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Zhihui Zhang Date

Metal Mediated Cross-Coupling Reactions for Carbon-Carbon and Carbon-Nitrogen Bonds Formation under Neutral pH Conditions

By

Zhihui Zhang

Doctor of Philosophy

Chemistry

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Dr. Lanny S. Liebeskind, Advisor

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Dr. Simon B. Blakey, Committee Member

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Accepted:

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Lisa A. Tedesco, Ph.D.
Dean of the Graduate School

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Date

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By

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B.Sc., Lanzhou University, Lanzhou, China, 2001

M.Sc., Lanzhou University, Lanzhou, China, 2004

Advisor: Lanny S. Liebeskind, Ph.D.

An abstract of

A dissertation submitted to the Faculty of the Graduate School of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry

2009

Abstract

Metal Mediated Cross-Coupling Reactions for Carbon-Carbon and Carbon-Nitrogen Bonds Formation under Neutral pH Conditions

By

Zhihui Zhang

The transition metal-catalyzed cross-coupling of thioorganics with boronic acids or organostannanes under neutral conditions for the construction of C-C bond has found various applications in modern organic synthesis. As an extension of this strategy, a novel cyanide-free cyanation reaction through the palladium(0)-catalyzed, copper(I)-mediated coupling of boronic acids with thiocyanates was developed. This non-basic desulfitative process provides a useful complement to the traditional synthesis of nitriles through metal-catalyzed cross-coupling of aryl halides with cyanide sources.

Based on the extensive study on previous thioorganic-boronic acid cross-couplings, a mechanistically unprecedented desulfitative protocol was developed which was completely catalytic in copper or palladium. A general ketone synthesis through the copper(I)-catalyzed cross-coupling of thiol esters with organoborons or organostannanes was reported. The application of this mechanism to the palladium-catalyzed desulfitative reaction of more thioorganic substrates was proven promising. Present results demonstrated the efficient coupling of heteroaromatic thioethers with boronic acids.

In addition to the selective functionalization of C-S bonds, a novel N-O bond cleavage to give C-N bond products was investigated. Under non-basic and non-oxidative conditions, *O*-acetyl hydroxamic acids couple efficiently with a variety of organostannanes or boronic acids in the presence of copper(I) sources to generate *N*-substituted amides and enamides in good yields.

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Table of Contents

Chapter 3

List of Schemes

Chapter 1

Chapter 2

Chapter 3

List of Tables

Chapter 1

Chapter 2

Chapter 3

List of Figures

Chapter 2

List of Abbreviations

app	apparent
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
br	broad
Bu	butyl
ºC	degrees Celsius
calcd	calculated
Cbz	benzyloxycarbonyl
CuTC	copper(I) thiophene-2-carboxylate
CuMeSal	copper(I) methyl salicylate
CuDPP	copper(I) diphenyl phosphinate
cm^{-1}	wavenumber unit
Cy	cyclohexyl
δ	chemical shift (in ppm for NMR)
d	doublet
dba	dibenzylideneacetone
DCC	1,3-dicyclohexylcarbodiimide
DMF	dimethylformamide
DMAP	*N*,*N*-dimethylaminopyridine
DMSO	dimethylsulfoxide
EDC	*N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride
equiv.	equivalent

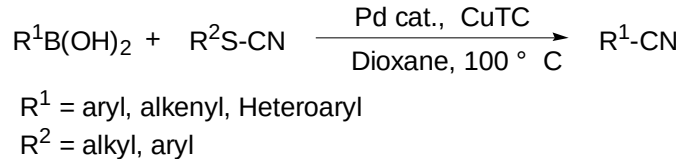
Et	ethyl
EtOAc	ethyl acetate
Hex	hexane
HPLC	high pressure liquid chromatography
hrs	hour(s)
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
L	liter
M	molar
Me	methyl
MeCN	acetonitrile
mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimole
mol %	mole percent
mol	mole
Mp	melting point
OAc	acetate
Ph	phenyl
py	pyridine
q	quartet
s	singlet
t	triplet

TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	toluene
w	weak

Chapter 1

Palladium-Catalyzed, Copper-Mediated Coupling of Boronic Acids and Thiocyanate. A Cyanide-Free Cyanation of Boronic Acids

***Abstract**: A new method for the synthesis of nitriles has been accomplished. As a complement to the classic metal-catalyzed cyanation of aryl halides with cyanide, the palladium-catalyzed, Cu (I) thiophene-2-carboxylate (CuTC)-mediated coupling of thiocyanates with boronic acids proceeds under neutral conditions affording nitriles in good to excellent yields.*



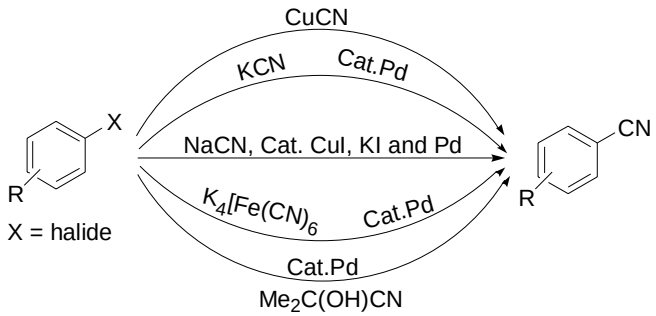
Scheme 1.1 Nitrile Synthesis: Boronic Acid-Thiocyanate Coupling

1.1 Introduction and Background

Aryl nitriles are an important class of compounds that are not only functional constituents of dyes and herbicides but also useful components of many natural products and pharmaceuticals.[1] As a consequence of the essential role played by nitriles in pharmaceutical chemistry and materials science, as well as their utility as synthetic building blocks, a number of useful strategies for introduction of cyanide functionality into aromatic compounds have been described.[2-3] The traditional method for preparing aryl nitriles involves direct reaction of copper (I) cyanide with aryl halides (mostly

[1] Sundermeier, M.; Zapf, A.; Beller, M.; Sans, S. *Tetrahedron Lett*. **2001**, *42*, 6707.
[2] (a) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513 and references therein. (b) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779.
[3] (a) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887. (b) Maligres, P. E.; Waters, M. S.; Flietz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193. (c) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224. (d) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661. (e) Okano, T.; Kiji, J.; Toyooka, Y. *Chem Lett.* **1998**, 425. (f) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441.

expensive aryl iodides are required), known as the Rosenmund-von Braun reaction (**Scheme 1.2**).[4] The reaction usually proceeds at high

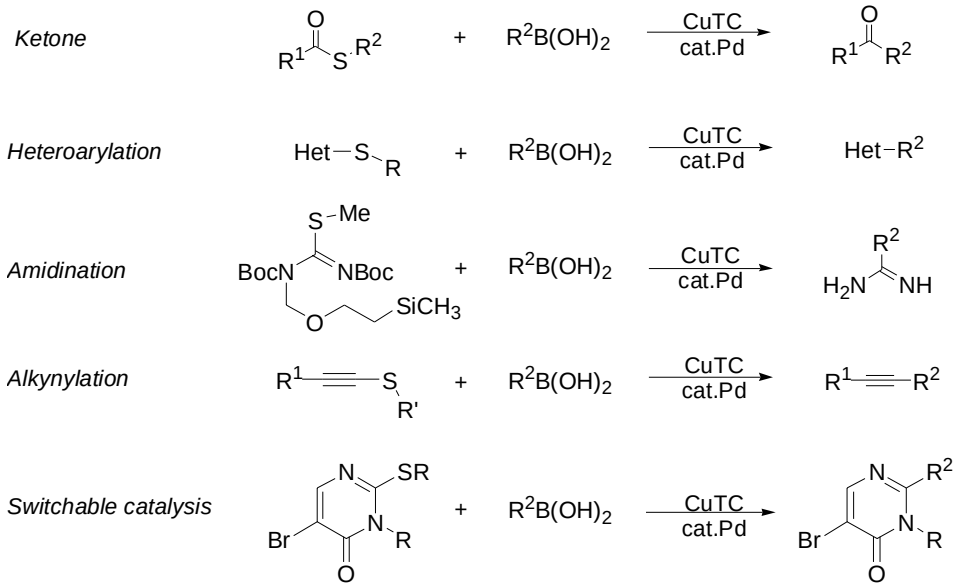


Scheme 1.2 Several Representative Methods for the Synthesis of Nitriles

temperature with prolonged times. More recently, transition-metal-catalyzed cyanations of aryl halides have been developed as a useful alternative for the preparation of aryl nitriles. Unfortunately, various problems limit the efficiency of this process. For example, mechanistic studies revealed excess cyanide ions significantly inhibit the transition metal catalyst by formation of inactive cyano complexes,[5] and the metal cyanides are highly poisonous. This problem can be prevented by careful control of the concentration of dissolved cyanide ions. Thus, nonpolar solvent such as toluene or xylene were used to dissolve low concentrations of cyanide salts (like KCN, $Zn(CN)_2$).[6] Another novel way to overcome this problem was achieved by employing slow dosage of liquid cyanide sources such as TMSCN or acetone cyanohydrin to control the low concentration of

[4] (a) Mowry, D. T. *Chem. Rev*. **1948**, *42*, 189. (b) Friedman, L.; Shechter, H. *J. Org. Chem*. **1961**, *26*, 2522. (c) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193.
[5] (a) Sekiya, A.; Ishikawa, N. *Chem. Lett*. **1975**, 277. (b) Takagi, K.; Okamoto, T,; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1972**, *49*, 3177.
[6] (a) Okano, T.; Kiji, J.; Toyooka, Y. *Chem. Lett*. **1998**, 425. (b) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193. (c) Veauthier, J. M.; Carlson, C. N.; Collis, G. E.; Kiplinger, J. L.; John, K. D. *Synthesis* **2005**, 2683.

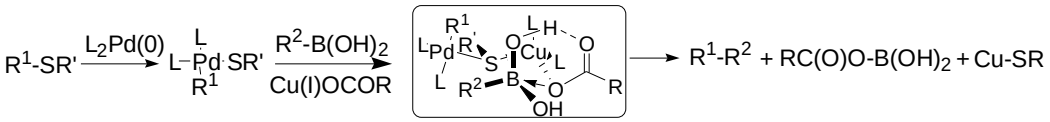
cyanide, but these cyanide sources are prone to liberate hydrogen cyanide (**Scheme 1.2**).[7] Recently, potassium hexacyanoferrate ($K_4[Fe(CN)_6]$) has been introduced as a nontoxic cyanide source (**Scheme 1.2**).[8] Other progresses such as cyanation of aryl bromides by copper-catalyzed domino halide exchange and the use of certain amines (tetramethylethylenediamine or 1,1-methylenedipiperidine) as co-catalysts have also been developed.[9-10] Herein is described the cyanide-free cyanation of boronic acids with organic thiocyanates as a complementary method for the synthesis of nitriles. This mild and general protocol is an extension of a growing family of thioorganic/boronic acid cross-couplings discovered in the Liebeskind laboratory.



Scheme 1.3 A Family of Pd-Catalyzed Thioorganic-Boronic Acid Couplings

[7] (a) Cassar, L.; Ferrara, S.; Foa, M. *Adv. Chem. Ser*. **1974**, *132*, 252. (b) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem.*, *Int. Ed*. **2003**, *42*, 1661.
[8] (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Comm.* **2004**, 1388-1389. (b) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem*. **2005**, *70*, 1508-1510. (c) Grossman, O.; Gelman, D. *Org. Lett.* **2006**, *8*, 1189.
[9] Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890.
[10] Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, S.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 165.

The Liebeskind laboratory has been interested in uncovering new metal catalyzed/mediated C-C bond formations that involve C-S bond cleavege during the process. Recent studies have demonstrated the efficient Pd-catalyzed, Cu-mediated cross-couplings of a variety of thioorganic compounds with boronic acids [11] or organostannanes[12] under non-basic conditions (**Scheme 1.3**).



Scheme 1.4 Thioorganic-Boronic Acid Coupling through Dual Thio/Borophilic Activation

The proposed reaction mechanism for these Cu(I)-mediated, Pd(0)-catalyzed thioorganic couplings is shown in **Scheme 1.4**.[11a] After oxidative addition of the thioorganic to the Pd(0) catalyst, the copper(I) carboxylate functions as a unique dual activator, acting through the soft Cu(I) ion as a thiophilic agent to polarize the palladium thiolate bond, while simultaneously providing borophilic activation through the hard carboxylate counterion. The much greater reactivity of boronic acids over boronate esters and anhydrides, and the deleterious effect of added oxygen bases on the coupling reaction led to the proposal of the hydrogen bonded, ternary complex as the reactive intermediate. A full equivalent of the copper carboxylate is required to scavenge the thiolate (-SR) and

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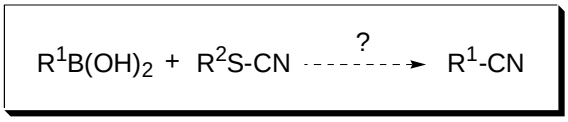
[11] (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000,** *122*, 11260. (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett*. **2001**, *3*, 91. (c) Savarin, C.; Liebeskind, L. S. *Org. Lett*. **2001**, *3*, 2149. (d) Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 979. (e) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett*. **2002**, *4*, 983. (f) Liebeskind, L. S.; Srogl, J.; Savarin, C.; Polanco, C. *Pure Appl. Chem.* **2002**, *74*, 115. (g) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Let.* **2003**, *5*, 4349. (h) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007,** *129*, 1132.

[12] (a) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033. (b) Egi, M. Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801. (c) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803. (d) Li, H.; Yang, H.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 4375.

pair with boronic acid residue (-$B(OH)_2$) as the reaction proceeds. CuTC was used because it is cheap and relatively air-stable. To avoid any undesired oxidation of the Cu^I cofactor to a Cu^{II} species, the reaction generally has to be performed under an inert atmosphere. As an extension of previously described thioorganic/boronic acid cross-coupling in this laboratory, the coupling of a boronic acid and a thiocyanate would be of value to synthetic and pharmaceutical chemists by providing a cyanide-free cyanation reaction. (**Scheme 1.5**)



Scheme 1.5 New Cyanide-Free Cyanation Reaction?

1.2 Results and Discussion

1.2.1 Preparation of Starting Materials

Aryl thiocyanates used herein were prepared from the corresponding aryl thiols.[13] The aryl thiols were treaded with SO_2Cl_2 in dichloromethane at 0℃ in the presense of triethylamine. Replacement of the dichloromethane by acetonitrile, followed by slow addition of trimethylsilyl cyanide (TMSCN), led rapidly to the formation of the desired aryl thiocyanates (**Table 1.1**).

Table 1.1 Synthesis of aryl thiocyanates from corresponding thiols

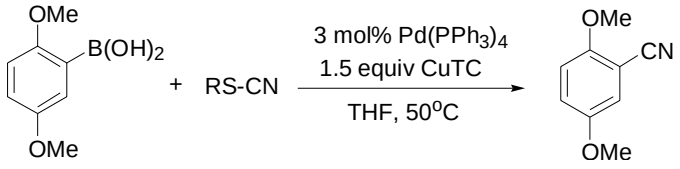
[13] Still, Ian W. J.; Watson, Iain D. G. *Synth. Commun.* **2001**, *31*, 1355.

entry	Ar	isolated yield (%)
1	phenyl	85
2	4-(trifluoromethyl)phenyl	82
3	4-nitrophenyl	78
4	2,4-dichlorophenyl	80

1.2.2 Thiocyanates/Boronic acid Coupling

In the initial stage of the experiments, the coupling of 2,5-dimethoxylphenyl boronic acid with several thiocyanates was investigated. In accordance with earlier reports from the Liebeskind laboratory, both catalytic palladium and stoichiometric copper carboxylate were required for the thiooganic-boronic acid cross-coupling.[11] Among the catalytic

Table 1.2 Variation of Thiocyanates for the Cyanation of Boronic acids

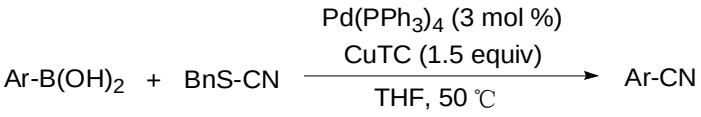


entry	R	isolated yield (%)
1	ethyl	70
2	benzyl	90
3	phenyl	90
4	4-nitrophenyl	92
5	4-(trifluoromethyl)phenyl	91
6	2,4-dichlorophenyl	85

systems studied for the cyanative cross-coupling, the $Pd(PPh_3)_4$/CuTC system gave the best results, and 1.5 equiv of boronic acid was used to optimize the cross-coupling yields. As shown in **Table 1.2**, in all cases, the cyanation products were obtained in good to excellent yields (70-92%) in THF at 50℃. The nature of the organic thiocyanates did not seem critical to the reaction, so commmercially available benzyl thiocyanate was employed as the cyanide source in the subsequent experiments and served as an excellent cyanide source in boronic acid cross-coupling reactions.

With these results in hand, the scope and the possible limitations of this new protocol were studied. As shown in **Table 1.3**, a variety of boronic acids (1.5 equiv) were tested in the copper-mediated, palladium-catalyzed cyanation reaction with benzyl thiocyanate. Very efficient transformations of activated (electron–rich)

Table 1.3 Cyanation of Various Boronic Acids



entry	Ar	isolated yield (%)
1	4-(*N*,*N*-dimethylamino)phenyl	88
2	2,3,4-trimethoxylphenyl	82
3	phenyl	76
5	4-(methoxylcarbonyl)phenyl	50
6	4-chlorophenyl	47

(entries 1-2) and unactivated (electron-neutral) aryl boronic acids (entries 3) were observed under the above conditions (1.5 equiv CuTC, THF/50℃). However, deactivated

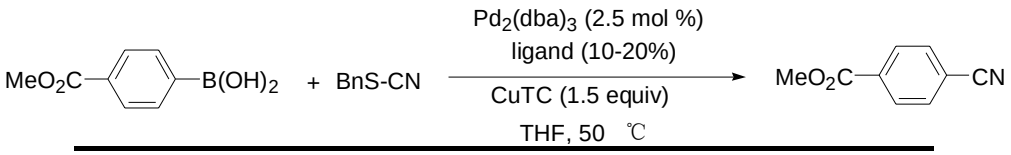
(electron-deficient) aryl boronic acids were generally less reactive and led to incomplete conversion under the same condition (entries 5-6). The staring material benzyl thiocyanate and homocoupling products of the boronic acids were detected along with the desired aryl nitriles. The coupling of electron-deficient boronic acids is also difficult in Suzuki-Miyaura coupling, because they are less nucleophilic and undergo transmetallation at a slower rate than electron-neutral and –rich aryl boronic acids.[14] Additionally, electron-poor aryl boronic acids are prone to homocoupling[15] and more susceptible to metal-catalyzed protodeboronation.[16] Therefore, the study was then focused on the development of reaction conditions under which electron-poor aryl boronic acids could effectively participate in the cross-coupling with benzyl thiocyanate.

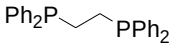
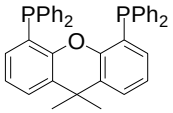
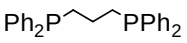
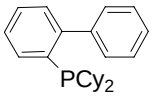
First, the palladium catalyst systems were screened. The nature of the palladium complex can greatly affect cross-coupling efficiency. Electron-rich palladium complexes more readily undergo oxidative addition of carbon-heteroatom bond[17] and bulky or bidentate ligands could accelerate the reductive elimination of the new carbon-carbon bond.[18] The cross-coupling of 4-(methoxycarbonyl)phenyl boronic acid with benzyl thiocyanate was carried out using $Pd_2(dba)_3$ as a pre-catalyst in combination with mono- and bidentate phosphine ligands with different electronic and steric properties (**Table 1.4**). In most cases, however, unreacted benzyl thiocyanate was still recovered. The catalysts explored did not lead to a significant improvement of the cross-coupling efficiency. These observations suggested that the poor reactivity of electron-deficient boronic acid

[14] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
[15] Wong, M. S.; Zhang, X. L. *Tetrahedron Lett*. **2001**, *42*, 4087-4089.
[16] Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am Chem. Soc.* **1964,** *86,* 2666-2670.
[17] (a)Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211. (b) Fu, G. C. *Acc. Chem. Res.* **2008**, *42,* 155-164.
[18] van Leeuwen, P. W. N. M.; Birkholz, M-N.; Freixa, Z. *Chem. Soc. Rev.*, **2009**, *38*, 1099 – 1118.

could be caused by their sluggish transmetallation with the RS-Pd$(L)_2$-CN intermediate rather than the oxidative addition or reductive elimination step.

Table 1.4 Catalyst Screening Cross-Coupling

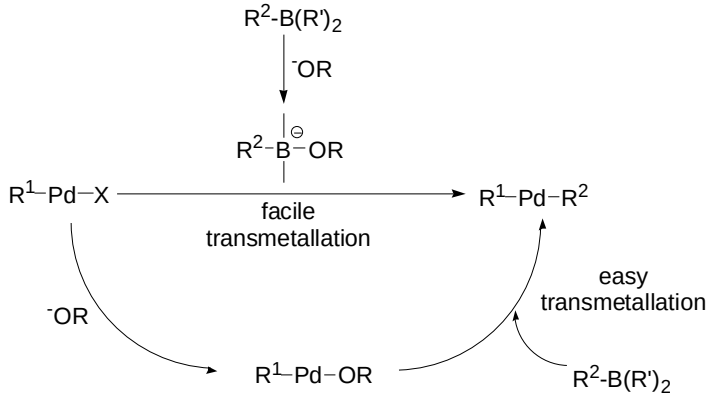


entry	ligand	yield[c]
1[a]	TFP	42
2[b]		15
3[b]		12
4[a]	$P(OPh)_3$	16
5[a]	P(*n*-Bu)$_3$	31
6[a]	PCy_3	23
7[b]		10
8[a]	P(*t*-Bu)$_3$	22
9[a]		18
10[a]	$P(OEt)_3$	38

a. 20 mol% ligand; b. 10 mol% ligand;
c. ^{1}H NMR yield, with *para*-dimethoxybenzene as the internal standard

The presence of an oxygen base exerts a remarkable effect on the traditional Suzuki-Miyaura reactions. An oxygen base can enhance the nucleophilicity of the group on the boron atom through coordination of the anionic base to the boron, giving the corresponding '-ate' complexes. Therefore, the transmetallation between the boron and

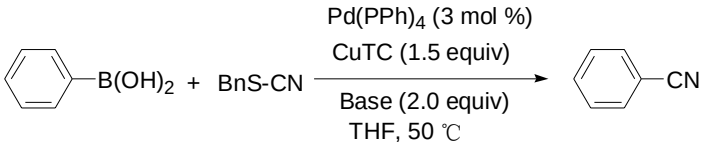
the palladium is facilitated. Another possibility is that an oxygen base would perform a ligand exchange and form the (alkoxo)palladium intermediate, to which the organoboron compounds readily transfer the organic groups (**Scheme 1.6**).[14]



Scheme 1.6 Bases Promote the Transmetallation from Boron to Palladium

With this in mind, a number of bases were screened in this reaction and the results are summarized in **Table 1.5**.

Table 1.5 The Effect of Base on the Cross-Coupling

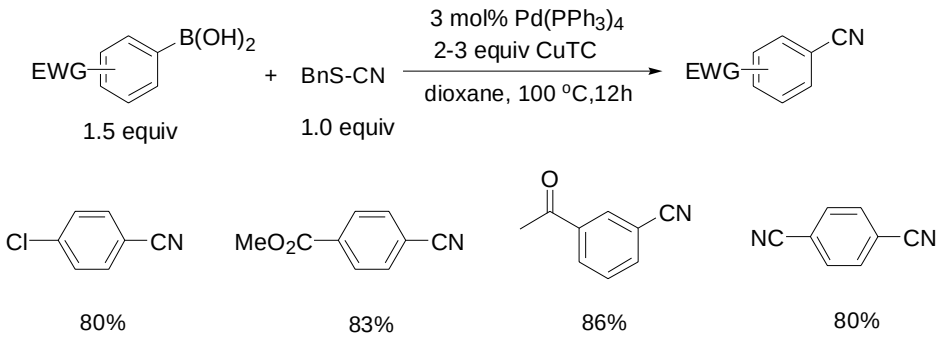


entry	Base	yield (%)
1	-	75[a]
2	KCO_3	trace[b]
3	wet KCO_3	trace[b]
4	Cs_2CO_3	trace[b]
5	Et_3N	trace[b]
6	DABCO	trace[b]

a. isolated yield; b. detected by GC-MS

As shown above, the addition of bases remarkably retarded the reaction. This result was consistent with previous studies indicating that bases were deleterious to the palladium-catalyzed, copper mediated couplings of boronic acids with thioorganics.[11] In the subsequent efforts to improve the cyanation of electron-deficient boronic acids, the use of excess of CuTC (2-3 equiv) at higher temperature (100 ℃) in 1,4-dioxane was discovered to afford much better results (**Scheme 1.7**). Other solvents tested (DMF, DMA, NMP, toluene) gave lower yields.

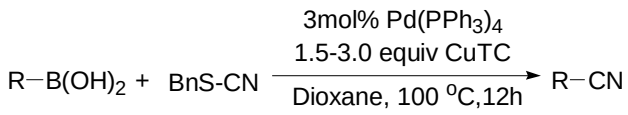
Scheme 1.7 Cyanation of Electron-Deficient Boronic Acids

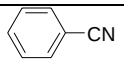
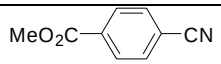
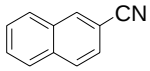
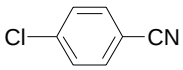
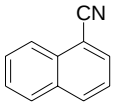
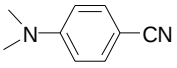
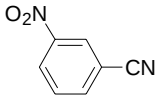
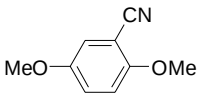
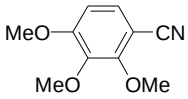
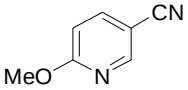
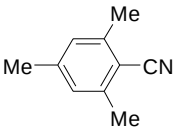
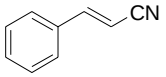
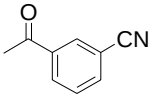
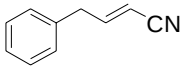


Under such conditions, very effective cyanation of unactivated (electron-neutral) (**Table 1.6,** entries 1-3) and activated (electron-rich) aryl boronic acids (entries 4-6) was observed. Most electron-deficient aryl boronic acids gave corresponding benzonitriles in good yields (entries 8-12) except the *m*-nitrophenyl boronic acid. This reaction only afforded trace of benzonitrile product and the unreacted starting benzylthiocyanate was recovered. The poor reactivity of the highly electron-deficient *m*-nitrophenyl boronic acid presumably could be ascribed to its extremely low nucleophilicity that resulted in the hard transmetallation. The cyanation of heteroaryl boronic acids was also possible. 3-Thiopheneboronic acid and 2-methoxy-5-pyridineboronic acid gave the corresponding

nitriles in 86% and 84% yields respectively (entry 13-14). It was worth noting that alkenyl nitriles can be obtained by this method in good yields as well (entry 15-16). Moreover, sterically congested substrates (entry 5-7) underwent cyanation efficiently.

Table 1.6 Pd-Catalyzed Cyanation of Boronic Acids Mediated by CuTC



entry	R-CN	yield[e] (%)	entry	R-CN	yield[e] (%)
1[a]		90	9[b]		83
2[a]		90	10[c]		80
3[a]		82	11[c]		80
4[a]		95	12[c]		trace[d]
5[a]		90	13[c]		86
6[a]		85	14[c]		84
7[c]		76	15[c]		82
8[b]		86	16[c]		75

[a]1.5 equiv CuTC; [b]2.0 equiv CuTC; [c] 3.0 equiv CuTC; [d] detected by GC-MS
[e] isolated yields

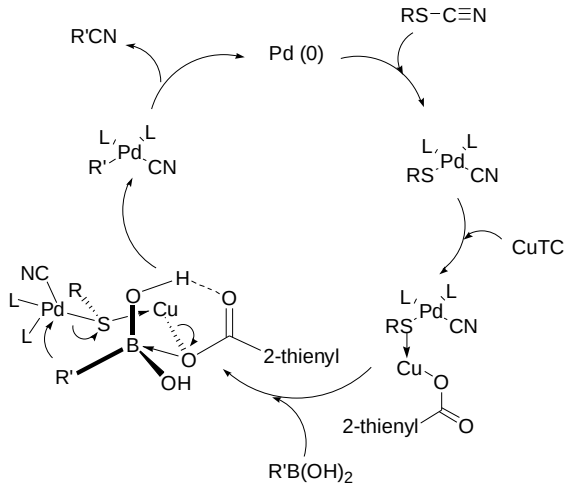
Remarkably, unlike most other Pd-catalyzed organoboron cross-coupling chemistry, where the presence of a base is essential,[14] the thiocyanate/boronic acid coupling can proceed well under neutral conditions without the aid of base. This offers the possibility

of the synthesis of base-sensitive compounds. Finally, in contrast to boronic acids, neither boronate esters and nor boroxines were effective in this new cyanative coupling.

1.2.3 Mechanistic Consideration

From a mechanistic perspective, the coupling may start with an oxidative addition of the thiocyanate to Pd(0), followed by a transmetallation from boron to palladium. Carbon-cyanide reductive elimination would afford the nitrile and regenerate a catalytically active Pd(0). It is suggested by early results that the copper(I) carboxylate used here functioned as a unique dual activator, acting through the soft Cu(I) ion as a thiophilic agent to help polarize the palladium thiolate bond, while simultaneously providing borophilic activation by coordination of the carboxylate to the trivalent boron atom.[11a] The much greater reactivity of boronic acids over boronate esters and anhydrides led to the proposal of the hydrogen bonded, ternary, complex depicted in **Scheme 1.8** as the reactive intermediate.

Scheme 1.8 Proposed Mechanism for Thiocyanate-Boronic Acid Coupling



1.3 Conclusion

In summary, a new cyanide-free cyanation of boronic acids has been developed through the use of a palladium-catalyzed, copper(I)-mediated coupling of organothiocyanate with boronic acids. Using this protocol, a variety of nitriles can be easily synthesized in high yields. The method is a useful complement to the traditional synthesis of nitriles through transition-metal-catalyzed cross-coupling of aryl halides/sulfonates with cyanide sources.

