NEW METHODS FOR HETEROCYCLE SYNTHESIS

by

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NEW METHODS FOR HETEROCYCLE SYNTHESIS

John Paul Maciejewski, Ph.D.

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This dissertation will describe the development and application of novel methods for heterocycle synthesis. The first chapter will outline the development of a titanocene catalyzed epoxide-opening rearrangement to prepare indolines from epoxyanilines. A discussion of the reaction development, along with the substrate scope and limitations will be reported.

The second chapter will describe progress toward expanding the scope of a Staudinger/*aza*-Wittig reaction used to prepare substituted 1,2,4-triazines. This methodology has been applied towards the synthesis of a model system for the DEF rings of the natural product noelaquinone. The challenges associated with the Staudinger/*aza*-Wittig reaction, and the late-stage oxidation strategy to prepare the DEF rings of the noelaquinone model system will be discussed.

The third chapter will describe the importance and general preparation of (*E*)-alkene peptide isosteres. Using compounds prepared in the UPCMLD and published on PubChem as a reference, we present our ongoing initiative to expand the library of α,β-cyclopropyl-γ-amino acid analogs.

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ABBREVIATIONS

$(t\text{-BuO})_2$	*t*-Butyl peroxide
))))	Sonication
Ac	Acetyl
ADDP	Azodicarboxylic dipiperidide
AIBN	2,2′-Azobis(2-methylpropionitrile)
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Cbz	Benzyloxycarbonyl
Coll-HCl	Collidine hydrochloride
Cp	Cyclopentadienyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPPB	1,4-bis(Diphenylphosphino)butane
dr	Diastereomeric ratio
EDCI	(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EI	Electron ionization
er	Enantiomeric ratio
ESI	Electrospray ionization
EtOAc	Ethyl acetate
$LiAlH_4$	Lithium aluminum hydride
m-CPBA	*m*-Chloroperbenzoic acid

NaH	Sodium hydride
NBS	*N*-Bromosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMP	*N*-Methyl-2-pyrrolidone
Nos	4-Nitrobenzenesulfonyl
o-DCB	*o*-Dichlorobenzene
OsO_4	Osmium tetroxide
PBu_3	Tributylphosphine
PG	Protecting group
PIFA	Phenyliodonium *bis*(trifluoroacetate)
p-Ts_2O	*p*-Toluenesulfonyl anhydride
py	Pyridine
PyBroP	Bromotripyrrolidinophosphonium hexafluorophosphate
rt	Room temperature
SmI_2	Samarium diiodide
T3P	Propane phosphoric acid anhydride
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*t*-Butyldiphenylsilyl
t-BuOK	Potassium *t*-butoxide
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy free radical
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	*p*-Toluenesulfonyl

ACKNOWLEDGEMENTS

To have the ability to complete a journey that some may never have the opportunity to begin is quite a humbling experience. I thank my research advisor Professor Peter Wipf for his patience and guidance throughout my graduate studies at the University of Pittsburgh. I am extremely fortunate to have benefited from Professor Wipf's unwavering commitment toward mentoring his students, and his ability to provide an outstanding educational experience. In addition to Professor Wipf, I wish to thank all of my co-workers at the University of Pittsburgh who have helped me learn and achieve during my graduate studies.

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This dissertation is dedicated to my grandfather John, who passed away during the last six months of my graduate studies. He was my best friend, and one of my biggest supporters. I am grateful to my Mom and Dad, sister Joanne, Irene, Bob, Mike, Prema and Gwen for their unconditional support throughout my graduate studies. I also thank Yanni and Pauline, and John and Lynn who treated me as part of their family. Finally, for upholding my freedom to pursue organic chemistry, I wish to thank the active and retired members of the U.S. Armed Forces for their service to my country.

1.0 TITANOCENE(III)-CATALYZED CONVERSION OF EPOXYANILINES TO INDOLINES

1.1 INTRODUCTION

1.1.1 Indolines: The Preparation and Applications of a Privileged Scaffold

Natural products that contain the indole and dihydroindole (indoline) scaffolds (outlined in bold in Figure 1-1) are ubiquitous in nature. In addition, the indoline and its nitrogen-containing isostere, the azaindoline,[1] have long been studied for their tremendous therapeutic potential, and are considered to be a privileged scaffolds.[2] One of the well-known biologically active indolines of the *Vinca* alkaloids include the potent anticancer agent vinblastine **1-1**.[3] In addition to being biologically active, there exist many structurally complex and thus synthetically challenging indoline-containing molecules that have been recent targets for total synthesis. Two of such molecules include the cytotoxic chlorinated marine metabolite diazonamide A **1-2**,[4,5] and the highly substituted core of kapakahine F **1-3**.[6] Many strategies have been developed to prepare indoline-containing heterocycles, however, due to the important biological activity often associated with these heterocyclic building blocks,[7,8] there remains a strong initiative to develop novel methods for their preparation.

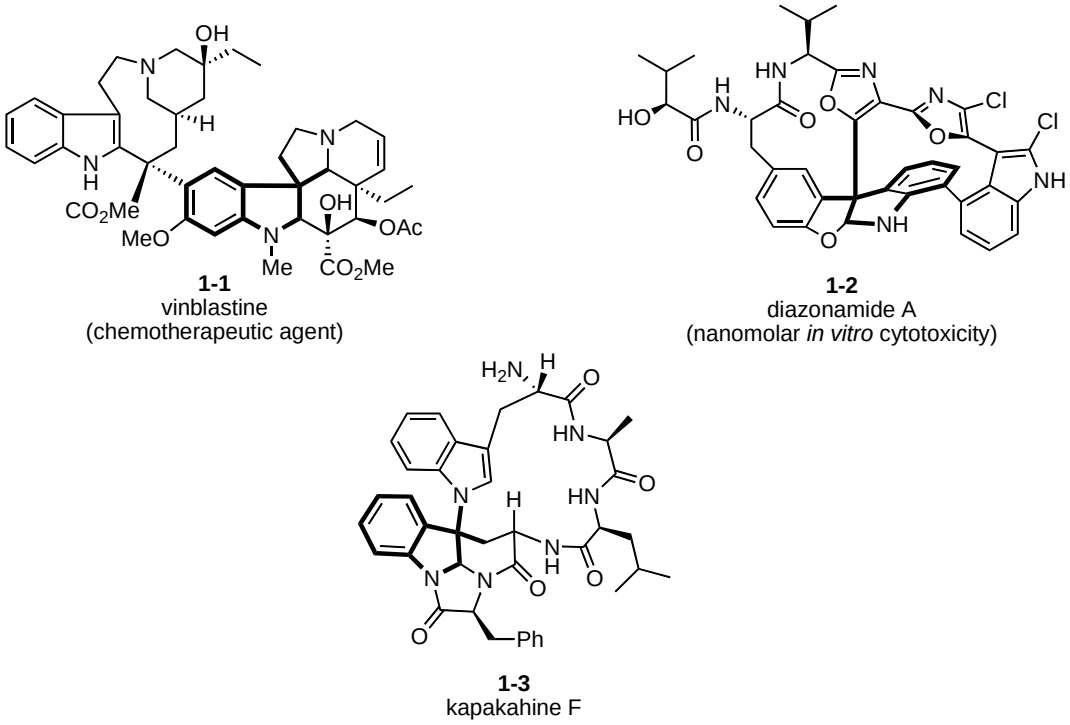
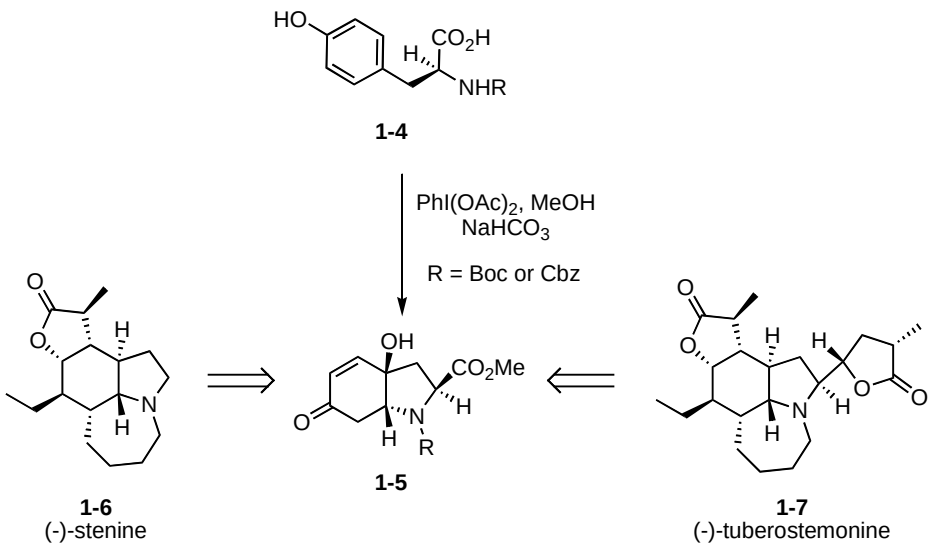


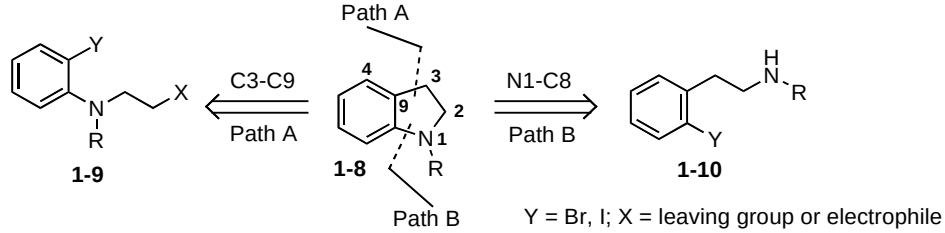
Figure 1-1. Natural products containing the 3,3-disubstituted indoline core (outlined in bold)

The Wipf research group has had an extensive interest in developing methods to prepare indolines and their derivatives for broad applications that range from S*temona* alkaloid synthesis to botulinum neurotoxin metalloprotease inhibitors.[9] One particularly useful method for indoline preparation involves the oxidative cyclization[10] of *N*-protected tyrosine **1-4** and subsequent methanolysis to yield the hydroindoline derivative **1-5**. This reaction has been widely utilized in the Wipf group for the preparation of *Stemona* alkaloids that include stenine **1-6**[11] and tuberostemonine **1-7**[12] (Scheme 1-1) and progress toward the preparation of tuberostemonone[13] and parvistemoline.[14]



Scheme 1-1. Oxidative cyclization of protected tyrosine **1-4** to form hydroindoline **1-5**

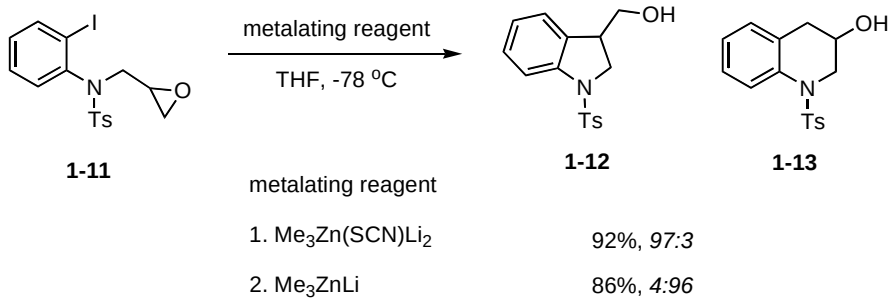
The preparation of indoles and indolines has been a topic of recent reviews,[2,15] where the synthetic strategies utilized in their preparation have also been evaluated.[16,17] In general, most one-step protocols to prepare indolines **1-8** (not including methods that begin with the indole core) are accomplished through either carbon-carbon bond formation (Path A) from aniline derivative **1-9** or carbon-nitrogen bond formation (Path B) *via* amine **1-10** (Scheme 1-2).



Scheme 1-2. General bond disconnections for indoline formation

The carbon-carbon bond formation reaction between C9 and C3 often involves activation of the aryl ring to function as a nucleophile. This is commonly achieved through metal/halogen

exchange with an aryl halide[18] followed by the trapping of the reactive intermediate with an appended electrophile. Sakamoto and co-workers[19] have demonstrated that zinc-ate complexes can undergo metal/halogen exchange to promote a 5-*exo* or 6-*endo* cyclization[20] with epoxide **1-11** to prepare the indoline **1-12** or hydroquinoline **1-13** scaffolds, respectively (Scheme 1-3). Substituted indolines have also been prepared using intramolecular Michael additions and carbozincation reactions.[19]



Scheme 1-3. Indoline formation using metal/halogen exchange

Natural products of the duocarmycin family represent a well-studied class of cytotoxic molecules that contain the indoline core (Scheme 1-4). The parent natural product from this family is CC-1065 **1-14**, which was isolated by Martin and co-workers[21] in 1981. Duocarmycin SA **1-15** is one of the most potent cytotoxic agents of its class, with an IC_{50} value of 10 pM in a L1210 (mouse lymphocytic leukemia cell line) cell assay.[22]. These compounds derive their cytotoxicity from selective binding to the minor groove of the DNA backbone and subsequently alkylating the N-3 of the adenine residue through the opening of the electrophilic cyclopropane.[23]

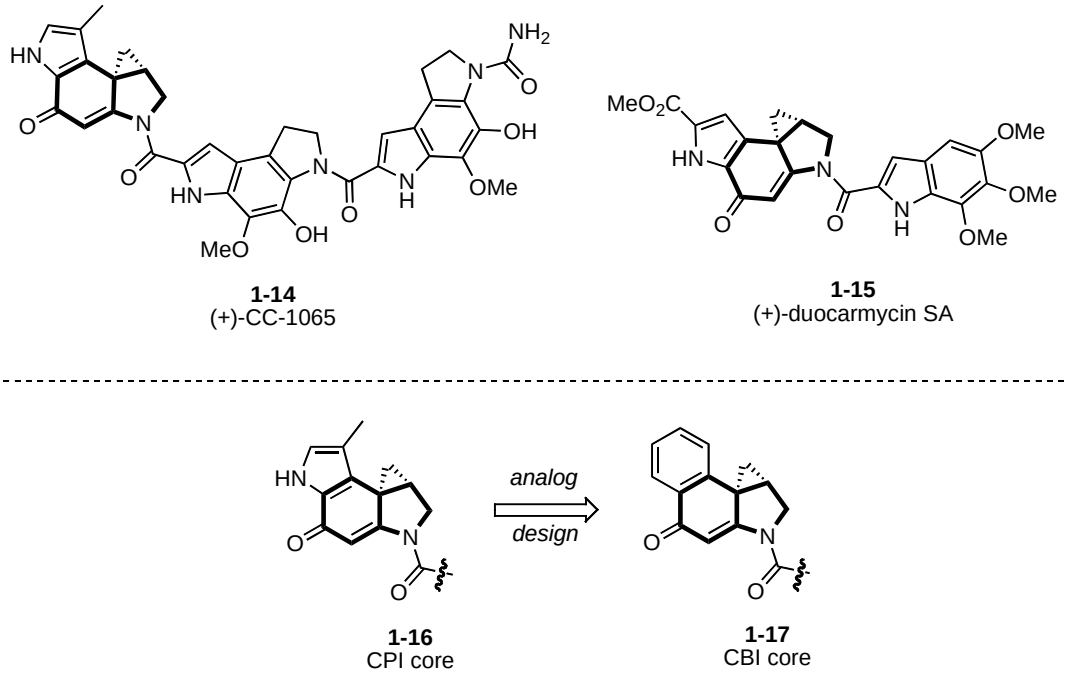
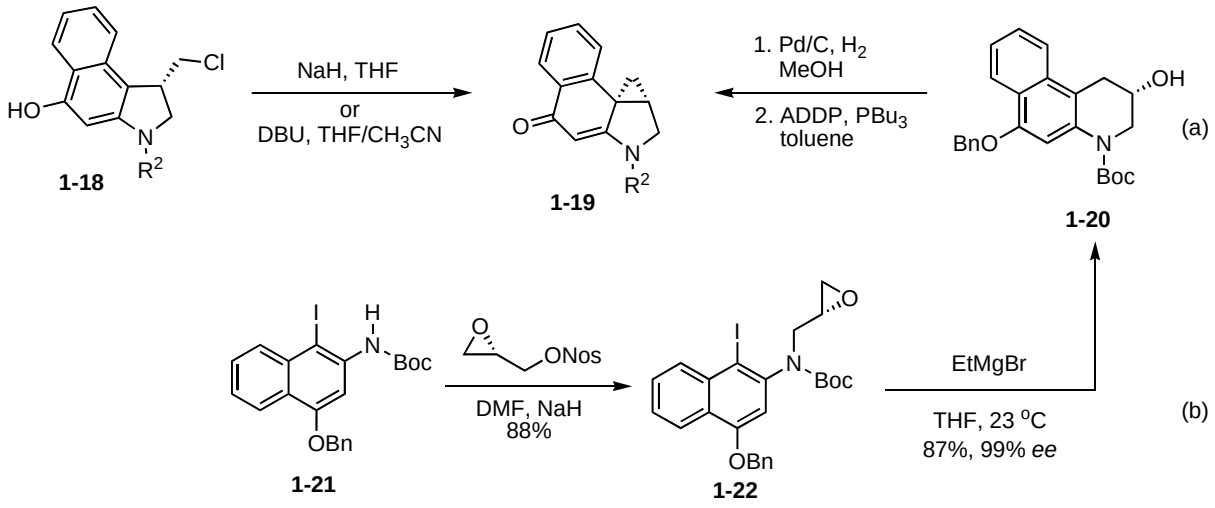


Figure 1-2. Natural products containing the CPI core

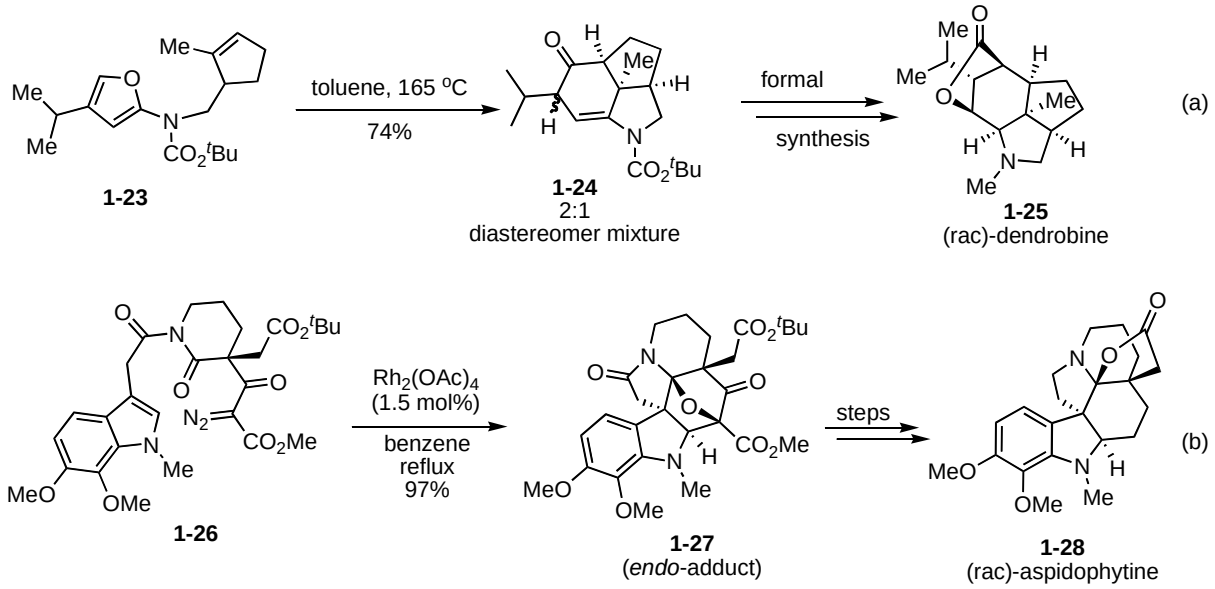
Boger and co-workers have made significant contributions toward optimizing the synthesis[24] and studying the biological activity[23] of these natural products that contain the CPI (1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-*e*]indol-4-one) core **1-16** (Figure 1-2). In the course of their studies, they designed an analog of the reactive cyclopropane core, the CBI (1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one) series **1-17**, which is four times more stable, four times more potent, and easier to synthesize than **1-16**.[25] The formation of the activated indoline-cyclopropane group can be accomplished through a 3-*exo*-tet cyclization using substrate **1-18**, or a ring contraction of the hydroquinoline **1-20** to yield **1-19** (Scheme 1-4). Although there have been numerous approaches to prepare the CPI and CBI cores, two common methods Boger has accomplished this transformation are shown in Scheme 1-4. In the past, enantiopure samples of **1-18** and/or **1-20** have been prepared either *via* separation using chiral HPLC or through various

forms of asymmetric catalysis.[25] A recent publication by Boger[26] demonstrates that the precursor to the CBI core can be prepared in a convergent manner by alkylating **1-21** with the enantiopure nosylated (*S*)-glycidol derivative to yield **1-22** in 87% yield and 99% *ee* (Scheme 1-4b).



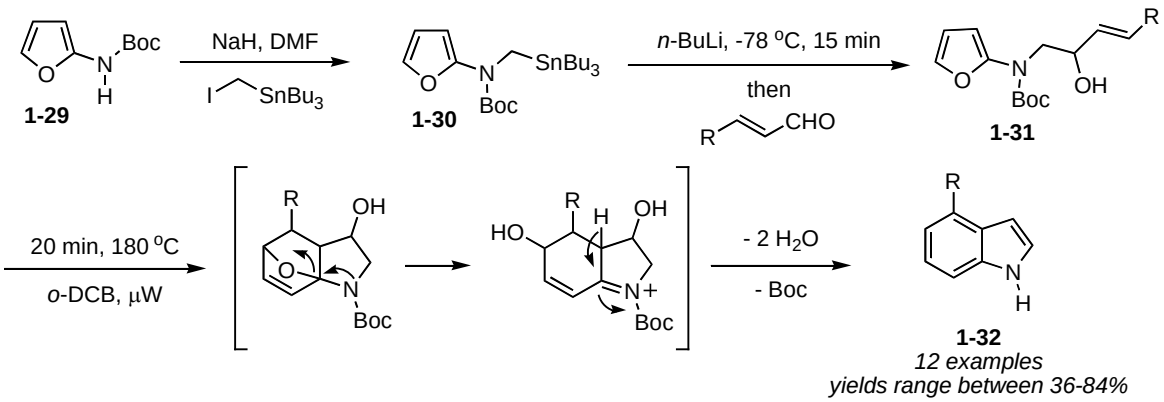
Scheme 1-4. Methods for obtaining the CBI core

In an alternative approach toward the indoline core, Padwa and co-workers utilized an intramolecular [4+2] cycloaddition reaction to access various alkaloids, including classical targets of the *Strychnos* family.[27,28] Scheme 1-5a shows one of the many examples from the Padwa group where researchers have used high temperatures to promote a cycloaddition reaction between the amino furan **1-23** and the appended olefin to produce a variant of the indoline core **1-24**. This methodology has recently been used in a (racemic) formal synthesis of the natural product dendrobine **1-25**.[29,30] An extension of this cycloaddition methodology involves the rhodium-catalyzed *in situ* generation of a carbonyl ylide from **1-26** that undergoes a [3+2] cycloaddition reaction to yield indoline **1-27** in 97% yield.[31] This intermediate was further elaborated to complete a racemic synthesis of aspidophytine **1-28** shown in Scheme 1-5b.



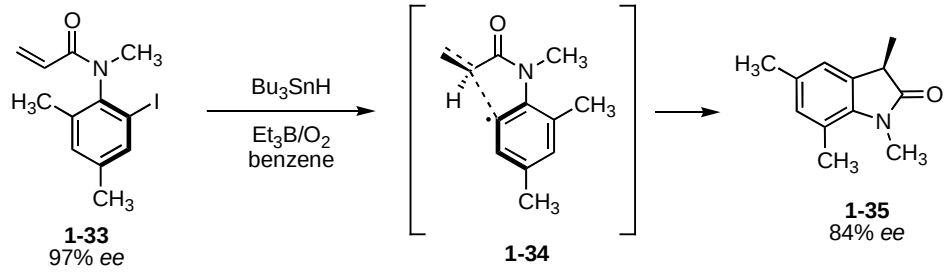
Scheme 1-5. Padwa's synthesis of natural products using a cycloaddition approach

Wipf and co-workers[32] have developed a methodology to prepare substituted indoles using a similar intramolecular [4+2] cycloaddition reaction. It was found that heating allylic alcohols of type **1-31** in *o*-DCB using microwave irradiation provides substituted indoles **1-32** in modest to good yields (Scheme 1-6). This methodology is currently being applied toward the synthesis of natural products.



Scheme 1-6. Wipf's method for indole synthesis

When exploring indoline formation through a radical manifold, activation of the aryl ring (path A, Scheme 1-2) can also be accomplished by treating aryl bromides or iodides with $Bu_3SnH/AIBN$,[33] $Bu_3SnH/BEt_3/O_2$,[34] or SmI_2.[35,36] These reactive intermediates are able to add onto an appended olefin acceptor, thereby forming the 5-membered ring. One recent example published by Curran and co-workers[37] involves the transfer of axial chirality of **1-33** to indolinone **1-35** (Scheme 1-7).[38,39]



Scheme 1-7. Curran's method to prepare indolines using chirality transfer

1.1.2 Intramolecular Radical Reactions onto Aromatic Rings

Radical cyclizations onto aromatic and heteroaromatic rings are known processes,[40,41] and, in particular, the intramolecular alkyl[42] and phenyl[43] radical additions onto heteroarenes have found many applications.[44] The intermolecular rate constants for radical addition onto phenyl rings with triethylsilyl, tributylstannyl, primary alkyl, and methyl groups have been measured and are summarized in Table 1-1. The intramolecular rates for alkyl radical additions onto arenes are estimated to be near 4×10^{-5} s^{-1}.[45]

Table 1-1. Rate constants for radical additions onto phenyl rings

radical species	rate constant
Et_3Si[46]	4.6×10^5 $M^{-1}s^{-1}$
Bu_3Sn[47]	$<2 \times 10^4$ $M^{-1}s^{-1}$
1^o Alkyl[48]	3.8×10^2 $M^{-1}s^{-1}$
Methyl[49]	4.6×10^1 $M^{-1}s^{-1}$

When compared to alkyl radicals, aryl and alkenyl radicals have a greater propensity to cyclize onto aromatic rings due to their higher reactivity. This is supported by the data shown in Table 1-2, where the difference between the carbon-hydrogen bond dissociation energy (BDE) between sp^2 and sp^3 hybridized carbon atoms is *ca*. 15 kcal/mol. Another factor limiting the ability of alkyl radicals to cyclize onto the aromatic nucleus has been attributed to the SOMO/LUMO energy gap between the alkyl radical and the aromatic ring.[48]

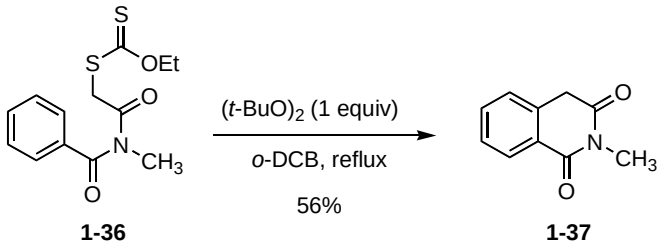
Table 1-2. Comparison of relevant bond dissociation energies (BDE).

bond (R-R)	BDE (kcal/mol)	bond (R-R)	BDE (kcal/mol)
(Ar)sp^2C-H	112	Methyl Csp^3-Csp^3	90
(Ar)sp^2C-Csp^3	102[b]	Methyl Csp^3-OH	93
Methyl Csp^3-H	105	2^o Csp^3-H	98.5
1^o Csp^3-H	101	3^o Csp^3-H	96.5

[a]Data used from Vollhardt *et al.*[50] except where noted. [b]Data used from Togo[51]

There exist few general methods to promote the addition of alkyl radicals onto substituted benzene rings since the process is often difficult to control.[52] One exception lies in the field of xanthate transfer reactions where Zard and Quiclet-Sire[53] have published a method that utilizes the xanthate fragmentation of **1-36** to generate an alkyl radical which then cyclizes to afford

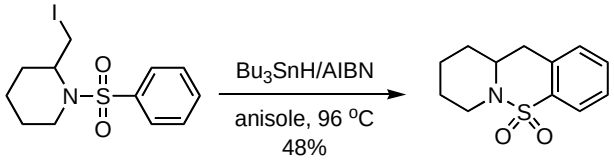
homophthalimide **1-37** (Scheme 1-8). Additionally, this methodology has been used to construct spirolactams[54] and tetrahydroisoquinolinones.[55] Although proven to be efficient, this methodology requires the use of a stoichiometric amount of oxidant that must be added throughout the duration of the reaction making experimental protocol rather cumbersome.



1-36 **1-37**

Scheme 1-8. Zard's method of alkyl radical cyclization onto aromatic rings

Köhler and Speckamp[45] have demonstrated that upon treatment of iodide **1-38** with Bu_3SnH/AIBN, the resulting alkyl radical cyclizes onto the aromatic ring to afford the tricyclic sultam **1-39** in 48% yield (Scheme 1-9). The drawbacks to this methodology include a limited reaction scope, in addition to the use of anisole as the solvent.

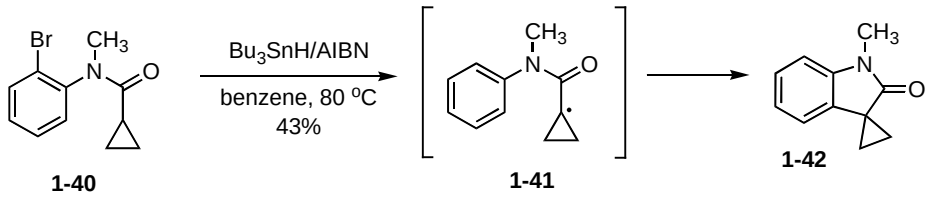


1-38 **1-39**

Scheme 1-9. Köhler's method of alkyl radical cyclization onto aromatic rings

Beckwith and Storey[56] have shown that alkyl radical cyclization can be accomplished through treatment of aryl bromide **1-40** with Bu_3SnH/AIBN, promoting a 1,5-H atom transfer to

quench the resulting aryl radical. The cyclopropyl radical intermediate **1-41** then cyclizes onto the aromatic nucleus to afford **1-42** in 43% yield (Scheme 1-10). As of today, the mechanism of oxidative rearomatization under reductive conditions is still not well understood.

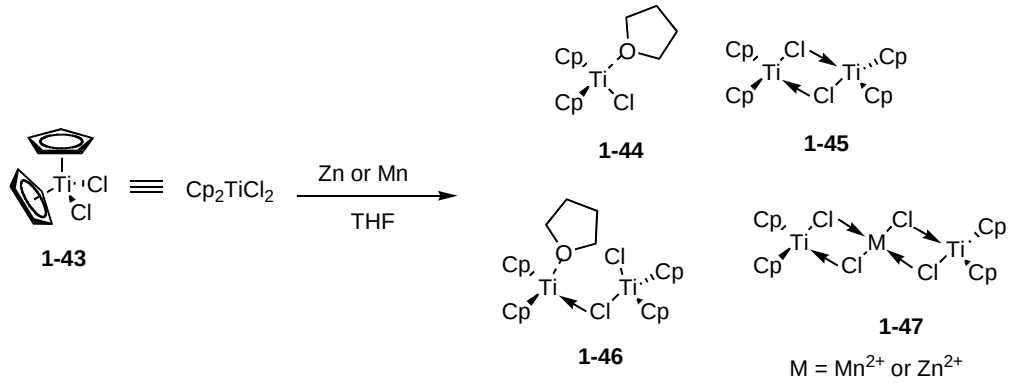


1-40 **1-41** **1-42**

Scheme 1-10. Beckwith's alkyl radical cyclization through aryl radical translocation

1.1.3 Titanocene(III) Chloride and Radical Chemistry

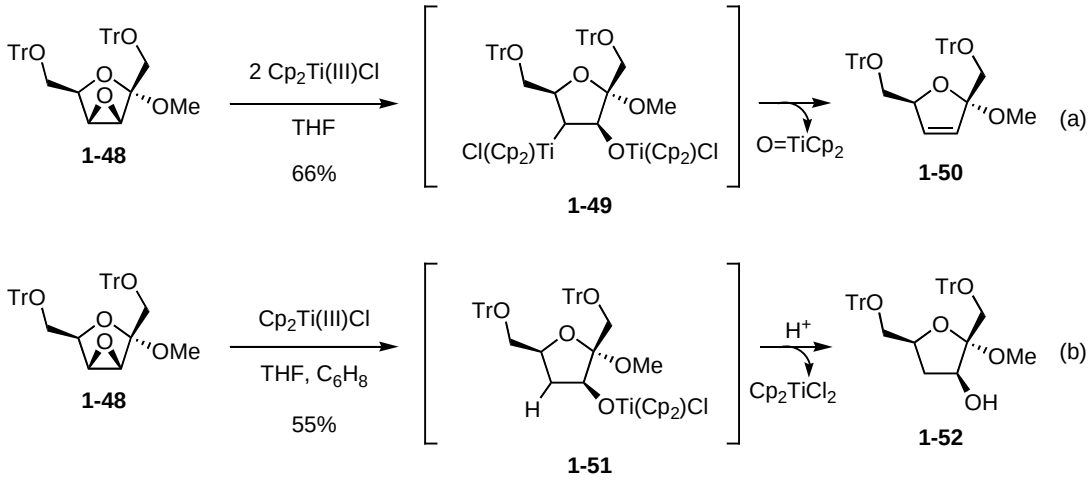
Titanocene(III) chloride is commonly prepared by mixing titanocene(IV) dichloride **1-43** with a reductant such as zinc or manganese metal in oxygen-free THF. The reagent is proposed to exist in equilibrium with its monomer **1-44**, bridged dimeric species **1-45** and **1-46**, and trinuclear species **1-47** (Scheme 1-11).[57,58]



1-43 **1-44** **1-45** **1-46** **1-47**

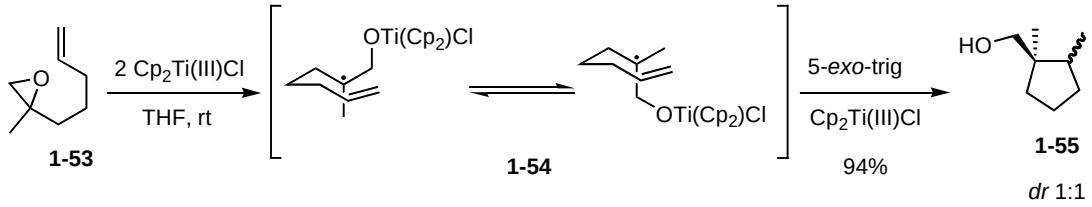
Scheme 1-11. Preparation of titanocene(III) chloride

The use of titanocene(III) chloride to reductively open epoxides was first described by RajanBabu and Nugent.[59] Early applications of the reductive epoxide opening reaction include the free radical deoxygenation of the methyl furanoside **1-48** as described in Scheme 1-12a. Here the epoxide was subjected to two equivalents of titanocene(III) chloride to afford intermediate **1-49**, which eliminates to form the internal olefin **1-50** in 66% yield.[60,61] The transformation of **1-48** into alcohol **1-52** is illustrated in Scheme 1-12b, where the epoxide was treated with one equivalent of titanocene(III) chloride in the presence of 1,4-cyclohexadiene to afford the reduced intermediate **1-51**. Upon acidic workup, the intermediate becomes protodemetallated to produce **1-52** in 55% yield.[59,62]



Scheme 1-12. Applications of titanocene(III) chloride

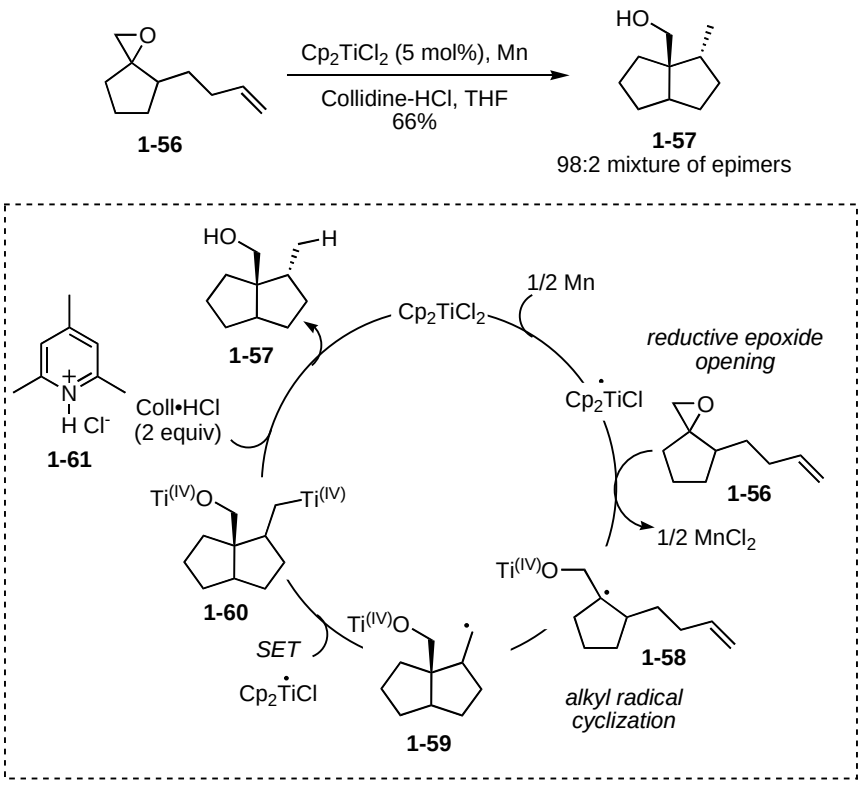
In addition to the epoxide opening reaction, RajanBabu and Nugent reported a hexenyl radical cyclization of radical intermediate **1-54** (derived from epoxide **1-53**) to form the substituted cyclopentanol **1-55** (Scheme 1-13).[59]



Scheme 1-13. Synthesis of cyclopentanol **1-55** using titanocene(III) chloride

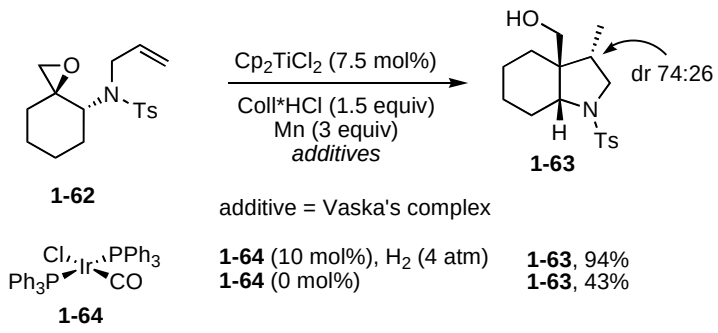
Building on the initial work by RajanBabu and Nugent, Gansäuer developed a catalytic variant of the titanocene(III) epoxide-opening reaction.[63,64] This technology can also be used to promote a 5-*exo*-trig radical cyclization, transforming epoxide **1-56** into alcohol **1-57** in 66% yield (Scheme 1-14). The proposed catalytic cycle for this titanocene(III) chloride annulation begins with the reductive opening of **1-56** to form the *β*-titanoxyradical **1-58**. This radical then undergoes a 5-*exo*-trig cyclization onto the olefin, and the resulting radical intermediate **1-59** is reduced by titanocene(III) chloride to form **1-60**. Subsequent protodemetallation by collidine hydrochloride **1-61** liberates the product **1-57**, allowing for the titanocene(IV) dichloride to re-enter the catalytic cycle.

When compared to other single electron transfer (SET) reagents known to open epoxides, titanocene(III) chloride was shown to be superior when performing epoxide-opening radical-mediated cyclizations.[65] Recent advances in titanocene(III)-mediated transformations include the work by Cuerva who has demonstrated that the titanocene(III)-mediated SET works well in oxygen-free, aqueous media to synthesize γ-lactols.[66]



Scheme 1-14. Gansäuer's proposed catalytic cycle for the titanocene(III) chloride catalyzed annulation

Since then, titanocene(III) chloride catalysis has become widely investigated and utilized,[67-74] where many applications prior to 2006 are summarized in a review by Barrero.[75] In addition to detailed mechanistic investigations of the reductive epoxide opening process,[76] and the use of chiral titanocene(III) complexes in asymmetric catalysis,[77] recent advancements in titanocene(III) chloride catalysis include the use of metal hydride complexes as hydrogen atom transfer reagents. The technology of hydrogen atom transfer has been improved through the use of catalytic amounts of Vaska's complex[78] $(IrCl(CO)PPh_3)_2$ **1-64** in the presence of a hydrogen atmosphere as shown in Scheme 1-15. This example shows how the yields for the transformation of epoxide **1-62** into bicycle **1-63** are improved by the presence of an *in situ* metal hydride complex used to trap reactive alkyl radical intermediates.[79]

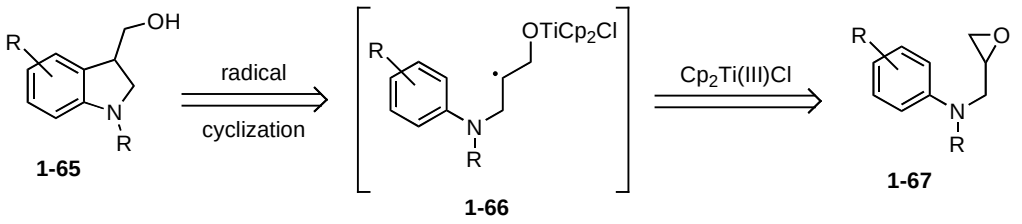


Scheme 1-15. Recent applications of the radical cyclization

1.2 RESULTS AND DISCUSSION

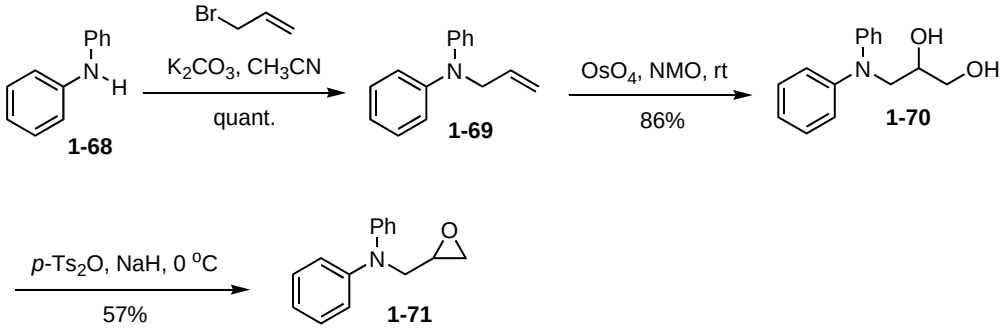
1.2.1 Initial Methodology Development Using *N,N*-Diphenyl Substrates

A new methodology[80,81] has been developed that uses a catalytic amount of *in situ* generated titanocene(III) chloride to promote a novel epoxide-opening rearrangement transforming epoxyanilines into indolines. We envisioned exploring an unconventional approach toward indoline preparation that uses a radical process to install a quaternary carbon simultaneously with pyrrolidine formation, starting with readily available epoxidized allylic amines.[10] Scheme 1-16 outlines our initial approach toward indoline formation. Treatment of **1-67** with titanocene(III) chloride will promote a reductive epoxide opening and thereby generate a persistent[82] radical intermediate **1-66**. The intermediate will then cyclize onto the aromatic ring to form the key bond between C3 and C9 (see Scheme 1-2, path A), producing indoline **1-65**.



Scheme 1-16. Proposed retrosynthesis for indoline methodology

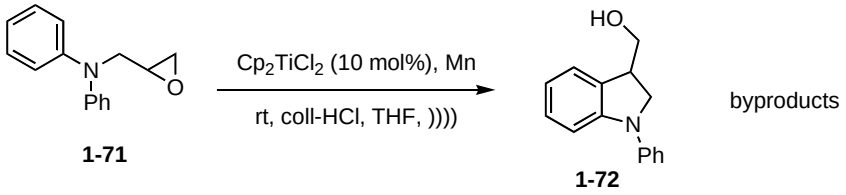
We began exploring the feasibility of our proposed methodology by preparing the *N*-phenyl epoxide **1-71** using a three-step reaction sequence beginning with the alkylation of **1-68** with allyl bromide to afford **1-69**. Subsequent dihydroxylation using OsO_4/NMO to afford diol **1-70** and epoxide formation using *p*-Ts_2O/NaH readily provided the product (Scheme 1-17).



Scheme 1-17. Synthesis of diphenyl epoxide **1-71**

When attempting the radical cyclization with substrate **1-71** using conventional magnetic stirring, multiple products were observed by TLC analysis including the desired indoline. The low indoline selectivity was initially attributed to the insolubility of the collidine hydrochloride and metal reductant in the reaction mixture. To remedy this, sonication was employed as a more aggressive method of mixing, but TLC analysis following sonication still showed a complex mixture of byproducts (Scheme 1-18). These complex mixtures were separated using column

chromatography and further purified by HPLC if necessary. After analysis, six of the seven major products from the reaction mixture were identified and characterized. In addition to starting material, the byproducts detected (shown in Table 1-3) included diphenylamine **1-68**, *N*-allyl diphenylamine **1-69**, the reduced epoxide **1-73**, hydroquinoline **1-74**, and the desired indoline **1-72**. The presence of these compounds was confirmed by using either $^{1}H/^{13}C$ NMR spectroscopy and/or comparison of GC retention times of authentic samples. In addition to these compounds, there remained one unknown product (single peak in GC) that could not be assigned.

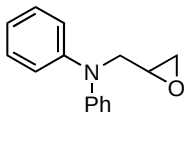


Scheme 1-18. Scheme for radical cyclization on model system

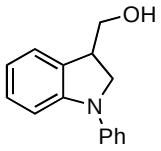
Although 3-alkyl indolines are known to be air sensitive and potentially undergo aerobic oxidation,[83] we postulate the formation of the undesired compounds to originate from competitive radical fragmentation pathways of the initial radical species. During our initial studies it was observed that using excess reductant in the cyclization reaction afforded olefin **1-69** as the major product and the cyclized products **1-72** and **1-74** as minor products in an average ~3:1 ratio, respectively. To explain the numerous byproducts detected, we concluded that the titanocene(III) chloride catalyzed annulation was occurring at a slower rate than other radical fragmentation pathways. Table 1-3 outlines the product ratios detected as a result of changing both the reaction concentration and the manganese stoichiometry. During our attempts to

optimize the transformation to favor the desired indoline, we observed that when using sub-stoichiometric amounts of reductant, the reaction proceeded with higher selectivity and produced only a minor percentage of the olefin **1-69**. While this modification minimized the formation of the undesired olefin, in some cases the reaction did not proceed to completion (entry 1, Table 1-3).

Table 1-3. GC analysis of products from titanocene(III) chloride catalyzed radical cyclization

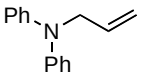


1-71

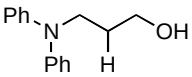


1-72

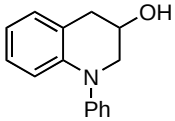
1-68



1-69



1-73



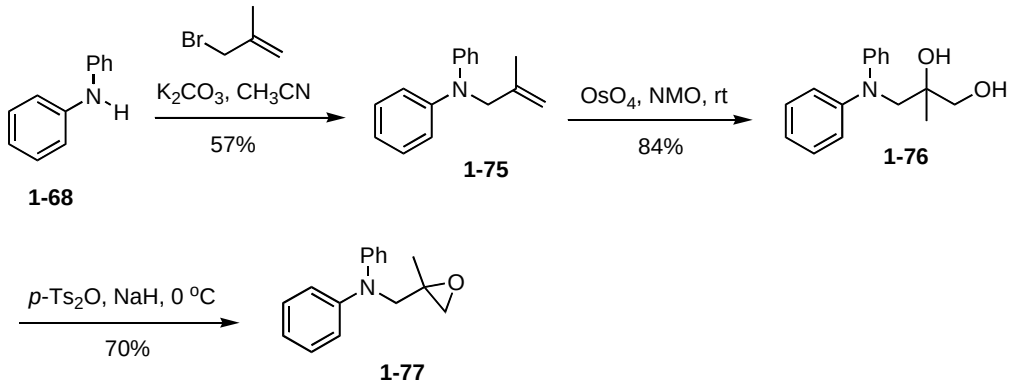
1-74

entry[a]	conc. [M][b]	Mn (mol%)	**1-71** (%)	**1-72** (%)	**1-68** (%)	**1-69** (%)	**1-73** (%)	**1-74** (%)	ratio of **1-72**:**1-74**
1	0.03	10	73.1	17.0	1.7	0.8	0	5.2	3.2:1
2	0.10	20	35.9	38.6	5.4	4.1	3.2	11.7	3.2:1
3	0.03	80	0.6	51.7	10.2	15.0	5.3	16.6	3.1:1
4	0.03	50	1.9	38.3	5.6	5.2	1.6	12.5	3.0:1
5	0.02	65	16.2	15.8	1.7	1.0	0.6	5.8	2.7:1
6	0.03	65	7.2	57.3	3.4	3.2	2.9	13.2	4.3:1

[a]Percentages relative to constituents in crude reaction mixture; sonication at 40-60% maximum output of 130 W was used as the means of mixing for all entries. [b]Reaction times ranged between 1-2 h.

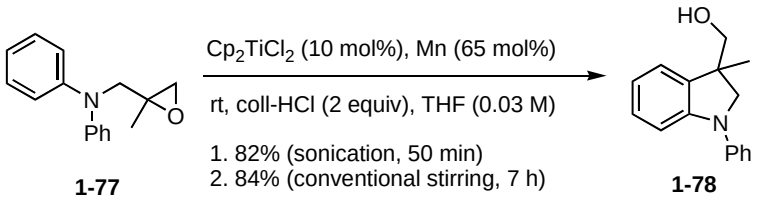
The reaction concentration and the stoichiometry of the manganese metal were altered until the starting material was nearly consumed and the olefin formation was minimized according to GC analysis of the crude reaction mixtures. However, a mixture of the desired indoline **1-72** and undesired hydroquinoline **1-74** (entry 6, Table 1-3) were still observed. Focusing on obtaining solely the indoline, conditions involving the use of sub-stoichiometric amounts of reductant were applied to the methyl substituted epoxide **1-77**, which was prepared

using our standard procedure of alkylation of **1-68** with 3-bromo-2-methylpropene, dihydroxylation of **1-75** using OsO_4/NMO to afford diol **1-76**, and epoxide formation using *p*-Ts_2O/NaH to afford **1-77** (Scheme 1-19).



Scheme 1-19. Synthesis of disubstituted epoxide **1-77**

We theorized that the reductive opening of **1-77** should form a more stabilized tertiary radical, therefore promoting a more selective cyclization to afford the desired 3,3-disubstituted indoline. When subjecting **1-77** to our reaction conditions, we qualitatively observed a faster reaction rate, as well as exclusive selectivity for the indoline (Scheme 1-20).

