The Development of Reactions for the Stereoselective Synthesis of Heterocycles and Benzylic Amines, and Exploration of Bisisoxazolidines as Small Molecule Transcriptional Activation Domains

by

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Dedication

To My Family

Table of Contents

List of Figures

List of Tables

List of Schemes

List of Abbreviations

Ac ..... Acyl

acac ..... acetylacetonate

Ar ..... aryl

BINAP ..... 2,2'-bis(diphenylphosphino)-1,1'-biphenyl

BINOL ..... 1,1'-bi-2-napthol

Bn ..... benzyl

Boc ..... *tert*-butyloxycarbonyl

Bu ..... butyl

Bz ..... benzoyl

ca ..... approximately

Cbz ..... carboxybenzyl

Cy ..... cyclohexyl

dba ..... dibenzylideneacetone

DBU ..... 1,8-diazabicyclo[5.4.0]undec-7-ene

DBD ..... deoxyribonucleic acid binding domain

DIAD ..... diisopropyl azodicarboxylate

DIPEA ..... diisopropylethylamine

DMAP ..... dimethylaminopyridine

DME 1,2-dimethoxyethane

DMF ..... dimethylformamide

DNA ..... deoxyribonucleic acid

Dpe-phos ..... bis(2-diphenylphosphinophenyl)ether

DPPA ..... diphenylphosphoryl azide

dppb ..... 1,4-bis(diphenylphosphino)butane

dppe ..... 1,2-bis(diphenylphosphino)ethane

dppf ..... 1,1'-bis(diphenylphosphino)ferrocene

dr ..... diastereomeric ratio

EDC ..... 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

ee ..... enantiomeric excess

equiv ..... equivalents

ESI ..... electrospray ionization

Et ..... ethyl

FMoc ..... fluorenylmethyloxycarbonyl

h ..... hour(s)

HBTu ..... *O*-(Benzotriazol-1-yl)-*N*,*N*,*N'N'*-tetramethyluronium hexafluorophosphate

HOBt ..... hydroxybenzotriazole

HMDS ..... hexamethyldisilazane

HPLC ..... high performance liquid chromatography

IMes ..... *N*,*N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene

i-Pr ..... isopropyl

IPr ..... *N*,*N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene

LA ..... lewis acid

LAH .....lithium aluminum hydride

LC-MS ..... liquid chromatography – mass spectrometry

LDA .....lithium diisopropylamide

Ln .....ligand

LRMS.....low resolution mass spectrometry

M .....molarity

Me ..... methyl

MOM..... methoxymethyl

Ms .....mesyl

NMP.....1-methyl-2-pyrrolidinone

NMR ..... nuclear magnetic resonance

nOe..... nuclear Overhauser effect

nu.....nucleophile

OxDex..... oxidized dexamethasone

tol ..... tolyl

pg..... protecting group

Ph .....phenyl

PMB .....*para*-methoxybenzyl

PMP.....*para*-methoxyphenyl

pr ..... propyl

RD..... regulatory domain

RNA .....ribonucleic acid

rt .....room temperature

SEMOH..... 2-(trimethylsilyl)ethanol

TAD .....transcriptional activation domain

TBS .....*tert*-butyl-dimethylsilyl

TEA..... triethylamine

Tf.....trifluoromethanesulfonyl

TF.....transcription factor

TFA ..... trifluoroacetic acid

THF .....tetrahedrofuran

TMG..... 1,1,3,3-tetramethylguanidine

TMS .....trimethylsilyl

Ts.....tosyl

Xantphos 9,9-dimethyl-bis-4,5-diphenylphosphinoxantphene

Abstract

Chapter 1 provides a brief introduction. Chapters 2 and 3 of this thesis describe the development new methods for the synthesis of nitrogen containing heterocycles *via* palladium catalyzed carboamination reactions. The development of conditions for the synthesis of functionalized pyrrolidines from *N*-protected γ–aminoalkenes and aryl bromides or triflates mediated by weak base and palladium catalysis is described in Chapter 2. These conditions, which use Cs_2CO_3 or K_3PO_4 in place of the strong base NaO*t*Bu, tolerate the presence of a broad array of functional groups and significantly expand the scope of the methodology. Chapter 3 describes the development of a four-step synthesis of *cis*-3,5-disubstituted morpholines from enantiomerically pure amino alcohols. The key step in the synthesis is a Pd-catalyzed carboamination reaction between a substituted ethanolamine derivative and an aryl or alkenyl bromide. The morpholine products are generated in good diastereoselectivity with full retention of enantiopurity. This chapter also describes the synthesis of fused bicyclic morpholines, 2,3- and 2,5-disubstituted morpholines, and 3,4-dihydro-2*H*-1,4-oxazine products.

Chapter 4 describes the development of a simple step-wise procedure to achieve a room temperature Curtius rearrangement of benzylic and heteroarylmethyl carboxylic acids. The developed conditions provide an alternative to previously described one-pot procedures that require heating or the use of Lewis acids, and the mild conditions allow

the Curtius rearrangement to occur while preventing the formation of unwanted ester byproducts or other deleterious side reactions.

The investigation of synthetic small molecule transcription activation domains (TADs) is described in Chapter 5. The synthesis of a small library of compounds intended to replicate key aspects of potent natural TADs is described. The compounds are functionally evaluated as either activators or inhibitors of transcription in cells.

Chapter 6 describes efforts to expand the scope of tandem Wittig rearrangement/aldol reactions to allow the synthesis of *anti*-α-alkyl-α,β-dihydroxy esters and *anti*-α-alkyl-α,γ-dihydroxy esters. Strategies focusing on the use of dialkyl acetals or Lewis acid activated aldehydes as electrophiles are discussed. An alternative approach involving use of Ti, Al, or Sc enolates as nucleophiles is reported. Preliminary work on the utilization of pyridinium salt electrophiles for the preparation of substituted piperidines is also discussed.

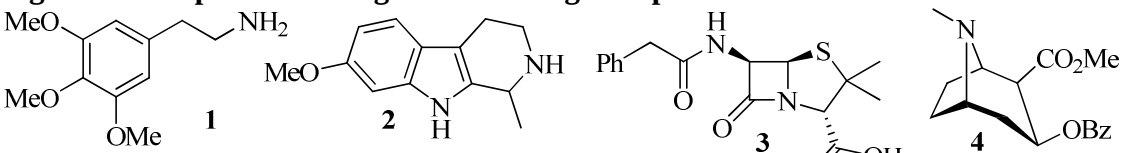
Chapter 1

Introduction

1.1 Importance of Alkaloids and Nitrogen-Containing Compounds

Alkaloids and nitrogen-containing natural compounds have potent activity in many different biological systems. As a result of their biological activity, these compounds have played a profound role in the course of human society. These compounds are found at the heart of some religious rituals, various healing therapies, and some recreational activities (Figure 1-1). For example mescaline (**1**), a natural product found in the peyote cactus, has been used for over 3000 years as an entheogen and supplement to various transcendence practices including meditation, psychonautics, and psychedelic psychotherapy.[1] In a similar fashion, tetrahydroharmine (**2**) is an active ingredient in the drink ayahuasca, a brew used for divinatory and healing purposes by the native peoples of the Amazonian Colombia.[2] Alternatively, penicillin (**3**) was discovered in 1928 and is the most widely used antibiotic in the world.[3] Cocaine (**4**) is a highly addictive recreational drug with activity as a serotonine reuptake inhibitor.[4]

Figure 1-1: Important Nitrogen-Containing Compounds

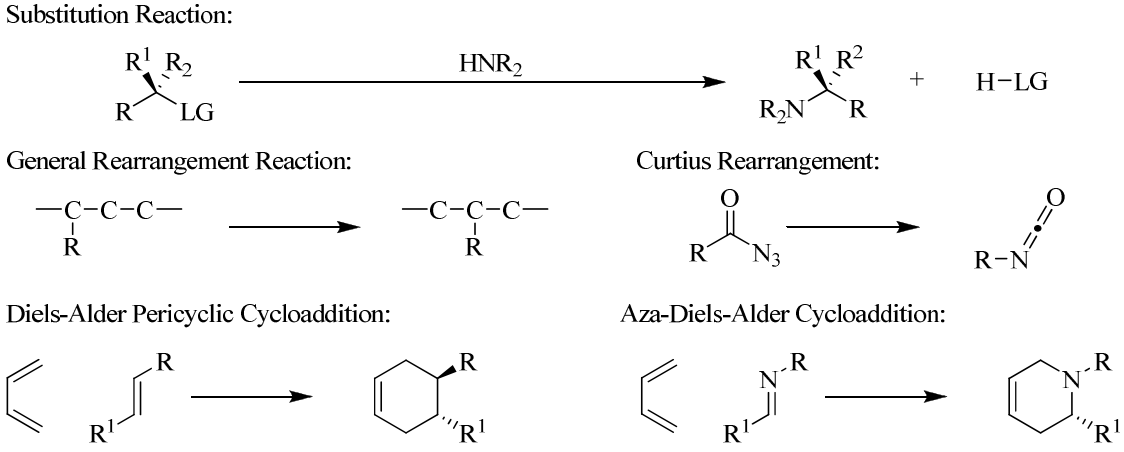


The chemical methods for preparing alkaloids and nitrogen-containing natural compounds are diverse. A key aspect of any method for the preparation of these compounds is the need to form new carbon-nitrogen bonds. This chapter will highlight some of the most useful and widely used methods for the formation of this important linkage.

1.2 Standard Methods for Forming New Carbon-Nitrogen Bonds

Early chemical methods for the formation of carbon-nitrogen bonds include substitution reactions, chemical rearrangements, or pericyclic reactions (Figure 1-2).[5] Nucleophilic substitution reactions are one of the most basic and broadly used transformations in organic chemistry. Chemical rearrangements are a powerful alternative to substitution reactions, as many chemical rearrangements form new carbon-nitrogen bonds from structures not suitable for displacement chemistry. Pericyclic reactions are a type of chemical rearrangement that proceeds through a cyclic transition state while simultaneously forming and breaking both σ- and π-bonds.

Figure 1-2: Some Standard Methods That Can Form Carbon-Nitrogen Bonds



Nucleophilic substitution reactions require substrates containing a carbon-bound leaving group, where nitrogen nucleophiles can attack the electrophilic carbon to form a new carbon-nitrogen bond. Bimolecular nucleophilic substitution reactions proceed with inversion of the carbon stereocenter, so the stereochemistry of the product is controlled by the stereochemistry of the substrate.

Many different chemical rearrangements are known to produce new carbon-nitrogen bonds. These rearrangements include the Beckmann rearrangement, Curtius rearrangement, the Lossen rearrangement, the Hofmann rearrangement, and the Schmidt rearrangement. These rearrangement reactions allow the migration of an alkyl group by the intermediate formation of a nitrogen bound leaving group. In contrast to the bimolecular nucleophilic substitution reactions, rearrangement reactions typically proceed with retention of the relative stereochemistry at the migrating carbon center.

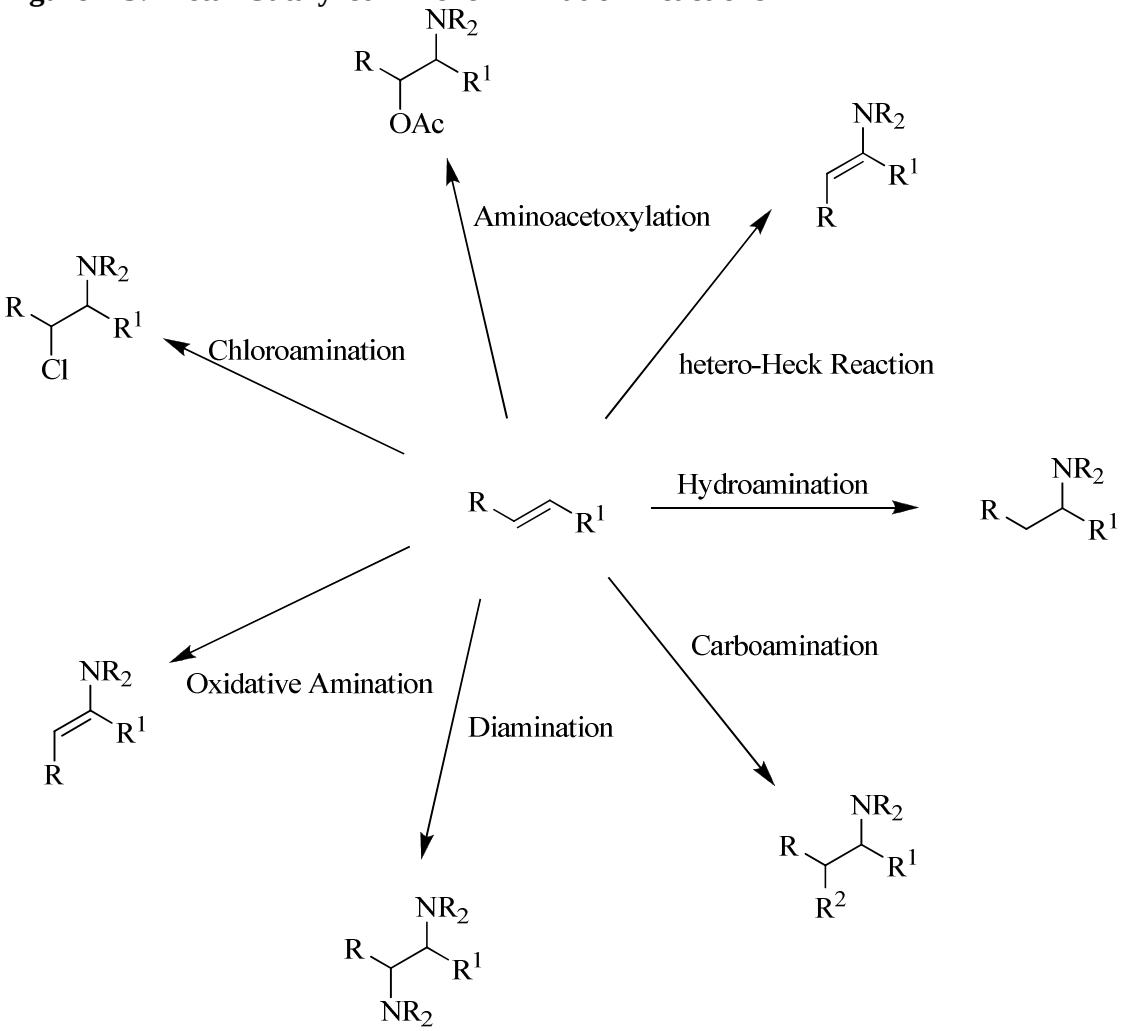
Pericyclic reactions have been widely used in chemical syntheses because they can be used to generate multiple new stereocenters with excellent diastereoselectivity. While the Diels-Alder cycloaddition for the formation of two new carbon-carbon σ-bonds in cyclohexene is one of the most widely known and used pericyclic reactions, this class of reactions can be used to form new carbon-nitrogen σ-bonds as well. Example pericyclic reactions include: electrocyclic reactions, cycloadditions, sigmatropic reactions, group transfer reactions, cheletropic reactions, and dyotropic reactions.

1.3 Metal-Catalyzed Methods for Forming New Carbon-Nitrogen Bonds

Work with metal catalysts has led to the development of new types of reactions for the formation of carbon-nitrogen bonds.[6] Transition metals can facility carbon-nitrogen

bond formation *via* insertion reactions and reductive elimination reactions. Key metals in this field include copper, nickel, palladium, gold, and rhodium. Focusing on palladium, this metal has been used effectively in alkene hydroaminations,[7] carboaminations,[8] diaminations,[9] oxidative aminations,[10] chloroaminations,[11] aminoacetoxylations,[12] and hetero-Heck transformations[13] (Figure 1-3). Further advancements in these methodologies are important for the development of useful and highly efficient chemical methodologies.

Figure 1-3: Metal-Catalyzed Alkene Amination Reactions



1.4 Conclusions

While many methods are known for the efficient preparation of new carbon-nitrogen bonds in biologically important molecules, challenges still remain in this area of research. Much of the work presented in this thesis is focused on the discovery and application of new or improved methods for addressing some challenges in the current field of chemistry. A unifying feature in the methods developed in Chapters 2, 3, and 4 of this thesis is the formation of new carbon-nitrogen bonds. Alternatively, Chapter 5 investigates nitrogen-containing heterocyclic isoxazolidines and isoxazolines as small molecule compounds with potential activity as artificial transcriptional activation domains (TADs). The final chapter of this thesis (Chapter 6) focuses on the formation of new carbon-carbon bonds through Wittig rearrangements and aldol condensations.

1.5 References

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Chapter 2

Mild Conditions for the Synthesis of Functionalized Pyrrolidines *via* Palladium Catalyzed Carboamination Reactions

2.1 Introduction

The development of synthetic methods for the construction of substituted pyrrolidines has been of longstanding importance in organic chemistry due to the prevalence of this moiety in biologically active molecules and natural products (Figure 2-1).[1] For example, the natural product preussin (**1**) has antifungal, antiviral, and antitumor activity.[2] Anisomycin (**2**) is a pyrrolidine natural product that has antifungal and cytotoxic activity, while broussonetine C (**3**) is a potent glycosidase inhibitor.[3,4] Captopril (**4**) is an angiotensin converting enzyme (ACE) inhibitor that is marketed as a hypertension therapeutic and accounted for $1.1 billion in sales in 1996.[5] Compound **5** has been identified as a potent BACE-1 inhibitor and is a potential therapeutic for Alzheimer's disease.[6]

Over the past several years, the palladium-catalyzed carboamination of γ-aminoalkenes with aryl bromides has emerged as an efficient and stereoselective method for the construction of substituted pyrrolidine derivatives.[7,8] These transformations effect tandem cyclization and coupling in a process that generates a C–N bond, a C–C bond, and up to two stereocenters in one step. For example, treatment of Boc-protected amine **6**

with 4-bromoanisole in the presence of NaO*t*Bu and catalytic amounts of $Pd_2(dba)_3$ and dppb afforded pyrrolidine **7** in 60% yield with >20:1 dr (Figure 2-2).[7c]

Figure 2-1: Biologically Active Pyrrolidines

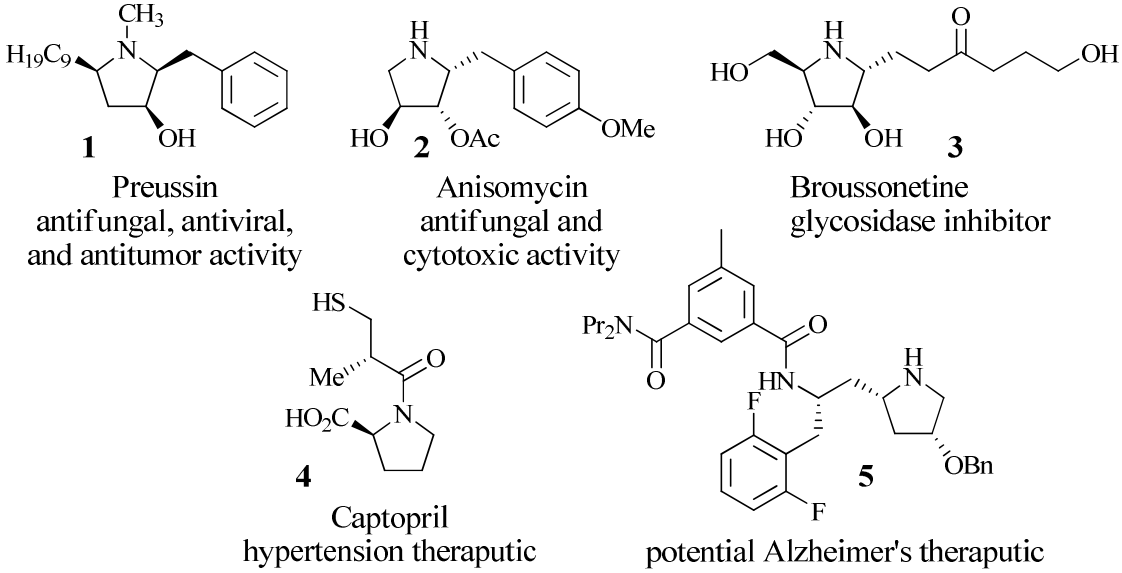
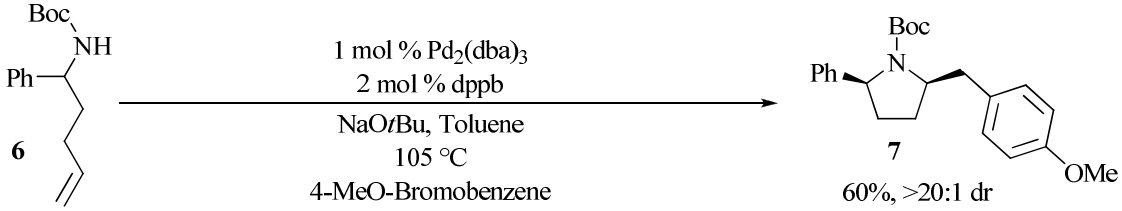


Figure 2-2: Pyrrolidine Synthesis *via* Palladium-Catalyzed Carboamination



Despite the synthetic utility of these transformations, the reactions are typically conducted in the presence of the strong base NaO*t*Bu, which limits the scope of this method. For example, the use of NaO*t*Bu restricts the functional group tolerance of these reactions, and transformations of aryl triflate electrophiles, which decompose in the presence of strong base, have not been reported. Additionally, Cbz protecting groups, which are frequently employed in the synthesis of complex alkaloids, are incompatible with the strongly basic conditions. This chapter describes the development of new

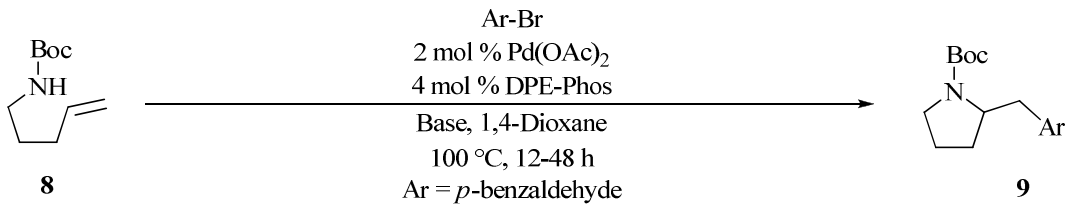
conditions that replace NaO*t*Bu with weaker bases (Cs_2CO_3 or K_3PO_4), which significantly expands the scope of the carboamination method.

The work for this chapter was conducted in collaboration with another graduate student, Myra Bertrand.[9] My contribution to the project consisted of optimization of reaction conditions and partial establishment of reaction scope.

2.2 Development of Reaction Conditions Utilizing Weak Base

The use of weak bases in Pd-catalyzed *N*-arylation reactions of amines with aryl halides had been previously established.[10] Using the reported weak base *N*-arylation conditions in combination with our conditions for pyrrolidine synthesis, an initial screen of potential weak bases was conducted (Table 2-1). Both Cs_2CO_3 and K_2CO_3 generated the desired pyrrolidines (**9**) in moderate yield (Table 2-1, entries 1-2). The other inorganic bases (Na_2CO_3, K_3PO_4) and KOAc generated a complex mixture of products (Table 2-1, entries 3-5), while soluble nitrogen bases did not induce catalytic turnover and only led to recovery of starting material (Table 2-1, entries 6-8). While K_2CO_3 provided the best crude yield of the desired pyrrolidine, inseperable impurities prevented the isolation of clean product. The Cs_2CO_3 reaction led to isolation of clean product and was therefore selected for further optimization through a solvent screen.

Table 2-1: Base Optimization[a]



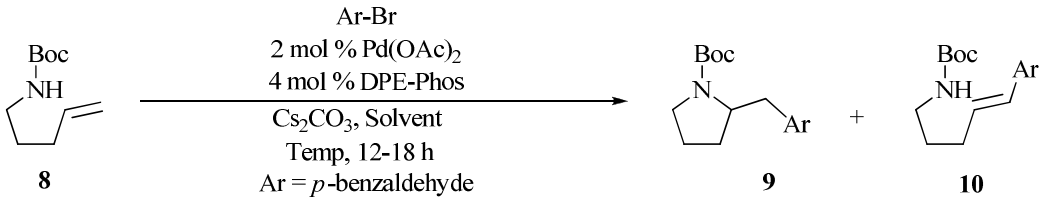
8 **9**

entry	Base	Result[b]
1	Cs_2CO_3	61% **9**[c]
2	K_2CO_3	69% **9**[d]
3	Na_2CO_3	Complex mixture[e]
4	K_3PO_4	Complex mixture[e]
5	KOAc	Complex mixture[e]
6	DBU	No reaction[e]
7	TEA	No reaction[e]
8	TMG	No reaction[e]

[a] Conditions: 1.0 equiv **8**, 2.3 equiv base, 1.2 equiv ArBr, 2 mol % $Pd(OAc)_2$, 4 mol % DPE-Phos, 1,4-Dioxane (0.2 M), 105 °C. DBU = 1,8-Diazabicycloundec-7-ene. TMG = Tetramethylguanidine. [b] Isolated yields. [c] Heck-type side product isolated in 20% yield. [d] Containes 10% inseperable impurity. [e] GC characterization.

Results from the solvent screen are shown in Table 2-2. Reaction temperature played an important role in reaction selectivity and yield. Temperature was initially varied to maintain reactions below the boiling point of the main solvent. Reducing the temperature to 65 °C for THF led to a greatly reduced reaction rate (Table 2-2, entry 8). The optimal result was obtained using dioxane as solvent at 85 °C, while dimethoxyethane provided a nearly comparable yield (Table 2-2, entries 5-6). After changing solvent, the weak base K_2CO_3 provided a significantly reduced yield of desired product, as compared to Cs_2CO_3 (Table 2-2, entries 6-7).

Table 2-2: Solvent Optimization[a]



8 **9** **10**

entry	solvent	T °C	yield **9** (%)[b]	yield **10** (%)[b]
1	Toluene	100	60	0
2	NMP	100	10	2
3	DMF	100	53	10
4	1,4-Dioxane	100	61	20
5	1,4-Dioxane	85	79	0
6	DME	85	75	1
7	DME	85	40[c]	0
8	THF	65	57[d]	0

[a] Conditions: 1.0 equiv **8**, 2.3 equiv Cs_2CO_3, 1.2 equiv ArBr, 2 mol % $Pd(OAc)_2$, 4 mol % DPE-Phos, solvent (0.2 M), 100 °C. NMP = *N*-Methylpyrrolidone. DMF = Dimethylformamide. DME = 1,2-Dimethoxyethane. [b] Isolated yields. [c] K_2CO_3 used as base instead of Cs_2CO_3. [d] Reaction time = 42h.

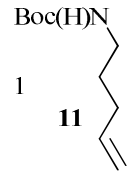
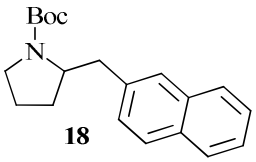
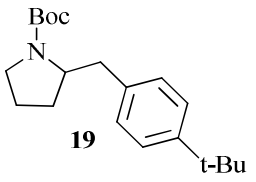
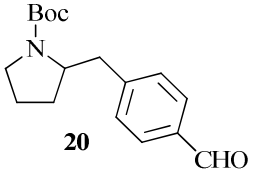
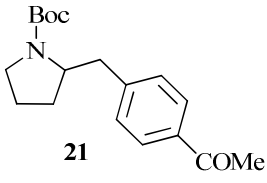
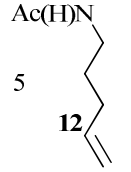
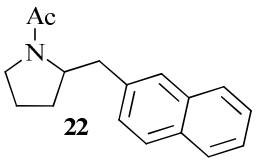
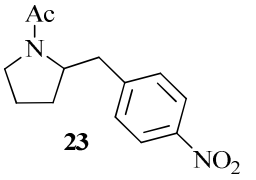
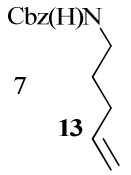
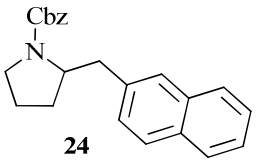
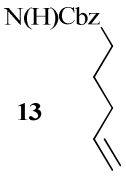
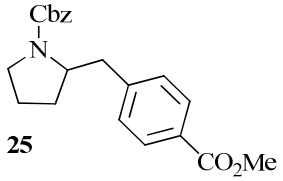
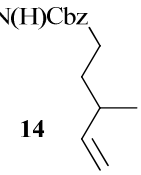
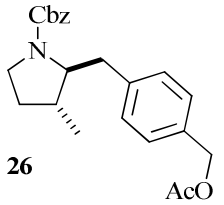
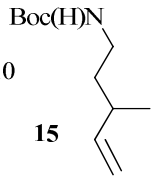
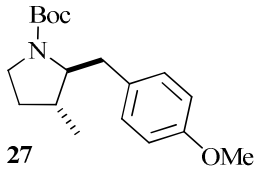
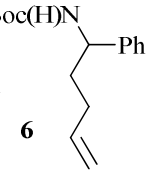
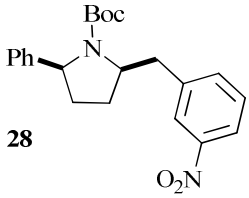
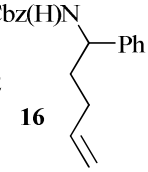
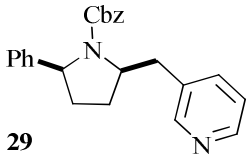
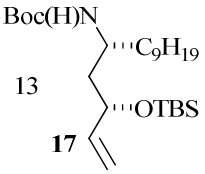
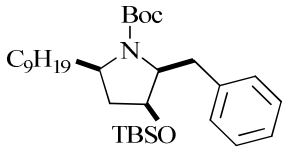
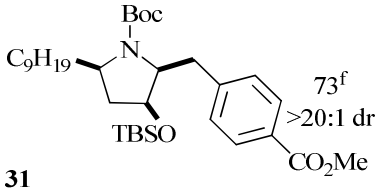
2.3 Exploration of Scope

With optimal reaction conditions established for an initial substrate and aryl halide combination, the full reaction scope was explored (Table 2-3). Reactions utilizing weak base are effective for the transformation of a number of different substrate combinations. Many functional groups are tolerated under these mild conditions, including aldehydes (Table 2-3, entry 3), enolizable ketones (Table 2-3, entry 4), nitro groups (Table 2-3, entries 6 and 11), methyl esters (Table 2-3, entries 8 and 14), and alkyl acetates (Table 2-3, entry 9). In addition, the carboamination reactions of electron-rich (Table 2-3, entry 10), electron-neutral (Table 2-3, entries 1, 2, 5, 7, and 13), and heterocyclic (Table 2-3, entry 12) aryl bromides proceed with good chemical yield. The mild conditions also are effective for stereoselective reactions, and provide selectivities

that are comparable to those observed in reactions that use NaO*t*Bu as base. For example, transformations of starting materials **6** and **16**, which bear a substituent adjacent to the nitrogen atom, provide *cis*-2,5-disubstituted products **28** and **29** with excellent (>20:1) diastereoselectivity (Table 2-3, entries 11–12). Similarly, substrates **14** and **15**, which are substituted at the allylic position, are transformed to *trans*-2,3-disubstituted products **26** and **27** with good stereocontrol (12 to 15:1).

In addition to providing increased tolerance of base-sensitive functional groups, the new reaction conditions also allow for the efficient carboamination of substrates bearing Cbz-protecting groups. For example, the Pd-catalyzed coupling of **13** with 2-bromonaphthalene using Cs_2CO_3 as base provided the desired product **24** in 88% isolated yield (Table 2-3, entry 7). In contrast, cleavage of the Cbz-group from the substrate was problematic when reactions were conducted with NaO*t*Bu as base; these conditions provided only a 17% yield of **24**. More complex γ-aminoalkene substrates are also efficiently transformed using the new reaction conditions. As shown in Table 2-3 (entries 13–14), Pd-catalyzed reactions of **17** with bromobenzene or methyl-4-bromobenzoate proceeded smoothly to provide **30** and **31** with excellent stereoselectivity. Trisubstituted pyrrolidine **30** has been previously employed as an intermediate in the synthesis of the natural product (+)-preussin.[7g,11]

Table 2-3: Palladium-Catalyzed Carboamination of *N*-Protected γ-Aminoalkenes with Functionalized Aryl Bromides[a]

entry	amine	product	yield (%)[b]
1	 **11**	 **18**	75
2		 **19**	82
3		 **20**	78[e]
4		 **21**	76[e,f]
5	 **12**	 **22**	79
6		 **23**	76[c,e]
7	 **13**	 **24**	88[f] 17[d,f]
8	 **13**	 **25**	88[e]
9	 **14**	 **26**	80[f] 12:1 dr
10	 **15**	 **27**	76 15:1 dr
11	 **6**	 **28**	75[f] >20:1 dr
12	 **16**	 **29**	74[f] >20:1 dr
13	 **17**	 **30**	71[f] >20:1 dr
14		 **31**	73[f] >20:1 dr

[a] Conditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.3 equiv Cs_2CO_3, 2 mol % $Pd(OAc)_2$, 4 mol % Dpe-phos, dioxane (0.2-0.25 M), 100 °C. [b] Yield refers to average isolated yield obtained in two or more experiments. [c] Dppe used in place of Dpe-phos. [d] NaO*t*Bu used in place of Cs_2CO_3. [e] The reaction was conducted at 85 °C in DME solvent. [f] This example established by Myra Bertrand.

The main limitations of these new reaction conditions involve transformations of sterically encumbered substrate combinations. For example, attempts to convert substrates bearing internal alkenes to pyrrolidines were unsuccessful under these conditions. In addition, the reaction of methyl 2-bromobenzoate with **6**, which bears a substituent on C-1 (adjacent to the nitrogen atom), was not effective. However, Myra Bertrand demonstrated that this *o*-substituted aryl bromide was effectively coupled with the less hindered carbamate **15**.[9] This limitation was later overcome in subsequent studies in the lab.[12]

In addition to greatly expanding the scope of Pd-catalyzed carboamination reactions involving aryl bromide substrates, the use of mildly basic reaction conditions also allows for the first Pd-catalyzed carboamination reactions with aryl triflates, as demonstrated by Myra Bertrand.[9]

2.4 Conclusions

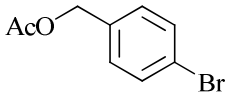
In conclusion, we have developed new conditions for palladium-catalyzed carboamination reactions of *N*-protected γ–aminoalkenes with aryl bromides and triflates. These conditions, which use Cs_2CO_3 (or K_3PO_4 for aryl triflates) in place of the strong base NaO*t*Bu, tolerate the presence of a broad array of functional groups, and significantly expand the scope of this method.

2.5 Experimental Section

General: All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All catalysts, reagents, anhydrous dioxane, and

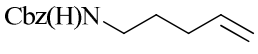
anhydrous DME were obtained from commercial sources and were used without further purification. Pent-4-enyl-carbamic acid *tert*-butyl ester (**11**),[13] *N*-pent-4-enylacetamide (**12**),[13] (3-methylpent-4-enyl)carbamic acid *tert*-butyl ester (**15**),[13] (1-phenylpent-4-enyl)carbamic acid *tert*-butyl ester (**6**),[13] 4-pentenylamine,[13] and (±)–(1*R*,3*S*)-3-(*tert*-butyldimethylsiloxy)-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (**17**)[14] were prepared according to published procedures. Ratios of regioisomers and/or diastereomers were determined by ^{1}H NMR and/or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and/or combustion analysis. The yields reported in the experimental section describe the result of a single experiment, whereas the yields reported in Table 2-3 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Table 2-3.

Synthesis of Substrates:

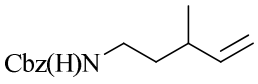


4-Bromobenzyl acetate.[15] A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 4-bromobenzyl alcohol (4.0 g, 21.4 mmol), acetic anhydride (20 mL), pyridine (20 mL), and DMAP (268 mg, 2.14 mmol, 10 mol %). The tube was purged with nitrogen, and the mixture was stirred at rt for 22 h until the starting material had been consumed as determined by TLC analysis. Water (10 mL) and ethyl acetate (10 mL) were added, and the layers were separated. The organic layer was washed with 1 M aqueous HCl (10 mL) and brine (10 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl acetate/hexanes

as the eluent to afford 4.4 g (90%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 5.03 (s, 2 H), 2.08 (s, 3 H).



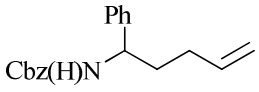
Pent-4-enylcarbamic acid benzyl ester (13).[16] A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of 4-pentenylamine (175 mL, 17.5 mmol, 0.1 M in diethyl ether). Triethylamine (7.4 mL, 52.5 mmol) and benzyl chloroformate (3.8 mL, 26.3 mmol) were added, and the resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 2 h). A solution of aqueous HCl (100 mL, 1.0 M) was added, the mixture was transferred to a separatory funnel, and was extracted with diethyl ether (100 mL). The layers were separated and the organic layer was washed with a solution of saturated aqueous Na_2CO_3 (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using 10% → 15% ethyl acetate/hexanes as the eluent to afford 1.9 g (50%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5 H), 5.86–5.70 (m, 1 H), 5.19–4.93 (m, 4 H), 4.92–4.62 (m, 1 H), 3.26–3.08 (m, 2 H), 2.16–2.00 (m, 2 H), 1.67–1.52 (m, 2 H).



3-Methylpent-4-enylcarbamic acid benzyl ester (14). A flame-dried flask was cooled under a stream of nitrogen and charged with 3-methylpent-4-enoic acid[17] (6.85 g, 60 mmol). The flask was purged with nitrogen, benzene (100 mL) was

added and the resulting solution was cooled to ca. 10 °C using an ice water bath. Oxalyl chloride (14 mL, 160 mmol) was added dropwise via syringe to the solution and the resulting mixture was warmed to rt, stirred for 1 h, and then concentrated *in vacuo*. The crude 3-methylpentenoyl chloride product of this reaction was dissolved in THF (100 mL), and slowly added to a separate flask containing aqueous ammonium hydroxide (100 mL) at 0 °C. The resulting mixture was stirred for 6 h and then concentrated *in vacuo.* The mixture was diluted with H_2O (50 mL) and ethyl acetate (100 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude 3-methylpent-4-enylcarboxamide was dissolved in THF (100 mL) and cooled to 0 °C. A solution of $LiAlH_4$ in THF (200 mL, 200 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to rt and stirred for 36 h, then was cooled to 0 °C, quenched with H_2O (16 mL), and diluted with ether (200 mL). An aqueous solution of NaOH (30 mL, 10 M) was added and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with ether (100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and filtered to afford a solution of 3-methylpentenylamine in diethyl ether (ca. 0.1 M). The solution of 3-methylpentenylamine (300 mL, 30 mmol, 0.1 M) was cooled to 0 °C, triethylamine (11.5 mL, 90 mmol) and benzyl chloroformate (6.6 mL, 45 mmol) were added, and the resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 16 h). A solution of 1.0 M aqueous HCl (200 mL) was added, the mixture was transferred to a separatory funnel, and was extracted with diethyl ether (100

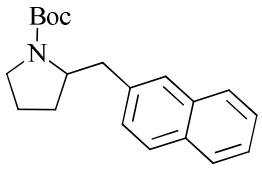
mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using 5% → 10% ethyl acetate/hexanes as the eluent to afford 1.2 g (17% over the five steps) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5 H), 5.73–5.60 (m, 1 H), 5.16–5.05 (m, 2 H), 5.02–4.90 (m, 2 H), 4.87–4.58 (m, 1 H), 3.27–3.08 (m, 2 H), 2.25–2.11 (m, 1 H), 1.58–1.40 (m, 2 H), 1.00 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 143.6, 136.6, 128.4, 128.1, 128.0, 113.4, 66.5, 39.2, 36.4, 35.6, 20.2; IR (film) 1706 cm^{-1}. Anal calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.28; H, 8.29; N, 6.08.



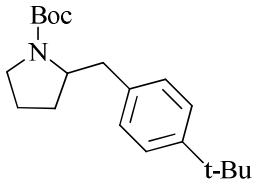
1-Phenylpent-4-enylcarbamic acid benzyl ester (16). Treatment of a solution of 1-phenylpent-4-enyl-amine[1] in diethyl ether (250 mL, 25 mmol, 0.1 M) with triethylamine (9.6 mL, 75 mmol) and benzyl chloroformate (5.5 mL, 37.5 mmol) using a procedure analogous to that described above for the synthesis of **6** afford 3.86 g (52%) of the title compound as a waxy white solid, m.p. 51–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–6.97 (m, 10 H), 5.86–5.65 (m, 1 H), 5.43–5.21 (m, 1 H), 5.14–4.90 (m, 4 H), 4.79–4.47 (m, 1 H), 2.12–1.94 (m, 2 H), 1.92–1.64 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 142.3, 137.4, 136.4, 128.5, 128.4, 128.0, 127.2, 126.3, 115.2, 66.6, 54.9, 35.6, 30.2 (two aromatic carbons are incidentally equivalent); IR (film) 1710 cm^{-1}. Anal calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.06; H, 7.19; N, 4.69.

Synthesis of Functionalized Pyrrolidines via Coupling with Aryl Bromides (Table 3)

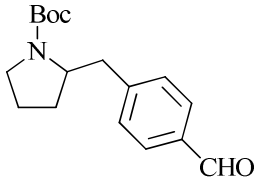
General Procedure for Pd-Catalyzed Carboamination Reactions of Aryl Bromides. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (2 mol %), dpe-phos (4 mol %) and Cs_2CO_3 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate (1.0 equiv) in dioxane (5 mL/mmol substrate) was then added via syringe. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



2-Napthalen-2-ylmethylpyrrolidine-1-carboxylic acid *tert*-butyl ester (18).[1] The general procedure was employed for the reaction of 2-bromonapthalene (62 mg, 0.30 mmol) with pent-4-enyl-carbamic acid *tert*-butyl ester (47 mg, 0.25 mmol). This procedure afforded 58 mg (75%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.74 (m, 3 H), 7.66–7.60 (m, 1 H), 7.51–7.40 (m, 2 H), 7.40–7.33 (m, 1 H), 4.16– 4.02 (m, 1 H), 3.43–3.21 (m, 3 H), 2.77–2.65 (m, 1 H), 1.83–1.70 (m, 4 H), 1.56–1.50 (s, 9 H).

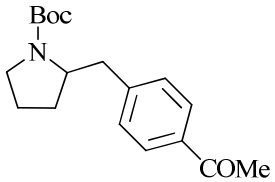


2-(4-*tert*-Butylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (19). The general procedure was employed for the reaction of 4-*tert*-butyl bromobenzene (52 μL, 0.30 mmol) with pent-4-enyl-carbamic acid *tert*-butyl ester (47 mg, 0.25 mmol). This procedure afforded 66 mg (83%) of the title compound as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.26 (m, 2 H), 7.22–7.07 (m, 2 H), 4.12–3.84 (m, 1 H), 3.49–3.23 (m, 2 H), 3.23–2.96 (m, 1 H), 2.60–2.42 (m, 1 H), 1.92–1.67 (m, 4 H), 1.55–1.48 (s, 9 H), 1.36–1.28 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 148.9, 136.1, 129.1, 125.2, 79.0, 58.8, 46.4, 40.0, 34.3, 31.4, 29.7, 28.6, 22.7; IR (film) 1695 cm^{-1}. Anal calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.46; H, 9.88; N, 4.38.

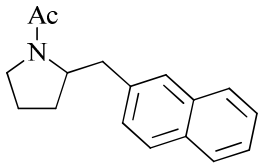


2-(4-Formylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (20). The general procedure was employed for the reaction of 4-bromobenzaldehyde (89 mg, 0.48 mmol) with pent-4-enyl-carbamic acid *tert*-butyl ester (74 mg, 0.40 mmol) except DME was used in place of dioxane and the reaction was conducted at 85 °C. This procedure afforded 94 mg (81%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{13}C NMR analysis; data are

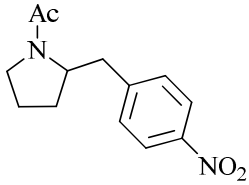
for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1 H), 7.80 (d, *J* = 8.0 Hz, 2 H), 7.41–7.29 (m, 2 H), 4.13–3.92 (m, 1 H), 3.46–3.01 (m, 3 H), 2.74–2.58 (m, 1 H), 1.85-1.60 (m, 4 H), 1.52–1.45 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 154.4, 146.6, 134.7, 130.1, 129.8, 79.3, 58.4, 46.3, 40.8, 39.9, 29.6, 28.5, 28.3, 23.4, 22.6; IR (film) 1693, 1606 cm^{-1}. Anal calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.45; H, 8.14; N, 4.72.



2-(4-Acetylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (21). The general procedure was employed for the reaction of 4-bromoacetophenone (120 mg, 0.60 mmol) with pent-4-enyl-carbamic acid *tert*-butyl ester (93 mg, 0.50 mmol) except DME was used in place of dioxane and the reaction was conducted at 85 °C. This procedure afforded 118 mg (78%) of the title compound as a white solid, m.p. 63–65 °C. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.85 (m, 2 H), 7.35–7.22 (m, 2 H), 4.11–3.94 (m, 1 H), 3.46–3.04 (m, 3 H), 2.74–2.55 (m, 4 H), 1.85–1.60 (m, 4 H), 1.51 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 197.7, 154.5, 154.4, 145.0, 144.9, 135.3, 135.2, 129.7, 129.5, 128.5, 128.3, 79.4, 79.1, 58.5, 58.3, 46.7, 46.2, 40.6, 39.6, 29.7, 28.9, 28.5, 26.5, 23.4, 22.6; IR (film) 1686, 1607 cm^{-1}. Anal calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.18; H, 8.30; N, 4.60.

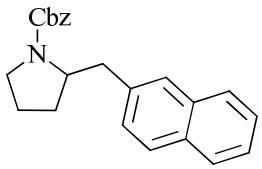


1-(2-(Naphthalen-2-ylmethyl)pyrrolidin-1-yl)ethanone (22).[1] The general procedure was employed for the reaction of 2-bromonapthalene (125 mg, 0.60 mmol) with *N*-pent-4-enyl-acetamide (64 mg, 0.50 mmol). This procedure afforded 101 mg (80%) of the title compound as a pale yellow oil. This compound was found to exist as a ~ 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.74 (m, 3 H), 7.66–7.58 (m, 1 H), 7.51–7.37 (m, 2.3 H), 7.32–7.27 (m, 0.7 H), 4.45–4.37 (m, 0.7 H), 4.17–4.09 (m, 0.3 H), 3.63–3.49 (m, 0.7 H), 3.45–3.32 (m, 2 H), 3.09–3.02 (m, 0.3 H), 2.86–2.69 (m, 1 H), 2.11 (s, 2 H), 2.06 (s, 1 H), 1.96–1.72 (m, 4 H).

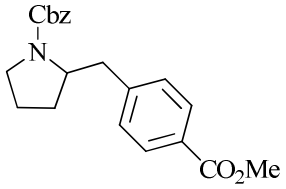


1-(2-(4-Nitrobenzyl)pyrrolidin-1-yl)ethanone (23). The general procedure was employed for the reaction of 1-bromo-4-nitrobenzene (97 mg, 0.48 mmol) with *N*-pent-4-enyl-acetamide (51 mg, 0.4 mmol) except dppe was used in place of Dpe-phos as ligand, DME was used in place of dioxane and the reaction was conducted at 85 °C. This procedure afforded 77 mg (77%) of the title compound as a white solid, m.p. 139–140 °C. This compound was found to exist as a ~ 7:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 0.3 H), 8.12 (d, J = 8.8 Hz, 1.7 H), 7.38 (d, J = 8.8 Hz, 1.7 H), 7.32 (d, J = 8.8

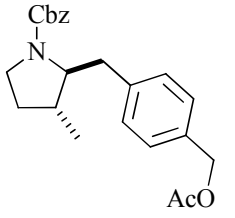
Hz, 0.3 H), 4.34–4.24 (m, 0.85 H), 4.11–4.03 (m, 0.15 H), 3.64–3.51 (m, 0.3 H), 3.50–3.35 (m, 1.7 H), 3.28 (dd, *J* = 3.4, 13.2 Hz, 0.85 H), 2.97 (dd, *J* = 5.2, 13.2 Hz, 0.15 H), 2.80 (dd, *J* = 8.8, 13.6 Hz, 0.15 H), 2.68 (dd, *J* = 9.2, 13.2 Hz, 0.85 H), 2.07 (s, 2.55 H), 1.99 (s, 0.45 H), 1.94–1.73 (m, 3.15 H), 1.71–1.60 (m, 0.85 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.9, 147.0, 146.5, 145.5, 130.2, 130.0, 123.8, 123.5, 59.4, 57.9, 47.8, 45.4, 40.6, 38.8, 30.1, 28.5, 23.7, 22.9 22.0, 21.7; IR (film) 1640, 1516 cm^{-1}. Anal calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.85; H, 6.44; N, 11.08.