1.4 Experimental

General Methods

All reactions were performed under an atmosphere of dry argon in oven-dried glassware. THF, DMA, DMF, NMP, toluene and 1,4-dioxane were dried over 4Å molecular sieves and titrated for water level prior to use with a Fisher Coulomatic K-F titrater. Et_3N was dried over KOH pellets. Hexanes, ethyl acetate (EtOAc), and ethyl ether (Et_2O) were obtained from EM Science and used as purchased. 'Brine' refers to a saturated aqueous solution of NaCl. Unless otherwise specified solutions. Purification by flash chromatography was performed using Whatman 60Å 230-400 mesh SiO_2 with compressed air as a source of positive pressure. Purification by plate chromatography was performed on EM Science Kieselgel 0.5 mm or 1 mm $60F_{254}$ plates. Analytical thin-layer chromatography (TLC) was carried out using Merck Kieselgel $60F_{254}$ plates with visualization by UV or phosphomolybdic acid.

^1H NMR spectra were recorded on a INOVA 400 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (7.27 ppm); ^{13}C NMR

spectra were recorded on a 100 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), hex (hextet), hept (heptet), m (multiplet), exch (exchangeable), app (apparent)); coupling constants, *J*, are reported (Hz); integration is provided. Infrared spectra were recorded using an ASI ReactIR 1000FT-IR spectrometer with a silicone probe. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium, 40-67%), w (weak, 20-40%) and br (broad). GC-MS spectra were recorded on a Shimadzu Gas Chromatograph GC-17A, Mass Spectrometer QP-5000. GC/MS analysis was carried out on a bonded 5% diphenylsiloxane capillary column (30 m, 0.25 mm id, 0.25 μm df). Uncalibrated melting points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes.

Starting materials

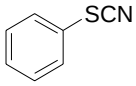
Benzenethiol, *p*-nitrylphenylthiol, *p*-trifluoromethylphenylthiol, 2,4-dichlorophenylthiol, triethylamine, sulfuryl chloride, trimethylsilyl cyanide, benzyl thiocyanate, ethylthiocyanate, $Pd(PPh_3)_4$, $Pd_2(dba)_3$ and phosphoros ligands were all obtained from Aldrich and used without further purification. All boronic acids were purchased from Frontier Scientific, Inc. Copper(I) thiophene-2-carboxylate(CuTC) [19] and aryl thiocyanate[13] were prepared following literature procedure.

General procedure for preparing aryl thiocyanate. Aryl thiol (1.0 mmol) was first treated with SO_2Cl_2 (1.1 mmol) at 0 ℃ in dry CH_2Cl_2 under argon. Triethylamine (1.2

[19] Allred, G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

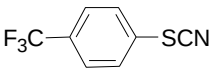
mmol) was also present. After stirring of solution at 0 ℃ for 30 min, the CH_2Cl_2 was removed by evaporation and replaced with CH_3CN, followed by the slow addition of TMSCN (1.1 mmol). The resulting brown solution was stirred at 25℃ for 1 h and concentrated. The crude product was chromatographed on silica gel to afford the corresponding aryl thiocyanates.

Benzenethiocyanate [20]



Purification by flash chromatography (hexane/EtOAc 20:1) afforded the title compound as an oil (1.23 g, 85%). ^{1}H NMR (300MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.42-7.41 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.1, 129.9, 129.3, 124.2, 110.4; IR (neat, cm^{-1}) 3060 (m), 2158 (s), 1583 (m), 1478(s), 1444 (s), 1023 (m), 999 (m), 752 (s), 687 (s);

***p*-Trifluoromethybenzenethiocyanate** [21]

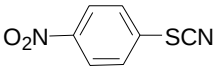


Purification by flash chromatography (hexane/EtOAc 20:1) afforded the title compound as a light yellow solid (1.42 g, 82%). Mp 30-31℃ (lit. {30-30.5℃}[21]); ^{1}H NMR (300MHz, $CDCl_3$) δ 7.72 (d, J = 6.9 Hz, 2H), 7.64 (d, J = 6.9 Hz, 2H); IR (neat, cm^{-1}) 3070 (w), 2162 (m), 1619 (s), 1405(s), 1011 (m),829 (s), 698 (m).

***p*-Nitrobenzenethiocyanate** [22]

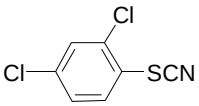
---

[20] M. Yokoyama, H. Ohteki, M. Kurauchi, K. Hoshi, E. Yanagisawa, A. Suzuki, and T. lmamoto. *J. Chem. Soc. Perkin Trans. I*, **1984**, 2635.
[21] T, Kentaro; T, Hideaki; Si, Ken. *J. Org. Chem*. **1995**, *60*, 6552.



Purification by flash chromatography (hexane/EtOAc 20:1) afforded the title compound as a yellow solid (1.28 g, 78%). Mp 128-129℃ (lit. {131-133℃}[22]); ^{1}H NMR (300MHz, $CDCl_3$) δ 8.31 (d, *J* = 6.9 Hz, 2H), 7.68 (d, *J* = 6.9 Hz, 2H); IR (neat, cm^{-1}) 3107 (m), 2165 (m), 1602 (m), 1579 (s), 1517 (s),1011 (m), 856 (s), 737 (m).

2,4-Dichlorobenzenethiocyanate [23]



Purification by flash chromatography (hexane/EtOAc 20:1) afforded the title compound as a yellow solid (1.11 g, 80%). Mp 69-70℃ (lit. {72℃}[23]); ^{1}H NMR (300MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.41-7.36 (m, 1H); IR (neat, cm^{-1}) 3060 (w), 2162 (m), 1559 (m), 1428 (s), 1405 (w), 1193 (m), 783 (s).

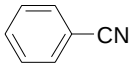
General Procedure for Thiocyanate-Boronic Acid Cross-Coupling Reaction. Thiocyanate (0.1 mmol), boronic acid (0.15 mmol), CuTC (0.15-0.30 mmol), and Pd $(PPh_3)_4$ (3 mol %) were added into a flask and then flushed with argon. Then dry and degassed 1,4-dioxane (2 mL) was added. The brown suspension was stirred under the protection of argon at 100 °C for 12 h. After cooling to room temperature, 10 mL Et_2O was added and the reaction was quenched with sat. NH_4Cl followed by sat. Na_2CO_3 and then brine. After evaporation of the solvent, the residue was purified by preparative plate

---

[22] M. Barbero; I. Degan; N. Dialgheroff; S. Dughero; R. Fochi. *Synthesis* **2001**, *4*, 585.
[23] K. Pilgram; D.Phillips. *J. Org. Chem*. **1965**, *30*, 2388.

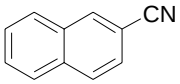
silica chromatography (SiO_2, 500 m, gradient of hexanes/EtOAc) to give the desired product.

Benzonitrile [24]



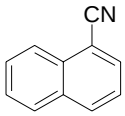
Purification by preparative TLC (Hexane/EtOAc 4:1) afforded the title compound as a colorless oil (9 mg, 90%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.67-7.59 (m, 3H), 7.50-7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0, 132.3, 129.3, 119.0, 112.6; IR (neat, cm^{-1}): 2231(s).

Naphthalene-2-carbonitrile [25]



Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (14 mg, 90%). Mp 65-66℃ (lit. {65-66℃}[25]); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.23 (d, J = 0.8 Hz, 1H), 7.92-7.88 (m, 3H); 7.67-7.59 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 134.3, 132.4, 129.4, 129.2, 128.6, 128.2, 127.8, 126.5, 119.4, 109.5; IR (neat, cm^{-1}): 2227(s).

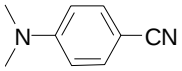
Naphthalene-1-carbonitrile [26]



[24] Fung, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 5713.
[25] House, H. O; Fisher, W. F. *J. Org. Chem,* **1969**, *34*, 3626.

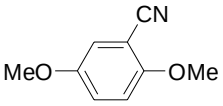
Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (12 mg, 82%). Mp 34-35℃ (lit. {33-34℃}[26]); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.95-7.92 (m, 2H); 7.73-7.69 (m, 1H), 7.65-7.61 (m, 1H), 7.55-7.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 133.1, 132.8, 132.5, 128.9, 128.8, 127.7, 125.3, 125.1, 118.0, 110.4; IR (neat, cm^{-1}): 2223 (s).

4-(Dimethylamino) benzonitrile [27]



Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a light blue solid (14 mg, 95%). Mp 75-76℃ (lit. {75-77℃}[27]); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H); 3.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 133.5, 121.0, 111.6, 97.5, 40.2; IR (neat, cm^{-1}): 2212 (s).

2, 5-Dimethoxybenzonitrile [28]



Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (15 mg, 90%). Mp 79-80℃ (lit. {80-81℃}[28]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (m, 2H), 6.92 (d, J=9.2 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 153.3, 121.0, 117.7, 116.6, 112.8, 102.0, 56.6, 56.1; IR (neat, cm^{-1}): 2227 (s).

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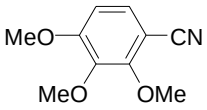
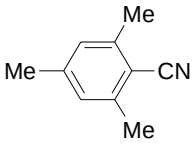
[26] Friedman, L.; Shechter, H. *J. Org. Chem*, **1961**, *25*, 2522.
[27] Chen, F.; Kuang. Y.; Dai. H.; Lu. L.; Huo. M. *Synthesis* **2003**, 2629.
[28] Wallenfels, K.; Hofmann, D.; Kern, R. *Tetrahedron* **1965**, *21*, 2231.

2,3,4-Trimethoxybenzonitrile [29]



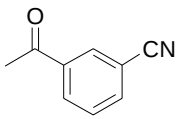
Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (16 mg, 85%). Mp 55-56℃ (lit. {52-55℃}[29]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 4.05 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 156.1, 142.1, 129.0, 107.7, 107.0, 99.3, 62.0, 61.3, 56.5; IR (neat, cm^{-1}): 2227 (s).

2,4,6-Trimethylbenzonitrile [30]



Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (11 mg, 76%). Mp 50-51℃ (lit. {50-52℃}[30]); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.93 (s, 2H), 2.48 (s, 6H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 142.2, 128.4, 117.8, 110.5, 21.8, 20.8; IR (neat, cm^{-1}): 2216 (s).

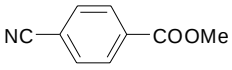
3-Acetylbenzonitrile [31]



[29] Kovach, E. G.; Barnes. D. E. *.J. Am. Chem. Soc.;* **1954**, *76*, 1176.
[30] Rutan, K. J.; Heldrich, F. J.; Borges, L. F. *J .Org. Chem.* **1995**, *60*, 2948.

Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (12 mg, 86%). Mp 97-98℃ (lit. {98 ℃}[31]); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.24-8.18 (m, 2H), 7.86-7.84 (m, 1H), 7.64-7.60 (m, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 137.6, 135.9, 132.1, 131.8, 129.7, 117.7, 113.0, 26.7; IR (neat, cm^{-1}): 2235 (m), 1683 (s).

4-Cyanobenzoic acid methyl ester [32]



Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (13 mg, 83%). Mp 65-66℃ (lit. {67-68℃}[32]); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.15 (m, 2H), 7.76 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 134.1, 132.4, 130.3, 118.1, 116.6, 52.9; IR (neat, cm^{-1}): 2231(m), 1725 (s).

4-Chlorobenzonitrile [33]

Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (11 mg, 80%). Mp 91-93 ℃ (lit. {90.5-91.5 ℃}[33]); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.62-7.60 (m, 1H), 7.48-7.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 133.6, 129.9, 118.2, 110.9; IR (neat, cm^{-1}): 2231 (s).

1,4-Dicyanobenzene [34]

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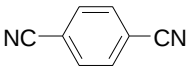
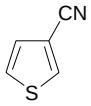
[31] Yamada, H. et al. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1459.
[32] Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 1118.
[33] Murahashi, S.; Naota, T.; Nakajima, N. *J. Org. Chem.* **1986**, *51*, 898.



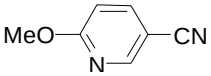
Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (10 mg, 80%). Mp 223-224℃ (lit. {226-227℃}[34]); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.80 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0, 117.2, 116.9; IR (neat, cm^{-1}): 2227 (s).

3-Cyanothiophene [35]



Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a light yellow oil (9 mg, 83%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.96 (dd, *J* = 3.2, 1.2 Hz, 1H), 7.45 (dd, *J* = 5.2, 3.2 Hz, 1H), 7.32 (dd, *J* = 5.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 128.9, 127.5, 115.3, 110.9; IR (neat, cm^{-1}): 2231(s), 1733(s).

6-Methoxynicotinonitrile [36]

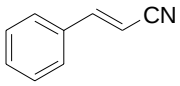


Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a white solid (11 mg, 84%). Mp 95-96℃ (lit. {97℃}[36]); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.4 Hz, 1H), 7.79 (dd, *J* = 8.8, 2.4 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 1H), 3.99 (s,

[34] Mulvaney, J. E.; Marvel, C. S. *J. Org. Chem.* **1961**, *26*, 95.
[35] Terui, Y.; Yamakawa, M.; Honma, T.; Yada, Y.; Tori, K. *Heterocycles*. **1982**, *19*, 221.
[36] Khanna, I. K.; Yu, Y.; Huff, R. M.; Weier, R. M.; Xu, X.; Koszyk, F. J.; Collins, P. W.; Cogburn, J. N.; Isakson, P. C.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Yuan, J.; Yang, D-C.; Zhang.Y. Y. *J. Med. Chem.* **2000**, *43*, 3168.

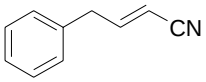
3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.25, 152.2, 141.0, 117.5, 112.0, 102.6, 54.5; IR (neat, cm^{-1}): 2231(s), 1602 (s).

trans-3-Phenyl-2-propenenitrile [37]



Purification by preparative TLC (hexane/EtOAc 4:1) afforded the title compound as a colorless oil (10 mg, 82%). ^{1}H NMR (400MHz, $CDCl_3$) δ7.46-7.39 (m, 6H), 5.85 (d, J = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15 0.8, 133.7, 131.4, 129.3, 127.5, 118.3, 96.5. IR (neat, cm^{-1}): 2219(s).

trans-4-Phenyl-2-butenenitrile [38]



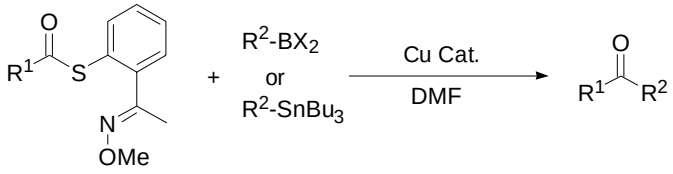
Purification by preparative TLC (hexane/EtOAc 4:1) afforded a colorless oil (11 mg, 75%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.36-7.14 (m, 5H), 6.92 (dt, J = 16.4, 6.4 Hz, 1H), 5.31 (dt, J = 16.4, 1.6 Hz, 1H), 3.55 (dd, J = 6.4, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 136.2, 129.1, 129.0, 127.4, 117.5, 101.0, 39.5; IR (neat, cm^{-1}): 2223(s).

[37] Hamza, K.; Abu-Reziq, R.; Avnir, D.; Blum, J. *Org. Lett*. **2004,** *6*, 925.
[38] Inaba, S.; Matsumoto, H.; Rieke, R. *J. Org. Chem.* **1984***, 49*, 2093.

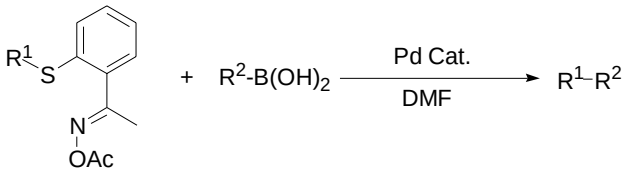
Chapter 2

Metal-Catalyzed Desulfitative Cross-Coupling Reactions for Carbon-Carbon Bonds Formation

***Abstract**: Modeled from a biochemical process of metallothioneins (MT), in which the Cu(I) is rapidly released from the strongly binding thiolate by exposure to an exogenous disulfide ligand, a novel MT-mimic catalyst system has been developed for the construction of new C-C bonds through the Cu or Pd-catalyzed desulfitative reaction. An efficient Cu-catalyzed cross-coupling of thiol esters containing an o-mercaptoacetophenone O-methyl oxime pendant with a wide range of aryl, heteroaryl, alkenyl and even alkyl boron as well as stannane reagents has been developed for the synthesis of ketones (Scheme 2.1). This study revealed the potential of more thioorganics to participate in the Pd-catalyzed desulfitative coupling with boronic acids using MT-mimic (Scheme 2.2). The application of this "metallothionein mimic" concept may prove useful for selective carbon-carbon bond formation in more complex molecules.*



Scheme 2.1 Cu-catalyzed Coupling of Thiol esters with Organoborons and Organostannanes

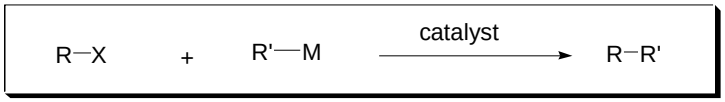


Scheme 2.2 Pd-Catalyzed Desulfitative Couplings

2.1 Introduction and Background

Carbon-carbon bond formations are the most important processes in the organic chemistry. Metal-mediated cross-coupling reactions between molecules provide powerful

methodologies for the construction of these bonds. In the recent decades, a variety of cross-coupling reactions have been developed and they are extensively employed in the area of organic synthesis. Most of these reactions utilize electrophilic organic halides or triflates reacting with a variety of nucleophilic organometallic reagents (**Scheme 2.3**).[39]



X= halogen, OTf ...

M= Li (Murahashi)
Mg (Kumada-Tamao)
B (Suzuki-Miyaura)
Zn (Negishi)
Cu (Normant)
Sn (Stille)
Si (Hiyama, Denmark)
Al, Zr...

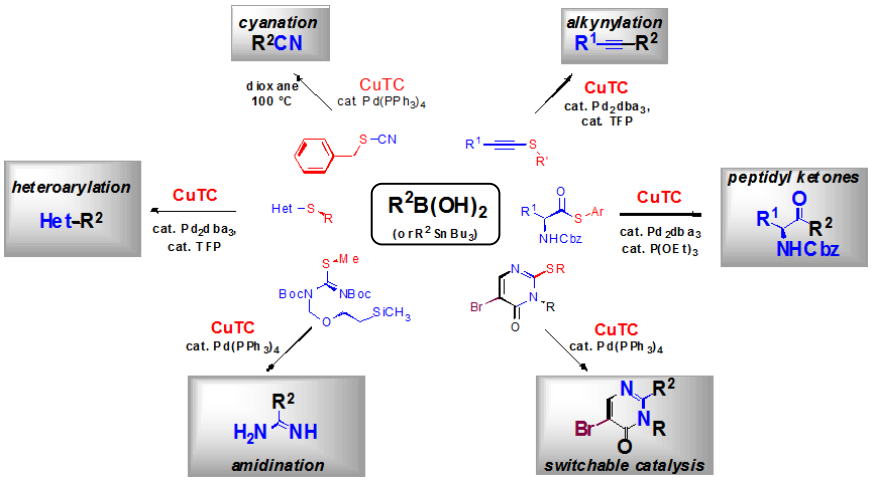
Scheme 2.3 General Transition Metal-Catalyzed Cross-Coupling Reaction of Organic Halides with Organometallic Reagents

For the last few years, the Liebeskind laboratory has focused on uncovering new C-C bond forming transformations through the cross-couplings of the thiooragnics with mild organometallic reagents such as organoboron or stannane under neutral conditions. The hypothesis was that the different polarizabilities of C-S bonds compared to those of C-halogen and C-O bonds would provide opportunities for unique chemoselectivities not achievable with halide and triflate-based couplings. Guided by this goal, cross-couplings of thioorganics with boronic acids (and organostannanes) have been developed by this laboratory and extended by others.[40] All reactions required catalytic amount of Pd and

[39] *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH, Weinheim, 1998.

[40] For selected examples see: (a) Srogl, J.; Liebeskind, L. S. *J. Am. Chem.Soc.* **2000,** *122*, 11260-11261. (b) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett*. **2002**, *4*, 983-985. (c) Zhang, Z.; Liebeskind, L. S. *Org. Lett.* **2006**, *8*, 4331-4333. (d) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007,** *129*, 1132-1140. (e) Li, H.; Yang, H.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 4375-4378. (f) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803. (g) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Synlett* **2002**, *3*, 447. (h)

stoichiometric amount of Cu^{I} carboxylate (or diphenylphosphinate) as reaction mediator (**Scheme 2.4**).



Scheme 2.4 A Family of Palladium-Catalyzed, Copper Carboxylate Mediated Desulfitative Couplings

In order to understand the mechanistic details of the first-generaion desulfitative couplings, computational studies by Dr. Djamaladdin Musaev were performed.[41] The previous speculations about the mechanism (**Scheme 1.8**) of palladium-catalyzed, Cu(I) carboxylate mediated couplings were generally derived from the experimental observations. In contrast to the hypothetical model suggested in Scheme 18, the computational study demonstrated an unprecedented attribute of the carboxylate counterion in this transformation.

Lengar, A.; Kappe, C. O. *Org. Lett.* **2004**, *6*, 771. (i) Oumouch, S.; Bourotte, M.; Schmitt, M.; Bourguignon, J.-J. *Synthesis* **2005**, 25. (j) Morita, A.; Kuwahara, S. *Org. Lett.* **2006**, *8*, 1613.; For selected reviews see: (a) Lory, P.; Gilbertson, S. R. *Chemtracts* **2005,** *18*, 569-583. (b) Prokopcova, H.; Kappe, C. O. *Angew. Chem. Int. Ed*. **2009**, *48*, 2276-2286

[41] Musaev, D. G.; Liebeskind, L. S. *Organometallics* **2009**, DOI**:** 10.1021/om900602b.

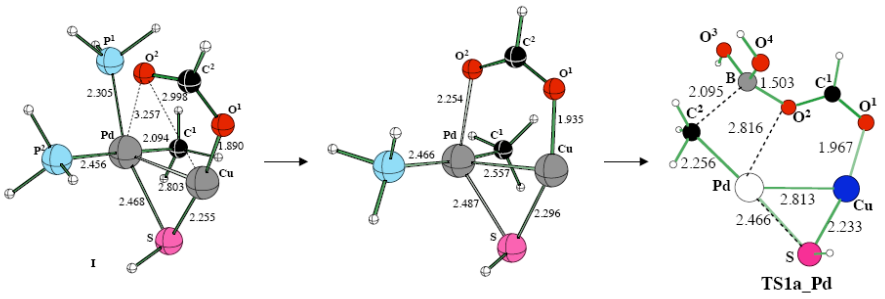
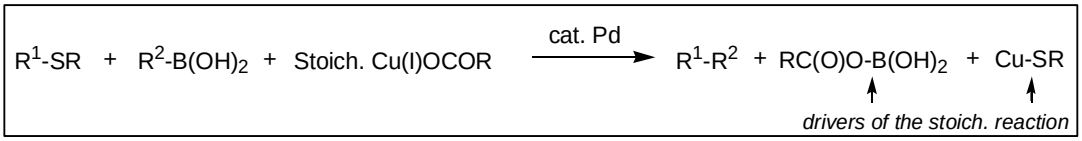


Figure 2.1 Computational Study of the Role of Cu(I) Carboxylate in the 1st Generation Desulfitative Coupling

As shown in **Figure 2.1**, the carboxylate on Cu displaces one phosphine ligand from the Pd-complex to form a more electrophilic and less hindered Pd monophosphine intermediate. This would be more effective at transmetallation with the boronic acid. The transmetallation from boron to palladium is enhanced by coordination of the carboxylate to the trivalent boron center, thus activating the boronic acid and bringing it in proximity to the Pd-complex. The Cu(I) center of the complex also thermodynamically promotes the transmetallation by forming a strong Cu－S bond. Comparing these computational results with the originally proposed mechanism (**Scheme 1.8**), we can see the Cu(I) still functions as a thiophilic agent to weaken the Pd－S bond and render the Pd-thiolate complex more electrophilic. And the carboxylate ligand serves dual roles, not only providing kinetic activation through RC(O)O－B interactions but also facilitating the dissociation of a phosphine ligand from the palladium center.

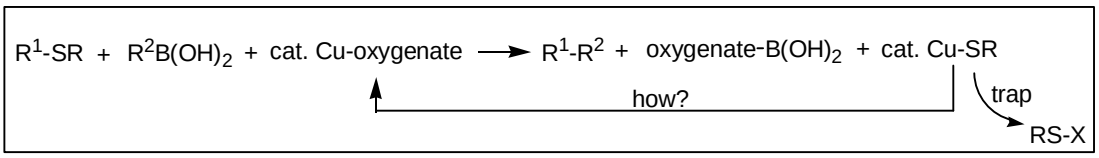
All first-generation Pd catalyzed desulfitative chemistries require at least stoichiometric quantity of a Cu(I) carboxylate cofactor. In addition to providing the dual kinetic activations through the Cu(I) － S (soft-soft) and RC(O)O － B (hard-hard) interactions to enhance the transmetallation, the stoichiometry of Cu(I) carboxylate could be rationalized by the simple balancing of a generic reaction equation. Cu(I) carboxylate

was used to completely scavenge the thiolate by forming CuSR, and thermodynamically balance the reaction by providing a full equivalent of carboxylate counterion to pair with -$B(OH)_2$ moiety (**Scheme 2.5**).



Scheme 2.5 Stoichiometry of the First-Generation Desulfitative Couplings

Based on the understanding of the first-generation desulfitative coupling of thioorganics with boronic acids, the challenge to develop the second-generation cross-couplings that are catalytic in Cu would be how to convert the formed Cu-SR to a catalytically viable Cu-oxygenate and, in the meantime, trap the thiolate (-SR) as a weekly binding species (X-SR) to Cu (**Scheme 2.6**).



Scheme 2.6 The Catalytic Challenge

The second-generation Cu-catalyzed desulfitative coupling system was inspired by the biochemical and bioinorganic literature on metallothioneins (**MT**).[42] (**Figure 2.2**) Metallothioneins are relatively small proteins comprised of roughly 30% cystein residues; they bind up to 7 equivalents of divalent metals such as Zn and Cu. Although surrounded by 4 tightly bound thiol/thiolate ligands, the metal is rapidly released when an MT is exposed to an exogenous disulfide (**Scheme 2.7**).[43] The release of metal is assumed to

[42] (a) Blindauer, C. A.; Sadler, P. J. *Acc. Chem. Res.* **2005,** *38*, 62-69. (b) Henkel, G.; Krebs, B. *Chem. Rev.* **2004,** *104*, 801 - 824. (c) Kägi, J. H. R.; Schäffer, A. *Biochemistry* **1988,** *27*, 8509 - 8515.
[43] (a) Maret, W.; Vallee, B. L. *Proc. Nat. Acad. Sci.* **1998**, 95, 3478 - 3482. (b) Jacob, C.; Maret, W.; Vallee,

proceed by way of “oxidation” of a bound cysteinate ligand to a more weakly binding disulfide ligand through a disulfide exchange mechanism.

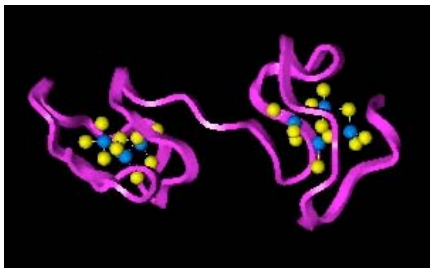
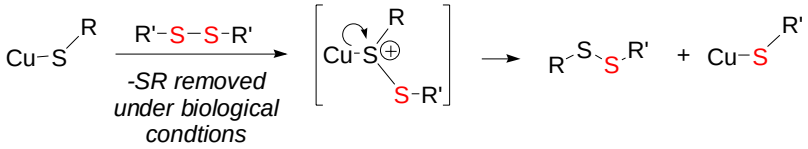


Figure 2.2 A Representative Metallothioneins (yellow=S, blue=Cu)



Thiolate → Disulfide: an "oxidative trap” of a strong thiolate ligand

Scheme 2.7 Liberating Cu from the Thiolate Ligand by Oxidative Trap of Thiolate

This "natural" means of liberating a strongly bound metal from a sulfur-rich environment suggests a partial laboratory-based solution to the catalytic challenge of the second-generation desulfitative cross-coupling. The exposure of metallothioneins to exogenous disulfides could remove the strongly binding thiolate (-SR) from Cu by forming a weakly binding disulfide, but the released Cu was re-bonded to a new thiolate (Cu-SR’) rather than generating a catalytically active Cu-oxygenate for the chemical catalysis. Therefore, to fulfill the catalytic requirements, we should find a disulfide variant that could not only transform the thiolate to a weakly binding disulfide or disulfide equivalent but also convert the liberated Cu to a catalytically viable Cu-oxygenate. From chemical literature, we found a practical thiolate trap process from the

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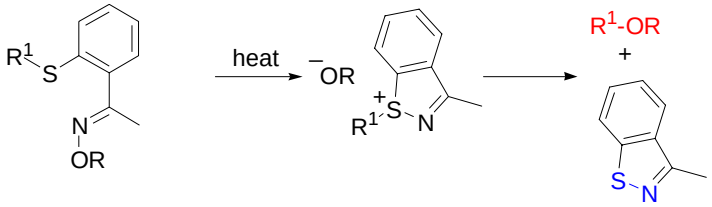
B. L. *Proc. Nat. Acad. Sci.* **1998**, 95, 3489 - 3494. (c) Maret, W. *Neurochem. Int.* **1995**, *27*, 111-117.

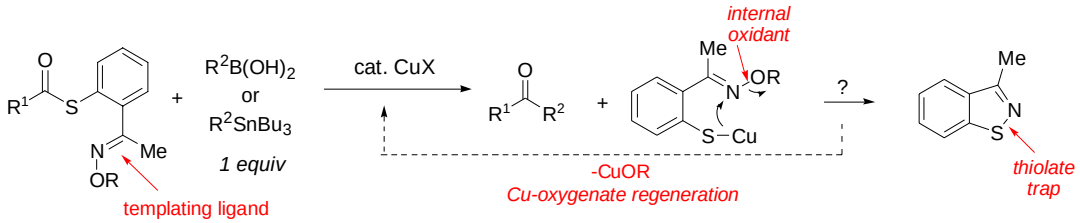
conversion of 2-(alkylthio)phenyl ketoxime derivatives to 1,2-benzisothiazole through a S→N closure. (**Scheme 2.8**).[44] Moreover, this transformation generated an oxygenate counterion (-OR) which is required in thioorganics-boronic acid cross-coupling under neutral conditions. These results shed light on the way to solve the challenge of developing second-generation thioorganic-boronic acid cross-couplings that use only catalytic amount of Cu.



