extended to the synthesis of high enantiopurity peptidyl ketones from peptidyl thiol esters.[12] In this palladium-catalyzed Cu^{I} carboxylate-mediated ketone synthesis, the thiolate which is generated in the reaction is trapped by stoichiometric Cu^{I} carboxylate to drive the coupling to the thermodynamic sink (**Scheme 2.7**). For the organostannane system the reaction might be rendered catalytic in copper, if the thiolate generated in the proposed reaction could be trapped by Bu_3Sn- to form thermodynamically stable tributylstannyl thiolate (**Scheme 2.8**). To explore the feasibility of this proposed chemistry as well as its application in a secondary alkyl transfer reaction, a study of the scope and limitations of the new stereocontrolled copper-catalyzed α,α′-aminoalkoxy ketone synthesis was undertaken in this chapter.

Scheme 2.7 1st Generation System Requires Stoichiometric Cu^{I} Carboxylate



Scheme 2.8 This Proposed Chemistry: Thiolate Paired with Bu_3Sn-

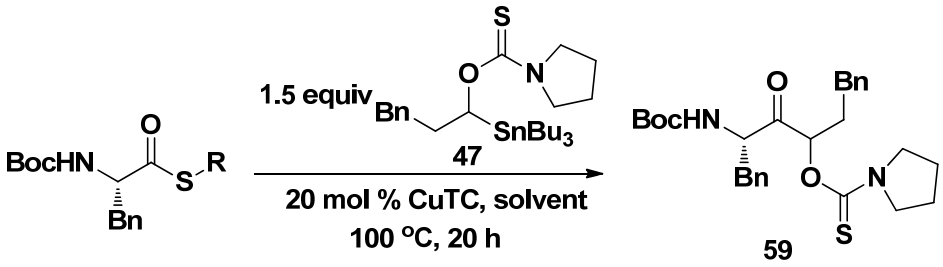


2.2 Results and Discussion

2.2.1 Preliminary Study

The project was initiated by exploring the cross-coupling of amino acid thiol esters and racemic pyrrolidinylthionocarbamoyl (PTC)-protected α-alkoxyalkylstannane **47,** which was proven to be a highly active coupling partner in copper-catalyzed cross-couplings.[10a] Results are depicted in **Table 2.1**. The coupling of L-Boc-Phe-SPh (**46**) with stannane **47** produced the desired α-alkoxy ketone **59** in 43% yield using CuTC as catalyst (**Table 2.1**, **entry 2**), while the corresponding L-Boc-Phe-SEt (**45**) generated no ketone product (**Table 2.1**, **entry 1**). Switching to a more electrophilic thiol ester L-Boc-Phe-S-*p*-NO_2Ph (**53**) led to an improved ketone yield (**Table 2.1**, **entry 3**). Upon screening solvents, *p*-dioxane was found to be the optimal solvent for the reaction and completely inhibited the decomposition of stannane **47** *via* an undesired O-S rearrangement.[13]

Table 2.1 Optimization Studies

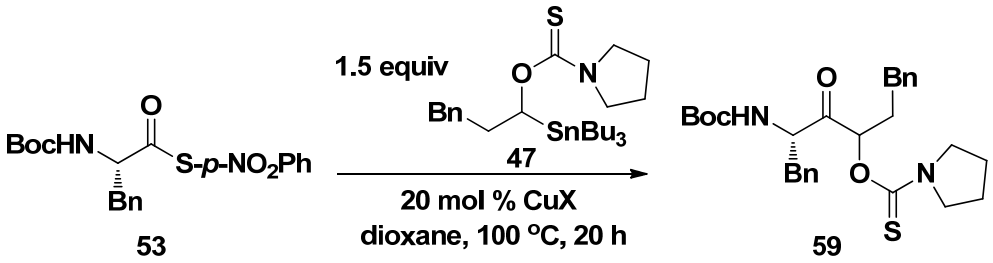


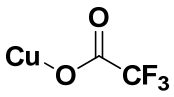
entry	R	solvent	yield[a] (%)
1	Et (**45**)	dioxane	0
2	Ph (**46**)	""	43
3	*p*-NO_2Ph (**53**)	""	87
4	**53**	toluene	61
5	**53**	1,2-dichloroethane	48
6	**53**	DMF	52

[a] Isolated yield.

In addition, different copper sources such as $CuOC(O)CF_3$, CuTC, CuI, CuCl, CuCN, $Cu(OAc)_2$, and $CuCl_2$ were investigated in the cross-coupling (**Table 2.2**). All the copper salts worked efficiently for the reaction although CuTC produced slightly higher yields of the ketone products. Control experiments revealed that no ketone product was formed without copper catalysts, in which both of thiol ester **53** and stannane **47** were completely recovered.

Table 2.2 Copper Source Screening

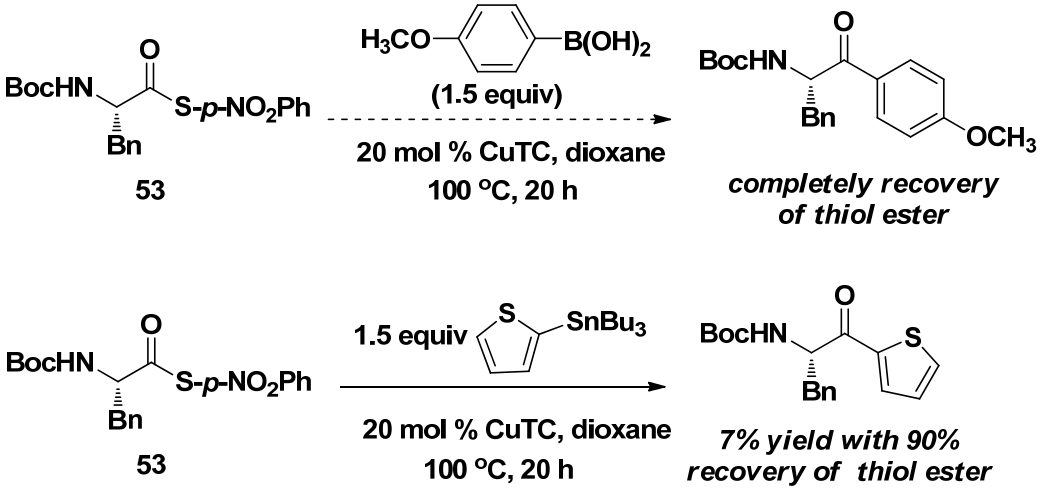


entry	CuX	yield[a] (%)
1		82
2	CuTC	87
3	CuI	82
4	CuCl	84
5	CuCN	83
6	$Cu(OAc)_2$	83
7	$CuCl_2$	84
8	10 mol% CuTC	89
9	5 mol% CuTC	92
10	No CuTC	0

[a] Isolated yield.

sp^2-Hydridized boronic acids and stannanes did not work efficiently in this copper-catalyzed cross-coupling (**Scheme 2.9**). The higher reactivity of PTC-protected α-alkoxyalkylstannes could result from intramolecular stabilization of the *in situ* generated copper intermediate by the thionocarbamate pendant.[10a]

Scheme 2.9 Control Experiments with sp^2-Hydridized Coupling Partners



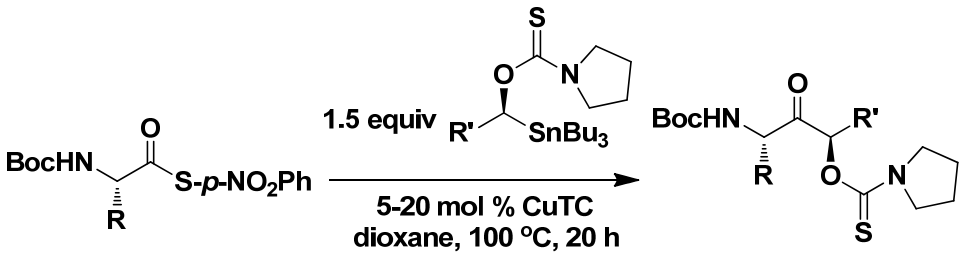
2.2.2 Stereocontrolled Desulfitative Coupling of Amino Acid Thiol Esters and Enantioenriched α-Alkoxyalkylstanne

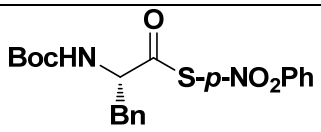
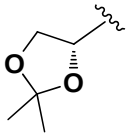
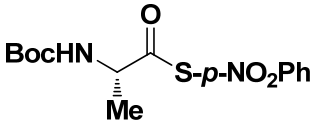
The scope of the desulfitative coupling of amino acid thiol esters and enantioenriched α-alkoxyalkylstanne was then explored. Results are summarized in **Table 2.3**. Enantioenriched PTC-protected stannane **48** (**Table 2.3**, **entries 1**, **4**, **9**, **and 12**) and stannane **51** (**Table 2.3**, **entry 7**) reacted efficiently. Cyclohexyl-substituted stannane **49** also participated in the reaction providing good yields of products (**Table 2.3**, **entries 2**, **5**, **8**, **10**, **and 13**). α,β-Dialkoxystannane **50** (**Table 2.3**, **entries 3**, **6**, **and 14**), a functional group relationship which is prone to β-elimination,[14] reacted smoothly with amino acid thiol esters to generate the corresponding trialkoxyketones in modest yields. The more robust α-alkoxy-β-aminostannane **58** (**Table 2.3**, **entries 11 and 15**) gave α-alkoxy-β-amino ketones in excellent yields. In most reactions, 20 mol % CuTC catalyst loading was

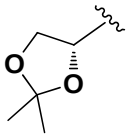
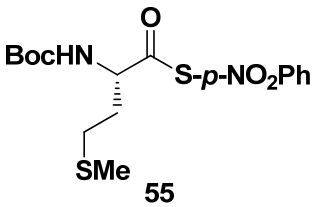
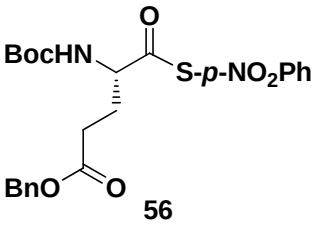
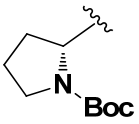
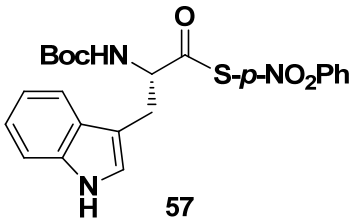
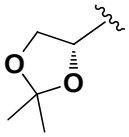
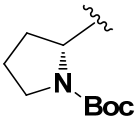
used though 5 mol % catalyst loading afforded the ketone products with slightly higher yields in some cases (**Table 2.3**, **entry 1**: 92% *vs* 87%; **entry 12**: 89% *vs* 85%).

A variety of *N*-protected amino acid thiol esters derived from naturally occuring amino acids such as Phe (**Table 2.3**, **entries 1-3**), Ala (**Table 2.3**, **entries 4-6**), Met (**Table 2.3**, **entries 7 and 8**), Glu (**Table 2.3**, **entries 9-11**) and Trp (**Table 2.3**, **entries 12-15**) coupled efficiently with α-alkoxyalkylstannes. Carbamate, ester, free indole, thiol ether, and acetal functional groups were well-tolerated using this pH-neutral reaction. The stereochemistry of the cross-coupling was investigated when enantioenriched stannanes **48**, **49** and **51** were employed. In all cases no epimerization was observed at the newly formed stereocenters from HPLC analysis.

Table 2.3 α,α′-Aminoalkoxy Ketone Synthesis by Stereocontrolled Thiol Ester–Alkoxyalkylstannane Cross-Coupling



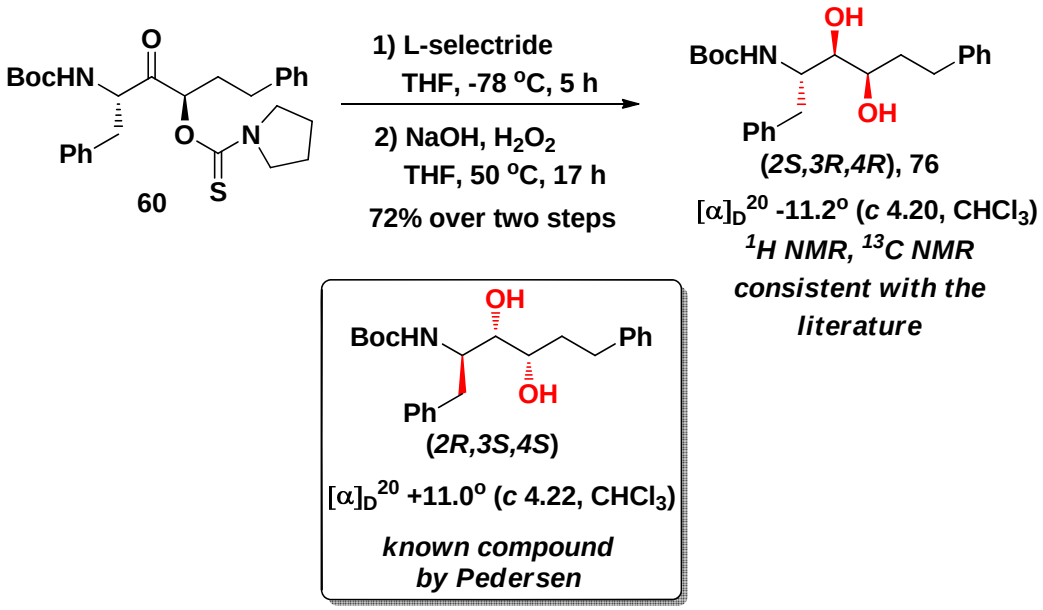
entry	thiol ester	R′	yield[a] (%)	dr[b]
1[c]	 **53**	phenylethyl[e]	92	58 : 1
2[d]	**53**	cyclohexyl[f]	67	99 : 1
3[d]	**53**		57	--
4[d]	 **54**	phenylethyl[e]	80	58 : 1
5[d]	**54**	cyclohexyl[f]	88	99 : 1

6[d]	**54**		48	--
7[d]	 **55**	phenylethyl[g]	82	28 : 1
8[d]	**55**	cyclohexyl[f]	70	99 : 1
9[d]	 **56**	phenylethyl[e]	73	58 : 1
10[d]	**56**	cyclohexyl[f]	76	99 : 1
11[d]	**56**		95	--
12[c]	 **57**	phenylethyl[e]	89	58 : 1
13[d]	**57**	cyclohexyl[f]	70	99 : 1
14[d]	**57**		60	--
15[d]	**57**		80	--

[a] Isolated yield. [b] dr determined by HPLC chiral OJ reversed phase column using diastereomeric mixtures derived from racemic α-alkoxystannanes as standards. [c] 5 mol% CuTC, dioxane, 100 °C, 20 h. [d] 20 mol% CuTC, dioxane, 100 °C, 20 h. [e] (*S*)-*O*-3-Phenyl-1-(tributylstannyl)propyl pyrrolidine-1-carbothioate **48** (ee 96.6%) was used. [f] (*S*)-*O*-Cyclohexyl(tributylstannyl)methyl pyrrolidine-1-carbothioate **49** (ee 98%) was used. [g] (*R*)-*O*-3-Phenyl-1-(tributylstannyl)propyl pyrrolidine-1-carbothioate **51** (ee 93%) was used.

In order to prove the stereochemistry of this new amino acid thiol ester–α-alkoxyalkylstannane coupling, L-selectride reduction of the α,α′-aminoalkoxy ketone **60** with Felkin-Ahn selectivity[15] followed by removal of the thionocarbamate group[16] afforded the *syn*,*syn*-aminodiol **76**. This is the enantiomer of a known compound prepared by Pedersen and co-workers (**Scheme 2.10**).[17] This result suggested the cross-coupling proceeded with retention of stereochemistry for the newly formed stereocenters of α,α′-aminoalkoxy ketones.

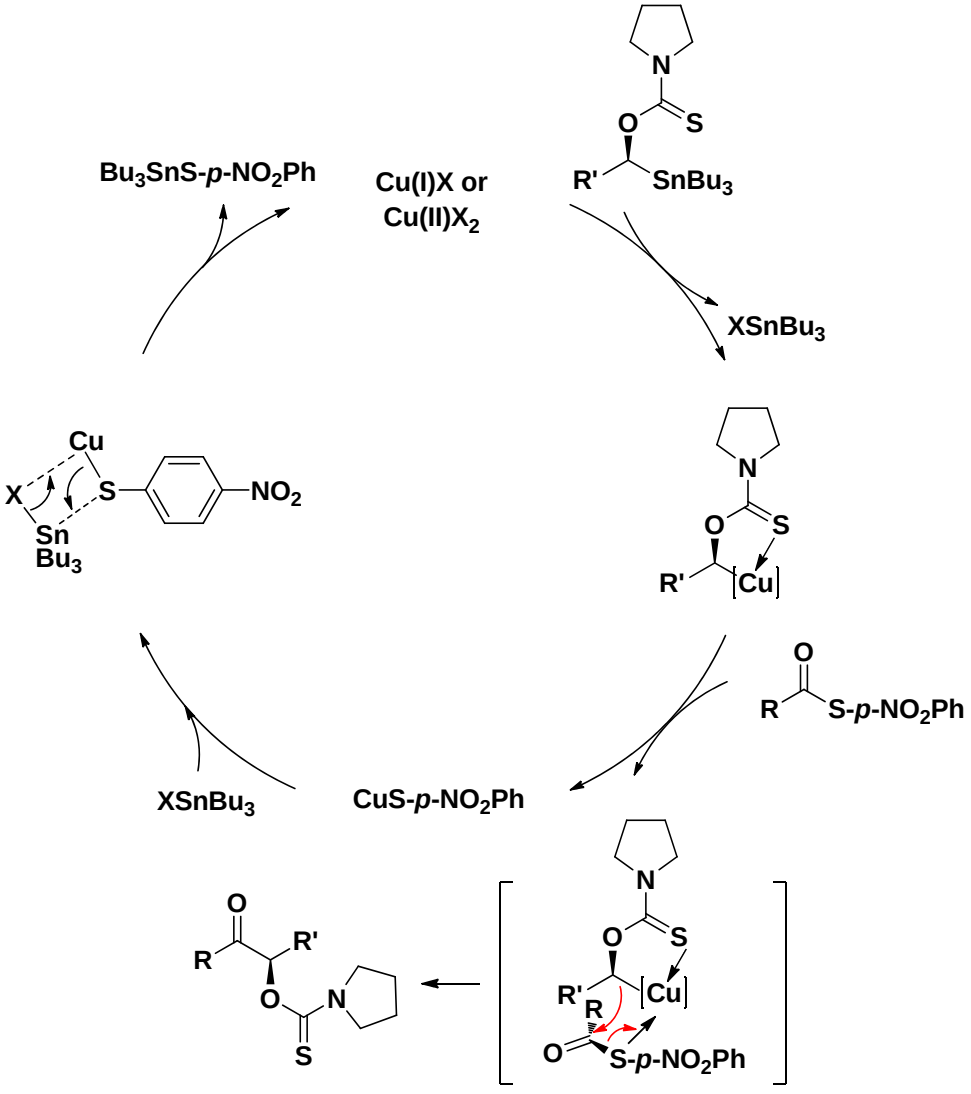
Scheme 2.10 Confirmation of Stereochemistry



A reasonable mechanistic pathway for the CuTC-catalyzed cross-coupling of amino acid thiol esters and enantioenriched α-alkoxyalkylstannanes is proposed in **Figure 2.1**. Similar to related tin-lithium transmetallation,[18] the tin-copper transmetallation with retention of configuration is precedented.[10a-c] After the formation of a thionocarbamate pendant-stabilized organocopper intermediate, nucleophilic addition to the thiol ester would afford the desired enantioenriched α,α′-aminoalkoxy ketones and copper thiolate. Finally, the thiolate would be trapped by Bu_3Sn- to generate a

catalytically active copper catalyst. This assumption was supported by the formation of Bu_3SnS-*p*-NO_2Ph (**61**) in approximately 1:1 ratio to the desired ketone products. Upon addition of 1.2 equiv Bu_3SnS-*p*-NO_2Ph (**61**) into the reaction of thiol ester L-Boc-Phe-S-*p*-NO_2Ph (**53**) and racemic stannane **47** at the beginning, the cross-coupling was retarded resulting in a lower ketone yield (48% vs 87%). This supports the hypothesis that at higher concentrations Bu_3SnS-*p*-NO_2Ph (**61**) can act as a coordinating ligand to copper and inhibit cross-coupling.

Figure 2.1 Proposed Mechanism



2.3 Conclusion

In summary, a highly efficient α,α′-aminoalkoxy ketone synthesis *via* secondary alkyl transfer has been developed using amino acid thiol esters and enantioenriched α-alkoxyalkylstannanes. A variety of ketones with epimerization-sensitive functionalities were prepared in good to excellent yield with complete retention of configuration at α-stannyl- and α-alkoxy-substituted stereocenters. This method could be a facile approach to construct epimerization-sensitive acyclic molecules with contiguous mulfunctionalities in a stereocontrolled manner.

2.4 Experimental Section

2.4.1 General Experimental

^{1}H and ^{13}C NMR spectra were recorded on Unity 600 MHz, Varian Inova 600 MHz, 400 MHz spectrometers, Mercury 300 MHz spectrometer, and VNMRS 400 MHz spectrometer in deuteriochloroform ($CDCl_3$) with the solvent residual peak ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.23 ppm; $(CD_3)_2SO$: ^{1}H = 2.50 ppm, ^{13}C = 39.51 ppm) as internal reference unless otherwise stated. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broad), 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 510 FT-IT or ASI ReactIR 1000 spectrometer. 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. HPLC analyses were carried out using an Agilent 1100 system with a

quarternary pump. Separations were achieved on a Zorbax Eclipse XDB C8 4.6 x 150 mm column or DAICEL chiral OD, OJ reversed phase column.