2-(Naphthalen-2-ylmethyl)pyrrolidine-1-carboxylic acid benzyl ester (24). The general procedure was employed for the reaction of 2-bromonaphthalene (125 mg, 0.6 mmol) with pent-4-enylcarbamic acid benzyl ester (110 mg, 0.5 mmol). This procedure afforded 151 mg (88%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.63 (m, 3.5 H), 7.56–7.32 (m, 7.5 H), 7.25–7.19 (m, 1 H), 5.27–5.16 (m, 2 H), 4.28–4.12 (m, 1 H), 3.54–3.35 (m, 2.5 H), 3.25–3.16 (m, 0.5 H), 2.82–2.69 (m, 1 H), 1.87–1.72 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 154.8, 137.1, 136.8, 136.5, 136.4, 133.4, 132.1, 128.4, 128.1, 128.0, 127.9, 127.85, 127.79, 127.74, 127.65, 127.6, 127.4, 125.93, 125.86, 125.34, 125.26, 67.0, 66.5, 59.3, 58.8, 46.8, 46.6, 40.8, 39.6, 29.7, 28.9, 23.5, 22.7; IR (film) 1698 cm^{-1}. Anal calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 80.01; H, 6.78; N, 4.11.



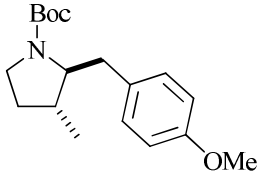
2-(4-(Methoxycarbonyl)benzyl)pyrrolidine-1-carboxylic acid benzyl ester (25). The general procedure was employed for the reaction of 4-bromobenzoate (129 mg, 0.6 mmol) with pent-4-enylcarbamic acid benzyl ester (110 mg, 0.5 mmol) except DME was used in place of dioxane and the reaction was conducted at 85 °C. This procedure afforded 152 mg (86%) of the title compound as a pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.86 (m, 2 H), 7.44–7.23 (m, 6 H), 7.16–7.08 (m, 1 H), 5.22–5.11 (m, 2 H), 4.18–4.02 (m, 1 H), 3.90 (s, 3 H), 3.51–3.31 (m, 2 H), 3.28–3.17 (m, 0.5 H), 3.11–3.00 (m, 0.5 H), 2.76–2.58 (m, 1 H), 1.88–1.61 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 167.0, 154.8, 144.4, 144.3, 137.0, 136.7, 129.64, 129.56, 129.3, 128.5, 128.2, 128.1, 127.9, 127.8, 67.0, 66.5, 58.9, 58.5, 52.0, 46.8, 46.6, 40.7, 39.5, 29.8, 28.9, 23.5, 22.7; IR (film) 1721, 1700 cm^{-1}. Anal calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.15; H, 6.62; N, 4.03.



(±)–(2*R*,3*S*)-2-(4-(Acetoxymethyl)benzyl)-3-methylpyrrolidine-1-carboxylic acid benzyl ester (26). The general procedure was employed for the reaction of 4-bromobenzyl acetate (138 mg, 0.6 mmol) with 3-methylpent-4-enylcarbamic acid

benzyl ester (117 mg, 0.5 mmol). The diastereoselectivity of the transformation was assessed by LAH reduction of the crude product obtained in a duplicate reaction, and was found to be 12:1 dr as judged by ^{1}H NMR analysis. The minor diastereomer was separated upon chromatographic purification to afford 143 mg (82%) of the title compound as a colorless oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5 H), 7.28–7.13 (m, 3 H), 7.09–7.02 (m, 1 H), 5.23–5.10 (m, 2 H), 5.09–5.02 (m, 2 H), 3.73–3.48 (m, 2 H), 3.34–3.18 (m, 1 H), 3.15–3.07 (m, 0.5 H), 3.01–2.92 (m, 0.5 H), 2.82–2.73 (m, 0.5 H), 2.70–2.61 (m, 0.5 H), 2.12–1.99 (m, 4 H), 1.94–1.80 (m, 1 H), 1.50–1.37 (m, 1 H), 0.87 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 155.1, 154.9, 138.8, 137.1, 136.8, 133.9, 133.7, 129.8, 129.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 67.0, 66.5, 66.15, 66.09, 65.9, 65.7, 45.4, 45.2, 39.9, 38.3, 36.8, 35.8, 31.1, 30.2, 21.0, 19.3, 19.1. IR (film) 1740, 1698 cm^{-1}. MS (ESI): 404.1839 (404.1838 calculated for $C_{20}H_{27}NO_4$, M + Na^+).

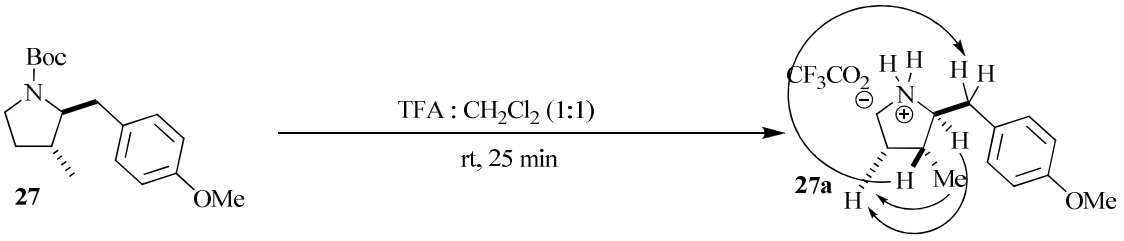
The stereochemistry of the above compound was assigned based on comparison of ^{1}H and ^{13}C NMR spectra to those obtained for the related product (±)–(2*R*,3*S*)-2-(4-Acetylbenzyl)-3-methylpyrrolidine-1-carboxylic acid benzyl ester, the stereochemistry of which was elucidated through ^{1}H NMR nOe experiments.[9]



(±)–(2*R*,3*S*)-2-(4-Methoxybenzyl)-3-methylpyrrolidine-1-carboxylic acid *tert*-butyl ester (27). The general procedure was employed for the

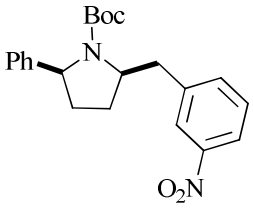
reaction of 4-bromoanisole (38 μL, 0.3 mmol) with 3-methylpent-4-enylcarbamic acid benzyl ester (50 mg, 0.25 mmol). The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be 15:1 dr as judged by ^{1}H NMR analysis. The minor diastereomer was separated upon chromatographic purification to afford 58 mg (78%) of the title compound as a pale yellow oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the rotamers mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.03 (m, 2 H), 6.86–6.78 (m, 2 H), 3.79 (s, 3 H), 3.63–3.34 (m, 2 H), 3.26–3.06 (m, 1 H), 3.05–2.89 (m, 1 H), 2.75–2.52 (m, 1 H), 2.09–1.95 (m, 1 H), 1.91–1.75 (m, 1 H), 1.51 (s, 9 H), 1.45–1.30 (m, 1 H), 0.85 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 154.7, 131.0, 130.6, 130.3, 113.8, 113.6, 79.2, 78.9, 65.9, 65.5, 55.2, 45.5, 44.9, 39.1, 37.7, 36.7, 35.8, 31.1, 30.3, 28.6, 19.4, 19.2; IR (film) 1692 cm^{-1}. Anal calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.56; H, 8.87; N, 4.60.

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **27** with TFA to afford **27a** as shown below.



(±)–(2*R*,3*S*)-2-(4-Methoxybenzyl)-3-methylpyrrolidinium-2,2,2-trifluoroacetate (**27a**). A flame-dried flask was cooled under a stream of nitrogen and charged with **27** (42 mg, 0.14 mmol). Methylene chloride (1 mL) was added and the mixture was cooled to 0

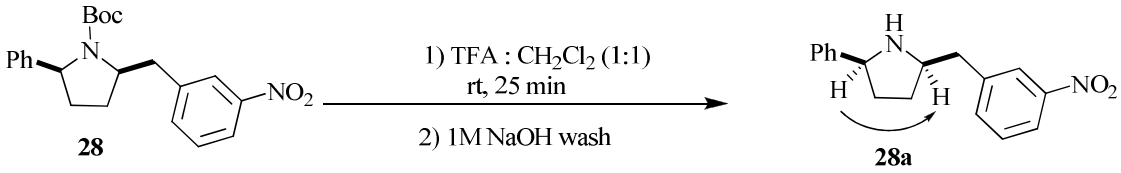
°C. Trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 25 min. The crude mixture was concentrated *in vacuo* to afford 41 mg (96%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, br, 1 H), 8.74 (s, br, 1 H), 7.10 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 6.72 (s, br, 1 H), 3.74 (s, 3 H), 3.28–3.18 (m, 1 H), 3.15–3.07 (m, 2 H), 3.00–2.86 (m, 2 H), 2.23–2.15 (m, 1 H), 2.14–2.05 (m, 1 H), 1.66–1.57 (m, 1 H), 0.99 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (q, *J* = 36.8 Hz), 158.8, 129.9, 127.6, 116.1 (q, *J* = 290.4 Hz), 114.2, 66.8, 55.1, 43.4, 38.3, 36.0, 32.2, 16.8; IR (film) 3502, 1690 cm^{-1}; MS (ESI): 206.1541 (206.1545 calculated for $C_{13}H_{19}NO$, M + H^+).



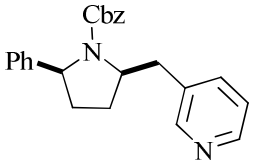
(±)–(2*R*,5*S*)-2-(3-Nitrobenzyl)-5-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (28). The general procedure was employed for the reaction of 1-bromo-3-nitrobenzene (122 mg, 0.6 mmol) with (1-phenylpent-4-enyl)carbamic acid *tert*-butyl ester (131 mg, 0.5 mmol). The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 151 mg (79%) of the title compound as a colorless oil with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–8.05 (m, 2 H), 7.72–7.52 (m, 1 H), 7.50–7.44 (m, 1 H), 7.36–7.16 (m, 5 H), 5.08–4.68 (m, 1 H), 4.28–4.09 (m, 1 H), 3.69–3.43 (m, 1 H), 2.88–2.76 (m, 1 H), 2.36–2.24 (m, 1 H), 2.01–1.92 (m, 1 H), 1.91–1.81 (m, 1 H), 1.75–

1.66 (m, 1 H), 1.65–1.05 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 148.2, 144.3, 141.1, 135.7, 129.3, 128.2, 126.6, 125.5, 124.1, 121.4, 79.7, 63.0, 60.4, 40.6, 34.3, 28.1 (two aliphatic carbons are accidentally equivalent); IR (film) 1687, 1530 cm^{-1}. Anal calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.97; H, 6.98; N, 7.19.

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **28** with TFA, followed by aqueous NaOH, to afford **28a** as shown below.

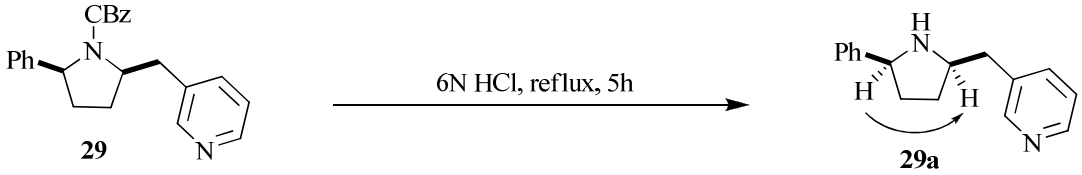


(±)–(2*R*,5*S*)-2-(3-Nitrobenzyl)-5-phenylpyrrolidine (**28a**). Treatment of **28** (100 mg, 0.26 mmol) with TFA/CH_2Cl_2 was effected using a procedure analogous to that described above for the preparation of compound **27a**, with the following modification. The crude residue obtained upon removal of TFA/CH_2Cl_2 was dissolved in CH_2Cl_2 (10 mL), and washed with 1.0 M NaOH (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. This procedure afforded 65 mg (88%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–8.12 (m, 1 H), 8.09–8.02 (m, 1 H), 7.63–7.57 (m, 1 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.40–7.35 (m, 2 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 7.25–7.18 (m, 1 H), 4.15 (t, *J* = 7.4 Hz, 1 H), 3.55–3.44 (m, 1 H), 2.99–2.86 (m, 2 H), 2.20–2.09 (m, 1 H), 2.00–1.91 (m, 1 H), 1.85 (s, 1 H), 1.75–1.55 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 144.9, 142.3, 135.5, 129.1, 128.2, 126.8, 126.5, 123.9, 121.2, 62.2, 59.6, 42.9, 33.9, 30.9; IR (film) 1526 cm^{-1}; MS (ESI): 283.1435 (283.1447 calculated for $C_{17}H_{18}N_2O_2$, M + H^+).

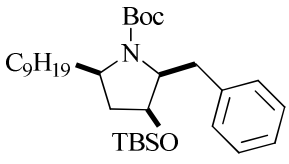


(±)–(2*S*,5*R*)-2-Phenyl-5-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylic acid benzyl ester (29). The general procedure was employed for the reaction of 3-bromopyridine (60 μL, 0.6 mmol) with 1-phenylpent-4-enylcarbamate benzyl ester (148 mg, 0.5 mmol). The diastereoselectivity of the transformation was assessed by HCl-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 144 mg (78%) of the title compound as a colorless oil with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59–8.31 (m, 2 H), 7.77–6.76 (m, 12 H), 5.29–4.85 (m, 3 H), 4.30–4.09 (m, 1 H), 3.67–3.27 (m, 1 H), 2.77–2.64 (m, 1 H), 2.35–2.24 (m, 1 H), 2.04–1.80 (m, 2 H), 1.76–1.65 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 150.5, 147.9, 143.6, 136.7, 136.5, 134.3, 128.4, 128.3, 127.5, 127.3, 126.8, 125.6, 123.4, 66.7, 63.0, 61.1, 38.1, 34.3, 28.6; IR (film) 1698 cm^{-1}; MS (ESI): 395.1736 (395.1735 calculated for $C_{24}H_{24}N_2O_2$, M + Na^+).

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **29** with 6N HCl, followed by aqueous NaOH, to afford **29a** as shown below.

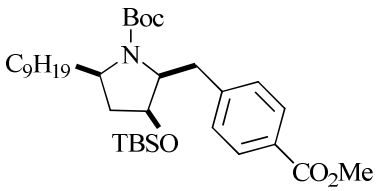


(±)–(2*R*,5*S*)-3-(5-Phenylpyrrolidin-2-ylmethyl)pyridine (**29a**). A flask was charged with **29** (40 mg, 0.11 mmol) and 6 N HCl (5 mL). The mixture was heated to reflux for 5 h, and then was cooled to rt. Distilled water was then added (2 mL), the crude mixture was washed with ether (3 x 10 mL), and the ether layers were discarded. The aqueous layer was then basified with 1M NaOH to pH 11 and extracted twice with ether (10 mL). The combined ether layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using 5% → 10% methanol/dichloromethane as the eluent to afford 22 mg (87%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55–8.42 (m, 2 H), 7.61–7.55 (m, 1 H), 7.43–7.36 (m, 2 H), 7.34–7.25 (m, 2 H), 7.24–7.17 (m, 2 H), 4.19 (t, *J* = 8.0 Hz, 1 H), 3.56–3.43 (m, 1 H), 3.25–2.89 (m, 1 H), 2.82 (d, *J* = 6.6 Hz, 2 H), 2.23–2.11 (m, 1 H), 2.02–1.90 (m, 1 H), 1.85–1.73 (m, 1 H), 1.72–1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 147.7, 136.6, 135.1, 128.3, 127.1, 126.7, 123.3, 62.3, 60.0, 39.7, 33.3, 30.6 (two aromatic carbons are incidentally equivalent); IR (film) 3410 cm^{-1}; MS (ESI): 239.1537 (239.1548 calculated for $C_{16}H_{18}N_2$, M + H$^+$).



(±)–(2*S*,3*S*,5*R*)-2-Benzyl-3-(*tert*-butyldimethylsiloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (30).[2] The general procedure was employed for the reaction of bromobenzene (26 μL, 0.24 mmol) with (±)–(1*R*,3*S*)-3-(*tert*-butyldimethylsiloxy)-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (89 mg, 0.20 mmol). ^{1}H NMR analysis of the crude material obtained upon workup showed the

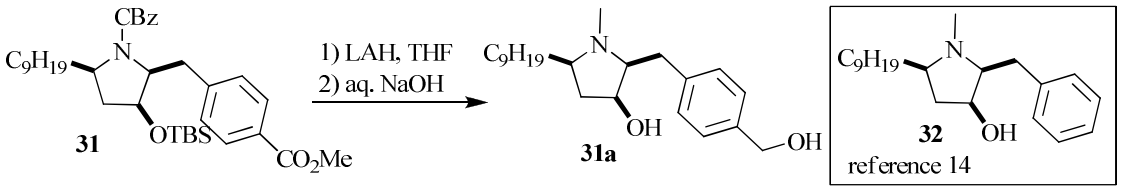
formation of the desired product as a >20:1 mixture of diastereomers. This procedure afforded 74 mg (71%) of the title compound as a colorless oil with >20:1 dr. The stereochemistry was assigned by comparison of the ^{1}H NMR spectrum to data previously reported in the literature.[14] This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.06 (m, 5 H), 4.32– 4.15 (m, 1.25 H), 4.08–3.95 (m, 0.75 H), 3.83–3.44 (m, 1 H), 3.06–2.96 (m, 1 H), 2.82–2.68 (m, 0.25 H), 2.61–2.47 (m, 0.75 H), 2.32–2.12 (m, 1.75 H), 2.05–1.93 (m, 0.25 H), 1.67–1.54 (m, 1 H), 1.51–1.03 (m, 24 H), 0.97–0.84 (m, 12 H), 0.13– -0.08 (m, 6 H).



(±)–(2*S*,3*S*,5*R*)-3-(*tert*-Butyldimethylsiloxy)-2-(4-methoxycarbonylbenzyl)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (31). The general procedure was employed for the reaction of methyl 4-bromobenzoate (52 mg, 0.24 mmol) with (±)–(1*R*,3*S*)-3-(*tert*-butyldimethylsiloxy)-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (89 mg, 0.20 mmol). The diastereoselectivity of the transformation was assessed by LAH reduction of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 83 mg (72%) of the title compound as a colorless oil with >20:1 dr. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.99–7.88 (m, 2 H), 7.39–7.22 (m, 2 H), 4.32–4.19 (m, 1.3 H), 4.07–3.98 (m, 0.7 H), 3.90 (s, 3 H), 3.72–3.51 (m, 1 H), 3.11–3.01 (m, 1 H), 2.87–2.75 (m, 0.3 H), 2.67–2.53 (m, 0.7 H), 2.33–2.12 (m, 1.7 H), 2.07–1.93 (m, 0.3 H), 1.65–1.55 (m, 1 H), 1.46–1.05 (m, 24 H), 0.96–0.81 (m, 12 H), 0.12– -0.12 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 154.8, 145.9, 129.9, 129.4, 127.6, 79.2, 71.4, 62.1, 55.7, 51.9, 38.0, 37.2, 36.3, 31.9, 29.7, 29.6, 29.3, 28.1, 26.5, 25.8, 22.7, 18.1, 14.1, -4.7, -5.0; IR (film) 1726, 1694 cm^{-1}. Anal calcd for $C_{33}H_{57}NO_5Si$: C, 68.82; H, 9.98; N, 2.43. Found: C, 68.43; H, 9.98; N, 2.42.

The stereochemistry of the above compound was determined through $LiAlH_4$ reduction of **31** to afford **31a** as shown below. The stereochemistry of **31a** was assigned by comparison of the ^{1}H NMR spectrum of **31** to that previously obtained for the related molecule **32**.[14]



(±)–(2*S*,3*S*,5*R*)-2-(4-Hydroxymethylbenzyl)-1-methyl-5-nonylpyrrolidin-3-ol (31a). A flame-dried flask was cooled under a steam of nitrogen and charged with **31** (70 mg, 0.12 mmol) and tetrahydrofuran (3 mL). The resulting solution was cooled to 0 °C and $LiAlH_4$ (1.2 mL, 1.2 mmol, 1 M in tetrahydrofuran) was added dropwise via syringe. The resulting mixture was heated to reflux until the starting material was consumed as judged by TLC analysis (ca. 21 h). The reaction mixture was cooled to 0 °C, slowly quenched with water (0.3 mL) and diluted with diethyl ether (5 mL). Aqueous NaOH (0.3 mL, 10

M) and water (0.3 mL) were added sequentially and an insoluble white precipitate formed. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil obtained was purified by flash chromatography using 10% → 20% methanol/dichloromethane as the eluent to afford 38 mg (91%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 4 H), 4.66 (s, 2 H), 3.83–3.75 (m, 1 H), 2.94–2.80 (m, 2 H), 2.33 (s, 3 H), 2.30–2.03 (m, 5 H), 1.77–1.66 (m, 1 H), 1.46–1.38 (m, 1 H), 1.37–1.15 (m, 15 H), 0.88 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 129.5, 127.1, 73.7, 70.2, 65.9, 64.9, 39.5, 38.6, 34.7, 33.1, 31.9, 29.9, 29.6, 29.5, 29.3, 26.4, 22.6, 14.1 (two aromatic carbons are incidentally equivalent); IR (film) 3384 cm^{-1}; MS (ESI): 348.2900 (348.2903 calculated for $C_{22}H_{37}NO_2$, M + H^+).

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Chapter 3

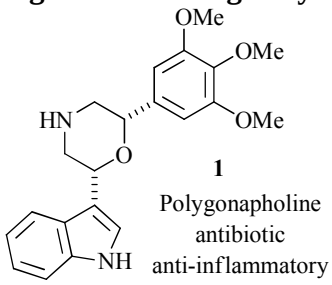
Synthesis of Substituted Morpholines *via* Palladium Catalyzed Carboamination Reactions

3.1 Background

In recent years drug discovery efforts have revealed several interesting biologically active compounds that contain C-substituted morpholine units (Figure 3-1).[1,2] Specifically, Polygonapholine (**1**), the first reported 2,6-disubstituted morpholine natural product was collected from the marine sponge *Chelonaplysilla sp.* from a marine lake in the nation of Palau. Compound **1** exhibits antimicrobial activity against *Bacillus subtilis* and shows in vivo anti-inflammatory activity.[3] Compound **2** was found to be the most potent compound in a screen for new centrally acting α1 agonists and has potential therapeutic value in the treatment of dementia and other central nervous system disorders characterized by symptoms of noradrenergic insufficiency.[4] Phendimetrazine (**3**) is a widely prescribed appetite suppressant with annual sales of 3.1 million dollars for one of the generic varieties in 2007.[5] The remaining compounds in Figure (**4**, **5**) contain *cis*-3,5-disubstituted morpholines. Compound **4** acts as a selective cholecystokinin-2 receptor antagonists, with potential for treatment of gastrointestinal adenocarcinomas, such as Barrett's metaplasia and pancreatic cancer, as well as gastroesophageal reflux disease and peptic ulcers.[2b] The meso-*cis*-3,5-dimethyl morpholine subunit was obtained by chromatographic separation of diastereomers from a non-selective morpholine

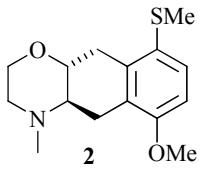
cyclization. Compound **5** has shown nanomolar activity as a caspase-1 inhibitor and is a potential therapeutic for inflammatory diseases such as rheumatoid arthritis or osteoarthritis.[2a]

Figure 3-1: Biologically Important Morpholines



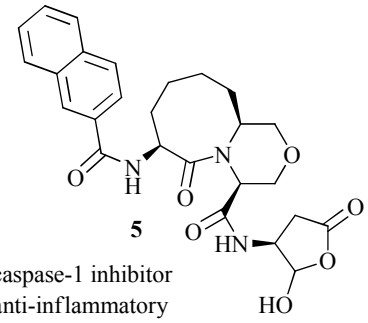
1

Polygonapholine
antibiotic
anti-inflammatory



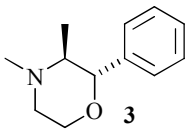
2

centrally acting α1 agonist
dementia or CNS theraputic



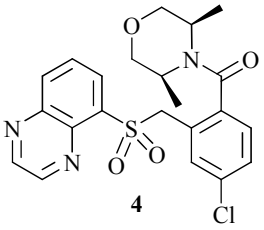
5

caspase-1 inhibitor
anti-inflammatory



3

Phendimetrazine
appetite suppressant

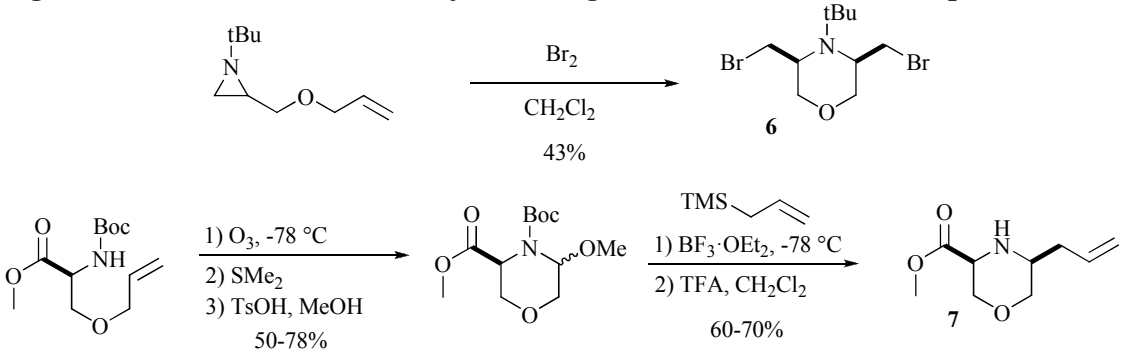


4

selective cholecystokinin-2 receptor antagonist
gastrointestinal adenocarcinomas, peptic ulcers

Despite the medicinal importance of these molecules, the development of new approaches for their synthesis remains relatively unexplored.[1,6] For example, few methods allow the preparation of 3,5-disubstituted morpholines,[7] and only two approaches for the stereoselective synthesis of *cis*-3,5-disubstituted derivatives have been described (Figure 3-2).[2a,8] Both of these strategies are limited in scope, as one affords symmetrically disubstituted (meso) products (**6**),[8] and the other was used only for the generation of a single monocyclic morpholine (***7***) in route to biologically active compound **5**.[2a] Development of a new, efficient, method for the diastereoselective synthesis of these types of compounds would be a valuable advancement in synthetic chemistry.

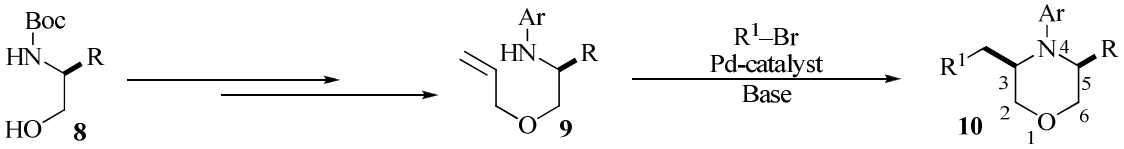
Figure 3-2: Known Methods for Synthesizing *cis*-3,5-Disubstituted Morpholines



3.2 Introduction

Previous work in the Wolfe lab established a concise asymmetric synthesis of *cis*-2,6-disubstituted piperazines that involves Pd-catalyzed carboamination reactions of *N*-allyl ethylenediamine derivatives.[9,10] It was hypothesized that a similar strategy may be applied to the construction of 3,5-disubstituted morpholines. As shown in Scheme 3-1, enantiopure *N*-Boc amino alcohols (**8**) could be converted to *O*-allyl ethanolamines **9** using standard methods. These compounds could then be transformed to the desired heterocycles **10** through Pd-catalyzed coupling with an aryl or alkenyl halide.[11] This strategy should provide access to a broad array of enantiopure *cis*-3,5-disubstituted morpholines that are difficult to generate using existing methods.

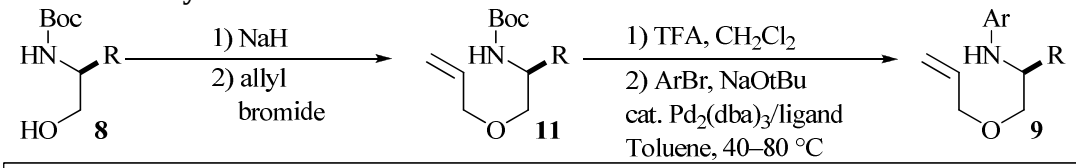
Scheme 3-1: Synthetic strategy



The substrates for the Pd-catalyzed carboamination reactions were synthesized in three steps from commercially available starting materials **8a–e** (Scheme 2). Treatment of the *N*-protected amino alcohols with NaH and allyl bromide afforded allyl ethers **11a–e**.

Cleavage of the Boc-group followed by Pd-catalyzed *N*-arylation of the resulting amine trifluoroacetate salts provided **9a–f** in moderate to good yield. For a representative reaction sequence, chiral HPLC analysis indicated complete retention of enantiomeric purity (99% ee) during the preparation of substrate **9a** from **8a**.

Scheme 3-2: Synthesis of Substrates



8a: R = Me	11a: 73%	9a: Ar = Ph (73%)[a]
8b: R = Bn	11b: 86%	9b: Ar = p-MeOPh (57%)[b]
		9c: Ar = Ph (59%)[c]
8c: R = $(CH_2)_2SMe$	11c: 59%	9d: Ar = Ph (71%)[a]
8d: R = CH_2OBn	11d: 73%	9e: Ar = p-Cl-Ph (59%)[c]
8e: R = CH_2[(N-Bn)-3-indolyl]	11e: 71%	9f: Ar = m-CN-Ph (60%)[c]

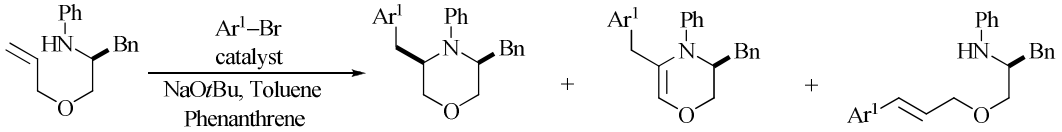
[a] Ligand = (o-biphenyl)P*t*Bu_2. [b] Ligand = P(*t*Bu)$_3$•HBF_4. [c] Ligand = (±)-BINAP.

3.3 Exploration of Reaction Conditions

Initial studies examined the coupling of a simple substrate and aryl bromide under reaction conditions similar to those used in the related piperazine-forming carboamination reactions.[9] A preliminary ligand screen revealed the formation of three main products (Table 3-1, Entry 1-5). The desired 3,5-disubstituted morpholine (**10**) formed in most cases, but an unsaturated morpholine (**12**) and Heck-type alkene arylation product (**13**) were also generated. Small amounts of several other unidentified side products were detected. The ratio of ligand to palladium played an important role in reaction selectivity (Table 3-1, Entries 4,5). Increasing the amount of base and aryl bromide helped the reactions proceed to full completion (Table 3-1, Entries 5,6). Other

ligands surveyed did not provide improved results for the desired morpholine product (Table 3-1, Entries 7-17). The initial choice of ligand based on the related piperazine system proved to be the optimal catalyst.

Table 3-1: Ligand Screen[a]



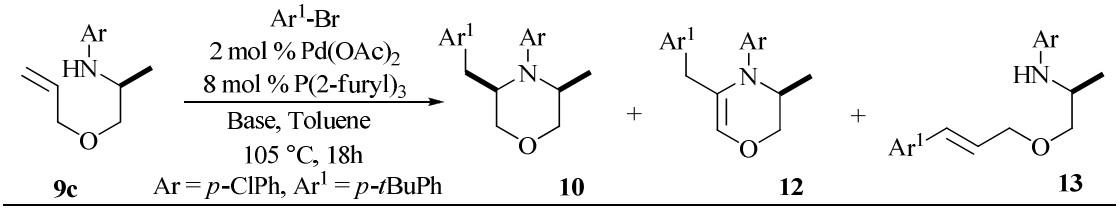
9c **10** **12** **13**

entry	catalyst	Ar^1–Br	Equiv Ar^1Br	conversion (%)	Product ratio **10**:**12**:**13**[c]
1	2% $Pd(OAc)_2$/4% Xantphos	*p*-*t*BuPh	1.2	73%	49 : 51 : 0
2	2%$Pd(OAc)_2$/8% P(*o*-tol)$_3$	*p*-*t*BuPh	1.2	26%	0 : 0 : 0
3	2% $Pd(OAc)_2$/8% TTMPP	*p*-*t*BuPh	1.2	12%	0 : 0 : 0
4	2% $Pd(OAc)_2$/2% P(2-furyl)$_3$	*p*-*t*BuPh	1.2	100%	33 : 11 : 56
5	2% $Pd(OAc)_2$/8% P(2-furyl)$_3$	*p*-*t*BuPh	1.2	75%	63 : 37 : 0
6	2% $Pd(OAc)_2$/8% P(2-furyl)$_3$	*o*-MePh	2.0	100%	82 : 18 : 0
7	2% $Pd(OAc)_2$/4% TDBPP	*p*-*t*BuPh	2.0	100%	0 : 78 : 22
8	2%$Pd(OAc)_2$/8% $BiPh_3$	*p*-*t*BuPh	2.0	79%	0 : 0 : 0
9	2% $Pd(OAc)_2$/8% $AsPh_3$	*p*-*t*BuPh	2.0	90%	54 : 15 : 31
10	2%$Pd(OAc)_2$/8% PPh_3	*o*-MePh	2.0	72%	83 : 17 : 0
11	2% $Pd(OAc)_2$/4% dppe	*o*-MePh	2.0	55%	80 : 20 : 0
12	2% $Pd(OAc)_2$/4% Dpe-Phos	*o*-MePh	2.0	42%	56 : 24 : 20
13	2% $Pd(OAc)_2$/4% dppf	*o*-MePh	2.0	89%	18 : 31 : 51
14	2% $Pd(OAc)_2$/2% IMes•HCl	*p*-*t*BuPh	2.0	100%	15 : 45 : 40
15[b]	5% $Pd(OAc)_2$/5% IPr•HCl	*p*-*t*BuPh	2.0	100%	20 : 80 : 0
16[b]	5% [(IPr)Pd(acac)Cl]	Ph	2.0	100%	0 : 100 : 0
17[b]	5% [(IPr)Pd(acac)Cl]	*o*-MePh	2.0	88%	34 : 44 : 22

[a] Conditions: 1.0 equiv **9c**, 2.0 equiv NaO*t*Bu, catalyst (as indicated), toluene (0.4 M), 105 °C. TTMPP = Tris(2,4,6-trimethoxyphenyl)phosphine. TDBPP = Tris(2,4-di-*t*Buphenyl)phosphite. [b] KO*t*Bu was used in place of NaO*t*Bu. [c] Product ratios were determined by ^{1}H NMR analysis of crude product mixtures after workup.

With a preferred catalytic system established, the remaining reaction conditions were investigated. Testing alternative bases known to facilitate similar palladium catalyzed reactions confirmed that NaO*t*Bu was the best choice (Table 3-2). Similarly, the screening of other potential solvents demonstrated a preference for toluene (Table 3-3).

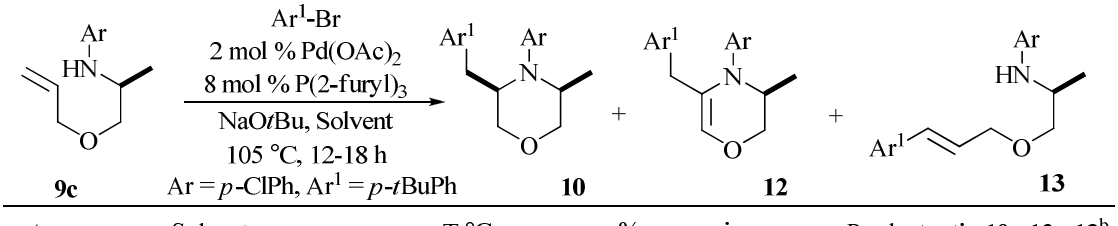
Table 3-2: Base Screen[a]



entry	Base	% conversion	Product ratio **10**:**12**:**13**[b]
1	Cs_2CO_3	100	27 : 0 : 73
2	K_3PO_4	100	24 : 0 : 76
3	KO*t*Bu	100	43 : 32 : 25
4	NaO*t*Bu	100	73 : 22 : 5

[a] Conditions: 1.0 equiv **9c**, 2.0 equiv Base, 2 mol % $Pd(OAc)_2$, 8 mol % P(2-furyl)$_3$, toluene (0.4 M), 105 °C. [b] Product ratios were determined by ^{1}H NMR analysis of crude product mixtures after workup.

Table 3-3: Solvent Screen[a]



entry	Solvent	T °C	% conversion	Product ratio **10** : **12** : **13**[b]
1	THF	65	0	0 : 0 : 0
2	DME	80	100	0 : 0 : 0
3	*t*-Amyl-OH	95	87	0 : 0 : 100
4	1,4-Dioxane	95	100	46 : 30 : 24
5	Benzotrifluoride	95	94	70 : 21 : 9
6	Toluene	105	100	73 : 22 : 5

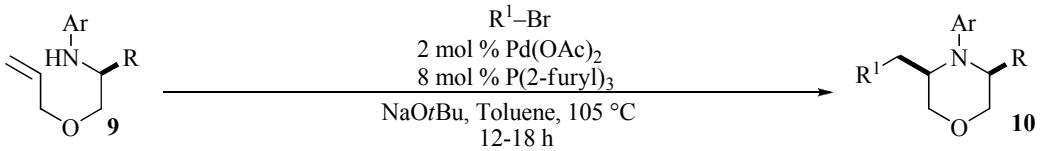
[a] Conditions: 1.0 equiv **9c**, 2.0 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 8 mol % P(2-furyl)$_3$, toluene (0.4 M), 105 °C. [b] Product ratios were determined by ^{1}H NMR analysis of crude product mixtures after workup.

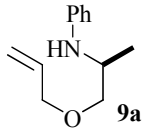
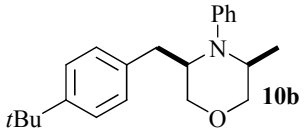
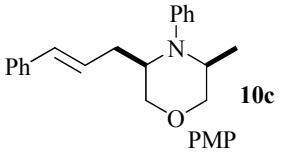
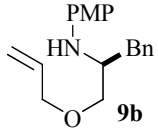
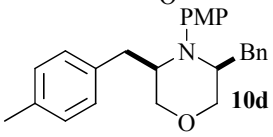
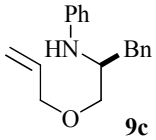
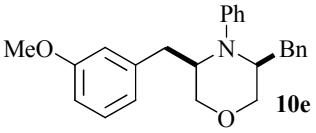
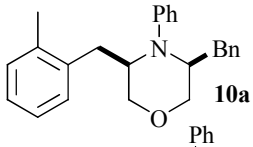
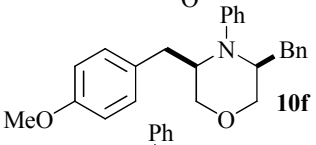
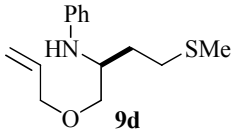
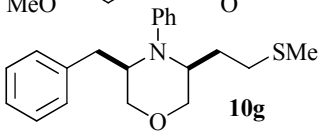
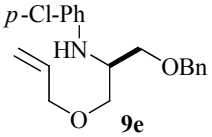
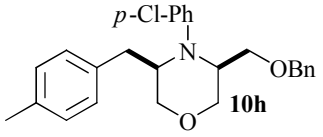
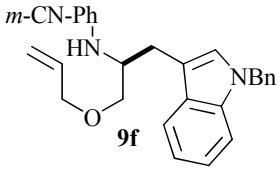
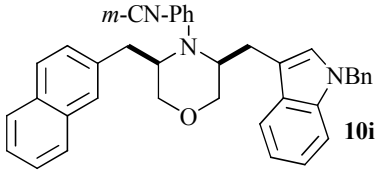
3.4 Synthesis of *cis*-3,5-Disubstituted Morpholines

The results of studies on the scope of 3,5-disubstituted morpholine-forming carboamination reactions are illustrated in Table 3-4. Several different 2-subsituted *O*-allylethanolamines were effectively converted to the desired heterocycles, including

heteroatom-containing substrates derived from methionine (Table 3-4, Entry 7), serine (Table 3-4, Entry 8), and tryptophan (Table 3-4, Entry 9). Although the yields in these reactions were modest (46–66%), the diastereoselectivities were uniformly high (> 20:1 dr). As a representative example, the Pd-catalyzed carboamination reaction of **9a** to **10b** proceeded with no erosion of enantiopurity. Side products of general structure **12** were observed in crude reaction mixtures, accounting for reduced yield of the desired morpholines. Spectroscopic analysis (^{1}H-NMR) of crude reaction mixtures indicated these side products were formed as 10–35% of the mixture (Table 3-5). The presence of electron-neutral or slightly electron-deficient *N*-aryl groups on the substrates was tolerated. However, efforts to employ a morpholine precursor bearing an *N*-(*p*-methoxyphenyl) moiety led to a poor yield of **10d** due to competing *N*-arylation or Heck arylation of the substrate (Table 3-4, Entry 3). In some instances side products resulting from sequential *N*-arylation and Heck arylation of the substrate were also isolated. Low yields were also obtained when starting materials with *N*-(*p*-cyanophenyl) groups were used, as competing Heck arylation of the substrate alkene group was again problematic. Similarly, efforts to couple *N*-Boc-protected substrate **11a** with 1-bromo-4-*tert*-butylbenzene afforded only a Heck arylation product.

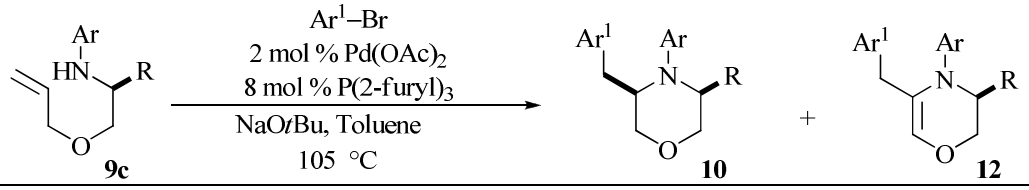
Table 3-4: Synthesis of *cis*-3,5-Disubstituted Morpholines[a]



entry	substrate	product	yield[b]
1	 **9a**	 **10b**	53%
2	**9a**	 **10c**	46%[c]
3	 **9b**	 **10d**	21%
4	 **9c**	 **10e**	48%
5	**9c**	 **10a**	66%
6	**9c**	 **10f**	47%
7	 **9d**	 **10g**	58%
8	 **9e**	 **10h**	49%
9	 **9f**	 **10i**	57%

[a] Conditions: 1.0 equiv substrate, 2.0 equiv R^1Br, 2.0 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 8 mol % P(2-furyl)$_3$, toluene (0.4 M), 105 °C. [b] Isolated yield (average of two experiments). All products were formed with >20:1 dr as judged by ^1H NMR analysis of crude products prior to purification. [c] The reaction was conducted using 4.0 equiv of β-bromostyrene, 4.0 equiv of NaOtBu, 4 mol % $Pd(OAc)_2$ and 16 mol % P(2-furyl)$_3$.

Table 3-5: Reaction Product Ratios



entry	R, Ar	Ar^1–Br	Product ratio **10** : **12**
1	Me, Ph	*p*-*t*BuPh	74 : 26
2	Me,Ph	β–Styrene	100 : 0
3	Bn, Ph	*o*-MePh	89 : 11
4	Bn, Ph	*m*-OMePh	66 : 34
5	Bn, Ph	*p*-OMePh	68 : 32
6	$CH_2CH_2SCH_3$, Ph	Ph	90 : 10
7	CH_2OBn, *p*-ClPh	*p*-ClPh	74 : 26
8	*N*-Bn-3-indolyl, *m*-CNPh	2-Napthyl	85 : 15

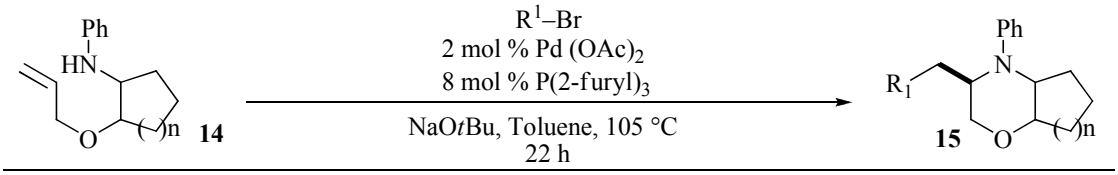
3.5 Expansion to Bicyclic Morpholines and Other Substitution Patterns.

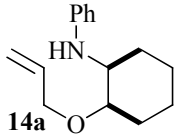
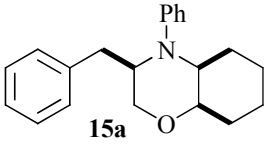
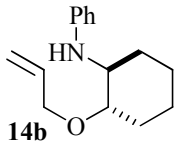
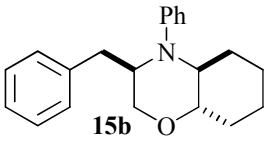
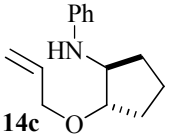
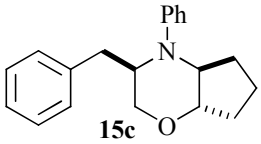
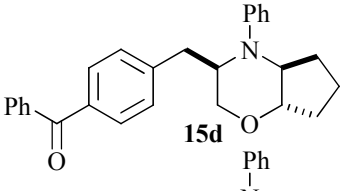
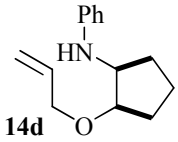
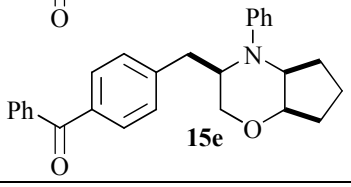
In order to further explore the utility of this method for the synthesis of other substituted morpholines, reactions of several *N*-aryl ethanolamine derivatives with different substitution patterns were examined. The synthetic work for the bicyclic morpholine examples was conducted by Brandon Rosen, an undergraduate co-worker on this project. Substrates **14a**–**d** were prepared by *O*-allylation of 2-(*N*-phenylamino)cyclohexanol or –cyclopentanol. The known *trans*-2-(*N*-phenylamino)cycloalkanols were prepared in one step from aniline and cyclohexene oxide or cyclopentene oxide. As shown in Table 3-6, the substrates were coupled with aryl bromides using the optimized reaction conditions. These transformations afforded the desired bicyclic morpholines **15a**–**e** in moderate to good yields with excellent diastereoselectivities (>20:1 dr). Alternatively, compounds **16** and **18** were converted into

2,3-disubstituted morpholine **17** and 2,5-disubstituted morpholine **19** (Scheme 3-3). However, both **17** and **19** were produced with only modest (2:1) diastereoselectivity.

The nature of the aryl halide coupling partner had a significant effect on the yield of the morpholine-forming reactions. Use of electron-rich or electron-neutral derivatives provided acceptable yields of the desired heterocycles. In addition, the coupling of **9a** with an alkenyl halide (Table 3-4, entry 2) was also successful. However, most attempts to employ electron-poor aryl bromides led to complex mixtures of products, although the carboamination reactions of **14c–d** with 4-bromobenzophenone (Table 3-6, entries 4–5) and of **16** with 3-bromobenzonitrile (Scheme 3-3) gave useful quantities of desired products. The coupling of **9c** with the sterically hindered 2-bromotoluene provided a 66% yield of **10a** (Table 3-4, entry 5), but 1-bromo-2-methylnaphthalene failed to react with **9c** under similar conditions.