Scheme 2.8 Cyclization of 2-(alkylthio)phenyl ketoxime derivatives

Based on these processes, a "metallothionein mimic" thiol ester was designed, which possesses an oxime functionality as the templating ligand for Cu and internal oxidative trap for the thiolate (**Scheme 2.9**). In this way, the resulting Cu-thiolate would react with the *ortho* oxime functional group to form a 3-methyl-1,2-benzisothiazole through the similar process to the 2-(alkylthio)phenyl ketoxime shown in **Scheme 2.8** and generate a viable Cu-oxygenate. The internal oxime pendant also provides stoichiometric oxygenate (-OR) to pair with boronic acid (-$B(OH)_2$) or organostannane (-$SnBu_3$) residue. In principle, the reaction could proceed under neutral conditions without adding any oxygenate bases.

[44] (a) Pedras, M. Soledade. C.; Suchy, Mojmir. *Bio & Med Chem*, **2006**, *14*, 714. (b) Creed, T; Leardini, R; McNab, H; Nanni, D; Nicolson, I. S.; Reed, D. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 1079. (c) Lawson, A.J. *Phosphorus and Sulfur*, **1982**,12, 357-367.

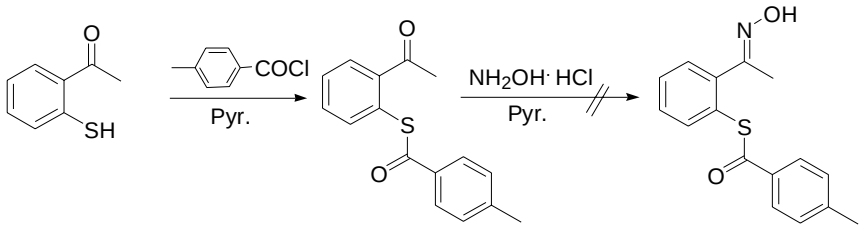


Scheme 2.9 Design of a 'MT mimic' Cu-Catalyzed Desulfitative Coupling System

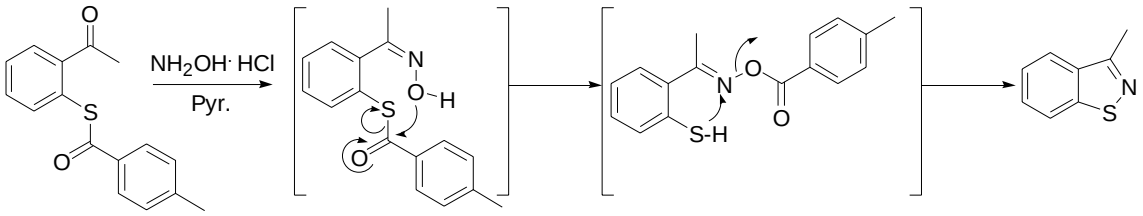
2.2 Results and Discussion

2.2.1 Preparation of Starting Materials

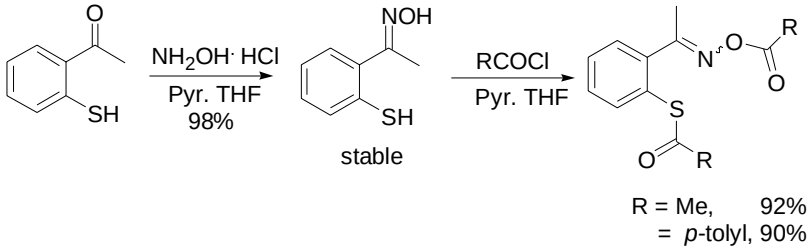
The thiol esters with oxime pendants were prepared from 2-mercaptoacetophenone. In the initial route, the commercially available 2-mercaptoacetophenone was treated with acid chloride to give the corresponding thiol ester in good yield. However, the reaction of the resulting 2-acetyl phenyl thiol ester with hydroxylamine did not lead to the desired oxime (**Scheme 2.10**). The only product obtained from this reaction was 3-methyl-1,2-benzisothiazole. A possible explanation of this observation is that after condensation the oxime oxygen rapidly attacked the neighboring thiol ester through a intramolecular ester exchange mechanism. The resulting thiol could cyclize with *O*-acyl oxime affording the observed 3-methyl-1,2-benzisothiazole (**Scheme 2.11**). To solve this problem, the following procedure was utilized to prepare the thiol esters containing an *O*-acyl oxime pendant. First, 2-mercaptoacetophenone was treated with hydroxylamine and the resulting 2-mercaptoacetophenone oxime was converted to the thiol ester and *O*-acyl oxime via exposure to acid chloride. This route furnished the required starting materials in high yields (**Scheme 2.12**).



Scheme 2.10 Unsuccessful Preparation of Oxime

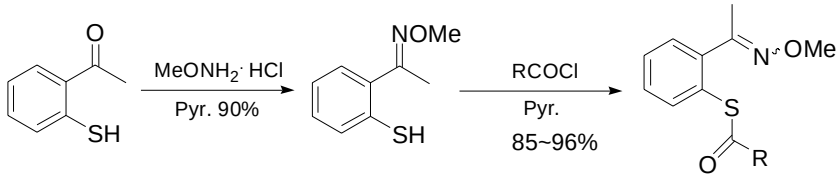


Scheme 2.11 Proposed Reaction Passway



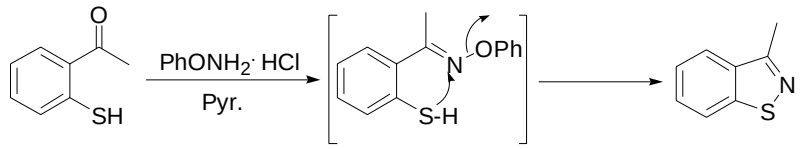
Scheme 2.12 Preparation of Thiol Esters with *O*-Acyl Oxime Pendant

Following a similar procedure, the reaction of 2-mercaptoacetophenone and *O*-methylhydroxylamine hydrochloride generated the corresponding 2-mercaptoacetophenone *O*-methyl oxime, which was treated with acid chlorides to give a variety of thiol esters with an *O*-methyl oxime pendant (**Scheme 2.13**).

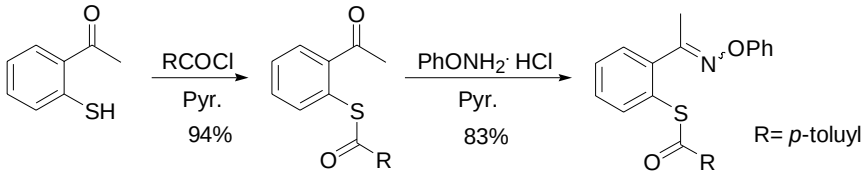


Scheme 2.13 Preparation of Thiol Esters with *O*-Methyl Oxime Pendant

An unexpected cyclization took place in the preparation of thiol esters containing an *O*-phenyl oxime pendant. As shown in **Scheme 2.14**, treatment of 2-mercaptoacetophenone with *O*-phenyl hydroxylamine led to the formation of 3-methyl-1,2-benzisothiazole. The generated 2-mercaptoacetophenone *O*-phenyl oxime may be more reactive for the cyclization than the *O*-methyl oxime counterpart. After experimentation, an optimized method was developed for the preparation of thiol esters containing the *O*-phenyl oxime pendant. The S→N closure was suppressed by acylation of 2-mercaptoacetophenone to give the corresponding thiol ester. The ketone was converted to the *O*-phenyl oxime by treatment with *O*-phenyl hydroxylamine hydrochloride under basic conditions (**Scheme 2.15**).



Scheme 2.14 An Unexpected Cyclization

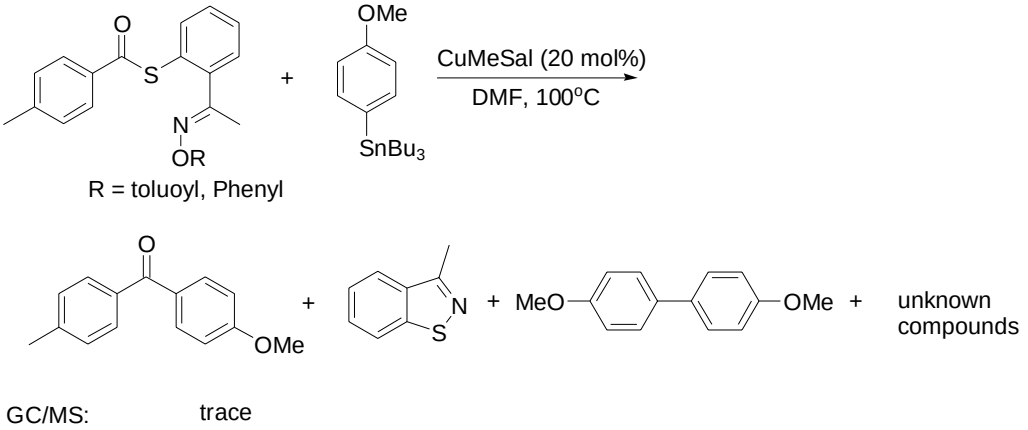


Scheme 2.15 Preparation of Thiol Esters with *O*-Phenyl Oxime Pendant

2.2.2 Cu-Catalyzed Cross-Coupling of Thiol esters with Organostannanes

It was assumed that electron withdrawing *O*-substitutions would weaken the N-O bond and facilitate its cleavage. Thus, thiol esters containing an *O*-acyl oxime pendant were tried first in the Cu-catalyzed cross-coupling with *p*-methoxyphenyltributylstannane and 20 mol% of Cu^{I}-3-methylsalicylate (CuMeSal) in DMF at 100℃. As shown in **Scheme**

2.16, only a trace of the desired ketone product was observed along with 3-methyl-1,2-benzisothiazole. The homocoupling product of *p*-methoxyphenyltributylstannane was present as well as some unidentifiable compounds. Similar results were noted when thiol esters with *O*-phenyl oxime pendant were employed in this reaction.

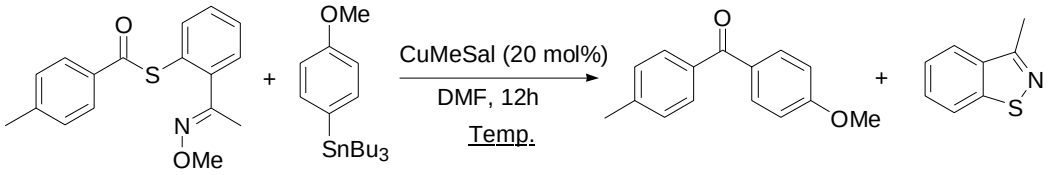


Scheme 2.16 Coupling of Thiol Esters with *O*-Acyl or *O*-Phenyl Oxime Pendant

Although ketones were produced in very low yields from above couplings, the starting thiol esters were not recovered. This result indicated that some side-reactions were taking place that predominated over the desired cross-coupling at C-S bond of the thiol ester. Previous studies in our laboratory have discovered the efficient Cu^{I}-mediated C-N bond formation through N-O bond cleavage of hydroxylamine derivatives.[45,46,47] Thus, the precedented N-O bond cleavage chemistry could possibly interfere with the desired thiol ester cross-coupling. The efforts towards to suppressing this side-reaction at the N-O bond were then focused on optimizing the oxime pendant. After a series of control experiments, it was found that the electron-rich *O*-methyl oxime did not react with boronic acid or organostannane in the presence of Cu^{I}. As a result, *O*-methyl oxime was

[45] Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007,** *9,* 1947-1950.
[46] Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008,** *10*, 3005-3008.
[47] See **Chapter 3**

employed as the *S*-pendant for thiol esters in this cross-coupling. When heating the thiol ester containing the *O*-methyl oxime pendant with 1.1 equiv *p*-methoxyphenyltributylstannane and 20 mol% CuMeSal in DMF at 100℃, the desired ketone product and 3-methyl-1,2-benzisothiazole were obtained in 80% and 72% yields respectively (**Scheme 2.17**). So the incorporated oxime pendant works both as a templating ligand of Cu and a internal trap of thiolate.

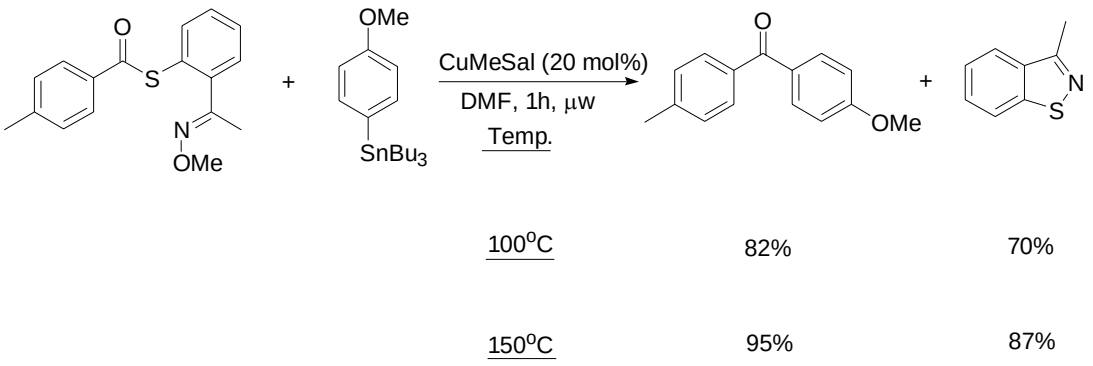


Temp.		
100°C	80%	72%
80°C	61%	58%
60°C	28%	24%

Scheme 2.17 Cu-catalyzed Coupling of the Thiol Ester with the Organostannane

Although the *O*-methyl oxime exists as a mixture of *E/Z* isomers in 6:1 ratio, they inter-convert under the reaction conditions[48] allowing both isomers to participate in the coupling. At lower temperature the reaction did not reach completion and the products were isolated in low to moderate yields (**Scheme 2.17**). Further optimization revealed that the reaction could be significantly accelerated under microwave irradiation at 150 °C (**Scheme 2.18**).

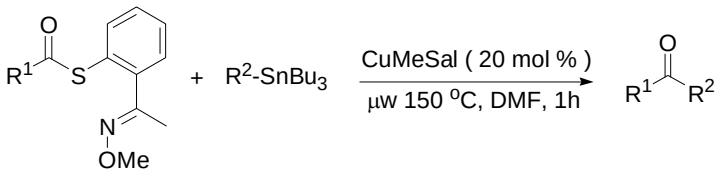
[48] (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.*, **2004**, *126*, 9542–9543; (b) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett*. **2006**, *8*, 1141-1144.



Scheme 2.18 Microwave Promoted Cross-coupling

Under the optimal conditions the generality of this new "metallothionein mimic" cross-coupling was studied through the reaction of various thiol esters and organostannanes with 20 mol% CuMeSal. As shown in **Table 2.1**, aromatic, heteroaromatic, and aliphatic thiol esters could be coupled with electron-rich and electron-poor aromatic and heteroaromatic stannanes providing the desired ketones in good yields. The 4-iodophenyl moiety (entry 3) was tolerated as was modest steric hindrance in the organostannanes (entry 5).

Table 2.1 Cu-Catalyzed Cross-Coupling of Thiol Esters with Organostannanes



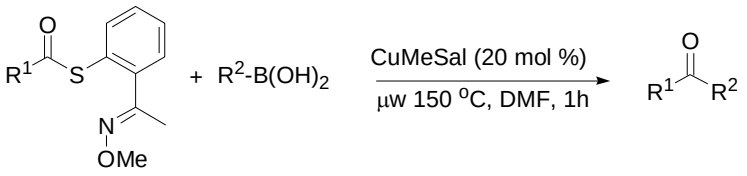
entry	R^1	R^2	ketone (%)[a]
1	*p*-toluyl	4-methoxyphenyl	95
2	*p*-toluyl	4-fluoro-3-methylphenyl	81
3	*p*-toluyl	4-iodophenyl	68
4	thienyl	4-methoxyphenyl	86
5	*n*-propyl	3-methoxypyridin-2-yl	70
7	*cyclo*-hexyl	4-methoxyphenyl	62

a. isolated yield

2.2.3 Cu-Catalyzed Cross-Coupling of Thiol esters with Boronic Acids

Boronic acids also proved to be excellent reaction partners in Cu-catalyzed couplings with thiol esters under the same reaction conditions (**Table 2.2**).

Table 2.2 Cu-Catalyzed Cross-Coupling of Thiol Esters with Boronic acids



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

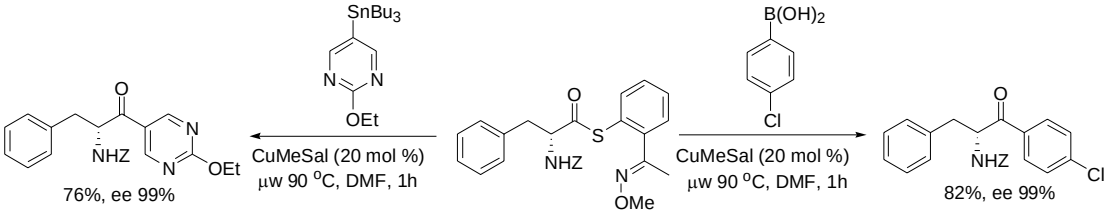
a. isolated yield

Electron-deficient (entries 1-5) and electron-rich (entries 6-7) aryl boronic acids participated efficiently in the reaction. The coupling of alkenyl (entry 8) and heteroaryl (entry 10) boronic acids was also possible. This reaction can accommodate significant variation in the nature of the acyl moiety (entries 8-12). The protocol could tolerate a variety of functional groups such as chloro, cyano, ester, ketone, aldehyde and phenol (entry 1-6).

2.2.4 Synthesis of High Enantiopurity Peptidyl Ketones

The generality and functional group compatibility led to the extension of this coupling to the phenylalanine derived thiol ester with boronic acids and organostananes for the

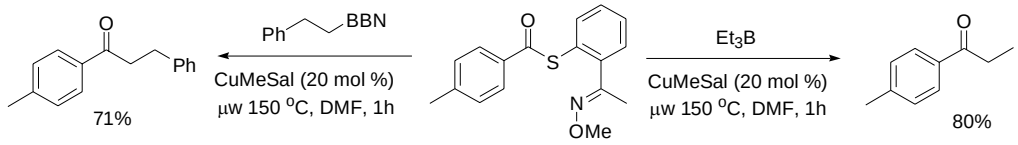
synthesis of high enantiopurity peptidyl ketones (**Scheme 2.19**). Both reactions proceeded well to afford α-amino ketones in good yields. No racemization was detected during the cross-coupling process. Compared with the previous coupling of thiol esters (**Table 2.2**), the reaction of amino acid derived thiol ester took place at lower temperature.



Scheme 2.19 Synthesis of High Enantiopurity Peptidyl Ketones

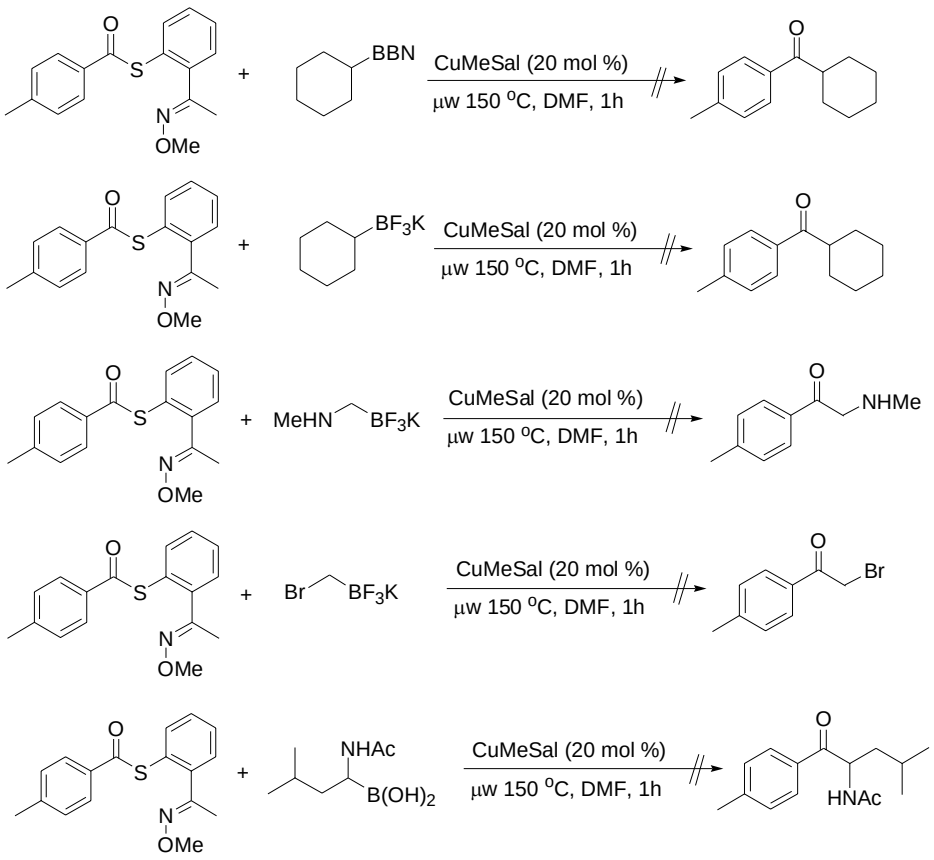
2.2.5 Cu-Catalyzed Cross-Coupling of Thiol esters with Alkyl Boron Reagents

It is worth noting that under the same reaction conditions, aliphatic boron reagents were also suitable reaction partners in this chemistry. *B*-2-Phenylethyl-9-BBN and triethyl boron gave the corresponding ketones in 71 and 80% yields respectively (**Scheme 2.20**).



Scheme 2.20 Cu-Catalyzed Cross-Coupling with Alkyl Boron Reagents

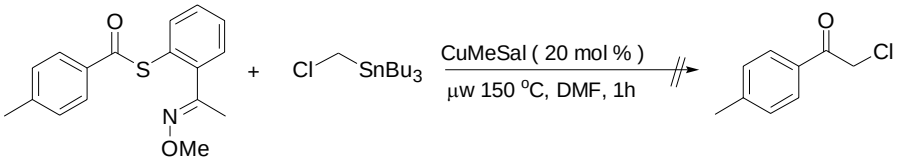
However the coupling of secondary alkyl boron reagents and α-functionalized alkyl boron reagents was not successful (**Scheme 2.21**). The starting material and 3-methyl-1,2-benzisothiazole were recovered after attempted reactions.



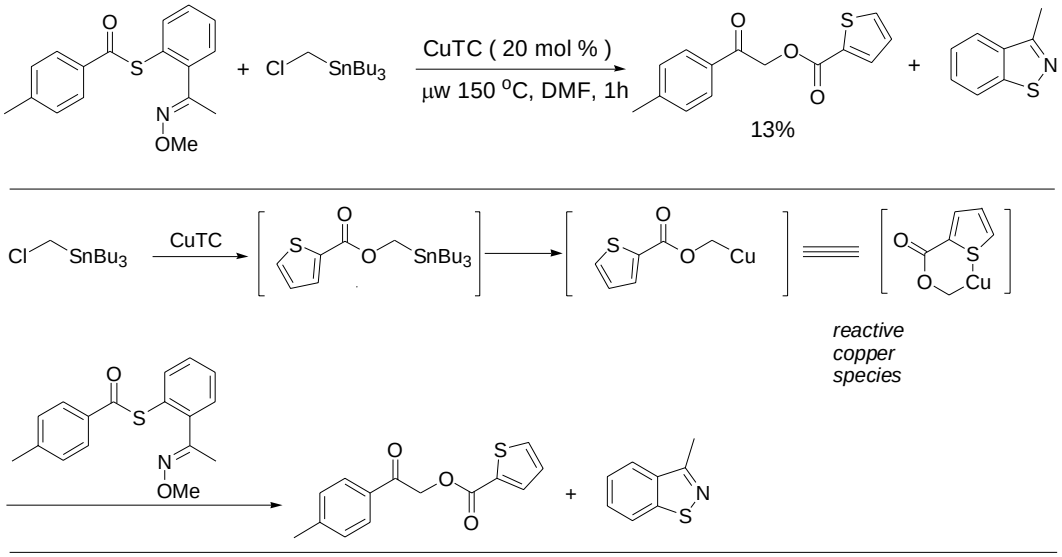
Scheme 2.21 *B-sec*-Alkyl and α-Functionalized Alkyl Boron Reagents in Coupling

2.2.6 Cu-Catalyzed Cross-Coupling of Thiol esters with Alkyl Tin Reagents

CuMeSal-catalyzed coupling of thiol esters with alkyl tin reagents were also studied. Specifically, the coupling of chloromethyltributylstannane was initially carried out but no ketone product was detected (**Scheme 2.22**). Unexpectedly, the coupling afforded an α-hydroxyl ketone derivative in 13% yield when CuTC was employed. (**Scheme 2.23**). This unusual reactivity was rationalized by the displacement of chlorine by TC- (thiophene carboxylate) followed by transmetallation generating a active copper species which would react with the thiol ester to provide the observed ketone. This result suggested that the α-functional group of the alkyl stannane played a key role in the reaction.



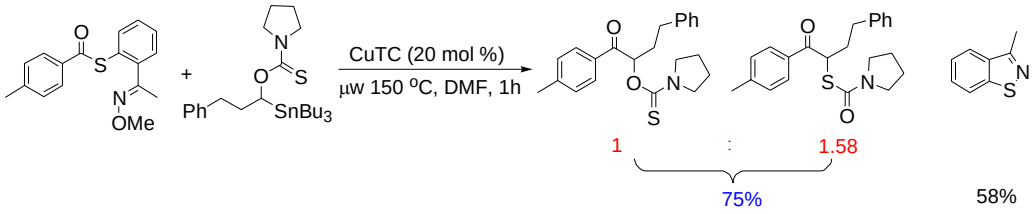
Scheme 2.22 CuMeSal-Mediated Coupling of Chloromethyltributylstannane



Scheme 2.23 CuTC-Mediated Coupling of Chloromethyltributylstannane

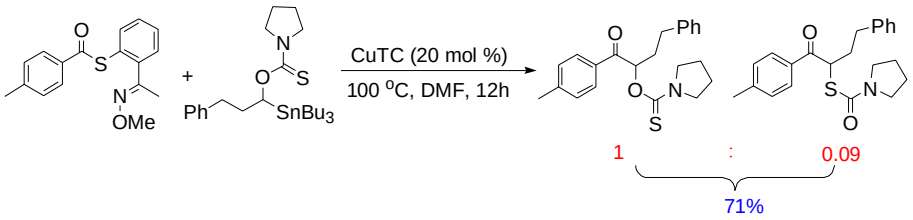
In the unpublished results of this laboratory, Mr. Hao Li discovered a Cu-mediated cross-coupling of α-(thiocarbamoyl)organostannanes with thiol esters.[49] In this chemistry the α-(thiocarbamoyl) group of the alkyl stanane is very important to facilitate the reaction. Due to its high reactivity in the cross-coupling, α-(thiocarbamoyl)organostannanes was employed in the reaction of thiol esters containing an *O*-methyl oxime pendant. As expected, this process was catalytic in copper affording the desired ketone in good yield. Unfortunately, S→O rearrangement was observed during the process (**Scheme 2.24)**.

[49] Unpublished results of the Liebeskind group.



Scheme 2.24 Coupling of α-(Thiocarbamoyl)organostannanes

Further experiments towards to suppressing this S→O rearrangement led to some observations. Different Cu sources (CuMeSal, CuCl) did not significantly alter the ratio of the two ketone products; Decreasing the copper catalyst loading could diminish the S→O rearrangement slightly, but it also reduced the product yield; The best result was obtained when the reaction was treated with 20 mol% of CuTC at 100℃. The S→O rearrangement was significantly reduced and the coupling gave desired α-hydroxyl ketone in good yields (**Scheme 2.25**).

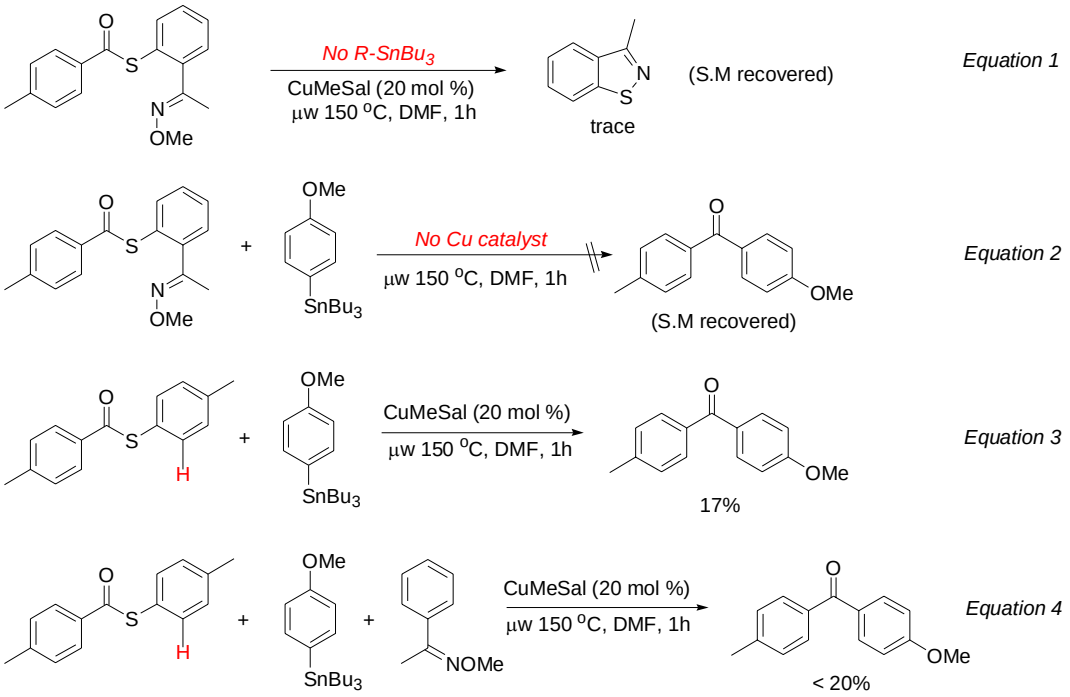


Scheme 2.25. Cu-catalyzed Coupling of α-(Thiocarbamoyl)organostannanes

2.2.7 Mechanistic Study

To probe the mechanism of this Cu-catalyzed desulfitative coupling some control experiments were carried out and led to the following observations (**Scheme 2.26**). Heating a mixture of thiol ester with the *O*-methyl oxime pendant and CuMeSal only produced a trace of 3-methyl-1,2-benzisothiazole and most of the starting material was recovered (Equation 1). This result suggested the facile S→N closure in Cu-catalyzed thiol ester cross-couplings could proceed through a Cu-thiolate intermediate; The copper

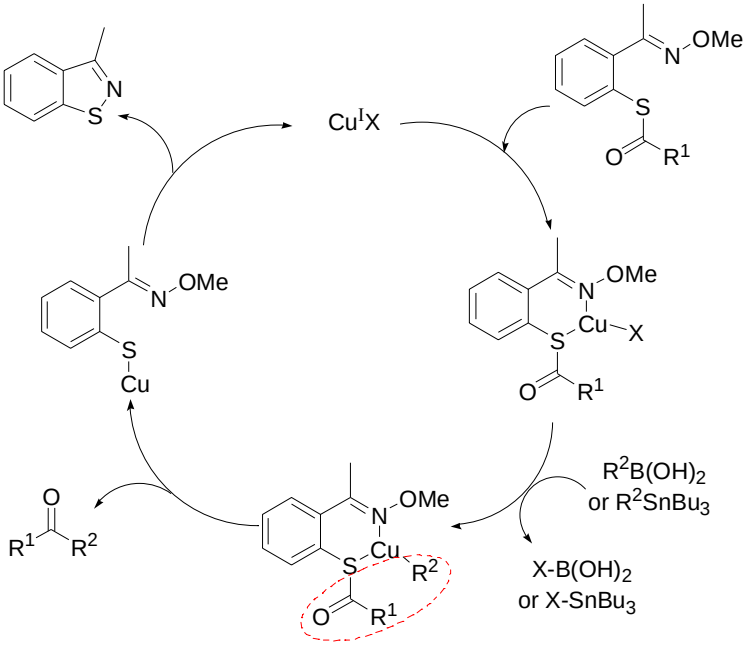
catalyst is necessary for the cross-coupling since the thiol ester did not react with the organostanane in the absence of the catalyst (Equation 2). The incorporated 2-mercapto-acetophenone *O*-methyl oxime pendant is crucial for the catalysis, otherwise reactions appeared to be stoichiometric in Cu (Equations 3 and 4). Equation 4 also indicated that the internal oxime pendant could not be replaced by an exogenous oxime species.