2.4.2 Starting Materials

All protected amino acids, solvents, 1,1′-thiocarbonyldiimidazole, pyrrolidine, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), L-selectride (1.0 M in tetrahydrofuran), hydrogen peroxide (30 wt% in water), copper(I) chloride, copper(I) iodide, copper(I) acetate, copper(I) cyanide, copper(II) chloride, copper(II) acetate and 4-dimethylaminopyridine (DMAP) were purchased from Sigma-Aldrich. 4-Nitrobenzenethiol was purchased from TCI. Copper(I) thiophene-2-carboxylate (CuTC), *p*-methoxyphenyl boronic acid and 2-(tri-*n*-butylstannyl)thiophene was provided by Dr. Gary Allred of Synthonix. L-Phe-Boc-SEt (**45**),[19] L-Phe-Boc-SPh (**46**),[20] (±)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate (**47**),[21] (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate (**48**),[22] (+)-(*S*)-*O*-cyclohexyl(tri-*n*-butylstannyl)methyl pyrrolidine-1-carbothioate (**49**),[22] (*S*)-*O*-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl](tri-*n*-butylstannyl)methyl pyrrolidine-1-carbothioate (**50**),[14] (-)-(*R*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate (**51**),[22] and (*R*)-*tert*-butyl 2-(*S*)-hydroxy(tri-*n*-butylstannyl) methyl pyrrolidine-1-carboxylate (**52**)[14] were prepared according to literature procedures.

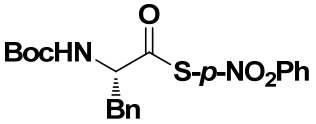
2.4.3 Experimental

General Procedure for the Preparation of Thiol Esters Derived from *N*-Protected Amino Acids

4-Nitrobenzenethiol (1.05 equiv) was added to a solution of *N*-protected amino acid in dry dichloromethane (2 mL/mmol) at 0 °C followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI, 1.0 equiv) in

dichloromethane (2 mL/mmol) over 15 min. The mixture was stirred for 24 h at room temperature. The reaction mixture was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, dichloromethane or ethyl acetate in hexanes) and then crystallization from 1 : 1 dichloromethane/hexanes affording the desired product.

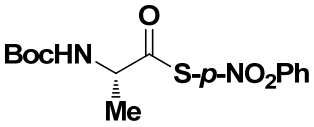
(-)-(*S*)-*S*-4-Nitrophenyl 2-(*tert*-butoxycarbonyl)amino-3-phenylpropanethioate, 53



Following the general procedure, 4-nitrobenzenethiol (1.700 g, 10.5 mmol) was added to a solution of *N*-Boc-L-phenylalanine (2.650 g, 10.0 mmol) in dry dichloromethane (20 mL) at 0 °C followed by EDCI (1.920g, 10.0 mmol) in dichloromethane (20 mL) over 15 min. The mixture was stirred for 24 h at room temperature. The reaction mixture was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, dichloromethane) and then crystallized from 1 : 1 dichloromethane/hexanes affording the title compound as a white solid. Yield: 2.010 g (50%). TLC (R_f = 0.60, silica gel, dichloromethane). Mp = 163-164 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 9.3 min, D-isomer t_R = 8.7 min, ee > 99%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 4.96 (d, *J* = 7.8 Hz, 1H), 4.76-4.74 (m, 1H), 3.19-3.14 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ

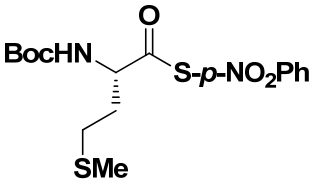
198.1, 155.1, 148.4, 136.4, 135.3, 135.2, 129.5, 129.0, 127.6, 124.1, 81.1, 61.4, 38.1, 28.4. IR (neat, cm^{-1}) 1714 (s), 1695 (vs), 1521 (s). HRMS (FAB) Calcd for $C_{20}H_{23}N_2O_5S$ ($[M+H]^+$): 403.1318. Found: 403.1322. $[\alpha]_D^{20}$ -141.5 (*c* 1.00, $CHCl_3$).

(-)-(*S*)-*S*-4-Nitrophenyl 2-[(*tert*-butoxycarbonyl)amino]propanethioate, 54



Following the general procedure, the title compound was prepared as a white solid. Yield: 1.630 g (50%). TLC (R_f = 0.53, silica gel, 5% diethyl ether in dichloromethane). Mp = 104-105 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 5.00 (s, 1H), 4.51-4.49 (m, 1H), 1.49 (s, 9H), 1.46 (d, *J* = 7.8 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.7, 155.1, 148.3, 136.4, 135.2, 124.1, 81.0, 56.8, 28.5, 18.4. IR (neat, cm^{-1}) 1714 (s), 1691 (vs), 1521 (s). HRMS (FAB) Calcd for $C_{14}H_{19}N_2O_5S$ ($[M+H]^+$): 327.1005. Found: 327.1009. $[\alpha]_D^{20}$ -58.3 (*c* 1.00, $CHCl_3$).

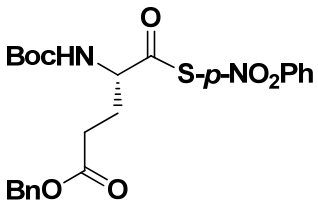
(-)-(*S*)-*S*-4-Nitrophenyl 2-(*tert*-butoxycarbonyl)amino-4-(methylthio)butane-thioate, 55



Following the general procedure, the title compound was prepared as a white solid. Yield: 1.891 g (49%). TLC (R_f = 0.57, silica gel, 5% diethyl ether in dichloromethane). Mp = 131.5-132.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.8 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 5.25 (d, *J* = 7.8 Hz, 1H), 4.62-4.61 (m, 1H), 2.64-2.56 (m, 2H), 2.24-2.21 (m, 1H), 2.11 (s, 3H), 2.01-1.97 (m, 1H), 1.49 (s, 9H). ^{13}C NMR (150 MHz,

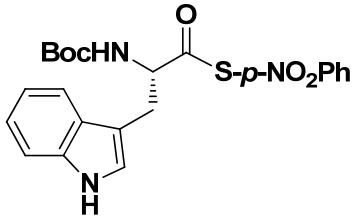
$CDCl_3$) δ 198.0, 155.2, 148.4, 136.3, 135.2, 124.1, 81.2, 60.2, 31.5, 30.2, 28.5, 15.6. IR (neat, cm^{-1}) 1702 (s), 1517 (s). HRMS (FAB) Calcd for $C_{16}H_{23}N_2O_5S_2$ ($[M+H]^+$): 387.1038. Found: 387.1042. $[\alpha]_D^{20}$ -60.2 (*c* 1.00, $CHCl_3$).

(-)-(*S*)-Benzyl 4-(*tert*-butoxycarbonyl)amino-5-(4-nitrophenyl)thio-5-oxo-pentanoate, 56



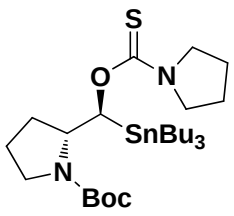
Following the general procedure, the title compound was prepared as a white solid. Yield: 1.943 g (41%). TLC (R_f = 0.57, silica gel, 33% ethyl acetate in hexanes). Mp = 107.5-108.5 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 11.0 min, D-isomer t_R = 10.5 min, ee > 99%. ^1H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.37-7.33 (m, 5H), 5.31 (d, *J* = 8.4 Hz, 1H), 5.14 (s, 2H), 4.51-4.48 (m, 1H), 2.59-2.48 (m, 2H), 2.31-2.26 (m, 1H), 2.06-2.00 (m, 1H), 1.48 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.8, 172.8, 155.3, 148.4, 136.1, 135.6, 135.2, 128.8, 128.6, 128.5, 124.1, 81.1, 66.9, 60.5, 30.5, 28.5, 27.2. IR (neat, cm^{-1}) 1710 (s), 1521 (s). HRMS (FAB) Calcd for $C_{23}H_{27}N_2O_7S$ ($[M+H]^+$): 475.1528. Found: 475.1533. $[\alpha]_D^{20}$ -52.7 (*c* 1.00, $CHCl_3$).

(-)-(*S*)-*S*-4-Nitrophenyl 2-(*tert*-Butoxycarbonyl)amino-3-(1*H*-indol-3-yl)propane-thioate, 57

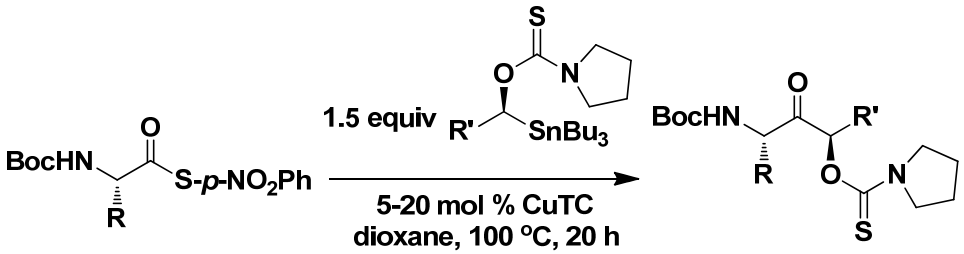


Following the general procedure, the title compound was prepared as an orange solid. Yield: 2.205 g (50%). TLC (R_f= 0.38, silica gel, 33% ethyl acetate in hexanes). Mp = 141-142 °C. HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 14.1 min, D-isomer t_R = 14.7 min, ee > 99%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 8.19 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.40 (app d, *J* = 7.8 Hz, 3H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.08 (s, 1H), 5.13 (d, *J* = 7.8 Hz, 1H), 4.81-4.78 (m, 1H), 3.44 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.28 (dd, *J* = 14.4, 5.4 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.0, 155.3, 148.3, 136.5, 136.4, 135.3, 127.6, 124.0, 123.4, 122.7, 120.1, 119.1, 111.5, 109.5, 81.0, 60.9, 28.5, 28.1. IR (neat, cm^{-1}) 1698 (s), 1521 (s). HRMS (FAB) Calcd for $C_{22}H_{24}N_3O_5S$ ($[M+H]^+$): 442.1426. Found: 442.1431. $[\alpha]_D^{20}$ -150.3 (*c* 1.00, $CHCl_3$).

(+)-(*R*)-*tert*-Butyl 2-(*S*)-[(pyrrolidine-1-carbonothioyl)oxy](tributylstannyl) methylpyrrolidine-1-carboxylate, 58



1,1'-Thiocarbonyldiimidazole (196 mg, 1.1 mmol, 1.1 equiv) was added to a stirring solution of (*R*)-*tert*-butyl 2-(*S*)-hydroxy(tri-*n*-butylstannyl)methyl pyrrolidine-1-carboxylate **52** (490 mg, 1 mmol, 1.0 equiv) in dry CH_2Cl_2 (5 mL) containing DMAP (12 mg, 0.1 mmol, 0.1 equiv) under an argon atmosphere. After 24 h, the reaction mixture was filtered through a short plug of silica gel and the filter cake was washed with EtOAc (5 mL). The combined filtrate was concentrated under reduced pressure and the residue was dissolved in pyrrolidine (2 mL). After 2 h, all volatiles were removed *in vacuo*. The crude product was purified by flash chromatography (silica gel, 25% ethyl acetate in hexanes) affording the title compound as a colorless oil. Yield: 476 mg (79%). TLC (R_f = 0.54, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 1H), 4.00-3.99 (m, 1H), 3.66 (app s, 2H), 3.53-3.39 (m, 3H), 3.32-3.26 (m, 1H), 2.16-1.75 (m, 8H), 1.51-1.42 (m, 15H), 1.31-1.26 (m, 6H), 0.92 (t, *J* = 8.0 Hz, 6H), 0.87 (t, *J* = 7.6 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 154.5, 79.9, 61.0, 52.2, 47.8, 47.5, 30.2, 29.3, 28.8, 27.7, 26.0, 24.7, 24.2, 13.8, 11.1. IR (neat, cm^{-1}) 2957 (s), 1695 (s), 1475 (s). HRMS (FAB) Calcd for $C_{27}H_{53}N_2O_3SSn$ ($[M+H]^+$): 605.2796. Found: 605.2796. $[\alpha]_D^{20}$ +107.1 (*c* 3.10, $CHCl_3$).

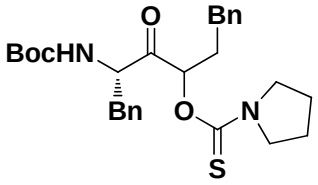


General Procedure for Thiol Ester and α-Alkoxyalkylstannane Cross-Coupling

N-Protected amino acid thiol ester (0.05 mmol, 1.0 equiv) and CuTC (2.0 mg, 0.01 mmol, 0.2 equiv) were placed in a 5 mL round bottom flask under an argon

atmosphere. Then dioxane (2 mL, degassed and dried over 4Å molecular sieves) was added followed by addition of α-alkoxyalkylstannane (0.075 mmol, 1.5 equiv) *via* syringe at room temperature. The reaction mixture was stirred for 20 h at 100 ^{o}C and then evaporated. The residue was suspended in CH_2Cl_2 (10 mL) and the suspension was filtered through a plug of Celite™. The organic layer was evaporated and purified by SiO_2 column chromatography to give the desired product.

_O_-(5_S_)-5-(_tert_-Butoxycarbonyl)amino-4-oxo-1,6-diphenylhexan-3-yl pyrrolidine-1-carbothioate, 59



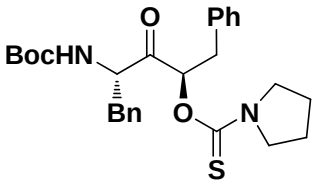
Following the general procedure, *N*-Boc-L-Phe-S-*p*-NO_2Ph (20 mg, 0.05 mmol, 1.0 equiv) was coupled with (±)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **47** (40 mg, 0.075 mmol, 1.5 equiv) using CuTC (2.0 mg, 0.01 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 22 mg (87%). The two diastereomers were easily separated by silica gel chromatography using 5% ether in dichloromethane as the eluting solvent.

Less polar diastereomer, TLC (R_f= 0.66, silica gel, 5% ether in dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 7.19-7.16 (m, 4H), 7.13 (d, *J* = 7.2 Hz, 2H), 6.09 (dd, *J* = 7.8, 4.2 Hz, 1H), 5.14 (d, *J* = 9.0 Hz, 1H), 4.82-4.78 (m, 1H), 3.74-3.65 (m, 3H), 3.47-3.43 (m, 1H), 3.29 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.80 (dd, *J* = 14.4, 7.8 Hz, 1H), 2.71-2.63 (m, 2H), 2.19-2.05 (m, 2H), 1.99-1.95 (m, 4H), 1.36 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.9, 183.9, 155.4, 141.0, 136.9, 129.6, 128.6, 128.5, 126.8, 126.2, 81.0, 80.1, 57.6, 52.6, 48.3, 37.3, 32.3, 31.8, 28.4, 25.8, 24.7. IR

(neat, cm^{-1}) 1710 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{28}H_{37}N_2O_4S$ ($[M+H]^+$): 497.2463. Found: 497.2468. $[\alpha]_D^{20}$ -45.8 (*c* 0.80, $CHCl_3$).

More polar diastereomer, TLC (R_f = 0.59, silica gel, dichloromethane). ^1H NMR (600 MHz, $CDCl_3$) two diastereomers δ 7.29-7.14 (m, 10H), 6.01 (dd, *J* = 7.8, 3.0 Hz, 1H), 4.95 (d, *J* = 8.4 Hz, 1H), 4.82-4.78 (m, 1H), 3.74-3.65 (m, 3H), 3.47-3.43 (m, 1H), 3.36 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.84 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.71-2.65 (m, 2H), 2.21-2.08 (m, 2H), 1.99-1.95 (m, 4H), 1.35 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 184.0, 155.2, 140.9, 136.7, 129.6, 128.6, 128.5, 126.9, 126.3, 81.6, 80.0, 57.2, 52.4, 48.2, 37.5, 32.8, 32.0, 28.4, 25.8, 24.7. IR (neat, cm^{-1}) 1710 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{28}H_{37}N_2O_4S$ ($[M+H]^+$): 497.2463. Found: 497.2459. $[\alpha]_D^{20}$ +81.4 (*c* 0.80, $CHCl_3$).

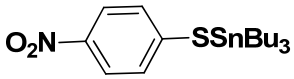
(-)-*O*-(3*R*,5*S*)-5-(*tert*-Butoxycarbonyl)amino-4-oxo-1,6-diphenylhexan-3-yl pyrrolidine-1-carbothioate, 60



Following the general procedure, *N*-Boc-L-Phe-S-*p*-NO_2Ph (336 mg, 0.836 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **48** (675 mg, 1.254 mmol, 1.5 equiv) using CuTC (8 mg, 0.042 mmol, 0.05 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 382 mg (92%). TLC (R_f = 0.66, silica gel, 5% ether in dichloromethane). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, 1,3-*syn*-isomer t_R = 10.2 min, 1,3-*anti*-isomer t_R = 10.8 min, dr =

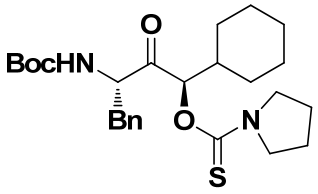
58 : 1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 7.19-7.16 (m, 4H), 7.13 (d, *J* = 7.2 Hz, 2H), 6.09 (dd, *J* = 7.8, 4.2 Hz, 1H), 5.14 (d, *J* = 9.0 Hz, 1H), 4.82-4.78 (m, 1H), 3.74-3.65 (m, 3H), 3.47-3.43 (m, 1H), 3.29 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.80 (dd, *J* = 14.4, 7.8 Hz, 1H), 2.71-2.63 (m, 2H), 2.19-2.05 (m, 2H), 1.99-1.95 (m, 4H), 1.36 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.9, 183.9, 155.4, 141.0, 136.9, 129.6, 128.6, 128.5, 126.8, 126.2, 81.0, 80.1, 57.6, 52.6, 48.3, 37.3, 32.3, 31.8, 28.4, 25.8, 24.7. IR (neat, cm^{-1}) 1710 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{28}H_{37}N_2O_4S$ ($[M+H]^+$): 497.2463. Found: 497.2468. $[\alpha]_D^{20}$ -45.8 (*c* 0.80, $CHCl_3$).

Tri-*n*-Butyl[(4-nitrophenyl)thio]stannane,[23] 61



The title compound was isolated as the side product of the coupling from *N*-Boc-L-Phe-S-*p*-NO_2Ph and stannane **48** as a bright yellow oil. Yield: 290 mg (78%). TLC (R_f = 0.90, silica gel, 5% ether in dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 9.2 Hz, 2H), 1.56-1.52 (m, 6H), 1.33-1.28 (m, 6H), 1.20-1.16 (m, 6H), 0.88 (t, *J* = 7.2 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 145.7, 134.4, 123.5, 28.6, 27.1, 15.0, 13.7. IR (neat, cm^{-1}) 2957 (m), 1575 (s).

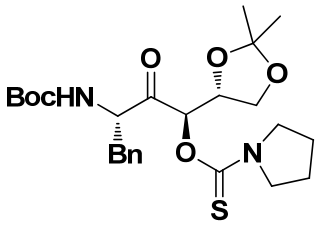
(-)-*O*-(1*R*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1-cyclohexyl-2-oxo-4-phenylbutyl pyrrolidine-1-carbothioate, 62



Following the general procedure, *N*-Boc-L-Phe-S-*p*-NO_2Ph (10 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-cyclohexyl(tri-*n*-butylstannyl)methyl

pyrrolidine-1-carbothioate **49** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 8 mg (67%). TLC (R_f = 0.65, silica gel, 5% ether in dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.23 (m, 2H), 7.19-7.18 (m, 3H), 5.89 (d, *J* = 4.0 Hz, 1H), 5.22 (d, *J* = 9.6 Hz, 1H), 4.78-4.72 (m, 1H), 3.75-3.69 (m, 3H), 3.62-3.56 (m, 1H), 3.29 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.78 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.01-1.88 (m, 5H), 1.72-1.62 (m, 4H), 1.37 (s, 9H), 1.21-1.06 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7, 184.4, 155.4, 137.1, 129.7, 128.4, 126.7, 85.2, 80.0, 57.9, 52.5, 48.3, 39.7, 37.4, 30.0, 28.4, 27.6, 26.3, 26.2, 26.1, 25.8, 24.7. IR (neat, cm^{-1}) 1710 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{26}H_{39}N_2O_4S$ ($[M+H]^+$): 475.2620. Found: 475.2625. $[\alpha]_D^{20}$ -182.8 (*c* 0.29, $CHCl_3$).

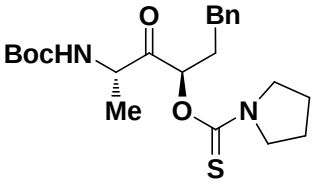
(-)-*O*-(1*R*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-4-phenylbutyl pyrrolidine-1-carbothioate, 63



Following the general procedure, *N*-Boc-L-Phe-S-*p*-NO_2Ph (10 mg, 0.025 mmol, 1.0 equiv) was coupled with (*S*)-*O*-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl] (tri-*n*-butylstannyl) methyl pyrrolidine-1-carbothioate **50** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 7 mg (57%). TLC (R_f= 0.36, silica gel, 5% ether in dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27-7.24 (m, 2H), 7.20-7.19 (m, 3H), 6.11 (d, *J* = 4.8 Hz, 1H), 5.39 (d, *J* = 9.6 Hz, 1H), 4.81-4.77 (m, 1H), 4.41 (dd, *J* = 11.4, 5.4 Hz, 1H), 4.00-3.96 (m, 2H), 3.74-3.66 (m, 3H), 3.62-3.58 (m, 1H), 3.35

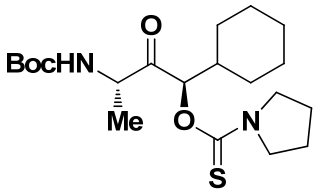
(dd, *J* = 14.4, 5.4 Hz, 1H), 2.84 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.01-1.94 (m, 4H), 1.38 (s, 3H), 1.33 (s, 9H), 1.30 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.9, 183.4, 155.3, 137.1, 129.8, 128.4, 126.7, 110.3, 79.9, 79.3, 75.1, 66.1, 59.3, 52.8, 48.5, 37.5, 28.4, 26.3, 25.9, 25.0, 24.7. IR (neat, cm^{-1}) 1710 (s), 1502 (vs). HRMS (FAB) Calcd for $C_{25}H_{37}N_2O_6S$ ($[M+H]^+$): 493.2360. Found: 493.2366. $[\alpha]_D^{20}$ -44.9 (*c* 0.70, $CHCl_3$).