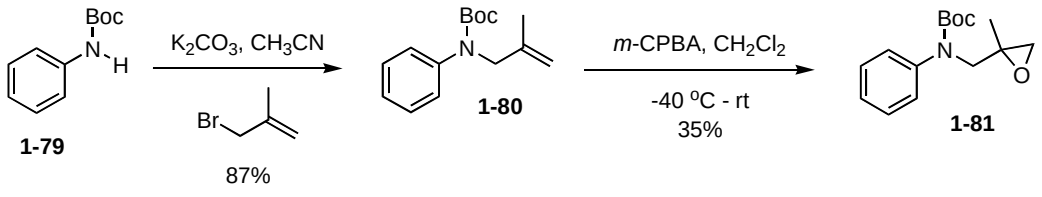


Scheme 1-20. Radical cyclization to form indoline **1-78**

Indoline **1-78** was formed in less than 1 h when using the sonication protocol, and was isolated in 82% yield. We also tested to see if this substrate would undergo the desired transformation when using conventional magnetic stirring. This would allow for the use of standard laboratory equipment and protocol when performing these oxygen-sensitive transformations, and eliminate the need for a specialized setup to perform oxygen-sensitive reactions utilizing sonication. Gratifyingly, under otherwise identical conditions, the desired product was obtained after 7 h, and isolated in 84% yield. At this point, we were pleased with the reproducible yields obtained with the *N*-phenyl system and decided to further expand the scope of this methodology.

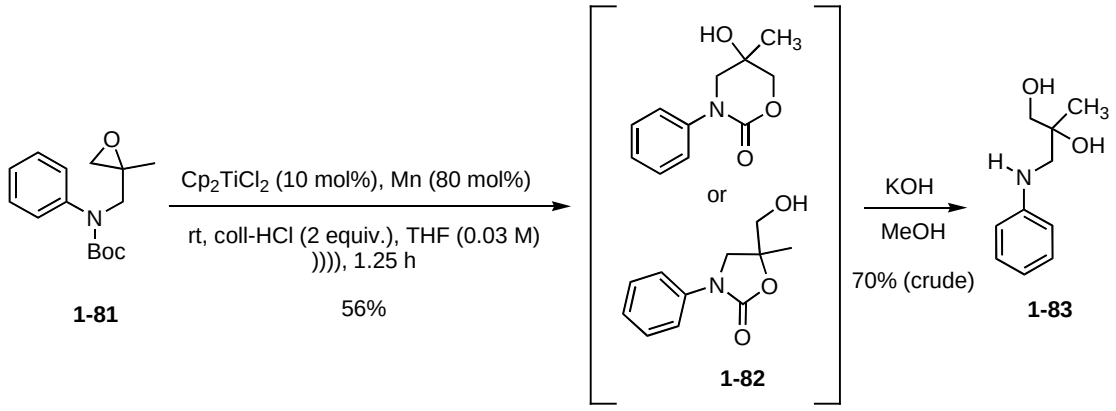
1.2.2 Screening Protecting Groups and Reaction Optimization

The use of an *N*-protected epoxide would allow access to free (N-H) indoline substrates. Since the methyl-substituted epoxide substrate reacted to form the desired indoline cleanly, it was chosen as a benchmark for further investigations. To begin the search for a compatible protecting group, the Boc-protected epoxide was prepared. This was accomplished in two steps, beginning with alkylation of Boc-protected aniline **1-79** to afford **1-80**, followed by subsequent oxidation with *m*-CPBA (Scheme 1-21).



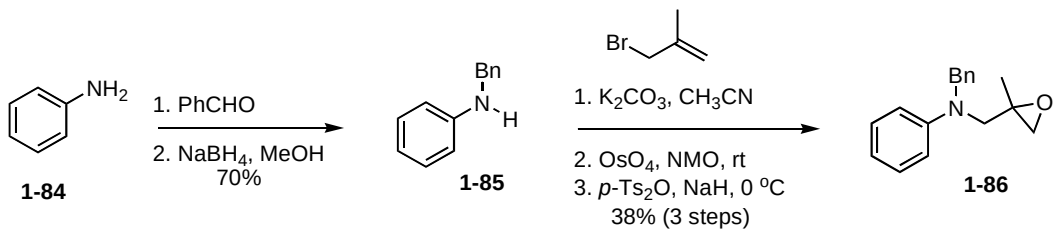
Scheme 1-21. Synthesis of Boc-protected epoxide **1-81**

Subjecting this substrate to the optimized radical cyclization conditions, the major product of the reaction was an acid-catalyzed cyclization of the Boc group onto the epoxide (Scheme 1-22) to form intermediate **1-82**. This intermediate was treated with KOH/MeOH to afford **1-83**, according to ^{1}H NMR and MS analysis of the crude reaction mixture. Due to the undesired side reaction observed, the Boc protecting group was dismissed as a possible candidate for our methodology.



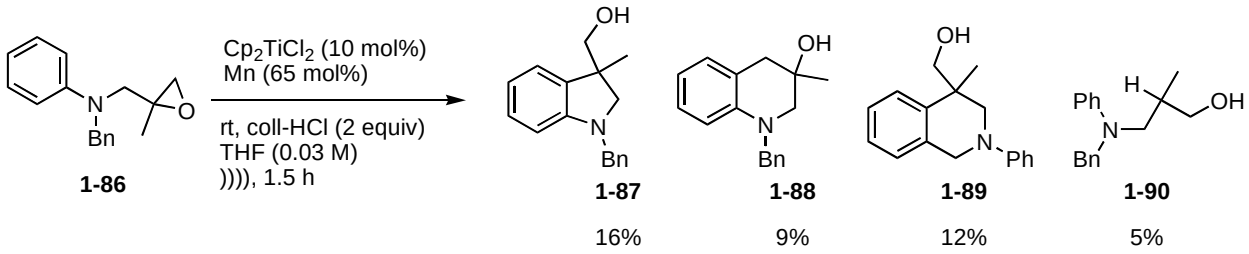
Scheme 1-22. Radical cyclization attempt using Boc-protected epoxide **1-81**

The benzyl-protected epoxide **1-86** was prepared over four steps, beginning with a reductive amination of benzaldehyde with aniline to give **1-85**, followed by a three step sequence of alkylation, dihydroxylation and epoxide formation (Scheme 1-23).



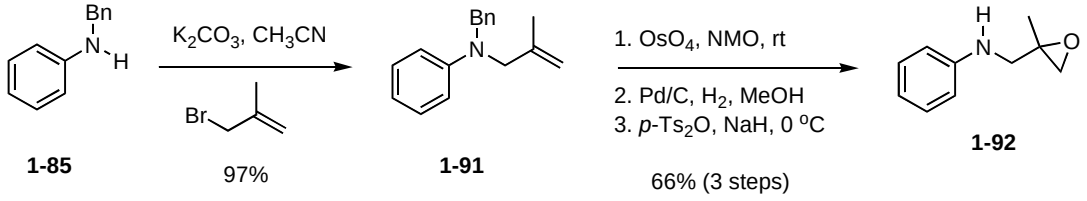
Scheme 1-23. Preparation of benzyl-protected epoxide **1-86**

After subjecting epoxide **1-86** to titanocene catalysis, a complex mixture of products was observed (Scheme 1-24). These products were separated by chromatography, and characterized by ^{1}H NMR. Based on the tentatively assigned side products **1-87**-**1-90**, it was evident that a benzyl protecting group on nitrogen would not be tolerated under the reaction conditions.



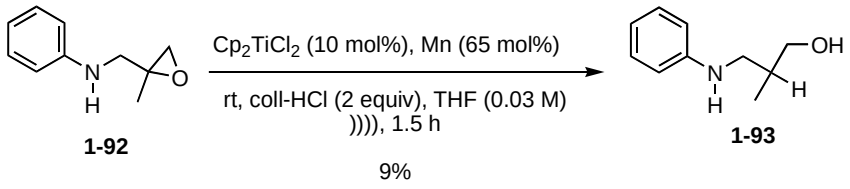
Scheme 1-24. Isolated products from radical cyclization of epoxide **1-86**

We briefly investigated the reactivity of the unprotected epoxide **1-92**, prepared by alkylation of the benzyl-protected intermediate **1-85** to afford olefin **1-91**. In a 3-step sequence, the olefin was dihydroxylated, the benzyl group was removed by using Pd/C and H_2, and transformed into the epoxide through the standard epoxidation conditions to give **1-92** in 66% yield over 3 steps (Scheme 1-25).



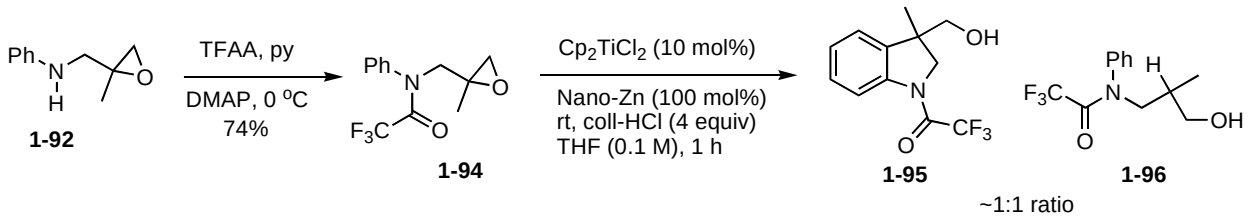
Scheme 1-25. Preparation of unprotected epoxide **1-92**

After subjecting **1-92** to titanocene(III) chloride catalysis, the only identifiable product recovered from the complex reaction mixture was the reduced alcohol **1-93** (Scheme 1-26). It is possible that the Thorpe-Ingold effect[84] may play a role to promote the cyclization reaction. It was concluded that the incorporation of a bulky protecting group was necessary to promote the annulation reaction.



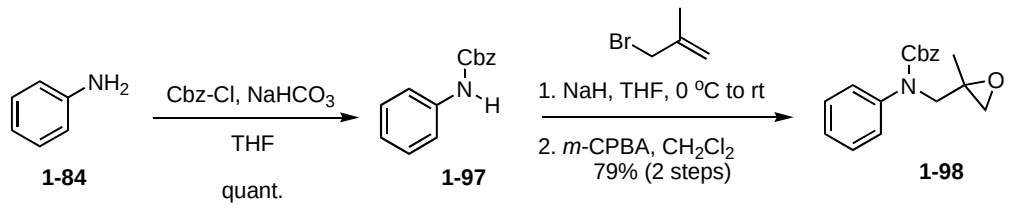
Scheme 1-26. Titanocene(III) chloride catalyzed reaction with unprotected epoxide **1-92**

The next protecting group of interest became the trifluoroacetamide, due to its ability to be hydrolyzed over the parent acetamide. The epoxide **1-94** was prepared by treating **1-92** to TFAA in pyridine (Scheme 1-27).



Scheme 1-27. Synthesis and radical cyclization using the trifluoroacetamide epoxide **1-94**

During this trial, it was difficult to initiate the radical reaction through the use of our standard conditions. Using Nano-Zinc[1] in place of manganese,[85] the epoxide was subjected to the cyclization conditions where the ^{1}H NMR analysis of the crude reaction mixture showed a ~1:1 ratio of cyclized **1-95** to reduced **1-96** compound. These results were promising since we were able to minimize the amount of side products produced. In addition, it appeared that only one competing radical pathway was in operation. Aiming to employ a bulkier protecting group that can be removed under mild conditions, the Cbz-protected epoxide **1-98** was prepared in three steps from Cbz-protection of aniline using our general protocol (Scheme 1-28).



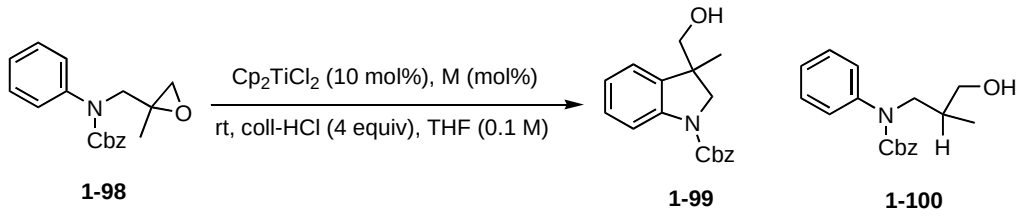
1-84 **1-97** **1-98**

Scheme 1-28. Synthesis of Cbz-protected epoxide **1-98**

When subjecting epoxide **1-98** to the cyclization conditions, a decrease in reactivity and selectivity was observed for the desired product **1-99**, versus the reduced product **1-100**. This was a significant problem because, in addition to not fully consuming the starting material, there were often different ratios of the desired indoline to reduced product, as outlined in Table 1-4.

[1] Nano-Zinc is a high purity metal of small particle size (100 nm) and greater reactivity than most commercially available zinc metal, and was obtained as a gift from Umicore Zinc Chemicals.

Table 1-4. Reductant screening for radical cyclization of Cbz-protected epoxide **1-98**



1-98 **1-99** **1-100**

entry	M (mol%)	conversion (TLC)	**1-99**:**1-100** (determined by ^{1}H NMR of crude)
1	Mn (150)	complete	~2:1
2	Nano-Zn (70)	complete	~1:1
3	Zn (70)	complete	~1:1
4	Li (150)	messy	inconclusive
5	Mg (156)	no rxn.	-
6	Fe (150)	no rxn.	-
7	Sm (150)	incomplete	inconclusive

In the cyclization of alkyl radicals onto aromatic systems, the ratios of the cyclized product to the reduced product can reflect the relative rates of cyclization versus the relative rates of reduction.[42] Therefore, it was necessary to optimize the reaction conditions to promote the cyclization, while avoiding reduction of the β–titanoxy radical through either hydrogen atom abstraction or SET to the tertiary radical intermediate.[74] As shown in Table 1-4, varying the choice of reductant did not significantly affect the ratio of cyclized to reduced products, and starting material remained in some cases (according to TLC analysis).

In addition to qualitative analysis, consumption of starting material was determined by ^{1}H NMR through the disappearance of the hydrogen resonance at δ = 2.50 (A of AB, 1 H, J = 4.8 Hz) on the epoxide methylene group of **1-98**; however, in most cases it was difficult to determine

due to the presence of the broad singlet of the collidine methyl peak (δ = 2.45). Therefore, crude ratios were determined from integration of δ = 4.12 (A of AB, 1 H, *J* = 11.8 Hz) of the indoline **1-99** compared to the methyl group (δ = 0.88 (d, 3 H, *J* = 6.9 Hz)) of **1-100**. The diagnostic chemical shifts observed in ^{1}H NMR spectra of the crude material are assigned to the appropriate structures as shown in Figure 1-3.

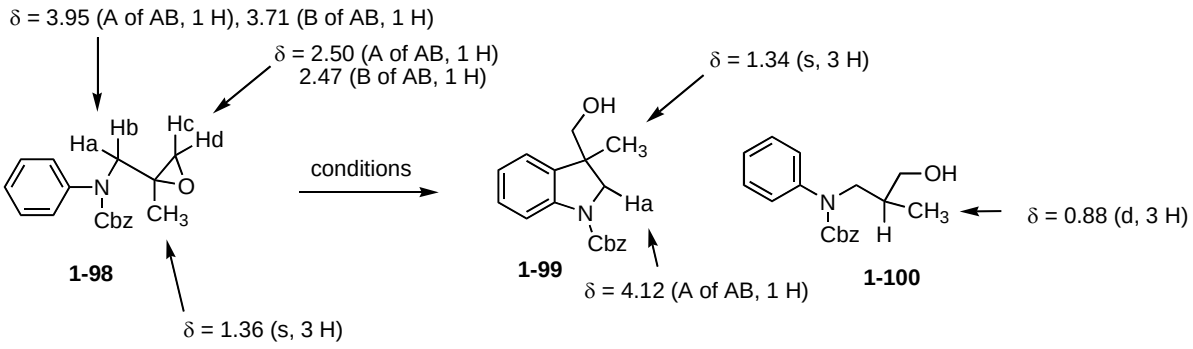
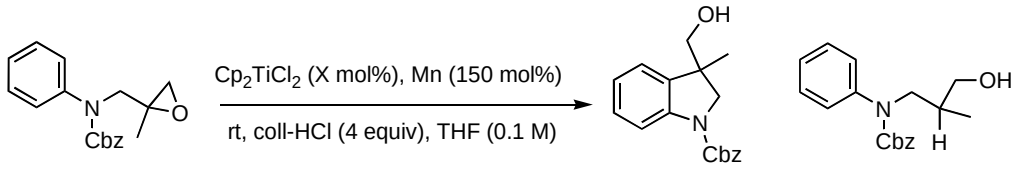


Figure 1-3. Diagnostic chemical shifts used to determine product ratios of **1-99**:**1-100**

Since no significant change in indoline selectivity could be achieved through varying the reductant, our focus was shifted toward varying the loading of the precatalyst. The standard precatalyst loading in all aforementioned titanocene(III) chloride catalyzed reactions was 10 mol% of titanocene dichloride. When using 5 mol% of precatalyst, the starting material was consumed and an increase in the indoline to reduced substrate selectivity from ~2:1 to ~3:1 was observed, determined by ^{1}H NMR of the crude reaction mixture (Table 1-5). When the loading was lowered further to 3 mol%, the selectivity determined by ^{1}H NMR of the crude reaction mixture was a ~7:1 ratio of **1-99**:**1-100**, but the reaction did not proceed to completion. Finally, with a loading of 1 mol%, only **1-100** (35% conversion) was observed in the ^{1}H NMR of the crude reaction mixture, in addition to unconsumed starting material (entry 3, Table 1-5). Based

on these results, it was clear that the precatalyst loading played a crucial role in the selective formation of the desired indoline product.

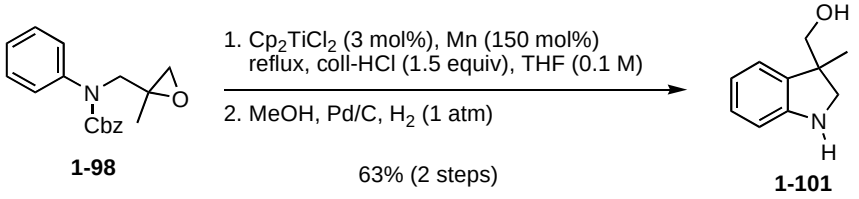
Table 1-5. Optimizing precatalyst loading for titanocene(III) catalyzed indoline formation



1-98 **1-99** **1-100**

entry	Cp_2TiCl_2 (mol%)	product ratio (**1-99**:**1-100**) (crude ^{1}H NMR)	product ratio (**1-99**:**1-100**) (^{1}H NMR, isolated)	unconsumed starting material **1-98**	reaction time (h)
1	5	~3:1	3.6:1	consumed	24
2	3	~7:1	10.3:1	18% (isolated)	18
3	1	**1-99** only	-	65% (crude ^{1}H NMR)	21

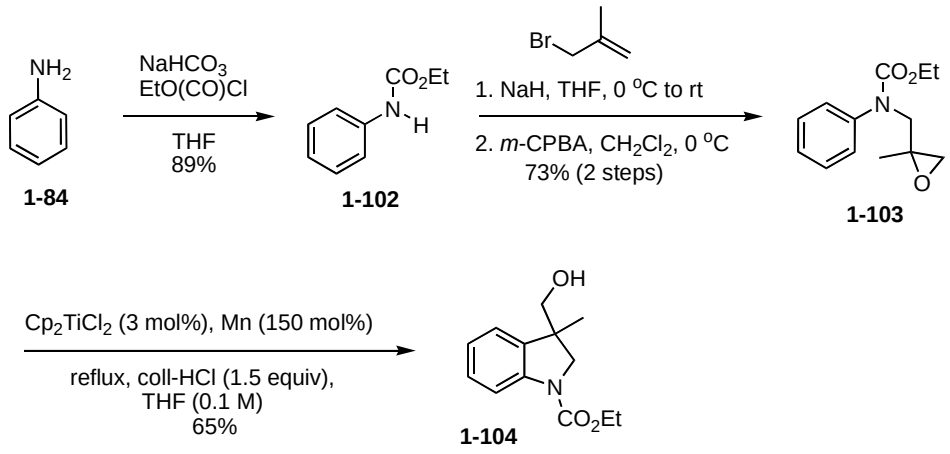
When using 3 mol% of the precatalyst, we observed complete consumption of the starting material, in addition to preserving the isolated ~10:1 ratio of **1-99**:**1-100**. The crude mixture was then subjected to Cbz-deprotection using Pd/C and H_2, providing 63% (2 steps) of indoline **1-101** after purification (Scheme 1-29).



1-98 **1-101**

Scheme 1-29. Radical cyclization to prepare indoline **1-101**

In addition to using **1-98** as a model system, the ethyl carbamate **1-103** was prepared in three steps, beginning with carbamate formation using ethyl chloroformate followed by alkylation and oxidation to give the epoxide in 65% over 3 steps (Scheme 1-30). Epoxide **1-103** was subjected to the optimized conditions and displayed similar reactivity to the Cbz-protected substrate **1-98** providing the desired indoline product **1-104** in 65% yield. We were satisfied with these results when using the benzyloxycarbamate and ethoxycarbamate groups as protecting groups and set out to expand the scope of the methodology.



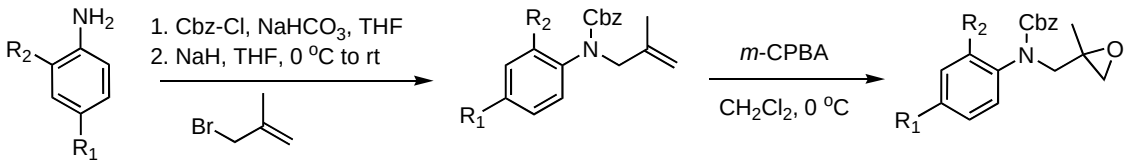
Scheme 1-30. Synthesis of indoline **1-104**

1.2.3 Preparation of Substituted Indolines

After developing the optimized procedure to prepare the desired indolines, the next challenge was to test the synthetic utility of this transformation by using substituted epoxyanilines. The reaction scope was explored by varying both the sterics and electronics around the aromatic ring. A series of Cbz-protected epoxides were prepared using a general three-step protocol that begins with carbamate formation from the requisite aniline, followed by

methallylation and epoxidation to prepare the desired epoxides (Table 1-6). The epoxyanilines were subjected to titanocene(III) chloride catalysis to afford the respective indolines (Table 1-7). The *para*- and *ortho*-methyl substituted epoxides **1-106** and **1-108** (entries 1 and 2, respectively) provided indolines in good to modest yields. A potential reason for the lower observed yield in entry 2 may be from the fact that the radical generated has only one reactive site available due to the *o*-substituted methyl group.

Table 1-6. General preparation for substituted Cbz-protected epoxides

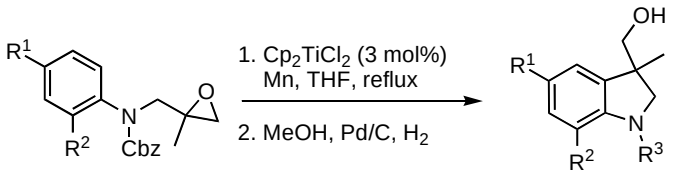


entry	carbamate	R^1	R^2	epoxide	yield (3 steps)
1	**1-105**	CH_3	H	**1-106**	68%
2	**1-107**	H	CH_3	**1-108**	72%
3	**1-109**	OCH_3	H	**1-110**	73%
4[a]	**1-111**	Cl	H	**1-112**	66%
5	**1-113**	CO_2CH_3	H	**1-114**	75%

[a]DMF was used as solvent for alkylation.

The 5-methoxyindoline **1-117** was isolated in low yield (21%, 2 steps). It is possible that the electron-rich molecule decomposed through air oxidation, since it was observed that the product was isolated as a purple oil after purification. Electron-deficient substrates underwent the epoxide-opening rearrangement to afford indolines in good yields (entries 4 and 5).[80,81] When epoxide **1-112** was subjected to radical cyclization conditions and subsequent Cbz deprotection, indoline **1-101** was isolated, which lacked the chlorine substituent.

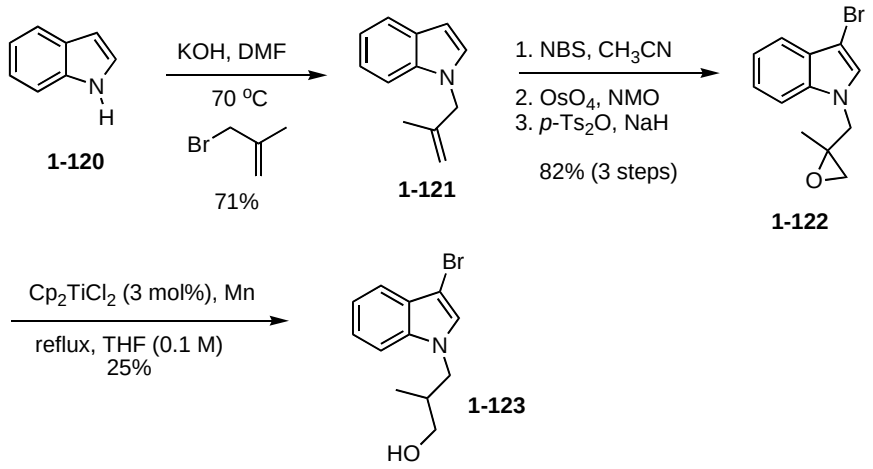
Table 1-7. Indolines prepared using titanocene(III) catalysis



entry	epoxide[a]	R^1	R^2	R^3	product	yield
1	**1-106**	CH_3	H	H	**1-115**	62%[b]
2	**1-108**	H	CH_3	H	**1-116**	35%[b]
3	**1-110**	OCH_3	H	H	**1-117**	21%[b]
4	**1-112**	Cl	H	Cbz	**1-118**	41%[c]
5	**1-114**	CO_2CH_3	H	H	**1-119**	56%[b]

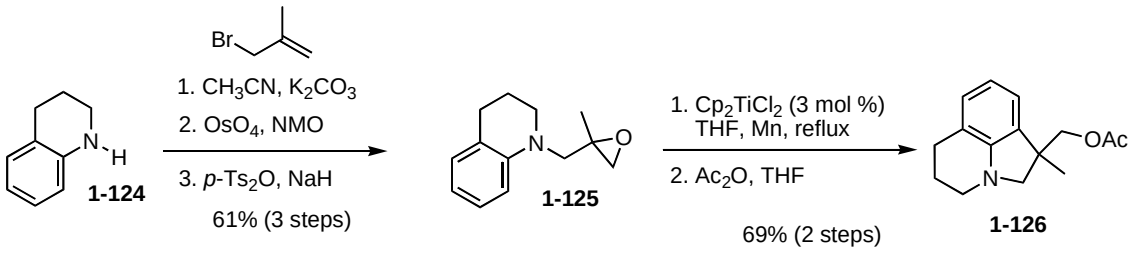
[a]See experimental section for epoxide preparation. [b]Yield determined over 2 steps. [c]Cbz group was not removed using Pd/C and H_2.

Further investigation of the cyclization with epoxide **1-112** showed that the chloride remained intact for the cyclization and that Cbz-protected indoline **1-118** could be isolated in 41% (entry 4, Table 1-7). It is likely that the aryl chloride is reduced upon subjecting the crude mixture to the Cbz deprotection conditions.[86] Although not investigated, alternative methods that facilitate Cbz deprotection in the presence of aryl halides are known.[87,88] To expand the scope of our reaction to heteroaromatic systems, the epoxide **1-122** was prepared in four steps from **1-120** beginning with alkylation using KOH/DMF to afford **1-121**, followed by a 3-step sequence of NBS bromination, dihydroxylation and epoxide formation (Scheme 1-31). This substrate was tested in the cyclization where a messy reaction mixture was observed by TLC analysis. In this case, only the reduced alcohol **1-123** was isolated in 25% yield.



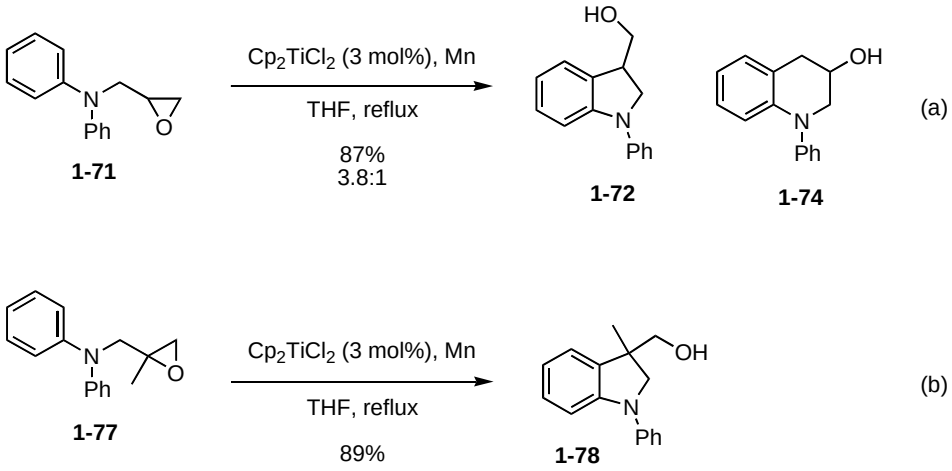
Scheme 1-31. Synthesis of epoxide **1-122** and attempted radical annulation

We were successful in the preparation of the slightly more complex indoline scaffold **1-126** shown in Scheme 1-32 beginning with **1-124**. Through the use of a 3-step protocol involving alkylation, dihydroxylation and epoxide formation, **1-125** was isolated in 61% yield over 3 steps. When the epoxide was treated with 3 mol% of *in situ* generated titanocene(III) chloride, followed by acetic anhydride, **1-126** was obtained in 69% over 2 steps. In this case, the acylation of the alcohol was performed to aid in the purification the indoline product.



Scheme 1-32. Synthesis of tetrahydroquinoline **1-126**

When applying our optimized conditions to epoxide **1-71**, the reaction was complete within 45 min according to TLC analysis and subsequent ^{1}H NMR of the crude reaction mixture showed a ~3.3:1 ratio between the desired indoline **1-72** and hydroquinoline **1-74** (Scheme 1-33a). Purification by chromatography on neutral alumina afforded a 3.8:1 mixture of **1-72** to **1-74** in 87% yield. Additionally, upon submitting epoxide **1-77** to the optimized conditions, the desired indoline **1-78** was isolated in an excellent 89% yield (Scheme 1-33b).



Scheme 1-33. Applying optimized reaction conditions to model substrates **1-71** and **1-77**

1.2.4 Preparation of Azaindolines

Azaindole (outlined in bold) and azaindoline natural products are less common in nature, however, these scaffolds are attractive isosteres of indoles and indolines in pharmaceutical research.[89] Two examples of azaindole natural products are variolin B **1-127**, and deoxyvariolin B **1-128**, which have been isolated from the rare Antarctic sponge, *Kirkpatricka varialosa* (Figure 1-4). Compounds containing the azaindole core have found many therapeutic

applications that include HIV-1 attachment inhibitors[90,91] (**1-129** and **1-130**) and treatment for neurological diseases[92] (**1-131**) (Figure 1-4).

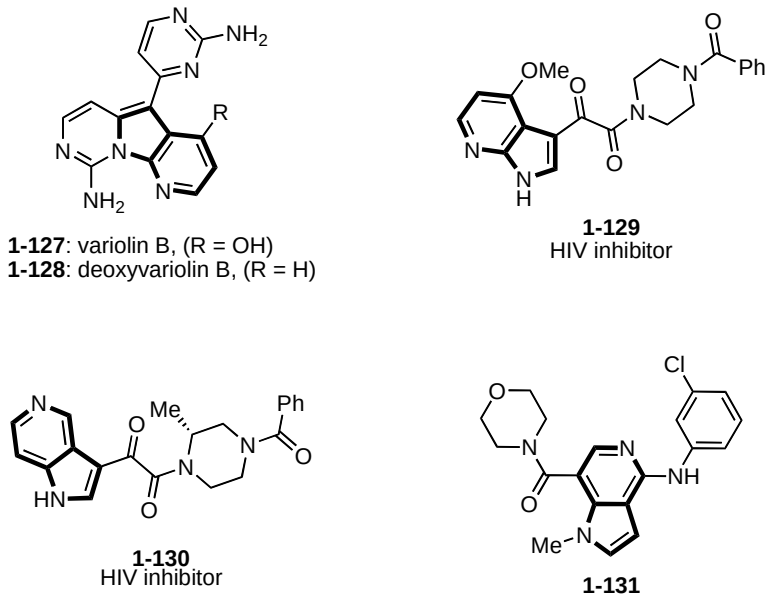
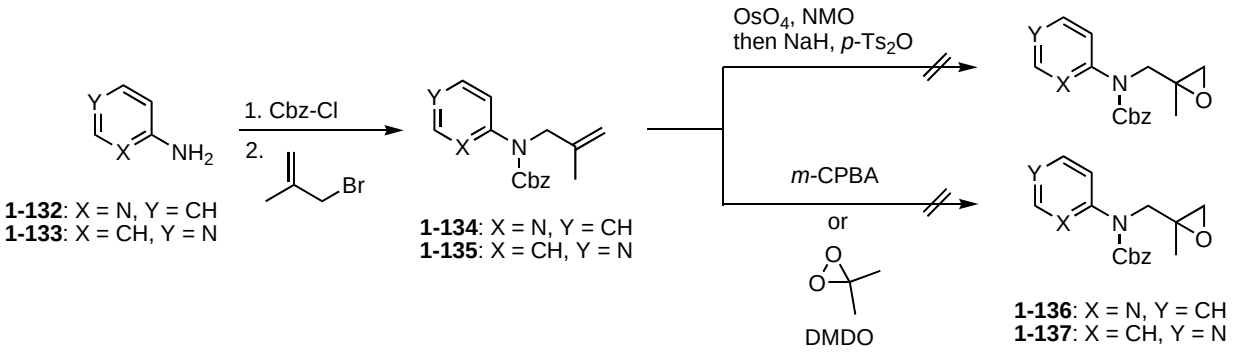


Figure 1-4. Biologically active azaindoles (outlined in bold)

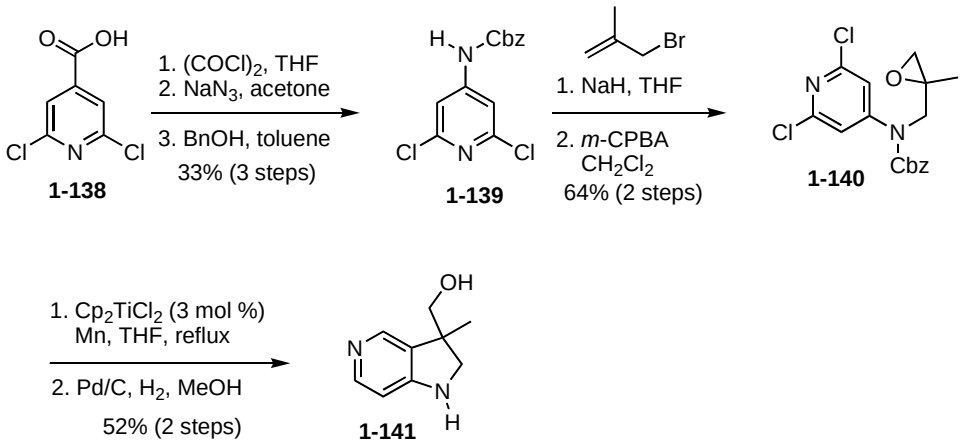
The next step toward broadening the scope and application of our methodology was to prepare azaindolines. This could be accomplished by using aminopyridines in place of anilines. Azaindoline precursors (2- and 4-aminopyridine **1-132** and **1-133**, respectively) are shown in Scheme 1-34. Although the Cbz protection and subsequent alkylation of the carbamates using methallyl bromide to produce **1-134** and **1-135** occurred without a problem, epoxide formation to produce **1-136** and **1-137** using either a 2-step dihydroxylation/ring closure protocol, or a direct epoxidation using *m*-CPBA or DMDO could not be accomplished.



Scheme 1-34. Initial attempts to prepare pyridine epoxides

Although chemoselective epoxidation of alkenes in the presence of the pyridine ring is precedented, attempts to efficiently prepare **1-136** and/or **1-137** were unsuccessful. It was found that exposure of either **1-134** or **1-135** to dihydroxylation conditions using osmium tetroxide resulted in no reaction. In contrast, treating the olefins with *m*-CPBA or DMDO produced polar compounds that were difficult to isolate.[80,81] These observations were attributed to the Lewis basic nature of the pyridine nitrogen, which is known to react with both *m*-CPBA or DMDO to form *N*-oxide products.[93]

In contrast, an *ortho*-chlorine substitution[94] proved to be sufficient to attenuate the reactivity of the pyridine nitrogen. Curtius rearrangement of the known carboxylic acid **1-138**[95] followed by subsequent trapping of the intermediate isocyanate with benzyl alcohol afforded the Cbz-protected aminopyridine **1-139** in 33% yield over 3 steps (Scheme 1-35). Subsequent methallylation and epoxidation using *m*-CPBA led to epoxide **1-140**, which, when treated with catalytic titanocene(III) chloride, provided an intermediate 4,6-dichloro-5-azaindoline. This was then treated with Pd/C under an atmosphere of H_2 to give azaindoline **1-141** in 52% yield over 2 steps.[80,81]

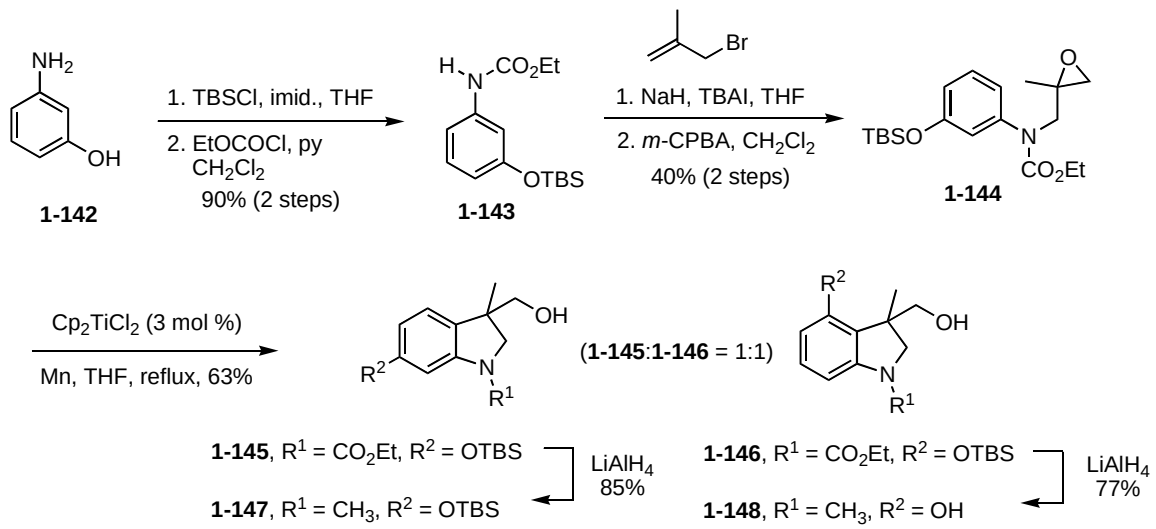


1-138 **1-139** **1-140** **1-141**

Scheme 1-35. Preparation of 5-azaindoline **1-141**

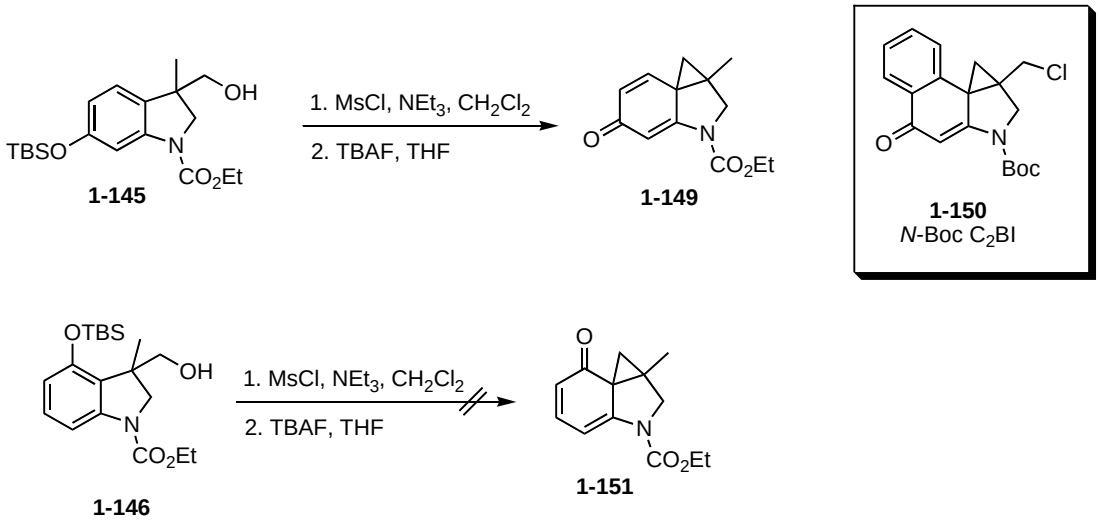
1.2.5 Regioselectivity Studies and Potential Applications

To further expand the scope of the methodology, the regioselectivity and diastereoselectivity of the annulation were investigated. Epoxide **1-144** (prepared in 4 steps from **1-142**) was subjected to titanocene(III) catalysis, which afforded a 1:1 mixture of regioisomers **1-145** and **1-146** in 63% yield. Subsequent reduction of the ethyl carbamates using $LiAlH_4$ provided *N*-methyl indolines **1-147** and **1-148**, respectively (Scheme 1-36).[81] Reduction of the carbamates was necessary since the materials were not stable to high temperature ^{1}H NMR analysis in DMSO-d_6.



Scheme 1-36. Regioselectivity studies for radical annulation reaction

With access to indolines **1-145** and **1-146**, the preparation of cyclopropanes similar to those found in the duocarmycin family of natural products (Figure 1-2) was attempted. It was observed that after the treatment of **1-145** with MsCl, followed by treating the crude reaction mixture to TBAF in THF, the desired product **1-149** could be detected by ^{1}H NMR as well as MS analysis (Scheme 1-37). Unfortunately, the cyclopropane proved to be an unstable compound to fully characterize, although similar C_2BI analogs **1-150** are known to be stable and have been prepared by Boger.[96] Furthermore, when exposing **1-146** to the same reaction conditions, the mixture appeared to have decomposed and **1-151** was not observed.

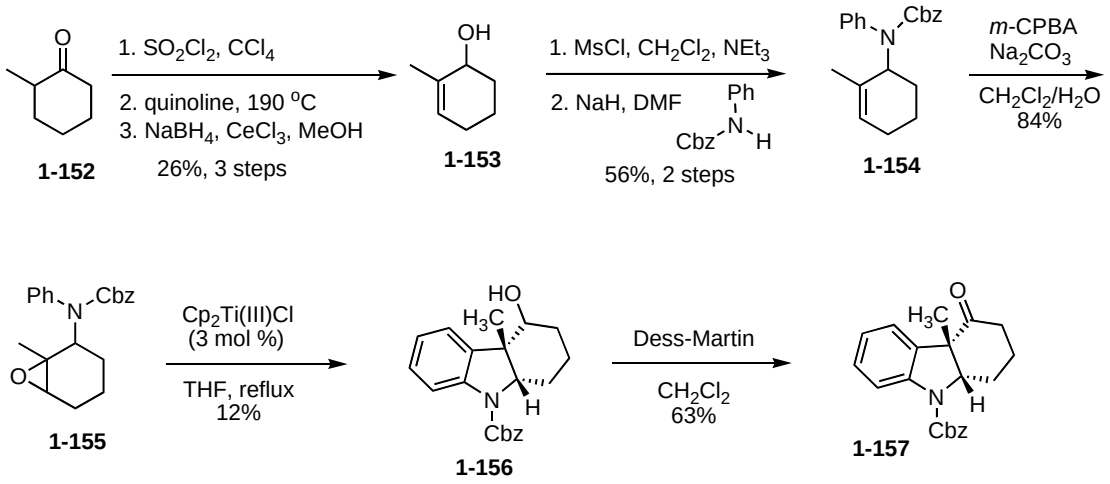


Scheme 1-37. Attempts to prepare CPI analogs

1.2.6 Diastereoselectivity Studies

The cyclic epoxide **1-155** was prepared in an effort to probe the diastereoselectivity of the cyclization reaction. To begin, allylic alcohol **1-153** was prepared in 3 steps[97] from **1-152** by oxidation to the unsaturated ketone followed by Luche reduction (Scheme 1-38).[98] Activation of the alcohol using MsCl followed by displacement with Cbz-aniline afforded the olefin **1-154** in 56% yield over 2 steps. Epoxidation of the olefin using *m*-CPBA yields **1-155** in 84%. Presumably the epoxidation reaction produces **1-155** as a mixture of diastereomers, however, due to the instability of the epoxide, the diastereoselectivity was not determined. Instead, the product was used immediately following purification in the key titanocene(III) chloride catalyzed cyclization reaction to provide **1-156** in a low 12% yield. Efforts to optimize this reaction were unsuccessful and the isolated yields were reproducibly low. When monitoring the cyclization reaction by TLC analysis there appeared to be multiple compounds formed in addition to the

desired hydrocarbazole **1-156**. The resulting alcohol was oxidized using Dess-Martin periodinane to yield ketone **1-157** in 63% yield. The relative stereochemistry of the ketone was confirmed to be *syn* due to the strong nOe observed between the tertiary methyl group and the methine hydrogen using 2D-NOESY NMR.[81] This low isolated yield represents a limitation for this methodology to construct hydrocarbazoles.

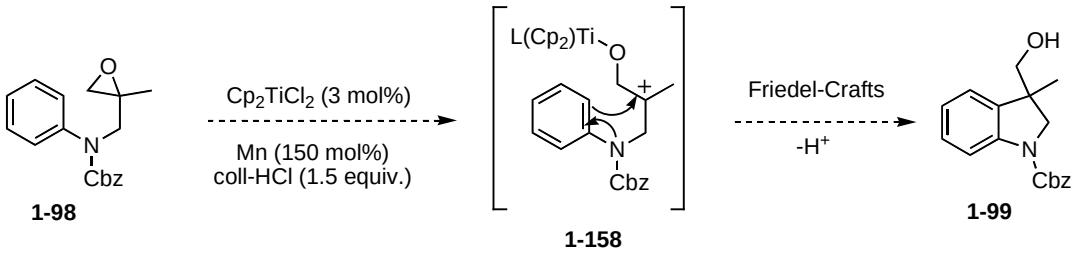


Scheme 1-38. Preparation of hydrocarbazole scaffold

1.2.7 Potential Reaction Mechanisms

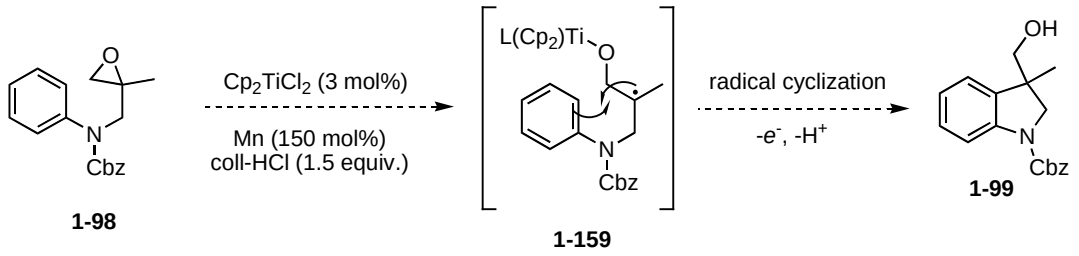
Various mechanisms for the titanocene-catalyzed annulation can be postulated. The first one involves the Lewis acid activation of the epoxide by the precatalyst or catalyst to promote an electrophilic aromatic substitution. The second involves the reductive opening of the epoxide *via* SET followed by radical cyclization onto the aromatic ring. The former is demonstrated in Scheme 1-39 where epoxide **1-98** may be activated by titanocene dichloride to provide

intermediate **1-158**, which is predisposed to undergo a Friedel-Crafts[99-101] (FC) rearrangement to afford indoline **1-99**. Although present in the reaction mixture, the manganese salts are not believed to play a role in the FC manifold.



Scheme 1-39. Proposed scheme for indoline **1-99** formation through FC manifold

In contrast, after the reductive epoxide opening of **1-98** to generate **1-159**, the radical can cyclize onto the aromatic ring and undergo oxidative rearomatization to provide indoline **1-99** (Scheme 1-40).



Scheme 1-40. Proposed formation of indoline **1-99** through the radical cyclization manifold

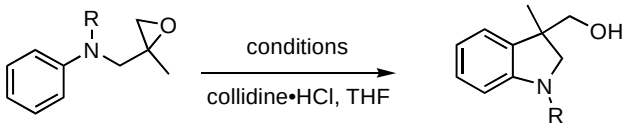
Preliminary results indicate that the path in Scheme 1-40 is the general pathway operating in our system since: 1) although the activated *p*-methoxy aromatic substrate **1-110** is suited for FC-type reactions, when performing the cyclization reaction only about a 20% yield of desired indoline **1-117** was observed; 2) it is known in the literature, as well as through our unreported

results, that using the FC alkylation reaction to form indanes and indolines through an acyclic aliphatic epoxide tether often results in low yields with multiple side products, including the aldehyde.[102-104] Unfortunately, under our optimized conditions, neither of these compounds were detected in the ^{1}H NMR analysis of our crude reaction mixtures.

The sensitivity of the reaction to both ambient oxygen and water was investigated. When subjecting **1-98** to titanocene(III) catalysis in a reaction flask open to ambient air, **1-99** was isolated in 14% yield, in addition to 43% of recovered starting material (Table 1-8, entry 1). This observation suggested that the desired reaction is inhibited by ambient oxygen, thus requiring the rigorous deoxygenation of the reaction solvent. To test the sensitivity of the reaction to water, epoxide **1-103** was subjected to titanocene(III) catalysis using a degassed mixture of distilled THF:H_2O in an equivolume ratio. The experiment resulted in the recovery of 89% of the starting material, and indicated that the reaction was sensitive to water (entry 2). Although some titanocene(III) chloride-mediated processes utilize water as a co-solvent,[105] this catalytic process appears to be inhibited by its presence. Additional control experiments using either only 3 mol% of the precatalyst (entry 3) or only 1.5 equiv of manganese metal (entry 4) under otherwise identical reaction conditions failed to afford indolines.[80,81] These observations suggest that the *in situ* generated titanocene(III) chloride reagent is responsible for promoting the annulation *via* a radical pathway.

In order to further elucidate the mechanism of oxidative rearomatization under the reductive conditions, we tested whether the precatalyst would be able to oxidize the hypothesized cyclohexadienyl radical intermediate, thereby regenerating the titanocene(III) catalyst and facilitating the rearomatization.