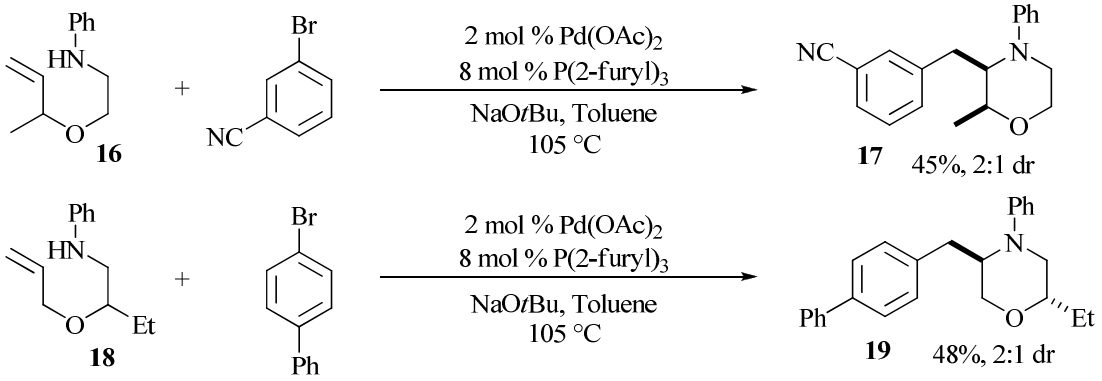
Table 3-6: Synthesis of Bicyclic Morpholines[a]



entry	substrate	product	yield[b]
1	 **14a**	 **15a**	65%
2	 **14b**	 **15b**	56%
3	 **14c**	 **15c**	73%
4	**14c**	 **15d**	54%
5	 **14d**	 **15e**	77%

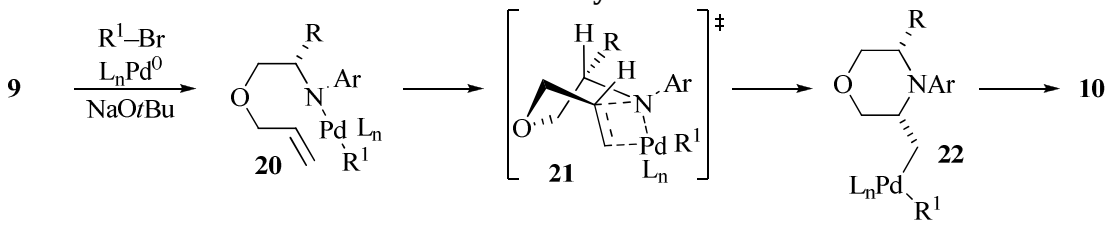
[a] Conditions: 1.0 equiv substrate, 2.0 equiv R^1Br, 2.0-2.7 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 8 mol % P(2-furyl)$_3$, toluene (0.3 M), 105 °C. [b] Isolated yield (average of two or more experiments). All products were formed with >20:1 dr as judged by ^1H NMR analysis of crude products prior to purification.

Scheme 3-3: Disubstituted Morpholines with Poor Diastereoselectivity

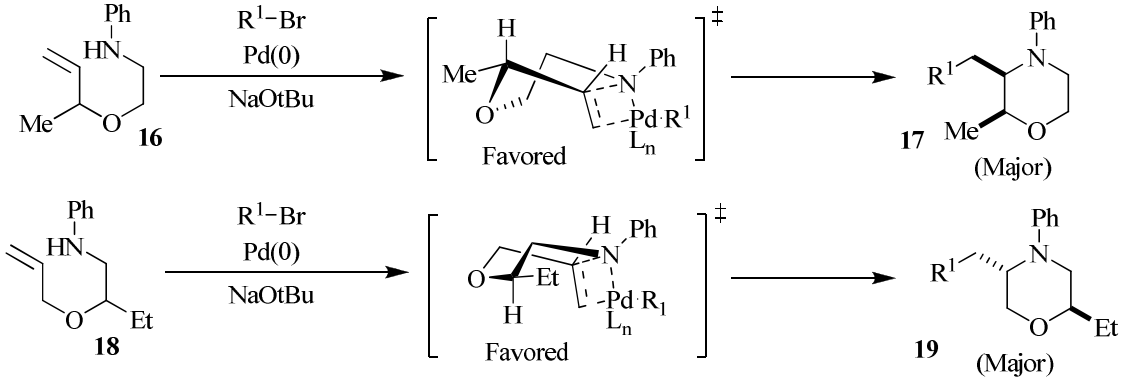


The mechanism of the morpholine-forming carboamination reactions is likely similar to that of related transformations that generate piperazines, pyrrolidines, and other nitrogen heterocycles.[9,11] As shown in Scheme 3-4, the key intermediate in the conversion of **9** to **10** is palladium(aryl)(amido) complex **20**, which is produced by oxidative addition of the aryl bromide to Pd(0) followed by Pd–N bond formation.[12] The relative stereochemistry of the substituted morpholine products is most consistent with a pathway involving *syn*-aminopalladation of **20** through a boat-like transition state (**21**) to afford **22**. Chair-like transition states for intramolecular *syn*-aminopalladation reactions that generate six-membered rings appear to be less favorable than boat-like transition states due to poor overlap between the alkene π-system and the Pd–N bond.[9b] Reductive elimination from **22** would provide the *cis*-3,5-disubstituted morpholine products **10**. This mechanism also accounts for the conversion of **16** to *cis*-2,3-disubstituted morpholine **17**, and **18** to *trans*-2,5-disubstituted morpholine **19** (Scheme 3-5). The modest diastereoselectivities observed in the reactions of **16** and **18** are presumably due to relatively small differences in the energies of transition states in which the substrate R-group is oriented in a psueduoaxial vs. pseudoequatorial position.[9b]

Scheme 3-4: Mechanism and Stereochemistry

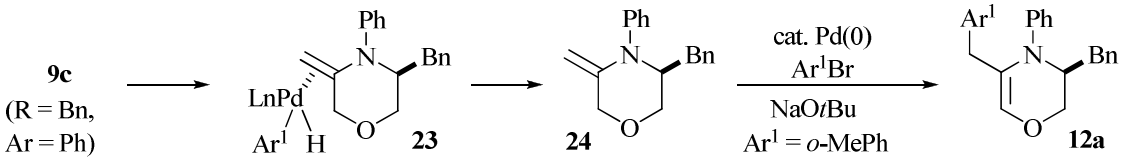


Scheme 3-5: Stereochemical Rational for 2,3- and 2,5-Disubstituted Morpholines



As noted above in Table 3-1, we observed the formation of 3,4-dihydro-2*H*-1,4-oxazine **5a** as a side product in the Pd/P(2-furyl)$_3$ catalyzed coupling of **9c** with 2-bromotoluene. This compound is presumably generated via β-hydride elimination from intermediate **22** to provide **23** (Scheme 3-6). This complex could then be transformed into unsaturated heterocycle **12a** by alkene dissociation and subsequent Heck arylation[13] of the resulting product **24**.

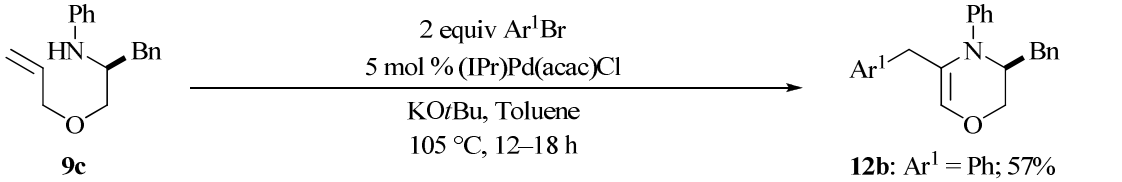
Scheme 3-6: Formation of 3,4-dihydro-*2H*-1,4-oxazine 12a



We felt that it may be possible to optimize conditions so that unsaturated compounds such as **12a** would be generated as the major products in coupling reactions between **9** and aryl bromides. The mechanism outlined in Scheme 3-6 suggests that catalysts or ligands that either slow C–C bond-forming reductive elimination, facilitate β–hydride elimination, or both, may favor the conversion of **22** to **23**, which in turn leads to generation of **12**. Thus, we examined the use of catalysts supported by relatively electron rich monodentate ligands. The rate of reductive elimination from Pd(II)

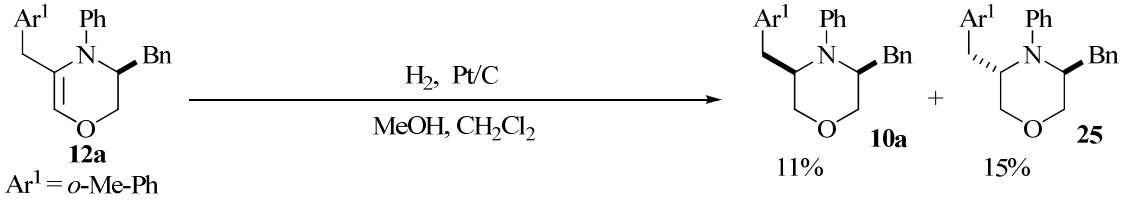
decreases as ligand basicity increases and ligand size decreases. However, steric effects can outweigh electronic effects, as electron-rich ligands that are sterically bulky are known to promote reductive elimination.[13] While a phosphite ligand showed improved selectivity for **12**, the best result was obtained after switching to an *N*-heterocyclic carbene based system (Table 3-1, Entries 15-16). Reaction conditions that generated the catalytic system *in situ* led to poor reproducibility. Utilization of the premade catalyst (IPr)Pd(acac)Cl[14] provided consistent results for the coupling of bromobenzene with **9c**, providing clean selectivity for the unsaturated product **12b** with a 57% isolated yield (Scheme 3-7). The scope of this reaction is currently limited, as use of 2-bromotoluene as the electrophile afforded only 21% yield of **12a**. Increased sterics bulk on the aryl coupling partner appears to promote C—C bond forming reductive elimination leading to the substituted morpholine products. Purification of the unsaturated morpholine products is also difficult due to their hydrolytic lability. Preliminary efforts to further manipulate the 3,4-dihydro-2*H*-1,4-oxazines proved unsuccessful. Further optimization of conditions or use of this transformation in tandem/sequenced reactions may improve synthetic utility. A catalytic hydrogenation reduced **12a** with no selectivity, providing a roughly equal mixture of both product diastereomers (Scheme 3-8). An ionic hydrogenation has been accomplished by the Zhou group, but the reaction was likely facilitated by protection of the ring nitrogen with the strong electron withdrawing tosyl group (**26**, Scheme 3-9).[15] While good diastereoselectivity was attained with a sterically demanding isopropyl side chain, no selectivity was observed with the less crowded isobutyl side chain.

Scheme 3-7: Steric Influence on 3,4-Dihydro-2*H*-1,4-oxazine Synthesis

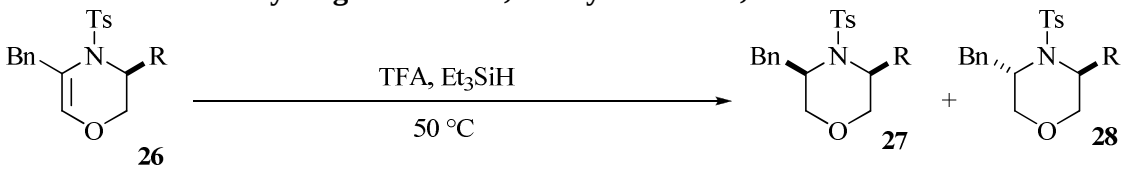


12b: Ar^1 = Ph; 57%
12a: Ar^1 = *o*-Me-Ph; 21%

Scheme 3-8: Hydrogenation of 3,4-Dihydro-2*H*-1a,4-oxazine



Scheme 3-9: Ionic Hydrogenation of 3,4-Dihydro-2*H*-1a,4-oxazine



R = *i*Pr; 73%, dr > 20:1
R = *i*Bu; 92%, dr 1:1

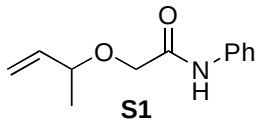
3.6 Conclusions

In conclusion, a new method has been developed for the concise asymmetric synthesis of *cis*-3,5-disubstituted morpholines from readily available enantiopure amino alcohol precursors. The modular nature of this approach permits variation of the morpholine substituents, and also provides access to fused-ring morpholine derivatives. In addition, modification of catalyst structure can lead to potentially useful 3,4-dihydro-2*H*-1,4-oxazine products. The strategies described in this chapter significantly expand the range of substituted morpholines that can be prepared in a concise, stereocontrolled manner.

3.7 Experimental Section

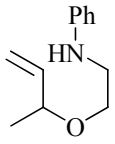
General: All reactions were carried out under a nitrogen atmosphere in oven or flame dried glassware. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides were obtained from commercial sources (Aldrich Chemical CO or Acros Chemical CO) and were used as obtained. *N*-phenyl-α-bromoacetamide,[16] (*S*)-2-(Boc-amino)-1-propanol,[17] N_{α}-Boc-L-tryptophan,[18] (*R*)-*tert*-butyl 1-(benzyloxy)-3-hydroxypropan-2-ylcarbamate,[19] (S)-*tert*-butyl 1-hydroxy-3-phenylpropan-2-ylcarbamate,[20] (*S*)-*tert*-butyl 1-hydroxy-4-(methylthio)butan-2-ylcarbamate,[21] and 1-(phenylamino)butan-2-ol,[22] were prepared according to published procedures. (±)-*trans*-2-(phenylamino)cyclohexanol[23] and (±)-*trans*-2-(phenylamino)cyclopentanol[24] were synthesized via ring-opening of cyclohexene oxide or cyclopentene oxide with aniline.[23] Toluene and THF were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, and either capillary GC (known compounds) or ESI Mass Spectrometry (new compounds). The yields reported in the Supporting Information describe the result of a single experiment, whereas the yields reported in Table 3-4, Table 3-5, and Table 6 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 3-4, Table 3-5, and Table 6.

Synthesis of Substrates

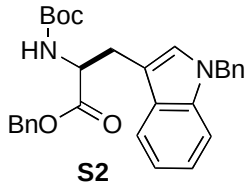


S1

(±)-*N*-Phenyl-2-(but-3-en-2-yloxy)acetamide (S1). A flame-dried flask was cooled under a stream of nitrogen and charged with 3-butene-2-ol (0.73 mL, 8.41 mmol) and THF (3.5 mL). The resulting solution was cooled to 0 °C in an ice/H_2O bath and sodium hydride (60% dispersion in mineral oil, 336 mg, 8.41 mmol) was added. The resulting mixture was stirred at 0 °C for 30 min, then a solution of phenyl bromoacetamide[16] (1.50 g, 7.0 mmol) in THF (13.5 mL) was added dropwise. The reaction mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (ca. 1 h). The reaction mixture was then quenched with saturated aqueous NH_4Cl (10 mL), diluted with EtOAc (10 mL), filtered by suction filtration to remove insoluble material, and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 10% EtOAc/hexanes as the eluent to afford the title compound (220 mg, 15%) as colorless crystals, m.p. 48−50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, br, 1 H), 7.57 (d, *J* = 7.8 Hz, 2 H), 7.31 (t, *J* = 7.8 Hz, 2 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 5.74 (ddd, *J* = 7.5, 10.1, 17.2 Hz, 1 H), 5.28−5.18 (m, 2 H), 4.05 (d, *J* = 15.7 Hz, 1 H), 3.98−3.89 (m, 2 H), 1.34 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 138.4, 137.0, 128.8, 124.2, 119.6, 117.2, 78.0, 67.5, 20.9; IR (film) 3386, 1682 cm^{-1}; MS (ESI) 228.0996 (228.1000 calcd for $C_{12}H_{15}NO_2$, M + Na^+).

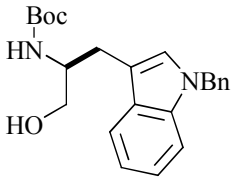


(±)-*N*-[2-(But-3-en-2-yloxy)ethyl]aniline (16). A flame-dried flask was cooled under a stream of nitrogen and charged with **S1** (450 mg, 2.2 mmol) and THF (4.4 mL). The resulting solution was cooled to 0 °C in an ice/H_2O bath, and $LiAlH_4$ (1M in THF, 4.4 mL, 4.4 mmol) was added. The reaction mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (ca. 23 h). The mixture was then cooled to 0 °C, quenched with H_2O (0.2 mL) and diluted with diethyl ether (10 mL). An aqueous solution of NaOH (0.2 mL, 10 M) was added followed by H_2O (0.6 mL), and an insoluble white solid precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with diethyl ether (10 mL). The combined organic layers were concentrated in vacuo to afford an amber oil. The crude material was purified by flash chromatography using 10% EtOAc/hexanes as the eluent to afford the title compound (263 mg, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.7 Hz, 2 H), 6.68 (t, *J* = 7.4 Hz, 1 H), 6.59 (t, *J* = 8.1 Hz, 2 H), 5.71 (ddd, *J* = 7.1, 10.2, 17.2 Hz, 1 H), 5.19−5.07 (m, 2 H), 4.00 (s, br, 1 H), 3.86−3.77 (m, 1 H), 3.66−3.59 (m, 1 H), 3.52−3.44 (m, 1 H), 3.29−3.16 (m, 2 H), 1.24 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 140.0, 129.0, 117.3, 115.8, 112.9, 77.0, 66.4, 43.6, 21.1; IR (film) 3403, 1604 cm^{-1}; MS (ESI) 192.1382 (192.1388 calcd for $C_{12}H_{17}NO$, M + H^+).

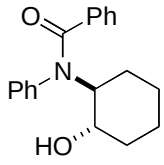


S2

(–)-(*S*)-Benzyl 3-(1-benzyl-1*H*-indol-3-yl)-2-(*tert*-butoxycarbonylamino)propanoate (S2). A flame-dried flask was cooled under a stream of nitrogen and charged with N_α-Boc-L-tryptophan[18] (1.00 g, 3.29 mmol, 1.0 equiv) and DMF (3.3 mL). The resulting solution was cooled to 0 °C in an ice/H_2O bath, and sodium hydride (60% dispersion in mineral oil, 389 mg, 9.73 mmol) was added. The resulting mixture was allowed to stir at 0 °C for 30 min, then benzyl bromide (1.4 mL, 11.8 mmol) was added dropwise. The reaction mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (ca. 36 h). The reaction was quenched with saturated aqueous NH_4Cl (10 mL), diluted with EtOAc (10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with brine (3 x 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude yellow oil was purified by flash chromatography on silica gel using 15% EtOAc/hexanes as the eluent to afford the title compound (1.25 g, 78%) as a white solid, m.p. 98−99 °C. $[\alpha]^{23}_D$ − 3.2 (*c* = 2.88, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.8 Hz, 1 H), 7.20−6.89 (m, 13 H), 6.61 (s, 1 H), 5.05 (s, 2 H), 5.00−4.87 (m, 3 H), 4.63−4.51 (m, 1 H), 3.25−3.09 (m, 2 H), 1.30 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 155.1, 137.4, 136.4, 135.3, 128.7, 128.5, 128.4, 128.3, 127.5, 126.9, 126.6, 121.9, 119.3, 119.0, 109.6, 109.2, 79.7, 66.9, 54.4, 49.8, 28.3, 27.9 (two aromatic carbon signals are incidentally equivalent); IR (film) 3427, 1713 cm^{-1}; MS (ESI) 507.2249 (507.2260 calcd for $C_{30}H_{32}N_2O_4$, M + Na^+).



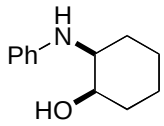
(–)-(*S*)-*tert*-Butyl 1-(1-benzyl-1*H*-indol-3-yl)-3-hydroxypropan-2-ylcarbamate (8e). The reduction of **S2** (10.82 g, 22.3 mmol) was conducted for 18 h using a procedure analogous to that described above for the preparation of **16**. This procedure afforded the title compound (7.22 g, 85%) as a colorless solid, m.p. 94−96 °C. $[\alpha]^{23}_{D}$ − 7.0 (*c* = 1.43, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.9 Hz, 1 H), 7.31–7.21 (m, 4 H), 7.20–7.07 (m, 4 H), 6.98 (s, 1 H), 5.26 (s, 2 H), 4.84 (d, *J* = 7.7 Hz, 1 H), 4.03–3.91 (m, 1 H), 3.73–3.53 (m, 2 H), 2.98 (d, *J* = 6.8 Hz, 2 H), 2.60 (s, br, 1 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 137.5, 136.6, 128.7, 128.3, 127.6, 126.8, 126.7, 121.9, 119.3, 119.1, 111.0, 109.7, 79.6, 64.9, 53.0, 49.9, 28.3, 26.9; IR (film) 3356, 1686 cm^{-1}; MS (ESI) 403.2006 (403.1998 calcd for $C_{23}H_{28}N_2O_3$, M + Na^+).



S3

(±)-(1*S,2*S**)-*N*-(2-hydroxycyclohexyl)-*N*-phenylbenzamide (S3)**. A solution of *trans*-2-(phenylamino)cyclohexanol[23] (956 mg, 5.0 mmol) and triethylamine (2.1 mL, 15 mmol), in dichloromethane (10 mL), was cooled to 0 °C and benzoyl chloride (0.6 mL, 4.9 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 48 h, then was transferred to a separatory funnel. The mixture was washed with 2 M HCl (2 x 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and

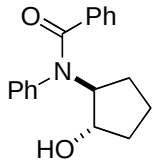
concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel using 2.5% MeOH/dichloromethane as the eluant to afford 1.13 g (77%) of the title compound as a white solid, m.p. 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2 H), 7.24–7.06 (m, 8 H), 4.77–4.61 (m, 1 H), 3.53–3.37 (m, 1 H), 2.76 (s, br, 1 H), 2.12 (d, *J* = 12.0 Hz, 1 H), 2.01–1.89 (m, 1 H), 1.78–1.63 (m, 2 H), 1.52–1.29 (m, 2 H), 1.29–1.00 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 139.5, 136.8, 130.8, 129.1, 128.7, 128.3, 127.63, 127.56, 71.7, 61.5, 35.7, 30.2, 25.2, 24.3; IR (film) 3319, 1622, cm^{-1}; MS (ESI) 318.1465 (318.1470 calcd for $C_{19}H_{21}NO_2$ M + Na^+).



S4

(±)-*cis*-2-(phenylamino)cyclohexanol (S4). A solution of **S3** (3.0 g, 10.2 mmol) in dichloromethane (50 mL) under nitrogen was cooled to 0 °C and thionyl chloride (4.4 mL, 61 mmol) was added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated *in vacuo*, and 6 N HCl (50 mL) was added. The resulting mixture was heated to reflux with vigorous stirring for 6 h, then was cooled to rt, filtered, and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined ethyl acetate layers were discarded, and the aqueous layer was basified to pH > 9 using 5 M NaOH. The aqueous layer was then extracted with ether (3 x 50 mL), and the combined ether layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 15% EtOAc/hexanes as the eluant to afford 1.5 g (77%) of the title compound as a white solid, m.p. 75–77 °C (lit.[25] m.p. 72–74 °C).

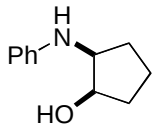
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.17 (m, 2 H), 6.79–6.72 (m, 1 H), 6.68 (dd, *J* = 1.0, 7.8 Hz, 2 H), 4.09–4.02 (m, 1 H), 3.73 (s, br, 1 H), 3.44–3.37 (m, 1 H), 2.31 (s, br, 1 H), 1.90–1.80 (m, 1 H), 1.76–1.56 (m, 5 H), 1.52–1.28 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 129.2, 117.6, 113.7, 67.6, 54.8, 31.3, 27.0, 23.5, 20.0; IR (film) 3397, 1505 cm^{-1}; MS (ESI) 214.1211 (214.1208 calcd for $C_{12}H_{17}NO$, M + Na^+).



S5

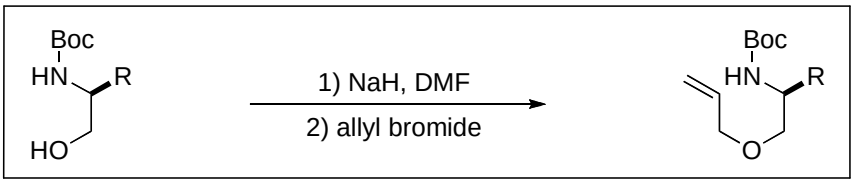
(±)-(1*S,2*S**)-*N*-(2-hydroxycyclopentyl)-*N*-phenylbenzamide (S5)**. A solution of *trans*-2-(phenylamino)cyclopentanol[24] (1.78 g, 10 mmol) and triethylamine (8.4 mL, 60 mmol) in dichloromethane (20 mL), was cooled to 0 °C with stirring and benzoyl chloride (3.5 mL, 30 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred overnight. The mixture was transferred to a separatory funnel then washed with 2 M HCl (2 x 10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was dissolved in methanol (25 mL) and potassium carbonate (6.9 g, 50 mmol) was added slowly at room temperature. The reaction mixture was stirred at rt for 48 h, then was quenched with saturated ammonium chloride (25 mL). The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a red-orange oil. The crude material was dissolved in a minimal amount of hot ethyl acetate and then cooled in a –20 °C freezer until crystals formed. Filtration afforded 2.27 g (81%) of the title

compound as a white solid, mp 109–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.03 (m, 10 H), 4.79–4.69 (m, 1 H), 4.28–4.18 (m, 1 H), 4.02 (s, br, 1 H), 1.97–1.86 (m, 2 H), 1.82–1.63 (m, 2 H), 1.61–1.50 (m, 1 H), 1.47–1.34 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 140.1, 136.4, 130.3, 129.3, 128.8, 128.3, 127.64, 127.57, 76.8, 67.5, 32.5, 28.4, 21.0; IR (film) 3401, 1633 cm^{-1}; MS (ESI) 304.1312 (304.1313 calcd for $C_{18}H_{19}NO_2$, M + Na^+).

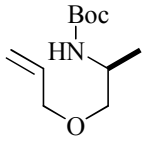


S6

(±)-*cis*-2-(phenylamino)cyclopentanol (S6). The conversion of **S5** (1.41 g, 5.0 mmol) to the title compound was accomplished using a procedure analogous to that described above for the synthesis of **S4**. This procedure afforded 880 mg (99%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.14 (m, 2 H), 6.81–6.61 (m, 3 H), 4.33–4.23 (m, 1 H), 3.69–3.53 (m, 1 H), 3.05 (s, br, 1 H), 2.17–2.01 (m, 1 H), 2.00–1.75 (m, 3 H), 1.69–1.49 (m, 2 H) (the OH signal was not observed due to broadening); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 129.3, 118.1, 113.5, 71.3, 59.4, 32.5 30.1, 20.3; IR (film) 3398, 1504 cm^{-1}; MS (ESI) 178.1225 (178.1232 calcd for $C_{11}H_{15}NO$ M + H^+).

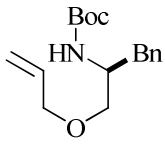


General Procedure 1: Conversion of *N*-Boc-2-aminoethanols to *N*-Boc-1-allyloxy-2-aminoethanes. A flame-dried flask was cooled under a stream of nitrogen and charged with *N*-Boc-2-aminoethanol (1 equiv) and a sufficient volume of DMF to provide a 0.5 M solution. The resulting solution was cooled to 0 °C in an ice/H_2O bath, and sodium hydride (1.1 equiv, 60% dispersion in mineral oil) was added. The resulting mixture was allowed to stir 5–10 min, then allyl bromide (1.1 equiv) was added. The mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 2 h). The reaction mixture was then quenched with saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

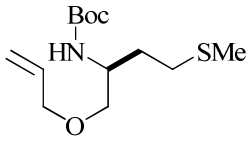


(–)-(*S*)-*tert*-Butyl (2-allyloxy-1-methylethyl)carbamate (11a). General Procedure 1 was conducted on (*S*)-2-(Boc-amino)-1-propanol[17] **8a** (3.00 g, 17.1 mmol), and gave the title compound (2.71 g, 73%) as a colorless oil after purification by chromatography using 10% EtOAc/hexanes as the eluant. $[\alpha]^{23}_{D}$ − 15.9 (*c* = 1.33,

CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94−5.83 (m, 1 H), 5.30−5.23 (m, 1 H), 5.20−5.15 (m, 1 H), 4.71 (s, br, 1 H), 4.04−3.92 (m, 2 H), 3.82 (s, br, 1 H), 3.44−3.33 (m, 2 H), 1.44 (s, 9 H), 1.17 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 134.3, 116.3, 78.3, 72.9, 71.5, 45.6, 28.0, 17.5; IR (film) 3345, 1715 cm^{-1}; MS (ESI) 238.1415 (238.1419 calcd for $C_{11}H_{21}NO_3$, M + Na^+).

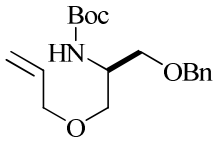


(–)-(*S*)-*tert*-Butyl 1-(allyloxy)-3-phenylpropan-2-ylcarbamate (11b). General Procedure 1 was conducted on (*S*)-*tert*-butyl 1-hydroxy-3-phenylpropan-2-ylcarbamate[20] **8a** (10.30 g, 41.0 mmol), and gave the title compound (10.21 g, 86%) as a colorless oil after purification by chromatography with 10% EtOAc/hexanes as the eluant. $[\alpha]^{23}_D$ − 21.8 (*c* = 2.85, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.18 (m, 5 H), 5.97−5.85 (m, 1 H), 5.31−5.24 (m, 1 H), 5.21−5.16 (m, 1 H), 4.85 (s, br, 1 H), 4.02−3.88 (m, 3 H), 3.39−3.30 (m, 2 H), 2.95−2.80 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 138.0, 134.3, 129.2, 128.1, 126.0, 116.7, 78.7, 71.8, 69.8, 51.4, 37.6, 28.1; IR (film) 3348, 1714 cm^{-1}; MS (ESI) 314.1735 (314.1732 calcd for $C_{17}H_{25}NO_3$, M + Na^+).

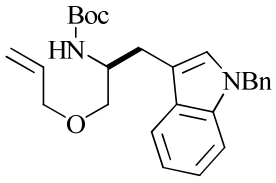


(–)-(*S*)-*tert*-Butyl 1-(allyloxy)-4-(methylthio)butan-2-ylcarbamate (11c). General Procedure 1 was conducted on (*S*)-*tert*-butyl 1-hydroxy-4-(methylthio)butan-2-ylcarbamate[21] **8c** (510.8 mg, 2.17 mmol) using THF as solvent and

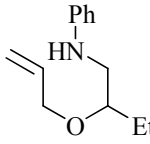
2.0 equiv of sodium hydride. This modified procedure gave the title compound (353.7 mg, 59%) as a yellow oil after purification by chromatography with 10% EtOAc/hexanes as the eluant. $[\alpha]^{23}_{D}$ − 17.6 (*c* = 0.59, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94−5.82 (m, 1 H), 5.30−5.22 (m, 1 H), 5.21−5.15 (m, 1 H), 4.86−4.73 (m, 1 H), 4.04−3.91 (m, 2 H), 3.82 (s, br, 1 H), 3.49−3.40 (m, 2 H), 2.61−2.46 (m, 2 H), 2.11 (s, 3 H), 1.95−1.72 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 134.5, 117.0, 79.2, 72.1, 71.7, 49.7, 31.9, 30.7, 28.3, 15.5; IR (film) 3342, 1714 cm^{-1}; MS (ESI) 298.1445 (298.1453 calcd for $C_{13}H_{25}NO_3S$, M + Na^+).



(+)-(*R*)-*tert*-Butyl 1-(allyloxy)-3-(benzyloxy)propan-2-ylcarbamate (11d). General Procedure 1 was conducted on (*R*)-*tert*-butyl 1-(benzyloxy)-3-hydroxypropan-2-ylcarbamate[19] **8d** (2.00 g, 7.11 mmol) using NaO*t*Bu (1.1 equiv) in place of sodium hydride. This modified procedure gave the title compound (1.66 g, 73%) as a colorless oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. $[\alpha]^{23}_{D}$ + 2.6 (*c* = 2.93, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5 H), 5.92−5.81 (m, 1 H), 5.28−5.21 (m, 1 H), 5.19−5.13 (m, 1 H), 4.92 (s, br, 1 H), 4.52 (s, 2 H), 4.03−3.84 (m, 3 H), 3.64−3.45 (m, 4 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 138.2, 134.6, 128.3, 127.6, 127.5, 116.9, 79.3, 73.1, 72.0, 68.9, 68.8, 49.7, 28.3; IR (film) 3345, 1714 cm^{-1}; MS (ESI) 344.1833 (344.1838 calcd for $C_{18}H_{27}NO_4$, M + Na^+).

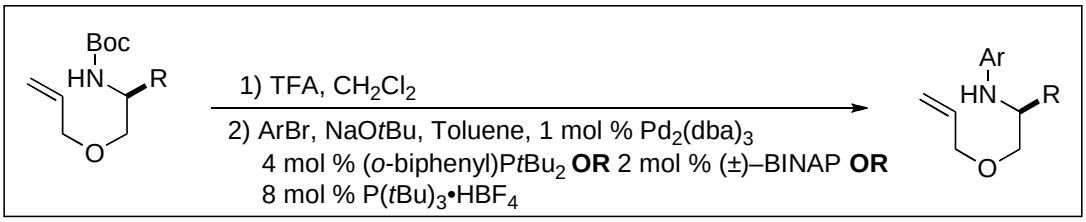


(–)-(*S*)-*tert*-Butyl 1-(allyloxy)-3-(1-benzyl-1*H*-indol-3-yl)propan-2-ylcarbamate (11e). General Procedure 1 was conducted on **8e** (3.00 g, 7.88 mmol), and gave the title compound (2.37 g, 71%) as a colorless oil after purification by chromatography using 10% EtOAc/hexanes as the eluant. $[\alpha]^{23}_{D}$ − 10.4 (*c* = 0.96, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 1 H), 7.28−7.18 (m, 4 H), 7.18−7.02 (m, 4 H), 6.94 (s, 1 H), 5.93−5.82 (m, 1 H), 5.28−5.19 (m, 3 H), 5.16−5.11 (m, 1 H), 4.99−4.89 (m, 1 H), 4.04 (s, br, 1 H), 3.96−3.84 (m, 2 H), 3.39−3.29 (m, 2 H), 3.10−2.95 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 137.5, 136.4, 134.6, 128.6, 128.5, 127.4, 126.7, 126.6, 121.6, 119.2, 119.0, 116.8, 111.4, 109.4, 78.9, 71.9, 70.2, 50.8, 49.7, 28.3, 27.0; IR (film) 3425, 1709 cm^{-1}; MS (ESI) 443.2314 (443.2311 calcd for $C_{30}H_{32}N_2O_4$, M + Na^+).



(±)-*N*-[2-(Allyloxy)butyl]aniline (18). General Procedure 1 was conducted on 1-(phenylamino)butan-2-ol[22] (1.00 g, 6.05 mmol) using THF as solvent. This modified procedure gave the title compound (0.639 g, 51%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.14 (m, 2 H), 6.74−6.67 (m, 1 H), 6.66−6.59 (m, 2 H), 5.99−5.87 (m, 1 H), 5.32−5.24 (m, 1 H), 5.20−5.14 (m, 1 H), 4.10−3.94 (m, 3 H), 3.57−3.48 (m, 1 H), 3.33−3.23 (m, 1 H), 3.13−3.04 (m, 1 H), 1.74−1.52 (m, 2 H), 0.96 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 135.1, 129.2, 117.4, 116.9, 113.0, 78.7, 70.2, 46.2,

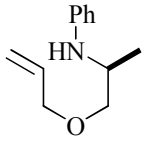
25.0, 9.8; IR (film) 3402, 1604 cm^{-1}; MS (ESI) 206.1535 (206.1545 calcd for $C_{13}H_{19}NO$, $M + H^+$).



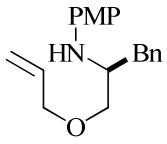
General Procedure 2: Conversion of *N*-Boc-2-(allyloxy)ethylamines to *N*-aryl-2-(allyloxy)ethylamines. A flame-dried flask was cooled under a stream of nitrogen and charged with the *N*-Boc-2-(allyloxy)ethylamine (1.0 equiv) and a sufficient volume of CH_2Cl_2 to provide a 2 M solution. The resulting solution was cooled to 0 °C in an ice/H_2O bath and an equal volume of trifluoroacetic acid was added dropwise. The solution was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (ca. 1 h). The reaction was concentrated in vacuo, then azeotroped twice with toluene to remove any remaining trifluoroacetic acid. The crude 2-(allyloxy)ethylammonium trifluoroacetate was immediately carried on without further purification.

A Schlenk tube was evacuated, flame dried, and backfilled with nitrogen. The tube was charged with NaO*t*Bu (2.4 equiv), $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), and either (*o*-biphenyl)P(*t*-Bu)$_2$ (4 mol %), (±)-BINAP (2 mol %), or P(*t*Bu)$_3$•HBF_4 (8 mol %). The tube was then evacuated and backfilled with nitrogen, and the aryl bromide (1.0 equiv) and a 0.5 M solution of the 2-(allyloxy)ethylammonium trifluoroacetate (1.0 equiv) in toluene were added (aryl bromides that were solids at room temperature were added as

solids following the addition of NaO*t*Bu). The mixture was heated to 50–80 °C with stirring until the amine was consumed as judged by GC analysis (12–18 h). The mixture was cooled to rt, diluted with ether (5 mL), filtered through Celite, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

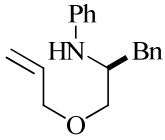


(–)-(*S*)-*N*-[1-(Allyloxy)propan-2-yl]aniline (9a). General Procedure 2 was employed for the coupling of **11a** (278 mg, 1.29 mmol), and bromobenzene using (*o*-biphenyl)P(*t*-Bu)$_2$ as ligand and a reaction temperature of 50 °C. This procedure gave the title compound (180 mg, 73%) as a light yellow oil after purification by chromatography with 7.5% EtOAc/hexanes as the eluant. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OD column, 0.5% isopropanol/hexanes, 2.0 mL/min, RT = 5.71 min and 8.39 min), $[\alpha]^{23}_{D}$ – 9.0 (*c* = 0.30, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.11 (m, 2 H), 6.70−6.65 (m, 1 H), 6.63−6.58 (m, 2 H), 5.96−5.84 (m, 1 H), 5.30−5.22 (m, 1 H), 5.20−5.14 (m, 1 H), 4.01−3.96 (m, 2 H), 3.78 (s, br, 1 H), 3.71−3.61 (m, 1 H), 3.48 (dd, *J* = 4.4, 9.3 Hz, 1 H), 3.40 (dd, *J* = 5.3, 9.3 Hz, 1 H), 1.23 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 134.7, 129.3, 117.3, 117.0, 113.4, 73.5, 72.2, 48.3, 18.1; IR (film) 3401, 1603 cm^{-1}; MS (ESI) 214.1204 (214.1208 calcd for $C_{12}H_{17}NO$, M + Na^+).

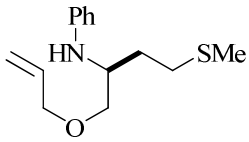


(±)-*N*-[1-(Allyloxy)-3-phenylpropan-2-yl]-4-methoxyaniline (9b). General Procedure 2 was employed for the coupling of **11b** (1.00 g, 3.43 mmol) with 4-bromoanisole using tri-*tert*-butylphosphonium tetrafluoroborate as ligand and a reaction

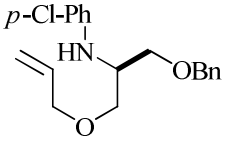
temperature of 40 °C. This procedure gave the title compound (581 mg, 57%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.26 (m, 2 H), 7.24−7.18 (m, 3 H), 6.82−6.76 (m, 2 H), 6.65−6.60 (m, 2 H), 5.98−5.87 (m, 1 H), 5.31−5.24 (m, 1 H), 5.21−5.16 (m, 1 H), 3.98 (d, *J* = 5.6 Hz, 2 H), 3.75 (s, 3 H), 3.72−3.63 (m, 1 H), 3.39 (d, *J* = 4.0 Hz, 2 H), 2.98−2.85 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 141.1, 138.6, 134.6, 129.3, 128.2, 126.1, 116.7, 115.0, 114.8, 71.9, 70.0, 55.5, 55.0, 37.0; IR (film) 3386, 2932, 1513 cm^{-1}; MS (ESI) 298.1794 (298.1807 calcd for $C_{19}H_{23}NO_2$, M + H^+).



(–)-(*S*)-*N*-[1-(Allyloxy)-3-phenylpropan-2-yl]aniline (9c). General Procedure 2 was employed for the coupling of **11b** (1.50 g, 5.15 mmol) with bromobenzene using (±)-BINAP as ligand and a reaction temperature of 80 °C. This procedure gave the title compound (806 mg, 59%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. $[\alpha]^{23}_D$ − 42.9 (*c* = 0.92, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.28 (m, 2 H), 7.23 (d, *J* = 7.5 Hz, 3 H), 7.21−7.16 (m, 2 H), 6.73−6.68 (m, 1 H), 6.68−6.63 (m, 2 H), 5.98−5.88 (m, 1 H), 5.31−5.25 (m, 1 H), 5.21−5.17 (m, 1 H), 4.04−3.91 (m, 3 H), 3.81−3.73 (m, 1 H), 3.45−3.37 (m, 2 H), 3.00−2.88 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 138.5, 134.6, 129.4, 129.3, 128.4, 126.3, 117.4, 117.0, 113.5, 72.2, 70.0, 53.9, 37.1; IR (film) 3406, 1602 cm^{-1}; MS (ESI) 268.1690 (268.1701 calcd for $C_{18}H_{21}NO$, M + H^+).

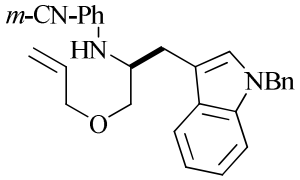


(–)-(*S*)-*N*-[1-(Allyloxy)-4-(methylthio)butan-2-yl]aniline (9d). General Procedure 2 was employed for the coupling of **11c** (165 mg, 0.60 mmol), with bromobenzene using (*o*-biphenyl)P(*t*-Bu)$_2$ as ligand and a reaction temperature of 50 °C. This procedure gave the title compound (107 mg, 71%) as a light amber oil after purification by chromatography using 5% EtOAc/hexanes as the eluant. $[\alpha]^{23}_{D}$ − 31.8 (*c* = 0.76, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.9 Hz, 2 H), 6.75−6.69 (m, 1 H), 6.69−6.65 (m, 2 H), 5.98−5.86 (m, 1 H), 5.33−5.25 (m, 1 H), 5.23−5.18 (m, 1 H), 4.01 (d, *J* = 5.3 Hz, 2 H), 3.85 (s, br, 1 H), 3.77−3.70 (m, 1 H), 3.56 (dd, *J* = 3.6, 9.4 Hz, 1 H), 3.49 (dd, *J* = 5.1, 9.4 Hz, 1 H), 2.71−2.58 (m, 2 H), 2.12 (s, 3 H), 2.09−1.96 (m, 1 H), 1.93−1.82 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 134.5, 129.1, 117.2, 116.8, 113.2, 72.0, 71.1, 51.6, 31.4, 30.9, 15.4; IR (film) 3391, 1602 cm^{-1}; MS (ESI) 252.1419 (252.1422 calcd for $C_{14}H_{21}NOS$, M + H$^+$).

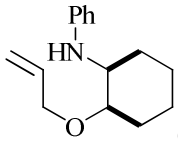


(+)-(*R*)-*N*-[1-(Allyloxy)-3-(benzyloxy)propan-2-yl]-4-chloroaniline (9e). General Procedure 2 was employed for the coupling of **11d** (1.50 g, 4.67 mmol) with 4-chlorobromobenzene using (±)-BINAP as ligand and a reaction temperature of 80 °C. This procedure gave the title compound (910 mg, 59%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. $[\alpha]^{23}_{D}$ + 2.8 (*c* = 0.95, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5 H), 7.11−7.06 (m, 2 H), 6.56−6.50 (m, 2 H), 5.94−5.82 (m, 1 H), 5.26 (dq, *J* = 1.6, 17.2 Hz, 1 H), 5.20−5.16 (m, 1 H), 4.54 (s, 2 H), 4.12−4.06 (m, 1 H), 3.98 (dt, *J* = 1.6, 5.5 Hz, 2 H), 3.68−3.51 (m, 5 H);

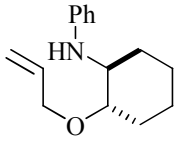
^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 138.1, 134.5, 129.1, 128.4, 127.7, 127.6, 121.9, 117.1, 114.3, 73.3, 72.2, 68.8, 68.7, 52.8; IR (film) 3414, 1600 cm^{-1}; MS (ESI) 332.1403 (332.1417 calcd for $C_{19}H_{22}ClNO_2$, M + Na^+).



(–)-(*S*)-3-[1-(Allyloxy)-3-(1-benzyl-1*H*-indol-3-yl)propan-2-ylamino]benzonitrile (9f). General Procedure 2 was employed for the coupling of **11e** (249.6 mg, 0.593 mmol), with 3-bromobenzonitrile using (±)-BINAP as ligand and a reaction temperature of 80 °C. This procedure gave the title compound (151.0 mg, 60%) as a yellow oil after purification by chromatography with 7.5% EtOAc/hexanes as the eluant followed by heating under vacuum in a Kugelrohr apparatus (185 °C, 0.3 Torr) to remove hydrocarbon impurities. $[\alpha]^{23}_D$ – 45.4 (*c* = 0.53, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.8 Hz, 1 H), 7.32−7.24 (m, 4 H), 7.23−7.11 (m, 3 H), 7.10−7.06 (m, 2 H), 6.95−6.90 (m, 2 H), 6.81−6.73 (m, 2 H), 5.97−5.85 (m, 1 H), 5.32−5.23 (m, 3 H), 5.21−5.16 (m, 1 H), 4.18 (d, *J* = 8.5 Hz, 1 H), 3.99−3.95 (m, 2 H), 3.88−3.79 (m, 1 H), 3.49−3.39 (m, 2 H), 3.16−3.03 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 137.4, 136.5, 134.4, 129.9, 128.7, 128.5, 127.6, 126.8, 126.7, 121.9, 120.4, 119.4, 119.3, 118.8, 117.4, 117.2, 115.4, 112.8, 110.8, 109.7, 72.1, 70.3, 53.0, 49.8, 26.5; IR (film) 3391, 2227, 1602 cm^{-1}; MS (ESI) 444.2053 (444.2052 calcd for $C_{28}H_{27}N_3O$, M + Na^+).

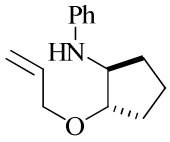


***cis*-2-(allyloxy)cyclohexylaniline (14a).** A solution of **S4** (764 mg, 4.0 mmol) in THF (16 mL) cooled to 0 °C under nitrogen with stirring. Solid NaH (216 mg, 5.6 mmol, 60% suspension in mineral oil) was added slowly and the resulting mixture was stirred for 30 minutes at 0 °C. Allyl bromide (0.4 mL, 4.4 mmol) was added, and the mixture was warmed to rt. After the starting material had been completely consumed as judged by TLC analysis, the reaction mixture was quenched with saturated aqueous NH_4Cl and transferred to a separatory funnel. The mixture was extracted with EtOAc (3 x 15 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 2% EtOAc/hexanes as the eluant to afford 610 mg (66%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.13 (m, 2 H), 6.70–6.60 (m, 3 H), 5.98–5.86 (m, 1 H), 5.31–5.24 (m, 1 H), 5.17–5.12 (m, 1 H), 4.16–4.03 (m, 2 H), 3.93–3.86 (m, 1 H), 3.71–3.66 (m, 1 H), 3.45–3.37 (m, 1 H), 2.05–1.97 (m, 1 H), 1.81–1.68 (m, 2 H), 1.67–1.50 (m, 2 H), 1.48–1.26 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 135.4, 129.2, 117.0, 116.2, 113.6, 75.5, 69.6, 53.7, 28.3, 27.4, 24.2, 20.2; IR (film) 3402, 1505 cm^{-1}; MS (ESI) 232.1707 (232.1701 calcd for $C_{15}H_{21}NO$, $M + H^+$).