Scheme 2.26 Some Control Experiments

Control experiments with other copper (I) salts showed that they were all able to catalyze this desulfitative cross-coupling, regardless of the nature of counterion (X= Cl, I, TC). All reactions were carried out under an inert atmosphere, so Cu^{I} would be the reactive catalyst. Since there is no precedent for the oxidative addition of a thiol ester to Cu^{I}, this new Cu catalysis could follow a mechanism different from the traditional metal-mediated cross-coupling mechanism (oxidative addition-transmetallation-reductive elimination). Based on the control experiments and previous studies of the aerobic Cu-

mediated coupling,[50] a 'metallothionein mimic' Cu^I-templated cross-coupling of the thiol ester with the organoboron and organostannane was proposed (**Scheme 2.27**).



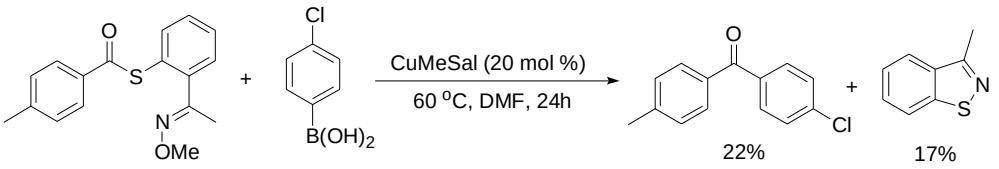
Scheme 2.27 Proposed Mechanism

It was assumed that the coupling starts with coordination of Cu^I to the thiol ester, followed by a transmetallation from boron/tin to Cu^I.[51] Templating by Cu through *S,N*-chelation brings the two reactive centers (thiol ester and R_2) in proximity and simultaneously provides double activation of electrophilic thiol ester and nucleophilic organometallic moiety (R_2) through electronic resonance. The ketone is formed through this Cu-templated interaction along with a Cu-thiolate. The Cu catalyst is regenerated by the reaction of the Cu-thiolate with the internal oxime functionality through a 'metallothionein mimic' mechanism. Therefore, the incorporated coordinating oxime pendant can not only preassociate the reactants and lower the energetic barrier to

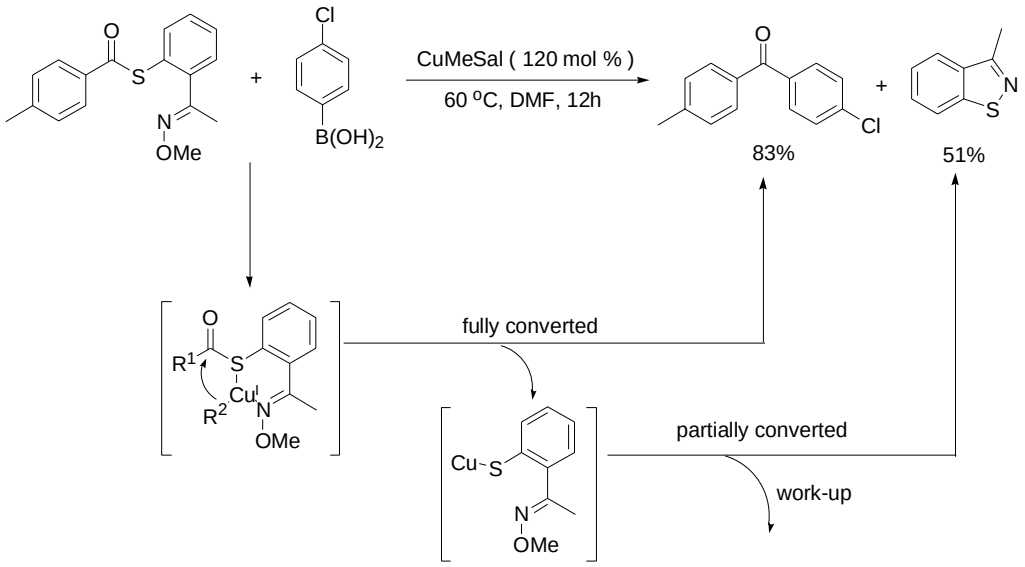
[50] Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007,** *129*, 15734-15735; Liebeskind, L. S.; Yang, H.; Li, H. *Angew. Chem. Int, Ed.* **2009**, *48*, 1417－1421.
[51] Allred, G. D. Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748-2748

reaction, but also oxidatively scavenge the thiolate and regenerate the active copper catalyst.

One possible limitation of this novel Cu catalysis is that the reaction usually proceeds at high temperature. According to the above suggested mechanism, the rate-determining step (RDS) in the catalytic cycle could reside in any of the following processes: B(Sn)→Cu transmetallation, templated C-C formation and S→N closure for the regeneration of catalyst. To determine the RDS in this transformation, two cross-couplings of the thiol ester with 4-chlorophenyl boronic acid were carried out by applying catalytic (**Scheme 2.28**) and stoichiometric (**Scheme 2.29**) amount of CuMeSal at 60 ℃. As shown, the catalytic transformation gave a very low yield of ketone even after prolonged time. Conversely, the stoichiometric reaction went to completion affording the ketone in 83% yield. Interestingly, a greater amount of ketone (83%) was obtained than of 3-methyl-1,2-benzisothiazole (51%). The reaction going to completion suggests that the B→Cu transmetallation and the templated C-C formation take place at 60℃， so the thiol ester was fully converted to the ketone. In the proposed catalytic cycle (**Scheme 2.27**), the Cu-thiolate would react with the oxime functionality to regenerate the copper catalyst and scavenge the thiolate as 3-methyl-1,2-benzisothiazole. As a result, the ketone and 3-methyl-1,2-benzisothiazole should be formed in 1:1 ratio. However, in the stoichiometric reaction 3-methyl-1,2-benzisothiazole was produced in a lower yield than ketone, which implied that the Cu-thiolate was only partially converted to 3-methyl-1,2-benzisothiazole. These observations pointed to the S→N closure/catalyst regeneration as the rate-determining step in the catalytic cycle, which requires high temperature to take place.



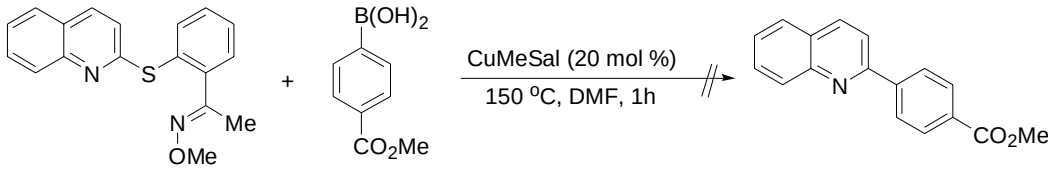
Scheme 2.28 Cu-catalyzed Coupling at Lower Temperature



Scheme 2.29 Incomplete Regeneration of Copper Oxygenate at Lower Temperature

2.2.8 Pd-Catalyzed Couplings of Thiol Esters with Boronic Acids

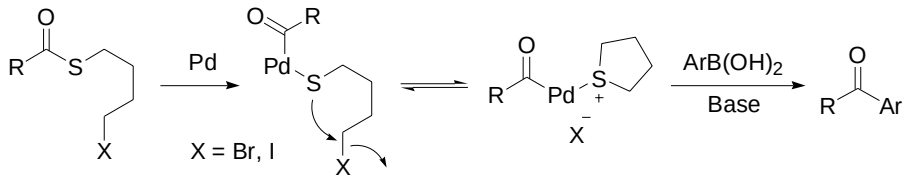
Due to their unique chemoselectivities and mild reaction conditions, the metallothionein mimic Cu-catalyzed desulfitative couplings hold great promise if they can be ported to a broad range of thioorganic reactants. However, studies showed this system could only be used in the reaction of thiol esters. As an example shown in **Scheme 2.30**, under standard conditions, the coupling of 2-quinoline thioether with boronic acid failed to produce any arylation product.



Scheme 2.30 Coupling of the Heteroaromatic Thioether with the Boronic Acid

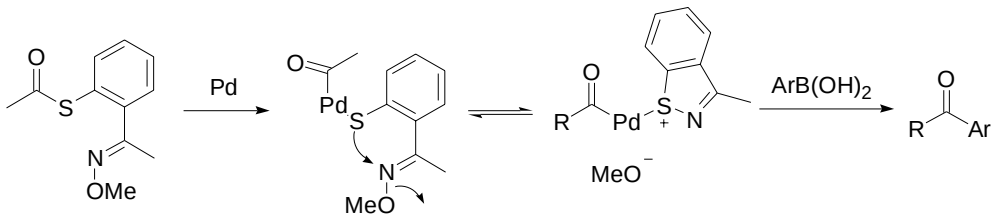
Therefore an investigation was initiated to find thioorganics, other than thiol esters, that would participate in Pd-catalyzed second-generation desulfitative couplings with boronic acids or organostannanes using the MT-mimic concept. Our previous studies on thioorganic-boronic acid cross-coupling have discovered the reactivity difference between thiol esters and other thioorganic derivatives. Thiol esters are better electrophiles than thioethers. With a proper *S*-pendant, they can directly couple with boronic acids under Cu-only conditions without using Pd. However, thioethers are not reactive enough to couple with a weak nucleophile like boronic acid. But such thioorganics could be activated by using a low valent Pd which could undergo the oxidative insertion to the C-S bond thus forming a potential electrophile R-Pd-SR'. The resulting Pd-thiolate intermediate (R-Pd-SR') would not be able to react with boronic acids unless it is further activated to be more electrophilic for transmetallation, and at the same time the poorly nucleophilic boronic acid should be activated in some fashion to make the transmetallation taking place from B to Pd. Furthermore, the overall reaction should be thermodynamically balanced by both fully scavenging the thiolate and providing stoichiometric oxygenate to bond with boronic acid residue. To achieve these goals, a stoichiometric quantity of Cu-carboxylate was employed as a key reaction cofactor in the first generation thioorganic-boronic acid coupling chemistry (see Chapter 1). Another feasible tactic to meet these requirements is to use alkylative activation of the palladium

thiolate intermediate (**Scheme 2.31**).[52] In this thiol ester-boronic acid cross-coupling, the alkylative conversion of a stable palladium-thiolate bond to a labile palladium-thioether bond is crucial to the catalysis. In the meantime, the thiolate was internally scavenged by alkylation and an oxygenate base is required to pair with boronic acid residue $-B(OH)_2$.



Scheme 2.31 Thiol Ester Cross-Coupling using Alkylative Activation

By comparison with the above system, the second generation metallothionein mimics were perfectly suited to activate the palladium-thiolate *via in situ* formation of sulfonium salt-like reactive intermediates. Moreover, the incorporated pendant would scavenge thiolate and generate a third valence oxygenate ligand for boron through trapping of the thiolate by the internal N-O bond (**Scheme 2.32**). This would allow the coupling to take place under neutral conditions without the use of oxygenate bases.

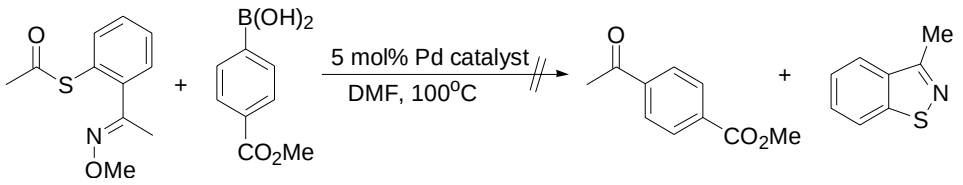


Scheme 2.32 Proposed Pd-catalyzed Cross-Coupling Using Metallothionein Mimic System

Therefore, it was anticipated that using only catalytic quantities of palladium, the MT-mimic coupling system would serve to generalize the 2nd generation desulfitative couplings to a full range of thioorganics. However, the initial experiments showed the

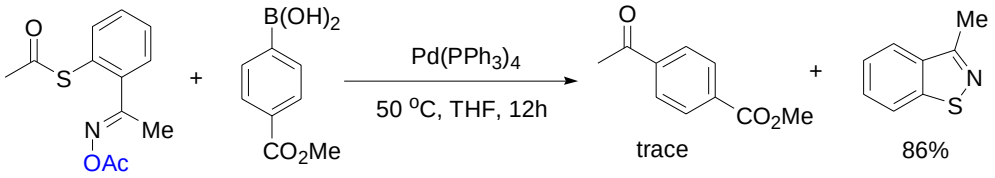
[52] Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229

thiol ester was reluctant to couple with boronic acid in the presence of any Pd catalysts (**Scheme 2.38**).



Scheme 2.33 Unsuccessful Pd-Catalyzed Thiol Ester Coupling

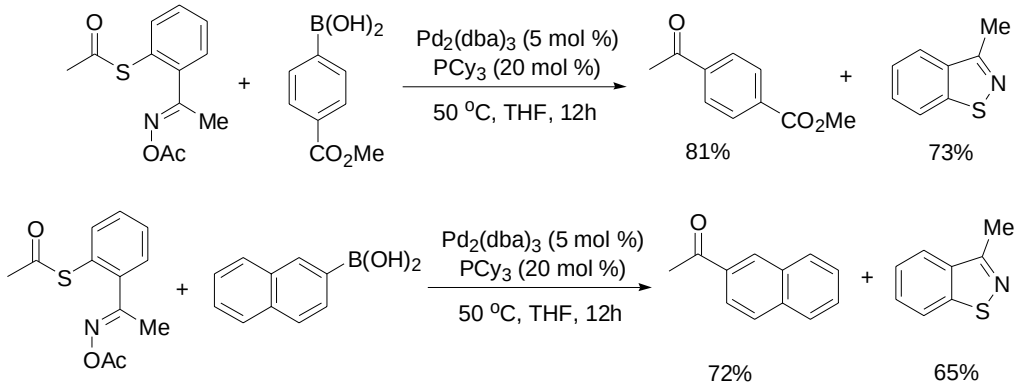
To optimize this reaction, it was assumed that a better oxygenate leaving group on the oxime (=N-OR) could facilitate the alkylative activation of the thiolate (**Scheme 2.39**) and promote the overall transformation. Therefore, a thiol ester bearing an *O*-acetyl oxime *S*-pendant was prepared and applied in the Pd-catalyzed coupling with boronic acid. Unfortunately, only a trace of ketone was observed from this process, but the 3-methyl-1,2-benzisothiazole was obtained in high yield (**Scheme 2.34**).



Scheme 2.34 Optimized Pd-Catalyzed Cross-Coupling

This result suggested the *O*-acetyl oxime did play a positive role in the alkylative activation of thiolate, which resulted in the efficient formation of 3-methyl-1,2-benzisothiazole. Since the oxidative addition of Pd(0) to thiol ester has ample precedent, the low yield of ketone could imply the transmetallation or reductive elimination was problematic in the catalytic process. Thus, a variety of Pd catalysts and supporting ligands were explored. After significant experimentation, $Pd_2(dba)_3/PCy_3$ (1:4 ratio) was

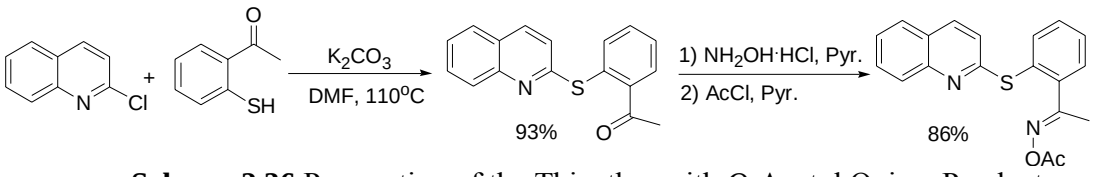
identified as the optimal catalyst system. Aryl boronic acids coupled well with thiol esters producing corresponding ketones (**Scheme 2.35**).



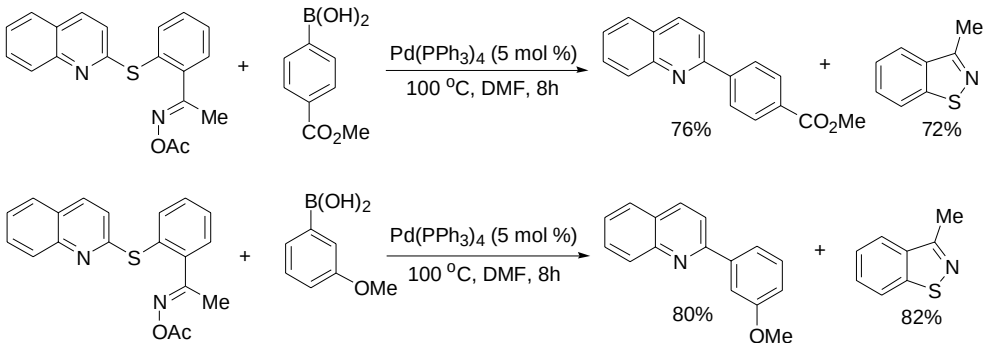
Scheme 2.35 Pd-catalyzed Cross-Coupling of the Thiol Ester with Boronic Acids

2.2.9 Pd-catalyzed Coupling of Heteroaromatic Thioether with Boronic Acid

To study the generality of the Pd-catalyzed metallothionein mimic system, heteroaromatic thioethers containing an *O*-acetyl oxime pendant were prepared. As depicted in **Scheme 2.36**, 2-chloroquinoline was heated with 2'-mercaptoacetophenone and potassium carbonate in DMF at 110℃ to yield the corresponding thioether. The thioether was subjected to hydroxylamine hydrochloride and pyridine to afford the oxime. Acetylation with acetyl chloride and base generated desired product in high yield. With staring materials in hand, the cross-coupling of heteroaryl thioethers with boronic acids was performed. In contrast to the Cu-catalyzed reaction, the Pd-catalyzed coupling was very efficient (**Scheme 2.37**). The 2-quinoline thioether was heated with 5 mol% $Pd(PPh_3)_4$ and 1.2 equiv aryl boronic acid producing the desired 2-aryl quinolines in good yields. As a proof of principle, this result fulfills our criteria to expanding the MT-mimic system to the desulfitative coupling of thioorganics other than thiol esters.



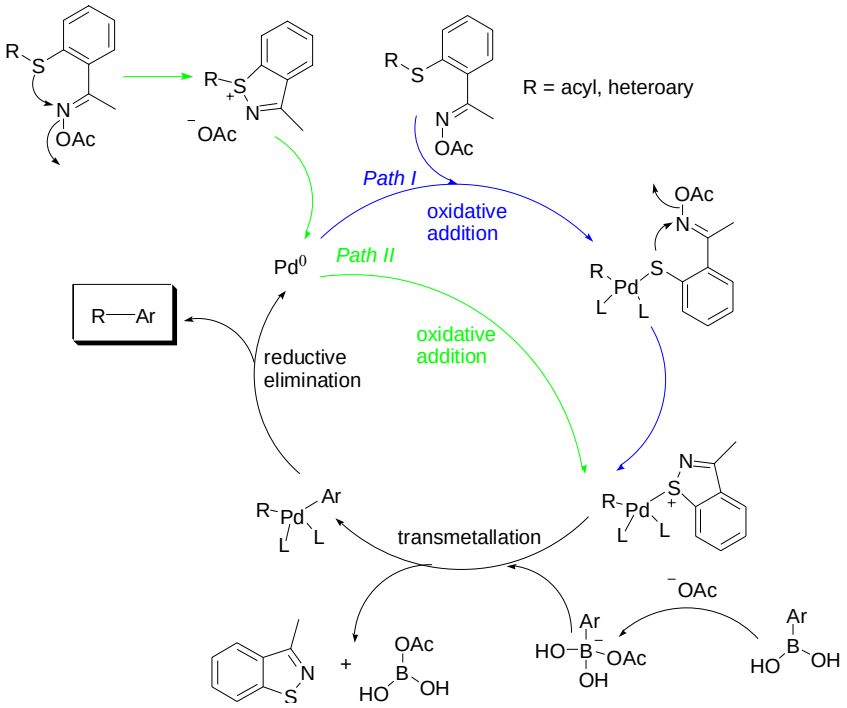
Scheme 2.36 Preparation of the Thioether with *O*-Acetyl Oxime Pendant



Scheme 2.37 Pd-catalyzed Cross-Coupling of the Heteroaromatic Thioether with Boronic Acids

2.2.10 Mechanistic Speculation

Based on previous studies of thioorganic couplings involving alkylative activation of palladium-thiolate intermediates,[52] a mechanism could be proposed for the Pd-catalyzed desulfitative couplings using the metallothionein mimic (**Scheme 2.38**).



Scheme 2.38 Proposed Mechanism

Oxidative addition of the C-S bond to Pd(0) followed by S→N closure would give a more electrophilic cationic palladium-sulfonium salt intermediate along with the release of an acetate counterion ⁻OAc (path I). This "alkylative activation" of a refractory metal thiolate intermediate works as a way to weaken the metal-sulfur bond and overcome the low thiophilicity of boron. The trivalent boron was then activated by the coordination of the released acetate (⁻OAc) to boron. Affected by these double activations, the transmetallation from boron to palladium efficiently occurred. Finally, reductive elimination would afford the desired C-C bond and regenerate a catalytically active Pd(0). Alternatively, the S→N closure to a sulfonium salt intermediate could precede oxidative addition by Pd(0) (path II). The earlier studies in the Liebeskind laboratory proved that a diverse variety of sulfonium salts are prone to oxidative addition and can participate in a

broad range of Pd-catalyzed couplings with boron and tin reagents.[53]

2.3 Conclusions

A metallothionein-mimic system has been developed for the construction of new C-C bond through a desulfitative reaction. With an *O*-methyl oxime *S*-pendant, an efficient Cu-catalyzed cross-coupling of thiol esters with organoborons and stannanes has been described. In this chemistry, the incorporated oxime pendant functions as a scavenger of the thiolate while simultaneously providing stoichiometric oxygenate for pairing with the boronic acid or stannane residue. This protocol is quite general and has a wide substrate scope and tolerates a variety of functional groups. The study of Pd-catalyzed desulfitative couplings demonstrated that the MT-mimic system has the potential to be applied to a broad range of thioorganic reactants under mild, pH-neutral conditions.

2.4 Experimental

General Methods

All reactions were performed under an atmosphere of dry Argon in oven-dried glassware. THF, DMA, DMF, and toluene were dried over 4Å molecular sieves and titrated for water level prior to use with a Fisher Coulomatic K-F titrater. Hexanes, ethyl acetate (EtOAc), and ethyl ether (Et_2O) were obtained from Aldrich and used as purchased. 'Brine' refers to a saturated aqueous solution of NaCl unless otherwise specified solutions. Purification by flash chromatography was performed using Whatman 60Å 230-400 mesh SiO_2 with compressed air as a source of positive pressure. Purification by plate

[53] Srogl, J.; Allred,G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.

chromatography was performed on EM Science Kieselgel 0.5 mm or 1 mm $60F_{254}$ plates. Analytical thin-layer chromatography (TLC) was carried out using Merck Kieselgel $60F_{254}$ plates with visualization by UV or phosphomolybdic acid. 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.

^{1}H NMR spectra were recorded on a Varian Inova 400 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (7.26 ppm); ^{13}C NMR spectra were recorded on a Varian Inova 100 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (77.23 ppm). ^{19}F NMR spectra were recorded on a Varian Inova 375 MHz NMR spectrometer at room temperature in CDCl3 without a reference. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), hex (hextet), hept (heptet), m (multiplet), exch (exchangeable), app (apparent)); coupling constants, *J*, are reported (Hz); integration is provided. Infrared spectra were recorded ASI ReactIR 1000FT-IR spectrometer with a silicone probe. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium, 40-67%), w (weak, 20-40%) and br (broad). GC-MS spectra were recorded on a Shimadzu Gas Chromatograph GC-17A, Mass Spectrometer QP-5000. GC/MS analysis was carried out on a bonded 5% diphenylsiloxane capillary column (30

m, 0.25 mm id, 0.25 μm df). Uncalibrated melting points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes

Microwave Irradiation Experiments

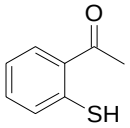
Microwave irradiation experiments were carried out using a Discover microwave reactor from CEM. All experiments were performed in sealed tubes (capacity 10 mL) under argon atmosphere utilizing microwave irradiation of 300 W. The temperature was ramped from room temperature to 150 °C in 1 minute. Once this temperature was reached, the reaction mixture was held at 150 °C for 60 minutes.

Starting materials

Thiosalicylic acid, *O*-methylhydroxylamine hydrochloride, *O*-phenylhydroxylamine hydrochloride, hydroxylamine hydrochloride, triethylborane, styrene, 9-BBN (0.5 M in THF), *p*-toluoyl chloride， thiophene-2-carbonyl chloride， butyryl chloride， cyclohexanecarbonyl chloride，but-2-enoyl chloride，acetic acid chlorocarbonylmethyl ester， *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), L-phenylalanine and D-phenylalanine were purchased from Aldrich and used without future purification. All boronic acids, organostannanes and Cu^{I}-3-methylsalicylate (CuMeSal) were obtained from Synthonix, Inc. *B*-2-phenylethyl-9-BBN was prepared following the known procedure.[54]

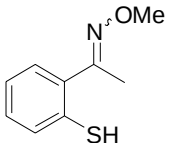
[54] Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554–3557.

2'-Mercaptoacetophenone [17]



2'-Mercaptoacetophenone was prepared using the method of Topolski.[55] Purification by flash chromatography (silica gel, 20:1 hexanes:EtOAc) afforded the title compound as a yellow oil (2.31g, 75%) for a 20 mmol reaction scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.33-7.31 (m, 2H), 7.23-7.19 (m, 1H), 4.45 (s, 1H), 2.64 (s, 3H); IR (neat, cm^{-1}): 3061 (m), 2536 (m), 1668 (s).

1-(2-Mercaptophenyl)ethanone *O*-methyloxime

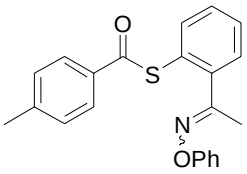


2'-Mercaptoacetophenone (3.04 g, 20 mmol) and *O*-methylhydroxylamine hydrochloride (2.51 g, 30 mmol) were dissolved in 60 mL MeOH. Pyridine (2.77 g, 35 mmol) was slowly added *via* syringe. After stirring at room temperature overnight the solvent was evaporated. The residue was dissolved into diethyl ether and the organic phase was washed with 1 M HCl (20 mL), water and brine. After drying over $MgSO_4$ the solvent was evaporated. Purification by flash chromatography (silica gel, 20:1 hexanes:EtOAc) afforded the title compound as a yellow oil (6:1 mixture of *E/Z* isomers, 3.11 g, 86%). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.16-7.14 (m, 2H), 4.01 (s, 3H), 3.97 (s, 1H), 2.22 (s, 3H); characteristic signals for minor isomer: ^{1}H NMR δ 2.16 (s, 3H), 3.84 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 135.8,

[55] Topolski , M. *J. Org. Chem.* **1995**, *60*, 5588–5594.

131.2, 129.2, 128.9, 125.7, 62.2, 15.3; IR (neat, cm^{-1}): 3061 (m), 2937 (s), 2548 (m), 1613 (m); HRMS (FAB) Calcd for $C_9H_{12}ONS$ ($M+H^+$): 182.0634. Found: 182.0632.

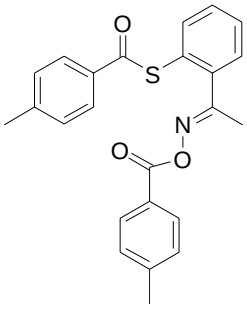
_S_-2-(1-(Phenoxyimino)ethyl)phenyl 4-methylbenzothioate



2'-Mercaptoacetophenone (152 mg, 1.0 mmol) and *p*-toluoyl chloride (162 mg, 1.05 mmol) were dissolved in 20 mL THF. Pyridine (87 mg, 1.1 mmol) was added slowly *via* syringe and after stirring at room temperature for 4 h the white precipitate was removed by filtration. The filtrate was washed with water, brine and dried over $MgSO_4$. The solvent was evaporated to give corresponding thiol ester derivative that was used without futher purification. The thiol ester derivative and *O*-phenylhydroxylamine hydrochloride (125 mg, 1.5 mmol) was dissolved in 10 mL MeOH. Pyridine (126 mg, 1.6 mmol) was added slowly *via* syringe and after stirring at room temperature overnight the solvent was evaporated. The residue was dissolved in diethyl ether and the organic phase was washed with 1 M HCl (10 mL), water and brine. After drying over $MgSO_4$ the solvent was evaporated. Purification by flash chromatography (silica gel, 10:1 hexanes:EtOAc) afforded the title compound as a clear oil (7:1 mixture of *E/Z* isomers, 318 mg, 88%). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.64-7.61 (m, 1H), 7.52-7.49 (m, 3H), 7.29-7.20 (m, 6H), 7.01-6.98 (m, 1H), 2.43 (s, 3H), 2.38 (s, 3H); characteristic signals for minor isomer: ^{1}H NMR δ 2.41 (s, 3H), 2.27 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4, 160.0, 159.5, 145.0, 142.0, 137.8, 134.1, 130.1, 129.81, 129.80, 129.7, 129.4, 127.9, 126.4, 122.4, 115.0, 22.0, 17.5; IR (neat, cm^-

[1]): 3061 (m), 1729 (s), 1671 (s); HRMS (FAB) Calcd for $C_{22}H_{20}O_2NS$ ($M+H^+$): 362.1209. Found: 362.1211.