Table 1-8. Condition used in control experiments to determine reaction sensitivity



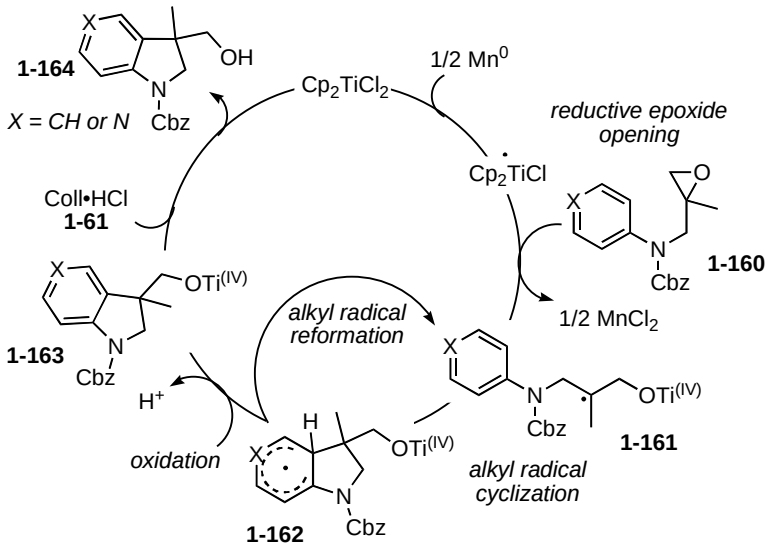
entry	epoxide	R	Cp_2TiCl_2 (mol%)	Mn (equiv)	product(s), yield
1	**1-98**	Cbz	3	1.5	**1-99**, 14% (**1-98**, 43%)[a,c]
2	**1-103**	CO_2Et	3	1.5	**1-104**, 0% (**1-103**, 89%)[b,c]
3	**1-98**	Cbz	3	0	**1-99**, 0%
4	**1-98**	Cbz	0	3	**1-99**, 0%
5	**1-98**	Cbz	3	0.15	**1-99**, 35% (**1-98**, 38%)[c]

[a]Reaction performed in a flask open to the atmosphere in distilled, non-degassed THF; [b]Reaction performed in a degassed mixture of distilled THF:H_2O (1:1); [c]Starting material was recovered from the reaction.

When epoxide **1-98** was subjected to 15 mol% of manganese reductant, **1-99** was isolated in 35% yield, in addition to 38% of starting material (entry 5, Table 1-8). This result indicates that a stoichiometric amount of manganese reductant is required to achieve optimal yields during the cyclization reaction.

In accordance with the general mechanism published on titanocene(III) chloride catalysis (shown in Scheme 1-14 above), it is envisioned that our transformation may proceed through the sequence shown in Scheme 1-41. The reagents required for the reaction include the titanocene dichloride precatalyst, collidine hydrochloride and manganese metal. We believe the sequence begins with the generation of the titanocene(III) chloride species, followed by the reductive epoxide opening of **1-160** to form radical **1-161**. This intermediate likely undergoes a reversible cyclization onto the aromatic ring, which may proceed through a chair-like Beckwith-Houk transition state[106,107] to afford intermediate **1-162**. This species then undergoes an oxidation to provide the rearomatized compound **1-163**.[108] The indoline is then liberated from the catalyst by

protodemetallation of the alkoxide by using **1-61**. This provides the product **1-164**, and the precatalyst, which is eligible to be reduced to $Cp_2Ti(III)Cl$ and re-enter the catalytic cycle.



Scheme 1-41. Proposed catalytic cycle for titanocene(III) chloride radical cyclization

Although the mechanism of oxidative rearomatization process under reductive conditions remains to be established,[108] two main pathways have been postulated. The first is applicable to our system and involves the single-electron oxidation of the cyclohexadienyl radical **1-162** and subsequent proton loss to afford the rearomatized compound **1-163**.[106,109-111] The second pathway may involve the loss of a hydrogen atom from intermediate **1-162**, which may then undergo a radical recombination to provide the aromatic product **1-163**.[112,113] The postulated mechanistic pathways remain speculative in the absence of additional rigorous mechanistic investigations.

1.3 CONCLUSIONS

In conclusion, a new method to prepare indolines and azaindolines utilizing an epoxide-opening rearrangement catalyzed by *in situ* generated titanocene(III) chloride was developed. Although this reaction was not regioselective, many of the desired indolines could be prepared in good to moderate yields. Control experiments indicate that the reaction is sensitive to both water and ambient air, and requires the presence of both the precatalyst and the manganese metal to promote the annulation.

The substrate scope of the reaction has been limited to the use of 1,1-disubstituted epoxyanilines to prepare 3,3-disubstututed indolines. One 5-azaindoline has been prepared using the analogous 4-aminopyridine group as the radical acceptor. In general, the azaindoline scaffold was more difficult to access due to the challenges associated with the preparation of the requisite epoxide starting materials.

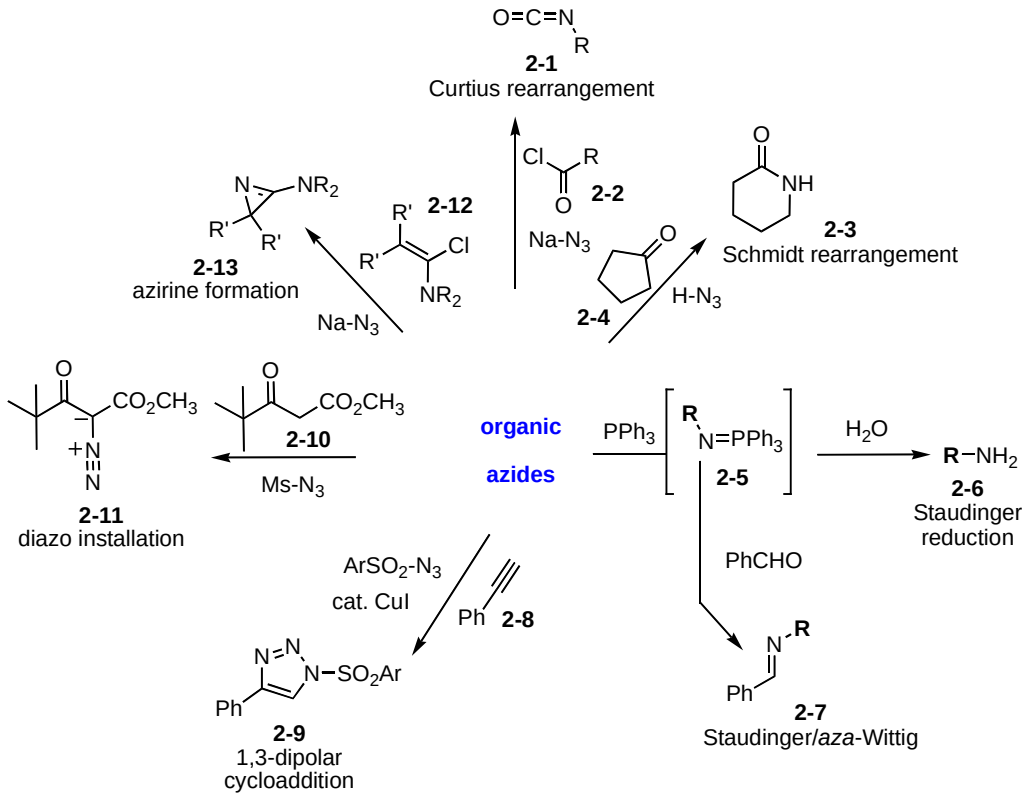
2.0 1,2,4-TRIAZINE SYNTHESIS USING THE STAUDINGER/*AZA*-WITTIG REACTION

2.1 INTRODUCTION

2.1.1 Applications of the Staudinger/*aza*-Wittig (SAW) Reaction

The azide is a versatile functional group in organic synthesis, and methods for its preparation[114] and synthetic applications have been reviewed.[115] Figure 2-1 shows general examples of the organic azide being used in synthesis that include the preparation of isocyanates **2-1** from acid chlorides **2-2** (Curtius rearrangement),[116] lactams **2-3** from ketones **2-4** (Schmidt reaction),[116] and diazo compounds **2-11** from β-ketoesters **2-10**.[31] Additional applications include the 1,2,3-triazole **2-9** synthesis using a copper-catalyzed [3+2] cycloaddition with alkynes **2-8** ("click chemistry"),[117] and transforming chloroenamines **2-12** into 3-amino-2*H*-azirines **2-13**, which serve as efficient precursors for α,α-disubstituted amino acids.[118] For this chapter, the relevant transformation involving the organic azide is the Staudinger/*aza*-Wittig (SAW) reaction.[116] This tandem reaction begins with the decomposition of organic azides to reactive iminophosphoranes **2-5** through treatment with trialkyl/triaryl phosphines and phosphites. These intermediates may be hydrolyzed to the corresponding amines **2-6**, or in the absence of water and the presence of a reactive carbonyl group, may undergo the *aza*-Wittig reaction to yield **2-7**. In

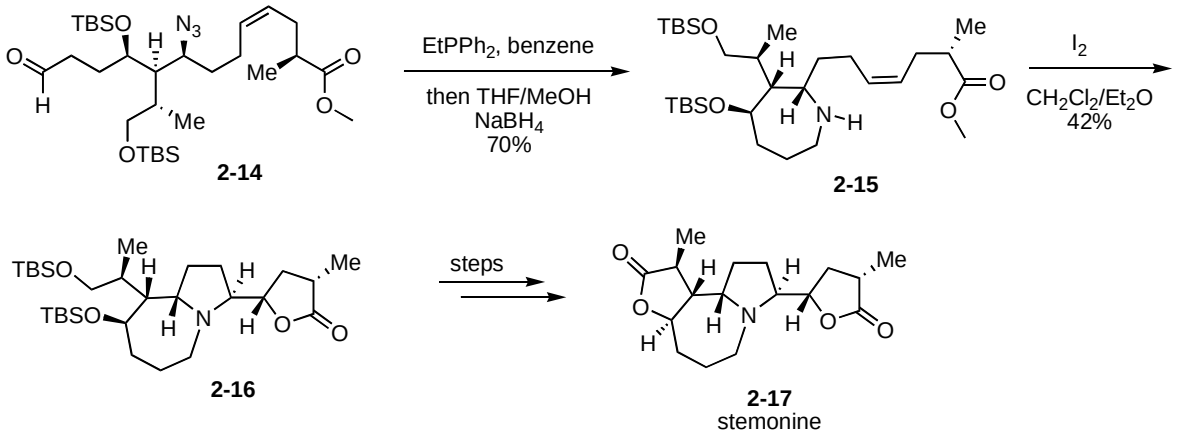
both the hydrolysis and *aza*-Wittig reactions, the phosphine oxide byproducts are often difficult to remove during purification. To aid in their removal, polymer support variants have been developed.[119]



Scheme 2-1. General applications of the organic azide functional group

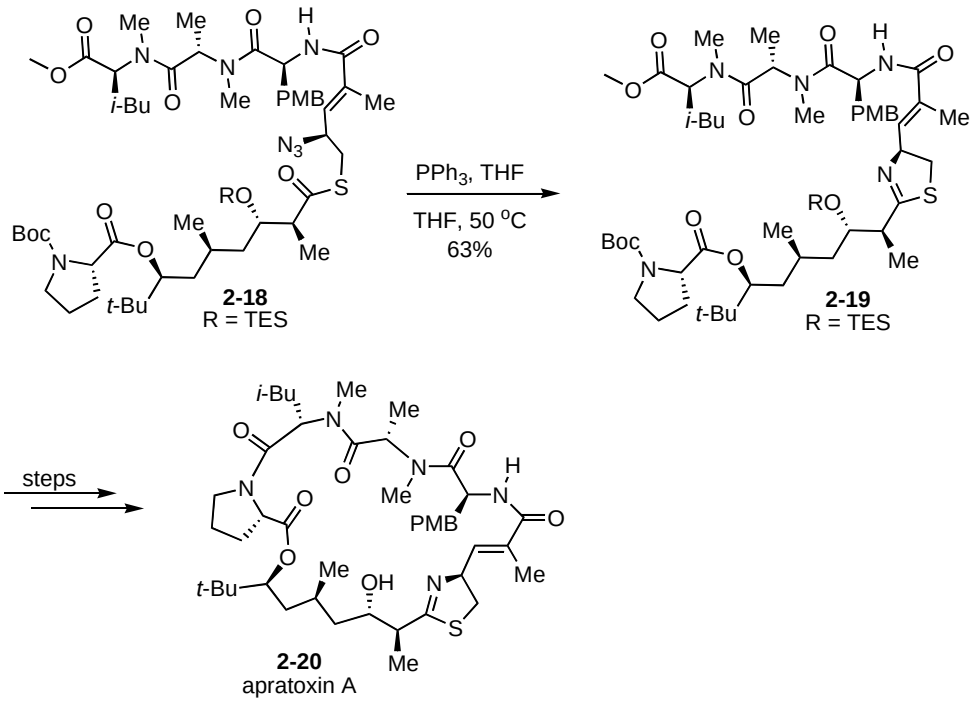
The reactivity profile of the iminophosphorane intermediate **2-5** lends itself to an intermolecular *aza*-Wittig reaction in the presence of an aldehyde, ketone, acid halide, or heterocumulene to afford the respective product represented as **2-7**.[120] Less reactive functional groups such the imide, ester, and amide may react with **2-5** in an intramolecular fashion. Applications of the SAW reaction in natural product synthesis include the work by Williams and co-workers[121] to prepare members of the *Stemona* alkaloid family such as (-)-stemonine **2-17** and

(-)-stemospironine.[122] Highlights of the preparation of stemonine include the treatment of the advanced intermediate **2-14** with $EtPPh_2$ in benzene, followed by reduction of the imine using $NaBH_4$ in THF and MeOH. The pyrrolidino-butyrolactone system **2-16** was installed using an iodine-induced cyclization event, where the product was further converted to the natural product **2-17**.



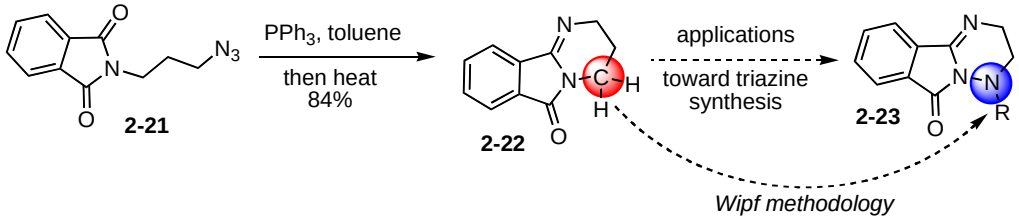
Scheme 2-2. Williams' preparation of stemonine **2-17**

During the preparation of the potent anticancer agent apratoxin A, Forsyth and Chen[123] installed the sensitive thiazoline ring using the SAW reaction in the late stages of their synthesis. Treating the advanced intermediate **2-18** with PPh_3 and THF promoted the Staudinger/*aza*-Wittig reaction with the thioester to provide the thiazoline **2-19** in 63% yield (Scheme 2-3). Subsequent protecting group removal and macrolactonization afforded apratoxin A **2-20**.



Scheme 2-3. Thiazoline formation using the Staudinger/*aza*-Wittig reaction

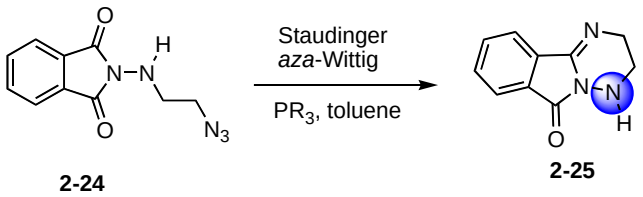
Eguchi and Takeuchi[124] have demonstrated that azides such as **2-21** can be transformed into iminolactam derivatives **2-22** in a one-pot process in good yields as shown in Scheme 2-4. This transformation provides precedence for the *aza*-Wittig reaction with phthalimides, and the inspiration to expand the methodology for the synthesis of 1,2,4-triazines similar to **2-23**.



Scheme 2-4. Staudinger/*aza*-Wittig reaction to form iminolactam derivatives

2.1.2 Wipf Group Methodology: 1,2,4-Triazine Synthesis

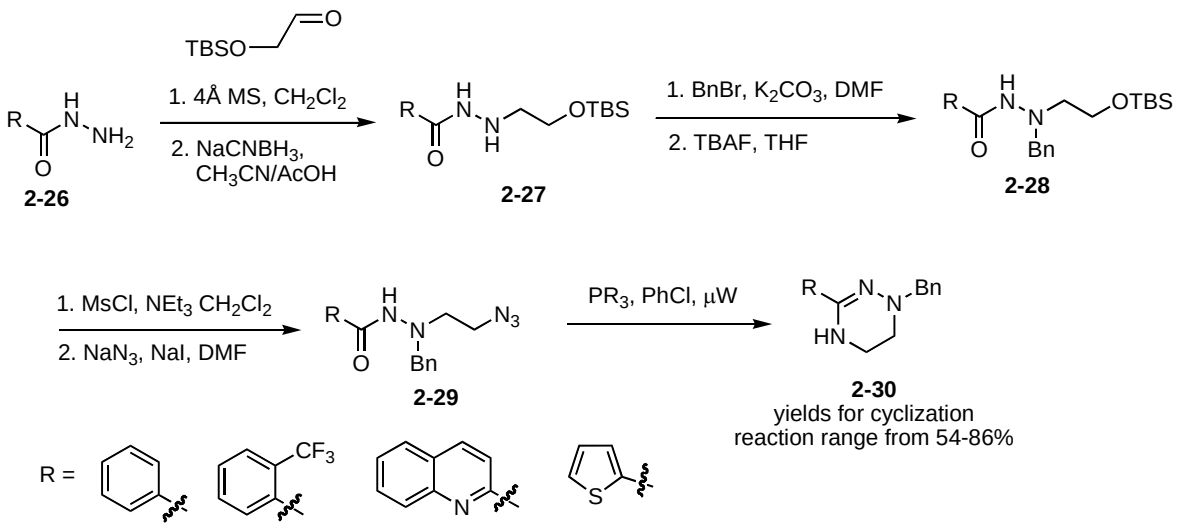
The synthesis of 1,2,4-triazines in the Wipf group began with studies conducted by Dr. David Amantini, Dr. Stephan Elzner and Dhezi Fu, who have demonstrated that alkyl azides such as **2-24** shown in Scheme 2-5 can be treated with trialkyl/aryl phosphines to afford 1,2,4-triazines such as **2-25**. Under this reaction manifold, a series of substituted triazines of this class have been successfully prepared (unpublished results).



2-24 **2-25**

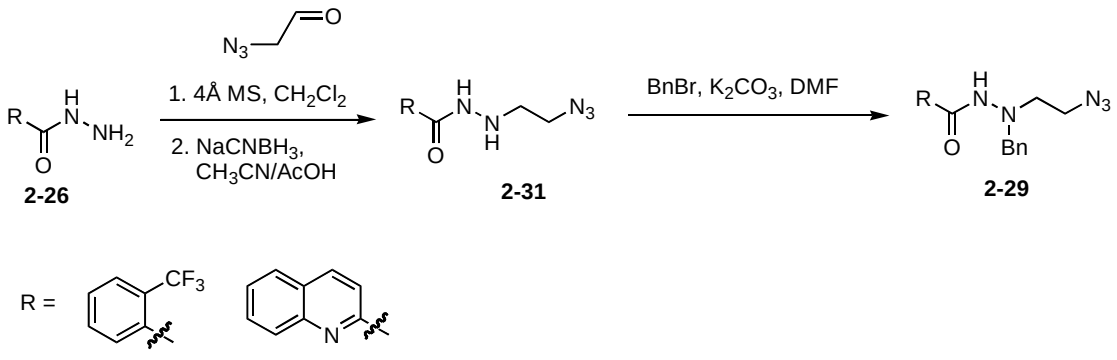
Scheme 2-5. Staudinger/*aza*-Wittig reaction to prepare 1,2,4-triazines

In addition to the studies using cyclic imides, Amantini, Elzner and Fu demonstrated that aryl hydrazides **2-26** could undergo reductive amination to prepare hydrazide derivatives similar to **2-27**. After alkylation and subsequent TBS deprotection to provide **2-28**, alcohol activation and azide displacement yields **2-29**. The azides were finally treated with trialkylphosphines to promote a SAW reaction, thereby forming triazines **2-30** in 54-86% yields for the R-groups shown in Scheme 2-6.



Scheme 2-6. Preparation of substituted 1,2,4-triazines

During their studies, a second-generation approach toward hydrazides similar to **2-29** was developed. This method employs the azido aldehyde in the reductive amination reaction step (Scheme 2-7). After alkylation with benzyl bromide to afford **2-29**, the azides have been transformed into triazines in the same manner as previously shown in Scheme 2-6.

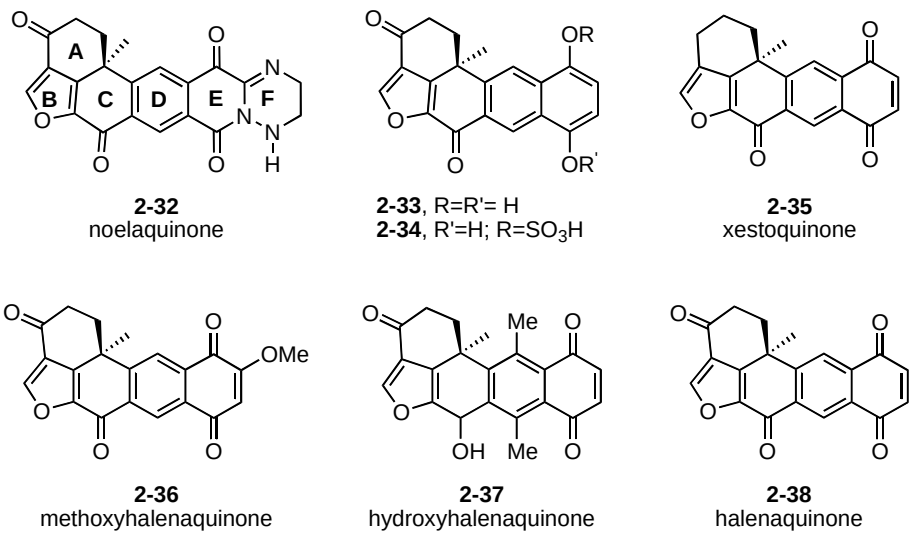


Scheme 2-7. Alternative approach toward preparing hydrazide **2-31**

Both linear approaches are effective in the preparation of **2-30**, although we envisioned developing a convergent approach toward the synthesis of similar hydrazides. This could be accomplished by the coupling of a functionalized 1,1-disubstituted hydrazine with an activated carboxylic acid to arrive at **2-29**.

2.1.3 *Xestospongia* Metabolites: Noelaquinone and Related Structures

In addition to developing a novel methodology, this SAW reaction could potentially be used toward natural product synthesis. Noelaquinone **1-32** was isolated in 1996 from an undescribed species of *Xestospongia* by Scheuer at Derawan Island, Indonesia (Scheme 2-8).[125] This marine metabolite has the potential to be biologically active since a similar natural product, halenaquinone **2-38** has been shown to possess antibiotic,[126] cytotoxic and antifungal activity.[127] Halenaquinone and xestoquinone are also known inhibitors of Pfnek-1,[128] a kinase responsible for the phosphorylation of Pfmap-2. This phosphorylation sequence has been identified as a critical step in the life cycle of the parasite and is being targeted as a method to treat malaria.[129] Although no total synthesis of noelaquinone has been published to date, halenaquinone has been a target for synthetic chemists.[130,131] Additional natural products isolated by Scheuer from the undescribed species of *Xestospongia* include the previously reported halenaquinone[132] **2-38**, Kitagawa's quinol **2-33** and monosulfate[133] **2-34**, xestoquinone[134] **2-35**, and the discovery of methoxyhalenaquinone **2-36** and hydroxyhalenaquinone **2-37**.



2-32
noelaquinone

2-33, R=R'= H
2-34, R'=H; R=SO_3H

2-35
xestoquinone

2-36
methoxyhalenaquinone

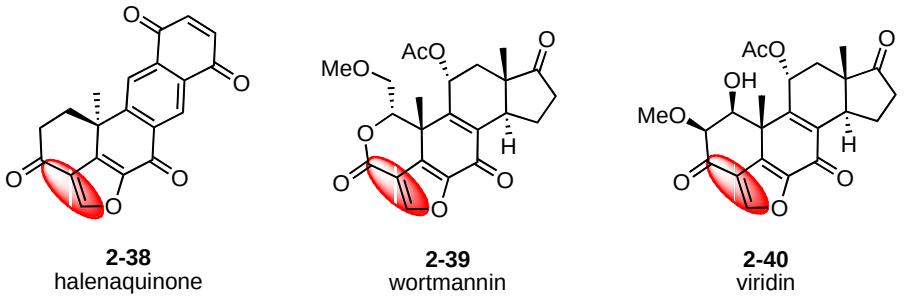
2-37
hydroxyhalenaquinone

2-38
halenaquinone

Scheme 2-8. Noelaquinone and other natural products isolated by Scheuer

2.1.4 Wortmannin and Halenaquinone Analogs Prepared in the Wipf Group

A group of natural products that contains the tricyclic furan group similar to halenaquinone is the viridin family,[135] which includes wortmannin **2-39** and viridin **2-40** (Figure 2-1). Wortmannin and viridin are classified as potent kinase inhibitors, however, their inhibition is not selective, thus making them poor candidates for therapeutics.[136] The Wipf research group maintains initiatives to design protein tyrosine kinase inhibitors[137] and phosphatidylinositol 3-kinase (PI-3 kinase) inhibitors,[138] since the development of selective as well as potent inhibitors for the PI-3 kinase family is believed to have therapeutic potential.[139]



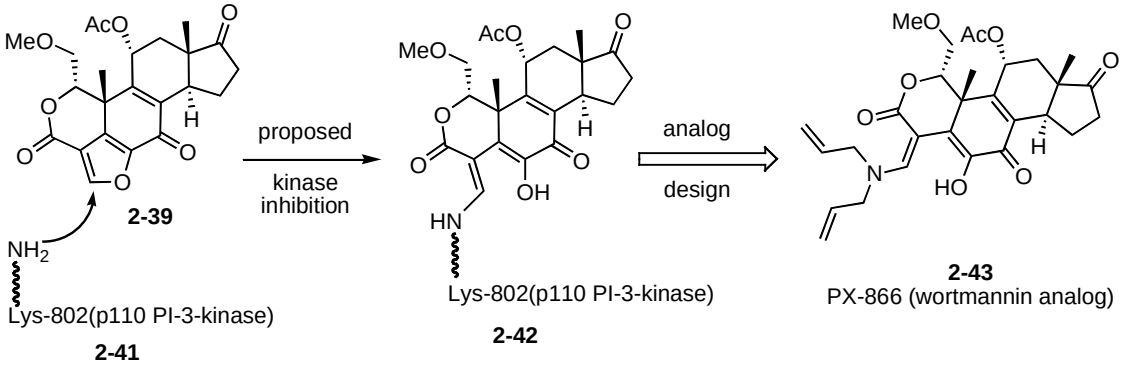
2-38
halenaquinone

2-39
wortmannin

2-40
viridin

Figure 2-1. Natural products containing the reactive tricyclic furan group

The proposed biological activity of the molecules shown in Figure 2-1 is believed to arise from the addition of a kinase residue **2-41** to the reactive Michael acceptor of wortmannin (highlighted) thereby forming a covalent adduct **2-42** that inhibits the protein function (Scheme 2-9).[140,141] Researchers in the Wipf group have prepared and analyzed a library of nucleophilic adducts of wortmannin and found that analog PX-866 **2-43** is a potent phosphoinositide (PtdIns)-3-kinase inhibition. The *N*,*N*-diallylamine adduct of wortmannin exhibited an IC_{50} value of 0.1 nM against PtdIns-3-kinase.[142]



Scheme 2-9. Proposed mechanism of action for kinase inhibition and the design of inhibitor PX-866 **2-43**

The Wipf research group has also studied halenaquinone and derivatives to function as kinase inhibitors in *Plasmodium falciparum*, the parasite responsible for malaria in humans.[143] Malaria is estimated to result in 300-500 million clinical cases every year, and over two million people infected will die as a result.[144,145] The U.S. Army is also actively involved in research to further understand and prevent malaria since many of its personnel are at risk of contracting the disease while deployed. Researchers at the Walter Reed Army Institute of Research (WRAIR) continue to study and develop new treatments for drug-resistant strains of malaria.[146] In an effort to develop a new kinase inhibitor, Wipf[147] and Wakefield[148] published the synthesis of a thiophene-containing analog of halenaquinone, thiohalenaquinone **2-44**. The rationale behind the analog design was to attenuate the reactivity of the Michael acceptor by replacing the furan ring with thiophene. Computational analysis showed that **2-44** is 2.6 kcal/mol lower in relative strain energy than **2-38**, which, in part, was theorized to increase the selectivity profile of the molecule for the targeted kinase (Figure 2-2).

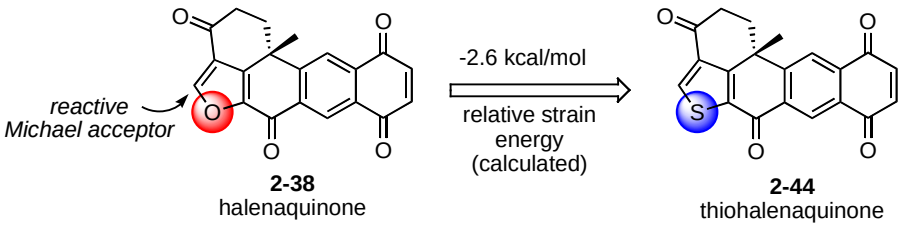
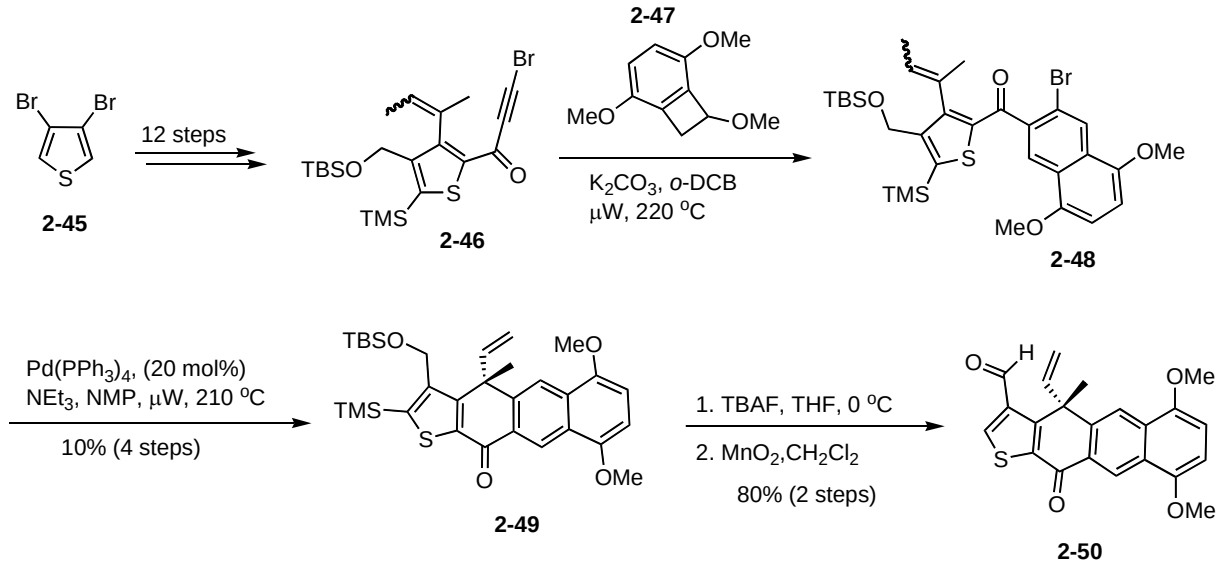


Figure 2-2. Proposed analog of halenaquinone, thiohalenaquinone **2-44**

The synthesis of thiohalenaquinone was accomplished by treating **2-46** (prepared in 12 linear steps from 2,3-dibromothiophene **2-45**) with the diene precursor **2-47** to promote a Diels-Alder reaction followed by a palladium-catalyzed Heck cyclization to provide **2-49** in 10% yield

over 4 steps. After a global desilation, the resulting alcohol was oxidized using MnO_2 to give aldehyde **2-50** (Scheme 2-10).

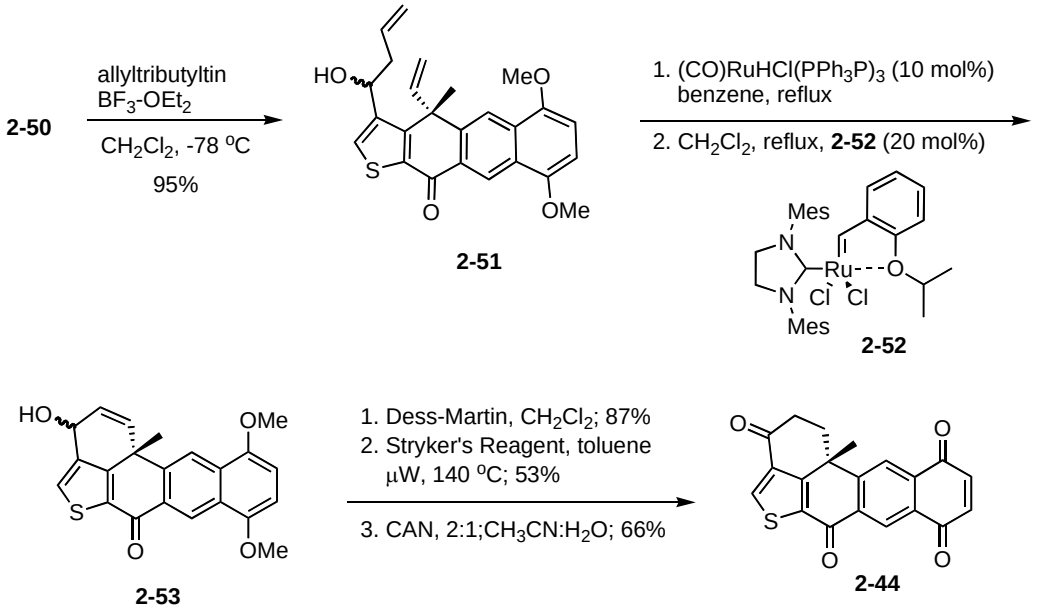


Scheme 2-10. Preparation of thiohalenaquinone

The allylation using allyltributyltin afforded alcohol **2-51** as an inconsequential mixture of diastereomers. The endgame of the synthesis includes a ruthenium[2] catalyzed olefin isomerization/metathesis sequence to form the A ring of thiohalenaquinone, where after a series of oxidation state adjustments around the periphery of the core the preparation of **2-44** was completed (Scheme 2-11). In collaboration with the Dow group at the Walter Reed Army Institute of Research (WRAIR), a series of samples that were prepared by Wakefield were screened against Pfnek-1. The natural product analog **2-44** inhibited Pfnek-1 with an IC_{90} value of 4.6-6.7 μM,[148] which is similar to the IC_{50} values of xestoquinone **2-35** and halenaquinone **2-**

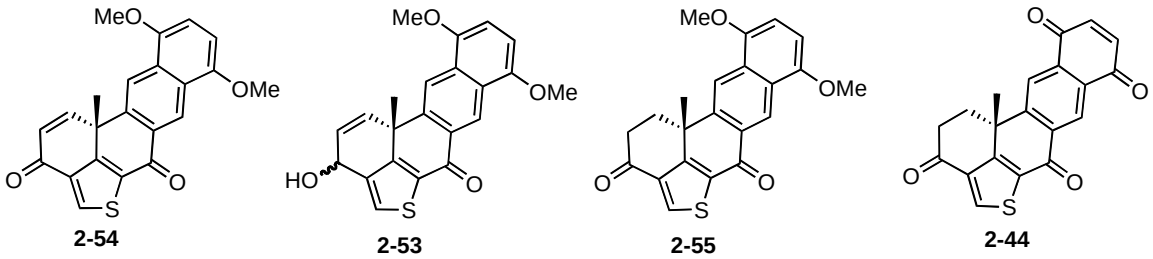
[2] The catalyst used in this transformation is the Hoveyda-Grubbs 2nd generation.

38, which are 1.1 μM and 3.0 μM, respectively.[148] Additional molecules prepared in the endgame of the synthesis were also screened, and the results are presented in Table 2-1.



Scheme 2-11. Preparation of thiohalenaquinone

Table 2-1. IC_{90} values of thiohalenaquinone analogs prepared by Wakefield

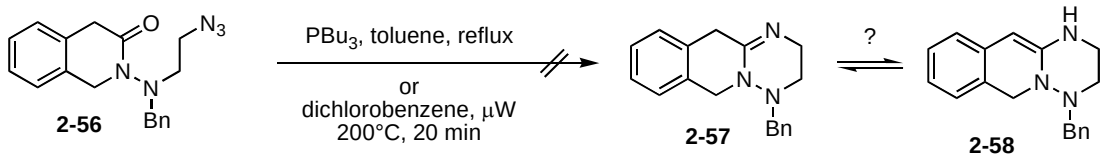


entry	thiohalenaquinone analog	IC_{90} (μM)
1	**2-54**	2.8-3.9
2	**2-53**	>2500
3	**2-55**	>2500
4	**2-44**	4.6-6.7

2.2 RESULTS AND DISCUSSION

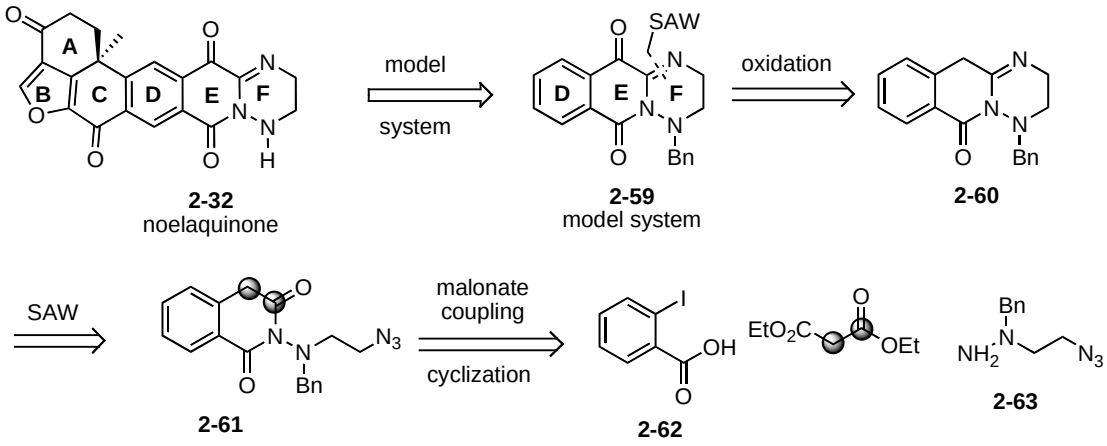
2.2.1 Model System Studies for the DEF Rings of Noelaquinone

In the Wipf group, the SAW methodology was being applied toward the synthesis of the 1,2,4-triazine-containing natural product noelaquinone. Amantini and Elzner began studies toward the preparation of a model system of noelaquinone. They reported subjecting **2-56** to the SAW conditions outlined in Scheme 2-12, however, no triazine products **2-57** or **2-58** were observed.



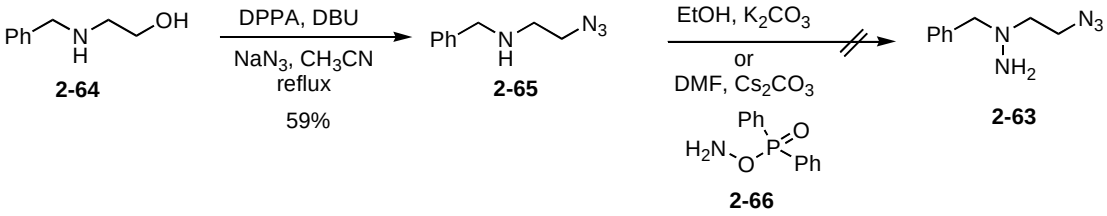
Scheme 2-12. Screening the SAW reaction conditions on substituted lactams

This failed result inspired the design of a second-generation approach toward preparing model system **2-59**, which is derived from homophthalimide **2-61** rather than the lactam **2-56**. The homophthalimide could be prepared through hydrazide formation between acid **2-62** and hydrazine **2-63**, followed by an annulation using diethylmalonate as the source for the remaining carbons (Scheme 2-13). The first step toward assembling **2-59** would be to prepare **2-63** as the requisite coupling partner.



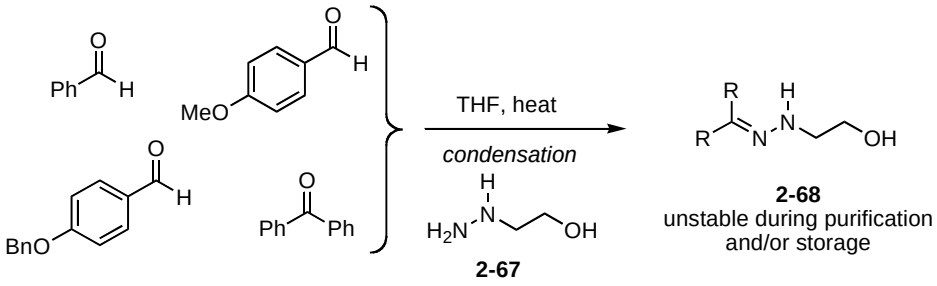
Scheme 2-13. General retrosynthesis of the model system for noelaquinone

Two approaches were investigated for the preparation of **2-63**. The first approach involved hydrazine formation through an electrophilic amination protocol. Using this protocol allowed us to prepare the target in a convergent manner. Although there are many reagents known to promote electrophilic amination reactions,[149] the *O*-diphenylphosphinylhydroxylamine[150] **2-66** was prepared and utilized for the task. Upon treatment of azide **2-65**[151] with **2-66** using either EtOH and potassium carbonate or DMF and cesium carbonate,[152] no desired hydrazine product was detected (Scheme 2-14).



Scheme 2-14. First approach toward preparation of hydrazine **2-63**

The second approach began with screening conditions for the preparation of a stable hydrazone from the commercially available 2-hydroxyethylhydrazine **2-67**. It was necessary to protect the hydrazine to prevent undesired side reactions during the conversion of the distal hydroxy group into the azide. Using this approach with the hydrazine group already in place eliminated the need for electrophilic amination protocols. A series of aldehydes and ketones[153] were screened in search of a stable protecting group for **2-67** in its hydrazone form. It was observed that the resulting hydrazones **2-68** (derived from the aldehydes and ketones shown in Scheme 2-15) were unstable during purification by chromatography on SiO_2, or during subsequent steps in the linear sequence.

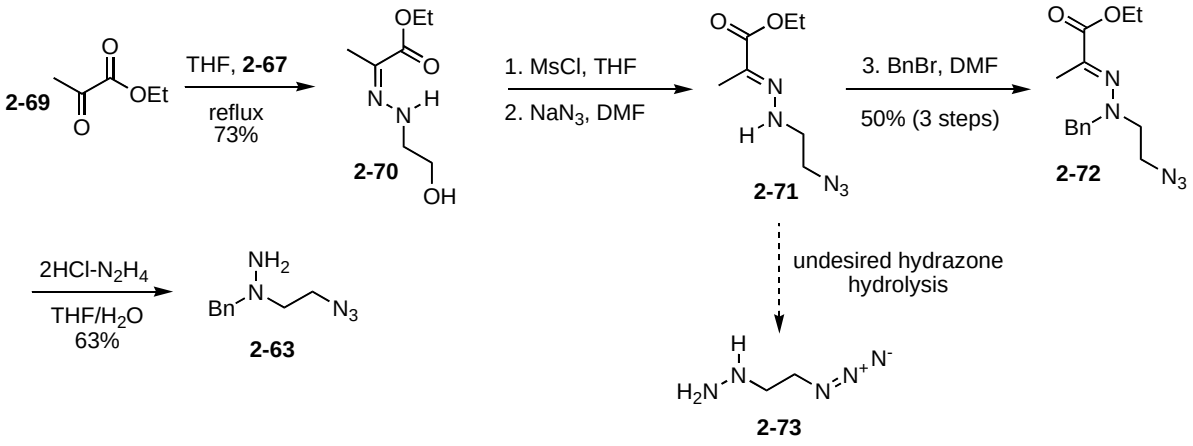


Scheme 2-15. Initial protecting group study for **2-67**

It was later realized that the condensation of **2-67** with ethyl pyruvate **2-69** provided a hydrazone that was stable to hydrolysis upon workup, as well as column chromatography (Scheme 2-16).[154] Identifying a stable hydrazone was critical since the sequence involves the handling of intermediate **2-71**, where if hydrolysis occurs during the purification step after azide displacement, the formation of **2-73** could be dangerous due to the explosive nature of low molecular weight organic azides.[115]

Activation of alcohol **2-70** with MsCl followed by azide displacement provided an intermediate that, after purification to remove the residual sodium azide, was treated with BnBr and K_2CO_3 in DMF to afford the *N*-benzylhydrazone **2-72** in 50% yield over 3 steps. This 3-step sequence was performed without incident using 45 g of alcohol **2-70** to prepare azide **2-72**. The hydrazone was stable to storage on the benchtop for months without noticeable decomposition by ^{1}H NMR.

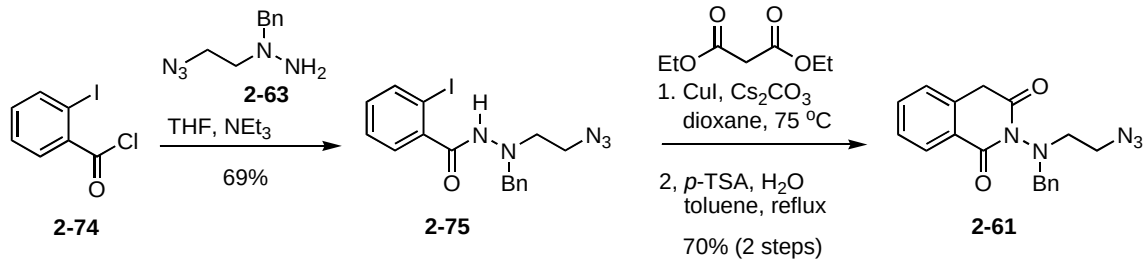
To cleave the hydrazone, **2-72** was treated with excess hydrazine dihydrochloride in aqueous THF to yield **2-63** in 63% yield.[155] During the scale up of this reaction, it was found that excess hydrazine dihydrochloride, or conc. HCl and hydrazine hydrate needed to be added to drive the reaction to completion. Yields could be obtained as high as 91% for this deprotection. Changing the acid source to acetic acid ensured complete conversion to **2-63** from **2-72**. This compound proved to be unstable to storage and was used immediately after purification by column chromatography.



Scheme 2-16. Synthesis of hydrazine synthon **2-63**

2.2.2 Preparing the Precursor for the Staudinger/*aza*-Wittig Reaction

After developing a sequence to obtain the hydrazine on preparative scale, our efforts became focused toward the preparation of **2-61**. In accordance to Scheme 2-17, the preparation was accomplished in a convergent manner beginning with the coupling of acid chloride **2-74** with hydrazine **2-63** to afford hydrazide **2-75** in 69% yield after recrystallization. Treatment of **2-75** with 5 mol% of CuI, 10 mol% of picolinic acid, 2 equiv of diethylmalonate and 3 equiv of Cs_2CO_3 in dioxane afforded the α-aryl malonate (not shown).[156,157] This intermediate was used crude after workup, and treatment with cat. *p*-TSA in aqueous toluene promoted a cyclization/decarboxylation to yield **2-61** in 70% over 2 steps.

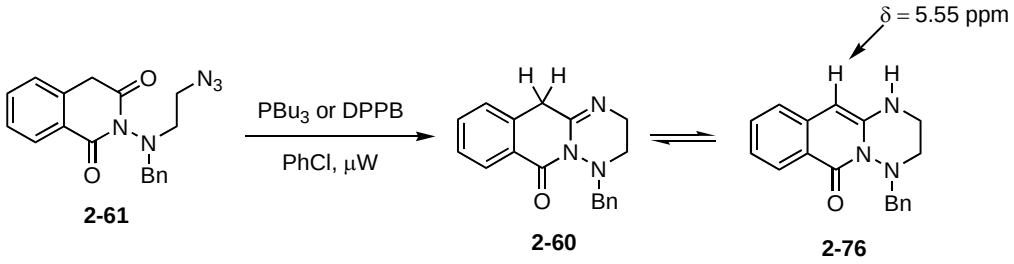


Scheme 2-17. Preparation of homophthalimide **2-61**

The resulting homophthalimide served as a key intermediate in the approach to complete the model system of noelaquinone. The remaining two steps consisted of the Staudinger/*aza*-Wittig reaction and the subsequent oxidation at the benzylic position to arrive at the DEF ring system **2-59**.

2.2.3 Testing the Staudinger/*aza*-Wittig Reaction/Enamine Oxidation

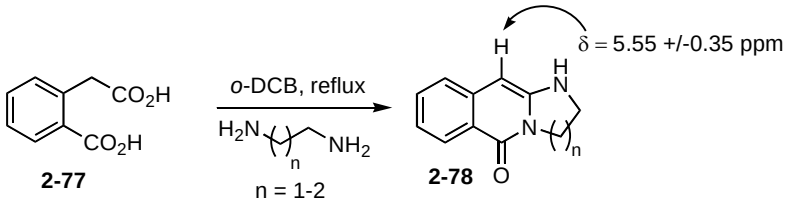
Our initial approach toward the model system involved performing the SAW reaction followed by oxidation at the benzylic position of the product to arrive at **2-59**. In general, either PBu_3 or DPPB as the phosphine source promotes the SAW reaction. Microwave irradiation of the reaction in place of conventional heating greatly decreases reaction times, as established by Amantini and Elzner. In experiments using the homophthalimide **2-61** in the SAW reaction, the isolation of **2-76** was quite challenging due to rapid (aerobic) oxidative decomposition of the substrate. Additionally, the removal of the phosphine oxide impurities was problematic since they often co-eluted with the product during purification. The ^{1}H NMR analysis of the purified material from the SAW reaction typically showed the diagnostic chemical shift of the vinyl methine singlet at 5.55 ppm (1 H), indicating that compound **2-76** was the preferred tautomer over **2-60** (Scheme 2-18).[3]



Scheme 2-18. Staudinger/*aza*-Wittig then oxidation approach

[3] See Scheme 2-19 below for reference compounds.

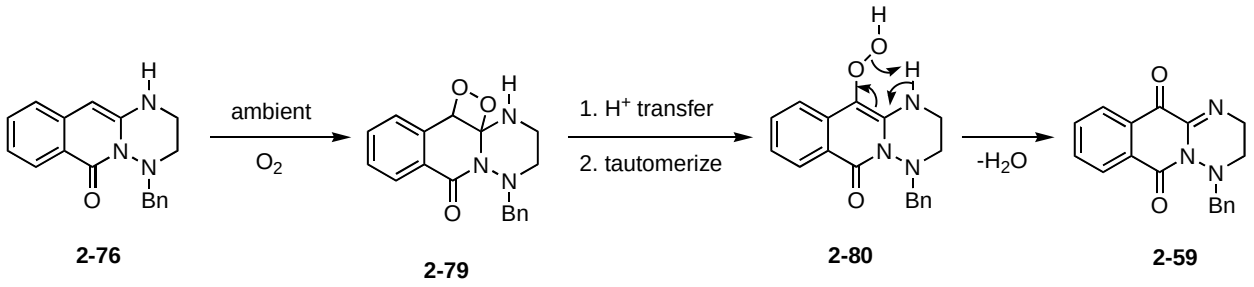
Molecules with cores similar to **2-76** have been prepared by Fritz and co-workers[158] through the condensation of homophthalic acid **2-77** and various diamines in refluxing *o*-DCB. The products from the SAW reaction were characterized to have a vinyl methine of similar chemical shift to those observed in **2-78** (Scheme 2-19).



Scheme 2-19. Fritz's preparation of ketene aminals **2-78**

During the storage of enamine **2-76** at room temperature, the desired triazine **2-59** was obtained. These conditions presumably allow for the aerobic oxidation of the DEF ring system. Although isolated by purification using SiO_2 and characterized as the enamine, a purity check by ^{1}H NMR of the sample after several days showed the disappearance of the singlet at 5.55 ppm and the presence of two new doublets at 8.39 ppm (1 H, J = 7.8 Hz) and 8.22 ppm (1 H, J = 8.4 Hz).