(-)-*O*-(3R,5S)-5-(*tert*-Butoxycarbonyl)amino-4-oxo-1-phenylhexan-3-yl pyrrolidine-1-carbothioate, 64



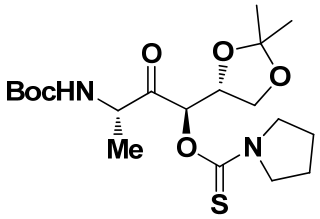
Following the general procedure, *N*-Boc-L-Ala-S-*p*-NO_2Ph (9 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **48** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 9 mg (80%). TLC (R_f = 0.49, silica gel, 5% ether in dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.19-7.16 (m, 3H), 6.02 (dd, *J* = 7.8, 4.2 Hz, 1H), 5.31 (d, *J* = 9.0 Hz, 1H), 4.59-4.57 (m, 1H), 3.74-3.66 (m, 3H), 3.47-3.44 (m, 1H), 2.72 (t, *J* = 7.8 Hz, 2H), 2.21-2.05 (m, 2H), 2.03-1.88 (m, 4H), 1.45 (s, 9H), 1.32 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 183.9, 155.4, 141.0, 128.6, 128.5, 126.3, 80.4, 80.1, 52.8, 52.6, 48.3, 32.5, 31.9, 28.5, 25.9, 24.7, 17.9. IR (neat, cm^{-1}) 1710 (s), 1502 (vs). HRMS (FAB) Calcd for $C_{22}H_{33}N_2O_4S$ ($[M+H]^+$): 421.2150. Found: 421.2155. $[\alpha]_D^{20}$ -35.0 (*c* 0.24, $CHCl_3$).

(-)-*O*-(1*R*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1-cyclohexyl-2-oxobutyl pyrrolidine-1-carbothioate, 65



Following the general procedure, *N*-Boc-L-Ala-S-*p*-NO_2Ph (9 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-cyclohexyl(tri-*n*-butylstannyl)methyl pyrrolidine-1-carbothioate **49** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 9 mg (88%). TLC (R_f = 0.58, silica gel, 5% ether in dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (d, *J* = 4.0 Hz, 1H), 5.40 (d, *J* = 9.2 Hz, 1H), 4.54-4.47 (m, 1H), 3.76-3.67 (m, 3H), 3.63-3.57 (m, 1H), 2.03-1.91 (m, 5H), 1.72-1.61 (m, 5H), 1.45 (s, 9H), 1.30 (d, *J* = 7.2 Hz, 3H), 1.24-1.14 (m, 5H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 184.4, 155.4, 84.6, 80.0, 53.3, 52.5, 48.3, 39.7, 28.5, 27.8, 26.3, 26.2, 26.1, 25.8, 24.7. IR (neat, cm^{-1}) 1710 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{20}H_{35}N_2O_4S$ ($[M+H]^+$): 399.2307. Found: 399.2312. $[\alpha]_D^{20}$ -61.5 (*c* 0.88, $CHCl_3$).

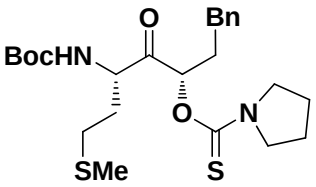
(-)-*O*-(1*R*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxobutyl pyrrolidine-1-carbothioate, 66



Following the general procedure, *N*-Boc-L-Ala-S-*p*-NO_2Ph (9 mg, 0.025 mmol, 1.0 equiv) was coupled with (*S*)-*O*-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]

(tri-*n*-butylstannyl) methyl pyrrolidine-1-carbothioate **50** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 5 mg (48%). TLC (R_f= 0.33, silica gel, 5% ether in dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 5.6 Hz, 1H), 5.62 (d, *J* = 9.2 Hz, 1H), 4.58-4.53 (m, 1H), 4.43 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.08-4.00 (m, 2H), 3.73-3.64 (m, 3H), 3.62-3.56 (m, 1H), 1.97-1.94 (m, 4H), 1.44 (s, 9H), 1.41 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.0, 183.4, 155.4, 110.3, 79.9, 78.7, 75.1, 66.2, 54.6, 52.7, 48.5, 28.5, 26.4, 25.9, 25.0, 24.7, 17.7. IR (neat, cm^{-1}) 1714 (s), 1502 (vs). HRMS (FAB) Calcd for $C_{19}H_{33}N_2O_6S$ ($[M+H]^+$): 417.2048. Found: 417.2053. $[\alpha]_D^{20}$ -32.4 (*c* 0.50, $CHCl_3$).

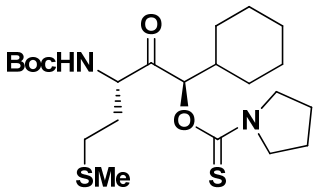
(+)-*O*-(3*S*,5*S*)-5-(*tert*-Butoxycarbonyl)amino-7-methylthio-4-oxo-1-phenylheptan-3-yl pyrrolidine-1-carbothioate, 67



Following the general procedure, *N*-Boc-L-Met-S-*p*-NO_2Ph (10 mg, 0.025 mmol, 1.0 equiv) was coupled with (-)-(*R*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **51** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 11 mg (82%). TLC (R_f= 0.51, silica gel, 5% ether in dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.2 Hz, 3H), 5.96 (dd, *J* = 8.4, 3.6 Hz, 1H), 5.10 (d, *J* = 9.0 Hz, 1H), 4.70-4.67 (m, 1H), 3.74-3.67 (m, 3H), 3.50-3.46 (m, 1H), 2.74 (t, *J* = 7.8 Hz, 2H), 2.61-2.56 (m, 1H), 2.53-2.48 (m, 1H), 2.32-2.30 (m, 2H), 2.24-2.19 (m, 1H), 2.06 (s, 3H), 2.03-1.93 (m, 4H), 1.79-1.76 (m,

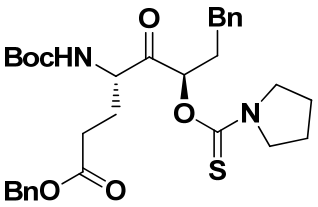
1H), 1.42 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.1, 184.0, 155.5, 140.7, 128.7, 126.4, 81.3, 80.2, 55.4, 52.4, 48.2, 32.9, 32.0, 31.7, 30.3, 28.5, 25.8, 24.7, 15.6. IR (neat, cm^{-1}) 1710 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{24}H_{37}N_2O_4S_2$ ($[M+H]^+$): 481.2183. Found: 481.2189. $[\alpha]_D^{20}$ +40.1 (*c* 0.76, $CHCl_3$).

(-)-*O*-(1*R*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1-cyclohexyl-5-methylthio-2-oxopentyl pyrrolidine-1-carbothioate, 68



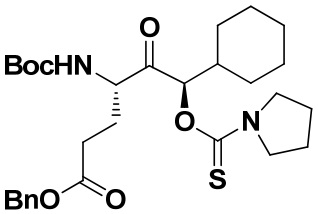
Following the general procedure, *N*-Boc-L-Met-S-*p*-NO_2Ph (10 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-cyclohexyl(tri-*n*-butylstannyl)methyl pyrrolidine-1-carbothioate **49** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 8 mg (70%). TLC (R_f = 0.61, silica gel, 5% ether in dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 (d, *J* = 4.2 Hz, 1H), 5.38 (d, *J* = 9.6 Hz, 1H), 4.65-4.61 (m, 1H), 3.81-3.77 (m, 1H), 3.69 (t, *J* = 6.6 Hz, 2H), 3.62-3.58 (m, 1H), 2.58-2.46 (m, 2H), 2.23-2.20 (m, 1H), 2.08 (s, 3H), 2.02-1.93 (m, 5H), 1.75-1.59 (m, 6H), 1.45 (s, 9H), 1.30-1.08 (m, 5H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.6, 184.3, 155.7, 84.8, 80.2, 56.3, 52.5, 48.4, 39.8, 31.5, 30.5, 30.0, 28.5, 27.8, 26.3, 26.2, 26.1, 25.8, 24.7, 15.7. IR (neat, cm^{-1}) 1710 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{22}H_{39}N_2O_4S_2$ ($[M+H]^+$): 459.2341. Found: 459.2345. $[\alpha]_D^{20}$ -68.2 (*c* 0.65, $CHCl_3$).

(-)-(4*S*,6*R*)-Benzyl 4-(*tert*-butoxycarbonyl)amino-5-oxo-8-phenyl-6-[(pyrrolidine-1-carbonothioyl)oxy]octanoate, 69



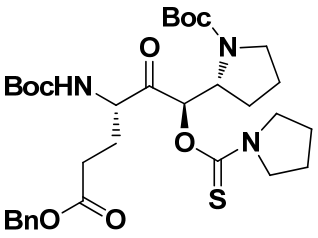
Following the general procedure, *N*-Boc-L-Glu-S-*p*-NO_2Ph (12 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **48** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 11 mg (73%). TLC (R_f = 0.54, silica gel, 5% ether in dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 7.27-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.98 (dd, *J* = 9.0, 4.2 Hz, 1H), 5.30 (d, *J* = 9.6 Hz, 1H), 5.13 (AB q, *J* = 15.6 Hz, 1H), 5.07 (AB q, *J* = 15.6 Hz, 1H), 4.62-4.58 (m, 1H), 3.73-3.66 (m, 3H), 3.45-3.42 (m, 1H), 2.73-2.70 (m, 2H), 2.44-2.42 (m, 2H), 2.33-2.28 (m, 1H), 2.20-2.11 (m, 2H), 2.01-1.92 (m, 4H), 1.81-1.77 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.1, 183.8, 172.8, 155.7, 140.9, 136.1, 128.7, 128.6, 128.5, 128.4, 126.3, 80.5, 80.3, 66.5, 55.9, 52.6, 48.3, 32.5, 32.0, 30.3, 28.5, 26.6, 25.8, 24.7. IR (neat, cm^{-1}) 1710 (s), 1502 (vs). HRMS (FAB) Calcd for $C_{31}H_{41}N_2O_6S$ ($[M+H]^+$): 569.2676. Found: 569.2679. $[\alpha]_D^{20}$ -47.7 (*c* 0.57, $CHCl_3$).

(-)-(4*S*,6*R*)-Benzyl 4-(*tert*-butoxycarbonyl)amino-6-cyclohexyl-5-oxo-6-[(pyrrolidine-1-carbonothioyl)oxy]hexanoate, 70



Following the general procedure, *N*-Boc-L-Glu-S-*p*-NO_2Ph (12 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-cyclohexyl(tri-*n*-butylstannyl)methyl pyrrolidine-1-carbothioate **49** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 10 mg (76%). TLC (R_f= 0.82, silica gel, 5% ether in dichloromethane). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, 1,3-*syn*-isomer t_R = 10.0 min, 1,3-*anti*-isomer t_R = 10.7 min, dr = 99 : 1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 5.79 (d, *J* = 4.8 Hz, 1H), 5.41 (d, *J* = 10.2 Hz, 1H), 5.10 (s, 2H), 4.54-4.50 (m, 1H), 3.79-3.75 (m, 1H), 3.72-3.64 (m, 2H), 3.60-3.55 (m, 1H), 2.43 (t, *J* = 7.8 Hz, 2H), 2.32-2.29 (m, 1H), 2.02-1.91 (m, 5H), 1.80-1.60 (m, 6H), 1.44 (s, 9H), 1.26-1.16 (m, 5H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.1, 184.3, 172.9, 155.7, 136.1, 128.7, 128.4, 84.6, 80.2, 66.5, 56.5, 52.5, 48.4, 39.7, 30.3, 30.0, 28.5, 27.8, 26.9, 26.3, 26.2, 26.1, 25.8, 24.7. IR (neat, cm^{-1}) 1710 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{29}H_{43}N_2O_6S$ ($[M+H]^+$): 547.2831. Found: 547.2836. $[\alpha]_D^{20}$ -61.4 (*c* 0.73, $CHCl_3$).

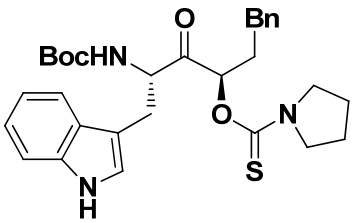
(-)-(*R*)-*tert*-Butyl 2-(1*R*,3*S*)-6-benzyloxy-3-(*tert*-butoxycarbonyl)amino-2,6-dioxo -1-[(pyrrolidine-1-carbonothioyl)oxy]hexylpyrrolidine-1-carboxylate, 71



Following the general procedure, *N*-Boc-L-Glu-S-*p*-NO_2Ph (12 mg, 0.025 mmol, 1.0 equiv) was coupled with (*R*)-*tert*-butyl 2-(*S*)-[(pyrrolidine-1-carbonothioyl)oxy] (tributylstannyl)methylpyrrolidine-1-carboxylate **58** (23 mg, 0.038 mmol, 1.5 equiv)

using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a colorless oil. Yield: 15 mg (95%). TLC (R_f= 0.40, silica gel, 33% ethyl acetate in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) two rotamers δ 7.33-7.30 (m, 5H), 6.57 (s, 0.4H), 6.41 (d, *J* = 10.2 Hz, 0.6H), 5.55 (d, *J* = 7.8 Hz, 0.6H), 5.26 (d, *J* = 9.0 Hz, 0.4H), 5.10 (s, 2H), 4.55 (br s, 1H), 4.27-4.26 (m, 1H), 3.83-3.66 (m, 3H), 3.54-3.39 (m, 2H), 3.33-3.24 (m, 1H), 2.45-2.37 (m, 2H), 2.30-2.20 (m, 1H), 1.99-1.74 (m, 9H), 1.45-1.44 (m, 11H), 1.41 (s, 7H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.4, 204.1, 184.1, 183.8, 173.3, 172.1, 155.9, 155.7, 155.0, 154.1, 136.3, 136.0, 128.7, 128.6, 128.4, 128.2, 82.8, 81.4, 80.7, 80.3, 79.5, 66.5, 66.2, 58.9, 57.2, 56.6, 55.7, 52.7, 48.4, 48.2, 47.2, 46.5, 30.5, 30.1, 28.6, 28.5, 28.0, 27.4, 26.7, 26.4, 25.8, 24.6, 23.7, 23.3. IR (neat, cm^{-1}) 1702 (s), 1679 (s), 1502 (vs). HRMS (FAB) Calcd for $C_{32}H_{48}N_3O_8S$ ($[M+H]^+$): 634.3151. Found: 634.3156. $[\alpha]_D^{20}$ -41.0 (*c* 1.06, $CHCl_3$).

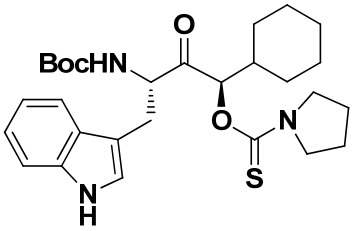
(-)-*O*-(3*R*,5*S*)-5-(*tert*-Butoxycarbonyl)amino-6-(1*H*-indol-3-yl)-4-oxo-1-phenylhexan-3-yl pyrrolidine-1-carbothioate, 72



Following the general procedure, *N*-Boc-L-Trp-S-*p*-NO_2Ph (22 mg, 0.05 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **48** (40 mg, 0.075 mmol, 1.5 equiv) using CuTC (0.5 mg, 0.003 mmol, 0.05 equiv) as the catalyst to give the title compound as a pale yellow oil. Yield: 24 mg (89%). TLC (R_f= 0.33, silica gel, 5% ether in dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.18-7.14 (m, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.05-7.04

(m, 3H), 6.09 (dd, *J* = 7.2, 4.2 Hz, 1H), 5.21 (d, *J* = 9.0 Hz, 1H), 4.97-4.93 (m, 1H), 3.67-3.65 (m, 2H), 3.61-3.57 (m, 1H), 3.43-3.38 (m, 1H), 3.36 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.08 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.69-2.56 (m, 2H), 2.16-2.02 (m, 2H), 1.95-1.90 (m, 4H), 1.40 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.4, 183.8, 155.6, 141.0, 136.2, 128.5, 128.0, 126.1, 123.1, 122.2, 119.7, 119.0, 111.2, 110.9, 81.5, 80.0, 56.8, 52.5, 48.2, 32.3, 31.6, 28.5, 27.2, 25.8, 24.6. IR (neat, cm^{-1}) 1695 (s), 1502 (vs). HRMS (FAB) Calcd for $C_{30}H_{38}N_3O_4S$ ($[M+H]^+$): 536.2571. Found: 536.2577. $[\alpha]_D^{20}$ -51.7 (*c* 0.90, $CHCl_3$).

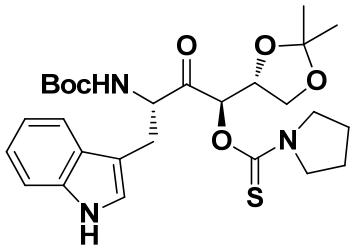
(-)-*O*-(1*R*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1-cyclohexyl-4-(1*H*-indol-3-yl)-2-oxo butyl pyrrolidine-1-carbothioate, 73



Following the general procedure, *N*-Boc-L-Trp-S-*p*-NO_2Ph (11 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-cyclohexyl(tri-*n*-butylstannyl)methyl pyrrolidine-1-carbothioate **49** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a pale yellow oil. Yield: 9 mg (70%). TLC (R_f = 0.47, silica gel, 33% ethyl acetate in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 5.91 (d, *J* = 3.6 Hz, 1H), 5.25 (d, *J* = 9.6 Hz, 1H), 4.93-4.89 (m, 1H), 3.69-3.61 (m, 3H), 3.58-3.54 (m, 1H), 3.37 (dd, *J* = 15.0, 7.2 Hz, 1H), 3.04 (dd, *J* = 15.0, 7.2 Hz, 1H), 1.96-1.86 (m, 5H), 1.68-1.57 (m, 3H), 1.40 (s, 9H), 1.34-1.29 (m, 1H), 1.19-0.90 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.2, 184.4, 155.5, 136.2, 128.0, 123.2, 122.1, 119.6, 119.1,

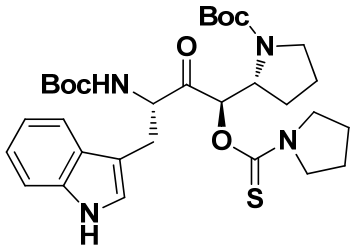
111.1, 111.0, 85.7, 79.9, 56.8, 52.4, 48.3, 39.8, 30.0, 28.5, 27.5, 27.1, 26.3, 26.1, 26.0, 25.7, 24.6. IR (neat, cm^{-1}) 1695 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{28}H_{40}N_3O_4S$ ($[M+H]^+$): 514.2727. Found: 514.2734. $[\alpha]_D^{20}$ -82.5 (*c* 0.76, $CHCl_3$).

(-)-*O*-(1*R*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-(1*H*-indol-3-yl)-2-oxobutyl pyrrolidine-1-carbothioate, 74



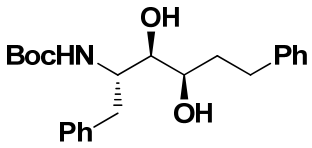
Following the general procedure, *N*-Boc-L-Trp-S-*p*-NO_2Ph (11 mg, 0.025 mmol, 1.0 equiv) was coupled with (*S*)-*O*-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl] (tri-*n*-butylstannyl) methyl pyrrolidine-1-carbothioate **50** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a pale yellow oil. Yield: 8 mg (60%). TLC (R_f = 0.55, silica gel, 50% ethyl acetate in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.11-7.07 (m, 2H), 6.21 (d, *J* = 4.2 Hz, 1H), 5.35 (d, *J* = 9.6 Hz, 1H), 4.93-4.90 (m, 1H), 4.43 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.97 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.91 (t, *J* = 7.8 Hz, 1H), 3.68-3.60 (m, 4H), 3.41 (dd, *J* = 15.0, 5.4 Hz, 1H), 3.14 (dd, *J* = 15.6, 6.6 Hz, 1H), 1.95-1.90 (m, 4H), 1.35 (app s, 12H), 1.25 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.2, 183.6, 155.5, 136.2, 128.1, 123.3, 122.1, 119.6, 119.1, 111.2, 110.9, 110.1, 80.0, 79.9, 75.1, 65.8, 58.3, 52.7, 48.4, 28.4, 26.8, 26.2, 25.8, 24.8, 24.7. IR (neat, cm^{-1}) 1702 (s), 1505 (vs). HRMS (FAB) Calcd for $C_{27}H_{38}N_3O_6S$ ($[M+H]^+$): 532.2469. Found: 532.2475. $[\alpha]_D^{20}$ -52.8 (*c* 0.80, $CHCl_3$).

(-)-(*R*)-*tert*-Butyl 2-(1*R*,3*S*)-3-(*tert*-butoxycarbonyl)amino-4-(1*H*-indol-3-yl)-2-oxo -1-[(pyrrolidine-1-carbonothioyl)oxy]butylpyrrolidine-1-carboxylate, 75



Following the general procedure, *N*-Boc-L-Trp-S-*p*-NO_2Ph (11 mg, 0.025 mmol, 1.0 equiv) was coupled with (*R*)-*tert*-butyl 2-(*S*)-[(pyrrolidine-1-carbonothioyl)oxy] (tributylstannyl)methylpyrrolidine-1-carboxylate **58** (23 mg, 0.038 mmol, 1.5 equiv) using CuTC (1 mg, 0.005 mmol, 0.2 equiv) as the catalyst to give the title compound as a pale yellow oil. Yield: 12 mg (80%). TLC (R_f = 0.47, silica gel, 50% ethyl acetate in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) two rotamers δ 8.07 (s, 0.5H), 8.00 (s, 0.5H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.33-7.29 (m, 1H), 7.18-7.05 (m, 3H), 6.67 (s, 0.5H), 6.03 (d, *J* = 9.6 Hz, 0.5H), 5.95 (d, *J* = 6.6 Hz, 0.5H), 5.15 (d, *J* = 8.4 Hz, 0.5H), 4.86-4.85 (m, 1H), 4.36 (app s, 0.5H), 4.12-4.11 (m, 0.5H), 3.70-3.63 (m, 3H), 3.49-3.47 (m, 1.5H), 3.37-3.32 (m, 2H), 3.20-3.17 (m, 0.5H), 3.12 (dd, *J* = 15.0, 6.0 Hz, 0.5H), 2.98 (dd, *J* = 15.0, 7.8 Hz, 0.5H), 1.95-1.56 (m, 8H), 1.51 (s, 5H), 1.47 (s, 4H), 1.38 (s, 4H), 1.25 (s, 5H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.3, 205.3, 184.2, 184.0, 155.7, 154.8, 154.1, 136.2, 128.5, 127.9, 123.3, 123.1, 122.3, 121.8, 119.7, 119.3, 119.1, 111.6, 111.2, 111.0, 110.8, 82.9, 82.3, 80.7, 80.1, 79.2, 58.7, 57.7, 57.6, 57.1, 52.6, 48.3, 48.1, 47.1, 46.6, 28.6, 28.4, 27.6, 27.0, 26.8, 25.8, 24.6, 23.7, 23.6. IR (neat, cm^{-1}) 1702 (s), 1502 (vs). HRMS (FAB) Calcd for $C_{31}H_{45}N_4O_6S$ ($[M+H]^+$): 601.3048. Found: 601.3055. $[\alpha]_D^{20}$ -25.0 (*c* 1.20, $CHCl_3$).

