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Hao Yang Date

Ambient Temperature Synthesis of High Enantiopurity N-Protected Peptidyl Ketone by Desulfitative Cross Coupling of Peptidyl Thiol Esters and Boronic Acids

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Doctor of Philosophy
Chemistry

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B.E., East China University of Science and Technology, 1999
M.E., East China University of Science and Technology, 2002
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An Abstract of
A dissertation submitted to the Faculty of the Graduate School of
Emory University in partial fulfillment of
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In
Chemistry

2009

Abstract

Ambient Temperature Synthesis of High Enantiopurity N-Protected Peptidyl Ketone by Desulfitative Cross Coupling of Peptidyl Thiol Esters and Boronic Acids

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Two efficient desulfitative cross coupling methodologies were developed to synthesize high enantiopurity peptidyl ketones. The first methodology was developed from the first generation of the Liebeskind-Srogl desulfitative cross coupling reaction. In the presence of catalytic $Pd_2(dba)_3$/triethyl phosphite and stoichiometric Cu(I)-thiophene-2-carboxylate, a great variety of N-protected peptidyl thiol esters couple efficiently with boronic acids to yield the corresponding peptidyl ketones in satisfactory yields without racemization or epimerization. In the second generation of desulfitative peptidyl ketone synthesis, high enantiopurity peptidyl ketones were synthesized from peptidyl *S*-acylthiosalicylamide esters and boronic acids by using Cu(I)-3-methylsalicylate as the only metal catalyst. The reaction takes place at room temperature under air. Eighteen examples have been synthesized to demonstrate the efficiency and a broad tolerance of functional groups for this new reaction.

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List of Abbreviations

app	apparent
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
ºC	degrees Celsius
calcd	calculated
Cbz	benzyloxycarbonyl
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
DIPEA	diisopropylethylamine
DMF	dimethylformamide
DMAP	*N*,*N*-dimethylaminopyridine
DMSO	dimethylsulfoxide
equiv.	equivalent
Et	ethyl
EtOAc	ethyl acetate

Fmoc	9-fluorenylmethoxycarbonyl
g	gram(s)
Hex	hexane
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
hrs	hour(s)
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
L	liter
M	molar
Me	methyl
MeCN	acetonitrile
mg	milligram
MHz	megahertz
ml	milliliter
mmol	millimole
mol %	mole percent
mol	mole
Mp	melting point
N	normal
N_3	azide
NMM	*N*-methyl morpholine
OAc	acetate
Ph	phenyl

PMB	*p*-methoxybenzyl
ppm	parts per million
py	pyridine
q	quartet
s	singlet
Ser	serine
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	toluene
Trityl	triphenylmethyl
UV	ultraviolet
w	weak

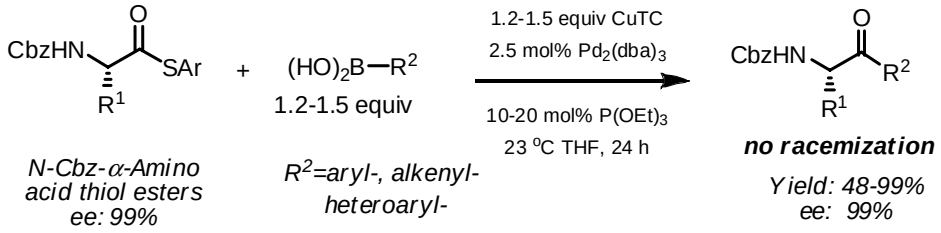
Chapter 1

Ambient Temperature Synthesis of High Enantiopurity N-Protected α-Amino Ketones by Thiol Ester–Boronic Acid Cross-Coupling

Abstract

N-Protected α-amino thiophenyl esters couple with aryl, π-electron-rich heteroaryl and alkenyl boronic acids in the presence of stoichiometric Cu(I) thiophene-2-carboxylate and catalytic $Pd_2(dba)_3$/triethylphosphite to generate the corresponding N-protected α-amino ketones in good-to-excellent yields without racemization of the resulting N-protected α-amino ketone. Triethylphosphite plays an important role as a supporting ligand by mitigating an undesired palladium-catalyzed decarbonylation-β-elimination of the α-amino thiol esters. This α-amino ketone synthesis proceeds at room temperature under pH neutral conditions and demonstrates a high tolerance to a wide range of functional groups (**Scheme 1.1**).

Scheme 1.1 N-Protected α-Amino Thiol esters and Boronic Acids Cross Coupling



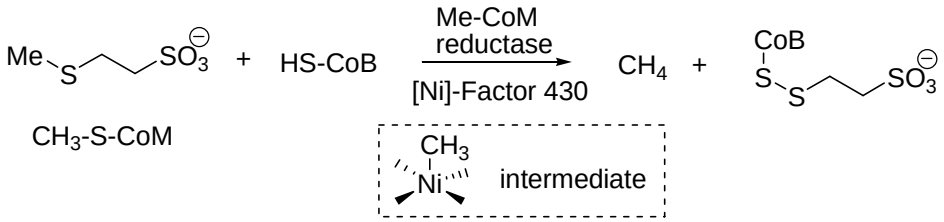
1.1 Introduction

1.1.1 Desulfitative Thioorganic and Boronic Acid Cross Coupling

Thioorganic compounds are widely present in nature. They are essential materials for protein such as cysteine and methionine. They also participate in a number of biochemical transformations either as an enzyme or as a substrate.[1] The unique chemical properties of thioorganic compounds have determined their important roles for many

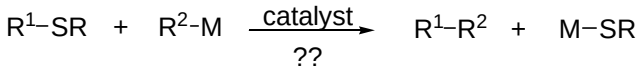
biochemical transformations. The C-S bond is longer and softer than the C-O bond. The C-S bond is polarizable in a hard environment.[2] More importantly, thiolate ligand shows a high affinity toward metals such as Ni, Fe, Cu and Zn. As for an example, methyl-coenzyme Metal reductase (MCR) is the enzyme responsible for the microbial formation of methane.[3] It was believed that an activated nickel hydrocorphinoid cofactor (F430) cleaves the Me-S bond of $MeSCH_2CH_2SO_3^-$ to generate a [Ni]-Me intermediate, which undergoes a rapid protonation in the presence of HS-CoB to release methane (**Scheme 1.2**) .[4] Based on this microbial process, more than 10^9 tons of methane are produced annually in Nature.[5]

Scheme 1.2 MCR Catalyzed Production of Methane



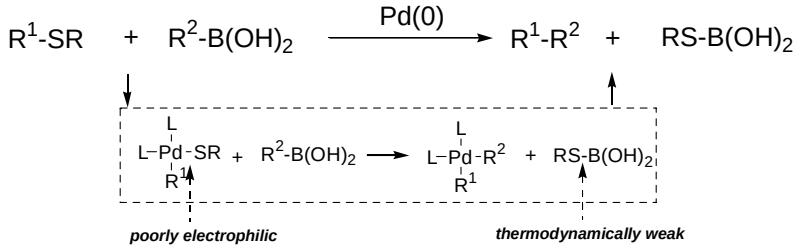
From the perspective of organic chemistry, this enzymatic process transformed the carbon-sulfur bond into the carbon-hydrogen bond from a nickel catalyzed oxidative addition and protonation sequence. Inspired by this biomolecular prototype, the Liebeskind research group has developed a series of novel desulfitative reactions to construct carbon-carbon bonds under pH-neutral conditions.

Scheme 1.3 A Typical Desulfitative C-C Coupling



The reaction shown in **Scheme 1.3** displays a representative disulfitative carbon-carbon cross-coupling. A transition metal catalyst selectively cleaves the C-S bond to generate an R^1-M-SR intermediate. The subsequent transmetalation will replace the thiolate (SR) with R^2 to produce R^1-M-R^2, and the final product R^1-R^2 is formed by reductive elimination. In fact, the desulfitative cross-coupling is not unprecedented. Wenkert[6], Okamura[7] and Ronzini[8] have published a variety of Ni- and Fe-catalyzed thioorganics and Grignard reagent cross couplings. In addition to Grignard reagents, organozinc reagents could also be used as the desulfitative cross coupling partner which was studied by Luh[9], Fukuyama[10] and Jacobi.[11]

Scheme 1.4 Assumption of Thioorganic-Boronic Acid Cross Coupling

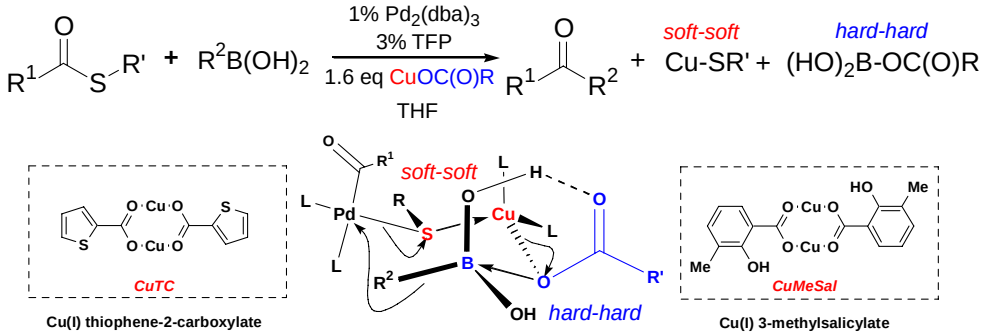


The current synthetic application of desulfitative cross coupling was largely limited to simple ketone substrates because Grignard and organozinc reagents are strongly nucleophilic and moisture sensitive. Under this circumstance, boronic acids would be better replacements for Grignard and organozinc reagent because of their wide commercial availability and broad tolerance to most functional groups, and most boronic acids are solids and air stable. However, to realize thioorganic and boronic acid cross coupling is still a tough challenge in the family of transition metal mediated carbon-carbon cross couplings. Assuming this cross coupling does occur, a thiol boronic acid ($RS\text{-}B(OH)_2$) should be formed to balance the reaction. In fact, the S-B bond, a soft-hard interaction, is not thermodynamically favored. Additionally, the transmetalation requires

the boronic acid to break the poorly electrophilic Pd-SR bond, which is assumed to be thermodynamically strong (**Scheme 1.4**).

To address this challenge, Liebeskind and Srogl introduced the use of a stoichiometric Cu(I) carboxylate to a reaction of thiol ester and boronic acid cross coupling shown in **Scheme 1.5**, which resulted in ketone formation.[12]

Scheme 1.5 Liebeskind-Srogl Cross Coupling

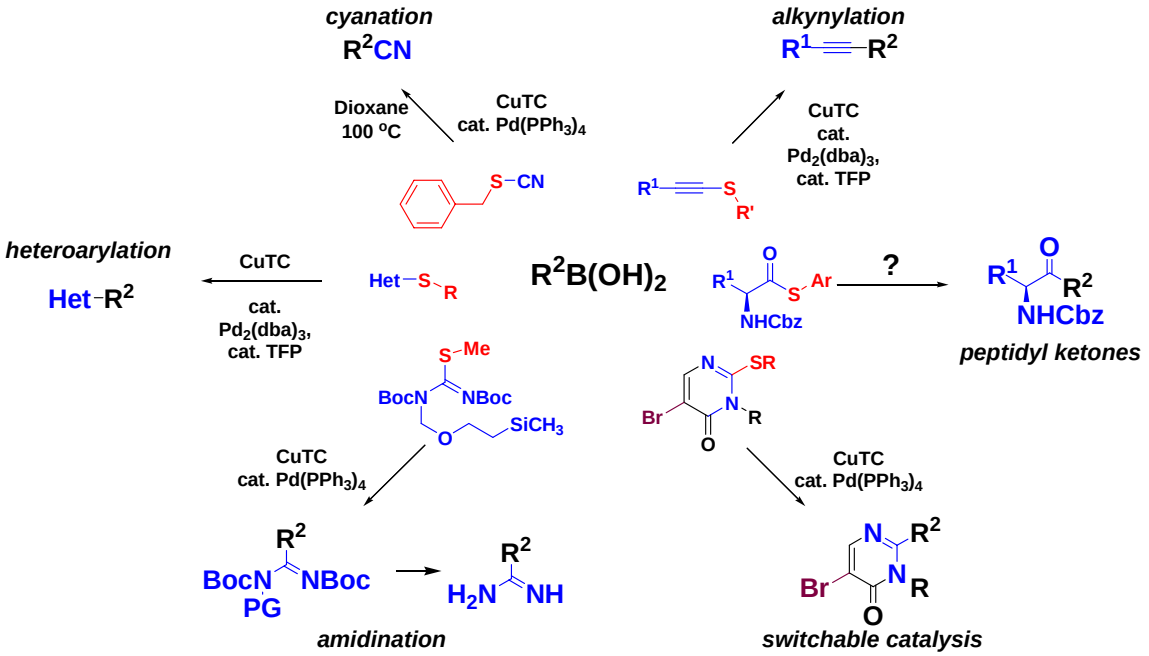


The whole chemistry is initialized from the palladium catalyzed oxidative addition to generate an acetyl palladium thiolate (R^1CO-Pd-SR'). In the absence of Cu(I) carboxylate, the crucial transmetalation from boronic acid to the palladium is not thermodynamically favorable. However, the introduction of the Cu(I) carboxylate to the system could actually allow the transmetalation to occur by dual activations: S→Cu soft-soft interaction and O→B hard-hard interaction. The S-Cu soft-soft activation improves the electrophilicity of the acetyl palladium thiolate, and the O-B hard-hard interaction enhances the nucleophilicity of boronic acid. The overall effects favor a six member open ring transition state which facilitates the transmetalation (**Scheme 1.5**). In results, the ketone product was generated by reductive elimination.

Based on the same principle, the Liebeskind group has developed a family of desulfitative thioorganic and boronic acid cross coupling shown in **Scheme 1.6**[13]. All of

these desulfitative thioorganic cross coupling reactions take place under pH-neutral conditions which suggests their potential application to the functionality rich and base-sensitive systems such as peptidyl thioorganic cross coupling (middle right, **Scheme 1.6**).

Scheme 1.6 Liebeskind-Srogl Desulfitative Thioorganic Cross Coupling



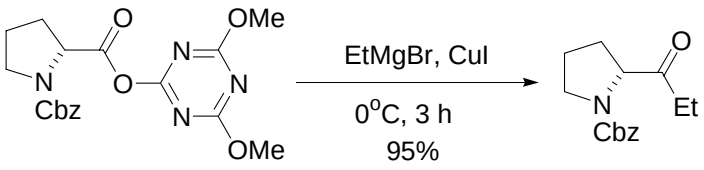
1.1.2 Current Progress of Synthesis of High Enantiopurity N-Protected α-Amino Ketone

Enantiomerically pure N-protected α-amino ketones are valuable compounds that can be used as chiral, non-racemic building blocks to construct a great diversity of molecules such as amino alcohol[14], heterocycles[15] and various natural products.[16] These peptidyl α-ketoheterocycles have displayed potent inhibition toward a large number of enzymes.[17]

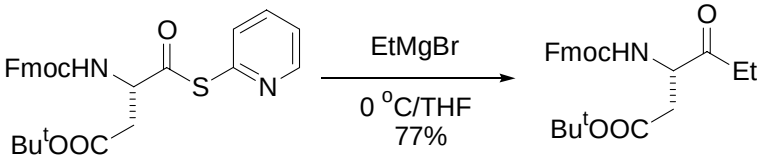
For decades, the transformation of α-amino acids and small peptides to the corresponding *C*-terminal ketones without epimerization has been an ongoing challenge

to synthetic chemists. From various derivatives of *N*-protected α-amino acids, most published methodologies are restricted to use strong basic/nucleophilic organometallic reagents such as Grignard, organolithium and organozinc reagent.[18]

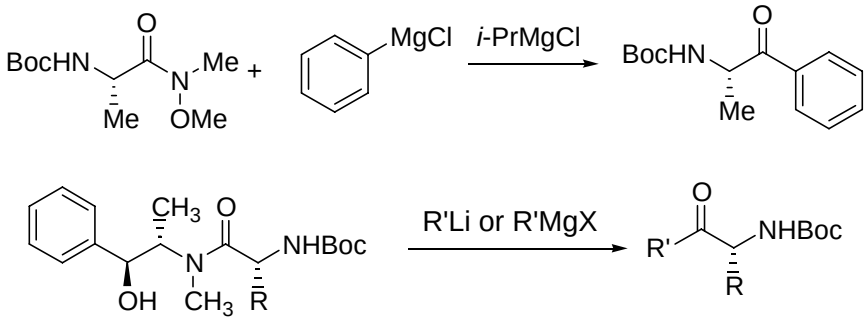
Scheme 1.7 Ketone Synthesis via Triazine Ester



Scheme 1.8 Ketone Synthesis via 2-Pyridyl Thiol Ester



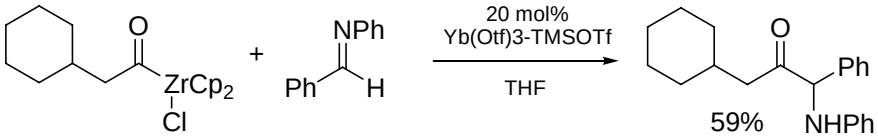
Scheme 1.9 Ketone Synthesis via Weinreb-like Amides



Giacomelli found an activated acid triazine ester could be converted to the ketone by reacting with Grignard/CuI reagent (**Scheme 1.7**).[19] Recently, Albericio disclosed a general protocol to prepare Fmoc-protected amino ketone from amino thiol (2-pyridyl) ester and Grignard reagent (**Scheme 1.8**).[20] In fact, most of these methods were based on Weinreb amide and its analogue (**Scheme 1.9**).[21] Although these established methodologies are of value in the synthesis of simple α-amino ketones from α-amino

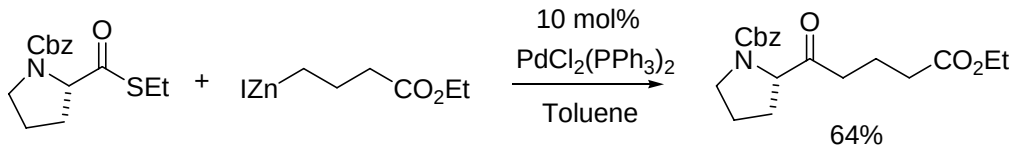
acid derivatives, the use of strongly nucleophilic and basic organomagnesium and -lithium reagents precludes the practice of this chemistry in the synthesis of more complex molecules containing base-sensitive stereogenic centers and electrophilic functional groups such as an aldehyde. Hanzawa and Taguchi introduced a novel solution to the problem: the preparation of α-amino ketones using acylzirconocene chloride complexes as acyl anion equivalents for the addition to substituted *N*-benzylideneaniline derivatives, but the reactivity is not high and enantioselectivity was not addressed (**Scheme 1.10**).[22]

Scheme 1.10 Ketone Synthesis via Acylzirconocene Chloride



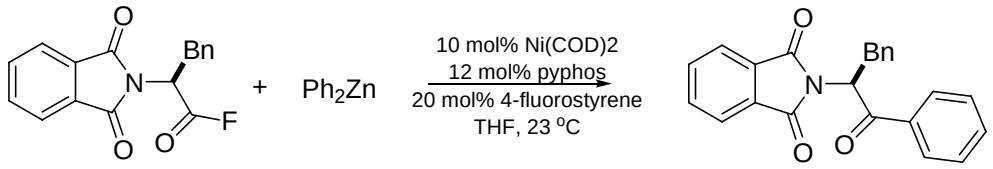
To further generalize the synthesis of α-amino ketones under mild reaction conditions, a small number of transition metal-catalyzed cross-coupling protocols have been developed. By far the mildest method for the synthesis of α-amino ketones from α-amino acids and small peptides is the palladium-catalyzed coupling of thiol esters with organozinc reagents developed by Fukuyama and Tokuyama.[10] Using this cross-coupling procedure, the authors prepared a few examples of α-amino ketones from alkylzinc reagents (**Scheme 1.11**).

Scheme 1.11 Fukuyama Ketone Synthesis



In a related study, Rovis employed a Ni catalyst for the coupling of α-amino acid fluorides with organozinc reagents to give ketones (**Scheme 1.12**).[23]

Scheme 1.12 Ni Catalyzed Acid Fluoride and Organozinc Cross Coupling



While organozinc reagents provide superior functional group compatibility relative to organolithium and organomagnesium reagents, they are, nevertheless, still basic and nucleophilic.

As described above, a new, non-basic desulfitative cross coupling of thiol esters and boronic acids was recently developed by the Liebeskind laboratory. In the presence of a Pd catalyst and copper(I) thiophene-2-carboxylate (CuTC) or related Cu(I) oxygenates, thiol esters react with boronic acids to give ketones in good to excellent yields.[12] In contrast to organolithium, -magnesium, and -zinc reagents, boronic acids are non-basic and non-nucleophilic, and they are easily prepared and handled.[24] A great variety of aryl, heteroaryl, and alkenyl boronic acids are now commercially available. Since boronic acids are nonbasic and the disulfitative thiol ester-boronic acid cross-coupling reaction conditions are mild, boronic acids could be superior partners in cross-couplings with functionally-rich and epimerization-sensitive peptidyl thiol esters. In fact there are related reactions of boronic acids with a variety of acid equivalents such as anhydrides,[25] esters, [26] acid fluorides,[23] and acid chlorides; [27] however, none of the published transformations use acyl reactants or take place under reaction conditions that would be suitable for application to pH sensitive α-amino ketone. Described herein in this chapter

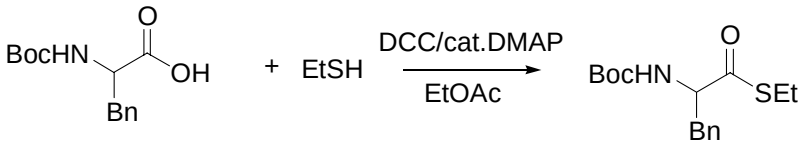
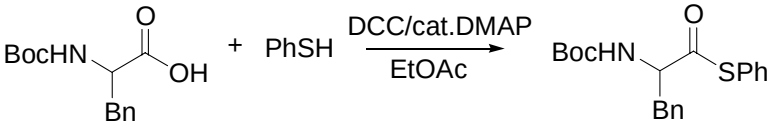
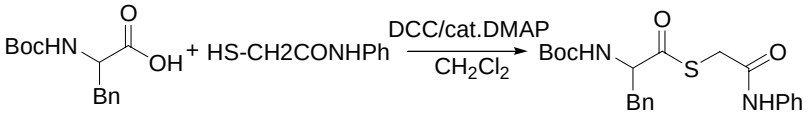
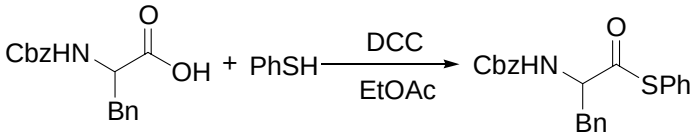
is a study of the scope and limitations of N-protected α-amino ketone synthesis from monopeptidyl thiol esters and boronic acids (**Scheme 1.1**).

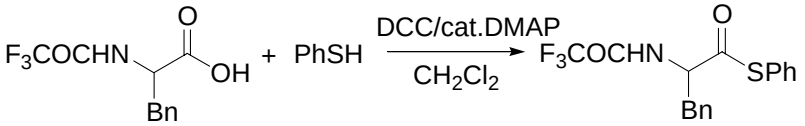
1.2 Results and discussion

1.2.1 Preliminary Study

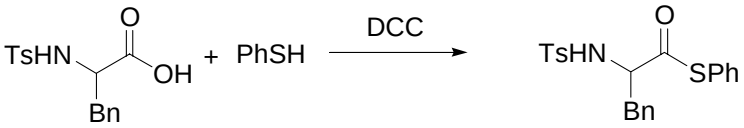
In order to investigate the possibility of mono N-protected α-amino thiol esters and boronic acids cross coupling, N-protected phenylalanine derived thiol esters were prepared to probe the reactivity toward the cross coupling reaction with phenyl boronic acids under standard conditions. For synthesis of these phenylalanine thiol esters, satisfactory yields were obtained by using reported methods from Fukuyama,[28] Steglich,[29] Weygand[30] and Takemura.[31]

Table 1.1 Synthesis of N-Protected α-Amino Thiol Esters

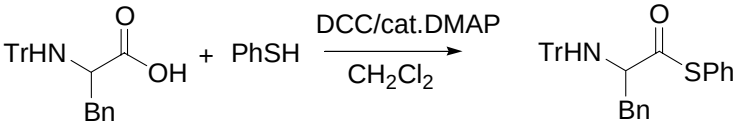
entry	reaction	yield
1	 **1.1**	76%
2	 **1.2**	68%
3	 **1.3**	63%
4	 **1.4**	85%

5  82%

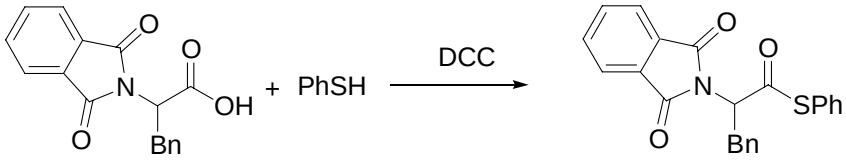
1.5

6  71%

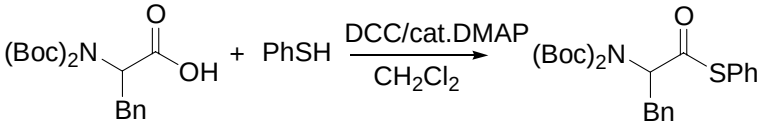
1.6

7  72%

1.7

8  88%

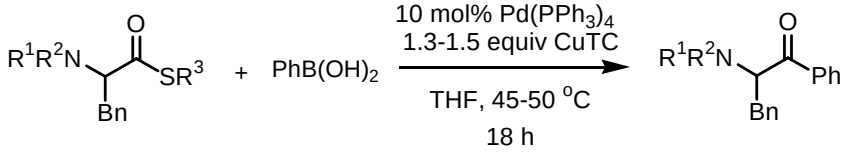
1.8

9  86%

1.9

From those thiol esters above, a standard cross coupling was conducted with phenyl boronic acid in the presence of 10 mol% $Pd(PPh_3)_4$, 1.3-1.5 equiv CuTC under argon atmosphere for 18 hours. Although highly efficient cross couplings were observed from non-peptidyl derived thiol esters and boronic acids, very low ketone yields were obtained from monopeptidyl thiol ester substrates in **Table 1.2**.

Table 1.2 *N*-Protected Phenylalanine Thiol Ester-Boronic Acid Cross Coupling



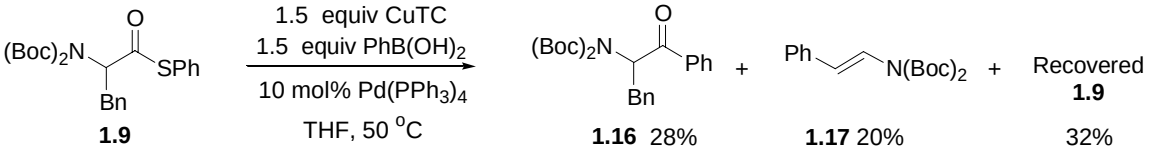
entry	Thiol ester	R^1	R^2	R^3	ketone	yield (%)
1	**1.1**	Boc	H	Et	**1.10**	10[a]
2	**1.2**	Boc	H	Ph	**1.10**	19[b]
3	**1.3**	Boc	H	$CH_2CONHPh$	**1.10**	15[b]
4	**1.4**	Cbz	H	Ph	**1.11**	18[b]

5	**1.5**	CF_3CO	H	Ph	**1.12**	20[b]
6	**1.6**	tosyl	H	Ph	**1.13**	15[b]
7	**1.7**	trityl	H	Ph	**1.14**	0[b]
8	**1.8**	phthaloyl		Ph	**1.15**	54[a]
9	**1.9**	Boc	Boc	Ph	**1.16**	28[a]

[a] Isolated yield. [b] Not isolated or fully characterized. Determined by ^{1}H NMR using pentamethylbenzene as an internal standard.

As shown in **Table 1.2** (entry 1-3), no significant difference was produced by the choice of thiol ester -SR moiety from either alkyl or aryl group. Other than *tert*-butoxycarbonyl protecting group, typical mono-*N*-protected phenylalanine derived thiol esters were also surveyed. While a trityl-protected, basic nitrogen gave no coupling product (**Table 1**, entry 7), *N*-Cbz, *N*-CF_3CO, and *N*-tosyl produced low yields (**Table1**, entries 4-6). Regardless of the low yields, a doubly protected *N,N-bis*-Boc-Phe-SPh (**Table 1**, entry 8,9) helped to reveal the problem by isolating a significant side product **1.17** (**Scheme 1.13**). Guided by the formation of enimide **1.17**, a putative understanding of this reaction mechanism is necessary to develop a more efficient cross coupling protocol.

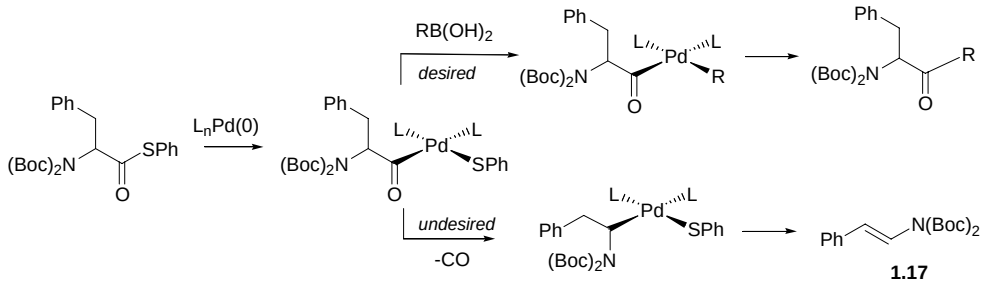
Scheme 1.13 Identification of a Decarbonylation Side Product



From a proposed mechanism for this reaction, the generation of the enimide side product **1.17** should follow a rapid palladium-catalyzed decarbonylation-β-hydride elimination sequence (**Scheme 1.14**). In the first stage, acylpalladium(II) intermediate ($RCOPdL_2SR$) would be formed by oxidative addition of the thiol ester to $L_nPd(0)$. The desired route of the upper half of **Scheme 1.14** requires transmetalation from boronic acid to the acylpalladium(II) intermediate. However, if the transmetalation is slow, and if the

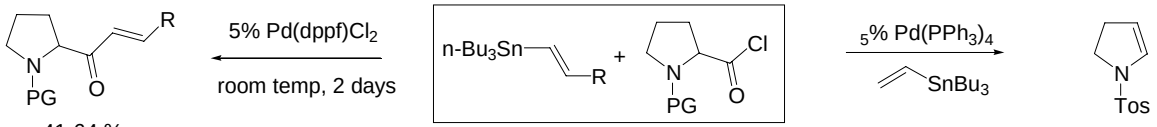
decarbonylation of the acylpalladium thiolate occurs at a reasonable rate,[32] then the enimide **1.17** can be produced by the reaction sequence depicted in the lower half of **Scheme 1.14**.

Scheme 1.14 The Decarbonylation Pathway



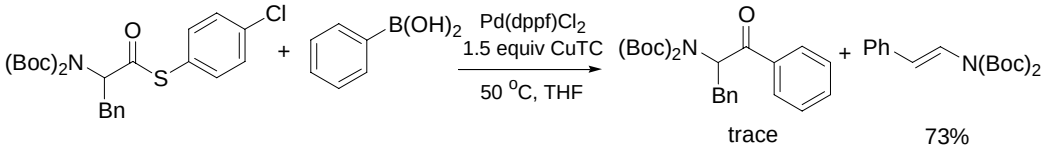
In fact, a similar enimide formation was also observed by Crisp as the only product in a $Pd(PPh_3)_4$-catalyzed cross-coupling of N-tosyl protected proline acid chloride with vinyl(tri-*n*-butyl)stannane (**Scheme 1.15**).[33] Although the undesired decarbonylation route was suppressed by using a bidentate ligand involved $Pd(dppf)Cl_2$ as the catalyst in the Crisp system, the use of $Pd(dppf)Cl_2$ did not solve the decarbonylation problem in our system (**Scheme 1.16**).

Scheme 1.15 Precedent for the Decarbonylation Pathway



PG = Fmoc, tosyl; dppf = 1,1'-bis(diphenylphosphino)ferrocene

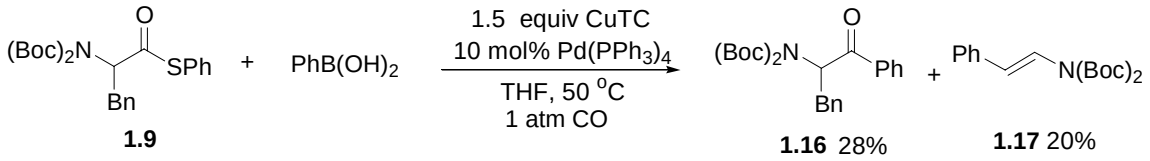
Scheme 1.16 Bidentate Ligand Prefers Decarbonylation



Metal catalyzed decarbonylation is an equilibrium reaction which can be reversed by conducting reactions in the presence of high concentrations of CO. A control cross

coupling reaction was conducted under 1 atm of CO (**Scheme 1.17**), however, the results showed no improvement to the ketone formation. Control experiments under high pressure CO were not carried out because it would not be practically useful.

Scheme 1.17 Control Experiment under CO

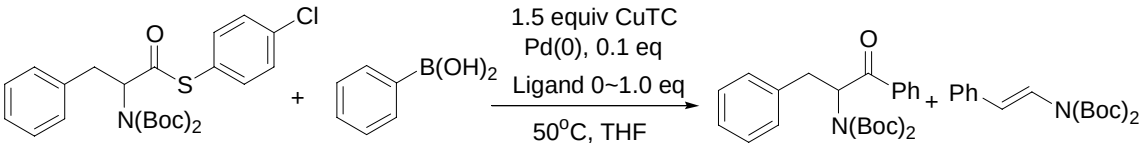


As the acyl (M-CO-R) ⇆ metal alkyl (M-R) equilibrium is not easy to perturb under simple experimental conditions, the reaction outcome might instead be adjusted by influencing the rate of the decarbonylation. From the perspective of the reaction rates, decarbonylation is problematic in the cross-couplings of α-amino acid-derived thiol esters with boronic acids because the rate of boron to palladium transmetalation is slower than that of decarbonylation. Therefore, to achieve a more selective cross-coupling one must either increase the rate of boron to palladium transmetalation or decrease the rate of decarbonylation. Since both the transmetalation and decarbonylation mechanisms require an open coordination site at palladium,[34] both rates should be affected by the ligands present in the reaction system (solvent as ligand, added supporting ligands, intramolecular ligation at Pd by the N-protecting group). Assuming that the decarbonylation and transmetalation pathways can respond differently to variations in the electronic and steric effects of added ligands, it might be possible to develop a successful cross-coupling by probing these ligand effects to retard the decarbonylation without hindering the rate of the transmetalation.

1.2.2 Ligand Screening

A ligand screening was conducted to probe the efficiency of the ketone formation based on the palladium precatalyst ($Pd(PPh_3)_4$, $Pd_2(dba)_3$ or $Pd(dppf)Cl_2$) with or without various added supporting ligand (PPh_3, $PMePh_2$, PMe_2Ph, PEt_3, and $P(OPh)_3$).

Table 1.3 Control Experiment Based on Various Pd/Ligand Ratio



1.46 1.5 equiv **1.16** **1.17**

Entry	Pd/Supporting Ligand and ratio		Yield (**1.16**)	**1.17**
1	$Pd(PPh_3)_4/Et_3P$	1/0	38%	22%
2		1/2	59%	10%
3		1/4	56%	2%
4		1/10	36%	trace
5	$Pd_2(dba)_3/Me_2PPh$	1/4	54%	trace
6		1/6	51%	trace
7		1/8	51%	trace
8	$Pd(PPh_3)_4/Me_2PPh$	1/4	61%	5%
9	$Pd_2(dba)_3/(Me_2PPh+PPh_3)$	1/8	65%	16%
10	$Pd_2(dba)_3/P(OPh)_3$	1/4	38%	13%
11	$Pd(dppf)Cl_2$	1/0	trace	73%

[a] Yields were determined by ^1H NMR using pentamethylbenzene as an internal standard.

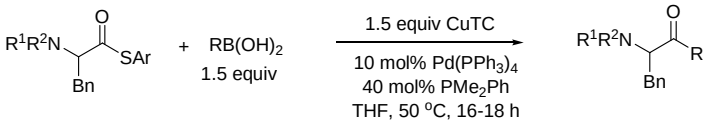
From the entries 1-4 shown in the **Table 1.3**, formation of the undesired enimide side product **1.17** was suppressed as ligand loadings were increased. Stronger electron donating ligands (Me_2PPh) gave higher ratios of ketone to enimide, but this was counterbalanced by the recovery of significant portions of unreacted thiol ester(entry 5-7, **Table 1.3**). Increasing the reaction temperature led to an increase in the decarbonylation side reaction. A bidentate ligand such as diphenylphosphinoferrocene (dppf) completely

prevented formation of the ketone and gave a high yield of the undesired enimide. Finally, of the various precatalyst/ligand systems tried, $Pd(PPh_3)_4$:PMe_2Ph (1:4 ratio, or 1:8 palladium/total phosphine) gave the best ratio of ketone to enimide to starting material (61:5:20).

1.2.3 A General Synthesis of N-*bis*-Boc Protected α-Amino Ketone

To examine the generality of this catalyst system, various cross coupling reactions were performed based on N-protected phenylalanine thiol esters and boronic acids by using $Pd(PPh_3)_4$:PMe_2Ph (1:4 ratio) as the catalyst. The results are shown in **Table 1.4**.