A potential mechanism for this auto-oxidation process is proposed in Scheme 2-20. In the presence of ambient oxygen the hydroperoxy intermediate **2-79** may be formed.[159] After opening the cyclic peroxide and proton transfer to form **2-80**, a dehydration event can afford the desired DEF ring system. Due to the rapid decomposition during purification as well as the phosphine oxide impurities that often accompanied the desired product, a quantitative assessment of the SAW reaction was not obtained. It was evident that the initial approach toward the DEF ring system needed to be revised.

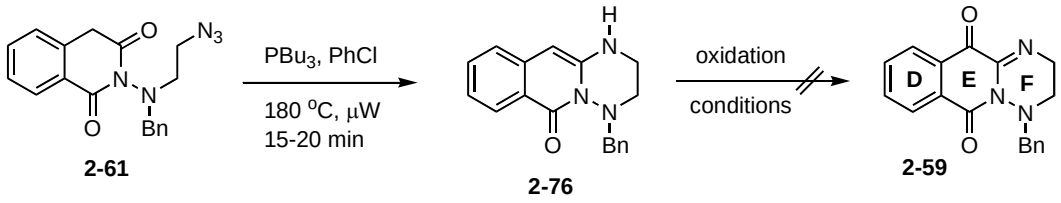


Scheme 2-20. Proposed mechanism for auto-oxidation of enamine **2-76**

Our strategy changed from initially trying to isolate and characterize the unstable enamine toward directly oxidizing the intermediate to the ketone under controlled conditions. Ideally, it was envisioned performing a one-pot SAW reaction/oxidation sequence to afford **2-59** directly. Table 2-2 summarizes some of the conditions screened to promote the SAW reaction/oxidation of the enamine intermediate to arrive at **2-59**. The SAW step was accomplished using conditions outlined in Table 2-2 below.

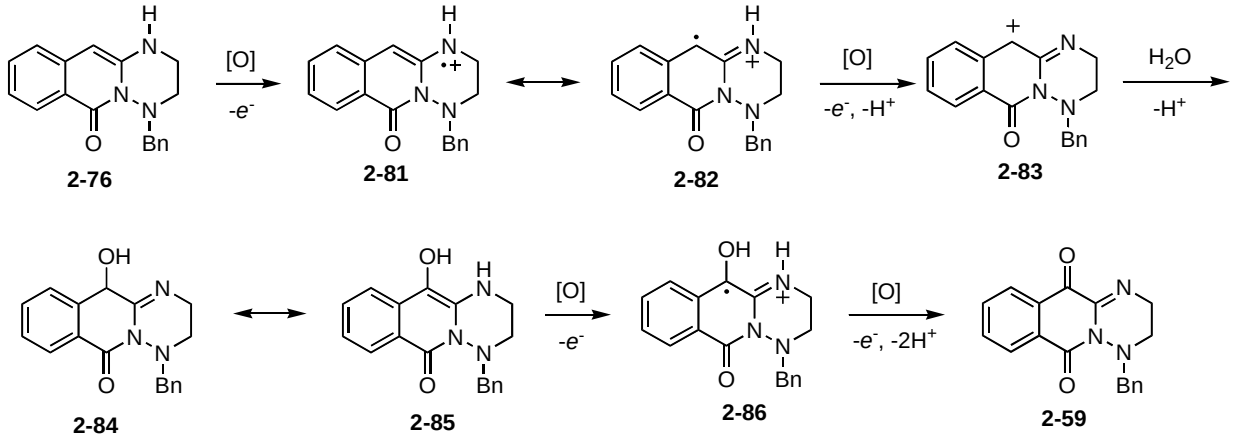
The subsequent oxidation step was problematic when using both organic oxidants such as Fremy's salt or inorganic oxidants such as CAN in aqueous media. In both cases, we failed to isolate **2-59**. In general, the reactions resulted in decomposition of the enamine intermediate into compounds that were difficult to isolate and characterize. These results indicated that promoting a controlled 4-electron oxidation on **2-76** was not reproducible.

Table 2-2. Staudinger/*aza*-Wittig reaction and oxidation sequence



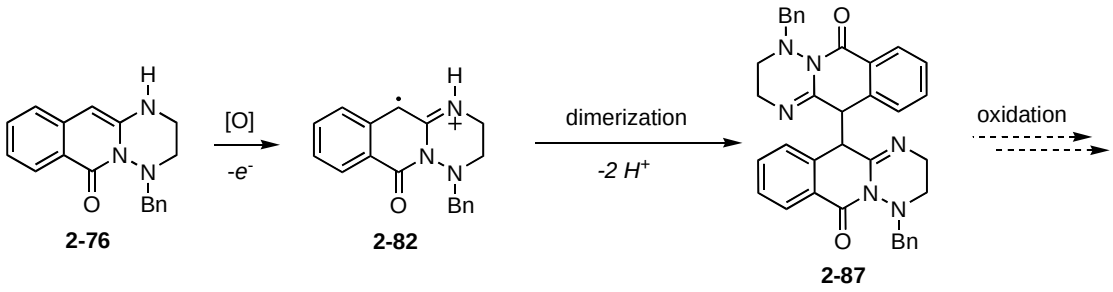
entry	oxidation conditions
1	Fremy's salt, EtOH(aq.)[160]
2	CAN, THF (aq.)[161]
3	CAN on alumina, THF (aq.)
4	$K_3Fe(CN)_6$, Cs_2CO_3, THF (aq.)
5	5% CAN, $NaBrO_3$, THF (aq.)

Based upon the proposed mechanisms of oxidative enamine coupling chemistry utilized in MacMillan's research group,[162-164] a possible mechanism for the *desired* oxidation pathway begins with the single electron oxidation of the enamine nitrogen to give the radical cation **2-81** and its tautomer **2-82**. This intermediate then may be oxidized again, forming a transient benzylic cation that is immediately quenched by the aqueous media. The α-hydroxy imide **2-84** can then tautomerize to **2-85**, which may then undergo the same 2-electron oxidation sequence to arrive at the desired product **2-59** (Scheme 2-21).



Scheme 2-21. Proposed mechanism for 4-electron oxidation of enamine **2-76**

It is precedented that enamines undergo dimerization/oligomerization under oxidative conditions.[165,166] Another explanation of possible decomposition pathways involves the oxidative dimerization of intermediate **2-82** to generate **2-87**, which may become oxidized further under the reaction conditions (Scheme 2-22).



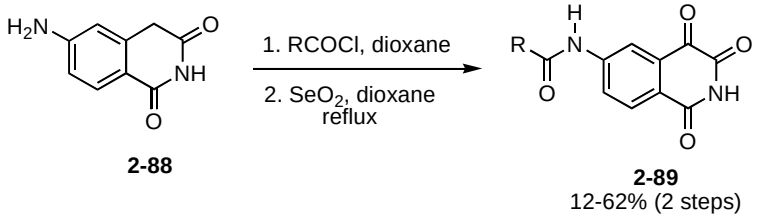
Scheme 2-22. Possible oxidation pathways of **2-76**

Efforts to promote the enamine oxidation by bubbling air through a solution of the isolated SAW product at 23 ^{o}C were also unsuccessful. At this point, our synthetic strategy was

redirected toward oxidizing the benzylic position to the ketone *before* performing the SAW reaction.

2.2.4 Oxidation to Ketone Followed by the Staudinger/*aza*-Wittig Reaction

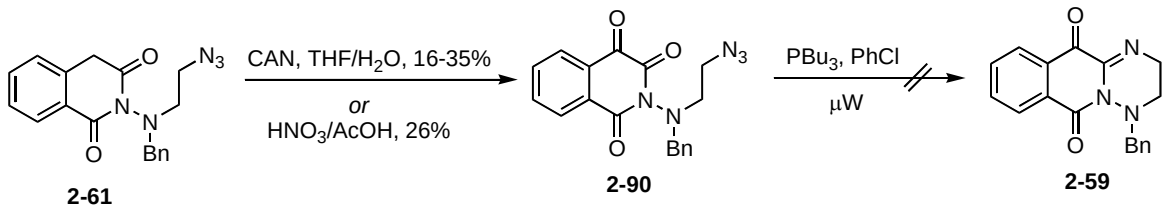
A second-generation endgame sequence was developed, which involved the oxidation of **2-61** to the trione **2-90**, as outlined in Scheme 2-24. In this case, performing the SAW reaction on the trione would lead directly to the DEF ring system. Oxidation reactions of similar homophthalimides to triones have been accomplished, as shown in Scheme 2-23, where the yields for the SeO_2 oxidation range in 12-62% (over 2 steps).[167] In addition to this method, oxidations using dye-sensitized photochemical conditions also afford homophthalimides; however, the reaction is often not selective.[168]



Scheme 2-23. Preparation of homophthalimides using benzylic oxidation

An alternative approach toward the oxidation of **2-61** involved the use of CAN in aqueous THF to afford the trione. According to qualitative analysis (TLC), the oxidation of the benzylic position was a clean reaction; however, the isolated yields of the desired compounds were near 30% at best when using either CAN or a mixture of HNO_3/AcOH (Scheme 2-24). When attempting to promote the SAW reaction using trione **2-90** under our established

conditions (Table 2-2), no desired triazine was detected by ^{1}H NMR analysis (even though the azide starting material was usually consumed according to TLC analysis of the reaction mixtures).

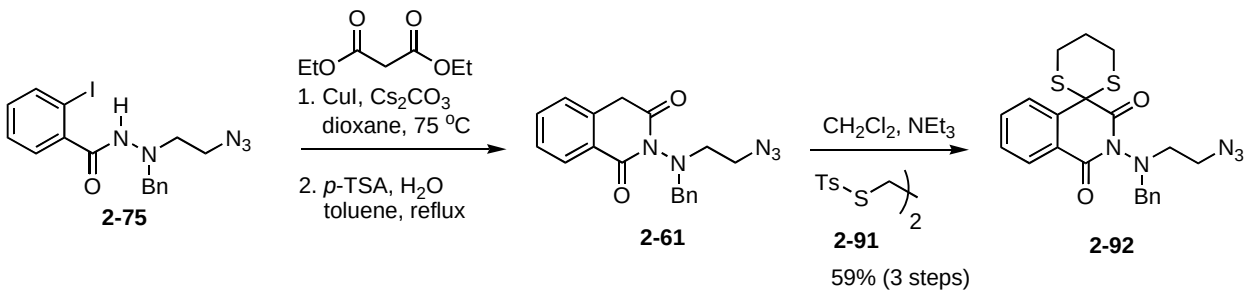


Scheme 2-24. Preparation of **2-59** using a 2-step oxidation/SAW sequence

The standard microwave irradiation conditions may have been too harsh for the potentially sensitive trione, although when screening lower temperatures for the SAW by using thermal heating in place of microwave irradiation no desired product was observed. These results indicated that using the homophthalimide at the necessary oxidation state in the SAW reaction allows for an efficient approach toward the construction of **2-59**; however, an alternative functional group would need to be used in place of the ketone.

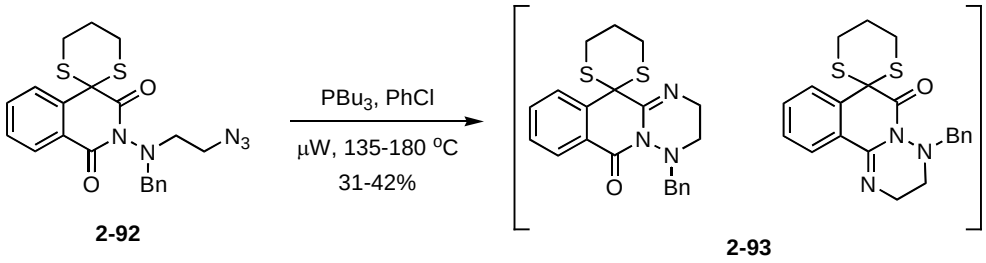
2.2.5 Oxidation to Thioketal Followed by the Staudinger/*aza*-Wittig Reaction

A third-generation approach was developed by installing a cyclic thioketal through treatment of **2-61** with **2-91**.[169] The thioketal approach would allow for incorporation of the necessary oxidation state at the benzylic position and presumably provide a more robust substrate to perform the SAW reaction.



Scheme 2-25. Preparation of thioketal **2-92**

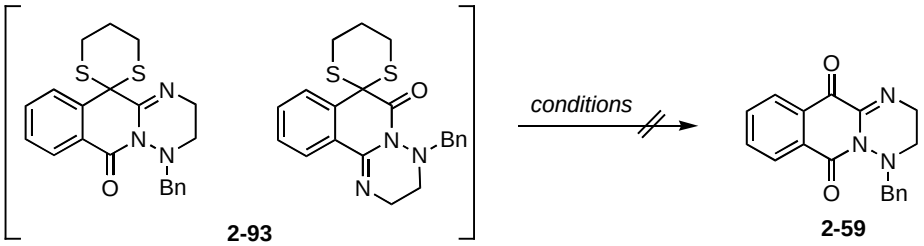
Thioketal incorporation occurred in high yields to provide **2-92** in 59% yield over 3 steps from **2-75**. When subjected to the SAW conditions, the azide was transformed into triazine **2-93** in low to moderate yields (Scheme 2-26). Inspection of the (600/150 MHz) $^{1}H/^{13}C$ NMR spectra of **2-93** indicated a mixture of compounds (inseparable by column chromatography) in a 1.7:1 ratio (determined from the integration of the AB methylene of the benzyl group). Based on the ^{13}C NMR, it appeared that the isolated material was comprised of a mixture of two regioisomers, which were putatively assigned as **2-93**. Through the use of high temperature ^{1}H NMR analysis it was not possible to conclusively determine the composition of the apparent mixture. Further chromatographic analysis must be done in order to confirm the presence of either conformational isomers or regioisomeric products.



Scheme 2-26. Putative products from the Staudinger/*aza*-Wittig reaction when using azide **2-92**

We felt that removing the thioketal might provide a less complex NMR spectrum, and therefore the products from the SAW reaction (when using azide **2-92**) were used in the deprotection reaction as isolated. In general, the thioketal removal was problematic since the conditions screened either did not react with the substrate or caused complete decomposition.

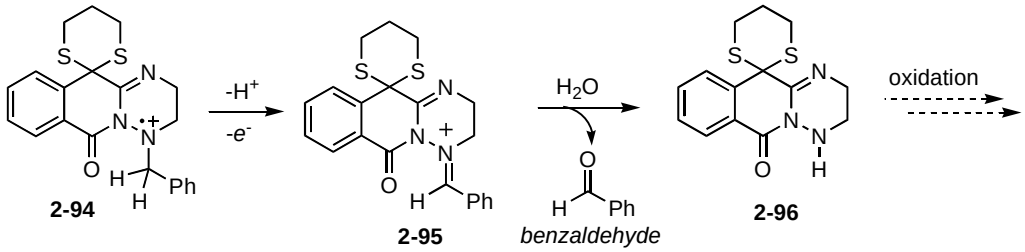
Table 2-3. Conditions to remove thioketal from SAW product **2-93**



entry	conditions
1	PIFA, CH_3CN/H_2O[170]
2	NBS, acetone/H_2O[171]
3	$CuCl_2$, CuO, acetone/H_2O[172]
4	I_2, DMSO[173]
5	PIFA, MeOH/H_2O
6	CAN, CH_3CN/H_2O[174]
7	PIFA, THF H_2O, AcOH
8	30% H_2O_2, MeOH
9	$Hg(OAc)_2$, CH_3CN/H_2O[175]
10	$AgNO_3$, NCS, CH_3CN/H_2O
11	Chloramine T, EtOH/H_2O[176]
12	$NaNO_2$, TFA/ H_2O[177]

Conditions screened for the desulfurization of **2-93** involved mercury salts, copper salts, hypervalent iodine, and silver nitrate/halosuccinimide mixtures, most of which were used in stoichiometric excess. The conditions outlined in Table 2-3 were applied to **2-93**, but resulted in the decomposition of starting material. It is important to note that many of the ^{1}H NMR spectra of the crude material isolated from the oxidative desulfurization contained a singlet (δ = 9.93) and doublet (δ = 7.80, J = 8.4 Hz) that are characteristic of benzaldehyde. This hypothesis was confirmed by addition of benzaldehyde to the ^{1}H NMR sample containing the crude reaction mixture for entry 12 (Table 2-3), resulting in an increased signal intensity for the singlet (δ = 9.93) and doublet (δ = 7.80, J = 8.4 Hz) in the ^{1}H NMR (600 MHz) of the crude reaction mixture and supporting the oxidative cleavage of the *N*-benzyl group.

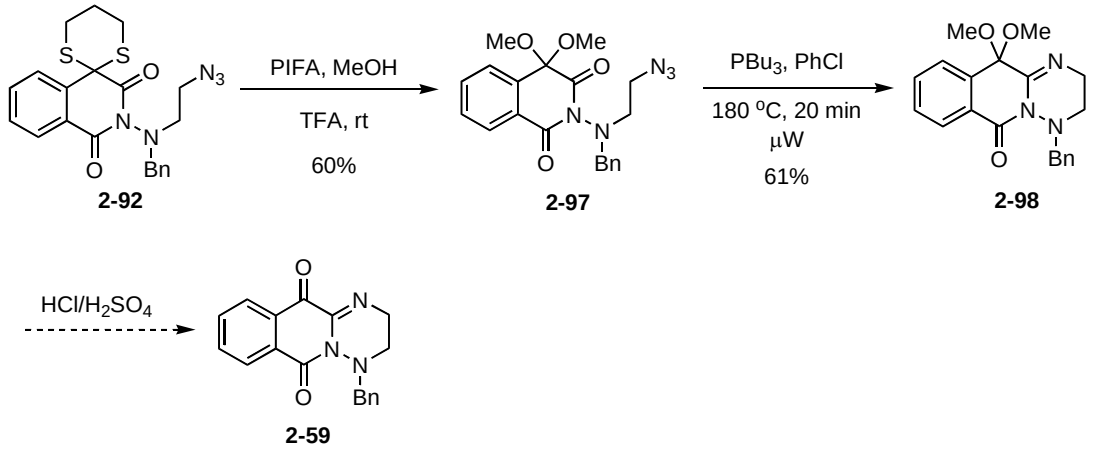
It is well precedented that the *p*-methoxybenzyl group can be removed from amines under oxidative conditions.[178] Although not as common, there are examples where tertiary *N*-benzyl groups are removed using CAN in aqueous THF[179] and aqueous acetonitrile solutions.[180] It may be possible that the *N*-benzyl group is being cleaved under the conditions intended to oxidize the thioketal through a pathway proposed in Scheme 2-27, where the *N*-benzyl amine **2-93** gets oxidized to give intermediate **2-94**. This compound can then undergo a second single electron oxidation to afford **2-95**, which, when hydrolyzed may explain the source of benzaldehyde in the crude reaction mixture. In all cases, it was not clear whether or not the sulfur atoms on **2-93** were being oxidized but not hydrolyzed, or not oxidized at all. It appeared that the conditions to remove the thioketal group on **2-93** must be orthogonal to the basic nitrogen atoms present. A window of reactivity could not be found to allow for the selective desulfurization of **2-93** without oxidative decomposition, and therefore this approach was discontinued.



Scheme 2-27. Potential oxidative pathway for benzaldehyde formation

2.2.6 Oxidation to Dimethoxyketal Followed by the Staudinger/*aza*-Wittig Reaction

In an effort to identify a protecting group that could be removed under conditions tolerant to the basic nitrogen atoms, the desulfurization event was performed *prior* to the SAW reaction. Gratifyingly, the transformation of **2-92** into the dimethoxyketal using PIFA in dry MeOH[170] was complete in less than 1 h, providing **2-97** in an unoptimized 60% yield (Scheme 2-28). This result was significant since it indicated that the methanolysis of the thioketal seemed to be substrate dependent. It also indicated that the *aza*-Wittig product **2-93** may have been oxidized but was not readily hydrolyzed due to sterics or electronic effects before oxidative decomposition. The dimethoxyketal was subjected to the SAW conditions, and the desired triazine **2-98** was isolated in 61% yield after recrystallization. This was the first time we were able to cleanly remove the thioketal protecting group as well as to characterize the product from the SAW reaction. The last step was to hydrolize the dimethoxyketal to the ketone, which turned out to be challenging.



Scheme 2-28. Desulfurization/SAW sequence to arrive at **2-59**

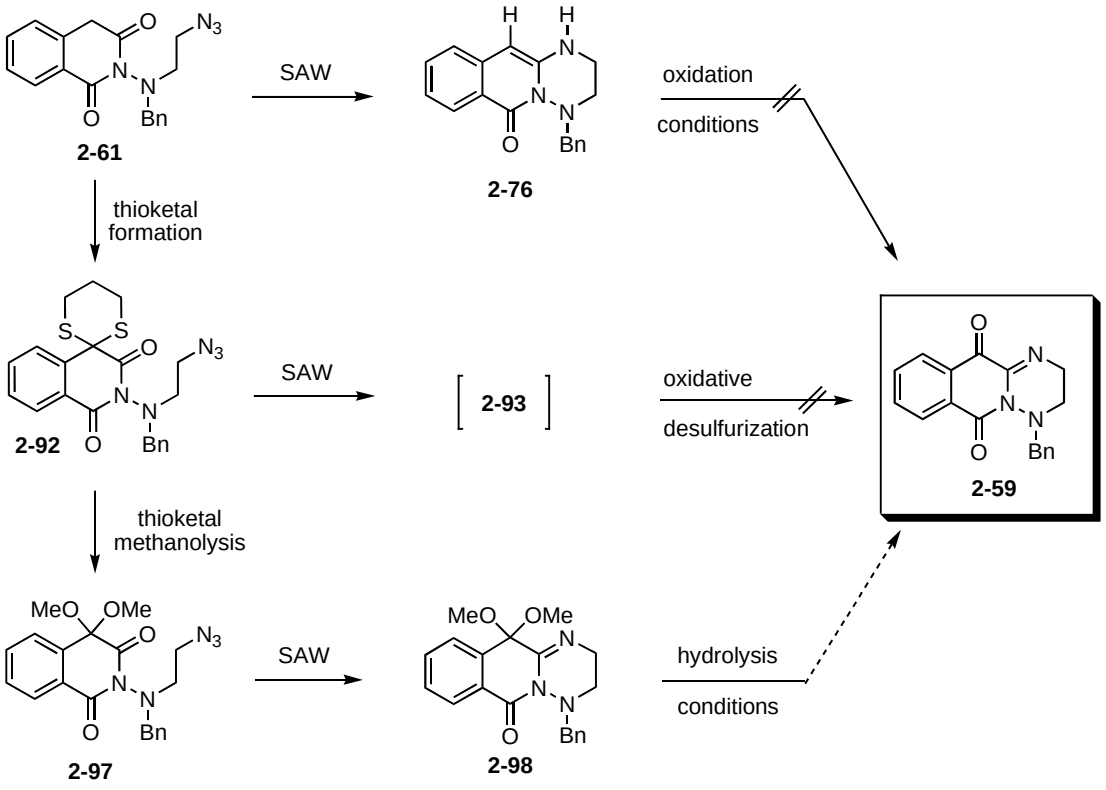
Qualitative reactions monitored by ^{1}H NMR showed that the conversion of **2-98** to **2-59** could be accomplished using HCl/H_2SO_4 to promote the hydrolysis, although this result has not been reproducible. It is important to note that the spectrum obtained from the hydrolysis of **2-98** was superimposable to that of the product isolated from the auto-oxidation product **2-59** obtained through the pathway described in Scheme 2-21. At this time, conditions to promote the hydrolysis of **2-98** to give a sample of pure **2-59** have not been identified. If the deprotection reaction is successful, this would demonstrate our first-generation sequence toward preparing a model DEF system of the natural product noelaquinone.

2.3 CONCLUSIONS

In summary, a method to prepare an advanced hydrazine intermediate has been developed. This intermediate can be readily transformed into the homophthalimide **2-61** (Scheme 2-17). The azide undergoes the SAW reaction to produce the enamine product **2-76** (Scheme 2-

29). It was observed that aerobic oxidation of the enamine produces the desired triazine product **2-59**, unfortunately, attempts to promote a controlled oxidation of **2-76** into **2-59** failed.

Subjecting the benzylic thioketal **2-92** to the SAW reaction produced a putative mixture of **2-93**, which, when treated to oxidative desulfurization conditions, led to a complete decomposition of the substrate. Removal of the thioketal *prior* to the SAW reaction to produce **2-97** occurred with ease, and the subsequent SAW reaction could be accomplished to prepare **2-98** in moderate yields. Although a qualitative result shows that the dimethoxyketal **2-98** can be hydrolyzed using harsh acidic conditions, a procedure needs to be developed to reproducibly facilitate this process. If this problem can be solved, we could demonstrate access to the core of the natural product noelaquinone.



Scheme 2-29. Summary of progress toward the preparation of **2-59**

3.0 PREPARATION OF α,β-CYCLOPROPYL-γ-AMINO ACIDS

3.1 INTRODUCTION

3.1.1 Peptide Mimetics: A Frontier in Therapeutic Agents

The amide bond is one of the most common covalent linkages found in proteins, many of which are responsible for critical biological functions. The dipeptide linkage is represented as **3-1** in Figure 3-1, where the two torsion angles in the peptide bonds are ϕ (C_α-N bond angle) and ψ (C_α-C bond) with respect to the amide bond plane, and the amide bond angle, ω, with is typically 180^o.[181,182] In the lab, amide bonds may be formed under mild conditions;[183,184] however, these bonds can only be hydrolyzed using strongly acidic or basic conditions.[178] Nature, on the other hand, employs a wide variety of enzymes (proteases) that are responsible for amide bond hydrolysis under physiological conditions. Due to this relative ease of degradation by nature, molecules containing amide bond linkages are not often practical pharmaceutical candidates.[182] Since nature's machinery is adept in the scission of the amide bond, chemists have studied its properties and developed bioisosteres to replace this ubiquitous functional group.

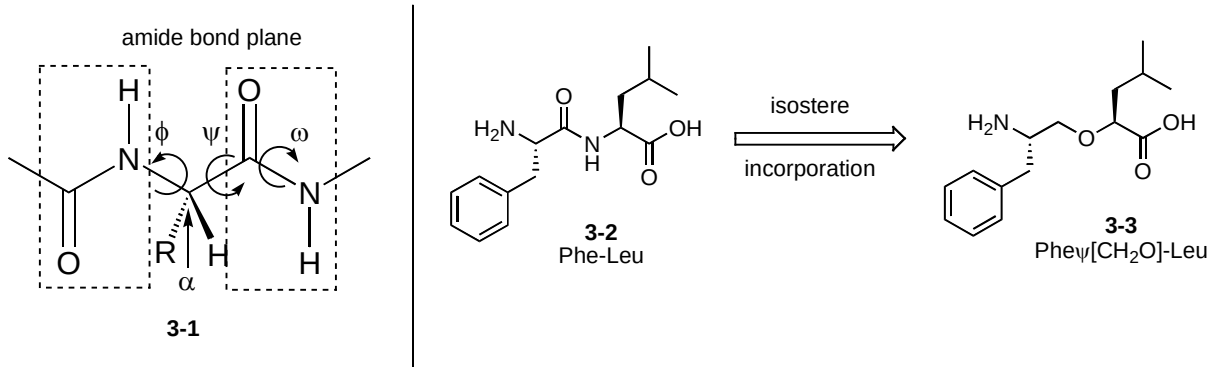


Figure 3-1. Dipeptide bond angles and peptide isosteres

Figure 3-1 shows an example of a parent dipeptide (Phe-Leu) **3-2** and a peptide mimic (Pheψ[CH_2O]-Leu) **3-3**, where the amide bond has been replaced by a methyleneoxy group.[182] Figure 3-2 shows a generic amide (outlined) and a variety peptide isosteres that mimic the amide functionality.[182] The analogs are often isoelectronic to the amide bond, but less susceptible to enzymatic hydrolysis. Peptide mimics continue to be developed to treat diseases that range from malaria[144,185] and AIDS[186] to renin inhibitors to treat hypertension[187] and kinase inhibitors to treat cancer.[188]

One common amide bond isomers is the aminomethylene group (ψ[CH_2N]). Methods for installing this group involve the reductive amination of an amine with an aldehyde. This approach has been used by Fairlie and co-workers[189] to prepare peptide mimics that inhibit the cysteine protease caspase-1. Cysteine proteases are responsible for a multitude of cellular functions. The ability to inhibit caspase-1 could treat diseases such as chronic inflammation[190] and malaria as well as triggering apoptosis.[191]

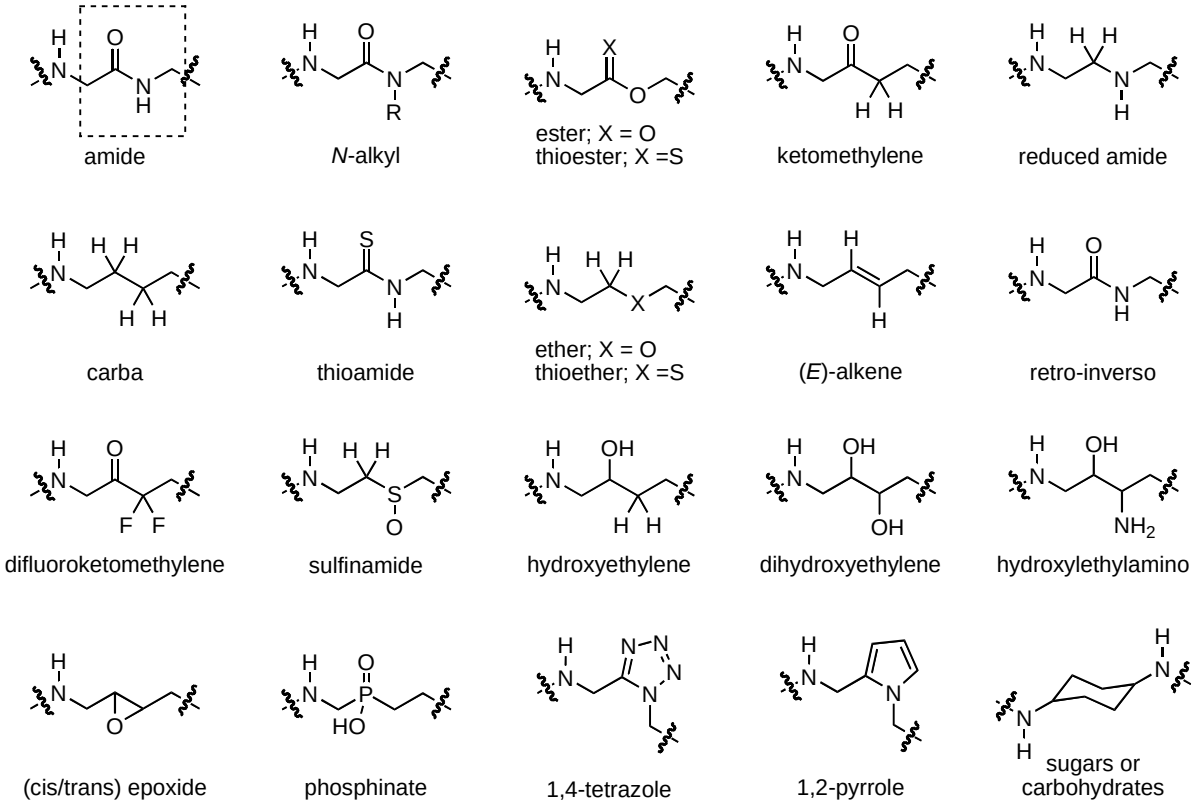
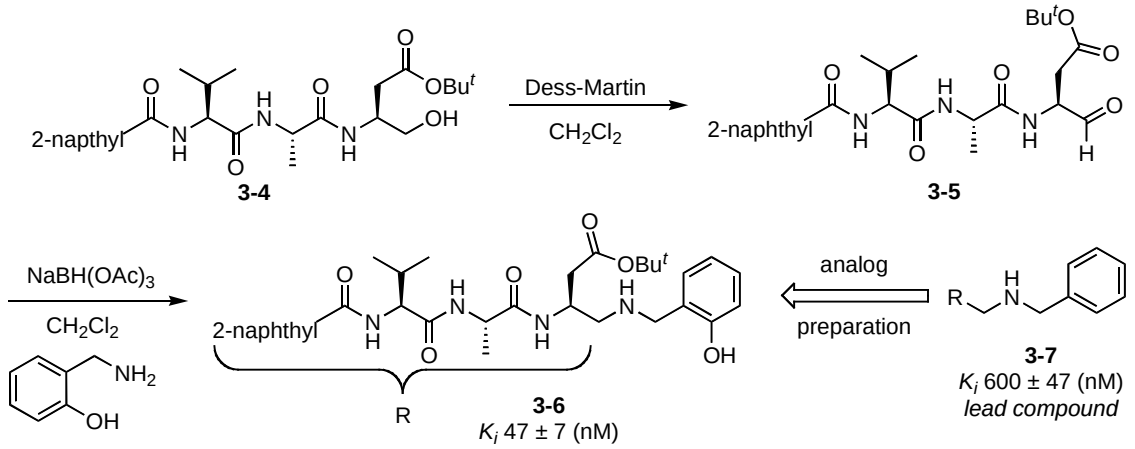


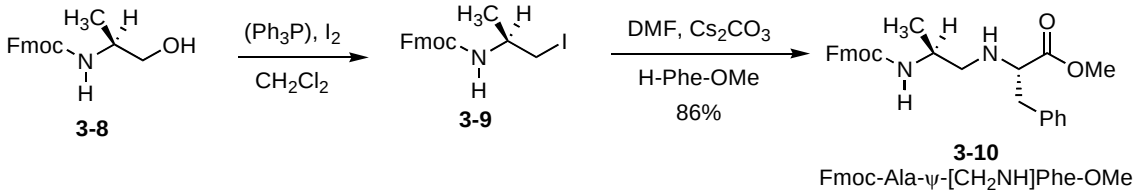
Figure 3-2. Peptide bioisosteres

The reductive amination methodology has been applied toward analogs of the lead peptide mimic ($\psi[CH_2N]$) **3-7** (Scheme 3-1).[189] Oxidation of the advanced intermediate **3-4** with the Dess-Martin reagent provides aldehyde **3-5**. This product was converted into analog **3-6** through a reductive amination protocol using $NaBH(OAc)_3$. The incorporation of the 2-hydroxybenzylamine onto the lead benzylamine analog increased the inhibition of caspase-1 by a factor of 12.



Scheme 3-1. Preparation of analogs for non-covalent caspase-1 inhibitors

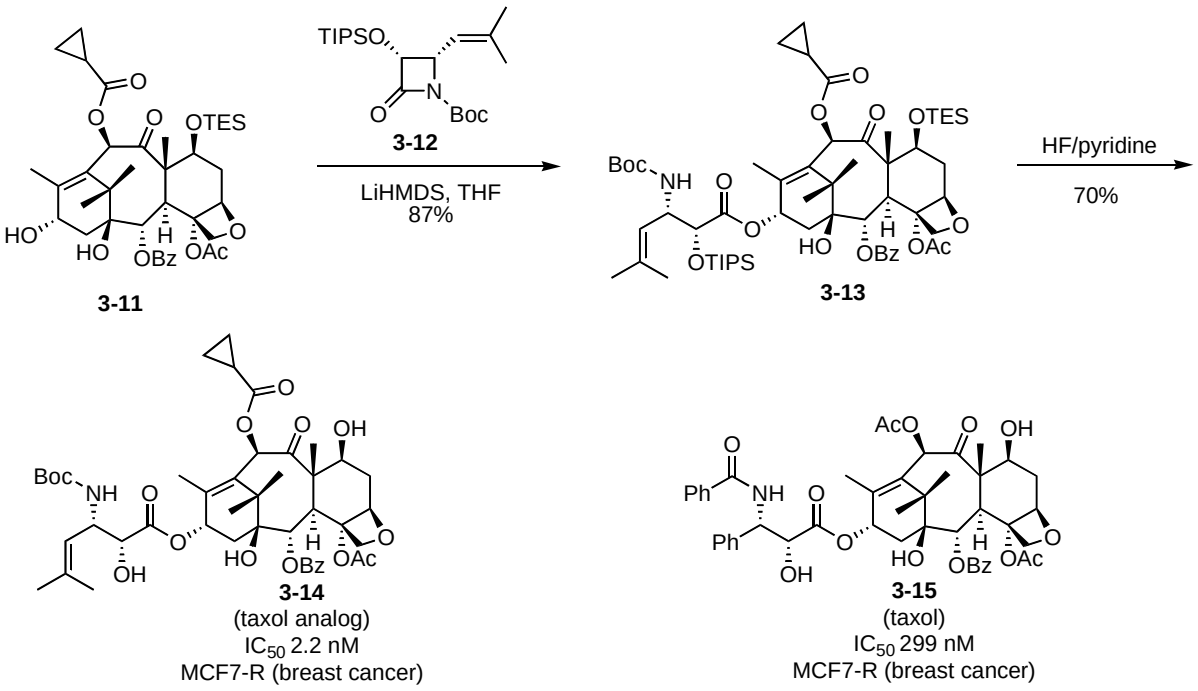
An alternative method for preparing (ψ[CH_2N]) amide bond isosteres involves the reaction of 1,2-aminoiodides **3-9** with protected amino acids to form dipeptides **3-10** (Scheme 3-2). In this case, Campiglia and Grieco[192] prepared 11 examples by using this methodology. The coupled products showed no racemization by analytical HPLC analysis.



Scheme 3-2. Preparation of aminomethylene peptide isosteres

Peptide isosteres have also been incorporated into the synthesis of natural product analogs.[193] The β-lactam **3-12** was prepared in high enantiopurity using a [2+2] reaction between an imine and an α-siloxy ester bearing a chiral auxiliary.[194,195] Scheme 3-3 shows the preparation of an analog to the antitumor agent taxol **3-15**. After the acylation of the secondary alcohol **3-11**

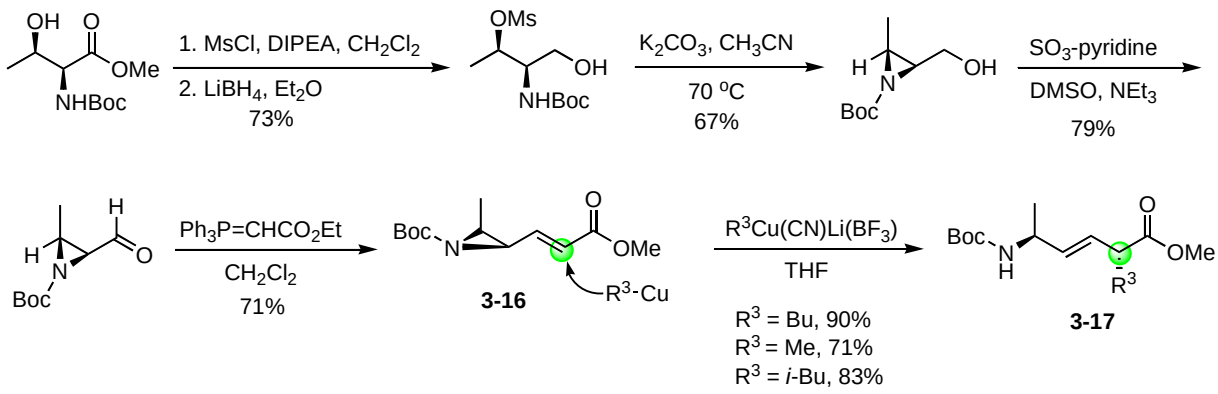
with the β-lactam **3-12** and global silyl deprotection of **3-13**, analog **3-14** was shown to be up to 100 times more potent than the parent natural product.[196]



Scheme 3-3. Preparation of taxol analogs using an enantiopure β-lactam

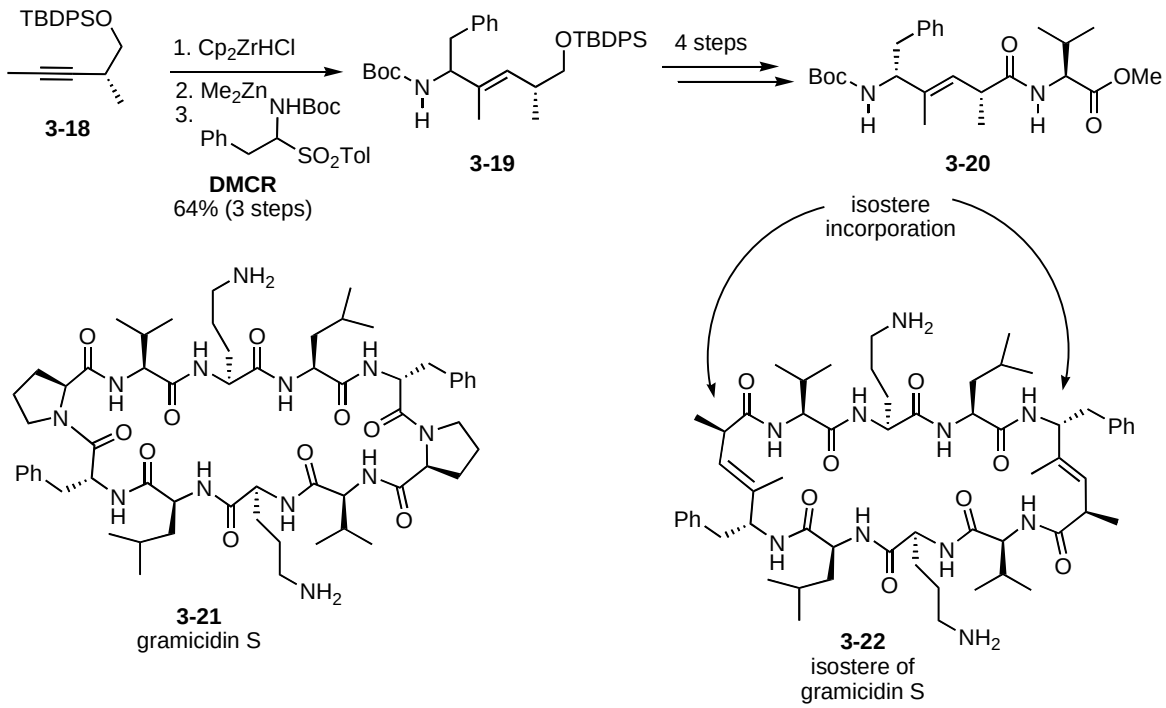
3.1.2 Peptide Mimetics in the Wipf Research Group

The Wipf group has made significant contributions to the field of peptidomimetics. Initial research involving the development of methods to prepare (*E*)-alkene dipeptide isosteres (ψ[RC=CH]) began with the S_N2'cuprate additions to vinyl aziridines **3-16**.[197] This methodology provided access to allylic amines of the type **3-17**, as shown in Scheme 3-4.



Scheme 3-4. Peptide isostere preparation using aziridines

Wipf's approach toward the preparation of (*E*)-alkene dipeptide isosteres has elegantly evolved through the use of a divergent multi-component reaction (DMCR).[198,199] To prepare the allylic amine **3-19**, alkyne **3-18** is hydrozirconated and the resulting vinyl zirconocene is then transmetalated to zinc. This vinyl zinc species undergoes an addition to the *in situ* generated imine to afford **3-19** in 64% over 3 steps. The intermediate is transformed into **3-20** over 4 steps. This fragment has been incorporated into analogs of the natural product gramicidin S (**3-21**). Gramicidin S is a cyclic decapeptide that exhibits a wide variety of biological activities, including antibiotic and antimicrobial properties.[200] The ψ-[(*E*)-C(CH_3)=CH] replacement for the D-Phe-Pro represented as **3-22** was found to uphold the secondary structure (β-sheet) of the parent gramicidin S. This was confirmed through the use of circular dichroism analysis. Earlier work by Wipf and Xiao[201] involved the preparation and characterization of gramicidin S analogs **3-23** and **3-24**, i.e *cyclo*(-Val-Orn-Leu-ψ[(*E*)-C(R)=CH]-^{D}Phe-Pro-)$_2$ where R = CH_3 and CF_3, respectively (Figure 3-3).



Scheme 3-5. Preparation of isosteres of gramicidin S

These gramicidin S analogs were prepared by using the methodology outlined in Scheme 3-5. The secondary structural features of the bis-CF_3 analog **3-24** closely resembled the natural product according to solution and solid-state analysis.

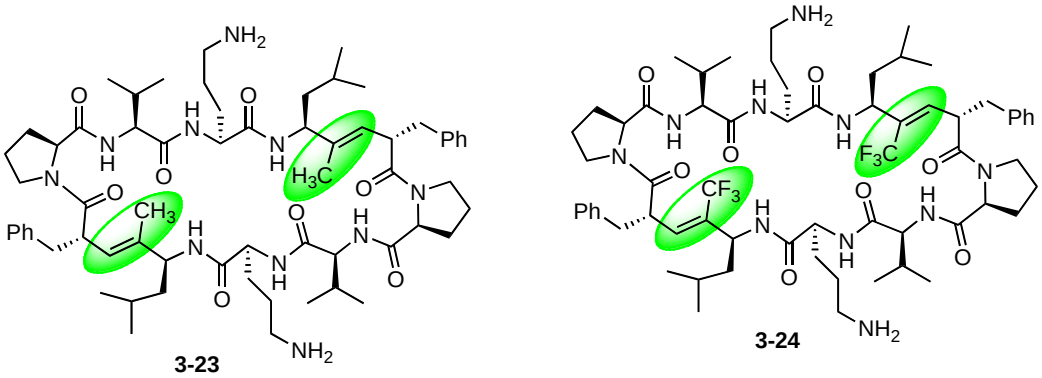
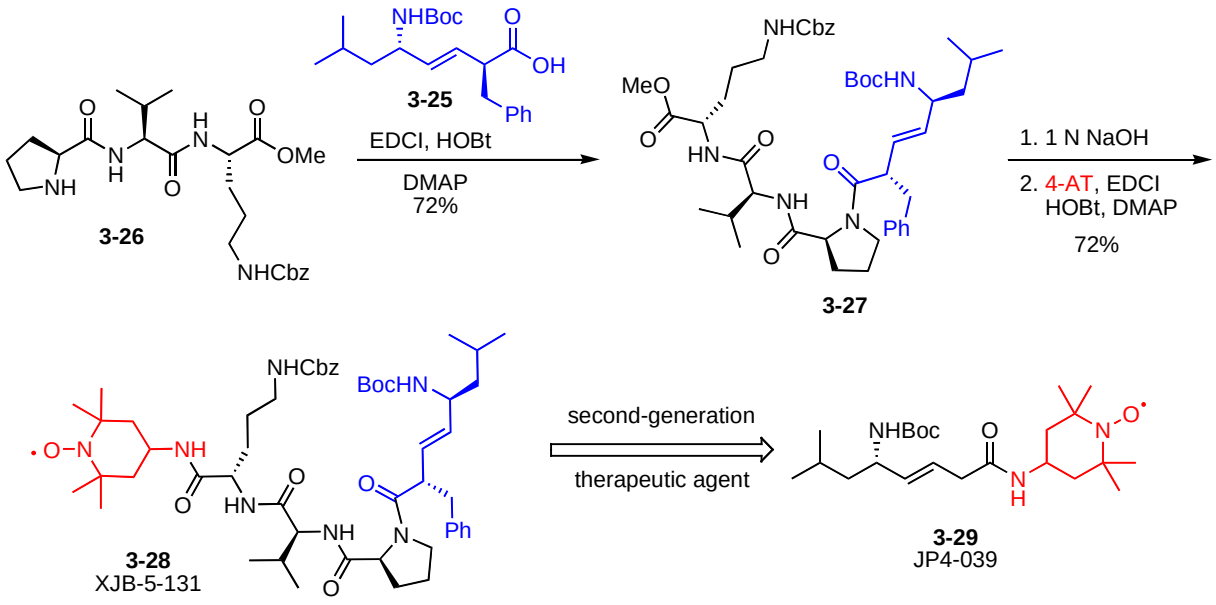


Figure 3-3. Gramicidin S analogs **3-23** and **3-24**

The ability for gramicidin S and its peptide isosteres to selectively target the mitochondria in the cell led to the development of truncated analogs of **3-21**. Two examples of gramicidin S analogs prepared in the Wipf research group are XJB-5-131 **3-28** and a lower molecular weight analog, JP4-039 **3-29**. These peptide mimics have the ability to protect cells from reactive oxygen species (ROS) that cause oxidative stress,[202] and are effective at treating hemorrhagic shock and radiation exposure; two properties that offer a wide array of therapeutic applications.[203] The analogs were prepared by coupling the peptide isostere **3-25** with peptide **3-26**. After saponification of the methyl ester, the 4-amino-TEMPO group (4-AT), which is believed to be critical for the biological activity, was coupled to prepare XJB-5-131 **3-28** in 72% yield. A similar approach has been used to prepare the XJB-5-131 analog JP4-039 **3-29**.[13] Additional examples of applications of peptide bond isosteres developed in the Wipf research group have been a topic of a recent review.[204]



Scheme 3-6. Gramicidin S peptide mimics with therapeutic properties

3.1.3 First Generation Preparation of α,β-Cyclopropyl-γ-amino Acids

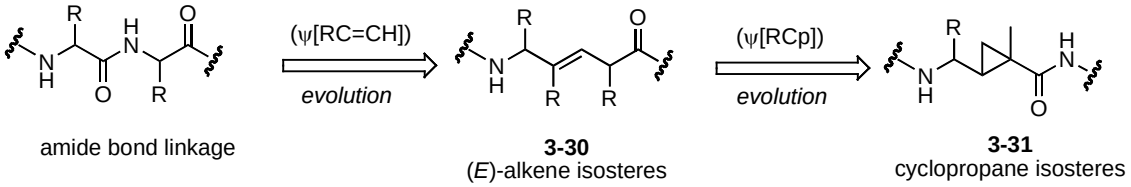
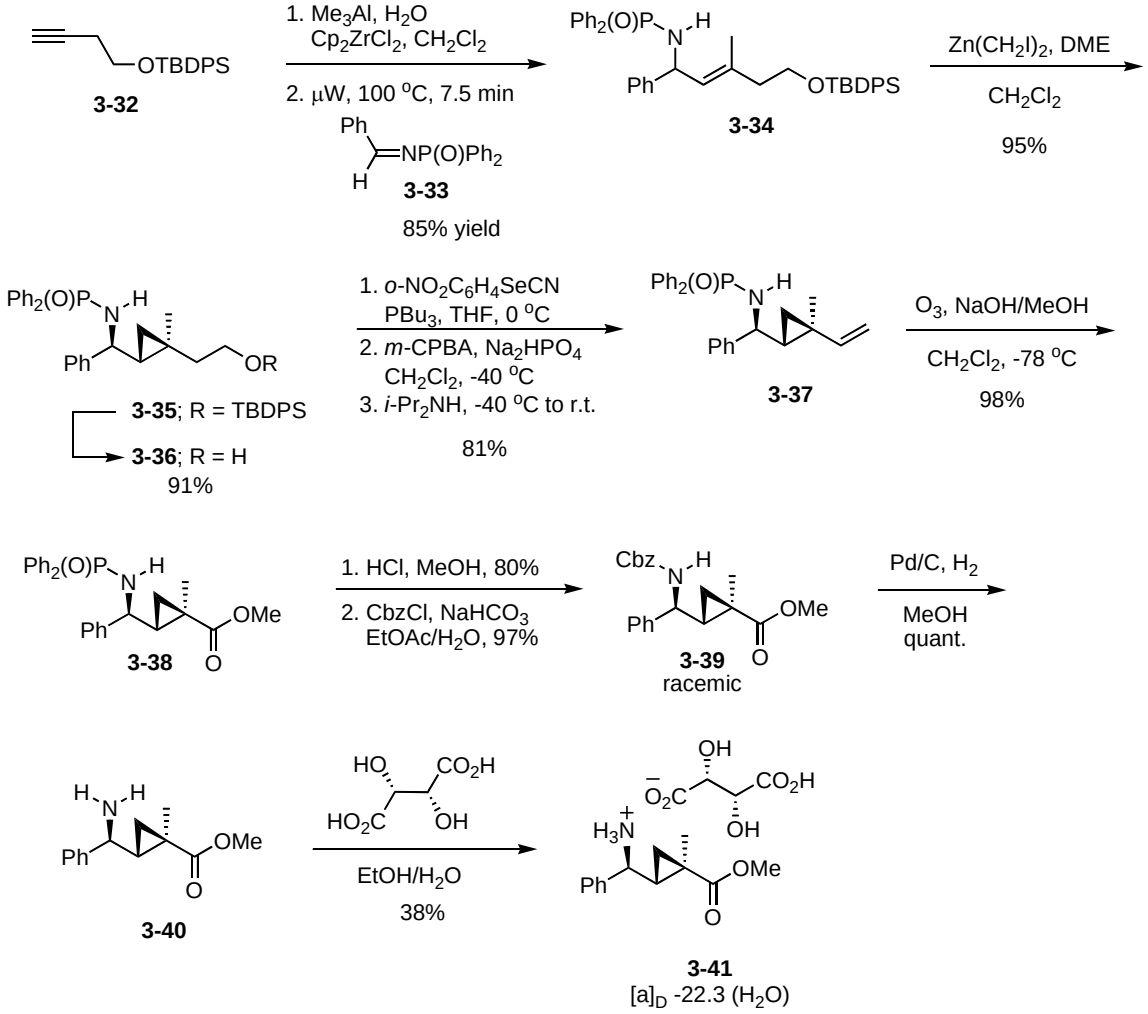


Figure 3-4. Evolution of dipeptide isosteres in the Wipf research group

As an extension of the DMCR methodology, the concept of cyclopropane dipeptide isosteres (ψ[RCp], **3-31**, shown in Figure 3-4) was developed. Cyclopropane analogs are proposed to be less susceptible to oxidation than the (*E*)-alkene isosteres **3-30**.[205] In 2005, Wipf[206] and Stephenson[207] demonstrated the synthesis of α,β-cyclopropyl-γ-amino acids derived from allylic amines.

