Of Palladium Catalysis and Stereochemical Strategies:
A Collection of Synthetic and Educational Chemistry Studies

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Chemistry)
in the University of Michigan
2017

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Dedication

To My Family and Friends, Old and New

You have been immensely supportive leading up to and throughout this process; I would not have made it this far without that support.

I will be grateful always.

Acknowledgments

First and foremost, I would like to give thanks to my doctoral advisor, Professor John P. Wolfe, for giving me the opportunity to complete my graduate studies in his lab. Without his support and guidance, I would not have been able to make it through my graduate studies, and I would not have had the opportunity to pursue the many side projects and educational research projects I have been fortunate to participate in. I have been able to pursue new directions, broaden my horizons, and advance as an independent researcher over the last five years. I continue to be astounded by his patience, resolve, and cunning. He truly is one of the greatest mentors a chemist could hope for.

I would also like to acknowledge the many others that have helped my development as a chemist. Beginning at the University of California, Davis, Professor Annaliese K. Franz provided me the opportunity to work in her laboratory, and alongside Dr. Megan Danielewicz I was able to conduct my first chemical biology and synthetic chemistry in a research laboratory. The lab work intrigued me, and led me toward my current trajectory as a chemist. I would also like to thank Professor Pavel Nagorny for allowing me the chance to rotate in his lab, and conduct research on thiourea-inspired organocatalysts. I am grateful for the opportunity that you provided, and your continued support throughout the last several years as I have advanced through the doctoral program. I owe a debt of gratitude to my former committee members, Professor John Montgomery and Professor Matthew Soellner, who served on my committee for three years. I appreciate the time and energy you have provided to help me develop as a chemist and as a person. Thanks to Professor Montgomery, I was able to spend a summer abroat in Tarragona Spain working at the Catalonian Institute of Chemical Technology (ICIQ) – while this work will not be part of this thesis, I appreciate Professor Antonio Echavarren's allowing me to work in his lab, as well as Pili Calleja Ramos for her mentorship, and the entire Echavarren Lab. Pili defends her thesis the day after me, so I hope that gives us some good luck for the future!

As a synthetic chemist, I have been fortunate to have exceptional mentors throughout the years at Michigan, including Dr. Nick Babij, Dr. John Hutt, Dr. Gracie Winschel, and Dr. Nate Cicowicz. The skill of these synthetic chemists has pushed me to strive for the excellence that they have shown to me during my time here. I have been granted a wonderful opportunity to work in the Wolfe group, and I owe so many great experiences to the time spent with my colleagues. In particular, I want to thank my fellow graduate students Zac Garlets, Derick White, and Luke Peterson. To Zac, I will always remember our rotations together, and I cherish your friendship and kindness throughout the years. To Derick, I have always appreciated your ability to bring joy to people, through music, jokes, and games, and I am grateful for your ability to cheer me up on a rough day. And to Luke, I have felt a particular kinship as we share so many interests, hobbies, and a sense of humor that is unparalleled. I appreciate all the fun we have had throughout the years, as well as your feedback and input on educational research. I would like to thank the former Wolfe Group undergraduates that I have worked with, including Grace McKenna, Kaia Parenti, Blane Zavesky, and Madeline Herman. I wish you the best of luck in your future graduate school endeavors, and a lifetime of happiness. We have had some great times together, and I will always appreciate the time we have had together, both in lab and out. I would like to particularly thank visiting student Yifan Shen for his expanding the scope of the Lactam cyclization chemistry in Chapter 2 of this thesis.

Thank you to Dr. Brett Hopkins and Dr. Renata Everett, who helped me develop as a synthetic chemist in the early days of my PhD. You are both bright and helpful people, and I appreciate your kindness. Mr. Jeremiah Alicea, as both a roommate and labmate, you have provided me countless hours of joy and fun to offset our hours spent working at the bench. I would also like to thank Elsa Hinds, my fellow California native in lab, for being the longest-standing labmate still left in my room, as well as Janelle Kirsch, Evan Bornowski, and all the rotators that have come through our lab. You have all brought a unique style to the lab, and I wish you the best in your future endeavors.

In recent years, the emphasis on educational research has allowed greater interaction with colleagues in chemical education. Thank you, Assistant Professor Leah Bricker, not only for being a great master's degree advisor (for my Master's in Postsecondary Science Education), but also for being the instructor of several of my classes, and for providing substantive feedback on educational research I have conducted throughout the last three years. Thank you to Professor Brian Coppola for improving my teaching and sparking an interest in education-based research – without your guidance, I would not have been able to improve my teaching practice, and likely would not have become involved in educational research to begin with. I also owe a debt of gratitude to Dr. Rachel Barnard for her patience and guidance in helping me develop as an educational researcher. Without your drive, mentorship, and skillset, I would be lost amidst the mountains of data these projects have provided.

Of course, I would like to thank my friends and family for helping make this possible. In particular, I would like to thank my mom and dad for being supportive of me along my journey. Through the many late-night conversations and early mornings, I cherish your time and thoughtfulness as parents. I would also like to thank Jeff, Benjamin, and Granny for your support and love. I want to give a special shoutout to those grandparents who always supported me, but were unable to see the completion of this journey – I wish I could share these moments with you in person, but I know you have been here in spirit. Finally, I would like to thank my wonderful wife Hilary. Throughout the ups and downs of graduate school and life, you have been the light that helps keep me going. You have been particularly helpful during the preparation of this thesis, and I look forward to repaying the favor next year and beyond.

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List of Abbreviations

Ac	acetyl
All	allyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
n-Bu	butyl
^{t}Bu	*tert*-butyl
CAN	ceric ammonium nitrate
Cbz	carboxybenzyl
mCPBA	*meta*-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DTBP	2,6-di-*tert*-butylpyridine
Et	ethyl
KHMDS	potassium hexamethyldisilazide
LG	leaving group
Me	methyl

(Me)4t-BuXPhos	2-di-t*ert*-butylphosphino-3,4,5,6-tetramethyl-2’,4’,6’-tri-*iso*-propylbiphenyl
MeOTf	methyl trifluoromethanesulfonate
Ms	methanesulfonyl
NMO	*N*-methylmorpholine 4-oxide
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
p-TSOH	*para*-toluenesulfonic acid
XPhos	2-di-t*ert*-butylphosphino-2’,4’,6’-tri-*iso*-propylbiphenyl

Abstract

The importance of organic chemistry is realized primarily in two disciplines: synthetic application and education of chemical concepts, including scientific thought and diagnostic thinking. Mono- and polycyclic lactams, ureas, and sulfamides serve both as synthetic intermediates, and bioactive compounds in their own right. This thesis describes new methodology to access these compounds in a rapid and straightforward manner through the use of palladium-catalyzed carboamination reactions.

In this thesis, Chapter 2 describes the development of palladium-catalyzed carboamination reactions toward the synthesis of γ- and δ-lactams, and Chapter 3 advances carboamination methodologies to the construction of bicyclic ureas and sulfamides. This stereodivergent synthetic methodology provides access to multiple stereoisomeric products, which serve as attractive synthetic intermediates toward the construction of tricyclic guanidine natural products, as well as additional alkaloids of the tetraponerine family.

Chapter 4 focuses on the impact of implementing a companion course (CHEM 220) to aid the peer-led study group program at the University of Michigan. This study was guided by three questions we had regarding course implementation, focused on facilitator perceptions of value, how facilitation has changed with course implementation, and how content knowledge or confidence may have changed. This is a mixed-methods study that draws from facilitator perceptions, course evaluations of teaching, facilitator surveys, as well as targeted surveys for those both without and with course implementation.

Chapter 5 continues this investigation into the impact of course-support by using audiovisual analysis to investigate facilitator interactions in study group and the support course, and uses this audiovisual data to trace conceptual correctness and instructional coherence. We sought to answer several research questions with this audiovisual data, with an emphasis on tracing how facilitator error in CHEM 220 is resolved, how facilitator error arises in study group, and tracing what facilitators were doing when topics they err in are covered in CHEM 220.

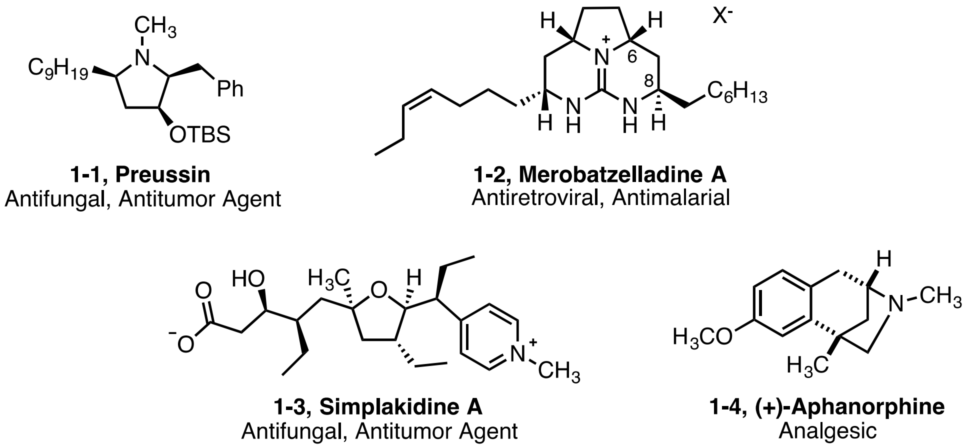
Chapter 1

Synthesis of Heterocycles Via Palladium-Catalyzed Cyclization Reactions

1-1 Introduction

Hetercycles and carbocycles are ubiquitous in biologically active compounds. Nitrogen- and oxygen-containing heterocycles are present in a large array of pharmaceuticals and agrochemicals, including preussin **1-1**,[1] merobatzelladine A **1-2**,[2] simplakidine A **1-3**,[3] and aphanorpine **1-4**[4] (**Figure 1.1**). These compounds elicit a range of bioactivities, including antifungal, antibacterial, and analgesic properties.

Figure 1.1 Biologically Active Heterocycles



1-1, Preussin
Antifungal, Antitumor Agent

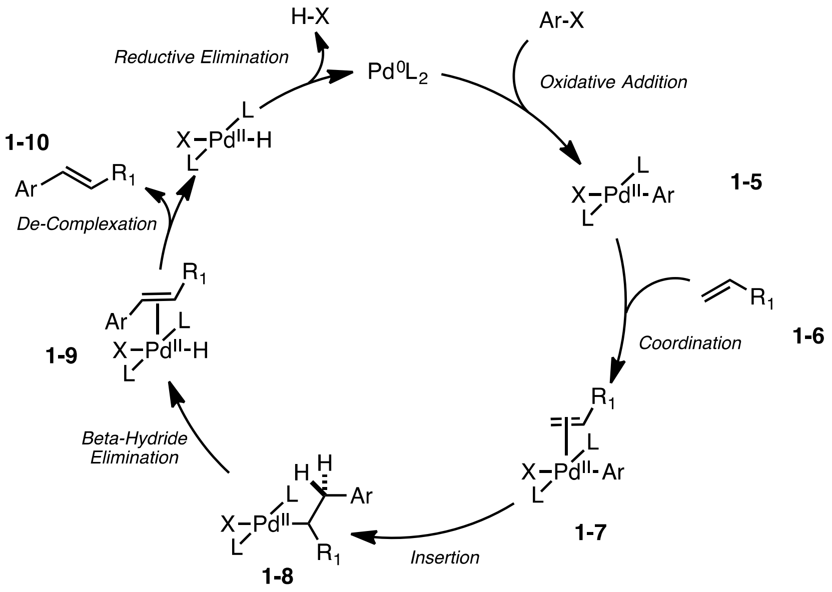
1-2, Merobatzelladine A
Antiretroviral, Antimalarial

1-3, Simplakidine A
Antifungal, Antitumor Agent

1-4, (+)-Aphanorphine
Analgesic

Transition metal catalysis has been used for decades to construct complex organic compounds. For more than a century, copper-catalyzed (Glaser,[5] Meerwein,[6] Sonogashira[7]), nickel-catalyzed (Wurtz,[8] Kumada[9]), and palladium-catalyzed (Negishi,[10] Stille,[11] Hiyama[12]) C-C cross-coupling reactions have been used in molecular assembly of heterocyclic compounds. Over the years, refinements in organometallic chemistry have led to lower catalyst loadings, higher yields, and greatly expanded scope.[13]

Scheme 1.1 Catalytic Cycle of the Heck Reaction

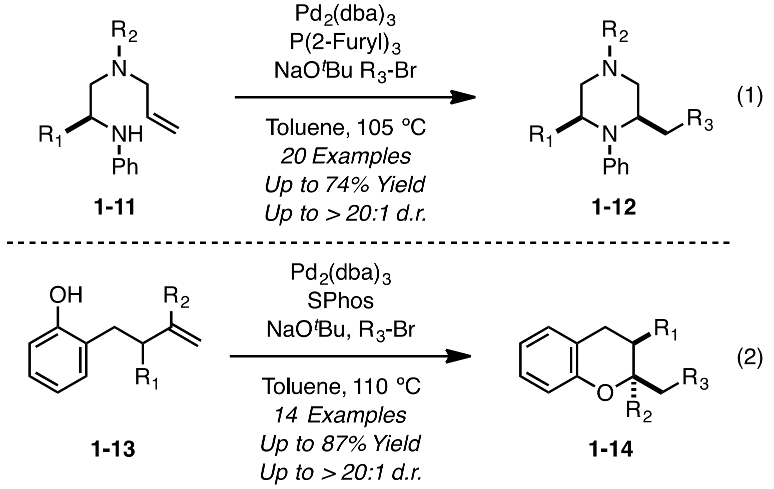


The Heck reaction is one of the most powerful cross-coupling reactions developed during this time. Initially developed by Tsutomu Mizoroki in 1971 this reaction uses palladium to couple styrenes with aryl halides, forming a bond between two sp^2-hybridized carbon atoms (**Scheme 1.1**).[14] Richard Heck from the University of Delaware improved the reaction in 1972 by introducing phosphine ligands,[15] later receiving the 2010 Nobel Prize in Chemistry alongside Akira Suzuki and Ei-ichi Negishi for their work on palladium-catalyzed cross-coupling reactions.[16] This reaction proceeds via an initial oxidative addition into the aryl halide bond to give intermediate **1-5**, followed by coordination to alkene **1-6** and migratory insertion of **1-7** to get to intermediate **1-8**. From intermediate **1-8**, subsequent beta-hydride elimination and de-complexation yields product **1-10**. Importantly, these active organopalladium intermediates have been attractive targets for several branches of cross-coupling chemistry and form the foundation for many active areas of research worldwide, including work done by the Hartwig,[17] Buchwald,[18] and Wolfe laboratories[19] (among many others).

1-2 Palladium-Catalyzed Carboamination and Carboetherification Reactions

Over the past decade, the Wolfe Group at the University of Michigan has developed a series of palladium-catalyzed carboamination and carboetherification reactions.[20] Analogous to other cross-coupling reactions, these transformations couple together an aryl halide and an alkene bearing a pendant heteroatom-hydrogen bond (**Scheme 1.2**). This reaction diastereoselectively forms a carbon-carbon and carbon-heteroatom bond in a single step, serving as a powerful entry point into highly substituted heterocycles.

Scheme 1.2 Representative Carboamination and Carboetherification Reactions

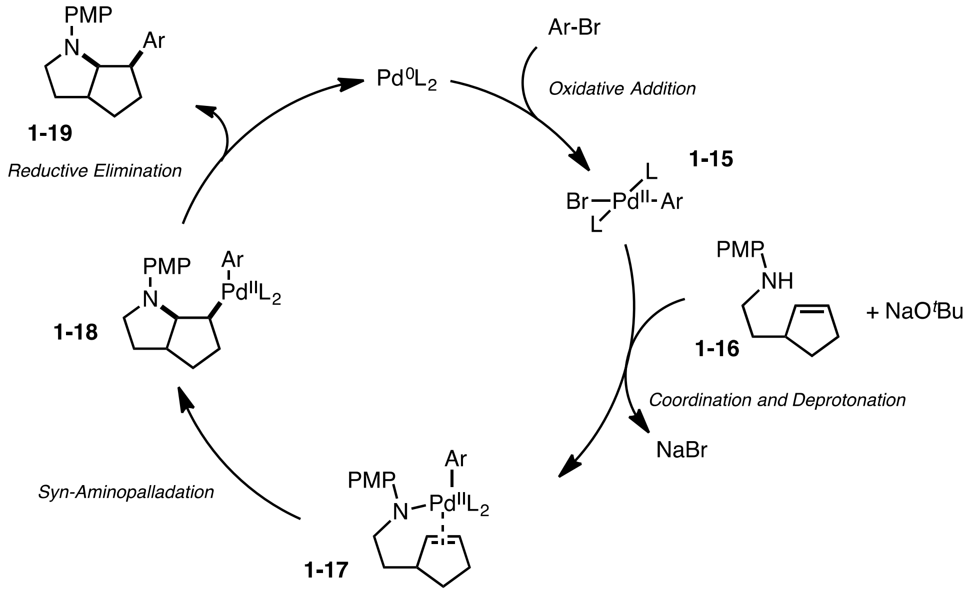


Palladium-catalyzed carboamination and carboetherification reactions have been leveraged to synthesize a wide variety of 5- and 6-membered heterocyclic compounds such as piperazines **1-12**[21] and chromans **1-14**,[22] among many others. Good diastereoselectivity may be observed from initial substitution at positions on the substrate adjacent either to the cyclizing group or at the allylic position of the tethered alkene, with selectivities up to greater than 20:1. Importantly, when chiral enantioenriched substrates are used, the stereochemical information is retained and conferred to the desired product, which is an important feature necessary for use in efficient total syntheses of bioactive molecules and natural products.[23]

1-3 Cyclization Events Proceeding Via *Syn*-Aminopalladation

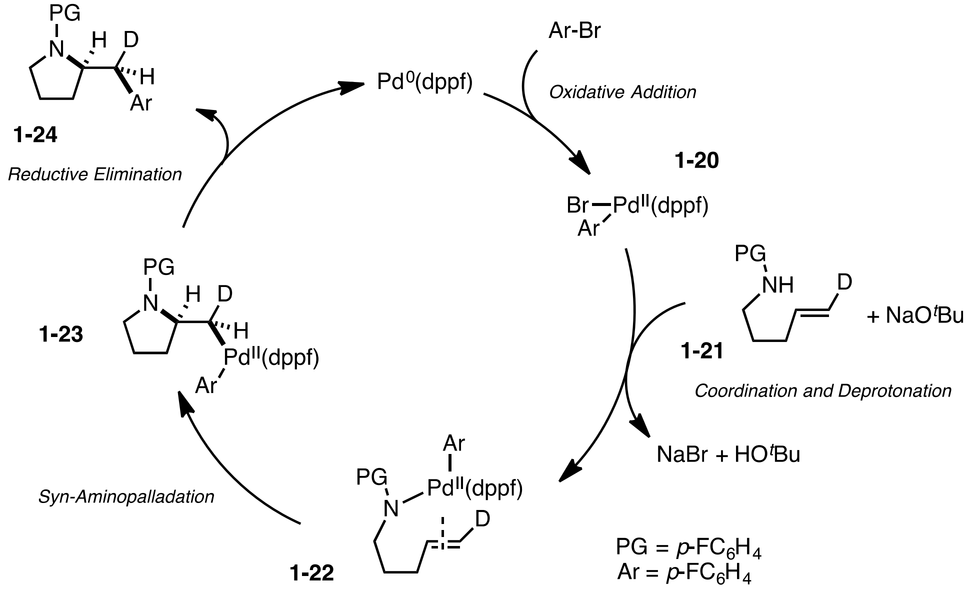
Initial investigations into the reaction mechanism for carboamination were conducted using substrates bearing cyclic alkenes.[24] These reactions afford products with a *cis* or *syn* relationship between the nitrogen and the aryl group. The outcome of these reactions led to a proposed catalytic cycle whereby the initial oxidative addition step of the aryl halide leads to intermediate **1-15** (**Scheme 1.3**). From there, the proposed mechanism proceeds via deprotonation of the nitrogen of substrate **1-16** and coordination of palladium to the nitrogen to give intermediate **1-17**, which will subsequently undergo *syn*-aminopalladation to the alkene and arrive at **1-18**. Finally, reductive elimination of **1-18** yields desired product **1-19**, and palladium (0) may re-enter the catalytic cycle. The aminopalladation step of the carboamination reaction resembles caarbopalladation undergone by intermediate **1-8** of the Heck reaction (**Scheme 1.1**). At this point, the intermediate is then captured by the nucleophilic portion of the substrate (e.g.; amine, alcohol). As such, the carboamination reaction may be viewed as an interrupted Heck reaction, trapping the arylpalladium complex from initial oxidative addition with the tethered nucleophile/alkene substrate and leading to increas-

Scheme 1.3 Proposed Catalytic Cycle of *N*-PMP Pyrrolidine Formation



ed molecular complexity compared to its paternal reaction, in contrast to undergoing the beta-hydrogen step in the Heck reaction.

Scheme 1.4 Deuterium Labelling Studies of Acyclic Aminoalkene Substrates

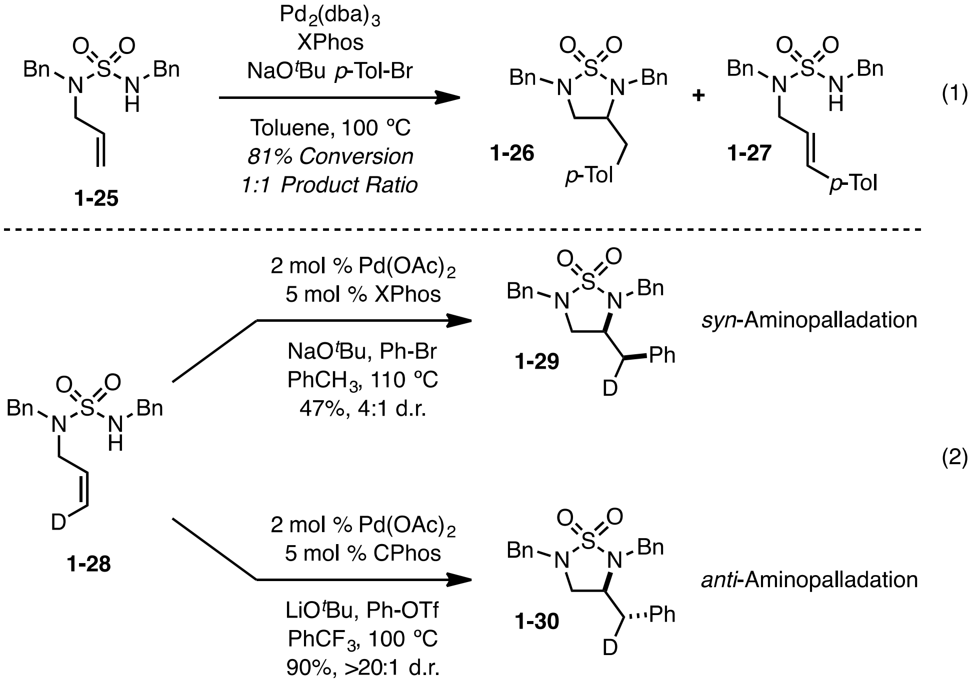


To further probe reaction mechanism in systems lacking a cyclic alkene, deuterated substrate **1-21** was examined, and the results indicated that the *syn*-addition mechanism is operational with acyclic substrates.[25] Extensive kinetic studies on palladium complexes related to **1-22** and **1-23** indicated that (a) increased nucleophilicity of the nitrogen increases reaction rate, and (b) insertion proceeds via a 4-coordinate palladium species.[17,18] The configuration of product **1-24** supported the *syn*-aminopalladation reaction mechanism put forth for substrates bearing a cyclic alkene, wherein the palladium and nitrogen would add to the same side of the alkene via intermediate **1-22**, resulting in the product shown in **Scheme 1.4**.

1-4 Palladium-Catalyzed Carboamination Events That Proceed Via *Anti*-Aminopalladation

After several successful optimizations of a broad array of substrate and product

Scheme 1.5 Limitations of Reactions Proceeding via *Syn*-Aminopalladation

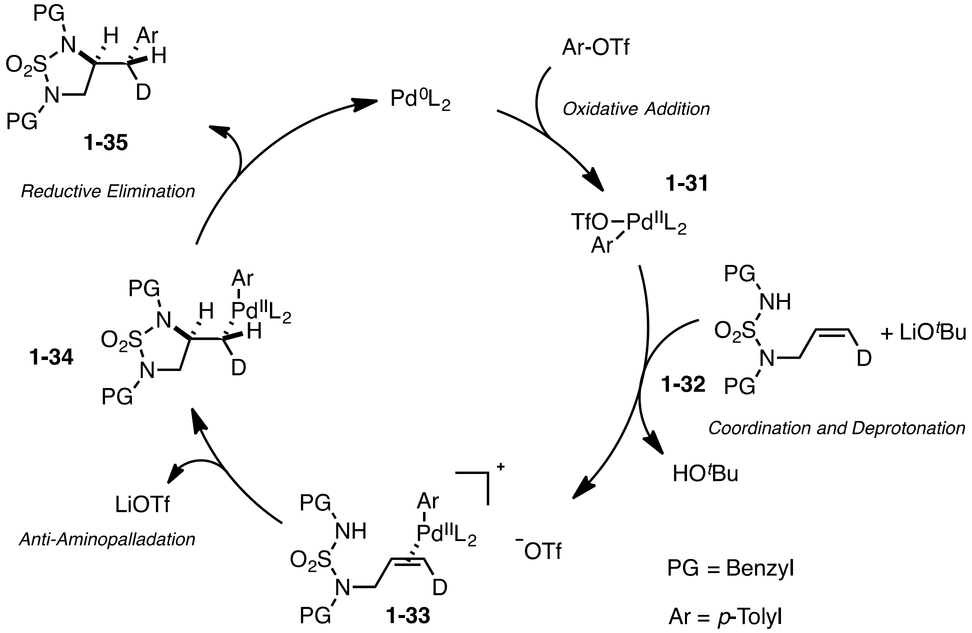


classes, some limitations began to surface. One of the largest limitations of carboheterocyclization reactions was the nature of both steric and electronic properties of the cyclizing heteroatom. While sterics seemed to be an intuitive issue (given the congested nature of the proposed palladium-heteroatom-complexed intermediates), the electronic trends indicated that a sweet spot of pKa proved to be most useful. For example, primary amine substrates failed to cyclize unless first protected by either an aryl or carbamate protecting group. Additionally, weakly nucleophilic substrates (such as amides, sulfamides **1-25**, or carboxylic acids) failed to cyclize in appreciable yields, in part due to competitive formation of the Heck side product (**Scheme 1.5, Equation 1**).

A discovery made by Mr. Ryan Fornwald in the early years of my PhD studies revealed that by altering several reaction conditions, *N*-protected sulfamide substrates would undergo carboamination with minimal Heck side product formation.[26] After deuterium labeling studies, it was determined that sulfamide cyclization could undergo either *syn*- or *anti*-aminopalladation reaction mechanisms depending on the choice of ligand, solvent, coupling partner, base, and palladium source (**Scheme 1.5, Equation 2**).

To promote cyclization via the via *anti*-aminopalladation pathway, it was important to employ biaryl phosphine ligands, in conjunction with palladium (II) acetate, lithium *tert*-butoxide, an aryl triflate (as opposed to aryl halide) coupling partner, with benzotrifluoride or *tert*-butanol as solvents (both of which have higher dielectric constants than the toluene previously employed in these reactions).

Scheme 1.6 Carboamination Proceeding Via Anti-Aminopalladation Mechanism



At present, we hypothesize that carboamination reactions that result in anti-addition to the alkene proceed via the catalytic cycle shown in **Scheme 1.6**. This catalytic cycle is initiated by oxidative addition to the aryl triflate to afford complex **1-31**. Subsequent coordination to the alkene and deprotonation of substrate **1-32** affords intermediate **1-33**. *Anti*-aminopalladation results in intermediate **1-34**, which undergoes reductive elimination to afford product **1-35**.

After these deuterium-labeled studies, investigations into substrate scope revealed that electron-poor substrates were more prone to undergo *anti*-aminopalladation. New substrate classes were probed, including tosyl-protected amines and guanidines, as well as amides and carboxylic acids.

1-5 Looking to the Future

In the following chapters, substrates that have been observed to proceed via both *syn*- and *anti*-aminopalladation pathways are presented. The products of these reactions may be used either as synthetic intermediates, or demonstrate use as potential pharmacophores. As a consistent theme, these reactions involve palladium-catalyzed cyclizations, and leverage the power of carboheterofunctionalization to construct complex products rapidly from synthetically accessible substrates.

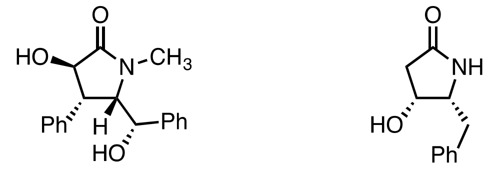
Chapter 2

Synthesis of γ- and δ-Lactams Via Palladium-Catalyzed Carboamination Reactions

2-1 Introduction

γ-Lactams (pyrrolidin-2-ones) are a common motif present in a variety of biologically active compounds and natural products including clausenamide[27,28] (**2-1**, nootropic agent) and streptopyrrolidine[29] (**2-2**, angiogenesis inhibitor) (**Figure 2.1**).

Figure 2.1 Biologically Active 4-Benzylpyrrolidin-2-one Derivatives



2-1, Clausenamide
Nootropic Agent

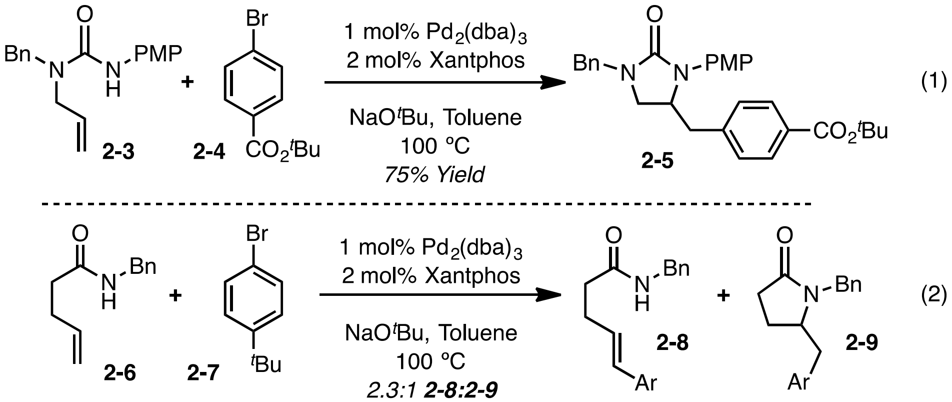
2-2, Streptopyrrolidine
Angiogenesis Inhibitor

Given the significance of these molecules, a variety of synthetic techniques have been employed for their construction[30] including alkene hydroamination,[31,32] intramolecular N-arylation of amides,[33] N-centered radical cyclizations of 4-pentenamides,[34,35] four-component coupling reactions,[36] and reductive amination strategies.[37]

2-2 Previous Carboamination Attempts

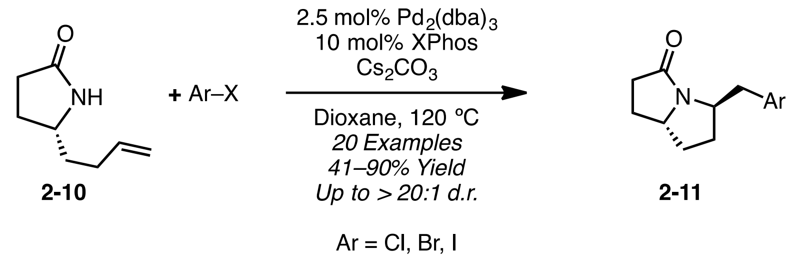
Over the past 12 years our group has developed a series of palladium-catalyzed alkene carboamination reactions between alkenes bearing pendant nitrogen nucleophiles and aryl/alkenyl halides/triflates.[19] These transformations generate both a C–N and a C–C bond during the ring-forming step and afford the heterocyclic products in generally good chemical yield, typically with high diastereoselectivity. For example, treatment of *N*-allyl urea **2-3** with **2-4** in the presence of a Pd/Xantphos catalyst afforded **2-5** in 75% yield (**Scheme 2.1, Equation 1**).[38,39,40]

Scheme 2.1 Palladium-Catalyzed Alkene Carboamination of Urea vs. Amide



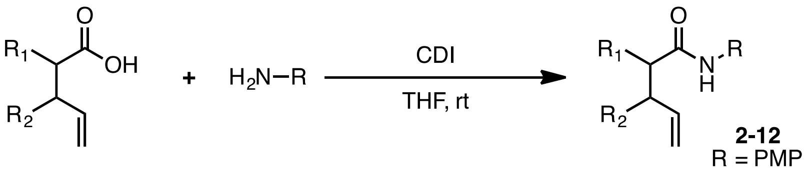
We felt that this approach could be employed for the construction of γ-lactams from *N*-protected 4-pentenamides (**Scheme 2.1**, **Equation 2**). However, although we have successfully employed a number of different nitrogen nucleophiles in these reactions, including anilines,[24] guanidines,[41] carbamates,[42] and *N*-acylated amines,[42] our early efforts to extend this method to 4-pentenamides were largely unsuccessful as products were formed in very low yields due to competing Heck-arylation of the alkene. For example, attempts to couple amide **2-6** with **2-7** under conditions that proved optimal with urea substrate **2-3** afforded a mixture of Heck arylation product **2-8** and desired product **2-9** in an unfavourable 2.3:1 ratio.[43,44]

Scheme 2.2 Cacchi's Palladium-Catalyzed Alkene Carboamination of Lactam **2-10**



Given our unsatisfactory results for the conversion of **2-6** to **2-9**, we were quite surprised when Cacchi reported a series of palladium-catalyzed carboamination reactions of **2-10** that afford substituted (5*R*, 7a*R*)-5-aryl hexahydropyrrolizidin-3-ones **2-11** (**Scheme 2.2**).[45] Although only a single alkene substrate was examined in these transformations, the coupling of **2-10** with a range of different aryl halides provided the bicyclic lactam products **2-11** in generally good yield (41–90%). Given Cacchi's success with this system, coupled with the fact that the scope of the amide carboamination reactions (with respect to amide substrate structure) was not fully explored, we elected to re-examine palladium-catalyzed alkene carboamination reactions of pentenamide-derived substrates related to **2-6**.

Scheme 2.3 Synthesis of N-PMP Pentenamides

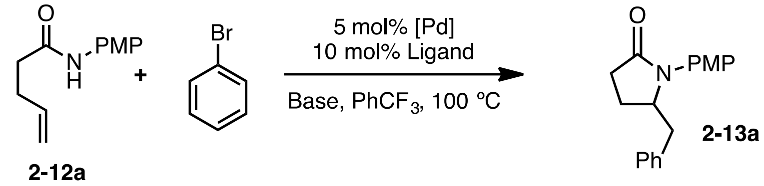


Pentenamide-derived substrates **2-12** were synthesized from the related carboxylic acids via an amide coupling of acid and amine in the presence of 1,1'-carbonyldiimidazole (**Scheme 2.3**).[46] 4-Pent-enoic acid and 2-methyl-4-pentenoic acid were used as-is from commercial sources, while 3-methyl-4-pentenoic acid and 3-phenyl-4-pentenoic acid were synthesized in 2 steps from the croyl alcohol and cinnamyl alcohol (respectively) as reported in the literature via a Claisen rearrangement and subsequent ester hydrolysis.[47] After initial optimization, substrates bearing a PMP protecting group were chosen for their effectiveness and ability to be deprotected.

2-3 Optimization Studies

In order to develop satisfactory conditions for palladium-catalyzed alkene

Table 2.1 Optimization Studies for the Carboaminations of Aliphatic Lactams



Entry	[Pd]	Ligand	Base	Solvent	Yield[b]
1	$Pd_2(dba)_3$ (2.5 mol %)	XPhos	Cs_2CO_3	Dioxane (120 °C)	<5%[c]
2	$PdCl_2(MeCN)_2$ (5 mol %)	CPhos	LiO*t*Bu	$PhCF_3$	34%[d]
3	$Pd(OAc)_2$ (5 mol %)	XPhos	LiO*t*Bu	$PhCF_3$	15%[d]
4	$PdBr_2$ (5 mol %)	XPhos	LiO*t*Bu	$PhCF_3$	69%[d]
5	$Pd(OAc)_2$ (5 mol %)	XPhos	LiO*t*Bu	$PhCF_3$	<5%[c]
6	$Pd(OAc)_2$ (5 mol %)	RuPhos	LiO*t*Bu	$PhCF_3$	58%
7	**$PdBr_2$** **(5 mol %)**	**XPhos**	**LiO*t*Bu**	**$PhCF_3$**	**79%**

[a]Conditions: 1 equiv **2-12a**, 2.0 equiv PhBr, 2.0 equiv base, 2.5 mol % $Pd_2(dba)_3$ or 5 mol % $Pd(OAc)_2$ or 5 mol %$PdBr_2$, 10 mol % ligand, solvent (0.1 M), 100 °C, 4–16 h. [b]Yields were determined by ^1H NMR

using phenanthrene as an internal standard. [c]Yields reported as <5% indicate the desired product was not observed by ^{1}H NMR analysis of the crude reaction mixture.

reactions of pentenamide derivatives we explored the coupling of *N*-PMP-substituted pentenamide substrate **12a** with bromobenzene (**Table 2.1**).[48] We first examined the conditions reported by Cacchi, however these conditions failed to produce the desired lactam product; unreacted starting material was observed along with Heck arylation of the alkene (**Table 2.1**, entry 1). We subsequently varied the palladium source, base, solvent, and phosphine ligand, to ultimately arrive at optimized conditions that employed $PdBr_2$/XPhos as the catalyst, LiO^{t}Bu as base, and $PhCF_3$ as solvent (**Table 2.1**, Entry 7). These conditions afforded 79% yield of the desired product **13a**.

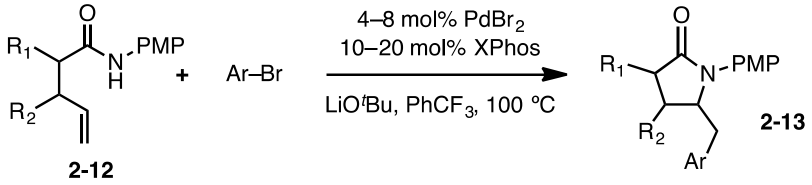
2-4 Scope

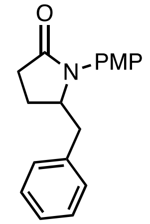
Once we had discovered conditions that provided satisfactory results for the coupling of **2-12a** with bromobenzene we began to explore the scope of the amide carboamination reactions. As shown in **Table 2.2**, both aryl chlorides and aryl bromides could be employed as coupling partners, and the reaction was effective with electron-rich, electron-neutral, and electron-poor electrophiles. The coupling of heteroaryl halides was also accomplished, albeit in modest yields.

Substrates **12c** (R = H, R^1 = Me) and **12d** (R = H, R^1 = Ph) bearing a substituent at the allylic position were transformed to *trans*-disubstituted lactams **2-13d** through **2-13j** in good yield with good to excellent diastereoselectivity. Not surprisingly, increasing the size of the allylic group from methyl to phenyl led to increased diastereoselectivities. In contrast, diastereoselectivities were poor in reactions of **2-12b** (R = Me, R^1 = H) due to base-mediated scrambling of the α-stereocenter in the lactam products **2-12b** and **2-**

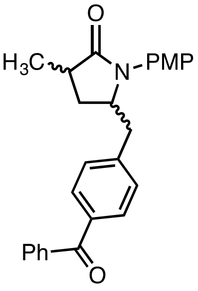
12c.[49] Unfortunately, efforts to employ weaker bases were unsuccessful. Although substitution on the backbone of the substrate was tolerated, efforts to transform substrates bearing a substituent at the internal or terminal alkene carbon atom failed to generate the desired products.

Table 2.2 Palladium-Catalyzed Synthesis of γ-Lactams[a]

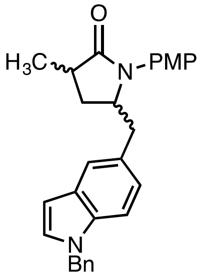




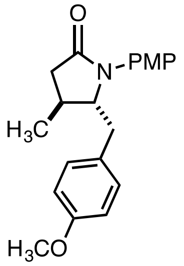
2-13a, 79%



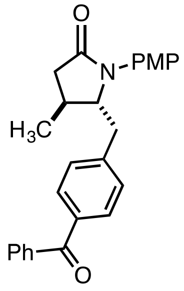
2-13b, 84%
1:1 d.r.



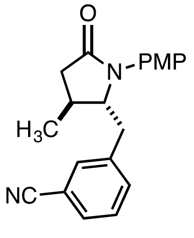
2-13c, 46%[b]
1:1 d.r.



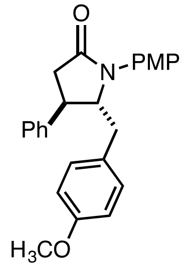
2-13d, 48%
8:1 d.r.



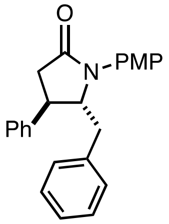
2-13e, 79%
6:1 d.r.



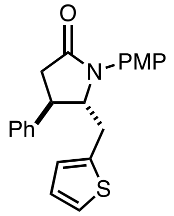
2-13f, 63%
6:1 d.r.