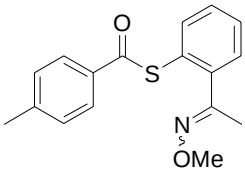
_S_-2-(1-(4-Methylbenzoyloxyimino)ethyl)phenyl 4-methylbenzothioate



2'-Mercaptoacetophenone (152 mg, 1.0 mmol) and hydroxylamine hydrochloride (104 mg, 1.5 mmol) were dissolved in 10 mL MeOH. Pyridine (127 mg, 1.6 mmol) was slowly added *via* syringe and after stirring at room temperature overnight the solvent was evaporated. The residue was dissolved in diethyl ether and the organic phase was washed with 1 M HCl (10 mL), water and brine. After drying over $MgSO_4$ the solvent was evaporated to give corresponding oxime derivative that was directly used in next reaction without further purification. The resulted oxime derivative and *p*-toluoyl chloride (339 mg, 2.2 mmol) were dissolved in 15 mL THF. Pyridine (190 mg, 2.4 mmol) was added slowly *via* syringe and after stirring at room temperature for 4h the white precipitate was removed by filtration. The filtrate was washed with water and brine. After drying over $MgSO_4$ the solvent was evaporated. Purification by flash chromatography (silica gel, 10:1 hexanes:EtOAc) afforded the title compound as a clear oil (343 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.60-7.58 (m, 1H), 7.53-7.49 (m, 3H), 7.27-7.24 (m, 4H), 2.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 165.6, 163.8, 145.1, 144.3, 141.1, 137.8, 133.9, 130.3, 130.2, 129.9, 129.8, 129.7, 129.4,

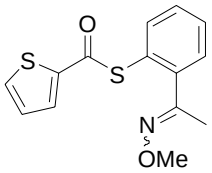
127.9, 126.47, 126.40, 31.0, 21.9, 18.5; IR (neat, cm^{-1}): 3065 (m), 2918 (m), 1745 (s), 1671 (s); HRMS (FAB) Calcd for $C_{24}H_{22}O_3NS$ ($M+H^+$): 404.1314. Found: 404.1319.

_S_-2-(1-(Methoxyimino)ethyl)phenyl 4-methylbenzothioate



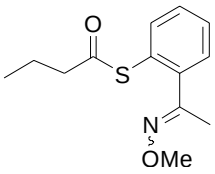
1-(2-Mercaptophenyl)ethanone *O*-methyloxime (181 mg, 1.0 mmol) and *p*-toluoyl chloride (162 mg, 1.05 mmol) were dissolved in 20 mL THF. Pyridine (87 mg, 1.1 mmol) was added slowly *via* syringe and after stirring at room temperature for 4 h the white precipitate was removed by filtration. The filtrate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

_S_-2-(1-(Methoxyimino)ethyl)phenyl thiophene-2-carbothioate



1-(2-Mercaptophenyl)ethanone *O*-methyloxime (181 mg, 1.0 mmol) and thiophene-2-carbonyl chloride (153 mg, 1.05 mmol) were dissolved in 20 mL THF. Pyridine (87 mg, 1.1 mmol) was added slowly *via* syringe and after stirring at room temperature for 4 h the white precipitate was removed by filtration. The filtrate was washed with water, brine and then dried over $MgSO_4$. The solvent was evaporated to give yellow oil. Purification by flash chromatography (silica gel 10:1 hexanes:EtOAc) afforded the title compound as a yellow oil (5:1 mixture of *E/Z* isomers, 276 mg, 95%). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.63 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.58 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.46-7.39 (m, 3H), 7.14-7.12 (m, 1H), 3.93 (s, 3H), 2.14 (s, 3H); characteristic signals for minor isomer: ^{1}H NMR δ 3.77 (s, 3H), 2.12 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 156.4, 142.4, 141.4, 137.6, 133.6, 132.0, 130.2, 129.6, 129.4, 128.3, 125.7, 62.1, 16.7; IR (neat, cm^{-1}): 3069 (m), 1660 (s), 1617 (s); HRMS (FAB) Calcd for $C_{14}H_{14}O_2NS$ ($M+H^+$): 292.0460. Found: 292.0463.

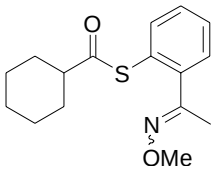
_S_-2-(1-(Methoxyimino)ethyl)phenyl butanethioate



1-(2-Mercaptophenyl)ethanone *O*-methyloxime (181 mg, 1.0 mmol) and butyryl chloride (111 mg, 1.05 mmol) were dissolved in 20 mL THF. Pyridine (87 mg, 1.1 mmol) was

added slowly *via* syringe and after stirring at room temperature for 4 h the white precipitate was removed by filtration. The filtrate was washed with water, brine and then dried over $MgSO_4$. The solvent was evaporated to give yellow oil. Purification by flash chromatography (silica gel 10:1 hexanes:EtOAc) afforded the title compound as a clear oil (4:1 mixture of *E/Z* isomers, 241 mg, 96%). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.36 (m, 4H), 3.94 (s, 3H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 1.72 (q, 2 H), 0.98 (t, *J* = 7.6, 3H); characteristic signals for minor isomer: ^{1}H NMR δ 3.76 (s, 3H), 2.08 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 156.4, 142.0, 137.0, 129.9, 129.5, 129.3, 126.7, 62.1, 45.7, 19.4, 16.7, 13.6; IR (neat, cm^{-1}): 3061 (m), 2964 (s), 1702 (s); HRMS (FAB) Calcd for $C_{13}H_{18}O_2NS$ ($M+H^+$): 252.1052. Found: 252.1054

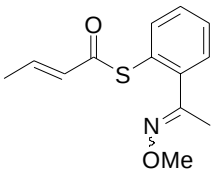
_S_-2-(1-(Methoxyimino)ethyl)phenyl cyclohexanecarbothioate



1-(2-Mercaptophenyl)ethanone *O*-methyloxime (181 mg, 1.0 mmol) and cyclohexanecarbonyl chloride (154 mg, 1.05 mmol) were dissolved in 20 mL THF. Pyridine (87 mg, 1.1 mmol) was added slowly *via* syringe and after stirring at room temperature for 4 h the white precipitate was removed by filtration. The filtrate was washed with water, brine and then dried over $MgSO_4$. The solvent was evaporated to give yellow oil. Purification by flash chromatography (silica gel 10:1 hexanes:EtOAc) afforded the title compound as a clear oil (6:1 mixture of *E/Z* isomers, 268 mg, 92%). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.34 (m, 4H), 3.96 (s, 3H), 2.62 (m, 1H), 2.11 (s, 3H), 1.97 (m, 2H), 1.81 (m, 2H), 1.52 (m, 2H), 1.30 (m, 4H); characteristic

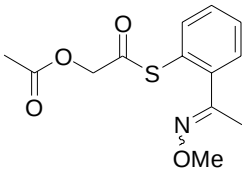
signals for minor isomer: ^{1}H NMR δ 3.78 (s, 3H), 2.08 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 156.4, 142.2, 137.2, 129.8, 129.5, 129.2, 126.7, 62.0, 52.7, 29.7, 25.8, 25.6, 16.6; IR (neat, cm^{-1}): 3065 (m), 2934 (s), 1698 (s), 1633 (s); HRMS (FAB) Calcd for $C_{16}H_{22}O_2NS$ ($M+H^+$): 292.1365. Found: 292.1369.

(*2E*)-*S*-2-(1-(Methoxyimino)ethyl)phenyl but-2-enethioate



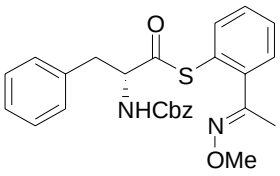
1-(2-Mercaptophenyl)ethanone *O*-methyloxime (181 mg, 1.0 mmol) and but-2-enoyl chloride (109 mg, 1.05 mmol) were dissolved in 20 mL THF. Pyridine (87 mg, 1.1 mmol) was added slowly *via* syringe and after stirring at room temperature for 4 h the white precipitate was removed by filtration. The filtrate was washed with water, brine and then dried over $MgSO_4$. The solvent was evaporated to give yellow oil. Purification by flash chromatography (silica gel 10:1 hexanes:EtOAc) afforded the title compound as a clear oil (5:1 mixture of *E/Z* isomers, 226 mg, 90%). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.34 (m, 4H), 7.03-6.94 (m, 1H), 6.22-6.17 (m, 1H), 3.96 (s, 3H), 2.12 (s, 3H), 1.93 (dd, *J* = 6.8, 1.2 Hz, 3H); characteristic signals for minor isomer: ^{1}H NMR δ 3.77 (s, 3H), 2.09 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 156.4, 142.5, 142.1, 137.2, 129.9, 129.5, 129.4, 129.3, 126.4, 62.0, 18.3, 16.6; IR (neat, cm^{-1}): 3061 (m), 2937 (s), 1683 (s), 1637 (s); HRMS (FAB) Calcd for $C_{13}H_{16}O_2NS$ ($M+H^+$): 250.0896. Found: 250.0898.

2-(2-(1-(Methoxyimino)ethyl)phenylthio)-2-oxoethyl acetate



1-(2-Mercaptophenyl)ethanone *O*-methyloxime (181 mg, 1.0 mmol) and acetic acid chlorocarbonylmethyl ester (143 mg, 1.05 mmol) were dissolved in 20 mL THF. Pyridine (87 mg, 1.1 mmol) was added slowly *via* syringe and after stirring at room temperature for 4 h the white precipitate was removed by filtration. The filtrate was washed with water, brine and then dried over $MgSO_4$. The solvent was evaporated to give yellow oil. Purification by flash chromatography (silica gel 10:1 hexanes:EtOAc) afforded the title compound as a clear oil (6:1 mixture of *E/Z* isomers, 256 mg, 91%). Major Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.39 (m, 4H), 4.81 (s, 2 H), 3.97 (s, 3 H), 2.20 (s, 3H), 2.12 (s, 3H); characteristic signals for minor isomer: ^{1}H NMR δ 3.79 (s, 3H), 2.09 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 170.0, 155.9, 142.3, 137.3, 130.4, 129.7, 129.5, 124.5, 67.7, 62.1, 20.7, 16.5; IR (neat, cm^{-1}): 2937 (s), 1756 (s), 1710 (s); HRMS (FAB) Calcd for $C_{13}H_{16}O_4NS$ ($M+H^+$): 282.0797. Found: 282.0797.

(+)-(*R,E*)-*S*-2-(1-(Methoxyimino)ethyl)phenyl-2-(benzyloxycarbonylamino)-3-phenylpropanethioate



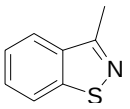
To a solution of 1-(2-mercaptophenyl)ethanone *O*-methyl-oxime (181 mg, 1.0 mmol) and *N*-Cbz-D-phenylalanine (299 mg, 1.0 mmol) in ethyl acetate (10 mL) was added EDC

(192 mg, 1.0 mmol in 10 mL CH_2Cl_2) dropwise at 0 ºC. After addition of EDC, the ice bath was removed and the reaction was stirred at room temperature overnight. The reaction crude was washed by 1M HCl, $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated. Purification by flash chromatography (silica gel 6:1 hexanes:EtOAc) afforded the title compound as a white solid (286 mg, 62%). Mp 50-51 °C； HPLC Chiral OJ-RH, λ= 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 25 min to 75% CH_3CN, during 28 min to 100% CH_3CN hold for 2 min, D-isomer t_R =13.8 min, L-isomer t_R =15.3 min, ee > 99%. ^{1}H NMR (400 MHz, $CDCl_3$) 7.48-7.27 (m, 12H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.19-5.09 (m, 3H), 4.83-4.81 (m, 1H), 3.95 (s, 3H), 3.18-3.13 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 156.2, 155.8, 142.3, 137.1, 136.2, 135.5, 130.2, 129.7, 129.6, 129.4, 129.0, 128.8, 128.5, 128.3, 127.5, 125.8, 67.5, 62.1, 61.7, 38.3, 16.7; IR (neat, cm^{-1}): 3327 (m), 3034 (m), 2937 (m), 1698 (s). HRMS (FAB) Calcd for $C_{26}H_{27}O_4N_2S$ ($M+H^+$): 463.1686. Found: 463.1692. $[\alpha]_D^{20}$ +57.7 (*c* 2.1, $CHCl_3$).

General Procedure for Cu-Catalyzed Cross-Coupling of Thiol Esters with Organostananes. A dry microwave tube was charged with a stir bar. To the tube were added the corresponding thiol ester (0.1 mmol) and CuMeSal (0.02 mmol). The reaction vessel was flushed with argon and sealed. Through the septum organostanane (0.11 mmol) and anhydrous and degassed DMF (1 mL) was added. The mixture was subsequently heated in a microwave reactor at 150 ^{o}C for 1 h. After cooling, the reaction mixture was diluted by ethyl ether (10 mL), washed with water, brine, dried over $MgSO_4$ and

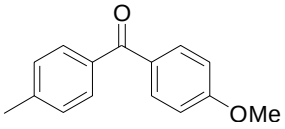
evaporated. The residue was then subjected to preparative plate silica chromatography using hexanes/EtOAc as the eluent.

3-Methyl-1,2-benzisothiazole [56]



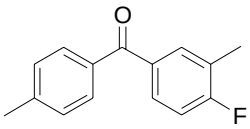
Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.89 (m, 2H), 7.52-7.48 (m, 1H), 7.43-7.39 (m, 1H), 2.74 (s, 3 H); IR (neat, cm^{-1}): 3065 (m), 1733 (s), 1633 (s).

4-Methyl-4'-methoxybenzophenone [57]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded title compound as a white solid (22 mg, 95%). Mp 91-92 °C (lit. {91.3-91.9 °C}[19]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3 H), 2.42 (s, 3 H); IR (neat, cm^{-1}) 1648 (s).

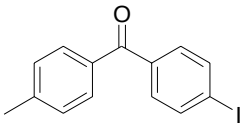
4-Fluoro-3-methyl-4'-methylbenzophenone



[56] Buchwald, S. L.; Watson, B. T.; Lum, R. T. *J. Am. Chem. Soc.* **1987**, *109*, 7137-7141.
[57] Atkinson, G. E.; Fischer, P. M.; Chan, W. C. *J. Org. Chem.* **2000,** 65, 5048-5056.

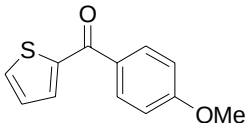
Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (19 mg, 81%). Mp 92-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.67 (m, 3H), 7.63-7.59 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 8.8 Hz, 1H), 2.45 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 165.3 (d, *J* = 251 Hz), 143.4, 135.1, 134.0, 133.9 (d, *J* = 6.0 Hz), 130.3, 130.1 (d, *J* = 8.9 Hz), 129.2, 125.4 (d, *J* = 18 Hz), 115.1 (d, *J* = 22 Hz), 21.8, 14.8; ^{19}F NMR (375 MHz, $CDCl_3$) δ -120.8. IR (neat, cm^{-1}) 1648 (s). HRMS (FAB) Calcd for $C_{15}H_{14}OF$ ($M+H^+$): 229.1023. Found: 229.1024.

4-Iodo-4'-methylbenzophenone [58]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (22 mg, 68%). Mp 149-150 °C (lit. {157.5-158 °C}[20]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3 H); IR (neat, cm^{-1}) 1644 (s).

2-(4-Methoxybenzoyl)thiophene [59]

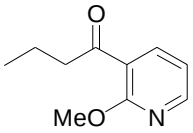


Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (19 mg, 86%). Mp 73-74 °C (lit. {74-75 °C}[21]); ^{1}H NMR (400 MHz, $CDCl_3$)

[58] Kikukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1511-1514.
[59] Zhao, W.; Carreira, E. M. *Chem. Eur. J.* **2007**, *13*, 2671-2685.

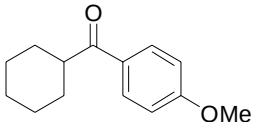
δ 7.85 (d, *J* = 9.2 Hz, 2H), 7.63 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.58 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.10 (dd, *J* = 4.8, 4.0 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 2H), 3.82 (s, 3 H); IR (neat, cm^{-1}) 1656 (s).

1-(2-Methoxy-pyridin-3-yl)-butan-1-one



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a clear oil (13 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.8 Hz, 1H), 8.07-8.05 (m, 1H), 6.99-6.96 (m, 1H), 4.05 (s, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 1.74-1.68 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 162.0, 150.5, 139.9, 122.2, 117.2, 53.9, 45.4, 17.7, 14.0; IR (neat, cm^{-1}) 1679 (s); HRMS (FAB) Calcd for $C_{10}H_{14}O_2N$ ($M+H^+$): 180.1019. Found: 180.1017.

Cyclohexyl *p*-methoxyphenyl ketone [60]

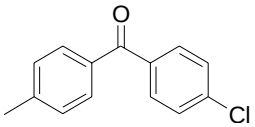


Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (14 mg, 62%). Mp 60-62 °C (lit. {61-63 °C}[22]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.2 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 3.85 (s, 3H), 3.23-3.16 (m, 1H), 1.85-1.20 (m, 10H); IR (neat, cm^{-1}) 1671 (s).

[60] Rao, M. L. N.; Venkatesh, V.; Banerjee, D. *Tetrahedron* **2007**, *63*, 12917-12926.

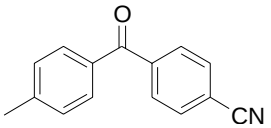
General Procedure for Cu-Catalyzed Cross-Coupling of Thiol Esters with Boronic Acids. A dry microwave tube was charged with a stir bar. To the tube were added the corresponding thiol ester (0.1 mmol), boronic acid (0.12 mmol) and CuMeSal (0.02 mmol). The reaction tube was flushed with argon and sealed. Through the septum anhydrous and degassed DMF (1 mL) was added. The mixture was subsequently heated in a microwave reactor at 150 ^{o}C for 1 h. After cooling, the reaction mixture was diluted with ethyl ether (10 mL), washed with water, brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative plate silica chromatography using hexanes/EtOAc as the eluent.

4-Chloro-4'-methylbenzophenone [61]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (21 mg, 91%). Mp 126-127 °C (lit. {123-125°C}[23]); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3 H); IR (neat, cm^{-1}) 1644 (s).

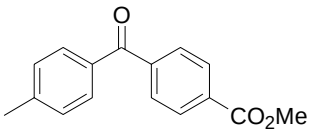
4-(4-Methylbenzoyl)benzonitrile [62]



[61] Rao, Maddali L. N.; Venkatesh, V.; Banerjee, D. *Tetrahedron* **2007**, *63*, 12917-12926.
[62] Wagner, G.; Voigt, B.; Steinbrueck, K.; Sekt. B. *Pharmazie* **1976**, *31*, 354-360.

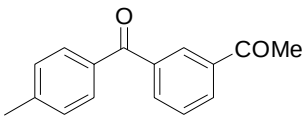
Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as white solid (19 mg, 88%). Mp 160-161°C (lit. {165-167 °C}[24]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3 H); IR (neat, cm^{-1}) 2227 (m), 1648 (s)

4-(4-Methylbenzoyl)benzoic acid methyl ester [63]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as white solid (22 mg, 86%). Mp 119-120 °C (lit. {122-124 °C}[25]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.8 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 3.95 (s, 3H), 2.43 (s, 3 H); IR (neat, cm^{-1}) 1710 (s), 1660 (s).

1-[3-(4-Methylbenzoyl)phenyl] ethanone [64]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (17 mg, 71%). Mp 72-73 °C (lit. {77.8-78 °C}[26]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (t, *J* = 1.2 Hz, 1H), 8.19 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.99 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz,1H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.66 (s, 3H), 2.46 (s, 3 H); IR (neat, cm^{-1}) 1687 (s), 1656 (s).

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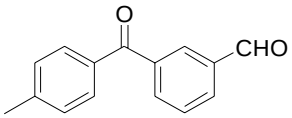
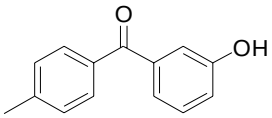
[63] Gogoll, A.; Schaefer, H**.** *Liebigs Ann. Chem.* **1987**, *7*, 589-696.
[64] Zhao, X.; Semenova, E. A.; Liao, C.; Nicklaus, M.; Pommier, Y.; Burke, T. R. *Bioorg. Med. Chem.* **2006**, *14*, 7816-7825.

3-Benzoylbenzaldehyde [65]



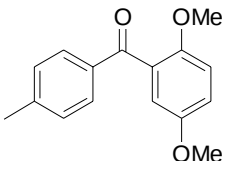
Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (16 mg, 69%). Mp 88-90 °C (lit. {91-99 °C}[27]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.27 (s, 1H), 8.13-8.07 (m, 2H), 7.74-7.67 (m, 3H), 7.34 (d, *J* = 8.4 Hz, 2H), 2.47 (s, 3 H); IR (neat, cm^{-1}) 1702 (s), 1656 (s).

3-Hydroxy-4'-methylbenzophenone [66]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (15 mg, 70%). Mp 120-122 °C (lit. {126 °C}[28]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.31-7.25 (m, 5H), 7.07-7.04 (m, 1H), 2.42 (s, 3 H); IR (neat, cm^{-1}) 1644 (s)

2,5-Dimethoxy-1-(4-methylbenzoyl)benzene [67]

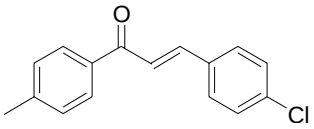


Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (17 mg, 68%). Mp 60-61 °C (lit. {63°C}[29]); ^{1}H NMR (400 MHz, $CDCl_3$) δ

[65] Miziak, P.; Zon, J.; Amrhein, N.; Gancarz, R. *Phytochemistry* **2007**, *68*, 407-415.
[66] Astoin, J.; Lepage, F.; Fromantin, J. P.; Poisson, M. *Eur. J. Med. Chem.* **1980**, *15*, 457-462.
[67] Waterlot, C.; Hasiak, B.; Couturier, D.; Rigo, B. *Tetrahedron* **2001**, *57*, 4889-4902.

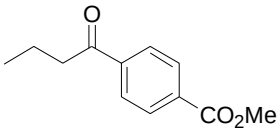
7.72 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.67-6.86 (m, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 2.39 (s, 3H); IR (neat, cm^{-1}) 1660 (s)

(*E*)-3-(4-Chlorophenyl)-1-p-tolylprop-2-en-1-one [68]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (13 mg, 52%). Mp 146-147 °C (lit. {148-150 °C}[30]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 15.6 Hz, 1H), 7.41-7.39 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H); IR (neat, cm^{-1}) 1656 (s).

4-Butyrylbenzoic acid methyl ester [69]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (17mg, 82%). Mp 81-82 °C (lit. {84°C}[31]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 3.93 (s, 3H), 2.96 (t, *J* = 7.6 Hz, 2H), 1.78-1.75 (m, 2H), 1.01 (t, *J* = 7.6 Hz, 3H); IR (neat, cm^{-1}) 1722 (s), 1675 (s).

Acetoxymethyl 2-furyl ketone [70]

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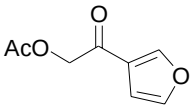
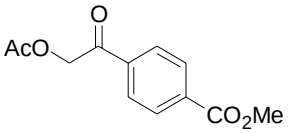
[68] Madapa, S.; Sridhar, D.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Eur. J. Org. Chem.* **2007**, *26*, 4343-4351.
[69] Sumida, Y.; Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2008**, *3*, 119-125.



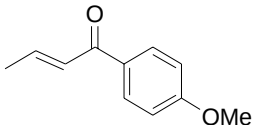
Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a clear oil (12 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (t, *J* = 0.8 Hz, 1H), 7.46 (t, *J* = 2.0 Hz, 1H), 6.78 (dd, *J* = 2.0, 0.8 Hz, 1H), 5.01 (s, 2H), 2.20 (s, 3H); IR (neat, cm^{-1}) 1729 (s), 1629 (s).

4-Carbomethoxyphenacyl acetate [71]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (18 mg, 78%). Mp 78-80 °C (lit. {80-82 °C}[33]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H), 5.35 (s, 2H), 3.96 (s, 3H), 2.24 (s, 3H); IR (neat, cm^{-1}) 1752 (s), 1698 (s).

(*E*)-1-(4-Methoxyphenyl)-2-buten-1-one [72]

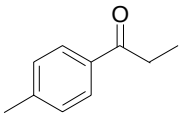


Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a clear oil (14 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.09-7.02 (m,

[70] Allcock, H. W.; Kipnis, F.; Ornfelt, J.; Allen, P. *J. Am. Chem. Soc.* **1948**, *70,* 3949-3950.
[71] Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122,*11260-11261.
[72] Ochiai, M.; Yoshimura, A.; Mori, T.; Nishi, Y.; Hirobe, M. *J. Am. Chem. Soc.* **2008**, *130,* 3742-3743.

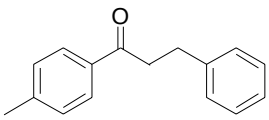
1H),6.97-6.90 (m, 3H), 3.88 (s, 3H), 2.01 (dd, *J* = 6.8, 1.6 Hz, 3H); IR (neat, cm^{-1}) 1668 (s).

Ethyl 4-methylphenyl ketone [73]



A dry microwave tube was charged with a stir bar. To the tube were added 4-methyl-thiobenzoic acid *S*-[2-(1-methoxyiminoethyl)phenyl] ester (30 mg, 0.1 mmol) and CuMeSal (4 mg, 0.02 mmol). The reaction tube was flushed with argon and sealed. Through the septum triethylborane (11 mg, 0.11 mmol) and anhydrous and degassed DMF (1 mL) was added. The mixture was subsequently heated in a microwave reactor at 150 ^{o}C for 1 h. After cooling, the reaction mixture was diluted with ethyl ether (10 mL), washed with water, brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative plate silica chromatography using CH_2Cl_2 as the eluent to afford the title compound as a clear oil (12 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 3.01 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); IR (neat, cm^{-1}) 1683 (s).

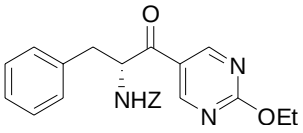
4-Methylphenyl phenethyl ketone [74]



[73] Olah, G. A.; Forsyth, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 3137-3141.
[74] Li, J-P.; Zhang, Y-X.; Ji, Y. *J. Chin. Chem. Soc.* **2008**, *55*, 390-393.

A dry microwave tube was charged with a stir bar. To the tube were added 4-methyl-thiobenzoic acid *S*-[2-(1-methoxyiminoethyl)phenyl] ester (30 mg, 0.1 mmol) and CuMeSal (4 mg, 0.02 mmol). The reaction tube was flushed with argon and sealed. Through the septum *B*-2-phenylethyl-9-BBN (0.22 mL [0.5 M in THF], 0.11 mmol) and anhydrous and degassed DMF (1 mL) was added. The mixture was subsequently heated in a microwave reactor at 150 ^{o}C for 1 h. After cooling, the reaction mixture was diluted with ethyl ether (10 mL), washed with water, brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative plate silica chromatography using hexanes/EtOAc (4:1) as the eluent to afford the title compound as a white solid (16 mg, 71%). Mp 64-65 °C (lit. {62-64 °C}[36]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.32-7.20 (m, 7H), 3.39 (t, *J* = 8.0 Hz, 2H), 3.08 (t, *J* = 8.0 Hz, 2H), 2.40 (s, 3H); IR (neat, cm^{-1}) 1683 (s).

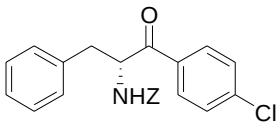
(-)-(*R*)-Benzyl 1-(2-ethoxypyrimidin-5-yl)-1-oxo-3-phenylpropan-2-ylcarbamate



A dry microwave tube was charged with a stir bar. To the tube were added 2-benzyloxycarbonylamino-3-phenylthiopropionic acid *S*-[2-(1-methoxyiminoethyl)phenyl] ester (46 mg, 0.1 mmol) and CuMeSal (4 mg, 0.02 mmol). The reaction tube was flushed with argon and sealed. Through the septum 2-ethoxyl-5-(tributylstannyl)pyrimidine (45 mg, 0.11 mmol) and anhydrous and degassed DMF (1 mL) was added. The mixture was subsequently heated in a microwave reactor at 150 ^{o}C for 1 h. After cooling, reaction mixture was diluted with ethyl ether (10 mL), washed with water, brine, dried over

$MgSO_4$ and evaporated. The residue was purified by preparative plate silica chromatography using hexanes/EtOAc (4:1) as the eluent to afford the title compound as a white solid (31 mg, 76%). Mp 91-92 °C; HPLC Chiral OJ-RH, λ= 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 25 min to 75% CH_3CN, during 28 min to 100% CH_3CN hold for 2 min, D-isomer t_R =15.3 min, L-isomer t_R =12.1 min, ee > 99%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 2H), 7.37-7.33 (m, 5H), 7.24-7.19 (m, 3H), 7.05-7.03 (m, 2H), 5.62 (d, *J* = 8.4 Hz, 1H), 5.41-5.36 (m, 1H), 5.14 (AB q, *J* = 12 Hz, 2H), 4.54 (q, *J* = 6.8 Hz, 2H), 3.20 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.10 (dd, *J* = 13.6, 5.6 Hz, 1H), 1.48 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 167.0, 160.7, 155.8, 136.2, 135.2, 129.5, 128.9, 128.7, 128.5, 128.3, 127.5, 123.0, 67.3, 65.0, 56.8, 39.3, 14.5; IR (neat, cm^{-1}) 1718 (s), 1687 (s), 1590 (s) 1498 (s). HRMS (FAB) Calcd for $C_{23}H_{24}O_4N_3$ ($M+H^+$): 406.1761. Found: 406.1765. $[\alpha]_D^{20}$ -36.4 (*c* 0.5, $CHCl_3$).