Table 1.4 Cross-Couplings Examples

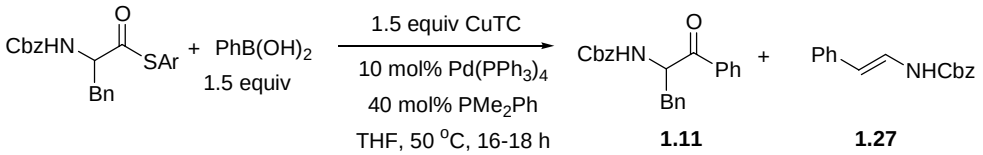


entry	thiol ester	R^1	R^2	Ar	boronic acid, R	ketone	yield (%)
1	**1.8**	phthaloyl		Ph	4-methoxyphenyl	**1.20**	98
2	"	"		"	4-carbomethoxyphenyl	**1.21**	74
3	**1.9**	Boc	Boc	*p*-NO_2Ph	phenyl	**1.16**	73
4	"	"	"	"	3,4-methylenedioxyphenyl	**1.22**	77
5	"	"	"	"	4-methoxyphenyl	**1.23**	91
6	"	"	"	"	3-nitrophenyl	**1.24**	58
7	"	"	"	"	2-formyl-4-methoxy	**1.25**	62
8	"	"	"	"	*E*-1-hexenyl	**1.26**	99

Doubly N-protected α-amino acid thiol esters (entry 1-8, **Table 1.4**) gave good yields of ketone products, which were not influenced by the electronic nature of the thiol ester – SAr used. As shown in **Table 1.4**, electronic donating aryl boronic acids (entry 1, 4, 5), electronic withdrawing aryl boronic acids (entry 2, 6) and alkenyl boronic acids (entry 10)

coupled with phenylalanine derived thiol esters to give ketones from satisfactory to excellent yields.

Table 1.5 Cross-Couplings Examples



entry	Thiol ester	Ar	ketone	Ketone yield(%)	**1.27** Yield(%)
1	**1.4**	Ph	**1.11**	49	25
2	**1.19**	*p*-NO_2Ph	**1.11**	20	34

Unfortunately, the same Pd/PPh_3/PMe_2Ph mixed ligand system did not provide satisfactory cross-coupling yields of the synthetically more practical mono-N-Cbz-protected systems (**Table 1.5**): N-Cbz-Phe-SPh coupled with phenyl boronic acid producing the desired ketone Cbz-Phe-COPh in only 49% yield as well as a significant yield of 25% (*E*)-PhCH=CH-NHCbz, **1.27**, the enimide product generated by a decarbonylation-β-elimination pathway. Changing to a more reactive *p*-nitrophenylthiol ester moiety did not improve the outcome of the reaction (entry 2, **Table 1.5**).

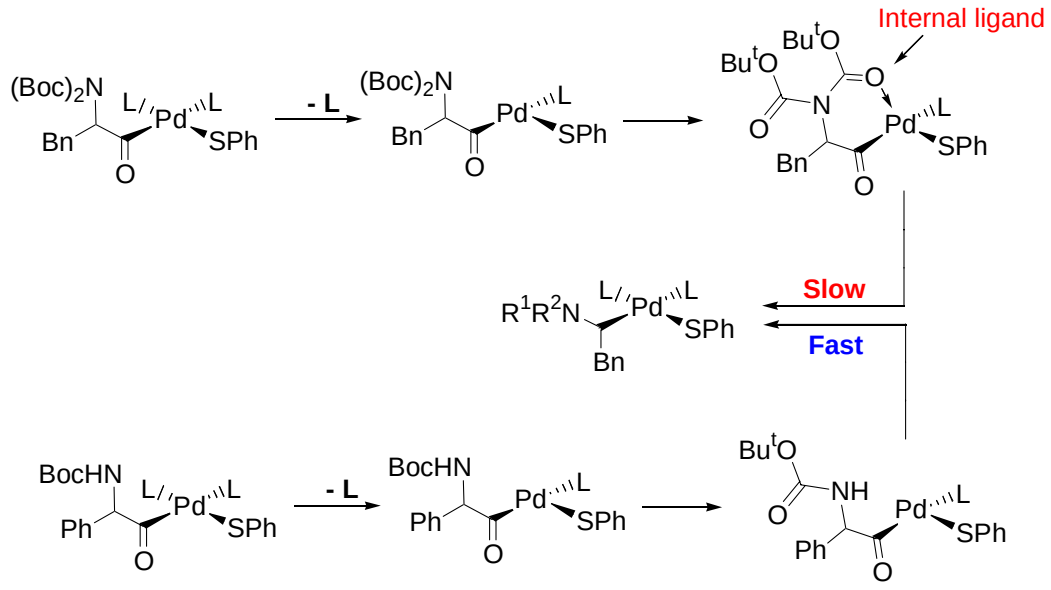
1.2.4 A Room Temperature Synthesis of High Enantiopurity *N*-Cbz α-Amino Ketones

From the data observed in **Table 1.4** and **Table 1.5**, although the Pd(PPh_3)$_4$/PMe_2Ph catalyst system provides good to excellent yields of product based on doubly N,N'-*bis*-protected phenylalanine thiol esters, this catalyst and ligand system is still inefficient toward synthetically more valuable *N*-Cbz (or *N*-Boc)-protected α-amino thiol esters. In order to provide more valuable applications in the synthesis of high enantiopurity α-

amino ketones, it is essential to develop a robust catalyst system to enable the efficient cross coupling based on α-amino acid thiol esters bearing simple N-Cbz (or N-Boc) protecting groups.

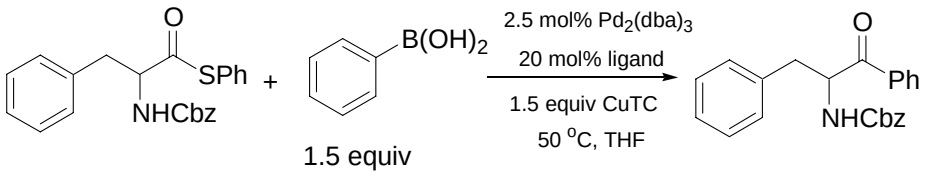
It was evident in **Table 1.3** that increased ligand loadings are effective in suppressing the undesired β-elimination pathway; however product yields are compromised on the other hand. More likely, it is because the boron to palladium transmetalation would be retarded by (1) an increase in the steric bulk around palladium when large ligands are used, and (2) a decrease in the electrophilicity at palladium when strong donor ligands are used. That is to say the electronic and steric feature of the ligand will still determine the outcome of the cross coupling reaction. What makes the $Pd(PPh_3)_4/PMe_2Ph$ catalyst system effective only toward those doubly N-protected N,N-*bis*-Boc and N-phthaloyl α-amino acid thiol esters? To disentangle this question, the structural analysis of the doubly and mono N-protected substrates is helpful to reveal their difference of cross coupling efficiency.

Scheme 1.18 Internal Ligand Effect



As shown in **Scheme 1.18**, N,N-*bis*-Boc protecting groups can act effectively as the "internal equivalent" of high loadings of small, but *weakly-donating* external ligands. This might enforce 4-coordination at palladium and block decarbonylation, but not sterically or electronically retard transmetalation. Based on this assumption, the use of a small, weakly-donating, external supporting ligand might be ideal for the palladium-catalyzed cross-coupling of N-Cbz (or N-Boc) protected α-amino thiol esters. A poorly basic and small phosphine or phosphite would fill coordination sites at Pd, but not attenuate electrophilicity and thus not suppress transmetalation (perhaps directly to a 4-coordinate, 16-electron $RCOPdL_2SR$ intermediate), even at higher ligand loadings.

Table 1.6 Ligand Effects



entry	ligand	yield (%)[a]
1	PPh_3	11
2	$P(OMe)_3$	34
3	$P(OEt)_3$	61 (81[b])
4	$P(OBu)_3$	31
5	$P(OPh)_3$	16

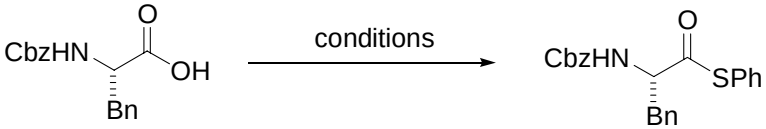
a.isolated yield b.reaction conducted at room temperature

To test this hypothesis, cross-coupling experiments (with N-Cbz-Phe-SPh, $PhB(OH)_2$ and CuTC) were carried out in the presence of 2.5 mol% $Pd_2(dba)_3$ as a precatalyst in combination with various phosphorus ligands. Among PPh_3, $P(OMe)_3$, $P(OEt)_3$, $P(OBu)_3$, and $P(OPh)_3$ as supporting ligands (20 mol% each), $P(OEt)_3$ delivered the

highest yield (61%, **Table 1.6**). It is even better when the reaction was conducted at room temperature (entry 3, **Table 1.6**).

In order to explore the generality of $Pd_2(dba)_3/P(OEt)_3$ catalyst system, a variety of N-Cbz protected amino acid thiophenyl esters were synthesized. Thiol esters can be easily prepared from N-protected amino acids and thiophenol by employing a dehydration reagent. Four methods have been used to synthesize thiol ester **1.13** (**Table 1.**7). All of these methods gave satisfactory thiol ester yields. A 6% racemization of thiol ester was observed when the N-Cbz phenyl alanine was treated with diphenyl disulfide mediated by triphenyl phosphine. No racemization occurred if CDI or DCC was used as the dehydration reagent. An attempt to boost the yield by addition of catalytical DMAP (**Table 1.7**, entry 3), however caused serious racemization of the resulting ketone.

Table 1.7 Thiol Esters

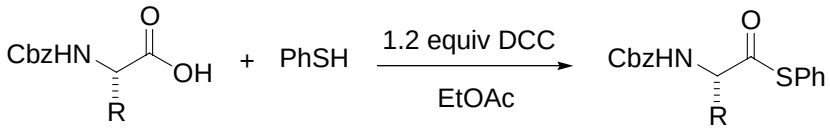


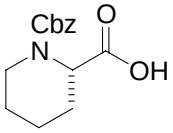
1.13

entry	condition	yield (%)	enantiopurity (%)
1	a.CDI,DMF/b.PhSH	72	>99
2	PhSSPh, PEt3	80	88
3	DCC,DMAP,PhSH	87	42
4	DCC, PhSH	85	>99

Finally, various N-Cbz protected α-amino acid derived thiophenyl esters were synthesized from the corresponding N-Cbz amino acid and thiophenol in the presence of DCC at room temperature to give N-Cbz amino acid thiophenyl ester with excellent yield and high enantiopurity (ee > 99%).

Table 1.8 Synthesis of N-Cbz Protected α-Amino Thiophenyl Ester



entry	amino acid	thiol ester	yield (%)	ee (%)[a]
1	(L)-Z-Phe-OH	**1.13**	85	>99
2	(d)-Z-Phe-OH	**1.28**	87	>99
3	(L)-Z-Val-OH	**1.29**	77	>99
4	(L)-Z-Tyr-OH	**1.30**	83	>99
5	(L)-Z-Trp-OH	**1.31**	96	>99
6		**1.32**	73	>99

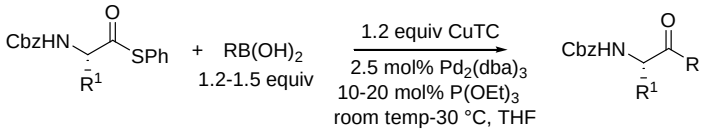
a. ee was determined by HPLC chiral OD, AD or AS column using racemic mixtures

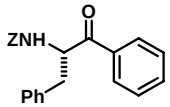
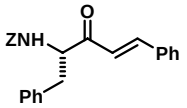
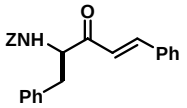
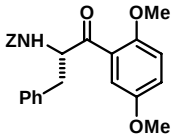
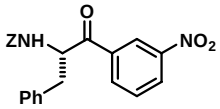
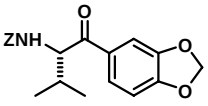
As shown in **Table 1.6**, 2.5 mol% $Pd_2(dba)_3$ and between 10-20 mol% triethyl-phosphite (1:2 - 1:4 Pd:P ratio) proved to be the best catalyst system for the cross-coupling of *N*-Cbz-Phe-SPh and phenyl boronic acid under room temperature. In fact, this $Pd_2(dba)_3/P(OEt)_3$ system is generally effective toward the mono-N-Cbz protected thiophenyl esters and boronic acids cross coupling. Due to the mild and neutral condition of this cross coupling reaction, all ketone produced from thiol esters completely preserved the stereochemistry without racemization. Of significance, higher reaction temperatures caused increased proportions of the undesired decarbonylation side product, suggesting, in retrospect, that the ability of triethylphosphite to support *ambient temperature* cross-couplings is probably an important factor in the development of a general cross-coupling protocol for the *N*-Cbz protected systems.

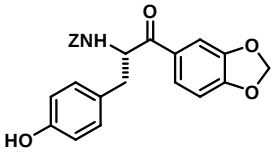
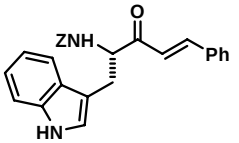
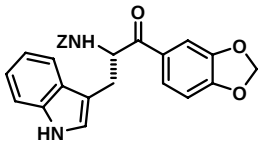
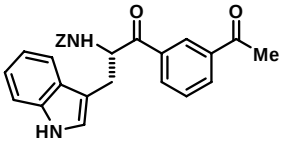
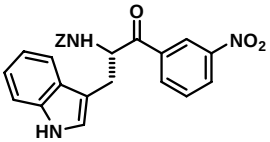
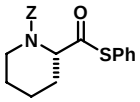
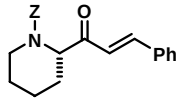
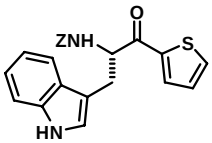
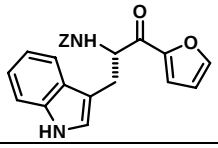
A variety of aryl (electron-rich, electron-deficient) and heteroaryl (thienyl and furyl) boronic acids and (*E*)-β-styrylboronic acid were efficiently coupled with thiophenyl esters of *N*-Cbz protected α-amino acids (**Table 1.9**). No racemization was detected

during the cross-coupling process (the ketonic product was formed with the same ee as the thiol esters precursor) reinforcing, once again, the very mild and non-basic nature of the Cu(I) carboxylate-mediated couplings of thioorganics and boronic acids.[49] Moreover, even unprotected tyrosine and tryptophan thiol esters were excellent cross-coupling substrates highlighting the compatibility of unprotected phenolic and indolic residues in this chemistry (**Table 1.9**, entries 7-11, 13, 14). Unfortunately, π-deficient heteroaromatic boronic acids were not effective substrates giving only low yields of ketone products in this cross-coupling.

Table 1.9 Synthesis of *N*-Cbz α-Amino Ketones in High Enantiomeric Purity



entry	thiol ester (ee)	boronic acid	product	isolated yld (%)	ee[a]
1[b]	(L)-Z-Phe-SPh **1.13** (99)	phenyl		81	99
2	(L)-Z-Phe-SPh **1.13** (99)	(*E*)-β-styryl		79	99
3	(D)-Z-Phe-SPh **1.14** (99)	(*E*)-β-styryl		75	99
4	(L)-Z-Phe-SPh **1.13** (99)	2,5-dimethoxyphenyl		72	99
5[b]	(L)-Z-Phe-SPh **1.13** (99)	3-nitrophenyl		48	99
6	(L)-Z-Val-SPh **1.29** (99)	3,4-methylenedioxyphenyl		64	99

7	(L)-Z-Tyr-SPh **1.30** (99)	3,4-methylenedioxyphenyl		81	99
8	(L)-Z-Trp-SPh **1.31** (99)	(*E*)-β-styryl		96	99
9[b]	(L)-Z-Trp-SPh **1.31** (99)	3,4-methylenedioxyphenyl		70	99
10[b]	(L)-Z-Trp-SPh **1.31** (99)	3-acetylphenyl		68	99
11[b]	(L)-Z-Trp-SPh **1.31** (99)	3-nitrophenyl		60	99
12	 **1.32** (99)	(*E*)-β-styryl[c]		72	99
13	(L)-Z-Trp-SPh **1.31** (99)	2-thienyl[c]		96	99
14	(L)-Z-Trp-SPh **1.31** (99)	2-furyl[c]		99	99

[a] ee was determined by HPLC chiral OD, AD or AS column using racemic mixtures. [b] Reaction carried out at 30 ˚C using 10 mol% $P(OEt)_3$ as supporting ligand. All others at room temperature in the presence of 20% $P(OEt)_3$. [c] 1.5 equiv of boronic acid used; all other reactions conducted with 1.2 equiv of boronic acid.

1.3 Conclusion

In summary, a mild, efficient and general method for synthesis of high enantiopurity N-protected α-amino ketones was developed from corresponding thiol esters and aryl, heteroaryl, or alkenyl boronic acids cross coupling which utilizes only catalytic $Pd_2(dba)_3/P(OEt)_3$ and stoichiometric CuTC at ambient temperature. As a result from this

mild and neutral reaction condition, no racemization was detected throughout the cross-coupling process and the configuration of the stereogenic centers was completely reserved. This efficient cross coupling produced aryl, heteroaryl and alkenyl ketones from moderate to excellent yields. Importantly, various nonprotected polar functional groups were well tolerated by this reaction system.

1.4 Experimental Section

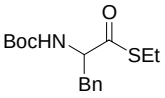
Starting Materials. All boronic acids were obtained from Frontier Scientific Inc. All protected amino acids, *N*,*N*'-dicyclohexylcarbodiimide (DCC), 1,1'-carbonyldiimidazole (CDI), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), thiophenol, 4-nitrothiophenol, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), tetrakis(triphenylphosphine)palladium(0), methyldiphenylphosphine, trimethyl-, tributyl-, and triphenylphosphite, dimethylphenylphosphine, triphenylphosphine, triphenylantimony, triethylphosphine, and *tris*-2-furylphosphine were purchased from Sigma-Aldrich. *N*-Trifluoroacetylphenylalanine, *tris*(dibenzylideneacetone)dipalladium(0), 1-hydroxybenzotriazole (HOBt), and triethylphosphite were purchased from Acros. *N*-Tosylphenylalanine was purchased from TCI. Triethylphosphite was purified by distillation at 1 atm (157 °C).[35] Cu(I) thiophene-2-carboxylate (CuTC) was prepared by using a previous procedure.[36] *N*,*N*-*Bis*-Boc-L-Phe and *N*,*N*-phthaloyl-L-Phe-SPh were prepared according to literature procedures.[37]

HPLC analyses were carried out using an Agilent 1100 system with a quaternary pump. Separations were achieved on a Zorbax Eclipse XDB C8 4.6 x 150 mm column or DAICEL chiral AD, AS, OD reversed phase column (Standard Method: λ= 254 nm;

Flow: 1.0 mL/min; T= 30 °C; Gradient: 50 % H_2O in CH_3CN during 10 min to 75 % CH_3CN during 12.5 min to 100 % CH_3CN hold for 4.5 min).

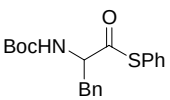
*Thiol esters **1.1-1.9** were prepared from the corresponding* N*-protected α-amino acids.*

(±)-2-*tert*-Butoxycarbonylamino-3-phenyl-thiopropionic acid ethyl ester, 1.1



N-Boc-Phe-SEt **1.1** was prepared using a procedure reported for a similar compound.[38] Yield: 945 mg (76%) for a 4.0 mmol reaction scale. TLC (R_f = 0.65, silica gel, 20% ethyl acetate in hexanes). White solid. Mp = 77-78 ˚C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.23 (m, 3H), 7.16 (d, *J* = 7.2 Hz, 2H), 4.89 (d, *J* = 8.4 Hz, 1H), 4.62 (m, 1H), 3.13 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.04 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.86 (q, *J* = 7.2 Hz, 2H), 1.40 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 155.1, 135.9, 129.5, 128.7, 127.1, 80.4, 61.0, 38.5, 28.4, 23.5, 14.6. IR (neat, cm^{-1}) 3347 (w), 2930 (m), 1718 (s), 1513 (m), 1455 (m), 1170 (s). HRMS (FAB) Calcd for $C_{16}H_{24}NO_3S$ ($[M+H]^+$): 310.1471. Found: 310.1472.

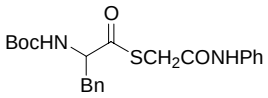
(±)-2-*tert*-Butoxycarbonylamino-3-phenyl-thiopropionic acid phenyl ester, 1.2



N-Boc-Phe-SPh **1.2** was prepared using general procedure reported for the similar compound.[8] Yield: 122 mg (68%) for a 0.5 mmol reaction scale. TLC (R_f = 0.60, silica

gel, 20% ethyl acetate in hexanes). White solid. Mp = 111-113 ˚C [Lit. 102-103 ˚C[39]]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42-7.32 (m, 7H), 7.29-7.19 (m, 3H), 4.99 (d, *J* = 9.0 Hz, 1H), 4.76 (m, 1H), 3.19-3.10 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.5, 155.1, 135.7, 134.8, 129.7, 129.6, 129.4, 128.8, 127.4, 127.3, 80.6, 61.1, 38.5, 28.4. IR (neat, cm^{-1}) 3347 (w), 2980 (w), 1702 (s), 1498 (m), 1166 (m). HRMS (FAB) Calcd for $C_{20}H_{24}NO_3S$ ($[M+H]^+$): 358.1471. Found: 358.1472.

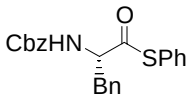
(±)-2-*tert*-Butoxycarbonylamino-3-phenyl-thiopropionic acid phenylcarbamoyl methyl ester, 1.3



Following the method of Steglich,[40] a solution of (±)-N-Boc-phenylalanine (620 mg, 2.3 mmol), 4-dimethylaminopyridine (DMAP) (28 mg, 0.2 mmol), and $HSCH_2CONHPh$[41] (420 mg, 2.8 mmol) in dry CH_2Cl_2 (2 mL for 1 mmol of amino acid) was treated with *N,N'*-dicyclohexylcarbodiimide (DCC) (338 mg, 2.8 mmol) at 0 °C. The precipitated urea was filtered off and the filtrate was evaporated. The residue was taken up in ethyl acetate and the ethyl acetate solution was washed twice with brine and then dried over $MgSO_4$. The solvent was removed by evaporation and the crude product was purified by flash chromatography (silica gel, 33% ethyl acetate in hexanes) afforded thiol ester **1.3** as a white solid. Yield: 612 mg (63%). TLC (R_f = 0.50, silica gel, 33% ethyl acetate in hexanes). Mp = 122-124 ˚C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.22 (m, 3H), 7.12 (m, 3H), 5.03 (d, *J* = 7.8 Hz, 1H), 4.62 (m, 1H), 3.68 (m, 2H), 3.17-3.07 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 202.2, 166.1, 155.4, 137.8, 135.3, 129.3, 129.1, 129.0, 127.5, 124.7, 120.1, 81.1, 61.5, 37.8, 33.6, 28.4. IR (neat, cm^{-1}) 3320 (w), 1691 (s), 1602 (m), 1544 (m), 1498 (m), 1166 (m). HRMS (FAB) Calcd for $C_{22}H_{27}N_2O_4S$ ($[M+H]^+$): 415.1686. Found: 415.1698.

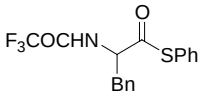
(-)-L-Cbz-Phenylalanine thiophenyl ester, 1.4



Thiophenol (0.529 g, 4.8 mmol) was added to a solution of *N*-Cbz-L-phenylalanine (1.197 g, 4.0 mmol) in dry ethyl acetate (2 mL/mmol) at 0 ˚C followed by *N*,*N*′-dicyclohexylcarbodiimide (990 mg, 4.8 mmol). The mixture was stirred for 24 h at room temperature and the reaction progress was monitored by HPLC analysis. At the end of the reaction a few drops of 50 % acetic acid in ethyl acetate were added. The reaction mixture was filtered through a short plug of Celite™ and concentrated *in vacuo*. The crude product was triturated with hexanes to remove excess thiophenol and then dissolved in MeOH. Crystallization was induced by addition of water. After filtration and drying at high vacuum the title compound **1.4** was obtained as a white solid. Yield: 1.331 g (85%). TLC (R_f = 0.51, silica gel, 25% ethyl acetate in hexanes). Mp = 120-122 ˚C [Lit. 117-118 ˚C[42]]. HPLC Chiral OD-RH standard method: L-isomer t_R = 13.2 min, D-isomer t_R = 14.2 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.27 (m, 13H), 7.19-7.16 (m, 2H), 5.19 (d, *J* = 8.8 Hz, 1H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 4.87-4.81 (m, 1H), 3.22-3.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 155.6, 136.0, 135.2, 134.6, 129.6, 129.4, 129.2, 128.7, 128.5, 128.2, 128.0, 127.3, 126.9, 67.2, 61.3, 38.3. IR (neat, cm^{-1}) 3323 (w), 3065 (w), 3034 (w), 1695 (vs), 1525 (s), 1498 (s), 1455 (m), 1247 (s), 1050 (m), 745 (s). HRMS (FAB) Calcd for $C_{23}H_{21}NO_3SLi$ ($[M+Li]^+$):

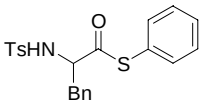
398.1402. Found: 398.1413. $[\alpha]^{20}_D$ = -60.4 (c = 0.96, $CHCl_3$) [Lit. $[\alpha]^{20}_D$ = -60.8 (c = 1.92, $CHCl_3$)].

(±)-3-Phenyl-2-(2,2,2-trifluoro-acetylamino)-thiopropionic acid phenyl ester, 1.5



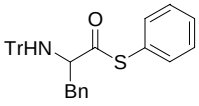
Following method of Steglich, a solution of (±)-N-trifluoroacetyl-phenylalanine (1.228 g, 4.7 mmol), 4-dimethylaminopyridine (DMAP) (57 mg, 0.5 mmol), thiophenol (0.642 g, 5.6 mmol) in dry CH_2Cl_2 (2 mL for 1 mmol of amino acid) was treated with *N,N'*-dicyclohexylcarbodiimide (1.213 g, 5.9 mmol) at 0 °C. The precipitated urea was filtered off and the filtrate was evaporated. The residue was taken up in ethyl acetate and the ethyl acetate solution was washed twice with brine and then dried over $MgSO_4$. The solvent was removed by evaporation and the crude product was purified by flash chromatography (silica gel, 50% ethyl acetate in hexanes) to afford thiol ester **1.5** as a white solid. Yield: 1.012 g (82%). TLC (R_f = 0.50, silica gel, 20% ethyl acetate in hexanes). Mp = 114-115 ˚C [Lit. 113 ˚C[43]]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47-7.42 (m, 3H), 7.38-7.30 (m, 5H), 7.18 (d, *J* = 7.2 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.10 (m, 1H), 3.30-3.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 169.6, 156.6, 134.7, 134.2, 130.3, 129.6, 129.5, 129.1, 127.9, 125.7, 59.7, 38.4. IR (neat, cm^{-1}) 3320 (m), 1702 (s), 1548 (m), 1212 (m), 1171 (s).

(±)-3-Phenyl-2-(toluene-4-sulfonylamino)-thiopropionic acid phenyl ester, 1.6



N-Tosyl-Phe-SPh **1.6** was prepared from *N*-tosyl-Phe-OH by using a general procedure reported for thiol ester formation.[44] TLC (R_f = 0.30, silica gel, 20% ethyl acetate in hexanes). Mp = 145-147 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.42-7.36 (m, 3H), 7.26-7.24 (m, 5H), 7.19-7.17 (m, 2H), 7.05-7.04 (m, 2H), 5.12 (d, *J* = 9.0 Hz, 1H), 4.36 (dt, *J* = 9.6, 6.0 Hz, 1H), 3.04 (m, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 143.9, 136.7, 134.6, 134.4, 129.9, 129.8, 129.7, 129.4, 128.9, 127.6, 127.5, 126.7, 63.0, 39.5, 21.7. IR (KCl cell, $CDCl_3$, cm^{-1}) 3277 (m), 3065 (w), 2926 (w), 1698 (s), 1339 (s), 1162 (s). HRMS (FAB) Calcd for $C_{22}H_{22}NO_3S$ ($[M+H]^+$): 412.1035. Found: 412.1037.

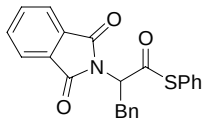
(±)-*N*-Trityl phenylalanine thiophenyl ester, 1.7



Following the method of Steglich method, a solution of (±)-N-trityl-phenylalanine (407 mg, 1.0 mmol), 4-dimethylaminopyridine (DMAP) (12 mg, 0.1 mmol), thiophenol (132 mg, 1.2 mmol) in dry CH_2Cl_2 (2 mL for 1 mmol of amino acid) was treated with *N,N'*-dicyclohexylcarbodiimide (252 mg, 1.2 mmol) at 0 °C. The precipitated urea was filtered off and the filtrate was evaporated. The residue was taken up in ethyl acetate and the ethyl acetate solution was washed twice with brine and then dried over $MgSO_4$. The solvent was removed by evaporation and the crude product was purified by flash chromatography (silica gel, 20% ethyl acetate in hexanes) to afford thiol ester **1.7** as a

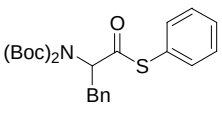
white solid. Yield: 359 mg (72%). TLC (R_f = 0.70, silica gel, 20% ethyl acetate in hexanes). Mp = 127-128 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 6H), 7.38-7.35 (m, 3H), 7.33-7.21 (m, 12H), 7.17 (m, 2H), 7.09 (m, 2H), 3.88 (m, 1H), 2.89 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.72 (br s, 1H), 2.48 (dd, *J* = 13.8, 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 146.5, 136.8, 135.0, 130.7, 129.6, 129.5, 129.2, 128.9, 128.6, 128.5, 127.8, 127.5, 127.2,72.2, 65.0, 41.6. IR (KCl cell, $CDCl_3$, cm^{-1}) 3327 (m), 3061 (m), 2934 (w), 1698 (s), 1494 (s), 1447 (s), 911 (m).

(±)-2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-phenyl-thiopropionic acid phenyl ester, 1.8



N-Phthaloyl-Phe-SPh **1.8** was prepared following the method of Weygand. TLC (R_f = 0.45, silica gel, 20% ethyl acetate in hexanes). White solid. Mp = 99-100 ˚C [Lit. 95-96 ˚C[45]]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.72 (m, 2H), 7.41 (s, 5H), 7.20-7.12 (m, 5H), 5.34 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.69-3.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 167.5, 136.4, 135.0, 134.5, 131.6, 129.9, 129.4, 129.0, 128.8, 127.1, 126.4, 123.8, 60.8, 34.3. IR (neat, cm^{-1}) 1779 (w), 1718 (s), 1382 (m), 1100 (w). HRMS (FAB) Calcd for $C_{23}H_{18}NO_3S$ ($[M+H]^+$): 388.1001. Found: 388.1001.

(±)-2-*Bis*(*tert*-butoxycarbonyl)amino-3-phenyl-thiopropionic acid phenyl ester, 1.9



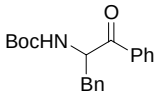
Following the method of Steglich, a solution of (±)-*N,N-bis*-Boc-phenylalanine (562 mg, 1.54 mmol), 4-dimethylaminopyridine (DMAP) (19 mg, 0.1 mmol), thiophenol (203 mg, 1.85 mmol) in dry CH_2Cl_2 (2 mL for 1 mmol of amino acid) was treated with *N,N'*-dicyclohexylcarbodiimide (395 mg, 1.9 mmol) at 0 °C. The precipitated urea was filtered off and the filtrate was evaporated. The residue was taken up in ethyl acetate and the ethyl acetate solution was washed twice with brine and then dried over $MgSO_4$. The solvent was removed by evaporation and the crude product was purified by flash chromatography (silica gel, 20 % ethyl acetate in hexanes) affording *N,N'-bis*-Boc-Phe-SPh **1.9** as a white solid. Yield: 606 mg (86%). TLC (R_f = 0.52, silica gel, 20% ethyl acetate in hexanes). Mp = 81-82 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 5H), 7.27-7.16 (m, 5H), 5.30 (dd, *J* = 9.8, 4.7 Hz, 1H), 3.47 (dd, *J* = 13.9, 4.7 Hz, 1H), 3.22 (dd, *J* = 13.9, 9.8 Hz, 1H), 1.44 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 151.2, 137.2, 134.7, 129.5, 129.3, 129.1, 128.4, 127.2, 126.6, 83.5, 66.9, 35.6, 27.8. IR (KCl cell, $CDCl_3$, cm^{-1}) 1790.4 (s), 1747.8 (s), 1733.6 (s), 1712.4 (s), 1694.6 (s). Anal. Calcd for $C_{25}H_{31}NO_5S$: C 65.62, H 6.83, N 3.06, S 7.01. Found: C 65.74, H 6.81, N 3.12, S 6.99.

N-*Protected phenylalanine ketones* ***1.10-1.16*** *were generated from the thiol esters* ***1.1-1.9*** *by the following general procedure.*

Thiol esters **1.1-1.9** (0.1 mmol), Cu(I) thiophenecarboxylate (CuTC) (28 mg, 0.15 mmol), phenylboronic acid (19 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) were placed in a Schlenk tube under argon. THF (2 mL) was added via syringe and the reaction mixture was stirred at 50 ˚C for 12 h. Diethyl ether (20 mL) was added and the suspension was washed with $NaHCO_3$ solution and brine. The organic layer was dried

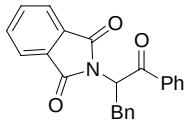
over $MgSO_4$. Filtration and concentration on rotary evaporator afforded a crude product. *Ketones **1.10**, **1.15**, and **1.16** were purified by preparative TLC (silica gel, 20 x 20 cm, 0.5 mm, 20% ethyl acetate in hexanes) and fully characterized. Ketones **1.11**, **1.12**, **1.13**, and were observed and in situ quantified (using pentamethylbenzene as an internal standard) by ^1H NMR. Full characterization data for **1.11** is described below (Table 4, entry 1).*

(±) 2-*tert*-Butyloxycarbonylamino-1,3-diphenyl-propan-1-one, 1.10



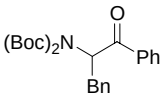
N-Boc-Phe-SEt **1.1** (31 mg, 0.1 mmol), Cu(I) thiophenecarboxylate (CuTC) (28 mg, 0.15 mmol), phenylboronic acid (19 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) afforded ketone **1.10** as a colorless oil. Yield: 4 mg (10%). TLC (R_f = 0.60, silica gel, 20% ethyl acetate in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.22-7.18 (m, 3H), 7.01 (d, *J* = 7.2 Hz, 2H), 5.54 (AB q, *J* = 7.8 Hz, 1H), 5.40 (d, *J* = 7.2 Hz, 1H), 3.24 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.97 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 155.7, 136.4, 135.4, 134.2, 130.0, 129.4, 129.2, 128.8, 127.3, 80.3, 56.5, 39.6, 28.8. IR (KCl cell, $CDCl_3$, cm^{-1}) 3428 (w), 3065 (w), 2980 (w), 2930 (w), 1714 (s), 1683 (s), 1498 (s), 1366 (s), 1170 (s), 698 (m). HRMS (FAB) Calcd for $C_{20}H_{23}NO_3$ ($[M+H]^+$): 326.1750. Found: 326.1753.

(±) 2-(1-Benzyl-2-oxo-2-phenyl-ethyl)-isoindole-1,3-dione, 1.15



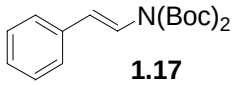
N-Phthaloyl-Phe-SPh **1.8** (45 mg, 0.1 mmol), Cu(I) thiophenecarboxylate (CuTC) (28 mg, 0.15 mmol), phenylboronic acid (19 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.01 mmol) afforded ketone **1.15** as a white solid. Yield: 21 mg (54%). TLC (R_f = 0.30, silica gel, 50% ethyl acetate in hexanes). Mp = 121-122 ˚C (Lit. 112-113 ˚C[15]]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.72 (m, 2H), 7.64 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 8.4 Hz, 2H), 7.22-7.13 (m, 3H), 5.82 (q, *J* = 5.4 Hz, 1H), 3.57 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 167.9, 137.6, 135.8, 134.6, 133.7, 131.9, 129.6, 129.3, 129.1, 128.6, 127.3, 124.0, 57.2, 34.8. IR (KCl cell, $CDCl_3$, cm^{-1}) 3065 (w), 2960 (w), 2930 (w), 1776 (s), 1714 (s), 1386 (s), 721 (m), 698 (m). HRMS (FAB) Calcd for $C_{23}H_{18}NO_3$ ($[M+H]^+$): 356.1281. Found: 356.1282.

(±)-2-*Bis*(*t*-butoxycarbonyl)amino-1, 3-diphenyl-propane-1-one, 1.16



Thiol ester **1.9** (±)-*N,N-bis*-Boc-Phe-SPh (75 mg, 0.16 mmol, 1.0 equiv), CuTC (41 mg, 0.22 mmol, 1.3 equiv), phenylboronic acid (25 mg, 0.21 mmol, 1.3 equiv) and $Pd(PPh_3)_4$ (18 mg, 0.016 mmol, 0.1 equiv) afforded after preparative thin layer chromatography (silica gel, 20 x 20 cm, 0.5 mm thickness, 20% ethyl acetate in hexanes) ketone **1.16** in 28% yield as a white solid. TLC (R_f = 0.53, silica gel, 20% ethyl acetate in hexanes). Mp = 102-104 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.53 (m, 2H), 7.50-7.46 (m, 1H),

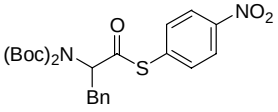
7.39-7.35 (m, 2H), 7.30-7.18 (m, 5H), 5.62 (dd, *J* = 9.8, 4.8 Hz, 1H), 3.58 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.16 (dd, *J* = 14.0, 9.5 Hz, 1H), 1.28 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 151.2, 137.9, 136.1, 132.3, 129.8, 128.3, 128.2, 127.8, 126.4, 83.3, 63.1, 35.4, 27.6. IR (KCl cell, $CDCl_3$, cm^{-1}) 2983 (w), 1786 (m), 1749 (m), 1730 (m), 1698 (s), 1370 (s), 1138 (s). HRMS (FAB) Calcd for $C_{25}H_{31}NO_5Na$ ($[M+Na]^+$): 448.2100. Found: 448.2104. Also isolated from this reaction was the decarbonylation side product (*E*)-$(Boc)_2NCH$=CH-Ph, **1.17** ***trans*-1-*Bis*(*t*-butoxycarbonyl)amino-2-phenyl-(*E*)-ethylene**



1.17

Enimide **1.17** is a colorless oil. Yield: 10 mg (20%). TLC (R_f = 0.55, silica gel, 20% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) 7.34-7.20 (s, 5H), 7.08 (d, *J* = 14.9 Hz, 1H), 6.31 (d, *J* = 14.6 Hz, 1H), 1.55 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) 151.3, 136.1, 128.5, 126.8, 125.8, 124.5, 117.0, 83.4, 27.8. IR (KCl cell, $CDCl_3$, cm^{-1}) 2981 (w), 1752(s), 1714 (s), 1370 (s), 1352 (s).