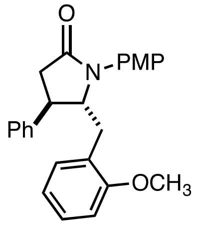
2-13g, 73%
>20:1 d.r.



2-13h, 65%
>20:1 d.r.



2-13i, 44%
>20:1 d.r.

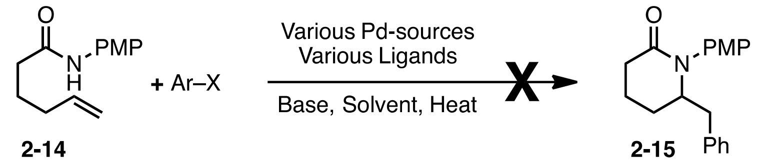


2-13j, 67%[b]
>20:1 d.r.

[a]Conditions: 1 equiv **2-12**, 2.0 equiv ArBr, 2.0 equiv base, 4–10 mol % [Pd], 8–20 mol % ligand, solvent (0.1 M), 100 °C, 4–16 h. Yields are isolated yields (average of two or more experiments). [b]The reaction was conducted using an aryl chloride rather than an aryl bromide.

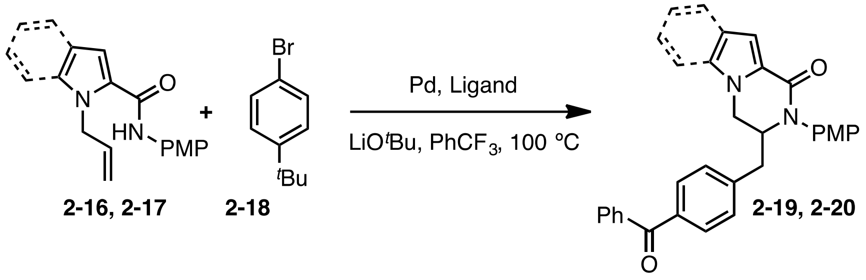
To further explore the scope of these transformations, we elected to investigate the synthesis of six-membered lactams from substituted hex-5-eneamide derivatives. As such, we prepared substrate **2-14** and investigated its reactivity in the palladium-catalyzed alkene carboamination reactions. Unfortunately, despite extensive studies with a number of different catalyst systems and reaction conditions, efforts to couple **2-14** with bromobenzene provided little or none of the desired product **2-15** (**Scheme 2.4**).

Scheme 2.4 Unsuccessful Palladium-Catalyzed Carboamination of **2-14**



We reasoned that the failure of substrate **2-14** to undergo the desired transformation may be due to entropic factors associated with generating the larger sized ring. It seemed that substrates with less conformational flexibility would therefore be more likely to undergo the palladium-catalyzed carboamination, so our attention turned to substrates **2-16** and **2-17** derived from *N*-allylindole-2-carboxylic acid and the analogous pyrrole derivative. As shown in Table 3, the conditions that proved optimal for the generation of γ-lactams provided unsatisfactory results in the coupling of **2-16** or **2-17** with 4-bromobenzophenone **2-18** (entry 1). However, use of $Pd(OAc)_2$ in place of $PdBr_2$ led to improved results, and after examining a few biarylphosphine derivatives we found that the SPhos ligand provided excellent results for the formation of both **19a** (94 % NMR yield) and **20a** (91% NMR yield).

Table 2.3 Optimization Studies[50,a]

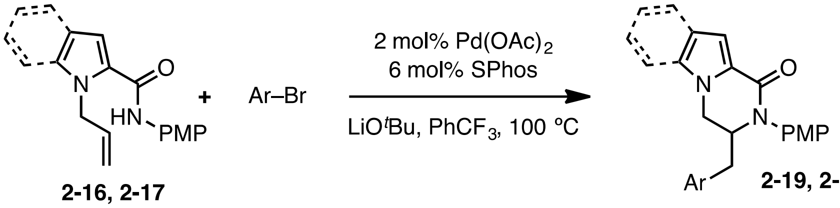


Entry	[Pd]	Ligand	Base	**19a** Yield[b]	**20a** Yield[b]
1	PdBr$_2$	XPhos	LiO^{t}Bu	10%	<5%
2	Pd(OAc)$_2$	XPhos	LiO^{t}Bu	<5%[c]	24%
3	Pd(OAc)$_2$	CPhos	LiO^{t}Bu	<5%[c]	60%
4	Pd(OAc)$_2$	RuPhos	LiO^{t}Bu	17%	29%
5	Pd(OAc)$_2$	BrettPhos	LiO^{t}Bu	42%	87%
6	PdBr$_2$	SPhos	LiO^{t}Bu	<5%[c]	39%
7	**Pd(OAc)$_2$**	**SPhos**	**LiO^{t}Bu**	**94%** **(98%)[d]**	**91%** **(96%)[d]**

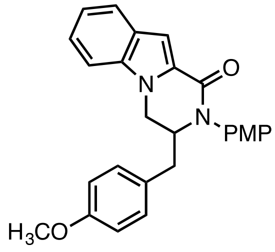
[a] Conditions: 1 equiv **2-16** or **2-17**, 2.0 equiv 4-Bromobenzophenone, 2.0 equiv base, 2 mol % [Pd], 8 mol % ligand, solvent (0.1 M), 100 °C, 4–16 h. [b] Yields were determined by ^{1}H NMR using phenanthrene as an internal standard. [c] Yields reported as <5% indicate the desired product was not observed by ^{1}H NMR analysis of the crude reaction mixture. [d] Isolated yield. The differences between NMR yields and isolated yields reflect experimental error in the measurement of NMR yields.

Having successfully optimized conditions, we proceeded to explore the coupling of **2-16** and **2-17** with a range of different aryl bromides. As shown in **Table 2.4**, these reactions were effective with electron-rich, electron-poor, *o*-substituted, and heteroaromatic electrophiles.

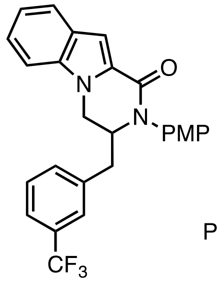
Table 2.4 Palladium-Catalyzed Synthesis of δ-Lactams[51,a]



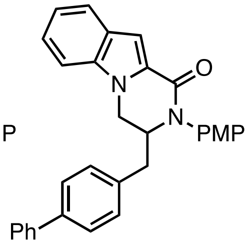
2-16, 2-17 **2-19, 2-20**



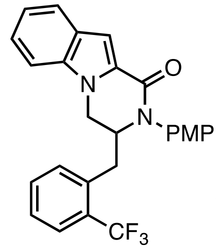
2-19b, 90%



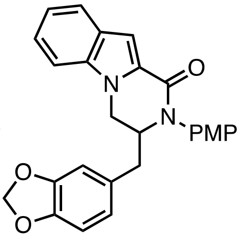
2-19c, 95%



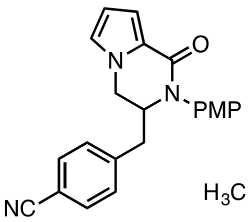
2-19d, 86%



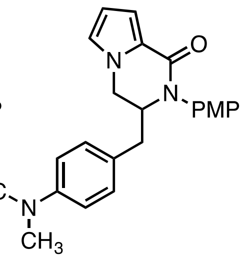
2-19e, 85%[b]



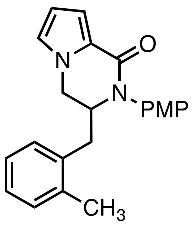
2-19f, 92%



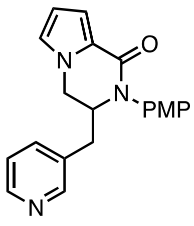
2-20b, 94%



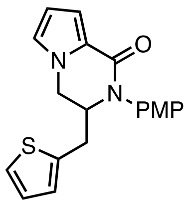
2-20c, 88%[c]



2-20d, 87%



2-20e, 94%

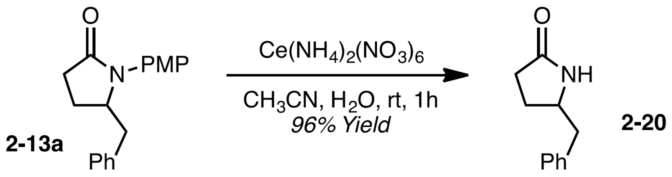


2-20f, 93%

[a]Conditions: 1 equiv **2-16** or **2-17**, 2.0 equiv ArBr, 2.0 equiv base, 2 mol % Pd(OAc)$_2$, 6 mol % S-Phos, PhCF$_3$ (0.2 M), 100 °C, 4–16 h. Yields are isolated yields (average of two or more experiments). [b]The reaction was conducted using *tert*-butyl alcohol as solvent. [c]The reaction was conducted using toluene as solvent.

The substituted lactam products were generally formed in good to excellent yields under our standard conditions, although use of *tert*-butanol as solvent provided optimal results for the reaction of **2-16** with 2-brombenzotrifluoride to afford **2-19e**, and toluene was superior to PhCF$_3$ as a solvent for the coupling of **2-17** with *N,N*-dimethyl-4-bromoaniline to afford **2-20c**.

Scheme 2.5 Removal of PMP protecting group from **2-13a**

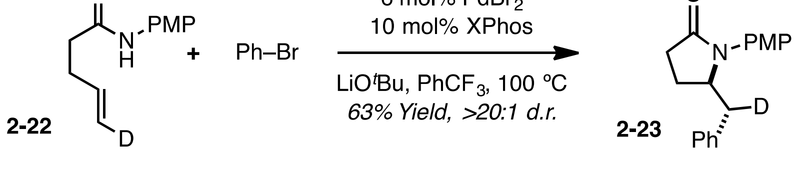


Having successfully prepared a range of PMP-protected lactams, we sought to illustrate the feasibility of removing the PMP protecting group. Fortunately, this proved to be straightforward (**Scheme 2.5**), as treatment of product **2-13a** with cerium(IV)ammonium nitrate in acetonitrile/water led to clean deprotection after 1 h, affording product **2-21** in 96% isolated yield (76% overall yield from **2-12a** over the two step carboamination/deprotection sequence).

2-5 Mechanistic Studies

Finally, we sought to obtain information about the mechanism of the carboamination reaction and the key C–N bond forming step, which in principle may occur via either *syn*- or *anti*-aminopalladation of the alkene.[20,26] As such, deuterated 4-pentenamide substrate **2-22** was synthesized and subjected to our optimized reaction conditions (**Scheme 2.6**). This transformation afforded deuterated lactam **2-23**, which results from *anti*-addition to the alkene, in 63% yield with >20:1 dr.[52,53]

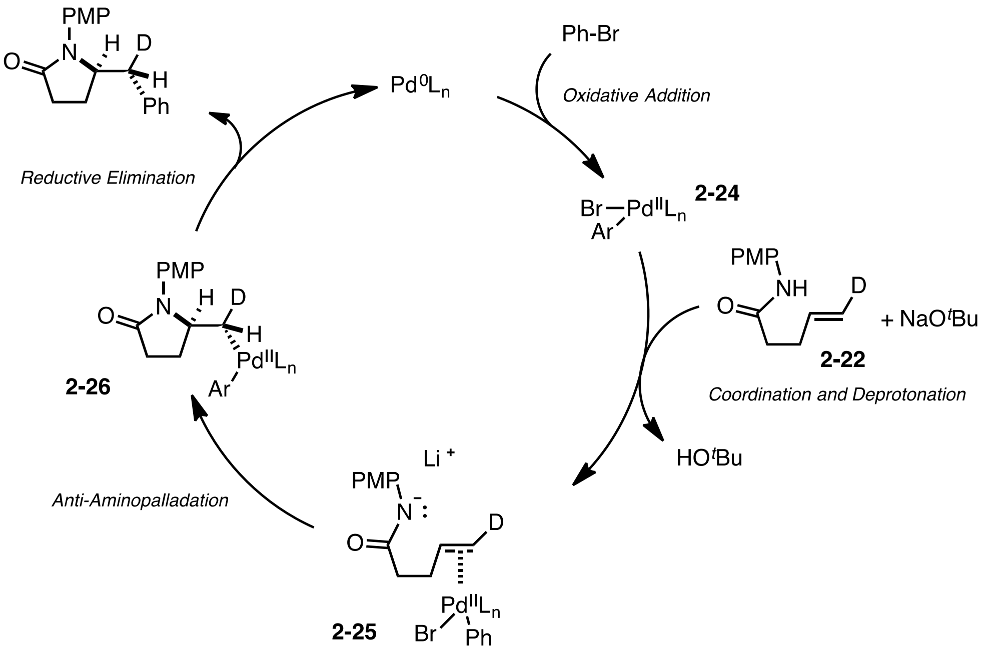
Scheme 2.6 Stereochemistry of Alkene Addition



The result of this stereochemical probe indicates the products of these reactions are generated via *anti*-aminopalladation of the alkene,[26] rather than *syn*-

aminopalladation[25,54,55,56] As such, the mechanism of the amide-forming reactions appears to be similar to related transformations of other electron-deficient nitrogen nucleophiles such as sulfamides[26,57] and sulfonamides,[58] and likely proceeds as illustrated in **Scheme 2.7**. The catalytic cycle is initiated by oxidative addition of the aryl bromide to Pd(0) to afford **2-24**.

Scheme 2.7 Catalytic Cycle of Palladium-Catalyzed Carboamination of Lactams



Coordination of the alkene to the metal activates the alkene for attack by the pendant amide nucleophile, and *anti*-aminopalladation of resulting intermediate **2-25** ensues to provide **2-26**. Finally, C–C bond-forming reductive elimination of **2-26** yields the lactam product and regenerates the Pd(0) catalyst.

2-6 Conclusion

In conclusion, we have explored and significantly expanded the scope of palladium-catalyzed alkene carboamination reactions of amide nucleophiles. These transformations afford substituted γ- and δ-lactam derivatives in good yield with moderate diastereoselectivity. The reactions are effective with a range of different aryl bromide electrophiles, and deuterium labelling studies indicate the mechanism of C–N bond formation involves *anti*-aminopalladation of the alkene.

2-7 Note from the Author

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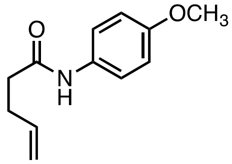
2-8 Experimental

General: All reactions were carried out under nitrogen atmosphere in flame- or oven-dried glassware. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. Palladium (II) bromide and palladium (II) acetate were purchased from Strem Chemical Co. and used without further purification. SPhos and XPhos were purchased from Sigma-Aldrich Chemical Co. and used without further purification. Dichloromethane, toluene, and tetrahydrofuran were purified using a GlassContour solvent purification system. Pent-4-eneamide,[42] *N*-methylpent-4-eneamide,[24] *tert*-butyl pent-4-enoyl carbamate,[59] and (*E*)-*tert*-butyl-5-d-pent-4-enylcarbamate[60] were synthesized according to published procedures. Benzotrifluoride was purified by distillation from CaH_2 prior to use. Structural and stereochemical assignments were based on 2-D COSY and NOESY experiments. Ratios of diastereomers were determined by ^{1}H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in **Tables 2.2** and **2.4** and **Schemes 2.4** and **2.5** are averages of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in **Tables 2.2** and **2.4** and **Schemes 2.4** and **2.5**.

Experimental Procedures and Compound Characterization Data for Substrates

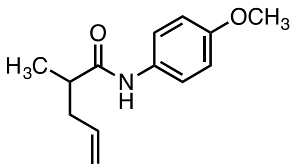
General Procedure 2.1[24] A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with the appropriate carboxylic acid (1.0 equiv), 1,1'-carbonyldiimidazole (1.0 equiv), and tetrahydrofuran (0.95 M). The resulting mixture was stirred at rt for 2 h then the appropriate aniline (1.0 equiv) was added slowly and the mixture was stirred at rt for 16 h. Water was then added and the mixture was transferred to a separatory funnel. The mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), then were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel using 30–40% ethyl acetate/hexanes as the eluent, unless otherwise noted.

***N*-(4-Methoxyphenyl)-pent-4-enamide (2-12a).**[61]



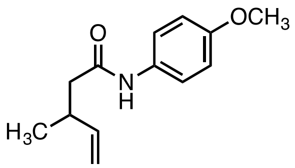
The title compound was prepared from 4-pentenoic acid (0.98 g, 9.7 mmol), and *p*-anisidine (1.20 g, 9.7 mmol) according to **General Procedure 2.1**. This procedure afforded 1.62 g (87%) of the title compound as a light brown solid, mp 91–92 °C (lit.[61] mp 86–88 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 2.7, 9.7 Hz, 2 H), 7.07 (s, 1 H), 6.87–6.82 (m, 2 H), 5.92–5.85 (m, 1 H), 5.19–5.09 (m, 2 H), 3.78 (s, 3 H), 2.51–2.45 (m, 2 H), 2.43 (dd, *J* = 6.3, 7.8 Hz, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.2, 156.4, 136.9, 121.7, 115.9, 114.1, 55.5, 36.7, 29.5.

***N*-(4-Methoxyphenyl)-2-methylpent-4-enamide (2-12b).**[61]



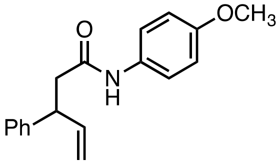
The title compound was prepared from 2-methyl 4-pentenoic acid (2.22 g, 19.4 mmol), and *p*-anisidine (2.40 g, 19.4 mmol) according to **General Procedure 2-1**. This procedure afforded 2.06 g (95%) of the title compound as light brown solid, mp 82–83 °C (lit.[61] mp 65–68 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42–7.35 (m, 2 H), 7.14 (s, br, 1 H), 6.86–6.82 (m, 2 H), 5.87–5.76 (m, 1 H), 5.16–5.09 (m, 2 H), 3.73 (s, 3 H), 2.53–2.43 (m, 1 H), 2.42–2.33 (m, 1 H), 2.22 (dt, *J* = 7.0, 14.1 Hz, 1 H), 1.23 (s, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.8, 135.7, 130.9, 121.7, 117.2, 114.1, 55.5, 42.1, 38.5, 17.5.

***N*-(4-Methoxyphenyl)-3-methylpent-4-enamide (2-12c).**[61]



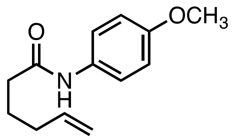
The title compound was prepared from 3-methyl-4-pentenoic acid (1.11 g, 9.7 mmol), and *p*-anisidine (1.20 g, 9.7 mmol) according to **General Procedure 2.1**. This procedure afforded 0.87 g (78%) of the title compound as pale brown solid, mp 91–92 °C (lit.[61] mp 57–60 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2 H), 7.05 (s, br, 1 H), 6.91–6.82 (m, 2 H), 5.88–5.80 (m, 1 H), 5.12–4.99 (m, 2 H), 3.77 (s, 3 H), 2.83–2.74 (m, 1 H), 2.38–2.33 (m, 1 H), 2.31–2.22 (m, 1 H), 1.11 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (176 MHz, CDCl3) δ 142.7, 121.8, 114.1, 113.9, 55.5, 44.6, 34.9, 19.7.

***N*-(4-Methoxyphenyl)-3-phenylpent-4-enamide (2-12d).**[24]



The title compound was prepared from 3-phenyl-4-pentenoic acid (1.71 g, 9.7 mmol), and *p*-anisidine (1.20 g, 9.7 mmol) according to **General Procedure 2.1**. This procedure afforded 0.95 g (35%) of the title compound as pale brown solid, mp 109–110 °C (lit. mp not reported[24]). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.6 Hz, 2 H), 7.28–7.18 (m, 5 H), 6.80 (d, 2 H), 6.11–5.99 (m, 1 H), 5.15–5.10 (m, 2 H), 3.95 (q, *J* = 7.3 Hz, 1 H), 3.76 (s, 3 H), 2.77 (dd, *J* = 7.2, 14.1 Hz, 1 H), 2.67 (dd, *J* = 7.8, 14.1 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.2, 140.2, 130.6, 128.8, 127.6, 126.9, 122.0, 115.2, 114.0, 55.4, 46.1, 43.8.

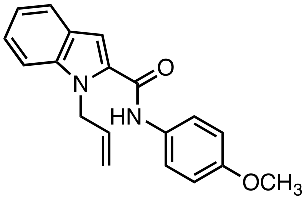
***N*-(4-Methoxyphenyl)hex-5-enamide (2-14).**[61]



A flame-dried round bottom flask and stirbar was charged with 5-hexenoic acid (0.7 mL, 5.9 mmol), benzene (15 mL), and triethylamine (3 mL, 21.5 mmol). Oxalyl chloride (0.8 mL, 9.3 mmol) was slowly added, and the reaction was stirred overnight at rt (12 h).

Neat *p*-anisidine (3.0 g, 24.4 mmol) was then added, and the reaction mixture was stirred at rt for 2 h. The reaction was slowly quenched through addition of water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 50 mL), and the organic layers were combined, dried over anhydrous sodium sulfate, and concenterated *in vacuo* to afford 524 mg (41%) of the title compound as an off-yellow solid, mp 69–71°C (lit.[61] mp 61–63 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.38 (m, 2 H), 7.05 (s, 1 H), 6.93–6.91–6.82 (m, 2 H), 5.82 (ddt, *J* = 6.7, 10.2, 17.0 Hz, 1 H), 5.12–4.99 (m, 2 H), 3.80 (s, 3 H), 2.35 (t, *J* = 7.5 Hz, 2 H), 2.22–2.15 (m, 2 H), 1.85 (p, *J* = 7.4 Hz, 2 H).

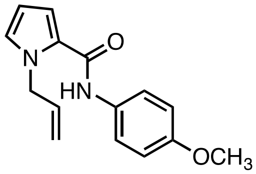
1-Allyl-*N*-(4-methoxyphenyl)-1*H*-indole-2-carboxamide (2-16).[62]



Ethyl indole-2-carboxylate (1.91 g, 10.1 mmol) was dissolved in *N,N*-dimethylformamide (10 mL) and the resulting solution was added dropwise to a suspension of sodium hydride (470 mg, 11.8 mmol) in *N,N*-dimethylformamide (10 mL) at 0 °C. The mixture was stirred for 30 min at rt, then a solution of allyl bromide (1.3 mL, 15.0 mmol) was added dropwise. The mixture was stirred at 50 °C overnight, and then was cooled to rt, poured into a mixture of ice and water (20 mL), diethyl ether (20 mL) was added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was then extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with water (5 x 25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a mixture of ethyl 1-allyl-indole-2-carboxylate and *N,N*-dimethylformamide, which was not further purified. Ethanol (15 mL) and 5 M sodium hydroxide (15 mL) were added to the mixture, which was then heaterd to reflux overnight. The mixture was and then cooled to rt, ethanol was evaporated under reduced pressure, and the aqueous layer was acidified with 5 M hydrochloric acid until pH 1 was achieved. The resulting mixture was extracted with ethyl acetate (3 x 30 mL), the organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 1-allyl-indole-2-carboxylic acid which was used without further purification.

1,1′-Carbonyldiimidazole (1.65 g, 10.1 mmol) was added to a solution of 1-allyl-indole-2-carboxylic acid in tetrahydrofuran (20 mL), and the resulting mixture was stirred at rt for 2 h. Neat *p*-anisidine (1.42 g, 11.5 mmol) was added, and the resulting mixture was stirred at rt overnight. The mixture was then transferred to a separatory funnel and washed with a saturated aqueous $NaHCO_3$ (20 mL), ethyl acetate (3 x 25 mL) and brine (20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford the title compound (2.02 g, 66% yield over three steps) as a white solid, mp 177–178 °C (lit.[62] mp not reported). ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.59–7.49 (m, 2 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.35 (ddd, *J* = 1.2, 6.9, 8.2 Hz, 1 H), 7.25–7.13 (m, 1 H), 7.02 (s, 1 H), 6.95–6.89 (m, 2 H), 6.06 (ddt, *J* = 5.1, 10.2, 17.0 Hz, 1 H), 5.24 (dt, *J* = 1.8, 5.2 Hz, 2 H), 5.13 (dq, *J* = 1.6, 10.3 Hz, 1 H), 4.98 (dq, *J* = 1.6, 17.1 Hz, 1H), 3.83 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 156.6, 138.7, 134.1, 131.7, 130.7, 126.2, 124.4, 122.0, 120.8, 116.2, 114.3, 114.2, 110.7, 104.6, 55.5, 46.9, 14.6.

1-Allyl-*N*-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxamide (2-17).



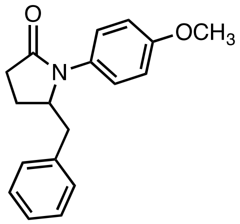
The title compound was prepared using a procedure analogous to that employed for the preparation of **2-16**, except methyl pyrrole-2-carboxylate (1.40 g, 10.1 mmol) was used as the starting material. This procedure afforded the title compound (1.92 g, 75% over three steps) as a yellow solid, mp 117–118 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (s, 1 H), 7.48–7.39 (m, 2 H), 7.24 (s, 1 H), 6.93–6.79 (m, 3 H), 6.67 (dt, *J* = 1.8, 3.8 Hz, 1 H), 6.16 (dt, *J* = 2.1, 4.1 Hz, 1 H), 6.08–5.93 (m, 1 H), 5.13 (dt, *J* = 1.6, 10.3 Hz, 1 H), 5.01 (ddq, *J* = 1.7, 5.3, 8.8 Hz, 2 H), 3.78 (d, *J* = 1.8 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.7, 156.3, 134.9, 131.0, 127.4, 125.3, 122.0, 116.5, 114.2, 112.1, 107.8, 77.2, 55.5, 51.0; IR (film) 3320, 1638 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{15}H_{16}N_2O_2$ 257.1285; found 257.1288.

Experimental Procedures and Compound Characterization Data for Lactam Products

General Procedure 2.2 – Synthesis of 5-Membered Lactams. A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the amide substrate (1.0 equiv), the aryl halide (2.0 equiv), LiO*^{t}*Bu (2.0 equiv), PdBr$_2$ (4-10 mol %), and XPhos (8-20 mol %). The tube was purged with nitrogen and benzotrifluoride (5 mL/mmol substrate) was added via syringe. The mixture was heated to 100 ºC with stirring until the reaction was complete as determined by TLC analysis. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (3 mL) and extracted with dichloromethane (3 x

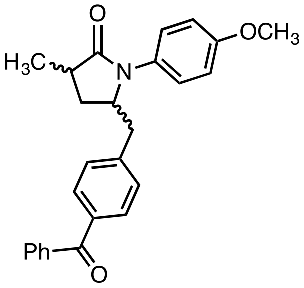
2 mL). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and subsequently purified by flash chromatography on silica gel using 30–60% ethyl acetate/hexanes as the eluent unless otherwise noted.

(±)-5-Benzyl-1-(4-methoxyphenyl)pyrrolidine-2-one (2-13a).



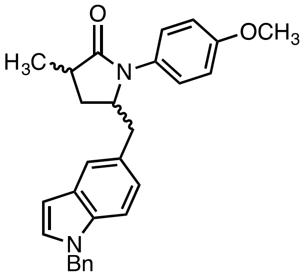
The title compound was prepared from substrate **2-12a** (40 mg, 0.20 mmol), bromobenzene (42 µL, 0.40 mmol), LiO*t*Bu (32 mg, 0.40 mmol), $PdBr_2$ (1.5 mg, 0.006 mmol), and XPhos (8.4 mg, 0.018 mmol) according to **General Procedure 2.2**. This procedure afforded 39 mg (69%) of the title compound as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 2.5, 9.0 Hz, 2 H), 7.28 (td, *J* = 2.3, 7.6 Hz, 2 H), 7.26–7.19 (m, 1 H), 7.10 (dd, *J* = 2.3, 7.8 Hz, 2 H), 7.00–6.92 (m, 2 H), 4.41–4.31 (m, 1 H), 3.82 (s, 3 H), 3.02–2.93 (m, 1 H), 2.64–2.55 (m, 1 H), 2.45–2.34 (m, 2 H), 2.17–2.05 (m, 1 H), 1.94–1.84 (m, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 136.9, 130.4, 129.2, 128.5, 126.7, 125.7, 114.5, 61.2, 55.5, 39.4, 30.8, 23.4; IR (film) 1682.8, 1506.4, 1239.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{18}H_{19}NO_2$ 282.1489; Found 282.1488.

(±)-5-(4-Benzoylbenzyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (2-13b).



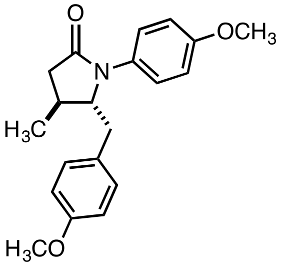
The title compound was prepared from substrate **2-12b** (35 mg, 0.16 mmol), 4-bromobenzophenone (110 mg, 0.42 mmol), LiO*t*Bu (38 mg, 0.45 mmol), $PdBr_2$ (1.9 mg, 0.007 mmol), and XPhos (8.8 mg, 0.018 mmol) according to **General Procedure 2.2**. This procedure afforded 50 mg (79%) of the title compound as a pale yellow foam. The compound was obtained as a 1:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78–7.68 (m, 4 H), 7.57 (dd, *J* = 5.3, 9.0 Hz, 2 H), 7.48 (d, *J* = 2.7 Hz, 2 H), 7.47 (s, 2 H), 7.48–7.41 (m, 2 H), 7.44–7.36 (m, 2 H), 7.27–7.13 (m, 8 H), 6.96–6.91 (m, 4 H), 4.42–4.35 (m, 1 H), 4.30–4.24 (m, 1 H), 3.80 (s, 6 H), 3.15–3.10 (m, 1 H), 3.03–2.98 (m, 1 H), 2.76–2.69 (m, 1 H), 2.59–2.52 (m, 1 H), 2.52–2.45 (m, 1 H), 2.42–2.30 (m, 1 H), 2.18–2.12 (m, 1 H), 1.87–1.76 (m, 3 H), 1.71 (s, 1 H), 1.47–1.41 (m, 1 H), 1.30–1.21 (m, 3 H), 1.24–1.17 (m, 3 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.2, 176.9, 176.4, 157.3, 142.2, 142.0, 137.6, 136.0, 136.0, 132.4, 130.6, 130.4, 130.3, 129.9, 129.2, 129.1, 128.3, 126.4, 125.0, 114.4, 58.9, 58.7, 55.5, 40.8, 38.9, 36.8, 35.9, 33.9, 31.9, 25.9, 16.7, 16.2; IR (film) 1659.1, 1510.2, 1249.2 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{26}H_{25}NO_3$ 400.1907; found 400.1917.

(±)-5-[(1-Benzyl-1*H*-indol-5-yl)methyl]-1-(4-methoxyphenyl)-3-methyl-pyrrolidin-2-one (2-13c).



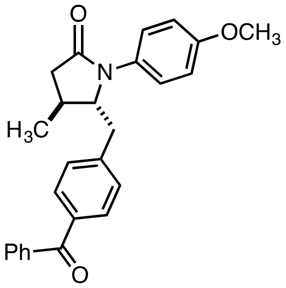
The title compound was prepared from substrate **2-12b** (43 mg, 0.20 mmol), *N*-benzyl-5-chloroindole (122 mg, 0.50 mmol), LiO*t*Bu (39 mg, 0.49 mmol), $PdBr_2$ (1.9 mg, 0.007 mmol), and XPhos (8.8 mg, 0.018 mmol) according to **General Procedure 2.2**. This procedure afforded 50 mg (43%) of the title compound as an orange oil. The compound was obtained as a 1:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51–7.47 (m, 2 H), 7.37 (dd, *J* = 1.6, 18.0 Hz, 2 H), 7.34–7.23 (m, 8 H), 7.18 (dd, *J* = 5.1, 8.4 Hz, 2 H), 7.13–7.05 (m, 6 H), 6.99–6.93 (m, 4 H), 6.89 (ddd, *J* = 1.6, 8.3, 10.8 Hz, 2 H), 6.52 (s, 2 H), 5.29 (s, 4 H), 4.38–4.30 (m, 1 H), 4.26–4.19 (m, 1 H), 3.82 (d, *J* = 2.4 Hz, 6 H), 3.19 (dd, *J* = 3.7, 13.5 Hz, 1 H), 3.03 (dd, *J* = 3.4, 13.7 Hz, 1 H), 2.67 (dd, *J* = 9.3, 13.7 Hz, 1 H), 2.55–2.43 (m, 3 H), 2.32–2.19 (m, 2 H), 1.76–1.68 (m, 1 H), 1.54–1.47 (m, 1 H), 1.33–1.21 (m, 3 H), 1.16 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 137.4, 135.3, 128.8, 128.75, 128.69, 127.6, 126.79, 126.77, 126.3, 124.8, 123.1, 121.3, 121.2, 114.4, 114.3, 109.7, 109.6, 101.3, 59.7, 59.6, 55.5, 50.2, 40.8, 38.6, 35.9, 34.0, 31.8, 16.7, 16.3; IR (film) 1688.4, 1509.1, 1244.9, 1178.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{28}H_{28}N_2O_2$ 425.2224; found 425.2234.

(±)-(4*S,5*R**)-5-(4-Methoxybenzyl)-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (13d).**



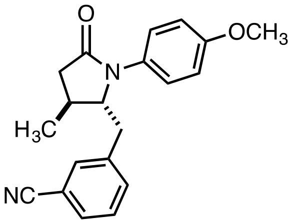
The title compound was prepared from substrate **2-12c** (54 mg, 0.25 mmol), 4-bromoanisole (60 µL, 0.48 mmol), LiO^{t}Bu (31 mg, 0.39 mmol), $PdBr_2$ (2.4 mg, 0.009 mmol), and XPhos (14.2 mg, 0.029 mmol) according to **General Procedure 2.2**. This procedure afforded 52 mg (66%) of the title compound as an orange oil. The compound was obtained as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 2.7, 9.5 Hz, 2 H), 7.02–6.92 (m, 4 H), 6.86–6.77 (m, 2 H), 3.88 (dt, *J* = 3.6, 7.8 Hz, 1 H), 3.83–3.72 (m, 6 H), 2.86 (dd, *J* = 3.7, 13.9 Hz, 1 H), 2.64–2.56 (m, 1 H), 2.53 (dd, *J* = 8.6, 17.0 Hz, 1 H), 2.23 (t, *J* = 9.3 Hz, 1 H), 2.07–2.01 (m, 1 H), 1.01 (t, *J* = 5.2 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.5, 158.4, 157.4, 130.6, 130.2, 129.8, 128.8, 126.3, 125.5, 114.4, 114.3, 113.9, 113.8, 68.7, 64.4, 55.5, 55.2, 39.7, 39.2, 37.7, 37.7, 33.5, 30.2, 29.7, 20.7, 15.1; IR (film) 1681.4, 1509.3, 1242.3, 1177.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{20}H_{23}NO_3$ 326.1751; found 326.1748.

(±)-(4*S**,5*R**)-5-(4-Benzoylbenzyl)-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (2-13e).



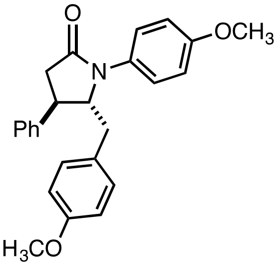
The title compound was prepared from substrate **2-12c** (54 mg, 0.25 mmol), 4-bromobenzophenone (113 mg, 0.43 mmol), LiO*t*Bu (36 mg, 0.45 mmol), $PdBr_2$ (5.2 mg, 0.02 mmol), and XPhos (12.4 mg, 0.026 mmol) according to **General Procedure 2.2**. This procedure afforded 59 mg (60%) of the title compound as a yellow oil. The compound was obtained as an 8:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.77–7.68 (m, 4 H), 7.63–7.54 (m, 1 H), 7.49–7.43 (m, 2 H), 7.35–7.29 (m, 2 H), 7.20–7.14 (m, 2 H), 6.96–6.90 (m, 2 H), 4.00–3.97 (m, 1 H), 3.79 (s, 3 H), 3.00 (dd, *J* = 4.2, 13.8 Hz, 1 H), 2.78 (dd, *J* = 8.0, 13.8 Hz, 1 H), 2.71–2.59 (m, 1 H), 2.31–2.21 (m, 1 H), 2.10 (dd, *J* = 4.9, 17.1 Hz, 1 H), 1.05 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.2, 173.4, 157.7, 142.1, 137.6, 136.0, 132.4, 130.3, 130.2, 129.9, 129.2, 128.8, 128.3, 126.4, 125.7, 114.5, 114.2, 68.4, 64.3, 55.5, 39.0, 38.9, 30.6, 20.5; IR (film) 1675.6, 1510.7, 1249.0, 909.6 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{26}H_{25}NO_3$ 422.1727; found 422.1739.

(±)-(2*R**,3*S**)-3-{[1-(4-Methoxyphenyl)-3-methyl-5-oxopyrrolidin-2-yl]methyl} benzonitrile (2-13f).



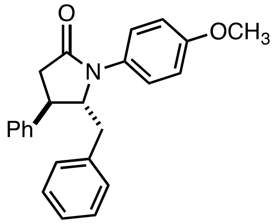
The title compound was prepared from substrate **2-12c** (41 mg, 0.19 mmol), 3-bromobenzonitrile (70 mg, 0.39 mmol), LiO^{t}Bu (42 mg, 0.52 mmol), $PdBr_2$ (4.2 mg, 0.016 mmol), and XPhos (15.1 mg, 0.032 mmol) according to **General Procedure 2.2**. This procedure afforded 35 mg (52%) of the title compound as a colorless oil. The compound was obtained as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51–7.47 (m, 1 H), 7.41–7.32 (m, 1 H), 7.31–7.24 (m, 4 H), 6.92 (dd, *J* = 2.7, 9.5 Hz, 2 H), 3.96–3.91 (m, 1 H), 3.80 (s, 3 H), 2.93 (dd, *J* = 4.3, 14.0 Hz, 1 H), 2.76 (dd, *J* = 7.7, 14.0 Hz, 1 H), 2.69–2.56 (m, 1 H), 2.23–2.18 (m, 1 H), 2.18–2.07 (m, 2 H), 1.09–1.05 (m, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 168.2, 138.5, 133.7, 132.8, 131.0, 130.4, 130.1, 129.3, 125.8, 121.9, 118.5, 114.5, 114.1, 112.6, 68.2, 55.49, 55.45, 38.9, 38.5, 30.7, 24.3, 20.3; IR (film) 2226.8, 1682.0, 1509.8, 1244.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{20}H_{20}N_2O_2$ 321.1598; found 321.1595.

(±)-(4*R,5*R**)-5-(4-Methoxyphenyl)-1-(4-methoxyphenyl)-4-phenylpyrrolidin-2-one (2-13g).**



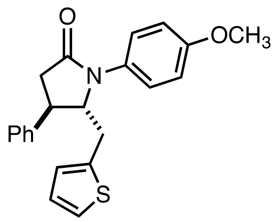
The title compound was prepared from substrate **2-12d** (54 mg, 0.19 mmol), 4-bromoanisole (50 µL, 0.40 mmol), LiO^{t}Bu (35 mg, 0.43 mmol), PdBr$_2$ (4.1 mg, 0.015 mmol), and XPhos (13.5 mg, 0.028 mmol) according to **General Procedure 2.2**. This procedure afforded 51 mg (75%) of the title compound as a yellow oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.38 (dd, J = 2.5, 9.1 Hz, 2 H), 7.32–7.24 (m, 2 H), 7.24–7.19 (m, 1 H), 7.08 (dd, J = 2.2, 7.9 Hz, 2 H), 7.03–6.94 (m, 4 H), 6.80 (dd, J = 2.4, 8.7 Hz, 2 H), 4.37–4.31 (m, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.32–3.27 (m, 1 H), 2.94–2.88 (m, 1 H), 2.83–2.76 (m, 2 H), 2.58–2.51 (m, 1 H); ^{13}C NMR (176 MHz, CDCl$_3$) δ 157.5, 130.5, 128.9, 126.9, 126.6, 125.3, 114.4, 114.0, 69.1, 55.5, 55.2, 40.5, 38.9, 37.4; IR (film) 1688.0, 1510.4, 1246.8, 1032.2 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{25}H_{25}NO_3$ 388.1907; found 388.1905.

(±)-(4*R,5*R**)-5-(4-Methoxybenzyl)-1-(4-methoxyphenyl)-4-phenylpyrrolidin-2-one (2-13h).**



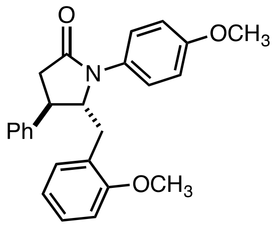
The title compound was prepared from substrate **2-12d** (54 mg, 0.19 mmol), bromobenzene (42 µL, 0.40 mmol), LiO*^t*Bu (38 mg, 0.47 mmol), PdBr$_2$ (2.1 mg, 0.078 mmol), and XPhos (13.5 mg, 0.028 mmol) according to **General Procedure 2.2**. This procedure afforded 48 mg (65%) of the title compound as a yellow oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.46–7.36 (m, 2 H), 7.29–7.25 (m, 4 H), 7.27–7.15 (m, 2 H), 7.09–7.02 (m, 4 H), 6.99–6.93 (m, 2 H), 4.40–4.33 (m, 1 H), 3.82 (s, 3 H), 3.33–3.26 (m, 1 H), 3.01–2.96 (m, 1 H), 2.87–2.80 (m, 2 H), 2.56 (dd, *J* = 6.9, 17.4 Hz, 1 H); ^{13}C NMR (176 MHz, CDCl$_3$) δ 172.9, 157.8, 141.5, 136.0, 132.4, 130.3, 130.1, 130.0, 129.3, 129.0, 128.5, 127.1, 126.6, 125.7, 114.5, 68.6, 55.5, 41.5, 39.2, 39.0; IR (film) 1684.2, 1509.8, 1246.3, 1176.0 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{24}H_{23}NO_2$ 358.1802; found 358.1801.