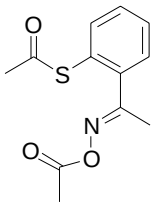
(-)-(*R*)-Benzyl 1-(4-chlorophenyl)-1-oxo-3-phenylpropan-2-ylcarbamate



A dry microwave tube was charged with a stir bar. To the tube were added 2-benzyloxycarbonylamino-3-phenylthiopropionic acid *S*-[2-(1-methoxyiminoethyl)phenyl] ester (46 mg, 0.1 mmol), 4-chlorophenylboronic acid (17 mg, 0.11 mmol) and CuMeSal (4 mg, 0.02 mmol). The reaction tube was flushed with argon and sealed. Through the septum anhydrous and degassed DMF (1 mL) was added. The mixture was subsequently heated in a microwave reactor at 90 ^oC for 1 h. After cooling, reaction mixture was

diluted with ethyl ether (10 mL), washed with water, brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative plate silica chromatography using hexanes/EtOAc (4:1) as the eluent to afford the title compound as a white solid (33 mg, 82%). Mp 87-88 °C; HPLC Chiral OJ-RH, λ= 254 nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 25 min to 75% CH_3CN, during 28 min to 100% CH_3CN hold for 2 min, D-isomer t_R =18.3 min, L-isomer t_R =23.7 min, ee > 99%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.39-7.31 (m, 5H), 7.21-7.18 (m, 3H), 6.98-6.96 (m, 2H), 5.65 (d, *J* = 8.0 Hz, 1H), 5.57-5.53 (m, 1H), 5.15 (AB q, *J* = 12 Hz, 2H), 3.26 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.10 (dd, *J* = 14.0, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 155.8, 140.5, 136.4, 135.5, 133.2, 130.2, 129.6, 129.4, 128.7, 128.6, 128.4, 128.2, 127.3, 67.1, 56.5, 39.2; IR (neat, cm^{-1}) 1722 (s), 1687 (s), 1498 (s). HRMS (FAB) Calcd for $C_{23}H_{21}O_3NCl$ ($M+H^+$): 394.1204. Found: 394.1209. $[\alpha]_D^{20}$ -21.0 (*c* 0.4, $CHCl_3$).

_S_-2-(1-(Acetoxyimino)ethyl)phenyl ethanethioate



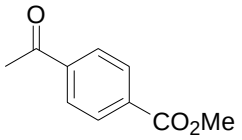
2'-Mercaptoacetophenone (152 mg, 1.0 mmol) and hydroxylamine hydrochloride (104 mg, 1.5 mmol) were dissolved in 10 mL MeOH. Pyridine (127 mg, 1.6 mmol) was slowly added *via* syringe and after stirring at room temperature overnight the solvent was evaporated. The residue was dissolved into diethyl ether and the organic phase was washed with 1 M HCl (10 mL), water and brine. After drying over $MgSO_4$ the solvent

was evaporated to give corresponding oxime derivative that was used without further purification. The resulted oxime derivative and acetyl chloride (174 mg, 2.2 mmol) were dissolved in 15 mL THF. Pyridine (190 mg, 2.4 mmol) was added slowly *via* syringe and after stirring at room temperature for 4h the white precipitate was removed by filtration. The filtrate was washed with water and then brine. After drying over $MgSO_4$ the solvent was evaporated. Purification by flash chromatography (silica gel, 10:1 hexanes:EtOAc) afforded the title compound as a clear oil (208 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.39 (m, 4H), 2.39 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H); IR (neat, cm^{-1}): 3061 (m), 2964 (s), 1768 (s), 1702 (s); $C_{12}H_{14}O_3NS$ ($M+H^+$): 252.0689. Found: 252.0693.

General Procedure for Pd-Catalyzed Thiol Ester-Boronic Acid Cross-Coupling.

Thiol ester (0.1 mmol), boronic acid (0.12 mmol), $Pd_2(dba)_3$ (0.005 mmol) and PCy_3 (0.02 mmol) were added into a flask and flushed with argon. Then 2 mL dry and degassed THF was added. The mixture was stirred under the protection of argon at 50 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with ethyl ether (10 mL), washed with water, brine, dried over $MgSO_4$. The solvent was evaporated to give a crude product that was purified by preparative plate silica chromatography using hexanes/EtOAc as the eluent.

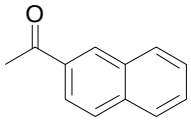
4-Acetyl-benzoic acid methyl ester [75]



[75] Emerson, W. S.; Heyd, J. W.; Lucas, V. E.; Chapin, E. C.; Owens, G. R.; Shortridge, R. W. *J. Am. Chem. Soc.* ***1946,*** *68*, 674-676.

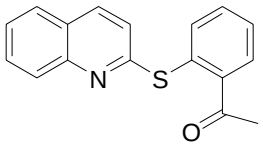
Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (14 mg, 81%). Mp 93-95℃ (lit. {95.2-95.4℃}[37]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 2.62 (s, 3H); IR (neat, cm^{-1}): 2961 (m), 1722 (s), 1679 (s).

1-Naphthalen-2-yl-ethanone [76]



Purification by preparative TLC (hexanes/EtOAc 4:1) afforded the title compound as a white solid (12 mg, 72%). Mp 50-52℃ (lit. {49-51℃}[38]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.02 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.87-7.85 (m, 2H), 7.59 (td, *J* = 7.2, 1.2 Hz, 1H), 7.55 (td, *J* = 7.2, 1.2 Hz, 1H), 2.71 (s, 3H); IR (neat, cm^{-1}): 3068 (m), 2996 (m), 1695 (s).

1-[2-(Quinolin-2-ylsulfanyl)-phenyl]ethanone

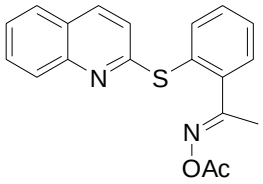


A suspension of 2-chloroquinoline (326 mg, 2.0 mmol) and 2'-mercaptoacetophenone (312 mg, 2.1 mmol), and potassium carbonate (297 mg, 3.0 mmol) in DMF (5 mL) was stirred at 110 ℃ overnight. After cooling to room temperature, the reaction mixture was diluted with ethyl ether (10 mL), washed with water, brine, dried over $MgSO_4$ and evaporated. Purification by flash chromatography (silica gel, 2:1 hexanes:EtOAc)

[76] Zoeller, J. R.; Sumner, C. E. *J.Org. Chem.* **1990**, *55*, 319-324.

afforded the title compound as red crystals (519 mg, 93%). H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.73-7.63 (m, 3H), 7.55-7.52 (m, 1H), 7.48-7.40 (m, 3H), 7.20 (d, *J* = 8.8 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 158.5, 147.5, 140.8, 136.2, 133.7, 131.1, 131.0, 129.5, 128.7, 127.7, 127.4, 127.2, 125.7, 121.26, 121.22, 28.8; IR (neat, cm^{-1}): 3061 (m), 2968 (m), 1695 (s), 1586 (m). $C_{17}H_{14}ONS$ ($M+H^+$): 280.0790. Found: 280.0786.

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

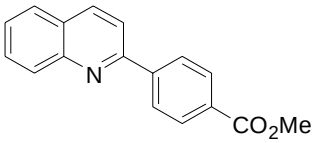


1-[2-(Quinolin-2-ylsulfanyl)-phenyl]ethanone (279 mg, 1.0 mmol) and hydroxylamine hydrochloride (104 mg, 1.5 mmol) were dissolved in 6 mL EtOH. Pyridine (158 mg, 2.0 mmol) was slowly added *via* syringe and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was extracted into diethyl ether (10 mL). The organic solution was washed with 1 M HCl (5mL), water, and brine. After drying over $MgSO_4$ the solvent was evaporated to give the corresponding oxime derivative that was used without further purification. The resulted oxime and AcCl (94 mg, 1.2mmol) was dissolved in 10 mL THF followed by addition of pyridine (119 mg, 1.5 mmol). After stirring at room temperature for 5 h, the white precipitate was removed by filtration. The filtrate was washed with water, brine, dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash chromatography (silica gel, 2:1 hexanes:EtOAc) to afford the title compound as a clear oil (6:1 mixture of *E/Z* isomers, 289 mg, 86%). Major Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.92-7.48 (m, 2H), 7.72-

7.63 (m, 3H), 7.52-7.43 (m, 4H), 6.98 (d, *J* = 8.8 Hz, 2H), 2.34 (s, 3H), 2.10 (s, 3H); characteristic signals for minor isomer: ^{1}H NMR δ 2.31 (s, 3H), 1.85 (s, 3H); Major Isomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 164.5, 160.3, 147.7, 141.0, 137.0, 136.6, 130.3, 129.9, 129.8, 129.7, 128.9, 128.0, 127.5, 125.8, 119.57, 119.53, 19.5, 18.3; IR (neat, cm^{-1}): 3057 (m), 2926 (m), 1768 (s), 1590 (s); HRMS (FAB) Calcd for $C_{19}H_{17}O_2N_2S$ ($M+H^+$): 337.1005. Found: 337.1001.

General Procedure for Pd-Catalyzed Heteroaromatic Thioether-Boronic Acid Cross-Coupling. Thioether (0.1 mmol), boronic acid (0.13 mmol) and $Pd(PPh_4)_4$ (0.005 mmol) were added into a flask and then flushed with argon. Then 2 mL dry and degassed DMF was added. The mixture was stirred under the protection of argon at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with ethyl ether (10 mL), washed with water, brine, dried over $MgSO_4$. The solvent was evaporated to give a crude product that was purified by preparative plate silica chromatography using hexanes/EtOAc as the eluent.

4-Quinolin-2-yl-benzoic acid methyl ester [77]

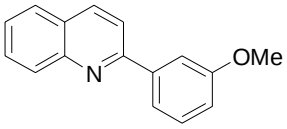


Purification by preparative TLC (hexanes/EtOAc 1:1) afforded the title compound as a light yellow solid (20 mg, 76%). Mp 146-148℃ (lit. {151-153℃}[39]); ^{1}H NMR (400 MHz,

[77] Ishikura, M.; Oda, I.; Terashima, M. *Heterocycles* **1985**, *23*, 2375-2386.

$CDCl_3$) δ 8.28-8.18 (m, 4H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.78-7.74 (m, 1H), 7.58-7.54 (m, 1H), 3.96 (s, 3H); IR (neat, cm^{-1}): 2946 (m), 1722 (s), 1598 (m).

2-(3-Methoxyphenyl)-quinoline [78]



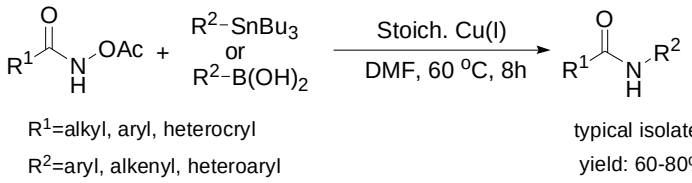
Purification by preparative TLC (hexanes/EtOAc 1:1) afforded a light yellow solid (19 mg, 80%). Mp 106-108℃ (lit. {110℃}[40]); ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.77-7.69 (m, 3H), 7.55-7.51 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.03-7.01 (m, 1H), 3.94 (s, 3H); IR (neat, cm^{-1}): 3061 (m), 2957 (m), 1598 (s), 1556 (m).

[78] Cho, C. S.; Lee, N. Y.; Kim, T-J.; Shim, S. C. *J. Heterocycl. Chem.* **2004**, *41*, 409-411.

Chapter 3

New Amidation Reaction by the Copper-Mediated Cross-Coupling of Organostannanes and Boronic Acids with *O*-Acetyl Hydroxamic Acids

Abstract: *A general nonoxidative N-amidation of organostannanes and boronic acids has been developed. Under nonbasic conditions a wide variety of aryl, alkenyl, and heteroaryl organostannanes and boronic acids couple efficiently with O-acetyl hydroxamic acids in the presence of Cu(I) sources.*



Scheme 3.1 Cu(I)-Mediated Amidation of Organostannanes and Boronic Acids with O-Acetyl Hydroxamic Acids

3.1 Introduction and Background

Mild methods for the formation of carbon-heteroatom bonds are of considerable interest to the synthetic organic community. A great diversity of carbon-heteroatom bonds can now be easily generated by transition-metal-catalyzed protocols.[79] Buchwald and Hartwig led the exploration of metal-catalyzed cross-coupling of heteroatom nucleophiles with organic halides and their equivalents.[80] A complementary oxidative coupling of boronic acid with amine, amide, alcohol, phenol and thiol has also been initiated by Lam, Chan, Evans and others (**Scheme 3.2)**.[81]

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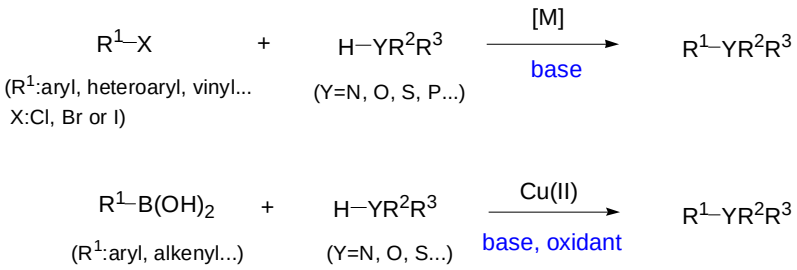
[79] For some reviews see: (a) Beletskaya, I. P. *Pure Appl. Chem.* **2005**, *77*, 2021. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.

[80] Leading reviews: (a) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholzc, U. *Adv. Synth. Catal.* **2006,** *348*, 23. (b) Hartwig, J. F. *Synlett.* **2006,** *9*, 1283. (c) Muci, A. R.; Buchwald, S. L. In *Topics in Current Chemistry*, 2002; Vol. 219, pp 131. (d) Hartwig, J. F. *Comprehensive Coordination Chemistry II* **2004**, *9*, 369. (e) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004,** *346*, 1599.

[81] For some examples see: (a) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927. (b) Chan, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, *44*, 3863. (c) Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 1691. (d) Evans, D. A. Katz, J. L. West, T. R. *Tetrahedron Lett* **.1998,** *44*, 2937.



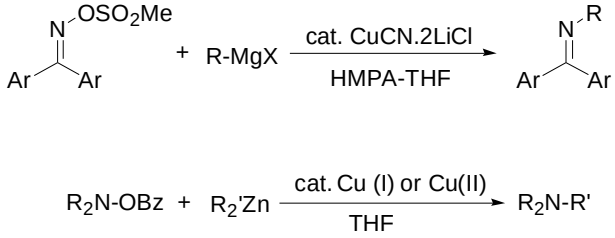
Scheme 3.2 Metal-Catalyzed Cross-Coupling Reactions for the Carbon-Heteroatom Bond Formation

Although Buchwald-Hartwig and Lam-like couplings are very powerful and broadly useful, a complementary protocol differentiated from existing C-N bond forming reactions by providing a non-basic protocol under non-oxidizing conditions is always of value in complex synthetic settings. The development of suitably mild reaction conditions for metal-tuned C-N bond formation could be useful in the development of small molecule therapeutics or chemical modification and/or tagging of more complex biomolecules. It is for these reasons that new C-N bond forming reactions are being pursued, particularly those that selectively target N-O bonded functional groups.

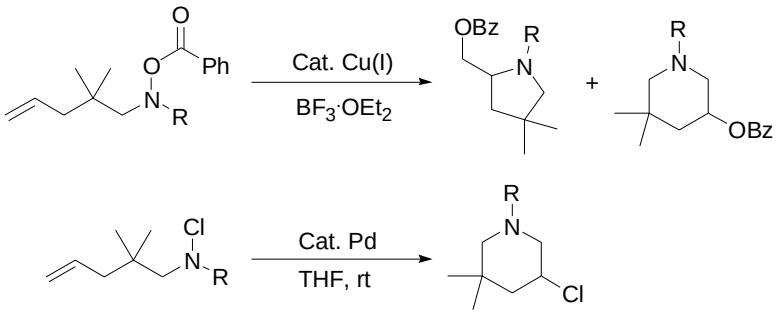
To date, using traditional carbon nucleophilic reagents, Narasaka (organomagnesium) [82] and Johnson (organozinc)[83] have shown that hydroxylamine derivatives can be cleaved by organometallic reagents in the presence of metal catalysts and provide a very general process for C-N bond formation (**Scheme 3.3**). Göttlich and coworkers also reported the metal induced N-O and N-Cl bond cleavage followed by cyclization with olefin to form C-N bonds (**Scheme 3.4**).[84] But, significantly, the direct formation of the C-N bond under

[82] (a) Kitamura, M.; Suga, T.; Chiba, S.; Narasaka, K. *Org. Lett.* **2004,** *6*, 4619. (b) Narasaka, K. *Pure Appl. Chem.* **2002,** *74*, 143. (c) Tsutsui, H.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, 317.
[83] (a) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007,** *9*, 1521. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006,** *71*, 219. (c) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680.
[84] Noack, M.; Göttlich, R. *Chem. Commun.* **2002**, 536.

neutral reaction conditions of the synthetically versatile boronic acids and organostannane is still desired.

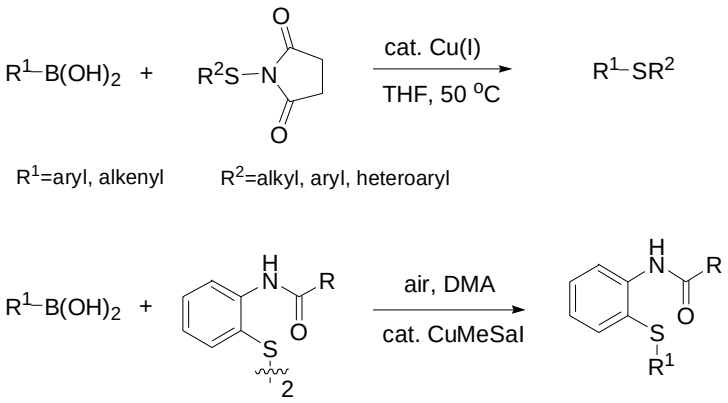


Scheme 3.3 Known Metal-Mediated Cross-Coupling Reactions of N-O Bond



Scheme 3.4 Göttlich's Study of Metal Induced N-O and N-Cl bonds cleavage

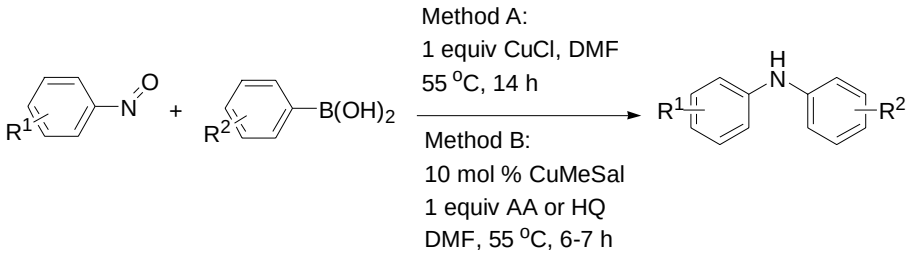
The Liebeskind laboratory has initiated the study of metal-catalyzed reactions of various heteroatom-heteroatom reactants with mild reaction partners such as boronic acids to seek out new approaches to carbon-heteroatom bond formations (**Scheme 3.5**).



Scheme 3.5 Cu-Catalyzed N-S and S-S bonds Cleavage and Formation of C-S Bond

A previous study demonstrated the efficient Cu-catalyzed cross-coupling of *N*-thioimide derivatives with boronic acids to give thioethers through cleavage of the N-S bond.[85] The reaction of disulfide and boronic acids in the presence of Cu(I) catalyst was also observed.[86]

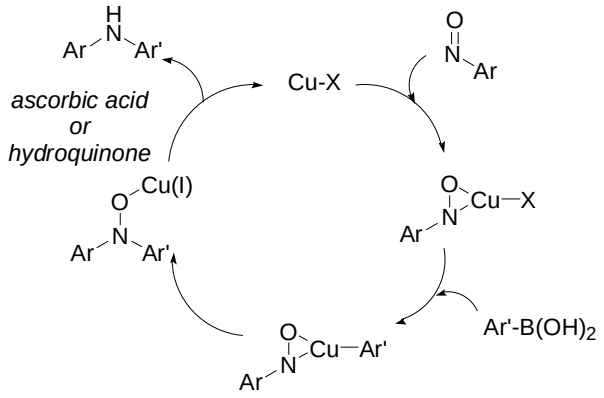
The study of N-O bond chemistry in our laboratory has uncovered the Cu-mediated reductive amination of aryl boronic acids with nitroso aromatic compounds (**Scheme 3.6**).[87] This C-N bond formation was mediated by a stoichiometric amount of CuCl as both a catalyst and a reducing agent. Alternatively,



Scheme 3.6 Cu(I)-Mediated Reductive Amination of Boronic Acids with Nitroso Aromatic Compounds

10% Cu(I)-3-methylsalicylate (CuMeSal) catalyzed the same reaction in the presence of either ascorbic acid or hydroquinone as the terminal reducing agent. A variety of unsymmetrical diarylamines bearing different functional groups were prepared in good yields.

[85] Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309.
[86] Unpublished results of Liebeskind group.
[87] Yu, Y.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2004**, *6*, 2631.

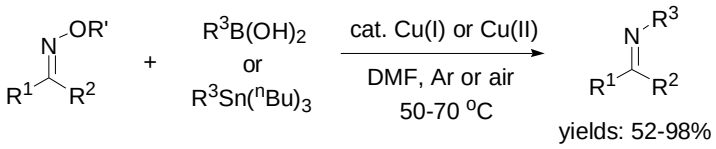


Scheme 3.7 Suggested Mechanism of Cu(I)-Mediated Amination of Boronic Acids

A suggested mechanism is depicted in **Scheme 3.7**, side-on complexation of Cu(I) with the nitroso moiety generates a formal Cu(III) intermediate that would be susceptible to transmetallation by the boronic acid. Reductive elimination would then generate a Cu(I) alkoxide of an *N*,*N*-diarylhydroxylamine.

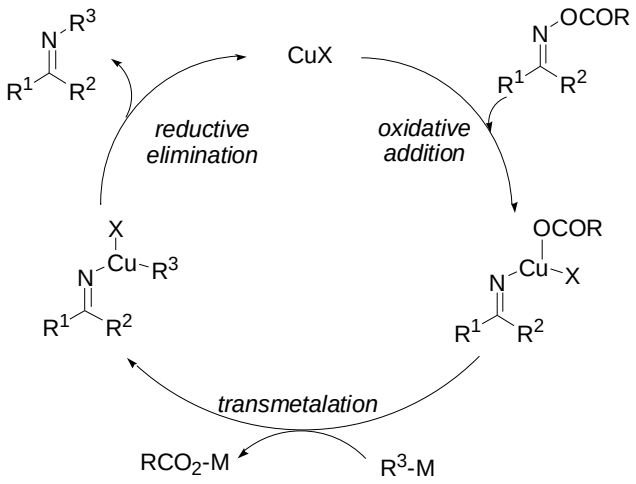
More recently the Liebeskind laboratory disclosed a mild Cu-catalyzed *N*-imination of boronic acids and organostannanes through reaction with oxime *O*-carboxylates under non-basic conditions.[88] This method tolerates various functional groups and proceeds using aryl, heteroaryl, and alkenyl boronic acids and stannanes (**Scheme 3.8**). A reasonable mechanistic pathway for the copper catalyzed coupling of oxime *O*-carboxylates with boronic acids or organostannanes is shown in **Scheme 3.9**. Oxidative addition of N–O bond to Cu(I) is followed by transmetallation of either the boronic acid or the organostannane to the putative Cu(III) intermediate. Reductive elimination would produce the desired C-N bond and regenerate a catalytically active Cu(I). The requisite Cu(I) catalyst is either added to the reaction system or generated *in situ* through reduction of a Cu(II) precatalyst by the coupling agent.

[88] Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007,** *9*, 1947.



R^1, R^2 = aryl, heteroaromatic, alkyl
R^3 = aryl and alkenyl for B; aryl, heteroaryl, and alkenyl for Sn
R' = Ac, COC_6F_5

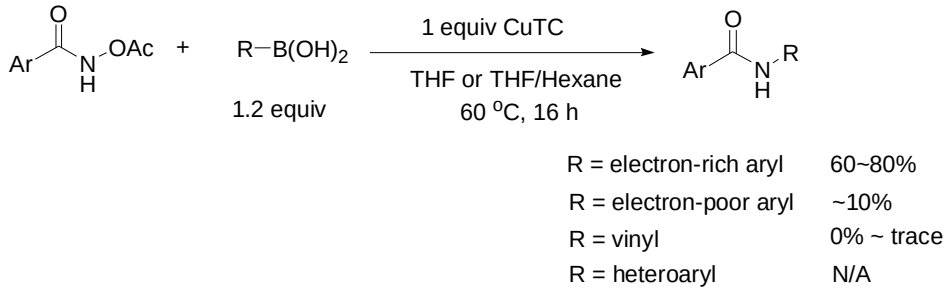
Scheme 3.8 Cu(I)-Catalyzed *N*-Imination of Boronic Acids and Organostannanes



Scheme 3.9 Suggested Mechanism of Cu(I)-Catalyzed *N*-Imination of Boronic Acids and Organostannanes

This Cu-catalyzed *N*-imination reaction provides a means of generalizing the 'oxidative' amination of boronic acids or organostannane by using an oxidized form of the amine coupling partner rather than an external oxidant. (Lam-like transformations require external oxidant like stoichiometric Cu^{II} or air) under neutral condition. Furthermore, as another important category of N-O compounds, hydroxamic acid derivatives were explored in the metal-mediated reaction with boronic acids and organostannanes to fulfill this C-N bond formation protocol. Dr. Ying Yu's preliminary results demonstrated that CuTC-mediated amidation of electron-rich aryl boronic acids proceeds well to give amide products in good yields (**Scheme 3.10**). However, the

reactions of the electron-deficient aryl, vinyl and heteroaryl boronic acid were not satisfactorily developed. To build up a more powerful methodology for this C-N bond formation, it is essential to generalize the reaction from a limited number of arylboronic acids to other mild organometallic reagents like organostannanes and expand the substrate scope from aromatic to olefinic and heteroaromatic types. Reaching these goals formed the substance of the research described in this chapter.

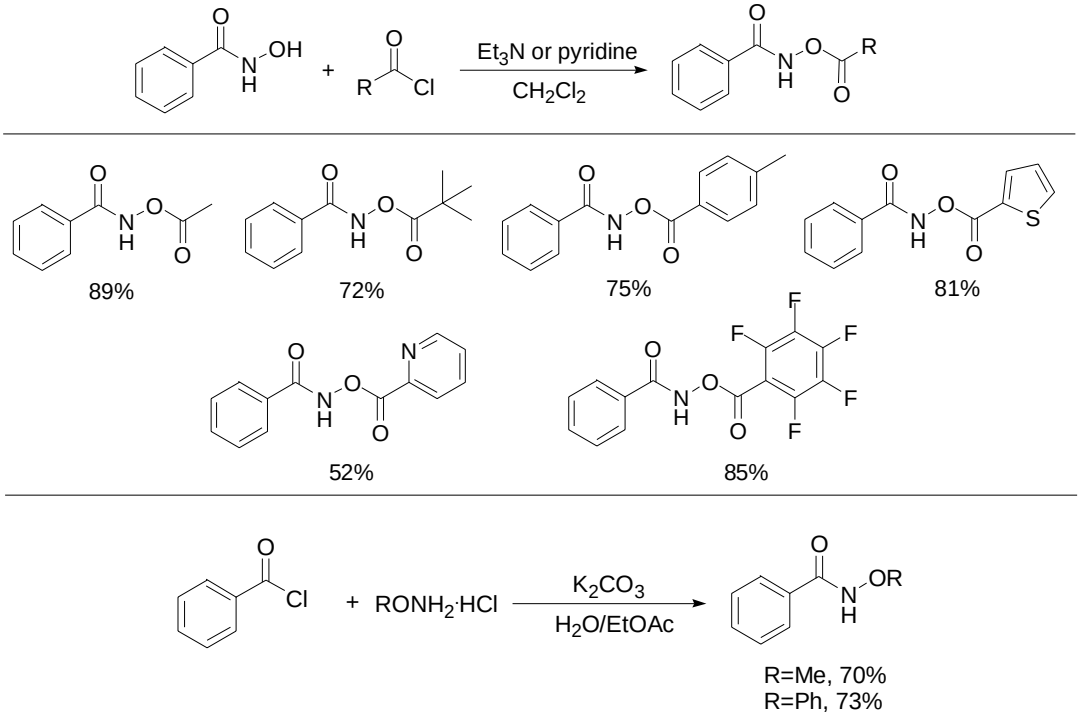


Scheme 3.10 Preliminary Study of Cu(I)-Mediated *N*-Amidation of Boronic Acids with *O*-Aceyl Hydroxamic Acids

3.2 Results and Discussion

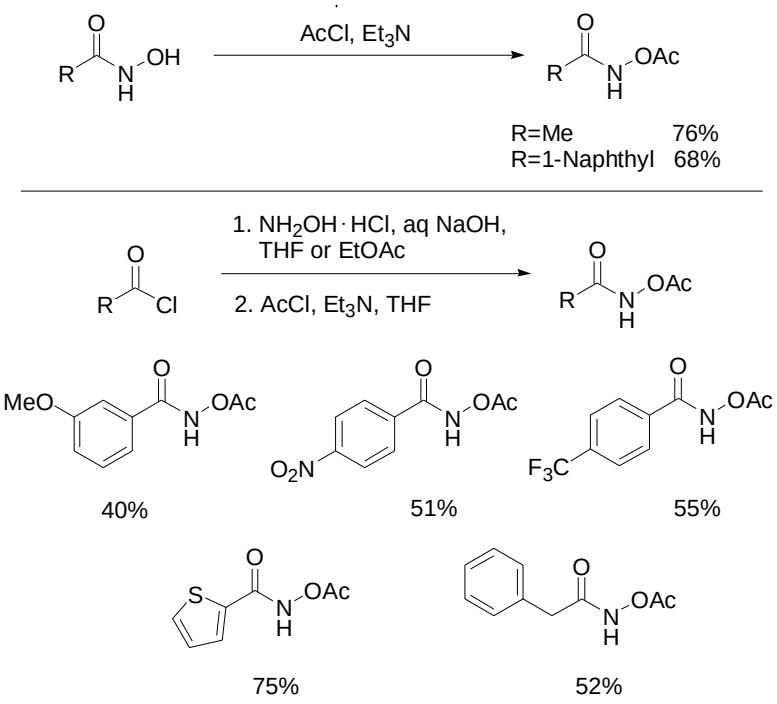
3.2.1 Preparation of *O*-Substituted Benzohydroxamic Acids

The *O*-acyl benzohydroxamic acids were prepared from benzohydroxamic acid and the corresponding acyl chloride (**Scheme 3.11**). *O*-methyl and *O*-phenyl benzohydroxamic acids were synthesized from the corresponding hydroxylamine hydrochloride and benzoyl chloride (**Scheme 3.11**).