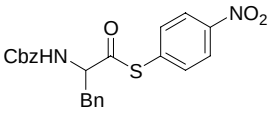
(±)-2-*Bis*(*tert*-Butoxycarbonyl)amino-3-phenyl-thiopropionic acid *p*-nitrophenyl ester, 1.18



Following the same procedure used to prepare **1.3**, (±)-*N*,*N*-*bis*-Boc-phenylalanine (0.825 g, 2.26 mmol, 1.0 equiv) was allowed to react with *p*-nitrophenylthiol (80% purity, 0.565 g, 2.92 mmol, 1.3 equiv) at 0 ˚C for 5 min then at room temperature overnight. The crude

product was dissolved in CH_2Cl_2 (20 mL). The reaction crude solution was washed with $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$. Filtration and concentration on a rotary evaporator afforded the crude product. Further purification by chromatography (Chromatotron™, silica gel, 2 mm plate, 20% ethyl acetate in hexanes) afforded thiol ester **1.18** as a white solid. Yield: 0.8667 g (76%). TLC (R_f = 0.45, silica gel, 20% ethyl acetate in hexanes). Mp = 114-115 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.23 (m, 2H), 7.61-7.58 (m, 2H), 7.29-7.15 (m, 5H), 5.31 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.45 (dd, *J* = 14.2, 5.0 Hz, 1H), 3.22 (dd, *J* = 13.9, 9.8 Hz, 1H), 1.43 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 151.2, 148.1, 136.7, 136.1, 135.0, 129.4, 128.5, 126.7, 123.9, 83.9, 67.0, 35.4, 27.8. IR (KCl cell, $CDCl_3$, cm^{-1}) 2976.5 (w), 1790.4 (m), 1754.4 (s), 1733.3 (s), 1523.1 (s), 1369.6 (s), 1345.3 (s), 1238.4 (m), 1137.6 (s).

(±)-2-Benzyloxycarbonylamino-3-phenyl-thiopropionic acid (4-nitrophenyl) ester, 1.19

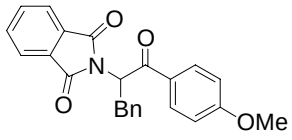


Following the same procedure used to prepare **1.3**, (±)-N-Cbz-phenylalanine (401 mg, 1.0 mmol) was allowed to react with *p*-nitrophenylthiol (202 mg, 1.3 mmol) at 0 ˚C for 5 min then at room temperature overnight. The crude product was dissolved in CH_2Cl_2 20 mL. The reaction crude solution was washed with $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$. Filtration and concentration on a rotary evaporator afforded the crude product. Further purification by chromatography (Chromatotron™, silica gel, 2 mm plate, 20% ethyl acetate in hexanes) afforded thiol ester **1.19** as a white solid. Yield: (357

mg , 83%). TLC (R_f = 0.30, silica gel, 20% ethyl acetate in hexanes). Mp = 159-161 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.37-7.28 (m, 8H), 7.16 (d, *J* = 7.2 Hz, 2H), 5.22 (d, *J* = 8.4 Hz, 1H), 5.14 (AB q, *J* = 9.0 Hz, 2H), 4.83 (m, 1H), 3.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 156.2, 148.8, 136.3, 135.6, 135.4, 129.9, 129.5, 129.2, 128.9, 128.7, 128.1, 124.5, 68.1, 62.2, 38.6. IR (KCl cell, $CDCl_3$, cm^{-1}) 3316 (w), 3065 (w), 2930 (w), 1710 (s), 1521 (s), 1343 (s), 1261 (m).

THE KETONE PRODUCTS IN TABLE 1.4

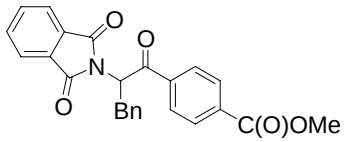
TABLE 1.4, ENTRY 1. (±)-*N*-(1-Benzyl-2-oxo-2-(*p*-methoxyphenyl)-ethyl)-phthalimide, 1.20



N,*N*-Phthaloyl-L-Phe-SPh[5] (112 mg, 0.29 mmol), CuTC (83 mg, 0.44 mmol), *p*-methoxyphenylboronic acid (66 mg, 0.44 mmol), $Pd(PPh_3)_4$ (33 mg, 0.029 mmol) and $PhPMe_2$ (16.5 µl, 0.12mmol) were placed in a Schlenk tube under argon. THF (5 mL) was added *via* syringe and the reaction mixture was stirred at 50 ˚C for 16 h. Diethyl ether (20 mL) was added and the suspension was washed with $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$. Filtration and concentration on rotary evaporator afforded a crude product. Purification by preparative TLC (silica gel, 20 x 20cm, 1.0 mm, 30% ethyl acetate in hexanes) afforded ketone **1.20** as a white solid. Yield: 109 mg (98%). TLC (R_f = 0.33, silica gel, 30% ethyl acetate in hexanes). Mp = 119-120 ˚C. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2H), 7.74-7.64 (m, 4H), 7.24-7.11 (m, 5H), 6.89-6.86 (m, 2H), 5.79 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.81 (s, 3H), 3.57 (d, *J* = 5.7 Hz, 1H), 3.56 (d, *J* = 9.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 193.4, 167.4, 163.5, 137.2, 134.0, 131.4, 130.4, 129.0, 128.5, 127.8, 126.7, 123.4, 113.9, 56.4, 55.4, 34.3. IR (KCl cell, $CDCl_3$) 1717 (s), 1602 (m), 1386 (m). Anal. for $C_{24}H_{19}NO_4$: C 74.79, H 4.97, N 3.63. Found C 74.92, H 4.92, N 3.70.

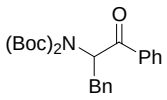
TABLE 1.4, ENTRY 2. (±)-*N*-(1-Benzyl-2-oxo-2-(4-methoxycarbonylphenyl)-ethyl)-phthalimide, 1.21



N,*N*-Phthaloyl-L-Phe-SPh[5] (127 mg, 0.33 mmol), CuTC (94 mg, 0.49 mmol), 4-methoxycarbonylphenylboronic acid (88 mg, 0.49 mmol), $Pd(PPh_3)_4$ (38 mg, 0.033 mmol) and $PhPMe_2$ (18.1 µl, 0.13 mmol) were placed in a Schlenk tube under argon. THF (5 mL) was added via syringe and the reaction mixture was stirred at 50 ˚C for 16 h. Diethyl ether (20 mL) was added and the suspension was washed with $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$. Filtration and concentration on rotary evaporator afforded a crude product. Purification by flash chromatography (silica gel, 30% ethyl acetate in hexane) afforded ketone **1.21** as a white solid. Yield: 100 mg (74%). TLC (R_f = 0.66, silica gel, 50% ethyl acetate in hexane). Mp = 180-181 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.72-7.64 (m, 4H), 7.40-7.15 (m, 5H), 5.77 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.88 (s, 3H), 3.63 (dd, *J* =

14.6, 5.0 Hz, 1H), 3.46 (dd, *J* = 14.2, 10.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 167.2, 166.0, 138.8, 136.7, 134.2, 133.8, 131.1, 129.8, 129.0, 128.5, 127.8, 126.9, 123.5, 56.7, 52.4, 34.2. IR (KCl cell, $CDCl_3$, cm^{-1}) 3032 (w), 2955 (w), 1718 (s), 1385 (s), 1281 (s), 1111 (m).

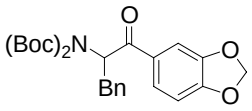
TABLE 1.4, ENTRY 3. (±)-2-*Bis*(*t*-butoxycarbonyl)amino-1, 3-diphenyl-propane-1-one, 1.16



(±)-*N*,*N*-*Bis*-Boc-Phe-S(*p*-nitrophenyl) **1.18** (60 mg, 0.12 mmol), Cu(I) thiophenecarboxylate (CuTC) (1.5 equiv), $Pd(PPh_3)_4$ (0.1 equiv), and PMe_2Ph (0.4 equiv), phenylboronic acid (21 mg, 0.18 mmol), and THF (3 mL) were placed in a Schlenk tube under argon. The reaction mixture was stirred at 50 ˚C for 16 h. Diethyl ether (20 mL) was added and the suspension was washed with $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$. Filtration and concentration on rotary evaporator afforded a crude product. Purification by preparative TLC (silica gel, 20 x 20 cm, 0.5 mm, 10% ethyl acetate in hexanes) afforded ketone **1.16** as a white solid. Yield: 36 mg (73%). TLC (R_f = 0.53, silica gel, 20% ethyl acetate in hexanes). Mp = 102-104 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.53 (m, 2H), 7.50-7.46 (m, 1H), 7.39-7.35 (m, 2H), 7.30-7.18 (m, 5H), 5.62 (dd, *J* = 9.8, 4.8 Hz, 1H), 3.58 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.16 (dd, *J* = 14.0, 9.5 Hz, 1H), 1.28 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 151.2, 137.9, 136.1, 132.3, 129.8, 128.3, 128.2, 127.8, 126.4, 83.3, 63.1, 35.4, 27.6. IR (KCl cell, $CDCl_3$, cm^{-1})

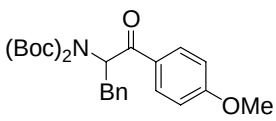
2983 (w), 1786 (m), 1749 (m), 1730 (m), 1698 (s), 1370 (s), 1138 (s). HRMS (FAB) Calcd for $C_{25}H_{31}NO_5Na$ ($[M+Na]^+$): 448.2100. Found: 448.2104.

TABLE 1.4, ENTRY 4. (±)-2-*Bis*(t-butoxycarbonyl)amino-1-(3,4-methylenedioxyphenyl)-3-phenyl-propane-1-one, 1.22



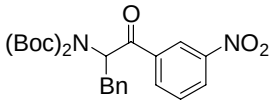
Following the same procedure used to prepared **1.16**, (±)-*N,N-bis*-Boc-Phe-S(*p*-nitrophenyl) **1.18** (60 mg, 0.12 mmol) coupled with 3,4-methylenedioxyphenylboronic acid (29 mg, 0.18 mmol) at 50 ˚C for 16 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 0.5 mm, 20% ethyl acetate in hexanes) afforded ketone **1.22** as a gum. Yield: 42 mg (77%). TLC (R_f = 0.34, silica gel, 20% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.29-7.17 (m, 6H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.60 (d, *J* = 1.2 Hz, 1H), 5.99 (d, *J* = 1.3 Hz, 1H), 5.54 (dd, *J* = 9.8, 4.8 Hz, 1H), 3.50 (dd, *J* = 14.3, 4.8 Hz, 1H), 3.14 (dd, *J* = 14.0, 9.8 Hz, 1H), 1.31 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 151.2, 151.2, 147.8, 138.0, 130.3, 129.8, 128.3, 126.4, 123.7, 108.1, 107.8, 101.6, 83.4, 62.8, 35.5, 27.6. IR (KCl cell, $CDCl_3$, cm^{-1}) 2983 (w), 1786 (s), 1748 (s), 1695 (s), 1370 (s), 1254 (s), 1138 (s).

TABLE 1.4, ENTRY 5. (±)-2-*Bis*(*t*-butoxycarbonyl)amino-1-(*p*-methoxyphenyl)-3-phenyl-propane-1-one, 1.23



Following the same procedure used to prepared **1.16**, (±)-*N,N-bis*-Boc-Phe-S(*p*-nitrophenyl) **1.18** (55 mg, 0.11 mmol) coupled with 4-methoxyphenylboronic acid (25 mg, 0.16 mmol) at 50 ˚C for 16 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 0.5 mm, 20% ethyl acetate in hexanes) afforded ketone **1.25** as a gum. Yield: 46 mg (91%). TLC (R_f = 0.37, silica gel, 20% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.78 (m, 2H), 7.30-7.20 (m, 5H), 6.88-6.85 (m, 2H), 5.58 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.84 (s, 3H), 3.53 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.17 (dd, *J* = 14.0, 9.5 Hz, 1H), 1.30 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 162.9, 151.3, 138.1, 130.1, 129.8, 128.6, 128.3, 126.3, 113.5, 83.2, 62.9, 55.9, 35.5, 27.6. IR (KCl cell, $CDCl_3$, cm^{-1}) 2983 (w), 1784 (s), 1747 (s), 1693 (s), 1603 (s),1370 (s), 1252 (s), 1138 (s).

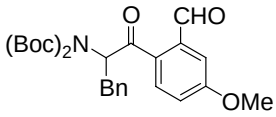
TABLE 1.4, ENTRY 6. (±)-2-*Bis*(*t*-butoxycarbonyl)amino-1-(*m*-nitrophenyl)-3-phenyl-propane-1-one, 1.24



Following the same procedure used to prepared **1.16**, (±)-*N,N-bis*-Boc-Phe-S(*p*-nitrophenyl) **1.18**(55 mg, 0.11 mmol) coupled with 3-nitrophenylboronic acid (27 mg, 0.16 mmol) at 50 ˚C for 16 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 0.5 mm, 20% ethyl acetate in hexanes) afforded ketone **1.24** as a yellow solid. Yield: 31 mg (58%). TLC (R_f = 0.37, silica gel, 20% ethyl acetate in hexanes). Mp = 96-99 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 1.9, 1.5 Hz, 1H), 8.37 (ddd, *J* = 8.2, 2.2, 1.2 Hz, 1H), 8.14 (ddd, *J* = 8.2, 1.5, 0.9 Hz, 1H), 7.62 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.32-7.22 (m, 5H), 5.66 (dd, *J* = 9.5, 4.4 Hz, 1H), 3.59 (dd, *J* = 13.9, 4.7 Hz, 1H), 3.18 (dd, *J* = 13.9,

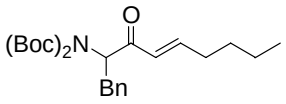
9.5 Hz, 1H), 1.29 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 151.2, 147.9, 137.6, 137.3, 133.7, 129.8, 129.6, 128.5, 126.7, 126.6, 122.5, 84.0, 63.3, 35.1, 27.6. IR (KCl cell, $CDCl_3$, cm^{-1}) 2984 (w), 1788 (m), 1753 (m), 1708 (s), 1535 (s), 1370 (s), 1353 (s), 1138 (s).

TABLE 1.4, ENTRY 7. (±)-2-*Bis*(*t*-butoxycarbonyl)amino-1-(4'-methyloxy-2'-formylphenyl)-3-phenyl-propane-1-one, 1.25



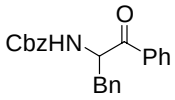
Following the same procedure used to prepared **1.16**, (±)-*N,N-bis*-Boc-Phe-S(*p*-nitrophenyl) **1.18** (65 mg, 0.13 mmol) coupled with 2,4-dimethoxyphenylboronic acid (35 mg, 0.20 mmol) at 50 ˚C for 16 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 0.5 mm, 20% ethyl acetate in hexanes) afforded ketone **1.25** as a gum. Yield: 38 mg (62%). TLC (R_f = 0.31, silica gel, 20% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.61 (d, *J* = 8.6 Hz, 1H), 7.47 (d, *J*= 2.9 Hz, 1H), 7.30-7.21 (m, 5H), 7.00 (dd, *J* = 8.5 Hz, 1H), 5.60 (dd, *J* = 9.8, 4.7 Hz, 1H), 3.88 (s, 3H), 3.60 (dd, *J* = 13.9, 4.7 Hz, 1H), 3.24 (dd, *J* = 14.2, 9.8 Hz, 1H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 192.2, 161.6, 152.1, 138.3, 137.8, 132.7, 129.7, 128.8, 128.3, 126.4, 118.3, 111.9, 83.3, 63.6, 55.7, 34.8, 27.7. IR (KCl cell, $CDCl_3$, cm^{-1}) 2981 (w), 1726 (m), 1685 (s), 1593 (m), 1368 (s), 1137 (s).

TABLE 1.4, ENTRY 8. (±)-2-*Bis*(*t*-butoxycarbonyl)amino-1-phenyl-4-(*E*)-nonen-3-one, 1.26



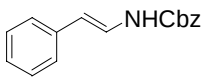
Following the same procedure used to prepared **1.16**, (±)-*N*,*N*-*bis*-Boc-Phe-S(*p*-nitrophenyl) **1.18** (60 mg, 0.12 mmol) coupled with (*E*)-1-hexenylboronic acid (23 mg, 0.18 mmol) at 50 ˚C for 16 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 0.5 mm, 20% ethyl acetate in hexanes) afforded ketone **1.26** as a gum. Yield: 50 mg (99%). TLC (R_f = 0.51, silica gel, 20% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.14 (m, 5H), 6.95 (dt, *J* = 15.5, 7.3 Hz, 1H), 6.24 (dt, *J* = 15.5 Hz, 1.5 Hz, 1H), 4.98 (dd, *J* = 9.8, 4.7 Hz, 1H), 3.44 (dd, *J* = 14.2, 4.7 Hz, 1H), 3.03 (dd, *J* = 14.2, 9.8 Hz, 1H), 2.17 (ddt, *J* = 7.3, 6.9, 1.5 Hz, 2H), 1.44-1.24 (m, 4H), 1.34 (s, 18H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 151.4, 148.2, 138.1, 129.6, 128.3, 126.3, 125.0, 83.3, 65.3, 34.9, 32.1, 30.2, 27.7, 22.1, 13.7. IR (KCl cell, $CDCl_3$, cm^{-1}) 2925 (w), 1783 (s), 1742 (s), 1701 (s), 1624 (s), 1368 (s), 1245 (s), 1143 (s).

TABLE 1.5 ENTRIES 1 and 2: (±) 2-Benzyloxycarbonylamino-1,3-diphenyl-propan-1-one, 1.11



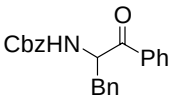
Following the same procedure used to prepared **1.16**, *N*-Cbz-Phe-SPh (39 mg, 0.1 mmol) coupled with phenylboronic acid (19 mg, 0.15 mmol) at 50 ˚C for 16 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 0.5 mm, 25% ethyl acetate in hexanes) afforded ketone **1.11** as a colorless oil. Yield: 18 mg (49%). See below for high yield procedure and full characterization data. The decarbonylation product **1.27** was also isolated. Yield:

9 mg (25%). Also isolated from this reaction was ***N*-benzyloxycarbonylamino-2-phenyl-(*E*)-ethylene, 1.27**



Colorless oil. TLC (R_f = 0.50, silica gel, 25% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) 7.38-7.13 (m, 11H), 6.64 (d, J = 10.5 Hz, 1H), 5.97 (d, J =14.9 Hz, 1H), 5.19 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 153.4, 136.1, 135.7, 128.6, 128.4, 128.3, 126.34, 125.2, 123.8, 110.8, 67.4. IR (KCl cell, $CDCl_3$, cm^{-1}) 3320 (br w), 3034 (w), 2922 (m), 1710 (s), 1660 (s), 1525 (m), 1251 (s), 1054 (m). HRMS (FAB) Calcd for $C_{16}H_{15}NO_2Li$ ($[M+Li]^+$): 260.1263. Found: 260.1270.

TABLE 1.5, ENTRY 2, 1.11

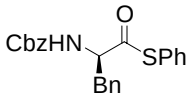


Following the same procedure used to prepared **1.16**, *N*-Cbz-Phe-S(*p*-nitrophenyl) (43 mg, 0.1 mmol) coupled with phenylboronic acid (19 mg, 0.15 mmol) at 50 ˚C for 16 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 0.5 mm, 25% ethyl acetate in hexanes) afforded ketone **1.11** as a colorless oil. Ketone Yield: 7 mg (20%). See below for high yield procedure and full characterization data. The decarbonylation product **1.27** was also isolated. Yield: 8 mg (34%). See above.

PREPARATION OF THE THIOL ESTERS IN TABLE 1.8

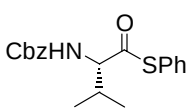
TABLE 1.8, ENTRIES 2, 3, 4, 5 AND 6. The preparation of L-Z-Phe-SPh (**1.13**) is described above.

TABLE 1.8, ENTRY 2. (+)-D-Cbz-Phenylalanine thiophenyl ester , 1.28



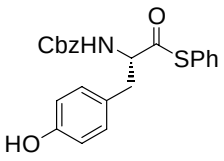
N-Cbz-D-Phenylalanine (299 mg, 1.0 mmol) and thiophenol (132 mg, 1.2 mmol) were dissolved in dry ethyl acetate (2 mL/mmol) at 0 ˚C, then *N,N'*-dicyclohexylcarbodiimide (250 mg, 1.2 mmol) was added. The reaction was stirred at 0 ˚C for the first 30 min and then at room temperature overnight. Progress was monitored by HPLC analysis. At the end of the reaction a few drops of 50 % acetic acid in ethyl acetate were added. The reaction mixture was filtered through a short plug of Celite™ and concentrated *in vacuo*. The crude product was triturated with hexanes to remove excess thiophenol and then dissolved in MeOH and crystallized by addition of water. Filtration and drying under vacuum afforded thiol ester *N*-Cbz-D-Phe-SPh as a white solid. Yield: 341 mg (87%). TLC (R_f = 0.51, silica gel, 25% ethyl acetate in hexanes). Mp = 117-118 ˚C. HPLC Chiral OD-RH standard method: D-isomer t_R = 14.2 min, L-isomer t_R = 13.2 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.27 (m, 13H), 7.19-7.16 (m, 2H), 5.19 (d, *J* = 8.8 Hz, 1H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 4.87-4.81 (m, 1H), 3.22-3.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 155.6, 136.0, 135.2, 134.6, 129.6, 129.4, 129.2, 128.7, 128.5, 128.2, 128.0, 127.3, 126.9, 67.2, 61.3, 38.3. IR (neat, cm^{-1}) 3323 (w), 3065 (w), 3034 (w), 1695 (vs), 1525 (s), 1498 (s), 1455 (m), 1247 (s), 1050 (m), 745 (s). HRMS (FAB) Calcd for $C_{23}H_{22}NO_3S$ ($[M+H]^+$): 392.1320. Found: 392.1313. $[\alpha]^{20}_D$ = +60.6 (c = 1.0, $CHCl_3$).

TABLE 1.8, ENTRY 3. (-)-L-Cbz-Valine thiophenyl ester, 1.29



Following the same procedure used to prepare (+)-D-Cbz-phenylalanine thiophenyl ester, above, *N*-Cbz-L-valine (1.433 g, 5.7mmol) was allowed to react with thiophenol (0.753 g, 6.8 mmol) at 0 ˚C for the first 30 min and the reaction mixture was stirred at room temperature overnight. Purification by recrystallization from MeOH (induced by addition water) afforded thiol ester *N*-Cbz-L-Val-SPh as a white solid. Yield: 1.507 g (77%). TLC (R_f = 0.51, silica gel, 25% ethyl acetate in hexanes). Mp = 63-64 ˚C. HPLC Chiral OD-RH standard method: L-isomer t_R = 10.6 min, D-isomer t_R = 11.1 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.28 (m, 10H), 5.28 (d, *J* = 9.4 Hz, 1H), 5.17 (s, 2H), 4.50 (dd, *J* = 9.5, 4.5 Hz, 1H), 2.40-2.31 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 156.2, 136.0, 134.5, 129.5, 129.2, 128.5, 128.2, 128.1, 127.0, 67.3, 65.7, 31.1, 19.4, 16.8. IR (neat, cm^{-1}) 3323 (m), 3065 (w), 2964 (m), 2934 (m), 1695 (vs), 1521 (vs), 1227 (vs), 1096 (s), 776 (vs). HRMS (FAB) Calcd for $C_{19}H_{21}NO_3SLi$ ($[M+Li]^+$): 350.1402. Found: 350.1406. $[\alpha]^{20}_D$ = -45.8 (c = 2.05, $CHCl_3$).

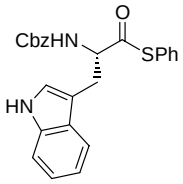
TABLE 1.8, ENTRY 4. (-)-L-Cbz-Tyrosine thiophenyl ester, 1.30



Following the same procedure used to prepare (+)-D-Cbz-phenylalanine thiophenyl ester, above, *N*-Cbz-L-tyrosine (5.455 g, 17.3mmol) was allowed to react with thiophenol (2.287 g, 20.7 mmol) at 0 ˚C for the first 30 min and the reaction mixture was stirred at room temperature overnight. Purification by recrystallization from MeOH (induced by addition water) afforded thiol ester *N*-Cbz-L-Tyr-SPh as a white solid. Yield: 5.890 g (83%). TLC (R_f = 0.17, silica gel, 25% ethyl acetate in hexanes). Mp = 189-190 ˚C.

HPLC Chiral OD-RH standard method: L-isomer t_R = 9.0 min, D-isomer t_R = 10.1 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ two rotamers 7.45-7.30 (m, 10 H), 7.1-6.9 (m, 2H), 6.8-6.6 (m, 2H), 5.3 (d, 1H), 5.1 (m, 2H), 4.8 (m, 1H), 3.1 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 156.0, 155.3, 134.8, 130.8, 129.9, 129.5, 128.8, 128.5, 128.3, 127.1, 115.9, 67.6, 61.8, 37.9. IR (neat, cm^{-1}) 3335 (br m), 3065 (w), 2957 (w), 1695 (vs), 1613 (m), 1513 (vs), 1444 (s), 1336 (m), 1243 (br s), 1054 (s), 826 (m), 749 (s). HRMS (FAB) Calcd for $C_{23}H_{21}NO_4SLi$ ($[M+Li]^+$): 414.1351. Found: 414.1359. $[\alpha]^{20}_D$ = –66.8 (c = 1.13, $CHCl_3$).

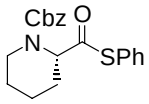
TABLE 1.8, ENTRIES 5 (-)-L-Cbz-Tryptophan thiophenyl ester, 1.31



Following the same procedure used to prepare (+)-D-Cbz-phenylalanine thiophenyl ester, above, *N*-Cbz-L-tryptophan (3.384 g, 10.0 mmol) was allowed to react with thiophenol (1.322 g, 12.0 mmol) at 0 ˚C for the first 30 min and the reaction mixture was stirred at room temperature overnight. Purification by recrystallization from MeOH (induced by addition of water) afforded thiol ester *N*-Cbz-L-Trp-SPh as a white solid. Yield: 4.127 g (96%). TLC (R_f = 0.22, silica gel, 25% ethyl acetate in hexanes). Mp = 47-51 ˚C. HPLC Chiral OD-RH standard method: L-isomer t_R = 14.2 min, D-isomer t_R =15.2 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1 H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.42-7.25 (m, 11H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 5.33 (d, *J* = 9.1 Hz, 1H), 5.14 (s, 2H), 4.92-4.85 (m, 1H), 3.43 (dd, *J* = 15.0 , 5.9 Hz, 1H), 3.32 (dd, *J* = 14.7, 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6,155.8, 136.1, 136.1,

134.6, 129.5, 129.2, 128.5, 128.2, 128.0, 127.4, 127.1, 123.2, 122.3, 119.8, 118.8, 111.3, 109.2, 67.2, 61.0, 28.2. IR (neat, cm^{-1}) 3405 (m), 3061 (w), 1698 (vs), 1502 (s), 1455 (m), 1239 (s), 1061 (m), 741 (s). HRMS (FAB) Calcd for $C_{25}H_{22}N_2O_3SLi$ ($[M+Li]^+$): 437.1511. Found: 437.1515. $[\alpha]^{20}_D$ = -68.4 (c = 1.02, $CHCl_3$).

Table 1.8, Entry 6. (-)-2-Phenylsulfanylcarbonyl-piperidine-1-carboxylic acid benzyl ester, 1.32

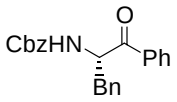


Following the same procedure used to prepare (+)-D-Cbz-phenylalanine thiophenyl ester, above, *N*-Cbz-(*S*)-piperidinecarboxylic acid (0.263 g, 1.0 mmol) was allowed to react with thiophenol (0.132 g, 1.2 mmol) at 0 ˚C for the first 30 min and the reaction mixture was stirred at room temperature overnight. Purification by chromatography (flash column, 3.5 x 15 cm, silica gel, 33% ethyl acetate in hexanes) afforded thiol ester (-)-2-phenylsulfanylcarbonyl-piperidine-1-carboxylic acid benzyl ester as a colorless oil. Yield: 0.261 g (73%). TLC (R_f = 0.22, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral AD-RH standard method: L-isomer t_R = 12.0 min, D-isomer t_R =12.7 min, ee > 99%. ^{1}H NMR (600 MHz, $CDCl_3$) two rotamers δ 7.42-7.31 (m, 10H), 5.30-5.02 (m, 3H), 4.26 (d, *J* = 12.6Hz, 0.45H), 4.17 (d, *J* = 13.8 Hz, 0.55H), 3.15 (m, 1H), 2.39 (d, *J* = 12.6 Hz, 0.45H), 2.33 (d, *J* = 13.2 Hz, 0.55H), 1.71-1.36 (m, 5H). ^{13}C NMR (150 MHz, $CDCl_3$) two rotamers δ 194.5, 152.1, 151.4, 132.3, 130.7, 130.6, 125.3, 125.1, 124.4, 124.0, 123.9, 123.7, 123.2, 63.6, 63.6, 57.6, 57.3, 38.2, 37.9, 22.4, 22.2, 20.6, 20.3, 16.2, 16.0. IR (neat, cm^{-1}) 2945 (m), 2840 (m), 1702 (vs), 1413 (m), 1254 (m), 1170 (m), 1027 (w), 749 (w).

HRMS (FAB) Calcd for $C_{19}H_{21}NO_3SLi$ ($[M+Li]^+$): 356.1320. Found: 356.1318. $[\alpha]^{20}_D$ = -109.3 (c = 2.85, $CHCl_3$).

TABLE 1.9 KETONES

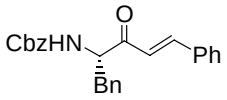
TABLE 1.9, ENTRY 1. (-)-(*2S*)-2-Benzyloxycarbonylamino-1,3-diphenyl-propan-1-one, 1.11



N-Cbz-L-Phe-SPh (78 mg, 0.2 mmol), phenylboronic acid (29 mg, 0.24 mmol), CuTC (1.2 equiv, 0.24 mmol), and $Pd_2(dba)_3$ (2.5 mol %, 5 mmol) were placed under an argon atmosphere. THF (3 mL, degassed and dried over 4Å molecular sieves) and $P(OEt)_3$ (3.4 µl, 20 µmol, 10 mol %) were added and the mixture was stirred at 30 ˚C overnight. The reaction progress was monitored by HPLC analysis. The reaction mixture was diluted with 25 mL of ether, washed with saturated aqueous $NaHCO_3$ and brine (15 mL each), followed by drying over $MgSO_4$. The drying agent was filtered off through a short plug of silica gel (to aid removal of metal containing products) and the filtrate was concentrated under vacuum. The crude product was purified by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 20% acetone in hexanes) afforded (-)-(*2S*)-2-benzyloxycarbonylamino-1,3-diphenyl-propan-1-one as a colorless oil. Yield: 58 mg (81%). TLC (R_f = 0.50, silica gel, 33% 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%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.40-

7.30 (m, 5H), 7.22-7.17 (m, 3H), 7.02-6.94 (m, 2H), 5.71 (d, J = 7.8 Hz, 1H), 5.65-5.59 (m, 1H), 5.15 and 5.09 (AB q, J = 12.2 Hz, 2H), 3.28 (dd, J = 13.9, 5.7 Hz, 1H), 3.02 (dd, J = 13.8, 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 155.6, 136.3, 135.4, 134.6, 133.8, 129.5, 128.9, 128.6, 128.5, 128.3, 128.1, 128.0, 126.9, 66.8, 56.4, 39.0. IR (neat, cm^{-1}) 3327 (w), 3065 (w), 1718 (s), 1683 (vs), 1498 (s), 1451 (m), 1254 (m), 1224 (s), 1058 (m), 748 (s), 695 (vs). HRMS (FAB) Calcd for $C_{23}H_{21}NO_3Li$ ($[M+Li]^+$): 366.1681. Found: 366.1669. $[\alpha]^{20}_D$ = -13.3 (c = 0.55, $CHCl_3$).

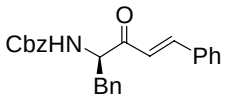
TABLE 1.9, ENTRY 2. (+)-(*4S*)-4-Benzyloxycarbonylamino-1,5-diphenyl-pent-1-en-3-one, 1.33



Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Phe-SPh (78 mg, 0.2 mmol) coupled with (*E*)-β-styreneboronic acid (35 mg, 0.24 mmol) using $P(OEt)_3$ (6.8 µl, 40 µmol, 20 mol %) at room temperature overnight. Purification by flash chromatography (silica gel, 25% hexanes in CH_2Cl_2) afforded (+)-(*4S*)-4-benzyloxycarbonylamino-1,5-diphenyl-pent-1-en-3-one as a off-white solid. Yield: 61 mg (79%). TLC (R_f = 0.18, silica gel, 25% hexane in CH_2Cl_2). Mp = 96-98 ˚C. HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.75 mL/min; T = 30 °C; Isogradient: 40 % H_2O in CH_3CN for 45 min., L-isomer t_R = 13.6 min; D-isomer t_R = 12.6 min; ee>99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 15.6 Hz, 1H), 7.48 (d, J = 7.8 Hz, 2H), 7.43-7.18 (m, 11H), 7.12 (d, J = 6.3 Hz, 2H), 6.71 (d, J = 16 Hz, 1H), 5.62 (d, J = 7.5 Hz, 1H), 5.14 and 5.10 (AB q, J = 12.4 Hz, 2H), 5.00-4.92 (m, 1H), 3.19 (dd, J = 14.0, 6.7 Hz, 1H), 3.13 (dd, J = 14.0, 5.5 Hz, 1H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 196.6, 155.6, 144.6, 136.3, 135.8, 134.0, 130.9, 129.5, 128.9, 128.7, 128.6, 128.5, 128.1, 128.0, 127.0, 122.6, 66.8, 59.5, 38.4. IR (neat, cm^{-1}) 3327 (w), 3030 (w), 1718 (s), 1687 (vs), 1610 (s), 1498 (vs), 1451 (m), 1247 (m), 1042 (m), 699 (vs). HRMS (FAB) Calcd for $C_{25}H_{23}NO_3Li$ ($[M+Li]^+$): 392.1838. Found: 392.1840. $[\alpha]^{20}_D$ = +5.4 (c = 2.24, $CHCl_3$).

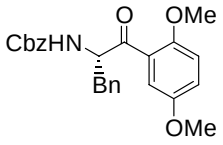
TABLE 1.9, ENTRY 3. (-)-(*4R*)-4-Benzyloxycarbonylamino-1,5-diphenyl-pent-1-en-3-one, 1.34



Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-D-Phe-SPh (39 mg, 0.1 mmol) coupled with (*E*)-β-styreneboronic acid (18 mg, 0.12 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature overnight. Purification by flash chromatography (silica gel, 25% hexanes in CH_2Cl_2) afforded (-)-(*4R*)-4-benzyloxycarbonylamino-1,5-diphenyl-pent-1-en-3-one as a white solid. Yield: 29 mg (75%). TLC (R_f = 0.18, silica gel, 25% hexane in CH_2Cl_2). Mp = 96-97 ˚C. HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.75 mL/min; T = 30 °C; Isogradient: 40 % H_2O in CH_3CN for 45 min., D-isomer t_R = 12.6 min, L-isomer t_R = 13.6 min, ee>99%. ^1H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 15.6 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.43-7.22 (m, 11H), 7.13 (d, *J* = 6.6 Hz, 2H), 6.71 (d, *J* = 15.6 Hz, 1H), 5.64 (d, *J* = 7.2 Hz, 1H), 5.14 and 5.10 (AB q, *J* = 12.4 Hz, 2H), 5.00-4.92 (m, 1H), 3.19 (dd, *J* = 14, 6.7 Hz, 1H), 3.13 (dd, *J* = 14.0, 5.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 155.9, 144.8, 136.6, 136.1, 134.3, 131.2, 129.7, 129.2, 128.8, 128.7, 128.6, 128.3, 128.2, 127.2, 122.9, 67.0, 59.8, 38.6. IR (neat, cm^{-1}) 3327 (w), 3030

(w), 1718 (s), 1687 (vs), 1610 (s), 1498 (vs), 1451 (m), 1247 (m), 1042 (m), 699 (vs). HRMS (FAB) Calcd for $C_{25}H_{23}NO_3Li$ ($[M+Li]^+$): 392.1838. Found: 392.1827. $[\alpha]^{20}_D$ = -5.4 (c = 1.45, $CHCl_3$).

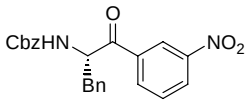
TABLE 1.9, ENTRY 4. (+)-(*2S*)-2-Benzyloxycarbonylamino-1-(2,5-dimethoxy-phenyl)-3-phenyl-propan-1-one, 1.35



Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Phe-SPh (78 mg, 0.2 mmol) coupled with 2,5-dimethoxyphenylboronic acid (43 mg, 0.24 mmol) using $P(OEt)_3$ (6.8 µl, 40 µmol, 20 mol %) at room temperature overnight. Purification by flash chromatography (silica gel, 33% ethyl acetate in hexanes) afforded (+)-(*2S*)-2-benzyloxycarbonylamino-1-(2,5-dimethoxy-phenyl)-3-phenyl-propan-1-one as a colorless oil. Yield: 60 mg (72%). TLC (R_f = 0.30, silica gel, 33% 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 45 min., L-isomer t_R = 36.5 min D-isomer t_R = 40.0 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 7.24-7.18 (m, 3H), 7.10 (dd, *J* = 12.1, 3.2 Hz, 1H), 7.01 (m, 3H), 6.93 (d, *J* = 9.2 Hz, 1H), 5.77 (m, 1H), 5.67 (d, *J* = 8.3 Hz, 1H), 5.09 (AB q, *J* = 12.4 Hz, 2H), 3.92 (s, 3H), 3.80 (s, 3H), 3.28 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.88 (dd, *J* = 14.3, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 155.7, 153.6, 153.2, 136.6, 136.3, 129.5, 128.4, 128.1, 128.0, 127.9, 126.6, 125.2, 121.4, 114.7, 113.1, 66.6, 60.5, 56.1, 55.8, 37.9. IR (neat, cm^{-1}) 3350 (br), 3034 (w), 2945 (m), 2837 (m), 1718 (s), 1671 (s), 1610 (m), 1583 (m), 1494 (vs), 1455 (s), 1413 (s), 1343 (s), 1224 (vs), 1046 (vs), 907 (s) 814 (s), 718 (s).