(±)-(4*R,5*R**)-1-(4-Methoxyphenyl)-4-phenyl-5-(thiophen-2-ylmethyl)pyrrolidin-2-one (2-13i).**



The title compound was prepared from substrate **2-12d** (41 mg, 0.15 mmol), 2-bromothiophene (30 µL, 0.31 mmol), LiO*^t*Bu (31 mg, 0.39 mmol), PdBr$_2$ (3.9 mg, 0.015 mmol), and XPhos (15.2 mg, 0.032 mmol) according to **General Procedure 2.2**. This procedure afforded 35 mg (49%) of the title compound as a pale yellow oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47–7.34 (m, 2H), 7.36–7.21 (m, 3H), 7.25–7.14 (m, 3H), 6.99–6.89 (m, 3H), 6.76 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.40–4.31 (m, 1H), 3.81 (s, 3H), 3.36 (dt, *J* = 4.5, 9.1 Hz, 1H), 3.11 (d, *J* = 5.1 Hz, 2H), 2.80 (dd, *J* = 9.4, 17.5 Hz, 1H), 2.57 (dd, *J* = 5.0, 17.5 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.2, 143.6, 137.6, 130.0, 129.0, 127.1, 127.0, 126.9, 126.7, 125.5, 124.8, 114.5, 68.4, 55.5, 40.6, 39.1, 32.0; IR (film) 2926.4, 1690.7, 1510.4, 1248.9 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{22}H_{21}NO_2S$ 364.1368; found 364.1368.

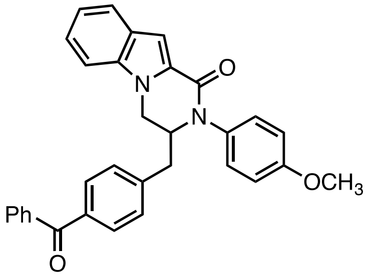
(±)-(4*R,5*R**)-5-(2-Methoxybenzyl)-1-(4-methoxyphenyl)-4-phenylpyrrolidin-2-one (2-13j).**



The title compound was prepared from substrate **2-12d** (42 mg, 0.15 mmol), 2-chloroanisole (45 µL, 0.35 mmol), LiO^{t}Bu (42 mg, 0.52 mmol), $PdBr_2$ (3.5 mg, 0.013 mmol), and XPhos (15.1 mg, 0.031 mmol) according to **General Procedure 2.2**. This procedure afforded 48 mg (81%) of the title compound as a yellow oil. The compound was obtained as an >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 2.4, 9.3 Hz, 2 H), 7.22–7.12 (m, 4 H), 7.03 (dd, *J* = 1.7, 7.4 Hz, 1 H), 6.99–6.94 (m, 2 H), 6.96–6.90 (m, 2 H), 6.87–6.83 (m, 1 H), 6.74 (dd, *J* = 1.0, 8.2 Hz, 1 H), 4.48–4.41 (m, 1 H), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.36–3.28 (m, 1 H), 3.21 (dd, *J* = 4.1, 13.4 Hz, 1 H), 3.05 (dd, *J* = 9.3, 17.4 Hz, 1 H), 2.67 (dd, *J* = 9.4, 13.4 Hz, 1 H), 2.60 (dd, *J* = 3.9, 17.4 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.1, 157.5, 157.3, 144.4, 131.1, 130.7, 128.7, 128.2, 126.59, 126.56, 126.5, 125.3, 125.0, 120.5, 114.2, 110.3, 67.7, 55.5, 55.1, 40.8, 39.0, 34.5; IR (film) 1680.2, 1601.1, 1492.4, 1242.8 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{25}H_{25}NO_3$ 388.1907; found 388.1910.

General Procedure 2.3 – Synthesis of 6-Membered Lactams. A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the amide substrate (1.0 equiv), the aryl halide (2.0 equiv), LiO^{t}Bu (2.0 equiv), Pd(OAc)$_2$ (2 mol %), and SPhos (6 mol %). The tube was purged with nitrogen, and benzotrifluoride (5 mL/mmol substrate) was added via syringe. The mixture was heated to 100 °C with stirring until the reaction was complete as determined by TLC analysis. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (3 mL) and extracted with dichloromethane (3 x 2 mL). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and subsequently purified by flash chromatography on silica gel using 30–60% ethyl acetate/hexanes as the eluent unless otherwise noted.

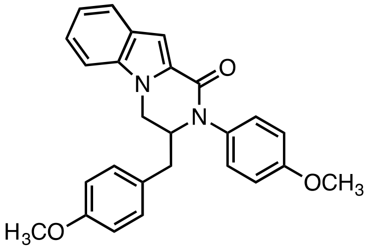
(±)-3-(4-Benzoylbenzyl)-2-(4-methoxyphenyl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (19a).



The title compound was prepared from substrate **2-16** (61 mg, 0.20 mmol), 4-bromobenzophenone (109 mg, 0.42 mmol), LiO^{t}Bu (35 mg, 0.44 mmol), Pd(OAc)$_2$ (1.0 mg, 0.004 mmol), and SPhos (5.1 mg, 0.012 mmol) according to **General Procedure 2.3**. This procedure afforded 95 mg (98%) of the title compound as a viscous yellow oil.

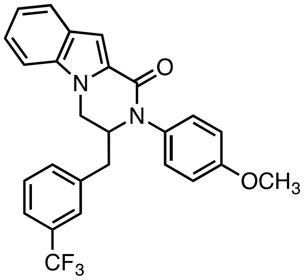
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.75 (m, 3 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.64–7.55 (m, 1H), 7.49 (t, *J* = 7.7 Hz, 2 H), 7.42–7.30 (m, 4 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 7.04 (d, *J* = 7.9 Hz, 2 H), 7.02–6.95 (m, 2 H), 4.34–4.28 (m, 1 H), 4.23 (qd, *J* = 2.9, 12.7 Hz, 2 H), 3.83 (s, 3 H), 3.20 (dd, *J* = 4.5, 13.4 Hz, 1 H), 2.83 (dd, *J* = 10.5, 13.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 158.8, 158.6, 141.5, 137.4, 136.7, 136.4, 133.5, 132.5, 130.6, 130.0, 129.3, 128.9, 128.6, 128.3, 127.6, 124.9, 122.8, 120.9, 114.6, 109.5, 107.0, 62.0, 55.5, 41.9, 37.5; IR (film) 1648.5, 1605.3 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{32}H_{26}N_2O_3$ 487.2016; found 487.2018.

(±)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (19b).



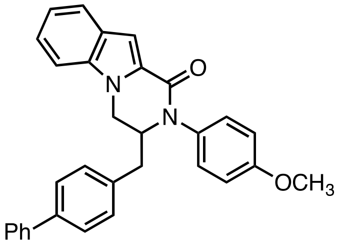
The title compound was prepared from substrate **2-16** (61 mg, 0.20 mmol), 4-bromoanisole (50 µL, 0.40 mmol), LiO^{t}Bu (37 mg, 0.46 mmol), Pd(OAc)$_2$ (1.0 mg, 0.004 mmol), and SPhos (5.2 mg, 0.013 mmol) according to **General Procedure 2.3**. This procedure afforded 71 mg (90%) of the title compound as a yellow solid, mp 140–142 ºC. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1 H), 7.41–7.31 (m, 4 H), 7.25–7.17 (m, 2 H), 7.03–6.97 (m, 2 H), 6.86–6.77 (m, 4 H), 4.27 (s, 1 H), 4.22–4.12 (m, 2 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.11 (dd, *J* = 4.1, 13.4 Hz, 1 H), 2.64 (dd, *J* = 10.9, 13.6 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.9, 158.7, 158.5, 136.8, 133.7, 130.3, 129.1, 128.8, 128.6, 127.6, 124.7, 122.8, 120.7, 114.6, 114.2, 109.5, 106.9, 62.7, 55.5, 55.3, 41.5, 36.4; IR (film) 1649 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{26}H_{24}N_2O_3$ 413.1860; found 413.1862.

(±)-2-(4-Methoxyphenyl)-3-[3-(trifluoromethyl)benzyl]-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (19c).



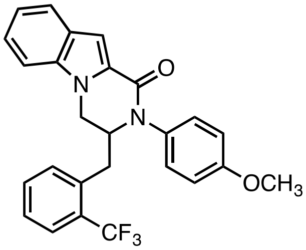
The title compound was prepared from substrate **2-16** (72 mg, 0.24 mmol), 3-bromobenzotrifluoride (60 µL, 0.43 mmol), LiO^{t}Bu (35 mg, 0.44 mmol), Pd(OAc)$_2$ (1.1 mg, 0.005 mmol), and SPhos (5.7 mg, 0.014 mmol) according to **General Procedure 2.3**. This procedure afforded 95 mg (95%) of the title compound as a brown solid, mp 164–165 ºC. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.77 (d, *J* = 8.0 Hz, 1 H), 7.51 (d, *J* = 7.8 Hz, 1 H), 7.42–7.34 (m, 3 H), 7.34–7.29 (m, 2 H), 7.24–7.14 (m, 3 H), 7.09 (d, *J* = 7.7 Hz, 1 H), 7.02–6.92 (m, 2 H), 4.24 (ddd, *J* = 2.5, 5.0, 10.5 Hz, 1 H), 4.19 (d, *J* = 2.8 Hz, 2 H), 3.83 (d, *J* = 1.9 Hz, 3 H), 3.19 (dd, *J* = 4.5, 13.6 Hz, 1 H), 2.79 (dd, *J* = 10.6, 13.5 Hz, 1 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.8, 158.6, 137.7, 136.7, 133.4, 132.8, 131.3 (q, *J* = 31.5 Hz), 129.4, 128.9, 128.6, 127.6, 126.0, 125.9 (q, 3.78 Hz), 125.0, 124.9, 124.0 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272 Hz), 122.8, 120.9, 114.7, 114.0, 109.4, 107.2, 62.1, 55.5, 41.7, 37.2, 29.7; IR (film) 1649 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{26}H_{21}F_3N_2O_2$ 451.1628; found 451.1631.

(±)-3-([1,1'-Biphenyl]-4-ylmethyl)-2-(4-methoxyphenyl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (19d).



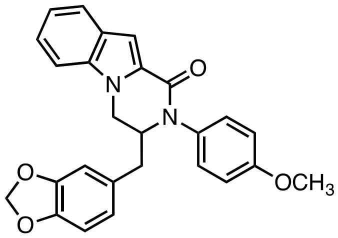
The title compound was prepared from substrate **2-16** (66 mg, 0.22 mmol), 4-bromobiphenyl (95 mg, 0.41 mmol), LiO*t*Bu (34 mg, 0.42 mmol), Pd(OAc)$_2$ (1.1 mg, 0.005 mmol), and SPhos (6.0 mg, 0.015 mmol) according to **General Procedure 2.3**. This procedure afforded 84 mg (86%) of the title compound as an off-yellow solid, mp 176–178 ºC. ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.59 (d, *J* = 7.9 Hz, 1 H), 7.39 (d, *J* = 7.6 Hz, 2 H), 7.31 (d, *J* = 7.7 Hz, 2 H), 7.28–7.22 (m, 3 H), 7.21–7.14 (m, 4 H), 7.07–7.00 (m, 3 H), 6.83–6.77 (m, 4 H), 4.10 (d, *J* = 12.4 Hz, 1 H), 4.07–4.02 (m, 1 H), 3.97 (dd, *J* = 3.3, 12.3 Hz, 1 H), 3.65 (d, *J* = 2.3 Hz, 3 H), 3.56 (t, *J* = 3.1 Hz, 1 H), 3.02–2.96 (m, 1 H), 2.55 (s, 1 H); ^{13}C NMR (176 MHz, CDCl$_3$) δ 158.8, 158.5, 140.3, 139.9, 136.7, 135.7, 133.5, 129.7, 129.6, 129.0, 128.73, 128.70, 128.50, 128.47, 127.50, 127.47, 127.37, 127.35, 127.31, 127.28, 126.85, 126.82, 124.71, 124.68, 122.68, 122.65, 120.7, 114.53, 114.51, 109.5, 106.84, 106.82, 77.2, 77.0, 76.8, 62.4, 62.3, 55.39, 55.36, 41.6, 36.9; IR (film) 1648 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{31}H_{26}N_2O_2$ 459.2067; found 459.2068.

2-(4-Methoxyphenyl)-3-(2-(trifluoromethyl)benzyl)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (19e).



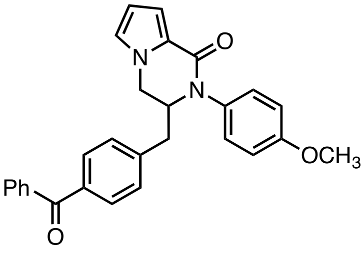
The title compound was prepared from substrate **2-16** (61 mg, 0.20 mmol), 2-bromobenzotrifluoride (60 µL, 0.44 mmol), LiO^{t}Bu (34 mg, 0.42 mmol), Pd(OAc)$_2$ (1.1 mg, 0.005 mmol), and SPhos (5.7 mg, 0.014 mmol) according to **General Procedure 2.3**, using *tert*-butyl alcohol as the solvent instead of benzotrifluoride. This procedure afforded 76 mg (85%) of the title compound as a yellow solid, mp 181–183 ºC. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.79 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.48–7.34 (m, 4 H), 7.28–7.20 (m, 3 H), 7.01–6.92 (m, 2 H), 6.89 (d, *J* = 7.6 Hz, 1 H), 4.40 (dt, *J* = 10.1, 4.3 Hz, 1 H), 4.33–4.20 (m, 2 H), 3.84 (s, 3 H), 3.43 (dd, *J* = 4.7, 14.0 Hz, 1 H), 2.91 (dd, *J* = 10.7, 13.8 Hz, 1 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.8, 158.5, 136.7, 135.0, 133.3, 133.2, 132.1, 129.2, 129.1, 129.1 (q, *J* = 13.9 Hz), 128.5, 127.7, 127.5, 126.6 (q, *J* = 6.3 Hz), 124.9, 124.1 (q, *J* = 273 Hz), 123.0, 122.9, 120.8, 114.5, 109.5, 107.2, 61.2, 55.5, 41.9, 34.7; IR (film) 1651 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{26}H_{21}F_3N_2O_2$ 451.1628; found 451.1637.

(±)-3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(4-methoxyphenyl)-3,4-dihydro pyrazino[1,2-*a*]indol-1(2*H*)-one (19f).



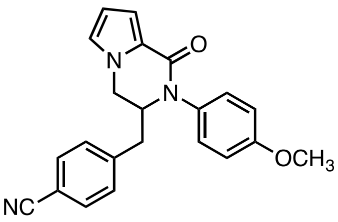
The title compound was prepared from substrate **2-16** (62 mg, 0.20 mmol), 5-bromobenzo[*d*][1,3]dioxole (80 µL, 0.66 mmol), LiO^{t}Bu (37 mg, 0.46 mmol), Pd(OAc)$_2$ (1.0 mg, 0.004 mmol), and SPhos (5.2 mg, 0.013 mmol) according to **General Procedure 2.3**. This procedure afforded 80 mg (92%) of the title compound as a yellow solid, mp 145–146 ºC. ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.76 (d, *J* = 8.0 Hz, 1 H), 7.43–7.29 (m, 4 H), 7.29–7.16 (m, 2 H), 6.99 (d, *J* = 8.3 Hz, 2 H), 6.69 (d, *J* = 7.7 Hz, 1 H), 6.40 (d, *J* = 1.7 Hz, 1 H), 6.34 (dd, *J* = 1.8, 7.8 Hz, 1 H), 5.92 (dt, *J* = 1.3, 9.8 Hz, 2 H), 4.29 (d, *J* = 12.2 Hz, 1 H), 4.23–4.11 (m, 2 H), 3.90–3.80 (m, 3 H), 3.06 (dd, *J* = 4.1, 13.6 Hz, 1 H), 2.61 (dd, *J* = 10.8, 13.6 Hz, 1 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.9, 158.6, 148.0, 146.7, 136.8, 133.6, 130.4, 129.1, 128.6, 127.6, 124.8, 122.8, 122.5, 120.8, 114.6, 109.5, 109.3, 108.5, 107.0, 101.1, 62.6, 55.5, 41.6, 37.0; IR (film) 1652 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{26}H_{22}N_2O_4$ 427.1652; found 427.1656.

(±)-3-(4-Benzoylbenzyl)-2-(4-methoxyphenyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (20a).



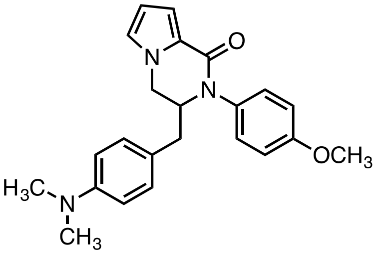
The title compound was prepared from substrate **2-17** (68 mg, 0.27 mmol), 4-bromobenzophenone (133 mg, 0.51 mmol), LiO^{t}Bu (41 mg, 0.52 mmol), Pd(OAc)$_2$ (1.5 mg, 0.006 mmol), and SPhos (6.0 mg, 0.014 mmol) according to **General Procedure 2.3**. This procedure afforded 113 mg (96%) of the title compound as a viscous yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83–7.63 (m, 4 H), 7.63–7.50 (m, 1 H), 7.50–7.40 (m, 2 H), 7.34–7.23 (m, 2 H), 7.14–7.06 (m, 2 H), 7.06–7.00 (m, 1 H), 6.98–6.91 (m, 2 H), 6.76–6.67 (m, 1 H), 6.29 (p, J = 2.3 Hz, 1 H), 4.29 (dd, J = 4.0, 12.9 Hz, 1 H), 4.16 (dt, J = 4.0, 9.1 Hz, 1 H), 3.92 (d, J = 12.8 Hz, 1 H), 3.82 (d, J= 2.1 Hz, 3 H), 3.24–3.13 (m, 1 H), 2.89–2.74 (m, 1 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 196.1, 158.4, 158.2, 141.7, 137.4, 136.4, 133.7, 132.5, 130.6, 129.9, 129.1, 128.7, 128.3, 124.4, 123.2, 114.5, 114.4, 110.3, 61.6, 55.5, 45.5, 37.2, 28.4, 14.1; IR (film) 1646 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{28}H_{24}N_2O_3$ 437.1860; found 437.1859.

(±)-4-{[2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-3-yl]methyl}benzo-nitrile (20b).



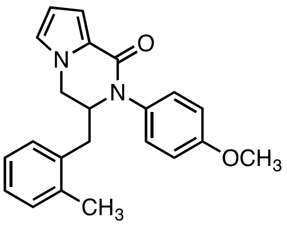
The title compound was prepared from substrate **2-17** (50 mg, 0.20 mmol), 4-bromobenzonitrile (72 mg, 0.40 mmol), LiO^{t}Bu (32 mg, 0.40 mmol), Pd(OAc)$_2$ (1.3 mg, 0.006 mmol), and SPhos (5.7 mg, 0.014 mmol) according to **General Procedure 2.3**. This procedure afforded 65 mg (94%) of the title compound as a yellow solid, mp 174–176 ^{o}C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (d, J = 7.9 Hz, 2 H), 7.20 (s, 1 H), 7.06 (d, J = 7.9 Hz, 2 H), 6.99–6.93 (m, 1 H), 6.88 (d, J = 8.6 Hz, 2 H), 6.68 (t, J = 2.0 Hz, 1 H), 6.29–6.22 (m, 1 H), 4.24 (dd, *J* = 4.1, 13.0 Hz, 1 H), 4.12 (dd, *J* = 4.9, 10.1 Hz, 1 H), 3.82 (dd, *J* = 1.7, 12.9 Hz, 1 H), 3.78 (s, 3 H), 3.09 (dd, *J* = 4.8, 13.6 Hz, 1 H), 2.75 (dd, *J* = 10.4, 13.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 158.1, 142.4, 133.5, 132.5, 130.0, 128.6, 124.2, 123.2, 118.5, 114.5, 114.4, 111.0, 110.3, 77.4, 61.3, 55.5, 45.6, 37.3; IR (film) 2227.3, 1641 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{22}H_{19}N_3O_2$ 358.1550; Found 358.1555.

(±)-3-[4-(Dimethylamino)benzyl]-2-(4-methoxyphenyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (20c).



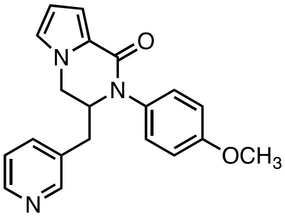
The title compound was prepared from substrate **2-17** (49 mg, 0.19 mmol), 4-bromo-*N*,*N*-dimethylaniline (82 mg, 0.41 mmol), LiO^{t}Bu (33 mg, 0.41 mmol), $Pd(OAc)_2$ (0.9 mg, 0.004 mmol), and SPhos (5.2 mg, 0.013 mmol) according to **General Procedure 2.3**, using toluene as the solvent rather than benzotrifluoride. This procedure afforded 63 mg (88%) of the title compound as a green liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.26 (m, 1 H), 7.03 (dd, *J* = 1.5, 3.9 Hz, 1 H), 6.96 (d, *J* = 8.8 Hz, 1 H), 6.86 (d, *J* = 8.3 Hz, 1 H), 6.72 (t, *J* = 2.0 Hz, 1 H), 6.67 (d, *J* = 7.3 Hz, 1 H), 6.29 (dd, *J* = 2.5, 3.9 Hz, 1 H), 4.19 (dd, *J* = 4.0, 12.6 Hz, 1 H), 4.05–3.93 (m, 1 H), 3.84 (s, 2 H), 3.03 (dd, *J* = 4.3, 13.7 Hz, 1 H), 2.92 (s, 6 H), 2.58 (dd, *J* = 11.3, 13.7 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 158.2, 149.5, 134.0, 129.9, 128.7, 124.52, 123.2, 114.5, 114.2, 114.0, 113.0, 109.9, 62.2, 55.5, 45.1, 40.7, 36.0, 29.7; IR (film) 1641 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]+ Calculated for $C_{23}H_{25}N_3O_2$ 376.2020; found 376.2028.

(±)-2-(4-Methoxyphenyl)-3-(2-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (20d).



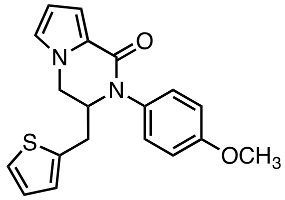
The title compound was prepared from substrate **2-17** (54 mg, 0.21 mmol), 2-bromotoluene (50 µL, 0.42 mmol), LiO^tBu (32 mg, 0.40 mmol), $Pd(OAc)_2$ (0.9 mg, 0.004 mmol), and SPhos (5.4 mg, 0.013 mmol) according to **General Procedure 2.3**. This procedure afforded 63mg (87%) of the title compound as a white solid, mp 130–131 ºC. ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.25 (m, 3 H), 7.13 (ddd, *J* = 1.8, 6.1, 12.6 Hz, 2 H), 7.12–7.02 (m, 1 H), 7.02–6.86 (m, 2 H), 6.85–6.70 (m, 1 H), 6.31 (dd, *J* = 2.5, 3.9 Hz, 1 H), 4.24 (dd, *J* = 4.2, 12.8 Hz, 1 H), 4.16–4.03 (m, 1 H), 3.96 (dd, *J* = 1.8, 12.7 Hz, 1 H), 3.84 (s, 2 H), 3.10 (dd, *J* = 4.0, 13.7 Hz, 1 H), 2.76 (dd, *J* = 11.3, 13.7 Hz, 1 H), 1.96 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.34, 158.27, 136.4, 135.1, 133.7, 130.8, 130.3, 128.8, 127.2, 126.3, 124.5, 123.2, 114.49, 114.48, 114.2, 110.1, 60.7, 55.5, 45.2, 34.1, 18.9; IR (film) 1641 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]+ Calculated for $C_{22}H_{22}N_2O_2$ 347.1754; found 347.1757.

(±)-2-(4-Methoxyphenyl)-3-(pyridin-3-ylmethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (20e).



The title compound was prepared from substrate **2-17** (51 mg, 0.20 mmol), 3-bromopyridine (40 µL, 0.42 mmol), LiO^{t}Bu (34 mg, 0.42 mmol), Pd(OAc)$_2$ (1.0 mg, 0.004 mmol), and SPhos (5.8 mg, 0.014 mmol) according to **General Procedure 2.3**. This procedure afforded 62 mg (94%) of the title compound as a yellow solid, mp 143–145 ºC. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.46 (d, *J* = 4.7 Hz, 1 H), 8.26 (s, 1 H), 7.32 (dt, *J* = 1.9, 7.8 Hz, 1 H), 7.27–7.16 (m, 3 H), 6.99 (dd, *J* = 1.5, 3.9 Hz, 1 H), 6.96–6.88 (m, 2 H), 6.71 (t, *J* = 2.0 Hz, 1 H), 6.28 (dd, *J* = 2.5, 3.9 Hz, 1 H), 4.28 (dd, *J* = 4.1, 12.9 Hz, 1 H), 4.11 (dtd, *J* = 1.6, 3.1, 3.8, 10.1 Hz, 1 H), 3.88 (dd, *J* = 1.9, 12.9 Hz, 1 H), 3.80 (s, 3 H), 3.07 (dd, *J* = 4.6, 13.8 Hz, 1 H), 2.73 (dd, *J* = 10.6, 13.8 Hz, 1 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.4, 158.1, 150.1, 148.2, 136.9, 133.6, 132.6, 128.6, 124.3, 123.7, 123.2, 114.6, 114.5, 110.3, 61.4, 55.5, 45.4, 34.4, 29.7; IR (film) 1638 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{20}H_{19}N_3O_2$ 334.1550; found 334.1556.

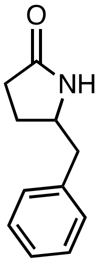
(±)-2-(4-Methoxyphenyl)-3-(thiophen-2-ylmethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (20f).



The title compound was prepared from substrate **2-17** (49 mg, 0.19 mmol), 2-bromothiophene (40 µL, 0.41 mmol), LiO*t*Bu (35 mg, 0.44 mmol), Pd(OAc)$_2$ (1.1 mg, 0.005 mmol), and SPhos (5.8 mg, 0.014 mmol) according to **General Procedure 2.3**. This procedure afforded 60 mg (93%) of the title compound as a yellow solid, mp 161–163 ºC. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30–7.24 (m, 2 H), 7.19–7.08 (m, 1H), 7.03 (dd, *J* = 1.5, 3.8 Hz, 1 H), 7.01–6.94 (m, 1 H), 6.96 (s, 1 H), 6.95 (s, 1 H), 6.95–6.82 (m, 2 H), 6.75–6.68 (m, 3 H), 6.29 (dd, *J* = 2.5, 3.8 Hz, 2 H), 4.28 (dd, *J* = 4.1, 12.8 Hz, 1 H), 4.12 (ddd, *J* = 2.0, 4.3, 8.9 Hz, 1 H), 4.12–3.99 (m, 2 H), 3.83 (s, 3 H), 3.25 (dd, *J* = 4.3, 14.6 Hz, 1 H), 2.98 (dd, *J* = 11.0, 14.6 Hz, 1 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.4, 158.2, 138.7, 133.7, 130.0, 128.6, 127.3, 126.7, 124.7, 124.3, 123.4, 117.9, 114.6, 114.55, 114.4, 112.1, 110.6, 110.1, 105.8, 61.8, 55.5, 55.48, 45.4, 31.0, 18.2; IR (film) 1640 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{19}H_{18}N_2O_2S$ 339.1162; found 339.1165.

Deprotection of the *N*-PMP Group From Product 13a

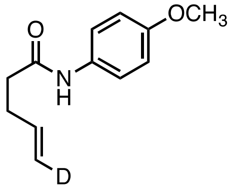
(±)-5-Benzylpyrrolidin-2-one (14).



A scintillation vial equipped with a stir bar was charged with **2-13a** (25 mg, 0.089 mmol), ammonium cerium(IV) nitrate (320 mg, 0.58 mmol), acetonitrile (1.75 mL), and water (0.35 mL). The resulting mixture was stirred at rt until the starting material had been completely consumed as judged by TLC analysis (ca. 1.5 h). Water (5 mL) was added and the resulting mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 5 mL). The organic layers were combined, dried over sodium sulfate, and concentrated. The crude product was then purified by flash chromatography on silica gel using 40–60% ethyl acetate/hexanes as the eluent to afford 15 mg (96%) of the title compound as a pale yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (s, 2 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 7.20 (s, 2 H), 6.73 (s, 1 H), 4.03 (s, 1 H), 2.88 (dd, *J* = 5.3, 13.7 Hz, 1 H), 2.77 (dd, *J* = 7.7, 13.6 Hz, 1 H), 2.48–2.43 (m, 2 H), 2.37–2.30 (m, 1 H).^{13}C NMR (176 MHz, $CDCl_3$) δ 136.5, 128.98, 128.95, 127.2, 77.2, 77.0, 76.8, 57.2, 42.4, 29.7, 26.0.

Synthesis and Reactivity of Deuterated Substrate 2-22

(*E*)-*N*-(4-methoxyphenyl)-pent-4-(5-*d*)-enamide (2-22).



This reaction was conducted with the hood light turned off. A flame-dried 3-neck round-bottom flask equipped with a stir bar was cooled under a stream of nitrogen, wrapped in aluminum foil, charged with THF (5 mL) bisdicyclopentylzirconium(IV)dichloride (1.5 g, 5.13 mmol), and cooled to 0 ºC. A solution of lithium triethylborohydride (4.9 mL, 4.9 mmol, x 1.0 M in THF) at 0 ºC via syringe. The resulting mixture was warmed to rt and stirred for 2 h with the hood light off. The reaction mixture was then cooled to 0º C, a solution of *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (502 mg, 2.52 mmol) in THF (5 mL) was added dropwise, and the resulting mixture was warmed to rt and stirred for 30 min. Deuterium oxide (2 mL, 93 mmol) was added, the mixture was stirred at rt for 15 min, then the mixture was diluted with hexanes (15 mL), filtered through a pad of silica gel, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel using 10% ethyl acetate/hexanes as the eluent to afford 382 mg (75%) of (*E*)-*tert*-butyldimethyl[(pent-4-en-1-yl-5-*d*)oxy]silane as a colorless oil. This material was judged to have undergone 95% d-incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (dt, *J* = 6.6, 15.4 Hz, 1 H), 5.00 (d, *J* = 1.6, 17.1 Hz, 1 H), 3.91 (q, *J* = 7.1 Hz, 2 H), 2.14–2.07 (m, 2 H), 1.63 (qd, *J* = 4.5, 7.3, 8.1 Hz, 2 H), 1.36–1.12 (m, 9 H), 1.04–0.84 (m, 6 H).

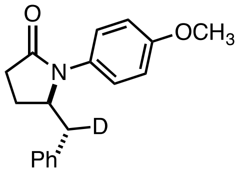
A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with (*E*)-*tert*-butyldimethyl[(pent-4-en-1-yl-5-*d*)oxy]silane (382 mg, 1.9 mmol) and THF (2 mL). A solution of tetrabutylammonium fluoride (5 mL, 1M in THF) was added and the resulting solution was stirred at rt until the starting material had been completely consumed as judged by TLC analysis (ca. 16 h). The mixture was then diluted with diethyl ether (15 mL), extracted with saturated sodium chloride (5 x 10 mL) and purified via column chromatography on silica gel using 5% ethyl acetate/hexanes as the eluent to afford (*E*)-pent-4-en-5-*d*-1-ol (143 mg, 84%).

Jones Reagent was prepared first by cooling a flame-dried 100 mL round bottom flask and stirbar under a stream of nitrogen. This vessel was then charged with chromium(VI) trioxide (13.3g, 133.0 mmol) and water (39 mL). The reaction vessel was cooled to room temperature and concentrated sulfuric acid (11 mL, 202.4 mmol) was slowly added, bringing the total volume to 50 mL.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with (*E*)-pent-4-en-5-*d*-1-ol (143 mg, 1.6 mmol) and acetone (50 mL). Subsequent drop-wise addition of Jones Reagent (4 mL, of prepared stock solution described above) at 0º C resulted in a murky solution, which was warmed to rt and stirred overnight. The mixture was then diluted with water (60 mL), and extracted with dichloromethane (3 x 15 mL) to afford a solution of (*E*)-pent-4-enoic-5-*d* acid in dichloromethane that was carried on in the next step without further purification.

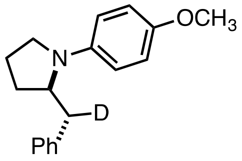
The title compound was prepared from the (*E*)-pent-4-en-5-*d*-oic acid solution and *p*-anisidine (0.7 g, 5.68 mmol) according to General Procedure 1. This procedure afforded 69 mg (21% over two steps) of the title compound as a pale brown solid, mp 83–85 °C, with 95% deuterium incorporation. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41–7.35 (m, 2 H), 7.11 (s, 1 H), 6.87–6.81 (m, 2 H), 5.90–5.85 (m, 1 H), 5.12–5.08 (m, 1 H), 3.77 (s, 3 H), 2.50–2.40 (m, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.3, 136.8, 130.9, 121.7, 114.1, 55.5, 36.6, 29.5; IR (film) 3296.5, 1650.0, 1514.5, 1251.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{12}H_{15}DNO_2$ 207.1238; found 207.1238.

(±)-(5*R,1'*R**)-1-(4-Methoxyphenyl)-5-(phenylmethyl-*d*)pyrrolidin-2-one (2-23).**



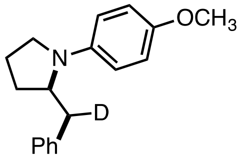
The title compound was prepared from substrate **2-22**[60] (49 mg, 0.24 mmol), bromobenzene (50 µL, 0.48 mmol), LiO^{t}Bu (31 mg, 0.39 mmol), $PdBr_2$ (4.2 mg, 0.016 mmol), and XPhos (18.2 mg, 0.038 mmol) according to General Procedure 2. This procedure afforded 30 mg (45%) of the title compound as a yellow oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41–7.34 (m, 2 H), 7.28 (d, *J* = 7.4 Hz, 2 H), 7.28–7.19 (m, 1 H), 7.13–7.08 (m, 2 H), 6.99–6.93 (m, 2 H), 4.40–4.31 (m, 1 H), 3.82 (s, 3 H), 2.56 (d, *J* = 9.1 Hz, 1 H), 2.45–2.34 (m, 2 H), 2.16–2.08 (m, 1 H), 1.91-1.85 (m, 1 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 174.4, 157.6, 136.8, 130.4, 129.2, 128.6, 126.7, 125.7, 121.7, 114.5, 114.0, 77.2, 77.0, 76.9, 61.2, 55.5, 39.2, 39.1, 30.9, 23.4. IR (film) 1679.7, 1508.8, 1242.8, 909.9 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{18}H_{18}DNO_2$ 283.1551; found 283.1557. The stereochemistry of this compound was assigned by reduction to the corresponding pyrrolidine **2-27** and then comparision of the NMR spectra of **2-27** to its diastereomer **2-28**, which was prepared via palladium-catalyzed carboamination of *tert*-butyl pent-4-enoyl carbamate followed by deprotection and *N*-arylation as described below.

(±)-(2*R,1'*R**)-1-(4-Methoxyphenyl)-2-(phenylmethyl-*d*)pyrrolidine (2-27).**



A flame-dried round-bottom flask was cooled with nitrogen and charged with pyrrolidin-2-one **2-23** (30 mg, 0.11 mmol) and tetrahydrofuran (0.5mL). A solution of lithium aluminum hydride (0.5 mL, 0.5 mmol, 1 M in THF) was then added and the resulting mixture was stirred at rt for 3 min then was heated to 45 ºC with stirring until the starting material had been completely consumed as judged by TLC analysis (ca 3 h). The solution was then was cooled to 0 °C, quenched with H_2O (0.5 mL), and diluted with diethyl ether (5 mL). A solution of aqueous NaOH (0.5 mL, 10 M) was added and an insoluble white material precipitated. The organic supernatant was decanted and the precipitate was washed with diethyl ether (5 mL). The combined organic washes were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via column chromatography on silica gel using 5% ethyl acetate/hexanes as the eluent to afford 7 mg (25%) of the title compound as a clear oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.7 Hz, 2 H), 7.29–7.22 (m, 3 H), 6.93–6.79 (m, 2 H), 6.65 (dd, *J* = 3.0, 9.8 Hz, 2 H), 3.91–3.86 (m, 1 H), 3.83 (s, 3 H), 3.43–3.37 (m, 1 H), 3.16–3.10 (m, 1 H), 2.53 (t, *J* = 10.2 Hz, 1 H), 1.93–1.81 (m, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.7, 142.0, 139.6, 129.3, 128.3, 126.1, 115.2, 112.6, 77.2, 77.0, 76.8, 60.2, 56.0, 55.7, 49.0, 29.6, 23.2. IR (film) 1510.6, 1241.8, 1039.6 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{18}H_{20}DNO$ 269.1759; found 269.1758.

(±)-(2*S,1'*R**)-1-(4-Methoxyphenyl)-2-(phenylmethyl-*d*)pyrrolidine (2-28).**



Prepared following previously reported procedures that have been shown to afford *syn*-addition products[60] via palladium-catalyzed carboamination reactions of carbamate substrates. A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with *tert*-butyl pent-4-enoyl carbamate (233 mg, 0.89 mmol), $Pd(OAc)_2$ (5.4 mg, 0.024 mmol), DPEphos (20.1 mg, 0.037 mmol), and NaO^{t}Bu (209 mg, 2.17 mmol). The tube was purged with nitrogen, and toluene (4 mL) and bromobenzene (100 µL, 0.95 mmol) were added via syringe. The mixture was heated to 100 °C with stirring until the reaction was complete as determined by TLC analysis. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (3 mL) and extracted with dichloromethane (3 x 2 mL). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and subsequently purified by flash chromatography on silica gel to afford 175 mg (53%) of (±)-(2*S**,1'*R**)-*tert*-butyl 2-(phenylmethyl-*d*)pyrrolidine-1-carboxylate as a clear oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.33–7.26 (m, 3 H), 7.21 (dd, *J* = 8.9, 16.0 Hz, 4 H), 4.06 (s, 1 H), 3.96 (s, 1 H), 3.40–3.35 (m, 2 H), 3.30 (s, 1 H), 3.16 (s, 1 H), 3.06 (d, *J* = 15.3 Hz, 1 H), 1.80–1.67 (m, 4 H), 1.64 (d, *J* = 3.2 Hz, 1 H), 1.61–1.56 (m, 1 H), 1.46 (d, *J* = 4.3 Hz, 1 H), 1.28 (d, *J* = 6.4 Hz, 1 H).

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with (±)-(2*S**,1'*R**)-*tert*-butyl 2-(phenylmethyl-*d*)pyrrolidine-1-carboxylate (75 mg, 0.29 mmol), 2 mL dichloromethane, and 2 mL trifluoroacetic acid. The reaction mixture was stirred until the starting material had been completely consumed as judged by TLC analysis (ca. 5 h), then was quenched with saturated ammonium hydroxide (10 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo*. The resulting crude pyrrolidine was then N-arylated:[63] A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2.0 mg, 0.009 mmol), (2-biphenyl)di-*tert*-butylphosphine (10.2 mg, 0.038 mmol), sodium *tert*-butoxide (90.8 mg, 0.94 mmol), 4-bromoanisole (50 µL, 0.40 mmol), and a solution of the crude pyrrolidine in toluene (1 mL). The mixture was heated to 110 °C until the starting material had been completely consumed as judged by TLC analysis. The reaction mixture was then worked up by addition of saturated aqueous ammonium chloride (2 mL), and extracted with ethyl acetate (3 x 3 mL). The organic layers were reserved, dried over sodium sulfate, and solvent removed *in vacuo*. The product was then purified by flash chromatography on silica gel to afford 23 mg (35% yield over two steps) of the title compound as a clear oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.17 (m, 5 H), 6.95–6.86 (m, 2 H), 6.68–6.64 (m, 2 H), 3.92–3.87 (m, 1 H), 3.81 (s, 3 H), 3.44–3.36 (m, 1 H), 3.18–3.10 (m, 1 H), 3.09–3.02 (m, 1 H), 1.92–1.82 (m, 2 H), 1.30 (d, *J* = 2.3 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.3, 128.3, 126.1, 125.3, 115.2, 113.8, 112.6, 77.2, 77.0, 76.7, 60.1, 56.0, 55.5, 49.0, 29.6, 28.7, 23.2. IR (film) 1510.6, 1241.8, 1039.6 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{18}H_{20}DNO$ 269.1759; found 269.1759.