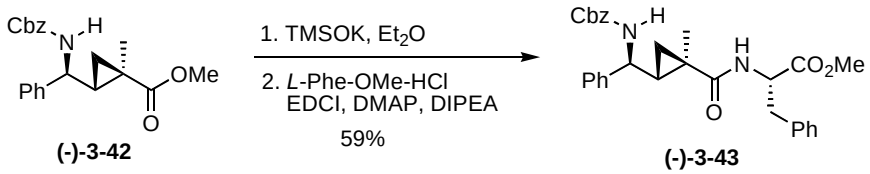
A water-accelerated carboalumination reaction[208] with alkyne **3-32** was followed by transmetalation to form the vinyl zirconocene and subsequent addition to imine **3-33** to afford **3-34** in 85% yield (Scheme 3-7). The allylic amine was treated under the Charette-modified Simmons-Smith cyclopropanation[209,210] conditions (which uses DME to stabilize the zinc carbenoid species) to afford **3-35** in 95% yield. The removal of the TBDPS ether in 91% liberated the free alcohol **3-36**, which was then eliminated to the olefin through a 3-step sequence that proceeded in 81% yield to form **3-37** *via* a modified Grieco protocol.[211] After ozonolysis of the olefin to the methyl ester **3-38** and a 2-step protecting group switch to the *N*-Cbz group, the racemic cyclopropane core of **3-39** was isolated. This methodology has been applied in the Wipf research group toward the preparation of a library of compounds containing cyclopropyl peptide mimics.[212]



Scheme 3-7. First generation preparation of the racemic cyclopropane core **3-39**

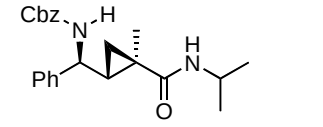
To obtain enantiopure material, a tartrate resolution was performed (using *L*-tartaric acid) with amine **3-40** to afford **3-41** in 38% yield (Scheme 3-7). The resolved material was then protected as benzyl carbamate **3-42**. After saponification and peptide coupling with *L*-Phe-OMe-HCl, the dipeptide **3-43** was isolated in 59% yield (Scheme 3-8). The crystal structure of **3-43** indicates that the peptide mimic adopts a β-sheet conformation. This secondary structural feature is often associated with promoting protein-protein interactions, and thus the potential for

biological activity. These results inspired us to synthesize a library of molecules that contain the chiral scaffold of **3-42**.

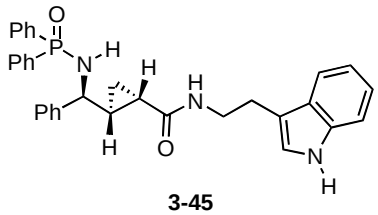


Scheme 3-8. Preparation of chiral dipeptide **3-43**

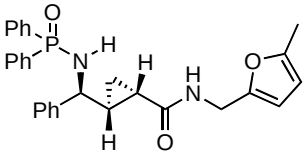
Molecules containing the phenylglycine derived α,β-cyclopropyl-γ-amino acid core **3-44** (shown in Figure 3-5) are known pregnane X receptor (PXR) agonists.[213] Some of these derivatives are active as inhibitors of cytochrome P450 (**3-45** and **3-46**), and inhibitors of the influenza NS1 protein function (H1N1 strain) (**3-47**).



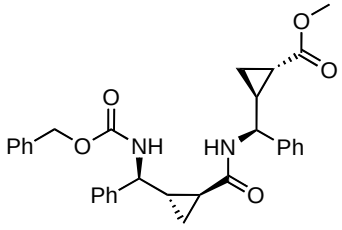
3-44
PXR agonist
(racemic)



3-45
UPCMLD04ASTW002131
CYP2C19 inhibition; AID 899
Activity concentration - 1.26 μM



3-46
UPCMLD04ASTW002128
CYP3A4 inhibition; AID 884
Activity concentration - 5.01 μM



3-47
UPCMLD00WCRS-5-231
Influenza NS1 protein function; AID 2326
Activity concentration - 10 μM

Figure 3-5. Phenylglycine derived α,β-cyclopropyl-γ-amino acids

Additional examples of molecules that contain the general scaffold of **3-48** (Figure 3-6) with biological activities are published in the NIH database, PubChem.[214] The goal for this research project was to diversify the pool of α,β-cyclopropyl-γ-amino acid derivatives available to biological screening. The R groups shown in **3-49** represent points of diversity for this scaffold. In our second-generation approach, the R^1 and R^3 groups represent the most versatile points of diversification. The R^2 group shown in **3-49** is inherent to the scaffold of the peptide mimic.

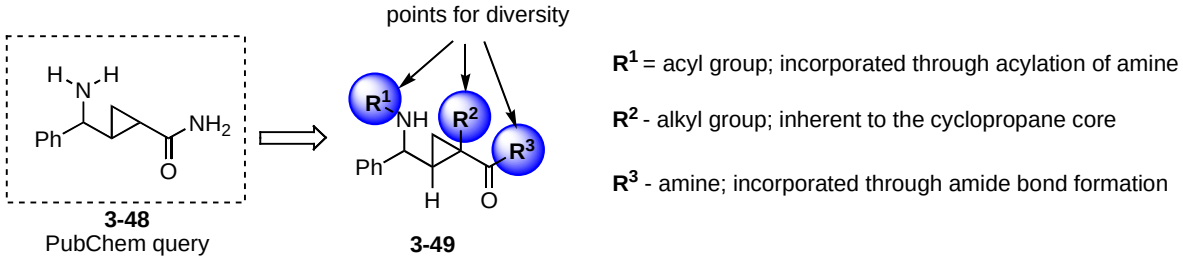


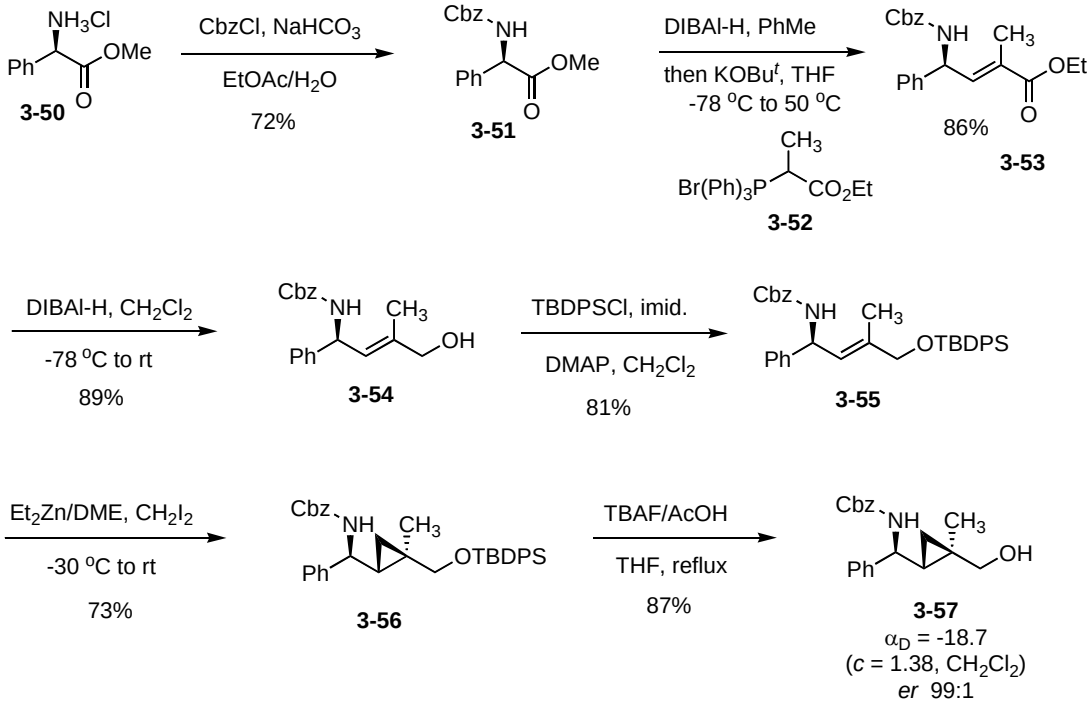
Figure 3-6. Phenylglycine α,β-cyclopropyl-γ-amino acid derivatives listed in the NIH database, PubChem

3.2 RESULTS AND DISCUSSION

3.2.1 Second Generation Preparation of α,β-Cyclopropyl-γ-amino Acids

A second-generation approach to the α,β-cyclopropyl-γ-amino acid core **3-57** (originally proposed by Wipf and Stephenson) was executed. This route to access the cyclopropyl amino acid core utilizes a Wittig olefination to access the chiral allylic amine in place of the

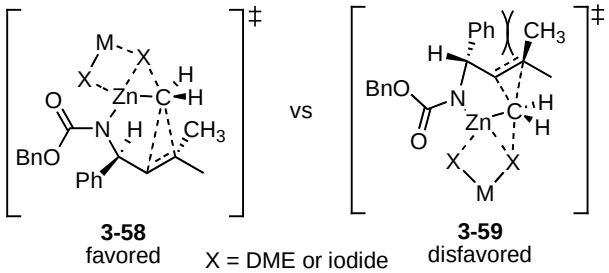
hydrozirconation/transmetalation and subsequent imine addition methodology (as shown in Scheme 3-9). The second-generation approach to the core of the chiral α,β-cyclopropyl-γ-amino acid derivatives began with the Cbz protection of *(R)*-phenylglycine methyl ester hydrochloride **3-50** followed by a 2-step Wittig-type olefination[215] involving the use of phosphonium salt **3-52** to afford the unsaturated ester **3-53** in 86% yield over 2 steps. Subsequent DIBAl-H reduction of the ester was accomplished in 89% yield, and the resulting alcohol **3-54** was protected as its TBDPS ether in 81% to afford **3-55** (Scheme 3-9).



Scheme 3-9. Preparation of chiral cyclopropane core

The key diastereoselective cyclopropanation step was executed using olefin **3-55** and employing the Charette-modified Simmons-Smith cyclopropanation[209,210] conditions provided **3-56** in 73% yield. The proposed origin of selectivity is shown in Figure 3-10. The transition state

of **3-58** is preferred due to the minimization of $A^{1,3}$ strain, as opposed to transition state of **3-59**, which involves a severe phenyl/methyl interaction. After treatment of the silyl ether with TBAF/AcOH in THF at reflux, alcohol **3-57** was isolated in 87% yield. This alcohol was used as the chiral building block for our library.



Scheme 3-10. Directed cyclopropanation of allylic amine to prepare cyclopropane **3-56**

A racemic sample of cyclopropane **3-57** was prepared according to the synthetic sequence outlined in Scheme 3-9.[4] The enantiopurity of **3-57** was determined by analytical HPLC analysis by using a Chiracel-OD column. The chromatogram showed one single, resolved peak indicating that the *er* was greater than 99:1.[5]

3.2.2 Preparation of Library Compounds

With access to gram quantities of alcohol **3-57**, reaction conditions to promote amide bond formation (to install the R^3 group) were investigated (Table 3-1). Oxidation of the alcohol

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[4] The ^1H and ^{13}C NMR data obtained for the racemic intermediates matched the data obtained from the respective chiral intermediates.

[5] For analytical HPLC conditions, see experimental section.

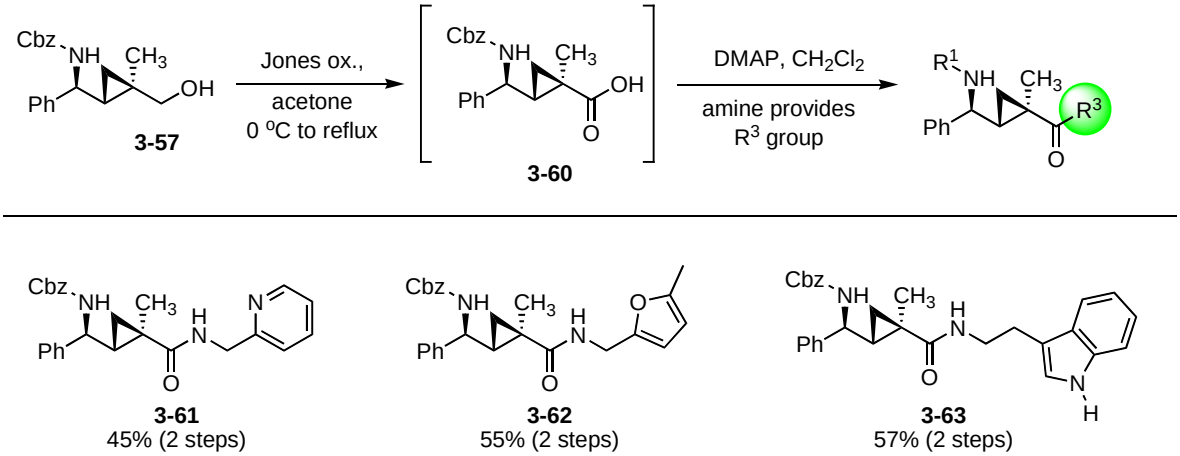
to the α,α-disubstituted carboxylic acid was accomplished using the Jones oxidation. When allowed to react at room temperature, the reaction took over 24 h to reach completion. To accelerate the reaction, the mixture was warmed from the initial temperature of 0 ^{o}C to reflux. The Jones oxidation reaction was carefully monitored by TLC analysis, and the reaction was quenched once **3-57** was consumed. In all cases the carboxylic acid **3-60** was used without purification in the following amine coupling.

To promote the amide bond formation, we initially screened modified coupling conditions employing the carbodiimide EDCI;[198] however, the yields for the coupling of tryptamine (to prepare **3-63**) were ~20% when performing the reaction on ~500 mg scale. When using PyBroP[216] to activate the carboxylic acid to couple the tryptamine, the yield was 57% (2 steps, entry 3). The coupling between 2-aminomethyl pyridine and carboxylic acid **3-60** to yield **3-61** was accomplished in slightly lower yields (45%, 2 steps, entry 1) than that of tryptamine when using PyBroP. When using T3P[217] to activate the carboxylic acid, the coupling reaction between **3-60** and 5-methylfurfurylamine to produce **3-62** was accomplished in 55% (2 steps, entry 2). Overall, the use of either PyBroP or T3P produced the desired amides in good yields. The advantage of using T3P was demonstrated in the ease of purification over removing the byproducts accompanied with the use of PyBroP (Table 3-1).

With the R^3 groups installed, the next step was to remove the Cbz group and acylate the resulting free amine. We initially envisioned performing this task in a one-pot process by using a palladium-catalyzed hydrogenolysis in the presence of an anhydride. However, there were two critical factors that caused this one-pot process to fail. The first major pitfall was the limited commercial availability of the requisite heterocyclic anhydrides, in addition to the low reactivity profile for their formation.[218] The second major problem we experienced was in the

hydrogenolysis reaction since the use of an anhydride-compatible solvent such as EtOAc in place of MeOH led to limited reactivity and decomposition of the reaction mixture, rather than an efficient Cbz removal. Additional conditions screened to remove the Cbz group included the use of either HBr in AcOH[88] or BBr_3 in dichloromethane.[219] Unfortunately, both of these methods worked with only modest results.

Table 3-1. Preparation of Cbz-protected cyclopropane cores



entry	coupling conditions[a]	product	yield[b]
1	DIPEA, PyBroP, 2-aminomethyl pyridine	**3-61**	45%
2	NEt_3, T3P, 5-methylfurfurylamine	**3-62**	55%
3	DIPEA, PyBroP, tryptamine	**3-63**	57%

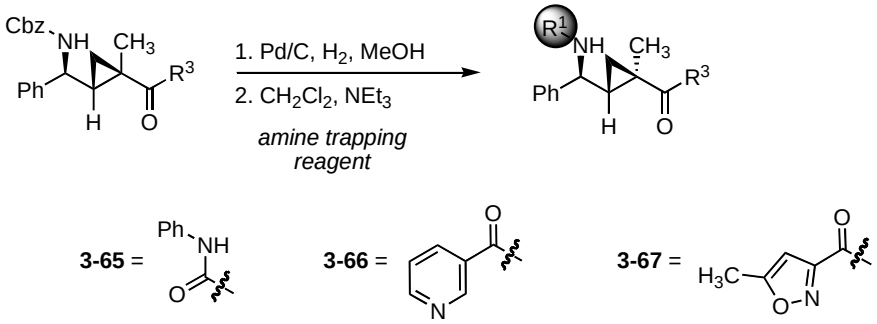
[a] See experimental section for reagent stoichiometry; [b]Yields determined over 2 steps.

We concluded that methanol was the optimal solvent for the Pd/C catalyzed hydrogenolysis of the Cbz group. Once complete, the reaction mixture was quenched with Celite, filtered and the free amine was dried on high vacuum to remove any residual methanol. The

acylation of the amine was accomplished by using a method published by Wipf and co-workers.[198]

The three cyclopropane scaffolds (**3-61**, **3-62**, and **3-63**) were transformed into a series of α,β-cyclopropyl-γ-amino acid derivatives shown in Table 3-2. In general, the products from the Cbz hydrogenolysis and subsequent acylation reactions were isolated in good yields (75-93%) over the 2 steps. When substituting BBr_3 in dichloromethane to deprotect the Cbz group in place of a hydrogenolysis, the desired compound can be isolated in a slightly lower yield (47%, 2 steps), underlining the superiority of the hydrogenolysis protocol.

Table 3-2. Synthesis of phenylglycine derived α,β-cyclopropyl-γ-amino acid derivatives



entry	starting material	R^1 group	product, yield (2 steps)
1	**3-63**	**3-64**	**3-68**, 90%
2	**3-63**	**3-65**	**3-69**, 89%
3	**3-63**	**3-66**	**3-70**, 75%
4	**3-63**	**3-67**	**3-71**, 77%
5	**3-61**	**3-65**	**3-72**, 85%
6	**3-61**	**3-66**	**3-73**, 47%[a]
7	**3-61**	**3-67**	**3-74**, 81%

[a]Conditions used: 1. BBr_3, CH_2Cl_2; 2. CH_2Cl_2, DIPEA, DMAP, **3-66**

3.3 CONCLUSIONS

We have prepared a series of *D*-phenylglycine derived α,β-cyclopropyl-γ-amino acid derivatives in high diastereoselectivity and enantiopurity. A 6-step sequence provided the cyclopropane scaffold **3-57** from commercially available material. We demonstrated that the chiral alcohol core can be oxidized to the requisite carboxylic acid, activated, and coupled with a primary amine. Subsequent Cbz removal in these advanced intermediates *via* hydrogenolysis, followed by acylation of the amine using acid chlorides, anhydrides and isocyanates, afforded a small library of α,β-cyclopropyl-γ-amino acid derivatives in good yields.

4.0 EXPERIMENTAL

4.1 GENERAL

All moisture-sensitive reactions were performed under an atmosphere of dry N_2 unless otherwise noted. All glassware was dried in an oven at >140 ^oC or flame-dried under an atmosphere of dry N_2 unless otherwise noted. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were dried by distillation over sodium/benzophenone under an argon atmosphere. Dry CH_2Cl_2 and toluene were purified by filtration through an activated alumina column. Unless otherwise stated, solvents and reagents were used as purchased without further purification. Benzyl alcohol was distilled prior to use. Collidine hydrochloride (coll-HCl) was recrystallized from absolute ethanol. Manganese and zinc metals were activated through washing with 1 M HCl, followed by rinsing with acetone and drying under vacuum. Titanocene dichloride was recrystallized from chloroform before use.

Analytical thin-layer chromatography (TLC) was preformed on pre-coated silica gel 60 F_{254} plates (250 μm layer thickness). Visualization was accomplished by using either a 254 nm UV lamp or by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\bullet 4\ H_2O$ and 0.2 g of

$Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4) or a potassium permanganate solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution).

NMR spectra were recorded at room temperature in $CDCl_3$ at 300 MHz/75 MHz ($^1H/^{13}C$ NMR) using a BRUKER AVANCE 300 MHz spectrometer unless stated otherwise. Chemical shifts (δ) are reported in parts per million and referenced from the residual solvent peak or tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity, integration and coupling constant(s). IR spectra were recorded on either a Nicolet AVATAR 360 FT-IR E.S.P. spectrometer (KBr or neat) or a Smiths Detection IdentifyIR FT-IR spectrometer (ATR). Melting points were uncorrected and determined using a Laboratory Devices Mel-Temp II.

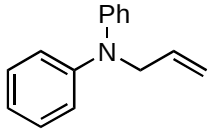
High-resolution mass spectrometry (HRMS) data (ESI/APCI technique) were recorded using a Waters Q-Tof ultima API-US instrument. HRMS data (EI technique) were recorded using a Micromass Autospec instrument. Mass spectrometry data were also recorded using an Applied Biosystems MDS SCIEX API 2000 LC/MS/MS system. Optical rotations were recorded on a Perkin-Elmer polarimeter (model 241).

Titanocene-catalyzed radical cyclization reactions were performed under rigorous exclusion of oxygen under a positive pressure of dry Ar. Tetrahydrofuran, in addition to being distilled, was deoxygenated (freeze-pump-thaw) three times and then stored under a positive pressure of dry argon. Sonication was accomplished with the Sonics Vibracell device (model VCX 130) equipped with a 2 mm microtip.

All organic azides and azide waste products should be considered highly toxic as well as potentially explosive and must be handled and stored with care. Avoid using halogenated solvents when performing reactions involving sodium azide, in addition to using halogenated solvents in reaction workup. Avoid quenching/manipulating/treating sodium azide reactions with

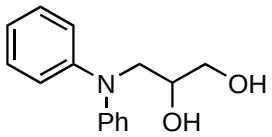
acid, as generation of trace amounts of hydrazoic acid (HN_3) may result in an explosion. In general, a safety shield must be used when conducting reactions involving either sodium azide or organic azide derivatives.

4.2 CHAPTER 1 EXPERIMENTAL



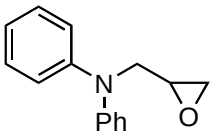
1-69

***N*-Allyl-*N*-phenylaniline (1-69).**[220,221] **General Protocol A.** According to a modified literature procedure, a solution of 5.07 g (29.9 mmol) of diphenylamine in 45 mL of acetonitrile was treated with 8.28 g (59.9 mmol) of K_2CO_3, 5.2 mL (60 mmol) of allyl bromide, and 533 mg (1.49 mmol) of TBAI. This reaction mixture was heated at reflux until the starting material was consumed according to TLC (hexanes). The solution was cooled to rt, diluted with 100 mL of H_2O and extracted with 3 x 15 mL of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexanes) to afford 6.24 g (29.8 mmol, quant.) of **1-69** as a golden oil: ^{1}H NMR δ 7.30-7.22 (m, 4 H), 7.06-6.91 (m, 6 H), 5.93 (ddt, 1 H, J = 14.7, J = 9.9 Hz, J = 4.5 Hz), 5.26 (d, 1 H, J = 17.4 Hz) 5.15 (d, 1 H, J = 10.2 Hz), 4.40-4.34 (m, 2 H); ^{13}C NMR δ 148.0, 134.4, 129.4, 121.4, 120.9, 116.6, 54.9.



1-70

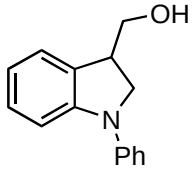
3-(Diphenylamino)propane-1,2-diol (1-70). General Protocol B. To a solution of 4.86 g (23.2 mmol) of *N*-allyl-*N*-phenylaniline (**1-69**) in 75 mL of a THF/acetone/pH 7.0 phosphate buffer solution (1:1:1) was added 3.53 g (30.1 mmol) of NMO and 700 μL of OsO_4 (1 mol%, 0.33 M in toluene). The reaction mixture was stirred overnight, quenched with a sodium bisulfite solution and extracted with 3 x 20 mL of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a white solid, which was recrystallized from hexane/EtOAc to afford 4.85 g (19.9 mmol, 86%) of **1-70** as a white solid: mp 96-98 ^oC; IR (KBr) 3297, 2927, 1589, 1497, 1323, 1070 cm^{-1}; ^1H NMR δ 7.28-7.22 (m, 4 H), 7.04-6.94 (m, 6 H), 4.05-3.95 (m, 1 H), 3.85-3.79 (m, 2 H), 3.73 (dd, 1 H, *J* = 10.6 Hz, *J* = 2.1 Hz), 3.55 (dd, 1 H, *J* = 11.1 Hz, *J* = 5.4 Hz), 2.62 (bs, 1 H), 2.21 (bs, 1 H); ^{13}C NMR δ 148.5, 129.6, 122.2, 121.6, 69.7, 64.4, 55.1; MS (EI) *m/z* 243 ($M^{+\bullet}$, 18), 182 (100), 167 (13), 91 (87); HRMS (EI) *m/z* calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1260.



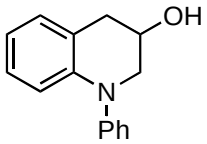
1-71

***N*-(Oxiran-2-ylmethyl)-*N*-phenylaniline (1-71).**[222] According to a modified literature procedure, a solution of 2.39 g (9.82 mmol) of **1-70** in 32 mL of THF was cooled to 0 ^oC and treated with 3.84 g (11.7 mmol) of *p*-Ts_2O followed by 545 mg (21.6 mmol) of NaH (95%). The

reaction mixture was stirred at 0 ^{o}C for 3 h, and an additional 1.17 g (29.4 mmol) of NaH (60% dispersion in mineral oil) was added. The solution was allowed to stir overnight at rt, cooled to 0 ^{o}C, and quenched with H_2O. The mixture was extracted with 3 x 20 mL of EtOAc. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 6:1) to afford 1.26 g (5.59 mmol, 57%) of **1-71** as a colorless oil: IR (neat) 3057, 2995, 2919, 1588, 1493, 1362, 1255, 748 cm^{-1}; ^{1}H NMR δ 7.25-7.19 (m, 4 H), 7.05-7.00 (m, 4 H), 6.93 (tt, 2 H, *J* = 7.2 Hz, *J* = 0.1 Hz), 3.91 (dd, 1 H, *J* = 15.9 Hz, *J* = 3.6 Hz), 3.79 (dd, 1 H, *J* = 15.6 Hz, *J* = 4.8 Hz), 3.19-3.14 (m, 1 H), 2.70 (app t, 1 H, *J* = 4.8 Hz), 2.50 (dd, 1 H, *J* = 5.1 Hz, *J* = 2.7 Hz); ^{13}C NMR δ 148.0, 129.4, 121.7, 121.1, 53.9, 50.4, 45.9; MS (EI) *m/z* 225 ($M^{+\bullet}$, 36), 182 (100), 167 (15), 104 (23); HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO$ 225.1153, found 225.1145.



1-72



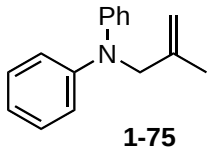
1-74

(1-Phenylindolin-3-yl)methanol (1-72) and 1-phenyl-1,2,3,4-tetrahydroquinolin-3-ol (1-74). General Protocol C. To a 3-neck flask was added 273 mg (1.21 mmol) of **1-71**, 9.0 mg (0.036 mmol) of Cp_2TiCl_2, 286 mg (1.81 mmol) of collidine hydrochloride, and 99 mg (1.8 mmol) of Mn. The vessel was fitted with a reflux condenser, and purged 3 times with Ar. After addition of 12.1 mL of THF (0.1 M), the reaction mixture was heated at reflux for 45 min. The color gradually changed from light orange to deep violet/blue. The mixture was cooled to rt, quenched with satd. NH_4Cl and extracted with 3 x 10 mL of Et_2O. The combined organic layers

were dried ($MgSO_4$), and concentrated *in vacuo.* The residue was purified by chromatography on neutral alumina (hexane:EtOAc; 3:1 to 1:3) to afford 237 mg (1.05 mmol, 87%) of **1-72** and **1-74** as a 3.8:1 mixture based on the integration of ^{1}H NMR peaks at 4.10 ppm for **1-72** vs. 3.15 ppm for **1-74**.

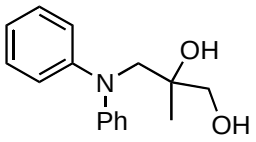
1-72: ^{1}H NMR δ 7.35-6.93 (m, 9 H), 6.75 (t, 1 H, *J* = 7.2 Hz), 4.10 (app t, 1 H, *J* = 7.8 Hz), 3.87-3.80 (m, 2 H), 3.57-3.48 (m, 1 H), 1.52 (t, 1 H, *J* = 4.2 Hz); ^{13}C NMR δ 147.5, 144.1, 131.2, 129.4, 128.3, 125.0, 121.4, 119.1, 117.9, 108.8, 65.3, 55.4, 43.0.

1-74: ^{1}H NMR δ 7.35-6.67 (m, 9 H), 4.38-4.28 (m, 1 H), 3.72 (bd, 1 H, *J* = 11.1 Hz), 3.55 (ddd, 1 H, *J* = 11.7 Hz, *J* = 4.5 Hz, *J* = 1.5 Hz), 3.15 (dd, 1 H, *J* = 16.5 Hz, *J* = 4.2 Hz), 2.88 (dd, 1 H, *J* = 16.5 Hz, *J* = 4.8 Hz), 2.13 (d, 1 H, *J* = 7.8 Hz); ^{13}C NMR δ 147.4, 143.9, 130.5, 129.6, 126.8, 125.2, 124.5, 120.8, 119.0, 115.0, 64.3, 56.4, 36.2.



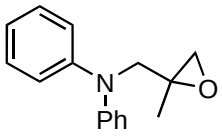
1-75

***N*-(2-Methylallyl)-*N*-phenylaniline (1-75).** According to General Protocol A, 4.20 g (24.8 mmol) of diphenylamine, 6.86 g (49.6 mmol) of K_2CO_3, 4.0 mL (40 mmol) of 3-bromo-2-methylpropene, and 1.83 g (4.96 mmol) of TBAI (reaction time 24 h) afforded 3.17 g (14.1 mmol, 57%) of **1-75** as a colorless oil: IR (neat) 3061, 3035, 2912, 2849, 2358, 1938, 1589, 1495, 1363, 1228, 894, 747 cm^{-1}; ^{1}H NMR δ 7.18 (t, 4 H, *J* = 7.5 Hz), 7.00 (bd, 4 H, *J* = 8.1 Hz), 6.87 (bt, 2 H, *J* = 6.9 Hz), 4.99 (bs, 1 H), 4.86-4.85 (m, 1 H), 4.19 (s, 2 H), 1.70 (s, 3 H); ^{13}C NMR δ 148.2, 141.4, 129.3, 121.3, 120.6, 111.3, 58.4, 20.3; MS (EI) *m/z* 223 ($M^{+\bullet}$, 75), 208 (19), 182 (100), 168 (57); HRMS (EI) *m/z* calcd for $C_{16}H_{17}N$ 223.1361, found 223.1351.



1-76

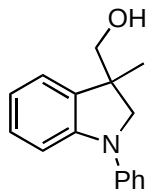
3-(Diphenylamino)-2-methylpropane-1,2-diol (1-76). According to General Protocol B, 1.61 g (7.20 mmol) of **1-75**, 1.26 g (10.8 mmol) of NMO and 218 μL of OsO_4 (1 mol%, 0.33 M in toluene) produced a brown solid that was recrystallized from chloroform/hexane to afford 1.55 g (6.05 mmol, 84%) of **1-76** as a white solid: mp 67-68 ^{o}C; IR (KBr) 3445, 3057, 2927, 2873, 1588, 1494, 1363, 1240, 1035, 749 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 7.35-7.20 (m, 4 H), 7.14-6.92 (m, 6 H), 3.97, 3.84 (AB, 2 H, *J* = 15.4 Hz), 3.50-3.32 (m, 2 H), 2.27 (bs, 1 H), 1.86 (dd, 1 H, *J* = 6.0 Hz, *J* = 1.2 Hz), 1.13 (s, 3 H); ^{13}C NMR (CD_2Cl_2) δ 150.1, 129.7, 122.2, 122.0, 74.6, 68.6, 59.8, 23.4; MS (EI) *m/z* 257 ($M^{+\bullet}$, 10), 182 (100), 169 (15), 104 (16); HRMS (EI) *m/z* calcd for $C_{16}H_{19}NO_2$ 257.1415, found 257.1419.



1-77

***N*-((2-Methyloxiran-2-yl)methyl)-*N*-phenylaniline (1-77).** To a solution of 430 mg (1.67 mmol) of **1-76** in 16 mL of THF at 0 ^{o}C was added 267 mg (6.68 mmol) of NaH (60% dispersion in mineral oil). The mixture was stirred for 10 min and 597 mg (1.83 mmol) of *p*-Ts_2O dissolved in 3 mL of THF was added dropwise. The disappearance of starting material was monitored by TLC (hexane:EtOAc; 2:1). The reaction mixture was quenched with H_2O and extracted with 3 x 10 mL of Et_2O. The combined organic layers were dried ($MgSO_4$),

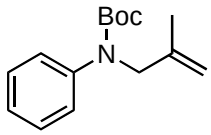
concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 10:1) to afford 279 mg (1.16 mmol, 70%) of **1-77** as a colorless oil: IR (neat) 3037, 2982, 2924, 1588, 1495, 1362, 1242, 749 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.31-7.23 (m, 4 H), 7.05-6.93 (m, 6 H), 3.96, 3.90 (AB, 2 H, *J* = 16.0 Hz), 2.68 (d, 1 H, *J* = 4.8 Hz), 2.57 (d, 1 H, *J* = 4.8 Hz), 1.38 (s, 3 H); ^{13}C NMR (CD_2Cl_2) δ 148.9, 129.6, 121.8, 121.3, 57.1, 56.8, 52.4, 19.8; MS (EI) *m/z* 239 ($M^{+\bullet}$, 30), 182 (100), 167 (15), 104 (23); HRMS (EI) *m/z* calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1311.



1-78

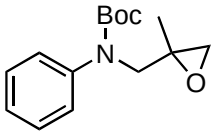
(3-Methyl-1-phenylindolin-3-yl)methanol (1-78). According to General Protocol C, 71 mg (0.29 mmol) of **1-77**, 2.2 mg (0.089 mmol) of Cp_2TiCl_2, 69 mg (0.44 mmol) of collidine hydrochloride and 24 mg (0.44 mmol) of Mn provided a mixture (reaction time 25 min) that was purified by chromatography on neutral alumina (hexane:EtOAc; 6:1 to EtOAc:EtOH; 5:1) to afford 63 mg (0.26 mmol, 89%) of **1-78** as a colorless oil: IR (neat) 3360, 3057, 2959, 2925, 2866, 1591, 1501, 1462, 1385, 1024, 744 cm^{-1}; ^1H NMR δ 7.32 (t, 2 H, *J* = 7.5 Hz), 7.22 (d, 2 H, *J* = 7.6 Hz), 7.15 (dt, 2 H, *J* = 6.9 Hz, *J* = 1.2 Hz), 7.10 (bt, 1 H, *J* = 6.9 Hz), 6.95 (t, 1 H, *J* = 7.2 Hz), 6.77 (t, 1 H, *J* = 6.9 Hz), 3.91, 3.66 (AB, 2 H, *J* = 9.6 Hz), 3.63 (A of ABX, 1 H, *J* = 10.5 Hz, *J* = 6.0), 3.56 (B of ABX, 1 H, *J* = 10.5 Hz, *J* = 6.3), 1.70-1.65 (m, 1 H), 1.37 (s, 3 H); ^{13}C NMR δ 146.9, 144.0, 135.6, 129.4, 128.2, 123.4, 121.2, 119.1, 117.8, 108.7, 69.1, 61.8, 45.6,

22.5; MS (EI) *m/z* 239 ($M^{+\bullet}$, 23), 208 (100), 193 (25), 130 (10); HRMS (EI) *m/z* calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1318.



1-80

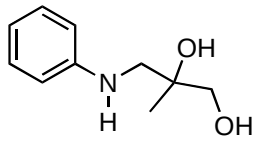
***t*-Butyl 2-methylallyl(phenyl)carbamate (1-80).** To a solution of 125 mg (0.646 mmol) of Boc-aniline in 7 mL of acetonitrile was added 51 mg (1.3 mmol) of NaH (60% dispersion in mineral oil) followed by 104 μL (1.03 mmol) of 3-bromo-2-methylpropene. The disappearance of starting material was monitored by TLC (hexane:EtOAc; 4:1). The reaction mixture was quenched with H_2O, extracted with 3 x 10 mL of Et_2O, concentrated *in vacuo,* and purified by chromatography on SiO_2 (hexane:EtOAc; 10:1) to afford 132 mg (0.534 mmol, 87%) of **1-80** as an oil: ^{1}H NMR δ 7.36-7.11 (m, 5 H), 4.84 (s, 1 H), 4.81 (s, 1 H), 4.16 (s, 2 H), 1.74 (s, 3 H), 1.44 (s, 9 H).



1-81

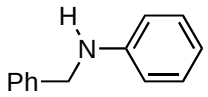
***t*-Butyl (2-methyloxiran-2-yl)methyl(phenyl)carbamate (1-81).**[25] According to a modified literature procedure, to a solution of 124 mg (0.501 mmol) of **1-80** in 5 mL of CH_2Cl_2 at -40 ^oC was added 185 mg (0.751 mmol) of *m*-CPBA (70%). The reaction mixture was warmed to rt over 4 h, quenched with $Na_2S_2O_3$ solution, extracted with 3 x 5 mL of CH_2Cl_2, dried ($MgSO_4$), concentrated *in vacuo,* and purified by chromatography on SiO_2 (hexane:EtOAc; 9:1 to 4:1) to

afford 46 mg (0.17 mmol, 35%) of **1-81**: ^{1}H NMR δ 7.35-7.17 (m, 5 H), 3.93, 3.64 (AB, 2 H, *J* = 15.0 Hz), 2.54, 2.52 (AB, 2 H, *J* = 4.5 Hz), 1.43 (s, 9 H), 1.39 (s, 3 H).



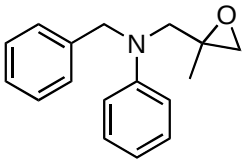
1-83

2-Methyl-3-(phenylamino)propane-1,2-diol (1-83). To a 10 mL flask was added 54 mg (0.34 mmol) of collidine hydrochloride, 4.3 mg (0.017 mmol) of Cp_2TiCl_2, followed by 46 mg (0.17 mmol) of **1-81** (in 1 mL of THF). The mixture was diluted with an additional 5 mL of THF (0.03 M) and 6.2 mg (0.11 mmol) of Mn was added before sonication was initiated (50% maximum power of 130 W). The reaction mixture was quenched after 75 min by addition of 10% HCl solution, extracted with 3 x 5 mL of Et_2O, washed with 2 x 5 mL of satd. $NaHCO_3$ solution, dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexane:EtOAc; 6:1) to afford 20 mg (0.09 mmol) of **1-82** as a white solid. This solid was dissolved in 3 mL of MeOH, treated with 50 mg (1.3 mmol) of NaOH, heated at reflux for 3 h, quenched with brine solution, neutralized with a HCl solution to pH 7, extracted with 3 x 20 mL of EtOAc, dried (Na_2SO_4), and concentrated *in vacuo* to afford 12 mg (0.067 mmol, 70%) of crude **1-83** that was analyzed without further purification: ^{1}H NMR δ 7.20 (t, 2 H, *J* = 7.8 Hz), 6.81-6.73 (m, 3 H), 3.65, 3.57 (AB, 2 H, *J* = 10.2 Hz), 3.35-3.10 (m, 5 H), 1.24 (s, 3 H); MS (ESI) *m/z* 182.10 (M+H).



1-85

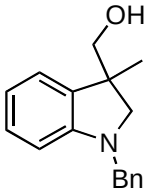
***N*-Benzylaniline (1-85).**[223,224] According to a modified literature procedure, to a solution of 2.75 g (29.5 mmol) of aniline in 30 mL of Et_2O was added 3.76 g (35.4 mmol) of freshly distilled benzaldehyde. The reaction mixture was stirred at rt for 1.5 h, diluted with 60 mL of MeOH and 10 mL of glacial acetic acid, and cooled to 0 ^oC when 1.11 g (29.5 mmol) of $NaBH_4$ was added slowly. Subsequently, the reaction mixture was warmed to rt, quenched with satd. $NaHCO_3$, extracted with 3 x 20 mL of Et_2O, dried ($MgSO_4$) and concentrated *in vacuo.* The residue was recrystallized from hexane to afford 3.73 g (20.3 mmol, 70%) of **1-85** as a tan solid: mp 36-38 ^oC (lit 35-38 ^oC); ^1H NMR δ 7.40-7.24 (m, 5 H), 7.17 (t, 2 H, J = 7.8 Hz), 6.71 (t, 1 H, J = 7.2 Hz), 6.63 (d, 2 H, J = 8.1 Hz), 4.32 (s, 2 H), 4.01 (bs, 1 H); ^{13}C NMR δ 148.4, 139.7, 129.5, 128.8, 127.7, 127.4, 117.8, 113.1, 48.5.



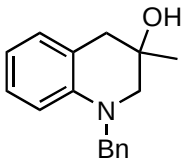
1-86

***N*-Benzyl-*N*-((2-methyloxiran-2-yl)methyl)aniline (1-86).** To a solution of 298 mg (1.62 mmol) of **1-85** in 5.5 mL of acetonitrile was added 450 mg (3.25 mmol) of K_2CO_3 and 295 μL (2.92 mmol) of 3-bromo-2-methylpropene. The reaction mixture was stirred at rt, and the disappearance of starting material was monitored by TLC (hexane:EtOAc; 4:1). The solution was quenched with H_2O, extracted with 3 x 10 mL of Et_2O, dried ($MgSO_4$), and concentrated *in*

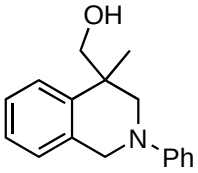
vacuo to afford an oil. According to General Protocol B, the crude residue, 342 mg (2.91 mmol) of NMO and 98 μL of OsO_4 (2 mol%, 0.33 M in toluene) afforded an oil that was dissolved in 16 mL of THF and cooled to 0 ^oC. After addition of 260 mg (6.50 mmol) of NaH (60% dispersion in mineral oil) the reaction was stirred for 15 min and 954 mg (2.92 mmol) of *p*-Ts_2O was added portionwise. The mixture was warmed to rt, quenched with H_2O, extracted with 3 x 10 mL of Et_2O, dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexane:EtOAc; 12:1) to afford 156 mg (0.616 mmol, 38%, 3 steps) of **1-86** as an oil: IR (neat) 3058, 3028, 2923, 1598, 1504, 1452, 1388, 1232, 1197 cm^{-1}; ^1H NMR δ 7.31-7.13 (m, 7 H), 6.71-6.66 (m, 3 H), 4.62 (s, 2 H), 3.65, 3.56 (AB, 2 H, *J* = 15.9 Hz), 2.68, 2.60 (AB, 2 H, *J* = 4.8 Hz), 1.38 (s, 3 H); ^{13}C NMR δ 149.1, 138.5, 129.4, 128.8, 126.9, 126.7, 117.0, 112.5, 56.9, 54.8, 54.7, 52.2, 19.8; MS (EI) *m/z* 253 ($M^{+\bullet}$, 11), 196 (35), 106 (14), 91 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{19}NO$ 253.1466, found 253.1469.



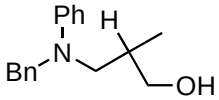
1-87



1-88



1-89



1-90

(1-Benzyl-3-methylindolin-3-yl)methanol (1-87). To a 10 mL flask was added 75 mg (0.48 mmol) of collidine hydrochloride, 5.9 mg (0.024 mmol) of Cp_2TiCl_2, followed by a solution of 61 mg (0.24 mmol) of **1-86** in 1 mL of THF. The mixture was diluted with 7 mL of THF (0.03 M), treated with 8.5 mg (0.15 mmol) of Mn, and sonicated at 50% of maximum power of 130 W. The reaction was quenched after 1.5 h by addition of 10% HCl solution, extracted with 3 x 5 mL of Et_2O, washed with 2 x 5 mL of satd. $NaHCO_3$, dried ($MgSO_4$), concentrated *in vacuo*, and

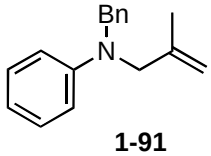
purified by chromatography on SiO_2 (hexane:EtOAc; 6:1) to afford 10.1 mg (0.0399 mmol, 16%) of **1-87**, 5.7 mg (0.022 mmol) of **1-88**, 7.5 mg (0.032 mmol) of **1-89**, and 3.2 mg (0.013 mmol) of **1-90** as impure oils:

1-87: ^{1}H NMR δ 7.31-7.13 (m, 6 H), 6.85 (d, 2 H, *J* = 8.1 Hz), 6.73 (t, 1 H, *J* = 7.2 Hz), 4.73 (s, 2 H), 3.67, 3.60 (AB, 2 H, *J* = 15.2 Hz), 3.55 (s, 2 H), 1.36 (s, 3 H).

1-Benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-3-ol (1-88): ^{1}H NMR δ 7.41-7.09 (m, 6 H), 6.85 (d, 2 H, *J* = 8.1 Hz), 6.73 (t, 1 H, *J* = 7.5 Hz), 4.76 (s, 2 H), 3.92, 3.83 (AB, 2 H, *J* = 15.6 Hz), 3.83-3.64 (m, 2 H), 1.63 (s, 3 H).

(4-Methyl-2-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methanol (1-89): ^{1}H NMR δ 7.36-7.25 (m, 5 H), 7.14-7.05 (m, 2 H), 6.72 (t, 1 H, *J* = 7.5 Hz), 6.53 (d, 1 H, *J* = 7.8 Hz), 4.35, 4.19 (AB, 2 H, *J* = 15.0 Hz), 3.64, 3.58 (AB, 2 H, *J* = 10.6 Hz), 3.42, 3.06 (AB, 2 H, *J* = 9.0 Hz), 1.29 (s, 3 H).

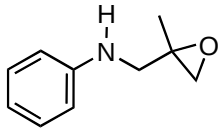
3-(Benzyl(phenyl)amino)-2-methylpropan-1-ol (1-90): ^{1}H NMR δ 7.35-7.17 (m, 8 H), 6.78-6.68 (m, 2 H), 4.61, 4.58 (AB, 2 H, *J* = 16.9 Hz), 3.61 (app d, 2 H, *J* = 5.1 Hz), 3.46 (dd, 1 H, *J* = 14.4 Hz, *J* = 8.1 Hz), 3.27 (dd, 1 H, *J* = 14.7 Hz, *J* = 6.3 Hz), 2.27-2.16 (m, 1 H), 0.98 (d, 3 H, *J* = 6.6 Hz).



1-91

***N*-benzyl-*N*-(2-methylallyl)aniline (1-91).** To a solution of 1.16 g (6.33 mmol) of **1-85** in 12 mL of acetonitrile was added 2.26 g (18.9 mmol) of K_2CO_3, and 1.0 mL (9.9 mmol) of 3-bromo-2-methylpropene. The mixture was stirred for 24 h at rt, quenched with H_2O, extracted with 3 x

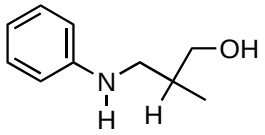
10 mL of Et_2O, dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexane:EtOAc; 20:1) to afford 1.46 g, (6.14 mmol, 97%) of **1-91** as an oil: IR (neat) 3061, 3027, 2910, 1655, 1598, 1504, 1357, 1230, 894 cm^{-1}; ^1H NMR δ 7.29-7.11 (m, 6 H), 6.65 (d, 4 H, *J* = 7.2 Hz), 4.86 (s, 1 H), 4.83 (s, 1 H), 4.54 (s, 2 H), 3.86 (s, 2 H), 1.71 (s, 3 H); ^{13}C NMR δ 149.2, 140.7, 139.0, 129.2, 128.8, 126.9, 126.7, 116.6, 112.4, 110.8, 56.7, 54.2, 20.3; MS (EI) *m/z* 237 ($M^{+\bullet}$, 13), 221 (10), 196 (11), 118 (26), 91 (94), 84 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{19}N$ 237.1517, found 237.1515.



1-92

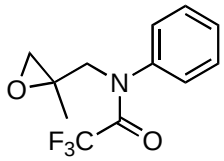
***N*-((2-Methyloxiran-2-yl)methyl)aniline (1-92).** According to General Protocol B, 979 mg (4.12 mmol) of **1-91**, 579 mg (4.94 mmol) of NMO, and 62 μL of OsO_4 (0.5 mol%, 0.33 M in toluene) afforded an oil that was dissolved in 4 mL of MeOH. The solution was treated with 110 mg (11% w/w, 0.05 mmol) of Pd/C and stirred under 1 atm of H_2 at rt. The disappearance of starting material was monitored by TLC (hexane:EtOAc; 1:1). After 3 h, the mixture was filtered through Celite® and concentrated *in vacuo*. The crude residue was dissolved in 35 mL of THF, cooled to 0 ^oC, and treated with 314 mg (7.85 mmol) of NaH (60% dispersion in mineral oil). The reaction mixture was stirred for 15 min, treated portionwise with 1.35 g (4.13 mmol) of *p*-Ts_2O, and quenched after 1 h by addition of H_2O. The mixture was extracted with 3 x 15 mL of Et_2O, dried ($MgSO_4$), concentrated *in vacuo,* and purified by chromatography on SiO_2 (hexane:EtOAc; 6:1) to afford 441 mg (2.70 mmol, 66%, 3 steps) of **1-92** as an oil: IR (neat) 3357, 3048, 2976, 2864, 1923, 1603, 1512, 1321, 1074 cm^{-1}; ^1H NMR δ 7.15 (t, 2 H, *J* = 7.2

Hz), 6.69 (t, 1 H, *J* = 7.2 Hz), 6.59 (d, 2 H, *J* = 8.4 Hz), 3.82 (bs, 1 H), 3.31, 3.28 (AB, 2 H, *J* = 13.6 Hz), 2.81, 2.61 (AB, 2 H, *J* = 4.8 Hz), 1.39 (s, 3 H); ^{13}C NMR δ 148.2, 129.4, 117.8, 113.0, 56.4, 52.0, 47.8, 19.9; MS (EI) *m/z* 163 ($M^{+\bullet}$, 37), 148 (6), 106 (40), 84 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{13}NO$ 163.0997, found 163.0994.