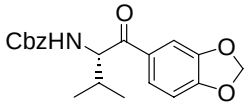
HRMS (FAB) Calcd for $C_{25}H_{25}NO_5Li$ ($[M+Li]^+$): 426.1893. Found: 426.1940. $[\alpha]^{20}_D$ = +69.1 (c = 0.58, $CHCl_3$).

TABLE 1.9, ENTRY 5. (+)-(*2S*)-2-Benzyloxycarbonylamino-1-(3-nitro-phenyl)-3-phenyl-propan-1-one, 1.36



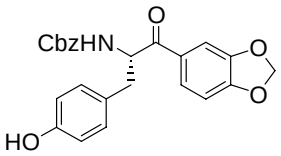
Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Phe-SPh (78 mg, 0.2 mmol) coupled with *m*-nitrophenylboronic acid (40 mg, 0.24 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 10 mol %) at 30 ˚C overnight. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 33% ethyl acetate in hexanes) afforded (+)-(*2S*)-2-benzyloxycarbonylamino-1-(3-nitro-phenyl)-3-phenyl-propan-1-one as a white solid. Yield: 39 mg (48%). TLC (R_f = 0.50, silica gel, 33% ethyl acetate in hexanes). Mp = 107-109 ˚C. HPLC Chiral OD-RH standard method: L-isomer t_R = 12.3 min, D-isomer t_R = 13.4 min, ee > 99%. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.40 (d, *J* = 8.1 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.40-7.28 (m, 5H), 7.22-7.14 (m, 3H), 7.04-6.98 (m, 2H), 5.65-5.53 (m, 2H), 5.14 and 5.10 (AB q, *J* = 12.5 Hz, 2H), 3.19 (dd, *J* = 13.8, 6.6 Hz, 1H), 3.09 (dd, *J* = 13.9, 5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 155.6, 148.3, 136.3, 136.1, 135.0, 134.0, 130.0, 129.3, 128.6, 128.5, 128.2, 127.7, 127.2, 123.5, 67.1, 56.8, 39.0. IR (neat, cm^{-1}) 3327 (m), 3034 (w), 1695 (vs), 1613 (m), 1532 (vs), 1351 (vs), 1251 (s), 1058 (m), 741 (s), 699 (vs). HRMS (FAB) Calcd for $C_{23}H_{20}N_2O_5Li$ ($[M+Li]^+$): 411.1532. Found: 411.1546. $[\alpha]^{20}_D$ = +32.1 (c = 1.66, $CHCl_3$).

TABLE 1.9, ENTRY 6. (+)-(*2S*)-2-Benzyloxycarbonylamino-1-benzo[1,3]dioxol-5-yl-3-methyl-butan-1-one, 1.37



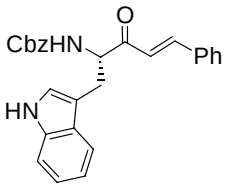
Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Val-SPh (68 mg, 0.2 mmol) coupled with 3,4-methylenedioxyphenylboronic acid (39 mg, 0.24 mmol) using $P(OEt)_3$ (6.8 μl, 40 μmol, 20 mol %) at room temperature overnight. Purification by flash chromatography (silica gel, 17% hexanes in CH_2Cl_2) afforded (+)-(*2S*)-2-benzyloxycarbonylamino-1-benzo[1,3]dioxol-5-yl-3-methyl-butan-1-one as a colorless oil. Yield: 46 mg (64%). TLC (R_f = 0.70, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral AS-RH, λ = 254nm, Method: Flow: 0.65 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN for 45 min, L-isomer t_R = 14.0 min, D-isomer t_R = 15.1 min, ee>99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.38-7.28 (m, 5H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.06 (s, 2H), 5.69 (d, *J* = 8.9 Hz, 1H), 5.19 (dd, *J* = 8.9, 4.1 Hz, 1H), 5.11 (AB q, *J* = 12.4 Hz, 2H), 2.15 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 156.5, 152.3, 148.4, 136.3, 129.8, 128.5, 128.1, 128.0,125.1, 108.2, 108.1, 102.0, 66.9, 59.8, 32.0, 20.0, 16.5. IR (neat, cm^{-1}) 3347 (w), 2964 (m), 2934 (m), 1718 (s), 1671 (s), 1606 (m), 1505 (s), 1444 (s), 1355 (s), 1243 (br s), 1089 (s), 1034 (s), 930 (s), 799 (s), 695 (s). HRMS (FAB) Calcd for $C_{20}H_{21}NO_5Li$ ($[M+Li]^+$): 362.1580. Found: 362.1582. $[\alpha]^{20}_D$ = +98.9 (c = 1.02, $CHCl_3$).

TABLE 1.9, ENTRY 7. (+)-(*2S*)-2-Benzyloxycarbonylamino-1-benzo[1,3]dioxol-5-yl-3-(4-hydroxy-phenyl)-propan-1-one, 1.38



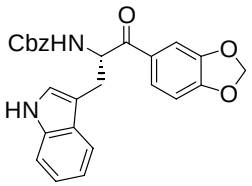
Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Tyr-SPh (81 mg, 0.2 mmol) coupled with 3,4-methylenedioxyphenylboronic acid (39 mg, 0.24 mmol) using $P(OEt)_3$ (6.8 μl, 40 μmol, 20 mol %) at room temperature overnight. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, CH_2Cl_2) afforded (+)-(*2S*)-2-benzyloxycarbonylamino-1-benzo[1,3]dioxol-5-yl-3-(4-hydroxy-phenyl)propan1-one as a yellow oil. Yield: 68 mg (81%). TLC (R_f = 0.46, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OD-RH standard method: L-isomer t_R = 7.9 min, D-isomer t_R = 9.1 min, ee>99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.41 (d, *J* = 1.6 Hz, 1H), 7.38-7.27 (m, 5H), 6.83 (app t, *J* = 7.9 Hz, 3H), 6.62 (d, *J* = 8.3 Hz, 2H), 6.03 (s, 2H), 5.83 (d, *J* = 8.4 Hz, 1H), 5.49 (m, 1H), 5.13 and 5.08 (AB q, *J* = 12.2 Hz, 2H), 3.15 (dd, *J* = 14.1, 5.7 Hz, 1H), 2.90 (dd, *J* = 14.1, 5.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 155.9, 154.9, 152.5, 148.4, 136.2, 130.6, 129.1, 128.5, 128.1, 128.0, 127.1, 125.3, 115.3, 108.3, 108.2, 102.1, 67.0, 56.3, 38.7. IR (neat, cm^{-1}) 3343 (br s), 3069 (w), 3038 (w), 1671 (s), 1613 (s), 1513 (vs), 1444 (vs), 1359 (s), 1251 (vs), 1038 (s), 907 (s), 807 (s). HRMS (FAB) Calcd for $C_{24}H_{21}NO_6Li$ ($[M+Li]^+$): 426.1529. Found: 426.1526. $[\alpha]^{20}_D$ = +36.3 (c = 3.12, $CHCl_3$).

TABLE 1.9, ENTRY 8. (-)-(*4S*)-4-Benzyloxycarbonylamino-5-(1*H*-indol-3-yl)-1-phenyl-pent-1-en-3-one, 1.39



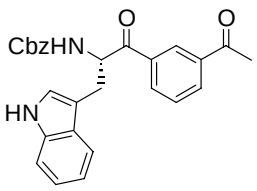
Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Trp-SPh (172 mg, 0.4 mmol) coupled with (*E*)-2-styreneboronic acid (71 mg, 0.48 mmol) using $P(OEt)_3$ (13.6 μl, 80 μmol, 20 mol %) at room temperature overnight. Purification by crystallisation from hexanes-CH_2Cl_2 (3:1) afforded (-)-(*4S*)-4-benzyloxycarbonylamino5-(1*H*-indol-3-yl)-1-phenyl-pent-1-en-3-one as yellow solid. Yield: 163 mg (96%). TLC (R_f = 0.60, silica gel, 50% ethyl acetate in hexanes). Mp = 162-163 ˚C. 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 = 19.8 min, D-isomer t_R = 18.2 min, ee>99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 16.0 Hz, 1H), 7.40-7.28 (m, 11H), 7.20 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 2.2 H, 1H), 6.67 (d, *J* = 16 Hz, 1H), 5.73 (d, *J* = 7.5 Hz, 1H), 5.16 and 5.12 (AB q, *J* = 12.2 Hz, 2H), 5.13-5.08 (m, 1H), 3.40-3.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 155.8, 144.3, 136.4, 136.1, 134.1, 130.8, 128.8, 128.5, 128.4, 128.1, 128.0, 127.6, 123.0, 122.9, 122.2, 119.7, 118.8, 111.2, 110.0, 66.8, 58.6, 28.5. IR (neat, cm^{-1}) 3408 (m), 3343 (m), 3034 (w), 1687 (s), 1610 (s), 1498 (s), 1455 (s). HRMS (FAB) Calcd for $C_{27}H_{24}N_2O_3Li$ ($[M+Li]^+$): 431.1947. Found: 431.1928. $[\alpha]^{20}_D$ = -7.8 (c = 1.1, $CHCl_3$).

TABLE 1.9, ENTRY 9. (+)-(*2S*)-2-Benzyloxycarbonylamino-1-benzo[1,3]dioxol-5-yl-3-(1*H*-indol-3-yl)-propan-1-one, 1.40



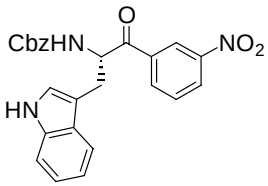
Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Trp-SPh (86 mg, 0.2 mmol) coupled with 3,4-methylenedioxyphenylboronic acid (39 mg, 0.24 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 10 mol %) at 30 ˚C overnight. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 33% ethyl acetate in hexanes) afforded (+)-(*2S*)-2-benzyloxycarbonylamino-1-benzo[1,3]dioxol-5-yl3-(1*H*-indol-3-yl)propan1-one as a yellow oil. Yield: 62 mg (70%). TLC (R_f = 0.55, silica gel, 50% 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 = 20.7 min, D-isomer t_R = 19.7 min, ee>99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.51 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.35 (m, 6H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.16 (app t, *J* = 7.2 Hz, 1H), 7.05 (app t, *J* = 7.2 Hz, 1H), 6.78 (m, 2H), 6.02 (m, 2H), 5.83 (d, *J* = 8.2 Hz, 1H), 5.60 (m, 1H), 5.13 (AB q, *J* = 12.2 Hz, 2H), 3.43 (dd, *J* = 14.9, 6.2 Hz, 1H), 3.22 (dd, *J* = 14.6, 5.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 155.8, 152.3, 148.3, 136.4, 135.9, 129.4, 128.5, 128.0, 127.6, 125.2, 122.9, 122.0, 119.5, 118.6, 111.1, 109.8, 108.2, 108.0, 101.9, 66.8, 55.7, 29.3. IR (neat, cm^{-1}) 3350 (br m), 3061 (w), 2914 (w), 1706 (s), 1675 (s), 1606 (m), 1505 (s), 1444 (s), 1355 (s), 1251 (vs), 1034 (vs), 930 (s), 807 (s). HRMS (FAB) Calcd for $C_{26}H_{22}N_2O_5Li$ ($[M+Li]^+$): 449.1689. Found: 449.1707. $[\alpha]^{20}_D$ = +32.0 (c = 1.12, $CHCl_3$).

TABLE 1.9, ENTRY 10. (+)-(*2S*)-1-(3-Acetyl-phenyl)-2-benzyloxycarbonylamino-3-(1*H*-indol-3-yl)-propan-1-one, 1.41



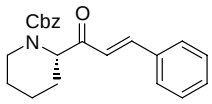
Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Trp-SPh (86 mg, 0.2 mmol) coupled with 3-acetylphenylboronic acid (39 mg, 0.24 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 10 mol %) at 30 ˚C overnight. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 33% ethyl acetate in hexanes) afforded ketone (+)-(*2S*)-1-(3-acetyl-phenyl)-2-benzyloxycarbonylamino-3-(1*H*-indol-3-yl)-propan-1-one as yellow oil. Yield: 60 mg (68%). TLC (R_f = 0.45, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral AS-RH standard method: L-isomer t_R = 7.3 min, D-isomer t_R = 6.8 min, ee>99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 8.03 (m, 2H), 7.48 (m, 2H), 7.40-7.28 (m, 5H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.14 (m ,1H), 7.05 (app t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 2.2Hz, 1H), 5.85 (d, *J* = 7.6 Hz, 1H), 5.71 (m, 1H), 5.17 and 5.13 (AB q, *J* = 12.1 Hz, 2H), 3.33 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 197.2, 155.8, 137.2, 136.3, 135.9, 135.4, 132.6, 129.0, 128.5, 128.2, 128.1, 127.3, 122.9, 122.2, 119.7, 118.6, 111.1, 109.7, 67.0, 56.0, 29.4, 26.4. IR (neat, cm^{-1}) 3350 (br m), 3061 (w), 2926 (w), 1683 (vs), 1598 (m), 1428 (m), 1278 (s), 1212 (s), 1061 (m), 745 (m), 698 (m). HRMS (FAB) Calcd for $C_{27}H_{25}N_2O_4$ ($[M+H]^+$): 441.1809. Found: 441.1815. $[\alpha]^{20}_D$ = +113.4 (c = 1.46, $CHCl_3$).

TABLE 1.9, ENTRY 11. (+)-(*2S*)-2-Benyloxycarbonylamino-3-(1*H*-indol-3-yl)-1-(3-nitro-phenyl)-propan-1-one, 1.42



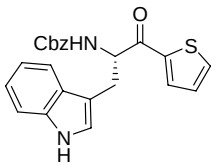
Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Trp-SPh (86 mg, 0.2 mmol) coupled with 3-nitrophenylboronic acid (40 mg, 0.24 mmol) using $P(OEt)_3$ (3.4 μl, 20 μmol, 10 mol %) at 30 ˚C overnight. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, CH_2Cl_2) afforded (+)-(*2S*)-2-benyloxycarbonylamino3-(1*H*-indol-3-yl)1-(3-nitro-phenyl)-propan-1-one as a yellow oil. Yield: 53 mg (60%). TLC (R_f = 0.15, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral AS-RH standard method: L-isomer t_R = 9.1 min, D-isomer t_R = 7.9 min, ee> 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 8.27 (app d, *J* = 8.3 Hz, 1H), 8.04 (m, 2H), 7.46 (d, *J* =7.9 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.40-7.27 (m, 5H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.31 (app t, *J* = 7.6 Hz, 1H), 7.04 (app t, *J* = 7.3 Hz, 1H), 6.81 (d, *J* = 1.9 Hz, 1H), 5.80 (d, *J* = 7.9 Hz, 1H), 5.65 (m, 1H), 5.15 and 5.12 (AB q, *J* = 12.4 Hz, 2H), 3.32 (app d, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 155.8, 148.0, 136.3, 136.1, 135.9, 133.8, 129.5, 128.5, 128.2, 128.1, 127.4, 127.1, 123.2, 122.9, 122.3, 119.8, 118.4, 111.1, 109.4, 67.1, 56.3, 29.1. IR (neat, cm^{-1}) 3408 (br m), 3065 (w), 2926 (w), 1695 (s), 1613 (m), 1532 (s), 1455 (m), 1351 (s), 1227 (m), 1061 (m), 748 (m), 698 (m). HRMS (FAB) Calcd for $C_{25}H_{21}N_3O_5Li$ ($[M+Li]^+$): 450.1641. Found: 450.1622. $[\alpha]^{20}_D$ = +62.0 (c = 0.56, $CHCl_3$).

TABLE 1.9, ENTRY 12. (-)-(*2S*)-3-Phenyl-1-benzyloxycarbonylpiperidin-2-yl-propenone, 1.43



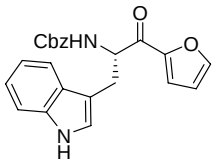
Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-(*S*)-2-piperidinecarbothiophenyl ester (54 mg, 0.15 mmol) coupled with (*E*)-2-styreneboronic acid (33 mg, 0.22 mmol) using $P(OEt)_3$ (5.1 µl, 30 µmol, 20 mol %) at room temperature overnight. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 33% ethyl acetate in hexanes) afforded ketone (-)-(*2S*)-3-phenyl-1-benzyloxycarbonylpiperidin-2-yl-propenone as yellow oil. Yield: 38 mg (72%). TLC (R_f = 0.50, silica gel, 33% ethyl acetate in hexanes). HPLC Chiral AD-RH standard method: L-isomer t_R = 12.4 min, D-isomer t_R = 13.7 min, ee > 99%. ^{1}H NMR (600 MHz, $CDCl_3$) two rotamers δ 7.60-7.55 (2d, *J* = 15.6 Hz, 1H), 7.40-7.22 (m, 10H), 6.79-6.72 (2d, *J* = 15.6 Hz, 1H), 5.12-4.83 (m, 3H), 4.09-3.98 (m, 0.4H+0.6H), 2.94-2.84 (2t, 0.6H+0.4H), 2.18 (2s, 0.4H+0.6H), 1.56-1.51 (m, 3H), 1.32-1.31 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) two rotamers δ 198.7, 156.7, 156.0, 144.2, 143.9, 136.9, 134.7, 130.8, 129.1, 128.7, 128.7, 128.2, 128.0, 122.2, 121.4, 67.6, 60.5, 60.0, 42.8, 25.7, 25.4, 25.3, 25.0, 20.5. IR (neat, cm^{-1}) 3065 (m), 3030 (m), 2941 (m), 2860 (m), 1695 (vs), 1610 (s), 1498 (m), 1420 (s), 1443 (m), 1274 (s), 1100 (m), 1077 (m), 764 (m), 694 (m). HRMS (FAB) Calcd for $C_{22}H_{23}NO_3Li$ ($[M+Li]^+$): 356.1838. Found: 356.1855. $[\alpha]^{20}_D$ = -121.6 (c = 1.99, $CHCl_3$).

TABLE 1.9, ENTRY 13. (+)-(*2S*)-2-Benzyloxycarbonylamino-3-(1*H*-indol-3-yl)-1-thiophen-2-yl-propan-1-one, 1.44



Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Trp-SPh (43 mg, 0.1 mmol) coupled with thiophene-2-boronic acid (19 mg, 0.15 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature for 30 min. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, CH_2Cl_2) afforded (+)-(*2S*)-2-benzyloxycarbonylamino3-(1*H*-indol-3-yl)-1-thiophen-2-yl-propan-1-one as a pale yellow oil. Yield: 39 mg (96%). 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* = 4.0, 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), 5.12 (AB q, *J* = 12.0 Hz, 2H), 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}) 3401 (m), 3061 (w), 2953 (w), 1702 (s), 1660 (s), 1505 (s), 1436 (s), 1235 (s), 1146 (m), 1061 (m), 849 (m), 698 (m). HRMS (FAB) Calcd for $C_{23}H_{21}N_2O_3S$ ($[M+H]^+$): 405.1267. Found: 405.1261. $[\alpha]^{20}_D$ = +112.6 (c = 1.25, $CHCl_3$).

TABLE 1.9, ENTRY 14. (+)-(*2S*)-2-Benzyloxycarbonylamino-1-furan-2-yl-3-(1*H*-indol-3-yl)-propan-1-one, 1.45



Following the same procedure used to prepare (-)-(*2S*)-2-benzyloxycarbonylamino1,3-diphenylpropan-1-one, above, *N*-Cbz-L-Trp-SPh (43 mg, 0.1 mmol) coupled with furan-2-boronic acid (16 mg, 0.15 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature for 30 min. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, CH_2Cl_2) afforded (+)-(*2S*)-2-benzyloxycarbonylamino1-furan-2-yl-3-(1*H*-indol-3-yl)-propan-1-one as a pale yellow oil. Yield: 38 mg (99%). TLC (R_f = 0.55, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.7 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN for 50 min, L-isomer t_R = 20.7 min, D-isomer t_R = 22.8 min, ee>99%. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.59 (d, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.37-7.29 (m, 6H), 7.18-7.15 (m, 2H), 7.09-7.05 (m, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.49 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.70 (d, *J* = 8.0 Hz, 1H), 5.45 (m, 1H), 5.11 (AB q, *J* = 12.0 Hz, 2H), 3.44 (dd, *J* = 6.0, 14.4 Hz, 1H), 3.29 (dd, *J* = 6.0, 14.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 187.1, 155.9, 151.1, 147.4, 136.4, 136.2, 128.6, 128.3, 128.2, 127.7, 123.1, 122.2, 119.7, 119.2, 118.6, 112.7, 111.3, 109.8, 67.0, 56.6, 28.9. IR (neat, cm^{-1}) 3408 (m), 3347 (s), 3061 (w), 2953 (w), 1702 (s), 1671 (s), 1505 (s), 1463 (s), 1231 (s), 1158 (m), 1061 (m), 841 (m), 698 (m). HRMS (FAB) Calcd for $C_{23}H_{21}N_2O_4$ ($[M+H]^+$): 389.1495. Found: 389.1490. $[\alpha]^{20}_D$ = +79.6 (c = 1.08, $CHCl_3$).

1.5 References

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Chapter 2

Room Temperature Synthesis of High Enantiopurity N-Protected Di, Tri-peptidyl Ketones by Peptidyl Thiol Ester–Boronic Acid Cross-Coupling

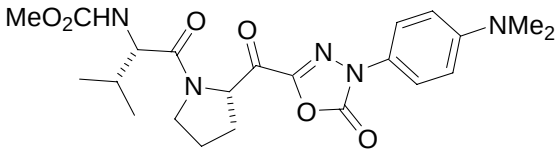
Abstract

Optically pure dipeptidyl and tripeptidyl thiophenyl esters coupled efficiently with aryl and alkenyl boronic acids to give the corresponding ketones with high yield. This C-terminal peptidyl ketone synthesis takes place in the presence of catalytic $Pd_2(dba)_3$ and $P(OEt)_3$ and stoichiometric CuTC at room temperature. No epimerization was found at the stereogenic centers of dipeptidyl and tripeptidyl ketones.

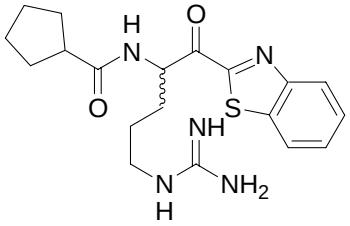
2.1 Introduction

As described in Chapter 1, N-protected α-amino ketones are of great value to act as chiral, non-racemic building blocks to construct various molecules with multiple purposes.[1] For example, as a class of molecules, peptidyl α-ketoheterocycles have been found to possess potent protease inhibition.[2]

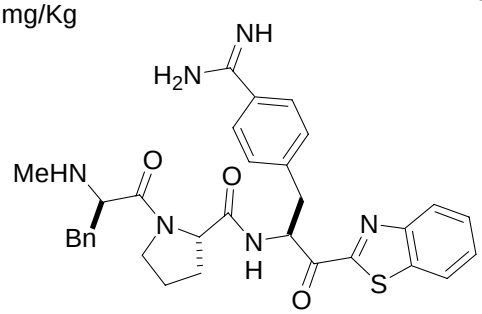
Figure 2.1 Protease Inhibitor



Elastase Inhibitor
Ki= 6.4nM ED50=7.5 mg/Kg



Serine protease inhibitor
Ki= 30nM



Thrombin inhibitor
Ki= 1nM

The therapeutic interests of these peptidyl α-ketoheterocycles have already generated several promising protease inhibitors in the pharmaceutical company pipeline for the purpose of treating HIV and hepatitis C (**Figure 2.1**). It is believed these electronic deficient heterocycle carbonyl would be electrophilic enough for nucleophilic addition of the active OH site of the protease.[3]

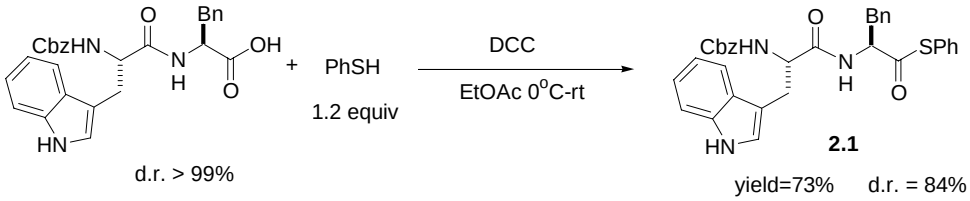
Methodologies to synthesize these therapeutically important peptidyl ketones are very limited. As described in the Chapter 1, all of the current methods (Weinreb amide, Fukuyama etc) are associated with low tolerance, low selectivity and racemization problems. The Liebeskind desulfitative cross coupling strategy has proved to be an efficient approach for the synthesis high enantiopurity N-protected α-amino ketones. It could be envisioned this pH neutral room temperature ketone synthesis would also be practical to the functionality more enriched peptidyl ketone system. Described herein Chapter 2 is the development of dipeptidyl and tripeptidyl ketone synthesis.

2.2 Results and Discussion

2.2.1 Synthesis of Dipeptidyl and Tripeptidyl Thiophenyl Esters

The successful synthesis of high enantiopurity N-Cbz protected α-amino ketones using 2.5 mol% $Pd_2(dba)_3$/20 mol% triethylphosphite and 1.2 equiv of CuTC encouraged us to investigate the synthesis of more complex structures such as dipeptidyl and tripeptidyl ketones. In order to achieve high efficient synthesis of peptidyl ketone with high enantiopurity, the first step is to develop a high enantiopurity synthesis of peptidyl thiophenyl ester.

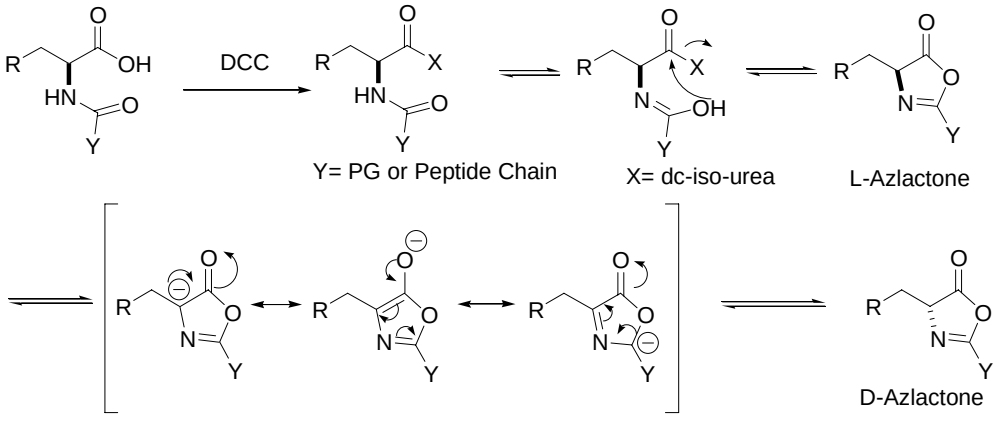
Scheme 2.1 N-Cbz-(L)-Trp-(L)-Phe Thiophenyl Ester



Under the same synthetic procedure of thiolester used in Chapter 1, dipeptide N-Cbz-(L)-Trp-(L)-Phe-OH was treated with 1.2 equivalent of thiophenol in the presence of 1 equivalent of DCC to generate N-Cbz-(L)-Trp-(L)-Phe-SPh in 73% isolated yield. However, more than 16 % epimerization of N-Cbz-(L)-Trp-(L)-Phe-SPh was detected by HPLC (**Scheme 2.1**).

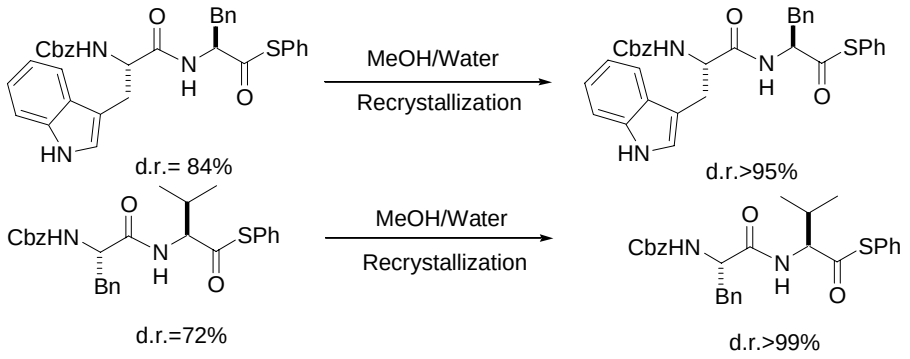
In fact, this epimerization associated with peptide synthesis is mechanistically caused by the formation of azlactone shown in **Scheme 2.2**.[4] When the amino acid was activated by DCC, the carbamide carbonyl group would attack the acyl isourea ester and cyclize intramolecularly to form L-azlactone. L-azlactone further undergoes a rapid tautomerization to epimerize the α-amino chiral center and thus to generate the D-azlactone.

Scheme 2.2 Racemization Mechanism of Peptide Synthesis



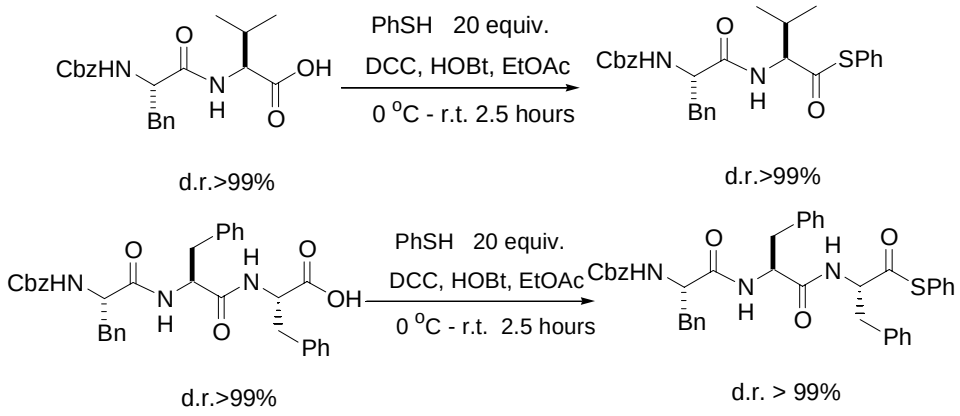
To address this epimerization problem, two approaches have been used to improve the diastereomeric purity of the peptidyl thiol esters. From a simple recrystallation in methanol and water, the diastereomeric purity was improved significantly. As shown in **Scheme 2.3**, diastereomeric ratio of N-Cbz-(L)-Trp-(L)-PheSPh was improved from 84% to 95%, while that of N-Cbz-(L)-Phe-(L)-ValSPh was increased from 72% to 99%.

Scheme 2.3 Recrystallization to Improve d.r. Value



However, N-Cbz-(L)-Phe-(L)-Phe-(L)-Phe-SPh failed to give a higher d.r. value by recrystallation. As described in **Scheme 2.2** about azlactone epimerization mechanism, it is likely to suppress the formation of azlactone by increasing the dehydration rate. As the reaction rate was determined by substrate concentration, the use of large excessive thiophenol will significantly enhance the rate of thiol ester formation rather than that of azlactone so that the azlactone epimerization will be eliminated. As a result, dipeptide or tripeptide was converted to the corresponding thiophenyl ester in satisfactory yields without epimerization (**Scheme 2.4**).

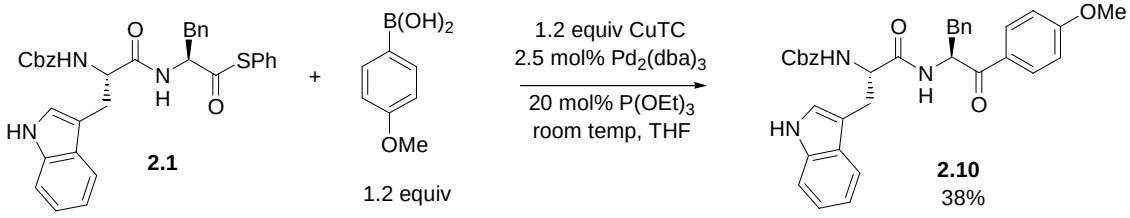
Scheme 2.4 Suppressing Epimerization



2.2.2 Peptidyl Thiophenyl Ester and Boronic Acid Cross Coupling

The $Pd_2(dba)_3/P(OEt)_3$ catalyst system has proved effective for the α-amino thiol ester and boronic acid cross coupling in Chapter 1. Is this protocol of ketone synthesis still efficient for dipeptide and tripeptide ketone synthesis? For our initial attempt to achieve this goal, *N*-Cbz-(L)-Trp-(L)-Phe-SPh was treated with 1.2 equiv of *p*-methoxylphenyl boronic acid in the presence of 2.5 mol% $Pd_2(dba)_3$, 20 mol% triethylphosphite and 1.2 equiv of CuTC in THF at room temperature (**Scheme 2.5**). In result, 38% of ketone was isolated by preparative TLC. A significant amount of N-Cbz-(L)-Trp-(L)-Phe-SPh was found unreacted.

Scheme 2.5 Cross Coupling



When the loading of triethyl phosphite was enhanced to 40 mol%, the ketone yield was improved slightly to 44%. On the contrary, very low ketone yield (10%) was obtained by using 10 mol% of triethyl phosphite.

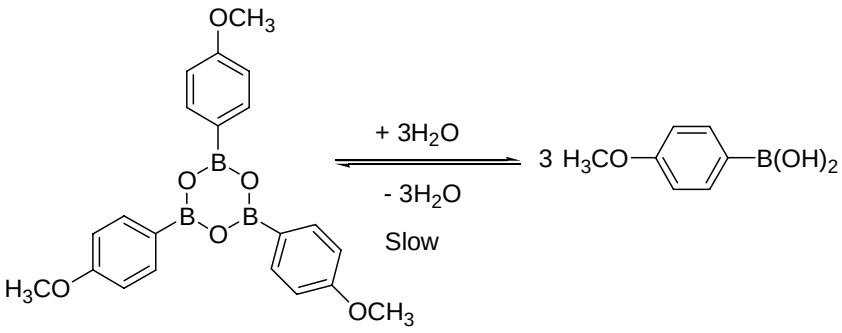
Further investigation revealed that the peptidyl ketone formed very rapidly during the first 3 hr of the reaction (according to HPLC monitoring), but the rate of the product formation dropped rapidly after that, even though significant quantities of the thiol ester and the boronic acid were still detectable in HPLC assay. The addition of *either* CuTC *or* the boronic acid *alone* did not restart the consumption of unreacted dipeptide thiol ester. However, charging the reaction mixture with an additional 0.5 equivalent of *both* Cu(I) thiophenecarboxylate *and* the boronic acid reactivated the cross-coupling to form more ketone led to almost complete consumption of the dipeptide thiol ester as determined by HPLC. These combined control experiments indicated that the palladium catalyst was still active, and that the well-known metal-binding affinity of polypeptides and proteins[5] was not the cause of the low conversion to ketone in this reaction system. However, the experiments gave no insight into why *additional* boronic acid was a necessary prerequisite to restart the cross-coupling reaction, in particular when HPLC traces indicated that boronic acid was still present in the reaction mixture.

Ultimately, the low conversions to ketone and the ambiguous stoichiometry of the boronic acid were associated with the unpreventable presence of boroxines (boronic acid cyclic trimers) in the boronic acid starting materials.[6] The synthesis of boronic acids uncontaminated by the corresponding boroxine is highly problematic in most cases.[7] Moreover, the facile boroxine ⇆ boronic acid equilibrium at acidic or basic pH complicates monitoring of the peptidyl thiol ester–boronic acid cross-couplings: HPLC

analysis is not able to differentiate between a boronic acid and its boroxine trimer, because the boroxine is easily transformed to the boronic acid by the HPLC eluent system (CH_3CN/H_2O/TFA).

Under standard Suzuki-Miyaura cross-coupling conditions[8], the boroxine ⇆ boronic acid equilibrium is not problematic because the boroxine can be shifted to the boronic acid under the reaction conditions by the presence of a requisite base (such as K_2CO_3) as well as the higher reaction temperatures typically used. A similar rapid *in situ* boroxine ⇆ boronic acid interconversion is *not* feasible under the non-basic, room temperature conditions of the Pd-catalyzed, Cu(I) carboxylate-mediated cross-couplings of peptidyl thiol esters and boronic acids.

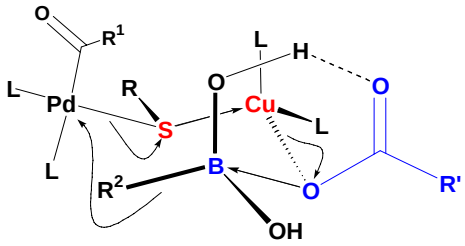
Scheme 2.6 Boroxine and Boronic Acid Equilibrium



It is known from earlier studies in the Liebeskind laboratories that *boronic acids and not boronate esters* are uniquely reactive with thiol esters under the mild and non-basic Pd-catalyzed, Cu(I) carboxylate-mediated conditions. As shown in **Figure 2.2**, the extra hydrogen bonding interaction of boronic acid and copper carboxylate helps to stabilize the transition state, which could be the reason that boronic acid is more reactive than boronate ester. Based on this rationale, boroxines are unreactive in Pd-catalyzed, Cu(I) carboxylate-mediated cross-couplings with thioorganics. Under ambient temperature and neutral pH reaction condition, it is impossible to establish a quick in-situ equilibrium of

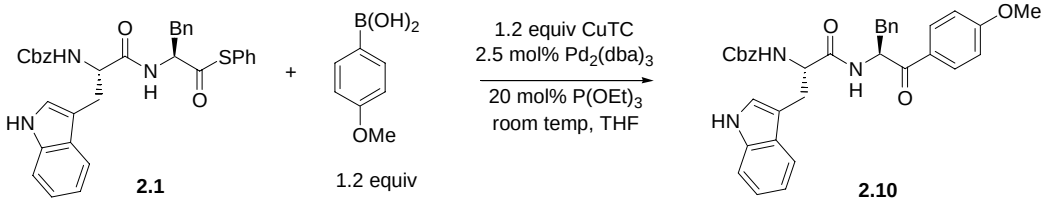
boroxine and boronic acid. In results, the production of high yields of peptidyl ketone was unsuccessful when only one equivalent of boronic acid is used.