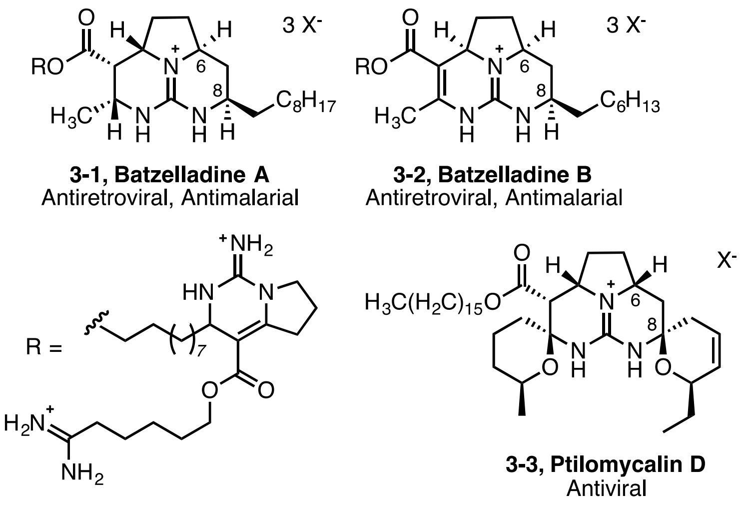
Chapter 3

Synthesis of Bicyclic Ureas and Sulfamides Via Palladium-Catalyzed Carboamination Reactions

3-1 Introduction

Bicyclic nitrogen-containing heterocycles represent a compelling class of compounds for chemical synthesis. These compounds have found use as synthetic intermediates in the synthesis of alkaloid natural products, such as the batzelladine alkaloids (e.g., batzelladines A **3-1** and B **3-2**),[64] and ptilomycalin **3-3** (**Figure 3.1**).[65]

Figure 3.1 Biologically Active Polycyclic Natural Products



3-1, Batzelladine A
Antiretroviral, Antimalarial

3-2, Batzelladine B
Antiretroviral, Antimalarial

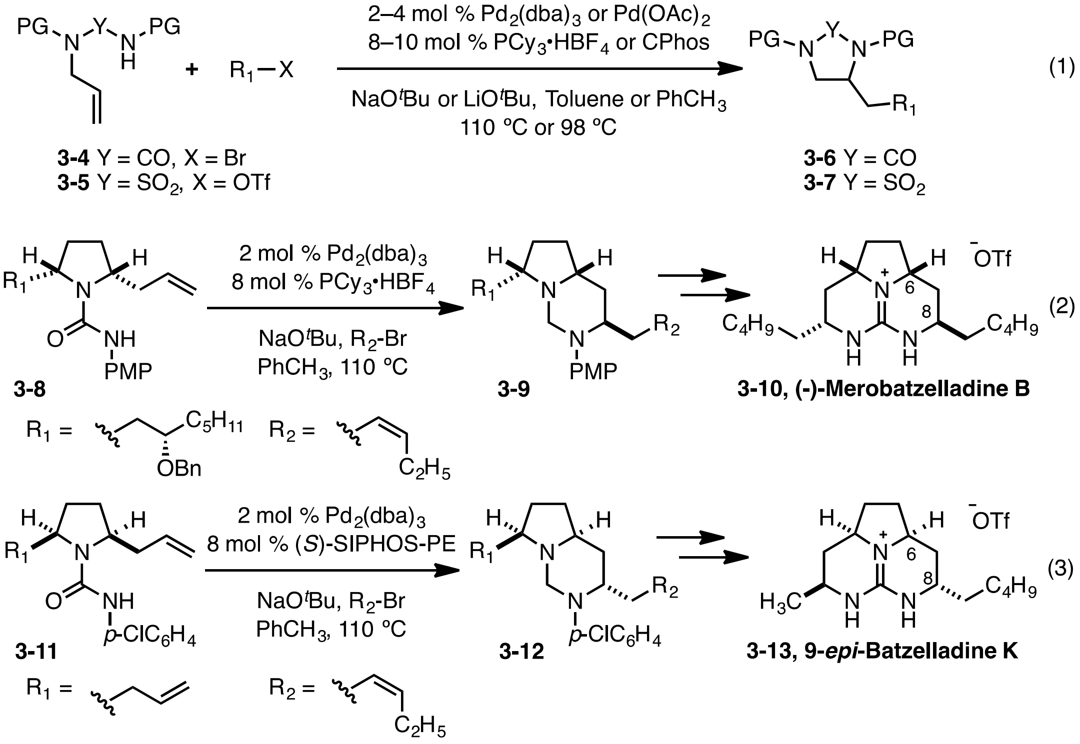
3-3, Ptilomycalin D
Antiviral

In addition to serving as useful synthetic intermediates, substituted bicyclic ureas and sulfamides act as peptidomimetics[66] that display a wide spectrum of biological activity, and interact as antivirals,[67] HIV protease inhibitors,[68] and hydroxysteroid dehydrogenase inhibitors.[69]

3-2 Previous Work

We have previously reported a new approach to the construction of cyclic ureas and sulfamides via palladium-catalyzed alkene carboamination reactions[19] between aryl/alkenyl halide/triflate electrophiles and alkenes bearing pendant ureas[38,39,40] or sulfamides (**Scheme 3.1, Equation 1**).[26,70] These transformations proceed in generally good yields with high diastereoselectivities, and the palladium-catalyzed carboamination of urea **3-8** was a key step in the asymmetric synthesis of (–)-merobatzelladine B (**Scheme 3.1, Equation 2**).[71]

Scheme 3.1 Synthesis of Cyclic Ureas and Sulfamides via Palladium-Catalyzed Alkene Carboamination Reactions



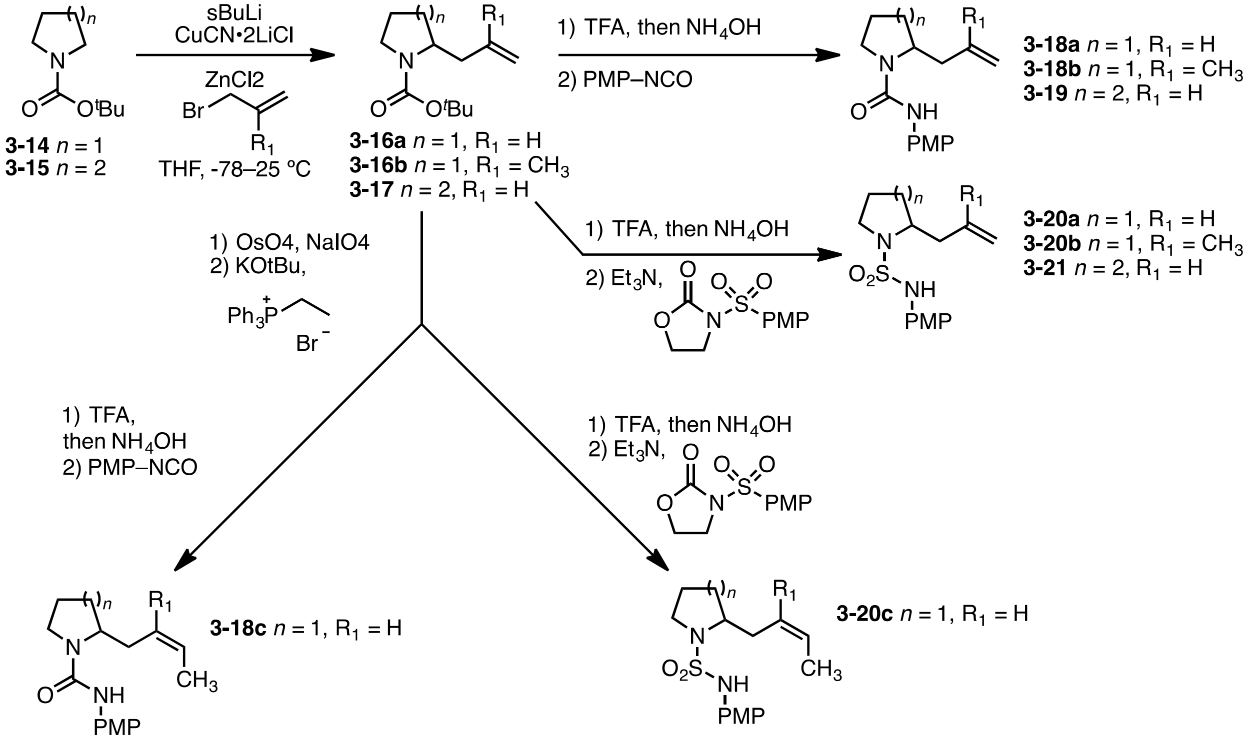
We have also described asymmetric desymmetrization reactions of ureas **3-11** derived from *cis*-2,5-diallylpyrrolidine afford products with high levels of enantioselectivity. This latter method was applied to the synthesis of an epimer of batzelladine K (**Scheme 3.1, Equation 3**).[72] Although these transformations have demonstrated utility, as illustrated through the syntheses shown in **Scheme 3.1**, the scope of this approach to the construction of bicyclic ureas remains largely unexplored (only three examples were reported).[71] Moreover, the synthesis of 9-*epi*-batzelladine K also illustrates a significant limitation of this method. We would have preferred to make the correct isomer of the natural product, but we have consistently observed complete substrate control in these reactions; in all cases the products contain a *cis*-relationship between the C^8 alkyl group and the C^6 H atom. These transformations do not provide access to the diastereomeric product with a *trans* relationship between the C^8 alkyl/ C^6 H substituents, which would be needed to access batzelledine K rather than its epimer.

In this chapter, the synthesis of bicyclic ureas, as well as the synthesis of bicyclic sulfamides is described, which provide access to sulfamide analogs related to **3-9,** but with the opposite relationship between the C^8 alkyl group and the C^6 H atom. These studies were conducted in collaboration with Dr. Nick Babij and Ms. Grace McKenna, and their individual contributions are noted both in footnotes and in references, when applicable.

3-3 Substrate Synthesis

Synthesis of substrates was generally accomplished in 2–5 steps from commercially available N-Boc pyrrolidines and piperidines (**Scheme 3.2**).[73] An initial allylation affords common intermediates **3-16** and **3-17**, which may deprotected and undergo urea formation to afford **3-18** and **3-19** or sulfamide formation to afford **3-20** and **3-21**. Alternately, common intermediate **3-18a** may be subjected to Lemieux-Johnson oxidation

Scheme 3.2 Substrate Synthesis

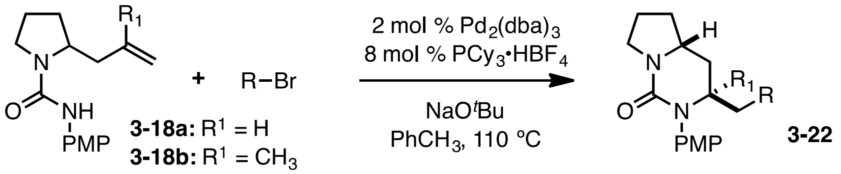


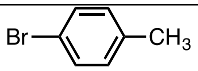
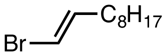
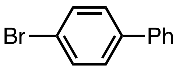
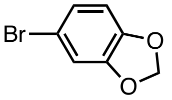
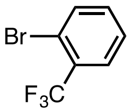
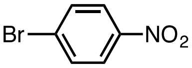
followed by a Wittig reaction, after which subsequent deprotection and functionalization affords substrates bearing an internal alkene (**3-18c** and **3-20c**).

3-4 Synthesis of 5,6- and 6,6-Bicyclic Ureas

During the course of model studies directed towards the synthesis of (–)-merobatzelladine B, we briefly examined palladium-catalyzed coupling reactions between **3-18a** and either *p*-tolylbromide or *E*-1-decenylbromide.[71] As shown in **Table 3.1**, entries 1 and 2, these transformations afforded desired products **3-22a** and **3-22b**, respectively, in good yield with high diastereoselectivity. In order to further explore the scope of palladium-catalyzed coupling reactions of ureas derived from cyclic amines, we treated **3-18a** with a range of different aryl halide electrophiles. Transformations of substrates bearing electron-donating groups proceeded in high yield, although lower yields were obtained with electron-poor and/or ortho-substituted aryl bromides.

Table 3.1 Palladium-Catalyzed Carboamination Reactions of 2-Allylpyrrolidinyl Ureas[a]

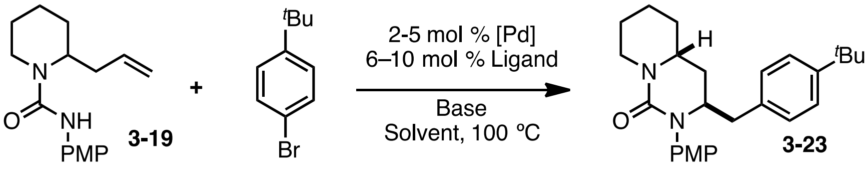


Entry	Urea Substrate	Aryl Halide	Product	Yield (%)[b]	d.r.
1	**3-18a**		**3-22a**	70	14:1[c]
2	**3-18a**		**3-22b**	77	18:1[c]
3	**3-18a**		**3-22c**	87	16:1
4	**3-18a**		**3-22d**	86	10:1
5	**3-18a**		**3-22e**	68	10:1
6	**3-18a**		**3-22f**	46	>20:1
7	**3-18b**		**3-22g**	97	15:1[d]

[a] Conditions: 1.0 equiv **3-18a**, 2 equiv NaO*t*Bu, 2 mol% $Pd_2(dba)_3$, 8 mol% PCy_3•HBF_4, 2 equiv, ArBr, toluene (0.2 M), 110 °C, 4–16 h. [b] Isolated yields (average of two or more experiments). [c] The reaction is previously published[71] and conducted by Dr. Nick Babij. [d] The reaction was conducted in xylenes solvent (0.2 M) at 125 °C.

Substrate **3-18b** bearing a methyl group at the internal alkene carbon was coupled with 4-bromobiphenyl to afford **3-22g** in excellent yield and dr, although a higher reaction temperature (125 °C) was required. In contrast, substrate **3-18c** bearing a 1,2-disubstituted alkene was found to be unreactive. In order to further explore the scope of the urea carboamination reactions we prepared 2-allylpiperidinylurea **3-19** and subjected it to our standard reacton conditions. Given the close structural similarities between **3-18a** and **3-19**, we were surprised to find the reaction conditions that afforded 70% yield in the coupling of **3-18a** with 4-bromotoluene failed to provide significant amounts of desired product in the attempted coupling of **3-19** with 4-*tert*-butylbromobenzene (**Table 3.2**, entry 1).

Table 3.2 Optimization of 2-Allylpiperidinyl Carboamination Reactions [a]

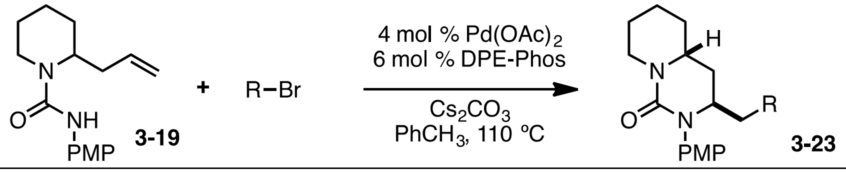


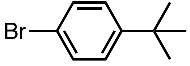
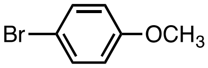
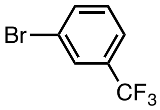
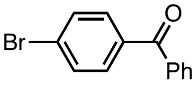
entry	[Pd]	ligand	base	solvent	yield (%)[b]	dr
1	$Pd_2(dba)_3$	PCy_3•HBF_4	NaO^{t}Bu	Toluene	<5%[c]	–
2	$Pd(OAc)_2$	PCy_3•HBF_4	Cs_2CO_3	Dioxane	11%	10:1
3	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	$PhCF_3$	<5%[c]	–
4	$PdBr_2$	DPE-Phos	Cs_2CO_3	Toluene	34%	8:1
5	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Toluene	6%	>20:1
6	$Pd(OAc)_2$	DPE-Phos	NaHMDS	Toluene	81%	2:1
7	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	49%	>20:1

[a] Conditions: 1 equiv **3-19**, 2.0 equiv 4-*tert*-butyl-1-bromobenzene, 2.0 equiv base, 2.5 mol % $Pd_2(dba)_3$ or 5 mol % Pd $(OAc)_2$, 6–10 mol % ligand, solvent (0.2 M), 100 °C, 4–16 h. [b] Yields were determined by ^1H NMR yield based on phenanthrene internal standard. [c] Yields reported as <5% indicate the desired product was not observed by ^1H NMR analysis of the crude reaction mixture.

Control experiments indicated the urea substrate decomposed when heated with NaO^{t}Bu, so we examined the use of other bases for coupling reactions of **3-19**. Use of Cs_2CO_3 as base and $Pd(OAc)_2$ as the palladium source, and dioxane solvent led to the formation of the desired product in low, but detectible, yield (entry 2). Use of wide-bite angle bidentate ligands led to further improvement when toluene was employed as solvent (entries 4-5 and 7). Interestingly, use of NaHMDS as base led to the formation of the desired product in 81% yield, but only 2:1 dr. The origin of this modest diastereoselectivity is unclear (although it is possible that hexamethyldisilazane or its conjugate base is serving as a ligand for palladium). Unfortunately use of other bases failed to provide improved results. As such, the combination of cesium carbonate, palladium acetate, DPE-Phos, and toluene solvent provided the highest combination of both yield and stereoselectivity (entry 7).

Table 3.3 Palladium-Catalyzed Carboamination Reactions of 2-Allylpiperidinyl Ureas[a]



Entry	Urea Substrate	Aryl Halide	Product	Yield (%)[b]	d.r.
1	**3-19**		**3-23a**	20	15:1
2	**3-19**		**3-23b**	35	>15:1
3	**3-19**		**3-23c**	47	>15:1
4	**3-19**		**3-23d**	59	10:1

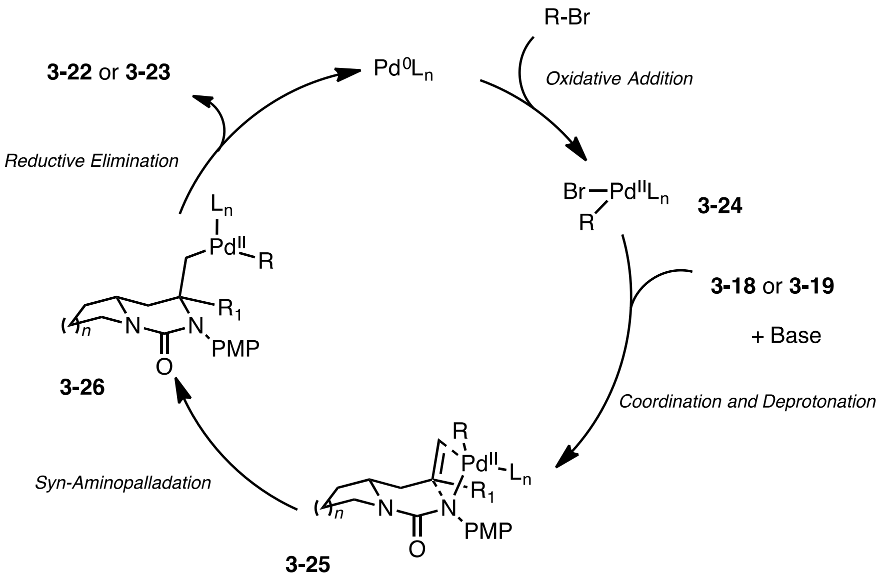
[a] Conditions: 1.0 equiv **3-19**, 2 equiv Cs_2CO_3, 4 mol% Pd $(OAc)_2$, 6 mol% DPE-Phos, 2 equiv, ArBr, toluene (0.2 M), 110 ºC, 4–16 h. [b] Isolated yields (average of two or more experiments).

As shown in **Table 3.3**, these optimized conditions provide satisfactory results with several different electron-rich or electron-poor aryl bromides. Unfortunately, lower conversion of starting material was observed despite investigating effects of changing temperature, solvent, stoichiometry of palladium and ligand, palladium source, ligand choice, and base. At this point, the reason for these disparate observations in reactivity are unclear, although this remains a point of interest for future investigations.

3-5 Mechanistic Considerations

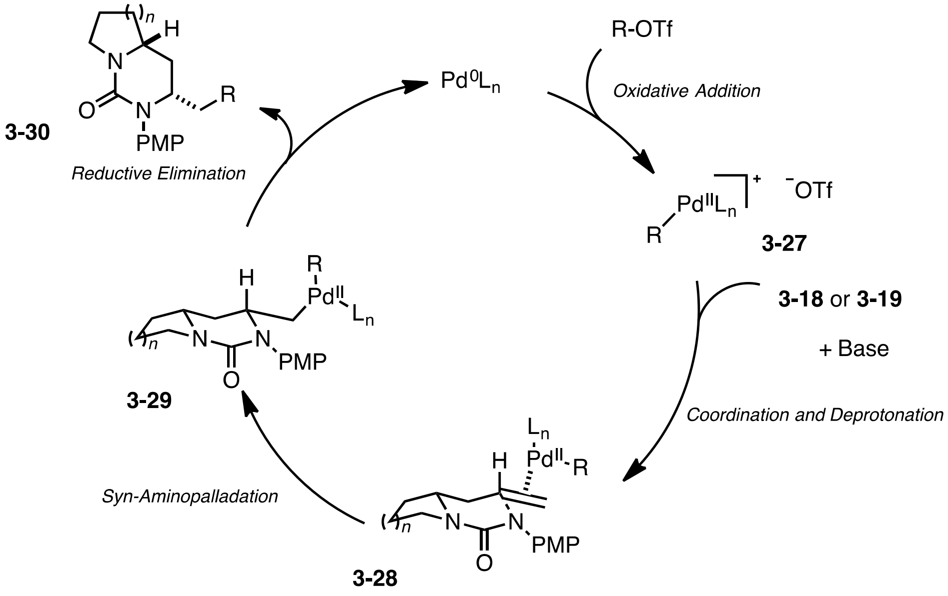
Our prior studies on urea carboamination reactions suggest the transformations described above likely proceed through the mechanism illustrated in Scheme 1. The reactions are initiated by oxidative addition of the aryl/alkeny halide to Pd(0) to afford intermediate **3-24**, which reacts with the urea substrate and base to afford amido complex **3-25**. The resulting palladium-amido complex undergoes *syn*-aminopalladation to provide **3-26**, which undergoes C–C bond-forming reductive elimination to afford the bicyclic urea product. The observed *cis*-relationship between the angular hydrogen atom and the arylmethyl group in the products derives from aminopalladation via boat-like transition state **3-25**.

Scheme 3.3 Proposed *syn*-Aminopalladation Catalytic Cycle



While this method is useful for the stereocontrolled construction bicyclic ureas, the stereoselectivity is substrate controlled. The conversion of **3-18** or **3-19** to bicyclic ureas with a *cis*-relationship between angular hydrogen atom and the arylmethyl group proceeds with generally high levels of stereocontrol, but the *syn*-aminopalladation mechanism allows for the selective formation of only this stereoisomer; diastereomeric

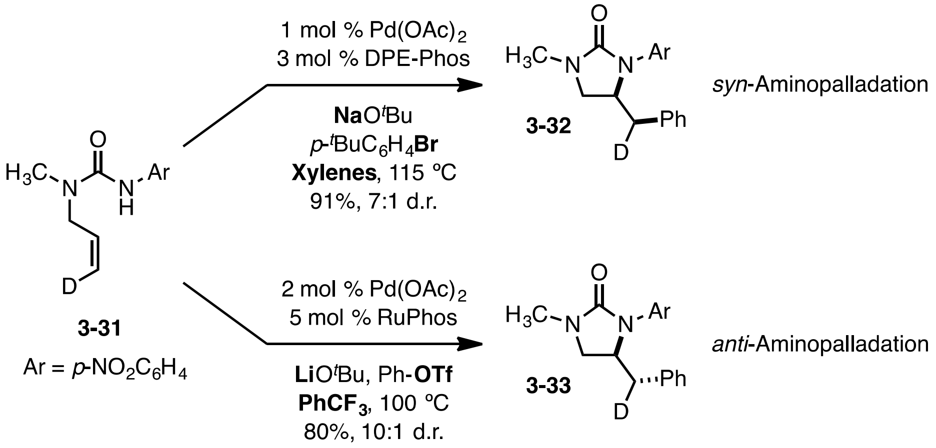
Scheme 3.4 Proposed *anti*-Aminopalladation Catalytic Cycle



molecules bearing a *trans*-relationship between angular hydrogen atom and the arylmethyl group are not accessible through this manifold.

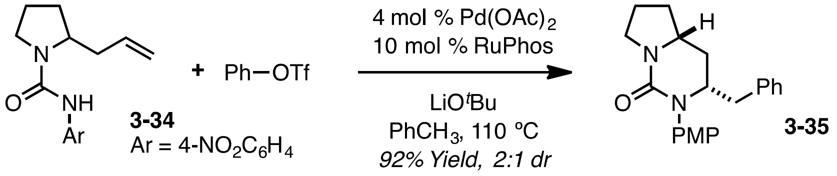
Although the *syn*-aminopalladation mechanism illustrated in **Scheme 3.3** provides access to only one product stereoisomer, we reasoned that it may be possible to access the opposite diastereomer by inducing the transformations to proceed via an alternative mechanistic pathway. As shown in **Scheme 3.4**, we reasoned that if the transformations could be induced to proceed via *anti*-aminopalladation of the alkene (following oxidative addition and alkene coordination to palladium), the *anti*-aminopalladation of palladium-alkene complex **3-28** would likely proceed via a chair-like transition state to afford **3-29**. Reductive elimination from **3-29** would then provide bicyclic urea product **3-30**, which contains a *trans*-relationship between the C^6 hydrogen atom and C^8 arylmethyl group. In addition, although most of our previously reported palladium-catalyzed alkene carboamination reactions proceed via *syn*-aminopalladation, we have observed that urea and sulfamide substrates can be induced to undergo carboamination via *anti*-aminopalladation under appropriate conditions. Specifically, factors that facilitate the formation of cationic intermediate palladium complexes (such as use of aryl triflates in place of aryl bromides, use of relatively polar solvents, etc). For example, treatment of urea **3-31** with an aryl bromide in toluene afforded *syn*-addition product **3-32** in 70 % yield and 7:1 dr using a Pd/Xantphos catalyst. In contrast, the Pd/RuPhos catalyzed coupling of **3-31** with phenyl triflate in benzotrifluoride solvent afforded *anti*-addition product **3-33** in 80% yield and 10:1 dr (**Scheme 3.5**).

Scheme 3.5 Urea Formation via *Syn*- vs *anti*-Aminopalladation Mechanisms



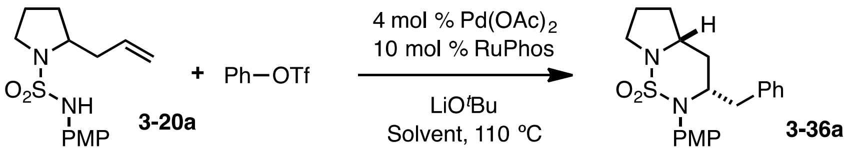
To test this hypothesis, we examined the coupling of urea **3-34** with phenyl triflate using the conditions optimized for *anti*-aminopalladation. As shown in **Scheme 3.6**, this transformation did lead to a change in product stereochemistry, as **3-35** was produced as the major stereoisomer. However, the diastereoselectivity of this transformation was low (2:1 dr), and efforts to improve the selectivity of the transformation through the use of other protecting groups, ligands, solvents, and reaction temperatures were largely ineffective.

Scheme 3.6 Bicyclic Urea Formation Under *anti*-Aminopalladation Conditions[74]



We postulated that two factors might be the cause of the modest diastereoselectivity observed for the coupling of **3-34** with phenyl triflate: (1) the rates of *syn*- and *anti*-aminopalladation may be comparable; and/or (2) the transition states/intermediates leading to the two possible stereoisomers may be close in energy. Both of these factors can be heavily influenced by the structural and electronic nature of the substrate. Many reports have illustrated that slight changes to substrate structure can dramatically influence the mechanism of aminopalladation reactions and in turn, the ratio of products resulting from *syn*- or *anti*-addition.[17,18] We reasoned that employing a less nucleophilic substrate, such as a sulfamide, might favor *anti*-aminopalladation by decreasing the likelihood that the substrate would form the Pd-N bond required to undergo *syn*-migratory insertion. Additionally, we expected that changing the hybridization of the substrate from the Csp^2 hybridized carbonyl group to the Ssp^3 hybridized sulfonyl group would influence the stereodetermining transition states/intermediates leading to the two possible stereoisomers, and consequently the selectivity of the desired transformation could potentially be improved. In order to test this hypothesis 2-allylpyrrolidinyl sulfamide substrate **3-20a** was synthesized and coupled with phenyl triflate using conditions we have previously shown to facilitate *anti*-aminopalladation pathways (**Scheme 3.7**).

Scheme 3.7 Palladium-Catalyzed Carboamination Reactions of Cyclic Sulfamides



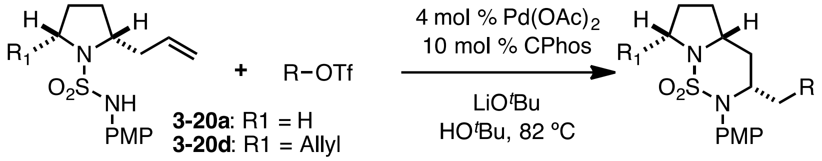
Solvent = $PhCF_3$: 80% NMR Yield, 6:1 dr
Solvent = ^{t}BuOH: 90% NMR Yield, 7:1 dr

We were gratified to discover that this substrate did react with significantly higher diastereoselectivity than urea **3-34**. Unfortunately, significant amounts of side products resulting from Heck-arylation of the alkene and/or oxidative amination of the alkene were observed. After some experimentation, we found that changing the solvent from benzotrifluoride to *tert*-butanol led to significantly improved and reproducible yields, and greatly diminished the formation of Heck arylation and oxidative amination side products. Finally, further optimization of ligand choice to CPhos resulted in greater product formation on a wider scope of aryl and alkenyl triflates.

3-6 Synthesis of 5,6- and 6,6-Bicyclic Sulfamides

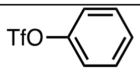
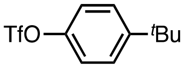
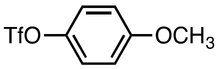
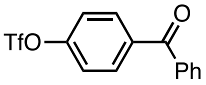
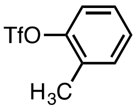
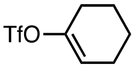
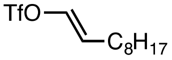
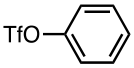
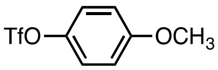
With suitable reaction conditions in hand, we proceeded to explore the scope of the bicyclic sulfamide-forming reactions. As shown in **Table 3.4**, these cyclization reactions tolerate aryl as well as alkenyl (**3-36g**) triflates as coupling partners. Electronically poor coupling partners, such as 4-benzophenone trifluoromethanesulfonate (**3-36d**) as well as electronically rich (4-methoxyphenyltrifluoromethanesulfonate, **3-36c**) are well tolerated. Additionally, sterically hindered coupling partners such as 2-tolyl trifluo- omethanesulfonate (**3-36e**)

Table 3.4 Palladium-Catalyzed Carboamination Reactions of 2-Allylpyrrolidinyl Sulfamides[a,b]



3-20a: R1 = H
3-20d: R1 = Allyl

3-36

Entry	Sulfamide Substrate	Aryl Triflate	Product	Yield (%)[d]	d.r.[e]
1	**3-20a**		**3-36a**	89	7:1
2	**3-20a**		**3-36b**	78	6:1
3	**3-20a**		**3-36c**	70	7:1
4	**3-20a**		**3-36d**	61[f]	8:1
5	**3-20a**		**3-36e**	87	5:1
6	**3-20a**		**3-36f**	63[f]	6:1
7	**3-20a**		**3-36g**	45[f]	10:1[g]
8	**3-20d**		**3-36h**	65	20:1
9	**3-20d**		**3-36i**	63	>20:1

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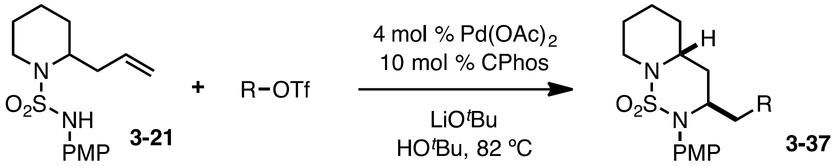
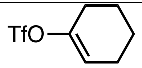
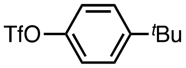
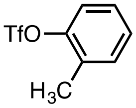
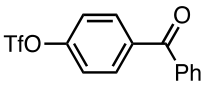
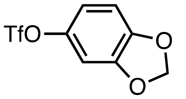
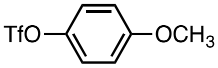
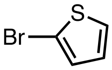
[a] Conditions: 1.0 equiv **3-18a**, 2 equiv LiO*t*Bu, 4 mol% $Pd(OAc)_2$, 10 mol% CPhos, 2 equiv, ArOTf, *tert*-butanol (0.2 M), 82 °C, 2–16 h. [b] Results in this table have been previously published by Dr. Nick Babij and Ms. Grace McKenna,[57] and are reproduced here for reference of past and future work. [c] Substrate **3-20d** was synthesized in an analogous fashion from N-Boc 2,5-diallylpyrrolidine[70] as other substrate pathways described above. [d] Isolated yields (average of two or more experiments). [e] Diastereomeric ratios are for isolated products unless otherwise noted. [f] This reaction was conducted with 3.0 equiv LiOtBu and 3.0 equiv R-OTf. [g] Decenyl triflate was used as a 5:1 mixture of *E*:*Z* isomers, and the related product diastereomeric ratio was determined after hydrogenation of the alkene.

proceeded in excellent chemical yield and good diastereoselectivity. Compared to our previous studies involving *syn*-aminopalladation, we noticed relatively modest diastereoselectivity, which may be attributed to the *anti*-aminopalladation proceeding through a less rigid transition state than the corresponding *syn*-aminopalladation cycle.

Table 3.5 Palladium-Catalyzed Carboamination Reactions of 2-Allylpiperidinyl Sulfamides[a]



Entry	Sulfamide Substrate	Aryl Triflate	Product	Yield (%)[b]	d.r.[c]
1	**3-21**		**3-37a**	85[d]	5:1
2	**3-21**		**3-37b**	71[d]	4:1
3	**3-21**		**3-37c**	83[d]	4:1
4	**3-21**		**3-37d**	71[d]	4:1
5	**3-21**		**3-37e**	83	6:1
6	**3-21**		**3-37f**	76[d]	3:1
7	**3-21**		**3-37g**	73[e]	6:1

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[a] Conditions: 1.0 equiv **3-21**, 2 equiv LiO*t*Bu, 4 mol% Pd(OAc)$_2$, 10 mol% CPhos, 2 equiv, ArOTf, *tert*-butanol (0.2 M), 82 °C, 2–16 h. [b] Isolated yields (average of two or more experiments). [c] Diastereomeric ratios are for isolated products unless otherwise noted. [d] Result in collaboration with Ms. Grace McKenna. [e] Reaction run with 2.0 equiv LiOTf and 2.0 equiv. aryl bromide.

Next, we wondered if we could also access analogous 6,6-bicyclic systems derived from 2-allylpiperidine with high yields and selectivity. Initial investigations revealed that under the same *anti*-aminopalladation reaction conditions that provided **3-36** in good chemical yield, substrate **3-21** was converted to product **3-37** in comparable yield and diastereoselectivity to the 5,6-bicyclic systems (**Table 3.5**). Similar to the reactions in **Table 3.4**, *N*-sulfonyl 2-allylpiperidines smoothly coupled with a range of aryl and alkenyl triflates. Again, we observe that sterically hindered (**3-37c**) coupling partners, as well as electronically rich (**3-37e**) and electronically poor (**3-37d**) triflates are all tolerated in similar chemical yield and diastereoselectivity to their 5,6-counterparts. Interestingly, with a lithium triflate additive coupling of heteraromatic bromides was also tolerated (**3-37g**). The diminished diastereoselectivity is likely attributable to the less constrained transition state present in *anti*-aminopalladation mechanisms.

3-7 Conclusion

In conclusion, a wide variety of substituted bicyclic ureas and sulfamides have been synthesized using palladium-catalyzed carboamination reactions. These carboamination reactions are tolerant of a variety of alkenyl and aryl coupling partners. This methodology provides robust access products possessing a *cis* relationship between the C^8 alkyl group and the C^6 H atom by use of a urea substrate, or access to the diastereomeric product with a *trans* relationship between the C^8 alkyl/ C^6 H substituents from a sulfamide substrate, both of which come from common parent amines. This control of relative stereochemistry should facilitate entry into potentially useful synthetic building blocks. Furthermore, reduction of the sulfonamide or urea in these products provides easy access to synthetically useful 1,3-diamines with defined stereochemistry, serving as additional intermediates in complex molecule synthesis.

3-8 Note from the Author

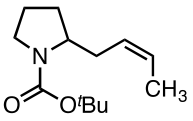
This thesis chapter represents work that is in preparation to be submitted as a manuscript to a peer-reviewed journal, which has been reproduced or adapted here with permission from the authors.

3-9 Experimental

General: All reactions were carried out under nitrogen atmosphere in flame- or oven-dried glassware. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. *Bis*-(dibenzylidineacetone) dipalladium(0), palladium (II) acetate, tricyclohexylphosphonium tetrafluoroborate, CPhos, and DPEphos were purchased from Strem Chemical Co. and used without further purification. Dichloromethane, toluene, and tetrahydrofuran were purified using a GlassContour solvent purification system. *N*-Boc-2-allylpyrrolidine, *N*-Boc-2-(2-methallyl)pyrrolidine and *N*-Boc-2-allylpiperidine were synthesized according to published procedures[75]. Benzotrifluoride and xylenes were purified by distillation from CaH_2 prior to use. Structural and stereochemical assignments were based on 2-D COSY and NOESY experiments. Ratios of diastereomers were determined by ^1H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^1H NMR analysis unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in **Tables 3.1, 3.3, 3.4** and **3.5** and **Schemes 3.6 and 3.7** are averages of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in **Tables 3.1, 3.3, 3.4** and **3.5** and **Schemes 3.6 and 3.7**.

Experimental Procedures and Compound Characterization Data for Substrates

(±)-*N*-Boc-(*Z*)-2-(but-2-en-1-yl)pyrrolidine.



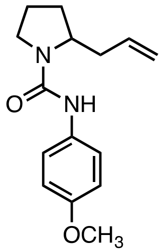
A clean, flame-dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with *N*-Boc-2-allylpiperidine (1.0 g, 4.7 mmol), sodium periodate (4.0 g, 18.8 mmol), and 2,6-lutidine (1.0 g, 9.4 mmol) in dioxane:water (3:1, 47 mL, 0.1 M in alkene). The reaction mixture was stirred overnight at 20 ºC, then diluted with water (25 mL) and extracted thrice with dichloromethane (20 mL x3). The organic layers were dried over sodium sulfate, solvent was removed until approximately 5 mL remained. The aldehyde intermediate was carried on directly without further purification, due to volatility concerns.

A clean, flame-dried round bottom flask equipped with a stir bar and under nitrogen was charged with ethyl triphenylphosphonium bromide (4.0 g, 10.8 mmol), tetrahydrofuran (150 mL), and cooled to 0 ºC. Potassium *tert*-butoxide (1.45 g, 12.9 mmol) was slowly added, and the mixture stirred at 0 ºC for 30 minutes. Then, the aldehyde was added and the mixture allowed to warm to room temperature and stir until judged as complete by TLC (ca. 8 hours). Solvent was evacuated, and a 1:1 mixture of diethyl ether:hexanes (3 x 100 mL) was added to the crude residue of the reaction flask. This organic solvent mixture was filtered through a silica gel plug, and concentrated *in vacuo*. Purification via flash column chromatography on silica gel (2–10% ethyl acetate/hexanes gradient) afforded 0.688 g (65% yield over two steps) as a clear oily liquid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.61–5.50 (m, 1H), 5.42–5.32 (m, 1H), 3.80 (s, 1H), 3.43–3.28 (m, 2H), 2.47 (dt, J = 4.6, 11.7 Hz, 1H), 2.15 (dt, J = 8.7, 14.9 Hz, 1H), 1.95–1.85 (m, 2H), 1.89–1.75 (m, 2H), 1.72–1.61 (m, 3H), 1.52–1.42 (m, 9H).

General Procedure 3.1 – Synthesized following previously established procedures.[73] A clean, flame-dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with *N*-Boc-2-allylpyrrolidine or *N*-Boc-2-allylpiperidine (1.0 equiv) and dichloromethane (0.2 M). The resulting solution was cooled to 0 ºC and trifluoroacetic acid (10.0 equiv) was added. The reaction mixture was stirred until judged as complete by thin layer chromatography (c.a. 4 hours), then diluted with water and quenched with ammonium hydroxide until pH reached 12. The organic layer was reserved, and the aqueous layer extracted with dichloromethane (2 x 30 mL). Organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting 2-allylpyrrolidine was then carried on to the next step without any additional purification.

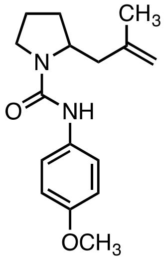
The crude allylpyrrolidine or allylpiperidine was re-dissolved in dichloromethane (0.2M) and charged to a new clean, dry round bottom flask with a stir bar. 4-Methoxyphenyl isocyanate (1.2 equiv) was added slowly, and the resulting reaction stirred at 20 ºC until judged as complete by TLC (ca. 4–14 hours). After concentration *in vacuo*, the resulting residue was purified via flash column chromatography on silica gel (20–40% ethyl acetate/hexanes gradient).

(±)-2-allyl-*N*-(4-methoxyphenyl)pyrrolidine-1-carboxamide (3-18a).