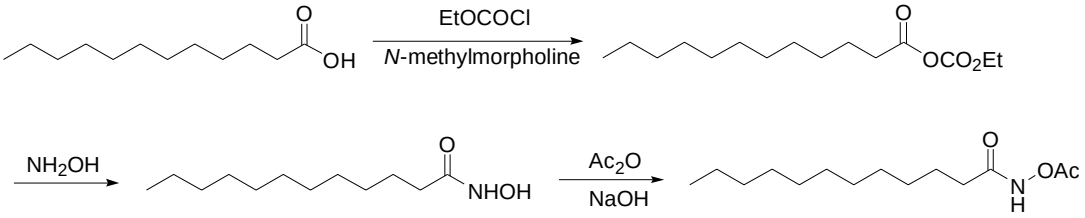
Scheme 3.11 Preparation of *O*-Substituted Benzohydroxamic Acids

O-Acetyl 1-naphthohydroxamic acid and *O*-acetyl acetylhydroxamic acid were obtained from acetylation of commercially available 1-naphthohydroxamic acid and acetyl hydroxamic acid, respectively. Non-commercially available aryl- and alkyl-hydroxamic acids can be prepared from an acyl chloride and hydroxylamine hydrochloride followed by acetylation with acetyl chloride to generate the corresponding *O*-acetyl hydroxamic acids in two steps (**Scheme 3.12**).



Scheme 3.12 Preparation of *O*-Acetyl Aryl- and Alkyl-Hydroxamic Acids

Laurohydroxamic acid was synthesized starting with lauric acid.[89] The lauric acid was treated with ethylchloroformate and *N*-methylmorpholine in diethyl ether. The resulted lauroyl ethyl carbonate was then subjected to freshly prepared hydroxylamine to afford laurohydroxamic acid. Acylation with acetic anhydride provides *O*-acetyl laurohydroxamic acid (**Scheme 3.13**).



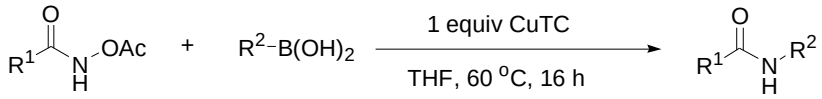
Scheme 3.13 Preparation of *O*-Acetyl Laurohydroxamic Acid

[89] Reddy, A. S.; Kumar, M. S.; Reddy, G. R. *Tetrahedron Lett*. **2000**, *41*, 6285-6288.

3.2.2 *N*-Amidation of Organostannanes with *O*-Acyl Hydroxamic Acids

According to Dr. Ying Yu's results, various *O*-acetyl hydroxamic acids and boronic acids were heated with 1 equiv CuTC in THF at 60 °C for 16 h to give amides resulting from C-N bond formation (**Table 3.1**). Electron-neutral and electron-rich aryl boronic acids generated amide products as desired (entry 1-4), but a low yield of the product was obtained when using an electronic deficient phenyl boronic acid (entry 5). The amidation of *E*-β-styrylboronic acid was not efficient either, and only a trace of the product was observed by GC/MS analysis (entry 6). In most cases, homocoupling and protodeborylation reaction of arylboronic acid were observed in significant quantities.[90]

Table 3.1 Amidation of Arylboronic Acids with *O*-Acetyl Hydroxamic Acids



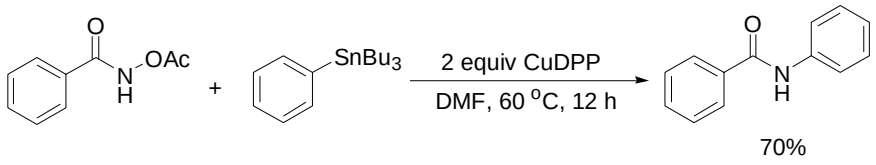
entry	R^1	R^2	yield(%)[a]
1	Ph-	Phenyl	74%[b]
2	Ph-	*p*-tolyl	77%[b]
3	Ph-	3,4-methylenedioxyphenyl	63%[b]
4	Ph-	4-phenoxyphenyl	68%[b]
5	Ph-	3-formylphenyl	10%[b,]
6	Ph-	*E*-β-styryl	trace[b,]
7	(*m*-OMe)Ph-	*p*-tolyl	58%[d]
8	(*p*-CF_3)Ph-	*p*-tolyl	81%[d]
9	$PhCH_2$-	*p*-tolyl	76%[d]
10	2-naphtho-	*p*-tolyl	65%[d]

a. Isolated yield; b. Hexane/THF (1:1) as solvent; c. GC/MS analysis; d. THF as solvent

To overcome the limitations associated with boronic acids and expand this protocol to other mild carbon nucleophiles, the study on the cross-coupling of *O*-acetyl hydroxamic acids with organostannanes was performed. This investigation was initiated by exploring the cross-coupling of *O*-acetyl benzohydroxamic acid with 1.1 equiv of tributylphenyltin

[90] Dr. Ying Yu's Ph.D Dissertation 2004, Emory University

(**Scheme 3.14**). A screen of different Cu(I) sources, solvents, additives, and reaction temperatures revealed that optimal yields were achieved with >1 equiv of Cu(I) diphenylphosphinate (CuDPP) in DMF at 60 °C. Therefore 2.0 equiv of CuDPP was routinely used for convenience. Increased loading of CuDPP did not lead to improved yields. CuTC, CuMeSal and CuOAc gave slightly lower yields, while non-oxygenate Cu(I) sources such as CuCl, CuI, and CuCN were ineffective. The beneficial pairing of Cu(I) diphenylphosphinate (CuDPP) with organostannanes in the cross-coupling reactions was ascribed to the precipitation of (n-$Bu_3SnO(O)PPh_2$) from the reaction mixture.[91] Solvents such as THF, DMA, and toluene were not as effective as DMF. The addition of Lewis acids ($BF_3{\cdot}Et_2O$, $Sc(OTf)_3$, $TiCl_4$, $SnCl_4$, ZnF_2, $Zn(OAc)_2$, or base (Et_3N, Cs_2CO3) dramatically reduced the product yield.



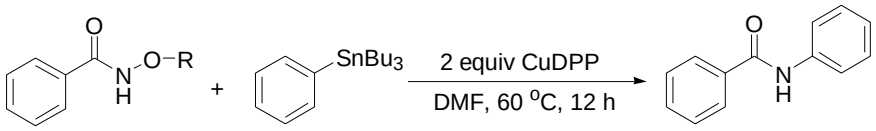
Scheme 3.14 CuDPP-Mediated Amidation of tributylphenyltin with *O*-Acetyl Benzohydroxamic Acids

The influence of the hydroxamic acid *O*-substituent on the reaction was probed by reacting the *O*-substituted benzohydroxamic acids with 1.1 equiv of tributylphenyltin and 2 equiv CuDPP in THF at 60 °C (**Table 3.2**). *O*-acetyl benzohydroxamic acid still gave the highest product yield (entry 1). *O*-(Pentafluorobenzoyl), *O*-(*t*-butylcarbonyl), *O*-(*p*-methylbenzoyl), *O*-(thiophene-2-carbonyl) and *O*-(2-pyridinylcarbonyl) substitutions resulted in moderate yields of amide (entries 2-6). Surprisingly, *O*-phenyl

[91] (a) Allred, G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749. (b) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033–3035.

benzohydroxamic acid also generated the *N*-substituted amide in about 65% yield (entry 8). The reaction of *O*-methyl benzohydroxamic acid gave very low yield of product and most starting material was recovered (entry 7).

Table 3.2 Amidation of tributylphenyltin with *O*-Substituted Benzohydroxamic Acids



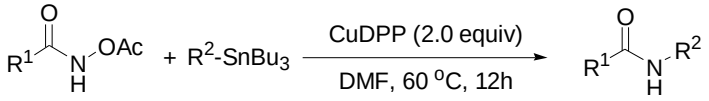
entry	-R'	amide (%)[a]
1	-COMe	70
2	-COC_6F_5	56
3	-CO(*t*-Bu)	62
4	-CO(*p*-totuyl)	60
5	-CO(2-thienyl)	52
6	-CO(2-pyridyl)	46
7	-Me	15
8	-Ph	65

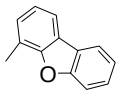
a. isolated yield

To investigate the generality of this reaction, various *O*-acetyl hydroxamates and organostannanes were exposed to the optimized reaction conditions, resulting in amides in moderate to good yields. In contrast to the boronic acid system which appeared limited to electron-rich aryl substituents, the reaction of organostannanes was very general. As shown in **Table 3.3**, *O*-acetyl benzohydroxamic acid coupled efficiently with aryl, heteroaryl, and alkenyl organostannanes providing the desired amides (entries 1-7), while slight lower yields of amides were obtained when using deactivated (electron-deficient) organostannane reagents (entries 3 and 7). Entries 8-14 show that significant variation in the nature of the acyl moiety is accommodated in this reaction. Heteroaryl *O*-acetyl hydroxamic acids reacted well (entries 11 and 12) and synthetically useful *N*-alkylsubstituted amides may also be obtained by this method (entries 13-18). Special

attention is drawn to entry 14 in which a 4-iodophenyl moiety is tolerated under the reaction conditions.

Table 3.3 CuDPP-Mediated Amidation of Organostannanes with *O*-Acetyl Hydroxamic Acids



entry	R^1	R^2	yield (%)[a]
1	phenyl	*p*-tolyl	80
2	phenyl	4-methoxyphenyl	76
3	phenyl	4-chlorophenyl	56
4	phenyl		73
5	phenyl	(Z)-1-propenyl	66
6	phenyl	2-thienyl	73
7	phenyl	2-pyrazinyl	42
8	4-nitrophenyl	*p*-tolyl	74
9	3-methoxyphenyl	*p*-tolyl	71
10	1-naphthyl	*p*-tolyl	83
11	2-thienyl	4-methoxyphenyl	90
12	2-thienyl	2-thienyl	60
13	benzyl	*p*-tolyl	74
14	benzyl	4-iodophenyl	60
15	benzyl	2-methyl-1-propenyl	64
16	methyl	*p*-tolyl	85
17	undecyl	*p*-tolyl	66
18	undecyl	(*E*)-β-styryl	52

a) isolated yield.

3.2.3 Mechanistic Consideration

Oxidative addition of the *O*-acetylhydroxamic acid to Cu(I)[92] is a likely first step in the mechanism of the previously described Cu(I)-catalyzed[9,10] as well as in the current Cu(I)-mediated cross-coupling of hydroxyl amine derivatives with boronic acids and organostannanes. Heating *O*-acetyl benzohydroxamic acid with 1 equiv of CuTC in THF resulted in complete conversion to $PhCONH_2$ after aqueous workup.[93] The reason at least a full equivalent of Cu(I) is required during cross-coupling reactions of *O*-acetylhydroxamic acids but is required in only catalytic quantities for cross-couplings with *O*-acyloximes[10] may reside in the nature of the two different amido Cu intermediates A and B shown in **Scheme 3.15**. Although the detailed mechanism of Cu-mediated coupling of hydroxylamine derivatives with boronic acids and organostannanes is not known, it is speculated that the imido intermediates $R_2C{=}NCuX_2$ are sufficiently electrophilic to engage in a fast transmetallation with boronic acids and organostannanes, while the amido $RCONHCuX_2$ species are likely to form relatively stable and less electrophilic amido bridging dimeric structures that would be more sluggish at transmetallation. This would rapidly consume a full equivalent of Cu(I) and could give the appearance of a noncatalytic process. In fact *N*-substituted *O*-acetyl hydroxamic acids do not participate in the Cu(I)-mediated cross-coupling, generating instead (after aqueous

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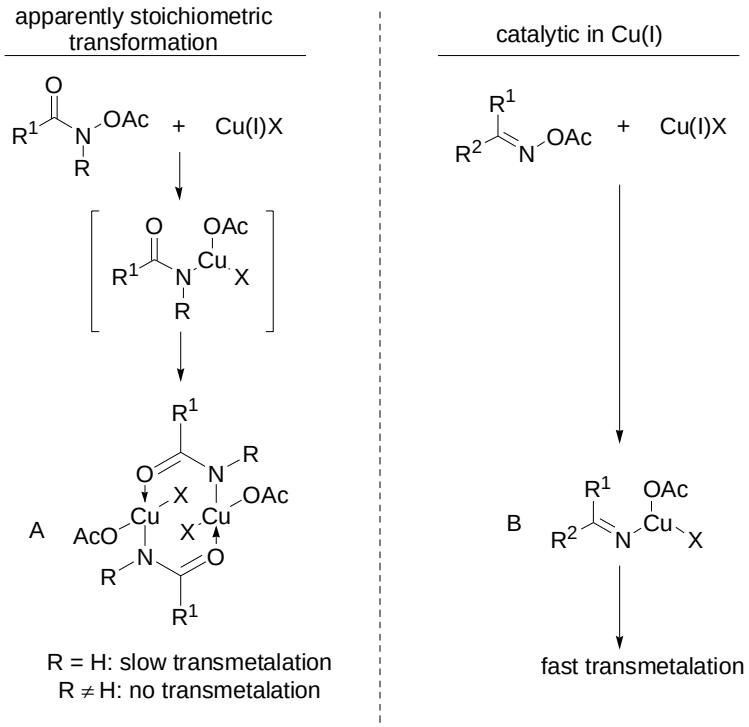
[92] For oxidative addition of N-O bond to various transition metals such as Re, Pd and Cu, see: (a) Kusama, H.; Yamashita, Y.; Uchiyama, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 965. (b)Ferreira, C. M. P.; Guedes da Silva, M. F. C.; Kukushkin, V. Y.; Fraústo da Silva, J. J. R.; Pombeiro, A. J. L. *J. Chem. Soc., Dalton Trans.* **1998**, 325. (c) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, 45. (d) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **2001**, 526. (e) Kitamura, M.; Zaman, S.; Narasaka, K. *Synlett* **2001**, 974. (f) Kitamura, M; Narasaka, K. *Chem. Rec.* **2002**, *2*, 268. (g) Chiba, S.; Kitamura, M.; Saku, O.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 785. (h) Tsutsui, H.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, 317. (i) Narasaka, K. *Pure Appl. Chem.* **2002**, *74*, 19.

[93] A Ti(III)-mediated reduction of *O*-methyl hydroxamic acid has been reported: Fisher, L. E.; Caroon, J. M.; Jahangir; Russell Stabler, J. S.; Lundberg, S.; Muchowski, J. M. *J. Org. Chem.* **1993**, *58*, 3643.

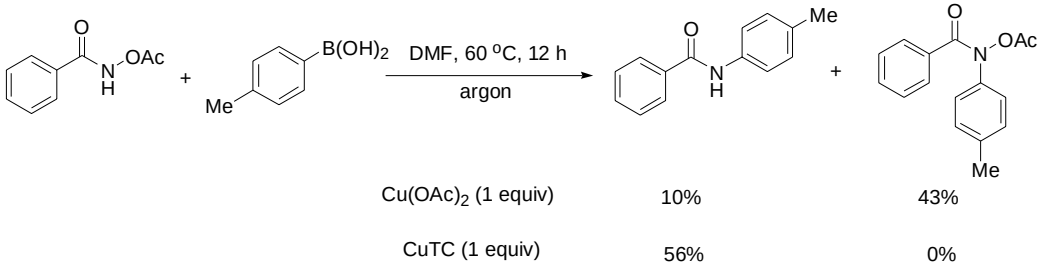
workup) the product of N-O bond reduction, suggesting that transmetallation is prevented by steric encumbrance in these cases.



Scheme 3.15 Mechanistic Speculations

3.2.4 Chemoselectivity Study

Interesting chemoselectivity of this new N-O-based cross-coupling was observed in the two reactions shown in **Scheme 3.16** (where DMF was used as solvent to ensure solubility of both Cu sources, rather than THF/hexanes as described in Table 3.1). Upon exposure of a mixture of *O*-acetyl benzohydroxamic acid and *p*-tolylboronic acid to Cu(II), Lam-like *N*-arylation reactivity is predominantly observed. In contrast, the use of Cu(I) allows divergence of this chemistry from Lam-like reactivity to exclusive formation of the product of cross-coupling at the N-O bond.



Scheme 3.16 Examples of Chemoselectivity

3.3 Conclusions

In summary, a general copper-mediated cross-coupling of *O*-acetyl hydroxamic acids with boronic acids and organostannanes under nonbasic and nonoxidizing conditions has been developed. This methodology allows a variety of amides to be easily prepared and is a useful complement to existing metal-catalyzed methods for C-N bond formation. Given the mild reaction conditions and its inherent chemoselectivity, this new method might be useful as a novel peptide ligation protocol of use in the construction of peptides and peptidomimetics.

3.4 Experimental

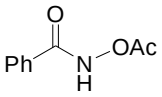
General Methods see **Chapter 1**

Starting Materials

N-Benzoyl-*N*-phenylhydroxylamine, benzoyl chloride, benzohydroxamic acid, acetic anhydride, acetyl chloride, 2-thiophene carbonyl chloride, *t*-butylcarbonyl chloride, *p*-toluoyl chloride, *O*-methylhydroxylamine hydrochloride, *O*-phenylhydroxylamine hydrochloride, phenylacetyl chloride, *m*-anisoyl chloride, *p*-nitrobenzoyl chloride, hydroxylamine hydrochloride, CuOAc, CuCl, CuI, CuCN, *p*-tolylboronic acid,

phenylboronic acid, 2-phenyl-1,3,2-dioxaborinane, $TiCl_4$, $Sc(OTf)_3$, $CuPF_6(CH_3CN)_4$ and boron trifuoride etherate were purchased from Aldrich. All boronic acids except *p*-tolylboronic acid and phenylboronic acid were obtained from Frontier Scientific, Inc. All organostannanes were obtained from Synthonix. 1-Naphthohydroxamic acid and 2-picolinoyl chloride hydrochloride were obtained from TCI America Inc. Copper(I) thiophene-2-carboxylate (CuTC)[94] and copper(I) diphenylphosphinate (CuDPP)[95] were prepared following the literature procedures.

_O_-Acetyl benzohydroxamic acid [96]



Benzohydroxamic acid (1.385 g, 10 mmol), CH_2Cl_2 (30 mL) and aqueous NaOH (2 M, 5.5 mL) were charged in a round bottomed flask. Ac_2O (1.12 g, 11 mmol) was added via syringe. After stirring at room temperature for 2 h, the CH_2Cl_2 layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined CH_2Cl_2 layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent afforded the title compound as a white solid (1.53 g, 86%). Mp 123-125 °C (ethyl ether, lit. {126.5 °C (hexanes/ether)}[18]). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.84 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 2.31 (s, 3H); IR (neat, cm^{-1}): 3147 (m), 2961 (m), 1793 (s), 1649 (s).

_N_-(2,2-Dimethyl-1-oxopropoxy)benzamide [97]

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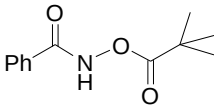
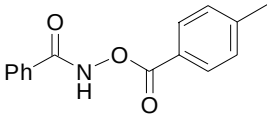
[94] Allred, G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748-2749.
[95] Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033-3035.
[96] Just, G.; Dahl, K. *Tetrahedron* **1968**, *24*, 5251-5269.



Benzohydroxamic acid (1.386 g, 10 mmol) was dissolved in THF (40 mL) in a round bottomed flask. *t*-Butylcarbonyl chloride (1.206 g, 10 mmol) was added via syringe, followed by Et_3N (1.214 g, 12 mmol). A white precipitate was observed. The suspension was stirred at room temperature for 2 h. Ethyl ether (20 mL) was added and the reaction was washed with water twice and then brine. After drying the organic layer over $MgSO_4$, evaporation of the solvent gave the product as an off-white solid. Recrystallization from hexanes/ether afforded the title compound as a white solid in (1.658 g, 75%). Mp 169-171 °C (lit. {170-171.5 °C}[19]). ^{1}H NMR δ (400 MHz, $CDCl_3$) 9.51 (s, 1H), 7.80 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 1.35 (s, 9H); IR (neat, cm^{-1}): 3204 (br), 2980 (s), 1783 (s), 1652 (s), 1517 (m), 1482 (m).

_N_-(4-Methylbenzoyloxy)benzamide [98]



Benzohydroxamic acid (1.386 g, 10 mmol) was dissolved in 1,4-dioxane (40 mL) in a round bottomed flask. Pyridine (0.800 g, 10 mmol) was added via syringe. After addition of *p*-toluoyl chloride (1.700 g, 11 mmol), a white precipitate was observed. The suspension was stirred at room temperature overnight. EtOAc (20 mL) was added and the reaction was washed with 1 M HCl, water and then brine. After drying the organic layer over $MgSO_4$, evaporation of the solvent afforded the title compound as white solid.

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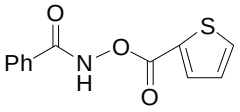
[97] Miller, M. J.; DeBons, F. E.; Loudon, G. M. *J. Org. Chem.* **1977**, *42*, 1750-1761.
[98] Alexandrou, N. E.; Nicolaides, D.N. *Tetrahedron Lett.* **1966**, *7*, 2497-2499.

Recrystallization from hexanes/EtOAc afforded colorless crystals (2.064 g, 81%). Mp 153-155°C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 9.86 (br, s, 1H), 8.03 (d, *J* = 10.8 Hz, 2H), 7.87 (d, *J* = 9.2 Hz, 2H), 7.57 (t, *J* = 10 Hz, 1H), 7.46 (t, *J* = 10 Hz, 2H), 7.28 (d, *J* = 10.8 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 165.5, 145.5, 132.9, 131.1, 130.3, 129.7, 129.0, 127.7, 123.9, 22.0; IR (neat, cm^{-1}): 3150 (m), 2953 (m), 1764 (s), 1706 (m), 1648 (s), 1583 (m). HRMS (FAB) Calcd for $C_{15}H_{13}O_3NLi$ ($M+Li^+$): 262.1055. Found: 262.1058.

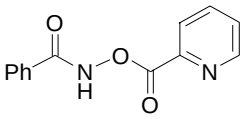
_N_-(Thiophene-2-carbonyloxy)benzamide [99]



Benzohydroxamic acid (1.386 g, 10 mmol) was dissolved in THF (30 mL) and CH_2Cl_2 (30 mL) in a round bottomed flask. 2-Thiophene carbonyl chloride (1.466 g, 10 mmol) was added to the solution via syringe, followed by Et_3N (1.214 g, 12 mmol). A white precipitate was observed. The suspension was stirred at 50 °C for 2 h after which CH_2Cl_2 (20 mL) was added and the reaction was washed with water twice then brine. After drying the organic layer over $MgSO_4$, evaporation of the solvent gave the product as a yellow solid. Recrystallization from hexanes/ether afforded the title compound as light yellow crystals (2.0 g, 80%). Mp 131-133 °C (lit. {133-133.5 °C (EtOAc)}[21]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (br, s, 1H), 8.02 (dd, *J* = 2.4, 1.2 Hz, 1H), 7.88-7.86 (m, 2H), 7.72 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.60 (tt, *J* = 7.2, 2.0 Hz, 1H), 7.51-7.47 (m, 2H), 7.19 (dd, *J* = 5.2, 4.0 Hz, 1H); IR (neat, cm^{-1}): 3188 (m), 2953 (m), 1752 (s), 1660 (s).

[99] Jones, L. W.; Hurd, C. D. *J. Am. Chem. Soc.* **1921**, *43*, 2422-2448.

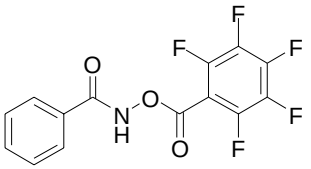
***N*-(2-Pyridinylcarbonyloxy)benzamide** [100]



2-Picolinoyl chloride hydrochloride (1.92 g, 10 mmol) was dissolved in THF (30 mL) in a round bottomed flask. Et_3N (1.011 g, 10 mmol) was added to the suspension via syringe, and a white precipitate was observed. Then benzohydroxamic acid (1.386 g, 10 mmol) was dissolved in THF (30 mL) and slowly added, followed by additional Et_3N (1.011 g, 10 mmol). More white precipitate was observed. After stirring at room temperature under argon overnight, the solid was filtered and washed with EtOAc (20 mL). The filtrate was washed with water and then brine. After drying over $MgSO_4$, evaporation of the solvent gave a light yellow solid. Recrystallization from Et_2O/CH_2Cl_2 afforded the title compound as an off-white solid (1.279 g, 55%). Mp 80-81°C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.82 (d, J = 4.8 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.09 (td, J = 8.0, 1.2 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.77-7.74 (m, 1H), 7.64 (t, J = 6.8 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H); ^{13}C NMR δ (100 MHz, d^6-DMSO) 164.9, 163.3, 150.3, 145.4, 138.0, 132.5, 130.9, 128.8, 128.4, 127.5, 125.7; IR (neat, cm^{-1}): 3157 (m), 2930 (m), 1776 (s), 1664 (s), 1282 (s), 1239 (s), 1061 (s), 695 (s). HRMS (FAB) Calcd for $C_{13}H_{11}O_3N_2$ ($M+H^+$): 243.0770. Found: 243.0771.

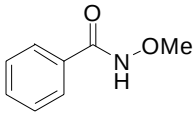
***N*-(Pentafluorobenzoyloxy)benzamide**

[100] Misra, B. N.; Sharma, R. P.; Diksha. *Indian J. Chem. Sec. B.* **1986**, *25*, 1182-1183.



Benzohydroxamic acid (1.38 g, 10 mmol) and Et_3N (1.21 g, 12 mmol) were dissolved in CH_2Cl_2 (30 mL) in a round-bottom flask and cooled to -78 °C under protection of argon. Pentafluorobenzoyl chloride (2.53 g, 11 mmol) in CH_2Cl_2 (10 mL) was added to the mixture via syringe. The suspension was stirred for 2 h and slowly warmed to room temperature. The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave the crude product. Recrystallization from CH_2Cl_2/hexanes afforded the title compound as a white solid (2.81 g, 85%) Mp 142-143 °C (ethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 158.2, 133.4, 130.1, 129.1, 127.8; IR (neat, cm^{-1}): 3244 (m), 1783 (s), 1654 (s), 1497 (s); HRMS (FAB) Calcd for $C_{14}H_7O_3NF_5$ ($M+H^+$): 332.0340. Found. 332.0336.

_O_-Methylbenzohydroxamic acid [101]

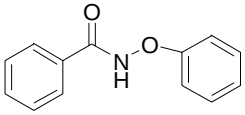


O-Methylhydroxylamine hydrochloride (0.852 g, 10 mmol) and K_2CO_3 (2.094 g, 20 mmol) were dissolved in water (20 mL) and EtOAc (20 mL) in a round bottomed flask. The solution was cooled to 0 °C in an ice bath. Benzoyl chloride (1.406 g, 10 mmol) was then added via syringe. After stirring at room temperature for 2 h, the aqueous layer was removed. The organic layer was washed with water then brine. After drying over $MgSO_4$,

[101] Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*, 252-259.

evaporation of the solvent gave a sticky residue. Recrystallization from hexanes/Et_2O gave afforded the title compound as a white solid (1.116 g, 72%). Mp 59-61 °C (lit. {61-62 °C (hexanes/Et_2O)}[23]). ^1H NMR (400 MHz, $CDCl_3$) δ 10.2 (br, s, 1H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 3.88 (s, 3H); IR (neat, cm^{-1}): 3196 (s), 2980 (m), 1648 (s), 1579 (m), 1517 (m).

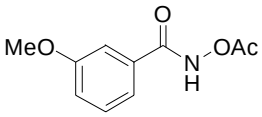
_O_-Phenylbenzohydroxamic acid [102]



O-Phenylhydroxylamine hydrochloride (1.500 g, 10 mmol) and Na_2CO_3 (1.590 g, 15 mmol) were dissolved in water (20 mL) and EtOAc (20 mL) in a round bottomed flask. Benzoyl chloride (1.406 g, 10 mmol) was added via syringe. After stirring at room temperature for 2 h, the aqueous layer was removed. The organic layer was washed with water then brine. After drying over $MgSO_4$, evaporation of the solvent gave a yellow solid. Recrystallization from hexanes/Et_2O afforded the title compound as a white solid (1.490 g, 70%). Mp 136-138 °C (lit. {137-139 °C (EtOAc)}[24]). ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (br, s, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.07-7.00 (m, 3 H); IR (neat, cm^{-1}): 3173 (s), 2953 (m), 1656 (s), 1590 (s), 1513 (m), 1486 (s).

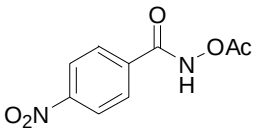
_O_-Acetyl-3-methoxybenzohydroxamic acid

[102] Baughman, R. G.; Fountain, K. R.; Fountain, D. P.; Tappmeyer, A. M. *J. Org. Chem.* **1989**, *54*, 5819-5821.



Hydroxylamine hydrochloride (2.78 g, 40 mmol) and NaOH pellets (2 g, 50 mmol) were dissolved in water (20 mL) and THF (20 mL). *m*-Methoxybenzoyl chloride (1.723 g, 10 mmol) was then added via syringe. After stirring the mixture at room temperature overnight, 2 M HCl was added to acidify the solution to pH=1. EtOAc (10 mL) was added to the organic layer that was washed with brine, then dried over $MgSO_4$. Evaporation of the solvent gave 0.939 g of a light orange solid, which was then dissolved in THF (30 mL). After purging with argon, AcCl (0.453 g, 5.8 mmol) and Et_3N (0.587 g, 5.8 mmol) were added subsequently via syringe. The suspension was stirred at room temperature overnight. After filtration of the solid, EtOAc (20 mL) was added to the filtrate that was washed with water, then brine. Drying over $MgSO_4$ and evaporation of the solvent gave a white solid. Recrystallization from hexanes/EtOAc afforded the title compound as white crystals (0.836 g, 40%). Mp 119-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (br, s, 1H), 7.35-7.29 (m, 3H), 7.07-7.04 (m, 1H), 3.80 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 166.4, 160.0, 132.1, 130.0, 119.6, 119.3, 112.5, 55.6, 18.5; IR (neat, cm^{-1}): 3181 (m), 2937 (m), 1795 (s), 1660 (s), 1583 (s), 1177 (s); HRMS (FAB) Calcd for $C_{10}H_{11}O_4NLi$ (M+Li$^+$): 216.0848. Found: 216.0848.

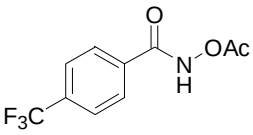
_O_-Acetyl-4-nitrobenzohydroxamic acid [103]



[103] (a) Dessolin, M.; Laloi-Diard, M.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1970**, *7*, 2573-2580. (b) Exner, O.; Simon, W. *Collect. Czech. Chem. Commun*. **1965**, *30*, 4078-4094.