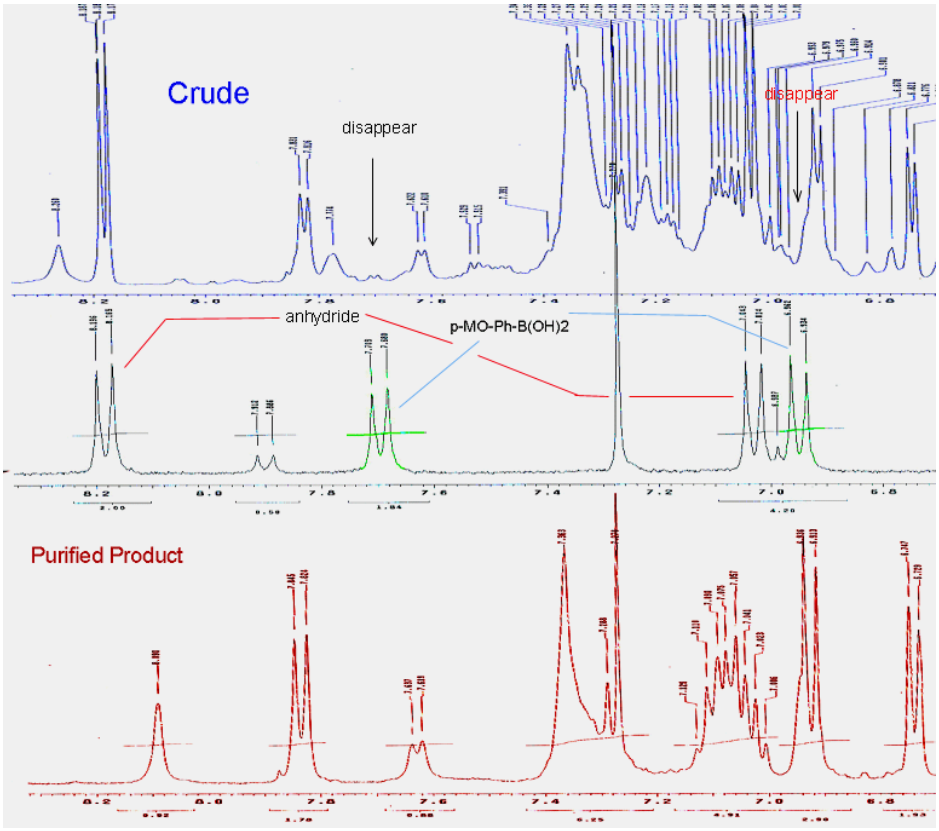
Figure 2.2 Proposed Transition State



Indirect proof of the presence of boroxines in the boronic acid samples and the low cross-coupling reactivity of boroxines under the current reaction conditions was obtained. A commercial sample of 4-methoxyphenyl boronic acid showed two pairs of ^{1}H NMR signals in $CDCl_3$, at 8.18 and 7.03 ppm and at 7.70 and 6.95 ppm. Addition of D_2O to the NMR tube led to an increase in the intensity of the 7.70/6.95 peaks and a decrease in intensity of those at 8.18/7.03. Therefore, the signals at 8.18 and 7.03 ppm are attributed to the boroxine and the others to the boronic acid.

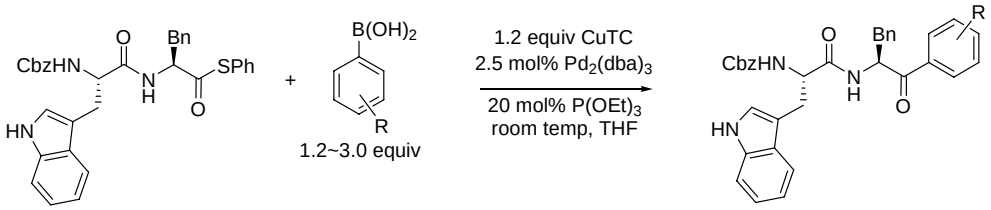
Scheme 2.7 Identification of boronic acids and boroxine on NMR study





Indeed, ^{1}H NMR analysis of the crude reaction mixture that resulted from the cross coupling reaction depicted in **Scheme 2.7** showed almost complete disappearance of the boronic acid resonances, while those of the boroxine appeared unchanged. Clearly the reactivity of boronic acid is much higher than that of the boroxine under the non-basic and room temperature reaction conditions of this cross-coupling.

Table 2.1 Probing Dipeptide Thiol Ester–Boronic Acid Cross-Coupling. Influence of Boronic Acid Stoichiometry on the Cross-Coupling Yield



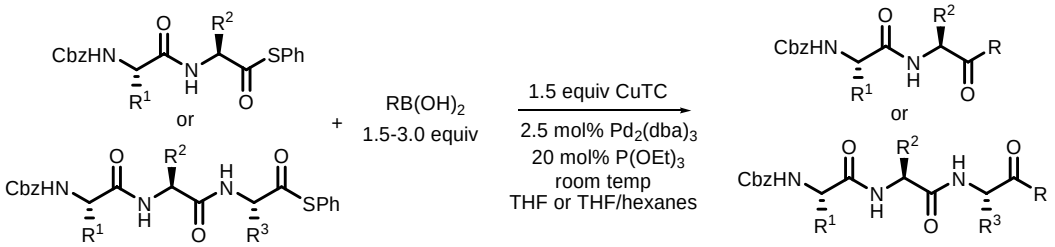
entry	boronic acid	ketone	equivalent	Yield (%)
1	*p*-methoxyphenyl	**2.10**	1.2 equiv	53
2	"	**2.10**	2.0 equiv	72
3	*p*-tolyl	**2.11**	1.2 equiv	26

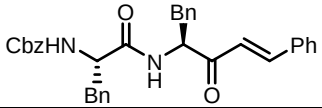
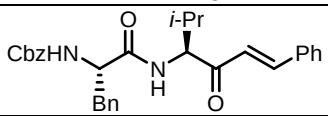
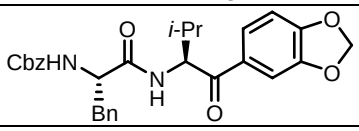
4	"	**2.11**	2.0 equiv	42
5	"	**2.11**	3.0 equiv	62

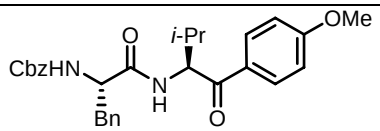
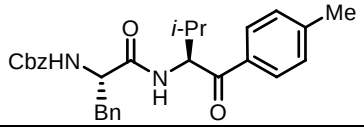
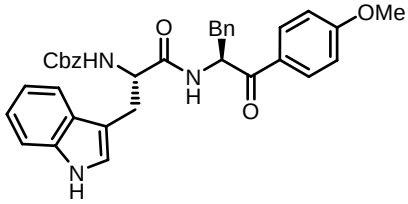
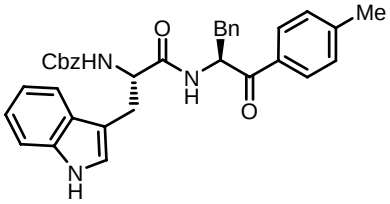
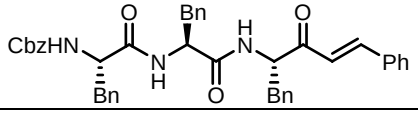
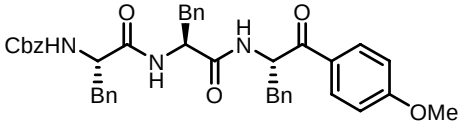
Unfortunately, the simple expedient of intentionally adding water or methanol to the non-basic cross-coupling reaction mixture did not improve the yield of peptidyl ketone. The overall observations suggest that the use of extra equivalents of freshly prepared boronic acid will be critical to any attempt to improve the yields of the peptidyl ketones. In fact, the simple expedient of increasing the amount of boronic acid compensated for any unreactive boroxine present in the starting material and led to much improved yields of the peptidyl ketones (**Table 2.1**, above, compare entries 1-2 and 3-5).

Finally, nine dipeptidyl and tripeptidyl ketones were easily prepared in good to excellent yields (**Table 2.2**) using 1.5-3.0 equiv of boronic acid, 2.5 mol% $Pd_2(dba)_3$, 20 mol% $P(OEt)_3$, and 1.5 equiv CuTC in THF at room temperature.

Table 2.2 Structures, Isolated Yields, and Diastereomeric Purity of Peptidyl Ketones



entry	thiol ester	peptidyl ketone	Yield (%)	d.r.[a]
1	**2.2**		94	>99
2	**2.3**		88	>99
3	**2.3**		74	>99

4	**2.3**		78	>99
5[b]	**2.3**		68	>99
6	**2.1**		72	>95
7	**2.1**		62	>95
8	**2.4**		85	>99
9	**2.4**		80	>99

[a] The d.r. of each ketone is identical to the d.r. of the thiol ester reactant; no epimerization occurred during the cross-coupling reaction. [b] The reaction was carried out in 1:1 THF:hexanes.

The diastereomeric purity of the peptidyl ketone product was identical to that of the starting thiol ester: no epimerization was detectable during the coupling reaction. In general THF was the best of those solvents explored, although a 1:1 THF:hexanes mixed solvent system gave an improved yield of product in one case shown in Table (40% in THF; 68% in 1:1 THF:hexanes). This mimics the same solvent effect observed in an earlier project,[9] where a 1:1 THF:hexanes mixture led to improved yields of ketone in some cases.[10]

2.3 Conclusion

A general and efficient synthesis of high enantiopurity *N*-Cbz protected di-, and tripeptidyl ketones was developed from the corresponding thiol esters and aryl, heteroaryl, or alkenyl boronic acids using the catalyst system $Pd_2(dba)_3/P(OEt)_3/CuTC$. Using this mild and versatile cross-coupling reaction, no epimerization was detected throughout the cross-coupling process and the configuration of stereogenic centers was completely preserved. Isolated yields ranged from moderate to excellent. Importantly, unprotected sensitive polar functional groups and variations in electronic nature of boronic acids were well tolerated by the reaction system. It is anticipated that the mild and non-basic features of this new ketone synthesis and its significant functional group compatibility will prove useful for the *C*-terminal or side-chain modification of proteins.

2.4 Experimental Section

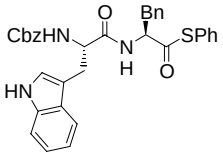
Starting Materials. All boronic acids were obtained from Frontier Scientific Inc. All protected amino acids, *N*,*N*'-dicyclohexylcarbodiimide (DCC) were purchased from Sigma-Aldrich. 1-hydroxybenzotriazole (HOBt), and triethylphosphite were purchased from Acros. Triethylphosphite was purified by distillation at 1 atm (157 °C).[11] Cu(I) thiophene-2-carboxylate (CuTC) was prepared by using a previous procedure.[12] *N*-Protected dipeptide and tripeptide acids were prepared using the standard DCC/HOBt method followed by hydrolysis with lithium hydroxide.[13]

For the synthesis of di- and tripeptidyl thiol esters an excess of the thiol (1.5-20.0 equiv) was employed in order to secure high diastereomeric purity (de 91-99%).

HPLC analyses were carried out using an Agilent 1100 system with a quaternary pump. Separations were achieved on a Zorbax Eclipse XDB C8 4.6 x 150 mm column or DAICEL chiral AD, AS, OD reversed phase column (Standard Method: λ= 254 nm; Flow: 1.0 mL/min; T= 30 °C; Gradient: 50 % H_2O in CH_3CN during 10 min to 75 % CH_3CN during 12.5 min to 100 % CH_3CN hold for 4.5 min).

THE THIOL ESTERS

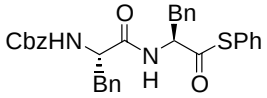
(-)-*N*-Cbz-L-Tryptophan-L-phenylalanine thiophenyl ester, 2.1



To a solution of the *N*-Cbz-L-Trp-L-Phe (945 mg, 2.0 mmol) in EtOAc (20 mL) was added HOBt (408 mg, 3.0 mmol), thiophenol (340 mg, 3.0 mmol), followed by the dropwise addition of 1,3-dicyclohexylcarbodiimide (415 mg, 2.0 mmol, in 10 mL EtOAc) at 0 ˚C for 30 minutes. The reaction progress was monitored by HPLC analysis. After stirring overnight at room temperature, the reaction was treated with 1 mL acetic acid (50% in ethyl acetate) for 30 min. The mixture was filtered through Celite™ and the organic phase was washed with 1M HCl, $NaHCO_3$ solution, and brine, dried over $MgSO_4$, filtered, and evaporated. The crude was purified by recrystallization from MeOH (induced by addition of water) afforded *N*-Cbz-L-Trp-L-Phe-SPh as a white solid. Yield: 1.066 g (95%). TLC (R_f = 0.54, silica gel, 50% ethyl acetate in hexanes). Mp = 159-160 ˚C. HPLC Chiral OD-RH standard method: L,L-isomer t_R = 13.8 min, de = 91% (determined by ^{1}H-NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.71 (d, 1H),

7.44-7.13 (m, 16H), 6.99 (s, 1H), 6.86 (d, *J* = 6.0 Hz, 2H), 6.24 (d, *J* = 6.4 Hz, 1H), 5.36 (s, 1H), 5.10 (s, 2H), 4.96 (dd, *J* = 14.8, 8.4 Hz, 1H), 4.55 (s, 1H), 3.34 (s, 1H), 3.16 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.95 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.8, 171.4, 156.2, 136.4, 135.3, 134.8, 129.8, 129.5, 128.8, 128.7, 128.4, 128.3, 127.4, 127.0, 123.6, 122.7, 120.2, 119.1, 111.5, 110.4, 67.3, 59.8, 55.4, 38.3, 28.2. IR (neat, cm^{-1}) 3405 (w), 3304 (w), 3061 (m), 3034 (m), 2926(m), 1698 (s), 1664 (s), 1513 (s), 1455 (m), 1343 (m), 1231 (s), 1054 (m), 1027 (m), 741 (s). HRMS (FAB) Calcd for $C_{34}H_{31}N_3O_4SLi$ ($[M+Li]^+$): 584.2195. Found: 584.2179. $[\alpha]^{20}_D$ = -28.8 (c = 0.57, $CHCl_3$).

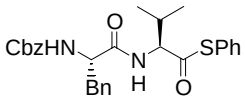
(-)-*N*-Cbz-L-Phenylalanino-L-phenylalanine thiophenyl ester, 2.2



To a solution of the *N*-Cbz-L-Phe-L-Phe (866 mg, 1.9 mmol) in EtOAc (20 mL) was added HOBt (390 mg, 2.9 mmol), thiophenol (3.9 mL, 38.8 mmol), followed by the dropwise addition of 1,3-dicyclohexylcarbodiimide (391 mg, 1.9 mmol, in 10 mL EtOAc) at 0 ˚C for 30 minutes. The reaction progress was monitored by HPLC analysis. After stirring overnight at room temperature, the reaction was treated with 1 mL acetic acid (50% in ethyl acetate) for 30 min. The mixture was filtered through Celite™ and the organic phase was washed with 1M HCl, $NaHCO_3$ solution, and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product (already crystalline) was triturated with hexanes to remove excess thiophenol. The crude was then purified by recrystallization from MeOH (induced by addition of water) to afford *N*-Cbz-L-Phe-L-Phe-SPh as a white solid. Yield: 1.001 g (96%). TLC (R_f = 0.24, silica gel, 25% ethyl acetate in hexanes). Mp = 177-178 ˚C. HPLC Chiral OD-RH standard method: L,L-isomer t_R = 13.1 min, L,D-isomer t_R = 13.7 min, de = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 3H), 7.36-

7.12 (m, 15H), 7.04 (m, 2H), 6.34 (d, *J* = 7.3 Hz, 1H), 5.13 (m, 1H), 5.06 (s, 2H), 5.00 (m, 1H), 4.41 (m, 1H), 3.15-3.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 170.7, 136.1, 135.2, 134.5, 129.6, 129.3, 129.3, 128.8, 128.7, 128.5, 128.2, 128.0, 127.2, 127.1, 126.7, 67.1, 59.5, 56.0, 38.2, 37.7. IR (neat, cm^{-1}) 3289 (m), 3061 (w), 3034 (w), 1695 (s), 1664 (vs), 1532 (s), 1285 (m), 1235 (m), 1042 (m), 745 (m), 648 (s); HRMS (FAB) Calcd for $C_{32}H_{30}N_2O_4SLi$ ([M+Li]$^+$): 545.2068. Found: 545.2087; α^{20}_D = -39.0 (c = 0.48, $CHCl_3$).

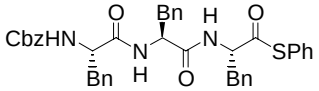
(-)-*N*-Cbz-L-Phenylalanine-L-valine thiophenyl ester, 2.3



To a solution of the *N*-Cbz-L-Phe-L-Val (610 mg, 1.5 mmol) in EtOAc (15 mL) was added HOBt (302 mg, 2.2 mmol), thiophenol (3.1 mL, 30.5 mmol), followed by the dropwise addition of 1,3-dicyclohexylcarbodiimide (310 mg, 1.5 mmol, in 8 mL EtOAc) at 0 ˚C for 30 minutes. The reaction progress was monitored by HPLC analysis. After stirring overnight at room temperature, the reaction was treated with 1 mL acetic acid (50% in ethyl acetate) for 30 min. The mixture was filtered through Celite™ and the organic phase was washed with 1M HCl, $NaHCO_3$ solution, and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product (already crystalline) was triturated with hexanes to remove excess thiophenol. The crude was then purified by recrystallization from MeOH (induced by addition of water) to afford *N*-Cbz-L-Phe-L-Val-SPh as a white solid. Yield: 583 mg (78%). TLC (R_f = 0.73, silica gel, 50% ethyl acetate in hexanes). Mp = 147-148 ˚C. HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 0.65 mL/min; T = 30 °C; Isogradient: 50 % H_2O in CH_3CN for 45 min., L,L-isomer t_R = 29.0 min, L,D-isomer t_R = 31.1 min, de = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.17 (m, 15H), 6.58

(d, *J* = 8.0 Hz, 1H), 5.35 (d, *J* = 7.2 Hz, 1H), 5.05 (dd, *J* = 18.4, 12.4 Hz, 2H), 4.65 (dd, *J* = 9.2, 5.2 Hz, 1H), 4.51 (d, *J* = 7.2 Hz, 1H), 3.09 (m, 2H), 2.23 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 171.5, 156.4, 136.4, 136.2, 134.7, 129.8, 129.6, 129.4, 129.0, 128.7, 128.4, 128.2, 127.3, 127.2, 67.4, 63.9, 56.5, 38.0, 31.4, 19.5, 17.2. IR (neat, cm^{-1}) 3408 (w), 3308 (w), 3061 (m), 2964 (m), 2930(m), 1698 (s), 1664 (s), 1513 (s), 1455 (m), 1343 (m), 1247 (s), 1050 (s), 1023 (m), 907.1(s), 741 (s). HRMS (FAB) Calcd for $C_{28}H_{30}N_2O_4SLi$ ($[M+Li]^+$): 497.2086. Found: 497.2105. $[\alpha]^{20}_D$ = -31.1 (c = 0.98, $CHCl_3$).

(-)-*N*-Cbz-L-Phenylalanine-L-phenylalanine-L-phenylalanine thiophenyl ester, 2.4

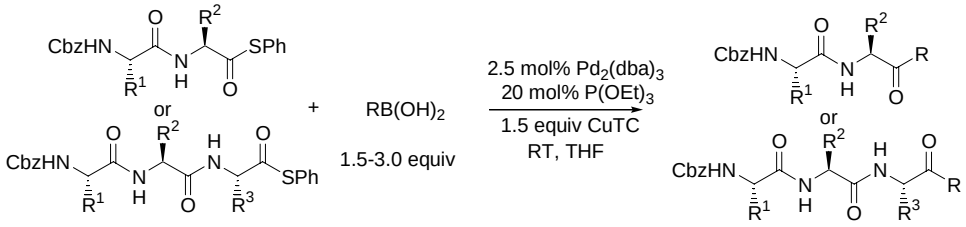


To a solution of the *N*-Cbz-L-Phe-L-Phe-L-Phe (718 mg, 1.2 mmol) in THF (12 mL) was added HOBt (240 mg, 1.8 mmol), thiophenol (2.5 mL, 24.0 mmol), followed by the dropwise addition of 1,3-dicyclohexylcarbodiimide (DCC) (250 mg, 1.2 mmol, in 6 mL THF) at 0 ˚C for 30 minutes. The reaction progress was monitored by HPLC analysis. After stirring overnight at room temperature for 3 h, the reaction was treated with 1 mL acetic acid (50% in ethyl acetate) for 30 min. The mixture was filtered through Celite™ and the organic phase was washed with 1M HCl, $NaHCO_3$ solution, and brine, dried over $MgSO_4$, filtered, and evaporated. The crude product (already solidified) was triturated with hexanes to remove excess thiophenol. The crude was then purified by recrystallization from $CHCl_3$ (induced by addition of hexane) afforded *N*-Cbz-L-Phe-L-Phe-L-Phe-SPh as a white solid. Yield: 514 mg (62%).TLC (R_f = 0.38, silica gel, 13% ethyl acetate in $CHCl_3$). Mp = 208-209 ˚C. HPLC Chiral AS-RH standard method: L,L,L-isomer t_R = 8.1 min, L,L,D-isomer t_R = 9.3 min, de = 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.43-7.07 (m, 25H), 6.51 (s, 1H), 6.37 (d, J = 7.6 Hz, 1H), 5.11 (d, J = 6.4 Hz, 1H), 5.02 (AB q, J = 12.0 Hz, 2H), 4,95 (dd, J = 7.2, 14.0 Hz, 1H), 4.62 (dd, J = 7.2, 14.4 Hz, 1H), 4.34 (d, J = 6.8 Hz, 1H), 3.18-2.93 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.7, 171.1, 170.6, 156.3, 136.3, 136.3, 136.1, 135.7, 134.8, 129.8, 129.5, 129.4, 129.0, 128.9, 128.8, 128.5, 128.3, 127.4, 127.4, 127.3, 127.1, 67.4, 60.1, 56.3, 54.5, 38.3, 38.0, 37.6. IR (neat, cm^{-1}) 3281 (br, m), 3065 (w), 3030 (w), 2922(w), 1695 (s), 1648 (s), 1544 (m), 1262 (m), 752 (s), 694 (w). HRMS (FAB) Calcd for $C_{41}H_{39}N_3O_5SLi$ ($[M+Li]^+$): 692.2770. Found: 692.2796. $[\alpha]^{20}_D$ = -51.1 (c = 1.12, $CHCl_3$).

THE DI- and TRIPEPTIDYL KETONES,

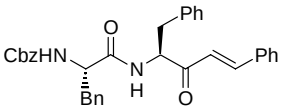
General Procedure for the Cross-Couplings of Di- and Tripeptidyl Thiophenyl Esters and Boronic Acids:



A mixture of *N*-Cbz-peptidyl-thiophenyl ester (0.1 mmol), boronic acid (1.5 to 3.0 equiv), CuTC (1.5 equiv), and $Pd_2(dba)_3$ (2.5 mol %, 2.5 μmol) were placed under an argon atmosphere. THF (3 mL, degassed and dried over 4Å molecular sieves) and triethylphosphite (20 mol %, 20 μmol) were added and the mixture was stirred at room temperature until the *N*-Cbz-peptidyl-thiophenyl ester was consumed (3 - 8 h). Reaction progress was monitored by HPLC analyses. The reaction mixture was diluted with ether (25 mL), washed with $NaHCO_3$ solution and brine (15 mL each), followed by drying over

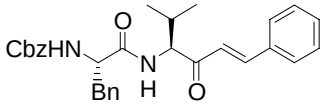
$MgSO_4$. The drying agent was filtered off through a short plug of silica gel (to aid removal of metal containing products) and concentrated under vacuum using a rotary evaporator. The crude material was subjected to preparative TLC or flash chromatography affording the title peptidyl ketone.

(-)-2-(*S*)-Benzyloxycarbonylamino-*N*-(1-(*S*)-benzyl-2-oxo-4-phenyl-but-3-enyl)-3-phenyl-propionamide, 2.5



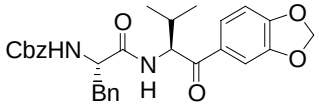
Following the general procedure, *N*-Cbz-L-Phe-L-Phe-SPh (107 mg, 0.2 mmol) coupled with (*E*)-2-styreneboronic acid (44 mg, 0.3 mmol) using $P(OEt)_3$ (6.8 µl, 40 µmol, 20 mol %) at room temperature for 3 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, CH_2Cl_2) afforded (-)-2-(*S*)-benzyloxycarbonylamino-*N*-(1-(*S*)-benzyl-2-oxo-4-phenyl-but-3-enyl)-3-phenyl-propionamide as a colorless oil. Yield: 100 mg (94%). TLC (R_f = 0.17, silica gel, 25% ethyl acetate in hexanes). HPLC Chiral OD-RH standard method: L,L-isomer t_R = 13.9 min, L,D-isomer t_R = 12.7 min, de = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 16.0 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.44-7.29 (m, 7H), 7.25-7.12 (m, 7H), 7.04 (dd, *J* = 7.6, 2.1 Hz, 2H), 6.64 (d, *J* = 16.0 Hz, 1H), 6.63 (br s, 1H), 5.30 (br, 1H), 5.14-5.01 (m, 3H), 4.07 (br m, 1H), 3.07 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 170.3, 144.8, 136.1, 135.7, 134.0, 131.0, 129.5, 129.3, 129.0, 128.7, 128.6, 128.52, 128.48, 128.2, 128.0, 127.0, 122.7, 67.1, 57.8, 56.1, 38.4, 38.1. IR (neat, cm^{-1}) 3293 (br s), 3065 (m), 2949 (w), 1695 (s), 1652 (vs), 1610 (s), 1532 (s), 1451 (s), 1386 (m), 1258 (s), 1046 (s), 984 (s), 907 (s), 760 (s). HRMS (FAB) Calcd for $C_{34}H_{32}N_2O_4Li$ ($[M+Li]^+$): 539.2522. Found: 539.2500. $[\alpha]^{20}_D$ = -2.6 (c = 1.03, $CHCl_3$).

(+)-2-(*S*)-Benzyloxycarbonylamino-*N*-(1-(*S*)-isopropyl-2-oxo-4-phenyl-but-3-enyl)-3-phenyl-propionamide, 2.6



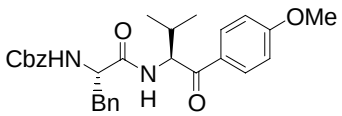
Following the general procedure, *N*-Cbz-L-Phe-L-Val-SPh (49 mg, 0.1 mmol) coupled with (*E*)-2-styreneboronic acid (29 mg, 0.20 mmol) using 20 mol % $P(OEt)_3$ (3.4 µl, 20 µmol) at room temperature for 3 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 50% ethyl acetate in hexane) afforded (+)-2-(*S*)-benzyloxycarbonylamino-*N*-(1-(*S*)-isopropyl-2-oxo-4-phenyl-but-3-enyl)3-phenyl-propionamide as a white solid. Yield: 42 mg (88%). TLC (R_f = 0.65, silica gel, 50% ethyl acetate in hexanes). Mp = 153-154 ˚C. HPLC Chiral AS-RH standard method: L,L-isomer t_R = 7.9 min, L,D-isomer t_R = 8.5 min, de = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 16.0 Hz, 1H), 7.43-6.70 (m, 15H), 6.62 (d, *J* = 15.6 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 5.27 (d, *J* = 8.0 Hz, 1H), 4.94 (s, 2H), 4.72 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.36 (d, *J* = 7.2 Hz, 1H), 2.92 (m, 2H), 2.02 (m, 1H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.60 (d, *J* = 5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 171.1, 156.1, 144.7, 136.4, 134.3, 131.2, 129.5, 129.2, 128.9, 128.8, 128.7, 128.4, 128.3, 127.2, 123.5, 67.2, 61.3, 56.5, 38.7, 31.2, 19.9, 17.3. IR (neat, cm^{-1}) 3300 (br w), 3065 (w), 3034 (w), 2934 (w), 2876 (w), 1702 (s), 1652 (s), 1610 (m), 1536 (s), 1455 (m), 1258 (m), 1069 (m), 741 (m), 699 (s). HRMS (FAB) Calcd for $C_{30}H_{32}N_2O_4Li$ ($[M+Li]^+$): 491.2522. Found: 491.2517. $[\alpha]^{20}_D$ = +71.0 (c = 1.02, $CHCl_3$).

(+)-2-(*S*)-Benzyloxycarbonylamino-*N*-[1-(benzo[1,3]dioxole-5-carbonyl)-2-methyl-(*S*)-propyl]-3-phenyl-propionamide, 2.7



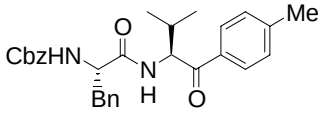
Following the general procedure, *N*-Cbz-L-Phe-L-Val-SPh (49 mg, 0.1 mmol) coupled with 3,4-methylenedioxyphenylboronic acid (33 mg, 0.20 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature overnight. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 50% ethyl acetate in hexane) afforded (+)-2-(*S*)-benzyloxycarbonylamino-*N*-[1-(benzo[1,3]dioxole-5-carbonyl)2-methyl-(*S*)-propyl]-3-phenyl-propionamide as reddish solid. Yield: 37 mg (74%). TLC (R_f = 0.60, silica gel, 50% ethyl acetate in hexanes). Mp = 152-153 ˚C. HPLC Chiral AS-RH standard method: L,L-isomer t_R = 7.7 min, L,D-isomer t_R = 9.2 min, de = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.53-7.21 (m, 11H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.17 (s, 2H), 5.56 (d, *J* = 8.0 Hz, 1H), 5.46 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.21 (s, 2H), 4.62 (d, *J* = 7.2 Hz, 1H), 3.16 (m, 2H), 2.20 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 171.1, 156.1, 152.6, 148.6, 136.3, 130.1, 129.4, 128.8, 128.7, 128.3, 128.2, 127.2, 125.5, 108.4, 108.3, 102.2, 67.2, 57.9, 56.6, 38.8, 32.2, 20.1, 17.1. IR (neat, cm^{-1}) 3296 (br w), 3065 (m), 3034 (m), 2964 (m), 2934 (m), 1702 (s), 1652 (s), 1606 (m), 1536 (s), 1444 (m), 1370 (m), 1247 (m), 1038 (m), 733 (m), 695 (s). HRMS (FAB) Calcd for $C_{29}H_{30}N_2O_6Li$ ($[M+Li]^+$): 509.2264. Found: 509.2264. $[\alpha]^{20}_D$ = +42.7 (c = 1.86, $CHCl_3$).

(+)-2-(*S*)-Benzyloxycarbonylamino-*N*-[1-(4-methoxy-benzoyl)-2-methyl-(*S*)-propyl]-3-phenyl-propionamide, 2.8



Following the general procedure, *N*-Cbz-L-Phe-L-Val-SPh (49 mg, 0.1 mmol) coupled with *p*-methoxyphenylboronic acid (30 mg, 0.20 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature for 3 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 50% ethyl acetate in hexane) afforded (+)-2-(*S*)-benzyloxycarbonylamino-*N*-[1-(4-methoxy-benzoyl)-2-methyl-(*S*)-propyl]3-phenyl-propionamide as a white solid. Yield: 41 mg (78%). TLC (R_f = 0.60, silica gel, 50% ethyl acetate in hexanes). Mp = 150-151 ˚C. HPLC Chiral AS-RH standard method: L,L-isomer t_R = 7.6 min, L,D-isomer t_R = 8.7 min, de = 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.2 Hz, 2H), 7.45 (m, 5H), 7.28-7.22 (m, 5H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 5.59 (d, *J* = 8.0 Hz, 1H), 5.53 (dd, *J* = 8.4, 4.8 Hz, 1H), 5.22 (s, 2H), 4.63 (d, *J* = 4.8 Hz, 1H), 4.00 (s, 3H), 3.18 (m, 2H), 2.23 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 171.1, 164.3, 156.0, 136.3, 131.2, 129.4, 128.8, 128.7, 128.3, 128.2, 127.2, 114.2, 67.2, 57.8, 56.6, 55.7, 38.8, 32.2, 20.1, 17.1. IR (neat, cm^{-1}) 3300 (w), 3065 (m), 3034 (m), 2964(m), 2934 (m), 1702 (s), 1652 (s), 1598 (s), 1513 (s), 1455 (m), 1370 (m), 1258 (s), 1146 (m), 1031 (m), 737 (s). HRMS (FAB) Calcd for $C_{29}H_{32}N_2O_5Li$ ($[M+Li]^+$): 495.2471. Found: 495.2466. $[\alpha]^{20}_D$ = +48.2 (c = 1.47, $CHCl_3$).

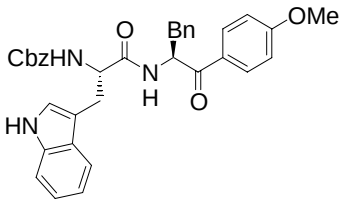
(+)-2-(*S*)-Benzyloxycarbonylamino-*N*-[2-methyl-1-(4-methyl-benzoyl)-(*S*)-propyl]-3-phenylpropionamide, 2.9



Following the general procedure, *N*-Cbz-L-Phe-L-Val-SPh (49 mg, 0.1 mmol) coupled with *p*-methylphenylboronic acid (40 mg, 0.30 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature for 3 h. Purification by preparative TLC (silica gel, 20 x 20

cm, 2 mm, 50% ethyl acetate in hexane) afforded (+)-2-(*S*)-benzyloxycarbonylamino-*N*-[2-methyl-1-(4-methyl-benzoyl)-(*S*)-propyl]3-phenyl-propionamide as a white solid. Yield: 32 mg (68%). TLC (R_f = 0.70, silica gel, 50% ethyl acetate in hexanes). Mp = 151-152 ˚C. HPLC Chiral AS-RH standard method: L,L-isomer t_R = 7.9 min, L,D-isomer t_R = 9.6 min, de = 99%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.31-7.23 (m, 7H), 7.15-7.09 (m, 5H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.40 (m, 2H), 5.08 (s, 2H), 4.47 (d, *J* = 7.2 Hz, 1H), 3.03 (m, 2H), 2.40 (s, 3H), 2.09 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.65 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.1, 171.1, 156.1, 145.0, 136.4, 132.8, 129.7, 129.4, 129.0, 128.9, 128.7, 128.4, 128.3, 127.2, 67.2, 58.1, 56.7, 38.8, 32.1, 21.9, 20.2, 17.0. IR (neat, cm^{-1}) 3296 (w), 3065 (m), 3034 (m), 2964 (m), 2930 (m), 1702 (s), 1652 (s), 1606 (m), 1536 (s), 1455 (m), 1370 (m), 1262 (m), 1227 (m), 1146 (m), 1042 (m), 741 (m), 699 (s). HRMS (FAB) Calcd for $C_{29}H_{32}N_2O_4Li$ ($[M+Li]^+$): 479.2522. Found: 479.2533. $[\alpha]^{20}_D$ = +41.8 (c = 0.82, $CHCl_3$).

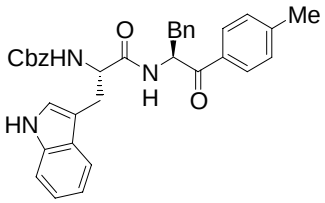
(+)-2-(*S*)-Benzyloxycarbonylamino-*N*-[1-(*S*)-benzyl-2-(4-methoxy-phenyl)-2-oxo-ethyl]-3-(1*H*-indol-3-yl)-propionamide, 2.10



Following the general procedure, *N*-Cbz-L-Trp-L-Phe-SPh (57 mg, 0.1 mmol) coupled with *p*-methoxylphenylboronic acid (30 mg, 0.20 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature for 3 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 50% ethyl acetate in hexane) afforded (+)-2-(*S*)-benzyloxycarbonylamino-*N*-[1-(*S*)-benzyl-2-(4-methoxy-phenyl)2-oxo-ethyl]3-(1*H*-indol-3-yl)-propionamide as a

colorless oil. Yield: 41 mg (72%). TLC (R_f = 0.32, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OD-RH standard method: L,L-isomer t_R = 13.3 min, L,D-isomer t_R = 12.7 min, de = 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.36-6.91 (m, 14H), 6.74 (d, *J* = 7.2 Hz, 2H), 6.61 (d, *J* = 7.6 Hz, 1H), 5.58 (m, 2H), 5.13 (m, 2H), 4.54 (d, *J* = 6.0 Hz, 1H), 3.89 (s, 3H), 3.33 (m, 1H), 3.12 (m, 2H), 2.88 (dd, *J* = 14.0, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 170.9, 164.3, 156.1, 136.4, 135.7, 131.2, 129.6, 128.7, 128.4, 128.3, 128.3, 127.6, 127.0, 123.4, 122.4, 119.9, 118.9, 114.2, 111.4, 110.5, 67.2, 55.7, 55.7, 54.6, 39.1, 28.8. IR (neat, cm^{-1}) 3327 (w), 3061 (m), 3034 (m), 2957 (m), 2934 (m), 1710 (s), 1652 (s), 1513 (s), 1455 (m), 1343 (m), 1258 (s), 1170 (m), 1027 (m), 737 (s). HRMS (FAB) Calcd for $C_{35}H_{33}N_3O_5Li$ ($[M+Li]^+$): 582.2580. Found: 582.2552. $[\alpha]^{20}_D$ = +13.2 (c = 0.68, $CHCl_3$).