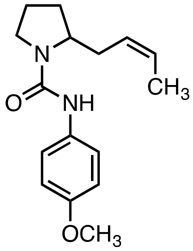
The title compound was prepared from *N*-Boc-2-allylpyrrolidine (1.3 g, 6.1 mmol) following **General Procedure 3.1**. This procedure afforded 997 mg (81% yield) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23–7.15 (m, 1H), 6.78–6.70 (m, 2H), 6.04 (s, 1H), 5.78–5.66 (m, 1H), 5.06–4.95 (m, 2H), 4.00–3.91 (m, 1H), 3.68 (d, *J* = 1.8 Hz, 3H), 3.63 (d, *J* = 1.7 Hz, 1H), 3.34 (ddq, *J* = 2.0, 4.6, 8.2 Hz, 2H), 2.15–2.04 (m, 1H), 1.98–1.79 (m, 2H), 1.71 (ddq, *J* = 2.7, 6.2, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.5, 154.2, 135.1, 132.1, 121.7, 117.3, 114.0, 57.1, 55.4, 46.3, 38.6, 29.5, 23.7.

(±)-*N*-(4-methoxyphenyl)-2-(2-methylallyl)pyrrolidine-1-carboxamide (3-18b).



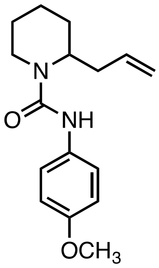
The title compound was prepared from *N*-Boc-2-(2-methallyl)pyrrolidine (663 mg, 2.9 mmol) following **General Procedure 3.1**. This procedure afforded 186 mg (23% yield) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34–7.19 (m, 2H), 6.90–6.79 (m, 2H), 6.11 (s, 1H), 4.83 (s, 1H), 4.76 (s, 1H), 4.22–4.16 (m, 1H), 3.79 (s, 3H), 3.52–3.40 (m, 2H), 2.60 (dd, *J* = 4.1, 13.6 Hz, 1H), 2.12–1.80 (m, 4H), 1.82 (s, 3H), 1.27 (d, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 154.4, 143.6, 132.3, 129.0, 126.9, 121.9, 118.2, 117.3, 114.0, 112.6, 57.1, 56.1, 55.5, 47.5, 46.0, 43.3, 42.5, 31.7, 30.1, 29.4, 24.4, 23.6, 22.7; IR (film) 2966.8, 1638.0, 1638.0, 1510.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{16}H_{22}N_2O_2$ 275.1754; found 275.1760.

(±)-(*Z*)-2-(but-2-en-1-yl)-*N*-(4-methoxyphenyl)pyrrolidine-1-carboxamide (3-18c).



The title compound was prepared from *N*-Boc-(*Z*)-2-(but-2-en-1-yl)pyrrolidine (685 mg, 3.0 mmol) following **General Procedure 3.1**. This procedure afforded 244 mg (30% yield) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.25 (m, 2H), 6.87–6.78 (m, 2H), 6.16 (s, 1H), 5.67–5.55 (m, 1H), 5.50–5.40 (m, 1H), 4.06–3.98 (m, 1H), 3.78 (s, 3H), 3.49–3.41 (m, 2H), 2.59–2.50 (m, 1H), 2.22 (dt, *J* = 8.4, 14.2 Hz, 1H), 2.16–1.89 (m, 2H), 1.95 (s, 1H), 1.81–1.72 (m, 1H), 1.71–1.64 (m, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.5, 154.4, 132.3, 127.6, 126.7, 121.7, 114.8, 114.1, 57.7, 55.5, 46.3, 31.6, 29.9, 23.8, 18.1, 13.1; IR (film) 2965.7, 1637.7, 1511.0, 1369.8 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{16}H_{22}N_2O_2$ 275.1754; found 275.1759.

(±)-2-allyl-*N*-(4-methoxyphenyl)piperidine-1-carboxamide (3-19).

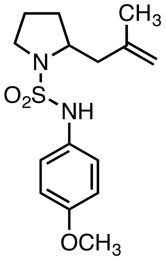


The title substrate was prepared by subjecting N-Boc-2-allylpiperidine (762 mg, 3.4 mmol) to **General Procedure 3.1**. This resulted in 355 mg (38% yield) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.17 (m, 2H), 6.85–6.75 (m, 2H), 6.32 (s, 1H), 5.79 (ddt, J = 7.2, 10.1, 17.2 Hz, 1H), 5.18–5.02 (m, 2H), 4.29–4.21 (m, 1H), 3.91 (dt, J = 3.1, 13.4 Hz, 1H), 3.76 (s, 3H), 2.93 (td, J = 2.8, 13.1 Hz, 1H), 2.52–2.47 (m, 1H), 2.32–2.27 (m, 1H), 1.71–1.52 (m, 5H), 1.54–1.40 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 135.4, 132.6, 122.2, 122.1, 117.3, 114.0, 77.3, 55.5, 51.1, 39.3, 34.3, 27.9, 25.5, 18.8; IR (film) 2934.8, 1628.9, 1509.5, 1416.8 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{16}H_{22}N_2O_2$ 275.1761; found 275.1761.

General Procedure 3.2 – Substrate was prepared according to a modification of a procedure previously published.[57] A clean, flame-dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with *N*-Boc-2-allylpyrrolidine or *N*-Boc-2-allylpiperidine[75,76] (1.0 equiv), dichloromethane (0.2 M), and trifluoroacetic acid (1.0 M). The reaction mixture was stirred until judged as complete by thin layer chromatography (c.a. 4 hours), then diluted with water and quenched with ammonium hydroxide until pH reached 12. The organic layer was reserved, and the aqueous layer extracted with dichloromethane (2 x 30 mL). Organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting 2-allylpyrrolidine or 2-allylpiperidine was then carried on to the next step without any additional purification.

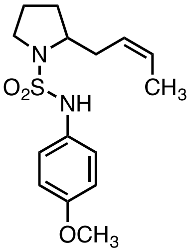
A separate clean, flame-dried round bottom flask was cooled under a stream of nitrogen, and charged with *N*-(4-methoxyphenyl)-2-oxo-oxazolidanone-3-sulfonamide (1.0 equiv), 4-dimethylaminopyridine (0.2 equiv), and a stir bar, and then was evacuated and backfilled with nitrogen. Acetonitrile (0.12 M resulting in added amine) was added, followed by triethylamine (3.0 equiv), and then the reaction vessel was heated in an oil bath to 75 ºC. After one hour at 75 ºC, the amine from above was added, and the reaction mixture stirred at 75 ºC overnight (approximately 16 hours). The mixture was cooled to 20 ºC, solvent was removed *in vacuo*, and the residue was partitioned between dichloromethane and 3M hydrochloric acid (aq). The organic layer was reserved, and the aqueous layer extracted with dichloromethane (2 x 30 mL). Organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo*, and the resulting residue purified via flash column chromatography on silica gel (20–40% ethyl acetate/hexanes gradient).

(±)-*N*-(4-methoxyphenyl)-2-(2-methylallyl)pyrrolidine-1-sulfonamide (3-20b).



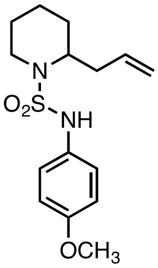
The title compound was prepared from *N*-Boc-2-(2-methallyl)pyrrolidine (332 mg, 1.5 mmol) following **General Procedure 3.2**. This procedure afforded 138 mg (30% yield) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.07 (m, 2H), 6.89–6.77 (m, 2H), 6.50 (br s, 1H), 4.69 (s, 1H), 4.58 (s, 1H), 3.85 (ddt, J = 3.6, 7.3, 10.8 Hz, 1H), 3.75 (s, 3H), 3.35–3.25 (m, 1H), 3.25–3.19 (m, 1H), 2.44 (dd, J = 3.7, 13.8 Hz, 1H), 1.90 (dd, J = 10.6, 13.7 Hz, 1H), 1.82–1.64 (m, 2H), 1.64 (s, 3H), 1.01 (t, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 142.8, 130.2, 123.8, 114.4, 112.6, 59.2, 55.4, 48.8, 43.8, 42.2, 29.9, 24.0, 22.3, 13.7; IR (film) 2973.2, 1507.8, 1245.8, 1142.1 cm^{-1}. HRMS (ESI^{+} TOF) m/z: [M + H]+ Calculated for $C_{15}H_{22}N_2O_3S$ 311.1424; found 311.1427.

(±)-(*Z*)-2-(but-2-en-1-yl)-*N*-(4-methoxyphenyl)pyrrolidine-1-sulfonamide (3-20c).



The title compound was prepared from *N*-Boc-(*Z*)-2-(but-2-en-1-yl)pyrrolidine (762 mg, 3.4 mmol) following **General Procedure 3.2**. This procedure afforded 414 mg (39% yield) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.12 (m, 2H), 6.90–6.81 (m, 2H), 6.63 (s, 1H), 5.56–5.44 (m, 1H), 5.34–5.18 (m, 1H), 3.78 (t, *J* = 1.4 Hz, 3H), 3.76–3.67 (m, 1H), 3.32 (tdd, *J* = 11.5, 9.5, 5.5, 9.5, 11.5 Hz, 2H), 2.42 (dt, *J* = 4.4, 10.8 Hz, 1H), 2.09 (dt, *J* = 8.7, 15.0 Hz, 1H), 1.91–1.69 (m, 3H), 1.69–1.52 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 135.4, 132.5, 122.2, 122.1, 117.3, 114.0, 77.3, 55.5, 51.1, 39.3, 34.3, 27.9, 25.5, 18.8; IR (film) 2972.6, 1508.0, 1246.1, 1145.4 cm^{-1}. HRMS (ESI^{+} TOF) m/z: [M + H]+ Calculated for $C_{15}H_{22}N_2O_3S$ 311.1424; found 311.1429.

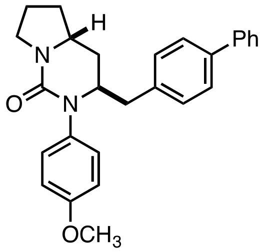
(±)-2-allyl-*N*-(4-methoxyphenyl)piperidine-1-sulfonamide (3-21).



The title compound was prepared from *N*-Boc-2-allylpiperidine (2.0 g, 8.9 mmol) following **General Procedure 3.2**. This afforded 1.25 g (45% yield) of the title compound as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.12–7.07 (m, 2H), 6.86–6.81 (m, 2H), 6.15 (s, 1H), 5.72–5.64 (m, 1H), 5.06–4.99 (m, 2H), 3.98–3.92 (m, 1H), 3.78 (s, 3H), 3.59 (dd, *J* = 4.5, 14.0 Hz, 1H), 2.97 (td, *J* = 2.8, 13.3 Hz, 1H), 2.41–2.30 (m, 2H), 1.59–1.49 (m, 2H), 1.50–1.37 (m, 2H), 1.33–1.22 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.1, 135.0, 130.1, 123.3, 117.3, 114.4, 55.5, 53.5, 41.4, 34.1, 26.7, 24.9, 18.0; IR (film) 3271.5, 1509.0, 1246.2, 1142.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{15}H_{22}N_2O_3S$ 311.1424; found 311.1422.

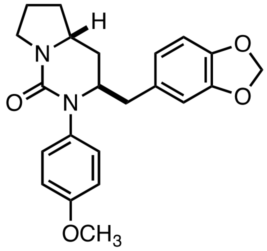
General Procedure 3.3 – A clean, flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the urea substrate, $Pd_2(dba)_3$, tricyclohexylphosphonium tetrafluoroborate, sodium *tert*-butoxide, and aryl bromide. The tube was purged with nitrogen and 2.5 mL toluene per 1 mmol substrate was added via syringe. The reaction mixture was heated to 110 ºC with stirring until judged complete as determined by TLC analysis. Subsequently, the crude reaction mixture was diluted with ethyl acetate (2 mL) and quenched with saturated aqueous ammonium chloride (3 mL). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (2 mL x 2). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and purified by flash chromatography on silica gel using 20–60% ethyl acetate/hexanes as the eluent unless otherwise noted.

(3*R,4a*R**)-3-([1,1'-biphenyl]-4-ylmethyl)-2-(4-methoxyphenyl)hexahydropyrrolo [1,2-*c*]pyrimidin-1(2*H*)-one (3-22c).**



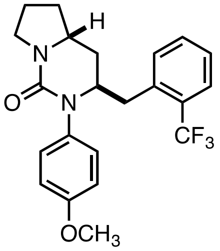
The title compound was prepared from substrate **3-18a** (53 mg, 0.20 mmol), 4-bromobiphenyl (95 mg, 0.41 mmol), NaO^{t}Bu (40 mg, 0.42 mmol), $Pd_2(dba)_3$ (3.4 mg, 0.007 mmol), and PCy_3•HBF_4 (6.8 mg, 0.018 mmol) according to **General Procedure 3.3**. This procedure afforded 64 mg (77%) of the title compound as a brown foamy solid. The compound was obtained as a 16:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 13.3 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.09–4.00 (m, 1H), 3.81 (s, 3H), 3.65–3.59 (m, 1H), 3.59–3.49 (m, 1H), 3.10 (dd, *J* = 4.2, 13.6 Hz, 1H), 2.74 (dd, *J* = 11.0, 13.6 Hz, 1H), 2.20–2.14 (m, 1H), 2.14–2.05 (m, 1H), 1.99 (dt, *J* = 7.2, 13.9 Hz, 1H), 1.92–1.80 (m, 1H), 1.60 (td, *J* = 5.1, 12.5 Hz, 1H), 1.55–1.41 (m, 1H), 1.26 (s, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.9, 154.7, 140.9, 139.6, 137.3, 135.8, 130.4, 129.7, 129.5, 129.0, 127.5, 127.2, 114.5, 60.7, 55.7, 52.9, 46.4, 38.6, 34.2, 30.0, 23.8; IR (film) 2931.6, 2228.0, 1627.9, 1447.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{27}H_{28}N_2O_2$ 413.2224; found 413.2220.

(3*R,4a*R**)-3-(benzo[d][1,3]dioxol-5-ylmethyl)-2-(4 methoxyphenyl) hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-22d).**



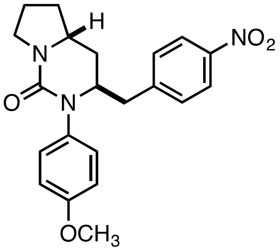
The title compound was prepared from substrate **3-18a** (41 mg, 0.16 mmol), 1-bromo-3,4-methylenedioxybenzene (48 µL, 0.40 mmol), NaO*ᵗ*Bu (40 mg, 0.42 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.008 mmol), and PCy_3•HBF_4 (6.7 mg, 0.018 mmol) according to General Procedure 1. This procedure afforded 48 mg (79%) of the title compound as a pale brown foamy solid. The compound was obtained as a 10:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.14 (m, 2H), 6.93–6.86 (m, 2H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.48 (dt, *J* = 2.0, 4.0 Hz, 2H), 5.90 (s, 2H), 3.97–3.89 (m, 1H), 3.81 (s, 3H), 3.79–3.71 (m, 1H), 3.65–3.48 (m, 2H), 2.96 (dd, *J* = 4.2, 13.7 Hz, 1H), 2.59 (dd, *J* = 11.1, 13.7 Hz, 1H), 2.20–1.91 (m, 1H), 1.93–1.84 (m, 1H), 1.84 (dd, *J* = 3.3, 9.6 Hz, 1H), 1.80–1.72 (m, 2H), 1.61–1.42 (m, 1H);^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 154.8, 148.1, 146.5, 135.9, 132.1, 129.6, 122.4, 114.6, 109.6, 108.7, 101.3, 60.9, 55.8, 53.0, 46.6, 38.8, 34.3, 30.0, 27.3, 23.9; IR (film) 2936.5, 1626.3, 1445.6, 1240.4 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{22}H_{24}N_2O_4$ 381.1809; found 381.1805.

(3*R**,4a*R**)-2-(4-methoxyphenyl)-3-(2-(trifluoromethyl)benzyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-22e).



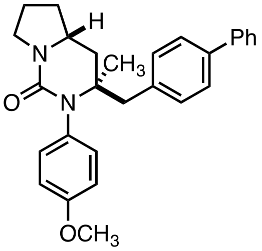
The title compound was prepared from substrate **3-18a** (41 mg, 0.16 mmol), 2-bromobenzotrifluoride (55 µL, 0.40 mmol), NaO^{t}Bu (41 mg, 0.42 mmol), $Pd_2(dba)_3$ (3.4 mg, 0.007 mmol), and PCy_3•HBF_4 (5.6 mg, 0.015 mmol) according to **General Procedure 3.1**. This procedure afforded 49 mg (78%) of the title compound as a brown foamy solid. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 12.8 Hz, 1H), 7.11 (t, *J* = 9.3 Hz, 3H), 6.85 (d, *J* = 8.3 Hz, 2H), 4.15 (dd, *J* = 10.6, 5.4 Hz, 1H), 3.78 (s, 3H), 3.55 (dt, *J* = 9.9, 35.7 Hz, 2H), 3.15 (d, *J* = 14.6 Hz, 1H), 2.96 (t, *J* = 12.4 Hz, 1H), 2.13 (dt, *J* = 5.7, 12.3 Hz, 1H), 2.05 (d, *J* = 13.6 Hz, 1H), 1.98–1.94 (m, 1H), 1.86 (d, *J* = 10.1 Hz, 1H), 1.60 (td, *J* = 13.4, 12.9, 5.0 Hz, 1H), 1.50–1.43 (m, 1H), 1.28–1.22 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.7, 157.7, 154.4, 136.6, 135.2, 131.7, 130.5, 129.2, 129.1 (q, 220 Hz), 114.7, 114.2, 113.9, 55.4, 54.1, 52.5, 46.1, 46.0, 35.2, 33.6, 30.2, 23.4, 21.8, 20.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -58.8; IR (film) 2934.5, 1628.7, 1510.6, 1450.1, 1342.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{22}H_{23}F_3N_2O_2$ 405.1784; found 405.1781.

(3*R**,4a*R**)-2-(4-methoxyphenyl)-3-(4-nitrobenzyl)hexahydropyrrolo[1,2-c] pyrimidin-1(2H)-one (3-22f).



The title compound was prepared from substrate **3-18a** (40 mg, 0.15 mmol), 1-bromo-4-nitrobenzene (83 mg, 0.41 mmol), NaO*^{t}*Bu (40 mg, 0.42 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.008 mmol), and PCy_3•HBF_4 (5.6 mg, 0.015 mmol) according to **General Procedure 3.1**. This procedure afforded 23 mg (39%) of the title compound as a sticky brown solid. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 2H), 7.18 (dd, *J* = 8.1, 15.4 Hz, 4H), 6.90 (dd, *J* = 3.0, 9.1 Hz, 2H), 4.09 (dt, *J* = 4.7, 10.0 Hz, 1H), 3.82 (s, 3H), 3.65–3.49 (m, 2H), 3.17 (dd, *J* = 4.5, 13.6 Hz, 1H), 2.85 (dd, *J* = 10.5, 13.7 Hz, 1H), 2.17 (dt, *J* = 5.7, 11.9 Hz, 1H), 2.06–1.94 (m, 2H), 1.93–1.83 (m, 1H), 1.67 (td, *J* = 4.9, 12.7 Hz, 1H), 1.49 (d, *J* = 13.1 Hz, 1H), 1.27 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 145.8, 135.2, 130.1, 129.8, 129.1, 124.1, 123.8, 114.4, 60.4, 60.0, 55.5, 52.6, 46.2, 38.9, 33.9, 30.1, 25.9, 23.4, 21.0, 14.2; IR (film) 2931.3, 1604.9, 1509.5, 1446.0 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{21}H_{23}N_3O_4$ 382.1761; found 382.1758.

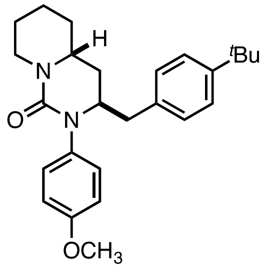
(3*R,4a*R**)-3-([1,1'-biphenyl]-4-ylmethyl)-2-(4-methoxyphenyl)-3-methylhexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-22g).**



The title compound was prepared from substrate **3-18b** (42 mg, 0.15 mmol), 4-bromobiphenyl (89 mg, 0.38 mmol), NaO^{t}Bu (38 mg, 0.40 mmol), $Pd_2(dba)_3$ (3.1 mg, 0.006 mmol), and PCy_3•HBF_4 (5.6 mg, 0.015 mmol) according to General Procedure 1. This procedure afforded 64 mg (77%) of the title compound as a brown solid, mp 73–74 ^oC. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 2H), 7.48–7.42 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.11 (dd, *J* = 8.0, 22.5 Hz, 4H), 6.88 (d, *J* = 8.3 Hz, 2H), 3.90 (td, *J* = 5.5, 10.7, 11.2 Hz, 1H), 3.79 (s, 3H), 3.64–3.58 (m, 1H), 3.51 (t, *J* = 10.2 Hz, 1H), 3.17 (d, *J* = 13.3 Hz, 1H), 3.00 (d, *J* = 13.3 Hz, 1H), 2.17 (td, *J* = 4.7, 13.1, 13.5 Hz, 1H), 1.98 (dt, *J* = 7.4, 14.4 Hz, 1H), 1.92–1.81 (m, 1H), 1.50–1.43 (m, 1H), 1.41–1.34 (m, 1H), 1.22 (s, 1H), 1.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ158.5, 155.3, 140.6, 139.5, 136.4, 132.2, 131.0, 128.8, 127.3, 126.9, 114.0, 59.3, 55.4, 52.6, 46.3, 43.8, 37.9, 34.0, 27.7, 26.9, 26.3, 26.1, 23.2; IR (film) 2930.4, 1603.5, 1509.9, 1435.6 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{28}H_{30}N_2O_2$ 427.2380; found 427.2376.

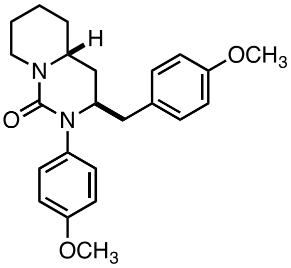
General Procedure 3.4 – A clean, flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the urea substrate, $Pd(OAc)_2$, DPEPhos, Cs_2CO_3, and aryl bromide. The tube was purged with nitrogen and 2.5 mL toluene per 1 mmol substrate was added via syringe. The reaction mixture was heated to 110 ºC with stirring until judged complete as determined by TLC analysis. Subsequently, the crude reaction mixture was diluted with ethyl acetate and quenched with saturated aqueous ammonium chloride (3 mL). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (2 mL x 2). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and purified by flash chromatography on silica gel using 20–60% ethyl acetate/hexanes as the eluent unless otherwise noted.

(3*R,4a*R**)-3-(4-(*tert*-butyl)benzyl)-2-(4-methoxyphenyl)octahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one (3-23a).**



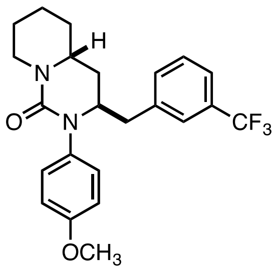
The title compound was prepared from substrate **3-19** (44 mg, 0.16 mmol), 1-bromo-4-*tert*-butylbenzene (70 µl, 0.40 mmol), Cs_2CO_3 (126 mg, 0.39 mmol), $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and DPEPhos (7.8 mg, 0.014 mmol) according to **General Procedure 3.4**. Isolated 19.6 mg (30% yield) product as a pale brown solid, mp 138–142 ºC. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.23 (m, 2H), 7.19–7.10 (m, 2H), 6.99 (d, *J* = 7.8 Hz, 2H), 6.92–6.82 (m, 2H), 4.69–4.59 (m, 1H), 3.80 (s, 3H), 3.45–3.36 (m, 1H), 3.05 (dd, *J* = 13.6, 4.5 Hz, 1H), 2.74 – 2.58 (m, 2H), 1.90 – 1.80 (m, 2H), 1.77 – 1.66 (m, 2H), 1.53 – 1.37 (m, 3H), 1.29 (s, 11H); IR (film) 1653.1, 1635.8, 1558.8, 1418.9 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]+ Calculated for $C_{26}H_{34}N_2O_2$ 407.2693; found 407.2690.

(3*R,4a*R**)-3-(4-methoxybenzyl)-2-(4-methoxyphenyl)octahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one (3-23b).**



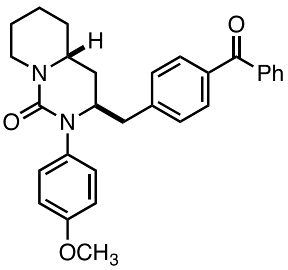
The title compound was prepared from substrate **3-19** (45 mg, 0.16 mmol), 4-bromoanisole (50 µl, 0.40 mmol), Cs_2CO_3 (126 mg, 0.39 mmol), $Pd(OAc)_2$ (1.7 mg, 0.008 mmol), and DPEPhos (7.5 mg, 0.014 mmol) according to **General Procedure 3.4**. This procedure afforded 23 mg (37%) of the title compound as a light brown oil. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.92–6.84 (m, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.66–4.57 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.43–3.34 (m, 1H), 3.08–2.99 (m, 1H), 2.68–2.56 (m, 2H), 1.90–1.82 (m, 2H), 1.70 (d, *J* = 12.0 Hz, 2H), 1.52–1.35 (m, 3H), 1.31–1.16 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 157.6, 154.9, 136.5, 130.1, 130.0, 129.0, 114.1, 114.0, 59.0, 55.4, 55.2, 50.7, 43.5, 38.4, 33.6, 32.1, 25.4, 24.0; IR (film) 1635.6, 1510.9, 1457.2, 1245.7 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]+ Calculated for $C_{23}H_{28}N_2O_3$ 381.2173; found 381.2170.

(3*R**,4a*R**)-2-(4-methoxyphenyl)-3-(3-(trifluoromethyl)benzyl)octahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one (3-23c).



The title compound was prepared from substrate **3-19** (48 mg, 0.17 mmol), 3-bromobenzotrifluoride (60 µl, 0.40 mmol), Cs_2CO_3 (117 mg, 0.36 mmol), $Pd(OAc)_2$ (1.4 mg, 0.006 mmol), and DPEPhos (5.8 mg, 0.011 mmol) according to **General Procedure 3.4**. Isolated 36 mg (56% yield) product as a sticky brown resin. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.39 (s, 1H), 7.29–7.22 (m, 2H), 7.18–7.10 (m, 2H), 6.95–6.84 (m, 2H), 4.63 (dd, *J* = 1.9, 13.2 Hz, 1H), 3.87 (dd, *J* = 3.3, 7.2 Hz, 1H), 3.81 (s, 3H), 3.41 (s, 1H), 3.16 (dd, *J* = 4.8, 13.6 Hz, 1H), 2.85–2.74 (m, 1H), 2.64 (d, *J* = 2.3 Hz, 1H), 1.98–1.81 (m, 3H), 1.77–1.69 (m, 2H), 1.45 (d, *J* = 2.1 Hz, 2H), 1.32–1.22 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.8, 154.7, 139.0, 136.2, 132.5, 130.8 (q, 234 Hz), 129.1, 129.0, 125.5, 124.8, 123.5, 114.2, 58.6, 55.4, 50.7, 43.5, 39.2, 33.6, 32.4, 25.3, 24.0, 14.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.6; IR (film) 1635.7, 1511.3, 1444.6, 1331.5, 1233.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{25}H_{25}C_3N_2O_3$ 419.1941; found 419.1938.

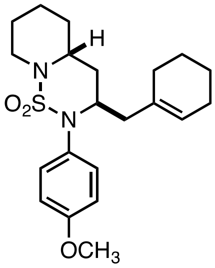
(3*R,4a*R**)-3-(4-benzoylbenzyl)-2-(4-methoxyphenyl)octahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one (3-23d).**



The title compound was prepared from substrate **3-19** (42 mg, 0.15 mmol), 4-bromobenzophenone (103.1 mg, 0.39 mmol), Cs_2CO_3 (122 mg, 0.37 mmol), $Pd(OAc)_2$ (1.4 mg, 0.006 mmol), and DPEPhos (6.6 mg, 0.012 mmol) according to **General Procedure 3.4**. Isolated 43 mg (54% yield) product as a sticky yellow resin. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 2H), 7.72–7.65 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.22–7.08 (m, 4H), 6.93–6.83 (m, 2H), 4.67–4.56 (m, 1H), 3.91–3.83 (m, 1H), 3.79 (s, 3H), 3.41 (t, *J* = 9.4 Hz, 1H), 3.16 (dd, *J* = 4.7, 13.6 Hz, 1H), 2.79 (dd, *J* = 10.3, 13.4 Hz, 1H), 2.62 (t, *J* = 11.8 Hz, 1H), 1.93–1.81 (m, 3H), 1.71 (t, *J* = 9.6 Hz, 2H), 1.52–1.37 (m, 2H), 1.25 (qd, *J* = 6.5, 12.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.2, 157.7, 154.8, 143.0, 137.5, 136.3, 135.9, 132.4, 130.5, 130.3, 129.9, 129.7, 129.0, 128.3, 114.3, 114.2, 58.7, 55.4, 50.8, 43.5, 39.5, 33.6, 32.4, 25.3, 24.0; IR (film) 1633.8, 1603.6, 1510.0, 1443.5, 1276.0 cm^{-1}. HRMS (ESI^+ TOF) m/z: [M + H]+ Calculated for $C_{29}H_{30}N_2O_3$ 455.2329; found 455.2324.

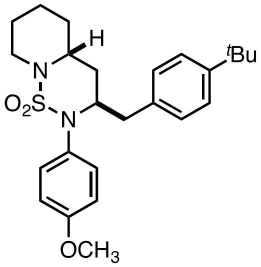
General Procedure 3.5 – A clean, flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with sulfamide substrate, $Pd(OAc)_2$, CPhos, LiO*t*-Bu, and aryl triflate. The tube was purged with nitrogen and 2.5 mL *tert*-butyl alcohol per 1 mmol substrate was added via syringe. The reaction mixture was heated to 82 ºC with stirring until judged complete as determined by TLC analysis. The reaction mixture was cooled to 20 ºC, and solvent was evaporated. Subsequently, the crude residue was diluted with ethyl acetate, and quenched with saturated aqueous ammonium chloride (3 mL). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (2 mL x 2). The collected organic layers were then dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* and subsequently purified by flash chromatography on silica gel using 20–40% ethyl acetate/hexanes as the eluent unless otherwise noted.

(3*S,4a*R**)-3-(cyclohex-1-en-1-ylmethyl)-2-(4-methoxyphenyl)octahydropyrido[1,2-*b*][1,2,6]thiadiazine 1,1-dioxide (3-37a).**



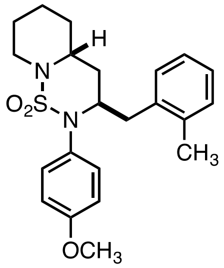
The title compound was prepared from substrate **3-21** (62 mg, 0.20 mmol), cyclohex-1-en-1-yl trifluoromethanesulfonate (70 µl, 0.40 mmol), LiO^{t}Bu (35 mg, 0.44 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), and CPhos (11.9 mg, 0.027 mmol) according to **General Procedure 3.5**. Isolated 60 mg (77% yield) product as a sticky off-white foam. The compound was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.32 (s, 1H), 4.26 (d, *J* = 3.2 Hz, 1H), 3.79 (s, 3H), 3.62–3.46 (m, 2H), 2.88 (s, 1H), 2.30 (s, 1H), 2.17 (d, *J* = 3.2 Hz, 1H), 1.94 (d, *J* = 5.2 Hz, 3H), 1.90–1.68 (m, 7H), 1.63–1.47 (m, 6H); ^{13}C NMR (176 MHz, CDCl$_3$) δ 159.3, 132.9, 131.2, 130.0, 128.7, 124.7, 118.4, 114.0, 57.1, 55.4, 44.4, 42.5, 40.5, 32.9, 32.1, 28.3, 27.5, 25.0, 24.8, 22.3, 21.6; IR (film) 1505.6, 1441.8, 1337.8, 1246.8 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{21}H_{30}N_2O_3S$ 391.2050; found 391.2049.

(3*S,4a*R**)-3-(4-(*tert*-butyl)benzyl)-2-(4-methoxyphenyl)octahydropyrido [1,2-*b*][1,2,6]thiadiazine 1,1-dioxide (3-37b).**



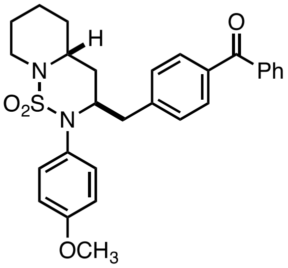
The title compound was prepared from substrate **3-21** (65 mg, 0.21 mmol), 4-(*tert*-butyl)phenyl trifluoromethanesulfonate (112 µl, 0.40 mmol), LiO^{t}Bu (40 mg, 0.50 mmol), Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (7.4 mg, 0.017 mmol) according to **General Procedure 3.5**. Isolated 80 mg (86% yield) product as a sticky light brown foam. The compound was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.44–4.32 (m, 1H), 3.81 (s, 3H), 3.58–3.50 (m, 1H), 3.47 (d, *J* = 3.6 Hz, 1H), 2.93–2.89 (m, 1H), 2.75 (dd, *J* = 4.7, 13.7 Hz, 1H), 2.08 (dd, *J* = 10.2, 13.7 Hz, 1H), 1.84–1.72 (m, 3H), 1.73–1.64 (m, 2H), 1.51–1.40 (m, 3H), 1.29 (s, 9H); ^{13}C NMR (176 MHz, CDCl$_3$) δ 159.4, 149.5, 134.0, 131.2, 130.1, 129.1, 128.7, 125.4, 114.3, 114.2, 66.2, 60.5, 57.1, 55.4, 54.2, 44.3, 44.2, 39.8, 34.4, 32.2, 31.9, 31.4, 29.6, 25.0, 21.9; IR (film) 1507.6, 1336.4, 1247.1, 1157.0 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{25}H_{34}N_2O_3S$ 443.2363; found 443.2364.

(3*S,4a*R**)-2-(4-methoxyphenyl)-3-(2-methylbenzyl)octahydropyrido[1,2-*b*][1,2,6]thiadiazine 1,1-dioxide (3-37c).**



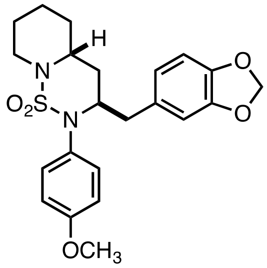
The title compound was prepared from substrate **3-21** (57 mg, 0.18 mmol), 2-tolyl trifluoromethanesulfonate (96 µl, 0.40 mmol), LiO^{t}Bu (30 mg, 0.37 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol), and CPhos (7.7 mg, 0.018 mmol) according to **General Procedure 3-5**. Isolated 49 mg (67% yield) product as a sticky off-white foam. The compound was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 2H), 7.14–7.06 (m, 4H), 6.95–6.87 (m, 2H), 4.41–4.36 (m, 1H), 3.79 (s, 3H), 3.54 (ddd, *J* = 3.7, 6.1, 10.7 Hz, 1H), 3.52–3.47 (m, 1H), 2.94 (ddd, *J* = 3.4, 9.0, 12.1 Hz, 1H), 2.72 (dd, *J* = 4.9, 14.0 Hz, 1H), 2.16 (s, 3H), 1.90 (dt, *J* = 14.4, 12.1 Hz, 1H), 1.77 (dddd, *J* = 20.1, 14.0, 7.2, 3.9 Hz, 2H), 1.73–1.64 (m, 2H), 1.55–1.38 (m, 4H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.5, 136.3, 135.4, 131.1, 130.5, 130.0, 128.6, 126.8, 126.0, 114.4, 64.5, 59.1, 57.0, 55.4, 37.6, 32.3, 31.8, 31.6, 25.0, 24.8, 21.8, 19.5; IR (film) 1606.1, 1506.1, 1463.5, 1338.8 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{22}H_{28}N_2O_3S$ 401.1893; found 401.1891.

(4-(((3*S,4a*R**)-2-(4-methoxyphenyl)-1,1-dioxidooctahydropyrido[1,2-*b*][1,2,6] thiadiazin-3-yl)methyl)phenyl)(phenyl)methanone (3-37d).**



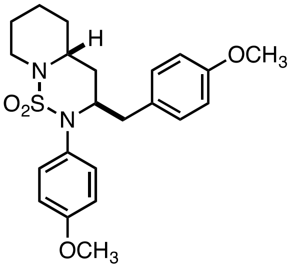
The title compound was prepared from substrate **3-21** (66 mg, 0.21 mmol), 4-benzoylphenyl trifluoromethanesulfonate (132 µl, 0.40 mmol), LiO*t*Bu (32 mg, 0.40 mmol), $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), and CPhos (7.4 mg, 0.017 mmol) according to **General Procedure 3.5**. Isolated 65 mg (62% yield) product as a sticky pale yellow foam. The compound was obtained as a 4:1 mixture of diastereomers as judged by ^1H NMR analysis. Data are for the major isomer. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81–7.72 (m, 4H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.47 (dd, *J* = 13.4, 6.2 Hz, 2H), 7.38 (dd, *J* = 8.3, 12.5 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 4.51–4.44 (m, 1H), 3.79 (s, 3H), 3.53 (tdd, *J* = 3.8, 10.2, 14.0 Hz, 2H), 2.98–2.87 (m, 1H), 2.83 (dd, *J* = 13.9, 5.4 Hz, 1H), 2.29 (dd, *J* = 13.9, 9.3 Hz, 1H), 1.90 (q, *J* = 12.7 Hz, 1H), 1.83–1.62 (m, 4H), 1.56–1.38 (m, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.6, 159.6, 137.4, 136.0, 132.9, 132.6, 132.5, 131.9, 131.2, 130.5, 130.4, 130.0, 129.8, 129.7, 129.6, 129.0, 128.4, 128.2, 114.4, 65.9, 60.0, 57.1, 55.5, 44.3, 40.1, 32.4, 24.9, 22.0; IR (film) 1709.3, 1651.9, 1602.8, 1505.9, 1443.7, 1276.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{28}H_{30}N_2O_4S$ 491.1999; found 491.1999.

(3*S,4a*R**)-3-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(4-methoxyphenyl) octahydropyrido[1,2-*b*][1,2,6]thiadiazine 1,1-dioxide (3-37e).**



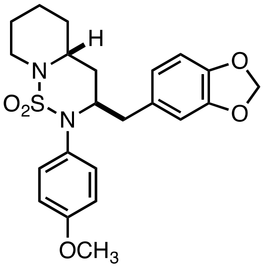
The title compound was prepared from substrate **3-21** (64 mg, 0.21 mmol), benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate (100 µl, 0.40 mmol), LiO^{t}Bu (35 mg, 0.44 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), and CPhos (10.0 mg, 0.023 mmol) according to **General Procedure 3.5**. Isolated 70 mg (79% yield) product as a sticky white foam. The compound was obtained as a 5:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47–7.34 (m, 2H), 6.97–6.86 (m, 2H), 6.68 (s, 2H), 6.55 (d, *J* = 1.8 Hz, 1H), 6.53–6.47 (m, 1H), 5.91 (s, 2H), 4.30 (d, *J* = 2.3 Hz, 1H), 3.80 (s, 3H), 3.50 (d, *J* = 3.7 Hz, 2H), 2.92 (d, *J* = 2.9 Hz, 1H), 2.68 (d, *J* = 13.7 Hz, 1H), 2.04 (dd, *J* = 10.1, 13.7 Hz, 1H), 1.84–1.65 (m, 5H), 1.54–1.40 (m, 3H).^{13}C NMR (126 MHz, CDCl$_3$) δ 159.4, 147.7, 146.3, 131.1, 130.0, 128.5, 122.1, 114.4, 109.3, 108.3, 101.0, 66.3, 60.5, 57.0, 55.4, 54.2, 44.3, 40.0, 38.0, 32.0 24.8, 21.8; IR (film) 1504.4, 1442.5, 1337.0, 1246.3 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{22}H_{26}N_2O_5S$ 431.1635; found 431.1634.

(3*S,4a*R**)-3-(4-methoxybenzyl)-2-(4-methoxyphenyl)octahydropyrido[1,2-*b*][1,2,6]thiadiazine 1,1-dioxide (3-37f).**



The title compound was prepared from substrate **3-21** (63 mg, 0.20 mmol), 4-methoxyphenyl trifluoromethanesulfonate (72 µl, 0.40 mmol), LiO^{t}Bu (30 mg, 0.37 mmol), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), and CPhos (10.1 mg, 0.023 mmol) according to **General Procedure 3.5**. Isolated 58 mg (72% yield) product as a sticky off-white foam. The compound was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.00–6.93 (m, 2H), 6.93–6.86 (m, 2H), 6.86–6.75 (m, 2H), 4.38–4.30 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.56–3.50 (m, 1H), 3.49–3.42 (m, 1H), 2.90 (ddd, *J* = 3.4, 9.5, 12.2 Hz, 1H), 2.71 (dd, *J* = 4.8, 13.8 Hz, 1H), 2.10–2.03 (m, 1H), 1.86–1.72 (m, 3H), 1.72–1.64 (m 2H), 1.56–1.39 (m, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.4, 158.3, 131.2, 130.5, 130.1, 130.0, 129.1, 128.5, 114.3, 113.9, 60.5, 57.1, 55.4, 44.3, 39.4, 32.2, 29.8, 25.0, 22.0; IR (film) 1506.8, 1442.4, 1338.2, 1338.2 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{22}H_{28}N_2O_4S$ 417.1837; found 417.1843.

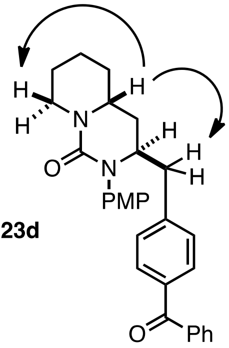
(3*R**,4a*R**)-2-(4-methoxyphenyl)-3-(thiophen-2-ylmethyl)octahydropyrido[1,2*b*][1,2,6]thiadiazine 1,1-dioxide (3-37g).