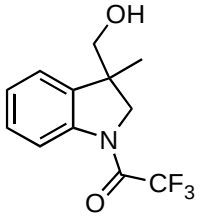
1-93

2-Methyl-3-(phenylamino)propan-1-ol (1-93). A mixture of 90 mg (0.57 mmol) of collidine hydrochloride, 7.1 mg (0.029 mmol) of Cp_2TiCl_2, and a solution of 47 mg (0.28 mmol) of **1-92** in 1 mL of THF was treated with 8.5 mL of THF, and 10.2 mg (0.187 mmol) of Mn. Sonication was initiated at 50% of the maximum power of 130 W. The reaction was quenched after 1.5 h with satd. NH_4Cl, extracted with 3 x 10 mL of Et_2O, concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexane:EtOAc; 6:1) to yield 4.3 mg (0.026 mmol, 9%) of **1-93** as an oil:[225] ^{1}H NMR δ 7.18 (t, 2 H, *J* = 7.5 Hz), 6.72 (t, 1 H, *J* = 7.2 Hz), 6.65 (d, 2 H, *J* = 7.5 Hz), 3.69 (dd, 1 H, *J* = 10.5 Hz, *J* = 4.8 Hz), 3.61 (dd, 1 H, *J* = 10.8 Hz, *J* = 6.9 Hz), 3.17 (dd, 1 H, *J* = 12.6 Hz, *J* = 7.5 Hz), 3.10 (dd, 1 H, *J* = 12.3 Hz, *J* = 5.4 Hz), 2.12-1.95 (m, 1 H), 0.99 (d, 3 H, *J* = 6.9 Hz).

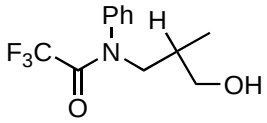


1-94

2,2,2-Trifluoro-*N*-((2-methyloxiran-2-yl)methyl)-*N*-phenylacetamide (1-94).[226] According to a modified literature procedure, to a solution of 147 mg (0.900 mmol) of **1-92** in 9 mL of pyridine at 0 ^{o}C was added 11 mg (0.090 mmol) of DMAP followed by 165 μL (1.17 mmol) of TFAA. After 2.5 h the mixture was quenched with H_2O, extracted with 3 x 10 mL of Et_2O, dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexane:EtOAc; 4:1) to afford 172 mg (0.667 mmol, 74%) of **1-94** as a white solid: ^{1}H NMR δ 7.46-7.41 (m, 3 H), 7.28-7.26 (m, 2 H), 3.99, 3.85 (AB, 2 H, J = 14.1 Hz), 2.56, 2.45 (AB, 2 H, J = 4.3 Hz), 1.42 (s, 3 H); MS (EI) *m/z* 259 ($M^{+\bullet}$, 26), 172 (41), 104 (93), 77 (100); ^{13}C NMR δ 157.3 (q, J_{C-P} = 35 Hz), 139.6, 129.4, 129.3, 128.3, 116.4 (q, J_{C-P} = 287 Hz), 56.8, 54.9, 52.2, 19.4.



1-95

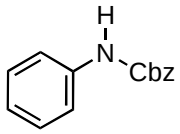


1-96

2,2,2-Trifluoro-1-(3-(hydroxymethyl)-3-methylindolin-1-yl)ethanone (1-95). According to General Protocol C, 61 mg (0.23 mmol) of **1-94**, 5.8 mg (0.024 mmol) of Cp_2TiCl_2, 147 mg (0.940 mmol) of collidine hydrochloride and 15 mg (0.23 mmol) of Nano-Zn (reaction time 1 h) provided a mixture that was purified by chromatography on SiO_2 (hexane:EtOAc; 4:1) to afford 10 mg (0.040 mmol, 17%) of **1-95** and 10 mg (0.040 mmol) of **1-96** as oils.

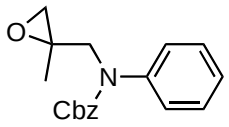
1-95: ^{1}H NMR δ 8.21 (d, 1 H, *J* = 7.8 Hz), 7.37-7.20 (m, 3 H), 4.38, 3.89 (AB, 2 H, *J* = 11.1 Hz), 3.68, 3.60 (AB, 2 H, *J* = 10.8 Hz), 1.61 (bs, 1 H), 1.40 (s, 3 H); MS (EI) *m/z* 259 ($M^{+\bullet}$, 14), 228 (100), 130 (42), 105 (25).

2,2,2-Trifluoro-*N*-(3-hydroxy-2-methylpropyl)-*N*-phenylacetamide (1-96): ^{1}H NMR δ 7.50-7.40 (m, 3 H), 7.25-7.15 (m, 2 H), 4.14 (dd, 1 H, *J* = 13.5 Hz, *J* = 9.9 Hz), 3.70-3.60 (m, 1 H), 3.51 (bd, 1 H, *J* = 9.0 Hz), 3.32 (dd, 1 H, *J* = 13.8 Hz, *J* = 5.4 Hz), 2.60 (bs, 1 H), 1.95-1.79 (m, 1 H), 0.96 (d, 3 H, *J* = 6.9 Hz); MS (EI) *m/z* 261 ($M^{+\bullet}$, 15), 202 (100), 105 (64).



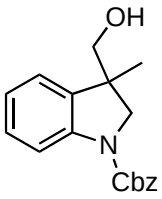
1-97

Benzyl phenylcarbamate (1-97).[227,228] **General Protocol D.** According to a modified literature procedure, a solution of 2.04 g (21.9 mmol) of aniline in 50 mL of THF at 0 °C was treated with 2.02 g (24.0 mmol) of $NaHCO_3$ followed by 3.4 mL (24 mmol) of benzyl chloroformate. After 15, min the reaction mixture was warmed to rt, quenched with H_2O and extracted with 3 x 20 mL of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford 4.97 g (21.9 mmol, quant.) of **1-97** as a white solid that was used without further purification: mp 76-77 ^{o}C (lit 80 ^{o}C); ^{1}H NMR δ 7.40-7.20 (m, 8 H), 7.01 (t, 2 H, *J* = 7.2 Hz), 6.94 (bs, 1 H), 5.13 (s, 2 H); ^{13}C NMR δ 153.6, 138.0, 136.2, 129.1, 128.7, 128.4, 123.6, 118.9, 67.1.

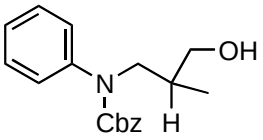


1-98

Benzyl (2-methyloxiran-2-yl)methyl(phenyl)carbamate (1-98). General Protocol E. To a solution of 2.91 g (12.8 mmol) of **1-97** in 60 mL of THF at 0 °C was added 1.02 g (25.6 mmol) of NaH (60% dispersion in mineral oil). The reaction mixture was warmed to rt over 15 min and 2.6 mL (26 mmol) of 3-bromo-2-methylpropene were added. The solution was stirred overnight, quenched with H_2O and extracted with 3 x 20 mL of Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 80 mL of CH_2Cl_2, cooled to 0 ^oC and 5.67 g (23.0 mmol) of *m*-CPBA (70%) was added portionwise. The reaction mixture was quenched with aq. $Na_2S_2O_3$ solution and extracted with 3 x 10 mL of Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 4:1 with 1% NEt_3) to afford 3.01 g (10.1 mmol, 79%, 2 steps) of **1-98** as an orange oil: IR (neat) 3520, 3036, 2934, 2360, 1706, 1597, 1494, 1405, 1273, 1147, 1020 cm^{-1}; ^1H NMR δ 7.38-7.20 (m, 10 H), 5.14 (s, 2 H), 3.95, 3.72 (AB, 2 H, *J* = 14.7 Hz), 2.50, 2.47 (AB, 2 H, *J* = 4.8 Hz), 1.36 (s, 3H); ^{13}C NMR δ 155.6, 142.2, 136.5, 129.0, 128.4, 128.0, 127.6, 127.2, 126.9, 67.5, 55.7, 55.5, 52.5, 19.4; MS (EI) *m/z* 297 ($M^{+\bullet}$, 23), 196 (71), 132 (47), 91 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{19}NO_3$ 297.1364, found 297.1351.



1-99

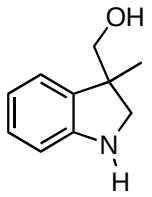


1-100

Benzyl 3-(hydroxymethyl)-3-methylindoline-1-carboxylate (1-99). A solution of 85 mg (0.28 mmol) of **1-98**, 7.0 mg (0.029 mmol) of Cp_2TiCl_2, 179 mg (1.14 mmol) of collidine hydrochloride, and 23.5 mg (0.427 mmol) of Mn in 2.8 mL of THF was stirred for 5 h at rt, quenched with satd. NH_4Cl and extracted with 3 x 5 mL of Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to provide a residue containing **1-99** and **1-100** (~2:1 ratio based on integration of the crude ^{1}H NMR peaks at 4.15 ppm (**1-99**) vs. 0.88 ppm (**1-100**)). The mixture was partially purified by chromatography on SiO_2 (hexane:EtOAc; 4:1) to afford 36 mg (0.12 mmol, 42%) of **1-99** in addition to 37 mg of an inseparable mixture of **1-99** and **1-100**.

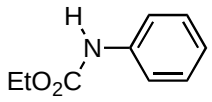
1-99: ^{1}H NMR δ 7.89 (bs, 1 H), 7.49-6.97 (m, 8 H), 5.24 (bs, 2 H), 4.12 (d, 1 H, *J* = 11.8 Hz), 3.68 (d, 1 H, *J* = 11.7 Hz), 3.61, 3.53 (AB, 2 H, *J* = 10.8 Hz), 1.70 (bs, 1 H), 1.34 (s, 3 H); MS (EI) *m/z* 297 ($M^{+\bullet}$, 28), 222 (55), 130 (40), 91 (100).

1-100: ^{1}H NMR δ 7.44-7.41 (m, 10 H), 5.15, 5.11 (AB, 2 H, *J* = 12.6 Hz), 3.96 (dd, 1 H, *J* = 14.4 Hz, *J* = 9.6 Hz), 3.71-3.30 (m, 3 H), 1.86-1.70 (m, 1 H), 0.89 (d, 3 H, *J* = 6.9 Hz); MS (EI) *m/z* 299 ($M^{+\bullet}$, 10), 191 (20), 91 (100).



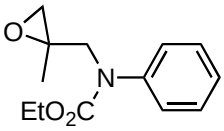
1-101

(3-Methylindolin-3-yl)methanol (1-101). General Protocol F. To a 2-neck flask was added 129 mg (0.433 mmol) of **1-98**, 3.2 mg (0.013 mmol) of Cp_2TiCl_2, 102 mg (0.649 mmol) of collidine hydrochloride, and 35.6 mg (0.649 mmol) of Mn. The vessel was fitted with a reflux condenser and purged 3 x with Ar. After addition of 4.3 mL of THF (0.1 M), the reaction mixture was placed in a preheated oil bath and heated at reflux for 3 h. During this time, the solution gradually changed from light pink to a dark violet color. The mixture was cooled to rt, quenched with satd. NH_4Cl and extracted with 3 x 10 mL of Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 5 mL of MeOH and treated with 30 mg (25% w/w, 0.01 mmol) of Pd/C. The mixture was stirred at rt under 1 atm of H_2 and the disappearance of starting material was monitored by TLC (hexane:EtOAc; 1:1). The solution was then quenched with Celite, filtered and purified by chromatography on SiO_2 (hexane:EtOAc; 1:2) to afford 44 mg (0.26 mmol, 63%, 2 steps) of **1-101** as a yellow oil: IR (neat) 3332, 2959, 2926, 2867, 1606, 1487, 1461, 1239, 1030, 747 cm^{-1}; ^1H NMR δ 7.08-7.02 (m, 2 H), 6.73 (t, 1 H, J = 6.6 Hz), 6.62 (d, 1 H, J = 7.5 Hz), 3.59, 3.53 (AB, 2 H, J = 10.5 Hz), 3.55, 3.26 (AB, 2 H, J = 9.0 Hz), 1.31 (s, 3 H); ^{13}C NMR δ 151.6, 133.7, 128.3, 123.2, 118.9, 110.0, 69.3, 56.9, 47.7, 22.4; MS (EI) *m/z* 163 ($M^{+\bullet}$, 32), 132 (100), 117 (59); HRMS (EI) *m/z* calcd for $C_{10}H_{13}NO$ 163.0997, found 163.0993.



1-102

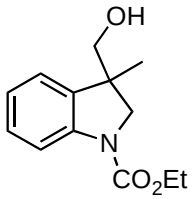
Ethyl phenylcarbamate (1-102).[229] According to a modified literature procedure, to a solution of 5.10 g (54.7 mmol) of aniline in 130 mL of THF at 0 ^{o}C was added 3.06 g (76.5 mmol) of NaH (60% dispersion in mineral oil) followed by 6.3 mL (66 mmol) of ethyl chloroformate. The reaction mixture was warmed to rt, quenched with H_2O after 3 h and extracted with 3 x 40 mL of Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 5:1 to 3:1) to afford 8.07 g (48.8 mmol, 89%) of **1-102** as a brown oil: ^{1}H NMR δ 7.39-7.25 (m, 4 H), 7.05 (t, 1 H, *J* = 6.9 Hz), 6.59 (bs, 1 H), 4.22 (q, 2 H, *J* = 7.2 Hz), 1.31 (t, 3 H, *J* = 7.2 Hz); MS (EI) *m/z* 165 ($M^{+\bullet}$, 78), 119 (34), 93 (100), 65 (50).



1-103

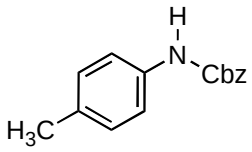
Ethyl (2-methyloxiran-2-yl)methyl(phenyl)carbamate (1-103). According to General Procedure E, 2.54 g (15.4 mmol) of **1-102**, 1.23 g (30.8 mmol) of NaH (60% dispersion in mineral oil), 2.8 mL (28 mmol) of 3-bromo-2-methylpropene, and 5.70 g (23.1 mmol) of *m*-CPBA (70%) provided an oil that was purified by chromatography on SiO_2 (hexane:EtOAc; 4:1) to afford 2.66 g (11.3 mmol, 73%, 2 steps) of **1-103** as a golden oil: IR (neat) 3043, 2981, 2933, 1702, 1597, 1536, 1408, 1299, 1023 cm^{-1}; ^{1}H NMR δ 7.35-7.18 (m, 5 H), 4.14 (q, 2 H, *J* = 6.9

Hz), 3.93 (A of ABX, 1 H, *J* = 14.7 Hz, *J* = 0.6 Hz), 3.71 (B of ABX, 1 H, *J* = 14.7 Hz, *J* = 0.9 Hz), 2.51 (m, 2 H), 1.37 (s, 3 H), 1.19 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 155.8, 142.4, 128.9, 127.1, 126.6, 61.9, 55.7, 55.3, 52.5, 19.4, 14.5; MS (EI) *m/z* 235 ($M^{+\bullet}$, 45), 178 (38), 134 (28), 106 (100); HRMS (EI) *m/z* calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1219.



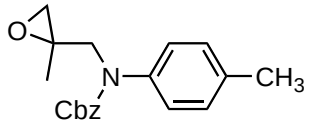
1-104

Ethyl 3-(hydroxymethyl)-3-methylindoline-1-carboxylate (1-104). According to General Protocol C, 125 mg (0.531 mmol) of **1-103**, 3.9 mg (0.016 mmol) of Cp_2TiCl_2, 125 mg (0.796 mmol) of collidine hydrochloride, and 43 mg (0.79 mmol) of Mn provided a mixture (reaction time 2 h) that was purified by chromatography on SiO_2 (hexane:EtOAc; 3:1) to afford 81 mg (0.34 mmol, 65%) of **1-104** as an oil: IR (neat) 3433, 2976, 2931, 1693, 1600, 1487, 1413, 1051cm^{-1}; ^{1}H NMR δ 7.85 (bs, 1 H), 7.24 (t, 1 H, *J* = 6.9 Hz), 7.11 (d, 1 H, *J* = 6.9 Hz), 6.98 (t, 1 H, *J* = 7.2 Hz), 4.26 (bs, 2 H), 4.07 (d, 1 H, *J* = 11.4 Hz), 3.64 (d, 1 H, *J* = 11.4 Hz), 3.61 (dd, 1 H, *J* = 11.4 Hz, *J* = 4.5 Hz), 3.52 (dd, 1 H, *J* = 10.5 Hz, *J* = 6.6 Hz), 1.97 (bs, 1 H), 1.34 (bs, 6 H); ^{13}C NMR δ 153.6, 142.9, 135.8, 128.6, 123.0, 122.8, 115.1, 69.7, 61.7, 57.7, 45.4, 23.2, 14.8; MS (EI) *m/z* 235 ($M^{+\bullet}$, 31), 204 (100), 160 (27), 130 (71), 117 (55); HRMS (EI) *m/z* calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1202.



1-105

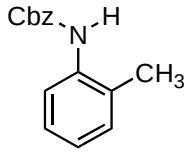
Benzyl *p*-tolylcarbamate (1-105). According to General Protocol D, 4.15 g (38.7 mmol) of *p*-toluidine, 3.57 g (42.6 mmol) of $NaHCO_3$, and 6.0 mL (42.6 mmol) of benzyl chloroformate (reaction time 30 min) afforded a solid that was recrystallized from chloroform/hexane to afford 8.12 g (33.6 mmol, 87%) of **1-105** as white needles: mp 82-84 ^oC; IR (KBr) 3319, 3195, 3032, 2943, 1730, 1707, 1602, 1543, 1406, 1232, 1067, 739 cm^{-1}; ^1H NMR δ 7.39-7.20 (m, 7 H), 7.06 (d, 2 H, *J* = 8.4 Hz), 6.72 (bs, 1 H), 5.15 (s, 2 H), 2.27 (s, 3 H); ^{13}C NMR δ 153.7, 136.3, 135.4, 133.2, 129.7, 128.7, 128.4, 119.1, 67.1, 20.9; MS (EI) *m/z* 241 ($M^{+\bullet}$, 49), 197 (45), 133 (34), 91 (100), 84 (91); HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO_2$ 241.1102, found 241.1106.



1-106

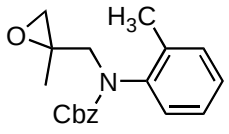
Benzyl (2-methyloxiran-2-yl)methyl(*p*-tolyl)carbamate (1-106). According to General Protocol E, 4.42 g (18.3 mmol) of **1-105**, 1.46 g (36.6 mmol) of NaH (60% dispersion in mineral oil), 2.8 mL (28 mmol) of 3-bromo-2-methylpropene, and 6.76 g (27.4 mmol) of *m*-CPBA (70%) provided an oil that was purified by chromatography on SiO_2 (hexane:EtOAc; 4:1) to afford 4.43 g (14.2 mmol, 78%, 2 steps) of **1-106** as a red oil: IR (neat) 3583, 3033, 2929, 1702, 1514, 1404, 1271, 1146 cm^{-1}; ^1H NMR δ 7.33-7.24 (m, 5 H), 7.16-7.09 (m, 4 H), 5.14 (bs, 2 H), 3.91, 3.69 (AB, 2 H, *J* = 14.7 Hz), 2.50, 2.47 (AB, 2 H, *J* = 4.6 Hz), 2.33 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR

δ 155.9, 139.7, 136.9, 136.7, 129.8, 128.6, 128.1, 127.8, 127.1, 67.6, 55.9, 55.8, 52.7, 21.2, 19.5; MS (EI) *m/z* 311 ($M^{+\bullet}$, 35), 210 (46), 146 (48), 91 (95), 84 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{21}NO_3$ 311.1521, found 311.1525.



1-107

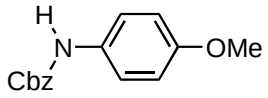
Benzyl *o*-tolylcarbamate (1-107). According to General Protocol D, 3.81 g (35.5 mmol) of *o*-toluidine, 3.28 g (39.1 mmol) of $NaHCO_3$, and 5.5 mL (39 mmol) of benzyl chloroformate (reaction time 1 h) provided a solid that was recrystallized from Et_2O to afford 7.41 g (30.7 mmol, 86%) of **1-107** as a white solid: mp 83-84 ^oC; IR (KBr) 3297, 3036, 2959, 1695, 1588, 1533, 1454, 1294, 1240, 1064 cm^{-1}; ^1H NMR (DMSO-d_6, 350 K) δ 8.64 (bs, 1 H), 7.47-7.30 (m, 6 H), 7.20-7.09 (m, 3 H), 5.16 (s, 2 H), 2.33 (s, 3 H); ^{13}C NMR (DMSO-d_6, 350 K) δ 153.9, 136.6, 136.0, 131.3, 129.8, 127.9, 127.3, 127.2, 125.5, 124.4, 124.2, 65.3, 17.1; MS (EI) *m/z* 241 ($M^{+\bullet}$, 13), 197 (13), 133 (18), 104 (16), 91 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO_2$ 241.1102, found 241.1107.



1-108

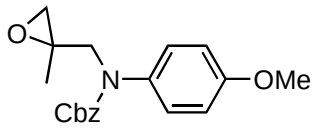
Benzyl (2-methyloxiran-2-yl)methyl(*o*-tolyl)carbamate (1-108). According to General Protocol E, 3.60 g (14.9 mmol) of **1-107**, 1.19 g (29.8 mmol) of NaH (60% dispersion in mineral

oil), 2.2 mL (22 mmol) of 3-bromo-2-methylpropene, and 5.51 g (22.3 mmol) of *m*-CPBA (70%) provided an oil that was purified by chromatography on SiO_2 (hexane:EtOAc; 4:1) to afford 3.88 g (12.4 mmol, 84%, 2 steps) of **1-108** as an oil: IR (neat) 3033, 2931, 1708, 1583, 1493, 1406, 1299, 1147, 1028 cm^{-1}; ^1H NMR (DMSO-d_6, 350 K) δ 7.34-7.20 (m, 9 H), 5.09 (s, 2 H), 4.10-3.20 (m, 2 H), 2.50, 2.41 (AB, 2 H, J = 4.7 Hz), 2.13 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (DMSO-d_6, 350 K) δ 154.6, 140.7, 136.3, 134.9, 130.2, 127.9, 127.8, 127.3, 126.9, 126.8, 126.0, 66.3, 54.7, 51.2, 18.9, 16.6; MS (EI) *m/z* 311 ($M^{+\bullet}$, 15), 210 (8), 118 (25), 91 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{21}NO_3$ 311.1521, found 311.1527.



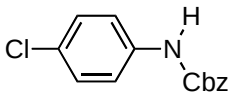
1-109

Benzyl 4-methoxyphenylcarbamate (1-109).[230] According to General Protocol D, 4.08 g (33.1 mmol) of *p*-anisidine, 3.06 g (36.4 mmol) of $NaHCO_3$, and 5.2 mL (36 mmol) of benzyl chloroformate (reaction time 30 min) provided a solid that was recrystallized (chloroform:hexane; 1:10) to afford 7.65 g (29.7 mmol, 90%) of **1-109** as a pink solid: mp 98 ^oC; IR (KBr) 3299, 3042, 2842, 1701, 1532, 1415, 1238, 1065, 1029, 825, 743 cm^{-1}; ^1H NMR δ 7.42-7.24 (m, 7 H), 6.86-6.81 (m, 2 H), 6.59 (bs, 1 H), 5.17 (s, 2 H), 3.77 (s, 3 H); ^{13}C NMR δ 156.3, 153.9, 136.4, 131.0, 128.8, 128.5, 121.0, 114.5, 67.1, 55.7; MS (EI) *m/z* 257 ($M^{+\bullet}$, 11), 213 (7), 122 (32), 91 (100), 65 (50); HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO_3$ 257.1051, found 257.1047.



1-110

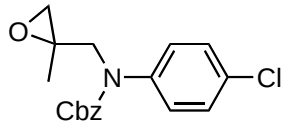
Benzyl 4-methoxyphenyl((2-methyloxiran-2-yl)methyl)carbamate (1-110). According to General Protocol E, 4.21 g (16.3 mmol) of **1-109**, 1.30 g (32.7 mmol) of NaH (60% dispersion in mineral oil), 2.5 mL (25 mmol) of 3-bromo-2-methylpropene, and 6.04 g (24.5 mmol) of *m*-CPBA (70%) provided an oil that was purified by chromatography on SiO_2 (hexane:EtOAc; 4:1) to afford 4.34 g (13.2 mmol, 81%, 2 steps) of **1-110** as an oil: IR (neat) 3520, 3037, 2935, 2837, 1701, 1609, 1585, 1512, 1444, 1428, 1294 cm^{-1}; ^1H NMR δ 7.32-7.12 (m, 7 H), 6.83 (d, 2 H, *J* = 12.3 Hz), 5.12 (bs, 2 H), 3.89, 3.65 (AB, 2 H, *J* = 14.7 Hz), 3.74 (s, 3 H), 2.47, 2.45 (AB, 2 H, *J* = 4.5 Hz), 1.34 (s, 3 H); ^{13}C NMR δ 158.2, 155.9, 136.6, 135.0, 128.4, 127.9, 127.5, 114.2, 67.4, 55.8, 55.6, 55.4, 52.4, 19.3; MS (EI) *m/z* 327 ($M^{+\bullet}$, 23), 192 (15), 146 (23), 91 (81), 84 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{21}NO_4$ 327.1470, found 327.1471.



1-111

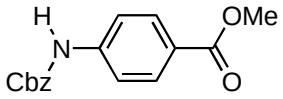
Benzyl 4-chlorophenylcarbamate (1-111). According to General Protocol D, 3.81 g (29.8 mmol) of *p*-chloroaniline, 2.57 g (32.8 mmol) of $NaHCO_3$, and 4.6 mL (33 mmol) of benzyl chloroformate provided a solid that was recrystallized (chloroform/hexane; 1:10) to afford 6.57 g (25.1 mmol, 84%) of **1-111** as pink needles: mp 109-111 ^oC; IR (KBr) 3320, 3112, 3037, 2954, 1707, 1594, 1528, 1403, 1237, 1065, 822, 737 cm^{-1}; ^1H NMR δ 7.41-7.23 (m, 9 H),

6.70 (bs, 1 H), 5.18 (s, 2 H); ^{13}C NMR δ 153.4, 136.6, 136.0, 129.3, 128.9, 128.8, 128.7, 128.5, 120.1, 67.4; MS (EI) *m/z* 261 ($M^{+\bullet}$, 20), 217 (15), 153 (79), 91 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{12}ClNO_2$ 261.0556, found 261.0561.



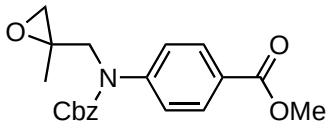
1-112

Benzyl 4-chlorophenyl((2-methyloxiran-2-yl)methyl)carbamate (1-112). According to General Protocol E, 3.96 g (15.1 mmol) of **1-111**, 1.21 g (30.2 mmol) of NaH (60% dispersion in mineral oil), 2.3 mL (23 mmol) of 3-bromo-2-methylpropene, and 5.58 g (22.6 mmol) of *m*-CPBA (70%) provided an oil that was purified by chromatography on SiO_2 (hexane:EtOAc; 4:1) to afford 3.96 g (11.9 mmol, 79%, 2 steps) of **1-112** as an orange solid: mp 58-60 ^{o}C; IR (KBr) 3319, 3400, 3036, 2968, 2279, 1702, 1412, 1263, 1148, 1090, 1011, 837, 734 cm^{-1}; ^{1}H NMR δ 7.32-7.16 (m, 9 H), 5.14 (s, 2 H), 3.86, 3.75 (AB, 2 H, *J* = 15.0 Hz), 2.51, 2.50 (AB, 2 H, *J* = 4.8 Hz), 1.34 (s, 3 H); ^{13}C NMR δ 155.5, 140.9, 136.3, 132.5, 129.2, 128.6, 128.5, 128.3, 127.9, 67.8, 55.8, 55.4, 52.3, 19.4; MS (EI) *m/z* 331 ($M^{+\bullet}$, 33), 230 (46), 111 (42), 91 (100), 84 (94); HRMS (EI) *m/z* calcd for $C_{18}H_{18}ClNO_3$ 331.0975, found 331.0975.



1-113

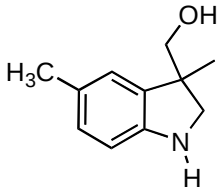
Methyl 4-(benzyloxycarbonylamino)benzoate (1-113). According to General Protocol D, 3.80 g (25.1 mmol) of methyl 4-aminobenzoate, 2.32 g (27.6 mmol) of $NaHCO_3$, and 3.9 mL (28 mmol) of benzyl chloroformate (reaction time 1 h) provided a solid that was recrystallized (chloroform/hexane; 1:10) to afford 6.47 g (22.6 mmol, 90%) of **1-113** as a white solid: mp 137-139 ^oC; IR (KBr) 3311, 3117, 2956, 1729, 1694, 1602, 1537, 1451, 1323, 1221, 1042 cm^{-1}; ^1H NMR δ 7.98 (d, 2 H, *J* = 8.7 Hz), 7.45 (d, 2 H, *J* = 8.7 Hz), 7.42-7.31 (m, 5 H), 6.99 (bs, 1 H), 5.20 (s, 2 H), 3.88 (s, 3 H); ^{13}C NMR δ 166.9, 153.1, 142.3, 135.9, 131.1, 128.9, 128.7, 128.6, 125.1, 117.8, 67.5, 52.2; MS (EI) *m/z* 285 ($M^{+\bullet}$, 38), 241 (43), 177 (77), 146 (88), 91 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{15}NO_4$ 285.1001, found 285.0999.



1-114

Methyl 4-((benzyloxycarbonyl)((2-methyloxiran-2-yl)methyl)amino)benzoate (1-114). To a solution of 1.96 g (6.87 mmol) of **1-113** in 20 mL of DMF at rt was added 190 mg (7.55 mmol) of NaH (95% dispersion in mineral oil). The reaction mixture was stirred until H_2 evolution ceased, then 900 μL (8.93 mmol) of 3-bromo-2-methylpropene was added. The mixture was stirred overnight at rt, quenched with H_2O, poured onto ice and extracted with 3 x 20 mL of CH_2Cl_2. The combined organic layers were washed with 50 mL of H_2O, dried

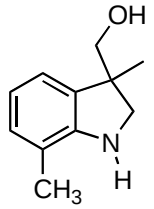
($MgSO_4$) and concentrated *in vacuo*. The crude residue was dissolved in 60 mL of CH_2Cl_2, cooled to 0 ^oC and treated portionwise with 2.03 g (8.24 mmol) of *m*-CPBA (70%). The disappearance of starting material was monitored by TLC (hexane:EtOAc; 2:1). The reaction mixture was quenched with aq. $Na_2S_2O_3$ solution and extracted with 3 x 15 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 5:1 to 3:1) to afford 2.06 g (5.79 mmol, 84%, 2 steps) of **1-114** as an oil: IR (neat) 3522, 3033, 2952, 1709, 1605, 1436, 1279, 1109, 1015, 773 cm^{-1}; ^1H NMR δ 8.01 (d, 2 H, *J* = 8.7 Hz), 7.37-7.25 (m, 7 H), 5.17 (s, 2 H), 3.92, 3.85 (AB, 2 H, *J* = 14.8 Hz), 3.89 (s, 3 H), 2.51 (app s, 2 H), 1.34 (s, 3 H); ^{13}C NMR δ 166.5, 155.2, 146.5, 136.1, 130.5, 128.6, 128.3, 128.2, 128.0, 126.6, 68.0, 55.9, 55.0, 52.3, 52.2, 19.4; MS (EI) *m/z* 355 ($M^{+\bullet}$, 62), 324 (30), 254 (55), 132 (49), 91 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{21}NO_5$ 355.1419, found 355.1415.



1-115

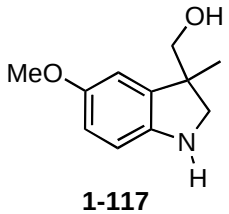
(3,5-Dimethylindolin-3-yl)methanol (1-115). According to General Protocol F, 163 mg (0.523 mmol) of **1-106**, 3.9 mg (0.016 mmol) of Cp_2TiCl_2, 123 mg (0.784 mmol) of collidine hydrochloride, and 43 mg (0.78 mmol) of Mn provided an oil (reaction time 3 h) that was purified first by chromatography on neutral alumina (hexane:EtOAc; 2:1) and then subjected to 111 mg (70% w/w, 0.0522 mmol) of Pd/C under 1 atm of H_2 (reaction time 2 h) to provide an oil that was purified by chromatography on SiO_2 (hexane:EtOAc; 1:1 with 1% NEt_3) to afford 57

mg (0.32 mmol, 62%, 2 steps) of **1-115** as an oil: IR (neat) 3327, 2958, 2922, 2864, 1614, 1495, 1463, 1238, 1033, 810 cm^{-1}; ^1H NMR δ 6.87-6.85 (m, 2 H), 6.56-6.53 (m, 1 H), 3.58, 3.51 (AB, 2 H, *J* = 10.6 Hz), 3.53, 3.22 (AB, 2 H, *J* = 9.1 Hz), 2.25 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR δ 149.3, 134.1, 128.7, 128.4, 123.8, 110.1, 69.4, 57.3, 47.7, 22.3, 21.0; MS (EI) *m/z* 177 ($M^{+\bullet}$, 45), 146 (100), 131 (69), 130 (38); HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO$ 177.1153, found 177.1154.



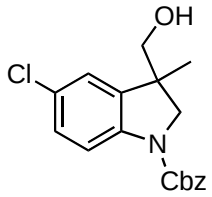
1-116

(3,7-Dimethylindolin-3-yl)methanol (1-116). According to General Protocol F, 230 mg (0.738 mmol) of **1-108**, 7.3 mg (0.030 mmol) of Cp_2TiCl_2, 174 mg (1.10 mmol) of collidine hydrochloride, and 60 mg (1.1 mmol) of Mn (reaction time 5 h) provided an oil that was purified by chromatography on neutral alumina (hexane:EtOAc; 4:1) and then subjected to 10 mg (10% w/w, 4.6 μmol) of Pd/C under 1 atm of H_2 to provide a mixture that was purified by chromatography on SiO_2 (hexane:EtOAc; 4:1 with 1% NEt_3) to afford 46 mg (0.25 mmol, 35%, 2 steps) of **1-116** as an oil: IR (neat) 3317, 2960, 2926, 2867, 1599, 1478, 1030, 749 cm^{-1}; ^1H NMR δ 6.91 (d, 2 H, *J* = 7.5 Hz), 6.69 (t, 1 H, *J* = 7.5 Hz), 3.61, 3.54 (AB, 2 H, *J* = 10.5 Hz), 3.60 (d, 1 H, *J* = 9.3 Hz), 3.29 (d, 1 H, *J* = 9.3 Hz), 2.12 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR δ 150.1, 133.0, 129.3, 120.6, 119.5, 119.2, 69.4, 56.9, 48.0, 22.6, 16.9; MS (EI) *m/z* 177 ($M^{+\bullet}$, 14), 146 (100), 131 (35); HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO$ 177.1153, found 177.1154.



1-117

(5-Methoxy-3-methylindolin-3-yl)methanol (1-117). According to General Protocol F, 236 mg (0.720 mmol) of **1-110**, 7.1 mg (0.028 mmol) of Cp_2TiCl_2, 170 mg (1.08 mmol) of collidine hydrochloride, and 59 mg (1.1 mmol) of Mn afforded an oil (reaction time 3 h) that was subjected to 46 mg (20% w/w, 0.022 mmol) of Pd/C and 1 atm of H_2 to provide an oil that was purified by chromatography on SiO_2 (hexane:EtOAc; 1:1) to afford 28 mg (0.14 mmol, 21%, 2 steps) of **1-117** as a purple oil: IR (neat) 3339, 2920, 2866, 1596, 1490, 1434, 1280, 1022 cm^{-1}; ^1H NMR δ 6.68-6.57 (m, 3 H), 3.74 (s, 3 H), 3.61, 3.54 (AB, 2 H, *J* = 10.8 Hz), 3.55, 3.25 (AB, 2 H, *J* = 9.3 Hz), 2.64 (bs, 2 H), 1.31 (s, 3 H); ^{13}C NMR δ 154.0, 145.3, 135.8, 113.1, 110.9, 110.2, 69.3, 57.6, 56.2, 48.2, 22.2; MS (EI) *m/z* 193 ($M^{+\bullet}$, 35), 162 (100), 147 (42), 118 (18); HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO_2$ 193.1102, found 193.1103.

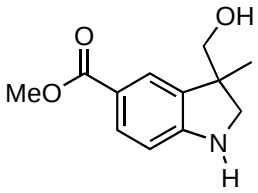


1-118

Benzyl 5-chloro-3-(hydroxymethyl)-3-methylindoline-1-carboxylate (1-118).

According to General Protocol C, 318 mg (0.958 mmol) of **1-112**, 7.1 mg (0.029 mmol) of Cp_2TiCl_2, 226 mg (1.43 mmol) of collidine hydrochloride, and 79 mg (1.4 mmol) of Mn

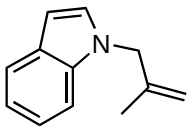
(reaction time 4 h) provided a mixture that was purified by chromatography on SiO_2 (hexane:EtOAc; 5:1 to 3:1) to afford 130 mg (0.392 mmol, 41%) of **1-118** as an oil: IR (neat) 3435, 2959, 1706, 1597, 1485, 1401, 1334, 1075 cm^{-1}; ^1H NMR (DMSO-d_6, 350 K) δ 7.64 (d, 1 H, *J* = 8.4 Hz), 7.46-7.29 (m, 5 H), 7.23 (d, 1 H, *J* = 2.1 Hz), 7.19 (dd, 1 H, *J* = 8.7 Hz, *J* = 2.4 Hz), 5.24 (s, 2 H), 4.71 (bs, 1 H), 4.06 (d, 1 H, *J* = 11.1 Hz), 3.64 (d, 1 H, *J* = 11.1 Hz), 3.45, 3.42 (AB, 2 H, *J* = 10.5 Hz), 1.27 (s, 3 H); ^{13}C NMR (DMSO-d_6, 350 K) δ 151.9, 140.5, 139.5, 136.0, 127.9, 127.5, 127.2, 126.9, 126.0, 123.1, 114.7, 67.3, 66.3, 57.2, 44.7, 22.6; MS (EI) *m/z* 331 ($M^{+\bullet}$, 40), 256 (14), 91 (100); HRMS (ESI) *m/z* calcd for $C_{18}H_{18}ClNO_3Na$ (M+Na) 354.0873, found 354.0851.



1-119

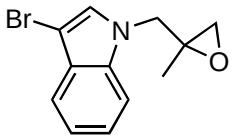
Methyl 3-(hydroxymethyl)-3-methylindoline-5-carboxylate (1-119). According to General Protocol F, 206 mg (0.579 mmol) of **1-114**, 4.3 mg (0.017 mmol) of Cp_2TiCl_2, 136 mg (0.868 mmol) of collidine hydrochloride, and 47 mg (0.86 mmol) of Mn (reaction time 5 h) provided an intermediate that was purified by chromatography on SiO_2 (hexane:EtOAc; 5:1). The intermediate was subjected to 20 mg (10% w/w, 9.3 μmol) of Pd/C and 1 atm of H_2, and the reaction mixture was purified by chromatography on SiO_2 (hexane:EtOAc; 1:1 with 1% NEt_3) to afford 72 mg (0.32 mmol, 56%, 2 steps) of **1-119** as an oil: IR (neat) 3368, 2952, 2868, 1687, 1610, 1502, 1293, 1253, 1110 cm^{-1}; ^1H NMR δ 7.78 (dd, 1 H, *J* = 8.4 Hz, *J* = 1.8 Hz), 7.68 (d, 1

H, *J* = 1.8 Hz), 6.53 (d, 1 H, *J* = 8.4 Hz), 4.21 (bs, 1 H), 3.83 (s, 3 H), 3.69 (d, 1 H, *J* = 9.1 Hz), 3.64, 3.54 (AB, 2 H, *J* = 11.1 Hz), 3.34 (d, 1 H, *J* = 9.3 Hz), 2.02 (bs, 1 H), 1.33 (s, 3 H); ^{13}C NMR δ 167.6, 155.8, 133.2, 131.7, 124.9, 119.6, 107.8, 69.1, 57.0, 51.8, 47.1, 22.8; MS (EI) *m/z* 221 ($M^{+\bullet}$, 23), 190 (81), 158 (100), 130 (68); HRMS (EI) *m/z* calcd for $C_{12}H_{15}NO_3$ 221.1051, found 221.1053.



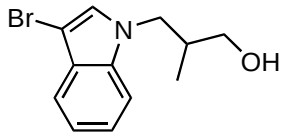
1-121

1-(2-Methylallyl)-1*H*-indole (1-121).[231] According to a modified literature procedure, a solution of 803 mg (6.85 mmol) of indole in 13 mL of DMF and 499 mg (8.90 mmol) of powdered KOH was stirred at 60 ^{o}C for 10 min, cooled to rt, and treated with 1.0 mL (10 mmol) of 3-bromo-2-methylpropene. The reaction mixture was stirred at 60 ^{o}C for 18 h, poured onto ice and diluted with 15 mL of EtOAc. The combined organic layers were washed with H_2O, brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane) to afford 832 mg (4.85 mmol, 71%) of **1-121** as a light green oil: IR (neat) 3054, 2913, 1657, 1612, 1462, 1333, 900, 739 cm^{-1}; ^{1}H NMR δ 7.61 (d, 1 H, *J* = 7.8 Hz), 7.27 (d, 1 H, *J* = 8.1 Hz), 7.19-7.05 (m, 2 H), 7.02 (d, 1 H, *J* = 3.3 Hz), 6.49 (d, 1 H, *J* = 3.3 Hz), 4.87 (s, 1 H), 4.69 (s, 1 H), 4.57 (s, 2 H), 1.63 (s, 3 H); ^{13}C NMR δ 141.4, 136.5, 128.8, 128.4, 121.7, 121.1, 119.6, 112.8, 109.9, 101.5, 52.7, 20.0; MS (EI) *m/z* 171 ($M^{+\bullet}$, 88), 156 (70), 130 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{13}N$ 171.1048, found 171.1046.



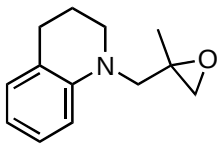
1-122

3-Bromo-1-((2-methyloxiran-2-yl)methyl)-1*H*-indole (1-122). To a solution of 746 mg (4.35 mmol) of **1-121** in 43 mL of acetonitrile was added 814 mg (4.57 mmol) of NBS. The reaction mixture was stirred overnight, quenched with H_2O and extracted with 3 x 10 mL of Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. According to General Protocol B, the crude oil, 765 mg (6.53 mmol) of NMO and 395 μL of OsO_4 (3 mol%, 0.33 M in toluene) were reacted and the disappearance of starting material was monitored by TLC (hexane:EtOAc; 2:1). The resulting golden oil was dissolved in 40 mL of THF and cooled to 0 ^oC. The solution was treated with 1.04 g (26.1 mmol) of NaH (60% dispersion in mineral oil) and stirred for 15 min. Upon addition of 1.70 g (5.22 mmol) of *p*-Ts_2O, the disappearance of starting material was monitored by TLC (hexane:EtOAc; 2:1). After 35 min, the reaction was quenched with H_2O and extracted with 3 x 15 mL of Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexane:EtOAc; 6:1) to afford 947 mg (3.55 mmol, 82%, 3 steps) of **1-122** as an oil: IR (neat) 3117, 3051, 2985, 2928, 1612, 1457, 1322, 1012 cm^{-1}; ^1H NMR δ 7.56 (app dt, 1 H, *J* = 8.1 Hz, *J* = 0.6 Hz), 7.36 (d, 1 H, *J* = 7.8 Hz), 7.30-7.17 (m, 2 H), 7.16 (s, 1 H), 4.30, 4.09 (AB, 2 H, *J* = 15.0 Hz), 2.65, 2.55 (AB, 2 H, *J* = 4.5 Hz), 1.26 (s, 3 H); ^{13}C NMR δ 136.4, 127.6, 127.5, 123.2, 120.6, 119.6, 110.0, 90.8, 56.4, 52.1, 51.6, 19.0; MS (EI) *m/z* 265 ($M^{+\bullet}$, 50), 208 (67), 186 (24), 129 (39), 69 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{12}NOBr$ 265.0102, found 265.0103.



1-123

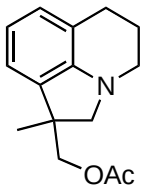
3-(3-Bromo-1*H*-indol-1-yl)-2-methylpropan-1-ol (1-123). According to General Protocol C, 171 mg (0.642 mmol) of **1-122**, 4.7 mg (0.019 mmol) of Cp_2TiCl_2, 151 mg (0.963 mmol) of collidine hydrochloride, and 52 mg (0.96 mmol) of Mn (reaction time 22 h) provided a mixture that was purified by chromatography on SiO_2 (hexane:EtOAc; 6:1) to afford 44 mg (0.16 mmol, 25%) of **1-123** as an oil: ^{1}H NMR δ 7.55 (d, 1 H, *J* = 8.1 Hz), 7.36 (d, 1 H, *J* = 7.8 Hz), 7.26-7.12 (m, 3 H), 4.22 (dd, 1 H, *J* = 15.0 Hz, *J* = 6.9 Hz), 3.95 (dd, 1 H, *J* = 14.4 Hz, *J* = 6.9 Hz), 3.47 (br s, 1 H), 3.43 (d, 1 H, *J* = 6.0 Hz), 2.30-2.15 (m, 1 H), 1.69 (bs, 1 H), 0.95 (d, 3 H, *J* = 6.9 Hz); MS (EI) *m/z* 269 ($M^{+\bullet}$, 13), 188 (14), 146 (46), 118 (100).



1-125

1-((2-Methyloxiran-2-yl)methyl)-1,2,3,4-tetrahydroquinoline (1-125). To a solution of 1.48 g (11.1 mmol) of 1,2,3,4-tetrahydroquinoline in 40 mL of acetonitrile was added 7.67 g (55.5 mmol) of K_2CO_3 and 1.6 mL (17 mmol) of 3-bromo-2-methylpropene at room temperature. The disappearance of starting material was monitored by TLC (hexane:EtOAc; 4:1). The reaction was quenched with H_2O and extracted with 3 x 20 mL of Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a brown oil that was used without purification. According to General Protocol B, the crude reaction mixture, 1.69 g (14.4 mmol) of

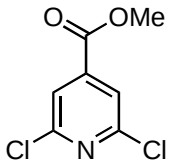
NMO and 370 μL of OsO_4 (1 mol%, 0.33 M in toluene) produced a residue that was filtered through a pad of Florisil, purified by chromatography on SiO_2 (hexane:EtOAc; 1:1) and concentrated *in vacuo*. The diol intermediate was subsequently dissolved in 89 mL of THF and cooled to 0 ^oC. To this solution was added 564 mg (22.3 mmol) of NaH (95%). The mixture was stirred for 15 min and 3.50 g (10.7 mmol) of *p*-Ts_2O was added in portions. The disappearance of starting material was monitored by TLC (hexane:EtOAc; 1:1). The reaction mixture was quenched with H_2O and extracted with 3 x 10 mL of EtOAc. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 8:1 with 1% NEt_3) to afford 1.38 g (6.78 mmol, 61%, 3 steps) of **1-125** as a colorless oil: IR (ATR) 2924, 1660, 1599, 1498, 1455, 1192 cm^{-1}; ^1H NMR δ 7.11 (t, 1 H, *J* = 7.5 H), 7.01 (d, 1 H, *J* = 8.1 Hz), 6.65 (t, 2 H, *J* = 8.1 Hz), 3.53, 3.41 (AB, 2 H, *J* = 15.9 Hz), 3.48-3.31 (m, 2 H), 2.82 (app t, 2 H, *J* = 6.0 Hz), 2.76, 2.66 (AB, 2 H, *J* = 4.8 Hz), 1.99 (app quint, 2 H, *J* = 6.0 Hz), 1.44 (s, 3 H); ^{13}C NMR δ 145.8, 129.2, 127.1, 122.2, 116.1, 111.0, 56.6, 55.9, 51.9, 50.9, 28.3, 22.2, 19.5; MS (EI) *m/z* 203 ($M^{+\bullet}$, 44), 146 (100), 130 (20); HRMS (EI) *m/z* calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1320.



1-126

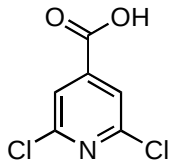
(1-Methyl-2,4,5,6-tetrahydro-1H-pyrrolo[3,2,1-ij]quinolin-1-yl)methyl acetate (1-126). According to General Protocol F, 206 mg (1.01 mmol) of **1-125**, 239 mg (1.52 mmol) of

collidine hydrochloride, 7.5 mg (0.030 mmol) of Cp_2TiCl_2, and 111 mg (2.02 mmol) of Mn afforded a crude reaction mixture that was subjected to 12 mg (0.10 mmol) of DMAP and 290 μL (3.04 mmol) of acetic anhydride in 10 mL of THF. The mixture was stirred for 5 h at rt until TLC analysis (hexane:EtOAc; 2:1) showed complete consumption of the alcohol. The reaction was quenched with satd. $NaHCO_3$ and extracted with 3 x 10 mL of Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc 12:1) to afford 172 mg (0.701 mmol, 69%, 2 steps) of **1-126** as an oil: IR (neat) 2936, 2806, 1740, 1599, 1489, 1236, 1034 cm^{-1}; ^1H NMR δ 6.87 (app t, 2 H, *J* = 6.8 Hz), 6.63 (t, 1 H, *J* = 7.5 Hz), 4.14, 4.06 (AB, 2 H, *J* = 10.8 Hz), 3.32 (d, 1 H, *J* = 8.7 Hz), 3.10-3.02 (m, 1 H), 2.93 (d, 1 H, *J* = 8.7 Hz), 2.87 (ddd, 1 H, *J* = 10.5 Hz, *J* = 7.2 Hz, *J* = 4.8 Hz), 2.68 (app t, 2 H, *J* = 6.6 Hz), 2.12-2.03 (m, 2 H), 2.08 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR δ 171.4, 149.5, 132.5, 127.4, 120.7, 119.9, 118.8, 69.3, 64.7, 46.9, 44.9, 24.0, 23.1, 22.0, 21.1; MS (EI) *m/z* 245 ($M^{+\bullet}$, 40), 172 (100), 170 (28), 144 (47); HRMS (EI) *m/z* calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1416.