(-)-*tert*-Butyl (2*S*,3*R*,4*R*)-3,4-dihydroxy-1,6-diphenylhexan-2-ylcarbamate,[17] 76



O-(3*R*,5*S*)-5-(*tert*-butoxycarbonyl)amino-4-oxo-1,6-diphenylhexan-3-yl pyrrolidine-1-carbothioate **60** (124 mg, 0.25 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) was added to a stirring solution of L-selectride (1.0 M in tetrahydrofuran, 0.5 mL, 0.5 mmol, 2.0 equiv) in dry tetrahydrofuran (5 mL) at -78 ^{o}C under an argon atmosphere. After 3 h, the reaction was quenched by 10% citric acid aqueous solution (10 mL). Then the reaction mixture was warmed to room temperature, and extracted with ethyl acetate (3*10 mL). The organic phases were combined and washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by passing through a short plug of silica gel (33% ethyl acetate in hexanes). The organic phase was concentrated *in vacuo*, and then the solution of the resulting residue in tetrahydrofuran (2 mL) was added to a solution of H_2O_2 (30 wt%, 0.5 mL, 5 mmol, 20 equiv) in tetrahydrofuran (2 mL) at 50 ^{o}C. After 4 h, 2 M NaOH aqueous solution (0.25 mL, 0.5 mmol, 2.0 equiv) was added at once to the reaction, and the reaction was stirred for 12 h. The reaction mixture was extracted with ethyl acetate (3*10 mL). The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 50% ethyl acetate in hexanes) affording the title compound as a white solid. Yield: 70 mg (72% over two steps). TLC (R_f = 0.50, silica gel, 50% ethyl acetate in hexanes). Mp = 131-132 °C (Lit.[17] 127.5-128.5 °C). ^{1}H NMR (600 MHz, $(CD_3)_2SO$, 98 ^{o}C) δ 7.26-7.13 (m, 10H), 5.82 (br s, 1H), 4.29-4.28 (m, 1H), 4.11-4.10 (m, 1H), 3.82-3.80 (m, 1H), 3.42 (br s, 1H), 3.26-3.22 (m, 1H), 2.83 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.73 (dd, *J* = 13.8, 7.8 Hz, 1H),

2.67 (ddd, J = 14.4, 10.2, 5.4 Hz, 1H), 2.57-2.52 (m, 1H), 1.80-1.79 (m, 1H), 1.54-1.53 (m, 1H), 1.30 (s, 9H). ^{13}C NMR (150 MHz, $(CD_3)_2SO$, 98 ^{o}C) δ 154.5, 141.9, 138.8, 128.7, 127.5, 127.3, 125.3, 125.0, 77.2, 73.6, 70.4, 52.6, 38.1, 34.2, 30.9, 27.6. HRMS (FAB) Calcd for $C_{23}H_{32}NO_4$ ($[M+H]^+$): 386.2324. Found: 386.2325. $[\alpha]_D^{20}$ -11.2 (*c* 4.20, $CHCl_3$) [Lit.[24] $[\alpha]_D^{20}$ +11.0 (*c* 4.22, $CHCl_3$)].

2.5 References

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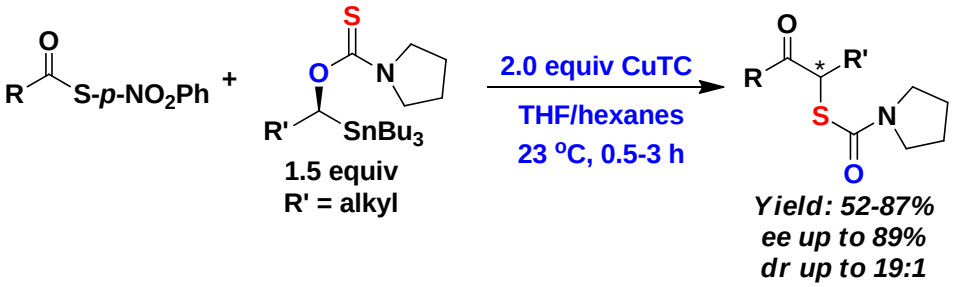
Chapter 3

Stereocontrolled α-Sulfenylated Ketone Synthesis by Thiol Ester–α-(Thiocarbamoyl)alkylstannane Cross-Coupling

Abstract: *Thiol esters derived from 4-nitrothiophenol were coupled with chiral α-alkoxyalkylstannanes in the presence of* ***stoichiometric*** *Cu(I) thiophene-2-carboxylate (CuTC) to give α-sulfenylated ketones in moderate to good yields through a stereocontrolled O-S rearrangement (**Scheme 3.1**). Compared with the α,α'-aminoalkoxy ketone synthesis using catalytic amounts of CuTC described in Chapter 2, this stoichiometric CuTC-mediated thiol ester–α-alkoxyalkylstannane cross-coupling/O-S rearrangement provided an efficient method for the construction of enantioenriched α-sulfenylated ketones. Using only CuTC in this alkylstannane coupling suggests a non-oxidative addition pathway.*

Scheme 3.1 Stoichiometric CuTC-Mediated Thiol Ester–α-Alkoxyalkylstannane Cross-Coupling/O-S Rearrangement

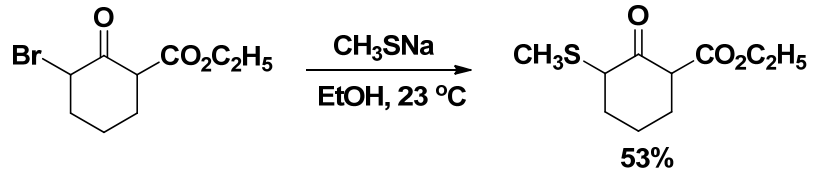


3.1 Introduction and Background

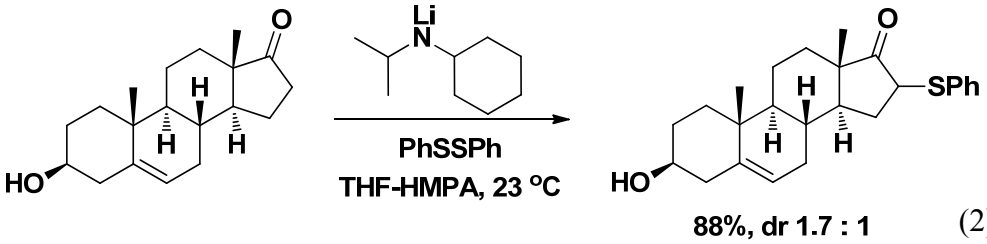
α-Sulfenylated ketones are important moieties in biologically active compounds.[1] They are also common intermediates in organic synthesis.[2] α-Sulfenylated ketones are usually prepared from the corresponding α-halo ketones or enolates. Gassman and co-workers reported a synthesis of β-keto sulfide by an S_N2 displacement of an α-bromoketone with a thiolate (**Scheme 3.2**, **equation 1**).[3] Trost and co-workers reported the direct sulfenylation of androst-5-en-3β-ol-l7-one (dehydroepiandrosterone) with a disulfide *via* a ketone enolate intermediate (**Scheme**

3.2, **equation 2**).[4] β-keto sulfides could also be prepared from silyl enol ethers using sulfenyl chlorides (**Scheme 3.2**, **equation 3**).[5] Kagoshima and co-workers developed a racemic synthesis of α-sulfenylated ketones *via* the cross-coupling of acyl chlorides and racemic α-mercaptoalkylstannanes without any metal catalyst (**Scheme 3.2**, **equation 4**).[6]

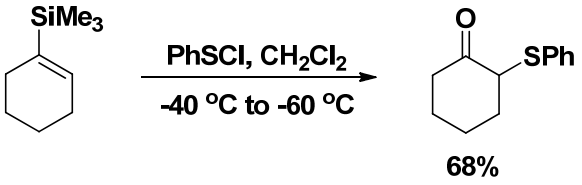
Scheme 3.2 Known Methods for the Construction of α-Sulfenylated Ketones



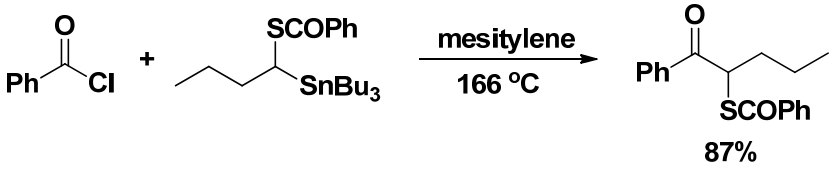
(1)



(2)



(3)

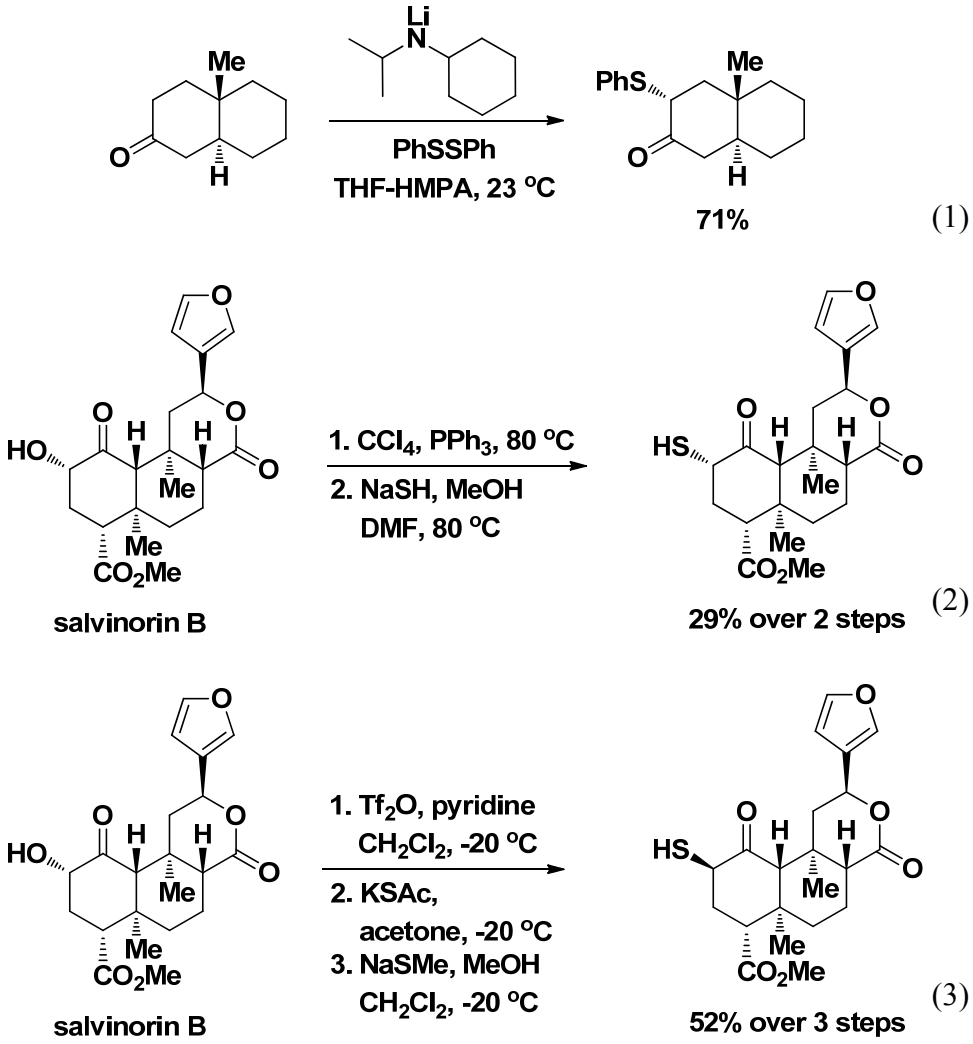


(4)

Although the preparation of racemic α-sulfenylated ketones is straightforward,[2] stereocontrolled construction of α-sulfenylated ketones is rare. The diastereoselective synthesis of α-sulfenylated ketones is precedented.[7] Trost and co-workers reported a diastereoselective sulfenylation of a *trans*-fused decalone with diphenyl disulfide (**Scheme 3.3**, **equation 1**). Alternatively, α-sulfenylated ketones were prepared from the corresponding enantioenriched α-alkoxy ketones by S_N2

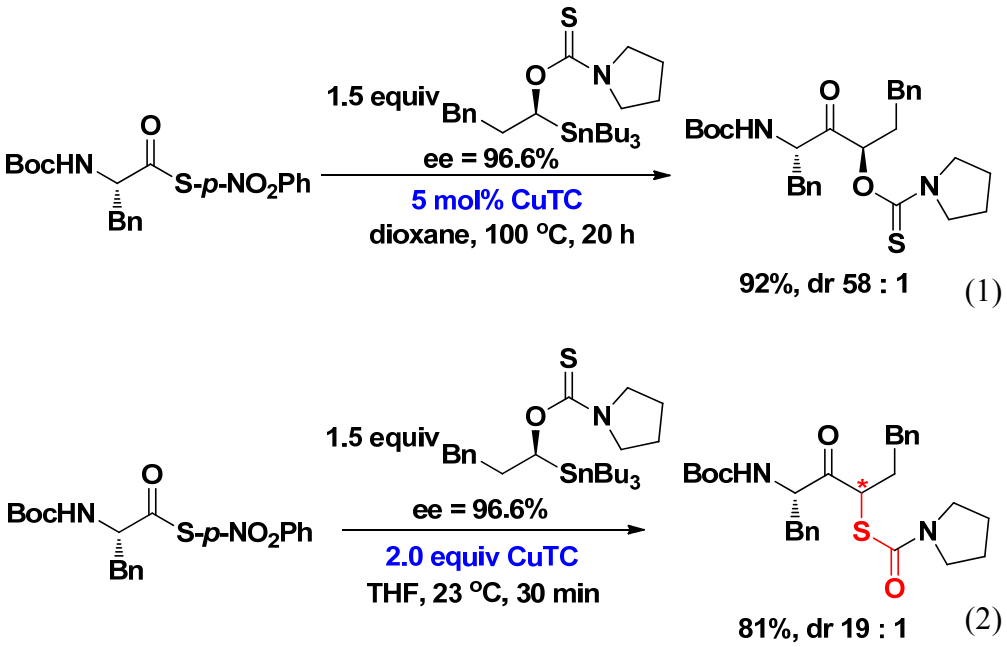
displacements. Zjawiony and co-workers developed a convenient synthesis of 2-thioanalogs of salvinorin B in which both epimers were efficiently prepared.[8] Chlorination of salvinorin B with CCl_4/PPh_3 followed by a S_N2 displacement of the corresponding chloride with NaSH afforded the 2α-sulfur analog of salvinorin B with retention of configuration (**Scheme 3.3**, **equation 2**). The 2β-sulfur analog of salvinorin B was prepared by a S_N2 displacement of triflated salvinorin B followed by deacetylation (**Scheme 3.3**, **equation 3**). Although these methods are efficient for the construction of a few α-sulfenylated ketones, their substrate scope is quite limited. No general method exists for the stereocontrolled synthesis of α-sulfenylated ketones.

Scheme 3.3 Stereocontrolled Construction of α-Sulfenylated Ketones



During the course of the study on the stereocontrolled α,α′-aminoalkyoxy ketone synthesis by amino acid thiol ester–chiral α-alkoxyalkylstannane cross-coupling (**Scheme 3.4**, **equation 1**), an unexpected O-S rearrangement was observed, which led to the formation of the α-sulfenylated ketone in a good yield with excellent diastereoselectivity when stoichiometric CuTC was used (**Scheme 3.4**, **equation 2**). The α-sulfenylated ketone has a very distinguishable IR peak at 1652 cm^{-1} for the thiocarbamate functional group, but the corresponding α,α′-aminoalkyoxy ketone has a strong IR peak at 1498 cm^{-1}. In addition, their NMR spectrums are quite different.

Scheme 3.4 An Unexpected O-S Rearrangement



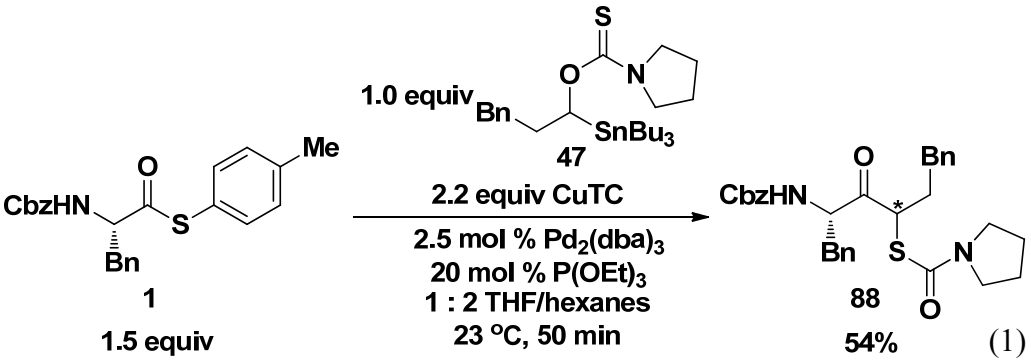
To explore the generality of this novel O-S rearrangement in the stereocontrolled construction of α-sulfenylated ketones, a study of the scope and mechanism of this unprecedented CuTC-mediated thiol ester–α-alkoxyalkylstannane cross-coupling/ O-S rearrangement was undertaken.

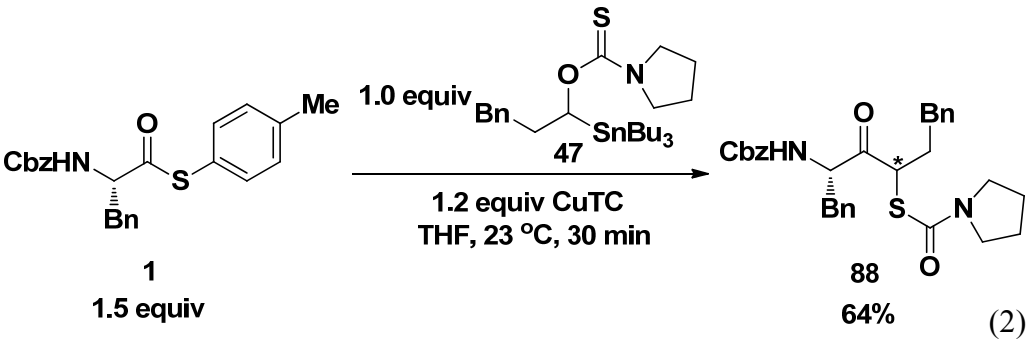
3.2 Results and Discussion

3.2.1 Preliminary Study

The project was initiated by exploring the cross-coupling of amino acid thiol esters and racemic pyrrolidinylthionocarbamoyl (PTC)-protected α-alkoxyalkylstannane **47** using Pd/Cu cocatalysts (**Scheme 3.5**, **equation 1**). The coupling of L-*Z*-Phe-S-*p*-tolyl (**1**) with stannane **47** produced the desired α-mercapto ketone **88** in 54% yield using $Pd_2(dba)_3$ as the palladium catalyst with $P(OEt)_3$ as the supporting ligand and 2.2 equiv CuTC as the cofactor. Control experiments revealed that this thiol ester–α-alkoxyalkylstannane cross-coupling/O-S rearrangement required only stoichiometric copper catalyst, the palladium species being unneccessary (**Scheme 3.5**, **equation 2**).