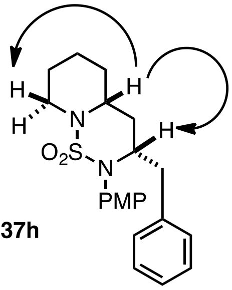
The title compound was prepared from substrate **3-21** (62 mg, 0.20 mmol), 2-bromothiophene (40 µl, 0.41 mmol), lithium trifluoromethanesulfonate (64 mg, 0.41 mmol), LiO*t*Bu (30 mg, 0.37 mmol), Pd(OAc)$_2$ (2.3 mg, 0.010 mmol), and CPhos (8.4 mg, 0.019 mmol) according to **General Procedure 3.5**. Isolated 58 mg (74% yield) product as a sticky light brown foam. The compound was obtained as a 6:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 5.2 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 3H), 6.74 (d, *J* = 3.4 Hz, 1H), 4.45–4.33 (m, 1H), 3.80 (s, 3H), 3.58 (d, *J* = 3.9 Hz, 1H), 3.55–3.46 (m, 1H), 2.96 (s, 1H), 2.90 (dd, *J* = 4.9, 14.8 Hz, 1H), 2.45 (dd, *J* = 9.5, 14.9 Hz, 1H), 1.87 (d, *J* = 14.3 Hz, 2H), 1.74–1.64 (m, 3H), 1.57–1.43 (m, 3H); ^{13}C NMR (176 MHz, CDCl$_3$) δ 159.5, 139.1, 131.1, 126.9, 126.4, 126.1, 124.3, 124.0, 114.4, 60.4, 56.8, 55.4, 44.2, 34.3, 32.6, 31.7, 29.7, 24.8, 21.6; IR (film) 1505.5, 1441.0, 1338.2, 1248.7 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]+ Calculated for $C_{19}H_{24}N_2O_3S_2$ 393.1301; found 393.1302.

Assignment of Stereochemistry

The stereochemistry of **3-23d** and **3-37h**[57,74] were assigned by 1H NMR nOe analysis. Key enhancements are illustrated below. The stereochemistry of **3-23** and **3-37** was assigned based on analogy to **3-23d** and **3-37h**, respectively.



3-23d



3-37h

Chapter 4

Investigating the Impact of a Companion Course for a Peer-Led Study Group Program

4-1 Introduction

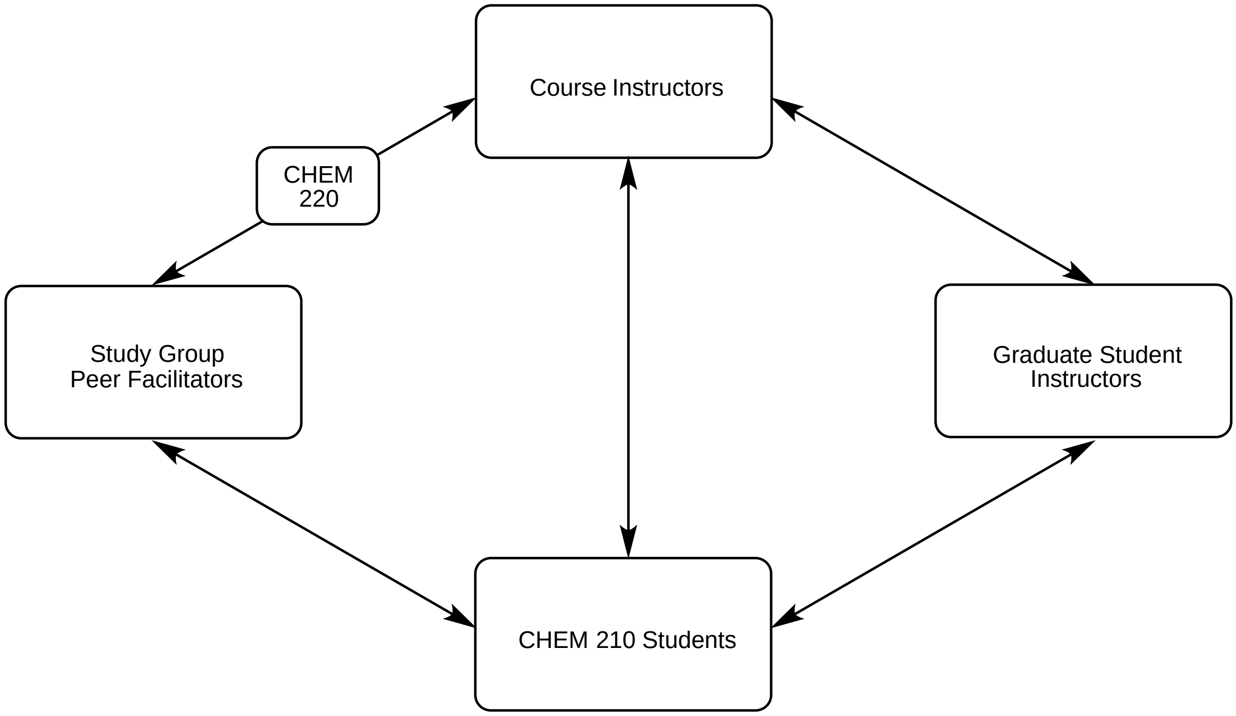
My thesis studies have been impacted not only by the synthetic work presented in previous chapters, but also by the chemistry education research I have conducted under the supervision of Professor Brian P. Coppola, and my Master's in Post-Secondary Science Education advisor Assistant Professor Leah A. Bricker. The focus of this education research is examining and studying a companion course developed to help oversee a peer-led study group (PLSG) program, that itself serves as a voluntary resource for students in the first-semester organic chemistry course at the University of Michigan.

In this chapter, I discuss results from a study my collaborators and I did to explore the impact of introducing a companion course for the PLSG program here at the University of Michigan. We thought this was important to investigate because of the broad impact of PLSG programs (affecting more than half of all introductory organic chemistry students), with a desire to gain insight on course effectiveness and facilitator perceptions of course impact, and facilitator's perceptions of their own usefulness. In what follows, I provide background for the study, including the structure and size of the instructional team for our first term organic chemistry course, the history of our peer-led study group program, and the reason for implementation of the companion course.

CHEM 210, or *Structure and Reactivity I*, is the first-term organic chemistry course offered by the University of Michigan. This course has on-cycle enrollment of 1300-1600 students, spread among four lecture sections, each given in three one-hour periods per week. The course grade comes from three in-term examinations and a comprehensive final examination. Graduate student instructors (GSIs) each lead six different one-hour discussion sections per week, in which all CHEM 210 students are enrolled but which have no graded component. Other structured resources for this course include open faculty discussions (ca. 6 hours/week), the peer-led study groups (PLSGs), and drop-in tutoring sessions offered through the Science Learning Center (SLC). The SLC is a dedicated location in the Chemistry building reserved for science, technology, and mathematics, that hires experienced undergraduate students to serve as peer-tutors and study group facilitators. The SLC also takes care of employment logistics, as well as providing training in facilitation techniques in the form of initial orientation for GSIs, as well as collaborative meetings that take place for one hour, once per month.

Until recently (Fall 2013), the undergraduate facilitators leading these PLSGs had no formal connection to the rest of the instructional team, guided only by their own experiences with course content. As a requirement for employment, all SLC employees (study group facilitators as well as peer tutors) are required to have received a grade of B+ or better in the course in which they facilitate (or tutor); however current employee knowledge was not tested before hiring. To help improve instructional coherence in a teaching system that includes this large number of undergraduate facilitators, the Department of Chemistry and the SLC collaborated to add more direct communication into the design of the instructional infrastructure (**Figure 4.1**).

Figure 4.1 Conceptual Diagram of the CHEM 210 Instructional Infrastructure[a]



[a] Arrows represent conversational flow between members of the teaching team; prior to the existence of CHEM 220, the link between Course Instructors and Study Group Peer Facilitators did not exist.

Our strategy to increase instructional coherence and improve facilitator subject matter knowledge was implemented by adding a new Graduate Student Instructor (GSI) position to the team, as a liaison between the course instructors and study group facilitators. Although the SLC handled the direct pedagogical training in facilitating group work, the CHEM 210 SLC facilitators and tutors were now required (with limited exceptions, e.g., being at the credit limit for the term) to enroll in a content-based course

(CHEM 220: “Teaching Experiences for Undergraduates”) as an additional condition of employment to facilitate or tutor CHEM 210. In the design for the new position, the liaison GSI offers a set of 5–7 sections into which the study group facilitators enroll (one hour/week; 5–12 facilitators per section). The agenda for each week’s session is developed cooperatively between the liaison GSI and the faculty member serving as the course coordinator, with the subject matter maintaining about a one week lead on the lecture pace of CHEM 210. The liaison GSI works with the facilitators, the SLC and the Department to reduce the flow of misinformation, or add clarity to some of the subtle differences in the CHEM 210 course that exist from term to term, ultimately seeking to better unite the message from the entire instructional team.

4-2 Background

Formal programs involving peer-led instruction are long-standing, prevalent, and well-studied in higher education contexts. Peer instruction (or facilitation, as we describe here) sits at the core of many of the “high-impact teaching practices” advocated for their positive effects on student learning.[77] One of the variables in these shared and distributed forms of teaching is the degree to which their work is directly connected with the core course.[78] These programs are directly rooted in constructivist, sociocultural-historical theoretical frameworks, with the majority citing the work of Soviet developmental psychologist Lev Vygotsky. One of Vygotsky’s major ideas is the concept of a learner’s zone of proximal development (ZPD), which is a representation of the learning potential of the learner.[79] The ZPD may be expanded and assisted with the presence of a more experienced other (including not only experts, such as instructors, but even more experienced peers, such as our PLSG facilitators). By leveraging the advantage conferred by a more experienced peer, a learner may expand their zone of proximal development, and ultimately be able to perform tasks on their own that they would not be able to do unassisted.

Several programs have developed in recent decades that leverage Vygotskian concepts of ZPD by inserting more experienced or advanced peers to work alongside undergraduates and expand their ability to learn. One such program is the PLSG program here at the University of Michigan. As described in previously published work,[80] the PLSG program run by the SLC at the University of Michigan “provides out-of-the-classroom programming and support for students enrolled in introductory natural science courses,” with particularly high participation in chemistry study groups compared to other disciplines.[80] All SLC programs, including PLSG, are voluntary and free for any students enrolled in a relevant course. Historically, peer-led study groups have been fully managed by the SLC staff. Each group is facilitated by an undergraduate who has previously take the course and is recruited, trained in collaborative group instructional strategies, and paid by the SLC. Facilitators are explicitly directed away from using didactic “telling” strategies during group sessions and encouraged to ask leading questions, providing scaffolding for learning and guiding students to their own understanding. PLSGs have evolved to sit alongside our courses as a service provided by the College of Literature Arts and Sciences. The introductory organic chemistry program has a consistently high participation in the PLSG program: F11 (Fall 2011) 876/1348 (65%) of students in 69 groups; F12 910/1452 (63%) in 70 groups; F13 824/1439 (57%) in 69 groups; F14 807/1368 (59%) 71 groups; and F15 786/1283 (61%) in 66 groups.

The PLSG program was an outgrowth of a project in the organic chemistry teaching program in the early 1990s.[81] The successful adoption, institutionalization and expansion of the program by the SLC, while quite positive for providing a peer-led instruction option for the campus, was also accompanied by its relative dissociation from the direct “pulse” of the courses being served. We have recently sought to recapture that sense of coherence, wherein the instructional team within the learning environment – 4 faculty members, 12 graduate student instructors, and approximately 70 undergraduate peer facilitators – is provided with the opportunity to increase coherence. The mere existence of peer-leaders, or facilitators as we will call them here, does not guarantee their understanding of, or instructional alignment with, the learning goals of, or pedagogical approaches to, the subject matter designed by the faculty instructors. To address the goal of improving coherence and subject matter correctness across the distributed team of instructors in our introductory organic chemistry courses, we recently created a companion class for all PLSG facilitators and student instructors in the SLC tutoring program who are associated with the organic chemistry courses. The focus of this chapter is to report and study implementation of a new collaborative model between what was, prior to 2013, a set of relatively independent instructional activities.

In thinking of the ca. 100 members of the instructional team for these courses as a single body, we had anecdotal evidence of disagreements between how the faculty, the graduate student instructors, and the study group facilitators were communicating about the instructional program. In order to address this issue, we strove for as much coherence as possible (course coordinator, single syllabus, common exams, and a single gradebook) while leaving room for instructor freedom with respect to day to day planning. The organic chemistry faculty members, as a group, have an internally generated, living document that captures an agreement about scope, depth, and sequence in the organic courses. Graduate student instructors usually attend one lecture section of CHEM 210, receive written overview summaries from the faculty, and attend a faculty-led 1–1.5-hour weekly staff meeting. In the fall term, one of the senior GSIs offers an open hour for the group of GSIs to attend a meeting and work through questions about teaching the subject.

In the next sections, I will describe the questions that arose regarding implementation of CHEM 220, and how we aimed to answer these questions. In order to determine the answers to these questions, a mixed-methods design was employed, in which surveys, interviews, and teaching evaluations present a mix of qualitative and quantitative data sources to inform facilitator perceptions of the course, impacts of implementing the course, and facilitator perceptions of usefulness.

4-3 Methods and Data Collection

In Fall 2013 (F13), the CHEM 220 class was initially structured to be a review of material covered in CHEM 210, with approximately one third of class time spent on lecture-style review, and two thirds of class time spent on problem review. In order to improve the quality of worksheets available to peer facilitators, this format was altered the following year to evenly split the time in discussion between problem generation and content review. In Fall of 2015 (F15) the course reverted to content review, as adequate problems were generated in F14. This chapter focuses on these first three semesters (F13, F14 & F15) of implementing CHEM 220 as support for CHEM 210 undergraduate PLSG facilitators and tutors.

We were interested in the following questions regarding our implementation:

1. Do PLSG facilitators find this course a valuable support to their work? If so, what aspects do they find valuable?
2. For those facilitators who have experienced pre- and post-CHEM 220, has this course changed how they experience working with a study group?
3. Does enrollment in this course influence the facilitators' perceptions about their course content knowledge and/or confidence about their understanding?

To understand the effect of introducing CHEM 220, we investigated three sources of data: (A) End-of-semester evaluations of the CHEM 220 sessions were administered F13 and F14 voluntarily, with free response questions. (B) Quantitative and qualitative information was solicited via email from nine undergraduates who had facilitated an organic chemistry SLC study group prior to the existence of CHEM 220 (F13) and had continued to facilitate with the support of CHEM 220, and (C) End-of-semester evaluations conducted by the SLC as a condition of participation in study groups comprising two fall semesters before CHEM 220 was implemented (F11 and F12), and the subsequent three fall semesters where facilitators were enrolled in CHEM 220 (F13, F14 and F15). How each data set correlates with each question is summarized below (**Figure 4.2**).

Figure 4.2 Questions with Correlated Data Sources Shown Below

Question 1: Do PLSG facilitators find this course a valuable support to their work? If so, what aspects do they find valuable?	**Question 2:** For those facilitators who have experienced pre- and post-CHEM 220, has this course changed how they experience working with a study group?	**Question 3:** Does enrollment in this course influence the facilitators' perceptions about their course content knowledge and/or confidence about their understanding?
Data Sources: (A) End of Term Evaluations from CHEM 220	**Data Sources:** (B) Targeted email survey from those who facilitated both without and with CHEM 220	**Data Sources:** (B) Targeted email survey from those who facilitated both without and with CHEM 220 (C) End of Semester Evaluations from the SLC

Empirical quantitative and qualitative data sets were collected. Quantitative data were collected using Likert-style surveys via Qualtrics, SurveyMonkey, and Google Surveys, where there are discreet categories a respondent may choose (e.g. Strongly Agree / Agree / Neutral / Disagree / Strongly Disagree ***or*** Increased / Decreased / Remained the Same). Qualitative data was also collected via open-ended survey questions collected via Qualtrics, SurveyMonkey, and Google Surveys. Relevant questions and all possible responses are reported in their respective tables in this Chapter. After collection, all qualitative data were coded for emergent themes related to our questions.[82] Subsequently, coding frequencies across data sets were analyzed and the results are reported below. Surveys were coded independently by Dr. Rachel Barnard and me, and then discussed until agreement for each code and response was found. Coding of qualitative data sets was performed based on a variety of emergent themes. After an initial read-through of *all* free-response data sets, analogous or similar responses were flagged and categorized together in order to provide numerical data that may be used for comparative purposes. Representative samples of how free response questions were coded have been included in the appendix for reference and reproducibility (**Section 4-7**). In addition, representative quotations and summaries from the data set have been used to highlight main assertions derived from the following findings.

4-4 Results

Question 1: Do PLSG facilitators find this course a valuable support to their work? If so, what aspects do they find valuable?

Overall, facilitators affirm that CHEM 220 is a valuable support to their work. Worksheets provided from the GSI with sample problems, and opportunity to have direct contact with the instructional liaison and ask content questions are reported as the most valuable aspects of the class. As shown in **Table 4.1**, most facilitators

Table 4.1 Summary of Quantitative Responses by Facilitators About CHEM 220 from Their Evaluations of CHEM 220 (A/SA: Agree/Strongly Agree; N: Neutral; D/SD: Disagree/Strongly Disagree)

	Fall 2013			***Fall 2014***			***Fall 2015***		
# of study groups/ # enrolled in CHEM 220/ # of responses	69/73/41			71/80/29			66/64/42		
	A/SA	**N**	**D/SD**	**A/SA**	**N**	**D/SD**	**A/SA**	**N**	**D/SD**
Overall, 220 was a useful class	41	0	0	22	4	3	40	1	1
Attending 220 sessions helped me prepare for my position in the SLC	40	1	0	17	7	5	40	1	1
Attending 220 for every term I facilitate/tutor would be useful	28	6	7	11	5	13	33	3	6

who completed the end of semester course evaluation found the course useful, especially when the focus was content review (F13 and F15). When asked to rank agreement with several statements, the vast majority (F13 41/41, F15 40/42) agreed or strongly agreed with the statement, "Overall CHEM 220 is a Useful Class." Additionally, facilitators had mostly positive responses regarding how CHEM 220 is helpful for preparing them for their position as an SLC employee. Facilitators felt that attendance every term was not necessary, although a majority in F13 and F15 felt it would be useful. In this data, F14 represents an enigma year, as the course focus was shifted to generating worksheets; relatively few facilitators found this exercise helpful.

Table 4.2 Summary of Code Frequencies Found in Free Response Answers from Facilitator Evaluations of CHEM 220 Based on a Question About How the Course Helped Them as a Tutor or Facilitator.

Code	F13	F14	F15
# of study groups/# enrolled in CHEM 220 / # of responses	*69/73/41*	*71/80/27*	*66/64/38*
Review of Content	26	11	28
Brought Up and Addressed Tricky or Detailed Content	8	2	7
Provided Physical Resources	11	11	8
Provided Human Resources	6	6	7
Lecture Pacing	9	8	4
Increased Confidence with Subject Matter	1	1	1

Free responses collected in these evaluations were coded in a manner similar to those previously published.[78,82] When given the free-response question "In what ways did attending CHEM 220 help you as a tutor or as a facilitator" facilitators wrote that they found the most useful parts of the course to be content review, lecture pacing, human resources (i.e. mentions of liaison GSI, or fellow peer facilitators), and physical resources, such as worksheets or practice exams (**Table 4.2**). Content review was provided by the liaison each week to refresh students on the material presented in the lecture; facilitator responses strongly reflected this as a crucial theme in CHEM 220. Facilitators noted that seeing problems, either presented (F13 and F15) or generated during discussion (F14), became a helpful resource because they could then use those with their study group members. From the liaison's perspective, having these problems helped to encourage whole group discussion of subject matter, allowing underlying errors and misunderstandings to become visible so that they could be discussed and corrected.

The additional weekly contact with their peers and the liaison was noted as valuable to study group facilitators. When asked about how attending CHEM 220 helped as a tutor or facilitator in the end of semester CHEM 220 course evaluations, sample responses included that CHEM 220 "provided a source of example problems and concept clarification" and that "if I had a random question, or if a student asked something that I wasn't sure about, it was helpful to be able to ask [the liaison] and get a direct answer." CHEM 220 clarified how they were able to ask the liaison with their own content questions and helped them to know what important concepts to review in their study groups.

Question 2: For those facilitators who have experienced pre- and post-CHEM 220, has this course changed how they experience working with a study group?

Experienced facilitators report feeling more confident with the subject matter when supported by CHEM 220. In W15 we emailed a survey to nine undergraduates who had been facilitators for organic chemistry SLC study groups before and after CHEM 220 existed. We asked these experienced facilitators questions about their subject matter knowledge confidence, confidence in facilitation, and understanding of course pace. In total, only nine facilitators met these qualifications (i.e. facilitators in either CHEM 210 or CHEM 215), and six of these facilitators responded. Of the four who responded and had experience with CHEM 210 (two respondents had previous worked with CHEM 215 only), three reported that CHEM 220 contributed positively to their confidence about these issues (**Table 4.3**). While this initial data set may be small with respect to the quantity of respondents, in this circumstance we are looking for an in-depth response, more adequately suited to a small sample of undergraduates that undergo a more rigorous line of questioning in order to verify claims and assumptions made in larger datasets. This type of sampling would be thought of as akin to a mechanistic study; a trend is observed in a larger population of data, and in order to gain insight into this trend, we take a more in-depth probe of a smaller subset of that population in order to gain insight. The smaller set is meant to *enhance the understanding of* a larger set, rather than to supplant it.

When asked about how their confidence in the subject matter changed while being enrolled in CHEM 220, one respondent elaborated in the open text portion of the survey that it “allowed facilitators to be exposed to challenging problems that caused them to dive deeper into the material and better understand the content of CHEM 210. In this way, better questions could then be asked of these facilitators’ study group members.”

Table 4.3 Quantitative Response from Survey of Those Who Facilitated With and Without CHEM 220.

Question Prompt	Increased	Remained the same	Decreased
How has your confidence with the subject matter changed from your time leading a group prior to CHEM 220, and with it?	3	1	0
How has your confidence in answering questions changed from your time leading a group prior to CHEM 220 and with it?	3	1	0
How has your ability to learn what is going on in the course changed from your time leading a group prior to CHEM 220, and with it?	3	1	0

Facilitators also expressed appreciation for the content review: "[CHEM 220] has given facilitators a refresh of content they NEED to know and this allows us to better answer questions." With respect to lecture pace, one facilitator explicitly mentioned that "[b]eing in CHEM 220 helped me keep track of the material covered in lecture on a weekly basis." Such quotes exemplify how the course helped the study group facilitators with their subject matter knowledge, a central goal of the course.

Question 3: Does enrollment in this course influence the facilitators' perceptions about their course content knowledge and/or confidence about their understanding?

From both the targeted survey of experienced facilitators and the semester-by-semester end of SLC evaluations by study group facilitators, students indicate that having additional exposure to a GSI was helpful in giving them greater confidence in study group.

(A) *Targeted survey of experienced facilitators*

After surveying just those who had taught with and without the support of CHEM 220, the four facilitators who had led CHEM 210 study groups indicated that contact with the liaison was helpful to their work as facilitators by providing a human resource with whom they can consult when they are confused. The facilitators were (and still are) encouraged to consult other facilitators for help, but the liaison seems to act as a more authoritative content (subject matter) expert. The facilitators also mentioned that the explicit connection to the liaison increased their students' confidence in them as study group leaders. Two of the four respondents mention perceived increases in trust from their study group members regarding their abilities as content knowledge experts. One stated that "having any degree, no matter how small, of official contact with the GSI's/Course Leader, really increases trust and makes your time and the students [sic] all the more valuable." Gaining study group members' trust is mentioned as a key component for functional study groups by facilitators, and the support of CHEM 220 helps bolster facilitators' resources for factual correctness. Supporting this idea, one student reflected the following: "[CHEM] 220 doesn't really help you answer your students' questions in the sense of giving them answers; rather, it allows facilitators to have a deep understanding of the content so that they can better direct discussion through the use of intelligent questions." Equipping study group leaders with an understanding of the material that helps them facilitate effective learning through group work is precisely the goal of CHEM 220.

(B) *Facilitators' evaluations of study group experience by the SLC*

Facilitators indicate a shift in their experiences in study group comparing before and during the implementation of CHEM 220. Facilitators report many positive experiences interacting with their study group members, including personal and professional aspects (**Table 4.4**).

Table 4.4 Summary of facilitators Reported Most Satisfying Experience(s) About Being a Study Group Leader.[a] The course was introduced in the Fall 2013 semester.

Code	**F11**	**F12**	**F13**	**F14**	**F15**
# of study groups/# enrolled in CHEM 220 / # of responses	*69/n.a./42*	*70/n.a./46*	*69/73/57*	*71/80/61*	*66/64/41*
Student Subject-matter Knowledge Gains	19	11	23	19	12
Student Increase in Confidence	7	3	1	1	0
Collaborative Team-Building	16	16	17	10	15
Student Expression of Study Group Appreciation	12	6	10	7	2
Student Expresses Personal Appreciation to Facilitator	6	5	12	14	9
Personal Satisfaction / Warm Fuzzies Expressed by Facilitator	6	14	9	13	11
Facilitator Expresses Feelings of Usefulness	3	4	8	10	5

[a] Numbers for a given code will not sum to the number of facilitators enrolled in CHEM 220 because each response could be coded with more than one code for most satisfying experience.

Many facilitators' self-reported that some of the most satisfying experiences in study group involved moments when students personally thanked the facilitators or when the facilitators had a constructive team-building moment, such as getting students to work together or feeling the group coalesce. Mentions of feeling more helpful or useful to study group members were more direct after the implementation of CHEM 220. One student expressed this as "[f]eeling like my group members think that coming to group was an important/useful use of time." CHEM 220 seems to have a positive influence on students' subject matter confidence and feelings of usefulness to their study group members.

Table 4.5 Summary of facilitators Reported Most Frustrating or Challenging Experience(s) About Being a Study Group Leader.[b] CHEM 220 was introduced in the Fall 2013 semester.

Code	**F11**	**F12**	**F13**	**F14**	**F15**
# of study groups/# enrolled in CHEM 220 / # of responses	*69/n.a./43*	*70/n.a./46*	*69/73/57*	*71/80/61*	*66/64/41*
Students' lack of content knowledge	5	6	0	2	1
Participation	27	29	30	33	26
Students' focus on answers not the process	5	2	2	1	2
Facilitators' lack of content knowledge	3	4	7	7	4
Facilitator's lack of confidence in content knowledge	n/a	n/a	1	4	0
Facilitators' struggle to facilitate and not teach	n/a	n/a	11	1	6
Facilitator's Issues with 210 Pace	3	3	1	3	1
Other	3	8	7	9	5

[a] Starting with the Fall 2013, the survey question addressing the facilitators' most frustrating experience was changed to inquire about their most challenging experience(s) as a study group facilitator. While these questions are clearly not identical, most students did report negative challenging experiences and as such these two questions were coded using the same set of codes. [b] Percentages for a given semester will not sum to 100% because each response could be coded with more than one code for a frustrating experience.

Several of the challenging aspects of facilitating that our study group facilitators report remained consistent across the years. These include issues such as trying to increase study group member participation, study group members pushing for direct answers, and facilitators feeling disconnected from the pace of the CHEM 210 lecture (**Table 4.5**). Perhaps one of the most striking observations after the implementation of CHEM 220 was the change in facilitators' perceptions of their own subject matter knowledge and difficulty in avoiding giving out answers. After the implementation of CHEM 220 in F13, there is more self-reported concern by the facilitators in their subject matter knowledge and confidence. As one student wrote, "[t]he most challenging part was the fear that I would give my group misinformation." By providing them a space to review the material and ask questions, CHEM 220 appears to provide a safe space in which study group facilitators may confront the gaps in their own content knowledge. Some capitalized on their direct connection to content experts and contacted the liaison when they found themselves in need of help outside of scheduled course time. "They came up with questions that I didn't know the answer to, so I just relayed the questions to [the liaison] or told them to ask their GSI."

Facilitators report student pressure for answers and their own increased desire to give students the answer instead of remaining in the role of peer facilitator. "Starting discussions during exam review sessions, students are mostly looking for answers to course pack and review questions quickly…so drawing a balance between what questions should just be given an answer to and which ones should be turned into a discussion was difficult at times but usually worked out well." Many of these tensions naturally arise in the transition from "good student" to "novice teacher" (or facilitator).

4-5 Conclusions and Future Directions

An explicit link between this peer-led study group (PLSG) program and the course it supports provides some important instructional advantages. The CHEM 220 course, in which the peer facilitators were enrolled, helped deepen the facilitator and tutors' perceived subject matter knowledge, ideally contributing to a better learning environment for our introductory organic chemistry students. Before implementation of CHEM 220, facilitators enjoyed their work and were confident in their ability to answer students' questions and facilitate study groups. Through their enrollment in CHEM 220, facilitators appear to confront their own understanding of the course content and have the resources they needed to resolve subject matter issues about which they were less confident.

Extending the usefulness of our experience beyond a large organic chemistry course is easy to imagine. Our work has drawn interest from other courses on campus with existing relationships with the SLC and efforts are already underway to replicate it across the array of courses served by the PLSG program. Treating the facilitators from any peer-led instruction program as members of the teaching team, regardless of the size of the course or its setting, is our core philosophical message, and could cut across multiple domains.

The ongoing design challenges of providing support to the SLC PLSG program include mandatory enrollment for tutors, role of repeat facilitators in the course, and scalability for lecture courses that have fewer PLSGs. In the organic teaching program, we wanted a stronger connection between the undergraduate facilitators and the rest of the instructional team to proactively and reactively ensure coherence in the overall instructional effort. Future work will include investigating an analogous program in our general chemistry course, and audiovisual analysis from both PLSG sessions and CHEM 220 classes to see how we may be able to best scaffold the development of our peer facilitators and tutors.

4-6 Note from the Author

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4-7 Appendices

Table 4.5 Representative Examples of Qualitative Data Analysis and Coding

Pedagogical Code	**Sample Response Corresponding with the Code**
Student Subject-matter Knowledge Gains	“Seeing students understand a concept after struggling”
Student Increase in Confidence	“You could just feel the confidence that I had built within each of the members…”
Students’ lack of content knowledge	“One group specifically ,every member seemed to be struggling with the material”
Students’ focus on answers not the process	“I had a few members who only wanted the answers to the coursepack…”
Facilitators’ lack of content knowledge	“Not being able to remember everything that I had learned…”
Facilitator’s lack of confidence in content knowledge	“Having the confidence to run the first few meetings initially”
Facilitators’ struggle to facilitate and not teach	“…for example, when we were going over stereochemistry…it was hard not to teach them”
Facilitator’s Issues with 210 Pace	“…making sure to prepare for the right thing”
Affect Code	**Sample Response Corresponding with the Code**
Collaborative Team-Building	“getting to know the members and building community”
Student Expression of Study Group Appreciation	“Members would often tell me that group has really helped them”
Student Expresses Personal Appreciation to Facilitator	“My study group members have been very thankful and appreciative of my hard work”
Personal Satisfaction / Warm Fuzzies Expressed by Facilitator	“Bonding with my group”
Facilitator Expresses Feelings of Usefulness	“When students say ‘Thanks, [Facilitator Name]. Today was really helpful’”
Participation	“This term, it was most challenging to get them to talk!”
Other	“…the room numbers in the basement are confusing and several leaders thought they had the same room”

Table 4.5, cont. Representative Examples of Qualitative Data Analysis and Coding

Code	Raw Data
Student Expresses Personal Appreciation to Facilitator, Student Expression of Study Group Appreciation	I got to know a study group member who was the same year as me and became good friends with him. I asked him once how he was doing in Orgo and he said that he was doing really well and that the study group was really helping him. I felt happy with that.
Student Expresses Personal Appreciation to Facilitator	My most satisfying experience would be when my study group members told me that I should lead study group again next semester, but for orgo 2 so that we could continue to work together.
Collaborative Team-Building, Student Subject-matter Knowledge Gains	Providing brain-teaser orgo questions and watching my members not only rally together to come up with the answer but also to come up with a good explanation of why
Collaborative Team-Building, Student Increase in Confidence	My most satisfying experience as a study group facilitator was when we were learning reactions for Chem 210. I played a game where we made 6 groups of 2 and each group would learn one reaction really well by themselves. Than one person from each group would go rotate to the next group and teach "their" reaction. By the end, everyone would learn all the reactions from other members. The members were laughing and feeling confident in teaching their reaction because by the end of the game, they ended up teaching their reaction about 5 times. They were smiling and I had never seen them so eager and confident before. The best part was that I just got to watch as they taught each other and I saw how they got more and more confident after each round.
Students' lack of content knowledge	My most frustrating time was at the beginning of the semester when it seemed like a lot of the members did not seem to have their basic foundation knowledge down and could not keep up with the course material.
Facilitator's Issues with 210 Pace	not knowing where the professors were in the material, not knowing exactly what had been covered that week
Facilitators' lack of content knowledge	Not knowing a part of the material and having to rely on the group's answer regardless if it was right/wrong
Students' focus on answers not the process	One member only wanted answers (did not care about the problem solving process).
Participation	Some members are naturally outgoing while others are more reluctant. Some frequently volunteer while others hesitant or never want to go to the board.
Facilitator Expresses Feelings of Usefulness	I enjoyed knowing that my knowledge of the material was in some cases essentially useful to my students.
Facilitators' struggle to facilitate and not teach	Not directly giving out answers

Table 4.6 Free Responses from CHEM 220 Surveys

Pedagogical Code	**Sample Response Corresponding with the Code**
Review of Content	"It helped keep me fresh with the material"
Brought Up and Addressed Tricky or Detailed Content	"It was really helpful to refresh on tricky material…"
Increased Confidence with Subject Matter	"…and answer questions with more confidence"
Resources Code	**Sample Response Corresponding with the Code**
Provided Physical Resources	"…gave me great examples to use in my own worksheets"
Provided Human Resources	"It also gave me with [sic] the opportunity to ask questions"
Lecture Pacing	"Helped me know what material was covered when…"

Table 4.6, cont. Free Responses from CHEM 220 Surveys

Code	**Raw Data**
Review of Content, Provided Physical Resources	Good review of the material and was it was useful to great worksheets [sic]
Review of Content, Lecture Pacing	220 helped jog my memory on what was going to be discussed in weeks to come
Review of Content, Provided Human Resources	I think that having the opportunity to review the week's material as a group was very valuable. I also found it helpful to have the opportunity to talk to other facilitators about problems we'd encountered in study group, etc… [sic]
Provided Physical Resources, Brought Up and Addressed Tricky or Detailed Content, Review of Content	I used almost all of the worksheets that we got in 220 as "challenge" problems in my study group. It also was a nice review of the concepts from Chem210, as it has been 2 years since I've taken the class myself"
Brought Up and Addressed Tricky or Detailed Content	It was very helpful to review challenging problems and more subtle details
Brought Up and Addressed Tricky or Detailed Content, Lecture Pacing	Kept me up to date and really helped to focus on the tough questions and big picture

Appendix 4.3 Free Responses from Targeted Experienced Facilitator Surveys

Question 1 asks for personal student information (e.g., name, student ID number, email address, which course they had previously facilitated), which has been anonymized for the purpose of this study. **Questions 2a**, **3a**, and **4a** are reported in the results section as Likert responses. **Questions 2b**, **3b**, **4b**, **5**, **6a**, and **6b** are free response questions from this survey.

Question 2a: How has your confidence with the subject matter changed from your time leading a group prior to CHEM 220, and with it?

Question 2b: Please explain your above choice using concrete examples and/or stories, whenever possible, to elaborate your reply.

Respondent A: Chem 220 allowed facilitators to ask questions on material they felt unsure about. For example, facilitators that were not sure on labeling stereochemistry with different methods (hand vs clockwise/counter-clockwise) were able to ask questions to the GSI and have him explain the proper techniques. It also allowed facilitators to be exposed to challenging problems that caused them to dive deeper into the material and better understand the content of Chem 210. In this way, better questions could then be asked of these facilitators' study group members.

Respondent B: The most useful thing for me that 220 offered was explanation for niche questions that I may be unsure of the answer. For example, I remember a complicated R/S labeling question that had two pathways that were difficult to discern which one took priority (the answer ended up being double bond > bonded to 2 carbons, which is a piece of knowledge that doesn't get tested often)

I found 220 most useful for getting these tricky questions answered, and in turn be able to confidently answer when a student asks it.

Respondent C: I'm usually pretty confident about the material covered in Chem 210, however, every once in a while I come across a question that I can't answer confidently. Chem 220 has been very helpful as a resource for asking questions about these challenging questions. This is particularly true when course material changes based on who is teaching that semester.

Respondent D: Overall, I felt my confidence with the subject before and with chem 220 remained the same. I feel this is because I really took the time to practice the material and teach it to others (friends, etc) before officially deciding to be a Chem 210 facilitator. Grace and Jordan were awesome GSIs, however, and I did appreciate the thorough replies to any questions I had, especially since the course material between Fall and Winter is not entirely the same. Many times, I would email Jordan or ask questions directly in section, and he really helped clarify many of the small things. However, as I've mentioned more than once in the past, I do not feel it is necessary to need to re-take this same 1-credit course every term. I can see the benefits for someone facilitating for the first time, but for returning facilitators, it really is just repetitive and unnecessary. Since there are obvious differences in the way the course is taught in the Fall and Winter, I would suggest the following (in order to help students): create a ctools site with a document that helps to address the changes and keep a chat room open where facilitators can communicate with instructors/GSIs should they need clarification on anything. The content was never the real issue, for me at least, it was more-so keeping up with the changes between the semesters, and I really think that if students are going to continuously be made to repeat chem 220, a large focus should be on clarifying these differences. The GSIs should be made aware of the changes, and should make it apart of their lesson plan so that facilitators aren't giving out "false answers".

Question 3a: How has your confidence in answering questions changed from your time leading a group prior to CHEM 220, and with it?

Question 3b: Please explain your above choice using concrete examples and/or stories, whenever possible, to elaborate your reply.

Respondent A: Chem 220 has given facilitators a refresh of content they NEED to know and this allows us to better answer questions. For example, from talking about acid base chemistry in Chem 220, most facilitators felt extremely comfortable about this topic and answers questions about it in Chem 220, which I believe translated into better study group environments later on.

Respondent B: I wish we would do more team-building exercises in Chem 220 to facilitate cooperation among facilitators and also teach them how to be better facilitators in their own study groups. I wish that Chem 220 and the course meetings could be combined.

Respondent C: I covered this is my previous answer. But overall, having direct GSI advice to provide a source for your information is great. When you say "The SLC Leader GSI told us this only a couple of days ago" a student is far more trusting of you than when you say "I seem to remember this should be the answer" or something along those lines if you aren't 100% confident in your answer.

Respondent D: Like I said on the previous page, it is usually questions from old coursepacks (available on the SLC resources page) that I encounter the most trouble with. It was helpful to be able to go to a GSI and ask him or her what is going on in the problem. Again, it seems to have a lot to do with who taught the course when the question was written. Sometimes there are excepts that one class will learn that another one won't learn and that's where the confusion can begin.

Respondent D: My confidence, again, remained the same because I practiced the material before applying for the position to be a Chem 210 facilitator. I will say, however, that my confidence in answering questions last term decreased a bit when I gave out "wrong" answers to students TWICE because of differences in course content between the two semesters. This didn't have anything to do with chem 220 specifically, though..

Question 4a: How has your your ability to learn what is going on in the course changed from your time leading a group prior to CHEM 220, and with it?

Question 4b: Please explain your above choice using concrete examples and/or stories, whenever possible, to elaborate your reply.

Question 5: From your perspective, how has your students' experience in your group changed from your time leading a group prior to CHEM 220, and with it?

Respondent A: I feel that the content is always more fresh when I'm in Chem 220 and I can better ask my study group students questions about the material. I believe chem 220 doesn't really help you answer your students' questions in the sense of giving them answers; rather, it allows facilitators to have a deep understanding of the content so that they can better direct discussion through the use of intelligent questions.

Respondent B: When the students know that you as a leader do have an official course to keep you up to date on the material, it enhances their trust in you and increases attentiveness and attendance to study group. Just having any degree, no matter how small, of official contact with the GSI's/Course Leader, really increases trust and makes your time and the students all the more valuable.

Respondent C: I think that Chem 220 almost acted as a liason between the Chem 210 professors and study group students. It helped me learn what the professors goals and policies were so that I could provide more accurate information for my students. I felt as though student were able to trust me more when I was in the Chem 220 course because my information about grading or material would be passed on from the GSI's rather than just speculation.

Respondent D: I facilitated Bio 172 last term while I was in chem 220, and I currently am not a facilitator for any course because of all that took place last term. I can comment on my students' experience after/during chem 219 over a year ago, and I'll say it was unchanged for the most part. I did use many of the examples/problems Grace presented in chem 219 to my group, so I'd assume my students benefited from those

Question 6a: Is there anthing else related to you or your students' experince before and after the introduction of CHEM 220 that you would like to share?

Respondent A: The GSI's you've picked for this course have been phenomenal! Keep up the quality work!

Respondent B: I would like to mention that the first time I had to take 220 I felt it was a lot more valuable to me than the 2nd time. I've been working for the SLC for three years, doing Chem 210 almost the entire time. Taking 220 for the 2nd time as a senior I really didn't feel the need to be there at all. I simply wish there was an option not to attend if you've already tutored the subject for more than two years or something of the like. 220 was very useful overall.

Respondent C: I wish we would do more team-building exercises in Chem 220 to facilitate cooperation among facilitators and also teach them how to be better facilitators in their own study groups. I wish that Chem 220 and the course meetings could be combined.