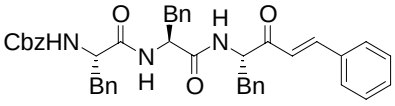
(+)-2-(*S*)-Benzyloxycarbonylamino-*N*-(1-(*S*)-benzyl-2-oxo-2-*p*-tolyl-ethyl)-3-(1*H*-indol-3-yl)-propionamide, 2.11



Following the general procedure, *N*-Cbz-L-Trp-L-Phe-SPh (57 mg, 0.1 mmol) coupled with *p*-methylphenylboronic acid (40 mg, 0.30 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature for 3 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 50% ethyl acetate in hexane) afforded (+)-2-(*S*)-benzyloxycarbonylamino-*N*-(1-(*S*)-benzyl-2-oxo-2-*p*-tolyl-ethyl)3-(1*H*-indol-3-yl)-propionamide as colorless oil. Yield: 35 mg (62%). TLC (R_f = 0.50, silica gel, 50% ethyl acetate in hexanes). HPLC Chiral OD-RH standard method: L,L-isomer t_R = 13.8 min, L,D-isomer t_R = 13.1min, de =

91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 6.8 Hz, 1H), 7.36-6.95 (m, 14H), 6.71 (d, *J* = 6.4 Hz, 2H), 6.56 (d, *J* = 7.2 Hz, 1H), 5.63 (dd, *J* = 12.8, 6.8 Hz, 1H), 5.54 (d, *J* = 7.2 Hz, 1H), 5.13 (m, 2H), 4.54 (d, *J* = 6.4 Hz, 1H), 3.33 (m, 1H), 3.13 (m, 2H), 2.88 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 170.8, 164.3, 156.1, 145.0, 136.4, 135.6, 132.2, 129.7, 129.6, 129.0, 128.7, 128.4, 128.3, 128.3, 127.0, 123.4, 122.4, 120.0, 118.9, 111.4, 110.5, 67.2, 55.8, 54.9, 38.9, 28.8, 21.9. IR (neat, cm^{-1}) 3327 (w), 3061 (m), 3034 (m), 2957 (m), 2926 (m), 2856 (m), 1710 (s), 1656 (s), 1505 (s), 1455 (m), 1343 (m), 1231 (m), 1181 (m), 1050 (m), 741 (s). HRMS (FAB) $C_{35}H_{33}N_3O_4Li$ Calcd for ($[M+Li]^+$): 566.2631. Found: 566.2618. $[\alpha]^{20}_D$ = +17.7 (c = 1.26, $CHCl_3$).

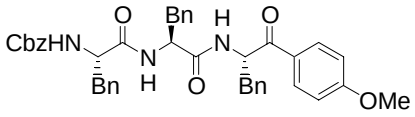
(-)-2-(*S*)-Benzyloxycarbonylamino-*N*-[1-(1-(*S*)-benzyl-2-oxo-4-phenyl-but-3-enylcarbamoyl)-2-phenyl-ethyl]-3-phenyl-(*2S*)-propionamide, 2.12



Following the general procedure, *N*-Cbz-L-Phe-L-Phe-L-Phe-SPh (49 mg, 0.1 mmol) coupled with (*E*)-2-styreneboronic acid (44 mg, 0.30 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature for 3 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 13% hexane in $CHCl_3$) afforded (-)-2-(*S*)-benzyloxycarbonylamino-*N*-[1-(1-(*S*)-benzyl-2-oxo-4-phenyl-but-3enylcarbamoyl)2-phenyl-ethyl]-3-phenyl-(*2S*)-propionamide as a white solid. Yield: 57 mg (85%). TLC (R_f = 0.65, silica gel, 13% hexane in $CHCl_3$). Mp = 182-184 ˚C. HPLC Chiral OD-RH standard method: L,L,L-isomer t_R = 14.2 min, L,L,D-isomer t_R = 12.7 min, de = 98%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 15.6 Hz, 1H), 7.50-7.04 (m, 25H), 6.66 (d, *J* = 16.2 Hz, 1H), 6.58 (s, 1H),

6.46 (d, *J* = 7.8 Hz, 1H), 5.23 (d, *J* = 7.2 Hz 1H), 5.05 (m, 3H), 4.62 (dd, *J* = 13.8, 6.6 Hz, 1H), 4.41 (d, *J* = 6.6 Hz, 1H), 3.11-2.96 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.3, 170.9, 170.1, 156.2, 144.9, 136.4, 136.2, 136.2, 134.4, 131.2, 129.7, 129.5, 129.4, 129.2, 129.0, 128.9, 128.8, 128.4, 128.3, 127.3, 127.3, 127.2, 123.0, 67.4, 58.2, 56.3, 54.7, 38.5, 38.3, 38.2. IR (neat, cm^{-1}) 3285 (br m), 3065 (w), 3030 (w), 2957(w), 2930 (w), 1698 (m), 1644 (s), 1613 (w), 1540 (m), 1455 (w), 1262 (m), 1046 (w), 741 (m), 699 (s). HRMS (FAB) Calcd for $C_{43}H_{41}N_3O_5Li$ ($[M+Li]^+$): 686.3206. Found: 686.3187. $[\alpha]^{20}_D$ = -10.4 (c = 1.20, $CHCl_3$).

(+)-2-(*S*)-Benzyloxycarbonylamino-*N*-[1-[1-(*S*)-benzyl-2-(4-methoxy-phenyl)-2-oxo-ethylcarbamoyl]-2-phenyl-ethyl]-3-phenyl-(*2S*)-propionamide, 2.13



Following the general procedure, *N*-Cbz-L-Phe-L-Phe-L-Phe-SPh (49 mg, 0.1 mmol) coupled with *p*-methoxyphenylboronic acid (45 mg, 0.30 mmol) using $P(OEt)_3$ (3.4 µl, 20 µmol, 20 mol %) at room temperature for 3 h. Purification by preparative TLC (silica gel, 20 x 20 cm, 2 mm, 13% hexane in $CHCl_3$) afforded (+)-2-(*S*)-benzyloxycarbonylamino-N-[1-[1-(*S*)-benzyl-2-(4-methoxy-phenyl)-2-oxo-ethylcarbamoyl]-2-phenyl-ethyl]-3-phenyl-(*2S*)-propionamide as a white solid. Yield: 49 mg (80%). TLC (R_f = 0.23, silica gel, 13% hexane in $CHCl_3$). Mp = 179-181 ˚C. HPLC Chiral AS-RH standard method: L,L,L-isomer t_R = 8.7 min, L,L,D-isomer t_R = 7.6 min, de = 98%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.37-7.13 (m, 16H), 7.01 (m, 2H), 6.95 (m, 4H), 6.64 (d, *J* = 6.0 Hz, 1H), 6.49 (d, *J* = 6.0 Hz, 1H), 5.64 (dd, *J* = 12.6, 6.0 Hz, 1H), 5.29 (s, 1H), 5.07 (AB q, *J* = 12.6 Hz, 2H), 4.62 (dd, *J* = 14.4, 7.2 Hz,

1H), 4.43 (d, J = 6.0 Hz, 1H), 3.89 (s, 3H), 3.20-2.94 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.6, 170.8, 169.8, 164.3, 136.5, 136.3, 136.3, 135.9, 131.3, 129.7, 129.5, 129.4, 129.0, 128.8, 128.8, 128.5, 128.4, 128.3, 127.7, 127.3, 127.2, 127.1, 114.3, 67.3, 56.2, 55.8, 54.8, 54.5, 39.1, 38.6, 38.4. IR (neat, cm^{-1}) 3285 (br m), 3065 (w), 3030 (w), 2930 (w), 2856 (w), 1695 (s), 1640 (s), 1602 (m), 1525 (s), 1455 (m), 1254 (s), 1173 (m), 1031 (m), 745 (m), 695 (s). HRMS (FAB) Calcd for $C_{42}H_{41}N_3O_6Li$ ($[M+Li]^+$): 690.3155. Found: 690.3167. $[\alpha]^{20}_D$ = +7.0 (c = 0.91, $CHCl_3$).

2.5 References

[1] See references in Chapter 1.

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[7] (a) Snyder, H. R.; Konecky, M. S.; Lennarz, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 3611-3615. (b) Snyder, H. R.; Kuck , J. A.; Johnson, J. R. *J. Am. Chem. Soc.* **1938**, *60*, 105-111.

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[9] Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033-3035.

[10] THF:hexanes solvent mixtures were used to maintain a low concentration of the active Cu(I) carboxylate in solution throughout the course of the cross-coupling reaction. Cu(I) carboxylate that is *not* complexed to the thiol ester or to the putative palladium(II) thiolate catalytic intermediate concentrations leads to competitive destruction of the boronic acid by a Cu-mediated protodeborylation.

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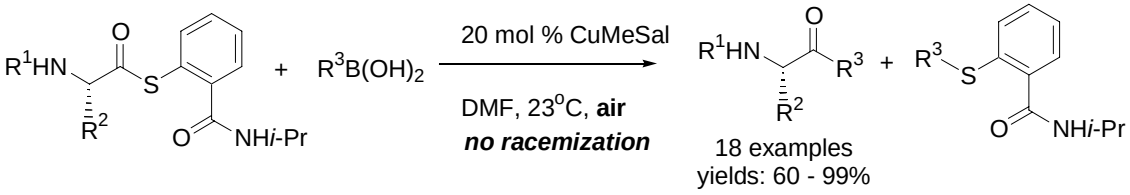
Chapter 3

Synthesis of High Enantiopurity Peptidyl Ketones from Copper Catalyzed, Aerobic, 2nd Generation Desulfitative Cross Coupling

Abstract

Peptidyl *S*-acylthiosalicylamides couple efficiently with aryl, alkenyl and heteroaryl boronic acids in the presence of catalytic Cu(I)-3-methylsalicylate (CuMeSal) under air at room temperature. This pH-neutral carbon-carbon cross coupling reaction produced a variety of high yield peptidyl ketone without racemization. The thiol ether co-product was easily removed by flash column. This mild reaction tolerates to a wide range of polar and non-polar functional groups (**Scheme 3.1**).

Scheme 3.1 Peptidyl Ketone Synthesis:2nd Generation of Desulfitative Cross Coupling

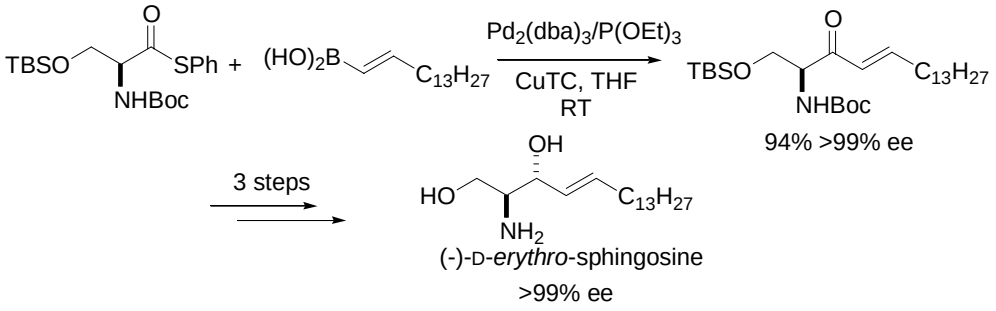


3.1 Introduction

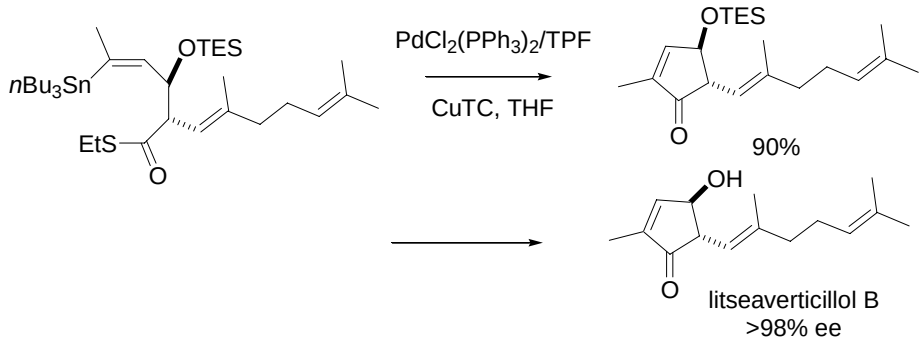
2nd Generation of Liebeskind Desulfitative Cross Coupling

The 1st generation of Liebeskind desulfitative cross coupling reactions described in Chapter 1 and 2[1] are of great value to generate various peptidyl ketones under neutral condition without racemization and epimerization. These highly efficient Liebeskind desulfitative C-C cross coupling reactions have also been successfully used as the key reactions for the total synthesis of (-)-D-*erythro*-sphingosine[2] (**Scheme 3.2**) and litseaverticillol B[3] (**Scheme 3.3**) with high enantiopurity.

Scheme 3.2 (-)-D-*erythro*-sphingosine



Scheme 3.3 Litsearverticillol B

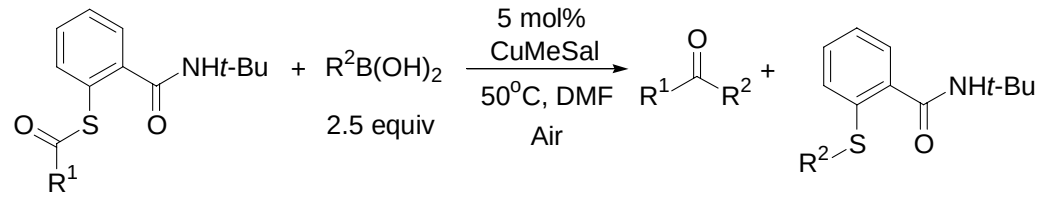


One of the ultimate goals of the Liebeskind laboratory is to seek high efficient reactions to realize the site-selective ketone transformation of functionality enriched biomolecular targets. The *in vivo* biological environment requires these reactions be catalytically efficient and globally tolerant of various functional groups under protic and aqueous conditions. To chase this goal, much effort has been made in the Liebeskind laboratory to develop a robust catalytic version of desulfitative thioorganic cross coupling reactions.

A novel templated thiol ester and boronic acid cross coupling has been developed in this lab. This second generation of desulfitative cross coupling utilizes only a catalytic amount of Cu^{I}-3-methylsalicylate without palladium and phosphine which are requisitive in the 1st generation desulfitative cross coupling described in Chapter 1 and 2.[4] This new reaction takes place in DMF at 50 ^{o}C, open to air, using 5 mol% Cu^{I}-3-methylsalicylate as the only metal catalyst. Alkyl, aryl and alkenyl *S*-acylthiosalicylamides couple

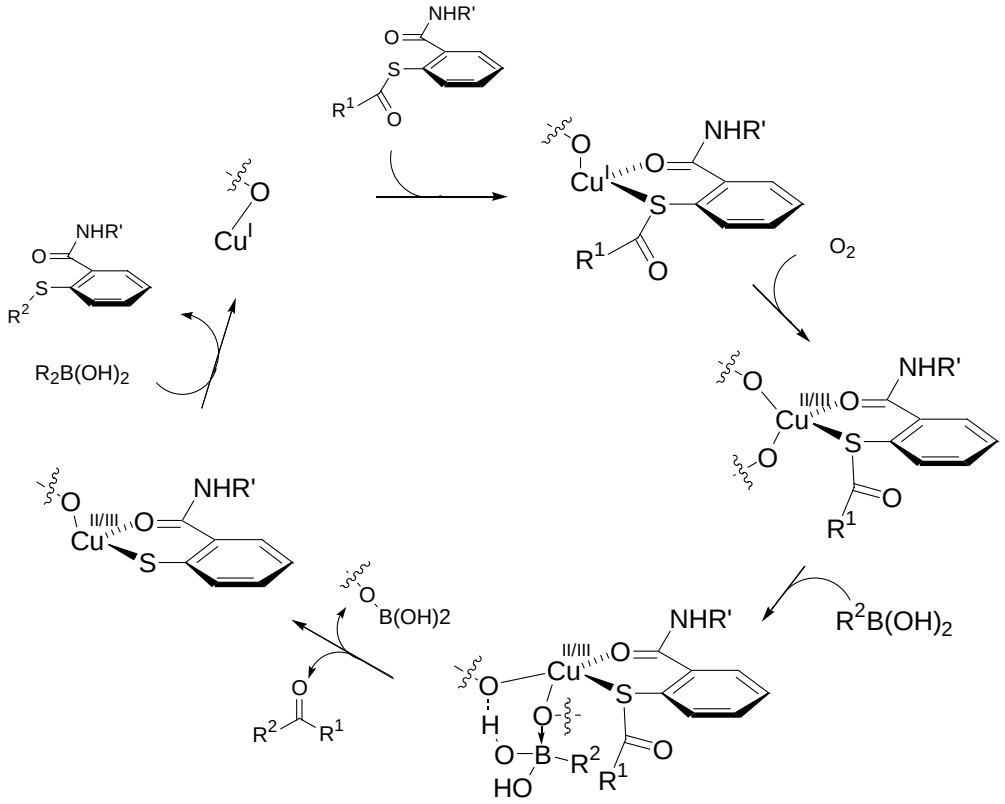
efficiently with aryl, heteroaryl and alkenyl boronic acids to give ketones with satisfactory yields (**Scheme 3.4**).[5]

Scheme 3.4 2nd Generation of Desulfitative Thiolester and Boronic Acid Cross Coupling



R^1	R^2	ketone yield	thiol ether yield
alkyl,aryl,alkenyl	aryl,heteroaryl,alkenyl	50%-97%	51%-92%

Figure 3.1 Mechanism



A proposed mechanism (**Figure 3.1**) suggests that this reaction is initialized by coordinative templating of *S*-acylthiosalicylamides and Cu^I-3-methylsalicylate to give

Cu-*S*-acylthiosalicylamides. This Cu^{I} species is oxidized under air to form a $Cu^{II/III}$-*S*-acylthiosalicylamides intermediate, which acts as an equivalent of a Lewis acid to activate the thiol carbonyl group by lowering the electron density on the sulfur atom. The oxidized $Cu^{II/III}$-*S*-acylthiosalicylamides can direct the boronic acid to approach the electrophilic thiol carbonyl center, which leads to the ketone formation. Finally, the resulting $Cu^{II/III}$ thiolate consumes a second equivalent of the boronic acid so that Cu^{I} is regenerated and turn into the next catalytic cycle.

This novel ketone synthesis can be described as Cu-catalyzed, pH-neutral, aerobic construction of a C-C bond. The condition to conduct this desulfitative cross coupling is so mild that this novel reaction is promising to provide significant value to address the challenging chemical transformation under biological environment. To unmask its potential application in C-terminal keto-transformation of peptide, we described herein the first application of this aerobic cross coupling in synthesis of high enantiopurity peptidyl ketone.

3.2 Results and Discussion

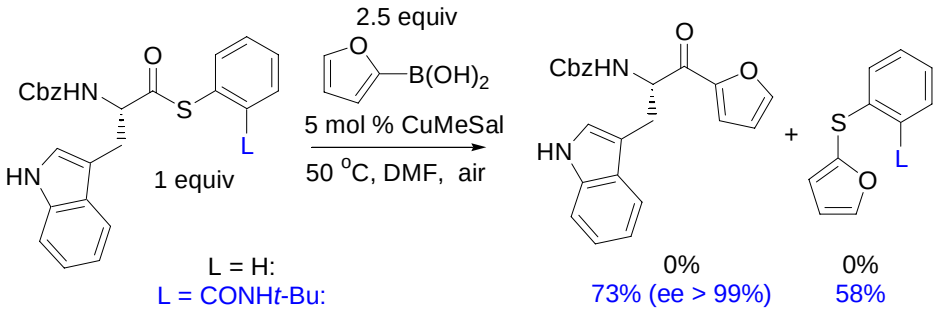
3.2.1 *S*-Pendant Structure and Reactivity Study

As disclosed in the mechanism paper of this "second generation" desulfitative cross coupling, [5] a coordinating moiety on the thiolate group of the thiol ester (*S*-pendant group) is a key factor to turn on this chemistry.

In order to validate the important *S*-pendant effect of the thiol ester that enables this Cu-catalyzed, aerobic, desulfitative coupling reaction, two control experiments were conducted. As shown in **Scheme 3.5**, N-Cbz-(L)-Trp-SPh was treated with 2.5 equiv of 2-

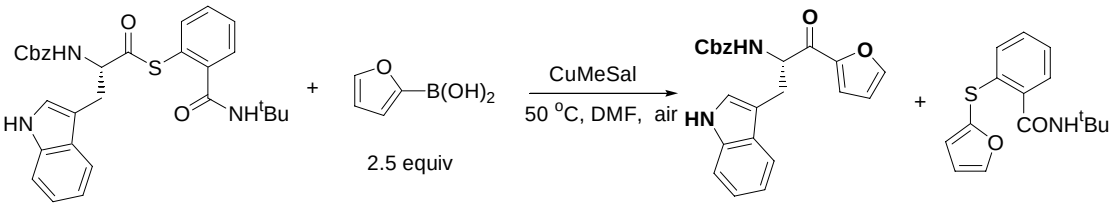
furyl boronic acid in the presence of 5 mol% Cu^{I}-3-methylsalicylate in DMF at 50 ^{o}C, open to air. No ketone and no thiol ether product were formed and thiol ester remained unreacted. However, under the same condition, N-Cbz-(L)-Trp-S-C_6H_4(*o*-CONH^{t}Bu) produced desired N-Cbz protected amino ketone and aryl thiol ether in 73% and 58% isolated yields respectively.

Scheme 3.5 Control Experiments



The control experiments observed in **Scheme 3.5** have clearly demonstrated this pendant group effect is crucial to a successful cross coupling reaction. In addition, further experiments in **Table 3.1** revealed that ketone yield was improved significantly to 87% when the loading of CuMeSal was increased from 5 mol% to 20 mol%.

Table 3.1 Cross Coupling and Catalyst Loading

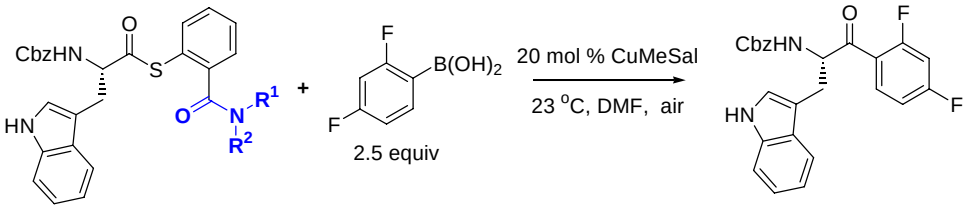


entry	CuMeSal	Ketone	Thio ether	Recovered SM
1	5 mol%	73%	58%	27%
2	10 mol%	82%	67%	15%
3	20 mol%	87%	72%	9%

a. isolated yield

A subsequent study was focused on the influence of various thiosalicyamides on the observed reaction rates and yields of peptidyl ketone formation. At room temperature, four N-Cbz-(L)-Trp-*S*-C_6H_4(*o*-$CONR^1R^2$) thiol esters coupled with 2,4-difluorophenyl-boronic acid in the presence of 20 mol% CuMeSal in DMF (**Table 3.2**).

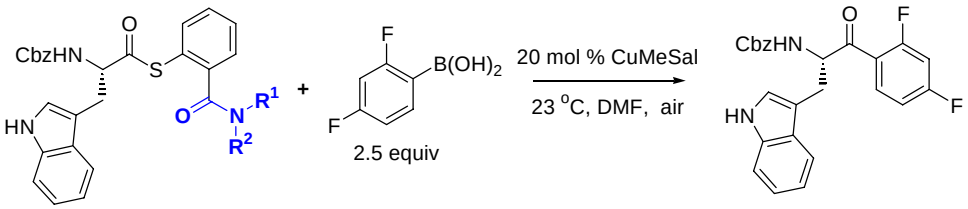
Table 3.2 Pendant Effect

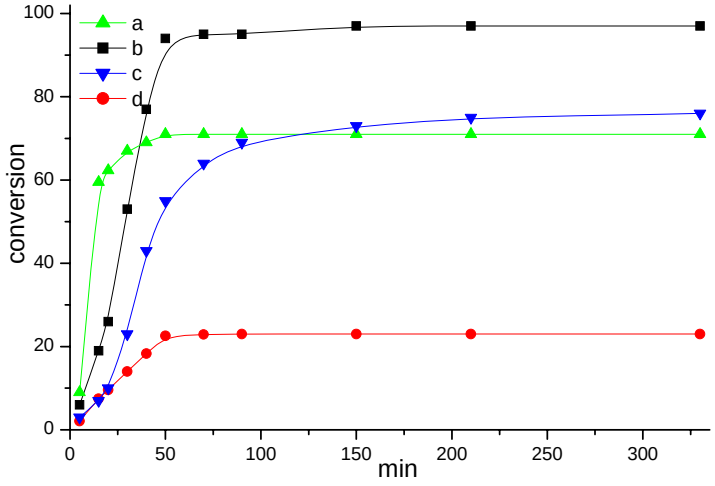


entry	$CONR^1R^2$	Ketone
1	$CONHCH_3$	71%
2	$CONH^iPr$	76%
3	$CONH^tBu$	97%
4	CON-morpholine	23%

Despite the fact that the N-morpholino 3° amide-derived thiol ester gave very low ketone yield, NHMe, NH^iPr and NH^tBu amide derived tryptophan thiol ester generated ketone in excellent yields.

Figure 3.2 Cross Coupling Study



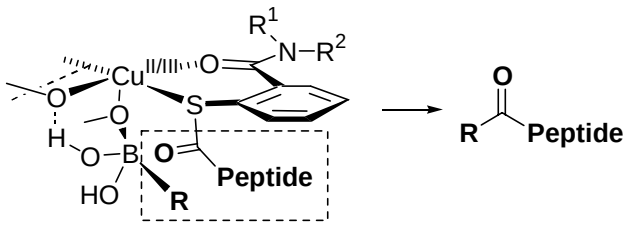


a. R^1 = H, R^2 = Me; b. R^1 = H, R^2 = *i*-Pr; c. R^1 = H, R^2 = *t*-Bu; d. R^1-R^2 = *N*-morpholinyl.

For a better understanding of the influence of the thiosalicylamides, these four experiments were carried out under the same conditions in the presence of decafluorobiphenyl as the internal standard, which was used to calculate ketone conversion rate by HPLC. A spotted reaction rate graph could be drawn in **Figure 3.2** from the data generated by HPLC sampling within 360 minutes of the reaction. All of the four thiol esters bearing amide pendants coupled rapidly with 2,4-difluorophenylboronic in about 6 hours. In fact, they reached reaction end point within the first three hours. The N-morpholino 3^o amide-derived thiol ester gave the slowest initial reaction rate and thiol esters with -NH^{t}Bu, -NH^{i}Pr and –NHMe pendant displayed a rapid conversion rate in the first hour. These observed initial rates are consistent with the putative mechanism of this Cu(I) catalyzed aerobic desulfitative cross coupling (**Figure 3.3**). Based on the proposed structure of reaction intermediate, the initial rates were determined by the non-bonded

steric effect of $CONHR^1R^2$, so that the –NHMe derived thiol ester started with the highest reaction rate.

Figure 3.3 Mechanism

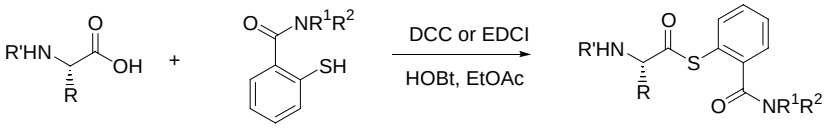


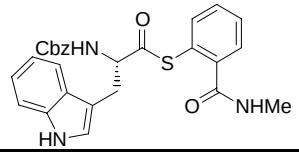
Although the difference of the final yield of the four reactions is still not completely understood, the best performing substrate was the sterically more hindered NH^iPr amide which gave the highest yield with in 90 minutes.

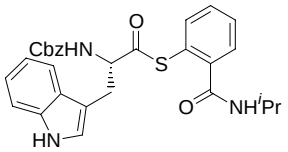
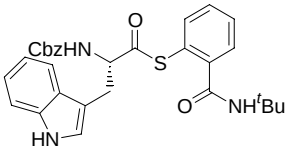
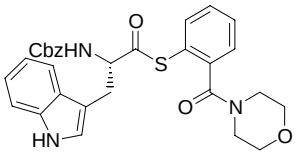
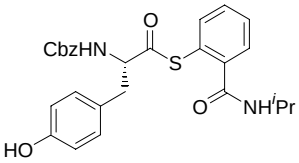
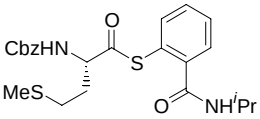
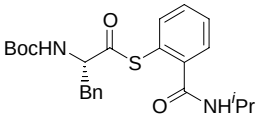
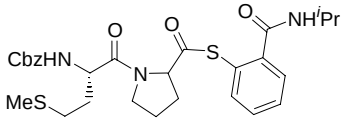
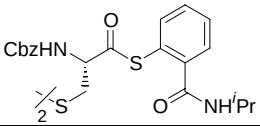
3.2.2 Synthesis of N-Cbz Protected Peptidyl *S*-Acylthiosalicylamide

In order to test this NH^iPr amide system for a general synthesis of peptidyl ketones, various N-protected peptidyl *S*-acylthiosalicylamides were synthesized. Either DCC or EDCI could be used to synthesize these peptidyl thiol esters without associated racemization problem (**Table 3.3**).

Table 3.3 Synthesis of peptidyl *S*-acylthiosalicylamides



entry	thiol ester	yield(%)	e.e. (%)
1[a]		45	NR

2[a]		83	>99
3[a]		95	>99
4[a]		68	NR
5[a]		56	>99
6[a]		86	NR
7[a]		75	>99
8[b]		31	NR
9[b]		34	NR

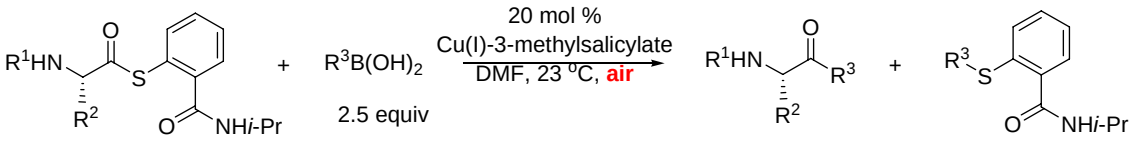
[a.] DCC was used; [b.] EDCI was used

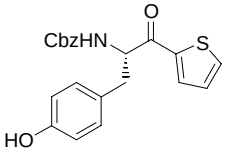
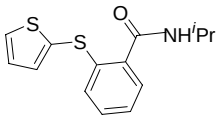
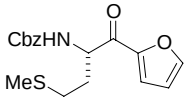
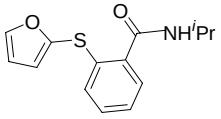
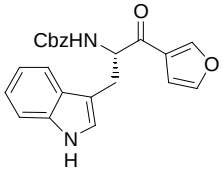
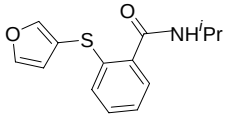
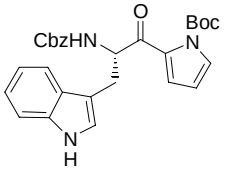
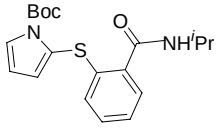
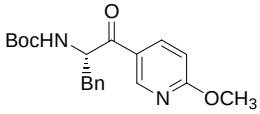
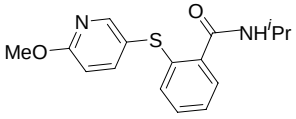
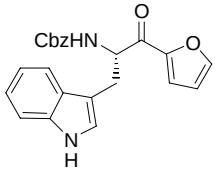
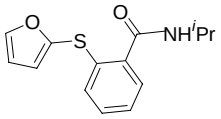
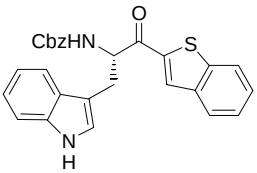
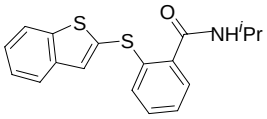
3.2.3 Examples and Scope of Cross Coupling

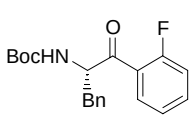
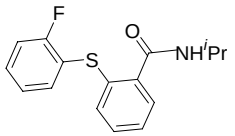
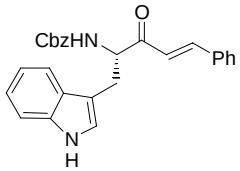
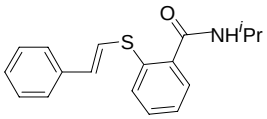
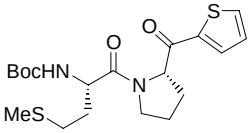
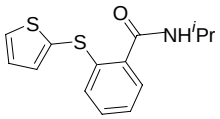
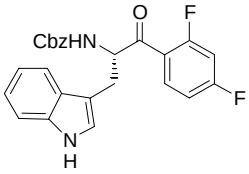
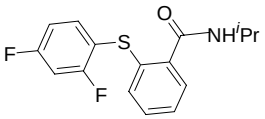
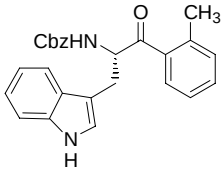
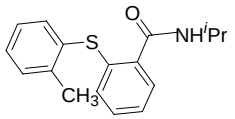
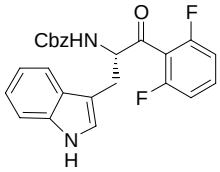
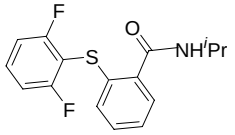
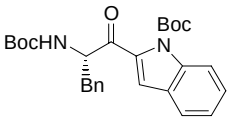
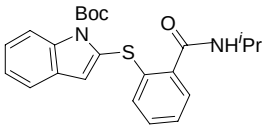
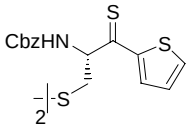
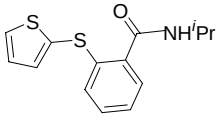
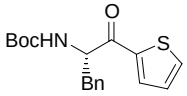
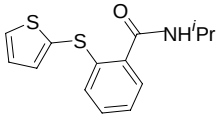
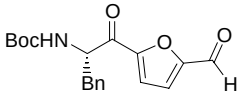
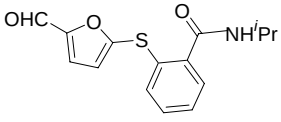
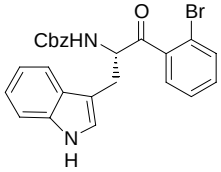
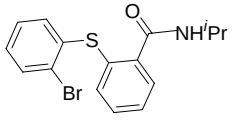
The scope and examples of this room temperature, Cu-catalyzed, aerobic, desulfitative cross coupling for the construction of peptidyl ketones are itemized in **Table 3.4**. A wide range of aryl (electron-rich, electon-deficient), heteroary (furyl, thienyl, benzothienyl, pyridinyl) and alkenyl boronic acids coupled efficiently with amino acid and a dipeptide derived thiol esters. Even sterically hindered boronic acids such as 2-tolyl boronic acid and 2-N-Boc-pyrolyl boronic acid generated ketones in satisfactory yields. Under the

same condition, *n*-butyl boronic acid was treated with N-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH^{i}Pr) giving no products. The most important value of this desulfitative cross coupling is that, the stereo profile of thiol ester was completely inherited by the resulting peptidyl ketone without detected any racemization or epimerization.

Table 3.4 Peptidyl Ketones[a,b,c,d]



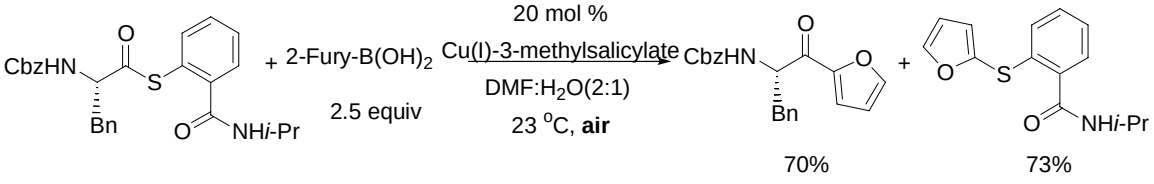
entry	ketone	yield (%)	e.e. (%)	thiol ether	yield (%)
1		71	>99		65%
2		67	NR		70%
3		99	>99		86
4		87	>99		81
5		97	NR		70
6		96	>99		73
7		99	NR		99

8		94	>99		70
9		60	>99		52
10		60	NR		53
11		97	>99		99
12		78	>99		59
13		92	>99		82
14		78	>99		83
15		64	NR		64
16		89	>99		73
17		60	>99		88
18		77	>99		90

[a] Isolated yields. [b] Conditions: 1.0 equiv peptidyl thiol ester, 2.5 equiv boronic acid and 20 mol % Cu^{I}-3-methylsalicylate in DMF open to air at room temperature for 0.5 h - 24 h. [c] ee was determined by reverse phase HPLC chiral OD, AD, AS and OJ column using racemic mixtures. In some cases the racemates were not resolved by HPLC and the ee's were not determined.

Although this reaction was carried out under aerobic conditions, these substrates bearing metal binding and oxidation sensitive functional groups such as methionine (thioether), cystine (disulfide), tryptophan (indole) and tyrosine (phenol) thiol ester coupled efficiently with boronic acids without any oxidized byproduct or poisoning of the Cu-catalyst. According to the observations above, this desulfitative coupling reaction displayed the potential to tolerate polar and protic functional groups in an aqueous medium which represents a typical biochemical environment. Is this reaction still effective under an aqueous media? To test this assumption, using DMF/H_2O as solvent, from a reaction of N-Cbz-L-Phe-*S*-C6H4(O-CONH^{i}Pr) and thiophene-2-boronic acid under standard condition was produced 70% ketone as well as 73% thiol ether co-product (**Scheme 3.6**).

Scheme 3.6 Cross Coupling in Aqueous Solvent

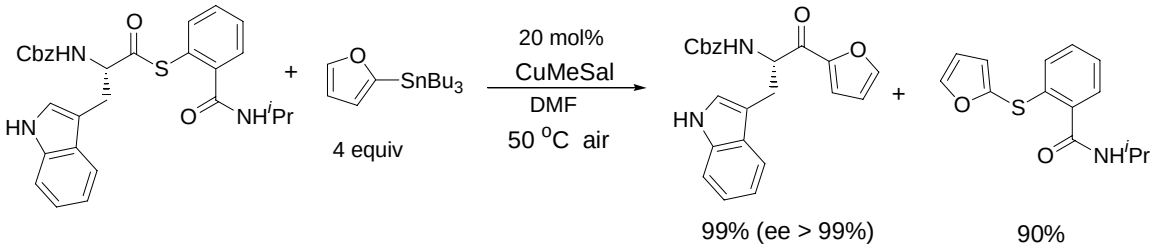


Further investigation reveals that the coupling reaction was unperturbed by the addition of stoichiometric quantities of a primary amine (benzylamine), a secondary amine (diisopropylamine) and a tertiary amine (triethylamine). The addition of a stoichiometric quantity of benzoic acid or of glucose did not suppress the formation of peptidyl ketone. However, the presence of salts like ammonium chloride and ammonium phosphate did inhibit the desired cross coupling reaction, possibly by the strong ionic interaction with CuMeSal so that catalytic cycle was blocked.