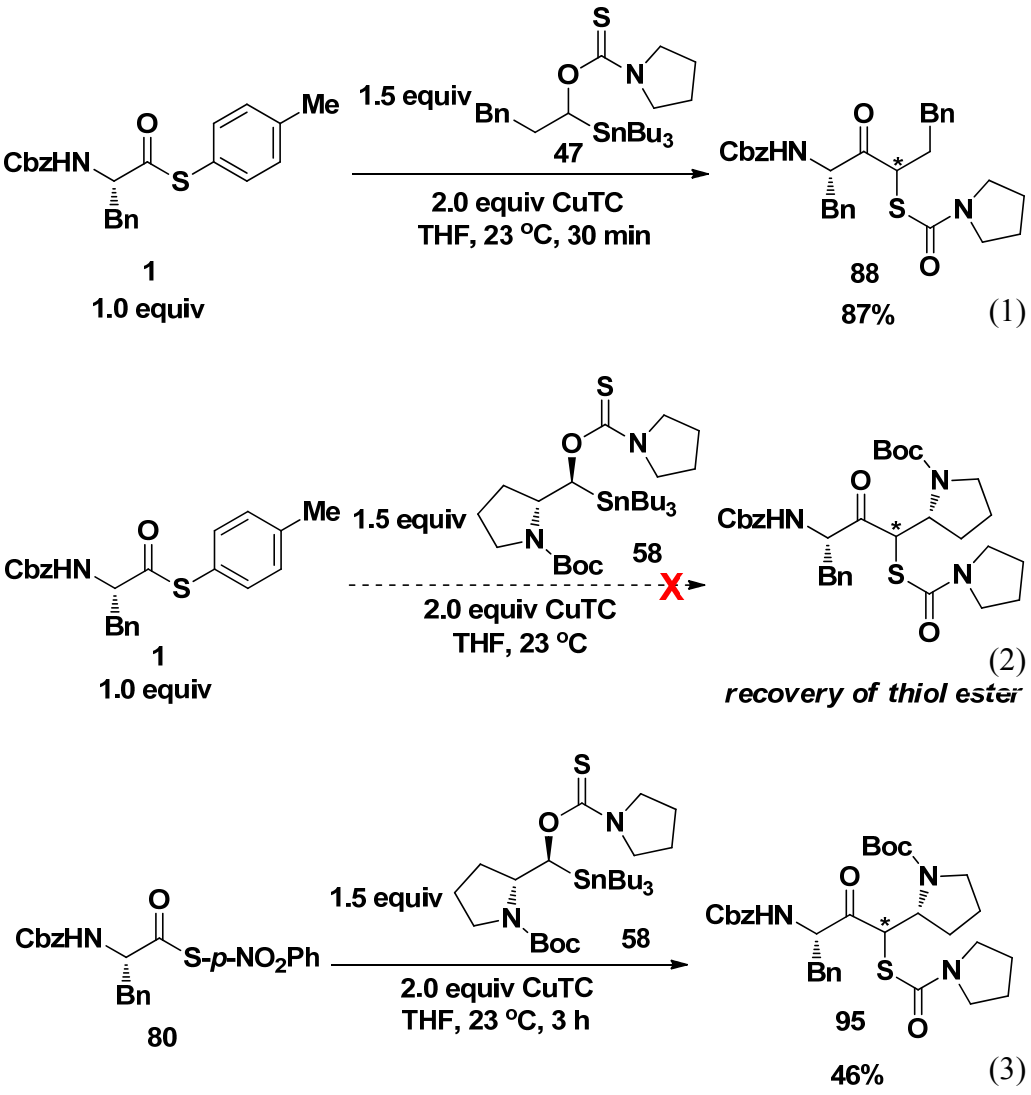
Scheme 3.5 Cbz-Protected Phenylalanine Thiol Ester–Alkylstannane Cross-Coupling





A variety of different conditions were screened for this new reaction. Copper sources such as copper(I) 3-methylsalicylate (CuMeSal), CuDPP, CuTC, CuCN, CuI, CuOAc, and $Cu(OAc)_2$ were tested, and CuTC proved to be the most efficient copper catalyst. It is noteworthy that CuCN and CuI did not give any O-S rearranged product though CuOAc and $Cu(OAc)_2$ generated trace O-S rearranged product. The unique reactivity of CuMeSal, CuDPP and CuTC could arise from their better solubility in THF compared with other copper salts. Stoichiometric CuTC is required for the completion of the reaction, catalytic amounts of CuTC gave lower yields (for example: 23% when 0.7 equiv CuTC was used). The reaction worked well in THF or dioxane as the solvent though no desired α-mercapto ketone was isolated when DMF was used. Typically, this cross-coupling reaction was complete within 30 minutes at room temperature. Additives such as LiCl completely inhibited the desired α-mercapto ketone formation. This brief study revealed that optimum yields of the desired ketone product were obtained using 1.0 equiv of thiol ester **1**, 1.5 equiv of stannane **47**, and 2.0 equiv of CuTC as the metal mediator (**Scheme 3.6**, **equation 1**). However, when thiol ester **1** was treated with α-alkoxy-β-aminostannane **58**, no desired ketone product was observed and the thiol ester starting material was recovered (**Scheme 3.6**, **equation 2**). To solve this problem, the more electrophilic thiol ester L-Cbz-Phe-S-*p*-NO_2Ph (**80**) was investigated in the coupling with α-alkoxy-β-aminostannane **58**. Fortunately, ketone **95** was isolated in 46% yield (**Scheme 3.6**, **equation 3**).

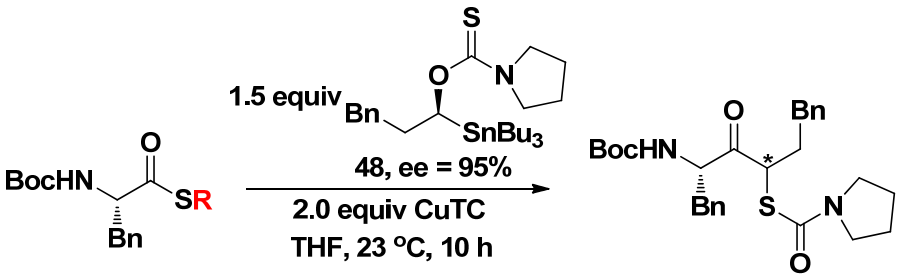
Scheme 3.6 Optimization Studies



Since Boc-protected amino acid thiol esters are easier to prepare as pure crystalline solids with high enantiopurity compared to Cbz-protected thiol esters, and control experiments showed that the *N*-protecting groups did not affect the nature of the cross-coupling, Boc-protected amino acid thiol esters were used in the probe reactions. Results are summarized in **Table 3.1**. The coupling of L-Boc-Phe-SPh (**46**) with enantioenriched stannane **48** produced the desired α-mercapto ketone **60** in 65% yield using 2.0 equiv of CuTC (**Table 3.1**, **entry 2**), while the corresponding L-Boc-Phe-SEt (**45)** generated no ketone product (**Table 3.1**, **entry 1**). Switching to a more electrophilic thiol ester L-Boc-Phe-S-*p*-NO_2Ph (**53**) led to a faster reaction

with a higher yield and good diastereoselectivity (**Table 3.1**, **entry 3**). Thiol ester **77** derived from 2-pyridyl thiol which provided a potentially stronger chelation group to copper gave an unsatisfactory yield (**Table 3.1**, **entry 4**). Using a highly electrophilic thiol ester L-Boc-Phe-S-C_6F_5 (**78**) provided an acceptable ketone yield but with complete epimerization at the α-mercapto carbon center (**Table 3.1**, **entry 5**). Therefore, thiol esters derived from 4-nitrobenzenethiol were used as standard substrates for investigating the O-S rearrangement in the synthesis of α-mercapto ketones.

Table 3.1 Changing Electrophilicity of Thiol Esters Derived from Phenylalanine



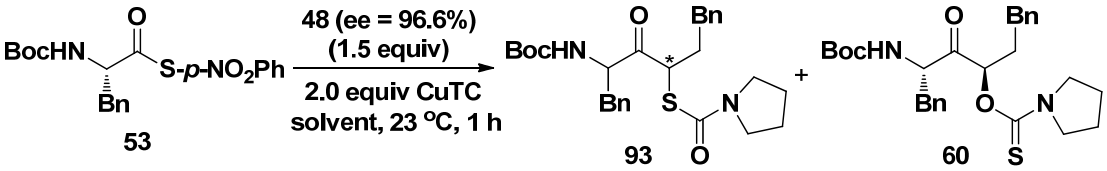
entry	R	yield[a] (%)	dr[b]
1	Et (**45**)	0	--
2	Ph (**46**)	65	13.3 : 1
3	*p*-NO_2Ph (**53**)	68	13.3 : 1
4	2-pyridyl (**77**)	30	--
5	pentafluorophenyl (**78**)	48	1 : 1

[a] Isolated yield of the major isomer. [b] dr determined by HPLC chiral OJ reversed phase column using diastereomeric mixtures derived from racemic α-alkoxystannanes as standards.

To further probe the solvent effect in this reaction, THF or THF/hexanes mixtures were surveyed (**Table 3.2**). Ketone **93** was formed in 68% yield when THF was used as the solvent for the reaction (**Table 3.2**, **entry 1**). Notably, α-alkoxy ketone **60** was formed in 19% yield with complete retention of configuration, which accounted for the modest yield of **93**. By switching to a 1 : 2 THF/hexanes mixture

as the solvent, the undesired ketone **60** was minimized to 10% (**Table 3.2**, **entry 2**). By decreasing further the polarity of the reaction solvent (a 1 : 4 THF/hexanes mixture), the optimum yield of α-mercapto ketone **93** was obtained with only trace amount of undesired ketone **60** (**Table 3.2**, **entry 3**).

Table 3.2 Solvent Effect



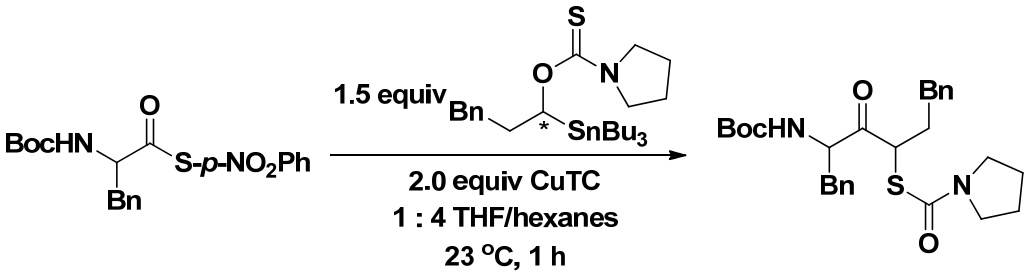
entry	solvent	yield[a] of **93** (dr)[b]	yield[c] of **60** (dr)[b]
1	THF	68% (13.3 : 1)	19% (58 : 1)
2	1 : 2 THF/hexanes	75% (19 : 1)	10% (58 : 1)
3	1 : 4 THF/hexanes	81% (19 : 1)	3% (58 : 1)

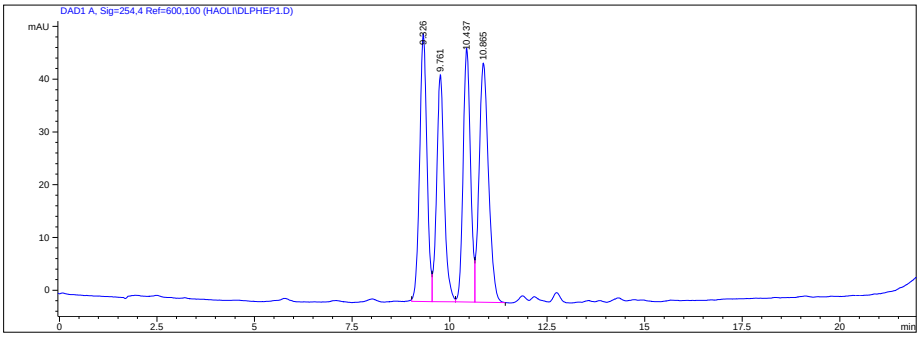
[a] Isolated yield of the major isomer. [b] dr determined by HPLC chiral OJ reversed phase column using diastereomeric mixtures derived from racemic α-alkoxystannanes as standards. [c] Yield determined by ^{1}H NMR from the ratio of **93** and **60**.

A brief study of the stereochemical outcome of the thiol ester–α-alkoxyalkylstannane cross-coupling/O-S rearrangement was carried out by using a chiral HPLC analysis of the α-mercapto ketone products (**Figure 3.1**). Two major issues needed to be checked: 1. retention of configuration of the α-amino carbon centers derived from the amino acid, and; 2. the stereoselectivity of the newly formed α-mercapto carbon centers. Racemic thiol ester (±)-*N*-Boc-Phe-S-*p*-NO_2Ph was coupled with racemic stannane **47** to give a mixture of four α-mercapto ketone isomers, separated by chiral HPLC column (t_R: 9.3 min, 9.7 min, 10.4 min, and 10.8 min, respectively) (**Figure 3.1**, **A**). The reaction of L-Boc-Phe-S-*p*-NO_2Ph (**53**) and racemic stannane **47** afforded a mixture of two α-mercapto ketone isomers (t_R: 9.3 min and 10.4 min, respectively) (**Figure 3.1**, **B**). These results proved that there was

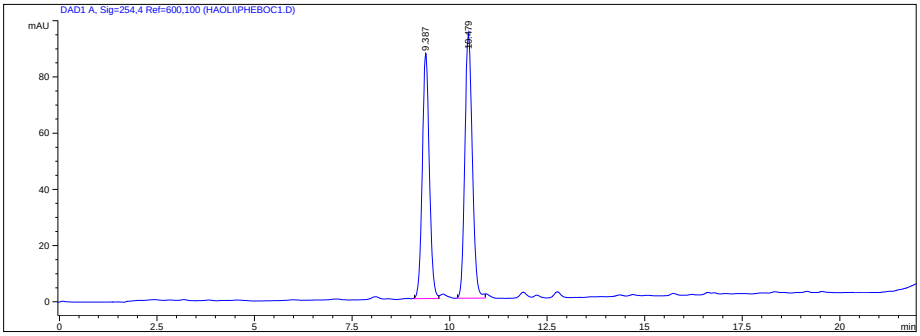
no epimerization at the α-amino carbon centers. Using enantioenriched stannane **48** (ee 95%), a mixture of two α-mercapto ketone isomers (t_R: 9.3 min and 10.4 min, respectively) was generated with 13.3 : 1 diastereoselectivity (**Figure 3.1**, **C**), which showed that the α-mercapto carbon centers were slightly epimerized.

Figure 3.1 HPLC Study of the Stereochemical Outcome of the Thiol Ester–α-Alkoxyalkylstannane Cross-Coupling/O-S Rearrangement

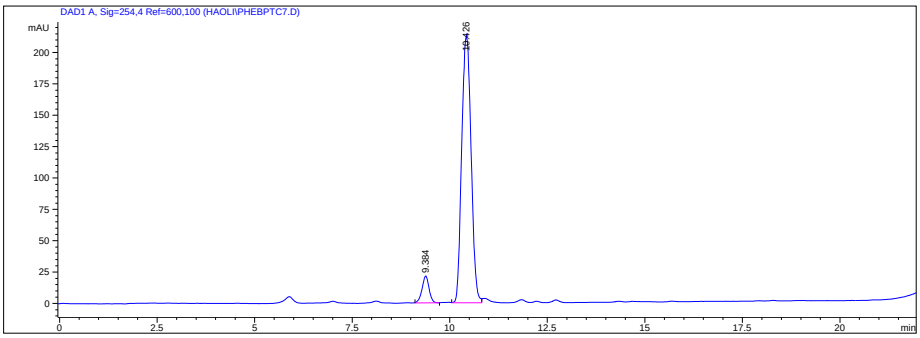




A. Mixture of four α-mercapto ketone isomers from racemic thiol ester (±)-*N*-Boc-Phe-S-*p*-NO_2Ph and racemic stannane **47**



B. Mixture of two α-mercapto ketone isomers from enantiopure thiol ester **53** and racemic stannane **47**



C. Mixture of two α-mercapto ketone isomers from enantiopure thiol ester **53** and enantioenriched stannane **48**

However, the absolute stereochemistry of α-mercapto ketone products remains to be determined. Attempts have been made to derivatize α-mercapto ketones derived from amino acid thiol esters by changing protecting groups on the α-amino group or chelation-controlled reduction of the ketone carbonyl group with $LiAlH(O\textit{t}\text{-}Bu)_3$.[9] Unfortunately, none of these efforts gave satisfactory crystalline solids to grow a single crystal for X-ray crystallographic analysis.

3.2.2 Scope and Limitations

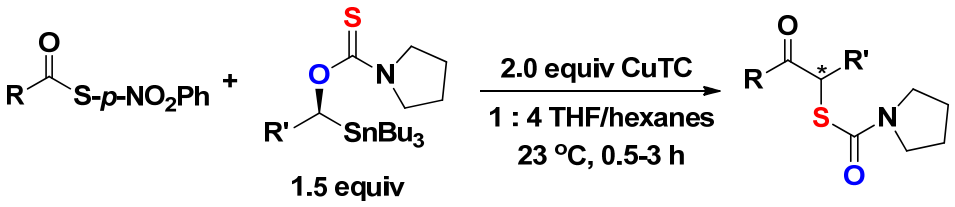
The scope and limitations of the thiol ester–α-alkoxyalkylstannane cross-coupling/O-S rearrangement was then explored. Results are depicted in **Table 3.3**. Enantioenriched PTC-protected stannane **48** reacted efficiently in the reaction (**Table 3.3**, **entries 1-5**, **8**, **10**, **and 13**). Cyclohexyl-substituted stannane **49** also participated in the reaction providing good yields (**Table 3.3**, **entries 6 and 9**). Highly functionalized α-alkoxy-β-aminostannane **58** gave α-alkoxy-β-amino ketone **95** in 60% yield (**Table 3.3**, **entry 7**). Racemic stannane **47** worked well in the cross-coupling with different thiol esters (**Table 3.3**, **entries 11**, **12**, **and 14**). In all the cases, a 1 : 4 THF/hexanes mixture was used as the solvent to suppress the

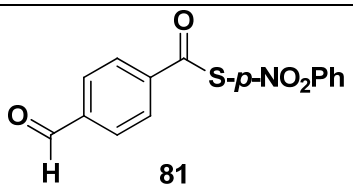
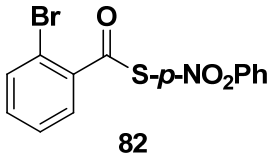
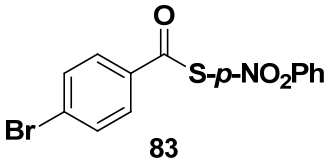
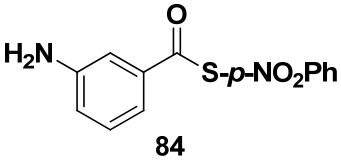
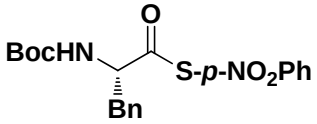
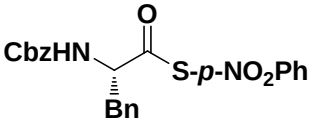
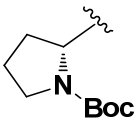
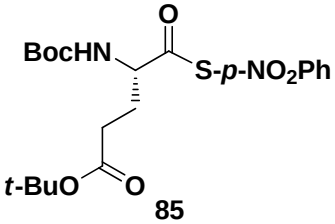
formation of α-alkoxy ketone as a side product. In addition, these reactions are usually finished in 0.5-3 h at room temperature.

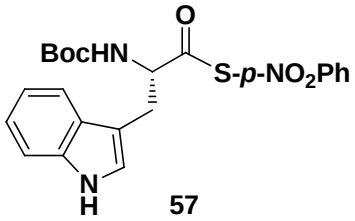
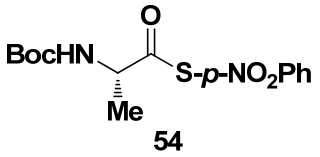
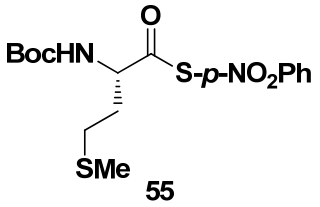
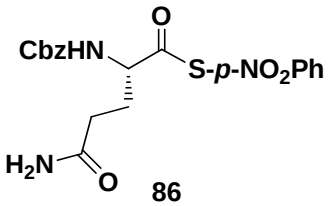
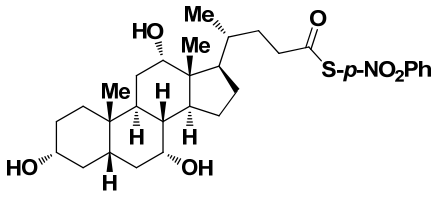
To explore the substrate scope of this O-S rearrangement, different thiol esters derived from substituted benzoic acids were investigated (**Table 3.3**, **entries 1-4**). Unprotected aldehyde, free amine, and bromide functional groups were well-tolerated using this pH-neutral reaction. When *S*-(4-nitrophenyl) 2-bromobenzothioate (**82**) was coupled with stannane **48**, the desired ketone was isolated in 74% yield with only 7% ee (**Table 3.3**, **entry 2**). Switching to *S*-(4-nitrophenyl) 4-bromobenzothioate (**83**), the corresponding α-mercapto ketone was obtained in a similar yield with a higher ee (**Table 3.3**, **entry 3**). A variety of *N*-protected amino acid thiol esters derived from natural occuring amino acid such as Phe (**Table 3.3**, **entries 5-7**), Glu (**Table 3.3**, **entries 8 and 9**), Trp (**Table 3.3**, **entry 10**), Ala (**Table 3.3**, **entry 11**), Met (**Table 3.3**, **entry 12**), and Gln (**Table 3.3**, **entry 13**) can couple with α-alkoxyalkylstannes. Importantly, thiol ester **87** derived from cholic acid participated in the reaction efficiently (**Table 3.3**, **entry 14**). Unprotected indole, free alcohol, primary amide, carbamate, esters, and thiol ether functionalities were tolerated under these mild conditions.

The thiol ester–α-alkoxyalkylstannane cross-coupling/O-S rearrangement provided α-mercapto ketones with good enantioselectivity (**Table 3.3**, **entries 1**, **3**, **and 4**) and diastereoselectivity (**Table 3.3**, **entries 5**, **6**, **8-10**, **and 13**) when enantioenriched α-alkoxyalkylstannanes were the coupling partners. This reaction could be a general method for the stereocontrolled construction of α-mercapto ketones.