Respondent D: [No Response]

Question 6b: Please explain your above choice using concrete examples and/or stories, whenever possible, to elaborate your reply.

[No Responses]

Chapter 5

Investigating Instructional Coherence in Peer-Led Study Groups via Analysis of Audiovisual Recordings

5-1 Introduction

After anecdotal evidence surfaced of conflicting information arising from the Peer Led Study Groups (PLSGs) at the University of Michigan (i.e., undergraduate reports to faculty members that peer facilitators were not covering material in the same way as faculty members), we became interested in improving instructional coherence, and correctness in the PLSG program. In order to ensure that peer leaders are kept up-to-date and refreshed on subject matter knowledge, an additional graduate student liaison position and course (titled CHEM 220: Teaching Experience for Undergraduates) was created. Once per week, peer facilitators attend a discussion course to refresh themselves on chemistry subject matter (for further background on peer-led study groups and the origins of CHEM 220, see **Chapter 4** of this thesis). While **Chapter 4** highlighted peer facilitator course perceptions, this chapter focuses on a central question: Is CHEM 220 helping reduce the errors made by peer facilitators, and if so, to what degree?

The approach we envisioned as best for answering this question falls into the category of a *case study*. The purpose of case studies (as opposed to other research methods, e.g. a randomized controlled study) is to gain depth, either longitudinally, or with a rich data source (such as audio, visual, or interview data).[83] Populations are generally smaller for case studies, but with a more limited population a researcher may gain greater depth and insight into their subjects. In analogy, this process mirrors many aspects of a mechanistic study in chemistry: as an in-depth study of one or more compounds subjected to reaction conditions provides insight into mechanism of a larger suite of reactions, so the depth of a case study may provide insight to educational practice at a deeper level that may influence broader views of practice. Case studies are, by their nature, not generalizable; they are in-depth investigations into the educational practices or interventions in a specific location, and often contain relatively small populations. However, the depth of analysis (including, but not limited to, collection and coding of audiovisual samples) allows for increased understanding of the specific situation. While any claims made in this document represent a narrow contribution to the broader chemistry education community, they simultaneously represent a much greater understanding of how the PLSG program works at the University of Michigan, thereby allowing us to improve upon our existing frameworks with higher levels of confidence than before, potentially providing insight to other PLSG or PLTL programs elsewhere. More detail on the types of case studies, as well as the details of our case study, are found in **5-3 Methods and Data Collection**. Importantly, we want to use this case study to improve instructional coherence, a concept we define as ensuring that all members of the instructional team are consistent and accurate in their discussion of subject matter with students (instructional coherence may also be thought of as “same-pageness”).

In thinking about how to capture instructional coherence, we wanted to somehow capture facilitator correctness and, more specifically, incorrectness (referred to as error herein) during CHEM 220 and their own study groups. This would allow us to capture (1) the nature of facilitator error, (2) how these errors are addressed in CHEM 220, and (3) how error correction in CHEM 220 affects study group facilitators' content knowledge (if it does). In order to capture facilitator error, we concluded that audiovisual recordings of both CHEM 220 and study group facilitators' associated study groups would be the most powerful way to sample facilitator conversations, aimed at determining error frequency, and be able to trace errors from CHEM 220 into study groups, and errors from study groups back to CHEM 220. Audiovisual analysis has been employed in educational settings as a rich source of data, wherein student conversations, interactions, and even gestures may be captured for further analysis.[84] After obtaining student consent, the audiovisual recordings (totaling over 30 hours of recorded data) could then be coded for strategies used (by the CHEM 220 GSI, study group facilitators, as well as peer study group members), facilitator correctness, and whether facilitator error is eliminated or persists between CHEM 220 and study groups. For this case, we hypothesized audiovisual capture and analysis would allow for significantly greater understanding of (a) how correctness (or error) traces between study groups, and (b) provide insight about whether (and if so, how) facilitators taking CHEM 220 use what they learned in CHEM 220 during their facilitation of study group.

5-2 Background

With a large teaching team serving a high-enrollment (ca. 1200–1400 student) introductory course such as *Structure and Reactivity I,* our primary goal in creating

CHEM 220 is to improve instructional coherence, or consistency in message (including presentation, representation, and discussion of subject matter) across the entire teaching team (4 course instructors, 12 GSIs, and 70–80 study group peer facilitators). At its core, we envision instructional coherence as derived from presenting a unified message of correctness regarding content knowledge to our students. Several other case studies have examined the importance of content knowledge when teaching in the science.[85,86,87,88] One study conducted in chemistry looked at chemistry teachers with varying levels of subject matter knowledge, and found that instructors who have limited content knowledge "are constrained in their teaching by the limitations of their understanding of the concept."[85] In circumstances where teachers with limited content knowledge are exposed to new concepts (e.g. a study group member asks a facilitator a question about a stereochemical strategy they are unfamiliar with), such teachers will fall back on rote teaching and learning due to their lack of confidence (i.e. facilitators will simply teach topics based on their limited knowledge, rather than facilitate study groups).[89] Therefore, by establishing CHEM 220, we envisioned that improving content knowledge amongst facilitators would provide a crucial step toward minimizing any potential conflicting ability to present information, therefore fostering instructional coherence.

Along this same track, we wanted (and continue to want) to provide good pedagogical foundations not only for course instructors and graduate student instructors, but also for peer facilitators – all of whom are involved in undergraduate instruction. In the domain of teacher expertise there are three categories of content knowledge: (a) subject matter content knowledge, defined as the amount and organization of knowledge about a subject, (b) pedagogical content knowledge, defined as the dimension of subject matter knowledge that “embodies the aspects of content most germane to its teachability,” and (c) curricular content knowledge, or knowledge of how the curriculum and its associated materials are used.[90] In the realm of stereochemistry, we would think of (a) subject matter knowledge as being able to assign R/S stereochemistry correctly to a chiral carbon. Continuing with stereochemistry examples, (b) pedagogical content knowledge (PCK) is the ability to explain multiple strategies of assigning R/S stereochemistry, such as visualization of the carbon as a clockface, visualization as a steering wheel, or use of the right-hand rule, as well as being able to switch between these strategies at any point as needed to help explain topics to students. Knowledge of how to order lecture topics effectively using all course-related materials including coursepack, would be (c) curricular content knowledge.

While the facilitators that lead our study groups are not intended to be fully fledged course instructors[80] (thus rendering any improvement on curricular content knowledge impractical), we surmised that the introduction of CHEM 220 would provide a scaffold to reinforce and refresh subject matter knowledge, as well as a space to reflect upon subject matter from the perspective of an instructor, in the presence of both the graduate student instructor and other facilitators. CHEM 220 provides access to a graduate student instructor (who has a direct line to faculty for any particularly challenging questions), faculty-approved worksheets and practice problems with answer keys for use in study group, undergraduate-generated explanations (in the form of fellow facilitators explaining their rationale and thinking aloud), and a safe opportunity to make mistakes and allow those errors to be discussed in the open and corrected. The goal of providing these resources for the facilitators taking CHEM 220 is to increase their fluency with course content knowledge, which provides a solid foundation for facilitators to continue to develop their PCK .

The collective PCK literature outlines that the greater a teacher's PCK, the more effective their instruction.[85,86,87,88] In the aforementioned chemistry content knowledge study, the authors note that a teacher with greater content knowledge "is able to display more powerful PCK where [his/her] nuanced SMK allow [him/her] the flexibility to produce innovative approaches."[85] Others have also noted the importance of subject matter knowledge and PCK in the realm of effective instruction. McDiarmid summarizes the overall concept particularly well:

> "To help learners develop integrated and meaningful understandings of subject matter, teachers need not only the substantive knowledge of their subject matter but understandings of what specialists in the field do, what constitutes knowledge in the discipline, how knowledge is generated and verified, and how knowledge is best taught and learned."[91]

Therefore, the introduction of CHEM 220 and the accompanying liaison seeks to (a) improve facilitator knowledge of subject matter, with the added potential to (b) learn how that knowledge is taught and learned, with the added potential to (c) learn what specialists in the field do based on their exposure to an actively researching organic chemist as their liaison GSI.

One of the best examples of how PCK influences study group may be drawn from an example found in our audiovisual data. During one study group, a student incorrectly assigned an *R* stereocenter as *S* and is asked by their facilitator to come to the board to walk through her assignment of the problem. In her explanation to her peers, she discusses how she (a) identified an atom as chiral by having 4 distinct substituents, (b) assigned priorities to each substituent, and (c) used the right-hand rule to assign stereochemistry. During her explanation, fellow study group peer members begin to question her assignment of priorities; as it turns out, she assigned priority based on *hybridization* as opposed to atomic number. This is an instance of one specific strategy of applying content knowledge to a practice problem is incorrect: her assignment of priorities to substituents. Embedded in the audiovisual data is evidence of the facilitator's content knowledge and the beginning shades of PCK. At its core, PCK is the knowledge, built upon an understanding of the subject matter, whereby an instructor considers the origin of a student's error and devises (usually based on instructor preparation ahead of class) an instructional strategy that will address, reveal, and correct the understanding: the facilitator identifies that the problem was done incorrectly, asks leading questions about how the student arrived at her answer, then proceeds to request the student show their thought process on the board. Throughout this recording, the facilitator's correct understanding of content knowledge provides the fundamental basis for facilitation; the student would not have been asked leading questions, nor asked to be at the board, without understanding the mistake in her problem and how to address it.

5-3 Methods and Data Collection

As mentioned in **Section 5-2**, the approach represented in this chapter is a case study. According to Robert Yin,[83] case studies traditionally fall into one of three different categories: descriptive, exploratory, and explanatory – much like experimental methods, each type of study conducted provides insight through a different lens. Descriptive case studies set out to provide descriptions of phenomena, (i.e. how student dynamics function in the classroom), exploratory case studies set out to detail a new phenomena or intervention (i.e. how does this new experiment help students learn?), and explanatory case studies set out to explain how a phenomena occurs and indicate how such explanations may be applied to other situations. Yin details how case study research is chosen based on the nature of the research questions, and that each study must be built upon a particular *case*. In the frame of this research project, we are investigating the case of correctness of SLC facilitators. The type of case study we have developed falls into the category of exploratory: we seek to get a glimpse into how often SLC facilitators correctly discuss stereochemistry problems, and in any instances of incorrect discussion, we want to trace what they were doing in CHEM 220 while this topic was covered, because this will help us to determine what we can do (if anything) to improve CHEM 220 implementation in the future to enhance instructional coherence.

From the perspective of a PCK framework with an emphasis on content understanding, we view correctness in content knowledge as being essential to instructional coherence, and focused our investigations on study group facilitator correctness. If CHEM 220 works as intended, providing a safe space for facilitators to confront their own errors *before* making those errors in their study groups, we will have maintained instructional coherence and improved facilitator content knowledge. Additionally, improved content knowledge serves to improve overall pedagogical content knowledge, potentially improving the effectiveness of our PLSG program.[91]

The video data used for this analysis were collected during a two-week period, during which the topics of three-dimensional representations of molecules, conformational analysis (rings, chairs, Newman projections), and stereochemistry (sources of stereochemistry, labeling stereocenters, stereoisomer relationships) were covered, along with brief review of electrophilic addition. Stereochemistry and conformational analysis was chosen as the ideal organic chemistry topic to study with respect to correctness, as stereochemical assignments are *binary* and *definite.*[92] In contrast to reaction mechanisms, which may have multiple possible products and pathways and require intense diagnostic heuristics to determine the *most correct products*, stereochemistry problems are comparatively facile to code for correctness and error propogation.

For example, a molecule containing three chiral carbons, each with substituents from one another, is represented as eight distinct stereoisomers (2^n where $n = 3$). If we choose one (for the sake of argument, the *RRR*), this molecule has a single enantiomer (*SSS*), and six diastereomers (*RSS, RRS, SRS, SRR, RSR, SRS*). The compound is not meso; all eight stereoisomers are optically active, and the *RRR* will have an equal and opposite (in sign) optical rotation value compared to the *SSS*…etc.

Audiovisual recordings were conducted with full IRB-approved consent from both members of CHEM 220 and the study groups themselves. All participants in the study were given the option to opt-out of being recorded, or being used in this study. All 58 facilitators and tutors consented to be recorded during the CHEM 220 discussion sections. Of those 58, 12 consented to be recorded during their study groups. We were able to attend and record study groups for a total of 10 different undergraduate facilitators. For this analysis, a total of twelve CHEM 220 sections and 18 study group sessions were ultimately collected during this two-week period. Finally, any study group peer members that did not wish to be filmed were either (a) positioned off-camera, or (b) their conversations were not used in the analysis of tapes.

To better understand how the flow of information currently exists in our PLSG program, we became interested in the following questions:

1. Do misunderstandings that the SLC facilitators demonstrate during their weekly CHEM 220 sessions and that are addressed during CHEM 220 persist during the study group sessions and if so, in what ways?
2. When facilitator misunderstandings and/or uncorrected SLC group member misunderstandings occur during study group, what was that facilitator doing during the relevant CHEM 220 discussion section?
3. If a facilitator is present when **another** facilitator makes an error in CHEM 220 and sees it resolved, how do they handle that topic if/when it arises later in their own study group?

Data was collected by a single researcher during a given recording session using a digital camcorder and tripod. The camcorder was placed as far off to the side/back of the study group space as was possible while still being able to see the boards that students worked on. During times of small group work the camcorder was panned to follow the study group facilitator as he/she made his/her way around the room. This allowed for the most optimal recording of facilitator/student interaction. All transcriptions were performed by the researchers conducting the study.

Table 5.1 Summary of Population of Study Group Facilitators Who Participated in Study.

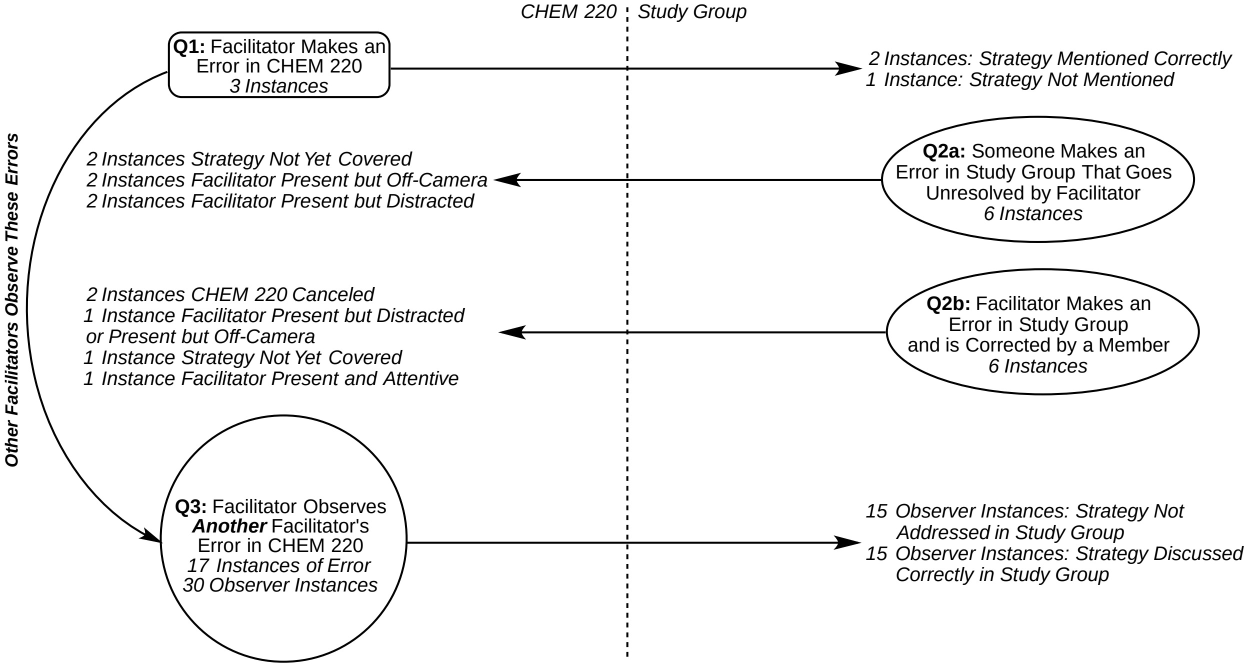
Pseudonym	Has the facilitator taken CHEM 220 prior to F15?	Number of study group sessions recorded
Adam	Yes	2
Andy	Yes	1
Carrie	Yes	2
Daisy	Yes	3
Lupita	Yes	1
Max	Yes	1
Gwen	No	2
Harrison	No	3
Mark	No	2
Oscar	No	3

Coding of audiovisual data was performed using NVivo 11, in analogue to other methods presented in literature and in accordance with qualitative coding procedures.[93] As mentioned under *Framing Student Errors*, each individual strategy involved in solving a stereochemistry problem was coded at each instance throughout all CHEM 220 and study group videos. Each strategy was coded for as long or as brief as the discussion was focused on the particular strategy. Data was not coded on simple utterances alone; rather, codes were applied when students used codes in the context of (a) solving practice problems, or (b) small-group, topic-centric theoretical discussions. Correctness codes were applied to all solved problems; theoretical discussions were not coded for correctness, but were reviewed for correctness when tracing occurred during analysis. Coding of strategies is not mutually exclusive if multiple strategies are discussed simultaneously in the recording. At least two researchers were present for the coding of audiovisual data to ensure agreement and consistency in coding. Passages were coded for one of six overarching topic codes (e.g. Stereoisomer Relationships), which are further differentiated into more specific strategy codes (e.g. assign diastereomer - change E/Z). In addition to the topic code and strategy code, video was coded for the source of the strategy (e.g. study group member, facilitator, CHEM 220 instructor), and fidelity of strategy implementation (i.e. was the strategy used correctly?). Throughout the following results and subsequent discussion, each research question is framed with how the collected data will provide insight as a collective whole, followed by individual descriptions of instances describing the origin of any applicable code along with supporting, relevant information. The code book that follows (**Appendix 5-1**) includes a combination of codes, including spoken words and gestures captured in the recording process. Due to the nature of the aforementioned coding process, and the difficulty in finding instances of non-overlapping codes, as well as representing gestural codes throughout the multitude of recordings in this study, descriptions of codes are listed as topical, with a subset of strategy codes listed below, along with key concepts that tell how that code emerged from the data, the number of instances of that code, and correctness in use. When applicable, descriptions of facilitator behavior have been included. For example, the “Present but Distracted” code indicates that a facilitator was in CHEM 220, but was distracted speaking with a colleague, playing on their phone, or otherwise obviously not participating in the discussion taking place in that moment around them.

5-4 Results

Several patterns emerged upon analysis of audiovisual recordings, with different subpatterns of coded datasets surfacing. In order to best answer each question presented above, three distinct traces of correctness were investigated: (1) For facilitators who incorrectly answered a question in CHEM 220, we look for those codes to appear in their own study groups, (2) for facilitators who incorrectly discuss content in their study groups, we want to know what they were doing during the discussion of this topic in CHEM 220, and (3) for facilitators who observe *another facilitator's error being corrected* in CHEM 220, we look to the study groups of the observing facilitators to see if those topics are correctly discussed (**Scheme 5.1**). Each trace represents a distinct instance that appears below. To clearly present the results of this study, each trace (and corresponding research question) is separated into a distinct section, with an initial description of observed traces, as well as a table of data and subsequent descriptions of each instance for clarity.

Scheme 5.1 Diagram of Research Questions' Correlation to Instances[a]



[a] Video sources are indicated by position (left CHEM 220, right Study Groups). Each Research Question corresponds with a specific type of video code, number of recorded instances, and an arrow which points to which video these codes were traced to, and the distribution of those instances.

Of the total 395 coded instances of facilitators addressing content, we observed eleven instances of facilitators incorrectly explaining, describing, or providing answers for study group peer members. Below are presented thirty-two instances that best highlight how facilitator correctness (or error) is carried between CHEM 220 and study group. These instances have been organized by how the data was correlated, with each data correlation method corresponding to a different research question. Data sets are further sub-categorized by the nature of error (or correctness) observed (e.g. if a facilitator describes something correctly on tape in study group that was covered in CHEM 220, or what the facilitator was doing on tape when this topic was discussed in CHEM 220 based on an error made in study group), which is outlined below each research question heading. Finally, each instance has one or more corresponding strategy, emergently coded from the data sets, that provides a method of determining when a facilitator has described, asked questions about, or explained a stereochemical strategy. The presence of these strategy tags provides a way of tracing correctness (or error) between CHEM 220 and study groups. The presence of a given strategy coded alongside the error tag (Strategy Applied Incorrectly) allowed us to link together segments of video that provided insight into when topics were covered in CHEM 220 and study groups, as well as when those topics were covered by a specific facilitator, and whether they were covered correctly or incorrectly.

Research Question 1: Do misunderstandings that the SLC facilitators demonstrate during the CHEM 220 discussion sections addressed during CHEM 220, persist during the study group sessions or have they been cleared up?

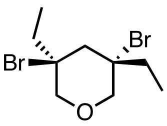
To answer whether facilitator misunderstandings that are corrected during CHEM 220 are presented correctly in study group (Question 1 from **5-3 Methods and Data Collection**), audiovisual recordings from CHEM 220 identified two facilitator problem solving errors and one facilitator conceptual question error; all three of these instances were made by facilitators for whom there is also audiovisual recording of their study groups, for which a summary is provided (**Table 5.2**). Of these three instances, two involved facilitators correctly utilizing the strategy (previously corrected in CHEM 220) in their own study group. One instance involved a facilitator for whom the strategies corresponding with the error made in CHEM 220 did not appear later in study group.

Table 5.2 Summary of Misunderstandings Seen During CHEM 220 by Study Group Facilitators.

Instance #	Pseudonym	Topic :: Strategy	Error persists into study group?
1	Lupita	Rings :: Preferences between chairs by substituent orientation. Rings :: Relative Keq	No
2	Adam	R/S Stereochemistry :: Assign - Right/sleft hand rule R/S Stereochemistry :: Assign - Clockwise/counterclockwise	No
3	Daisy	Stereoisomer Relationships :: Assign different molecule if new molecule is enantiomer or diastereomer of another Stereoisomer Relationships :: Assign different conformation if same molecule but sigma bond is rotated	Strategies not used

For **Instance 1**, facilitators in CHEM 220 are given a practice problem set to work on. One of the problems involves predicting the equilibrium constant between the two chair forms of a cyclohexane-like molecule. The molecule itself is shown below (**Figure 5.1**).

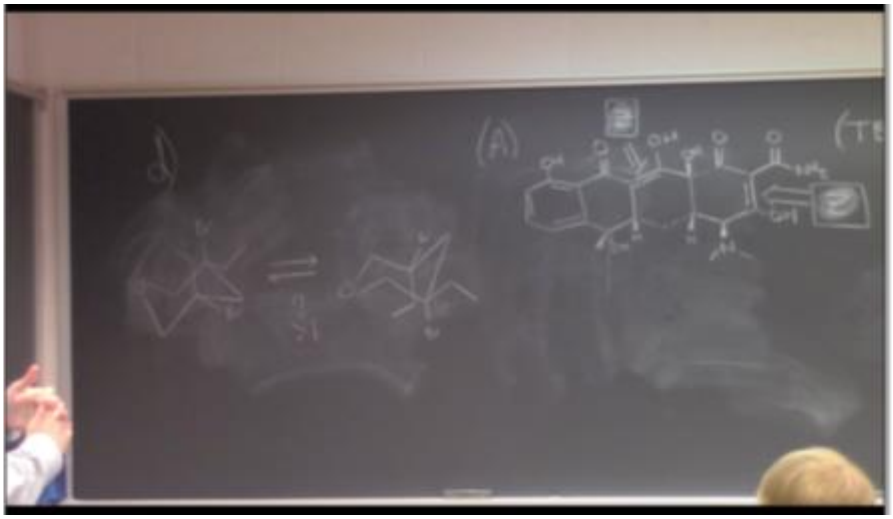
Figure 5.1 Example Compound Given to Study Group Facilitators for a “Chair-type” Practice Problem in CHEM 220.



(3*S*,5*S*)-3,5-dibromo-3,5-diethyltetrahydro-2*H*-pyran

Each chair form has one ethyl group in the axial position and one in the equatorial position (ditto for bromine substituents). This makes the chairs exactly equal in energy, and because of the nature of the molecule, the equilibrium constant should be 1 (as opposed to >1 or <1). When Lupita completes the problem at the board she correctly draws both chair forms, but when she is tasked with predicting the value of Keq (the equilibrium constant), she wrote the following in the board (**Figure 5.2**):

Figure 5.2 Lupita’s Answer She Provided to the “Chair-type” Practice Problem on the Blackboard.



Even if Lupita had given the correct answer, the presence of a “?” with her predicted value for Keq is indicative of her lack of confidence with this problem. The CHEM 220 instructor proceeded to walk through the problem in front of the class in order to address the incorrect answer:

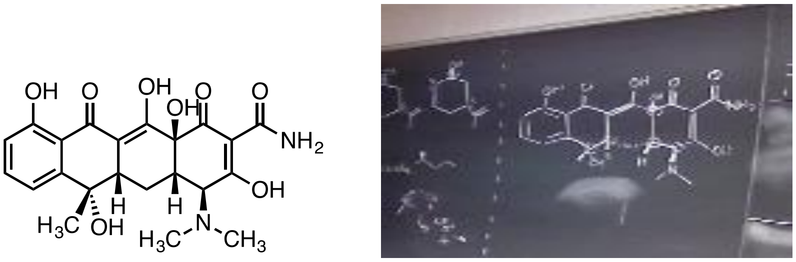
> **CHEM 220 Instructor:** *So, for our first sample. As previously stated, there are a ton of R/S stereochemistry problem on this exam, as most second exams have. And so this was one of the products that was formed from the reaction shown on the page. As we'll see next week, the rest of that problem discusses the stereoisomers of that and the different products that that has. And so, comparing these two different chair forms of the given product "A" I believe it is. What we see is that we have two carbons away from our oxygen we have a bromine and ethyl group. (pointing at the chair form to the left of the equilibrium arrows) and on the left hand side the bromine and ethyl group are axial and on the right hand side (pointing at chair to the right of the arrows) bromine and ethyl group are axial. So in this case, with this particular product, we actually see two products (chairs) that are in the same equilibrium ratio. Because we don't gain anything energetically one over the other. So in this circumstance (erases wrong answer and writes "Keq = 1") these are actually having a Keq equal to 1. And as a reminder on Keq stuff, because I think we've talked about it, but I'm not totally sure because it's something that took me a while to grasp, is that we want to determine where the equilibrium lies. If it's equivalent between the two, Keq is equal to one. If it favors the right hand side product (chair), then Keq will be greater than 1, and if it favors the left then Keq will be less than 1. More on that problem next week...*

During the correction of her given answer Lupita did not ask any clarification questions. Lupita cannot be seen during the mini lecture on Keq by the course instructor, but the instructor corroborates that Lupita was paying attention while the error was corrected.

<u>How this strategy was observed in study group:</u> There is one instance of "preference between chair by substituent orientation" in Lupita's study group. In response to an inaudible student question with a chair conformation on the board, she explains that the "bulkier" substituent is more stable in the equatorial position in a chair conformation. This interaction is also the only instance of "Relative Keq" that we have for Lupita. She uses the two chair conformations to illustrate the effect of bulky substituent orientation on the relative Keq.

Instance 2 involves the tetracycline shown below. While the facilitators are working on the practice problems for the day (a mix of individual work and group work) Adam can be seen working on a problem where he applies the "right hand rule" strategy and the "clockface" strategy. Adam then turns to talk to the facilitators next to him to ask about the problem (**Figure 5.3)**.

Figure 5.3 The Tetracycline Molecule Used for Study Group Facilitator R/S Assignment Practice



Other facilitator A: *Did you get all S?*

Adam: *Wait, I got R.*

Other facilitator B: *For which one?*

Adam: *The bottom right one.*

Other facilitator A: *[inaudible]*

Adam: *Yeah.*

Other facilitator C: *I got S for that one.*

Adam: *(Talking about priorities) So I've got the N is one, then going to the right is two…*

Other facilitator C: *Yeah, it's S though.*

Other facilitator A: *Yeah it's S. so you did it right (talking about priorities) one, two, three, but…*

Other facilitator B: *Because in this case the hydrogen's in the back, so...*

Adam: *Oh, right! Whoops! Duh!*

From the interaction between the facilitators it appears that Adam assigned his priorities correctly to the substituents, but he got mixed up with his R/S based on whether the priority 4 substituent was coming out of the plane or back behind the plane of the paper. [There are multiple other stereocenters in the molecule in question (tetracycline) that have the priority 4 substituent coming out of the plane of the paper (necessitating a reverse of the typical R/S assignment used for a strategy like "clockface"). Perhaps this caused Adam to be in the habit of assigning the opposite R/S than usual].

The other facilitators in the section are quick to point this out to him, and from his reaction it appears that once he was made aware of this he fully understood what his mistake was. Adam continues to discuss R/S assignments with the other facilitators, and he can be seen using the "right hand" rule along with the "clockface" rule in conjunction with "tripod arm" to visualize stereocenters. By discussing this strategy with his peers, Adam could go through stereochemical assignments using multiple strategies, and better understand how to use each one.

How this strategy was observed in study group: We have no recorded instances of the right hand rule strategy being used in Adam's study group. There are four instances of the clockwise/counter clockwise strategy for determine R/S assignment of a stereocenter recorded in Adam's study group session. The strategy was applied correctly three of four instances. In the fourth instance, Adam was gesturing at a student's paper and we could not determine if he was applying the strategy correctly to the molecule in question. Overall, it seems like Adam learned from his encounter in CHEM 220.

Instance 3 features Daisy working with other facilitators on a series of "box-check problems" in a semi-group/semi-individual manner at this point of the class. The facilitators are asking the CHEM 220 course liaison questions as they fill out the practice problems, and he is doing his best to answer the questions as the facilitators are working through the problems. Following a talk about optical activity, Daisy asks a question aloud to the group:

Daisy: *Should you say "different molecules" if there's different stereocenters?*

Other Facilitator A: *That's what I was wondering too.*

CHEM 220 Instructor: *Yes.*

Other Facilitator A: *They're different molecules if they have different stereocenters.*

Other Facilitator B: *The only time they're the same is if they're conformations.*

Daisy: *Like a chair flip?*

Other Facilitator B: *Exactly!*

In this case, Daisy did not actually make an error that we can observe. However, the fact that she raised a question to the group while working on a box-check problem indicates that she did not have complete command of the topic in question. After she asks her question about whether or not two compounds are “different molecules” if they contain different stereocenters another facilitator states that he had a similar question. This question is answered with a simple “yes” by the instructor, but it is also answered in a more thorough manner by a fellow facilitator. The other facilitator expands upon the answer to the question by stating that two compounds would in fact be the same molecule if they are conformational isomers/conformers (the example given is how chair flips are different conformations of the same cyclohexane ring).

How this strategy was observed in study group: There were no instances of the “Assign different molecule if new molecule is an enantiomer or diastereomer of another” being used in Daisy’s study group sessions. There was one instance of the “Assign different conformation if same molecule but sigma bond is rotated” strategy being used during Daisy’s study group, but correctness could not be determined because Daisy was gesturing to work on a student’s individual worksheet.

Research Question 1 sought to determine whether errors made in CHEM 220 are carried into study groups, or whether those strategies are used correctly after having been rectified in CHEM 220. From the available sample of three instances, we have no propagation of error, two instances where the strategy was used correctly in study group, and one instance for which that strategy did not come up in any of the audiovisual recording we have for that facilitator’s study groups. Fortunately, from the data we have available, this tells us that when facilitators make errors in CHEM 220 they are able to resolve misunderstandings before they cover those topics in their study groups – a good indicator that CHEM 220 is working the way we intended and desired.

Research Question 2: When facilitator misunderstandings and/or uncorrected SLC group member misunderstandings occur during study group, what was that facilitator doing during the relevant CHEM 220 discussion section?

Using the video data collected, all instances of error from study group were pooled, with both video and code identified. We found twelve instances of error in our sample: six instances of unresolved errors, where neither facilitator nor study group members notice any error (**Table 5.3**), and five instances of the facilitator being conceptually incorrect, where the facilitator is then corrected by a study group member (**Table 5.4**). These twelve instances are collected below and sort into several different categories according to whether the error was resolved or not, and what the facilitator was doing during CHEM 220.

Of the six instances of unresolved errors, we noted three different sources of error: two where the strategy was not yet covered in CHEM 220 (**Instances 4 & 5**), two where the facilitator is present but off camera (**Instances 6 & 7**), and two where the facilitator is present, but distracted and talking to a colleague (**Instances 8 & 9**). For the five instances of the facilitator being corrected by a study group member, these also sorted into distinct categories: two where the facilitator's CHEM 220 class on the topic was canceled and a handout was emailed out (**Instances 10 & 11**), one where the facilitator was present in CHEM 220 but the strategy was not covered (**Instance 12**), one where the facilitator was (a) present but distracted during class or (b) off-screen (**Instance 13**), and one where the facilitator was present and paying attention in CHEM 220 (**Instance 14**).

Unresolved Errors in Study Group

Unresolved errors in study group represent instances when a strategy is used incorrectly by either the facilitator or study group members, but the misunderstanding is never clarified or rectified in the audiovisual recording we have. These six instances are summarized below (**Table 5.3**).

Table 5.3 Summary of Unresolved Errors Found During Study Group for Sample Population.

Instance	**Pseudonym**	**Topic :: Strategy**	**Facilitator Behavior in CHEM 220**
4	Harrison	Rings :: Axial or equatorial by parallels	Strategy not yet covered
5	Lupita	Rings :: Chair flips by drawing both chairs	Strategy not yet covered
6	Oscar	Stereoisomer Relationships :: Assign Meso – two opposite SCs with same substituents and internal molecular symmetry	Present but off-camera
7	Daisy	E/Z :: Assign Priority to Substituents	Present but off-camera
8	Daisy	Stereoisomer Relationships :: Optically active – has RS stereocenter but isn't meso	Present but distracted
9	Daisy	Stereoisomer Relationships :: Assign optical active - if compound is chiral // Optically active - has RS stereocenter but isn't meso	Present but distracted

In **Instance 4**, a student in Harrison's section had just finished explaining how she converts from the planar version of a 6-membered ring to the chair version by numbering her carbons on each structure drawing on the blackboard (**Figure 5.4**). The molecule in question is a simple cyclohexane ring with only hydrogen substituents in all of the axial and equatorial positions:

> **Student A:** *(Discussing converting from planar version to chair version) Wedges will always be in the up position. And then whether you have this chair or the opposite chair will change whether it's equatorial or axial. Equatorial will always be going to the sides, while, wait, well yeah, and axial will always be going up or down. Let's see...*
>
> **Student B:** *You should also remember that when you're drawing, you know that equatorial H by 3? You would always want it to be parallel to 5 and 4.*
>
> **Harrison:** *Yeah, the side lines, sort of, yeah.*
>
> **Student B:** *That's just something to remember.*
>
> **Harrison:** *Yeah.*
>
> **Student A:** *This one? (pointing at her drawing).*
>
> **Student B:** *Yeah. No! Go to your equatorial H, the one on 3. And you see how it's parallel to 5 and 4?*
>
> **Student A:** *Oh! This! (pointing at a different spot).*
>
> **Student B:** *Yeah!*
>
> **Harrison:** *Yeah!*
>
> **Student B:** *So you always want that.*
>
> **Harrison:** *So your equatorial lines are always parallel to some other lines in your chair.*
>
> **Student B:** *Yeah. It's just important…*
>
> **Harrison:** *Yeah. You drew them right.*

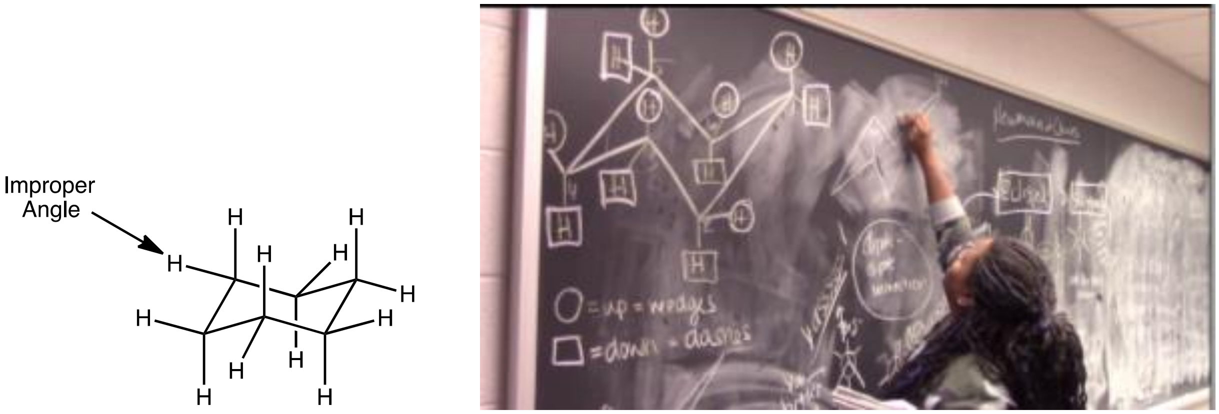
Student B: *You drew them perfect.*

Harrison: *You drew a really good chair. If your chair looks like that on the exam you should be very happy.*

Student A: *Cool.*

Even though both the facilitator and another student proclaim that the chair that was drawn is a perfect chair, the drawing in question did not have all equatorial H bonds drawn parallel to the corresponding bonds in the ring. This problem was coded as incorrect and unresolved because nobody pointed out the improper bond angle that exists for one of the equatorial hydrogens.

Figure 5.4 Cyclohexane Chair, as Drawn by a Study Group Member, that Contains an Incorrect Bond Angle.



Facilitator behavior during CHEM 220 when this strategy was covered: While this is a rather small point in proper representation of chair conformations, Harrison is emphasizing that this is a perfect drawing. In CHEM 220 the liaison said "I am operating under the assumption that the majority of you are very familiar with chairs, drawing chair, drawing substituents. If you have questions on that, feel free to let me know. I am mostly going to focus on the idea of chair flips 'cause that is something that students can get very confused on very quickly, and there are multiple methods for doing that."

In **Instance 5**, Lupita had just finished talking through how to accomplish a chair flip by drawing both chairs, and she asked the study group if anybody knew of a different way to do a chair flip (looking for someone to explain "chair flips by rotating around ring"). Nobody says anything for a few moments, then a student begins describing something that her discussion GSI showed her:

> **Lupita:** *What's the other way that we can chair flip? [silence] I'll give you a hint. I can draw the exact same chair (as before) and still chair flip this guy with the same shape. But what would happen to my substituents? [silence]*
>
> **Student:** *Is it like a mirror?*
>
> **Lupita:** *Explain.*
>
> **Student:** *I remember from discussion my GSI drew, like, two exactly the same just mirrored. And he said they're different because, it's like the hand. It's never going to be, like, exactly on top of one another. I don't know...*
>
> **Lupita:** *Okay.*
>
> **Student:** *It's difficult to understand.*
>
> **Lupita:** *No. Yeah. Maybe. I don't want to say I should know about, like, draw it up there and see [inaudible]. Anybody else?*

From the video it appears that Lupita does not know if the strategy presented by the student is a valid way to accomplish a chair flip. From the description given by the student, the strategy would not accomplish a chair flip, and would instead give you the enantiomer of the original chair structure that was given. For this reason the strategy described by the student was coded as "incorrect", and because Lupita's answer was essentially "maybe, draw it and see", we coded this instance as "unresolved".

Facilitator behavior during CHEM 220 when this strategy was covered: When this study group had occurred, Lupita had not yet been "refreshed" about enantiomers and diastereomers in CHEM 220. When the topic was addressed it was not done in the context of chair flips making this student's "strategy" especially challenging to troubleshoot.

Instance 6 occurred during Oscar's exam review, in which the students are working on box check problems. For one of the problems the molecule shown below is in question:

Figure 5.5 Example Compound Used in Oscar's Study Group.

(2R,5S)-2,5-dimethyl-1,4-dioxane

The students are talking amongst themselves about which boxes they have checked for this molecule:

Student A: *I have 'has at least one chiral diastereomer', 'a meso compound', and 'optically inactive'.*

Student B: *What?*

Student C: *Yeah, that's what I got.*

Student B: *I just got (boxes) 1 and 2… It's not meso.*

Student A: *It is meso.*

Oscar: *Hey, which one are we on?*

Student D: *Don't both have to be wedged or both have to be dashed?*

Other students: *No.*

Student E: *One has to be R and one has to be S.*

Oscar: *Okay, so let's... So what do we think about the first one?*

Student A: *We said the left one was R and the right one was S. Then I said it has at least one chiral diastereomer, it's a meso compound, and optically inactive.*

Oscar: *Why do we think it's meso?*

Student B: *It's not meso.*

Student F: *There's no line of symmetry.*

Oscar: *I'm going to draw something...*

Student E: *There is a line of symmetry.*

Student B: *Where?*

Student E: *There is. Right here (points towards her worksheet).*

The students continue to talk amongst themselves as Oscar draws the molecule in question on the board and then redraws it with the wedges/dashes flipped to (incorrectly) show that you cannot superimpose the two molecules:

Oscar: *(gesturing towards whiteboard) So I've switched R and S here and then I flipped it over. Are these things the same?*

Students: *No.*

Oscar: *Apparently not.*

Student E: *Wait, wait, wait. That's the problem, right? (pointing at original molecule).*

Oscar: *This is the problem. I switched R and S, and then I flipped this thing over (gesturing to show a rotation of the whole molecule, flipped like a pancake). Notice that this 'O' is now shifted over one.*

Student B: *So they're not meso. We were right.*

Oscar: *They are not meso.*

Oscar failed to execute the proper rotations that would have shown that the molecule is indeed meso. However, the answer key he was provided for the practice exam that he was going through with his students **incorrectly** claimed that this molecule is *not* meso. Oscar was, for the most part, just sticking with the answer that the key to the exam provided for him. For this reason he did not exhaust the possibilities for rotating the molecule to see if it was actually meso or not.