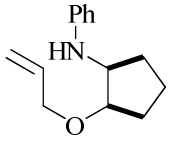


***trans*-2-(allyloxy)cyclohexylaniline (14b).**[26] The conversion of *trans*-2-(phenylamino)cyclohexanol[23] (500 mg, 2.62 mmol) to the title compound was accomplished using a procedure analogous to that described above for the synthesis of

14a. This procedure afforded 578 mg (95%) of the title compound as an amber oil. Spectroscopic properties were consistent with those reported in the literature.[26]



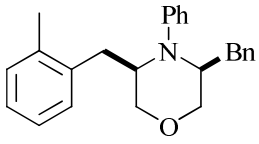
***trans*-2-(allyloxy)cyclopentylaniline (14c)**. The conversion of *trans*-2-(phenylamino)cyclopentanol[24] (500 mg, 2.82 mmol) to the title compound was accomplished using a procedure analogous to that described above for the synthesis of **14a**. This procedure afforded 535 mg (87%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.10 (m, 2 H), 6.71–6.57 (m, 3 H), 5.98–5.83 (m, 1 H), 5.26 (dd, *J* = 1.6, 17.2 Hz, 1 H), 5.13 (d, *J* = 10.0 Hz, 1 H), 4.04–3.89 (m, 2 H), 3.74–3.65 (m, 2 H), 3.48 (s, br, 1 H), 2.25–2.10 (m, 1 H), 1.87–1.59 (m, 4 H), 1.43–1.30 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 135.0, 129.0, 117.0, 116.4, 113.0, 84.9, 69.9, 59.8, 31.5, 30.0, 21.7; IR (film) 3404 cm^{-1}; MS (ESI) 218.1543 (218.1545 calcd for $C_{14}H_{19}NO$, $M + H^+$).



***cis*-2-(allyloxy)cyclopentylaniline (14d).** The conversion of **S6** (532 mg, 3 mmol) was accomplished using a procedure analogous to that described above for the synthesis of **14a**. This procedure afforded 601 mg (92%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.13 (m, 2 H), 6.70–6.59 (m, 3 H), 5.95–5.82 (m, 1 H), 5.26 (dq, *J* = 1.6, 15.3 Hz, 1 H), 5.15 (dq, *J* = 1.5, 9.0 Hz, 1 H), 4.34 (s, br, 1 H), 4.05–3.98 (m, 1 H), 3.96–3.89 (m, 2 H), 3.75–3.65 (m, 1 H), 2.07–1.94 (m, 1 H), 1.88–1.76 (m, 3 H), 1.71–1.51 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 135.0,

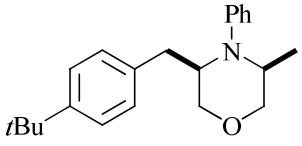
129.2, 116.9, 116.7, 113.3, 79.9, 70.3, 56.1, 29.8, 29.4, 20.3; IR (film) 3401, 1602, 1505 cm^{-1}; MS (ESI) 240.1366 (240.1364 calcd for $C_{14}H_{19}NO$, M + Na^+).

General Procedure 4: Synthesis of Morpholines via Pd-Catalyzed Carboamination. A Schlenk tube was evacuated, flame dried, and backfilled with nitrogen. The tube was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), P(2-furyl)$_3$ (9.3 mg, 0.04 mmol), and NaO*t*Bu (96.1 mg, 1.0 mmol). The tube was evacuated and backfilled with nitrogen, then the aryl bromide (1.0 mmol) and a solution of the amine substrate (0.50 mmol) in toluene (1.25 mL) were added to the schlenk tube (aryl bromides that were solids at room temperature were added as solids following the addition of NaO*t*Bu). The mixture was heated to 105 °C with stirring until the substrate was consumed as judged by GC analysis (12–18 h). The reaction mixture was cooled to rt, quenched with saturated aqueous NH_4Cl (3 mL), and extracted with EtOAc (3 x 3 mL). The combined organic layers were concentrated in vacuo and the crude product was purified by flash chromatography on silica gel.

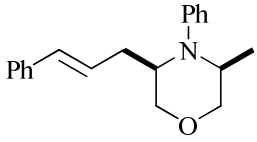


(–)-(3*S*,5*R*)-3-Benzyl-5-(2-methylbenzyl)-4-phenylmorpholine (10a). General Procedure 4 was employed for the coupling of 2-bromotoluene with **9c**. This procedure gave the title compound (121 mg, 68%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. $[\alpha]^{23}_D$ − 3.1 (*c* = 1.20, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.37 (m, 2 H), 7.31−7.14 (m, 7 H),

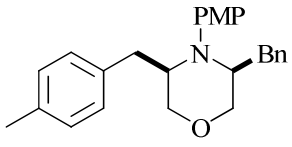
7.14−7.07 (m, 4 H), 7.07−7.00 (m, 1 H), 3.71 (dd, *J* = 5.4, 11.5 Hz, 1 H), 3.66−3.46 (m, 5 H), 2.81−2.66 (m, 4 H), 2.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 138.9, 137.0, 136.5, 130.4, 129.6, 129.5, 129.1, 128.5, 126.3, 126.3, 125.9, 121.7, 119.6, 69.6, 69.6, 57.9, 56.9, 37.0, 33.6, 19.6; IR (film) 1598 cm^{-1}; MS (ESI) 358.2174 (358.2171 calcd for $C_{25}H_{27}NO$, M + H^+).



(+)-(3*R*,5*S*)-3-(4-*tert*-Butylbenzyl)-5-methyl-4-phenylmorpholine (10b). General Procedure 4 was employed for the coupling of 1-bromo-4-*tert*-butylbenzene with **9a**. This procedure gave the title compound (88.7 mg, 55%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. The enantiopurity was judged to be 99% ee by chiral hplc analysis (chiralcel OD column, 0.05% isopropanol/hexanes as the eluant, 0.25 mL/min, RT = 51.29 min and 63.38 min), $[\alpha]^{23}_D$ + 112.1 (*c* = 0.90, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.32 (m, 2 H), 7.29−7.25 (m, 2 H), 7.15−7.11 (m, 2 H), 7.06−7.01 (m, 3 H), 3.79 (dd, *J* = 3.4, 11.1 Hz, 1 H), 3.68−3.59 (m, 2 H), 3.56 (dd, *J* = 6.4, 11.1 Hz, 1 H), 3.47−3.40 (m, 1 H), 3.40−3.32 (m, 1 H), 2.62 (dd, *J* = 3.0, 13.6 Hz, 1 H), 2.47 (dd, *J* = 10.8, 13.6 Hz, 1 H), 1.29 (s, 9 H), 0.96 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.0, 135.9, 129.2, 128.7, 125.3, 122.5, 121.6, 73.0, 70.1, 58.7, 52.7, 36.3, 34.3, 31.3, 16.4; IR (film) 1598 cm^{-1}; MS (ESI) 324.2330 (324.2327 calcd for $C_{22}H_{29}NO$, M + H^+).

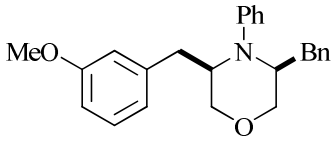


(+)-(3*R*,5*S*)-3-Cinnamyl-5-methyl-4-phenylmorpholine (10c). General Procedure 4 was employed for the coupling of β-bromostyrene (2.0 mmol, 4 equiv) with **9a** using 4 equiv of NaO*t*Bu and a catalyst composed of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 4 mol %), and P(2-furyl)$_3$ (18.6 mg, 0.08 mmol, 16 mol %). This modified procedure gave the title compound (70 mg, 47%) as a dark amber oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. $[\alpha]^{23}_D$ + 48.3 (*c* = 1.50, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.30 (m, 2 H), 7.30−7.24 (m, 4 H), 7.22−7.15 (m, 1 H), 7.12−7.03 (m, 3 H) 6.29 (d, *J* = 15.8 Hz, 1 H), 6.05 (dt, *J* = 7.3, 15.8 Hz, 1 H), 3.86 (dd, *J* = 7.3, 15.8 Hz, 1 H), 3.80 (dd, *J* = 7.3, 15.8 Hz, 1 H), 3.64 (dd, *J* = 7.3, 11.4 Hz, 1 H), 3.50 (dd, *J* = 7.3, 11.2 Hz, 1 H), 3.34−3.26 (m, 2 H), 2.18 (t, *J* = 6.8 Hz, 2 H), 0.86 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 137.3, 132.1, 129.1, 128.4, 127.1, 126.7, 125.9, 123.2, 122.7, 73.1, 70.7, 57.3, 53.4, 34.2, 16.2; IR (film) 1598 cm^{-1}; MS (ESI) 294.1858 (294.1858 calcd for $C_{20}H_{23}NO$, M + H$^+$).

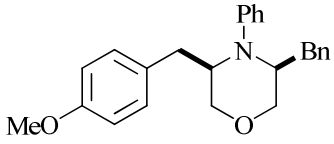


(±)-(3*S,5*R**)-3-Benzyl-4-(4-methoxyphenyl)-5-(4-methylbenzyl)morpholine (10d).** General Procedure 4 was employed for the coupling of 4-bromotoluene with **9b** on a 0.30 mmol scale. This procedure gave the title compound (27 mg, 23%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.19 (m, 4 H),

7.17−7.12 (m, 1 H), 7.05−7.00 (m, 4 H), 6.99−6.94 (m, 2 H), 6.93−6.89 (m, 2 H), 3.83 (s, 3 H), 3.67 (dt, *J* = 2.8, 11.3 Hz, 2 H), 3.49−3.43 (m, 2 H), 3.32−3.21 (m, 2 H), 2.67−2.57 (m, 2 H), 2.37−2.26 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 141.3, 138.7, 135.6, 135.6, 129.0, 129.0, 128.8, 128.3, 126.1, 125.9, 114.6, 71.1, 71.1, 61.4, 61.3, 55.5, 37.2, 36.8, 21.0; IR (film) 3436, 2924, 1509 cm^{-1}; MS (ESI) 388.2280 (388.2277 calcd for $C_{26}H_{29}NO_2$, M + H^+).

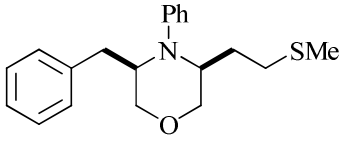


(+)-(3*S*,5*R*)-3-Benzyl-5-(3-methoxybenzyl)-4-phenylmorpholine (10e). General Procedure 4 was employed for the coupling of 3-bromoanisole with **9c**. This procedure gave the title compound (96.4 mg, 52%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. $[\alpha]^{23}_D$ + 3.5 (*c* = 1.28, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 7.25−7.18 (m, 4 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 6.97 (t, *J* = 7.3 Hz, 1 H), 6.82 (d, *J* = 7.5 Hz, 1 H), 6.79−6.74 (m, 2 H), 3.84−3.76 (m, 5 H), 3.62−3.53 (m, 4 H), 2.83−2.76 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 147.1, 140.7, 139.1, 129.6, 129.5, 129.2, 128.6, 126.3, 121.5, 120.1, 116.9, 115.1, 111.4, 68.8, 68.7, 56.3, 56.2, 55.1, 36.6, 36.6; IR (film) 1598 cm^{-1}; MS (ESI) 374.2117 (374.2120 calcd for $C_{25}H_{27}NO_2$, M + H^+).



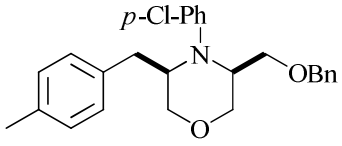
(+)-(3*S*,5*R*)-3-Benzyl-5-(4-methoxybenzyl)-4-phenylmorpholine (10f). General Procedure 4 was employed for the coupling of 4-

bromoanisole with **9c**. This procedure gave the title compound (96 mg, 51%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. $[\alpha]^{23}_D$ + 11.9 (*c* = 0.71, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.39 (m, 2 H), 7.35−7.29 (m, 2 H), 7.27−7.21 (m, 3 H), 7.18−7.12 (m, 4 H), 6.98 (t, *J* = 7.3 Hz, 1 H), 6.89−6.84 (m, 2 H), 3.86−3.76 (m, 5 H), 3.63−3.50 (m, 4 H), 2.87−2.73 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 147.2, 139.1, 131.1, 130.1, 129.6, 129.2, 128.6, 126.3, 120.0, 116.9, 114.0, 68.7, 56.5, 56.3, 55.2, 36.6, 35.7. (two aliphatic carbon signals are incidentally equivalent); IR (film) 1597 cm^{-1}; MS (ESI) 374.2113 (374.2120 calcd for $C_{25}H_{27}NO_2$, M + H$^+$).

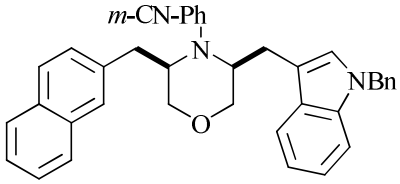


(+)-(3*R*,5*S*)-3-Benzyl-5-[2-(methylthio)ethyl]-4-phenylmorpholine (10g). General Procedure 4 was employed for the coupling of bromobenzene with **9d**. This procedure gave the title compound (100 mg, 61%) as a yellow oil after purification by chromatography with 10% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. $[\alpha]^{23}_D$ + 122.9 (*c* = 0.88, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.31 (m, 2 H), 7.28 (t, *J* = 7.5 Hz, 2 H), 7.22−7.15 (m, 3 H), 7.10 (d, *J* = 7.9 Hz, 2 H), 6.94 (t, *J* = 7.3 Hz, 1 H), 3.84−3.70 (m, 3 H), 3.58−3.49 (m, 3 H), 2.75−2.63 (m, 2 H), 2.58−2.51 (m, 1 H), 2.43−2.36 (m, 1 H), 2.02 (s, 3 H), 1.97−1.87 (m, 1 H), 1.76−1.67 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 139.0, 129.5, 129.1, 128.5, 126.3, 120.5, 117.7, 69.5,

68.9, 56.8, 53.9, 36.6, 31.3, 29.1, 15.5; IR (film) 1598 cm^{-1}; MS (ESI) 328.1725 (328.1735 calcd for $C_{20}H_{25}NOS$, M + Na^+).

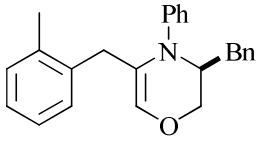


(+)-(3*S*,5*R*)-3-(Benzyloxymethyl)-4-(4-chlorophenyl)-5-(4-methylbenzyl)morpholine (10h). General Procedure 4 was employed for the coupling of 4-bromotoluene with **9e**. This procedure gave the title compound (108 mg, 51%) as an amber oil after purification by chromatography with 7.5% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. $[\alpha]^{23}_D$ + 136.8 (*c* = 0.93, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.22 (m, 7 H), 7.14−7.06 (m, 4 H), 6.87−6.83 (m, 2 H), 4.56 (d, *J* = 11.9 Hz, 1 H), 4.49 (d, *J* = 11.9 Hz, 1 H), 4.15−4.09 (m, 1 H), 3.84−3.79 (m, 1 H), 3.76−3.66 (m, 2 H), 3.61−3.55 (m, 1 H), 3.52−3.46 (m, 2 H), 3.42−3.37 (m, 1 H), 2.59 (d, *J* = 7.6 Hz, 2 H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 138.0, 136.0, 135.4, 129.4, 129.4, 129.0, 128.4, 127.8, 127.6, 123.7, 115.8, 73.4, 68.3, 67.8, 67.7, 54.9, 53.2, 35.7, 21.0; IR (film) 1595 cm^{-1}; MS (ESI) 422.1873 (422.1887 calcd for $C_{26}H_{28}ClNO_2$, M + H^+).

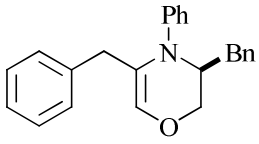


(+)-(3*S*,5*R*)-3-{3-[(1-Benzyl-1*H*-indol-3-yl)methyl]-5-(naphthalen-2-ylmethyl)morpholino}benzonitrile (10i). General Procedure 4 was employed for the coupling of 2-bromonaphthalene with **9f**. This procedure gave the title compound (159 mg, 58%) as a yellow solid after purification by chromatography with 15% EtOAc/hexanes as the eluant followed by heating under vacuum in a Kugelrohr

apparatus (195 °C, 0.3 Torr) to remove hydrocarbon impurities. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. m.p. 83−87 °C; $[\alpha]^{23}_D$ + 55.5 (*c* = 1.18, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.79 (m, 3 H), 7.77−7.72 (m, 2 H), 7.50−7.40 (m, 4 H), 7.33−7.19 (m, 8 H), 7.13−7.08 (m, 3 H), 7.05 (s, 1 H), 5.26 (s, 2 H), 4.09 (d, *J* = 11.5 Hz, 1 H), 3.99 (d, *J* = 11.5 Hz, 1 H), 3.69 (d, *J* = 11.2 Hz, 2 H), 3.51 (ddd, *J* = 2.2, 11.7, 26.1 Hz, 2 H), 3.33−3.21 (m, 2 H), 3.00−2.89 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 137.3, 136.6, 135.9, 133.5, 132.2, 130.4, 128.7, 128.6, 128.0, 127.9, 127.6, 127.5, 127.5, 127.2, 126.7, 126.5, 126.3, 125.6, 122.1, 121.2, 119.6, 119.4, 118.7, 117.8, 116.9, 113.5, 111.8, 109.9, 68.4, 67.6, 54.4, 54.0, 49.9, 36.6, 25.8; IR (film) 2228, 1596 cm^{-1}; MS (ESI) 570.2519 (570.2521 calcd for $C_{38}H_{33}N_3O$, M + Na^+).

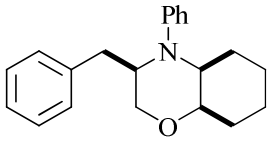


(+)-(*S*)-3-Benzyl-5-(2-methylbenzyl)-4-phenyl-3,4-dihydro-2*H*-1,4-oxazine (12a). The title compound was isolated as a side product in the above reaction of **9b** with 2-bromotoluene (yellow oil,14.6 mg, 8%). $[\alpha]^{23}_D$ + 74.9 (*c* = 1.02, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.02 (m, 8 H), 7.01–6.91 (m, 2 H), 6.80–6.74 (m, 2 H), 6.65–6.60 (m, 2 H), 6.23 (s, 1 H), 3.89 (dd, *J* = 1.1, 10.4 Hz, 1 H), 3.72 (dd, *J* = 2.3, 10.4 Hz, 1 H), 3.47–3.39 (m, 2 H), 3.23 (d, *J* = 15.2 Hz, 1 H), 2.78 (dd, *J* = 9.6, 13.6 Hz, 1 H), 2.61–2.54 (m, 1 H), 2.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 139.6, 137.5, 136.6, 130.7, 130.2, 129.7, 129.5, 128.9, 128.2, 126.3, 126.0, 125.7, 123.7, 122.7, 118.2, 64.1, 63.3, 36.2, 33.4, 19.3; IR (film) 1658, 1596 cm^{-1}; MS (ESI) 356.2012 (356.2014 calcd for $C_{25}H_{25}NO$, M + H^+).

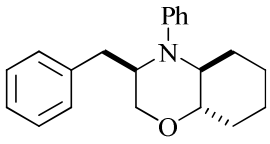


(*S*)-3,5-Dibenzyl-4-phenyl-3,4-dihydro-2*H*-1,4-oxazine (12b). A Schlenk tube was evacuated, flame dried, and backfilled with nitrogen. The tube was charged with [(IPr)Pd(acac)Cl][27] (15.7 mg, 0.025 mmol, 5 mol %), KO*t*Bu (112 mg, 1.0 mmol), and phenanthrene (89.1 mg, 0.50 mmol, 1.0 equiv) and evacuated and backfilled with nitrogen. Bromobenzene (105 μL, 1.0 mmol) and a solution of **9b** (133.7 mg, 0.50 mmol) in toluene (1.25 mL, 0.4 M) were added to the Schlenk tube. The mixture was heated to 105 °C with stirring until the amine substrate was consumed as judged by GC analysis (15 h). The mixture was cooled to rt, quenched with saturated aqueous NH_4Cl (3 mL), and extracted with EtOAc (3 x 3 mL). The combined organic layers were concentrated in vacuo. A crude yield of 79% was calculated as judged by ^{1}H-NMR analysis with phenanthrene as an internal standard The crude product was purified by flash chromatography on silica gel with 1.5% EtOAc/hexanes as the eluant to afford the title compound (97 mg, 57%) as a colorless oil. This material contained ca. 10% of an unknown impurity as judged by ^{1}H NMR analysis. This material readily decomposes on a TLC plate or in a chloroform solution open to air. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.16 (m, 8 H), 7.12–7.05 (m, 2 H), 7.04–6.98 (m, 1 H), 6.81–6.73 (m, 2 H), 6.69–6.62 (m, 2 H), 6.42 (s, 1 H), 3.93 (dd, *J* = 1.3, 10.3 Hz, 1 H), 3.75 (dd, *J* = 2.4, 10.2 Hz, 1 H), 3.51-3.41 (m, 2 H), 3.22 (d, *J* = 14.8 Hz, 1 H), 2.76 (dd, *J* = 9.4, 13.3 Hz, 1 H), 2.58 (dd, *J* = 5.1, 13.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 140.0, 139.6, 129.9, 129.5, 129.0, 128.9, 128.2, 128.1, 126.1, 126.0, 123.6, 122.7, 119.4, 64.2, 63.1, 36.2, 36.0; IR

(film) 1658, 1596, 1492 cm^{-1}; MS (ESI) 342.1861 (342.1858 calcd for $C_{24}H_{23}NO$, M + H^+).

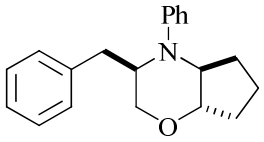


(±)-(3*R,4a*S**,8a*R**)-3-Benzyl-4-phenyloctahydro-2*H*-benzo[*b*][1,4]oxazine (15a).** General Procedure 4 was employed for the coupling of bromobenzene with **14a** (174 mg, 0.75 mmol). This procedure gave the title compound (150 mg, 65%) as white solid after purification by chromatography with 2% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. m.p. 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 6 H), 7.26–7.20 (m, 1 H), 6.93–6.83 (m, 2 H), 6.79–6.71 (m, 1 H), 4.04 (d, *J* = 12.0 Hz, 1 H), 3.73–3.53 (m, 4 H), 3.05 (t, *J* = 12.0 Hz, 1 H), 2.80 (d, *J* = 13.0 Hz, 1 H), 2.08 (d, *J* = 14.0 Hz, 1 H), 1.95 (d, *J* = 12.0 Hz, 1 H), 1.86–1.49 (m, 5 H), 1.34–1.20 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 139.9, 129.6, 129.3, 128.7, 126.3, 116.6, 111.8, 75.6, 67.8, 53.0, 37.2, 31.7, 25.4, 25.0, 20.9 (one aliphatic carbon signal is absent due to incidental equivalence); IR(film) 1598, 1503 cm^{-1}; MS (ESI) 308.2011 (308.2014 calcd for $C_{21}H_{15}NO + H^+$).

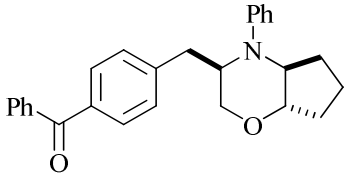


(±)-(3*R,4a*S**,8a*S**)-3-Benzyl-4-phenyloctahydro-2*H*-benzo[*b*][1,4]oxazine (15b)**. General Procedure 4 was employed for the coupling of bromobenzene with **14b** (174 mg, 0.75 mmol). This procedure gave the title compound (126 mg, 55%) as a white crystalline solid, after purification by chromatography with 2% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR

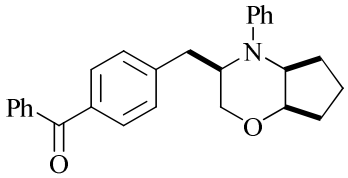
analysis before and after purification. m.p. 128–130 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.08 (m, 8 H), 6.99–6.91 (m, 2 H), 3.78 (d, *J* = 11.3 Hz, 1 H), 3.48 (t, *J* = 10.3 Hz, 1 H), 3.37–3.24 (m, 2 H), 2.56 (d, *J* = 13.0 Hz, 2 H), 2.21–2.09 (t, *J* = 11.7 Hz, 1 H), 1.92 (d, *J* = 10.3 Hz, 1 H), 1.68 (d, *J* = 10.3 Hz, 1 H), 1.54 (d, *J* = 11.7 Hz, 1 H), 1.42–1.20 (m, 3 H), 1.16–0.94 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 138.5, 129.1, 128.9, 128.2, 128.0, 126.3, 126.1, 80.8, 71.7, 66.6, 62.5, 37.5, 31.3, 29.7, 24.6, 24.5; IR (film) 1488, 1448 cm^{-1}; MS (ESI) 308.2018 (308.2014 calcd for $C_{21}H_{25}NO$, M + H^+).



(±)-(3*R,4a*S**,7a*S**)-3-benzyl-4-phenyloctahydrocyclopenta[*b*][1,4]oxazine (15c).** General Procedure 4 was employed for the coupling of bromobenzene with **14c** (54 mg, 0.25 mmol). This procedure gave the title compound (52 mg, 71%) as yellow solid after purification by chromatography with 15% EtOAc/hexanes as the eluant. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. m.p. 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 2 H), 7.30–7.26 (m, 2 H), 7.24–7.28 (m, 3 H), 7.17–7.12 (m, 1 H), 7.04–7.00 (m, 2 H), 3.87 (dd, *J* = 3.1, 8.2 Hz, 1 H), 3.59–3.47 (m, 2 H), 3.30 (tt, *J* = 3.6, 10.1 Hz, 1 H), 2.75–2.63 (m, 2 H), 2.23 (dd, *J* = 3.8, 10.2 Hz, 1 H), 1.98–1.89 (m, 1 H), 1.69–1.52 (m, 3 H), 1.37–1.29 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 138.6, 129.0, 128.9, 128.3, 126.5, 126.2, 126.0, 82.9, 72.8, 68.7, 61.8, 36.6, 26.7, 26.2, 17.4; IR (film) 1597, 1492, 1126 cm^{-1}; MS (ESI) 294.1844 (294.1858 calcd for $C_{20}H_{23}NO$, M + H^+).

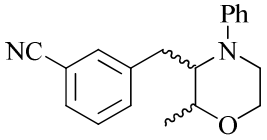


(±)-(3*R,4a*S**,7a*S**)-Phenyl 4-(4-phenyloctahydrocyclopenta[*b*][1,4]oxazin-3-ylmethyl)phenyl ketone (15d).** General Procedure 4 was employed for the coupling of 4-bromobenzophenone with **14c** (163 mg, 0.75 mmol). This procedure gave the title compound (151 mg, 51%) as yellow solid after purification by chromatography with 15% EtOAc/hexanes as the eluant followed by heating under vacuum in a Kugelrohr apparatus (180 °C, 0.3 Torr) to remove hydrocarbon impurities. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. m.p. 84–86 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.74 (m, 2 H), 7.69–7.65 (m, 2 H), 7.60–7.54 (m, 1 H), 7.49–7.44 (m, 2 H), 7.40–7.34 (m, 2 H), 7.30–7.25 (m, 2 H), 7.24–7.19 (m, 1 H), 7.15–7.10 (m, 2 H), 3.88 (dd, *J* = 3.3, 8.0 Hz, 1 H), 3.61–3.48 (m, 2 H), 3.40–3.31 (m, 1 H), 2.81–2.65 (m, 2 H), 2.37 (dd, *J* = 4.0, 10.0 Hz, 1 H), 2.00–1.89 (m, 1 H), 1.70–1.56 (m, 3 H), 1.38–1.29 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 149.1, 143.8, 137.7, 135.6, 132.3, 130.3, 129.9, 129.1, 128.8, 128.2, 126.5, 126.1, 82.9, 72.7, 68.6, 61.6, 36.7, 26.6, 26.2, 17.4; IR (film) 1658, 1606 cm^{-1}; MS (ESI) 398.2119 (398.2120 calcd for $C_{27}H_{27}NO_2$, M + H^+).



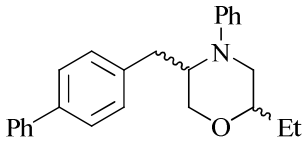
(±)-(3*R,4a*S**,7a*R**)-Phenyl 4-(4-phenyloctahydrocyclopenta[*b*][1,4]oxazin-3-ylmethyl)phenyl ketone (15e).** General Procedure 4 was employed for the coupling of 4-bromobenzophenone with **14d** (109 mg, 0.5 mmol). This procedure gave the title compound (150 mg, 75%) as yellow oil after

purification by chromatography with 10% EtOAc/hexanes as the eluant followed by heating under vacuum in a Kugelrohr apparatus (160 °C, 0.3 Torr) to remove hydrocarbon impurities. This material was judged to be of >20:1 dr by ^{1}H NMR analysis before and after purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.77 (m, 4 H), 7.63–7.56 (m, 1 H), 7.52–7.45 (m, 2 H), 7.44–7.40 (m, 2 H), 7.37–7.30 (m, 2 H), 6.91 (d, *J* = 8.3 Hz, 2 H), 6.79 (t, *J* = 7.0 Hz, 1 H), 4.01–3.96 (m, 1 H), 3.89 (d, *J* = 11.6 Hz, 1 H), 3.83–3.68 (m, 2 H), 3.58–3.50 (m, 1 H), 3.11 (dd, *J* = 1.2, 13.0, 1 H), 2.95 (d, *J* = 13.0, 1 H), 2.38–2.25 (m, 1 H), 2.12–1.86 (m, 3 H), 1.74–1.50 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 147.1, 144.7, 137.7, 135.8, 132.3, 130.6, 130.0, 129.6, 129.3, 128.3, 116.9, 111.9, 78.2, 66.0, 56.3, 52.7, 35.6, 31.3, 28.1, 21.6; IR (film) 1658, 1597 cm^{-1}; MS (ESI) 420.1925 (420.1939 calcd for $C_{27}H_{27}NO_2$, M + Na^+).

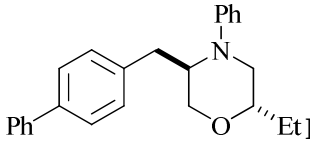


(±)-3-[(2-Methyl-4-phenylmorphlin-3-yl)methyl]benzonitrile (17). General Procedure 4 was employed for the coupling of 3-bromobenzonitrile with **16**. This procedure gave the title compound as an inseparable mixture of diastereomers. The crude material was judged to be of 1.3:1 dr by ^{1}H NMR analysis. Purification by chromatography with 15% EtOAc/hexanes as the eluant gave the title compound (65 mg, 45%) as a yellow oil. The pure material was judged to be of 2:1 dr by ^{1}H NMR analysis. **Major (*cis*) diastereomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 3 H), 7.24−7.13 (m, 3 H), 6.78–6.69 (m, 3 H), 4.07−3.89 (m, 3 H), 3.80 (dt, *J* = 3.3, 11.5 Hz, 1 H), 3.34 (dt, *J* = 3.8, 12.3 Hz, 1 H), 3.14 (dd, *J* = 3.3, 12.3 Hz, 1 H), 3.00 (dd, *J* = 6.2, 14.5 Hz, 1 H), 2.91 (dd, *J* = 6.2, 14.5 Hz, 1 H), 1.13 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 149.7, 141.6, 133.6, 132.7, 129.4, 129.3, 129.0, 119.2, 118.8, 116.1, 111.9, 75.2, 66.8, 62.0, 41.6, 29.8, 18.8. **Minor (*trans*) diastereomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.29 (m, 6 H), 6.96−6.87 (m, 3 H), 4.02 (dt, *J* = 3.9, 11.3 Hz, 1 H), 3.84–3.74 (m, 2 H), 3.56–3.50 (m, 1 H), 3.31–3.23 (m, 1 H), 3.18–3.10 (m, 2 H), 2.71 (dd, *J* = 3.8, 13.6 Hz, 1 H), 1.38 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 140.8, 133.9, 132.7, 129.8, 129.1, 128.7, 120.0, 118.7, 116.8, 112.3, 68.7, 67.9, 59.7, 43.9, 32.4, 16.9. IR (film) 2229, 1598 cm^{-1}; MS (ESI) 293.1656 (293.1654 calcd for $C_{19}H_{20}N_2O$, M + H^+).

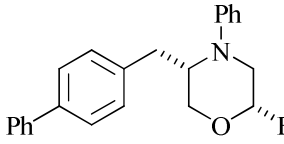


(±)-5-(Biphenyl-4-ylmethyl)-2-ethyl-4-phenylmorpholine (19). General Procedure 4 was employed for the coupling of 4-bromobiphenyl with **18**. This procedure gave the title compound as a separable mixture of diastereomers. The crude material was judged to be of 2:1 dr by ^{1}H NMR analysis. Purification by chromatography with 2→5% EtOAc/hexanes as the eluant gave the major diastereomer *trans*-**19** (57.2 mg, 32%) and minor diastereomer *cis*-**19** (30.1 mg, 17%) for a combined total mass of 87.3 mg (49%, 2:1 dr). The separated diastereomers were each judged to be of >20:1 dr by ^{1}H NMR analysis after purification.



Major diastereomer: *trans*-5-(Biphenyl-4-ylmethyl)-2-ethyl-4-phenylmorpholine (*trans*-19); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* =

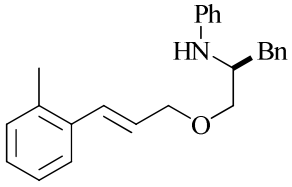
7.6 Hz, 2 H), 7.47 (d, *J* = 8.1 Hz, 2 H), 7.44−7.28 (m, 5 H), 7.23−7.13 (m, 4 H), 7.08 (t, *J* = 7.4 Hz, 1 H), 3.89 (dd, *J* = 2.6, 11.2 Hz, 1 H), 3.71–3.62 (m, 1H), 3.49 (dd, *J* = 7.8, 11.3 Hz, 1 H), 3.45−3.37 (m, 1 H), 3.19 (dd, *J* = 2.7, 11.7 Hz, 1 H), 2.83 (dd, *J* = 2.9,13.8 Hz, 1 H), 2.75 (dd, *J* = 8.2, 11.9 Hz, 1 H), 2.52 (dd, *J* = 9.8, 13.8 Hz, 1 H), 1.71−1.57 (m, 1 H), 1.52−1.37 (m, 1 H), 0.93 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 140.9, 139.1, 137.6, 129.5, 129.3, 128.7, 127.1, 127.0, 126.9, 123.3, 122.5, 76.8, 68.5, 58.5, 57.4, 34.8, 25.5, 9.9; IR (film) 1598 cm^{-1};MS (ESI) 358.2164 (358.2171 calcd for $C_{25}H_{27}NO$, M + H^+).



Minor diastereomer: *cis*-5-(Biphenyl-4-ylmethyl)-2-ethyl-4-phenylmorpholine (*cis*-19), yellow solid, m.p. 125−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.5 Hz, 2 H), 7.51 (d, *J* = 7.9 Hz, 2 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.37−7.29 (m, 3 H), 7.28−7.22 (m, 2 H), 6.97 (d, *J* = 8.3 Hz, 2 H), 6.87 (t, *J* = 7.2 Hz, 1 H), 3.93 (d, *J* = 11.4 Hz, 1 H), 3.84−3.77 (m, 1 H), 3.71−3.65 (m, 1 H), 3.56−3.48 (m, 1 H), 3.28 (dd, *J* = 2.8, 11.8 Hz, 1 H), 3.09 (dd, *J* = 11.3, 12.8 Hz, 1 H), 2.88 (t, *J* = 11.3 Hz, 1 H), 2.62 (d, *J* = 12.8 Hz, 1 H), 1.78−1.67 (m, 1 H), 1.67−1.57 (m, 1 H), 1.06 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 140.9, 139.0, 138.6, 129.8, 129.4, 128.7, 127.2, 127.1, 127.0, 118.9, 115.1, 77.2, 67.1, 57.2, 47.1, 30.7, 26.8, 9.9; IR (film) 1598 cm^{-1}; MS (ESI) 358.2171 (358.2171 calcd for $C_{25}H_{27}NO$ M + H^+).

Ligand Screen for the Synthesis of Morpholines via Pd-Catalyzed Carboamination. A Schlenk tube was evacuated, flame dried, and backfilled with nitrogen. The tube was

charged with the appropriate palladium catalyst or precatalyst, ligand (where appropriate), phenanthrene (1.0 equiv) as an internal standard, and NaO*t*Bu or KO*t*Bu (2.0 equiv). The tube was evacuated and backfilled with nitrogen, then the aryl bromide (2.0 equiv) and a solution of the amine substrate (1.0 equiv) in toluene (0.4 M) were added to the Schlenk tube. The mixture was heated to 105 °C with stirring for 15 h. The reaction mixture was cooled to rt, quenched with saturated aqueous NH_4Cl (3 mL), and extracted with EtOAc (3 x 3 mL). The combined organic layers were concentrated in vacuo and the crude product mixture was analyzed by ^1H NMR spectroscopy. Results are shown Table 3-1.

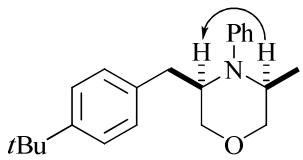


(–)-(*E*)-(2*S*)-*N*-(1-Phenyl-3-(3-*o*-tolylallyloxy)propan-2-yl)aniline (13). Isolation of **13** from the mixtures described in Table 3-1 proved to be difficult. As such, a sample of **13** was prepared by a modification of General Procedure 4. A Schlenk tube was evacuated, flame dried, and backfilled with nitrogen. The tube was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), dppf (4.4 mg, 0.04 mmol), and K_3PO_4 (212 mg, 1.0 mmol). The tube was evacuated and backfilled with nitrogen, then 2-bromotoluene (120 μL, 1.0 mmol) and a solution of **9b** (78 mg, 0.29 mmol) in toluene (1.25 mL) were added to the Schlenk tube. The mixture was heated to 105 °C with stirring until the substrate was consumed as judged by GC analysis (16 h). The reaction mixture was cooled to rt, quenched with saturated aqueous NH_4Cl (3 mL), and extracted with EtOAc (3 x 3 mL). The combined organic layers were concentrated in vacuo. The crude oil was purified by flash chromatography on silica gel using 5% EtOAc/hexanes as

the eluant to afford the title compound (8 mg, 7%) as a colorless oil. $[\alpha]^{23}_{D}$ – 21.7 (*c* = 0.69, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 1 H), 7.32–7.12 (m, 10 H), 6.85–6.77 (m, 1 H), 6.73–6.69 (m, 1 H), 6.69–6.63 (m, 2 H), 6.17 (dt, *J* =6.2, 15.9 Hz, 1 H), 4.22–4.12 (m, 2 H), 3.96 (s, br, 1 H), 3.80 (s, br, 1 H), 3.51–3.44 (m, 2 H), 3.03–2.90 (m, 2 H), 2.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 138.5, 135.7, 135.5, 130.4, 130.3, 129.4, 129.4, 128.4, 127.6, 127.2, 126.3, 126.1, 125.8, 117.5, 113.5, 72.0, 69.8, 54.0, 37.2, 19.8; IR (film) 3404, 1601, cm^{-1}; MS (ESI) 380.1986 (380.1990 calcd for $C_{25}H_{27}NO$, M + Na^+).

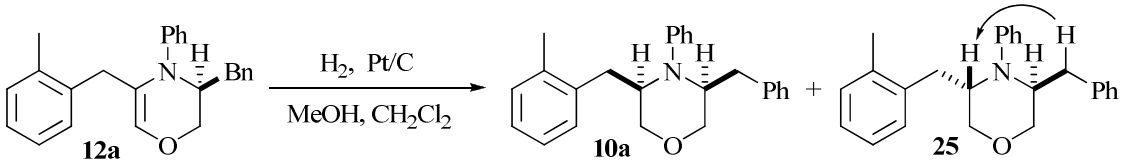
Assignment of Stereochemistry

***cis*-3,5-Disubstituted morpholines derived from alanine, methionine, and serine.** The stereochemistry of 5-methylmorpholine **10b** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below. The stereochemistry of morpholines **10c**, and **10g–h** were assigned based on analogy to **10b**.



***cis*-3,5-Disubstituted morpholines derived from phenylalanine, and tryptophan.** Due to overlap of key signals in the ^{1}H NMR spectra of *cis*-3,5-disubstituted morpholines derived from phenylalanine, the stereochemistry of these compounds was established through preparation of a 1:1.4 mixture of *cis*-isomer **10a** and *trans*-isomer **25** via hydrogenation of dihydro-2*H*-1,4-oxazine **12a**. The stereochemistry of *trans*-

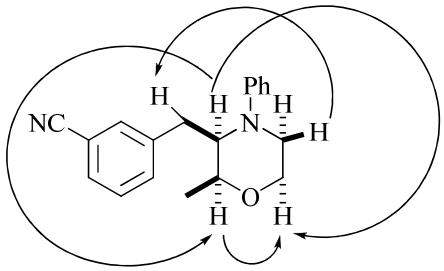
disubstituted 3-benzylmorpholine **25** was assigned on the basis of 2D NOESY and 1D NOESY experiments. The key nOe signals are shown below. The stereochemistry of *cis*-disubstituted morpholine **10a** was assigned by comparison to **25**. The stereochemistry of morpholines **10e–f**, and **10i** were assigned based on analogy to **10a**.



(3*S*,5*S*)-3-Benzyl-5-(2-methylbenzyl)-4-phenylmorpholine (25). A Schlenk tube was evacuated, flame dried, and backfilled with hydrogen. The tube was charged with platinum (2 mg, 10 wt. % on activated carbon), then evacuated and backfilled with hydrogen four times. A solution of **12a** (14.6 mg, 0.04 mmol) in MeOH:CH_2Cl_2 (2:1, 0.9 mL, 0.05 M) was added to the Schlenk tube. The mixture was stirred until the oxazine was consumed as judged by GC analysis (15 h). The mixture was diluted with CH_2Cl_2 (2 mL) and filtered through celite. The celite was washed with CH_2Cl_2 (2 x 2 mL) and the combined organic solutions were concentrated in vacuo to provide a yellow oil. This material was judged to be of 1.6:1 dr by ^{1}H NMR analysis. The crude product was purified by flash chromatography on silica gel with 5% EtOAc/hexanes as the eluant to yield the title compound **25** (2.2 mg, 15%) as a yellow oil along with **10a** (1.6 mg, 11%) as a yellow oil for a combined isolated yield (3.8 mg, 26%, 1.4:1 dr). The diastereomers were judged to be of >20:1 dr by ^{1}H NMR analysis after purification. The (3*S*,5*S*)-stereoisomer was characterized by ^{1}H NMR and MS for purposes of comparison to compound **10a** as described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2 H), 7.31–7.16 (m, 5 H), 7.15–6.98 (m, 7 H), 3.87 (dd, *J* = 3.4, 11.2 Hz, 1 H), 3.77–3.69 (m, 2

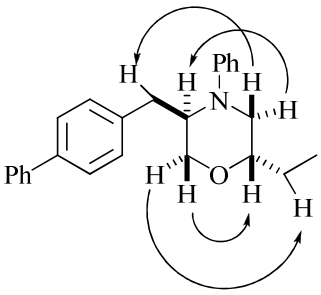
H), 3.63 (dd, *J* = 3.9, 11.2 Hz, 1 H), 3.54–3.46 (m, 2 H), 3.02 (dd, *J* = 2.9, 13.7 Hz, 1 H), 2.84 (dd, *J* = 10.6, 13.2 Hz, 1 H), 2.77 (dd, *J* = 3.5, 13.2 Hz, 1 H), 2.45 (dd, *J* = 11.1, 13.8 Hz, 1 H), 2.00 (s, 3 H); MS (ESI) 358.2163 (358.2171 calcd for $C_{25}H_{27}NO$, M + H^+).

(±)-*cis*-3-[(2-methyl-4-phenylmorphlin-3-yl)methylbenzonitrile (*cis*-17). The stereochemistry of cis-2,3-disubstituted morpholine ***cis*-17** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below.

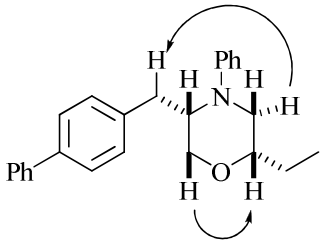


(±)-*trans*-5-(Biphenyl-4-ylmethyl)-2-ethyl-4-phenylmorpholine (*trans*-19) and (±)-[*cis*]-5-(Biphenyl-4-ylmethyl)-2-ethyl-4-phenylmorpholine (*cis*-19).

The stereochemistry of *trans*- and *cis*-2,5-disubstituted morpholines **19** were assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below.

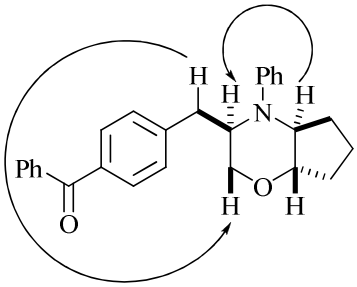


trans-**19**

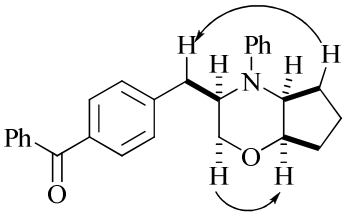


cis-**19**

***trans*-Fused bicyclic morpholines 15b–d.** The stereochemistry of **15d** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below. The stereochemistry of **15b** and **15c** was assigned based on analogy to **15d**.



***cis*-Fused bicyclic morpholines 15a and 15e.** The stereochemistry of **15e** was assigned on the basis of 2D NOESY experiments. The key nOe signals are shown below. The stereochemistry of **15a** was assigned based on analogy to **15e**.



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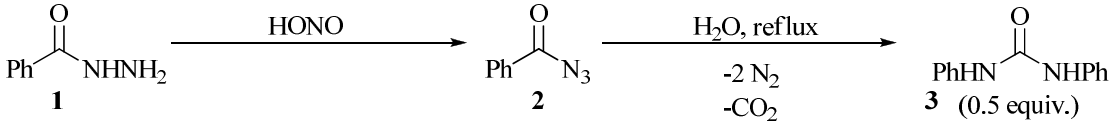
Chapter 4

Development of a Mild Curtius Rearrangement for the Synthesis of Benzylic and Heteroarylmethyl Amines

4.1 Introduction

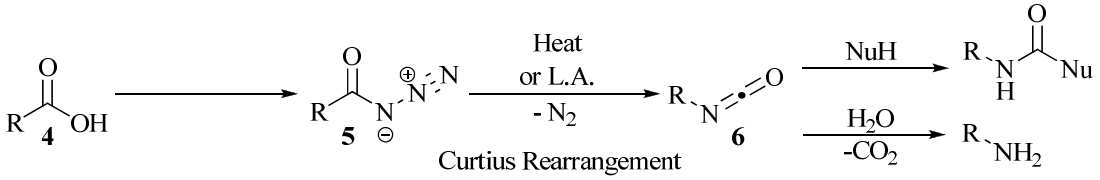
The Curtius rearrangement was first reported in 1890 when Thomas Curtius described the conversion of benzoylhydrazine (**1**) to diphenylurea (**3**) (Scheme 4-1).[1]

Scheme 4-1: Discovery of the Curtius Rearrangement



The defining step of the Curtius rearrangement is the conversion of an acyl azide (**5**) to an isocyanate (**6**) via a 1,2-carbon-to-nitrogen migration with extrusion of dinitrogen (Scheme 4-2).[2] Subsequent hydrolysis of the isocyanate generates primary amines, or trapping of the isocyanate with a nucleophile leads to ureas, carbamates, or amides. Converting a carboxylic acid to an amine functionality is fundamentally useful in organic synthesis, and as such, the Curtius rearrangement has been widely utilized and has been carefully investigated. Useful reviews summarizing the development and application of this rearrangement are available.[3] A key feature of the Curtius rearrangement is that it proceeds with retention of stereopurity.[4] Mechanistic studies indicate that the rearrangement proceeds through a concerted mechanism with an asynchronous transition state.[5]

Scheme 4-2: The Curtius Rearrangement



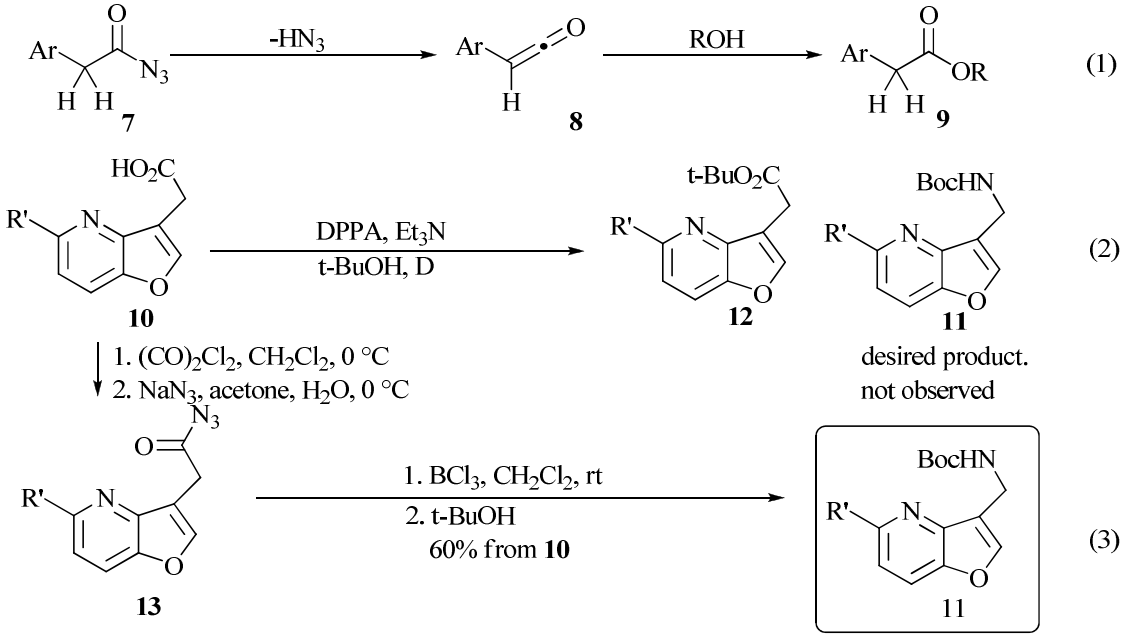
4.2 Modern Developments and Current Challenges

The Curtius rearrangement was quickly recognized as a highly useful transformation, but the potential for acyl azides to decompose explosively introduced a safety hazard and methodological challenge for some substrates. This limitation led to the development of reagents and methods that facilitate acyl azide generation, Curtius rearrangement, and isocyanate trapping in a single flask. The most commonly used reagent for this transformation is diphenylphosphorylazide (DPPA), which allows the direct transformation of carboxylic acids into carbamates.[6] Use of this reagent is potentially complicated by the high temperatures required to achieve conversion to the desired carbamate, which could compromise the stability of sensitive functionalities. Furthermore, substrates that contain acidic protons adjacent to the carboxylic acid undergoing rearrangement, such as benzylic or malonic acids (**7**), are problematic for the Curtius rearrangement using DPPA, often leading to ester byproducts (**9**) as judged by LC-MS characterization.[7] This could potentially occur through elimination of hydrazoic acid, formation of the ketene (**8**) and subsequent trapping with the alcohol nucleophile (Scheme 4-3, eq 1).[8]

For example, selective ester formation was observed by LC-MS when attempting to convert acid **10** to carbamate **11** by heating **10** with DPPA and triethylamine in *t*-BuOH

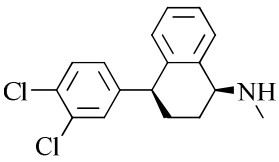
(Scheme 4-3, eq 2). To avoid this side reaction, it was found that sequential formation of the acyl azide **13** and treatment with BCl_3 at room temperature in CH_2Cl_2 followed by addition of *t*-BuOH led to the desired product in moderate yield (Scheme 4-3, eq 3).