Table 3.3 α-Mercapto Ketones from Thiol Esters and α-Alkoxyalkylstannanes



entry	thiol ester	R′	yield (%)	ee[a]	dr[b]
1[c]	 81	phenylethyl[f]	86[i]	89	--
2[c]	 82	phenylethyl[f]	74[i]	7	--
3[c]	 83	phenylethyl[f]	74[i]	83	--
4[c]	 84	phenylethyl[f]	87[i]	60	--
5[d]	 53	phenylethyl[f]	81[j]	--	19 : 1
6[c]	53	cyclohexyl[g]	84[j]	--	11.5 : 1
7[e]	 80		60[i]	--	--
8[d]	 85	phenylethyl[f]	75[j]	--	10.8 : 1
9[c]	85	cyclohexyl[g]	86[j]	--	5.9 : 1

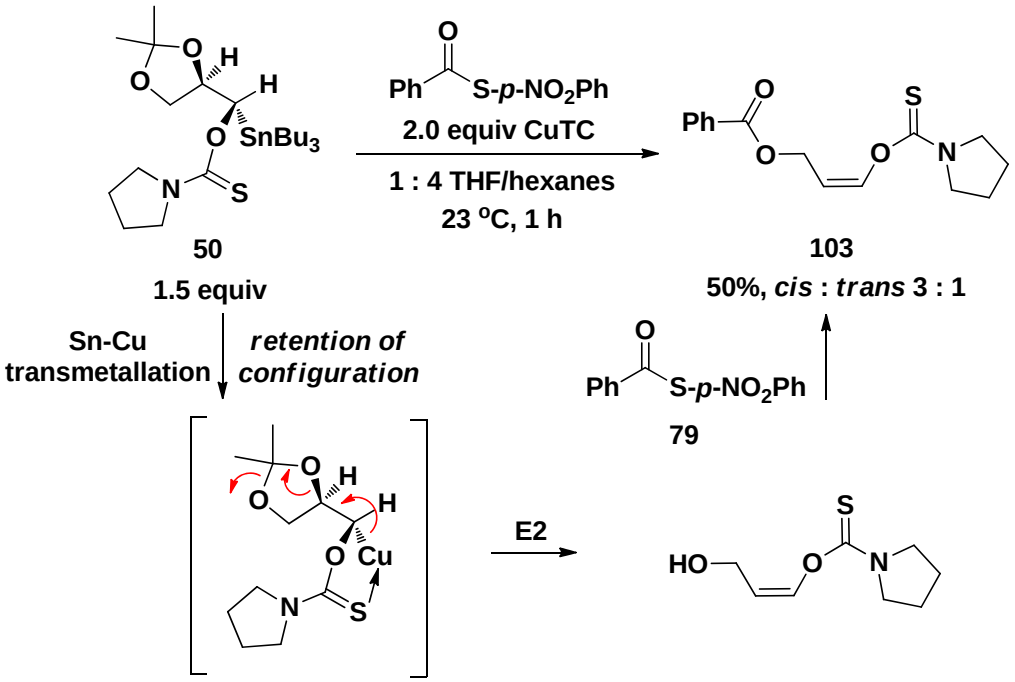
10[d]	 57	phenylethyl[f]	75[j]	--	7 : 1
11[d]	 54	phenylethyl[h]	63[k]	--	--
12[d]	 55	phenylethyl[h]	63[k]	--	--
13[e]	 86	phenylethyl[f]	67[j]	--	5.1 : 1
14[e]	 87	phenylethyl[h]	52[k]	--	--

[a] ee determined by HPLC chiral OJ, OD, and AD reversed phase column using racemic mixtures derived from racemic α-alkoxystannanes as standards. [b] dr determined by HPLC chiral OJ reversed phase column using diastereomeric mixtures derived from racemic α-alkoxystannanes as standards. [c] 1 h. [d] 30 min. [e] 3 h. [f] (*S*)-*O*-3-Phenyl-1-(tributylstannyl)propyl pyrrolidine-1-carbothioate **48** (ee 96.6%) was used. [g] (*S*)-*O*-Cyclohexyl(tributylstannyl)methyl pyrrolidine-1-carbothioate **49** (ee 98%) was used. [h] (±)-*O*-3-Phenyl-1-(tributylstannyl)propyl pyrrolidine-1-carbothioate **47** was used. [i] Isolated yield. [j] Isolated yield of the major isomer. [k] Isolated yield of the mixture of two diastereomers.

α,β-Dialkoxystannane **50** which worked well for the synthesis of α-alkoxy ketones in Chapter 2 suffered from facile β-elimination[10] to form allyl ester **103** with no desired α-mercapto ketone observed (**Scheme 3.7**). The formation of allyl ester **103**

as a mixture of *cis/trans* isomers could be rationalized by the working model shown in **Scheme 3.7**. Tin to copper transmetallation with retention of configuration followed by E2 elimination would afford the *cis* allylic alcohol which reacted with *S*-(4-nitrophenyl) benzothioate (**79**) to give allyl ester **103**.

Scheme 3.7 Facile β-Elimination

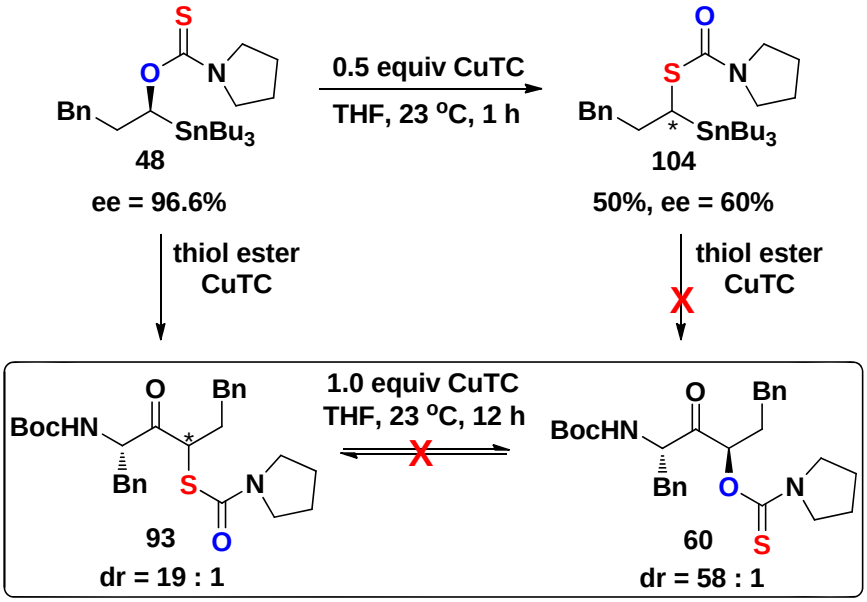


3.2.3 Mechanistic Study

To explore the mechanism of this stereocontrolled thiol ester–α-alkoxyalkylstannane cross-coupling/O-S rearrangement, the stability of enantioenriched α-alkoxyalkylstannane **48** and its corresponding α-mercapto and α-alkoxy ketone products were investigated (**Scheme 3.8**). Stannane **48** reacted with CuTC to give O-S rearranged stannane **104**[11] in 50% yield with 60 % ee. Alternatively, stannane **48** can react with L-Boc-Phe-S-*p*-NO_2Ph (**53**) to afford both α-mercapto ketone **93** and α-alkoxy ketone **60** with excellent stereoselectivity. In contrast, O-S rearranged stannane **104** did not react at all under the same conditions. Notably, both of the α-mercapto ketone **93** and α-alkoxy ketone **60** are stable under

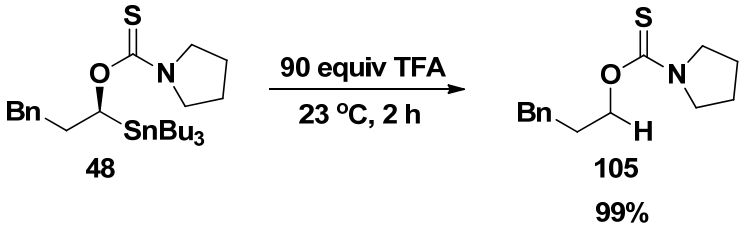
the reaction conditions, and there is neither interconversion between these two ketones nor epimerization of their stereocenters.

Scheme 3.8 Investigation of the Reaction Mechanism

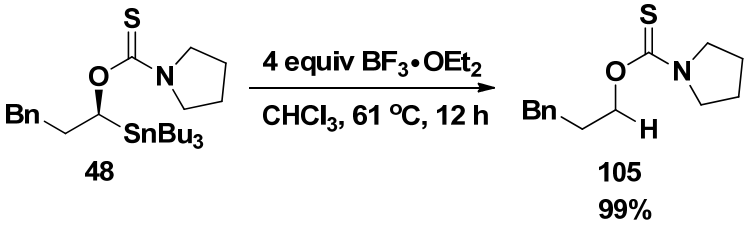


Lewis acid-mediated rearrangement of alkylthionocarbamates is known[12] as well as the related rearrangements of xanthates under thermal[13] or acidic conditions.[14] Control experiments supported that O-S rearrangement of α-alkoxyalkylstannanes was facilitated by CuTC,[11] but not by acids or Lewis acids (**Scheme 3.9**).

Scheme 3.9 Control Experiments



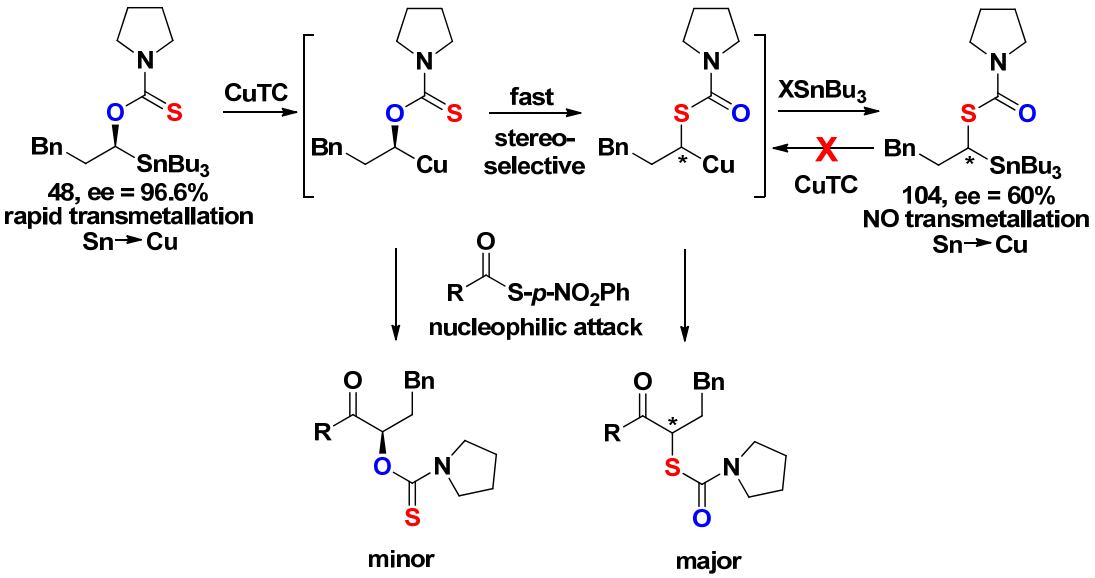
(1)



(2)

The proposed mechanism for the cross-coupling of thiol esters and stannane **48** with stoichiometric CuTC is shown in **Scheme 3.10**. Rapid tin-copper transmetallation with retention of configuration is well precedented.[15] After fast O-S rearrangement of the resulting α-alkoxyl copper intermediate to give α-mercapto copper intermediate stereoselectively, both of the organocopper intermediates could react with electrophilic thiol esters *via* nucleophilic attack to afford the corresponding ketone products. Alternatively, the α-mercapto copper intermediate could be converted to the O-S rearranged stannane **104** by a copper to tin transmetallation. Since it was not reactive toward the tin-copper transmetallation, O-S rearranged stannane **104** is not responsible for the formation of α-mercapto ketone products. In addition, control experiments revealed that pyrrolidinylcarbamoyl-protected α-alkoxyalkylstannanes did not react with thiol ester **53**, indicating that the sulfur atom of PTC protecting group enhances tin-copper transmetallation.

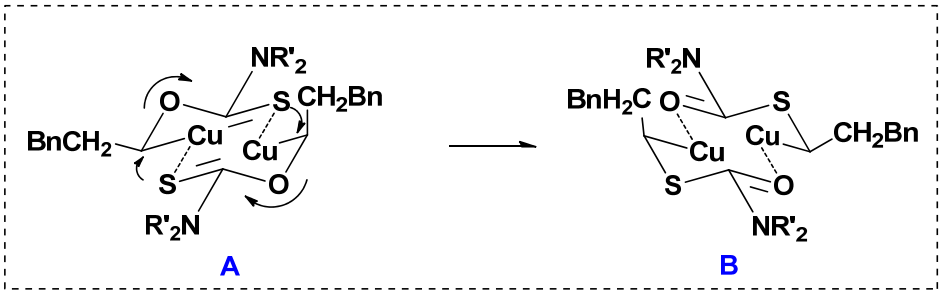
Scheme 3.10 Proposed Mechanism



A reasonable working model for the O-S rearrangement was shown in **Figure 3.2**. This O-S rearrangement could proceed *via* a bimolecular process which was shown as

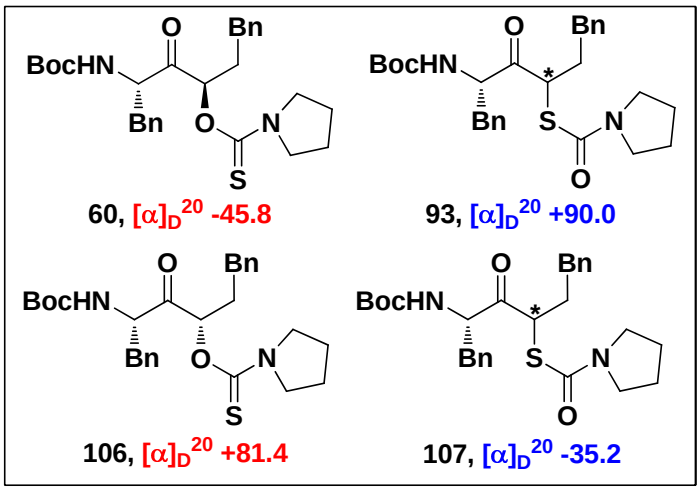
intermediate **A**. S_N2 displacement would afford the α-mercapto copper intermediate **B**.

Figure 3.2 Working Model for O-S Rearrangement



Possible inversion of configuration for this O-S rearrangement was supported by indirect evidence: i) this O-S rearrangement only occurs at high concentration of CuTC; ii) signs of the rotation values of enantioenriched α-alkoxyalkylstannane **48** ($[\alpha]_D^{20}$ +45.8) and its corresponding α-mercaptoalkylstannane **104** ($[\alpha]_D^{20}$ -8.4) are opposite; iii) α-alkoxy ketones and α-mercapto ketones prepared from the same enantioenriched α-alkoxyalkylstannane, signs of their rotation values are opposite. Representative rotation values of α-alkoxy ketones and their corresponding α-mercapto ketones were summarized in **Figure 3.3**. α-Alkoxy ketone **60** and α-mercapto ketone **93** derived from stannane **48** have opposite signs of their rotation values. α-Alkoxy ketone **106** and α-mercapto ketone **107** derived from stannane **51** also have opposite signs of their rotation values. All the data indicates that the O-S rearrangement might proceed with inversion of configuration which needs to be confirmed by further investigation.

Figure 3.3 Rotation Values Indicating Inversion of Configuration



3.3 Conclusion

In summary, a new α-sulfenylated ketone synthesis has been developed by cross-coupling of thiol esters and enantioenriched α-(thiocarbamoyl)alkylstannanes. A variety of α-sulfenylated ketones were prepared in good to excellent yields *via* the stereocontrolled O-S rearrangement. Unprotected aldehyde, bromide, free amine, free indole, free alcohol, primary amide, carbamate, ester, and thiol ether functional groups were well-tolerated under these mild, pH-neutral conditions. The absolute stereochemistry of α-sulfenylated ketones prepared in this chapter has not yet been determined. However, possible inversion of configuration was suggested for this O-S rearrangement. It is anticipated that these α-sulfenylated ketones will be related to sulfenylated derivatives of structure-defined α,α′-aminoalkoxy ketones *via* Mitsunobu reaction to confirm their absolute configuration.

3.4 Experimental Section

3.4.1 General Experimental

^{1}H and ^{13}C NMR spectra were recorded on Unity 600 MHz, Varian Inova 600 MHz, 400 MHz spectrometers, Mercury 300 MHz spectrometer, and VNMRS 400 MHz spectrometer in deuteriochloroform ($CDCl_3$) with the solvent residual peak ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.23 ppm; $(CD_3)_2SO$: ^{1}H = 2.50 ppm, ^{13}C = 39.51 ppm) as internal reference unless otherwise stated. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broad), 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 510 FT-IT or ASI ReactIR 1000 spectrometer. Peaks are reported (cm^{-1}) with the following relative intensities: vs (very strong), s (strong), m (medium), w (weak), and br (broad). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. 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 Merck silica gel glass plates with F-254 indicator. Visualization was accomplished by UV light, or phosphomolybdic acid in ethanol. Solvents for chromatography were reagent grade and used as received. Flash column chromatography was performed with 32-63 μm silica gel 60 (Woelm). HPLC analyses were carried out using an Agilent 1100 system with a quarternary pump. Separations were achieved on a Zorbax Eclipse XDB C8 4.6 x 150 mm column or DAICEL chiral OD, OJ reversed phase column. Solvents used as reaction media were purchased in > 99% purity purged for several minutes with

argon then dried and stored over 4Å molecular sieves (water content below 10 ppm). All reactions requiring inert atmospheres were carried out under dry argon in oven-dried glassware. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of NH_4Cl, $NaHCO_3$ refer to saturated solutions.

3.4.2 Starting Materials

All protected amino acids, solvents, 1,1′-thiocarbonyldiimidazole, pyrrolidine, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), L-selectride (1.0 M in tetrahydrofuran), lithium tri-*tert*-butoxyaluminohydride ($LiAlH(O\textit{t}\text{-}Bu)_3$), copper(I) iodide, copper(I) acetate, copper(I) cyanide, copper(II) acetate and 4-dimethylaminopyridine (DMAP) were purchased from Sigma-Aldrich. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) and triethylphosphite ($P(OEt)_3$) were purchased from Acros. 4-Nitrobenzenethiol was purchased from TCI. Copper(I) thiophene-2-carboxylate (CuTC), copper(I) 3-methylsalicylate (CuMeSal), and copper (I) diphenylphosphinate (CuDPP) were provided by Dr. Gary Allred of Synthonix. L-Boc-Phe-S-2-pyridyl (**77**),[16] L-Boc-Phe-S-C_6F_5 (**78**),[17] *S*-(4-nitrophenyl) benzothioate (**79**),[18] (+)-(*R*)-*tert*-Butyl 2-(*S*)-[(pyrrolidine-1-carbonothioyl)oxy] (tributylstannyl)methyl- pyrrolidine-1-carboxylate (**58**) was prepared according to the procedure described in Chapter 2.

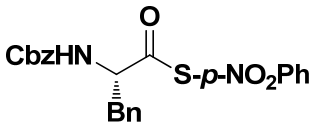
3.4.3 Experimental

General Procedure for the Preparation of Thiol Esters Derived from Substituted Benzoic Acids and *N*-Protected Amino Acids

4-Nitrobenzenethiol (1.05 equiv) was added to a solution of a substituted benzoic acid or *N*-protected amino acid in dry dichloromethane (2 mL/mmol) at 0 °C followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI, 1.0 equiv) in dichloromethane (2 mL/mmol) over 15 min. The mixture was stirred for 24 h at

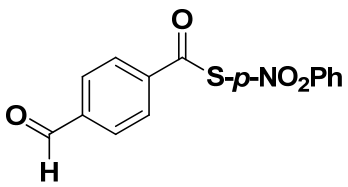
room temperature. The reaction mixture was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, dichloromethane or ethyl acetate in hexanes) and then crystallization from 1 : 1 dichloromethane/hexanes affording the desired product.

(-)-(*S*)-*S*-4-Nitrophenyl 2-(benzyloxycarbonyl)amino-3-phenylpropanethioate, 80



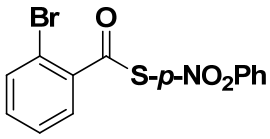
Following the general procedure, the title compound was prepared as a white solid. Yield: 240 mg (55%). TLC (R_f = 0.50, silica gel, 25% ethyl acetate in hexanes). Mp = 175-176 °C. HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 13.3 min, D-isomer t_R = 11.6 min, ee > 99%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.34-7.29 (m, 8H), 7.17 (d, *J* = 7.2 Hz, 2H), 5.24 (d, *J* = 8.4 Hz, 1H), 5.16 (AB q, *J* = 12.0 Hz, 1H), 5.12 (AB q, *J* = 12.0 Hz, 1H), 4.85-4.82 (m, 1H), 3.21-3.17 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.5, 155.8, 148.5, 136.0, 135.2, 135.0, 129.5, 129.1, 128.8, 128.6, 128.4, 127.7, 124.2, 67.7, 61.8, 38.2. IR (neat, cm^{-1}) 1715 (s), 1693 (vs), 1516 (s). HRMS (FAB) Calcd for $C_{23}H_{21}N_2O_5S$ ($[M+H]^+$): 437.1165. Found: 437.1168. $[\alpha]_D^{20}$ -82.7 (*c* 2.70, $CHCl_3$).

***S*-4-Nitrophenyl 4-formylbenzothioate, 81**



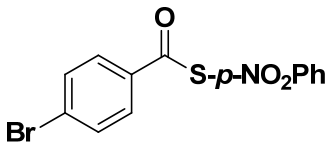
Following the general procedure, the title compound was prepared as a white solid. Yield: 170 mg (59%). TLC (R_f= 0.50, silica gel, 33% ethyl acetate in hexanes). Mp = 151-152 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.32 (d, *J* = 9.0 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 2H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.4, 187.8, 148.7, 140.4, 140.0, 135.6, 135.3, 130.2, 128.3, 124.3. IR (neat, cm^{-1}) 1701 (s), 1673 (vs). HRMS (FAB) Calcd for $C_{14}H_{10}NO_4S$ ($[M+H]^+$): 288.0325. Found: 288.0327.

_S_-4-Nitrophenyl 2-bromobenzothioate, 82



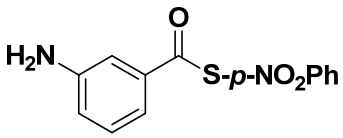
Following the general procedure, the title compound was prepared as a white solid. Yield: 184 mg (55%). TLC (R_f= 0.55, silica gel, 60% dichloromethane in hexanes). Mp = 140-141 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.7 Hz, 2H), 7.76-7.69 (m, 4H), 7.48-7.38 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.9, 148.5, 138.4, 135.1, 134.6, 133.2, 129.3, 127.7, 126.5, 124.6, 124.3. IR (neat, cm^{-1}) 1697 (s), 1515 (vs). HRMS (FAB) Calcd for $C_{13}H_9BrNO_3S$ ($[M+H]^+$): 337.9481. Found: 337.9484.