In addition to the boronic acid, an organostannane was reactive with peptidyl *S*-

acylthiosalicylamides. Thiol ester NCbz-Trp-*S*-C_6H_4(*o*-CONHiPr) was treated with 4 equiv of 2-furyl tributyltin in the presence of 20 mol% CuMeSal at 50 ^oC in DMF, open to air, resulting a quantitative isolation of the ketone product. Again, no racemization occurred from the reaction (**Scheme 3.7**).

Scheme 3.7 Cross Coupling with Organostannane



3.3 Conclusion

A mild, Cu-catalyzed, aerobic, room temperature synthesis of peptidyl ketone was successfully developed. Various peptidyl *S*-acylthiosalicylamide coupled efficiently with aryl, hetero aryl, alkenyl boronic acids to generate desired ketone with good to excellent yields. Importantly, neither racemization nor epimerization was detected throughout the reaction process.

3.4 Experiment Section

General Methods. ^1H and ^{13}C NMR spectra were recorded on Varian Inova 600 MHz and 400 MHz spectrometers or a Mercury 300 MHz spectrometer in deuteriochloroform ($CDCl_3$) with the solvent residual peak as internal reference unless otherwise stated ($CDCl_3$: ^1H = 7.26 ppm, ^{13}C = 77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (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.

Analytical thin-layer chromatography (TLC) was performed using 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 reactions and chromatography were reagent grade and used as received. Flash column chromatography was performed by the method of Still[6] with 32-63 μm silica gel 60 (Woelm). HPLC analyses were carried out using an Agilent 1100 system with a quaternary pump. Separations were achieved on a Zorbax Eclipse XDB C8 4.6 x 150 mm column or DAICEL chiral AD, AS, OD and OJ reversed phase column. Solvents used as reaction media were purchased in > 99% purity without further purification. All reactions requiring an inert atmosphere 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 and $NaHCO_3$ refer to saturated aqueous solutions.

Starting Materials. All protected amino acids and solvents were purchased from Sigma-Aldrich. Also purchased from Sigma-Aldrich were *N*,*N*′-dicyclohexylcarbodiimide (DCC), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), triethylamine, and magnesium sulfate. 1-Hydroxybenzotriazole (HOBt) was purchased from Acros. All boronic acids and Cu^{I}-3-methylsalicylate (CuMeSal) were provided by Dr. Gary Allred of Synthonix. *N*-Methyl-2-mercaptobenzamide, *N*-isopropyl-2-mercaptobenzamide, *N*-*tert*-butyl-2-mercaptobenz- amide, and *N*-morpholine-2-mercaptobenzamide were prepared from the corresponding disulfides by reduction with sodium borohydride in ethanol following previously published procedures.[5,7]

General Procedures.

Procedure A (Synthesis of* N-*Protected α-Amino Thiol Ester)

To a solution of the *N*-protected amino acid (1.0 equiv), *N*-isopropyl-2-mercaptobenzamide (1.0 equiv), and HOBt (1.5 equiv) in ethyl acetate (0.1 M based on amino acid) was added DCC (1.0 equiv, 0.5 M in ethyl acetate solution) dropwise at 0 ºC. After addition of DCC, the ice bath was removed and the reaction was stirred at room temperature overnight. The reaction mixture was then washed with 1M HCl, aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude was further purified by flash chromatography on silica gel to afford the thiol ester.

Procedure B (Synthesis of* N-*Protected Peptidyl Ketone)

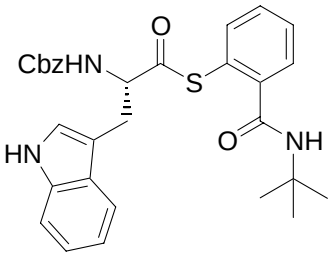
To a mixture of the *N*-protected amino acid thiol ester (1.0 equiv), boronic acid (2.5 or 5.0 equiv), and CuMeSal (20 mol %) was added DMF (0.1 M based on thiol ester) under air at room temperature. The reaction mixture was stirred for 30 minutes to 6 hours. The reaction mixture was concentrated under vacuum to remove most of the DMF. The crude concentrate was then diluted with 10 volumes of ether. The ether solution was washed with water and the aqueous solution was twice back extracted with same volume of ether. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was further purified by flash chromatography on silica gel to afford the pure ketone product.

Procedure C (Synthesis of Cystine and Dipeptidyl Thiol Ester)

To a mixture of the peptidyl acid (1.0 equiv) and *N*-isopropyl-2-mercaptobenzamide (1.0 equiv) was added ethyl acetate (0.1 M based on peptidyl acid). The solution was stirred at room temperature for 10 minutes. EDCI (1.0 equiv) in dichloromethane (same volume as the ethyl acetate) was slowly added into the reaction solution. The reaction mixture was stirred for another 4 hours then was then washed with 1M HCl, $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude was further purified by flash chromatography on silica gel to afford the thiol ester.

Experimental Procedure for Scheme 1.

(-)-*N*-Carbobenzyloxy-L-tryptophan-*S*-(2-*tert*-butylcarbamoyl-phenyl) thiol ester, 3.1

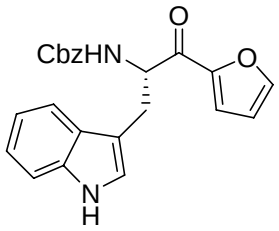


Following general procedure **A**, from *N*-Cbz-L-Trp-OH (0.3 mmol, 101 mg), *N-tert*-butyl-2-mercaptobenzamide (0.3 mmol, 63 mg), HOBt (0.45 mmol, 61 mg) and DCC (0.3 mmol, 62 mg) was obtained 152 mg of the pure thiol ester after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Yield 95%, white Solid, Mp = 151-152 ºC. TLC (silica gel, R_f = 0.50, hexanes : EtOAc = 1 : 1). HPLC Chiral AS-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 7.4 min, D-isomer t_R = 6.4 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.53-7.48 (m, 2H), 7.42-7.38 (m, 1H), 7.33-7.26 (m, 7H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.94-6.92 (m, 2H), 5.93 (s, 1H), 5.54 (d, *J* = 8.4 Hz, 1H), 5.13-5.05 (m, 2H), 4.86-4.80 (m, 1H), 3.38-3.25 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 168.0, 155.9, 143.5, 136.8, 136.5, 136.2, 130.5, 130.2, 128.8, 128.5, 128.3, 127.5, 123.8, 123.7, 122.3, 119.9, 118.8, 111.7, 108.8, 67.4, 61.4, 52.3, 28.8, 28.5. IR (neat, cm^{-1}) 3316 (br), 1702 (s), 1652 (m), 1521 (s), 1231 (m), 745 (m). HRMS (FAB) Calcd for $C_{30}H_{32}N_3O_4S$ ($[M+H]^+$): 530.2108. Found: 530.2189. $[\alpha]_D^{20}$ -18.6 (*c* 1.02, $CHCl_3$).

To a mixture of *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*t*-Bu) (0.05 mmol, 26 mg), 2-furylboronic acid (0.125 mmol, 14 mg) and CuMeSal (0.01 mmol, 2 mg) was added DMF (0.5 mL)

under air at room temperature. The reaction mixture was stirred for 16 hours at 50 ^{o}C. The reaction solution was concentrated under vacuum to remove most of the DMF. The crude material was then diluted with 10 volumes of ether. The ether solution was washed with water and the aqueous solution was twice back extracted with same volume of ether. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude material was further purified by flash chromatography on silica gel with 1 : 1 hexanes : EtOAc to afford the pure ketone product (14 mg, 73%) and S-Ar product (8 mg, 58%).

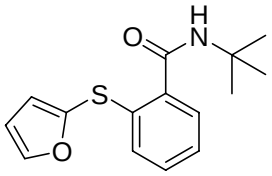
(+)-(*S*)-2-(Carbobenzyloxyamino)-1-(furan-2-yl)-3-(1*H*-indol-3-yl) propan-1-one, 3.2



Ketone yield 73%, pale yellow oil. TLC (silica gel, R_f = 0.55, 1 : 1 hexanes : EtOAc). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50% H_2O in CH_3CN for 50 min, L-isomer t_R = 20.7 min, D-isomer t_R = 22.8 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.59 (d, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.37-7.29 (m, 6H), 7.18-7.15 (m, 2H), 7.09-7.05 (m, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.49 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.70 (d, *J* = 8.0 Hz, 1H), 5.47-5.42 (m, 1H), 5.11 (AB q, *J* = 12.0 Hz, 2H), 3.44 (dd, *J* = 6.0, 14.4 Hz, 1H), 3.29 (dd, *J* = 6.0, 14.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 155.9, 151.1, 147.4, 136.4, 136.2, 128.6, 128.3, 128.2, 127.7, 123.1, 122.2, 119.7, 119.2, 118.6, 112.7, 111.3, 109.8, 67.0, 56.6, 28.9. IR

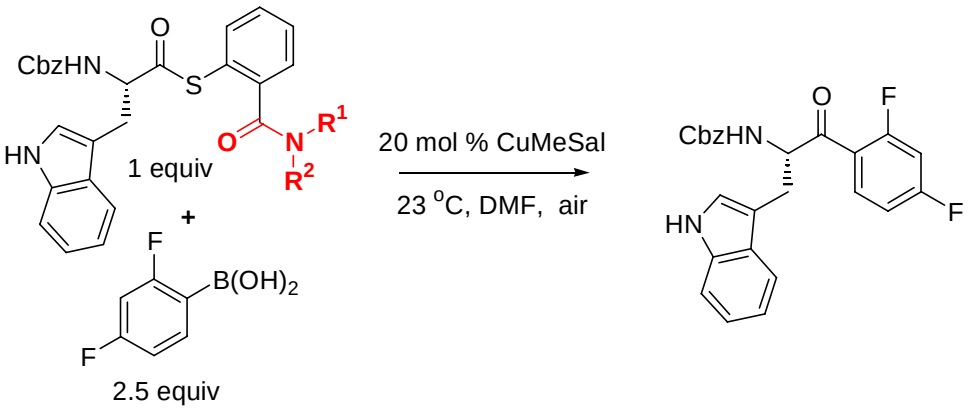
(neat, cm^{-1}) 3408 (m), 3347 (s), 3061 (w), 2953 (w), 1702 (s), 1671 (s), 1505 (s), 1463 (s), 1231 (s), 1158 (m), 1061 (m), 841 (m), 698 (m). HRMS (FAB) Calcd for $C_{23}H_{21}N_2O_4$ ($[M+H]^+$): 389.1495. Found: 389.1490. $[\alpha]_D^{20}$ +79.8 (*c* 1.00, $CHCl_3$) (Lit.[1] $[\alpha]_D^{20}$ +79.6 (*c* 1.08, $CHCl_3$).

N-tert-Butyl-2-(furan-2-ylthio)benzamide, 3.3



Yellow solid. Mp = 76-78 °C (lit.[2] 78 °C). TLC (silica gel, R_f = 0.22, hexanes : EtOAc = 10 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.45 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.24 (ddd, *J* = 7.4, 7.4, 1.5 Hz, 1H), 7.16 (ddd, *J* = 7.8, 7.8, 1.5 Hz, 1H), 6.86 (dd, *J* = 7.8, 0.8 Hz, 1H), 6.80 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.50 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.92 (br s, 1H), 1.51 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 146.9, 143.1, 136.1, 135.6, 130.7, 128.5, 127.8, 126.1, 120.5, 112.2, 52.3, 29.0. IR (neat, cm^{-1}): 3298 (m), 2972 (m), 1634 (s), 1531 (s). HRMS (ESI) Calcd for $C_{15}H_{18}NO_2S$ ($[M+H]^+$): 276.1056. Found: 276.1051.

Experimental for Figure 1.



Entry	R^1, R^2	Ketone yield
a	H, Me	71%
b	H, *i*Pr	97%
c	H, *t*Bu	76%
d	*N*-morpholino	23%

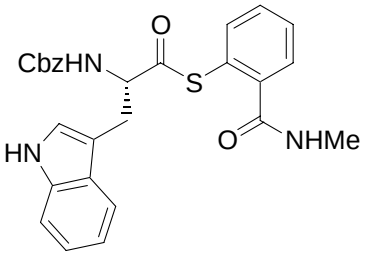
Conditions:

To a mixture of the thiol ester (0.05 mmol), 1,4-difluorophenylboronic acid (0.125 mmol, 20 mg), CuMeSal (0.01 mmol, 2 mg) and decafluorobiphenyl (30 mg) was added DMF (0.5 mL) under air at room temperature. The reaction mixture was stirred for 360 minutes. Using the above reaction conditions, two identical reactions were carried out for each entry (total of 8 reactions). One reaction was analyzed and recorded by HPLC with time. The other reaction was used to isolate the peptidyl ketone product at a reaction time of 360 minutes.

The preparation of the thiol ester used in entry c has been described in Scheme 1 above.

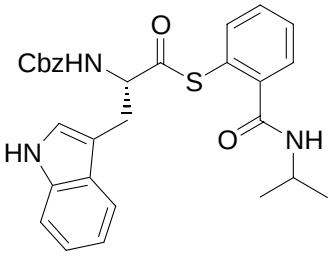
The preparations of other thiol esters used in Figure 1 are described here.

Entry a: (-)-*N*-Carbobenzyloxy-L-tryptophan-*S*-(2-methylcarbamoyl-phenyl) thiol ester, 3.4



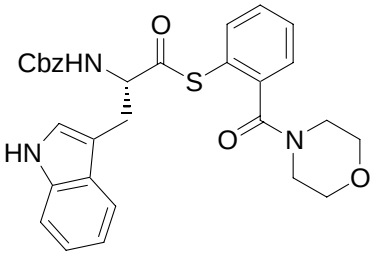
Following general procedure **A**, from *N*-Cbz-L-Trp-OH (1.0 mmol, 338 mg), *N*-methyl-2-mercaptobenzamide (1.0 mmol, 166 mg), HOBt (1.5 mmol, 204 mg), and DCC (1.0 mmol, 206 mg) was obtained 219 mg of the pure thiol ester after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Yield 45%, colorless oil. TLC (silica gel, R_f = 0.4, hexanes : EtOAc = 1 : 2). ^{1}H NMR (400 MHz, $CDCl_3$) shows 2 rotamers (8:2) δ 8.50 (s, 1H), 7.58-7.51 (m, 2H), 7.46-7.26 (m, 8H), 7.20-7.17 (m, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.00 (s, 1H), 5.99 (d, *J* = 4.8 Hz, 1H), 5.45 (d, *J* = 7.6 Hz, 1H), 5.13-5.06 (m, 2H), 4.80 (dd, *J* = 13.2, 6.0 Hz, 1H), 3.37-3.26 (m, 2H), 2.79 (d, *J* = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 169.0, 156.1, 142.1, 136.9, 136.4, 130.5, 130.4, 128.9, 128.8, 128.5, 128.3, 127.5, 123.7, 122.6, 120.0, 118.8, 111.7, 109.1, 124.2, 67.5, 61.4, 31.8, 28.1. IR (neat, cm^{-1}) 2922 (m), 1710 (s), 1251 (m), 1652 (m), 1529 (m). HRMS (FAB) Calcd for $C_{27}H_{26}N_3O_4S$ ($[M+H]^+$): 488.1638. Found: 488.1635. $[\alpha]_D^{20}$ -28.2 (*c* 1.05, $CHCl_3$).

Entry b: (-)-*N*-Carbobenzyloxy-L-tryptophan-*S*-(2-isopropylcarbamoyl-phenyl) thiol ester, 3.5



Following general procedure **A**, from *N*-Cbz-L-Trp-OH (1.0 mmol, 338 mg), *N*-isopropyl-2-mercaptobenzamide (1.0 mmol, 195 mg), HOBt (1.5 204 mg), and DCC (1.0 mmol, 206 mg) was obtained 428 mg of the pure thiol ester after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Yield 83%, white solid, Mp = 168-169 ºC. TLC (silica gel, R_f = 0.25, hexanes : EtOAc = 1 : 1). HPLC Chiral AD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R =9.3 min, D-isomer t_R =10.0 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.56-7.00 (m, 14H), 5.86 (d, *J* = 8.0 Hz, 1H), 5.38 (d, *J* = 8.8 Hz, 1H), 5.08 (s, 2H), 4.85-4.80 (m, 1H), 4.21-4.13 (m, 1H), 3.38-3.26 (m, 2H), 1.15 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 167.6, 155.9, 142.6, 136.8, 136.4, 136.2, 130.4, 128.7, 128.6, 128.5, 128.3, 127.5, 124.1, 123.6, 122.6, 120.1, 118.9, 111.6, 109.2, 67.5, 61.3, 42.3, 28.4, 22.7, 22.6. IR (neat, cm^{-1}) 3296 (br), 1702 (s), 1604 (m), 1529 (s), 1257 (m), 756 (m). HRMS (FAB) Calcd for $C_{29}H_{30}N_3O_4S$ ($[M+H]^+$): 516.1951. Found: 516.1949. $[\alpha]_D^{20}$ -19.0 (*c* 1.02, $CHCl_3$).

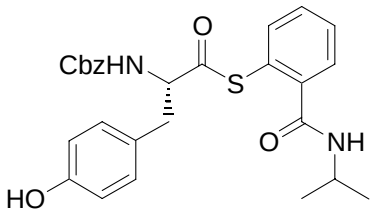
Entry d: (-)-*N*-Carbobenzyloxy-L-tryptophan-*S*-(2-*N*-morpholinocarbamoyl-phenyl) thiol ester, 3.6



Following general procedure **A**, from *N*-Cbz-L-Trp-OH (1.0 mmol, 338 mg), *N*-morpholine-2-mercaptobenzamide (1.0 mmol, 223 mg), HOBt (1.5 mmol, 204 mg), and DCC (1.0 mmol, 206 mg) was obtained 370 mg of the pure thiol ester after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Yield 68%, white solid, Mp = 105-106 ºC. TLC (silica gel, R_f = 0.20, hexanes : EtOAc = 1 : 2). ^{1}H NMR (400 MHz, $CDCl_3$) shows 2 rotamers (3:2) δ 8.55 (s, 0.6H), 8.42 (s, 0.4H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.47-7.26 (m, 9.5H), 7.21-7.00 (m, 3.5H), 5.50 (d, *J* = 8.0 Hz, 0.6H), 5.41 (d, *J* = 8.0 Hz, 0.4H), 5.16-5.05 (m, 2H), 4.85-4.75 (m, 1H), 3.76-3.66 (m, 4H), 3.52-3.47 (m, 2H), 3.41-3.09 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) shows 2 rotamers δ 200.6, 168.0, 156.1, 141.3, 137.2, 136.2, 130.3, 129.9, 128.8, 128.7, 128.4, 128.3, 128.2, 127.5, 127.2, 127.0, 124.7, 123.1, 122.5, 120.0, 118.8, 111.6, 109.2, 108.9, 67.4, 66.8, 61.5, 47.6, 42.1. IR (neat, cm^{-1}) 2922 (m), 1710 (s), 1621 (m), 1254 (m). HRMS (FAB) Calcd for $C_{30}H_{30}N_3O_5S$ ($[M+H]^+$): 544.1909. Found: 544.1897. $[\alpha]_D^{20}$ -53.7 (*c* 1.01, $CHCl_3$).

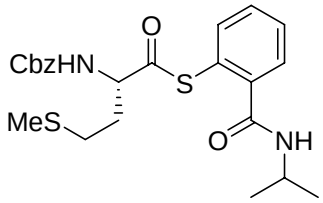
Thiol Esters used in Table 1.

(-)-*N*-Carbobenzyloxy-L-tyrosine-*S*-(2-isopropylcarbamoyl-phenyl) thiol ester, 3.7



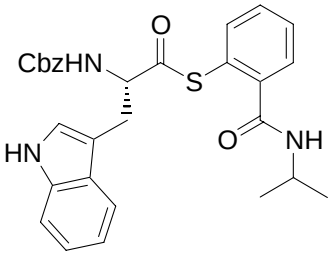
Following general procedure **A**, from *N*-Cbz-L-Tyr-OH (1.0 mmol, 315 mg), *N*-isopropyl-2-mercaptobenzamide (1.0 mmol, 195 mg), HOBt (1.5 mmol, 204 mg), and DCC (1.0 mmol, 206 mg) was obtained 280 mg of the pure thiol ester after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Yield 56%, white solid, Mp = 109-110 ºC. TLC (silica gel, R_f = 0.3, hexanes : EtOAc = 1 : 1). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R =6.4 min, D-isomer t_R =7.5 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) shows 2 rotamers (8:2) δ 7.54-7.26 (m, 9H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.00 (d, *J* = 8.0 Hz, 1H), 5.47 (d, *J* = 8.4 Hz, 1H), 5.08 (s, 2H), 4.73-4.68 (m, 1H), 4.21-4.11 (m, 1H), 3.09-2.93 (m, 2H), 1.18 (dd, *J* = 6.4, 3.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 168.0, 156.0, 155.8, 142.1, 136.8, 136.1, 130.6, 130.5, 128.8, 128.6, 128.5, 128.2, 126.5, 124.2, 116.0, 67.5, 62.0, 42.5, 37.6, 22.6 IR (neat, cm^{-1}) 3308 (br), 2922 (m), 1702 (s), 1637 (m), 1517 (s), 1251 (m). HRMS (FAB) Calcd for $C_{27}H_{29}N_2O_5S$ ($[M+H]^+$): 493.1791. Found: 493.1786. $[\alpha]_D^{20}$ -47.0 (*c* 1.01, $CHCl_3$).

(-)-*N*-Carbobenzyloxy-L-methionine-*S*-(2-isopropylcarbamoyl-phenyl) thiol ester, 3.8



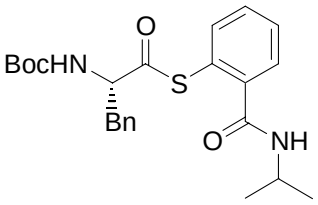
Following general procedure **A**, from *N*-Cbz-L-Met-OH (1.0 mmol, 280 mg), *N*-isopropyl-2-mercaptobenzamide (1.0 mmol, 195 mg), HOBt (1.5 mmol, 204 mg), and DCC (1.0 mmol, 206 mg) was obtained 395 mg of the pure thiol ester after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Yield 86%, white solid, Mp = 149-150 ºC. TLC (silica gel, R_f = 0.7, hexanes : EtOAc = 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.29 (m, 9H), 5.82 (d, *J* = 8.0 Hz, 1H), 5.63 (d, *J* = 8.4 Hz, 1H), 5.14 (s, 2H), 4.71-4.65 (m, 1H), 4.22-4.13 (m, 1H), 2.65-2.51 (m, 2H), 2.27-2.18 (m, 1H), 2.08 (s, 3H), 2.01-1.92 (m, 1H), 1.18 (dd, *J* = 6.0, 4.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 167.4, 155.9, 142.5, 136.8, 136.1, 130.5, 128.8, 128.5, 128.3, 124.1, 67.6, 60.4, 42.2, 32.0, 30.2, 22.7, 15.6. IR (neat, cm^{-1}) 2922 (m), 1702 (s), 1640 (m), 1529 (s), 1251 (m). HRMS (FAB) Calcd for $C_{23}H_{29}N_2O_4S_2$ ($[M+H]^+$): 461.1563. Found: 461.1558. $[\alpha]_D^{20}$ -42.5 (*c* 1.12, $CHCl_3$).

(-)-*N*-Carbobenzyloxy-L-tryptophan-*S*-(2-isopropylcarbamoyl-phenyl) thiol ester, 3.9



The preparation of this thiol ester was described in the experimental for **Figure 1** above.

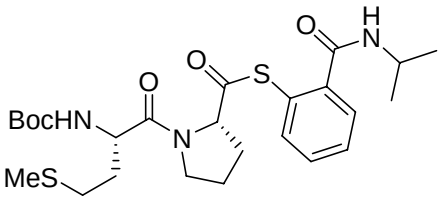
(-)-*N*-*tert*-Butoxycarbonyl-L-phenylalanine-*S*-(2-isopropylcarbamoyl-phenyl) thiol ester, 3.10



Following general procedure **A**, from *N*-Boc-L-Phe-OH (5.0 mmol, 1325 mg), *N*-isopropyl-2-mercaptobenzamide (5.0 mmol, 975 mg), HOBt (7.5 mmol, 1020 mg), and DCC (5.0 mmol, 1030 mg) was obtained 1657 mg of the pure thiol ester after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Yield 75%, white solid, Mp = 147-148 ºC. TLC (silica gel, R_f = 0.55, hexanes : EtOAc = 1 : 1). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R =7.1 min, D-isomer t_R =7.8 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 1H), 7.49-7.40 (m, 2H), 7.34-7.25 (m, 4H), 7.19-7.17 (m, 2H), 5.87 (d, *J* = 8.0 Hz, 1H), 4.97 (d, *J* = 8.8 Hz, 1H), 4.78-4.69 (m, 1H), 4.24-4.15 (m, 1H), 3.19 (dd, *J* =

14.4, 5.2 Hz, 1H), 3.04 (dd, *J* = 14.4, 5.2 Hz, 1H), 1.40 (s, 9H), 1.20 (dd, *J* = 6.4, 4.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 167.4, 161.8, 155.0, 142.7, 136.7, 135.7, 130.4, 129.5, 128.9, 128.7, 127.4, 124.3, 80.8, 61.3, 42.2, 38.5, 28.4, 22.8, 22.7. IR (neat, cm^{-1}) 3289 (br), 2976 (m), 1702 (s), 1644 (m), 1521 (s), 1170 (s), 756 (m). HRMS (FAB) Calcd for $C_{24}H_{31}N_2O_4S$ ($[M+H]^+$): 443.1999. Found: 443.1998. $[\alpha]_D^{20}$ -27.2 (*c* 1.03, $CHCl_3$).

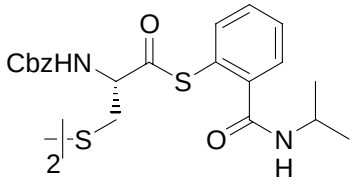
(-)-*N*-*tert*-Butoxycarbonyl-L-methionine-L-proline-*S*-(2-isopropylcarbamoyl-phenyl) thiol ester, 3.11



Following general procedure **C**, from *N*-Boc- L-Met-L-Pro-OH[8] (0.3 mmol, 105 mg), *N*-isopropyl-2-mercaptobenzamide (0.3 mmol, 60 mg), and EDCI (0.3 mmol, 60 mg) was obtained 48 mg of the pure thiol ester after flash chromatography on silica gel with 4 : 1 CH_2Cl_2 : EtOAc. Yield 31%, colorless oil. TLC (silica gel, R_f = 0.20, EtOAc : CH_2Cl_2 = 1 : 4). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53-7.50 (m, 1H), 7.45-7.26 (m, 3H), 5.93 (d, *J* = 5.7 Hz, 1H), 5.27 (d, *J* = 8.4 Hz, 1H), 4.78 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.69-4.64 (m, 1H), 4.23-4.14 (m, 1H), 3.85-3.78 (m, 2H), 2.65-2.56 (m, 2H), 2.26-2.03 (m, 8H), 1.93-1.82 (m, 1H), 1.42 (s, 9H), 1.23 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 171.7, 167.5, 155.7, 142.5, 137.0, 130.4, 128.7, 124.0, 80.1, 65.9, 51.0, 47.5, 42.3, 32.5, 30.3, 30.0, 28.5, 28.3, 24.9, 22.7, 22.7, 15.9. IR (neat, cm^{-1}) 2926 (s), 1459 (m), 1266 (s),

760 (m). HRMS (FAB) Calcd for $C_{25}H_{38}N_3O_5S_2$ ($[M+H]^+$): 524.2247. Found: 524.2251. $[\alpha]_D^{20}$ -95.1 (*c* 1.31, $CHCl_3$).

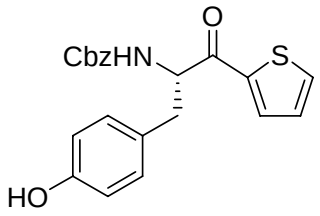
(-)-*N*-Carbobenzyloxy-L-cystine-*S*-(2-isopropylcarbamoyl-phenyl) bis thiol ester, 3.12



Following general procedure **C**, from (Z-L-Cys-OH)$_2$ (0.2 mmol, 100 mg), *N*-isopropyl-2-mercaptobenzamide (0.4 mmol, 80 mg), and EDCI (0.4 mmol, 80 mg) was obtained 60 mg of the pure thiol ester after flash chromatography on silica gel with 2 : 1 CH_2Cl_2 : EtOAc. Yield 34%, colorless oil. TLC (silica gel, R_f = 0.40, EtOAc : CH_2Cl_2 = 1 : 2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.29 (m, 18H), 5.98 (d, *J* = 8.4 Hz, 2H), 5.82 (d, *J* = 7.5 Hz, 2H), 5.18-5.09 (m, 4H), 4.81-4.74 (m, 2H), 4.12-4.10 (m, 2H), 3.17-3.15 (m, 4H), 1.20-1.15 (m, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 167.3, 156.0, 142.3, 136.8, 136.1, 130.5, 128.8, 128.5, 128.4, 124.0, 67.8, 60.5, 42.3, 40.9, 22.8. IR (neat, cm^{-1}) 3293 (br), 1702 (s), 1529 (s), 1258 (m), 752 (m). HRMS (FAB) Calcd for $C_{42}H_{47}N_4O_8S_4$ ($[M+H]^+$): 863.2271. Found: 863.2251. $[\alpha]_D^{20}$ -6.0 (*c* 0.61, $CHCl_3$)..

Ketones in Table 1.

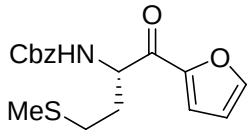
(+)-(*S*)-2-(Carbobenzyloxyamino)-3-(4-hydroxyphenyl)-1-(thiophen-2-yl) propan-1-one, 3.13



Following general procedure **B**, from *N*-Cbz-L-Tyr-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.1 mmol, 49 mg), thiophene-2-boronic acid (0.25 mmol, 32 mg), and CuMeSal (0.02 mmol, 4 mg) in 1 mL DMF after 6 hours was obtained 27 mg of the pure ketone and 18 mg of the S-Ar product after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Ketone yield 71%, colorless oil. TLC (R*f* = 0.54, hexanes : EtOAc = 1:1). 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), 5.10 (AB q, *J* = 12.4 Hz, 2H), 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-Ar product 18 mg, yield 65%. Analytical data see below at the thiol ether section.

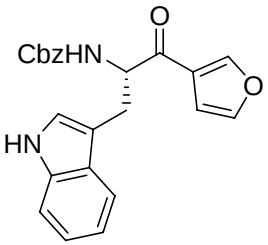
(+)-(*S*)-2-(Carbobenzyloxyamino)-1-(furan-2-yl)-4-(methylthio)butan-1-one, 3.14



Following general procedure **B**, from *N*-Cbz-L-Met-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 23 mg), furyl-2-boronic acid (0.125 mmol, 28 mg), and CuMeSal (0.01 mmol, 2 mg) after 2 hr was obtained 11 mg of the pure ketone and 9 mg of the S-Ar product after flash chromatography on silica gel with 2 : 1 hexanes : EtOAc. Ketone yield 67%, white solid, Mp = 70-72 ºC. TLC (R*f* = 0.75, 1 : 1 hexanes : EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.38-7.31 (m, 6H), 6.59-6.58 (m, 1H), 5.69 (d, *J* = 8.4 Hz, 1H), 5.28-5.23 (m, 1H), 5.11 (app s, 2H), 2.63-2.49 (m, 2H), 2.25-2.16 (m, 1H), 2.06 (s, 3H), 1.95-1.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 156.1, 150.7, 147.7, 136.3, 128.7, 128.4, 128.3, 119.6, 112.9, 67.3, 55.4, 33.2, 30.2, 15.7. IR (neat, cm^{-1}) 1718 (s), 1675 (s), 1517 (m), 1463 (s). HRMS (FAB) Calcd for $C_{17}H_{20}NO_4S$ ($[M+H]^+$): 334.1106. Found: 334.1107. $[\alpha]_D^{20}$ +26.7 (*c* 0.69, $CHCl_3$).

S-Ar product 9 mg, yield 70%. Analytical data see forward at thiol ether section.

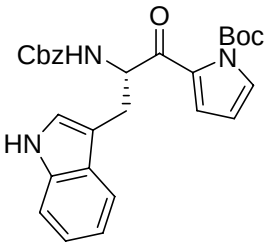
(+)-(*S*)-2-(Carbobenzyloxyamino)-1-(furan-3-yl)-3-(1*H*-indol-3-yl) propan-1-one, 3.15



Following general procedure **B**, from *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), furyl-3-boronic acid (0.125 mmol, 28 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF after 3 hours was obtained 21 mg of the pure ketone and 11 mg of S-Ar product after flash chromatography on silica gel with 20 : 1 : 5 $CHCl_3$: EtOAc : hexanes. Ketone yield 99%, colorless oil. TLC (R_f = 0.25, silica gel, $CHCl_3$: EtOAc = 20 : 1). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 9.5 min, D-isomer t_R = 10.0 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.87 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.37-7.28 (m, 7H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.70 (d, *J* = 1.2 Hz, 1H), 5.68 (d, *J* = 8.4 Hz, 1H), 5.19-5.05 (m, 3H), 3.36 (dd, *J* = 10.4, 6.8 Hz, 1H), 3.25 (dd, *J* = 10.4, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 155.9, 148.3, 144.5, 136.5, 136.2, 128.7, 128.4, 128.3, 127.7, 125.8, 123.1, 122.4, 119.9, 118.8, 111.4, 110.1, 108.8, 67.1, 58.1, 29.5. IR (neat, cm^{-1}) 3347 (m), 2926 (m), 1679 (s), 1509 (m), 745 (m). HRMS (FAB) Calcd for $C_{23}H_{21}N_2O_4$ ($[M+H]^+$): 389.1495. Found: 389.1498. $[\alpha]_D^{20}$ +64.4 (*c* 1.46, $CHCl_3$).

S-Ar product 11 mg, yield 86%. For the analytical data see below at thiol the ether section.

(+)-(*S*)-1-(1-*tert*-Butoxycarbonyl-1*H*-pyrrol-2-yl)-2-(carbobenzyloxyamino)-3-(1*H*-indol-3-yl)propan-1-one, 3.16

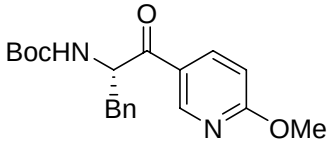


Following general procedure **B**, from *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), *N*-Boc-pyrole-2-boronic acid (0.125 mmol, 27 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF after 3 hours was obtained 22 mg of the pure ketone and 15 mg of S-Ar product after flash chromatography on silica gel with 20 : 1: 5 $CHCl_3$: EtOAc : hexanes. Ketone yield 92%, yellow oil. TLC (R_f = 0.40, silica gel, $CHCl_3$: EtOAc : hexanes = 10 : 2 : 2). HPLC Chiral AS-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 12.4 min, D-isomer t_R = 15.9 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.36-7.24 (m, 7H), 7.16 (t, *J* = 6.8 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.88-6.87 (m, 1H), 6.11 (t, *J* = 3.2 Hz, 1H), 5.64 (d, *J* = 8.4 Hz, 1H), 5.30-5.25 (m, 1H), 5.08-5.02 (m, 2H), 3.45 (dd, *J* = 14.8, 6.4 Hz, 1H), 3.18 (dd, *J* = 14.8, 6.4 Hz, 1H). 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 156.0, 148.7, 136.6, 136.2, 131.7, 129.5, 128.7, 128.2, 128.2, 127.8, 123.2, 123.1, 122.3, 119.8, 118.9, 111.3, 110.6, 85.3, 67.0, 57.7, 29.4, 27.8.

IR (neat, cm^{-1}) 3389 (m), 2930 (m), 1749 (s), 1710 (s), 1679 (s), 1316 (s), 1146 (s), 748 (m). HRMS (FAB) Calcd for $C_{28}H_{30}N_3O_5$ ($[M+H]^+$): 488.2180. Found: 488.2179. $[\alpha]_D^{20}$ +23.3 (*c* 1.20, $CHCl_3$).

S-Ar product 15 mg, yield 81%. For the analytical data see below at thiol the ether section.

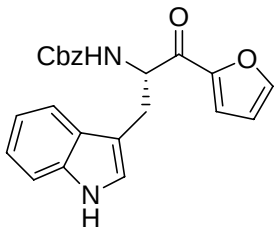
(+)-(*S*)-2-(*tert*-Butoxycarbonylamino)-1-(6-methoxypyridin-3-yl)-3-phenylpropan-1-one, 3.17



Following general procedure **B**, from *N*-Boc-L-Phe-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.1 mmol, 43 mg), 2-methoxyl 5-pyridyl boronic acid (0.25 mmol, 38 mg), and CuMeSal (0.02 mmol, 4 mg) in 1 mL DMF after 3 hours was obtained 35 mg of the pure ketone and 27 mg of S-Ar product after flash chromatography on silica gel with 20 : 1 : 5 $CHCl_3$: EtOAc : hexanes. Ketone yield 97%, white solid, Mp = 105-106 ˚C. TLC (R_f = 0.80, silica gel, hexanes : EtOAc = 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.0 Hz, 1H), 8.05 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.24-7.14 (m, 3H), 7.02 (d, *J* = 6.4 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 1H), 5.40-5.35 (m, 2H), 3.98 (s, 3H), 3.21-3.16 (m, 1H), 2.98-2.94 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 167.2, 149.8, 138.7, 135.9, 129.6, 128.6, 127.1, 126.0, 124.9, 111.6, 80.1, 56.1, 54.4, 39.5, 28.5. IR (neat, cm^{-1}) 3347 (br), 2953 (m), 1710 (s), 1679 (s), 1602 (s), 1498 (s), 1170 (m), 698 (m). HRMS (FAB) Calcd for $C_{20}H_{25}N_2O_4$ ($[M+H]^+$): 357.1808. Found: 357.1791. $[\alpha]_D^{20}$ +33.2 (*c* 1.50, $CHCl_3$).

S-Ar product 20 mg, yield 70%. For the analytical data see below at thiol the ether section.

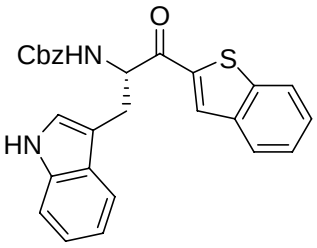
(+)-(*S*)-2-(Carbobenzyloxyamino)-1-(furan-2-yl)-3-(1*H*-indol-3-yl) propan-1-one, 3.18



Following general procedure **B**, from *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), 2-furyl boronic acid (0.125 mmol, 14 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF after 3 hours was obtained 19 mg of the pure ketone and 10 mg of S-Ar product after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Ketone yield 96%. For analytical data, please refer to the data presented in **Scheme 1** above.