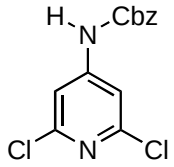
Methyl 2,6-dichloroisonicotinate.[95] According to a literature procedure, a flask was charged with 9.57 g (61.7 mmol) of citrazinic acid, 7.44 g (67.9 mmol) of Me_4NCl, and 17 mL (188 mmol) of $POCl_3$. The reaction mixture was heated to 130 ^oC for 18 h, cooled to 0 ^oC and quenched with 200 mL of freshly distilled MeOH. The solution was neutralized with powdered $NaHCO_3$, diluted with 200 mL of H_2O and concentrated *in vacuo*. The residue was extracted

with 2 x 150 mL of toluene, dried ($MgSO_4$), concentrated and filtered through a plug of SiO_2 (EtOAc/hexanes; 1:9) to afford 8.01 g (38.9 mmol, 63%) of methyl 2,6-dichloroisonicotinate as a pink solid that was used without further purification: mp 80-81 ^oC (lit. 80-81 ^oC); ^1H NMR δ 7.82 (s, 2 H), 3.98 (s, 3 H); MS (EI) *m/z* 209 ($[M+4]^{+\bullet}$) (5), 207 ($[M+2]^{+\bullet}$) (35), 205 ($M^{+\bullet}$, 54), 174 (100), 146 (53).



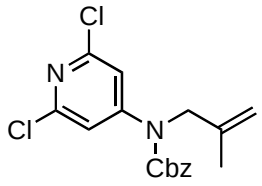
1-138

2,6-Dichloroisonicotinic acid (1-138).[95] According to a literature procedure, a solution of 8.91 g (43.2 mmol) of methyl 2,6-dichloroisonicotinate in 20 mL of THF was treated with 1.24 g (51.9 mmol) of LiOH in 60 mL of H_2O. The reaction mixture was stirred for 20 min at rt and concentrated *in vacuo* to remove the THF. The resulting solution was cooled to 0 ^oC and treated with 25 mL of 2 M HCl solution. After 2 h, the solid was filtered and dried to afford 6.05 g (31.5 mmol, 73%) of **1-138** as a tan solid: mp 208-210 ^oC (lit. 209-211 ^oC); ^1H NMR δ 7.86 (s, 2 H); MS (EI) *m/z* 195 ($[M+4]^{+\bullet}$) (28), 193 ($[M+2]^{+\bullet}$) (91), 191 ($M^{+\bullet}$, 100), 174 (61), 156 (43), 85 (56).

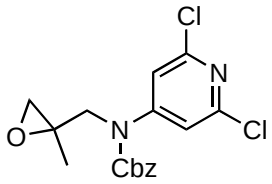


1-139

Benzyl 2,6-dichloropyridin-4-ylcarbamate (1-139). To a solution of 1.00 g (5.20 mmol) of **1-138** in 20 mL of THF was added 540 μL (6.35 mmol) of oxalyl chloride at rt. The reaction mixture was refluxed for 2 h, cooled to rt and concentrated *in vacuo*. The resulting oil was dissolved in 40 mL of freshly distilled acetone, cooled to 0 ^{o}C and treated dropwise with a solution of 1.01 g (15.6 mmol) of NaN_3 in 20 mL of H_2O. The mixture was stirred for 90 min, and the temperature was allowed to increase from 0 ^{o}C to 10 ^{o}C. The mixture was diluted with 15 mL of distilled Et_2O, and the aqueous layer was extracted with 2 x 10 mL of distilled Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to ~10% volume. After addition of 10 mL of toluene the remaining Et_2O and acetone were removed under reduced pressure. The residue was dissolved in 15 mL of toluene, stirred with $MgSO_4$ and treated with 1.1 mL (10 mmol) of benzyl alcohol. The mixture was heated at reflux for 15 h behind a blast shield, cooled to rt, diluted with water and extracted with 2 x 10 mL of EtOAc. The combined organic layers were dried ($MgSO_4$), concentrated and purified by chromatography on SiO_2 (hexane:EtOAc; 20:1 to 10:1 gradient) to afford 580 mg (1.95 mmol, 33%, 3 steps) of **1-139** as a brown oil: IR (ATR) 3302, 3259, 3153, 1699, 1572, 1505, 1250, 1218, 1071 cm^{-1}; ^{1}H NMR δ 7.37 (bs, 5 H), 7.36 (s, 2 H), 5.21 (s, 2 H); ^{13}C NMR δ 152.4, 151.4, 149.1, 135.1, 129.0, 128.9, 128.7, 111.4, 68.3; MS (EI) *m/z* 298 ([M+2]$^{+\bullet}$) (24), 296 (M$^{+\bullet}$, 37), 278 (82), 261 (61), 91 (100); HRMS (EI) *m/z* calcd for $C_{13}H_{10}Cl_2N_2O_2$ 296.0119, found 296.0112.

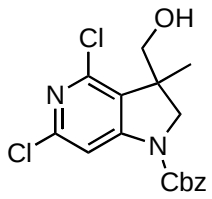


Benzyl 2,6-dichloropyridin-4-yl(2-methylallyl)carbamate. A solution of 547 mg (1.84 mmol) of **1-139** in 10 mL of THF at 0 ^{o}C was treated with 34 mg (0.092 mmol) of TBAI and 93 mg (3.7 mmol) of NaH (95%). The reaction mixture was stirred for 5 min, treated with 370 μL (3.68 mmol) of 3-bromo-2-methylpropene, warmed to rt and stirred for 16 h. After addition of 160 mg of NaH and 400 μL of 3-bromo-2-methylpropene, the mixture was stirred until starting material was consumed according to TLC (hexane:EtOAc; 4:1). The solution was then cooled to 0 ^{o}C, quenched with water and extracted with 3 x 10 mL of Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 15:1 to 10:1 gradient) to afford 497 mg (1.41 mmol, 77%) of benzyl 2,6-dichloropyridin-4-yl(2-methylallyl)carbamate as a colorless oil: IR (ATR) 3280, 1716, 1576, 1367, 1216, 1159 cm^{-1}; ^{1}H NMR δ 7.38-7.36 (m, 5 H), 7.30 (s, 2 H), 5.25 (s, 2 H), 4.94 (s, 1 H), 4.74 (s, 1 H), 4.26 (s, 2 H), 1.74 (s, 3 H); ^{13}C NMR δ 154.0, 153.4, 151.0, 139.5, 135.4, 128.9, 128.8, 128.4, 116.2, 111.8, 69.0, 54.4, 20.2; MS (EI) *m/z* 352 ([M+2] $^{+\bullet}$) (24), 350 ($M^{+\bullet}$, 38), 259 (30), 215 (80), 91 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{16}Cl_2N_2O_2$ 350.0588, found 350.0571.

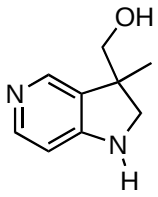


1-140

Benzyl 2,6-dichloropyridin-4-yl((2-methyloxiran-2-yl)methyl)carbamate (1-140). To a solution of 429 mg (1.22 mmol) of benzyl 2,6-dichloropyridin-4-yl(2-methylallyl)carbamate in 10 mL of CH_2Cl_2 at 0 ^oC was added 451 mg (1.83 mmol) of *m*-CPBA (70%). The reaction mixture was warmed to rt and after 6 h an additional 1 equiv (300 mg) of *m*-CPBA was added. The mixture was stirred for a total of 11 h, cooled to 0 ^oC, quenched with aq. $Na_2S_2O_3$ solution and extracted with 3 x 10 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 8:1) to afford 371 mg (1.01 mmol, 83%) of **1-140** as a colorless oil: IR (ATR) 3089, 1714, 1576, 1535, 1216, 1149, 1088 cm^{-1}; ^1H NMR δ 7.39 (s, 2 H), 7.39-7.37 (m, 5 H), 5.28, 5.21 (AB, 2 H, *J* = 12.0 Hz), 4.11, 3.78 (AB, 2 H, *J* = 15.6 Hz), 2.60, 2.58 (AB, 2 H, *J* = 4.2 Hz), 1.32 (s, 3 H); ^{13}C NMR δ 154.1, 153.6, 151.0, 135.1, 129.0, 129.0, 128.7, 117.8, 69.1, 56.1, 53.3, 51.7, 19.5; MS (ESI) *m/z* 389 $[M+Na]^+$ (14), 365 (22), 361 (100); HRMS (ESI) *m/z* calcd for $C_{17}H_{16}Cl_2O_3Na$ (M+Na) 389.0436, found 389.0467.



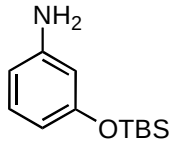
Benzyl 4,6-dichloro-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate. According to General Protocol F, 269 mg (0.733 mmol) of **1-140**, 5.5 mg (0.022 mmol) of Cp_2TiCl_2, 173 mg (1.10 mmol) of collidine hydrochloride, and 60 mg (1.1 mmol) of Mn (reaction time 3 h) afforded an oil that was purified by chromatography on SiO_2 (toluene:acetone; 8:1) to afford 147 mg (0.400 mmol, 55%) of benzyl 4,6-dichloro-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate as a waxy solid: IR (ATR) 3397, 2965, 2877, 1718, 1582, 1449, 1380, 1312 cm^{-1}; ^1H NMR δ 7.42-7.37 (m, 6 H), 5.30-5.20 (m, 2 H), 4.31, 3.74 (AB, 2 H, *J* = 11.1 Hz), 4.14, 3.58 (AB, 2H, *J* = 11.1 Hz), 2.62 (bs, 1 H), 1.41 (s, 3 H); ^{13}C NMR δ 154.8, 152.4, 150.7, 145.0, 135.3, 128.9, 128.9, 128.6, 127.3, 109.4, 68.5, 66.1, 59.1, 46.3 21.4; MS (EI) *m/z* 368 ($[M+2]^{+\bullet}$, 9), 366 ($M^{+\bullet}$, 15), 201 (10), 91 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{16}Cl_2N_2O_3$ 366.0538, found 366.0527.



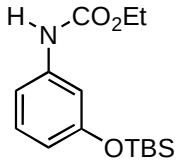
1-141

(3-Methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl)methanol (1-141). To a solution of 78 mg (0.21 mmol) of benzyl 4,6-dichloro-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate in 2 mL of MeOH at rt was added 22 mg (0.021 mmol) of

Pd/C. The reaction mixture was saturated with 1 atm of H_2, stirred for 21 h, quenched with Celite®, filtered, concentrated *in vacuo* and purified on neutral Al_2O_3 (hexane:EtOAc; 1:1 to 100% EtOH) to afford a white solid. This solid was washed once each (5 mL) with boiling acetone and boiling ethyl acetate. The organic extracts were combined and concentrated *in vacuo* to afford 33 mg (0.20 mmol, 95%) of **1-141** as a colorless oil: IR (ATR) 3248, 3160, 2925, 2866, 1649, 1608, 1522, 1030 cm^{-1}; ^1H NMR (CD_3OD) δ 7.94 (d, 1 H, *J* = 6.3 Hz), 7.90 (s, 1 H) 6.61 (d, 1 H, *J* = 6.3 Hz), 3.77, 3.47 (AB, 2 H, *J* = 10.5 Hz), 3.60, 3.53 (AB, 2 H, *J* = 10.8 Hz), 1.37 (s, 3 H); ^{13}C NMR δ 162.2, 144.3, 137.1, 133.1, 103.9, 69.1, 58.1, 47.0, 23.6; MS (ESI) *m/z* 165 ($[M+H]^+$, 100); HRMS (ESI) *m/z* calcd for $C_9H_{13}N_2O$ (M+H) 165.1028, found 165.1038.

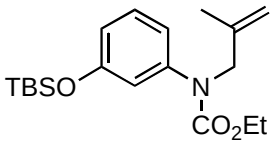


3-(*tert*-Butyldimethylsilyloxy)aniline. To a solution of 5.78 g (53.0 mmol) of 3-aminophenol (**1-142**) in 200 mL of THF was added 5.77 g (84.8 mmol) of imidazole, followed by 10.38 g (68.86 mmol) of TBSCl. The reaction mixture was stirred at rt overnight, quenched with 50 mL of satd. NH_4Cl, extracted with 3 x 50 mL of Et_2O, washed with brine, dried ($MgSO_4$), concentrated and purified by chromatography on SiO_2 (hexane:EtOAc; 15:1 to 5:1 gradient) to afford 11.06 g (49.50 mmol, 93%) of 3-(*tert*-butyldimethylsilyloxy)aniline as a tan oil: ^1H NMR (600 MHz) δ 6.99 (t, 1 H, *J* = 8.4 Hz), 6.30 (dd, 1 H, *J* = 7.8 Hz, *J* = 1.8 Hz), 6.25 (dd, 1 H, *J* = 7.8 Hz, *J* = 1.8 Hz), 6.20 (app t, 1 H, *J* = 1.8 Hz), 3.62 (br s, 2 H), 0.97 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR (150 MHz) δ 156.9, 147.8, 130.1, 110.7, 108.7, 107.4, 25.9, 18.4, -4.2.



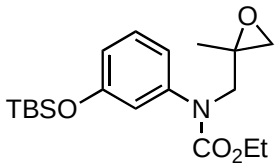
1-143

Ethyl 3-(*tert*-butyldimethylsilyloxy)phenylcarbamate (1-143). To a solution of 6.51 g (29.1 mmol) of 3-(*tert*-butyldimethylsilyloxy)aniline in 150 mL of CH_2Cl_2 cooled to 0 ^oC was added 3.9 mL of pyridine, followed by 2.9 mL (31 mmol) of ethylchloroformate dropwise over 1 h. The reaction was allowed to warm to rt, stirred for 1 h, and then quenched with 60 mL of satd. NH_4Cl. The mixture was diluted with 60 mL of H_2O, extracted with 2 x 20 mL of CH_2Cl_2, dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc; 10:1) to afford 8.34 g (28.2 mmol, 97%) of **1-143** as a golden oil: IR (ATR) 3321, 2957, 2930, 2859, 1704, 1596, 1540, 1220, 1063 cm^{-1}; ^1H NMR (600 MHz) δ 7.12 (t, 1 H, *J* = 7.8 Hz), 7.04 (br s, 1 H), 6.88 (br d, 1 H, *J* = 7.8 Hz), 6.68 (br s, 1 H), 6.54 (dd, 1 H, *J* = 8.1 Hz, *J* = 2.4 Hz), 4.21 (q, 2 H, *J* = 6.6 Hz), 1.29 (t, 3 H, *J* = 7.2 Hz), 0.97 (s, 9 H), 0.20 (s, 6 H); ^{13}C NMR (150 MHz) δ 156.5, 153.7, 139.3, 129.8, 115.2, 111.7, 110.8, 61.3, 25.9, 18.4, 14.7, -4.3; MS (ESI) *m/z* 318 ($[M+Na]^+$).



Ethyl 3-(*tert*-butyldimethylsilyloxy)phenyl(2-methylallyl)carbamate. To a solution of 6.09 g (20.6 mmol) of **1-143** in 100 mL of distilled THF cooled to 0 ^oC was added 380 mg (1.03 mmol) of TBAI, followed by 937 mg (37.1 mmol) of NaH 95% (added piecewise). The reaction

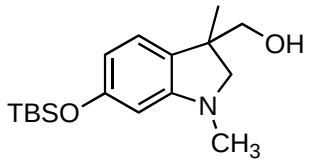
mixture was stirred at 0 ^{o}C for 20 min when 3.1 mL (31 mmol) of methallyl bromide was added. Upon addition of the methallyl bromide, the flask was removed from the ice bath and the mixture was stirred for a total of 3 h when TLC (hexane:EtOAc; 4:1) analysis showed the starting material was consumed. The mixture was then cooled to 0 ^{o}C, quenched with 10 mL of H_2O, extracted with 3 x 10 mL of Et_2O, washed with 10 mL of brine, dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 12:1) to afford 4.96 g (14.2 mmol, 69%) of ethyl 3-(*tert*-butyldimethylsilyloxy)phenyl(2-methylallyl)carbamate as a tan oil: IR (ATR) 2931, 1703, 1597, 1488, 1252, 1193 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.20 (t, 1 H, J = 7.8 Hz), 6.88 (dd, 1 H, J = 7.8 Hz, J = 1.2 Hz), 6.74 (s, 1 H), 6.68 (dd, 1 H, J = 7.8 Hz, J = 1.8 Hz), 4.79 (s, 1 H), 4.70 (s, 1 H), 4.18 (s, 2 H), 4.07 (q, 2 H, J = 7.2 Hz), 1.66 (s, 3 H), 1.14 (t, 3 H, J = 6.6 Hz), 0.93 (s, 9 H), 0.17 (s, 6 H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 155.0, 154.6, 142.8, 141.2, 129.3, 119.0, 118.0, 117.4, 111.6, 61.2, 55.0, 25.5, 19.8, 18.0, 14.4, -4.6; MS (ESI) *m/z* 372 ([M+Na]$^{+}$).



1-144

Ethyl 3-(*tert*-butyldimethylsilyloxy)phenyl((2-methyloxiran-2-yl)methyl)carbamate (1-144). To a solution of 388 mg (1.11 mmol) of ethyl 3-(*tert*-butyldimethylsilyloxy)phenyl(2-methylallyl)carbamate in 5 mL of CH_2Cl_2 cooled to 0 ^{o}C was added 235 mg (2.22 mmol) of Na_2CO_3 in 2 mL of water followed by 410 mg (1.67 mmol) of *m*-CPBA (70% purity). The mixture was allowed to warm from 0 ^{o}C to rt over 2 h. At this time, an additional 273 mg of *m*-

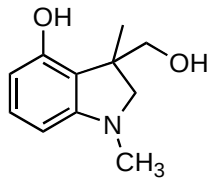
CPBA was added. After 30 min, the reaction was determined to be complete by TLC analysis (hexane:EtOAc; 2:1). The mixture was quenched with 15 mL of $Na_2S_2O_3$ solution, extracted with 3 x 10 mL of $CHCl_3$, dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexane:EtOAc; 10:1 to 6:1 gradient) to afford 236 mg (0.646 mmol, 58%) of **1-144** as a light yellow oil: IR (ATR) 2931, 2859, 1703, 1597, 1488, 1260, 954 cm^{-1}; ^1H NMR (600 MHz) δ 7.19 (t, 1 H, *J* = 7.8 Hz), 6.84 (d, 1 H, *J* = 7.8 Hz), 6.74-6.72 (m, 2 H), 4.16 (q, 2 H, *J* = 7.2 Hz), 3.99, 3.61 (AB, 2 H, *J* = 14.4 Hz), 2.54, 2.52 (AB, 2 H, *J* = 4.8 Hz), 1.38 (s, 3 H), 1.21 (bs, 3 H), 0.98 (s, 9 H), 0.20 (s, 6 H); ^{13}C NMR (150 MHz) δ 156.2, 156.0, 143.5, 129.6, 120.0, 119.5, 118.8, 62.1, 55.9, 55.6, 53.0, 25.9, 19.6, 18.4, 14.8, -4.2; MS (EI) *m/z* 365 ($M^{+\bullet}$, 77), 280 (55), 238 (67), 220 (100), 192 (97), 178 (65); HRMS (EI) *m/z* calcd for $C_{19}H_{31}NO_4Si$ 365.2022, found 365.2033.



1-147

(6-(*tert*-Butyldimethylsilyloxy)-1,3-dimethylindolin-3-yl)methanol (1-147). A mixture of 178 mg (0.486 mmol) of **1-144**, 115 mg (0.730 mmol) of coll-HCl, 40 mg (0.73 mmol) of Mn, and 3.6 mg (0.015 mmol) of Cp_2TiCl_2 was purged with argon 3 times, dissolved in 5.0 mL of distilled, degassed THF, and heated at reflux. After 4 h, the solution was allowed to cool to room temperature and was quenched with 10 mL of satd. NH_4Cl, extracted with 3 x 10 mL of EtOAc; washed with 10 mL of brine, dried (Na_2SO_4), concentrated, and purified on neutral alumina (hexane:EtOAc; 10:1 to 1:1 gradient) to afford 53 mg (0.14 mmol, 30%) of **1-145**. To a solution

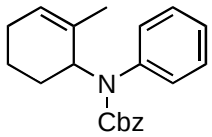
of 53 mg (0.14 mmol) of **1-145** in 3 mL of dry THF cooled to 0 ^{o}C was added 28 mg (0.72 mmol) of $LiAlH_4$. Upon addition, the mixture was stirred until no gas evolution was observed and then heated at reflux. TLC analysis (hexane:EtOAc; 1:1) after 50 min showed that the starting material was consumed. The solution was cooled to 0 ^{o}C, quenched with MeOH, diluted with 5 mL of H_2O, saturated with potassium sodium tartrate, and diluted with 5 mL of EtOAc. The solution was stirred until biphasic when it was partitioned and extracted with 3 x 5 mL of EtOAc. The combined organic extracts were washed with 5 mL of brine, dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc; 2:1) to afford 38 mg (0.12 mmol, 85%) of **1-147** as a colorless oil: IR (ATR) 3373, 2956, 1612, 1497, 1253, 985 cm^{-1}; ^{1}H NMR (600 MHz) δ 6.81 (d, 1 H, *J* = 7.8 Hz), 6.15 (dd, 1 H, *J* = 7.8 Hz, *J* = 1.8 Hz), 5.98 (d, 1 H, *J* = 1.8 Hz), 3.56, 3.51 (AB, 2 H, *J* = 10.8 Hz), 3.40, 2.98 (AB, 2 H, *J* = 9.0 Hz), 2.70 (s, 3 H), 1.65 (br s, 1 H), 1.28 (s, 3 H), 0.98 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR (150 MHz) δ 156.8, 154.6, 127.1, 122.8, 108.8, 100.4, 69.4, 66.0, 45.7, 35.9, 25.9, 22.3, 18.4, -4.2; MS (EI) *m/z* 307 ($M^{+\bullet}$, 40), 276 (100), 204 (20), 73 (24); HRMS (EI) *m/z* calcd for $C_{17}H_{29}NO_2Si$ 307.1968, found 307.1960.



1-148

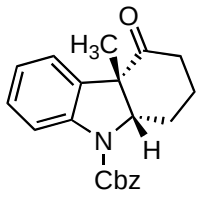
3-(Hydroxymethyl)-1,3-dimethylindolin-4-ol (1-148). A mixture of 178 mg (0.486 mmol) of **1-144**, 115 mg (0.730 mmol) of coll-HCl, 40 mg (0.73 mmol) of Mn, and 3.6 mg (0.015 mmol) of Cp_2TiCl_2 was purged with argon 3 times, dissolved in 5.0 mL of distilled,

degassed THF and heated at reflux. After 4 h, the reaction mixture was allowed to cool to room temperature and quenched with 10 mL of satd. NH_4Cl, extracted with 3 x 10 mL of EtOAc, washed with 10 mL of brine, dried (Na_2SO_4), concentrated, and purified by chromatography on neutral alumina (hexane:EtOAc; 10:1 to 1:1 gradient) to afford 59 mg (0.16 mmol, 33%) of **1-146**. To a solution of 59 mg (0.16 mmol) of **1-146** in 3 mL of dry THF cooled to 0 ^oC was added 31 mg (0.81 mmol) of $LiAlH_4$. Upon addition and after visible gas evolution had ceased, the mixture was heated at reflux. TLC analysis (hexane:EtOAc; 1:1) after 50 min showed that starting material was consumed. The mixture was cooled to 0 ^oC and then quenched dropwise with MeOH until no further gas evolution was observed. To this solution was added 2 mL of a satd. potassium sodium tartrate followed by 5 mL of EtOAc. The mixture was extracted with 3 x 5 mL of EtOAc, dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 2:1) to afford 24 mg (0.12 mmol, 77%, (25% over 2 steps) of **1-148** as a tan waxy solid: IR (ATR) 3206, 2959, 1617, 1595, 1477, 1246, 903 cm^{-1}; ^1H NMR (600 MHz) δ 8.37 (bs, 1 H), 7.01 (t, 1 H, *J* = 7.8 Hz), 6.28 (d, 1 H, *J* = 8.4 Hz), 6.07 (d, 1 H, *J* = 7.8 Hz), 3.90, 3.75 (AB, 2 H, *J* = 9.6 Hz), 3.09, 2.88 (AB, 2 H, *J* = 8.4 Hz), 2.85 (bs, 1 H), 2.73 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR (150 MHz) δ 154.1, 153.4, 129.9, 119.2, 107.5, 100.1, 70.1, 65.5, 46.3, 36.0, 21.5; MS (EI) *m/z* 193 ($M^{+\bullet}$, 26), 162 (100), 147 (29); HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO_2$ 193.1103, found 193.1100.



1-154

Benzyl 2-methylcyclohex-2-enyl(phenyl)carbamate (1-154). To a solution of 224 mg (2.00 mmol) of **1-153** in 5 mL of CH_2Cl_2 cooled to 0 ^oC was added 840 μL (6.03 mmol) of NEt_3 followed by 310 μL (4.01 mmol) of MsCl. Upon addition, the mixture was allowed to warm slowly to 25 ^oC overnight. The solution was quenched with 10 mL of H_2O, extracted with 3 x 5 mL of CH_2Cl_2, dried (Na_2SO_4), concentrated, and used without further purification. To a solution of 396 mg (2.40 mmol) of benzyl phenylcarbamate in 10 mL of dry DMF cooled to 0 ^oC was added 120 mg (3.00 mmol) of NaH (60%). The reaction mixture was stirred for 15 min at 0 ^oC and then the crude mesylate intermediate was added in 1 mL of dry DMF. The resulting yellow mixture was allowed to warm to 25 ^oC overnight, quenched with 10 mL of H_2O, extracted with 3 x 10 mL of EtOAc; washed with 10 mL of water and 10 mL of brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on SiO_2 (hexane:Et_2O; 10:1) to afford 361 mg (1.12 mmol, 56%, 2 steps) of **1-154** as a light yellow oil: IR (ATR) 3032, 1697, 1597, 1495, 1453, 1396, 1293, 1120, 1017 cm^{-1}; ^1H NMR (300 MHz, 350 K, DMSO-d_6) δ 7.39-7.22 (m, 8 H), 7.17-7.14 (m, 2 H), 5.57 (bs, 1 H), 5.11, 5.06 (AB, 2 H, J = 12.9 Hz), 4.68 (app t, 1 H, J = 7.2 Hz), 1.91-1.64 (m, 4 H), 1.76 (s, 3 H), 1.47-1.24 (m, 2 H); ^{13}C NMR (75 MHz, 350K, DMSO-d_6) δ 154.4, 140.1, 136.4, 133.0, 128.1, 127.7, 127.7, 127.1, 126.7, 126.3, 125.6, 65.9, 57.2, 27.4, 24.0, 19.9, 19.8; MS (ESI) *m/z* 322 ($[M+H]^+$).



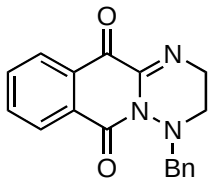
1-157

(4a*S*,9a*S*)-Benzyl 4a-methyl-4-oxo-2,3,4,4a-tetrahydro-1*H*-carbazole-9(9a*H*)-carboxylate (1-157). To a solution of 952 mg (2.96 mmol) of **1-154** in 12 mL of CH_2Cl_2 and 691 mg (6.52 mmol) of Na_2CO_3 (dissolved in 12 mL of water) at 0 ^oC was added 1.46 g (5.92 mmol) of *m*-CPBA (70%). Upon addition of the oxidant, the mixture was allowed to warm slowly to 25 ^oC. After 2 h, the reaction was quenched with 10 mL of a 1 M $Na_2S_2O_3$ solution, diluted with 5 mL of H_2O, extracted with 3 x 10 mL of CH_2Cl_2, washed with 10 mL of brine, dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc; 10:1 with 1% NEt_3 to hexane:EtOAc; 5:1 gradient) to afford 841 mg (2.49 mmol, 84%) of **1-155** as a colorless oil.

A mixture of 841 mg (2.49 mmol) of **1-155**, 18.9 mg (0.0759 mmol) of Cp_2TiCl_2, 589 mg (3.73 mmol) of Coll-HCl and 274 mg (4.99 mmol) of Mn was then purged 3 times with Ar, diluted with 24 mL of THF and placed in a pre-heated oil bath. After heating at reflux under Ar overnight, the solution was cooled to 25 ^oC, quenched with 10 mL of satd. NH_4Cl, extracted with 3 x 10 mL of EtOAc; washed with 10 mL of brine, dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc; 5:1 with 1% NEt_3 to hexane:EtOAc; 1:1) to afford 97 mg (0.29 mmol, 12%) of **1-156** as a light brown oil that was taken on to the Dess-Martin oxidation. To a solution of 97 mg (0.29 mmol) of the alcohol intermediate in 5 mL of CH_2Cl_2 was added 366 mg (0.862 mmol) of Dess-Martin periodinane reagent. This mixture was stirred under N_2 at 25 ^oC overnight and after 13 h reaction time, TLC analysis (hexane:EtOAc; 4:1) showed that the starting material had been consumed. The mixture was poured over 10 mL of

satd. $NaHCO_3$, partitioned, and extracted with 3 x 5 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc; 6:1) to afford 61 mg (0.18 mmol, 63%, 6% over 3 steps) of **1-157** as a colorless oil: IR (ATR) 2957, 1700, 1597, 1479, 1401, 1287, 1084 cm^{-1}; ^1H NMR (300 MHz, 365 K, DMSO-d_6) δ 7.71 (d, 1 H, J = 8.1 Hz), 7.48-7.33 (m, 5 H), 7.28-7.19 (m, 1 H), 7.04-6.96 (m, 2 H), 5.36-5.29 (m, 2 H), 4.47-4.43 (m, 1 H), 2.44-2.20 (m, 2 H), 2.13-2.00 (m, 1 H), 1.80-1.64 (m, 3 H), 1.33 (s, 3 H); ^{13}C NMR (75 MHz, 365 K, DMSO-d_6) δ 207.8, 151.5, 140.4, 135.8, 133.5, 127.9, 127.8, 127.3, 127.1, 122.6, 122.5, 114.4, 68.0, 66.3, 55.1, 37.1, 27.2, 24.5, 17.3; HRMS (TOF MS ES^+) *m/z* calcd for $C_{21}H_{21}NO_3$ 358.1419, found 358.1443.

4.3 CHAPTER 2 EXPERIMENTAL[6]



2-59

4-Benzyl-3,4-dihydro-2*H*-[1,2,4]triazino[2,3-*b*]isoquinoline-6,11-dione, (2-59).[7] To a solution of 230 mg (0.685 mmol) of **2-61** in PhCl (4 mL) was added 206 mg (0.483 mmol) of DPPB. Upon addition, the flask was placed in a pre-heated oil bath at 110 ^{o}C, and the mixture was stirred under a N_2 atmosphere overnight, cooled to 25 ^{o}C and extracted with 4 x 5 mL of 10% HCl. The combined acidic aqueous phases were washed once with 10 mL of CH_2Cl_2 and then basicified with 10% NaOH solution until the pH reached ~12. The alkaline solution was extracted with 4 x 10 mL of Et_2O, dried (Na_2SO_4), and concentrated *in vacuo* to afford a green/brown residue. The light yellow aqueous was extracted with 2 x 20 mL of CH_2Cl_2 and the combined Et_2O and CH_2Cl_2 extracts were concentrated *in vacuo* and purified by chromatography on SiO_2 (CH_2Cl_2:EtOH; 15:1) to afford 43 mg of a light brown residue. This residue was stored at room temperature for 10 d when a purity check revealed a new compound by 1H NMR analysis. This material was purified by chromatography on SiO_2 (CH_2Cl_2:EtOH, 30:1 to 15:1) to afford 25 mg (0.082 mmol, 12%) of **2-59** as a yellow/brown solid: ^{1}H NMR δ 8.38 (d, 1 H, *J* =

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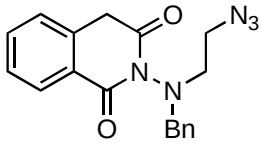
[6] All NMR data were recorded on a 600 MHz Bruker instrument in $CDCl_3$ unless otherwise noted.

[7] The results from this reaction are not reproducible. The product obtained has been tentatively assigned as **2-59**.

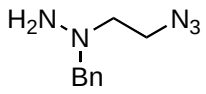
7.8 Hz), 8.28 (d, 1 H, *J* = 7.8 Hz), 7.88 (t, 1 H, *J* = 7.2 Hz), 7.80 (t, 1 H, *J* = 7.2 Hz), 7.55 (d, 2 H, *J* = 7.2 Hz), 7.38 (t, 2 H, *J* = 7.2 Hz), 7.34 (t, 1 H, *J* = 7.2 Hz), 4.08 (br s, 2 H), 3.98 (t, 2 H, *J* = 4.8 Hz), 3.13-3.12 (m, 2 H); ^{13}C NMR δ 176.2 157.6, 144.6, 135.8, 135.4, 133.9, 131.6, 130.2, 129.9, 129.6, 128.9, 128.5, 127.8, 58.9, 43.4, 40.8; MS (ESI) *m/z* 306 ($[M+H]^+$).



2-61

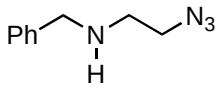
2-((2-Azidoethyl)(benzyl)amino)isoquinoline-1,3(2*H*,4*H*)-dione (2-61). To a flame-dried 100 mL flask was added 3.20 g (7.60 mmol) of **2-75**, 72 mg (0.37 mmol) of CuI, 94 mg (0.76 mmol) of 2-picolinic acid and 7.42 g (22.8 mmol) of Cs_2CO_3. The mixture was purged 3 times with N_2, diluted with 36 mL of anhydrous dioxane and heated with 2.3 mL (15 mmol) of diethyl malonate. The lime green solution was heated at 70 ^oC under a N_2 atmosphere. TLC analysis (hexane:EtOAc; 6:1) after 3 h showed that the starting material was consumed. The reaction mixture was cooled to 25 ^oC, quenched with 20 mL of saturated NH_4Cl solution, diluted with 20 mL of H_2O, and filtered through a coarse fritted filter. The collected solid was rinsed with EtOAc and the combined phases were partitioned. The aqueous phase was then extracted with 3 x 10 mL of EtOAc, and the combined organic phases were concentrated *in vacuo*. The residue was dissolved in 50 mL of toluene with 5 mL of H_2O when 433 mg (2.28 mmol) of *p*-TSA was added and the mixture was heated at reflux overnight. TLC analysis (hexane:EtOAc; 4:1) showed the streaky intermediate was converted to one UV active spot (stain with $KMnO_4$). The reaction mixture was cooled to 25 ^oC, quenched with 20 mL of satd. $NaHCO_3$, partitioned,

and then the aqueous phase was extracted with 3 x 15 mL of EtOAc. The combined organic phases were washed with 12 mL of brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexane:EtOAc; 10:1 to 5:1 gradient) to afford 1.87 g (5.57 mmol, 73%, 2 steps) of **2-61** as a light yellow/green oil: IR (ATR) 3063, 2924, 2098, 1730, 1683, 1605, 1462, 1345, 1228 cm^{-1}; ^1H NMR δ 8.17 (d, 1 H, *J* = 11.7 Hz), 7.55 (dd, 1 H, *J* = 7.2 Hz, *J* = 1.2 Hz), 7.47 (d, 2 H, *J* = 7.2 Hz), 7.42 (t, 1 H, *J* = 7.8 Hz), 7.28-7.26 (m, 2 H), 7.22-7.19 (m, 2 H), 4.45, 4.39 (AB, 2 H, *J* = 12.6 Hz), 4.00, 3.83 (AB, 2 H, *J* = 22.2 Hz), 3.50-3.38 (m, 4 H); ^{13}C NMR δ 169.9, 165.2, 137.0, 133.9, 133.8, 129.5, 129.4, 128.5, 127.9, 127.9, 127.2, 125.9, 60.2, 53.0, 50.4, 37.9; MS (ESI) *m/z* 336 ($[M+H]^+$).



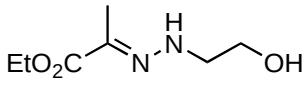
2-63

1-(2-Azidoethyl)-1-benzylhydrazine (2-63). To a solution of 87 mg (0.30 mmol) of **2-72** in 2.5 mL of THF and 500 µL of H_2O at 25 ^oC was added 96 mg (0.90 mmol) of hydrazine dihydrochloride. This mixture was stirred at 25 ^oC for 3 h, quenched with solid Na_2CO_3, and concentrated *in vacuo*. The resulting oil was immediately purified by chromatography on SiO_2 (hexane:EtOAc; 1:1 with 1% NEt_3) to afford 36 mg (0.19 mmol, 63%) of **2-63** as an unstable, colorless oil: IR (ATR) 3345, 2937, 2815, 2099, 1717, 1600, 1495, 1453, 1352, 1279 cm^{-1}; ^1H NMR δ 7.36-7.33 (m, 4 H), 7.31-7.27 (m, 1 H), 3.74 (s, 2 H), 3.48 (t, 2 H, *J* = 5.4 Hz), 2.75 (t, 2 H, *J* = 6.0 Hz), 2.74 (br s, 2 H); ^{13}C NMR δ 137.3, 129.2, 128.7, 127.7, 67.7, 58.8, 48.8; MS (ESI) *m/z* 192, ($[M+H]^+$).



2-65

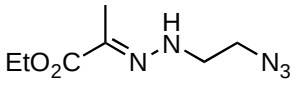
2-Azido-*N*-benzylethanamine (2-65). To a solution of 100 µL (0.704 mmol) of *N*-benzylethanolamine, 115 µL (0.774 mmol) of DBU, 457 mg (7.04 mmol) of NaN_3 in 5 mL of CH_3CN cooled to 0 ^oC was added 182 µL (0.845 mmol) of DPPA. Upon addition, the reaction mixture was heated at reflux for 7 h, cooled to rt and quenched with 10 mL of water. The reaction was then diluted with 5 mL of EtOAc and partitioned. The aqueous phase was extracted with 3 x 10 mL of EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4), concentrated under reduced pressure and filtered through a plug of neutral alumina using hexane:EtOAc; 4:1 as mobile phase to afford 58 mg (0.41 mmol, 59%) of **2-65** as a light golden oil: ^1H NMR δ 7.35-7.20 (m, 5 H), 3.81 (s, 2 H), 3.41 (t, 2 H, *J* = 5.4 Hz), 2.80 (t, 2 H, *J* = 6.0 Hz), 1.56 (br s, 1 H).



2-70

(*E*)-Ethyl 2-(2-(2-hydroxyethyl)hydrazono)propanoate (2-70). To a solution of 3.6 mL (32 mmol) of ethyl pyruvate in 75 mL of THF was added 1 mL of EtOH containing 3.0 mL (45 mmol) of 2-hydroxyethylhydrazine. This mixture was heated at reflux for 5 h, concentrated *in vacuo* to a thick oil, diluted with 10 mL of water and 10 mL of EtOAc and partitioned. The aqueous phase was extracted with 3 x 10 mL of EtOAc, washed with brine, dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on SiO_2 (100% EtOAc) to afford 3.32 g (19.1 mmol, 59%) of **2-70** as a pale oil: IR (ATR) 3308, 2938, 1697, 1561, 1442, 1369, 1313,

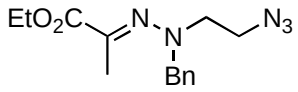
1144, 1054 cm^{-1}; ^1H NMR δ 6.08 (s, 1 H), 4.27 (q, 2 H, *J* = 7.2 Hz), 3.85 (t, 2 H, *J* = 4.8 Hz), 3.59-3.56 (m, 2 H), 2.98 (s, 1 H), 1.95 (s, 3 H), 1.32 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 165.2, 132.8, 62.5, 61.3, 52.4, 14.5, 10.3; MS (EI) *m/z* 174 ($M^{+\bullet}$, 9), 128 (30), 117 (69), 73 (88), 61 (100); HRMS (EI) *m/z* calcd for $C_7H_{14}N_2O_3$ 174.1004, found 174.1009.



2-71

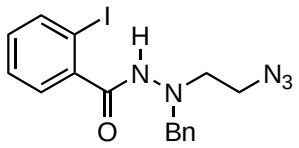
(*E*)-Ethyl 2-(2-(2-azidoethyl)hydrazono)propanoate (2-71). To a solution of 1.96 g (11.3 mmol) of **2-70** and 2.4 mL (17 mmol) of NEt_3 in 50 mL of THF was added 1.1 mL (15 mmol) of MsCl. This was stirred at 25 ^oC for 15 min, quenched with 20 mL of satd. $NaHCO_3$, diluted with 20 mL of water and extracted with 3 x 15 mL of Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil that was used without further purification. To the crude oil was added 70 mL of DMF followed by 2.19 g (33.8 mmol) of NaN_3. This mixture was heated to 50 ^oC behind a blast shield for 16 h when TLC analysis (hexane:EtOAc; 1:1) showed that the mesylate intermediate was completely consumed. The reaction was cooled to 25 ^oC, diluted with 50 mL of water and 30 mL of brine and extracted with 4 x 50 mL of EtOAc. The combined organic phases were washed with 50 mL of water, 50 mL of brine, dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on SiO_2 (100% hexane to hexane:EtOAc; 2:1 gradient with 1% NEt_3) to afford 1.57 g (7.88 mmol, 70%, 2 steps) of **2-71** as a yellow oil: IR (ATR) 3310, 2982, 2099, 1699, 1569, 1445, 1369, 1307, 1149 cm^{-1}; ^1H NMR δ 5.84 (s, 1 H), 4.29 (q, 2 H, *J* = 7.2 Hz), 3.63-3.60 (m, 2 H), 3.55-3.53 (m, 2 H), 1.96 (s, 3 H), 1.33 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 165.1, 134.0, 61.4, 51.5, 49.9, 14.6, 10.5; MS (EI)

m/z 184 ([M-CH_3]$^+$, 46), 174 (42), 130 (53), 117 (100), 56 (75); HRMS (EI) *m/z* calcd for $C_6H_{10}N_5O_2$ 184.0833 ([M-CH_3]), found 184.0835 ([M-CH_3]).



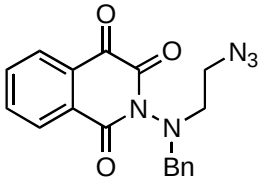
2-72

(*E*)-Ethyl 2-(2-(2-azidoethyl)-2-benzylhydrazono)propanoate (2-72). To a solution of 491 mg (2.46 mmol) of **2-71** in 10 mL of DMF was added 681 mg (4.92 mmol) of K_2CO_3, 369 mg (2.46 mmol) of NaI, and 1.8 mL (15 mmol) of benzyl bromide. The mixture was heated at 70 ^oC behind a blast shield for 17 h, cooled to 25 ^oC, quenched with 10 mL of water and extracted with 3 x 15 of EtOAc. The combined organic layers were washed with 20 mL of water, 20 mL of brine, dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on SiO_2 (100% hexane to hexane:EtOAc; 1:1 gradient with 1% NEt_3) to afford 510 mg (1.76 mmol, 72%) of **2-72** as a golden oil: IR (ATR) 2982, 2100, 1710, 1585, 1496, 1453, 1364, 1301, 1150, 1129, 1027 cm^{-1}; ^1H NMR δ 7.38-7.35 (m, 4 H), 7.32-7.29 (m, 1 H), 4.33 (q, 2 H, *J* = 7.2 Hz), 4.07 (s, 2 H), 3.34 (t, 2 H, *J* = 5.4 Hz), 3.23 (t, 2 H, *J* = 5.4 Hz), 2.22 (s, 3 H), 1.36 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 165.1, 153.2, 136.8, 128.9, 128.4, 127.9, 62.0, 61.1, 56.2, 49.9, 16.2, 14.5; MS (EI) *m/z* 289 ($M^{+\bullet}$, 27), 234 (62), 188 (54), 91 (71), 65 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{19}N_5O_2$ 289.1542, found 289.1539.



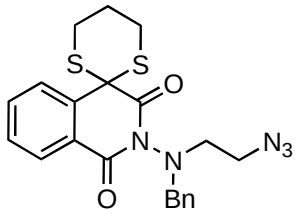
2-75

***N*'-(2-Azidoethyl)-*N*'-benzyl-2-iodobenzohydrazide (2-75).** To a solution of 4.33 g (16.3 mmol) of 2-iodobenzoyl chloride in 20 mL of CH_2Cl_2 cooled to 0 ^oC was added a solution of 3.27 g (17.1 mmol) of **2-63** in 5 mL of CH_2Cl_2 *via* syringe, followed by 3.0 mL (22 mmol) of NEt_3. After addition, the vessel was removed from the ice bath and the solution was allowed to warm to 25 ^oC overnight. After 12 h, the reaction was quenched with 15 mL of satd. $NaHCO_3$, partitioned, and extracted with 3 x 10 mL of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo*, and recrystallized using hexane:EtOAc to afford 4.74 g (11.3 mmol, 69%) of **2-75** as tiny cream colored needles: mp 100-101 ^oC; IR (ATR) 3232, 2871, 2104, 1658, 1580, 1513, 1461, 1278 cm^{-1}; ^1H NMR δ 7.82 (dd, 2 H, *J* = 7.9 Hz, *J* = 0.8 Hz), 7.45 (app d, 2 H, *J* = 7.2 Hz), 7.37 (app t, 2 H, *J* = 7.2 Hz), 7.33-7.27 (m, 2 H), 7.07, (td, 1 H, *J* = 7.8 Hz), 6.93 (dd, 1 H, *J* = 7.5 Hz, *J* = 1.2 Hz), 6.74 (s, 1 H), 4.35 (s, 2 H), 3.56 (t, 2 H, *J* = 6.0 Hz), 3.43 (t, 2 H, *J* = 6.0 Hz); ^{13}C NMR δ 169.2, 140.5 140.1, 136.9, 131.6, 129.6, 128.8, 128.3, 128.3, 128.0, 92.8, 60.5, 54.8, 49.2; MS (ESI) *m/z* 422 ($[M+H]^+$).



2-90

2-((2-Azidoethyl)(benzyl)amino)isoquinoline-1,3,4(2*H*)-trione, (2-90). To a solution of 251 mg (0.748 mmol) of **2-61** in 6 mL of 1:1;THF:H_2O was added 2.46 g (4.49 mmol) of CAN. The mixture was stirred at 25 ^oC, diluted with 10 mL of H_2O after 3.5 h, and extracted with 3 x 10 mL of EtOAc. The combined organic phases were washed with 10 mL of H_2O, dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc; 5:1 to 3:1 gradient) to afford 70 mg (0.20 mmol, 27%) of **2-90** as a light yellow oil: IR (ATR) 3065, 2925, 2100, 1693, 1596, 1336, 1283, 1165 cm^{-1}; ^1H NMR δ 8.34 (dd, 1 H, *J* = 8.1 Hz, *J* = 1.2 Hz), 8.16 (dd, 1 H, *J* = 7.8 Hz, *J* = 1.2 Hz), 7.90 (dt, 1 H, *J* = 7.5 Hz, *J* = 1.8 Hz), 7.81 (dt, 1 H, *J* = 7.2 Hz, *J* = 1.2 Hz), 7.45 (d, 2 H, *J* = 7.2 Hz), 7.28-7.25 (m, 2 H), 7.21 (t, 1 H, *J* = 7.8 Hz), 4.49-4.45 (m, 2 H), 3.50-3.47 (m, 2 H), 3.43-3.41 (m, 2 H); ^{13}C NMR δ 175.3, 162.5, 157.7, 136.4, 136.2, 134.7, 131.1, 130.3, 129.9, 129.5, 128.7, 128.2, 128.2, 60.3, 53.1, 50.5; MS (ESI) *m/z* 350 ($[M+H]^+$).



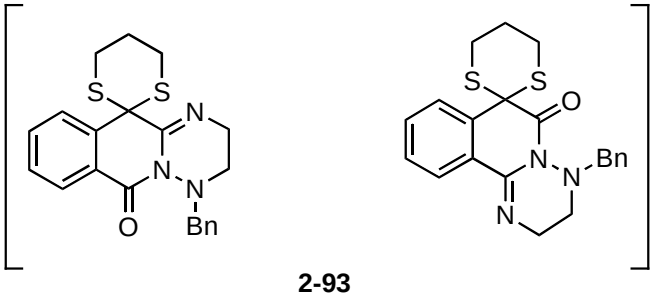
2-92

2'-((2-Azidoethyl)(benzyl)amino)-1'*H*-spiro[[1,3]dithiane-2,4'-isoquinoline]-1',3'(2'*H*)-dione (2-92). To a flame-dried 100 mL flask was added 1.61 g (3.81 mmol) of **2-75**, 36 mg (0.19 mmol) of CuI, 48 mg (0.39 mmol) of 2-picolinic acid and 3.72 g (11.4 mmol) of Cs_2CO_3. The mixture was purged 3 times with N_2, diluted with 19 mL of anhydrous dioxane and 1.2 mL (7.9 mmol) of diethyl malonate was added. After addition, the vessel was placed in a pre-

heated oil bath at 70 ^{o}C under a N_2 atmosphere. TLC analysis (hexane:EtOAc; 6:1) after 3 h showed that the starting material was consumed. The reaction was cooled to 25 ^{o}C, quenched with 10 mL of satd. NH_4Cl, extracted with 3 x 10 mL of EtOAc, washed with 20 mL of brine, and concentrated *in vacuo* to be used directly in the next step. The residue was dissolved in 13 mL of toluene and 3 mL of H_2O, and 225 mg (1.18 mmol) of *p*-TSA was added. The pink colored mixture was heated at reflux for 20 h, cooled to 25 ^{o}C, and quenched with 20 mL of satd. $NaHCO_3$. The biphasic mixture was partitioned and then the aqueous phase was extracted with 3 x 10 mL of EtOAc. The crude mixture showed to be one spot by TLC (hexane:EtOAc; 5:1). The combined organic phases were washed with 10 mL of brine, dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexane:EtOAc; 10:1 to 5:1 gradient) to afford 889 mg of **2-61** as a light brown oil.

To a solution of 889 mg (2.65 mmol) of **2-61** in 30 mL of CH_2Cl_2 at 25 ^{o}C was added 760 µL (5.45 mmol) of NEt_3 followed by 1.27 g (3.05 mmol) of *S,S*'-propane-1,3-diyl bis(4-methylbenzenesulfonothioate). The green/yellow solution was stirred at 25 ^{o}C under N_2 for 21 h, quenched with 10 mL of satd. NH_4Cl, extracted with 2 x 10 mL of CH_2Cl_2, dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc;4:1) to afford 989 mg (2.25 mmol, 59%, 3 steps) of **2-92** as a light green oil: IR (ATR) 2921, 2099, 1724, 1684, 1598, 1455, 1337, 1224 cm^{-1}; ^{1}H NMR δ 8.18 (dd, 1 H, *J* = 7.9 Hz, *J* = 1.8 Hz), 8.10 (app d, 1 H, *J* = 7.8 Hz), 7.65 (app dt, *J* = 7.5 Hz, *J* = 1.8 Hz), 7.52 (d, 2 H, *J* = 7.8 Hz), 7.53-7.49 (m, 1 H), 7.29 (app t, 2 H, *J* = 7.2 Hz), 7.22 (t, 1 H, *J* = 7.3 Hz), 4.46, 4.41 (AB, 2 H, *J* = 13.2 Hz), 3.82 (td, 1 H, *J* = 13.5 Hz, *J* = 2.5 Hz), 3.76 (td, 1 H, *J* = 13.5 Hz, *J* = 2.5 Hz), 3.50-3.32 (m, 4 H), 2.76 (dt, 1 H, *J* = 13.9 Hz, *J* = 3.7 Hz), 2.68 (dt, 1 H, *J* = 13.9 Hz, 3.7 Hz), 2.34-2.31 (m, 1 H), 2.07-1.99

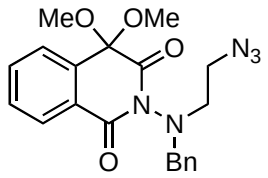
(m, 2 H); ^{13}C NMR δ 170.0, 163.3, 137.2, 137.0, 134.4, 129.9, 129.7, 129.6, 129.3, 128.5, 127.9, 125.1, 60.5, 52.5, 50.0, 49.6, 29.2, 29.1; MS (ESI) *m/z* 440 ([M+H]$^+$).