Scheme 4-3: Formation of undesired ester byproducts

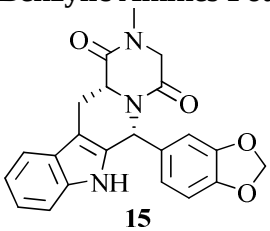


Benzylic amines are found in many important biologically active molecules.[9] For example, three highly profitable pharmaceutical products have chrial benzylic amines in their structures. Zoloft (**14**) helps treat depression and obsessive compulsive disorder (OCD); Cialis (**15**) is an erectile dysfunction therapeutic, and Sensipar (**16**) helps to treat hyperparathyroidism. Furthermore, benzylic amines bearing stereogenic centers have been used as ligands in asymmetric synthesis.[10] Optimization of this room temperature Curtius rearrangement was motivated by the broad importance of benzylic amines.

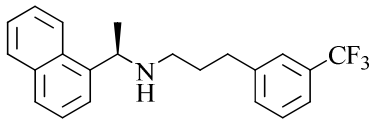
Figure 4-1: Example Chiral Benzylic Amines Found in Bilogically Active Molecules



14
Zoloft - Pfizer
$1.77 Billion (2006)
Depression and OCD



15
Cialis - Eli-Lilly
$560 Million (2008)
Erectile Dysfunction



16
Sensipar - Amgen
$350 Million (2008)
Hyperparathyroidism

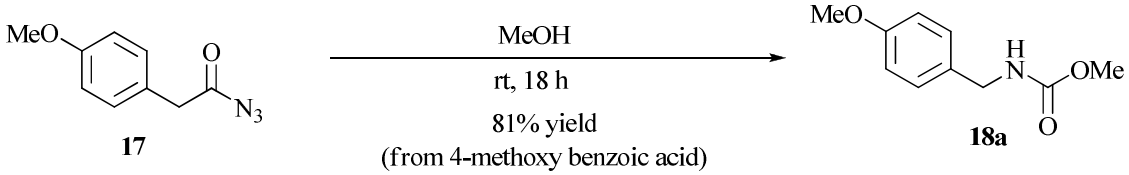
A general method for the formation of benzylic amines from readily available carboxylic acids would prove particularly useful, especially when considering the powerful asymmetric hydrogenation methods that have been developed for accessing α-chiral benzylic acids.[11] This chapter describes the development of a step-wise procedure for conversion of benzylic and heteroarylmethyl acids to carbamate protected amines via a room temperature Curtius rearrangement.

4.3 Initial Optimization

The first task in optimization was to screen a variety of Lewis acids and solvents with the aim of determining the optimal conditions for Curtius rearrangement of benzylic acyl azides. For this initial study, the acyl azide **17**, derived from 4-methoxybenzoic acid, was employed as a standard substrate, with MeOH as the nucleophile to trap the isocyanate. As a control, alternate Curtius conditions were tested (refluxing 4-methoxybenzoic acid, DPPA, Et_3N and MeOH or *t*BuOH), but they led to numerous side products instead of rearrangement product **18a**. A wide variety of Lewis acids and solvents were tested, with no improvement over the initial result. A key observation was made during these studies that in some instances, acyl azide **17** was not undergoing rearrangement to the isocyanate until after the addition of methanol. This observation led

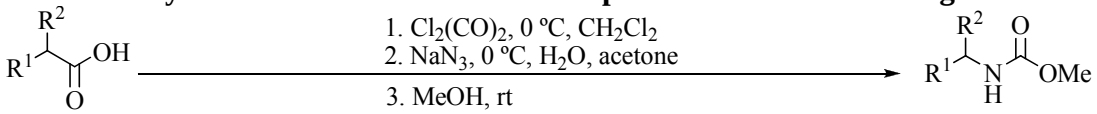
us to the discovery that in the presence of MeOH, **17** was cleanly converted to the desired methyl carbamate **18a** after 18 h at room temperature, in the absence of any additive (Figure 4-2). Attempts to increase the rate of conversion to **18a** by addition of catalytic HCl, and other more acidic alchohol solvents such as hexafluoroisopropanol and trifluoroethanol led in all cases to ester byproducts in addition to product **18a**.

Figure 4-2: Room temperature Curtius rearrangement in MeOH

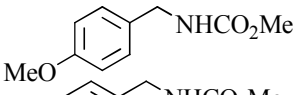
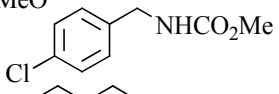
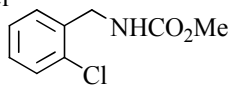
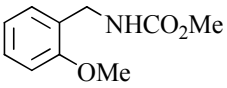
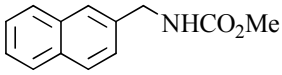
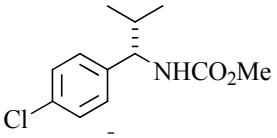
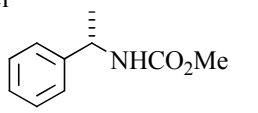
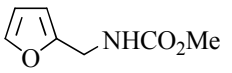
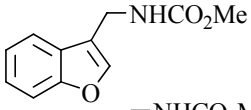
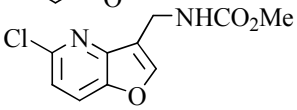
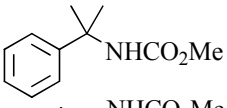
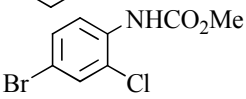


There are few reports of low temperature Curtius rearrangements; one notable exception is the work by Lebel and coworkers where they report a useful one-pot Curtius rearrangement using $TMSN_3$, Boc_2O and $Zn(OTf)_2$ at 40 °C.[12] The authors reveal that a benzylic acid substrate was problematic, leading to a mixture of desired product and the anticipated ester byproduct, thus highlighting the utility of this discovery. This simple solution to the problematic Curtius rearrangement of benzylic and heteroarylmethyl acyl azides is complementary to existing methods and provides an alternative procedure for more sensitive compounds that are unstable to heat or Lewis Acids. For example, the acyl azide derived from 2-(benzofuran-3-yl)acetic acid forms extensive side products in the presence of Lewis acids at room temperature or when heated with DPPA, but converts cleanly to carbamate **18i** at room temperature in methanol (Table 4-1, entry 9).

Table 4-1: Acyl azide formation and room temperature Curtius rearrangement.



19a-l **18a-l**

Entry	Time	Product		Yield (%)[a]
1	18 h		**18a**	81
2	24 h		**18b**	80
3	48 h		**18c**	78
4	48 h		**18d**	87
5	24 h		**18e**	85
6	18 h		**18f**	70 (>99% ee)
7	18 h		**18g**	85 (>99% ee)
8	24 h		**18h**	61
9	24 h		**18i**	78
10	48 h		**18j**	75
11	12 d		**18k**	86
12	24 h		**18l**	92

[a] Isolated yield starting from corresponding carboxylic acid.

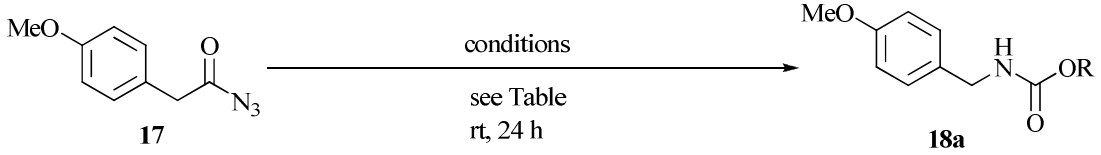
4.4 Synthesis of Methyl Carbamates

To determine the generality of the step-wise acyl azide formation and room temperature Curtius rearrangement in methanol, the scope of the transformation was investigated (Table 4-1). A wide variety of benzylic and heterocyclic acids convert to the corresponding methyl carbamates in good yield (Table 4-1). Chiral, non-racemic acids can also be converted to the corresponding protected amines without racemization of the adjacent stereogenic center (Table 4-1, entries 6 and 7). The reaction can be run under an air atmosphere without strict moisture exclusion, and purification of the resulting products is simplified by the absence of additives. In many applications, simply concentrating the reaction mixture provides product of sufficient purity for subsequent chemical transformations. Aromatic acids also undergo rearrangement cleanly in high yield (Table 4-1, entry 12), however aliphatic acids provide the corresponding carbamate in poor yields due to competetive hydrolysis of the acyl chloride during acyl azide formation. Substrates bearing a quarternary carbon center adjacent to the acyl azide undergo the rearrangement at a slower rate, achieving 86% yield after 12 days. (Table 4-1, entry 11). This limitation is not especially troubling, since substrates bearing quaternary carbons will not be susceptible to ester byproduct formation using established procedures.[13] It should also be noted that increasing the reaction temperature (40–60 °C) can shorten the reaction time considerably for substrates listed in Table 1, but often leads to increased formation of undesired byproducts.

4.5 Synthesis of Various Carbamates

The procedure described above provides a convenient and mild method for accessing benzylic and heteroarylmethyl amines without forming ester byproducts, however, removal of methyl carbamates can often require harsh basic conditions. Thus, conditions were sought to further expand this protocol so that alternative alcohol nucleophiles could be utilized to form more readily deprotected carbamates. A simple solution would be to perform the rearrangement in *t*-BuOH to form the Boc carbamate, however, it was found that both *i*-PrOH and *t*-BuOH provided slow conversion to products **18m** and **18n**, revealing that the steric nature of the alcohol nucleophile greatly effects the rate of product formation (Table 4-2, entries 9-11).

Table 4-2: Solvent screen



17 **18a**

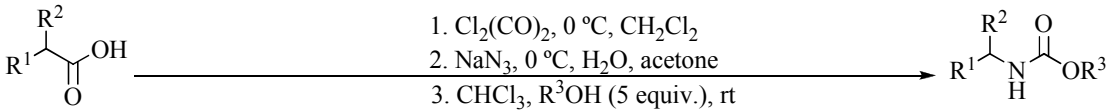
Entry	Solvent (condition)	Product	% Conv.[a]
1	THF, MeOH (5 equiv)	**18a**, R = Me	37
2	p-Dioxane, MeOH (5 equiv)	**18a**, R = Me	21
3	MeCN, MeOH (5 equiv)	**18a**, R = Me	46
4	Benzene, MeOH (5 equiv)	**18a**, R = Me	68
5	CH_2Cl_2, MeOH (5 equiv)	**18a**, R = Me	74
6	$CHCl_3$, MeOH (5 equiv)	**18a**, R = Me	87 (81)[b]
7	$CHCl_3$, MeOH (5 equiv)	**18a**, R = Me	75
8	$CHCl_3$, MeOH (5 equiv)	**18a**, R = Me	47
9	iPrOH	**18m**, R = iPr	48[b]
10	t-BuOH	**18n**, R = tBu	28[b]
11	$CHCl_3$, t-BuOH (5 equiv)	**18o**, R = tBu	Trace

[a] Conversion to product **18** measured by HPLC-LRMS.
[b] Isolated yield.

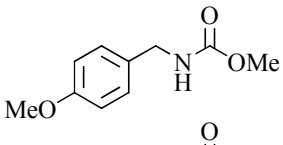
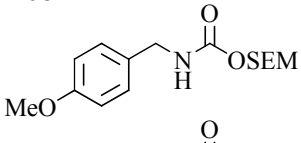
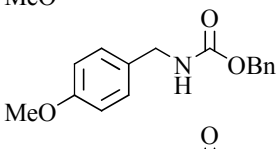
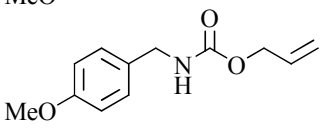
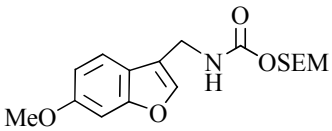
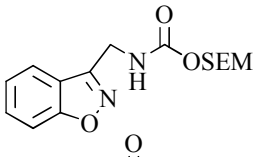
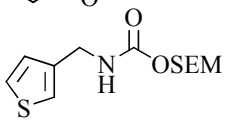
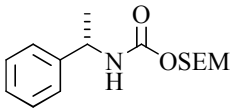
An important consideration was to determine whether the rearrangement would take place without using the desired alcohol as the solvent. This would allow preparation of alternative carbamates that could be deprotected under more mild conditions without using excessive amounts of potentially expensive alchohol nucleophiles. A variety of solvents were screened using 5 equivalents of MeOH as an additive. Chloroform was effective in providing the fastest rearrangement. Although it is possible that rearrangement could be promoted by trace amounts of HCl present in $CHCl_3$, we found that the product was formed with equal efficiency in base-washed $CHCl_3$. The hydrogen-bonding capability of $CHCl_3$ could also be responsible.[14] Comparison of entries 6–8 (Table 4-2) reveals that 5 equivalents of the alcohol nucleophile was the optimal condition to achieve a reasonable yield in 24 hours.

Using the optimal conditions from Table 4-2 (entry 6) a variety of substrates and different alcohol nucleophiles were tested (Table 4-3). Again, the transformation appears to be general for both benzylic and heteroaryl substrates with less sterically hindered nucleophiles. Note that the majority of commerically purchased chloroform is stabilized with added ethanol, even if unspecified. Ethanol can compete with other alcohol nucleophiles to trap the isocyanate intermediate. It is possible to use anhydrous chloroform stabilized with amylenes to avoid this complication. Carbamate derivatives bearing a variety of more easily deprotected side chains were formed in good yield.

Table 4-3: Formation of easily deprotected carbamates



19a, o-u → **18a, o-u**

Entry	Time	R^3OH	Product		Yield (%)[b]
1	18 h	MeOH		**18a**	77
2	18 h	SEMOH[a]		**18o**	80
3	18 h	BnOH		**18p**	82
4	18 h	Allyl-OH		**18q**	88
5	24 h	SEMOH		**18r**	90
6	72 h	SEMOH		**18s**	81
7	24 h	SEMOH		**18t**	76
8	24 h	SEMOH		**18u**	89 (99% ee)

[a] SEMOH = 2-(Trimethlsilyl)ethanol
[b] Isolated yields.

4.6 Conclusions

In conclusion, a simple step-wise procedure to achieve a room temperature Curtius rearrangement of benzylic and heteroarylmethyl carboxylic acids is reported. The conditions described in this chapter provide an alternative to already described one-pot

procedures that require heating or the use of Lewis acids. Hopefully this simple result will enable others to easily prepare benzylic and heteroarylmethyl carbamates without the formation of unwanted ester byproducts or other deleterious side reactions. The mild nature of these conditions and the ease of purification will hopefully encourage their use in more complicated synthetic applications.

4.7 Experimental Section

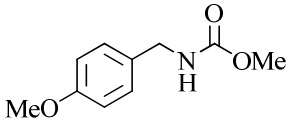
General: Unless otherwise noted, all material were obtained from commercial suppliers and used without further purification. Anhydrous solvents were purchased from Aldrich packaged under nitrogen in Sure/Seal™ bottles and used directly. Reactions were monitored using Agilent 1100 Series LCMS with UV detection at 254 nm and 215 nm and a low resonance electrospray mode (ESI). Medium pressure liquid chromatography (MPLC) was performed on a Combiflash® Companion® (Teledyne Isco) with Redisep® normal-phase silica gel (35 – 60 micron) columns and UV detection at 254 nM. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 (400 mHz) spectrometer at ambient temperature. Chemical shifts are recorded in ppm from the solvent resonance. Mass spectra were obtained on a high resonance Electrospray Time-of-Flight mass spectrometer. Enantiomeric excess was measured by chiral SFC.

General Procedure A (Acyl Azide Formation and Curtius Rearrangements in MeOH): To a flask under nitrogen atmosphere containing acetic acid (1.0 mmol) was added CH_2Cl_2 (5 mL, 0.2 M). The resulting solution was cooled to 0 °C and oxalyl chloride (175 µL, 2.0 mmol) was added followed by DMF (39 µL, 0.5 mmol). The

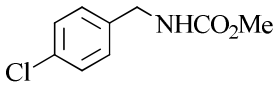
solution was allowed to warm to rt and maintained until gas evolution ceased (~1 h). The solution was concentrated *in vacuo* and the resulting residue was taken up in acetone (5 mL, 0.2 M) and transferred dropwise to a vigorously stirring aqueous solution (0.4 M) of sodium azide (130 mg, 2.0 mmol) at 0 °C. The resulting solution was maintained at 0 °C for 15 minutes at which time it was partitioned between EtOAc (10 mL) and H_2O (5 mL). CAUTION: the aqueous layer may contain hydrazoic acid (HN_3) as a byproduct.[15] The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with H_2O (10 mL), brine (5 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to provide acyl azide, which could be stored at rt for several hours, or at -20 ˚C for several days without decomposition or rearrangement. Although acyl azides are a widely used intermediate in organic synthesis, the authors caution that low molecular weight acyl azides can be potentially explosive if evaporated to dryness.[16] On larger scale, the authors recommend partial concentration of the acyl azide intermediate, followed by introduction of MeOH. The acyl azide residue was transferred to a vial using MeOH (5 mL, including rinses). The solution was maintained at 25 °C for 18 h, at which time it was concentrated *in vacuo*. The residue was purified by silica gel chromatography using a gradient of 2–80% EtOAc in hexanes to yield the desired product.

General Procedure B (Curtius rearrangement for alternative carbamates): To a flask charged with acyl azide (1.0 equiv., prepared from acetic acid) was added $CHCl_3$ (5 mL, anhydrous, stabilized with amylenes) followed by alcohol (5.0 equiv.). (Note that the majority of commercially purchased chloroform is stabilized with added ethanol, even if unspecified. Ethanol can compete with other alcohol nucleophiles to trap

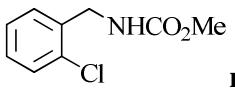
the isocyanate intermediate. It is recommended to use anhydrous chloroform stabilized with amylenes to avoid this complication.) The resulting solution was maintained at rt for 24 h, at which time it was concentrated *in vacuo*. The residue was purified by silica gel chromatography using a gradient of 2% EtOAc in hexanes –100% EtOAc to yield the desired product.



methyl 4-methoxybenzylcarbamate (18a). Prepared according to General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.68 (s, 3 H) 3.78 (s, 3 H) 4.28 (d, *J*=5.77 Hz, 2 H) 5.11 (br. s., 1 H) 6.81 - 6.91 (m, 2 H) 7.20 (d, *J*=8.51 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 44.48, 52.02, 55.17, 76.68, 77.00, 77.31, 113.92, 128.75, 130.61, 156.95, 158.90; IR (film) 3317, 2950, 1689, 1161 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}NO_3$ (M + Na) *m/z* 218.07876; found 218.07652.

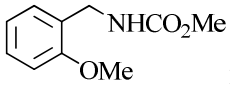


methyl 4-chlorobenzylcarbamate (18b). Prepared according to General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.70 (s, 3 H), 4.33 (d, *J*=6.06 Hz, 2 H), 5.21 (br. s., 1 H), 7.18 -7.26 (m, 2 H), 7.27 - 7.34 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 44.3, 52.2, 128.7, 128.7, 133.1, 137.1, 157.0; IR (film) 3308, 2948, 1686, 1538 cm^{-1}; HRMS (ESI) calcd for $C_9H_{10}Cl\ NO_2$ (M + Na) *m/z* 222.02923; found 222.02905.

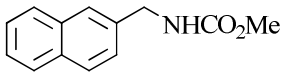


methyl 2-chlorobenzylcarbamate (18c). Prepared according to General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.69 (s, 3 H), 4.46 (d, *J*=6.26 Hz, 2 H), 5.31 (br. s., 1 H), 7.17 -7.32 (m, 2 H), 7.32 - 7.48 (m, 2 H); ^{13}C NMR (100

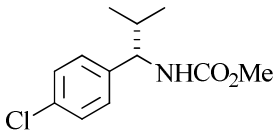
MHz, $CDCl_3$) δ ppm 42.9, 52.2, 126.9, 128.8, 129.4, 129.7, 133.4, 135.9, 156.9; IR (film) 3297, 3061, 2957, 1687, 1542 cm^{-1}; HRMS (ESI) calcd for $C_9H_{10}ClNO_2$ (M + H) *m/z* 200.04728; found 200.04718.



methyl 2-methoxybenzylcarbamate (18d). Prepared according to General Procedure A. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.67 (s, 3 H), 3.85 (s, 3 H), 4.37 (d, *J*=5.28 Hz, 2 H), 5.33 (br.s., 1 H), 6.88 (d, *J*=8.12 Hz, 1 H), 6.93 (td, *J*=7.43, 0.98 Hz, 1 H), 7.24 - 7.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 40.8, 51.8, 55.1, 76.7, 77.0, 77.3, 110.1, 120.4, 126.6, 128.6, 129.2, 156.9, 157.3; IR (film) 3331, 3006, 1701, 1603.

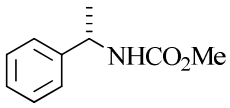


methyl naphthalen-2-ylmethylcarbamate (18e). Prepared according to General Procedure A. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.73 (s, 3 H), 4.51 (d, *J*=5.18 Hz, 2 H), 5.27 (br. s., 1 H), 7.40 (d, *J*=8.02 Hz, 1 H), 7.44 - 7.53 (m, 2 H), 7.71 (s, 1 H), 7.78 - 7.86 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 45.1; 52.2, 125.5, 125.8, 125.9, 126.1, 127.57, 127.64, 128.4, 132.7, 133.2, 135.9, 157.1; IR (film) 3325, 3005, 1690, 1534 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{13}NO_2$ (M + H) *m/z* 216.10191; found 216.10193.

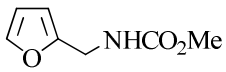


(S)-methyl 1-(4-chlorophenyl)-2-methylpropylcarbamate (18f). Prepared according to General Procedure A. $[\alpha]^{25}_D$ –64.9 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.85 (d, *J*=6.75 Hz, 3 H), 0.96 (d, *J*=6.65 Hz, 3 H), 1.90 - 2.05 (m, 1 H), 3.65 (s, 3 H), 4.43 (br. s., 1 H), 5.11 (br. s., 1 H), 7.17 (d, *J*=8.31 Hz, 2 H), 7.27 - 7.34

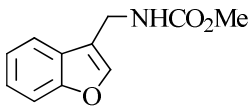
(m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.6, 33.4, 52.1, 60.6, 128.1, 128.5, 132.7, 140.5, 156.5; IR (film) 3329, 2963, 1690, 1534 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}ClNO_2$ (M + Na) *m/z* 264.07618; found 264.07586.



(S)-methyl 1-phenylethylcarbamate (18g). Prepared according to General Procedure A. $[\alpha]^{25}_D$ –76.8 (*c* 1.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (d, *J*=6.94 Hz, 3 H), 3.67 (s, 3 H), 4.88 (br. s., 1 H), 5.26 (br. s., 1 H), 7.24 - 7.30 (m, 1 H), 7.30 - 7.39 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 22.3, 50.5, 51.9, 125.8, 127.1, 128.4, 143.6, 156.1; IR (film) 3323, 2972, 1686, 1529 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}NO_2$ (M + Na) *m/z* 202.08385; found 202.08390.

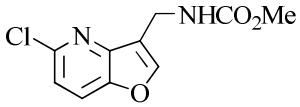


methyl furan-2-ylmethylcarbamate (18h). Prepared according to General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.67 (s, 3 H), 4.34 (d, *J*=5.48 Hz, 2 H), 5.17 (br. s., 1 H), 6.21 (d, *J*=2.45 Hz, 1 H), 6.30 (dd, *J*=3.13, 1.86 Hz, 1 H), 7.33 (dd, *J*=1.76, 0.78 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 37.9, 52.1, 106.9, 110.2, 142.0, 151.6, 156.8; IR (film) 3324, 3006, 1700, 1522 cm^{-1}; HRMS (ESI) calcd for $C_7H_9NO_3$ (M + Na) *m/z* 178.04746; found 178.04718.

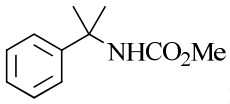


methyl benzofuran-3-ylmethylcarbamate (18i). Prepared according to General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.71 (s, 3 H), 4.48 (d, *J*=5.58 Hz, 2 H), 5.19 (br. s., 1 H), 7.24 -7.29 (m, 1 H), 7.33 (td, *J*=7.70, 1.32 Hz, 1 H), 7.47 - 7.52 (m, 1 H), 7.57 (s, 1 H), 7.63 (d, *J*=7.34 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 34.9, 52.1, 111.5, 117.9, 119.7, 122.7, 124.6, 126.6, 142.41, 155.45,

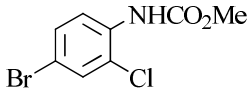
156.95; IR (film) 3332, 3006, 1683, 1534 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}NO_3$ (M + Na) *m/z* 228.06311; found 228.06298.



methyl (5-chlorofuro[3,2-b]pyridin-3-yl)methylcarbamate (18j). Prepared according to General Procedure A. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.64 (s, 3 H), 4.47 (dd, *J*=6.16, 0.88 Hz, 2 H), 5.72 (br. s., 1 H), 7.20 (d, *J*=8.51 Hz, 1 H), 7.67 (d, *J*=8.61 Hz, 1 H), 7.88 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 33.6, 52.1, 118.4, 119.4, 121.0, 146.3, 146.7, 147.0, 147.8, 157.0; IR (film) 3256, 3126, 3083, 2957, 1703, 1614 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_9ClN_2O_3$ (M + H) *m/z* 241.03745; found 241.03761.

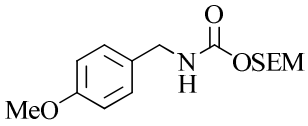


methyl 2-phenylpropan-2-ylcarbamate (18k). Prepared according to General Procedure A. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.58 (s, 6 H), 3.50 (s, 3 H), 5.08 (br. s., 1 H), 7.11 - 7.17 (m, 1H), 7.20 - 7.27 (m, 2 H), 7.29 - 7.35 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 29.3, 51.5, 55.1, 124.7, 126.6, 128.3, 146.98, 155.06; IR (film) 3335, 2977, 1697, 1525 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}NO_2$ (M + Na) *m/z* 216.09950; found 216.09955.

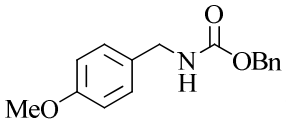


methyl 4-bromo-2-chlorophenylcarbamate (18l). Prepared according to General Procedure A. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.81 (s, 3 H), 7.10 (br. s., 1 H), 7.38 (dd, *J*=8.90, 2.25 Hz, 1 H), 7.50 (d, *J*=2.25 Hz, 1 H), 8.07 (d, *J*=8.90 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 52.7, 115.2, 120.9, 122.7, 130.8, 131.4,

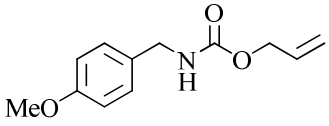
134.0, 153.4; IR (film) 3299, 1698, 1518, 1248, 1075, 1049; HRMS (ESI) calcd for $C_8H_7BrClNO_2$ (M + Na) *m/z* 285.92409; found 285.92363.



(2-(trimethylsilyl)ethoxy)methyl 4-methoxybenzylcarbamate (18o). Prepared according to General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.04 (s, 9 H), 0.94 - 1.03 (m, 2 H), 3.79 (s, 3 H), 4.13 - 4.23 (m, 2 H), 4.28 (d, *J*=5.77 Hz, 2 H), 5.00 (br. s., 1 H), 6.83 - 6.88 (m, 2 H), 7.21 (d, *J*=8.51 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm –1.5, 17.7, 44.4, 55.2, 63.0, 113.9, 128.8, 130.8, 156.7, 158.9; IR (film) 3328, 2952, 2897, 1691, 1511 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{23}NO_3Si$ (M + Na) *m/z* 304.13394; found 304.13188.

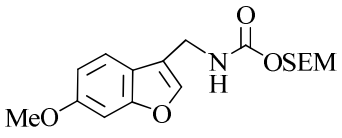


benzyl 4-methoxybenzylcarbamate (18p). Prepared according to General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.80 (s, 3 H), 4.32 (d, *J*=5.87 Hz, 2 H), 5.08 - 5.24 (m, 3 H), 6.83 - 6.91 (m, 2 H), 7.22 (d, *J*=8.12 Hz, 2 H), 7.30 - 7.43 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 44.5, 55.2, 66.7, 114.0, 128.0, 128.4, 128.8, 130.5, 136.5, 156.3, 158.9; IR (film) 3310, 3034, 2941, 1684, 1546 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}NO_3$ (M + Na) *m/z* 294.11006; found 294.10999.

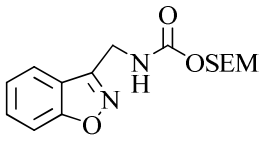


allyl 4-methoxybenzylcarbamate (18q).[17] Prepared according to General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.81 (s, 3 H), 4.32 (d, *J*=5.97 Hz, 2 H), 4.60 (d, *J*=5.38 Hz, 2H), 4.97 (br. s., 1 H), 5.22 (dq, *J*=10.47, 1.34 Hz, 1 H), 5.31 (dq, *J*=17.21, 1.57 Hz, 1 H), 5.87 - 6.01 (m, 1 H), 6.85 - 6.90 (m, 2 H),

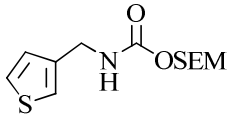
7.22 (d, *J*=8.41 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 44.6, 55.3, 65.6, 114.1, 117.6, 128.9, 130.5, 132.9, 156.2, 159.0; IR (film) 3305, 3017, 2955, 1684, 1649 cm^{-1}.



(2-(trimethylsilyl)ethoxy)methyl (6-methoxybenzofuran-3-yl)methylcarbamate (18r). Prepared according to General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.05 (s, 9 H), 0.90 - 1.07 (m, 2 H), 3.85 (s, 3 H), 4.12 - 4.28 (m, 2 H), 4.44 (d, *J*=5.67 Hz, 2 H), 4.90 (br. s., 1 H), 6.89 (dd, *J*=8.51, 2.25 Hz, 1 H), 7.00 (d, *J*=2.15 Hz, 1 H), 7.43 -7.52 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm –1.5, 17.7, 35.0, 55.7, 63.3, 96.1, 111.8, 118.0, 119.9, 120.0, 141.4, 156.6, 156.7, 158.3; IR (film) 3330, 3005, 1691, 1518 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{23}NO_4Si$ (M + Na) *m/z* 344.12886; found 344.12902.

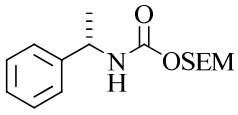


(2-(trimethylsilyl)ethoxy)methyl benzo[d]isoxazol-3-ylmethylcarbamate (18s). Prepared according to General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.00 (s, 9 H), 0.82 - 1.09 (m, 2 H), 4.11 - 4.27 (m, 2 H), 4.74 (d, *J*=6.16 Hz, 2 H), 5.49 (br. s., 1 H), 7.21 - 7.34 (m, 1 H), 7.45 - 7.58 (m, 2 H), 7.78 (d, *J*=7.82 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm –1.6, 17.6, 36.0, 63.6, 109.7, 120.2, 121.8, 123.5, 130.0, 156.1, 156.7, 163.3; IR (film) 3326, 2953, 3895, 1692, 1529 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}N_2O_3Si$ (M + H) *m/z* 293.13160; found 293.13193.

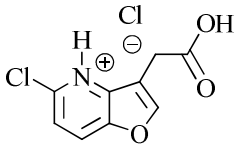


(2-(trimethylsilyl)ethoxy)methyl thiophen-3-ylmethylcarbamate (18t). Prepared according to General Procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm

0.04 (s, 9 H), 0.92 - 1.03 (m, 2 H), 4.12 - 4.23 (m, 2 H), 4.34 (d, *J*=5.87 Hz, 2 H), 5.13 (br. s., 1 H), 7.01 (d, *J*=4.70 Hz, 1 H), 7.12 (d, *J*=1.76 Hz, 1 H), 7.26 (dd, *J*=4.99, 2.93 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm –1.6, 17.7, 40.1, 63.0, 121.7, 126.1, 127.0, 139.6, 156.6; IR (film) 3329, 2952, 2896, 1691, 1517 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{19}NO_2SSi$ (M + Na) *m/z* 280.07980; found 280.08012.



(S)-(2-(trimethylsilyl)ethoxy)methyl 1-phenylethylcarbamate (18u).[18] Prepared according to General Procedure B. $[\alpha]^{25}_D$ –57.1 (*c* 1.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.00 (s, 9 H), 0.88 - 1.03 (m, 2 H), 1.45 (d, *J*=6.85 Hz, 3 H), 4.01 - 4.23 (m, 2 H), 4.81 (br. s., 1 H), 4.88 - 5.01 (m, 1 H), 7.14 - 7.41 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm –1.50, 17.74, 22.48, 50.52, 63.00, 125.90, 127.22, 128.57, 143.72, 155.93; HRMS (ESI) calcd for $C_{14}H_{23}NO_2Si$ (M + Na) *m/z* 288.13903; found 288.13928.



3-(carboxymethyl)-5-chlorofuro[3,2-b]pyridin-4-ium (11j). To a flask charged with MeOH (23 mL), water (7. mL), and NaOH (0.300 g, 7.5 mmol) was added methyl 2-(5-chlorofuro[3,2-b]pyridin-3-yl)acetate[19] (0.677 g, 3.0 mmol) as a solid in a single portion. The solution was maintained at rt for 18 h, at which time it was acidified (pH = 3.0) with conc. HCl. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to provide 3-(carboxymethyl)-5-chlorofuro[3,2-b]pyridin-4-ium (0.648 g, 87% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.70 (d, *J*=0.98 Hz, 2 H), 7.42 (d,

J=8.61 Hz, 1 H), 8.11 (d, *J*=8.61 Hz,1 H), 8.29 (s, 1 H), 12.51 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 27.4, 114.6, 119.3, 122.0, 145.7, 146.3, 146.7, 149.3, 171.2.

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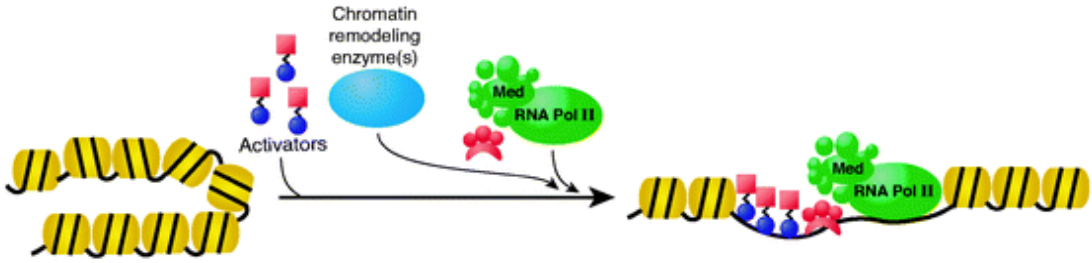
Chapter 5

Exploration of Bisisoxazolidines as Small Molecule Transcriptional Activation Domains

5.1 Introduction

Transcription is the process by which cells create an RNA sequence that is complementary to a DNA template.[1] Regulation of transcription plays a critical role in controlling the levels of gene expression in a cell and thus controlling cellular function and morphology. Transcription factor (TF) proteins serve to facilitate the activation or repression of transcription at specific genes.1 Activator TFs up-regulate gene expression by binding to specific sites on DNA, recruiting chromatin remodeling enzymes that modify DNA-histone complexes, and initiating transcription by assembling the RNA polymerase II holoenzyme (Figure 1).[2]

Figure 5-1: Activator TFs bind to DNA (black line) and recruit chromatin remodeling enzymes that help unwrap the DNA and allow initiation of transcription by RNA polymerase II



The misregulation of transcription is associated with many human diseases. For example, over 50% of all human cancers are found to have alterations in the function of the TF p53.[3] Similarly, NF-κB is found to be constitutively active and misregulated in inflammatory disorders and most cancers.[4] The development of artificial molecules capable of predictably manipulating the levels of transcription has good potential for disease therapy or for mechanistic investigations, and important progress has been made in both areas.[5]

Early experiments on TFs revealed that natural TFs are modular proteins minimally containing a DNA-binding domain (DBD) and a regulatory domain (RD), and each domain functions independently of the other one.[6] The DBD selectively targets specific DNA sequences for a given gene, localizing the RD near the gene to be regulated. The RD is either a transcriptional activation domain (TAD) that binds to and recruits components of the transcriptional machinery for activation, or it is a transcriptional repression domain that recruits components of the repression machinery.[1] Domain swapping experiments show that TF activity is maintained when the TAD of one TF is linked to the DBD of a different TF.[7] This result indicates that TADs and DBDs can be investigated independently. Excellent advances have been made in the development of artificial DBDs, including good sequence selectivity with polyamides, triplex-forming oligonucleotides, peptide nucleic acids, and designer proteins.[8] Progress in the development of artificial TADs has seen slower progress.

The development of artificial TADs has been challenging due to the limited amount of information known about natural RDs.[6,9] The largest class of natural activator RDs is the amphipathic class, containing a mix of polar and hydrophobic amino acid residues in

short repeats (Figure 2).[10] These natural activator RDs associate with multiple binding partners while facilitating the assembly of the transcriptional machinery. RD binding partners include components of the chromatin remodeling machinery, the proteasome, and the Mediator complex.[11]

Figure 5-2: Natural activation domains contain repeats of polar and hydrophobic residues

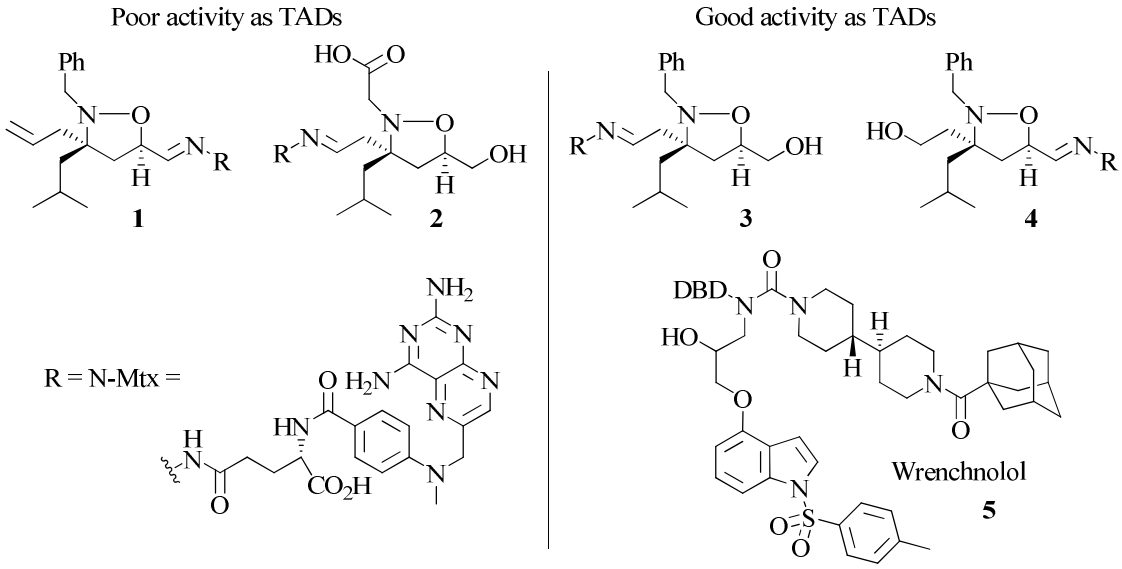
VP16 441 AspPheAspLeuAspMet…AspPheGluPheAspAsn 477
Gal4 843 GlnThrAlaTyrAsnAlaPheGly…AspAspValTyrGlnTyrLeuPhe 869

At least two different methods can be used to functionally evaluate small molecule artificial TADs. Artificial TADs can be linked to a functional DBD and evaluated by their ability to upregulate transcription and imitate natural TFs. Alternatively, natural and artificial TADs can be used to squelch activation levels by binding to transcriptional machinery and inhibiting the activity of activator TFs.

Previous work in the Mapp lab and the Uesugi lab has shown that small molecules are capable of functionally replacing TADs in artificial TFs for activation (Figure 5-3).[12] Isoxazolidine (**4**) was the first reported example of a small molecule TAD. In particular, a variety of isoxazolidines are capable of acting as TADs. While isoxazolidines functionalized with only polar or only hydrophobic groups show poor activation, compounds containing a combination of hydrophobic and polar groups show robust activation (Figure 5-3).[12a] Functional group position and ring stereochemistry did not strongly influence activation efficiency.[12b] The only other small molecule TAD known at the initiation of this research was wrenchnolol (**5**), reported by the Uesugi lab (Figure 5-3).[13] Wrenchnolol binds selectively to a subunit of the mediator complex, Sur-2 (Med23), and can function as part of an artificial TF *in vivo* at moderate levels. While the

Uesugi group demonstrated an entirely artificial TF based on **5** and a polyamide DBD, transcription levels only 3.5 times basal expression were attained.

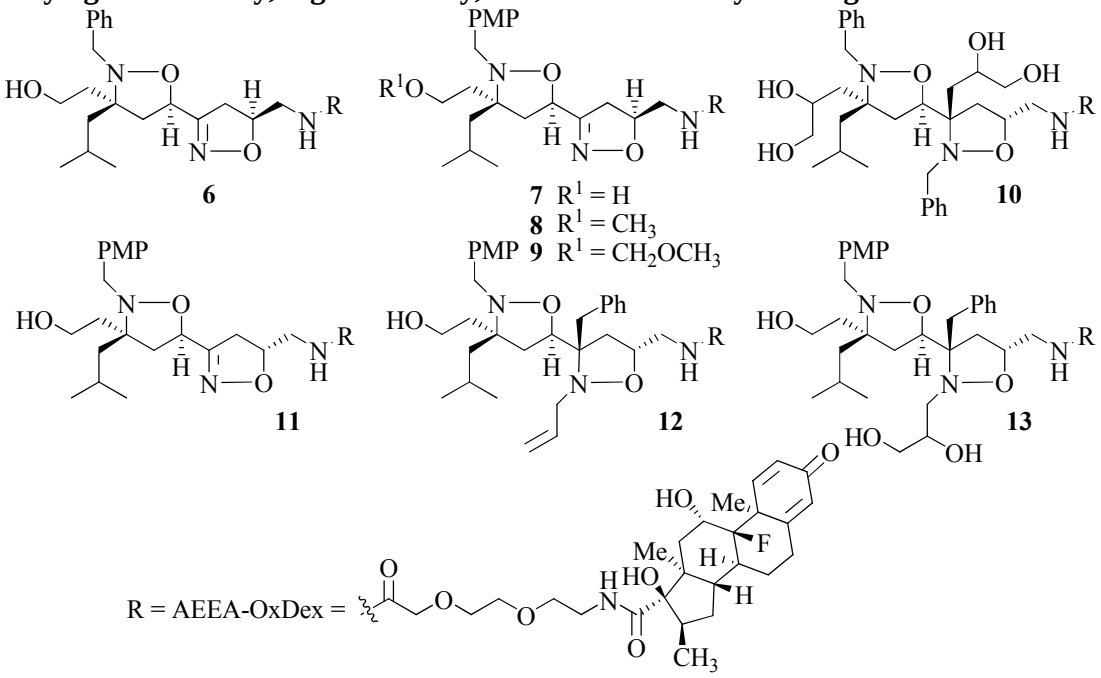
Figure 5-3: Isoxazolidines functionalized with mostly polar or hydrophobic functional groups are poor TADs. Amphipathic isoxazolidines robustly activate transcription



Development of an artificial TAD with potential for potent activity as part of an artificial TF or for squelching experiments remains a challenge limiting the potential utility of artificial TADs. A review of TAD potencies revealed that activation levels can be increased synergistically when a single TAD is repeatedly displayed as part of a TF.[14] The greater than additive improvement in activity demonstrated with natural TADs led the Mapp lab to hypothesize that bisisoxazolidine TADs would show improved potency. An array of bisisoxazolidines were targeted to probe this hypothesis. Since amphipathic mono-isoxazolidines showed much stronger activity than isoxazolidines functionalized with mainly hydrophobic or mainly polar substituents, compounds containing a mix of both polar and hydrophobic substituents were targeted (Figure 5-4). Initial experiments

would evaluate TADs by their ability to functionally upregulate transcription in cells as part of an artificial TF.