_S_-4-Nitrophenyl 4-bromobenzothioate[19], 83



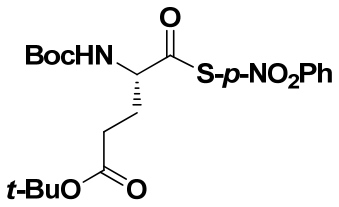
Following the general procedure, the title compound was prepared as a white solid. Yield: 270 mg (80%). TLC (R_f= 0.75, silica gel, dichloromethane). Mp = 181-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 9.2 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 9.2 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H). IR (neat, cm^{-1}) 1676 (s), 1511 (vs).

_S_-4-Nitrophenyl 3-aminobenzothioate, 84



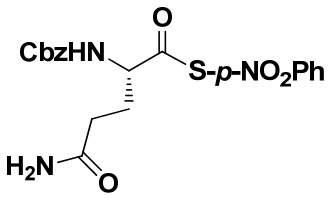
Following the general procedure, the title compound was prepared as a yellow solid. Yield: 120 mg (44%). TLC (R_f= 0.36, silica gel, 33% ethyl acetate in hexanes). Mp = 168-169.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.26 (s, 1H), 6.94 (d, J = 6.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.3, 148.4, 147.2, 137.2, 136.6, 135.6, 130.0, 124.1, 120.8, 118.0, 113.3. IR (neat, cm^{-1}) 3462 (w), 3376 (w), 1681 (s). HRMS (FAB) Calcd for $C_{13}H_{11}N_2O_3S$ ($[M+H]^+$): 275.0484. Found: 275.0486.

(-)-(*S*)-*tert*-Butyl 4-(*tert*-butoxycarbonyl)amino-5-(4-nitrophenyl)thio-5-oxo-pentanoate, 85



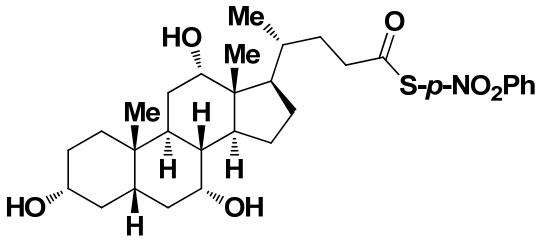
Following the general procedure, the title compound was prepared as a colorless oil. Yield: 1.4 g (53%). TLC (R_f= 0.65, silica gel, 33% ethyl acetate in hexanes). Mp = 80.0-81.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 5.38 (d, J = 7.8 Hz, 1H), 4.45-4.42 (m, 1H), 2.45-2.33 (m, 2H), 2.22-2.16 (m, 1H), 2.03-1.96 (m, 1H), 1.48 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.2, 172.4, 155.4, 148.4, 136.4, 135.2, 124.1, 81.1, 81.0, 60.8, 31.8, 28.5, 28.2, 27.0. IR (neat, cm^{-1}) 1709 (s), 1521 (s). HRMS (FAB) Calcd for $C_{20}H_{29}N_2O_7S$ ($[M+H]^+$): 441.1690. Found: 441.1692. $[\alpha]_D^{20}$ -50.3 (*c* 2.50, $CHCl_3$).

(-)-(*S*)-*S*-4-Nitrophenyl 5-amino-2-(benzyloxycarbonyl)amino-5-oxopentane-thioate, 86

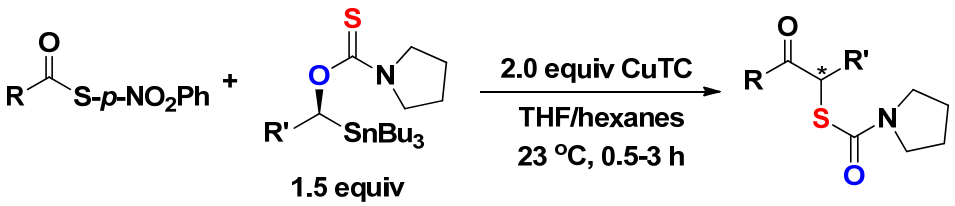


Following the general procedure, the title compound was prepared as a pale yellow solid. Yield: 140 mg (30%). TLC (R_f = 0.50, silica gel, 5% methanol in ethyl acetate). Mp = 154-155 °C. HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, L-isomer t_R = 10.7 min, D-isomer t_R = 11.5 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 9.2 Hz, 2H), 7.39-7.34 (m, 5H), 6.22 (d, *J* = 7.6 Hz, 1H), 5.52 (br s, 1H), 5.33 (br s, 1H), 5.18 (app s, 2H), 4.54-4.49 (m, 1H), 2.49-2.04 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.9, 174.3, 156.4, 148.4, 136.1, 136.0, 135.2, 128.7, 128.5, 128.4, 124.1, 67.6, 61.3, 31.5, 27.1. IR (neat, cm^{-1}) 1695 (vs), 1652 (s). HRMS (FAB) Calcd for $C_{19}H_{20}N_3O_6S$ ($[M+H]^+$): 418.1067. Found: 418.1070. $[\alpha]_D^{20}$ -51.8 (*c* 0.40, $CHCl_3$).

(+)-(*R*)-*S*-(4-Nitrophenyl) 4-[(3*R*,5*S*,7*R*,8*R*,9*S*,10*S*,12*S*,13*R*,14*S*,17*R*)-3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]pentanethioate, 87



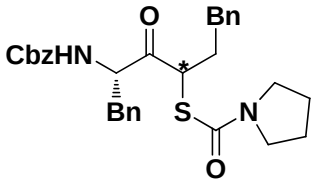
Following the general procedure, the title compound was prepared as a pale yellow solid. Yield: 180 mg (33%). TLC (R_f = 0.30, silica gel, ethyl acetate). Mp = 89-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 4.02 (br s, 1H), 3.88 (br s, 1H), 3.60 (br s, 1H), 2.76-2.67 (m, 2H), 2.22-1.18 (m, 22H), 1.03 (s, 3H), 0.90 (s, 3H), 0.70 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 148.1, 136.7, 134.7, 124.0, 73.2, 71.9, 68.5, 46.9, 46.5, 41.7, 41.5, 41.4, 39.5, 35.4, 35.3, 34.9, 34.8, 31.5, 30.4, 28.3, 27.7, 26.4, 23.3, 22.5, 17.5, 12.6. IR (neat, cm^{-1}) 3365 (br), 1713 (vs), 1599 (s). HRMS (FAB) Calcd for $C_{30}H_{44}NO_6S$ ([M+H]$^+$): 546.2883. Found: 546.2887. $[\alpha]_D^{20}$ +16.9 (*c* 1.90, $CHCl_3$).



General Procedure for Thiol Ester and α-Alkoxyalkylstannane Cross-Coupling

N-Protected amino acid thiol ester (0.05 mmol, 1.0 equiv) and CuTC (20 mg, 0.1 mmol, 2.0 equiv) were placed in a 5 mL round bottom flask under an argon atmosphere. Then a 1 : 4 THF/hexanes mixture (2 mL, degassed and dried over 4Å molecular sieves) was added, followed by addition of α-alkoxyalkylstannane (0.075 mmol, 1.5 equiv) *via* syringe at room temperature. The reaction mixture was stirred for 0.5-3 h and then evaporated. The residue was suspended in CH_2Cl_2 (10 mL) and the suspension was filtered through a plug of Celite™. The organic layer was evaporated and purified by SiO_2 column chromatography to give the desired product.

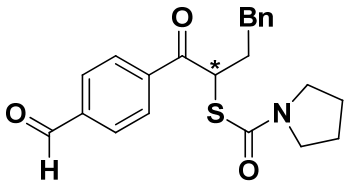
_S_-(5_S_)-5-(Benzyloxycarbonyl)amino-4-oxo-1,6-diphenylhexan-3-yl pyrrolidine-1-carbothioate, 88



Following the general procedure, *N*-Cbz-L-Phe-S-*p*-NO_2Ph (22 mg, 0.05 mmol, 1.0 equiv) was coupled with (±)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **47** (42 mg, 0.075 mmol, 1.5 equiv) using CuTC (20 mg, 0.1 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 23 mg (87%). TLC (R_f = 0.50, two diastereomers could not be separated, silica gel, 33% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) 3 : 2 ratio of two diastereomers, major isomer δ 7.34-7.27 (m, 6H), 7.24-7.05 (m, 9H), 5.70 (d, *J* = 8.4 Hz, 1H), 5.09 (AB q, *J* = 12.4 Hz, 1H), 5.04 (AB q, *J* = 12.4 Hz, 1H), 5.03-4.98 (m, 1H), 4.53 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.59-3.48 (m, 2H), 3.41-3.34 (m, 2H), 3.20 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.99 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.73-2.49 (m, 2H), 2.12-1.84 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 205.9, 163.9, 163.6, 155.8, 155.7, 141.2, 141.0, 136.7, 136.4, 136.2, 129.6, 128.7, 128.6, 128.3, 128.2, 128.1, 127.0, 126.3, 67.0, 66.9, 59.4, 58.6, 50.4, 48.1, 47.9, 47.6, 46.3, 46.2, 38.2, 37.1, 33.3, 33.0, 32.8, 31.6, 25.7, 24.7. IR (neat, cm^{-1}) 1714 (s), 1652 (vs). HRMS (FAB) Calcd for $C_{31}H_{35}N_2O_4S$ ($[M+H]^+$): 531.2312. Found: 531.2312.

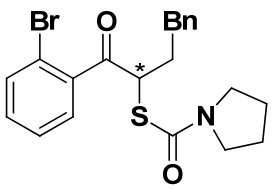
Characteristic data for the minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (d, *J* = 8.4 Hz, 1H), 4.61 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.29 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.85 (dd, *J* = 14.0, 8.0 Hz, 1H).

(+)-*S*-1-(4-Formylphenyl)-1-oxo-4-phenylbutan-2-yl pyrrolidine-1-carbothioate, 89



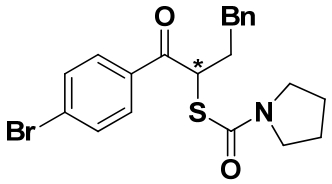
Following the general procedure, *S*-(4-nitrophenyl) 4-formylbenzothioate (14 mg, 0.05 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)-propyl pyrrolidine-1-carbothioate **48** (42 mg, 0.075 mmol, 1.5 equiv) using CuTC (20 mg, 0.1 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 16 mg (86%). TLC (R_f = 0.27, silica gel, 33% ethyl acetate in hexanes). HPLC Chiral AD-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, major isomer t_R = 23.0 min, minor isomer t_R = 28.3 min, ee = 89%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 2H), 7.28-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.26 (t, *J* = 7.2 Hz, 1H), 3.56-3.48 (m, 2H), 3.39-3.30 (m, 2H), 2.82-2.77 (m, 1H), 2.75-2.70 (m, 1H), 2.41-2.35 (m, 1H), 2.20-2.13 (m, 1H), 1.98-1.86 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 191.9, 163.7, 140.9, 140.2, 139.2, 130.0, 129.5, 128.7, 126.4, 47.8, 46.2, 33.6, 33.4, 25.7, 24.7. IR (neat, cm^{-1}) 1704 (s), 1683 (vs), 1653 (s). HRMS (FAB) Calcd for $C_{22}H_{24}NO_3S$ ($[M+H]^+$): 382.1471. Found: 382.1473. $[\alpha]_D^{20}$ +59.0 (*c* 0.80, $CHCl_3$).

***S*-1-(2-Bromophenyl)-1-oxo-4-phenylbutan-2-yl pyrrolidine-1-carbothioate, 90**



Following the general procedure, *S*-(4-nitrophenyl) 2-bromobenzothioate (9 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)-propyl pyrrolidine-1-carbothioate **48** (21 mg, 0.038 mmol, 1.5 equiv) using CuTC (10 mg, 0.05 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 8 mg (74%). TLC (R_f= 0.54, silica gel, 33% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, major isomer t_R = 11.2 min, minor isomer t_R = 11.8 min, ee = 7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 2H), 7.33 (td, *J* = 7.6, 1.2 Hz, 1H), 7.29-7.24 (m, 3H), 7.19-7.16 (m, 3H), 5.08 (dd, *J* = 7.2, 6.0 Hz, 1H), 3.51-3.35 (m, 4H), 2.89-2.82 (m, 1H), 2.78-2.71 (m, 1H), 2.42-2.33 (m, 1H), 2.18-2.09 (m, 1H), 1.98-1.82 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 163.7, 141.2, 140.0, 133.8, 131.9, 129.7, 128.7, 128.6, 127.3, 126.3, 120.2, 52.1, 47.6, 46.2, 33.4, 32.5, 25.7, 24.7. IR (neat, cm^{-1}) 1702 (s), 1656 (s). HRMS (FAB) Calcd for $C_{21}H_{23}BrNO_2S$ ($[M+H]^+$): 432.0627. Found: 432.0629.

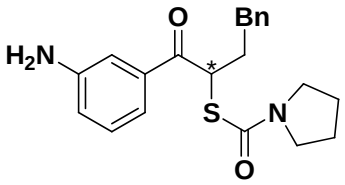
(+)-*S*-1-(4-Bromophenyl)-1-oxo-4-phenylbutan-2-yl pyrrolidine-1-carbothioate, 91



Following the general procedure, *S*-(4-nitrophenyl) 4-bromobenzothioate (9 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)-propyl pyrrolidine-1-carbothioate **48** (21 mg, 0.038 mmol, 1.5 equiv) using CuTC (10 mg, 0.05 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 8 mg

(74%). TLC (R_f= 0.55, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, major isomer t_R = 29.4 min, minor isomer t_R = 33.5 min, ee = 83%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.27-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.20 (t, *J* = 7.2 Hz, 1H), 3.56-3.48 (m, 2H), 3.38-3.30 (m, 2H), 2.79-2.74 (m, 1H), 2.72-2.67 (m, 1H), 2.39-2.33 (m, 1H), 2.17-2.11 (m, 1H), 1.98-1.86 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.0, 191.9, 163.8, 141.0, 134.4, 132.1, 130.5, 128.8, 128.6, 126.3, 47.7, 47.3, 46.1, 33.8, 33.5, 25.7, 24.7. IR (neat, cm^{-1}) 1681 (vs), 1653 (s). HRMS (FAB) Calcd for $C_{21}H_{23}BrNO_2S$ ($[M+H]^+$): 432.0627. Found: 432.0629. $[\alpha]_D^{20}$ +68.5 (*c* 0.80, $CHCl_3$).

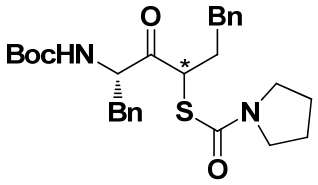
(+)-*S*-1-(3-Aminophenyl)-1-oxo-4-phenylbutan-2-yl pyrrolidine-1-carbothioate, 92



Following the general procedure, *S*-(4-nitrophenyl) 3-aminobenzothioate (14 mg, 0.05 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)-propyl pyrrolidine-1-carbothioate **48** (42 mg, 0.075 mmol, 1.5 equiv) using CuTC (20 mg, 0.1 mmol, 2.0 equiv) to give the title compound as a yellow oil. Yield: 16 mg (87%). TLC (R_f= 0.32, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, major isomer t_R = 6.9 min, minor isomer t_R = 8.6 min, ee = 60%. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.28-7.21 (m, 4H), 7.20-7.17 (m, 3H), 6.87-6.85 (m, 1H), 5.24 (t, *J* = 7.2 Hz, 1H), 3.56-3.48 (m, 2H), 3.38-3.30 (m, 2H), 2.80-2.65 (m, 2H), 2.40-2.31 (m, 1H), 2.18-2.09 (m, 1H), 1.98-1.84 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 164.2, 146.8, 141.3, 136.7, 129.7, 128.7, 128.6, 126.2, 120.1, 119.3, 114.9, 47.8, 47.6, 46.1, 34.2, 33.5, 25.7, 24.7. IR (neat, cm^{-1}) 3362 (w), 1648 (vs), 1602 (s). HRMS (FAB) Calcd for $C_{21}H_{25}N_2O_2S$ ($[M+H]^+$): 369.1631. Found: 369.1634. $[\alpha]_D^{20}$ +45.5 (*c* 0.80, $CHCl_3$).

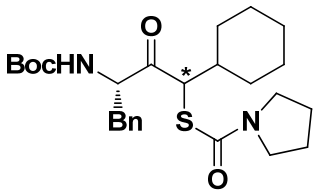
(+)-*S*-(5*S*)-5-(*tert*-Butoxycarbonyl)amino-4-oxo-1,6-diphenylhexan-3-yl pyrrolidine-1-carbothioate, 93



Following the general procedure, *N*-Boc-L-Phe-S-*p*-NO_2Ph (20 mg, 0.05 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **48** (42 mg, 0.075 mmol, 1.5 equiv) using CuTC (20 mg, 0.1 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 20 mg (81%). TLC (R_f = 0.36, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, major isomer t_R = 10.4 min, minor isomer t_R = 9.4 min, dr = 19 : 1. ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 7.29-7.27 (m, 2H), 7.23-7.14 (m, 6H), 7.09 (d, *J* = 7.2 Hz, 2H), 5.39 (d, *J* = 7.2 Hz, 1H), 4.97-4.92 (m, 1H), 4.53 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.61-3.49 (m, 2H), 3.42-3.35 (m, 2H), 3.19 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.96 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.72-2.65 (m, 1H), 2.56-2.48 (m, 1H), 2.11-1.89 (m, 6H), 1.39 (s,

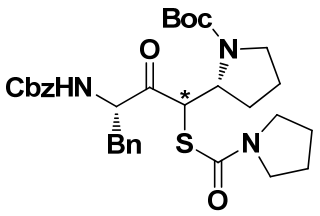
9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.4, 163.7, 155.2, 141.3, 136.6, 129.6, 128.6, 126.9, 126.2, 79.7, 58.2, 48.5, 47.8, 46.3, 38.4, 33.1, 31.7, 28.5, 25.8, 24.7. IR (neat, cm^{-1}) 1706 (s), 1652 (vs). HRMS (FAB) Calcd for $C_{28}H_{37}N_2O_4S$ ($[M+H]^+$): 497.2468. Found: 497.2472. $[\alpha]_D^{20}$ +90.0 (*c* 0.80, $CHCl_3$).

(+)-*S*-(3*S*)-3-(*tert*-Butoxycarbonyl)amino-1-cyclohexyl-2-oxo-4-phenylbutyl pyrrolidine-1-carbothioate, 94



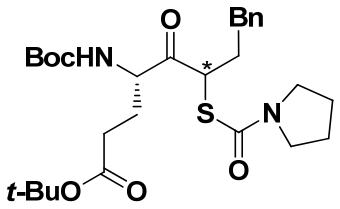
Following the general procedure, *N*-Boc-L-Phe-S-*p*-NO_2Ph (10 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-cyclohexyl(tri-*n*-butylstannyl)methyl pyrrolidine-1-carbothioate **49** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (10 mg, 0.05 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 10 mg (84%). TLC (R_f = 0.63, silica gel, 33% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, major isomer t_R = 9.0 min, minor isomer t_R = 8.3 min, dr = 11.5 : 1. ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 7.27-7.18 (m, 5H), 5.48 (d, *J* = 9.6 Hz, 1H), 4.82-4.74 (m, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 3.55-3.45 (m, 2H), 3.39-3.34 (m, 2H), 3.28 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.80 (dd, *J* = 14.0, 8.4 Hz, 1H), 1.97-1.82 (m, 5H), 1.69-1.60 (m, 4H), 1.35 (s, 9H), 1.21-1.06 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.6, 164.6, 155.3, 137.2, 129.7, 128.4, 126.6, 79.6, 59.5, 54.7, 52.5, 47.7, 46.3, 38.3, 37.9, 31.6, 28.4, 26.2, 25.8, 24.7. IR (neat, cm^{-1}) 1716 (s), 1653 (vs). HRMS (FAB) Calcd for $C_{26}H_{39}N_2O_4S$ ($[M+H]^+$): 475.2625. Found: 475.2626. $[\alpha]_D^{20}$ +36.4 (*c* 0.90, $CHCl_3$).

(+)-(2*R*)-*tert*-Butyl 2-(3*S*)-3-(benzyloxycarbonyl)amino-2-oxo-4-phenyl-1-[(pyrrolidine-1-carbonyl)thio]butylpyrrolidine-1-carboxylate, 95



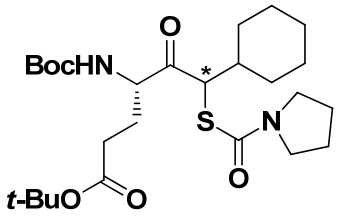
Following the general procedure, *N*-Cbz-L-Phe-S-*p*-NO_2Ph (22 mg, 0.05 mmol, 1.0 equiv) was coupled with (*R*)-*tert*-butyl 2-(*S*)-[(pyrrolidine-1-carbonothioyl)oxy](tributylstannyl)methylpyrrolidine-1-carboxylate **58** (46 mg, 0.075 mmol, 1.5 equiv) using CuTC (20 mg, 0.1 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 18 mg (60%). TLC (R_f = 0.63, silica gel, 40% ethyl acetate in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) two rotamers δ 7.33-7.16 (m, 10H), 5.55 (d, *J* = 7.8 Hz, 0.5H), 5.40-5.36 (m, 0.5H), 5.09-4.94 (m, 2.5H), 4.82-4.81 (m, 1H), 4.31-4.18 (m, 1.5H), 3.70-3.64 (m, 2H), 3.50-3.22 (m, 5H), 2.88 (dd, *J* = 14.4, 7.8 Hz, 0.5H), 2.66 (dd, *J* = 13.8, 9.6 Hz, 0.5H), 1.98-1.82 (m, 8H), 1.49 (s, 4H), 1.45 (s, 5H). ^{13}C NMR (150 MHz, $CDCl_3$) two rotamers δ 204.0, 163.9, 156.1, 155.1, 154.1, 137.7, 137.3, 136.3, 129.7, 129.6, 128.6, 128.5, 128.3, 128.1, 127.9, 127.7, 127.0, 126.4, 83.2, 81.8, 67.1, 66.4, 59.9, 59.0, 58.6, 58.2, 57.7, 57.2, 52.7, 48.0, 47.1, 46.5, 37.1, 36.8, 28.7, 28.6, 28.1, 27.2, 25.9, 24.6, 23.8, 23.2. IR (neat, cm^{-1}) 1695 (s), 1660 (vs). HRMS (FAB) Calcd for $C_{32}H_{42}N_3O_6S$ ($[M+H]^+$): 596.2788. Found: 596.2791. $[\alpha]_D^{20}$ +9.4 (*c* 0.50, $CHCl_3$).