2-93

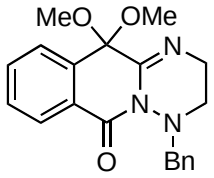
4-Benzyl-3,4-dihydrospiro[[1,2,4]triazino[2,3-*b*]isoquinoline-11,2'-[1,3]dithian]-6(2*H*)-one (2-93). To a flame dried microwave vial was added 51 mg (0.12 mmol) of **2-92** followed by 1.2 mL of dry PhCl. To this colorless solution was added 150 μL (0.161 mmol) of PBu_3 (1.07 M in PhCl). Upon addition of the phosphine at 25 ^{o}C, the reaction color changed to yellow. The vessel was then sealed and heated in the microwave at 180 ^{o}C for 20 min. The green solution was transferred to a 50 mL flask and the volatiles were removed under reduced pressure. The mixture was purified by chromatography on SiO_2 (hexane:EtOAc; 6:1 to 5:1 gradient) to afford 14 mg (0.035 mmol, 31%) of **2-93** as tan/light green oil as a (tentatively assigned) mixture of regioisomers. Further analysis is needed to confirm these putative structures. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15-8.13 (m, 0.93 H), 7.68 (d, 0.61 H, *J* = 7.8 Hz), 7.65 (d, 0.35 H, *J* = 7.5 Hz), 7.63-7.60 (m, 0.96 H), 7.53-7.50 (m, 1.8 H), 7.42 (app t, 1.0 H, *J* = 7.5 Hz), 7.31-7.26 (m, 2.3 H), 7.24-7.20 (m, 1.0 H), 4.46, 4.39 (AB of major, *J* = 12.6 Hz), 4.43, 4.40 (AB of minor, *J* = 13.8 Hz), 3.46-3.25 (m, 6.0 H), 2.90-2.87 (m, 0.35 H), 2.74-2.71 (m, 0.37 H), 2.58-2.34 (m, 2.8 H), 2.23-2.18 (m, 0.65 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 174.5, 164.1, 164.0, 141.6, 141.4, 137.5, 137.2, 134.5, 134.5, 129.6, 129.4, 129.1, 128.5, 128.5, 128.4, 128.3, 127.9, 127.8,

126.8, 126.8, 125.1, 125.1, 62.2, 61.3, 60.6, 60.1, 52.8, 52.6, 50.5, 49.8, 43.3, 42.9, 36.7, 36.4, 33.7, 33.1; MS (ESI) *m/z* 396 ($[M+H]^+$).



2-97

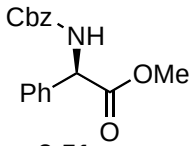
2-((2-Azidoethyl)(benzyl)amino)-4,4-dimethoxyisoquinoline-1,3(2*H*,4*H*)-dione, 2-97. To a solution of 343 mg (0.780 mmol) of **2-92** in 8 mL of dry MeOH was added 180 μL (2.35 mmol) of TFA, and 674 mg (2.35 mmol) of PIFA at 23 ^oC. The mixture was stirred for 15 min when TLC analysis (hexane:EtOAc; 4:1) of a Na_2CO_3 neutralized aliquot showed the starting material was consumed to a slightly more polar spot. After 20 min, the reaction was quenched with solid Na_2CO_3 until the pH was above 7, causing the yellow solution to change to colorless as the pH increased. The mixture was extracted with 4 x 10 mL of CH_2Cl_2, dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc: 5:1 to 3:1 gradient with 1% NEt_3) to afford 226 mg (0.571 mmol, 73%) of **2-97** as a pale yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, 1 H, *J* = 8.1 Hz), 7.68-7.65 (m, 2 H), 7.59-7.56 (m, 1 H), 7.45 (d, 2 H, *J* = 7.2 Hz), 7.25 (t, 2 H, *J* = 7.2 Hz), 7.19 (t, 1 H, *J* = 7.2 Hz), 4.46, 4.37 (AB, 2 H, *J* = 12.6 Hz), 3.54-3.49 (m, 1 H), 3.42-3.37 (m, 3 H), 3.32 (s, 3 H), 3.08 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 164.0, 136.6, 135.7, 133.9, 130.4, 129.8, 129.3, 128.5, 128.0, 126.6, 126.6, 96.0, 60.3, 52.9, 52.4, 52.2, 49.8.



2-98

4-Benzyl-11,11-dimethoxy-3,4-dihydro-2*H*-[1,2,4]triazino[2,3-*b*]isoquinolin-6(11*H*)-one, 2-98. To a flame-dried microwave vial was added 385 mg (0.974 mmol) of **2-97** in 2.5 mL of distilled PhCl, followed by 337 mg (1.67 mmol) of PBu_3 in 580 μL of PhCl. The green/brown mixture was stirred at rt for 10 min then heated at 180 ^oC for 20 min. TLC analysis (CH_2Cl_2:EtOH; 50:1) showed the starting material was consumed to a single, streaky more polar spot. The dark purple solution was concentrated under a stream of N_2 then purified by chromatography on SiO_2 (100% CH_2Cl_2 to CH_2Cl_2:EtOH; 100:1 to 25:1) to produce an oily semisolid that was triturated with hexanes and then recrystallized from Et_2O:hexanes to afford 210 mg (0.597 mmol, 61%) of **2-98** as tiny cream colored needles: mp 127-128 ^oC; IR (ATR) 2938, 2834, 1698, 1646, 1604, 1496, 1457, 1351, 1278, 1237, 1077 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.18 (dd, 1 H, *J* = 7.8 Hz, *J* = 0.6 Hz), 7.73 (d, 1 H, *J* = 7.2 Hz), 7.66 (dt, 1 H, *J* = 7.2 Hz, *J* = 1.2 Hz), 7.56-7.53 (m, 3 H), 7.36 (t, 2 H, *J* = 7.2 Hz), 7.31 (t, 1 H, *J* = 7.2 Hz), 4.07 (brs, 2 H), 3.80 (brs, 2 H), 3.39 (brs, 6 H), 3.18 (t, 2 H, *J* = 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 148.1, 135.8, 135.6, 133.0, 130.1, 130.0, 129.3, 128.7, 128.2, 127.3, 126.3, 96.4, 58.4, 45.7, 39.0; MS (ESI) *m/z* 352 ($[M+H]^+$).

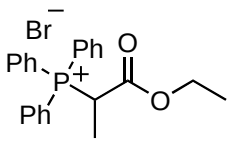
4.4 CHAPTER 3 EXPERIMENTAL[8]



3-51

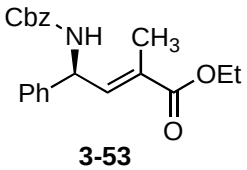
(*R*)-Methyl 2-(benzyloxycarbonylamino)-2-phenylacetate (3-51).[232] To a mixture of 24.0 g (119 mmol) of (*R*)-(-)-2-phenylglycine methyl ester hydrochloride in 1200 mL of EtOAc:H_2O (1:1) cooled to 0 ^oC was added 50.1 g (596 mmol) of $NaHCO_3$, followed by a solution of 24 mL (142 mmol) of benzyl chloroformate in 20 mL of EtOAc over 20 min. After 2 h, the mixture was quenched with 200 mL of H_2O, extracted with 3 x 150 mL of EtOAc and washed with 200 mL of brine. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to a solid. The solid was triturated with hexanes, filtered and dried to afford 25.6 g (85.4 mmol, 72%) of **3-51** as an amorphous solid: mp 64-65 ^oC; $[\alpha]_D$ -116.3 (*c* 1.78, CH_2Cl_2); ^1H NMR (300 MHz, CD_3OD) δ 7.40-7.27 (m, 10 H), 5.31 (brs, 1 H), 5.12, 5.07 (AB, 2 H, *J* = 12.6 Hz), 3.68 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 172.9, 158.1 138.1, 137.7, 129.8, 129.5, 129.4, 129.0, 128.8, 128.6, 67.8, 59.7, 53.0.

[8] All NMR data in this section were recorded on Bruker instruments at the indicated spectrometer frequency in the solvent listed.



3-52

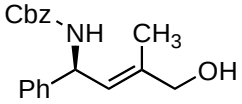
(1-Ethoxy-1-oxopropan-2-yl)triphenylphosphonium bromide (3-52).[233] To a solution of 50.0 g (191 mmol) of PPh_3 in 200 mL of acetone was added 30 mL (231 mmol) of ethyl 2-bromopropionate. The mixture was heated at reflux for 38 h, causing the formation of a white precipitate. The solvent was removed under reduced pressure and to the solid was added 20 mL of CH_2Cl_2 followed by 200 mL of Et_2O. The resulting solid was filtered, rinsed with Et_2O, ground into a fine powder and dried on high vacuum to afford 81.3 g (183 mmol, 96%) of **3-52** as an amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.75 (m, 6 H), 7.66-7.61 (m, 3 H), 7.56-7.51 (m, 6 H), 6.37 (dq, 1 H, J = 15.8 Hz, J = 7.6 Hz), 3.89-3.74 (m, 2 H), 1.50 (dd, 3 H, J = 18.4 Hz, J = 7.2 Hz), 0.80 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (d, $J_{C\text{-}P}$ = 1.9 Hz), 134.8 (d, $J_{C\text{-}P}$ = 3.0 Hz), 133.9 (d, $J_{C\text{-}P}$ = 9.9 Hz), 130.1 (d, $J_{C\text{-}P}$ = 12.7 Hz), 117.3 (d, $J_{C\text{-}P}$ = 85.6 Hz), 62.7, 36.4 (d, $J_{C\text{-}P}$ = 49.8 Hz), 13.4, 12.8 (d, $J_{C\text{-}P}$ = 2.9 Hz).



3-53

(*S*,*E*)-Ethyl 4-(benzyloxycarbonylamino)-2-methyl-4-phenylbut-2-enoate (3-53). To a suspension of 30.1 g (67.9 mmol) of **3-52** in 170 mL of distilled THF cooled to 0 °C was added 7.68 g (68.5 mmol) of KOBu^t in one portion. This caused the suspension to change to a partially homogenous yellow solution. The mixture was stirred at 0 °C for 1.5 h, and then used directly in

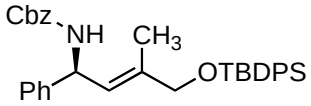
the next step. To a 3-neck flask charged with 10.1 g (33.9 mmol) of **3-51** dissolved in 200 mL of dry toluene and cooled to -78 ^{o}C was added dropwise *via* cannula a solution of 9.67 g, (68.0 mmol) of DIBAl-H in 20 mL of dry toluene over 25 min. After addition, the mixture was stirred at -78 ^{o}C for 1 h. After 1 h, the light green ylide solution (prepared as described above) was added dropwise *via* cannula over 30 min. After addition of the ylide, the mixture was allowed to stir for 45 min at -78 ^{o}C then removed from the cooling bath and allowed to warm to ambient temperature. The lime green/yellow mixture was then heated at 50 ^{o}C for 22 h. After cooling to rt, the mixture was quenched with 50 mL of H_2O and 200 mL of 1M HCl, stirred for 20 min, extracted with 3 x 100 mL of EtOAc, washed with 200 mL of brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexane:EtOAc; 10:1 to 5:1 gradient) to afford 10.3 g (29.1 mmol, 86%, 2 steps) of **3-53** as an oil: $[\alpha]_D$ -0.6 (*c* 0.94, CH_2Cl_2); IR (ATR) 3331, 3029, 1687, 1521, 1452, 1230,1126, 1023 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.36-7.24 (m, 10 H), 6.82 (dq, 1 H, *J* = 9.30 Hz, *J* = 1.48 Hz), 5.59 (app d, 1 H, *J* = 9.2 Hz), 5.09 (s, 2 H), 4.18 (q, 2 H, *J* = 7.11 Hz), 1.94 (s, 3 H), 1.27 (t, 3 H, *J* = 7.13 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 169.2, 158.2, 142.1, 141.4, 138.3, 130.2, 129.8, 129.5, 129.0, 128.8, 128.7, 127.7, 67.7, 62.0, 54.3, 14.5, 13.0; MS (ESI) *m/z* 354 ($[M+H]^+$); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}NO_4Na$ (M+Na) 376.1525, found 376.1501.



3-54

(*S*,*E*)-Benzyl 4-hydroxy-3-methyl-1-phenylbut-2-enylcarbamate (3-54). To a solution of 10.3 g (29.1 mmol) of **3-53** in 150 mL of dry CH_2Cl_2 cooled to -78 ^{o}C was added dropwise *via*

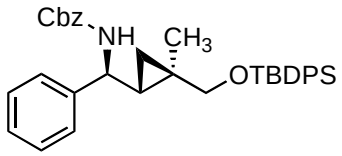
cannula a solution of 12.4 g (87.3 mmol) of DIBAl-H in 10 mL of dry CH_2Cl_2 over 10 min. After addition, the reaction mixture was allowed to stir at -78 ^oC for 1.5 h, removed from the cooling bath, warmed to rt, and after 2 h, the mixture was quenched by the dropwise addition of 100 mL of a satd. solution of potassium sodium tartrate. After being diluted 100 mL of EtOAc the cloudy mixture was stirred until it became biphasic and TLC analysis (hexane:EtOAc; 1:1) showed that the starting material was consumed. The mixture was extracted with 2 x 100 mL of EtOAc, washed with 50 mL of brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 2:1) to afford 8.61 g (25.9 mmol, 89%) of **3-54** as a tan oil: $[\alpha]_D$ +15.2 (*c* 0.38, CH_2Cl_2); IR (ATR) 3312, 3064, 3031, 1692, 1523, 1495, 1452, 1240, 1025 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.35-7.17 (m, 10 H), 5.64 (dq, 1 H, *J* = 9.2 Hz, *J* = 1.3 Hz), 5.57 (br d, 1 H, *J* = 9.1 Hz), 5.07, 5.03 (AB, 2 H, *J* = 12.4 Hz), 3.95 (s, 2 H), 1.76 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.0, 143.9, 138.5, 138.1, 129.4, 129.3, 128.9, 128.7, 128.0, 127.4, 125.8, 67.8, 67.4, 53.7, 14.2; MS (ESI) *m/z* 312 ($[M+H]^+$); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}NO_3$ (M+H) 312.1600, found 312.1604.



3-55

(*S*,*E*)-Benzyl-4-(*tert*-butyldiphenylsilyloxy)-3-methyl-1-phenylbut-2-enylcarbamate (3-55). To a solution of 8.06 g (25.9 mmol) of **3-54** in 100 mL of dry CH_2Cl_2 cooled to 0 ^oC was added 1.77 g (26.0 mmol) of imidazole, 510 mg (4.14 mmol) of DMAP, and 5.4 mL (21 mmol) of TBDPSCl. The mixture was allowed to warm to rt overnight. In the morning, the mixture was quenched with 50 mL of satd. $NaHCO_3$, and extracted with 3 x 20 mL of CH_2Cl_2. The combined

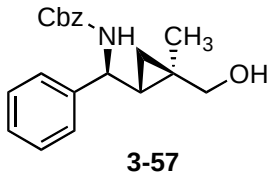
organic layers were washed with 50 mL of brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:Et_2O; 10:1) to afford 9.27 g (16.9 mmol, 81%) of **3-55**: $[\alpha]_D$ +23.1 (*c* 1.55, CH_2Cl_2); IR (ATR) 3066, 2928, 2854, 1694, 1493, 1426, 1105, 1023 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.64-7.60 (m, 4 H), 7.37-7.17 (m, 16 H), 5.72 (d, 1 H, *J* = 8.8 Hz), 5.59-5.57 (m, 1 H), 5.07, 5.03 (AB, 2 H, *J* = 12.8 Hz), 4.07, 4.03 (AB, 2 H, *J* = 15.2 Hz) 1.68 (brs, 3 H), 1.01 (s, 9 H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.1, 143.9, 138.2, 137.6, 136.5, 134.6, 134.6, 130.8, 129.5, 129.4, 128.9, 128.7, 128.0, 127.5, 157.7, 69.3, 67.5, 53.6, 27.3, 20.0, 14.2; MS (ESI) *m/z* 572 ($[M+Na]^+$); HRMS (ESI) *m/z* calcd for $C_{35}H_{39}NO_3NaSi$ (M+Na) 572.2597, found 572.2623.



3-56

Benzyl-(*S*)-((1*R*,2*R*)-2-((*tert*-butyldiphenylsilyloxy)methyl)-2-methylcyclopropyl) (phenyl)methylcarbamate (3-56). To a freshly prepared solution of 6.28 g (50.9 mmol) of Et_2Zn in 30 mL of dry CH_2Cl_2 was added 5.3 mL of freshly distilled DME. The solution was cooled to -30 ^oC (internal temperature) when 8.0 mL (100 mmol) of CH_2I_2 was added dropwise over 20 min. The temperature was maintained at or below -30 ^oC during the addition. After addition, the mixture was stirred for 10 min at -30 ^oC and a solution of 2.75 g (5.00 mmol) of **3-55** was added dropwise in 20 mL of CH_2Cl_2 *via* addition funnel over 20 min while maintaining the temperature. After addition, the reaction mixture was allowed to warm to rt overnight and stirred for a total of 25 h, before slowly quenching with 80 mL of satd. NH_4Cl. The mixture was partitioned and extracted with 4 x 20 mL of CH_2Cl_2. The combined organic layers were washed

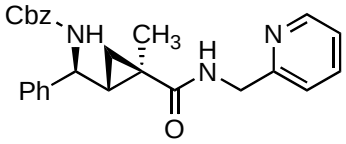
with 50 mL of brine, dried ($MgSO_4$) and concentrated *in vacuo*. The tan oil was purified by chromatography on SiO_2 (hexane:EtOAc; 10:1) to afford 2.05 g (3.64 mmol, 73%) of **3-56** as an oily foam: $[\alpha]_D$ -19.5 (*c* 0.47, CH_2Cl_2); IR (ATR) 3318, 2952, 2928, 1694, 1497, 1247, 1105, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 4 H), 7.48 (d, 2 H, *J* = 6.8 Hz), 7.43-7.24 (m, 14 H), 5.18 (app d, 1 H, *J* = 7.2 Hz), 5.13, 5.09 (AB, 2 H, *J* = 12.0 Hz), 4.46 (app t, 1 H, *J* = 8.8 Hz), 3.59, 3.24 (AB, 2 H, *J* = 10.0 Hz), 1.21, (s, 3 H), 1.02 (s, 9 H), 0.66 (dd, 1 H, *J* = 8.4 Hz, *J* = 4.8 Hz), 0.49 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 143.0, 136.8, 135.9, 135.8, 133.8, 133.7, 129.8, 128.7, 128.3, 127.8, 127.4, 126.8, 71.2, 67.0, 55.6, 27.6, 27.0, 23.4, 19.5, 16.4, 15.1; MS (ESI) *m/z* 586 ($[M+Na]^+$); HRMS (ESI) *m/z* calcd for $C_{36}H_{41}NO_3SiNa$ (M+Na) 586.2753, found 586.2766.



3-57

Benzyl(*S*)-((1*R*,2*R*)-2-(hydroxymethyl)-2-methylcyclopropyl) (phenyl)methylcarbamate (3-57). To a solution of 4.18 g (7.41 mmol) of **3-56** in 15 mL of TBAF (15.0 mmol) in THF was added 860 μL (14.9 mmol) of AcOH. The mixture was heated at reflux for 4 h, cooled to rt, quenched with 40 mL of satd. $NaHCO_3$, and extracted 3 x 15 mL of EtOAc. The combined organic layers were washed with 40 mL of brine, dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (hexane:EtOAc; 2:1 to 1:2 gradient) to afford 2.10 g (6.44 mmol, 87%) of **3-57** as a pale oily foam: HPLC analysis indicated one enantiomer (*er* >99:1; t_R major = 8.76

min; t_R minor = 11.18 min);[9] $[\alpha]_D$ -18.7 (*c* 1.38, CH_2Cl_2); IR (ATR) 3411, 3316, 2928, 1691, 1527, 1452, 1253, 1027 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.41-7.27 (m, 9 H), 7.24-7.20 (m, 1 H), 5.10, 5.05 (AB, 2 H, *J* = 12.8 Hz), 4.37-4.34 (m, 1 H), 3.34, 3.24 (AB, 2 H, *J* = 11.2 Hz), 1.26-1.19 (m, 1 H), 1.17 (s, 3 H), 0.74 (dd, 1, *J* = 8.6 Hz, *J* = 4.4 Hz), 0.42-0.39 (m, 1 H); ^{13}C NMR (150 MHz, CD_3OD) δ 158.6, 144.7, 138.5, 129.4, 129.4, 128.9, 128.7, 128.0, 127.7, 70.9, 67.4, 56.6, 28.1, 24.4, 16.4, 16.3; MS (ESI) *m/z* 348 ($[M+Na]^+$); HRMS (ESI) *m/z* calcd for $C_{20}H_{23}NO_3Na$ (M+Na) 348.1576, found 348.1551.

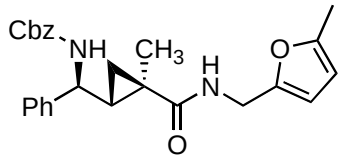


3-61

Benzyl-(*S*)-((1*R*,2*R*)-2-methyl-2-(pyridin-2-ylmethylcarbamoyl)cyclopropyl) (phenyl) methylcarbamate (3-61). To a solution of 467 mg (1.43 mmol) of **3-57** in 5 mL of acetone was added 3.8 mL (9.5 mmol, 2.5 M solution) of Jones reagent. After addition, the flask was heated at 50 ^oC for 3 h. TLC analysis (hexane:EtOAc; 1:1) showed starting material remained. To the reaction was added an additional 2 mL (5 mmol, 2.5 M) of Jones reagent, and the mixture was heated at reflux. After the starting material was consumed (TLC analysis), the mixture was cooled to rt, diluted with 10 mL of H_2O, and extracted with 3 x 10 mL of EtOAc. The combined organic layers were washed with 10 mL of brine, dried (Na_2SO_4), concentrated under reduced

[9] Analytical HPLC data was obtained by analysis of **3-57** through a Chiracel OD column (4.6 mm ID x 250 mm; 10 μm particle size; Daicel Chemical Industries, LTD.). The eluent was composed of 20% isopropanol in 80% hexane, with a flow rate of 1.0 mL/min on a Shimadzu instrument.

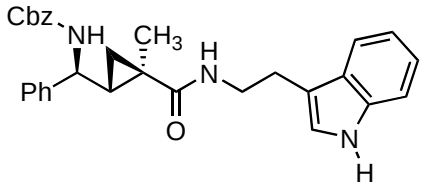
pressure, and used directly in the next coupling step. To a solution of the crude carboxylic in 5 mL of dry CH_2Cl_2 was added 871 mg (1.87 mmol) of PyBroP, 27.8 mg (0.227 mmol) of DMAP, 240 μL (2.32 mmol) of 2-aminomethylpyridine, and 750 μL (4.30 mmol) of DIPEA. The brown mixture was stirred at rt overnight, and then concentrated *in vacuo*. The residue was diluted with 15 mL of EtOAc, and the organic phase was washed with 20 mL of 5% solution of $NaHSO_4$, 20 mL of brine, and 20 mL of satd. $NaHCO_3$. The organic phase was dried (Na_2SO_4), and concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexane:EtOAc; 1:1 to 1:7 gradient with 1% NEt_3) to afford 287 mg (0.648 mmol, 45%, 2 steps) of **3-61** as a colorless oil: $[\alpha]_D$ -37.5 (*c* 1.57, CH_2Cl_2); IR (ATR) 3297, 3066, 3005, 1700, 1638, 1514, 1254, 1215, 1027, 844 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.40 (d, 1 H, *J* = 4.4 Hz), 7.65 (t, 1 H, *J* = 7.6 Hz), 7.40 (d, 2 H, *J* = 7.2 Hz), 7.32-7.22 (m, 8 H), 7.20-7.17 (m, 1 H), 7.12 (d, 1 H, *J* = 8.0 Hz), 5.09, 5.03 (AB, 2 H, *J* = 12.5 Hz), 4.51 (d, 1 H, *J* = 10.0 Hz), 4.49, 4.41 (AB, 2 H, *J* = 16.8 Hz), 2.02-1.96 (m, 1 H), 1.47 (dd, 1 H, *J* = 9.0 Hz, *J* = 4.4 Hz), 1.40 (s, 3 H), 0.81-0.79 (m, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.0, 159.3, 158.2, 149.5, 143.9, 138.5, 138.1, 129.5, 129.3, 128.8, 128.6, 128.3, 127.6, 123.4,122.1, 67.4, 56.1, 45.6, 32.4, 25.4, 20.9, 15.0; MS (ESI) *m/z* 452 ($[M+Na]^+$); HRMS (ESI) *m/z* calcd for $C_{26}H_{27}N_3O_3Na$ (M+Na) 452.1950, found 452.1934.



3-62

Benzyl-(*S*)-((1*R*,2*R*)-2-methyl-2-((5-methylfuran-2-yl)methylcarbamoyl) cyclopropyl)

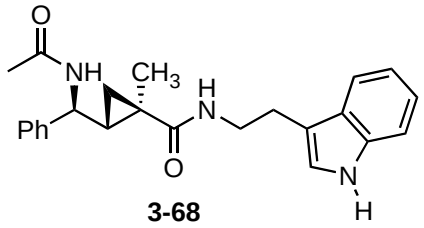
(phenyl)methylcarbamate (3-62). To a solution of 801 mg (2.46 mmol) of **3-57** in 10 mL of acetone cooled to 0 ^{o}C was added 6 mL (15.0 mmol, 2.5 M solution) of Jones reagent dropwise. After addition, the reaction mixture allowed to warm rt over 1.5 h, and then heated at reflux for 1 h. TLC analysis (hexane:EtOAc; 4:1) showed the starting material was consumed. The reaction was cooled to rt, quenched with 10 mL of H_2O, neutralized to pH of 3 with satd. $NaHCO_3$, and extracted with 3 x 10 mL of EtOAc. The combined organic layers were washed with 10 mL of brine, dried (Na_2SO_4), concentrated under reduced pressure, and used directly in the next coupling step. To a solution of the crude carboxylic acid in 8 mL of dry CH_2Cl_2 was added 92.6 mg (0.758 mmol) of DMAP, 510 μL (4.91 mmol) of 5-methylfurfurylamine, and 1 mL (7 mmol) of NEt_3. To this was added 2.2 mL (3.7 mmol) of T3P (50% w/w solution in ethyl acetate). After addition, the reaction mixture was allowed to warm to rt overnight. The reaction mixture was quenched with 10 mL of satd. $NaHCO_3$, extracted with 3 x 10 mL of CH_2Cl_2, washed with 10 mL of brine, dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on SiO_2 (hexane:EtOAc; 5:1 to 1:1 gradient) to afford 587 mg (1.36 mmol, 55%, 2 steps) of **3-62** as a colorless, foamy oil: $[\alpha]_D$ -5.1 (*c* 1.20, CH_2Cl_2); IR (ATR) 3295, 2945, 1694, 1635, 1523, 1452, 1256, 1021 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.35-7.19 (m, 10 H), 5.98 (d, 1 H, *J* = 2.8 Hz), 5.87 (dd, 1 H, *J* = 3.0 Hz, *J* = 0.8 Hz), 5.09, 5.04 (AB, 2 H, *J* = 12.4 Hz), 4.44 (br d, 1 H, *J* = 10.4 Hz), 4.29-4.22 (m, 2 H), 2.19 (s, 3 H), 1.94-1.88 (m, 1 H), 1.41 (dd, 1 H, *J* = 9.2 Hz, *J* = 4.4 Hz), 1.31 (s, 3 H), 0.75-0.73 (m, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.7, 158.4, 152.4, 151.5, 143.8, 138.3, 129.5, 129.4, 128.9, 128.7, 128.3, 127.7, 108.5, 107.1, 67.5, 56.0, 37.7, 32.1, 25.5, 20.8, 15.0, 13.4; MS (ESI) *m/z* 455 ([M+Na]$^{+}$); HRMS (ESI) *m/z* calcd for $C_{26}H_{28}N_2O_4Na$ (M+Na) 455.1947, found 455.1936.



3-63

Benzyl(*S*)-((1*R*,2*R*)-2-(2-(1*H*-indol-3-yl)ethylcarbamoyl)-2-methylcyclopropyl) (phenyl)methylcarbamate (3-63). To a solution of 563 mg (1.73 mmol) of **3-57** in 5 mL of acetone was added 4.6 mL (12 mmol, 2.5 M solution) of Jones reagent. The reaction was heated at 50 ^{o}C for 2 h. TLC analysis (hexane:EtOAc; 1:1) showed the starting material was consumed. The reaction was cooled to rt, diluted with 10 mL of H_2O, and extracted with 3 x 10 mL of EtOAc. The combined organic layers were washed with 10 mL of brine, dried (Na_2SO_4), concentrated under reduced pressure, and used directly in the next coupling step. To a solution of the crude carboxylic acid in 10 mL of dry CH_2Cl_2 was added 362 mg (2.26 mmol) of tryptamine, 21.6 mg (0.176 mmol) of DMAP, 893 mg (1.91 mmol) of PyBroP, and 670 μL (3.85 mmol) of DIPEA. The brown mixture was stirred at rt overnight, concentrated *in vacuo*, and the residue was diluted with 15 mL of EtOAc. The organic phase was washed with 20 mL of 5% solution of $NaHSO_4$, 20 mL of brine, 20 mL of satd. $NaHCO_3$, and dried (Na_2SO_4). The organic phase was concentrated *in vacuo*, and the residue was purified by chromatography on SiO_2 (hexane:EtOAc; 1:1) to afford 472 mg (0.981 mmol, 57%, 2 steps) of **3-63** as a white foam: $[\alpha]_D$ -18.8 (*c* 0.62, CH_2Cl_2); IR (ATR) 3284, 3062, 2937, 1694, 1637, 1517, 1454, 1256 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (d, 1 H, *J* = 8.0 Hz), 7.50 (app t, 1 H, *J* = 5.0Hz, N-H), 7.33-7.22 (m, 11 H), 7.07 (ddd, 1 H, *J* = 8.1 Hz, *J* = 7.0 Hz, *J* = 1.2 Hz), 6.96 (ddd, 1 H, *J* = 9.5 Hz, *J* = 4.0 Hz, *J* = 0.8 Hz), 6.95 (s, 1 H), 5.09, 5.04 (AB, 2 H, *J* = 12.4 Hz), 4.41 (d, 1 H, *J* = 10.4 Hz), 3.45 (app q, 2 H, *J* = 6.4 Hz), 2.89 (app t, 2 H, *J* = 7.4 Hz), 1.93-1.87 (m, 1 H), 1.38 (dd, 1 H, *J* = 9.2 Hz, *J* =

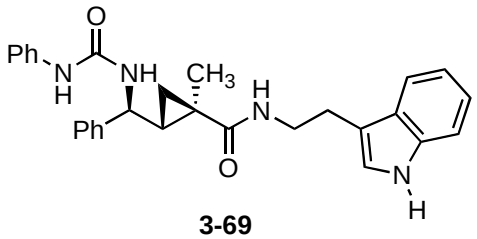
4.0 Hz), 1.24 (s, 3 H), 0.71 (app t, 1 H, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 177.0, 158.5, 143.9, 138.3, 138.1, 129.6, 129.4, 128.9, 128.8, 128.7, 128.3, 127.7, 123.4, 123.3, 119.6, 119.3, 113.3, 112.2, 67.5, 56.2, 42.1, 31.9, 26.2, 25.6, 20.8, 15.1; MS (ESI) *m/z* 504 ($[M+Na]^+$); HRMS (ESI) *m/z* calcd for $C_{30}H_{31}N_3O_3Na$ (M+Na) 504.2263, found 504.2226.



3-68

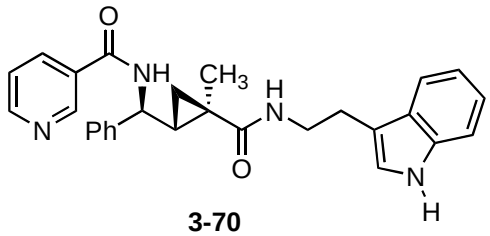
(1*R*,2*R*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-2-((*S*)-acetamido(phenyl)methyl)-1-methylcyclopropanecarboxamide (3-68). According to general protocol A, 106 mg (0.219 mmol) of **3-63**, and 46.2 mg (0.0434 mmol) of Pd/C (10%) in 2 mL of MeOH was stirred for 1 h to provide the amine intermediate. The residue was dissolved in 2 mL of dry CH_2Cl_2, and treated with 27 μL (0.29 mmol) of Ac_2O, and 40 μL (0.29 mmol) of NEt_3 to afford 76.7 mg (0.197 mmol, 90%, 2 steps) of **3-68** as a white foam: $[\alpha]_D$ -33.4 (*c* 1.19, CH_2Cl_2); IR (ATR) 3413, 3290, 3055, 1625, 1523, 1454, 1430, 1294 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 10.15 (br s, 1 H, N-H), 8.70 (d, 1 H, *J* = 8.4 Hz), 7.56-7.51 (m, 2 H), 7.34-7.20 (m, 6 H), 7.08 (ddd, 1 H, *J* = 8.5 Hz, *J* = 6.6 Hz, *J* = 1.2 Hz), 6.97 (ddd, 1 H, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.2 Hz), 6.96 (br s, 1 H), 4.76-4.71 (m, 1 H), 4.73 (dt, 1 H, *J* = 10.8 Hz, *J* = 6.0 Hz), 3.49-3.44 (m, 2 H), 2.91 (app dt, 2 H, *J* = 7.4 Hz, *J* = 1.2 Hz), 1.97 (s, 3 H), 1.94-1.89 (m, 1 H), 1.38 (dd, 1 H, *J* = 9.2 Hz, *J* = 4.0 Hz), 1.23 (s, 3 H), 0.69 (dd, 1 H, *J* = 6.4 Hz, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 176.9, 172.3, 143.4, 138.1, 129.6, 128.8, 128.4, 127.8, 123.3, 122.3, 119.6, 119.3, 113.3, 112.2, 54.1,

42.1, 31.4, 26.2, 25.6, 22.7, 20.8, 15.0; MS (ESI) *m/z* 412 ([M+Na]$^+$); HRMS (ESI) *m/z* calcd for $C_{24}H_{27}N_3O_2Na$ (M+Na) 412.2001, found 412.2035.



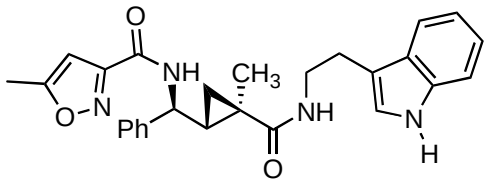
3-69

(1*R*,2*R*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-1-methyl-2-((*S*)-phenyl(3-phenylureido) methyl)cyclopropanecarboxamide (3-69). According to general protocol A, 99.0 mg (0.205 mmol) of **3-63** and 43.9 mg (0.0439 mmol) of Pd/C (10%) in 2 mL of MeOH was stirred for 1.5 h to provide the amine intermediate. The residue was dissolved in 2 mL of dry CH_2Cl_2, and treated with 29 μL (0.27 mmol) of PhNCO and 40 μL (0.29 mmol) of NEt_3 to afford 85.7 mg (0.184 mmol, 89%, 2 steps) of **3-69** as a white, waxy foam: $[\alpha]_D$ +14.5 (*c* 0.98, CH_2Cl_2); IR (ATR) 3316, 3051, 2937, 1616, 1543, 1497, 1439, 732 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.56-7.52 (m, 2 H), 7.36-7.19 (m, 10 H), 7.08 (ddd, 1 H, *J* = 8.1 Hz, *J* = 7.2 Hz, *J* = 1.2 Hz), 6.99-6.93 (m, 3 H), 6.73 (br d, 1 H, *J* = 8.8 Hz), 4.66-4.61 (m, 1 H), 3.49-3.44 (m, 2 H), 2.91 (app dt, 2 H, *J* = 7.2 Hz, *J* = 1.6 Hz), 1.89 (ddd, 1 H, *J* = 10.4 Hz, *J* = 9.0 Hz, *J* = 6.4 Hz), 1.41 (dd, 1 H, *J* = 9.2 Hz, *J* = 4.0 Hz), 1.27 (s, 3 H), 0.79 (dd, 1 H, *J* = 6.4 Hz, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 177.0, 157.5, 144.3, 140.8, 138.1, 129.8, 129.7, 128.6, 128.3, 127.6, 123.5, 123.3, 122.3, 120.1, 119.6, 119.3, 113.3, 112.2, 54.4, 42.1, 32.3, 26.2, 25.6, 20.9, 15.0; MS (ESI) *m/z* 489 ([M+Na]$^+$); HRMS (ESI) *m/z* calcd for $C_{29}H_{30}N_4O_2Na$ (M+Na) 489.2266, found 489.2263.



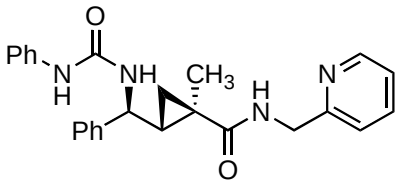
3-70

***N*-((*S*)-((1*R*,2*R*)-2-(2-(1*H*-Indol-3-yl)ethylcarbamoyl)-2-methylcyclopropyl) (phenyl)methyl)nicotinamide (3-70).** According to general protocol A, 101 mg (0.210 mmol) of **3-63**, and 45.4 mg (0.0426 mmol) of Pd/C (10%) in 2 mL of MeOH was stirred for 1.5 h to provide the amine intermediate. The residue was dissolved in 2 mL of dry CH_2Cl_2, and treated with 67.0 mg (0.376 mmol) of nicotinoyl chloride hydrochloride, 2.2 mg (0.018 mmol) of DMAP, and 90 μL (0.65 mmol) of NEt_3 to afford 70.9 mg (0.155 mmol, 75%, 2 steps) of **3-70** as a light yellow oil: $[\alpha]_D$ -11.5 (*c* 0.36, CH_2Cl_2); IR (ATR) 3279, 3049, 1627, 1528, 1431, 1338, 1029 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 9.38 (br d, 1 H, *J* = 8.0 Hz), 9.00 (dd, 1 H, *J* = 2.0 Hz, *J* = 0.8 Hz), 8.64 (dd, 1 H, *J* = 4.8 Hz, *J* = 1.6 Hz), 8.26 (ddd, 1 H, *J* = 8.0 Hz, *J* = 2.4 Hz, *J* = 1.6 Hz), 7.62 (t, 1 H, *J* = 5.6 Hz), 7.53 (dt, 1 H, *J* = 7.6 Hz, *J* = 1.2 Hz), 7.50 (ddd, 1 H, *J* = 8.0 Hz, *J* = 4.8 Hz, *J* = 0.8 Hz), 7.43-7.40 (m, 2 H), 7.33-7.23 (m, 4 H), 7.07 (ddd, 1 H, *J* = 8.1 Hz, *J* = 7.0 Hz, *J* = 0.8 Hz), 6.96 (ddd, 1 H, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 0.8 Hz), 6.97 (s, 1 H), 5.00 (dt, 1 H, *J* = 10.4 Hz, *J* = 5.6 Hz), 3.49-3.44 (m, 2 H), 2.93-2.90 (m, 2 H), 2.11 (ddd, 1 H, *J* = 10.8 Hz, *J* = 9.2 Hz, *J* = 6.4 Hz), 1.44 (dd, 1 H, *J* = 9.2 Hz, *J* = 4.4 Hz), 1.28 (s, 3 H), 0.77 (dd, 1 H, *J* = 6.6 Hz, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 176.8, 167.0, 152.4, 149.0, 143.2, 138.1, 137.3, 132.1, 129.7, 128.8, 128.5, 128.0, 125.2, 123.3, 122.3, 119.6, 119.3, 113.3, 112.2, 54.8, 42.1, 31.1, 26.2, 25.7, 20.9, 15.0; MS (ESI) *m/z* 453 ($[M+H]^+$); HRMS (ESI) *m/z* calcd for $C_{28}H_{29}N_4O_2$ (M+H) 453.2291, found 453.2293.



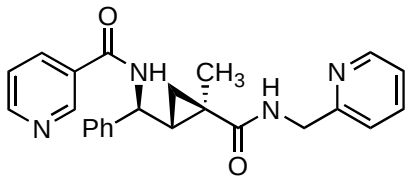
3-71

***N*-((*S*)-((1*R*,2*R*)-2-(2-(1*H*-Indol-3-yl)ethylcarbamoyl)-2-methylcyclopropyl) (phenyl)methyl)-5-methylisoxazole-3-carboxamide (3-71).** According to general protocol A, 99.9 mg (0.207 mmol) of **3-63**, and 44.8 mg (0.0421 mmol) of Pd/C (10%) in 2 mL of MeOH was stirred for 1 h to provide the amine intermediate. The residue was dissolved in 2 mL of dry CH_2Cl_2, and treated with 49.9 mg (0.342 mmol) of 5-methylisoxazole-3-carbonyl chloride, 25 mg (0.040 mmol) of DMAP, and 90 μL (0.65 mmol) of NEt_3 to afford 72.9 mg (0.160 mmol, 77%, 2 steps) of **3-71** as a light yellow oil: $[\alpha]_D$ -24.3 (*c* 1.11, CH_2Cl_2); IR (ATR) 3295, 3057, 2923, 2852, 1637, 1526, 1454, 1225 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.57-7.54 (m, 2 H), 7.40-7.36 (m, 2 H), 7.34-7.21 (m, 5 H), 7.07 (ddd, 1 H, *J* = 8.4 Hz, *J* = 7.2 Hz, *J* = 1.2 Hz), 6.98 (s, 1 H), 6.97 (ddd, 1 H, *J* = 7.9 Hz, *J* = 7.0 Hz, *J* = 1.2 Hz), 6.43 (d, 1 H, *J* = 1.2 Hz), 4.92 (d, 1 H, *J* = 10.8 Hz), 3.50-3.45 (m, 2 H), 2.94-2.90 (m, 2 H), 2.41 (d, 3 H, *J* = 0.8 Hz), 2.08 (ddd, 1 H, *J* = 10.8 Hz, *J* = 9.2 Hz, *J* = 6.4 Hz), 1.42 (dd, 1 H, *J* = 9.0 Hz, *J* = 4.0 Hz), 1.28 (s, 3 H), 0.74 (dd, 1 H, *J* = 6.4 Hz, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 176.8, 172.9, 160.9, 160.0, 142.8, 138.1, 129.7, 128.8, 128.6, 128.0, 123.3, 122.3, 119.6, 119.3, 113.3, 112.2, 102.0, 54.4, 42.1, 30.9, 26.2, 25.8, 20.8, 15.0, 12.0; MS (ESI) *m/z* 479 ($[M+Na]^+$); HRMS (ESI) *m/z* calcd for $C_{27}H_{28}N_4O_3Na$ (M+Na) 479.2059, found 479.2043.



3-72

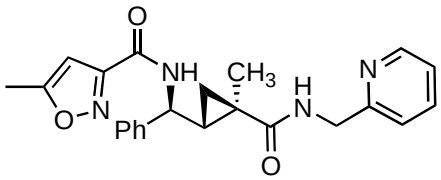
(1*R*,2*R*)-1-Methyl-2-((*S*)-phenyl(3-phenylureido)methyl)-*N*-(pyridin-2-ylmethyl) cyclopropanecarboxamide (3-72). General protocol A. To a solution of 68.7 mg (0.160 mmol) of **3-61** in 2 mL of MeOH was added 32.1 mg (0.0301 mmol) of Pd/C (10%). This was purged with H_2 (1 atm) and the mixture was stirred at rt for 1.5 h. TLC analysis (hexane:EtOAc; 1:4) showed the starting material was consumed. The mixture was quenched with Celite, filtered, and rinsed with MeOH. The filtrate was concentrated *in vacuo*, and dried on high vacuum to provide the amine intermediate. The residue was dissolved in 2 mL of dry CH_2Cl_2, and treated with 23 μL (0.21 mmol) of PhNCO, followed by 30 μL (0.22 mmol) of NEt_3. The reaction mixture was stirred at rt overnight, quenched with 5 mL of satd. $NaHCO_3$, extracted with 3 x 5 mL of CH_2Cl_2, dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on SiO_2 (2%-5% MeOH/CH_2Cl_2) to afford 57 mg (0.14 mmol, 85%, 2 steps) of **3-72** as a waxy oil: $[\alpha]_D$ +4.5 (*c* 1.25, CH_2Cl_2); IR (ATR) 3292, 3061, 1635, 1541, 1499, 1437, 1254, 1217, 950 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.43 (d, 1 H, *J* = 4.2 Hz), 7.72 (app dt, 1 H, *J* = 7.7 Hz, *J* = 1.8 Hz), 7.41-7.15 (m, 12 H), 6.95 (d, 1 H, *J* = 7.5 Hz), 4.68 (d, 1 H, *J* = 10.2 Hz), 4.52, 4.43 (AB, 2 H, *J* = 16.2 Hz), 1.94-1.85 (m, 1 H), 1.49-1.41 (m, 1 H), 1.45 (s, 3 H), 0.89 (dd, 1 H, *J* = 6.6 Hz, *J* = 4.2 Hz); ^{13}C NMR (150 MHz, CD_3OD) δ 177.4, 159.5, 157.5, 149.6, 144.4, 140.8, 138.7, 129.8, 129.7, 128.4, 127.6, 123.6, 123.5, 122.2, 120.1, 54.4, 45.8, 33.0, 25.6, 21.0, 15.1; MS (ESI) *m/z* 415 ($[M+H]^+$); HRMS (ESI) *m/z* calcd for $C_{25}H_{27}N_4O_2$ (M+H) 415.2134, found 415.2133.



3-73

***N*-((*S*)-((1*R*,2*R*)-2-Methyl-2-(pyridin-2-ylmethylcarbamoyl)cyclopropyl)(phenyl)methyl)nicotinamide (3-73).** To a solution of 108 mg (0.251 mmol) of **3-61** in 2 mL of dry CH_2Cl_2 was added 500 μL (0.500 mmol, 1.0 M solution in CH_2Cl_2) of BBr_3 at rt. The mixture was stirred vigorously at rt for 2 h, diluted with 2 mL of Et_2O, decanted, and rinsed with Et_2O to provide a solid that was dried under high vacuum and used directly in the next step. The solid was suspended in 2 mL of dry CH_2Cl_2, and 8.1 mg (0.066 mmol) of DMAP, 111 mg (0.624 mmol) of nicotinoyl chloride hydrochloride and 440 μL (2.52 mmol) of DIPEA were added at rt. The mixture was stirred at rt overnight, before it was slowly quenched with 5 mL of satd. $NaHCO_3$. The reaction mixture was extracted with 3 x 5 mL of CH_2Cl_2, dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on SiO_2 (2% MeOH in CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to afford 47.1 mg (0.117 mmol, 47%, 2 steps) of **3-73** as a light yellow oil: $[\alpha]_D$ -22.7 (*c* 1.00, CH_2Cl_2); IR (ATR) 3297, 3049, 2919, 1625, 1530, 1433, 1418, 1212, 1025 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 9.00 (dd, 1 H, *J* = 2.0 Hz, *J* = 0.8 Hz), 8.67 (dd, 1 H, *J* = 5.2 Hz, *J* = 1.6 Hz), 8.47 (ddd, 1 H, *J* = 5.0 Hz, *J* = 1.6 Hz, *J* = 0.8 Hz), 8.26 (ddd, 1 H, *J* = 8.0 Hz, *J* = 2.4 Hz, *J* = 1.6 Hz), 7.81 (td, 1 H, *J* = 7.6 Hz, *J* = 2.0 Hz), 7.52 (ddd, 1 H, *J* = 8.0 Hz, *J* = 4.8 Hz, *J* = 0.8 Hz), 7.48-7.45 (m, 2 H), 7.39-7.23 (m, 5 H), 5.03 (d, 1 H, *J* = 10.8 Hz), 4.54, 4.46 (AB, 2 H, *J* = 16.0 Hz), 2.10 (ddd, 1 H, *J* = 10.8 Hz, *J* = 9.0 Hz, *J* = 6.4 Hz), 1.52-1.48 (m, 1 H), 1.48 (s, 3 H), 0.87 (dd, 1 H, *J* = 6.4 Hz, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 177.3, 167.0, 159.3, 152.6, 149.2, 149.2, 143.3, 139.4, 137.2, 132.0, 129.8, 128.6, 128.0, 125.1, 123.8,

122.5, 54.8, 45.6, 31.8, 25.8, 21.0, 15.0; MS (ESI) *m/z* 423 ($[M+Na]^+$); HRMS (ESI) *m/z* calcd for $C_{24}H_{24}N_4O_2Na$ (M+Na) 423.1797, found 423.1797.



3-74

5-Methyl-*N*-((*S*)-((1*R*,2*R*)-2-methyl-2-(pyridin-2-ylmethylcarbamoyl) cyclopropyl)(phenyl)methyl)isoxazole-3-carboxamide (3-74). According to general protocol A, a mixture of 92.3 mg (0.215 mmol) of **3-61**, and 44.7 mg (0.0420 mmol) of Pd/C (10%) in 2 mL of MeOH was stirred for 1 h to provide the amine intermediate. The intermediate was dissolved in 2 mL of dry CH_2Cl_2, and treated with 45.5 mg (0.312 mmol) of 5-methylisoxazole-3-carbonyl chloride, 5.1 mg (0.041 mmol) of DMAP, and 40 μL (0.29 mmol) of NEt_3 to afford 70.6 mg (0.174 mmol, 81%, 2 steps) of **3-74** as a fine white powder: mp 171-172 ^oC; $[\alpha]_D$ -46.6 (*c* 1.79, CH_2Cl_2); IR (ATR) 3006, 1633, 1594, 1435, 1374, 1241 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.45 (d, 1H, *J* = 4.8 Hz), 7.76 (td, 1 H, *J* = 7.7 Hz, *J* = 1.2 Hz), 7.45 (d, 2 H, *J* = 7.2 Hz), 7.35 (t, 2 H, *J* = 7.8 Hz), 7.30-7.25 (m, 2 H), 7.20 (d, 1 H, *J* = 7.8 Hz), 6.44 (s, 1 H), 4.98 (d, 1 H, *J* = 10.8 Hz), 4.53, 4.44 (AB, 2 H, *J* = 16.2 Hz), 2.44 (s, 3 H), 2.16-2.07 (m, 1 H), 1.51-1.42 (m, 1 H), 1.45 (s, 3 H), 0.83 (dd, 1 H, *J* = 6.3 Hz, *J* = 4.5 Hz); ^{13}C NMR (150 MHz, CD_3OD) δ 177.1, 172.8, 160.8, 160.0, 159.5, 149.6, 142.9, 138.7, 129.7, 128.6, 128.0, 123.6, 122.2, 102.0, 54.3, 45.7, 31.5, 25.7, 21.0, 150, 12.0; MS (ESI) *m/z* 405 ($[M+H]^+$); HRMS (ESI) *m/z* calcd for $C_{23}H_{25}N_4O_3$ (M+H) 405.1927, found 405.1934.

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