Hydroxylamine hydrochloride (2.78 g, 40 mmol) and NaOH pellets (2 g, 50 mmol) were dissolved in water (20 mL) and THF (20 mL). *p*-Nitrobenzoyl chloride (1.874 g, 10 mmol) was dissolved in THF (30 mL) and added via syringe. After stirring the mixture at room temperature overnight, 2 M HCl was added to acidify the solution to pH=1. EtOAc (10 mL) was added to the organic layer that was washed with brine, then dried over $MgSO_4$. Evaporation of the solvent gave 1.290 g of an off-white solid, which was then dissolved in THF (30 mL). AcCl (0.569 g, 7.3 mmol) and Et_3N (0.739 g, 7.3 mmol) were added subsequently via syringe. The suspension was stirred at room temperature overnight. After filtration of the solid, EtOAc (10 mL) was added to the filtrate which was washed with water, then brine. Drying over $MgSO_4$ and evaporation of the solvent gave a white solid. Recrystallization from Et_2O/CH_2Cl_2 afforded the title compound as needle-shape yellow crystals (1.14 g, 51%). Mp 181-183 °C; ^{1}H NMR (400 MHz, d_6-acetone) δ 11.6 (br, s, 1H), 8.38 (d, J = 8.0 Hz, 2H), 8.13 (d, J = 8.0 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, *d*6-DMSO) δ 168.5, 162.7, 149.6, 136.6, 129.0, 123.9, 18.1; IR (neat, cm^{-1}): 3150 (s), 2964 (m), 1799 (s), 1671 (s), 1602 (m), 1571 (m); HRMS (FAB) Calcd for $C_9H_8O_5N_2Li$ (M+Li$^+$): 231.0593. Found: 231.0594.

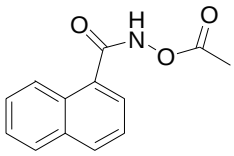
_O_-Acetyl-(4-trifluoromethyl)benzohydroxamic acid



Hydroxylamine hydrochloride (2.78 g, 40 mmol) and NaOH pellets (2 g, 50 mmol) were dissolved in water (20 mL) and THF (20 mL). *p*-(Trifluoromethyl)benzoyl chloride (2.150 g, 10 mmol) was added via syringe. After stirring the mixture at room temperature

overnight, 2 M HCl was added to acidify the solution to pH=1. EtOAc (10 mL) was added to the organic layer that was washed with brine, then dried over $MgSO_4$. Evaporation of the solvent gave 2.0 g of an off-white solid, which was then dissolved in THF (30 mL). AcCl (0.765 g, 9.8 mmol) and Et_3N (0.992 g, 9.8 mmol) were added subsequently via syringe. The suspension was stirred at room temperature overnight. After filtration of the solid, EtOAc (10 mL) was added to the filtrate that was washed with water, then brine. Drying over $MgSO_4$ and evaporation of the solvent gave a white solid. Recrystallization from EtOAc/CH_2Cl_2 afforded the title compound as needle-shaped white crystals (1.359 g, 55%). Mp 140-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (br, s, 1H), 7.93 (d, *J* = 11.2 Hz, 2H), 7.73 (d, *J* = 11.2 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.5, 163.3, 134.9, 132.0 (q, *J* = 31.9 Hz), 128.4, 125.7 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 270.8 Hz), 18.1; IR (neat, cm^{-1}): 3142 (m), 2961 (m), 1799 (s), 1710 (s), 1656 (m); HRMS (FAB) Calcd for $C_{10}H_8O_3NF_3Li$ (M+Li$^+$): 254.0616. Found: 254.0616.

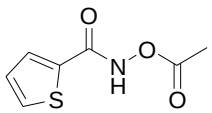
_O_-Acetyl 1-naphthohydroxamic acid



1-Naphthohydroxamic acid (0.936 g, 5 mmol) was dissolved in THF (60 mL) in a round bottomed flask. AcCl (0.408 g, 5.2 mmol) was added to the solution via syringe, followed by Et_3N (0.526 g, 5.2 mmol). The suspension was stirred at room temperature overnight. The precipitate was filtered and washed with EtOAc (20 mL). The filtrate was washed with water and then brine. After drying over $MgSO_4$, evaporation of the solvent gave a

light yellow solid. Recrystallization from Et_2O/CH_2Cl_2 afforded the title compound as a white solid (0.779 g, 68%). Mp 105-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (br, s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.77 (dd, *J* = 6.8, 1.2 Hz, 1H), 7.54-7.82 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 167.5, 133.6, 131.9, 130.4, 129.3, 128.4, 127.6, 126.8, 126.4, 125.2, 124.6, 18.3; IR (neat, cm^{-1}): 3150 (s), 2953 (m), 1791 (s), 1660 (s), 1513 (m); HRMS (FAB) Calcd for $C_{13}H_{11}O_3NLi$ ($M+Li^+$): 236.0899. Found: 236.0910.

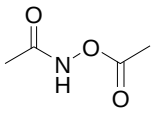
_N_-Acetoxy-2-thiophenecarboxamide



Hydroxylamine hydrochloride (2.78 g, 40 mmol) and NaOH pellets (2 g, 50 mmol) were dissolved in water (20 mL) and THF (20 mL). 2-Thiophenecarbonyl chloride (1.46 g, 10 mmol) was then added via syringe. After stirring the mixture at room temperature overnight, 2 M HCl was added to acidify the solution to pH=1. EtOAc (10 mL) was added to the organic layer that was washed with brine, then dried over $MgSO_4$. Evaporation of the solvent gave a yellow solid which was then dissolved in THF (30 mL). After purging with argon, AcCl (0.765 g, 9.8 mmol) and Et_3N (0.992 g, 9.8 mmol) were added subsequently via syringe. The suspension was stirred at room temperature overnight. After filtration of the solid, EtOAc (10 mL) was added to the filtrate that was washed with water, then brine. Drying over $MgSO_4$ and evaporation of the solvent gave a yellow solid. Recrystallization from hexanes/EtOAc afforded the title compound as a white crystal (1.39 g, 75%). Mp 93-94 °C (ethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$)

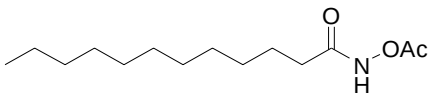
δ 9.37 (s, 1H), 7.69 (m, 1H), 7.61 (d, *J* = 5.6 Hz, 1H), 7.15 (m, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 161.7, 133.7, 132.1, 130.7, 128.1, 18.5; IR (neat, cm^{-1}): 3102 (w), 1782 (s), 1643 (s); HRMS (FAB) Calcd for $C_7H_8O_3NS$ ($M+H^+$): 186.0219. Found: 186.0215.

_O_-Acetyl acetylhydroxamic acid [26]



Acetyl hydroxamic acid (1.5 g, 20 mmol), CH_2Cl_2 (30 mL), and NaOH (2 M, 11 mL) were charged to a round bottomed flask. Ac_2O (2.2 g, 22 mmol) was added via syringe. After stirring at room temperature for 2 h, the CH_2Cl_2 layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the CH_2Cl_2 layers were combined and washed with brine and dried over $MgSO_4$. Evaporation of the solvent afforded the title compound as a white solid (1.72 g, 76%). Mp 85-86 °C (hexanes/EtOAc, lit. {88-90 °C (hexanes/ether)}[104]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 2.24 (s, 3H), 2.07 (s, 3H); IR (neat, cm^{-1}): 2957 (m), 1787 (s), 1668 (s).

_O_-Acetyl laurohydroxamic acid

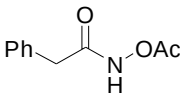


Laurohydroxamic acid[105] (2.2 g, 10 mmol), CH_2Cl_2 (30 mL) and NaOH (2 M, 11 mL) were charged to a round bottomed flask. Ac_2O (1.1 g, 11 mmol) was added via syringe.

[104] Narita, M.; Akiyama, M,; Okawara, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 437-441.
[105] Laurohydroxamic acid was prepared by the procedure: Reddy, A. S.; Kumar, M. S.; Reddy, G. R. *Tetrahedron Lett*. **2000**, *41*, 6285-6288.

After stirring at room temperature for 2 h, the CH_2Cl_2 layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL). The CH_2Cl_2 layers were combined and washed with brine and dried over $MgSO_4$. Evaporation of the solvent afforded the title compound as a white solid (2.23 g, 85%). Mp 95-96 °C (hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 2.24 (m, 5H), 1.68 (m, 2H), 1.28 (br, 16H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.0, 33.0, 32.1, 29.8, 29.6, 29.53, 29.50, 29.3, 25.3, 22.8, 18.4, 14.3; IR (neat, cm^{-1}): 2916 (s), 2847 (s), 1790 (s), 1661 (s); HRMS(FAB) Calcd for $C_{14}H_{28}O_3N$ ($M+H^+$): 258.2063. Found: 258.2057.

_N_-Acetoxy-2-phenylacetamide [106]



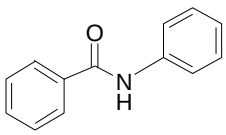
Hydroxylamine hydrochloride (2.78 g, 40 mmol) and NaOH pellets (2 g, 50 mmol) were dissolved in water (20 mL) and EtOAc (20 mL). Phenylacetyl chloride (1.578 g, 10 mmol) was then added via syringe. After stirring the mixture at room temperature overnight, 2 M HCl was added to acidify the solution to pH=1. The organic layer was separated, washed with brine then dried over $MgSO_4$. Evaporation of the solvent gave 0.830 g of an off-white solid, which was then dissolved in THF (30 mL). After purging with argon, AcCl (0.453 g, 5.8 mmol) and Et_3N (0.587 g, 5.8 mmol) were added subsequently via syringe. The suspension was stirred at room temperature overnight. After filtration of the solid, EtOAc (10 mL) was added to the filtrate which was washed with water, then brine. Drying over $MgSO_4$ and evaporation of the solvent gave a white solid. Recrystallization from hexanes/Et_2O afforded the title compound as needle-shape colorless crystals (1.04 g,

[106] Cherest, M.; Lusinchi, X. *Tetrahedron* **1986**, *42*, 3825-3840.

52%). Mp 139-140 °C (lit. {141-142 °C}[28]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (br, s, 1H), 7.38-7.30 (m, 5H), 3.65 (s, 2H), 2.18 (s, 3H); IR (neat, cm^{-1}): 3142 (s), 2937 (m), 1791 (s), 1702 (s), 1652 (s).

General Procedure for Cu(I) Mediated Reaction of *O*-Substituted Aryl/Alkylhydroxamic acids and Arylboronic acids. *O*-Substituted hydroxamic acid (0.2 mmol), boronic acid (0.24 mmol) and CuTC (0.2 mmol) were added to a Schlenk tube. After flushing with argon, THF (5 mL) was added via syringe. The reaction mixture was stirred under the protection of argon at 60 °C for 16 h. After cooling, ethyl ether (10 mL) was added to the mixture. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was then subjected to preparative plate silica gel chromatography using hexanes/EtOAc as eluent.

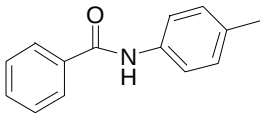
***N*-Phenylbenzamide**[107]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a light yellow solid (30 mg, 74%). Mp 160-162 °C (lit. {162-163 °C (ethanol)}[29]). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (br, s, 1H), 7.86 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H), 7.56-7.34 (m, 5H), 7.15 (t, J = 7.6 Hz, 1H); IR (neat, cm^{-1}): 3343 (s), 3053 (m), 2918 (m), 1656 (s), 1598 (s), 1525 (s), 1440 (s).

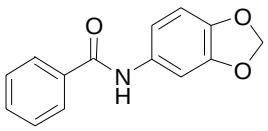
[107] Huang, H. H.; Tan, B. G. *J. Chem. Soc. Perkin Trans.2* **1983**, 233-235.

_N_-_p_-Tolylbenzamide[108]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a light yellow solid (32 mg, 77%). Mp 157-158 °C ({lit. 158 °C}[30]). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br, s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.53-7.42 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 2.34 (s, 3H); IR (neat, cm^{-1}): 3312 (s), 3053 (m), 2918 (m), 1648 (s), 1579 (m), 1513 (m).

_N_-(1,3-Benzodioxol-5-yl)benzamide[109]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a yellow solid (30 mg, 63%). Mp 134-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (br, s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.52-7.38 (m, 3H), 7.30 (d, J = 0.8 Hz, 1H), 6.90 (dd, J = 8.4, 2.0 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.93 (s, 2H); IR (neat, cm^{-1}): 3308 (s), 2891 (m), 1644 (s), 1540 (m), 1490 (m).

_N_-(4-Phenoxyphenyl)benzamide[110]

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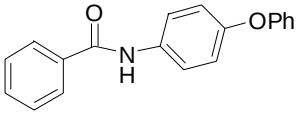
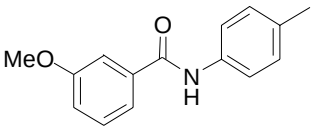
[108] Haridasan, V. K.; Ajayaghosh, A.; Pillai, V. N. Rajasekharan *J. Org. Chem.* **1987**, *52*, 2662-2665.
[109] (a) Commercially available from Exploratory Library. (b) Monteil, A.; Simond, J.; Combourieu, M. Eur. Pat. Appl. (1985), EP 84-401919 19840926.
[110] (a) Konieczny, J. M.; Wunder, S. L. *Macromolecules* **1996**, 29, 7613-7615. (b) Ruane, P. H.; Ahmed, A. R.; McClelland, R. A. *J. Chem. Soc. Perkin Trans. 2* **2002**, 312-317.



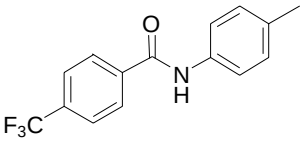
Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (40 mg, 68%). Mp 159-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br, s, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.61-7.45 (m, 5H), 7.36-7.31 (m, 2H), 7.12-6.99 (m, 5H); IR (neat, cm^{-1}): 3347 (m), 3057 (m), 1652 (s), 1606 (m), 1525 (m), 1505 (s), 1486 (s).

3-Methoxy-*N*-*p*-tolylbenzamide[111]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (28 mg, 58%). Mp 129-130 °C (lit. {132 °C (ethanol)}[33]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br, s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.42-7.31 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.05 (dq, *J* = 7.6 Hz, 1.4, 1H), 3.82 (s, 3H), 2.33 (s, 3H); IR (neat, cm^{-1}): 3296 (m), 2922 (m), 1648 (s), 1594 (s), 1517 (s).

***N*-(4-Methylphenyl)-4-(trifluoromethyl)benzamide**[112]

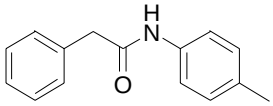


Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (46 mg, 81%). Mp 236-238 °C; ^{1}H NMR (400 MHz, d_6-acetone) δ 9.66 (br, s,

[111] Grammaticakis, P. *Bull. Soc. Chim. Fr.* **1964**, 5, 924-935.
[112] Commercially available from Exploratory Library.

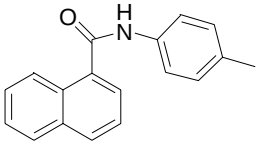
1H), 8.18 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 2.31 (s, 3H). IR (neat, cm^{-1}): 3424 (m), 3061 (m), 3007 (m), 1710 (s), 1420 (m), 1363 (s).

2-Phenyl-*N*-*p*-tolylacetamide[113]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a light yellow solid (34 mg, 76%). Mp 131-132.5 °C (lit. {132-133.8 °C}[35]); ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.40-7.30 (m, 7H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.70 (s, 2H), 2.29 (s, 3H); IR (neat, cm^{-1}): 3300 (m), 3034 (m), 1656 (s), 1606 (s), 1536 (s), 1517 (s).

Naphthalene-1-carboxylic acid *p*-tolylamide[114]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (34 mg, 65%). Mp 190-191 °C (lit. {191.9-192.9 °C}[36]); ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.36-8.34 (m, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.90-7.88 (m, 1H), 7.17 (d, *J* = 6.4 Hz, 2H), 7.58-7.53 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H); IR (neat, cm^{-1}): 3235 (m), 2922 (m), 1648 (s), 1598 (m), 1517 (s).

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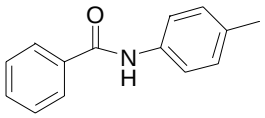
[113] House, H. O.; Berkowitz, W. F. *J. Org. Chem.* **1963**, *28*, 307-311.
[114] Jart, A. *Acta Polytech. Scand., Chem. Met. Ser.* **1965**, *44*, 1.

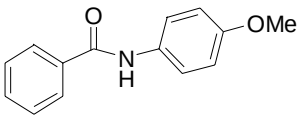
General Procedure for Cu(I) Mediated Reaction of *O*-Acetyl Aryl/Heteroaryl/Alkylhydroxamic Acids and Organostannanes. *O*-Substituted hydroxamic acid (0.2 mmol), organostannane (0.24 mmol) and CuDPP (0.4 mmol) were added to a Schlenk tube. After flushing with argon, DMF (5 mL) was added via syringe. The reaction mixture was stirred under the protection of argon at 60 °C for 12 h. After cooling, ethyl ether (10 mL) was added to the mixture. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was then subjected to preparative plate silica chromatography using hexanes/EtOAc as eluent.

***N*-*p*-Tolylbenzamide** [30]



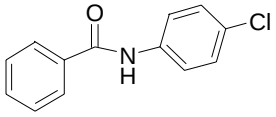
Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a light yellow solid (33 mg, 80%). Mp 157-158 °C ({lit. 158 °C}[30]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br, s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.53-7.42 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 2.34 (s, 3H); IR (neat, cm^{-1}): 3312 (s), 3053 (m), 2918 (m), 1648 (s), 1579 (m), 1513 (m).

***N*-*p*-Methoxyphenylbenzamide** [37]



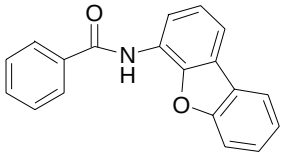
Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (34 mg, 76%). Mp 156-157 °C (lit. {156-157°C}[115]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.79 (s, 1H), 7.55-7.47 (m, 5H), 6.92 (d, *J* = 7.2 Hz, 2H), 3.82 (s, 3H); IR (neat, cm^{-1}): 3331 (m), 3053 (m), 1644 (s), 1602 (m), 1517 (s).

_N_-_p_-Chlorophenylbenzamide [38]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (26 mg, 56%). Mp 188-190 °C (lit. {190-191°C}[116]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 6.8 Hz, 2H), 7.80 (s, 1H), 7.62-7.49 (m, 5H), 7.36 (d, *J* = 8.8 Hz, 2H); IR (neat, cm^{-1}): 3335 (m), 1648 (s), 1594 (m), 1521 (s).

_N_-4-Dibenzofuranylbenzamide

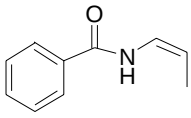


Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (42 mg, 73%). Mp 195-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 7.6 Hz, 1H), 8.48 (s, 1H), 8.05-7.97 (m, 3H), 7.74 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.65-7.56 (m, 4H), 7.52-7.48 (m, 1H), 7.42-7.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 155.9, 146.0, 134.9, 132.3, 129.1, 127.5, 127.4, 124.7, 124.5, 124.0, 123.8, 123.4, 121.2, 118.2,

[115] Katritzky, A. R. Cai, C.; Singh, S. K. *J. Org. Chem.* **2006**, *71*, 3375-3380.
[116] Singh, H; Aggarwal, S. K.; Malhotra, N. *Synthesis* **1983**, *10*, 791-793.

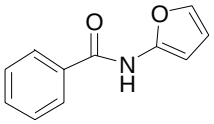
116.2, 111.8; IR (neat, cm^{-1}): 3239 (m), 1648 (s), 1525 (s); HRMS (FAB) Calcd for $C_{19}H_{14}O_2N$ ($M+H^+$): 288.1019. Found: 288.1015.

_N_-((Z)-Prop-1-enyl)benzamide [117]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as light yellow oil (22 mg, 66%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.81 (m, 2H), 7.58-7.46 (m, 4H), 6.99-6.93 (m, 1H), 4.98-4.94 (m, 1H), 1.73 (dd, *J* = 7.2, 2.0 Hz, 3H); IR (neat, cm^{-1}): 2926 (s), 1656 (s), 1606 (m), 1529 (s).

_N_-(Furan-2-yl)benzamide [40]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (27 mg, 73%). Mp 116-118 °C (lit. {121-122°C}[118]); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.59-7.48 (m, 3H), 7.12 (dd, *J* = 2.0, 1.2 Hz, 1H), 6.50 (d, *J* = 3.2 Hz, 1H), 6.49 (dd, *J* = 3.2, 2.0 Hz, 1H); IR (neat, cm^{-1}): 3065 (m), 1660 (s), 1606 (m), 1540 (s).

_N_-(Pyrazin-2-yl)benzamide [41]

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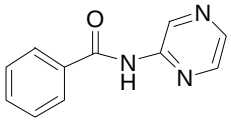
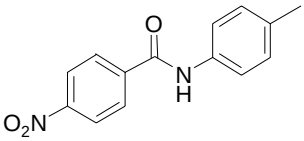
[117] Liskamp, R. M. J.; Blom, H. J.; Nivard, R. J. F.; Ottenheijm, H. C. J. *J. Org. Chem.* **1983**, *48*, 2733-2736.
[118] Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609-2617.



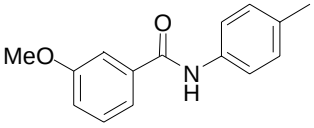
Purification by preparative TLC (hexanes/EtOAc 2:1) afforded a white solid (17 mg, 42%). Mp 169-170 °C (lit. {170°C}[119]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 8.51 (s, 1H), 8.41 (d, *J* = 2.4 Hz, 1H), 8.29 (s, 1H), 7.96-7.94 (m, 2H), 7.62-7.52 (m, 3H); IR (neat, cm^{-1}): 3242 (m), 3065 (m), 1675 (s), 1583 (m), 1532 (s).

_N_-(4-Methylphenyl)-4-nitrobenzamide [42]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (37 mg, 74%). Mp 198-199 °C (lit. {201-203°C}[120]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 9.2 Hz, 2H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.84 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H); IR (neat, cm^{-1}): 3312 (m), 1644 (s), 1598 (m), 1525 (s).

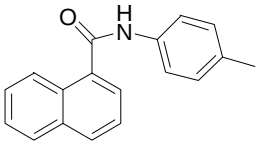
3-Methoxy-_N_-_p_-tolylbenzamide [121]



[119] Barlin, G. B.; Brown, D. J.; Kadunc, Z.; Petric, A.; Stanovnik, B.; Tisler, M. *Aust. J. Chem,* **1983***, 36*, 1215-1220.
[120] Han, K-J; Tae, B. S.; Kim, M. *Org. Prep. Proced. Int.* **2005**, *37*, 198-203.
[121] Grammaticakis, P. *Bull. Soc. Chim. Fr.* **1964**, 5, 924-935.

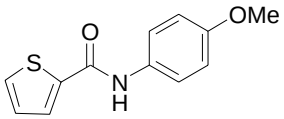
Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (34 mg 71%). Mp 125-126 °C (lit. {132 °C}[43]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.43-7.37 (m, 3H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.09 (m, 1H), 3.87 (s, 3H), 2.35 (s, 3H); IR (neat, cm^{-1}): 3296 (m), 3034 (m), 1648 (s), 1594 (s), 1517 (s).

Naphthalene-1-carboxylic acid *p*-tolylamide [122]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (43 mg 83%). Mp. 192-193 °C (lit. {191.9-192.9 °C}[44]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.92-7.90 (m, 1H), 7.76 (d, *J* = 6.8 Hz, 1H), 7.64-7.50 (m, 6H), 7.23 (d, *J* = 8.4 Hz, 2H), 2.37 (s, 3H); IR (neat, cm^{-1}): 3235 (m), 3046 (m), 1652 (s), 1598 (s), 1517 (s).

***N*-(4-Methoxyphenyl)thiophene-2-carboxamide** [123]

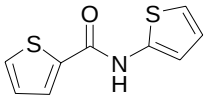


Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (42 mg, 90%). Mp 139-140 °C (lit. {137-140 °C }[45]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.62 (d, *J* = 3.6 Hz, 1H), 7.54-7.50 (m, 3H), 7.12 -7.10 (m, 1H),

[122] Jart, A. *Acta Polytech. Scand., Chem. Met. Ser.* **1965**, *44*, 1.
[123] Lee, C. K; Yu, J. S; Ji, Y. R. *J. Heterocycl. Chem*, **2002**, *39* ,1219-1227.

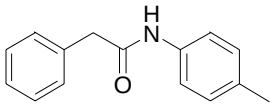
6.91-6.88 (m, 2H), 3.81 (s, 3H); IR (neat, cm^{-1}): 3281 (m), 3003 (m), 1633 (s), 1602 (m), 1513 (s).

_N_-(Thiophen-2-yl)thiophene-2-carboxamide [124]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (25 mg, 60%). Mp 205-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.68 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.58 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.15 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.95 (dd, *J* = 5.6, 1.2 Hz, 1H), 6.91(dd, *J* = 5.6, 3.6 Hz, 1H), 6.80 (dd, *J* = 3,6, 1.2 Hz, 1H); IR (neat, cm^{-1}): 3227 (m), 1617 (s), 1563 (s) 1513 (s).

2-Phenyl-*N*-*p*-tolylacetamide [35]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (33 mg, 74%). Mp 130-131 °C (lit. {132-133.8 °C }[35]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (m, 7H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.04 (s, 1H), 3.73 (s, 2H), 2.29 (s, 3H); IR (neat, cm^{-1}): 3300 (m), 1656 (s), 1606 (s), 1536 (s).

_N_-(4-Iodophenyl)-2-phenylacetamide [125]

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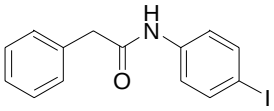
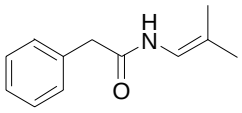
[124] Brovelli, F; del Valle, M. A.; Diaz, F. R.; Bernede, J. C. *Bol. Soc. Chil. Quim,* **2001**, *46*, 319-337.
[125] Chattaway, F. D.; Constable, A. *J. Chem. Soc.,Trans.,* **1914**, *105,* 124-131.



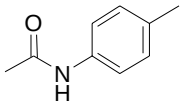
Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (40 mg, 60%). Mp 195-196 °C (lit. {200 °C}[47]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.44-7.32 (m, 5H), 7.21-7.19 (m, 2H), 7.02 (s, 1H), 3.74 (s, 2H); IR (neat, cm^{-1}): 3273 (m), 3026 (m), 1656 (s), 1583 (m), 1525 (s).

_N_-(2-Methylprop-1-enyl)-2-phenylacetamide [126]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (24 mg, 64%). Mp 98-99 °C (lit. {102 °C}[48]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 6.64 (s, 1H), 6.51-6.48 (m, 1H), 3.65 (s, 2H), 1.65 (s, 3H), 1.35 (s, 3H); IR (neat, cm^{-1}): 3300 (m), 2930 (m), 1660 (s), 1637 (s), 1529 (s).

_N-p_-Tolylacetamide [127]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (25 mg, 85%). Mp 146-147 °C (lit. {146-148 °C}[49]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 2.31 (s, 3H), 2.16 (s, 3H); IR (neat, cm^{-1}): 3289 (m), 2922 (m), 1660 (s), 1602 (s), 1532 (s).

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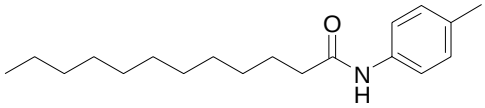
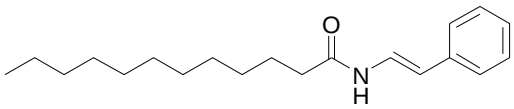
[126] Zehavi,U.; Ben-Ishai,D. *J.Org. Chem,* **1961**, *26,* 1097-1101.
[127] Lobo, A. M.; Marques, M. M; Prabhakar, S; Rzepa, H. S. *J.Org. Chem,* **1987**, *52,* 2925-2927.

_N_-_p_-Tolyldodecanamide [128]



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (38 mg, 66%).. Mp 83-84 °C (lit. {82-83 °C}[50]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 2H), 7.18 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 2.35-2.31 (m, 5H), 1.73-1.70 (m, 2H), 1.32-1.26 (br, 16H), 0.90 (t, J = 6.8 Hz, 3H); IR (neat, cm^{-1}): 3312 (m), 2922 (s), 1660 (s), 1529 (s).

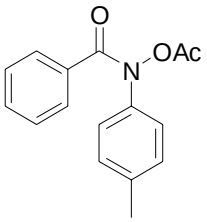
_N_-(_E_)-β-Styryldodecanamide



Purification by preparative TLC (hexanes/EtOAc 2:1) afforded the title compound as a white solid (31 mg, 52%). Mp 103-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 14.4, 10.8 Hz, 1H), 7.38-7.26 (m, 5H), 7.19-7.15 (m, 1H), 2.35-2.31 (m, 5H), 6.11 (d, J = 14.4 Hz, 1H), 2.31 (t, J = 7.6 Hz, 2H), 1.71-1.66 (m, 2H), 1.32-1.26 (br, 16H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 136.2, 128.8, 126.8, 125.7, 122.8, 112.5, 37.0, 32.1, 29.8, 29.6, 29.5, 29.4, 25.7, 22.8, 14.3; IR (neat, cm^{-1}): 3305 (m), 2916 (s), 2849 (m), 1664 (m), 1639 (s), 1522 (m); HRMS (FAB) Calcd for $C_{20}H_{32}ON$ ($M+H^+$): 302.2478. Found: 302.2474.

_N_-(acetyloxy)-_N_-(4-methylphenyl)benzamide

[128] Robertson. P. W. *J. Chem. Soc.,Trans.,* **1919**, *115,* 1210-1223.



O-Acetyl benzohydroxamic acid (36 mg, 0.2 mmol), *p*-tolyl boronic acid (33 mg, 0.24 mmol) and $Cu(OAc)_2$ (36 mg, 0.2 mmol) were added to a flask. DMF (5 mL) was added via syringe. The reaction mixture was stirred under air at 60 °C for 12 h. After cooling, ethyl ether (10 mL) was added to the mixture. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was then subjected to preparative plate silica gel chromatography using hexanes/EtOAc as eluent. The product was obtained as a yellow oil (23 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.29 (m, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 2.32 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 167.0, 139.1, 138.2, 133.4, 131.1, 130.0, 129.0, 128.2, 127.5, 21.3, 18.6. IR (neat, cm^{-1}): 3069 (m), 2964 (m), 1795 (s), 1675 (s), 1509 (m). HRMS (FAB) Calcd for $C_{16}H_{16}O_3N$ ($M+H^+$): 270.1124. Found: 270.1120.