(+)-(4*S*)-*tert*-Butyl 4-(*tert*-butoxycarbonyl)amino-5-oxo-8-phenyl-6-[(pyrrolidine-1-carbonyl)thio]octanoate, 96



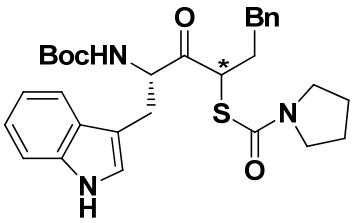
Following the general procedure, *N*-Boc-L-Glu-S-*p*-NO_2Ph (11 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **48** (21 mg, 0.038 mmol, 1.5 equiv) using CuTC (10 mg, 0.05 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 10 mg (75%). TLC (R_f = 0.50, silica gel, 33% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, major isomer t_R = 9.2 min, minor isomer t_R = 8.7 min, dr = 10.8 : 1. ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 7.28-7.24 (m, 2H), 7.18-7.16 (m, 3H), 5.47 (d, *J* = 9.2 Hz, 1H), 4.64-4.58 (m, 2H), 3.57-3.50 (m, 2H), 3.40-3.31 (m, 2H), 2.79-2.71 (m, 1H), 2.66-2.58 (m, 1H), 2.33-2.20 (m, 4H), 2.03-1.78 (m, 6H), 1.43 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 172.4, 163.9, 155.6, 141.1, 126.2, 80.7, 79.8, 47.8, 46.3, 33.5, 32.1, 31.6, 28.5, 28.2, 27.2, 25.7, 24.7. IR (neat, cm^{-1}) 1709 (vs), 1658 (s). HRMS (FAB) Calcd for $C_{28}H_{43}N_2O_6S$ ($[M+H]^+$): 535.2836. Found: 535.2840. $[\alpha]_D^{20}$ +59.5 (*c* 2.20, $CHCl_3$).

(+)-(4*S*)-*tert*-Butyl 4-(*tert*-butoxycarbonyl)amino-6-cyclohexyl-5-oxo-6-[(pyrrolidine-1-carbonyl)thio]hexanoate, 97



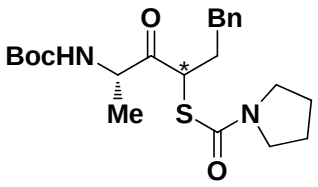
Following the general procedure, *N*-Boc-L-Glu-S-*p*-NO_2Ph (12 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-cyclohexyl(tri-*n*-butylstannyl)methyl pyrrolidine-1-carbothioate **48** (20 mg, 0.038 mmol, 1.5 equiv) using CuTC (10 mg, 0.05 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 11 mg (86%). TLC (R_f = 0.59, silica gel, 33% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, major isomer t_R = 16.6 min, minor isomer t_R = 16.0 min, dr = 5.9 : 1. ^{1}H NMR (600 MHz, $CDCl_3$) major isomer δ 5.55 (d, *J* = 9.6 Hz, 1H), 4.52-4.47 (m, 2H), 3.52-3.47 (m, 2H), 3.39-3.33 (m, 2H), 2.32-2.23 (m, 3H), 1.94-1.85 (m, 6H), 1.78-1.63 (m, 6H), 1.44 (s, 9H), 1.43 (s, 9H), 1.26-1.10 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.6, 172.5, 164.5, 155.6, 80.5, 79.7, 58.2, 54.0, 47.7, 46.3, 38.0, 31.9, 31.7, 30.3, 28.5, 28.4, 28.2, 27.3, 26.2, 26.1, 25.8, 24.7. IR (neat, cm^{-1}) 1715 (s), 1653 (vs). HRMS (FAB) Calcd for $C_{26}H_{45}N_2O_6S$ ($[M+H]^+$): 513.2992. Found: 513.2994. $[\alpha]_D^{20}$ +59.1 (*c* 0.80, $CHCl_3$).

(+)-*S*-(5*S*)-5-(*tert*-Butoxycarbonyl)amino-6-(1*H*-indol-3-yl)-4-oxo-1-phenylhexan-3-yl pyrrolidine-1-carbothioate, 98



Following the general procedure, *N*-Boc-L-Trp-S-*p*-NO_2Ph (11 mg, 0.025 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **48** (21 mg, 0.038 mmol, 1.5 equiv) using CuTC (10 mg, 0.05 mmol, 2.0 equiv) to give the title compound as a pale yellow oil. Yield: 10 mg (75%). TLC (R_f = 0.25, silica gel, 33% ethyl acetate in hexanes). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, major isomer t_R = 11.0 min, minor isomer t_R = 10.2 min, dr = 7 : 1. ^{1}H NMR (600 MHz, $CDCl_3$) major isomer δ 7.99 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.19-7.13 (m, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.06-7.03 (m, 2H), 6.88 (s, 1H), 5.49 (d, *J* = 7.8 Hz, 1H), 5.07-5.04 (m, 1H), 4.51 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.58-3.48 (m, 2H), 3.41-3.27 (m, 4H), 2.59-2.54 (m, 1H), 2.41-2.36 (m, 1H), 1.97-1.85 (m, 6H), 1.42 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.6, 163.7, 155.3, 141.5, 136.1, 128.6, 128.5, 126.1, 123.0, 122.2, 119.7, 119.2, 111.2, 110.7, 79.6, 57.7, 48.8, 47.8, 46.2, 32.9, 31.9, 28.5, 28.1, 25.7, 24.7. IR (neat, cm^{-1}) 1700 (vs), 1652 (s). HRMS (FAB) Calcd for $C_{30}H_{38}N_3O_4S$ ($[M+H]^+$): 536.2577. Found: 536.2581. $[\alpha]_D^{20}$ +61.2 (*c* 0.90, $CHCl_3$).

_S_-(5_S_)-5-(_tert_-Butoxycarbonyl)amino-4-oxo-1-phenylhexan-3-yl pyrrolidine-1-carbothioate, 99



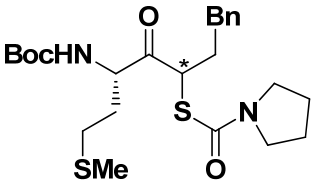
Following the general procedure, *N*-Boc-L-Ala-S-*p*-NO_2Ph (82 mg, 0.25 mmol, 1.0 equiv) was coupled with (±)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **47** (230 mg, 0.375 mmol, 1.5 equiv) using CuTC (95 mg, 0.5 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 71 mg (63%). The two diastereomers were easily separated by silica gel chromatography using 33% ethyl acetate in hexanes as the eluting solvent.

Less polar diastereomer, TLC (R_f= 0.55, silica gel, 33% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.49 (d, *J* = 6.8 Hz, 1H), 4.66 (t, *J* = 3.2 Hz, 1H), 4.59 (t, *J* = 7.2 Hz, 1H), 3.54-3.47 (m, 2H), 3.39-3.31 (m, 2H), 2.77-2.70 (m, 1H), 2.65-2.58 (m, 1H), 2.30-2.21 (m, 1H), 2.04-1.87 (m, 5H), 1.44 (s, 9H), 1.34 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.3, 163.8, 155.2, 141.1, 128.6, 128.5, 126.3, 79.7, 53.5, 47.8, 47.5, 46.3, 33.5, 32.3, 28.5, 25.7, 24.7, 18.5. IR (neat, cm^{-1}) 1700 (vs), 1653 (s). HRMS (FAB) Calcd for $C_{22}H_{33}N_2O_4S$ ($[M+H]^+$): 421.2155. Found: 421.2158.

More polar diastereomer, TLC (R_f= 0.46, silica gel, 33% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.14 (d, *J* = 6.8 Hz, 1H), 4.56-4.49 (m, 2H), 3.54-3.47 (m, 2H), 3.39-3.31 (m, 2H), 2.77-2.70 (m, 1H), 2.65-2.58 (m, 1H), 2.30-2.21 (m, 1H), 2.04-1.87 (m, 5H), 1.42 (s, 9H), 1.37 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) 207.3, 164.0, 155.2, 141.1, 128.6, 128.5, 126.3, 79.7, 54.1, 47.8, 47.5, 46.2, 33.3, 32.4, 28.6, 25.7, 24.7, 18.5. IR (neat, cm^{-1})

1700 (vs), 1653 (s). HRMS (FAB) Calcd for $C_{22}H_{33}N_2O_4S$ ($[M+H]^+$): 421.2155. Found: 421.2152.

_S_-(5_S_)-5-(_tert_-Butoxycarbonyl)amino-7-methylthio-4-oxo-1-phenylheptan-3-yl pyrrolidine-1-carbothioate, 100



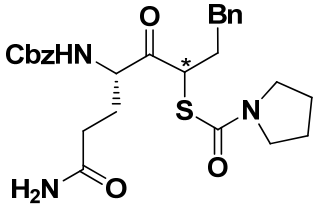
Following the general procedure, *N*-Boc-L-Met-S-*p*-NO_2Ph (97 mg, 0.25 mmol, 1.0 equiv) was coupled with (±)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **47** (230 mg, 0.375 mmol, 1.5 equiv) using CuTC (95 mg, 0.5 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 80 mg (63%).

Less polar diastereomer, TLC (R_f = 0.46, silica gel, 33% ethyl acetate in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.17 (app d, *J* = 7.8 Hz, 3H), 5.54 (d, *J* = 7.8 Hz, 1H), 4.76-4.72 (m, 1H), 4.61 (t, *J* = 7.2 Hz, 1H), 3.53-3.51 (m, 2H), 3.39-3.33 (m, 2H), 2.78-2.73 (m, 1H), 2.65-2.60 (m, 1H), 2.50-2.45 (m, 2H), 2.24-2.19 (m, 2H), 2.05 (s, 3H), 2.02-1.95 (m, 3H), 1.93-1.85 (m, 3H), 1.44 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.0, 163.8, 155.7, 141.1, 128.7, 128.6, 126.3, 79.9, 57.0, 47.8, 46.3, 33.4, 32.1, 32.0, 30.1, 28.5, 25.7, 24.7, 15.6. IR (neat, cm^{-1}) 1705 (vs), 1653 (s). HRMS (FAB) Calcd for $C_{24}H_{37}N_2O_4S_2$ ($[M+H]^+$): 481.2189. Found: 481.2193.

More polar diastereomer, TLC (R_f = 0.40, silica gel, 33% ethyl acetate in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.19 (app d, *J* = 7.2 Hz, 3H), 5.16 (d, *J* = 7.2 Hz, 1H), 4.62-4.60 (m, 1H), 4.55 (t, *J* = 7.2 Hz, 1H), 3.53-3.51 (m, 2H),

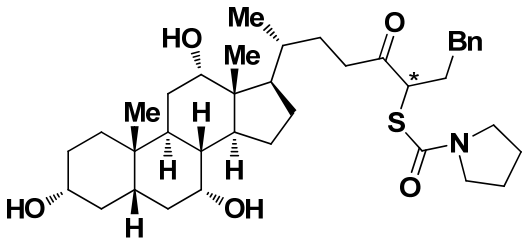
3.39-3.33 (m, 2H), 2.78-2.73 (m, 1H), 2.68-2.61 (m, 1H), 2.50-2.45 (m, 2H), 2.24-2.19 (m, 2H), 2.06 (s, 3H), 2.02-1.95 (m, 3H), 1.93-1.85 (m, 3H), 1.42 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.0, 163.8, 155.5, 141.0, 128.7, 128.6, 126.3, 80.1, 57.4, 50.4, 47.6, 46.2, 33.4, 33.1, 32.1, 30.4, 28.4, 25.7, 24.7, 15.5. IR (neat, cm^{-1}) 1705 (vs), 1653 (s). HRMS (FAB) Calcd for $C_{24}H_{37}N_2O_4S_2$ ($[M+H]^+$): 481.2189. Found: 481.2194.

(+)-*S*-(5*S*)-8-Amino-5-(benzyloxycarbonyl)amino-4,8-dioxo-1-phenyloctan-3-yl pyrrolidine-1-carbothioate, 101



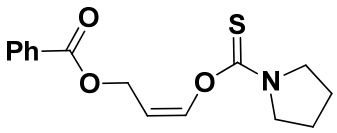
Following the general procedure, *N*-Cbz-L-Gln-S-*p*-NO_2Ph (42 mg, 0.1 mmol, 1.0 equiv) was coupled with (+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **48** (84 mg, 0.15 mmol, 1.5 equiv) using CuTC (38 mg, 0.2 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 34 mg (67%). TLC (R_f = 0.35, silica gel, 3% methanol in ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 6H), 7.19-7.15 (m, 4H), 6.04 (d, *J* = 8.0 Hz, 1H), 5.94 (s, 1H), 5.50 (s, 1H), 5.12 (AB q, *J* = 12.0 Hz, 1H), 5.06 (AB q, *J* = 12.0 Hz, 1H), 4.72-4.64 (m, 1H), 4.54 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.49 (t, *J* = 6.8 Hz, 2H), 3.37-3.33 (m, 2H), 2.79-2.71 (m, 1H), 2.65-2.57 (m, 1H), 2.32-2.10 (m, 4H), 2.04-1.83 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 174.6, 163.9, 156.5, 140.8, 136.4, 128.7, 128.6, 128.5, 128.3, 128.2, 126.3, 67.1, 57.7, 47.8, 46.4, 33.3, 31.9, 28.2, 25.7, 24.7. IR (neat, cm^{-1}) 3331 (br), 1706 (s), 1664 (vs). HRMS (FAB) Calcd for $C_{27}H_{34}N_3O_5S$ ($[M+H]^+$): 512.2213. Found: 512.2215. $[\alpha]_D^{20}$ +79.0 (*c* 2.60, $CHCl_3$).

_S_-(7_R_)-4-oxo-1-Phenyl-7-[(3_R_,5_S_,7_R_,8_R_,9_S_,10_S_,12_S_,13_R_,14_S_,17_R_)-3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1_H_-cyclopenta[_a_]phenanthren-17-yl]octan-3-yl pyrrolidine-1-carbothioate, 102



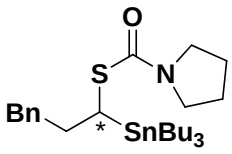
Following the general procedure, cholic acid thiol ester (42 mg, 0.075 mmol, 1.0 equiv) was coupled with (±)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **47** (70 mg, 0.113 mmol, 1.5 equiv) using CuTC (29 mg, 0.15 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 26 mg (52%). TLC (R_f = 0.35, two diastereomers could not be separated, silica gel, 10% methanol in ethyl acetate). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 0.5 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 15 min, 75% CH_3CN to 100 % CH_3CN in 15 min, hold for 10 min, major isomer t_R = 13.7 min, minor isomer t_R = 13.0 min, dr = 1.5 : 1. ^{1}H NMR (600 MHz, $CDCl_3$) two diastereomers could not be differentiated δ 7.28-7.26 (m, 2H), 7.19-7.17 (m, 3H), 4.33-4.30 (m, 1H), 3.95 (br s, 1H), 3.84 (br s, 1H), 3.52 (t, *J* = 6.8 Hz, 2H), 3.44-3.38 (m, 3H), 2.76-2.72 (m, 2H), 2.66-2.61 (m, 1H), 2.55-2.34 (m, 1H), 2.25-2.18 (m, 4H), 2.03-0.93 (m, 27H), 0.88 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.9, 164.4, 141.2, 128.6, 126.2, 73.1, 72.1, 68.6, 52.2, 51.9, 47.7, 47.2, 47.0, 46.7, 46.6, 46.3, 42.0, 41.6, 39.9, 39.7, 38.0, 37.7, 35.4, 35.1, 34.8, 34.7, 33.5, 32.4, 30.7, 30.0, 29.8, 28.4, 27.7, 27.5, 26.7, 25.8, 24.7, 23.4, 22.7, 17.7, 12.7. IR (neat, cm^{-1}) 3396 (br), 1706 (vs), 1652 (s). HRMS (FAB) Calcd for $C_{38}H_{58}NO_5S$ ($[M+H]^+$): 640.4030. Found: 640.4036.

(*Z*)-3-[(Pyrrolidine-1-carbonothioyl)oxy]allyl benzoate, 103



The title compound was isolated as a colorless oil. Yield: 9 mg (50%). TLC (R_f= 0.62, silica gel, 33% ethyl acetate in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 9.6 Hz, 1H), 6.02-5.98 (m, 1H), 4.90 (d, *J* = 6.6 Hz, 2H), 3.56 (t, *J* = 7.2 Hz, 2H), 3.41 (t, *J* = 6.6 Hz, 2H), 2.01-1.89 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.6, 173.2, 133.2, 129.9, 128.5, 124.3, 123.4, 117.0, 62.7, 47.6, 46.0, 25.7, 24.7. IR (neat, cm^{-1}) 1719 (vs), 1502 (s). HRMS (FAB) Calcd for $C_{15}H_{18}NO_3S$ ($[M+H]^+$): 292.1001. Found: 292.1004.

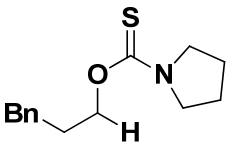
(-)-*S*-3-Phenyl-1-(tributylstannyl)propyl pyrrolidine-1-carbothioate[11], **104**



(+)-(*S*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **48** (21 mg, 0.038 mmol, 1.0 equiv) and CuTC (4 mg, 0.019 mmol, 0.5 equiv) were placed under an argon atmosphere. Then THF (2 mL, degassed and dried over 4Å molecular sieves) was added at room temperature. The reaction mixture was stirred for 1 h and then evaporated. The residue was purified by SiO_2 column chromatography to give the title compound as a colorless oil. Yield: 10 mg (50%). TLC (R_f= 0.30, silica gel, 5% ethyl acetate in hexanes). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN to 75% CH_3CN in 10 min, 75% CH_3CN to 100 % CH_3CN in 8 min, hold for 4 min, major isomer t_R = 20.9 min,

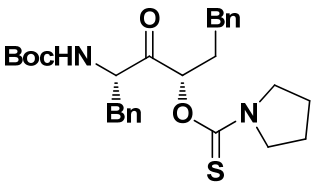
minor isomer t_R = 21.2 min, ee = 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.24 (m, 2H), 7.19-7.15 (m, 3H), 3.51 (t, *J* = 8.4 Hz, 2H), 3.38 (t, *J* = 6.4 Hz, 2H), 2.87 (t, *J* = 6.8 Hz, 1H), 2.71-2.66 (m, 2H), 2.10-2.05 (m, 2H), 1.96-1.85 (m, 4H), 1.51-1.47 (m, 6H), 1.33-1.27 (m, 6H), 0.95-0.91 (m, 6H), 0.88 (t, *J* = 7.2 Hz, 9H). IR (neat, cm^{-1}) 1633 (vs). $[\alpha]_D^{20}$ -8.4 (*c* 0.80, $CHCl_3$).[20]

_O_-3-Phenylpropyl pyrrolidine-1-carbothioate[21], 105



The title compound was isolated as a colorless oil. Yield: 19 mg (99%). TLC (R_f= 0.38, silica gel, 10% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H), 4.48 (t, *J* = 6.0 Hz, 2H), 3.72 (t, *J* = 6.4 Hz, 2H), 3.48 (t, *J* = 6.0 Hz, 2H), 2.73 (t, *J* = 8.0 Hz, 2H), 2.09-2.02 (m, 2H), 1.96-1.90 (m, 4H). IR (neat, cm^{-1}) 1490 (vs).

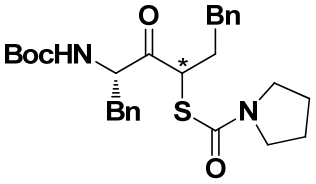
(+)-_O_-(3_S_,5_S_)-5-(_tert_-Butoxycarbonyl)amino-4-oxo-1,6-diphenylhexan-3-yl pyrrolidine-1-carbothioate, 106



TLC (R_f = 0.59, silica gel, dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$) two diastereomers δ 7.29-7.14 (m, 10H), 6.01 (dd, *J* = 7.8, 3.0 Hz, 1H), 4.95 (d, *J* = 8.4 Hz, 1H), 4.82-4.78 (m, 1H), 3.74-3.65 (m, 3H), 3.47-3.43 (m, 1H), 3.36 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.84 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.71-2.65 (m, 2H), 2.21-2.08 (m, 2H), 1.99-1.95 (m, 4H), 1.35 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 184.0, 155.2,

140.9, 136.7, 129.6, 128.6, 128.5, 126.9, 126.3, 81.6, 80.0, 57.2, 52.4, 48.2, 37.5, 32.8, 32.0, 28.4, 25.8, 24.7. IR (neat, cm^{-1}) 1710 (s), 1498 (vs). HRMS (FAB) Calcd for $C_{28}H_{37}N_2O_4S$ ($[M+H]^+$): 497.2463. Found: 497.2459. $[\alpha]_D^{20}$ +81.4 (*c* 0.80, $CHCl_3$).

(-)-*S*-(5*S*)-5-(*tert*-Butoxycarbonyl)amino-4-oxo-1,6-diphenylhexan-3-yl pyrrolidine-1-carbothioate, 107



Following the general procedure, *N*-Boc-L-Phe-S-*p*-NO_2Ph (20 mg, 0.05 mmol, 1.0 equiv) was coupled with (-)-(*R*)-*O*-3-phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate **51** (42 mg, 0.075 mmol, 1.5 equiv) using CuTC (20 mg, 0.1 mmol, 2.0 equiv) to give the title compound as a colorless oil. Yield: 20 mg (81%). TLC (R_f= 0.30, silica gel, 25% ethyl acetate in hexanes). $[\alpha]_D^{20}$ -35.2 (*c* 1.00, $CHCl_3$). IR (neat, cm^{-1}) 1706 (s), 1652 (vs).

3.5 References

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