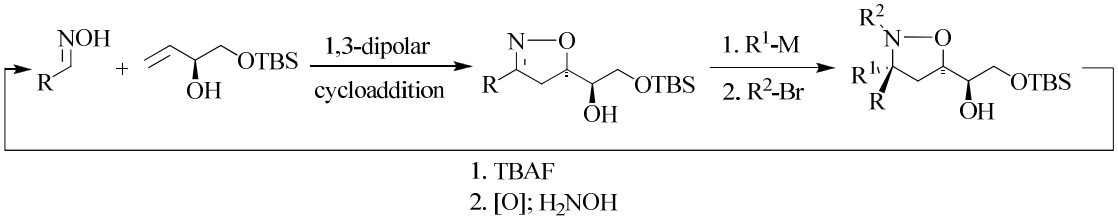
Figure 5-4: Compounds targeted for evaluation as TADs. Compounds containing varying functionality, regiochemistry, and stereochemistry are targeted



5.2 Synthesis of Bisisoxazolidines for Synergystic TAD Activity

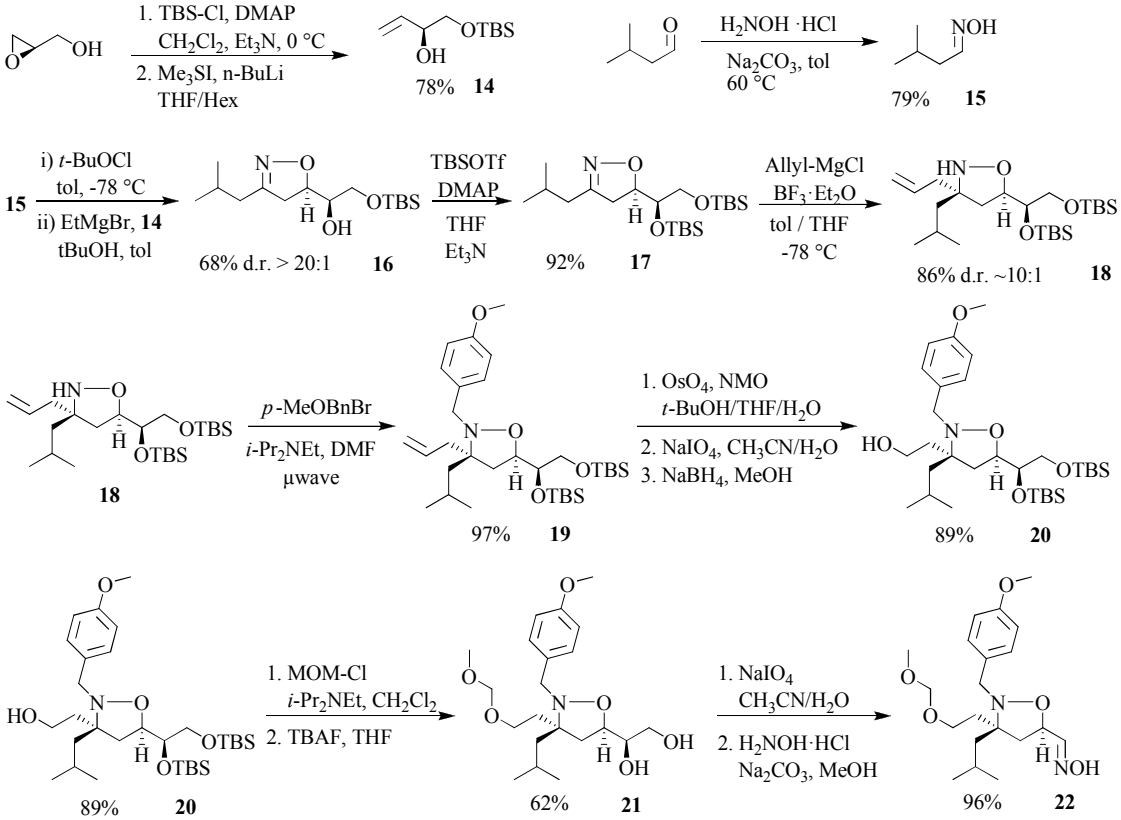
The synthetic strategy for preparation of bisisoxazolidines utilizes an iterative approach to construct the ring system (Figure 5-5). Isoxazolidines can be synthesized from a diastereoselective 1,3-dipolar cycloaddition of an oxime and allylic alcohol to build the heterocyclic scaffold.[5,6,19] Diastereoselective nucleophilic addition functionalizes C3, and alkylation of N2 introduces another substituent. Deprotection and oxidation of the alcohol side chain allows formation of another oxime, and the process is repeated to produce bisisoxazolidines.

Figure 5-5: Synthetic Strategy for Bisisoxazolidine Synthesis



In the forward direction, the commercially available chiral epoxide (R)-glycidol can be protected and ring opened to form a chiral allylic alcohol (**14,** Figure 5-6). Similarly, commercially available 3-methyl-butanal is efficiently converted to an oxime (**15**). Activation of **15** with *tert*-butyl hypochlorite forms a nitrile oxide that subsequently undergoes diastereoselective [3+2] cycloaddition with the allylic alcohol to form isoxazoline **16**. Protection of the free secondary alcohol followed by lewis-acid assisted grignard addition into C=N forms isoxazolidine **17** in excellent yield and good diastereoselectivity. Further functionalization of the isoxazolidine is accomplished by *N*-alkylation under microwave conditions with *p*-methoxybenzyl bromide to generate **18**. The allyl side chain is converted to an alcohol through the three step sequence of dihydroxylation with OsO_4, oxidative cleavage with $NaIO_4$ to form an aldehyde, and then reduction with sodium borohydride. Protection of the newly formed alcohol as a methoxy methyl ether, then silyl deprotection of the C5 diol forms isoxazolidine **21**. Oxidative cleavage with $NaIO_4$ and condensation with hydroxylamine leads to isoxazolidine **22**, fully functionalized for a second cycloaddition.

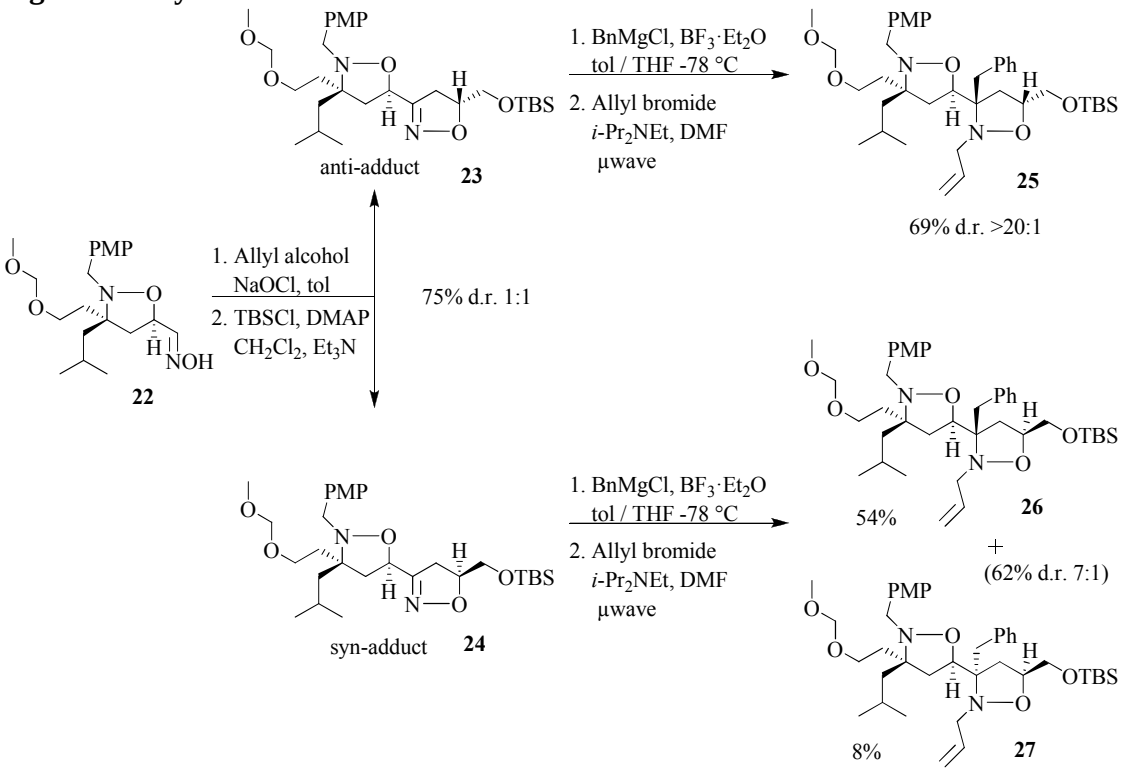
Figure 5-6: Synthesis of the first isoxazolidine ring



Formation of the second bisisoxazolidine ring is accomplished *via* a second [3+2] cycloaddition of the nitrile oxide of **22** with allyl alcohol (Figure 5-7). While previous efforts in the Mapp lab to establish diastereoselective conditions for the second cycloaddition were unsuccessful, both isoxazolidine-isoxazoline diastereomers were desired in order to evaluate the influence of stereochemistry on bisisoxazolidine TAD efficiency. While the initial mixture of *syn* and *anti*-adduct diastereomers were difficult to separate by chromatography on silica gel, silyl protection of the free alcohol led to easily separable diastereomeric products. Stereochemical assignment of the diastereomeric products is assigned based on analogy to the crystalographically established structure of **10** (Figure 5-4).[15] Benzyl grignard addition to *anti*-adduct **23**

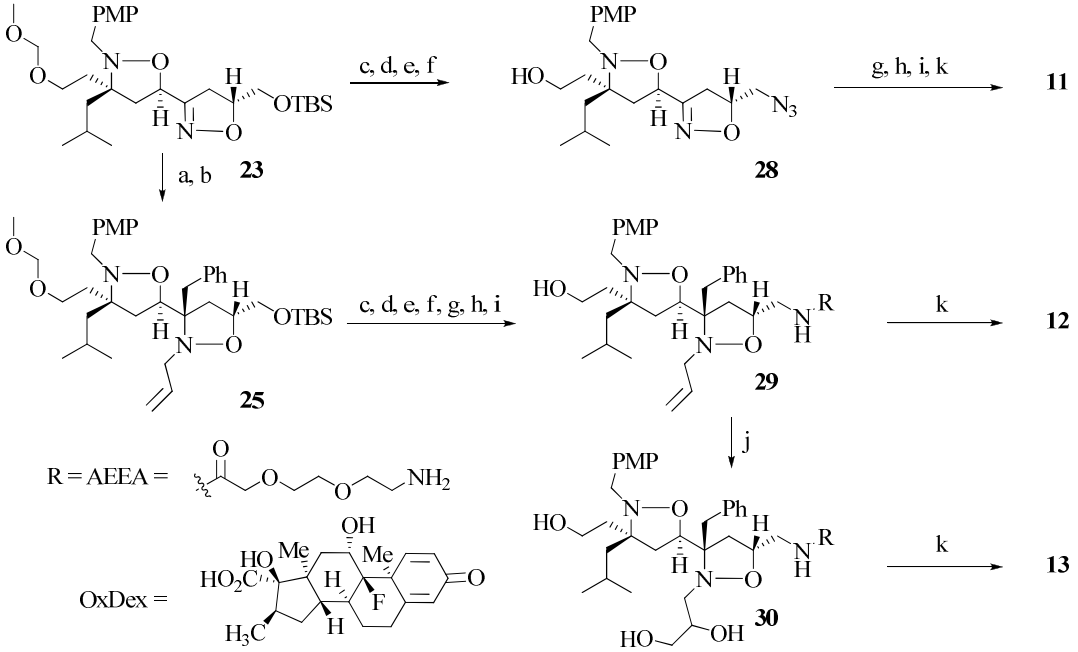
yielded a single diastereomers and provided **25** after microwave assisted *N*-allylation. Conversely, *syn*-adduct **24** provided both diastereomers, **26** and **27**, after *N*-allylation.

Figure 5-7: Synthesis of bisisoxazolidines



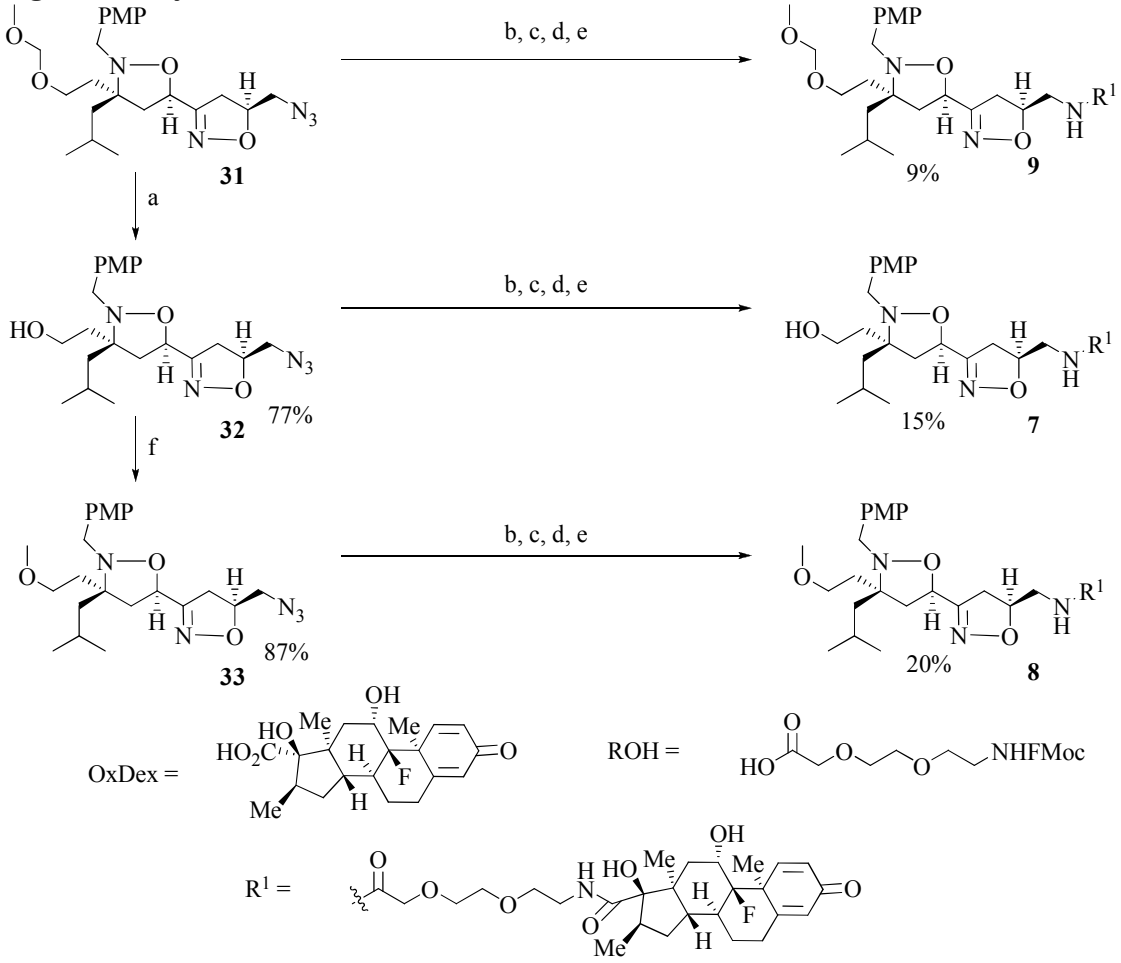
An initial series of bisisoxazolidines was prepared for functional evaluation as TADs by covalently attaching the compounds to oxidized dexamethasone (OxDex) via a short linker fragment (Figure 5-8). Standard functional group conversion and amide-bond formation techniques can be used to prepare appropriate compounds for evaluation in HeLa cell based transcription assays.[16] A similar series of compounds with variable functionalization of the alcohol side chain is shown in Figure 5-9.

Figure 5-8: Preparation of Targeted TADs for Activation Assay



Conditions: a) BnMgCl, BF_3•Et_2O, tol/THF -78 °C; b) Allyl bromide, *i*-Pr_2NEt, DMF, microwave; c) TBAF, THF; d) MsCl, Et_3N, CH_2Cl_2; e) NaN_3, DMSO, 100 °C; f) HCl (aq); g) PPh_3, H_2O, THF, 60 °C; h) ROH, HOBT HBTu, Et_3N; i) 1,3-diaminopropane; j) OsO_4, NMO, THF, H_2O, *t*BuOH; k) OxDex, HOBt, HBTu, Et_3N, DMF.

Figure 5-9: Synthesis of TADs with Variable Alcohol Functionalization



Conditions: a) HCl (aq); b) PPh_3, H_2O, THF, 60 °C; c) ROH, HOBT HBTu, Et_3N; d) 1,3-diaminopropane; e) OxDex, HOBt, HBTu, Et_3N, DMF; f) MeI, CH_2Cl_2, 0 °C.

Another isoxazolidine-isoxazoline TAD was prepared to probe the influence of para-methoxy benzyl N-substitution on the first ring compared to N-benzyl substitution as utilized in **4** (Figure 5-10). Alternatively, a TAD was prepared from a racemic mixture of the original isoxazolidine minor diastereomers (**43**), while a TAD from a racemic mixture of the isoxazolidine major diastereomer was synthesized (**42**, Figure 5-11).

Figure 5-10: Synthesis of a TAD to Probe the Influence of Nitrogen Substitution

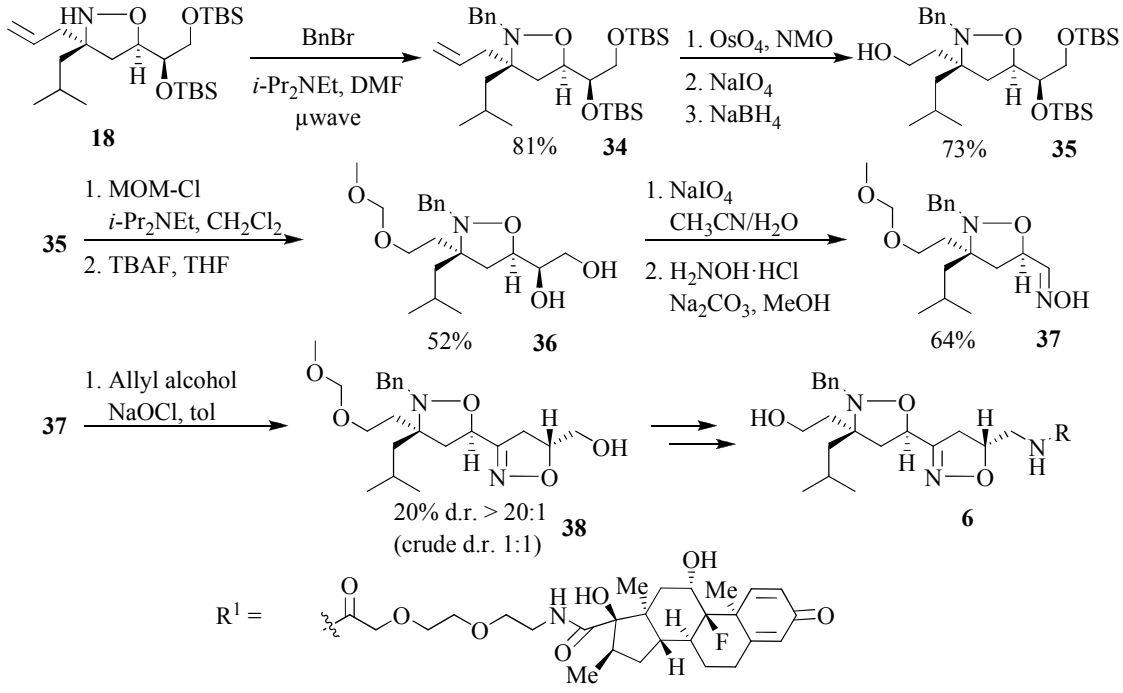
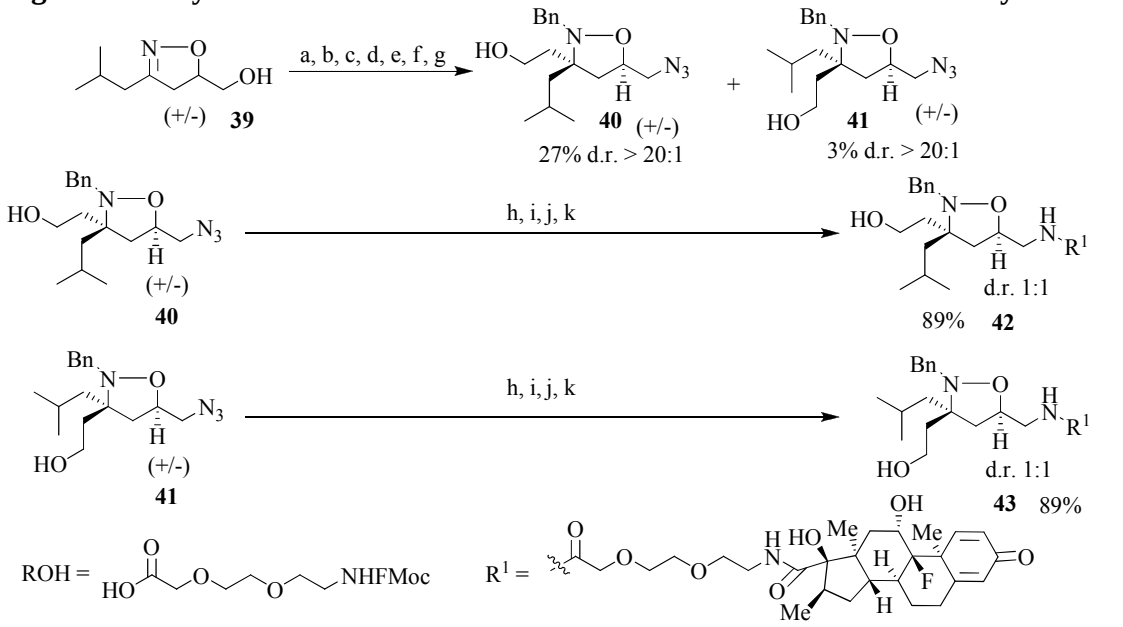


Figure 5-11: Synthesis of Isoxazolidine TADs with Variable Stereochemistry



Conditions: a) Allyl-MgCl, BF_3•Et_2O, tol/THF -78 °C; b) MsCl, Et_3N, CH_2Cl_2; c) NaN_3, DMSO, 100 °C; d) BnBr, *i*-Pr_2NEt, DMF, microwave; e) OsO_4, NMO THF, H_2O, *t*BuOH; f) $NaIO_4$, H_2O, CH_3CN; g) $NaBH_4$, MeOH; h) PPh_3, H_2O, THF, 60 °C; i) ROH, HOBT HBTu, Et_3N; j) 1,3-diaminopropane; k) OxDex, HOBt, HBTu, Et_3N, DMF.

5.3 Functional Evaluation of TADs

The TAD conjugates were assessed in a cell based transcriptional activation assay as a standard dual-reporter luciferase assay.[17] To test small molecule TADs in cells, an appropriate DNA-targeting moiety was required. The assay was established based on a system developed by Kodadek and co-workers in which a fusion protein consisting of the Gal4 DNA binding domain and the minimal ligand binding domain of the glucocorticoid receptor is constitutively expressed in the cells.[18] The small molecule TADs under examination are thus tagged with an oxidized form of dexamethasone (OxDex); upon binding of the TAD-OxDex conjugate, the complex localizes the small molecule to binding sites for Gal4 that control the activity of a reporter gene, firefly luciferase. A measurement of luciferase activity provides direct information regarding the ability of the small molecule to function as a TAD. Results from the luciferase assays in HeLa cell culture suggested that the targeted compounds were ineffective as TADs, producing very minimal increases in the transcriptional activity.

In the course of testing new small molecules for function as TADs, it became necessary to prepare a new batch of our positive control **42**. Two different diastereomers of the isoxazolidine TAD were prepared (Figure 5-11). Surprisingly, the new sample of **42** that I prepared showed no significant activity in the cell based assay. I carefully prepared a total of four batches of **42**, and each one showed no significant activity. Another member of the lab also prepared an inactive sample of **42** while conducting similar activation experiments. Alternatively, Dr. Ryan Casey, another graduate student at the time, later prepared an active batch of **42**. An explanation for this inconsistent activity has not been perfectly established. The Mapp lab is working towards testing the

effective binding of various OxDex conjugates with isolated Glucocorticoid Receptor (GR) in a collaboration with Professor Jorge Iniguez. These experiments will help probe an aspect of the transcriptional activation biological assay to help establish whether there are differences in binding between the active and inactive samples. Differences in binding affinity to the GR could influence activity through a conformational difference in binding or through an affect on trafficking of the liganded complex to the nucleus.

Further experiments have been conducted to functionally evaluate the small library of isoxazolidine-isoxazoline and bisisoxazolidine TAD mimics that I have synthesized. The isoxazolidine-isoxazoline and bisisoxazolidine azide intermediates have been evaluated in some initial NMR based experiments aimed at evaluating binding to components of the transcriptional machinery. Similarly, these compounds have been tested as inhibitors of transcriptional activation in squelching experiments against a VP16-derived activator. While none of these molecules have shown significant functional activity, the Mapp lab has many more targets against which to further evaluate these compounds as transcriptional inhibitors.

5.4 Conclusion

A small library of compounds has been synthesized in an effort to identify potent small molecule TADs. The compounds were designed in an effort to replicate the repetitive display of functionality that is known to generate a greater than additive improvement in potency from natural activators.

Initial functional evaluation of this library of compounds was conducted through a transcriptional activation assay in cells, but none of the compounds showed significant

activity. The resynthesis of a positive control for the activation assay revealed inconsistent activity between different batches of compounds for the assay. Further experiments have been targeted to probe whether the differently activating samples show different binding affinities to a key protein involved in the biological assay.

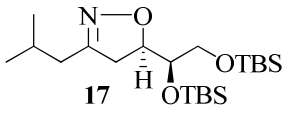
The targeted small molecule TAD mimics have also been evaluated as inhibitors of transcriptional activation through squelching experiments. While these compounds showed no activity against a VP16-derived activator, the Mapp lab is interested in testing their function against many other natural activators.

5.5 Experimental Section

General: Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. CH_2Cl_2, THF, CH_3CN and toluene were dried by passage through activated alumina columns and degassed by stirring under a dry N_2 atmosphere. NMP and DMF were used as purchased without further purification. BF_3•OEt_2 and Et_3N were distilled from CaH_2, MeOH was distilled from sodium metal, and t-BuOH was distilled from $MgSO_4$. All reactions involving air- or moisture-sensitive reagents were performed under a dry N_2 atmosphere. Purification by column chromatography was carried out with E. Merck Silica Gel 60 (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz and 125 MHz, respectively, unless otherwise specified. Reverse-phase HPLC purification was performed on a Varian ProStar 210 equipped with Rainin Dynamax UVD II detector using a C18 (8 x 100 mm) Radial-PakTM cartridge using a gradient of 0.1% TFA in H_2O and CH_3CN as the mobile phase. UVvis spectra were measured in MeOH. In order to

determine the concentration of all methotrexate conjugates (3-7), the characteristic UV-vis absorptions of methotrexate at λ_{max} = 257, 302, and 370 nm with extinction coefficients of 23,000, 22,000, and 7,100 $M^{-1}cm^{-1}$, respectively, was used. Once the concentration was determined, the sample was aliquoted, lyophilized, and stored at –78 °C. The in vitro transcription assays were carried out as previously described.[17] The buffer used for transcription assays contains 5 mM MgCl2, 400 mM of each NTP, 10 µg of salmon sperm carrier DNA, 10 mM HEPES (pH 7.9), 50 mM KCl, 0.1 mM EDTA, 0.25 mM DTT, and 10% glycerol. 3-Methylbutyraldehyde oxime (**15**),[19] (S)-1-(tert-butyldimethylsilyloxy)but-3-en-2-ol (**14**),[20] 2-(tert-Butyl-dimethyl-silanyloxy)-(1R)-1-[(5R)-3-isobutyl-4,5-dihydro-isoxazol-5-yl]-ethanol (**16**),[12b] and **42**[17] were prepared according to published procedures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR.

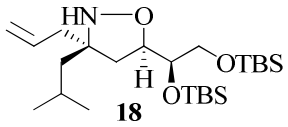
Synthesis of Compounds



17

(R)-3-isobutyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-4,5-dihydroisoxazole (**17**). To a solution of **16** (1.0 equiv) in THF (0.2 M) cooled in an ice-H_2O bath was added DMAP (0.10 eq) and Et_3N (2.2 equiv). TBSOTf (2.2 equiv) was then added dropwise and the solution slowly warmed to ambient temperature. The reaction was complete in 2 h as indicated by TLC analysis. The mixture was again cooled in an ice-H2O bath, diluted with sat. NH_4Cl (15 mL), and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (1 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure

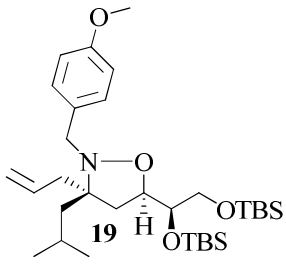
yielded the title compound **17** (10.58 g, 92%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63-4.56 (m, 1 H), 3.71-3.64 (m, 2 H), 3.61-3.54 (m, 1 H), 2.90-2.84 (m, 2 H), 2.25-2.12 (m, 2 H), 1.95-1.83 (m, 1 H), 0.97-0.93 (m, 6 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.06-0.04 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 80.3, 74.1, 64.4, 38.6, 36.7, 26.0, 25.9, 25.8, 22.6, 22.4, 18.3, 18.1, -4.4, -4.8, -5.5, -5.5.



18

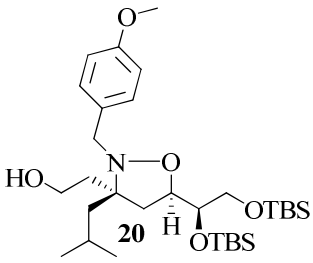
(3S,5R)-3-allyl-3-isobutyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)isoxazolidine (**18**). To a solution of isoxazoline **17** (1.0 eq) in toluene (0.1 M) cooled in a dry ice-acetone bath was added distilled BF_3•OEt_2 (3.0 eq) and the resultant mixture was stirred with continued cooling for 30 min. Allylmagnesium chloride (2.0 M solution in THF, 6.0 eq) was added dropwise over 10 min. The reaction mixture was allowed to stir with continued cooling until the reaction was complete by TLC analysis (6 h). H_2O (10 mL) was added and the mixture stirred for 20 min. H_2O (20 mL) was added and the aqueous and organic layers were separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with H_2O (1 x 20 mL) and brine (1 x 20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. A diastereomeric ratio of 10:1 was determined by crude ^{1}H NMR. This procedure yielded the title compound **18** (2.03 g, 79%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94−5.83 (m, 1 H), 5.11 (d, 6 Hz, 1 H), 5.09 (s, 1 H), 4.30 (t, 7 Hz, 1 H), 3.73 (dd, *J* = 9.5, 11 Hz, 1 H), 3.62−3.57 (m, 2 H), 2.39 (dd, *J* = 7, 15 Hz, 1 H), 2.23 (dd,

J = 8.5, 12.5 Hz, 1 H), 1.89−1.81 (m, 2H), 1.48 (dd, *J* = 6.5, 14 Hz, 1 H), 1.39 (dd, *J* = 6.5, 14 Hz, 1 H), 0.94 (d, *J* = 6.5 Hz, 6 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.11 (s, 6 H), 0.07−0.06 (m, 6 H).



19

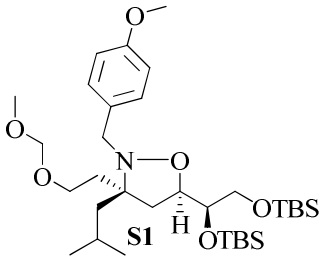
(3S,5R)-3-allyl-3-isobutyl-2-(4-methoxybenzyl)-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)isoxazolidine (**19**). To a solution of isoxazolidine 11 (210 mg, 0.61 mmol, 1.0 eq) in DMF (3.0 mL) was added iPr2NEt (0.31 mL, 1.8 mmol, 3.0 eq) and BnBr (0.48 mL, 3.7 mmol, 6.0 eq). The reaction mixture was irradiated in a 1000 W microwave (6 x 20 s) @ 20% power with mixing between each interval. Upon cooling to ambient temperature the solution was diluted with H2O (3 mL) and extracted with Et2O (3 x 5 mL). The combined organic extracts were washed with H_2O (1 x 5 mL) and brine (1 x 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compound **19** (14.72 g, 93%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2 H), 6.87-6.84 (m, 2 H), 6.02-5.92 (m, 1 H), 5.15-5.12 (m, 1 H), 5.11 (s, 1 H), 4.09 (dt, *J* = 5.0, 8.5 Hz, 1 H), 3.86-3.74 (m, 5 H), 3.71-3.63 (m, 2 H), 3.57 (dd, *J* = 6.0, 10 Hz, 1 H), 2.44-2.28 (m, 2 H), 2.19-2.09 (m, 2 H), 1.97-1.87 (m, 1 H), 1.64 (dd, *J* = 5.0, 14.5 Hz, 1 H), 1.38 (dd, J = 6.5, 14.5 Hz, 1 H), 1.02 (t, *J* = 6.5 Hz, 6 H), 0.91 (s, 18 H), 0.07 (s, 3 H), 0.42-0.29 (m, 6 H), -0.01 (s, 3 H).



20

2-((3S,5R)-3-isobutyl-2-(4-methoxybenzyl)-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)isoxazolidin-3-yl)ethanol (**20**). To a solution of isoxazolidine **19** (14.39 g, 24.9 mmol, 1.0 equiv) in t-BuOH (125 mL), THF (33.5 mL), and H_2O (8.3 mL) was added NMO (3.2 g, 27.4 mmol, 1.1 equiv) followed by OsO_4 (5 ml of a 2.5 wt% solution in t-BuOH, 1.25 mmol, 0.05 equiv). The reaction mixture was stirred at ambient temperature until complete by TLC analysis (24 h). The mixture was cooled in an ice-H_2O bath, Na_2SO_3 was added, and the mixture stirred 1 h. The mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude diol was taken up in 80 mL CH_3CN and 80 mL H_2O and cooled in an ice-H_2O bath. Sodium periodate (8.0 g, 37.3 mmol, 1.5 equiv) was added and the reaction mixture stirred at ambient temperature until complete by TLC analysis (30 min). The reaction mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with H_2O (1 x 50 mL) and brine (1 x 50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude aldehyde thus obtained was dissolved in 150 mL MeOH and cooled in an ice-H_2O bath prior to addition of $NaBH_4$ (1.41 g, 37.3 mmol, 1.5 equiv). Upon completion as noted by TLC analysis (1h), H_2O (50 mL) was added and the reaction extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered

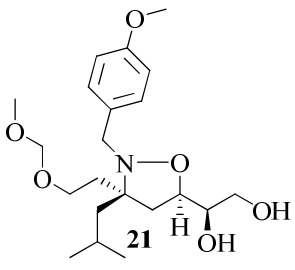
and concentrated in vacuo. This procedure yielded the title compound **20** (12.83 g, 89%) as a yellow oil after purification by chromatography with 20% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2 H), 6.84-6.80 (m, 2 H), 5.45 (bs, 1 H), 4.30-4.24 (m, 1 H), 3.94-3.87 (m, 1 H), 3.86-3.75 (m, 6 H), 3.71-3.66 (m, 1 H), 3.62-3.54 (m, 2 H), 2.27 (dd, *J* = 10, 12.5 Hz, 1 H), 2.08 (dd, *J* = 7.5, 12.5 Hz, 1 H), 2.05-1.97 (m, 1 H), 1.93-1.87 (m, 1 H), 1.77-1.68 (m, 1 H), 1.68-1.60 (m, 1 H), 1.38 (dd, *J* = 8.0, 13.5 Hz, 1 H), 1.02 (d, *J* = 6.5 Hz, 3 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 0.95 (s, 9 H), 0.87 (s, 9 H), 0.15 (s, 3 H), 0.09 (s, 3 H), -0.01 (s, 6 H).



S1

(3S,5R)-3-isobutyl-2-(4-methoxybenzyl)-3-(2-(methoxymethoxy)ethyl)-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)isoxazolidine (**S1**). A flame-dried flask was cooled under a stream of nitrogen and charged with **20** (11.86 g, 20.4 mmol, 1.0 equiv) and CH_2Cl_2. The resulting solution was cooled in an ice-water bath and DIPEA (5.3 mL, 30.6 mmol, 1.5 equiv) was added, followed by MOMCl (2.24 mL, 29.5 mmol, 1.45 equiv) dropwise. The reaction was allowed to come to rt and stired overnight. TLC analysis (20% EtOAc/hexanes) shows some **S1** remaining. The reaction was then cooled in an ice-water bath, and DIPEA (2.7 mL, 0.75 equiv) was added, followed by MOMCl (1.2 mL, 0.7 equiv). The reaction was allowed to warm to rt and stirred 24 h. The reaction was diluted with H_2O (100 mL), extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with 1

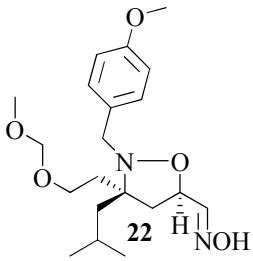
M HCl and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compound **S1** (10.0 g, 78%) as a yellow oil after purification by chromatography with 15% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 9.0 Hz, 2 H), 6.84 (d, *J* = 9.0 Hz, 2 H), 4.64 (s, 2 H), 4.15-4.09 (m, 1 H), 3.82-3.77 (m, 4 H), 3.76-3.70 (m, 3 H), 3.68 (q, *J* = 5.5 Hz, 1 H), 3.62 (dd, *J* = 5.0, 10 Hz, 1 H), 3.55 (dd, *J* = 6.0, 10 Hz, 1 H), 3.38 (s, 3 H), 2.24-2.10 (m, 2 H), 1.99-1.82 (m, 3 H), 1.64 (dd, *J* = 5.0, 14 Hz, 1 H), 1.34 (dd, *J* = 7.0, 14 Hz, 1 H), 1.03 (d, *J* = 7.0 Hz, 3 H), 1.00 (d, *J* = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.02 (m, 6 H), 0.01 (s, 3 H).



21

(R)-1-((3S,5R)-3-isobutyl-2-(4-methoxybenzyl)-3-(2-(methoxymethoxy)ethyl)isoxazolidin-5-yl)ethane-1,2-diol (**21**). A flame-dried flask was cooled under a stream of nitrogen and charged with **S1** (1.0 g, 1.6 mmol, 1.0 equiv) and THF (10 mL). TBAF (3.5 mL, 1 M in THF, 3.5 mmol, 2.2 equiv) was added slowly, and the reaction was stirred until TLC (33% EtOAc/hexanes) indicates reaction completion (2 h). The reaction was diluted with H_2O (10 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with H_2O (1 x 5 mL) and brine (1 x 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compound **21** (0.51 g, 80%) as a clear colorless oil after purification by chromatography with 66% EtOAc/hexanes as the eluant. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5

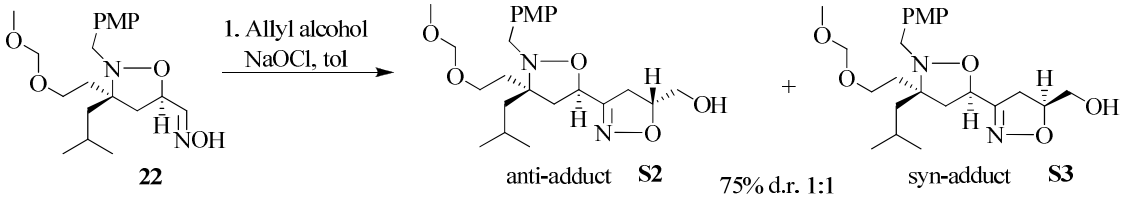
Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 4.60 (s, 2 H), 4.02-3.95 (m, 1 H), 3.80-3.72 (m, 5 H), 3.71 (s, 1 H), 3.68-3.60 (m, 1 H), 3.55-3.45 (m, 2 H), 3.44-3.38 (m, 1 H), 3.34 (s, 3 H), 3.23 (s, br, 1 H), 2.56 (s, br, 1 H), 2.33 (dd, *J* = 8.5, 12.4 Hz, 1 H), 2.18 (dd, *J* = 5.5, 12.4 Hz, 1 H), 1.98-1.78 (m, 3 H), 1.58 (dd, *J* = 4.5, 14.5 Hz, 1 H), 1.37 (dd, *J* = 7.0, 14.5 Hz, 1 H), 0.97 (t, *J* = 6.0 Hz, 6 H).



22

3-isobutyl-2-(4-methoxybenzyl)-3-(2-(methoxymethoxy)ethyl)isoxazolidine-5-carbaldehyde oxime (**22**). A flame-dried flask was cooled under a stream of nitrogen and charged with **21** (0.508 g, 1.28 mmol, 1.0 equiv), CH_3CN (5 mL), and H_2O (5 mL). Sodium periodate (0.424 g, 2 mmol, 1.5 equiv) was added and the reaction was stirred until TLC shows reaction completion (1 h). The reaction was diluted with H_2O (10 mL), extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude aldehydes intermediate was dissolved in MeOH (10 mL), and hydroxylamine•HCl (0.107 g, 1.5 mmol, 1.2 equiv) and potassium carbonate (0.213 g, 1.5 mmol, 1.2 equiv) were added. The reaction was stirred for 2 h, then the reaction was diluted with H_2O (10 mL), extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compound **22** (0.468 g, 96%) as a yellow oil after workup. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (s, 1 H), 7.33-7.29 (m, 2 H), 6.91-6.86 (m, 2

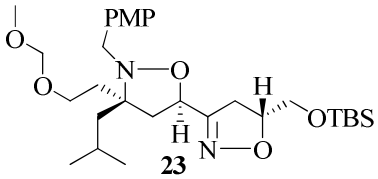
H), 4.65 (s, 2 H), 4.19 (dd, *J* = 5.5, 12 Hz, 1 H), 3.83-3.80 (m, 5 H), 3.80-3.65 (m, 3 H), 3.39 (s, 3 H), 2.52 (dd, *J* = 12, 16 Hz, 1 H), 2.38 (dd, *J* = 5.5, 16 Hz, 1 H), 2.04-1.94 (m, 1 H), 1.94-1.84 (m, 1 H), 1.84-1.74 (m, 1 H), 1.59 (dd, *J* = 6, 18 Hz, 1 H), 1.33 (dd, *J* = 8.5, 18 Hz, 1 H), 0.97 (dd, *J* = 8.5, 10.5 Hz, 6 H).



((R)-3-((3S,5R)-3-(2-(methoxymethoxy)ethyl)-2-(4-methoxybenzyl)-3-isobutylisoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)methanol (**S2**) and ((S)-3-((3S,5R)-3-(2-(methoxymethoxy)ethyl)-2-(4-methoxybenzyl)-3-isobutylisoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)methanol (**S3**). A flame-dried flask was cooled under a stream of nitrogen and charged with oxime (**22**, 468 mg, 1.23 mmol, 1.0 equiv) and toluene (10 mL). The solution was cooled in an ice-water bath, then allyl alcohol (0.84 mL, 12.3 mmol, 10 equiv) was added, followed by sodium hypochlorite (4.13 mL, 744 mM, 3.1 mmol, 2.5 equiv) dropwise over 20 min. A white precipitate forms and the reaction is stirred for 1 h. The reaction was diluted with H_2O (10 mL), extracted with Et_2O (4 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compounds **S2** (0.145 g, 27%) and **S3** (0.129 g, 24%) as clear colorless oils after purification by chromatography with 50% EtOAc/hexanes as the eluant and HPLC gradiation separated the diastereomers. **S2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 2 H),

4.72 (dd, *J* = 6.5, 8.0 Hz, 1 H), 4.62 (s, 2 H), 4.61-4.53 (m, 1 H), 3.81-3.66 (m, 7 H), 3.61 (d, br, *J* = 12 Hz, 1 H), 3.49 (dd, *J* = 5.0, 12 Hz, 1 H), 3.37 (s, 3 H), 2.82 (dd, *J* = 11, 17.5 Hz, 1 H), 2.70 (dd, *J* = 7.5, 17.5 Hz, 1 H), 2.53 (dd, *J* = 8.5, 13 Hz, 1 H), 2.49-2.39 (m, 2 H), 1.99-181 (m, 3 H), 1.61 (dd, *J* = 5.0, 14.5 Hz, 1 H), 1.36 (dd, *J* = 7.0, 14.5 Hz, 1 H), 0.99 (t, *J* = 6.0 Hz, 6 H).

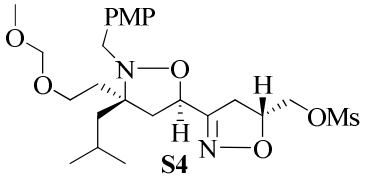
S3: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 4.70 (t, *J* = 7.5 Hz, 1 H), 4.64-4.57 (m, 3 H), 3.77 (s, 3 H), 3.76 (s, br, 2 H), 3.74-3.68 (m, 2 H), 3.59 (d, br, *J* = 11 Hz, 1 H), 3.45 (d, br, *J* = 11 Hz, 1 H), 3.37 (s, 3 H), 2.84 (dd, *J* = 11, 17.5 Hz, 1 H), 2.65 (dd, *J* = 7.5, 17.5 Hz, 1 H), 2.52 (d, *J* = 7.5 Hz, 2 H), 2.39 (s, br, 1 H), 1.98-1.89 (m, 2 H), 1.89-1.81 (m, 1 H), 1.63 (dd, *J* = 5.0, 14.5 Hz, 1 H), 1.37 (dd, *J* = 7.0, 14.5 Hz, 1 H), 0.99 (t, *J* = 7.0 Hz, 6 H).



23

((R)-3-((3S,5R)-3-(2-(methoxymethoxy)ethyl)-2-(4-methoxybenzyl)-3-isobutylisoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)(tert-butyldimethylsilyloxy)methane (**23**). A flame-dried flask was cooled under a stream of nitrogen and charged with **S2** (15 mg, 0.034 mmol, 1 equiv) and CH_2Cl_2 (0.2 mL). The solution was cooled in an ice-water bath and DMAP (0.2 mg, 0.001 mmol, 0.04 equiv) and Et_3N (9.4 μL, 0.069 mmol, 2.0 equiv) were added, followed by TBSCl (9.8 mg, 0.065 mmol, 1.9 equiv). A white precipitate forms, and the reaction is stirred until TLC indicates completion (2 h). The reaction is filtered, diluted with water, extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were washed with brine, dried

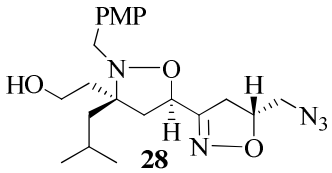
over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compound **23** (0.014 g, 74%) as a clear colorless oil after purification by chromatography with 15% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 4.79 (t, *J* = 8.0 Hz, 1 H), 4.64 (s, 2 H), 4.59-4.52 (m, 1 H), 3.84-3.70 (m, 7 H), 3.67 (dd, *J* = 5.0, 11.0 Hz, 1 H), 3.61 (dd, *J* = 5.0, 11.0 Hz, 1 H), 3.39 (s, 3 H), 2.85 (d, *J* = 9.0 Hz, 1 H), 2.55 (dd, *J* = 9.0, 12.5 Hz, 1 H), 2.41 (dd, *J* = 6.0, 13 Hz, 1 H), 2.01-183 (m, 3 H), 1.63 (dd, *J* = 5.0, 14.5 Hz, 1 H), 1.39 (dd, *J* = 7.0, 14.5 Hz, 1 H), 1.01 (t, *J* = 6.5 Hz, 6 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H).



S4

((R)-3-((3S,5R)-3-(2-(methoxymethoxy)ethyl)-2-(4-methoxybenzyl)-3-isobutylisoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)-methyl methanesulfonate (**S4**). A flame-dried flask was cooled under a stream of nitrogen and charged with **S2** (17.6 mg, 0.040 mmol, 1.0 equiv) and dichloromethane (1.0 mL, 0.1 M). The solution is cooled in an ice-water bath and Et_3N (16 μL, 0.117 mmol, 1.1 equiv) is added. Methylsulfonyl chloride (9 μL, 0.117 mmol, 1.1 equiv) is added, and the reaction is stirred until ESI-MS indicates reaction completion (1 h). The reaction is diluted with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 6 mL). The combined organic extracts were washed with aq. 1 M HCl, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compound **S4** (0.014 g, 68%) as a yellow oil after workup. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 4.74 (t, *J* = 7.0 Hz, 1 H), 4.70-4.62 (m, 3 H), 3.84-3.68

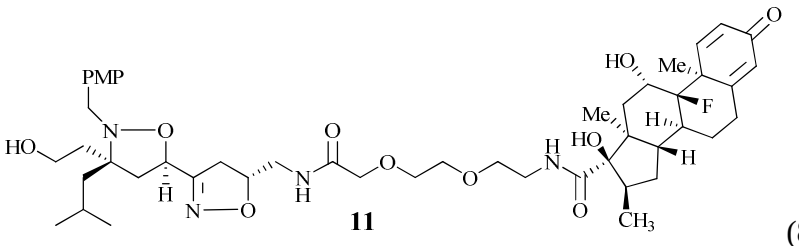
(m, 7 H), 3.40 (s, 3 H), 3.32 (dd, *J* = 4.0, 13.0 Hz, 1 H), 3.24 (dd, *J* = 5.5, 13.0 Hz, 1 H), 2.88 (dd, *J* = 11.0, 17.5 Hz, 1 H), 2.69 (dd, *J* = 6.5, 17.5 Hz, 1 H), 2.64-2.53 (m, 2 H), 2.03-195 (m, 1 H), 1.95-1.86 (m, 2 H), 1.64 (dd, *J* = 5.0, 15.0 Hz, 1 H), 1.40 (dd, *J* = 7.0, 14.5 Hz, 1 H), 1.02 (d, *J* = 6.5 Hz, 6 H).