S-Ar product 10 mg, yield 73%. For the analytical data see below at thiol the ether section.

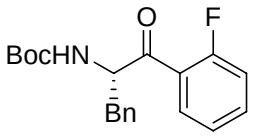
(+)-(*S*)-1-(Benzo[β]thiophen-2-yl)-2-(carbobenzyloxyamino)-3-(1*H*-indol-3-yl)propan-1-one, 3.19



Following general procedure **B**, from *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), 2-benzothiophene boronic acid (0.125 mmol, 22 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF after 3 hours was obtained 23 mg of the pure ketone and 18 mg of S-Ar product after flash chromatography on silica gel with 20 : 1 : 5 $CHCl_3$: EtOAc : hexanes. Ketone yield 99%, yellow solid, Mp = 189-190 ˚C. TLC (R_f = 0.50, silica gel, $CHCl_3$: EtOAc = 20 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.72 (d, *J* =7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.38-7.24 (m, 7H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 1.2 Hz, 1H), 5.71 (d, *J* = 8.4 Hz, 1H), 5.62 (q, *J* = 6.8 Hz, 1H), 5.11 (q, *J* = 11.6 Hz, 2H), 3.47-3.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 155.9, 142.9, 141.3, 139.1, 136.5, 136.2, 130.8, 128.7, 128.4, 128.3, 128.0, 127.7, 126.5, 125.3, 123.2, 123.0, 122.4, 120.0, 118.9, 111.4, 110.0, 67.2, 57.0, 30.1. IR (neat, cm^{-1}) 3401 (m), 2926 (m), 1710 (s), 1664 (s), 1509 (s), 1227 (m), 745 (m). HRMS (FAB) Calcd for $C_{27}H_{23}N_2O_3S$ ($[M+H]^+$): 455.1423. Found: 455.1424. $[\alpha]_D^{20}$ +64.7 (*c* 1.91, THF).

S-Ar product 11 mg, yield 99%. For the analytical data see below at thiol the ether section.

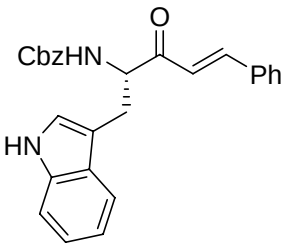
(+)-(*S*)-2-(*tert*-Butoxycarbonylamino)-1-(2-fluorophenyl)-3-phenylpropan-1-one, 3.20



Following general procedure **B**, from *N*-Boc-L-Phe-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.1 mmol, 43 mg), 2-fluorophenyl boronic acid (0.25 mmol, 35 mg), and CuMeSal (0.02 mmol, 4 mg) in 1 mL DMF after 3 hours was obtained 28 mg of the pure ketone and 20 mg of S-Ar product after flash chromatography on silica gel with 20 : 1 : 5 $CHCl_3$: EtOAc : hexanes. Ketone yield 94%, white solid, Mp = 123-124 ˚C. TLC (R_f = 0.70, silica gel, hexanes : EtOAc = 2 : 1). HPLC Chiral AS-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 7.2 min, D-isomer t_R = 6.6 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.58-7.52 (m, 1H), 7.27-7.13 (m, 5H), 7.03 (d, *J* = 6.4 Hz, 2H), 5.43-5.38 (m, 1H), 5.32 (d, *J* = 7.6 Hz, 1H), 3.27 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.86 (dd, *J* = 14.0, 5.2 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 162.9, 160.4, 155.3, 136.1, 135.5, 135.4, 131.6, 129.7, 128.5, 127.0, 125.0, 123.9, 123.8, 117.1, 116.9, 79.9, 60.3, 60.2, 38.0, 28.5. IR (neat, cm^{-1}) 3432 (w), 2980 (m), 1687 (s), 1494 (s), 1170 (m), 756 (m). HRMS (FAB) Calcd for $C_{20}H_{23}NO_3F$ ($[M+H]^+$): 344.1656. Found: 344.1658. $[\alpha]_D^{20}$ +43.3 (*c* 1.59, $CHCl_3$).

S-Ar product 20 mg, yield 70%. For the analytical data see below at thiol the ether section.

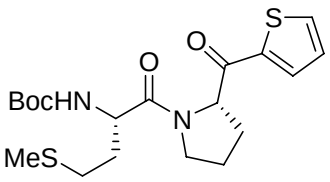
(-)-(*S*,*E*)-4-(Carbobenzyloxyamino)-5-(1*H*-indol-3-yl)-1-phenylpent-1-en-3-one, 3.21



Following general procedure **B**, from *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), *trans*-2-styrene boronic acid (0.125 mmol, 19 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF after 16 hours was obtained 13 mg of the pure ketone and 8 mg of S-Ar product after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Ketone yield 60%, white solid, Mp = 162-163 ˚C (Lit.[4] 162-163 °C). TLC (R_f = 0.60, silica gel, hexanes : EtOAc = 1 : 1). 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 = 19.8 min, D-isomer t_R = 18.2 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 16.0 Hz, 1H), 7.40-7.28 (m, 11H), 7.20 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.67 (d, *J* = 16 Hz, 1H), 5.73 (d, *J* = 7.5 Hz, 1H), 5.16 and 5.12 (AB q, *J* = 12.2 Hz, 2H), 5.13-5.08 (m, 1H), 3.40-3.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 155.8, 144.3, 136.4, 136.1, 134.1, 130.8, 128.8, 128.5, 128.4, 128.1, 128.0, 127.6, 123.0, 122.9, 122.2, 119.7, 118.8, 111.2, 110.0, 66.8, 58.6, 28.5. IR (neat, cm^{-1}) 3408 (m), 3343 (m), 3034 (w), 1687 (s), 1610 (s), 1498 (s), 1455 (s). HRMS (FAB) Calcd for $C_{27}H_{24}N_2O_3Li$ ($[M+Li]^+$): 431.1947. Found: 431.1928. $[\alpha]_D^{20}$ -7.8 (*c* 1.10, $CHCl_3$).

S-Ar product 8 mg, yield 52%. For the analytical data see below at thiol the ether section.

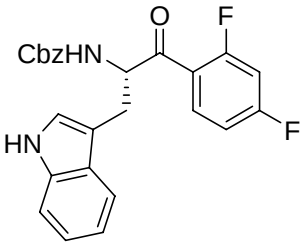
(-)-(*S*)-2-(*tert*-Butoxycarbonylamino)-4-(methylthio)-1-((*S*)-2-(thiophene-2-carbonyl)pyrrolidin-1-yl)butan-1-one, 3.22



Following general procedure **B**, from *N*-Boc-L-Met-L-Pro-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), thiophene-2-boronic acid (0.2 mmol, 26 mg), and CuMeSal (0.01 mmol, 2 mg) in 1 mL DMF after 16 hours was obtained 12 mg of the pure ketone and 7 mg of S-Ar product after flash chromatography on silica gel with 1 : 1 CH_2Cl_2: EtOAc. Ketone yield 60%, colorless oil. TLC (silica gel, R_f = 0.65, CH_2Cl_2: EtOAc = 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.65 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.13 (dd, *J* = 4.8, 4.0 Hz, 1H), 5.33 (dd, *J* = 8.4, 4.8 Hz, 1H), 5.25 (d, *J* = 9.2 Hz, 1H), 4.68-4.63 (m, 1H), 3.85-3.74 (m, 2H), 2.62-2.57 (m, 2H), 2.33-2.26 (m, 1H), 2.12 (s, 3H), 2.11-1.95 (m, 4H), 1.90-1.81 (m, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 170.7, 155.7, 141.4, 134.3, 132.6, 128.4, 79.9, 62.2, 51.0, 47.5, 32.8, 30.1, 29.8, 28.5, 25.2, 15.9. IR (neat, cm^{-1}) 3312 (br), 2926 (m), 1698 (s), 1640 (s), 1166 (s). HRMS (FAB) Calcd for $C_{19}H_{29}N_2O_4S_2$ ($[M+H]^+$): 413.1563. Found: 413.1555. $[\alpha]_D^{20}$ -8.0 (*c* 0.60, $CHCl_3$).

S-Ar product 7 mg, yield 53%. For the analytical data see below at thiol the ether section.

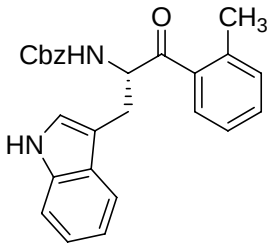
(+)-(*S*)-2-(Carbobenzyloxyamino)-1-(2,4-difluorophenyl)-3-(1*H*-indol-3-yl)propan-1-one, 3.23



Following general procedure **B**, from *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), 2,4-difluoro phenyl boronic acid (0.125 mmol, 20 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF after 3 hours was obtained 21 mg of the pure ketone and 16 mg of S-Ar product after flash chromatography on silica gel with 20 : 1 : 5 $CHCl_3$: EtOAc : hexanes. Ketone yield 97%, yellow oil. TLC (R_f = 0.20, silica gel, $CHCl_3$: EtOAc: hexanes = 20 : 1 : 5). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 13.8 min, D-isomer t_R = 12.2 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.81 (dd, *J* = 14.8, 8.4 Hz, 1H), 7.35-7.27 (m, 7H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.93-6.80 (m, 3H), 5.67 (d, *J* = 7.6 Hz, 1H), 5.51 (dd, *J* = 13.2, 5.6 Hz, 1H), 5.11-5.04 (m, 2H), 3.44 (dd, *J* = 15.2, 5.6 Hz, 1H), 3.16 (dd, *J* = 14.8, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 156.0, 136.6, 136.1, 133.5, 133.5, 128.7, 128.3, 127.7, 123.0, 122.3, 119.8, 118.7, 112.8, 112.6, 111.3, 109.8, 105.3, 105.1, 104.8, 67.1, 60.0, 59.9, 27.8. IR (neat, cm^{-1}) 3405 (m), 1687 (s), 1610 (s), 1502 (m), 1235 (m), 972 (m), 741 (m). HRMS (FAB) Calcd for $C_{25}H_{21}N_2O_3F_2$ ($[M+H]^+$): 435.1514. Found: 435.1513. $[\alpha]_D^{20}$ +33.6 (*c* 1.40, $CHCl_3$).

S-Ar product 16 mg, yield 99%. For the analytical data see below at thiol the ether section.

(+)-(*S*)-2-(Carbobenzyloxyamino)-3-(1*H*-indol-3-yl)-1-*o*-tolylpropan-1-one, 3.24

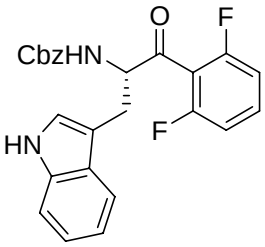


Following general procedure **B**, from *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), 2-tolyl boronic acid (0.125 mmol, 17 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF after 16 hours was obtained 16 mg of the pure ketone and 8 mg of S-Ar product after flash chromatography on silica gel with 20 : 1 : 5 $CHCl_3$: EtOAc : hexanes. Ketone yield 78%, yellow oil. TLC (R_f = 0.40, silica gel, $CHCl_3$: EtOAc: hexanes = 20 : 1 : 5). HPLC Chiral OJ-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 15.3 min, D-isomer t_R = 12.8 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.40-7.19 (m, 10H), 7.12 (t, *J* = 8.0 Hz, 1H)), 6.97 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 5.81 (d, *J* = 7.6 Hz, 1H), 5.58-5.54 (m, 1H), 5.16-5.08 (m, 2H), 3.35 (dd, *J* = 15.2, 5.6 Hz, 1H), 3.15 (dd, *J* = 15.2, 5.2 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 156.1, 139.8, 136.6, 136.1, 135.1, 132.4, 132.2, 129.2, 128.7, 128.3, 128.3, 127.6, 125.9, 122.8, 122.3, 119.7, 118.9, 111.1, 110.1, 67.0, 57.9, 28.3, 21.2. IR (neat, cm^{-1}) 3405 (m), 2926 (m),

1687 (s), 1505 (m), 1227 (m), 741 (m). HRMS (FAB) Calcd for $C_{26}H_{25}N_2O_3$ ($[M+H]^+$): 413.1859. Found: 413.1860. $[\alpha]_D^{20}$ +36.9 (*c* 0.98, $CHCl_3$).

S-Ar product 8 mg, yield 59%. For the analytical data see below at thiol the ether section.

(+)-(*S*)-2-(Carbobenzyloxyamino)-1-(2,6-difluorophenyl)-3-(1*H*-indol-3-yl)propan-1-one, 3.25

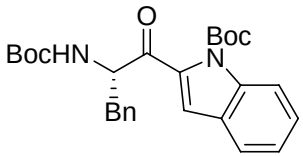


Following general procedure **B**, from *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), 2,6-difluorophenylboronic acid (0.125 mmol, 20 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF after 3 hours was obtained 19 mg of the pure ketone and 13 mg of S-Ar product after flash chromatography on silica gel with 20 : 1 : 5 $CHCl_3$: EtOAc : hexanes. Ketone yield 92%, yellow oil. TLC (R_f = 0.20, silica gel, $CHCl_3$: EtOAc : hexanes = 20 : 1 : 5). HPLC Chiral AS-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 12.9 min, D-isomer t_R = 10.5 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.81 (dd, *J* = 14.8, 8.4 Hz, 1H), 7.35-7.27 (m, 7H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.89-6.83 (m, 3H), 5.55 (d, *J* = 7.6 Hz, 1H), 5.36 (dd, *J* = 14.0, 6.0 Hz, 1H), 5.07 (s, 2H), 3.40 (dd, *J* = 14.8, 6.4 Hz, 1H), 3.23 (dd, *J* = 15.2, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 156.0,

136.5, 136.2, 133.4, 128.7, 128.3, 127.7, 123.0, 122.3, 119.8, 118.8, 112.4, 112.2, 111.2, 109.8, 67.1, 61.3, 27.4. IR (neat, cm^{-1}) 3385 (m), 1702 (s), 1621 (m), 1467 (m), 1239 (m), 741 (m). HRMS (FAB) Calcd for $C_{25}H_{21}N_2O_3F_2$ ($[M+H]^+$): 435.1514. Found: 435.1514. $[\alpha]_D^{20}$ +12.2 (*c* 0.70, $CHCl_3$).

S-Ar product 13 mg, yield 82%. For the analytical data see below at thiol the ether section.

(+)-(*S*)-1-(1-*tert*-Butoxycarbonyl-1*H*-indol-2-yl)-2-(*tert*-butoxycarbonylamino)-3-phenylpropan-1- one, 3.26

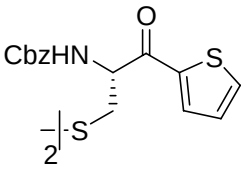


Following general procedure **B**, from *N*-Boc-L-Phe-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.1 mmol, 43 mg), *N*-Boc-2-indolyl-boronic acid (0.25 mmol, 65 mg), and CuMeSal (0.02 mmol, 4 mg) in 1 mL DMF after 16 hours was obtained 36 mg of the pure ketone and 34 mg of the S-Ar product after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Ketone yield 78%, yellow oil. TLC (silica gel, R_f = 0.50, hexanes : EtOAc = 1 : 1). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R =13.3 min, D-isomer t_R =12.6 min, ee > 99%. ^1H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.27-7.16 (m, 7H), 5.31 (d, *J* = 8.4 Hz, 1H), 5.25-5.21 (m, 1H), 3.22 (dd, *J* = 14.4, 6.0

Hz, 1H), 2.90 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.63 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 155.3, 149.6, 138.9, 136.9, 136.2, 129.5, 128.5, 127.9, 127.5, 126.9, 123.6, 123.0, 117.0, 115.0, 85.2, 80.0, 59.0, 39.2, 28.4, 28.0. IR (neat, cm^{-1}) 2980 (m), 1741 (s), 1695 (s). HRMS (FAB) Calcd for $C_{27}H_{33}N_2O_5$ ($[M+H]^+$): 465.2384. Found: 465.2383. $[\alpha]_D^{20}$ +21.8 (*c* 1.95, $CHCl_3$).

S-Ar product 34 mg, yield 83%. For the analytical data see below at thiol the ether section.

(+)-(2*S*,2'*S*)-3,3'-Disulfanediylbis(2-(carbobenzyloxyamino)-1-(thiophen-2-yl)propan-1-one), 3.27

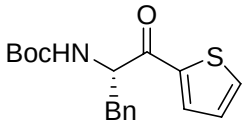


Following general procedure **B**, from *N*, *N*'-Cbz-L-cystine-bis-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.04 mmol, 32 mg), thiophene-2-boronic acid (0.2 mmol, 26 mg), and CuMeSal (0.02 mmol, 4 mg) in 1 mL DMF after 16 hours was obtained 28 mg of the pure ketone and 7 mg of S-Ar product after flash chromatography on silica gel with 10 : 1 CH_2Cl_2: EtOAc. Ketone yield 64%, colorless oil. TLC (silica gel, R_f = 0.90, CH_2Cl_2 : EtOAc = 10 : 1). ^{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, $CHCl_3$).

S-Ar product 7mg, yield 64%. For the analytical data see below at thiol the ether section.

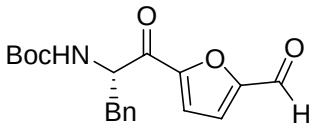
(+)-(*S*)-2-(*tert*-Butoxycarbonylamino)-3-phenyl-1-(thiophen-2-yl)propan-1-one, 3.28



Following general procedure **B**, from *N*-Boc-L-Phe-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 22 mg), thiophene-2-boronic acid (0.125 mmol, 16 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF for 16 hours was obtained 15 mg of the pure ketone and 12 mg of the S-Ar product after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Ketone yield 89%, white solid, Mp = 118-120 ºC. TLC (silica gel, R_f = 0.85, hexanes : EtOAc = 1 : 1). HPLC Chiral OD-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 8.3 min, D-isomer t_R = 9.7 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.66 (m, 2H), 7.24-7.16 (m, 3H), 7.10-7.07 (m, 3H), 5.31-5.29 (m, 2H), 3.23-3.19 (m, 1H), 3.05-3.00 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 155.3, 142.0, 136.2, 135.0, 133.3, 129.6, 128.6, 127.1, 80.1, 57.3, 40.1, 28.5. IR (neat, cm^{-1}) 3343 (br), 2980 (m), 1702 (s), 1664 (s), 1166 (s). HRMS (FAB) Calcd for $C_{18}H_{22}NO_4S_1$ ($[M+H]^+$): 332.1314. Found: 332.1306. $[\alpha]_D^{20}$ +76.3 (*c* 2.23, $CHCl_3$).

S-Ar product 12 mg, yield 73%. For the analytical data see below at thiol the ether section.

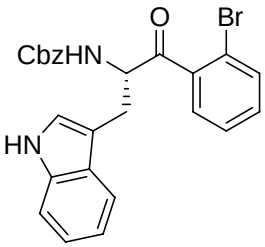
(+)-(*S*)-5-(2-(*tert*-Butoxycarbonylamino)-3-phenylpropanoyl)furan-2-carbaldehyde, 3.29



Following general procedure **B**, from *N*-Boc-L-Phe-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.1 mmol, 43 mg), 2-formyl-5-boronic acid (0.25 mmol, 35 mg), and CuMeSal (0.02 mmol, 4 mg) in 1 mL DMF after 16 hours was obtained 21 mg of the pure ketone and 26 mg of the S-Ar product after flash chromatography on silica gel with 1 : 1 hexanes : EtOAc. Ketone yield 60%, white solid, Mp = 158-159 ºC. TLC (silica gel, R_f = 0.60, hexanes : EtOAc = 1 : 1). HPLC Chiral OD-RH, λ = 210nm, Method: Flow: 1.0 mL/min; T = 30 °C; Isogradient: 50% H_2O in CH_3CN for 50 min, L-isomer t_R = 7.1 min, D-isomer t_R = 6.5 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.32-7.14 (m, 7H), 5.39 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.31 (d, *J* = 8.0 Hz, 1H), 3.24-3.09 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 179.2, 155.2, 153.8, 153.0, 135.7, 129.6, 128.7, 127.3, 119.1, 118.9, 80.4, 57.2, 39.1, 28.5. IR (neat, cm^{-1}) 3362 (br), 2980 (m), 1679 (s), 1498 (m), 1166 (m), 752.7 (m). HRMS (FAB) Calcd for $C_{19}H_{22}NO_5$ ($[M+H]^+$): 344.1492. Found: 344.1488. $[\alpha]_D^{20}$ +37.8 (*c* 1.41, $CHCl_3$).

S-Ar product 26 mg, yield 88%. For the analytical data see below at thiol the ether section.

(+)-(*S*)-1-(2-Bromophenyl)-2-(carbobenzyloxyamino)-3-(1*H*-indol-3-yl)propan-1-one, 3.30

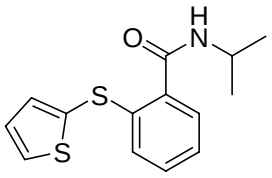


Following general procedure **B**, from *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg), 2-bromo phenyl boronic acid (0.125 mmol, 25 mg), and CuMeSal (0.01 mmol, 2 mg) in 0.5 mL DMF after 16 hours was obtained 19 mg of the pure ketone and 16 mg of S-Ar product after flash chromatography on silica gel with 20 : 1 : 5 $CHCl_3$: EtOAc : hexanes. Ketone yield 77%, yellow oil. TLC (R_f = 0.25, silica gel, $CHCl_3$: EtOAc : hexanes = 20 : 1 : 5). HPLC Chiral AS-RH, λ = 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN, during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 10.9 min, D-isomer t_R = 11.8 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.58-7.42 (m, 3H), 7.35-7.23 (m, 8H), 7.16-7.12 (m, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 5.62 (d, *J* = 8.0 Hz, 1H), 5.56-5.51 (m, 1H), 5.08 (s, 2H), 3.36-3.13 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 156.1, 138.6, 136.5, 136.2, 134.2, 132.4, 129.8, 128.7, 128.3, 128.2, 127.6, 127.4, 123.1, 122.3, 120.1, 119.8, 118.8, 111.3, 110.0, 67.1, 59.1, 27.6. IR (neat, cm^{-1}) 3389 (m), 2926 (m), 1698 (s), 1509 (m), 1224 (m), 741 (m). HRMS (FAB) Calcd for $C_{25}H_{22}N_2O_3Br$ ($[M+H]^+$): 477.0808. Found: 477.0814. $[\alpha]_D^{20}$ +10.7 (*c* 1.10, $CHCl_3$).

S-Ar product 16 mg, yield 90%. For the analytical data see below at the thiol ether section.

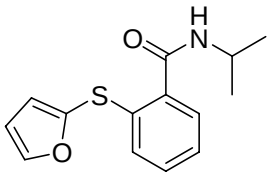
Thioethers in Table 1.

_N_-Isopropyl-2-(thiophen-2-ylthio)benzamide, 3.31



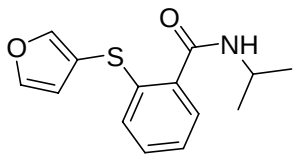
White solid. Mp = 115-117 ^{o}C. TLC (silica gel, R_f = 0.40, hexanes : EtOAc = 2 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 5.6, 1.2 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.30 (dd, *J* = 3.2, 1.2 Hz, 1H), 7.22 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.13 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.09 (dd, *J* = 5.2, 4.0 Hz, 1H), 6.93 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.90 (br d, *J* = 6.4 Hz, 1H), 4.34-4.25 (m, 1H), 1.28 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 138.9, 137.2, 134.0, 132.1, 130.9, 130.7, 128.4, 127.7, 125.6, 42.3, 23.0. IR (neat, cm^{-1}): 3281 (m), 2972 (m), 1633 (s), 1536 (s). HRMS (ESI) Calcd for $C_{14}H_{16}NO_2S_2$ ($[M+H]^+$): 278.0667. Found: 278.0667.

2-(Furan-2-ylthio)-*N*-isopropylbenzamide, 3.32



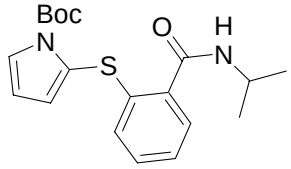
White solid. Mp = 94-96 ^{o}C. TLC (silica gel, R_f = 0.44 hexanes : EtOAc = 2 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (app t, *J* = 0.8 Hz, 1H), 7.45 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.25-7.22 (m, 1H), 7.16 (app t, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 2.8 Hz, 1H), 6.50-6.49 (m, 1H), 5.95 (br s , 1H), 4.34-4.26 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 146.9, 143.1, 136.5, 134.6, 130.9, 128.6, 127.9, 126.1, 120.5, 112.2, 42.3, 22.9. IR (neat, cm^{-1}): 3277 (m), 2972 (m), 1633 (s), 1536 (s). HRMS (ESI) Calcd for $C_{14}H_{16}NO_2S$ ($[M+H]^+$): 262.0896. Found: 262.0896.

2-(Furan-3-ylthio)-*N*-isopropylbenzamide, 3.33



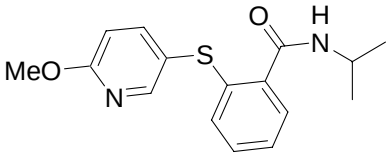
White solid, Mp = 120-121 ºC. TLC (R_f = 0.45, silica gel, $CHCl_3$: EtOAc = 20 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.51 (t, *J* = 1.6 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.05-7.02 (m, 1H), 6.41 (d, *J* = 2.0 Hz, 1H), 5.93 (s, 1H), 4.33-4.24 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 147.1, 144.6, 137.1, 134.4, 130.7, 128.0, 127.8, 125.4, 114.9, 113.6, 42.3, 23.0. IR (neat, cm^{-1}) 3254 (m), 2972 (m), 1629 (s), 1544 (m). HRMS (FAB) Calcd for $C_{14}H_{16}NO_2S$ ($[M+H]^+$): 262.0896. Found: 262.0894.

tert-Butyl 2-(2-(isopropylcarbamoyl)phenylthio)-1_H_-pyrrole-1-carboxylate, 3.34



Pale yellow oil. TLC (R_f = 0.60, silica gel, $CHCl_3$: EtOAc : hexanes = 10 : 2 : 2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.56 (m, 1H), 7.44-7.43 (m, 1H), 7.25-7.17 (m, 2H), 6.99-6.96 (m, 1H), 6.80 (d, *J* = 6.8 Hz, 1H), 6.43-6.41 (m, 1H), 6.22 (t, *J* = 3.6 Hz, 1H), 4.31-4.22 (m, 1H), 1.42 (s, 9H), 1.21(d, *J* = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 148.6, 135.7, 135.4, 130.5, 129.6, 129.2, 126.5, 125.4, 123.8, 121.7, 111.4, 84.8, 42.1, 27.9, 22.8. IR (neat, cm^{-1}) 3354 (m), 2976 (m), 1737 (s), 1633 (s), 1536 (s), 1324 (s), 1158 (s), 745 (m). HRMS (FAB) Calcd for $C_{19}H_{25}N_2O_3S$ ($[M+H]^+$): 361.1580. Found: 361.1567.

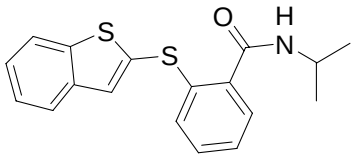
_N_-Isopropyl-2-(6-methoxypyridin-3-ylthio)benzamide, 3.35



White solid. Mp = 137-138 ˚C. TLC (R_f = 0.5, silica gel, hexanes : EtOAc = 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.45 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.19 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.13 (dt, *J* = 7.2, 1.2 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 9.0 Hz, 1H), 5.95 (d, *J* = 7.2 Hz, 1H), 4.29-4.24 (m, 1H), 3.92 (s, 3H), 1.25 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 164.6, 152.6, 144.9, 137.1, 135.2, 130.8, 128.9, 128.2, 125.9, 121.4, 122.4, 54.0, 42.3, 22.9. IR

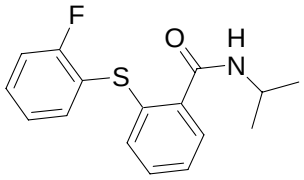
(neat, cm^{-1}) 3277 (br), 2972 (m), 1633 (s), 1536 (s), 1475 (s), 829 (m). HRMS (FAB) Calcd for $C_{16}H_{19}N_2O_2S$ ($[M+H]^+$): 303.1161. Found: 303.1157.

2-(Benzo[b]thiophen-2-ylthio)-*N*-isopropylbenzamide, 3.36



White solid. Mp = 131-132 ˚C. TLC (R_f = 0.60, silica gel, $CHCl_3$: EtOAc = 20 : 1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H), 7.53 (s, 1H), 7.48-7.45 (m, 1H), 7.37-7.32 (m, 2H), 7.25-7.15 (m, 3H), 5.93 (d, *J* = 7.2 Hz, 1H), 4.33-4.24 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 143.2, 139.8, 137.0, 135.0, 133.9, 132.8, 130.9, 129.3, 127.8, 126.3, 125.4, 124.8, 123.9, 122.3, 42.4, 22.9. IR (neat, cm^{-1}) 3269 (m), 2972 (m), 1637 (s), 1536 (s), 752 (m). HRMS (FAB) Calcd for $C_{18}H_{18}NOS_2$ ($[M+H]^+$): 328.0824. Found: 328.0821.

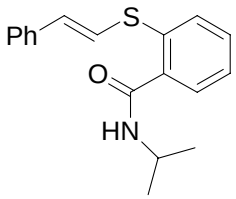
2-(2-Fluorophenylthio)-*N*-isopropylbenzamide, 3.37



White solid. Mp = 76-77 ˚C. TLC (R_f = 0.45, silica gel, hexanes : EtOAc = 2 : 1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.56 (m, 1H), 7.31-7.22 (m, 4H), 7.13-7.06 (m, 3H), 6.21 (d, *J* = 6.0 Hz, 1H), 4.26-4.17 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.4, 160.8, 137.1, 134.4, 132.8, 131.7, 130.8, 130.2, 129.1, 127.4, 125.2, 122.0, 116.3, 116.2, 42.3, 42.2, 22.7, 22.7. IR (neat, cm^{-1}) 3281 (m), 2972

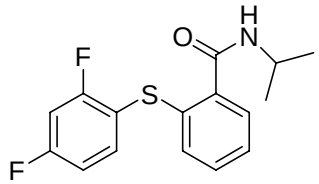
(m), 1633 (s), 1536 (s), 1471 (s), 756 (m). HRMS (FAB) Calcd for $C_{16}H_{17}NOFS$ ($[M+H]^+$): 290.1009. Found: 290.1006.

(*E*)-*N*-Isopropyl-2-(styrylthio)benzamide, 3.38



Yellow oil. TLC (R_f = 0.80, silica gel, hexanes : EtOAc = 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.43-7.21 (m, 8H), 6.79 (s, 2H), 6.03 (d, *J* = 6.4 Hz, 1H), 4.30-4.22 (m, 1H), 1.24 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 136.7, 136.4, 134.2, 134.0, 130.8, 130.7, 128.9, 128.7, 128.1, 127.0, 126.4, 122.7, 42.3, 22.9. IR (neat, cm^{-1}) 3281 (m), 2972 (m), 1633 (s), 1536 (s), 690 (m). HRMS (FAB) Calcd for $C_{18}H_{20}NOS$ ($[M+H]^+$): 298.1260. Found: 298.1257.

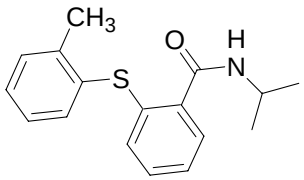
2-(2,4-Difluorophenylthio)-*N*-isopropylbenzamide, 3.39



White solid, Mp = 108-110 ºC. TLC (R_f = 0.55, silica gel, EtOAc: hexanes = 2 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 1H), 7.46-7.40 (m, 1H), 7.28-7.20 (m, 2H), 7.00 (dd, *J* = 6.8, 1.6 Hz, 1H), 6.93-6.87 (m, 2H), 6.07 (br s, 1H), 4.31-4.23 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 136.7, 136.2, 134.3, 130.8, 130.1, 128.6, 126.8, 112.8, 112.6, 105.4, 105.1, 104.8, 42.3, 22.8. IR (neat, cm^{-1})

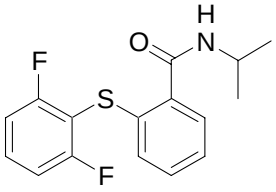
3285 (m), 1633 (s), 1594 (m), 1536 (m), 1482 (m). HRMS (FAB) Calcd for $C_{16}H_{16}F_2NOS$ ($[M+H]^+$): 308.0914. Found: 308.0915.

_N_-Isopropyl-2-(_o_-tolylthio)benzamide, 3.40



White solid, Mp = 117-118 ºC. TLC (R_f = 0.50, silica gel, $CHCl_3$: EtOAc: hexanes = 20 : 1 : 5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 1H), 7.25-7.11 (m, 6H), 6.98-6.95 (m, 1H), 6.10 (br s, 1H), 4.27-4.19 (m, 1H), 2.34 (s, 3H), 1.15 (d, J = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 140.1, 136.8, 134.1, 133.5, 132.9, 131.0, 130.9, 130.8, 129.1, 128.4, 127.2, 126.8, 42.2, 29.9, 22.8, 20.6. IR (neat, cm^{-1}) 3289 (m), 2972 (m), 1633 (s), 1536 (m), 752 (m). HRMS (FAB) Calcd for $C_{17}H_{20}NOS$ ($[M+H]^+$): 286.1260. Found: 286.1257.

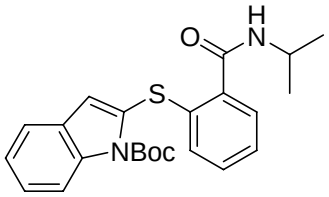
2-(2,6-Difluorophenylthio)-_N_-isopropylbenzamide, 3.41



Colorless oil. TLC (R_f = 0.40, silica gel, $CHCl_3$: EtOAc : hexanes = 20 : 1 : 5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.50 (m, 1H), 7.41-7.33 (m, 1H), 7.22-7.14 (m, 2H), 7.01-6.91 (m, 3H), 6.07 (d, J = 6.8 Hz, 1H), 4.36-4.27 (m, 1H), 1.28 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 135.7, 134.6, 131.7, 131.6, 130.8, 129.1, 128.3, 126.3, 112.4,

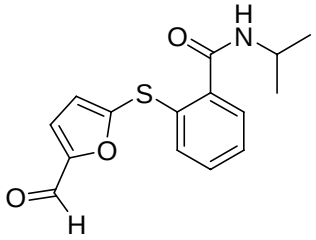
112.1, 42.3, 22.9. IR (neat, cm^{-1}) 3289 (m), 2972 (m), 1629 (s), 1540 (s), 1463 (s), 1235 (m), 992 (s), 787 (m). HRMS (FAB) Calcd for $C_{16}H_{16}NOF_2S$ ($[M+H]^+$): 308.0915. Found: 308.0911.

2-(1-*tert*-Butoxycarbonyl-1*H*-indol-2-ylthio)-*N*-isopropylbenzamide, 3.42



White solid. Mp = 141-143 °C. TLC (silica gel, R_f = 0.50, hexanes : EtOAc = 2 : 1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.73-7.70 (m, 1H), 7.42-7.34 (m, 4H), 7.24 (dt, *J* = 6.8, 1.6 Hz, 1H), 7.17 (dt, *J* = 7.2, 0.8 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H) 6.17 (s, 1H), 4.22-4.09 (m, 1H), 1.60 (s, 9H), 1.06 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 150.1, 138.7, 137.3, 134.2, 134.1, 131.4, 131.0, 130.0, 129.2, 128.9, 124.3, 123.3, 119.9, 115.4, 112.2, 85.4, 42.1, 28.3, 22.6. IR (neat, cm^{-1}): 3330 (m), 2976 (m), 1729 (s), 1637 (s), 1536 (s), 1328 (s). HRMS (ESI) Calcd for $C_{23}H_{27}N_2O_3S$ ($[M+H]^+$): 411.1736. Found: 411.1735.

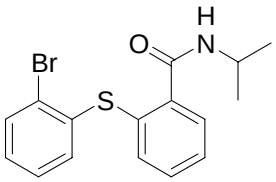
2-(5-Formylfuran-2-ylthio)-*N*-isopropylbenzamide, 3.43



Yellow solid. Mp = 112-113 °C. TLC (silica gel, R_f = 0.2, hexanes : EtOAc = 2 : 1). ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.48 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.31-7.23 (m,

3H), 7.10 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.79 (d, *J* = 3.2 Hz, 1H), 6.03 (d, *J* = 7.2 Hz, 1H), 4.30-4.22 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 167.0, 155.0, 136.7, 132.7, 131.1, 130.9, 128.1, 127.6, 122.4, 119.7, 42.4, 22.9. IR (neat, cm^{-1}): 3296 (m), 2976 (m), 1679 (s), 1637 (s), 1536 (s), 1459 (s). HRMS (ESI) Calcd for $C_{13}H_{16}NO_3S$ ($[M+H]^+$): 290.0845. Found: 290.0845.

2-(2-Bromophenylthio)-*N*-isopropylbenzamide, 3.44



Colorless oil. TLC (R_f = 0.50, silica gel, $CHCl_3$: EtOAc : hexanes = 20 : 1 : 5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.77 (m, 1H), 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.43-7.32 (m, 3H), 7.17 (dt, *J* = 8.8, 1.2 Hz, 1H), 7.05 (dt, *J* = 7.6, 1.6 Hz, 1H), 6.93 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.44 (br d, *J* = 6.4 Hz, 1H), 4.19-4.08 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138.9, 137.5, 134.8, 133.4, 131.3, 130.4, 130.2, 130.1, 129.1, 128.4, 128.1, 123.5, 42.2, 22.5. IR (neat, cm^{-1}) 3285 (m), 2972 (m), 1633 (s), 1536 (s), 1019 (m), 748 (m). HRMS (FAB) Calcd for $C_{16}H_{17}NOBrS$ ($[M+H]^+$): 350.0208. Found: 350.0205.

3.5 Refereces

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[7] These benzamides are easily oxidized back to the disulfide under air. They were freshly made and used directly in the subsequent synthesis of thiol esters.

[8] The dipeptide was made from *N*-Boc-L-Met-OH and L-Pro-OMe by using DCC as dehydration agent. The resulting methyl ester was hydrolyzed using LiOH to give the dipeptide.