28

2-((3S,5R)-5-((R)-5-(azidomethyl)-4,5-dihydroisoxazol-3-yl)-3-isobutyl-2-(4-methoxybenzyl)isoxazolidin-3-yl)ethanol (**28**). A flame-dried flask was cooled under a stream of nitrogen and charged with **S4** (14.0 mg, 0.027 mmol, 1 equiv), sodium azide (17.7 mg, 0.27 mmol, 10 equiv), and DMSO (0.27 mL, 0.1 M). The reaction flask was attached to a reflux condenser and heated to 100℃ for 3 h. The reaction was diluted with sat. aq. ammonium chloride (5 mL) and extracted with EtOAc (4 x 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a protected azide intermediate. The crude clear colorless oil was dissolved in isopropanol (0.25 mL) and conc. aq HCl (0.05 mL) was added. The solution was stirred until ESI-MS indicates reaction completion (6 h). The reaction was diluted with sat. aq. ammonium chloride (5 mL), extracted with EtOAc (4 x 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded compound **28** (0.0048 g, 58%%) as a clear colorless oil after after purification by chromatography with 2% MeOH/CH_2Cl_2 as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 4.79 (t, *J* = 8.0 Hz, 1 H), 4.76-4.69 (m, 1 H), 3.97 (d, *J* = 14.0

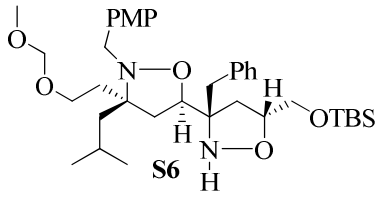
Hz, 1 H), 3.93-3.86 (m, 1 H), 3.86-3.75 (m, 5 H), 3.40 (dd, *J* = 3.5, 13.0 Hz, 1 H), 3.30 (dd, *J* = 5.0, 13.0 Hz, 1 H), 2.99-2.90 (m, 1 H), 2.82-2.68 (m, 2 H), 2.55 (dd, *J* = 8.5, 13.5 Hz, 1 H), 2.06-1.94 (m, 1 H), 1.88-1.72 (m, 3 H), 1.46 (dd, *J* = 8.5, 13.5 Hz, 1 H), 1.02 (dd, *J* = 2.0, 6.5 Hz, 6 H).



11

(8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-N-(2-(2-(2-(((R)-3-((3S,5R)-3-(2-hydroxyethyl)-3-isobutyl-2-(4-methoxybenzyl)isoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)methylamino)-2-oxoethoxy)ethoxy)ethyl)-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthrene-17-carboxamide (**11**). A flame-dried flask was cooled under a stream of nitrogen and charged with **28** (4.8 mg, 0.011 mmol, 1 equiv), triphenyl phosphine (6.0 mg, 0.023 mmol, 2.0 equiv), and THF (0.2 mL). The reaction was heated under a reflux condenser to 85℃ for 2 h. The mixture was allowed to cool to rt and was then transferred into a biphasic mixture of 1 M HCl (10 mL) and ether (10 mL). The layers were partitioned and the organic layer was extracted with 1 M HCl (2× 10 mL). The combined aqueous layers were basified with 3 M NaOH (until pH 10 or greater). The aqueous mixture was then extracted with CH_2Cl_2 (3× 15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. To a solution of 8-(9-fluorenylmethyloxycarbonyl-amino)-3,6-dioxaoctanoic acid (18 mg, 0.045 mmol, 3.0 equiv) dissolved in NMP (0.067 mL) were

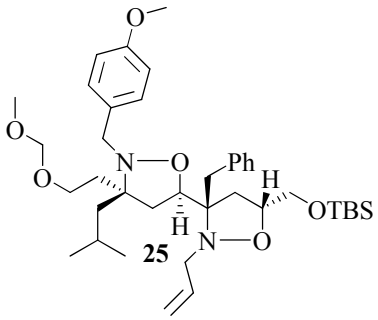
added HOBt (6.3 mg, 0.045 mmol, 3.0 equiv based) and HBTU (17 mg, 0.045 mmol, 3.0 equiv). This solution was agitated for 15 min. The solution of activated ester was added to the crude amine dissolved in NMP (0.067 mL) and the resulting mixture was allowed to stir for 12 h at which time the reaction was complete as judged by ESI-MS analysis. Excess reagents were quenched by the addition of 1M HCl (10 mL) and EtOAc (10 mL). The reaction vessel was washed with EtOAc (2 x 2 mL) to remove all residues. The resulting biphasic mixture was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oil was dissolved in a solution of 20% piperidine in DMF (0.037 mL, 0.076 mmol piperidine, 5.0 equiv) and was allowed to stir for 30 minutes. The resulting solution was diluted with aq 0.1% TFA (0.50 mL) and CH_3CN (0.50 mL) and partially purified by reverse-phase HPLC to remove Fmoc byproducts. The partially purified amine was used immediately in subsequent steps. To a solution of OxDex[21] (17 mg, 0.045 mmol, 3.0 equiv) dissolved in NMP (0.15 mL) were added HOBt (6.2 mg, 0.045 mmol, 3.0 equiv) and HBTU (17 mg, 0.045 mmol, 3.0 equiv) and the resulting mixture was agitated for 15 min. To this solution were added the amine dissolved in NMP (0.15 mL), 2,6-lutidine (35 μL, 0.30 mmol, 6.7 equiv), and DIPEA (49 μL, 0.30 mmol, 6.7 equiv). The resulting mixture was stirred for 12 h at rt. The product was isolated by reverse-phase HPLC purification to provide **11** as a white solid (2.7 mg, 26%). The purity of compound **11** was confirmed by analytical reverse-phase HPLC analysis. The identity was verified by mass spectral analysis of the isolated compound. LRMS (ESI) calcd for $[C_{48}H_{69}FN_4O_{11} + H]^+$: 897, found: 897.



S6

(3S,3'S,5R,5'R)-3-benzyl-5-((tert-butyldimethylsilyloxy)methyl)-3'-isobutyl-2'-(4-methoxybenzyl)-3'-(2-(methoxymethoxy)ethyl)-3,5'-biisoxazolidine (**S6**). A solution of compound **23** (109 mg, 0.198 mmol, 1.0 equiv) in toluene (2.8 mL) was cooled in a dry ice-acetone bath. BF_3•OEt_2 (75 μl, 0.59 mmol, 3.0 eq) was added dropwise over 15 min and the mixture was stirred with continued cooling for 30 min. Benzylmagnesium chloride (0.5 mL of a 2.0 M solution in THF, 1.0 mmol, 5.0 eq) was added dropwise over 30 min. The reaction mixture was stirred for 4 h with continued cooling at which point TLC analysis indicated complete consumption of starting material. Saturated aqueous NH_4Cl (5 mL) was added to the reaction and the resultant solution was transferred to an ice-H_2O bath. After slowly warming to rt the mixture was diluted with H_2O (5 mL) and Et_2O (5 mL) and the organic and aqueous layers separated. The aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compound **S6** (0.094 g, 73%) as a clear colorless oil after purification by chromatography with 15% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5 H), 7.19-7.14 (m, 2 H), 6.89-6.84 (m, 2 H), 6.02 (s, br, 1 H), 4.65 (s, 2 H), 4.10 (s, br, 1 H), 4.06-3.98 (m, 1 H), 3.82-3.72 (m, 5 H), 3.70-3.62 (m, 2 H), 3.39 (s, 3 H), 3.30-3.00 (m, 2 H), 2.85 (s, 2 H), 2.48-2.38 (m, 1 H), 2.32 (dd, *J* = 8.5, 12.5 Hz, 1 H), 2.08 (dd, *J* = 7.5, 12.5 Hz, 1 H), 2.02-1.78 (m,

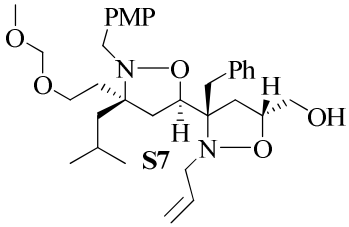
4 H), 1.67 (s, br, 1 H), 1.58 (dd, *J* = 5.0, 14.5 Hz, 1 H), 1.44-1.38 (m, 1 H), 1.01 (d, *J* = 6.5 Hz, 6 H), 0.87 (s, 9 H), 0.01 (s, 3 H), -0.01 (s, 3 H).



25

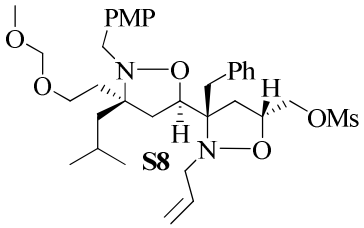
(3S,3'S,5R,5'R)-2-allyl-3-benzyl-5-((tert-butyldimethylsilyloxy)methyl)-3'-isobutyl-2'-(4-methoxybenzyl)-3'-(2-(methoxymethoxy)ethyl)-3,5'-biisoxazolidine (**25**). A flame-dried flask was cooled under a stream of nitrogen and charged with **S6** (94 mg, 0.145 mmol, 1 equiv), allyl bromide (126 μL, 1.46 mmol, 10 equiv), DIPEA (76 μL, 0.439 mmol, 3 equiv), and DMF (0.4 mL). The solution was irradiated in a 1000 W microwave at 10% power (10 x 10 s) with cooling and stirring between each interval until TLC shows reaction completion. Upon cooling to rt, the mixture was diluted with H_2O (5 ml) and extracted with Et_2O (3 x 5 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compound **25** (0.093 g, 94%) as a clear colorless oil after purification by chromatography with 7% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 9.0 Hz, 2 H), 7.24-7.15 (m, 5 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 5.95-5.85 (m, 1 H), 5.16-5.10 (m, 1 H), 5.09-5.03 (m, 1 H), 4.66 (s, 2 H), 4.31-4.24 (m, 1 H), 3.83-3.70 (m, 8 H), 3.62-3.50 (m, 3 H), 3.40 (s, 3 H), 3.39-3.33 (m, 1 H), 3.22 (dd, *J* = 6.5, 15.5 Hz, 1 H), 2.88 (d, *J* = 14.0 Hz, 1 H), 2.80 (d, *J* =14.0 Hz, 1 H), 2.28 (dd, *J* = 8.0, 12.5 Hz, 1 H), 2.20 (dd, *J* = 7.5, 12.5 Hz, 1 H), 2.06 (s, 2 H),

2.05-1.87 (m, 5 H), 1.78-1.71 (m, 1 H), 1.67-1.56 (m, 2 H), 1.51-1.44 (m, 1 H), 1.06 (d, *J* = 6.5 Hz, 3 H), 1.03 (d, *J* = 6.5 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H).



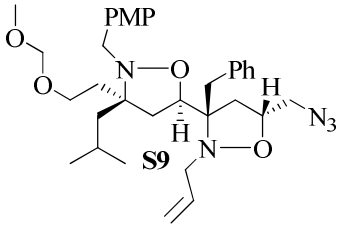
S7

((3S,3'S,5R,5'R)-2-allyl-3-benzyl-3'-isobutyl-2'-(4-methoxybenzyl)-3'-(2-(methoxymethoxy)ethyl)-3,5'-biisoxazolidin-5-yl)methanol (**S7**). The reaction of **25** was conducted using a procedure analogous to that described above for the preparation of **21**. This procedure yielded the title compound **S7** (0.061 g, 78%) as a clear colorless oil after purification by chromatography with 33% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 2 H), 7.25-7.17 (m, 5 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 5.96-5.86 (m, 1 H), 5.19-5.13 (m, 1 H), 5.12-5.07 (m, 1 H), 4.66 (s, 2 H), 4.24 (t, *J* = 8.0 Hz, 1 H), 3.83-3.78 (m, 4 H), 3.78-3.70 (m, 4 H), 3.69-3.64 (m, 1 H), 3.64-3.58 (m, 1 H), 3.48-3.39 (m, 5 H), 3.29 (dd, *J* = 6.0, 15.5 Hz, 1 H), 2.90 (d, *J* = 14.5 Hz, 1 H), 2.82 (d, *J* =14.5 Hz, 1 H), 2.30 (dd, *J* = 8.0, 12.5 Hz, 1 H), 2.26-2.14 (m, 2 H), 2.08 (dd, *J* = 7.5, 12.5 Hz, 1 H), 2.03-1.80 (m, 5 H), 1.62 (dd, *J* = 5.5, 14.5 Hz, 1 H), 1.48 (dd, *J* = 5.5, 14.5 Hz, 1 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 1.02 (d, *J* = 7.0 Hz, 3 H).



S8

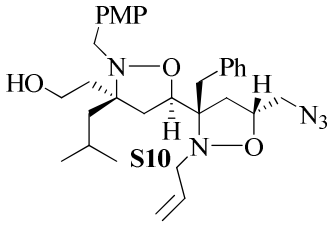
((3S,3'S,5R,5'R)-2-allyl-3-benzyl-3'-isobutyl-2'-(4-methoxybenzyl)-3'-(2-(methoxymethoxy)ethyl)-3,5'-biisoxazolidin-5-yl)methyl methanesulfonate (**S8**). The reaction of **S7** was conducted using a procedure analogous to that described above for the preparation of **S4**. This procedure yielded the title compound **S8** (0.053 g, 77%) as a yellow. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.12 (m, 5 H), 7.11-7.08 (m, 2 H) 6.78 (d, *J* = 9.0 Hz, 2 H), 5.86-5.76 (m, 1 H), 5.12-5.05 (m, 1 H), 5.04-4.99 (m, 1 H), 4.61 (s, 2 H), 4.18 (t, *J* = 8.0 Hz, 1 H), 4.13 (dd, *J* = 6.5, 11.5 Hz, 1 H), 4.03 (dd, *J* = 3.0, 11.5 Hz, 1 H), 3.76-3.63 (m, 8 H), 3.42-3.33 (m, 4 H), 3.25-3.18 (m, 1 H), 2.96 (s, 3 H), 2.82 (d, *J* = 14.0 Hz, 1 H), 2.75 (d, *J* =14.0 Hz, 1 H), 2.27 (dd, *J* = 8.0, 12.5 Hz, 1 H), 2.16-2.04 (m, 2 H), 1.98-1.90 (m, 1 H), 1.90-1.80 (m, 2 H), 1.64-1.55 (m, 2 H), 1.00 (d, *J* = 7.0 Hz, 3 H), 0.97 (d, *J* = 7.0 Hz, 3 H).



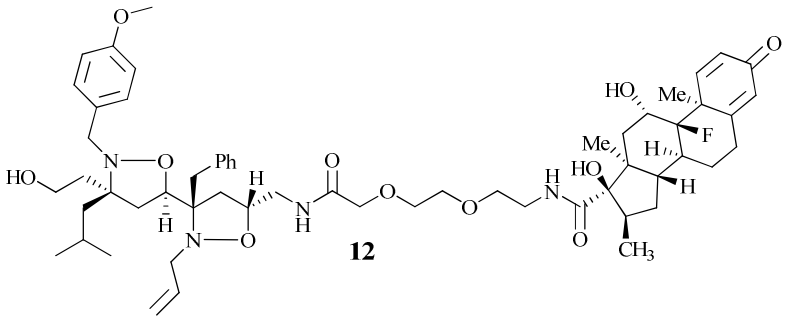
S9

(3S,3'S,5R,5'R)-2-allyl-5-(azidomethyl)-3-benzyl-3'-isobutyl-2'-(4-methoxybenzyl)-3'-(2-(methoxymethoxy)ethyl)-3,5'-biisoxazolidine (**S9**). The reaction of **S8** was conducted using a procedure analogous to that described above for the preparation of **28**. This procedure yielded the title compound **S9** (0.043 g, 84%) as a clear colorless oil after purification by chromatography with 15% EtOAc/hexanes as the

eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.0 Hz, 2 H), 7.25-7.14 (m, 5 H), 6.85 (d, *J* = 9.0 Hz, 2 H), 5.95-5.85 (m, 1 H), 5.19-5.12 (m, 1 H), 5.11-5.07 (m, 1 H), 4.66 (s, 2 H), 4.28 (t, *J* = 8.0 Hz, 1 H), 3.82-3.70 (m, 7 H), 3.68- 3.62 (m, 1 H), 3.46-3.39 (m, 4 H), 3.29-3.17 (m, 3 H), 2.88 (d, *J* = 14.0 Hz, 1 H), 2.80 (d, *J* =14.0 Hz, 1 H), 2.32 (dd, *J* = 8.0, 12.5 Hz, 1 H), 2.22 (dd, *J* = 8.5, 12.5 Hz, 1 H), 2.07 (dd, *J* = 8.5, 12.5 Hz, 1 H), 2.04-1.97 (m, 1 H), 1.96-1.86 (m, 2 H), 1.74 (dd, *J* = 7.5, 13.0 Hz, 1 H), 1.64 (dd, *J* = 5.5, 14.0 Hz, 1 H), 1.46 (dd, *J* = 5.5, 14.0 Hz, 1 H), 1.06 (d, *J* = 6.5 Hz, 3 H), 1.03 (d, *J* = 6.5 Hz, 3 H).

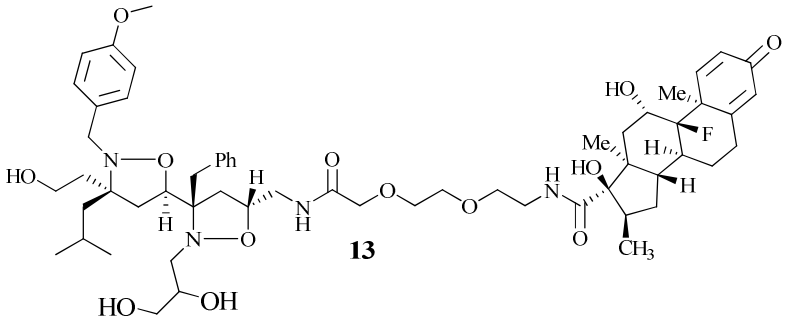


2-((3S,3'S,5R,5'R)-2-allyl-5-(azidomethyl)-3-benzyl-3'-isobutyl-2'-(4-methoxybenzyl)-3,5'-biisoxazolidin-3'-yl)ethanol (**S10**). The reaction of **S9** was conducted using a procedure analogous to that described above for the preparation of **28**. This procedure yielded the title compound **S10** (0.013 g, 67%) as a clear colorless oil after purification by chromatography with 3% MeOH/CH2Cl2 as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.19 (m, 6 H), 7.17-7.13 (m, 1 H), 6.91-6.85 (m, 2 H), 5.96-5.86 (m, 1 H), 5.19-5.08 (m, 2 H), 4.39-4.33 (m, 1 H), 4.24-4.14 (m, 1 H), 4.04-3.90 (m, 2 H), 3.89-3.62 (m, 8 H), 3.47-3.40 (m, 1 H), 3.31-3.10 (m, 3 H)4.28 (t, *J* = 8.0 Hz, 1 H), 3.82-3.70 (m, 7 H), 3.68- 3.62 (m, 1 H), 3.46-3.39 (m, 4 H), 3.29-3.02 (m, 4 H), 3.00-2.90 (m, 1 H), 2.86-2.76 (m, 1 H), 2.42-2.28 (m, 1 H), 2.23-2.09 (m, 2 H), 1.96-1.82 (m, 2 H), 1.82-1.70 (m, 2 H), 1.70-1.56 (m, 3 H), 1.08-1.04 (m, 6 H).



12

(8S,9R,10S,11S,13S,14S,16R,17R)-N-(2-(2-(2-(((3S,3'S,5R,5'R)-2-allyl-3-benzyl-3'-(2-hydroxyethyl)-3'-isobutyl-2'-(4-methoxybenzyl)-3,5'-biisoxazolidin-5-yl)methylamino)-2-oxoethoxy)ethoxy)ethyl)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthrene-17-carboxamide (**12**). The reaction of **S10** was conducted using a procedure analogous to that described above for the preparation of **11**. This procedure yielded the title compound **12** (2.5 mg, 25%) as a white solid. The purity of compound **12** was confirmed by analytical reverse-phase HPLC analysis. The identity was verified by mass spectral analysis of the isolated compound. LRMS (ESI) calcd for $[C_{58}H_{81}FN_4O_{11} + H]^+$: 1030, found: 1030.

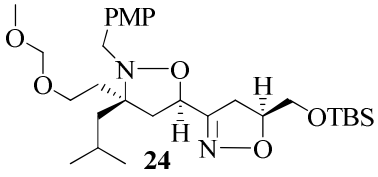


13

(8S,9R,10S,11S,13S,14S,16R,17R)-N-(2-(2-(2-(((3S,3'S,5R,5'R)-3-benzyl-2-(2,3-dihydroxypropyl)-3'-(2-hydroxyethyl)-3'-isobutyl-2'-(4-methoxybenzyl)-3,5'-

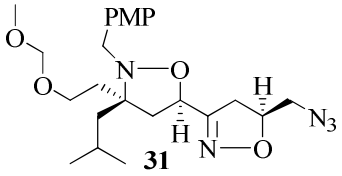
biisoxazolidin-5-yl)methylamino)-2-oxoethoxy)ethoxy)ethyl)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthrene-17-carboxamide (**13**). A flame-dried flask was cooled under a stream of nitrogen and charged with **S10** (19.0 mg, 0.035 mmol, 1 equiv), triphenyl phosphine (18 mg, 0.070 mmol, 2.0 equiv), and THF (0.35 mL). The reaction was heated under a reflux condenser to 85℃ for 2 h. The mixture was allowed to cool to rt and was then transferred into a biphasic mixture of 1 M HCl (10 mL) and ether (10 mL). The layers were partitioned and the organic layer was extracted with 1 M HCl (2× 10 mL). The combined aqueous layers were basified with 3 M NaOH (until pH 10 or greater). The aqueous mixture was then extracted with CH_2Cl_2 (3× 15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. To a solution of 8-(9-fluorenylmethyloxycarbonyl-amino)-3,6-dioxaoctanoic acid (20 mg, 0.05 mmol, 1.5 equiv) dissolved in NMP (0.067 mL) were added HOBt (7.0 mg, 0.05 mmol, 1.5 equiv based) and HBTU (20 mg, 0.05 mmol, 1.5 equiv). This solution was agitated for 15 min. The solution of activated ester was added to the crude amine dissolved in NMP (0.067 mL) and the resulting mixture was allowed to stir for 12 h at which time the reaction was complete as judged by ESI-MS analysis. Excess reagents were quenched by the addition of 1M HCl (10 mL) and EtOAc (10 mL). The reaction vessel was washed with EtOAc (2 x 2 mL) to remove all residues. The resulting biphasic mixture was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oil was dissolved in a solution of 20% piperidine in DMF (0.037 mL, 0.076 mmol piperidine, 5.0 equiv) and was allowed to stir for 30 minutes. The resulting

solution was diluted with aq 0.1% TFA (0.50 mL) and CH_3CN (0.50 mL) and partially purified by reverse-phase HPLC to remove Fmoc byproducts. The partially purified amine was used immediately in subsequent steps. The amine product was then dissolved in t-BuOH (0.3 mL), THF (0.1 mL), and H_2O (30 μL), then NMO (1.1 mg, 8.9 μmol, 1.1 equiv) was added followed by OsO_4 (3 μl of a 2.5 wt% solution in t-BuOH, 0.9 μmol, 0.1 equiv). The reaction mixture was stirred at ambient temperature until complete by ESI-MS analysis (1 h). The mixture was cooled in an ice-H_2O bath, Na_2SO_3 was added, and the mixture stirred 1 h. The mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to yield a trihydroxyamine. To a solution of OxDex[22] (17 mg, 0.045 mmol, 3.0 equiv) dissolved in NMP (0.15 mL) were added HOBt (6.2 mg, 0.045 mmol, 3.0 equiv) and HBTU (17 mg, 0.045 mmol, 3.0 equiv) and the resulting mixture was agitated for 15 min. To this solution were added the trihydroxyamine dissolved in NMP (0.15 mL), 2,6-lutidine (35 μL, 0.30 mmol, 6.7 equiv), and DIPEA (49 μL, 0.30 mmol, 6.7 equiv). The resulting mixture was stirred for 12 h at rt. The product was isolated by reverse-phase HPLC purification to provide **13** as a white solid (0.8 mg, 9%). The purity of compound **13** was confirmed by analytical reverse-phase HPLC analysis. The identity was verified by mass spectral analysis of the isolated compound. LRMS (ESI) calcd for $[C_{58}H_{83}FN_4O_{13} + H]^+$: 1064, found: 1064.



24

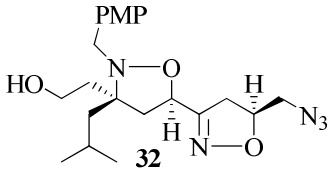
(S)-5-((tert-butyldimethylsilyloxy)methyl)-3-((3S,5R)-3-isobutyl-2-(4-methoxybenzyl)-3-(2-(methoxymethoxy)ethyl)isoxazolidin-5-yl)-4,5-dihydroisoxazole (**24**). The reaction of **S3** was conducted using a procedure analogous to that described above for the preparation of **23**. This procedure yielded the title compound **24** (0.062 g, 41%) as a clear colorless oil after purification by chromatography with 15% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 4.71 (t, *J* = 7.5 Hz, 1 H), 4.64 (s, 2 H), 4.62-4.55 (m, 1 H), 3.83-3.77 (m, 5 H), 3.77-3.70 (m, 2 H), 3.63-3.55 (m, 2 H), 3.39 (s, 3 H), 2.84 (dd, *J* = 11.0, 17.5 Hz, 1 H), 2.72 (dd, *J* = 7.0, 17.5 Hz, 1 H), 2.64-2.57 (m, 1 H), 2.52 (dd, *J* = 8.5, 12.5Hz, 1 H), 1.98-183 (m, 3 H), 1.65 (dd, *J* = 5.0, 14.0 Hz, 1 H), 1.40 (dd, *J* = 7.0, 14.5 Hz, 1 H), 1.00 (t, *J* = 6.5 Hz, 6 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).



31

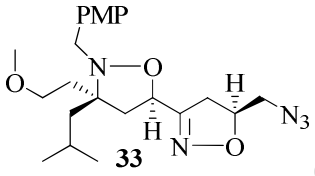
(S)-5-(azidomethyl)-3-((3S,5R)-3-isobutyl-2-(4-methoxybenzyl)-3-(2-(methoxymethoxy)ethyl)isoxazolidin-5-yl)-4,5-dihydroisoxazole (**31**). The reaction of **S3** was conducted using a two step procedure analogous to that described above for the preparation of **S4** and **28**. This procedure yielded the title compound **31** (0.043 g, 72%) as a clear colorless oil after purification by chromatography with 25% EtOAc/hexanes as the eluant. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 4.74 (t, *J* = 7.5 Hz, 1 H), 4.69-4.59

(m, 3 H), 3.85-3.67 (m, 7 H), 3.39 (s, 3 H), 3.31 (dd, *J* = 4.0, 13.0 Hz, 1 H), 3.23 (dd, *J* = 5.0, 13.0 Hz, 1 H), 2.87 (dd, *J* = 11.0, 17.5 Hz, 1 H), 2.69 (dd, *J* = 6.5, 17.5 Hz, 1 H), 2.61-2.52 (m, 2 H), 2.04-1.84 (m, 3 H), 1.64 (dd, *J* = 5.0, 14.5 Hz, 1 H), 1.40 (dd, *J* = 6.0, 14.5 Hz, 1 H), 1.02 (t, *J* = 6.0 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 158.6, 130.6, 129.6, 113.6, 96.5, 78.6, 71,0, 67.7, 64.6, 55.3, 55.2, 53.5, 53.1, 44.3, 42.0, 37.5, 34.0, 25.2, 24.4, 24.3.

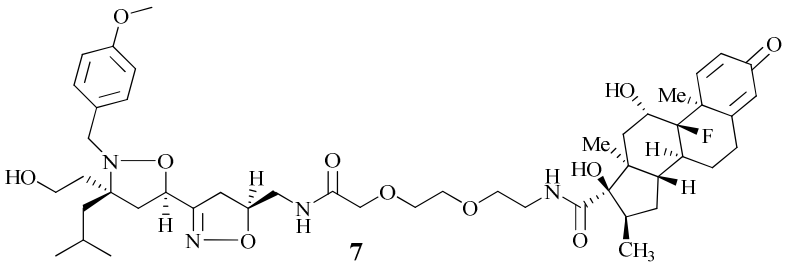


32

2-((3S,5R)-5-((S)-5-(azidomethyl)-4,5-dihydroisoxazol-3-yl)-3-isobutyl-2-(4-methoxybenzyl)isoxazolidin-3-yl)ethanol (**32**). The reaction of **31** was conducted using a procedure analogous to that described above for the preparation of **28**. This procedure yielded the title compound **32** (0.015 g, 77%) as a clear colorless oil after purification by chromatography with 2% MeOH/CH2Cl2 as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 4.79 (t, *J* = 8.0 Hz, 1 H), 4.76-4.68 (m, 1 H), 3.97 (d, *J* = 14.0 Hz, 1 H), 3.92-3.86 (m, 1 H), 3.86-3.76 (m, 5 H), 3.39 (dd, *J* = 4.0, 13.0 Hz, 1 H), 3.30 (dd, *J* = 5.0, 13.0 Hz, 1 H), 2.94 (dd, *J* = 11.0, 17.0 Hz, 1 H), 2.77 (dd, *J* = 7.0, 17.5 Hz, 1 H), 2.71 (dd, *J* = 7.5, 17.5 Hz, 1 H), 2.55 (dd, *J* = 7.5, 18.0 Hz, 1 H), 1.98 (s, br, 1 H), 1.86-1.70 (m, 3 H), 1.47 (dd, *J* = 7.5, 14.0 Hz, 1 H), 1.03 (d, *J* = 2.0 Hz, 3 H), 1.02 (d, *J* = 2.0 Hz, 3 H).

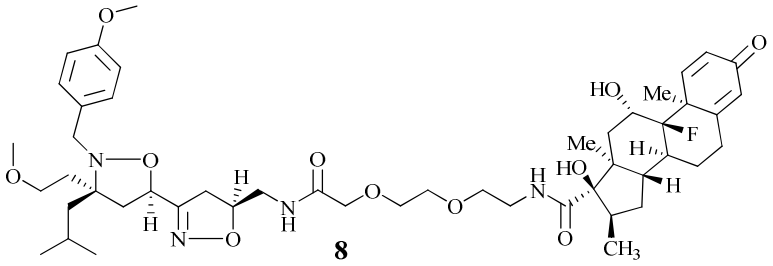


(S)-5-(azidomethyl)-3-((3S,5R)-3-isobutyl-2-(4-methoxybenzyl)-3-(2-methoxyethyl)isoxazolidin-5-yl)-4,5-dihydroisoxazole (**33**). A flame-dried flask was cooled under a stream of nitrogen and charged with **32** (7 mg, 0.017 mmol, 1 equiv) and THF (0.17 mL, 0.1 M). Sodium hydride (1.2 mg, 60% dispersion in mineral oil, 0.05 mmol, 3 equiv) was added and the mixture was allowed to stir for 10 min before addition of iodomethane (3 μL, 0.05 mmol, 3 equiv). After stirring 1 h, TLC analysis shows **32** remaining, so sodium hydride (2.4 mg, 6 equiv) and iodomethane (6 μL) were added. The mixture was stirred until TLC analysis indicated reaction completion, then the reaction was quenched with H_2O (5 mL), extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. This procedure yielded the title compound **33** (0.006 g, 87%) as a clear colorless oil after purification by chromatography with 25% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 4.77-4.71 (m, 1 H), 4.69-4.61 (m, 1 H), 3.85-3.72 (m, 5 H), 3.65-3.51 (m, 2 H), 3.38 (s, 3 H), 3.32 (dd, *J* = 4.5, 13.0 Hz, 1 H), 3.24 (dd, *J* = 5.0, 13.0 Hz, 1 H), 2.88 (dd, *J* = 11.0, 17.5 Hz, 1 H), 2.69 (dd, *J* = 7.0, 17.5 Hz, 1 H), 2.63-2.51 (m, 2 H), 2.01-1.82 (m, 3 H), 1.62 (dd, *J* = 5.0, 14.5 Hz, 1 H), 1.39 (dd, *J* = 6.0, 14.5 Hz, 1 H), 1.02 (d, *J* = 2.0 Hz, 3 H), 1.01 (d, *J* = 2.0 Hz, 3 H).



7

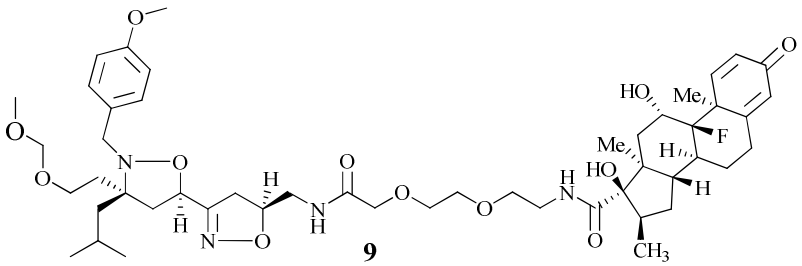
(8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-N-(2-(2-(2-(((S)-3-((3S,5R)-3-(2-hydroxyethyl)-3-isobutyl-2-(4-methoxybenzyl)isoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)methylamino)-2-oxoethoxy)ethoxy)ethyl)-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthrene-17-carboxamide (**7**). The reaction of **32** was conducted using a procedure analogous to that described above for the preparation of **11**. This procedure yielded the title compound **7** (1.4 mg, 15%) as a white solid. The purity of compound **7** was confirmed by analytical reverse-phase HPLC analysis. The identity was verified by mass spectral analysis of the isolated compound. LRMS (ESI) calcd for $[C_{48}H_{69}FN_4O_{11} + H]^+$: 897, found: 897.



8

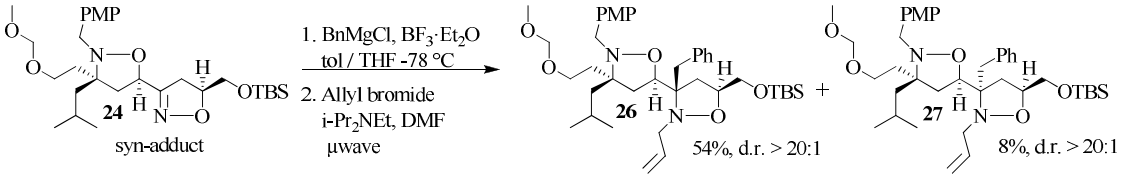
(8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-N-(2-(2-(2-(((S)-3-((3S,5R)-3-isobutyl-2-(4-methoxybenzyl)-3-(2-methoxyethyl)isoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)methylamino)-2-oxoethoxy)ethoxy)ethyl)-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthrene-17-

carboxamide (**8**). The reaction of **33** was conducted using a procedure analogous to that described above for the preparation of **11**. This procedure yielded the title compound **8** (1.9 mg, 20%) as a white solid. The purity of compound **8** was confirmed by analytical reverse-phase HPLC analysis. The identity was verified by mass spectral analysis of the isolated compound. LRMS (ESI) calcd for $[C_{49}H_{71}FN_4O_{11} + H]^+$: 912, found: 912.



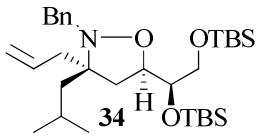
9

(8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-N-(2-(2-(2-(((S)-3-((3S,5R)-3-isobutyl-2-(4-methoxybenzyl)-3-(2-(methoxymethoxy)ethyl)isoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)methylamino)-2-oxoethoxy)ethoxy)ethyl)-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthrene-17-carboxamide (**9**). The reaction of **31** was conducted using a procedure analogous to that described above for the preparation of **11**. This procedure yielded the title compound **9** (1.2 mg, 11%) as a white solid. The purity of compound **9** was confirmed by analytical reverse-phase HPLC analysis. The identity was verified by mass spectral analysis of the isolated compound. LRMS (ESI) calcd for $[C_{50}H_{73}FN_4O_{12} + H]^+$: 942, found: 942.



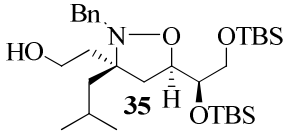
(3S,3'S,5S,5'R)-2-allyl-3-benzyl-5-((tert-butyldimethylsilyloxy)methyl)-3'-isobutyl-2'-(4-methoxybenzyl)-3'-(2-(methoxymethoxy)ethyl)-3,5'-biisoxazolidine (**26**) and (3R,3'S,5S,5'R)-2-allyl-3-benzyl-5-((tert-butyldimethylsilyloxy)methyl)-3'-isobutyl-2'-(4-methoxybenzyl)-3'-(2-(methoxymethoxy)ethyl)-3,5'-biisoxazolidine (**27**). The reaction of **24** was conducted using a two step procedure analogous to that described above for the preparation of **S6** and **25**. This procedure yielded the title compounds **26** (0.405 g, 54%) and **27** (0.057 g, 8%) as a clear colorless oils after purification by chromatography with 7% EtOAc/hexanes as the eluant. **26**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 9.0 Hz, 2 H), 7.23-7.17 (m, 3 H), 7.07-7.02 (m, 2 H), 6.90 (d, *J* = 9.0 Hz, 2 H), 6.00-5.91 (m, 1 H), 5.19 (d, *J* = 17.5 Hz, 1 H), 5.07 (d, *J* = 10.0 Hz, 1 H), 4.60 (s, 2 H), 4.15-4.08 (m, 1 H), 4.01-3.95 (m, 1 H), 3.83-3.64 (m, 10 H), 3.43 (dd, *J* = 6.0, 10.0 Hz, 1 H), 3.34 (s, 3 H), 3.26-3.18 (m, 1 H), 2.98 (d, *J* = 12.5 Hz, 1 H), 2.74-2.64 (m, 2 H), 2.19 (dd, *J* = 8.5, 13.0 Hz, 1 H), 1.98-1.84 (m, 4 H), 1.56-1.44 (m, 2 H), 1.31 (dd, *J* = 6.0, 13.0 Hz, 1 H), 1.04 (d, *J* = 3.0 Hz, 3 H), 1.03 (d, *J* = 3.0 Hz, 3 H), 0.89 (s, 9 H), 0.06 (d, *J* = 1.5 Hz, 6 H). **27:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 9.0 Hz, 2 H), 7.23-7.17 (m, 3 H), 7.10-7.07 (m, 2 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 5.92-5.83 (m, 1 H), 5.17-5.12 (m, 1 H), 5.07-5.03 (m, 1 H), 4.67-4.54 (m, 3 H), 4.22 (t, *J* = 8.0 Hz, 1 H), 3.88-3.78 (m, 6 H), 3.78-3.68 (m, 5 H), 3.46-3.30 (m, 5 H), 3.24 (dd, *J* = 7.0, 10.0 Hz, 1 H), 2.18 (dd, *J* = 6.5, 15.5 Hz, 1 H), 2.89 (dd, *J* = 5.5, 10.0 Hz, 1 H), 2.84 (d, *J* = 14.0 Hz, 1 H), 2.76 (d, *J* = 14 Hz, 1 H), 2.31 (dd, *J* = 8.0, 13.0 Hz, 1 H), 2.24-2.16 (m, 2 H), 1.99-1.92 (m, 2 H), 1.92-1.83

(m, 2 H), 1.74 (dd, *J* = 4.5, 13.5 Hz, 1 H), 1.67-1.59 (m, 1 H), 1.47 (dd, *J* = 5.0, 14.0 Hz, 1 H), 1.05 (d, *J* = 6.5 Hz, 3 H), 1.02 (d, *J* = 6.5 Hz, 3 H), 0.82 (s, 9 H), -0.06 (s, 3 H), -0.08 (s, 3 H).



34

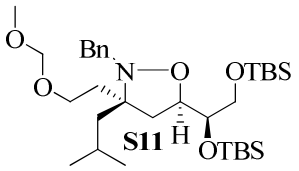
(3S,5R)-3-allyl-2-benzyl-3-isobutyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)isoxazolidine (**34**). The reaction of **18** was conducted using a procedure analogous to that described above for the preparation of **19**. This procedure yielded the title compound **34** (1.84 g, 81%) as a yellow oil after purification by chromatography with EtOAc/hexanes as the eluant. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2 H), 7.31-7.18 (m, 3 H), 6.03-5.87 (m, 1 H), 5.13 (d, *J* = 4.2 Hz, 1 H), 5.08 (s, 1 H), 4.11-4.01 (m, 1 H), 3.91-3.75 (m, 2 H), 3.69-3.50 (m, 3 H), 2.39-2.32 (m, 2 H), 2.12 (dd, *J* = 3.6, 8.4 Hz, 2 H), 1.97-1.83 (m, 1 H), 1.62 (dd, *J* = 5.1, 14.4 Hz, 1 H), 1.55 (s, 3 H), 1.35 (dd, *J* = 6.6, 14.1 Hz, 1 H), 0.99 (dd, *J* = 5.4, 6.6 Hz, 6 H), 0.88-0.86 (m, 18 H), 0.03- -0.02 (m, 9 H), -0.06 (s, 3 H).



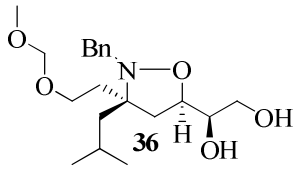
35

2-((3S,5R)-2-benzyl-3-isobutyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)isoxazolidin-3-yl)ethanol (**35**). The reaction of **34** was conducted using a procedure analogous to that described above for the preparation of **20**. This procedure yielded the title compound **35** (0.730 g, 73%) as a yellow oil after purification by chromatography with 10% EtOAc/hexanes as the eluant. ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 2 H), 7.31-7.26 (m, 2 H), 7.24-7.19 (m, 1 H), 5.35 (s, br, 1 H), 4.32-4.25 (m, 1 H), 3.96-3.85 (m, 3 H), 3.82-3.75 (m, 1 H), 3.69 (dt, *J* = 4.0, 6.0 Hz, 1 H), 3.57 (dt, *J* = 6.0, 10.0 Hz, 2 H), 2.29 (dd, *J*= 10.0, 12.5 Hz, 1 H), 2.10 (dd, *J*= 7.5, 12.5 Hz, 1 H), 2.07-1.98 (m, 1 H), 1.94-1.87 (m, 1 H), 1.79-1.70 (m, 1 H), 1.70-1.63 (m, 1 H), 1.39 (dd, *J*= 8.0, 13.5 Hz, 1 H), 1.03 (d, *J* = 6.5 Hz, 3 H), 1.00 (d, *J* = 6.5 Hz, 3 H), 0.95 (s, 9 H), 0.87 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H), -0.02 (s, 6 H).

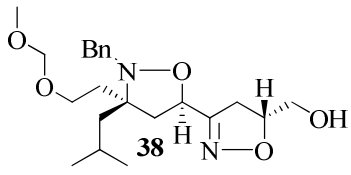


(3S,5R)-2-benzyl-3-isobutyl-3-(2-(methoxymethoxy)ethyl)-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)isoxazolidine (**S11**). The reaction of **35** was conducted using a procedure analogous to that described above for the preparation of **21**. This procedure yielded the title compound **S11** (0.493 g, 83%) as a yellow oil after purification by chromatography with 5% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2 H), 7.30-7.25 (m, 2 H), 7.22-7.18 (m, 1 H), 4.64 (s, 2 H), 4.11 (dt, *J* = 5.0, 8.5 Hz, 1 H), 3.86 (d, *J* = 14.0 Hz, 1 H), 3.79-3.70 (m, 3 H), 3.68-3.63 (m, 1 H), 3.59 (dd, *J* = 5.0, 10.5 Hz, 1 H), 3.53 (dd, *J* = 6.0, 12.5 Hz, 1 H), 3.38 (s, 3 H), 2.22-2.10 (m, 3 H), 1.99-1.82 (m, 3 H), 1.63 (dd, *J* = 5.0, 14.0 Hz, 1 H), 1.54 (s, 2 H), 1.34 (dd, *J* = 6.5, 14.0 Hz, 1.02 (d, *J* = 6.5 Hz, 3 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.01- -0.01 (m, 6 H), -0.03 (s, 3 H).



36

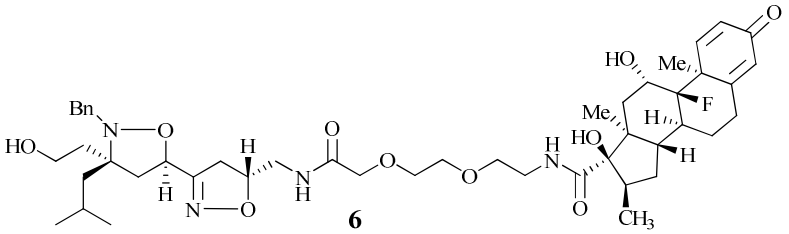
(R)-1-((3S,5R)-2-benzyl-3-isobutyl-3-(2-(methoxymethoxy)ethyl)isoxazolidin-5-yl)ethane-1,2-diol (**36**). The reaction of **S11** was conducted using a procedure analogous to that described above for the preparation of **21**. This procedure yielded the title compound **36** (0.051 g, 82%) as a yellow oil after purification by chromatography with 66% EtOAc/hexanes as the eluant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 4 H), 7.28-7.23 (m, 1 H), 4.64 (s, 2 H), 4.05-3.99 (m, 1 H), 3.87 (d, *J* = 14.5 Hz, 1 H), 3.84-3.76 (m, 2 H), 3.72-3.65 (m, 1 H), 3.59-3.52 (m, 2 H), 3.49-3.43 (m, 1 H), 3.39 (s, 3 H), 3.09 (s, br, 1 H), 2.39 (dd, *J* = 9.0, 12.5 Hz, 1 H), 2.24 (dd, *J* = 6.0, 12.5 Hz, 1 H), 2.16 (s, br, 1 H), 2.02-1.94 (m, 1 H), 1.93-1.85 (m, 2 H), 1.63 (dd, *J* = 5.0, 14.0 Hz, 1 H), 1.42 (dd, *J* = 7.5, 14.0 Hz, 1 H), 1.01 (t, *J* = 6.5 Hz, 6 H).



38

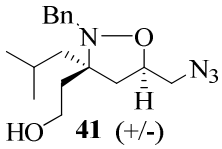
((R)-3-((3S,5R)-2-benzyl-3-isobutyl-3-(2-(methoxymethoxy)ethyl)isoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)methanol (**38**). The reaction of **36** was conducted using a procedure analogous to that described above for the preparation of **22** and **S2**. This procedure yielded the title compound **38** (0.014 g, 20%) as a clear colorless oil after purification by chromatography with 50% EtOAc/hexanes as the eluant and HPLC seperation of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 4 H), 7.27-7.23 (m, 1 H), 4.76-4.71 (m, 1 H), 4.66-4.60 (m, 3 H), 3.87-3.82 (m, 2 H), 3.78-3.71 (m, 2 H), 3.66-3.59 (m, 1 H), 3.50-3.43 (m, 1 H), 3.39 (s, 3 H), 2.85 (dd,

J = 11.0, 17.5 Hz, 1 H), 2.66 (dd, *J* = 7.5, 17.5 Hz, 1 H), 2.56 (d, *J* = 8.0 Hz, 2 H), 2.02-1.84 (m, 3 H), 1.77 (s, br, 1 H), 1.67 (dd, *J* = 5.0, 14.5 Hz, 1 H), 1.41 (dd, *J* = 7.0, 14.5 Hz, 1 H), 1.02 (t, *J* = 6.5 Hz, 6 H).



6

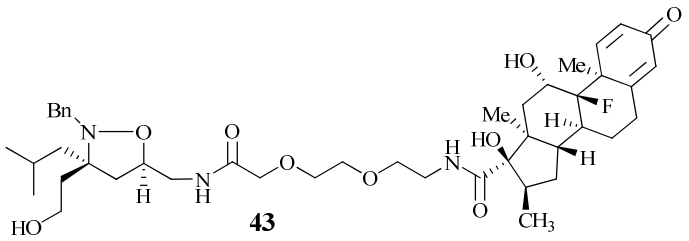
(8S,9R,10S,11S,13S,14S,16R,17R)-N-(2-(2-(2-(((R)-3-((3S,5R)-2-benzyl-3-(2-hydroxyethyl)-3-isobutylisoxazolidin-5-yl)-4,5-dihydroisoxazol-5-yl)methylamino)-2-oxoethoxy)ethoxy)ethyl)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthrene-17-carboxamide (**6**). The reaction of **38** was conducted using a procedure analogous to that described above for the preparation of **S4**, **28**, and **11**. This procedure yielded the title compound **6** (1.3 mg, 11%) as a white solid. The purity of compound **6** was confirmed by analytical reverse-phase HPLC analysis. The identity was verified by mass spectral analysis of the isolated compound. LRMS (ESI) calcd for $[C_{47}H_{67}FN_4O_{10} + H]^+$: 867, found: 867.



41 (+/-)

(±)-2-((3R*,5R*)-5-(azidomethyl)-2-benzyl-3-isobutylisoxazolidin-3-yl)ethanol (**41**). Compound **41** was prepared in a procedure analogous to those reported

previously.[17] It was isolated after HPLC separation of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 4 H), 7.24-7.19 (m, 1 H), 4.54 (s, br, 1 H), 4.39-4.31 (m, 1 H), 3.94 (d, *J* = 13.6 Hz, 1 H), 3.85-3.74 (m, 2 H), 3.69 (d, *J* = 13.6 Hz, 1 H), 3.42 (dd, *J* = 6.4, 12.8 Hz, 1 H), 3.22 (dd, *J* = 4.8, 12.8 Hz, 1 H), 2.35 (dd, *J* = 8.8, 12.8 Hz, 1 H), 2.09-1.96 (m, 2 H), 1.74-1.63 (m, 3 H), 1.52-1.44 (m, 1 H), 0.99-0.93 (m, 6 H).



43

(8S,9R,10S,11S,13S,14S,16R,17R)-N-(2-(2-(2-(((3RS,5RS)-2-benzyl-3-(2-hydroxyethyl)-3-isobutylisoxazolidin-5-yl)methylamino)-2-oxoethoxy)ethoxy)ethyl)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthrene-17-carboxamide (**43**). The reaction of **41** was conducted using a procedure analogous to that described above for the preparation of **11**. This procedure yielded the title compound **41** (0.3 mg). The purity of compound **43** was confirmed by analytical reverse-phase HPLC analysis. The identity was verified by mass spectral analysis of the isolated compound. LRMS (ESI) calcd for $[C_{44}H_{64}FN_3O_9 + H]^+$: 798, found: 798.

5.6 References

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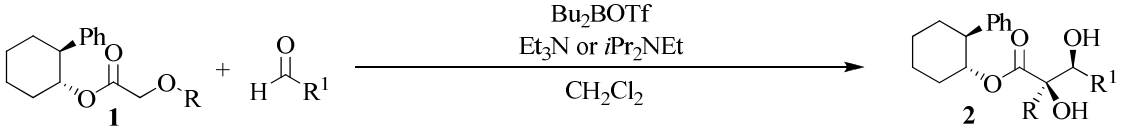
Chapter 6

Exploratory Studies on the Reactivity of Electrophiles with Enediol Diboronates

6.1 Introduction

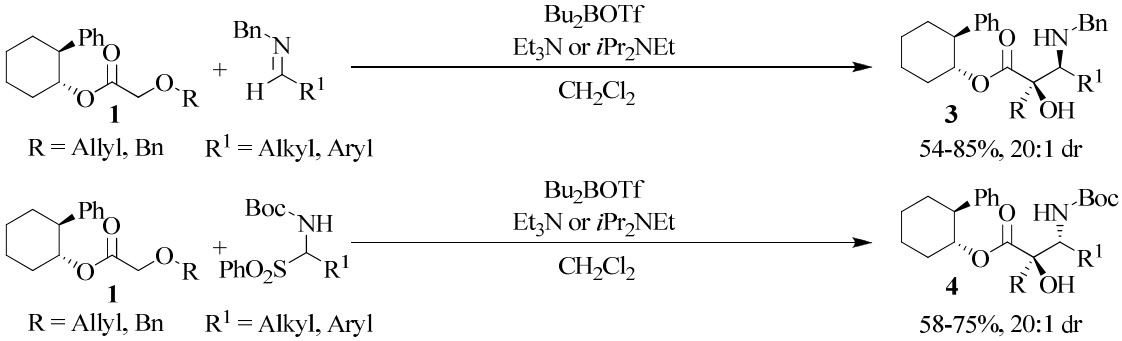
Tandem reactions in organic synthesis often allow for the rapid preparation of complex molecules in an efficient manner. Previous work in the Wolfe lab has explored tandem Wittig rearrangement/aldol reactions for the synthesis of glycolate aldols (Figure 6-1).[1] This reaction provided a new approach to the construction of α-alkyl-α,β-dihydroxy esters (**2**) through a tandem one-pot sequence of two different C−C bond-forming reactions.[1a] Further investigation of the reaction identified a chiral auxiliary that provided excellent stereoselectivity, and after cleavage, provides products in good yield and excellent enantiopurity.[1b] An improved synthesis of a key intermediate for the natural product alternaric acid was reported as a result of this development. Expansion to imine electrophiles provided selective access to both *syn*-α-alkyl-α-hydroxy-β-amino esters (**3**) and *anti*-α-alkyl-α-hydroxy-β-amino esters (**4**) (Figure 6-2).[1c] Interestingly, utilization of imines provided access to the *syn*-products, while use of *N*-Boc-2-(phenylsulfonyl)amines electrophiles led to formation of *anti*-products.

Figure 6-1: Asymmetric Tandem Wittig Rearrangement/Aldol Reactions



R = Allyl, Bn R^1 = Alkyl, Aryl, Alkenyl 59-88%, 20:1 dr

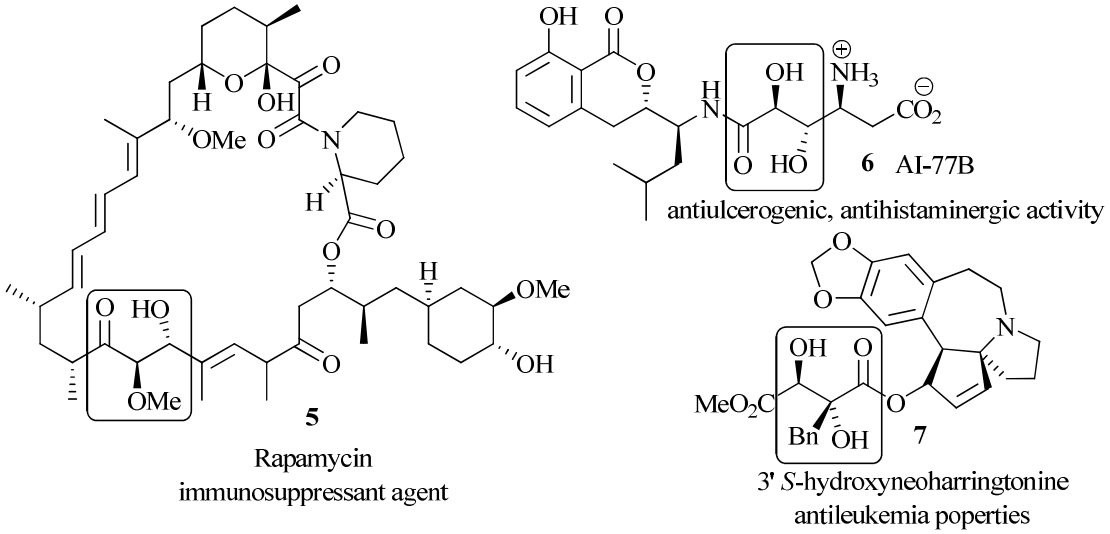
Figure 6-2: Asymmetric Tandem Wittig Rearrangement/Mannich Reactions



6.2 Importance of Aldol Addition with Anti Selectivity

Anti-α-alkyl-α,β-dihydroxy esters and *anti*-α,β-dihydroxy carbonyl compounds are important synthetic building blocks and can be found in biologically important compounds and natural products.[2-4] For example, Rapamycin[2] (**5**) is a natural product and immunosuppressant drug used to prevent rejection in organ transplantation, AI-77B[3] (**6**) is a natural product with antiulcerogenic and antihistaminergic activity, and 3'*S*-hydroxyneoharringtonine[4] (**7**) is a natural product with antileukemia activity. While reactions that selectively generate *anti*-aldol products are known, none of these reports included products containing unprotected tertiary alcohols, like those potentially formed by the tandem Wittig rearrangement/aldol reaction or found in 3'*S*-hydroxyneoharringtonine (**7**).[5]

Figure 6-3: Biologically Important Compounds that Contain 1,2-*anti*-aldol Fragments



6.3 Selection for Anti-Selective Aldol Reactions via Oxonium Electrophiles

The selectivity change in the tandem Wittig rearrangement/Mannich reactions suggested that the selective synthesis of *anti*-α-alkyl-α,β-dihydroxy esters should be possible. Consideration of the tandem Wittig Rearrangement/Mannich reactions indicated that the nature of the electrophile played a key role in determining diastereoselectivity. While *N*-benzyl- and *N*-Boc-imine electrophiles participate in a boat-like transition state leading to *syn*-products (**10**), it was hypothesized in these reactions that use of *N*-Boc-2-(phenylsulfonyl)amines led to formation of *anti*-products (**12**) through an *N*-Boc iminium mediated open transition state (**11**, Figure 6-4).[1c] Thus, I hypothesized that a similar strategy could be used for targeting the *anti*-α-alkyl-α,β-dihydroxy esters. The Sinha group has recently reported aldol-type reactions of ketone boron enolates with acetals both intermolecularly[6] and intramolecularly,[7] confirming the feasibility of this strategy. It was hypothesized that dialkyl acetals should play a similar role to *N*-Boc-2-

(phenylsulfonyl)amines in the reaction by generating electrophilic alkyl oxonium ion intermediates *in situ* that should preferentially participate in an open transition state and form the *anti*-type products. Execution of this strategy for the formation of *anti*-α-alkyl-α,β-dihydroxy esters showed improved selectivity for the *anti*-products, but the overall diastereoselectivity only shifted to 3:1 *syn*-to-*anti* under the best conditions explored to date (Figure 6-5). To unequivocally identify the major diastereomer as the *syn*-diol ester product (**16**), an authentic sample of the *syn*-diol ester product was synthesized for comparison (Figure 6-6). Use of 2-phenyl-1,3-dioxane (**17**) as electrophile showed no improvement in selectivity (Figure 6-5). It's not clear why *anti*-aldol selectivity for the reactions involving oxonium ion intermediates is not comparable to the reactions involving iminium ion intermediates. It is possible that transition state **11** has improved organization and stability due to an interaction between the *N*-Boc carbonyl and boron on the enolate, which results in higher stereocontrol for the iminium ion reactions than can be achieved in the oxonium ion cases.

Figure 6-4: Stereochemical Hypothesis for *syn*- and *anti*-Product Formation

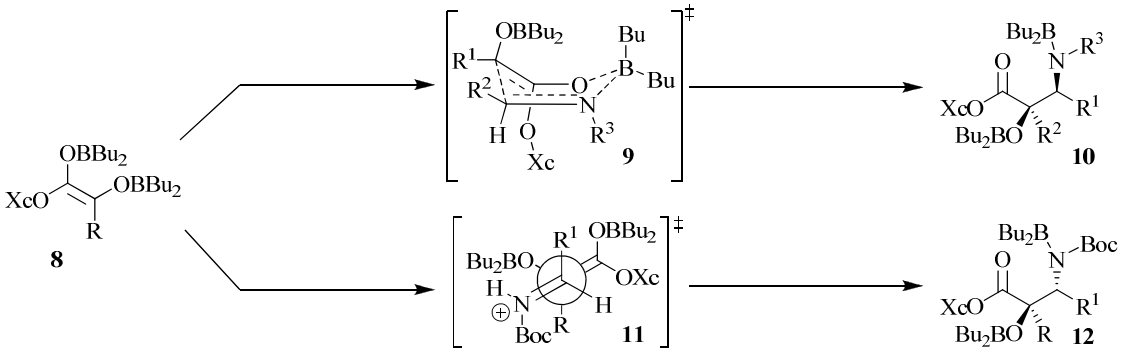


Figure 6-5: Tandem Wittig Rearrangement/Aldol Reaction

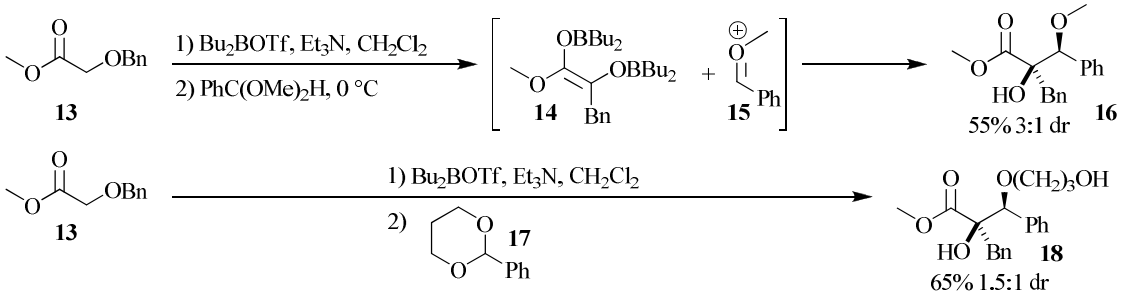
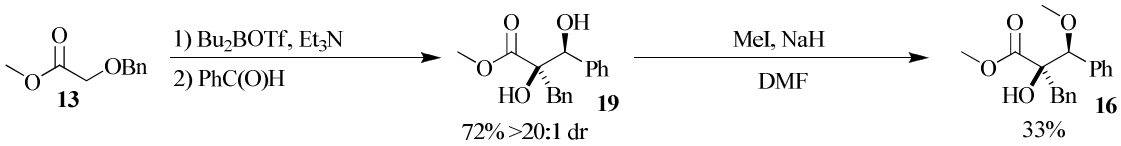


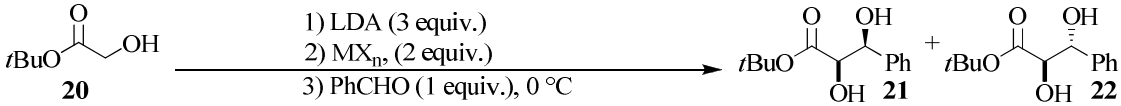
Figure 6-6: Authentic Synthesis of *Syn*-Diol Ester Product



6.4 Selection for Anti-Selective Aldol Reactions via Metal Enolates

Work with the dialkyl acetal electrophiles indicated that diastereoselectivity was influenced by the nature of the electrophile, but efforts to develop electrophiles strongly favoring the desired *anti*-aldol type products have not yet been successful. We therefore decided to more closely investigate aspects of the enolate nucleophile. While the previously developed tandem Wittig/aldol procedure proceeds through a diboron enolate intermediate (**14**) in route to *syn*-aldol type products, we thought it would be possible to favor production of *anti*-aldol type products by changing the reactivity of the enolate by switching to other metal enolates. Literature precedent indicates that aldol selectivity can be strongly influenced by the metal bound to the intermediate enolates.[8] In particular, the Kazmaier lab has shown that glycolate titanium enolates can preferentially form *anti*-aldol products (**22**, Figure 6-7). However, none of these reports included products containing unprotected tertiary alcohols (**2**, Figure 6-1), like those formed by the tandem Wittig rearrangement/aldol reactions.

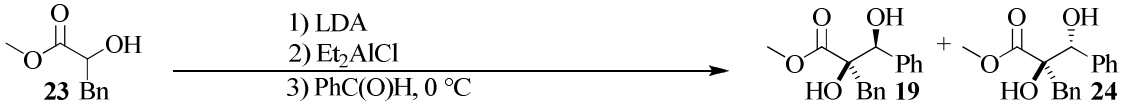
Figure 6-7: Selectivity for *anti*-aldol Products Controlled by Metal Enolate



MX_n, = $Ti(OiPr)_4$, dr = 68:32
= $TiCl(OiPr)_3$, dr = 1:99

The glycolate aldol reaction was investigated on its own with the intent of expanding to the tandem Wittig/aldol reaction system once conditions strongly favoring *anti*-aldol selectivity were identified. Starting from α-hydroxy ester **23**, addition of lithium diisopropyl amide generates a lithium enolate, then addition of Et_2AlCl followed by benzaldehyde yields products with a minor preference for the *anti*-aldol stereochemistry (**24**) as judged by crude ^{1}H-NMR analysis. Interestingly, it was found that the relative stoichiometry of base and Lewis acid mediated selectivity for the *anti*-aldol product (**24**, Table 6-1). However, further screening of other metals ($AlMe_3$, Me_2AlOTf, $TiCl(OiPr)_3$, Bu_2BOTf, $Sc(OTf)_3$, $LiClO_4$) showed no improvement in reaction selectivity.

Table 6-1: Lewis Acid Ratio Influence on Diastereoselectivity



entry	equiv. LDA	equiv. Et_2AlCl	ratio LDA:Et_2AlCl	dr **19**:**24**[a]
1	2.0	0.5	4:1	1 : 1.2
2	2.0	1.0	2:1	1 : 2.1
3	2.0	2.0	1:1	1 : 1.3
4	2.0	3.0	2:3	1 : 1.4
5	4.0	2.0	2:1	1 : 2.7
6	4.0	4.0	1:1	1 : 1.2

[a] Determined by ^{1}H-NMR.

6.5 Selection for Anti-Selective Aldol Reactions via Aldehyde Activation

Work from the Heathcock[9] and Oppolzer[10] labs has shown that reactions of enolates with Lewis acid coordinated aldehydes can provide products with good to excellent *anti*-selectivity. Although these conditions have not been reported in aldol reactions involving tetrasubstituted enolates or glycolates, application of this stereochemical model to our tandem Wittig/aldol process suggests that a similar strategy should work in our chemistry (Figure 6-8). The reported reactions are proposed to proceed through open transition states (**25** and **27**) with minimization of gauche interactions leading to good selectivity for the *anti*-aldol products (**26**). Both $TiCl_4$ and Et_2AlCl have been shown to promote *anti*-aldol selectivity, so our preliminary experiments tested these Lewis acids (Figure 6-9).[9-11] Conducting the Wittig rearrangement followed by reaction with precoordinated Lewis acids provided no evidence of the desired aldol products. Varying the order in which the components were mixed, either adding **14** to the activated aldehydes or adding the activated aldehydes to **14**, did not influence the result. It seems like the added steric bulk of the tetrasubstituted enolate is preventing the desired aldol reactivity, or exchange of boron and titanium may be occurring, reducing the enolate's reactivity. Reaction of a lithium enolate with Et_2AlCl activated benzaldehyde provided the aldol products with selectivity comparable to that observed with aluminum enolates as discussed in the previous section (Table 6-1).

Figure 6-8: Stereochemical Model for Selectivity with Aldehyde Activation

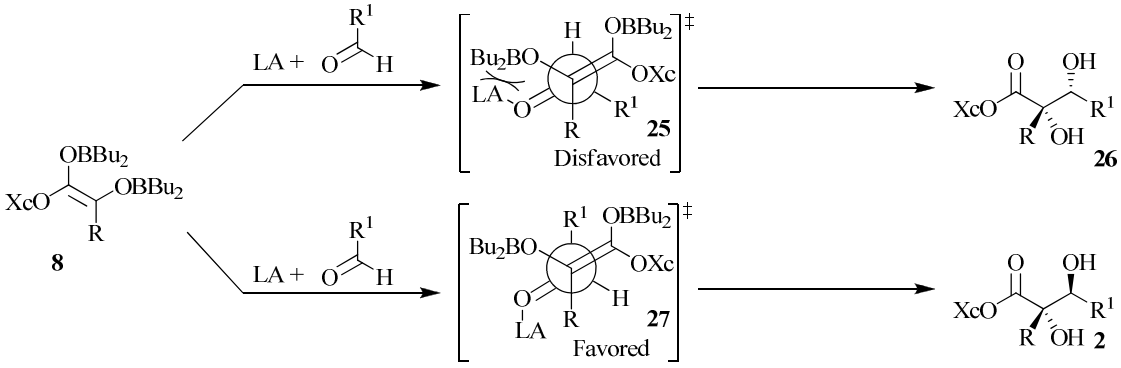
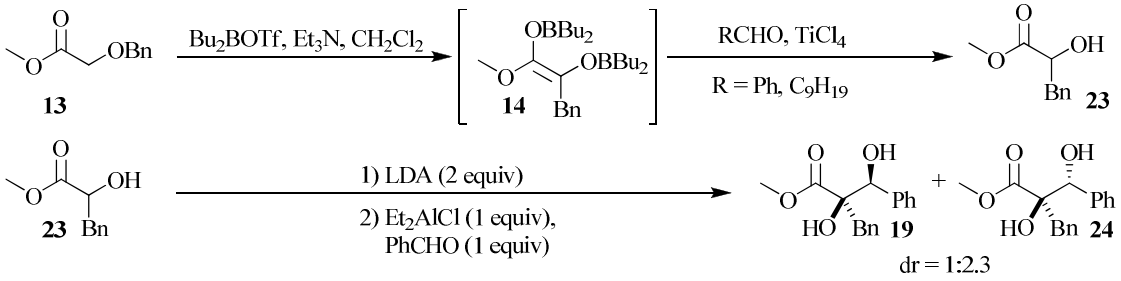


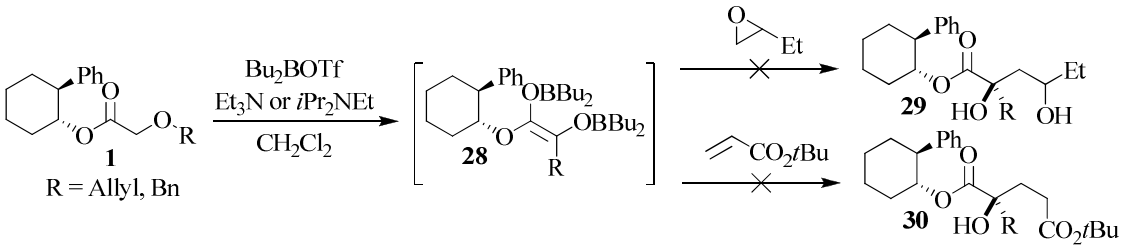
Figure 6-9: Exploring Enolate Addition to Activated Aldehydes



6.6 Investigating New Electrophiles for Tandem Wittig Rearrangment Reactions

Development of new tandem Wittig rearrangement/electrophilic alkyl reactions was sought as a way to gain access to new and useful products. Application of epoxide electrophiles was investigated as a route to 1,3-diols, but only Wittig rearrangement products were isolated from these reactions (Figure 6-10). Similarly, Michael acceptors were tested as electrophiles for the enolate intermediates (**28**), but no evidence of a tandem reaction was observed. Examples of epoxide ring opening and michael addition reactions are known with other metal enolates including Zn,[12] Al,[13] and Li,[14,15] so further exploration of these reactions from glycolate intermediates with other metals (such as Figure 6-7) may lead to formation of the desired products.

Figure 6-10: Testing Epoxides and Michael Acceptors in Tandem Reactions



Alternatively, pyridinium salts have been used as electrophiles for the formation of substituted piperidines.[16] Use of pyridinium salt **31** gave promising preliminary results for the construction of substituted piperidine **33** (Figure 6-11). Subjecting the 1,2-Wittig rearrangement enolate intermediate (**28**) to **31** generated intermediate **32**, which underwent an intramolecular condensation to form **33** in low yield. The α-hydroxy ester (**36**), which results from Wittig rearrangement without electrophilic trapping, is the other main product isolated from this reaction. Initial modifications of solvent, temperature, concentration, and order of addition have yet to provide improved results. Surprisingly, intermediates from the 2,3-Wittig rearrangement have not shown reactivity with **31** (Figure 6-12).

Figure 6-11: Tandem 1,2-Wittig Rearrangement/Pyridinium Addition Reaction

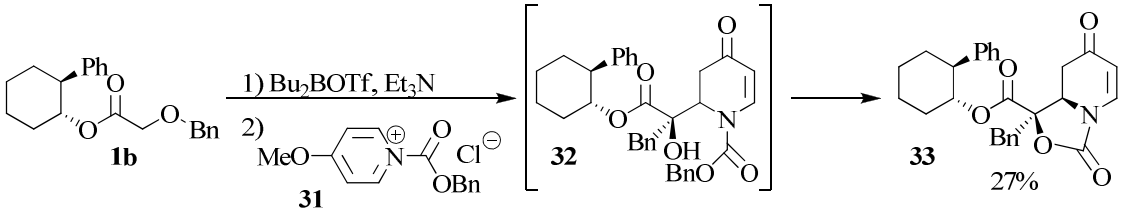
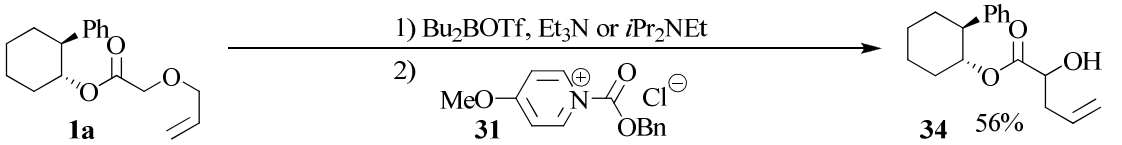
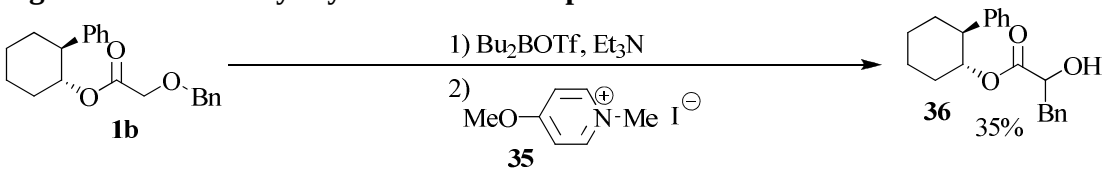


Figure 6-12: Tandem 2,3-Wittig Rearrangement/Pyridinium Addition Reaction



Extension of this tandem reaction to other pyridinium salts has not yet been successful. *N*-alkyl pyridinium salts[17] are isolable and are known electrophiles for nucleophilic addition, but tandem reaction conditions have only afforded α-hydroxy ester (**36**) along with substrate decomposition (Figure 6-13).

Figure 6-13: *N*-Methyl Pyridinium Electrophiles Fail to Provide Tandem Products



To improve the tandem Wittig rearrangement/Pyridinium addition reactions, improved conditions need to be identified that promote full conversion of the Wittig rearrangement intermediate to the tandem reaction product. It is anticipated that improving enolate stability while promoting nucleophilic addition to a pyridinium salt will provide the desired products in improved yields. Screening amine bases may improve results, as improved reactivity was achieved in the Wittig rearrangement/aldol reactions by switching from Et_3N to iPr_2NEt for the O-allyl glycolate ester substrate (**1a**). Exploration of solvent mixtures may help achieve improved results, as the pyridinium salts have low solubility in CH_2Cl_2, which is currently the best solvent for inducing the Wittig rearrangement. Further exploration of various pyridinium salts my improve conversion with adjustment of electrophelicity.

6.7 Conclusions

A range of conditions were explored for expanding the potential utility of tandem Wittig rearrangement/aldol reactions. Use of dialkyl acetal electrophiles led to lower

diastereoselectivity for *syn*-aldol type products, but a reversal of selectivity to afford the *anti*-stereoisomer was not achieved. Application of other α-hydroxy ester metal enolates shifted aldol selectivity in favor of the *anti*-aldol products, though the best conditions using aluminum enolates only preferred the *anti*-aldol products by 2.7:1. Attempts to promote *anti*-selectivity *via* open transition state aldol reactions through aldehyde activation with precoordinated Lewis acids were unsuccessful.

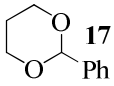
Extension of the Wittig rearrangement intermediates to new electrophiles with application towards 1,3-diols (epoxides) or tertiary alcohols (activated alkenes) did not show any evidence of successful reactivity. Pyridinium salt electrophiles have shown preliminary success with the benzyl rearrangement substrate, but low reaction conversion and an initially limited substrate scope indicate that more optimization is needed.

6.8 Experimental Section

General: All reactions were carried out under a nitrogen atmosphere in oven or flame dried glassware. Dibutylboron triflate (1.0 M solution in methylene chloride), *tert*-butyl acrylate, methyl iodide, sodium hydride, trifluoromethanesulfonic acid, and DMF were purchased from Aldrich Chemical Co. and used without further purification. All aldehydes, benzaldehyde dimethyl acetal, and 2-ethyl oxirane were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were purified by distillation from Ca_2SO_4. Triethylamine and diisopropylethylamine were obtained from Aldrich Chemical Co. and were purified by distillation from CaH. Phosphate buffer solution (pH 7) was obtained from Aldrich Chemical Co. Methylene chloride, toluene, and THF was purified using a GlassContour solvent purification system. (±)-(1R*,2S*)-

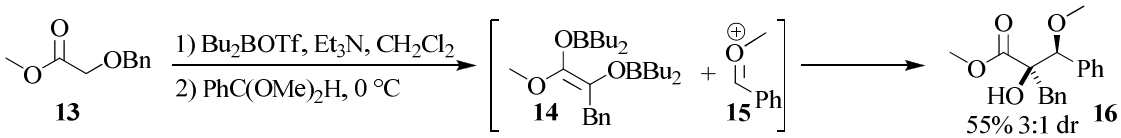
2-Phenylcyclohexyl-2'-(allyloxy)acetate (**1a**),[1a] (±)-(1R*,2S*)-2-Phenylcyclohexyl-2'-(benzyloxy)acetate (**1b**),[1b] Methyl 2-(benzyloxy)acetate (**13**),[1a] (±)-(2R*,3S*)-Methyl-2-benzyl-2,3-dihydroxypent-4-enoate (**19**),[1a] (±)-Methyl-2-hydroxy-3-phenylpropanoate (**23**),[1a] and 4-methoxy-1-methyl-pyridinium iodide (**35**),[17] were prepared according to published procedures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR.

Synthesis of Substrates



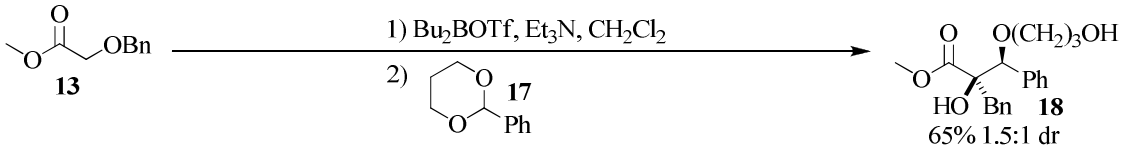
2-Phenyl-1, 3-dioxane (17). A flame-dried flask was cooled under a stream of nitrogen and charged with benzaldehyde (2.04 mL, 20.0 mmol, 1.0 equiv.), 1,3-propanediol (2.3 mL, 32.0 mmol, 1.6 equiv.), *p*-toluenesulfonic acid monohydrate (2 mg), and toluene (20 mL). The resulting solution was brought to reflux under a Dean-Stark trap until the starting material was consumed as judge by TLC analysis (ca. 24 h). The reaction was then cooled to rt, poured into a sat. aq. solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 10% EtOAc/hexanes as the eluent to afford the title compound (3.21 g, 98%) as a white solid. Spectroscopic properties were consistent with those reported in the literature.[18]

Selection for *anti*-selective aldol reactions via oxonium electrophiles



(±)-(2R*,3S*)-methyl 2-benzyl-2-hydroxy-3-methoxy-3-phenylpropanoate (16). A flame-dried flask was cooled under a stream of nitrogen and charged with a 1 M solution of dibutylboron triflate in dichloromethane (0.5 mL, 0.5 mmol, 3.2 equiv). The pale yellow solution was cooled to 0 °C, and triethylamine (0.625 mmol, 4.0 equiv) was added dropwise to afford a colorless solution. Methyl 2-(benzyloxy)acetate (**13**) (28.2 mg, 0.16 mmol, 1.0 equiv) in CH_2Cl_2 (0.25 mL) was then added dropwise, and the reaction mixture was warmed rt, stirred for 1.5 h, and then cooled to -78 °C. A second portion of Bu_2BOTf (0.5 mL, 0.5 mmol, 3.2 equiv) was added, then benzaldehyde dimethyl acetal in CH_2Cl_2 was added dropwise. The reaction was stired at -78 °C for 3 h, the warmed to 0 °C in an ice/water and stirred another 1 h. The reaction vessel was then opened to air, and pH 7 buffer (1 mL/mmol substrate), and methanol (2 mL/mmol substrate) were added. The resulting mixture was cooled to 0 °C, 30% aqueous H_2O_2 (2 mL/mmol substrate) was added slowly, and the reaction mixture was warmed to rt and stirred for 1 h. The mixture was diluted with ether (10 mL/mmol substrate) and water (5 mL/mmol substrate), then was transferred to a separatory funnel. The layers were separated, and the organic layer was washed with a saturated aqueous solution of $FeSO_4$ (4 x 5 mL/mmol substrate) until a red-orange aqueous phase no longer persisted in order to quench any remaining peroxide. Caution! This procedure is exothermic. The $FeSO_4$

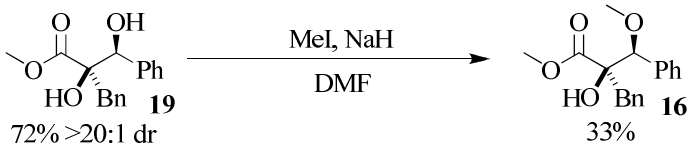
solution should be added via glass pipette SLOWLY DROPWISE. The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to yield the title compound **16** (25.8 mg, 55%, 3:1 dr) as a colorless oil. The pure material was judged to be of 3:1 dr by ^{1}H NMR analysis. **Major (*syn*) diastereomer (16):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.45 (m, 2 H), 7.43−7.36 (m, 3 H), 7.24−7.16 (m, 3 H), 7.12−7.08 (m, 2 H), 4.50 (s, 1 H), 3.71 (s, 3 H), 3.23−3.20 (m, 4 H), 2.97 (d, *J* = 13.5 Hz, 1 H), 2.48 (d, *J* = 13.5 Hz, 1 H). **Minor (*anti*) diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.45 (m, 2 H), 7.43−7.36 (m, 3 H), 7.24−7.16 (m, 3 H), 7.12−7.08 (m, 2 H), 4.50 (s, 1 H), 3.55 (s, 3 H), 3.47 (d, *J* = 13.5 Hz, 1 H), 3.33 (s, 3 H), 3.12 (d, *J* = 13.5 Hz, 1 H), 3.06 (s, br, 1 H).



(±)-(2R*,3S*)-methyl 2-benzyl-2-hydroxy-3-(3-hydroxypropoxy)-3-phenylpropanoate (18). The reaction of **13** (28.2 mg, 0.16 mmol) was conducted using a procedure analogous to that described above for the preparation of **16**. This procedure afforded the title compound **18** (35 mg, 65%, 1.5:1 dr) as a colorless oil. The pure material was judged to be of 1.5:1 dr by ^{1}H NMR analysis. **Major (*syn*) diastereomer (18):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.32 (m, 5 H), 7.25−7.16 (m, 4 H), 7.14−7.10 (m, 1 H), 4.55 (s, 1 H), 3.76−3.69 (m, 5 H), 3.56−3.47 (m, 2 H), 3.22 (s, br, 1 H), 3.02 (d, *J* = 13.5 Hz, 1 H), 2.56 (d, *J* = 13.5 Hz, 1 H), 2.29 (s, br, 1 H), 1.82−1.74 (m, 2 H). **Minor (*anti*) diastereomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.32 (m, 5 H),

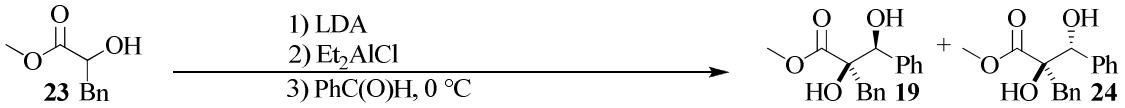
7.25−7.16 (m, 4 H), 7.14−7.10 (m, 1 H), 4.59 (s, 1 H), 3.83−3.69 (m, 5 H), 3.46−3.39 (m, 2 H), 3.38 (d, *J* = 13.5 Hz, 1 H), 3.14 (s, br, 1 H), 3.10 (d, *J* = 13.5 Hz, 1 H), 2.29 (s, br, 1 H), 1.92−1.82 (m, 2 H).

Authentic synthesis of *syn*-diol ester product



(±)-(2R*,3S*)-methyl 2-benzyl-2-hydroxy-3-methoxy-3-phenylpropanoate (16). A flame-dried flask was cooled under a stream of nitrogen and charged with (±)-(2R*,3S*)-Methyl-2-benzyl-2,3-dihydroxypent-4-enoate (**19**) (50 mg, 0.175 mmol, 1.0 equiv) and DMF (2 mL). The resulting solution was cooled in an ice/water bath and sodium hydride (60% dispersion in mineral oil, 7 mg, 0.175 mmol, 1.0 equiv) was added. After gas evolution ceased, methyl iodide (11 μL, 0.175 mmol, 1.0 equiv) was added. The reaction was stirred at 0 °C for 1 h, then warmed to rt and stirred for 1 h. The reaction mixture was then quenched with 1 M HCl (5 mL), diluted with EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 10% EtOAc/hexanes as the eluent to afford the title compound (17.4 mg, 33%) as a colorless oil. Spectroscopic data matched those reported above.

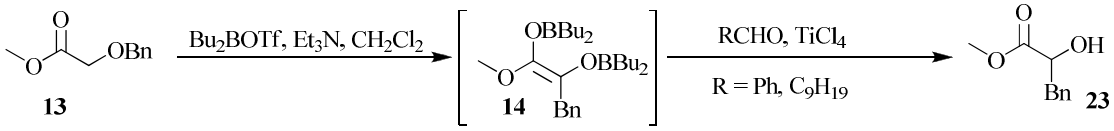
Selection for *anti*-selective aldol reactions *via* metal enolates



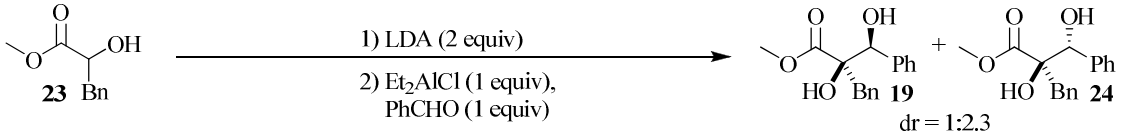
A flame-dried flask was cooled under a stream of nitrogen and charged with diisopropyl amine (148 μL, 1.05 mmol, 5.25 equiv) and THF (1.0 mL). The resulting solution was cooled in an ice/water bath and n-butyl lithium (2.00 M in hexanes, 0.5 mL, 1.0 mmol, 5.0 equiv) was added dropwise. The resulting stock LDA solution was stirred 15 minutes before use. A separate flame-dried flask was cooled under a stream of nitrogen and charged with (±)-Methyl-2-hydroxy-3-phenylpropanoate (**23**) (36 mg, 0.2 mmol, 1.0 equiv) and toluene (0.5 mL). The flask was cooled to 0 °C in an ice/water bath. Stock LDA (x equiv) was added dropwise, and the reaction was allowed to stir for 10 minutes. Diethyl aluminum chloride (1 M in hexanes, x equiv) was added dropwise to the yellow solution and white LiCl precipitated. The reaction mixture was stirred for 20 minutes, then benzaldehyde (61 μL, 0.60 mmol, 3.0 equiv) was added. The reaction was allowed to warm to rt and stirred 3 h. The reaction mixture was then quenched with 1 M HCl (5 mL), diluted with EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The reaction dr was determined by crude ^{1}H-NMR analysis. Spectroscopic properties for **(19)** were consistent with those reported in the literature.[1a] **Major (*anti*) diastereomer (24):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.42 (m, 2 H), 7.40−7.31 (m, 3 H), 7.24−7.15 (m, 3 H),

7.11−7.04 (m, 2 H), 4.88 (s, 1 H), 3.69 (s, 3 H), 3.38 (d, *J* = 13.5 Hz, 1 H), 3.18 (d, *J* = 13.5 Hz, 1 H), 2.04 (s, br, 1 H), 1.89 (s, br, 1 H).

Exploring Enolate Addition to Activated Aldehydes

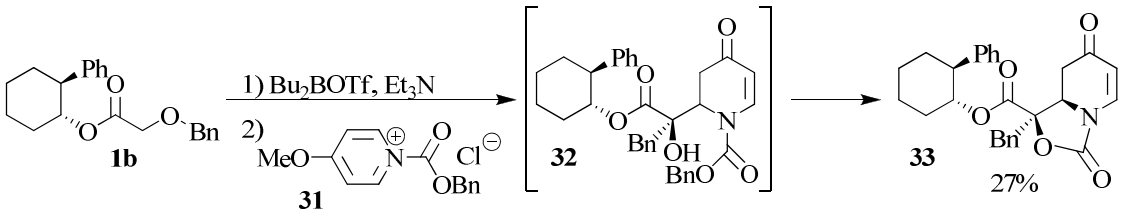


A flame-dried flask was cooled under a stream of nitrogen and charged with a 1 M solution of dibutylboron triflate in dichloromethane (0.5 mL, 0.5 mmol, 3.2 equiv). The pale yellow solution was cooled to 0 °C, and triethylamine (0.625 mmol, 4.0 equiv) was added dropwise to afford a colorless solution. Methyl 2-(benzyloxy)acetate (**13**) (28.2 mg, 0.16 mmol, 1.0 equiv) in CH_2Cl_2 (0.25 mL) was then added dropwise, and the reaction mixture was warmed rt, stirred for 1.5 h, and then cooled to -0 °C. A second flame-dried flask was cooled under a stream of nitrogen, cooled to -78 °C, and charged with aldehyde (2.0 equiv) and $TiCl_4$ (1 M in CH_2Cl_2, 4.0 equiv). Cannula transfer of **14** to the aldehydes or the aldehydes to **14** was conducted. The reaction was stired at -78 °C for 3 h, the warmed to 0 °C in an ice/water and stirred another 1 h. The reaction vessel was then opened to air, and pH 7 buffer (1 mL/mmol substrate), and methanol (2 mL/mmol substrate) were added. The resulting mixture was cooled to 0 °C, 30% aqueous H_2O_2 (2 mL/mmol substrate) was added slowly, and the reaction mixture was warmed to rt and stirred for 1 h. The reaction was worked up as described for **16** above. Crude ^{1}H-NMR analysis showed formation of **23**.



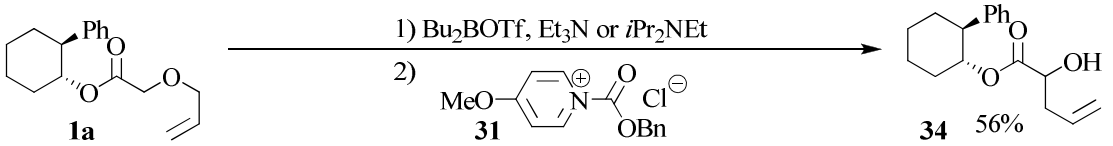
A flame-dried flask was cooled under a stream of nitrogen and charged with diisopropyl amine (148 μL, 1.05 mmol, 5.25 equiv) and THF (1.0 mL). The resulting solution was cooled in an ice/water bath and n-butyl lithium (2.00 M in hexanes, 0.5 mL, 1.0 mmol, 5.0 equiv) was added dropwise. The resulting stock LDA solution was stirred 15 minutes before use. A separate flame-dried flask was cooled under a stream of nitrogen and charged with (±)-Methyl-2-hydroxy-3-phenylpropanoate (**23**) (36 mg, 0.2 mmol, 1.0 equiv) and toluene (0.5 mL). The flask was cooled to 0 °C in an ice/water bath. Stock LDA (2.0 equiv) was added dropwise, and the reaction was allowed to stir for 10 minutes, then the reaction solution was cannula transferred to a 0 °C flask containing benzaldehyde (1.0 equiv) and Et_2AlCl (1 M in hexanes, 1.0 equiv). The reaction was allowed to warm to rt and stirred 3 h. The reaction mixture was then quenched with 1 M HCl (5 mL), diluted with EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The reaction dr was determined by crude ^{1}H-NMR analysis.

Investigating new electrophiles for tandem wittig rearrangement reactions



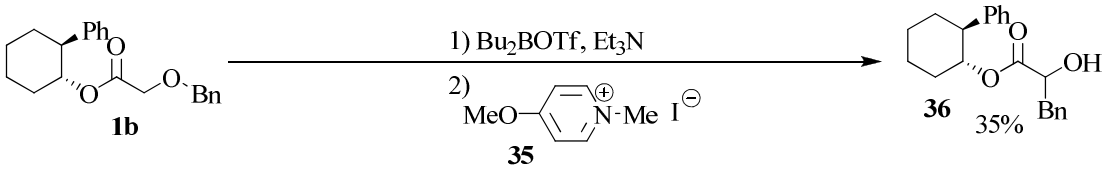
(±)-(1R*,8aR*)-((1R*,2S*)-2-phenylcyclohexyl) 1-benzyl-3,7-dioxo-3,7,8,8a-tetrahydro-1H-oxazolo[3,4-a]pyridine-1-carboxylate (33). A flame-dried flask was cooled under a stream of nitrogen and charged with a 1 M solution of dibutylboron triflate in dichloromethane (0.64 mL, 0.64 mmol, 3.2 equiv). The pale yellow solution was cooled to 0 °C, and triethylamine (112 μL, 0.80 mmol, 4.0 equiv) was added dropwise to afford a colorless solution. (±)-(1R*,2S*)-2-Phenylcyclohexyl-2'-(benzyloxy)acetate (**1b**) (65 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (0.40 mL) was then added dropwise, and the reaction was stirred for 1.5 h. The solution was cannulated into a solution (-40 °C) of pyridinium salt **31** which was formed from 4-methyoxypyridine (61 μL, 0.60 mmol, 3.0 equiv) and benzyl chloroformate (86 μL, 0.60 mmol, 3.0 equiv) in toluene (1 mL) at -23 °C for 40 min. After 2 h, the reaction mixture was then quenched with 1 M HCl (5 mL), diluted with EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to yield the title compound **33** (24.2 mg, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 1 H), 7.39−7.35 (m, 1 H), 7.30−7.25 (m, 3 H), 7.25−7.11 (m, 5 H), 5.39 (d, *J* = 8.0 Hz, 1 H),

5.17 (dt, *J* = 4.0, 11.0 Hz, 1 H), 3.03 (d, *J* = 14.5 Hz, 1 H), 2.97 (d, *J* = 14.5 Hz, 1 H), 2.89 (dd, *J* = 4.0, 15.5 Hz, 1 H), 2.73 (dt, *J* = 3.5, 11.5 Hz, 1 H), 2.55 (t, *J* = 15.5 Hz, 1 H), 2.20 (dd, *J* = 4.5, 15.5 Hz, 1 H), 2.04−1.87 (m, 2 H), 1.84−1.77 (m, 1 H), 1.60−1.33 (m, 5 H).



(±)-(1R*,2S*)-2-phenylcyclohexyl 2-hydroxypent-4-enoate (34). The reaction with (±)-(1R*,2S*)-2-Phenylcyclohexyl-2'-(allyloxy)acetate (**1a**) was conducted using a procedure analogous to that described above for the preparation of **33**. The crude product was purified by flash chromatography on silica gel using 25% EtOAc/hexanes as the eluent to afford the title compound (**34**) (28 mg, 56%). The pure material was judged to be of 1:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.24 (m, 2.5 H), 7.21−7.16 (m, 2.5 H), 5.63−5.54 (m, 0.5 H), 5.17−5.01 (m, 2.5 H), 4.89−4.85 (m, 0.5 H), 4.78−4.73 (m, 0.5 H), 2.73−2.65 (m, 1 H), 2.54 (s, br, 1 H), 2.42−2.35 (m, 0.5 H), 2.30−2.23 (m, 0.5 H), 2.20−2.09 (m, 1 H), 2.04−1.92 (m, 1.5 H), 1.91−1.85 (m, 1 H), 1.83−1.73 (m, 1.5 H), 1.63−1.30 (m, 5 H).

***N*-Methyl pyridinium electrophiles fail to provide tandem products**



(±)-(1R*,2S*)-2-phenylcyclohexyl 2-hydroxy-3-phenylpropanoate (36). The reaction with 4-methoxy-1-methyl-pyridinium iodide (**35**) was conducted using a procedure analogous to that described above for the preparation of **33**. The crude product was purified by flash chromatography on silica gel using 15% EtOAc/hexanes as the eluent to afford the title compound (**36**) (23 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.24 (m, 5 H), 7.17−7.15 (m, 5 H), 5.05−4.97 (m, 1 H), 4.06−4.00 (m, 1 H), 2.94 (dd, *J* = 4.5, 14.0 Hz, 1 H), 2.77−2.65 (m, 2 H), 2.49 (d, *J* = 4.5 Hz, 1 H), 2.12−2.06 (m, 1 H), 1.99−1.92 (m, 1 H), 1.92−1.85 (m, 1 H), 1.84−1.77 (m, 1 H), 1.65−1.56 (m, 1 H), 1.51−1.43 (m, 2 H), 1.43−1.33 (m, 1 H).

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