Facilitator behavior during CHEM 220 when this strategy was covered: The "Assign Meso - two opposite SCs with same substituents and internal molecular symmetry" strategy is touched on at the end of the second week of CHEM 220 along with several other features of meso compound determination. Oscar was present during this discussion of determining if a compound is meso, and received the complimentary handout via email after discussion. All students were off camera during this concept review.

In **Instance 7**, Daisy presented the structure shown above was to help students practice assigning R/S stereochemistry, and the study group member that presented the molecule correctly assigned both stereocenters as “S”. However, after Daisy affirms the “S” assignments, a student asks about also labeling the alkene stereochemistry:

Figure 5.6 A Compound Used by Daisy in Her study group for R/S and E/Z Assignment Practice.

(1*S*,1'*S*)-1,1'-(furan-2,5-diyl)bis(propan-1-ol)

Student: *Oh wait! Aren’t you also supposed to label the alkenes?*

Student A (that wrote down answer on board): *Oh yeah, I didn’t write that down. Sorry.*

Daisy: *Oh yeah! Yes, but in this case since it’s a small ring they’re always going to be “E”.*

Student A: *What?*

Daisy: *So you only label E or Z in a ring if it’s greater than eight carbons. So this ring, it has five. So I guess if you did it on an exam you wouldn’t be wrong, but in small rings they’re always going to be E. Because in small rings they’re flexible enough to be Z, because then you would have to break the bond, like, break the ring.*

Student B: *Do we have to label them in the ring?*

Daisy: *No. If it's greater than eight carbons.*

Student B: *Yeah. [inaudible]. So we're just not dealing with the ones in the rings now?*

Daisy: *I think for now, for the exam coming up, for tomorrow, I think that they're not going to give you any double bonds in rings. But you can do them in rings, but you assume the small rings are always going to be E.*

Student A: *But isn't that top one Z, though?*

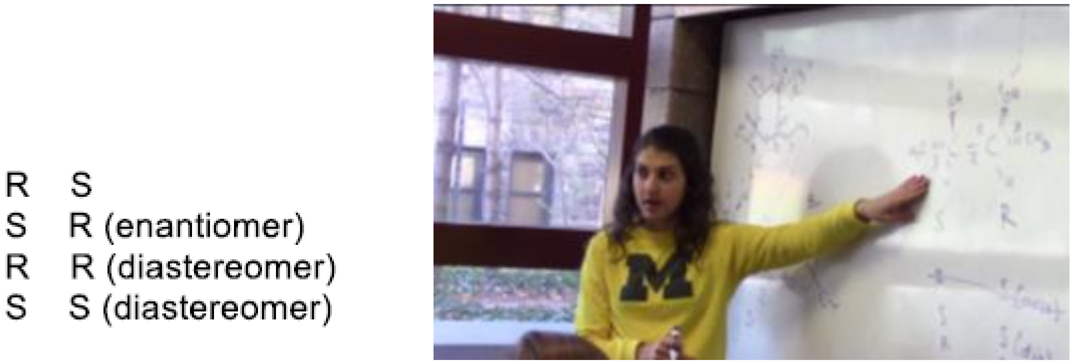
Daisy*: Yeah. But you're going to assume it's going to be E. So if it's in a small ring it's so strained that you're not going to have, like, a Z conformation in the ring. So that's why they don't ask you to label them. But if it's greater than eight carbons, then you would label it like you normally would. So if this was greater than eight carbons you guys could do it because you can label priories. I don't know if they are going to ask you that, but in this case you don't have to label them because it's less than eight.*

When Daisy is asked the question about labeling alkene stereochemistry in the ring of the compound, she mistakenly tells the students that alkenes in small rings can only ever have E stereochemistry. Even after she is confronted by a student about the alkenes in the example problem being Z, she still sticks with her answer that "you're going to assume it's going to be E". Because Daisy never deviates from her original, incorrect answer, this instance of incorrectness was never resolved.

Facilitator behavior during CHEM 220 when this strategy was covered: E/Z assignment within rings were discussed in CHEM 220 during the first week on stereochemical topics. Daisy was present, but off camera, as the CHEM 220 liaison discussed two examples of assigning Z stereochemistry to double bonds in the six membered rings of tetracycline.

Instance 8 occurred during Daisy's exam review session, during which she is leading students through a discussion about stereoisomers and their relationships such as enantiomers and diastereomers. On the whiteboard can be seen a diagram showing the relationships between all of the variations of a molecule with two stereocenters (**Figure 5.7**).

Figure 5.7 A Diagram Used by Daisy to Remember How Changing Stereocenters Factors into Stereoisomer Relationships



R S
S R (enantiomer)
R R (diastereomer)
S S (diastereomer)

This discussion leads to a question about meso compounds and how to identify them/their defining characteristics. The students and facilitators correctly state that if the compound in question was meso, then the S/R enantiomer would not exist (facilitator crosses this out on the diagram). Next, the facilitator asks the students about how to identify meso compounds:

Daisy: *How do you know if it's meso? What does meso mean?*

Student A: *It's...*

Daisy: *Yes?*

Student A: *Optically active but not chiral?*

Daisy: *(thinking) Um. Optically active... it itself can be optically active, but it does not have... yeah, that's right. But it's not chiral, so that's true.*

Daisy then begins to talk about how to identify a meso compound based on if it has two opposite stereocenters with internal symmetry. Her error of claiming that meso compounds are optically active goes either unnoticed or unchallenged by the students in her study group.

Facilitator behavior during CHEM 220 when this strategy was covered: Meso compounds lacking optical activity is addressed in the second week of CHEM 220 sessions on stereochemical topics. Several times the liaison implies that meso compounds are not chiral and are optically inactive. In one such example, the liaison says "We can think about having two products that are optically active that are enantiomers to one another, and then the meso compound as well." Another student had incorrectly identified a molecule in the worksheet as both chiral and meso on the board. The liaison corrects this, but during this correction Daisy can be overheard talking with another student indicating that meso compounds do not have enantiomers. She misses the most explicit statement disconnecting meso compounds and optical activity.

Instance 9's unresolved error stems from the same larger discussion that the previous error (**Instance 8**) came from. Daisy is still leading a discussion about meso compounds, diastereomers, and enantiomers with the study group members. During the talk about meso compounds the topic of optical activity is touched on once again:

> **Daisy:** *So in this case, this structure right here (pointing at board), since it is the meso compound it has chirality. No, it doesn't have, it's achiral but it is optically active. Because optical activity means that it has, like, a stereocenter, basically. So because it has two stereocenters, it is optically active. Or I mean... (thinking) it is optically active, but it is achiral. Okay?*
>
> **Student A:** *So something can be optically active but be achiral?*
>
> **Daisy:** *Only if it's meso.*
>
> **Student B:** *But otherwise being chiral means...*
>
> **Daisy:** *Being optically active (nodding).*
>
> **Student B:** *So it's like the one exception.*
>
> **Daisy:** *Yes, exactly.*

Once again this error goes unnoticed/unchallenged by the students in Daisy's study group. The discussion continues on about other kinds of molecules that are achiral (E/Z stereochem, cis/trans stereochem).

Facilitator behavior during CHEM 220 when this strategy was covered: See **Instance 8** for details.

Study Group Member Corrects an Error

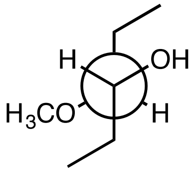
Another type of facilitator error observed in study group occurs when the facilitator makes an error, yet a student questions this incorrect statement, answer, or line of questioning. These six instances are collected in the table below (**Table 5.4**).

Table 5.4 Summary of Instances Where a Study Group Member Corrects a Conceptual Error Made by a Facilitator During Study Group.

Instance #	Pseudonym	Topic :: Strategy	Facilitator Behavior in CHEM 220
10	Andy	Newman Projections :: Assign or use gauche vs periplanar	CHEM 220 canceled, handouts emailed out
11	Mark	Newman Projections :: Convert to Newman from dash and wedge	CHEM 220 canceled, handouts emailed out
12	Daisy	R/S Stereochemistry :: Assign chiral atom - requires 4 different substituents	(1) present but distracted (2) off screen
13	Daisy	R/S Stereochemistry :: To get lowest priority in back - change perspective	Strategy not covered
14	Harrison	Stereoisomer Relationships :: Assign enantiomer - change all R/S but not E/Z Possibly: Stereoisomer Relationships :: Assign diastereomer - change E/Z	Yes.

During **Instance 10**, Andy's study group is going through the answers to the practice exam together. The facilitator is presenting the exam answer key projected on a screen at the front of the classroom. The problem in question involves identifying the destabilizing forces present in a Newman Projection (**Figure 5.8**). During the discussion, a student openly wonders why "gauche interactions between –OCH3 and the ethyl group" is not on the answer key. Instead of taking the study group member's answer into full consideration, the facilitator dismisses it:

Figure 5.8 Newman Projection Used in Andy's Study Group for a Practice Problem Concerning Destabilizing Forces.



(3*R*,4*S*)-4-methoxyhexan-3-ol

Andy: *If it's not on the answer key it's not a right answer.*

Student A: *Yeah, I'm trying to understand why.*

Andy*:* *If there are more answers, then they will say there are opportunities for more answers.*

(Pause)

Andy: *So the question is, "why can't gauche interactions between –OCH_3 and the ethyl group be an answer".*

Student B: *Is it because they're really far away?*

Andy: *Literally, that's it.*

Student A: *What did he say?*

Andy: *It's because they're on different molecules, and they're pretty far away.*

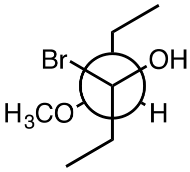
Student C: *One's in the front and one's in the back.*

Andy: *They're on different carbons.*

Student A: *But on the first problem that's an answer.*

Student A proceeds to show/explain to Andy how the preceding question that involved an extremely similar Newman Projection listed "gauche interactions between –OCH3 and the ethyl group" as a destabilizing force. The preceding Newman Projection can be seen in **Figure 5.9**:

Figure 5.9 Example Newman Projection Used by a Study Group Member to Explain His Thinking to Andy.



(3*S*,4*S*)-3-bromo-4-methoxyhexan-3-ol

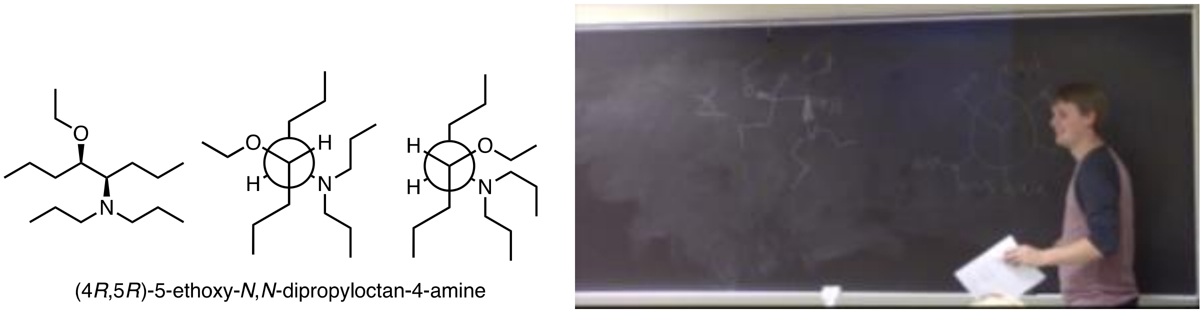
Andy: *Interesting... Good point.*

After the students made their case, Andy acknowledged that their original answer is an acceptable answer for this question. Andy was too “married” to the answer key at first, and instead of thinking through the possible answers put forth by the students he immediately assumed any answer not listed on the key was incorrect. However, after some explanation by the study group members he realized he was incorrect.

Facilitator behavior during CHEM 220 when this strategy was covered: We do not have audiovisual data for Newman Projections from CHEM 220, as they were covered the week before we started recording, but Andy’s section of CHEM 220 was canceled and handouts were emailed instead.

During **Instance 11**, Mark accidentally perpetuated an error made by a study group member when they were asked to take a dash/wedge drawing and convert it to a Newman Projection. Mark correctly identified the fact that the member made an error, and even erased the error. However, when he went to draw in the correct Newman he accidentally re-drew the incorrect Newman. This was pointed out to him by the members of the study group.

Figure 5.10 Practice Problem as Well as Incorrect Newman Projection (left) and Correct Newman Projection (right) from Mark's Study Group



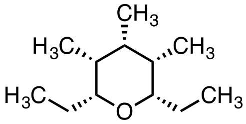
(4*R*,5*R*)-5-ethoxy-*N*,*N*-dipropyloctan-4-amine

Facilitator behavior during CHEM 220 when this strategy was covered: As with **Instance 10**, we do not have audiovisual data for these topics from CHEM 220; Newman Projections were covered the week before we started recording, but Mark's section of CHEM 220 was canceled and handouts were emailed instead.

Instance 12 was part of Daisy's exam review session the group is working on some check-box problems (**Figure 5.11**). The student standing up at the board asked the facilitator, Daisy, to help her get started on this problem. Daisy gave the member the advice to label the stereocenters first:

> **Daisy:** *Let's start at the basics, and label each stereocenter. Have you done that? Or no?*
>
> **Student A:** *No, but it's kind of hard because if you have something like this (pointing at molecule) and they're the same (pointing at the internal symmetry of the molecule in question).*
>
> **Daisy:** *Yeah, that's true. So there are no stereocenters, right?*

Figure 5.11 Example Compound Used in Daisy's Study Group for a Check-Box Problem



(2*R*,3*R*,4*r*,5*S*,6*S*)-2,6-diethyl-3,4,5-trimethyltetrahydro-2*H*-pyran

Student A: *Right.*

Daisy: *So there you go.*

Student A: *So it's not optically active?*

Daisy: *Exactly! So in this case, you don't have any stereocenters, because it's symmetrical around the whole way, right? There's not four different groups on a carbon, so it's not optically active...*

(Pause)

Student B: *Can't you have a stereocenter right here (pointing at molecule on board). Aren't these two, can't you make these two stereocenters? You have this hydrogen, four, one, two, three (counting out priorities).*

Daisy: *Oh yeah, technically, oh you're right.*

Student A: *So you have two.*

Student B: *Yeah, two (pointing at lower two stereocenters on molecule).*

Daisy: *And the top ones!*

Student B: *Yeah.*

Daisy: *You're right. She's right. So this one isn't a stereocenter (pointing at only carbon on ring that is not a stereocenter) because it's symmetrical. But these two and these two are. So you're actually right.*

Daisy failed to recognize that the internal molecular symmetry only prevents on carbon on the ring from being chiral. She did not realize her mistake on her own, and it was only after some argument from a student group member that Daisy saw her error.

Facilitator behavior during CHEM 220 when this strategy was covered: Daisy was present in CHEM 220 the week this topic was covered. She was having a conversation with her peer when the CHEM 220 liaison went over an example where dashes and wedges do NOT indicate chiral atoms. The second time the topic is mentioned, Daisy is present but off screen.

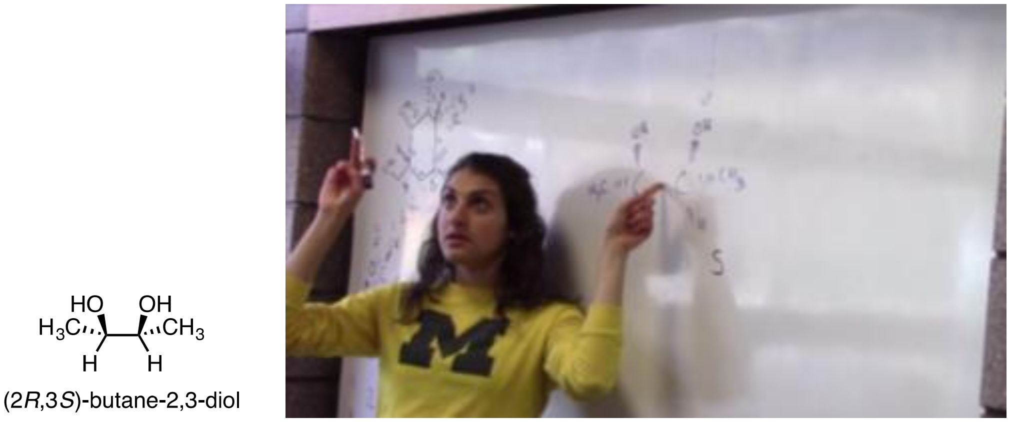
During **Instance 13**, Daisy and her students are looking at the molecule shown below in **Figure 5.12**. They are trying to determine the R/S assignments for the two stereocenters present in the molecule.

Daisy: *(pointing at the stereocenter on the right) Yes, that one is S I think. No, yes, that one is s. This one is S. Is that the one you were looking at?*

Student A: *Yes. It is S though.*

Student B: *Wait, how is that one S?*

Figure 5.12 Example Compound Used in Daisy's Study Group for R/S Assignment Practice.



(2*R*,3*S*)-butane-2,3-diol

Daisy: *Okay, so let's say you want the hydrogen in the back, right? So you're looking at it again from this way (draws line of perspective from top down). So you have oxygen, and you're going like this (motioning in a circle). Pretend like you're on the other side of the carbon, and you're going from one to this way (pauses to think).*

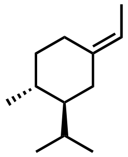
Student B: *Because the hydrogen is down, so if it's straight down and you stick your thumb towards it...*

Daisy: *No, you're right, it's R. It's R.*

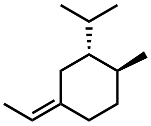
This seems to be a case of Daisy getting mixed up when she tried to change her perspective of the molecule in order to use the clockwise/counterclockwise method to assign stereocenters. Visualizing the molecule in 3D proves to be a challenge for her, and she is unable to properly apply the clockwise/counterclockwise strategy because of this. After another student questions her assignment and makes a comment about using the right hand rule, Daisy realizes her mistake.

<u>Facilitator behavior during CHEM 220 when this strategy was covered:</u> This strategy was not explicitly mentioned by the CHEM 220 liaison during discussion, though several other strategies for getting the lowest priority in the back were described. In Harrison's study group, **Instance 15** was observed during the discussion of the problem found in **Figure 5.13**. Harrison first tells the study group members that the two molecules in question are not enantiomers or diastereomers, because they are "different molecules":

Figure 5.13 Example Compounds Used in Harrison's Study Group for a Check-Box Problem.



(1*R*,2*S*,*E*)-4-ethylidene-2-isopropyl-1-methylcyclohexane



(1*S*,2*R*,*Z*)-4-ethylidene-2-isopropyl-1-methylcyclohexane

Harrison: *Oh wait, this just straight up isn't the same molecule.*

Student A: *What?!*

Student B: *Yeah, they are different molecules.*

Harrison: *They're just different molecules.*

Student A: *Wait, so they're not enantiomers?*

Harrison: *No, they're just different molecules. They're connected wrong.*

Student B: *The connectivity is wrong.*

Harrison: *Count between the double bond and the two other substituents.*

(Pause)

Harrison: *(Pointing at molecule and counting carbons) So there's one carbon between this and this (pointing at alkene and isopropyl group). There are two carbons between this feature and this feature (pointing at alkene and methyl group).*

Student A: *Yeah, but what if you just flipped it?*

Harrison: *Then there's two carbons here (pointing at alkene and isopropyl group). This has three carbons here (pointing at alkene and methyl group).*

Student A: *But what if flipped all the wedges to dashes and all the dashes to wedges. Then you would have the same count.*

Harrison: *No. It's connected in a different spot. Right? Or am I going insane?*

Student C: *I'm counting it, and it seems like the connectivity is the same.*

Student D: *I think the connectivity's the same.*

Student A: *You got us all riled up.*

Student D: *[inaudibly explaining is thinking and pointing at his worksheet].*

Harrison: *Yeah, but those are different features. One is a methyl group and one is an isopropyl group.*

[Lots of students talking at once]

Harrison: *Oh no, yeah, you're right. I'm just going insane. Oh my god. These are hard.*

Harrison was convinced that the two molecules in question were structural isomers because he thought they contained different connectivity. He was confused in his counting of carbons, as he was not consistent in his counting from the alkene to the other substituents. However, after multiple students explained their thinking to him, including one student showing Harrison his worksheet to help explain his thinking, Harrison realized that the two molecules do indeed have the same connectivity.

Facilitator behavior during CHEM 220 when this strategy was covered: The liaison gives a quick definitional coverage of this strategy, though it is not done in the context of a problem. Harrison is present and appears to be looking at the board/liaison during this time. An example of identifying two molecules as structural isomers is discussed in a “box checking” problem late in the discussion section. Harrison was present but off screen during the discussion of the problem.

Research Question 2 may be answered by investigating the observed errors made by facilitators during study groups, and subsequently determining what peer facilitators were doing during CHEM 220 when this topic was covered. In principle, this should inform the implementation of CHEM 220 and allow us to patch potential holes in instructional time, spend additional time on problematic topics, or encourage facilitator participation during particularly critical points of discussion. Of the twelve total instances of facilitator error observed, three involved topics that were not covered yet in CHEM 220, two instances where the facilitator’s CHEM 220 section had been canceled when this topic was taught, and one instance where the facilitator was present onscreen and attentive. Additionally, there are two instances where the facilitator is obviously distracted, two instances where the facilitator is off-camera, and one instance where (during each of the two times the topic was covered in CHEM 220) the facilitator is first obviously distracted, then later off-screen. Perhaps not surprisingly, when class is canceled, subject matter is not yet covered, and when a facilitator is obviously distracted, misunderstandings on content may translate to study groups.

The issue of subject matter coverage does give insight into the importance of pacing when implementing this companion course. CHEM 220 should always be significantly ahead of CHEM 210 pace in order to intercept these errors before they reach study groups. Interestingly, one attentive student from CHEM 220 does make an error in study group later on. Although there is only one instance of the several study group and CHEM 220 sections filmed, this still suggests that in situations where a facilitator does not speak up about content, does not participate in problem solving at the board, or perhaps even is unaware of their own content limitations, a classroom environment that promotes facilitator participation and engagement is optimal for surfacing errors in CHEM 220. Finally, there are a handful of instances where facilitators are off-screen during CHEM 220, which means no concrete conclusions as to their behavior during CHEM 220 may be made.

Research Question #3: If a facilitator is present when *another* facilitator makes an error in CHEM 220 and sees it resolved, how do they handle that topic if/when it arises later in their own study group?

In this third section, we wanted to trace the effect of *observing a fellow facilitator being corrected* on a facilitator's performance in their own study group. These final eighteen instances use facilitators for whom only CHEM 220 video is available (i.e. no study group video was collected) making a mistake in front of facilitators for whom we do have study group video. When tracing these errors to facilitators' study groups for whom we do have video, the use of these strategies generally fell into one of three different categories: (a) the strategy was correctly used in study group, (b) the strategy was used correctly in a *theoretical discussion*, or (c) the topic was not addressed in study group. For each individual incident of facilitator error from CHEM 220, there are one or more facilitators present; as such, for some instances there may be a single entry under column 4 (**Correctness maintained in study group?**), but for others there may be multiple entries. For convenience of organization, these results are collected together in **Table 5.5**.

Table 5.5 Summary of Instances When an Observing Facilitator is Present for an Error Made by a Fellow Facilitator in CHEM 220 and Saw that Error Corrected by Liaison GSI

Instance #	**Pseudonym of facilitator who saw another's error correction**	**Topic :: Stratxegy**	**Correctness maintained in study group?**
15	Mark	Chairs :: determining the relative preferences of chair substitutes and how that influences the relative Keq	Yes
16	Daisy	R/S Stereochemistry :: (1) Right/Sleft hand rule; (2) Assign clockwise/ counterclockwise; and (3) Tripod arm	Yes
17	Adam	R/S Stereochemistry :: Assign different molecule if new molecule is an enantiomer or diastereo of another // Assign different conformation if same molecule but sigma bond is rotate	Topic not addressed in study group
18	Oscar & Gwen	Electrophilic Addition :: Acid base rate is faster than EA	Yes
19	Mark & Lupita	R/S Stereochemistry :: Assign different molecule if new molecule is an enantiomer or diastereo of another // Assign different conformation if same molecule but sigma bond is rotate	Topic not addressed in study group
20	Mark & Lupita	R/S Stereochemistry :: Assign chiral Atom – req's 4 different subs'ts	Mark: Yes. Lupita: Topic not addressed in study group.

21	Harrison	R/S Stereochemistry :: Assign different molecule if new molecule is an enantiomer or diastereo of another // Assign different conformation if same molecule but sigma bond is rotate	Yes
22	Andy & Carrie	Rings :: Relative Keq	Topic not addressed in study group
23	Max	Stereoisomer Relationships :: Assign meso - mirror image is same compound Stereoisomer Relationships :: Assign meso - two opposite SCs with same substituents and internal molecule symmetry	Topics not addressed in study group
24	Max	Stereoisomer Relationships :: Assign enantiomer - change all R/S but not E/Z	Topic not addressed in study group
25	Max	Stereoisomer Relationships :: Assign diastereomer - change E/Z	Yes.
26	Max	Stereoisomer Relationships :: Assign different molecule if new molecule is enantiomer or diastereomer of other	Topic not addressed in study group
27	Max	Stereoisomer Relationships :: Assign optical activity from Enantiomer/ Diastereomer or conformational relationship to known compound	Topic not addressed in study group
28	Oscar & Gwen	Stereoisomer Relationships :: Assign different molecule if new molecule is enantiomer or diastereomer of other	Gwen: Yes. Oscar: Not addressed
29	Andy & Lupita Andy & Mark Andy & Mark	Stereoisomer Relationships :: Assign Optical Activity from Enat Diast or Conf relationship to known compound Stereoisomer Relationships :: Assign different molecule if new molecule is enantiomer or diastereomer of another Stereoisomer Relationships :: Assign different conformation if same molecule but sigma bond is rotated	Andy: Correct theoretical discussion. Lupita: Not addressed. Mark: Correct theoretical discussion. Andy: Not addressed. Mark: Correct theoretical discussion. Andy: Not addressed.
30	Daisy & Adam	Stereoisomer Relationships :: Assign meso – mirror image is the same compound Stereoisomer Relationships :: Assign Chiral – has RS stereocenters but isn't meso Stereoisomer Relationships :: Assign Optically Active – if compound is chiral	Daisy: Yes Adam: Not addressed. Daisy: Yes Adam: Not addressed. Daisy: Yes. Adam: Not addressed.
31	Harrison	Stereoisomer Relationships :: Assign different conformation if same molecule but sigma bond is rotated	Yes
32	Harrison	R/S :: Priority – double bonds count as two identical branches	Yes.

In **Instance 15**, Lupita was incorrect about determining the relative preferences of chair substitutes and how that influences the relative Keq. Mark was present during CHEM 220 when this happened, and we have video records of two sessions of Mark's study group. The concepts preference between chairs by substituent orientation and relative Keq comes up three times during the first study group session and not at all during the second study group.

In Mark's study group, they have a theoretical conversation concluding that bigger groups are more stable in equatorial positions. This concept undergirds the assigning of the Keq as greater than, less than, or equal to one. Later, they discuss the application of Keq to a pair chair conformations and correctly determine the relative Keq for the pair, and how the sign would change if they were written in a different arrangement (left/right). A study group member correctly determines the relative Keq for the pair of chair conformations that was drawn on the board. Mark affirms the member's answer and explanation. [[This is the EXACT same pair of chairs as was used in CHEM 220!]] Later in the same study group, Mark re-draws one of the stereocenters on the chair so that one chair has both bromines equatorial and both ethyl groups axial and they discuss how they would assign the relative Keq for these new compounds. A study group member correctly assigns the relative Keq, which Mark affirms as correct.

In **Instance 16**, Adam struggles to assign R/S to a chiral center in tetracycline during CHEM 220. He uses three strategies: (1) Right/Sleft hand rule; (2) Assign clockwise/counterclockwise; and (3) Tripod arm. We have video records of three sessions of Daisy's study group, and looked for each of these strategies being used in those sessions.

In one instance, the Daisy is at the board and trying to lead students through assigning R/S for a particular chiral center. She being by trying to apply the clockwise/counterclockwise strategy but because the lowest priority substituent is in the plane of the board, she struggles with the three-dimensional visualization of applying this strategy. A student quickly suggests using the right hand rule instead, which Daisy then incorrectly applies but is caught by the same student and corrected. There are also one instance of facilitator and member using this correctly, two instances of the facilitator using this strategy correctly, and one instance of the member using the strategy correctly across all three of Daisy's study group sessions. There were also two instances where they strategy was mentioned but was not applied to a particular problem or molecule.

In all fourteen usages of the assign clockwise/counterclockwise strategy in Daisy's three study group sessions, she correctly uses the strategy. The tripod arm strategy is not used in any of Daisy's study group sessions.

In **Instance 17**, Daisy is asking questions in CHEM 220 about checking the "different molecule" of something else is an enantiomer or diastereomer during a "box checking" problem, and that you should check "different conformation" if the molecules are only different by the rotation of a sigma bond. Adam was present in CHEM 220 during this conversation.

We have video from one of Adam's study group sessions. In this study group, neither "Assign different molecule if new molecule is an enantiomer or diastereomer of another" nor "Assign different conformation if same molecule but sigma bond is rotate" are used. Thus we cannot determine if Adam learned from the conversation that Daisy started during CHEM 220.

In **Instance 18**, a facilitator who didn't consent for us to come to her study group answers a problem on the board about a molecule with a double bond and basic amine and incorrectly did an electrophilic addition reaction instead of the acid/basic reaction that would take place. The liaison redirects the question to the facilitators with the tidbit that "acid/base reactions are the fastest kind of reactions" and asks if that changes how they would answer the question. The facilitators nod their head and the liaison proceeds to correct the problem on the board. Both Oscar and Gwen are present when this happens.

Oscar has one instance of this strategy in his study groups. He is using the same problem from CHEM 220 and handles it correctly when a study group member asks how the two reaction conditions could yield two different products.

Gwen has one instance of this strategy in her study group. She is using the same problem from CHEM 220 and handles it correctly when a student struggles to answer the question on the board.

In **Instance 19**, Mark and Lupita are present when the same error as in **Instance 17** occurs by another facilitator in CHEM 220. The liaison again gives the hint about relative reaction rates and corrects the problem at the board. As the hint is given, facilitators appear to quickly understand how this would impact the product of the reaction in question. We do not have any instances of this strategy being used in either Mark or Lupita’s study groups.

In **Instance 20**, an anonymous facilitator misidentifies an atom as chiral when it is not due to internal molecular symmetry. The liaison verbally corrects this error on the board when going over the practice problems. Both Mark and Lupita are present when this error is corrected. This strategy comes up in Mark’s study group five times and is handled correctly in all five occurrences. This strategy does not occur in any of the study group audiovisual data that we have for Lupita’s study group.

In **Instance 21**, an anonymous facilitator made same mistake as in **Instance 20** at the board. The liaison again corrects facilitator error when going over the practice problems. Harrison is present when this error is corrected. Two of the three times this strategy is used in Harrison’s study group, it is used correctly. The third time it was used in a theoretical conversation and was not applied to a specific problem.

In **Instance 22**, a facilitator drew both chair conformations but left blank the relative Keq between them. The liaison affirms the chair conformations and explains that the relative Keq is one and why. Both Andy and Carrie are present when this occurs. This strategy is used in neither Carrie nor Andy’s study groups.

In **Instance 23**, a facilitator asks for clarification about if a particular compound is meso. The liaison explains that the general ways he identifies a molecular as meso. Meso assignment is not discussed in the week of Max's study group that we were able to record.

In **Instance 24**, a facilitator asks for clarification from her peers about the stereochemical relationship between two compounds that are E/R and E/S. Her peers respond that the correct relationship is enantiomer. **Instance 24** is immediately followed by **Instance 25** where a different facilitator inquires about about the stereochemical relationship between two molecules which are E/R and Z/S. Facilitators immediately respond that the correct relationship is that of diastereomers. The liaison was not a part of either conversation. Max was present during this back and forth between his peers. The "Assign diasteromer - change EZ" strategy does come up three times in Max's study group and is handled correctly in all instances. There was no instances of "Assign enantiomer - change all RS but not EZ" in Max's study group session.

In **Instance 26**, a facilitator asks the liaison if stereoisomers are classified as different molecules. The liaison affirms that they are. Max is present during this conversation, but his strategy does not come up in his study group.

In **Instance 27**, a facilitator asks her peer about the how to determine experimental values of optical activity from known stereochemical relationships. Her peers answer her correctly that enantiomers have the same value but opposite sign for the optical activity and that you cannot determine the optical activity value for a molecule that is the diastereomer of a molecules whose optical activity you do know. The liaison was not a part of the conversation. Max was present during this conversation, but this strategy was not observed to occur in his study group.

In **Instance 28**, the liaison is going over a “box checking” problem where a facilitator correctly indicated that two molecules are diastereomers, but did not also indicate that they are different molecules. Oscar and Gwen were present (but off screen) when this happened. “Assign different molecule if new molecule is enant or diast of other”

This strategy is used once in Gwen’s study group when determining how E and Z alkenes are diastereomers that are also distinct products, different molecules. This strategy is not used in Oscar’s study group.

In **Instance 29**, Lupita and Mark have been working together. Mark asks how to determine the optical activity between two molecules which are enantiomers or diastereomers. The liaison tells them that you cannot determine the optical activity for the diastereomer of a compound, and enantiomers have optical activity of equal magnitude and opposite sign. Lupita asks the liaison if stereoisomers are different molecules and if different conformations are the same molecule. The liaison affirm both as true.

Andy is present but only paying attention during the discussion of different conformations being the same molecule with the sigma bond rotate. This strategy is used in Andy's study group, and while used correctly, it is discussed as a definitional, theoretical statement.

The strategy about assigning optical activity values from enantiomer/diastereomer relationship(s) is not used in the study groups that we have recorded for Lupita.

The strategy about assign different molecule if new molecule is enantiomer or diastereomer of other is used once in Mark's study group, but only as a theoretical conversation – once again, the theoretical discussion is correct. The strategy to assign different conformation if same molecule but sigma bond is rotated strategy comes up in the same conversation. It is also a correct, theoretical conversation.

In **Instance 30**, a facilitator incorrectly labeled a structure as meso when it was not. Because of this error, the facilitator also misses that the compound is chiral, has an enantiomer, is optically active, and has a diastereomer. Both Daisy and Adam are present.

The assign meso when the mirror image is the same compound strategy is used once in Daisy's study group. The strategy is used correctly by the facilitator. The strategy to assign "chiral" if the compound has RS stereocenter but is not meso is used four times in Daisy's study group. It is applied by the facilitator and is used correctly in all instances. The assign optically active if compound is chiral strategy is used once in Daisy's study group. The strategy is applied by Daisy and is used correctly.

The assign meso when the mirror image is the same compound strategy is not used in Adam's study group. The strategy to assign "chiral" if the compound has RS stereocenter but is not meso is not used in Adam's study group. The assign optically active if compound is chiral strategy is not used in Adam's study group.

In **Instance 31**, a facilitator incorrectly indicated that two compounds were different conformations. The liaison corrects this at the board during the problem review. Harrison is present (but off camera) during this correction

The assign different conformation if same molecule be sigma bond is rotated strategy is used three times in Harrison's study groups. In all three instances, it is used correctly by Harrison in response to a theoretical student question.

In **Instance 32**, a facilitator asks a clarification question about how to use "ghost atoms" as place holders when determining R/S priority around stereocenter. The liaison reviews again how to use "ghost atoms" as place holders. Harrison is present and appears to pay attention.

The strategy that when determining R/S around a stereocenter to count double bond as two identical branched atoms is used three times in Harrison's study group. Once it is used by a study group member, and the other two usages are by Harrison. In all instances the strategy is applied correctly.

Research Question 3 targeted facilitator error that is observed by other facilitator(s). The study group videos of these observing facilitators are then examined for the strategies of the errors they observed. These observer instances, where an observer instance comprises one facilitator observing another's error, and subsequently takes that back to their own individual study group, provide insight into the effects of observing a colleague's content knowledge corrected. The initial 17 instances of facilitator error from CHEM 220, this resulted in a total of 30 observer instances, where multiple different instances of observing facilitators's use of strategies is collected into a single observer instance. The results of these 30 observer instances split evenly, with 15 observer instances where the strategy was used (either in practice on a problem, or as part of a theoretical discussion) correctly by the observing facilitator. Additionally, there are 15 observer instances where these strategies are not addressed in the study group footage we have.

5-5 Discussion

When we initiated collection of audiovisual recording, we set out to capture peer facilitators' content correctness, both in the companion course (where the liaison is present) and their study groups (which are not usually attended by any graduate student instructors or faculty members). From the outset, we envisioned CHEM 220 to serve as a safe space for facilitators to ask questions, clarify misunderstandings, and refresh themselves on previously learned subject matter. Additionally, this course provides multiple strategies of subject matter explanation and discussion with both the liaison and other facilitators. While we understand the limits of this case study (small sample size, inability to generalize findings), it provides us with a deeper glimpse into how facilitators' enrollment in CHEM 220 impacts their study groups.

In trying to understand how any errors from CHEM 220 sessions may or may not persist into study groups, several distinct traces of facilitator error were made (represented above in **Figure 5.1**). We observed three specific instances (**Table 5.2**) of facilitators' answering questions incorrectly. When probing whether misunderstandings that arose in CHEM 220 (i.e; instances of peer facilitators incorrectly answering a question that are clarified by the CHEM 220 instructor) propagated to study group, in no instance did we observe this error carried into the facilitator's own study group. In two of the three instances, the strategy was observed in their own study groups, and in all cases the strategy was applied correctly. From the onset, one of the primary functions of CHEM 220 is to provide a place for peer facilitators to improve their subject matter knowledge. In the instances we are able to observe, facilitator subject matter error is intercepted and corrected in CHEM 220. This suggests CHEM 220 is working as intended to correct error and improve facilitator subject matter knowledge.

In examining the nature of errors made by facilitators in study groups, we aim to probe our instructional coherence, and improve our understanding of how peer facilitators approach subject matter. We observed two distinct types of error: (a) unresolved errors from study group, where neither facilitator nor study group peer members correct the error, and (b) errors made by facilitators that are corrected by study group peer members. In this data set, we found six instances of errors that arose and were not resolved by either the facilitator or a study group member (**Table 5.3**), and six instances of study group members correcting errors made by a study group facilitator (**Table 5.4**). These 12 instances are small in comparison to the 383 instances of correct usage of problem solving strategies employed during these recorded study groups, an encouraging sign of correct use of subject matter. Of these 12 instances, in 9 the incorrect topic was either (a) not covered in CHEM 220, or (b) the facilitator was not paying attention during CHEM 220. This suggests that CHEM 220 does help prevent misunderstandings from propagating into study groups, but a facilitator's presence alone in CHEM 220 is insufficient to prevent all error propagation. True engagement in discussions regarding subject matter, which Shulman suggests forms the foundation of pedagogical content knowledge, is not present surrounding the topics featured in any of these errors.[90]

In order to determine how engaged facilitators are with the course, we also wanted to turn our attention to instances where a facilitator whose study group we recorded observes *another* facilitator in CHEM 220 making an error, and subsequently having that error corrected by the liaison GSI. In fifteen of the thirty observer instances that we have observed, when another facilitator has a subject matter error clarified in CHEM 220, facilitators appear to recall and remember that clarification while leading their own study group. In the remaining fifteen observer instances the strategy is not used incorrectly, however it is not used correctly either (**Table 5.5**). By observing another facilitator's struggle with their own subject matter understanding in the group, peer facilitators in the room may also further their understanding. We cannot, however, know if the other facilitators present when their peer's error was addressed in CHEM 220 had that particular misunderstanding.

5-6 Conclusions and Future Directions

In the context of a large instructional team, CHEM 220 provides an effective way to address PLSG leader misunderstandings of course content. With an emphasis on and discussion of subject matter knowledge from a teaching perspective in CHEM 220, we were optimistic about the correctness level maintained by facilitators in peer-led study groups.

In the work presented above in **Chapter 4**, we demonstrated how CHEM 220 is effective at providing physical resources (such as handouts and problem sets) as well as human resources (including the liaison GSI and additional exposure to fellow peer facilitators) to PLSG leaders. The use of audiovisual data collection allows a much deeper look into the flow of subject matter knowledge from liaison to facilitator to study group member in our PLSG program, as well as insight into the correctness of subject matter usage within both CHEM 220 and study groups. While individual instances of incorrectness are observed in these peer-led study groups, the majority of instances (10/11 that could be observed) involve peer facilitators who did not attend the companion course, material that was not yet discussed, or those who were distracted and not paying attention during class. One of the most encouraging aspects observed in these recordings was that peer facilitators are able to learn not only from their mistakes in CHEM 220, but also from problems solved incorrectly or questions asked by their peers during class. Such errors do not propagate to study groups, and overwhelmingly these strategies are covered correctly by study group facilitators who actively observed the errors made by themselves or others being corrected by the liaison. However, some outstanding challenges to instructional coherence remain. Some errors result from topics or strategies not yet being covered in CHEM 220. In order to improve continuity in instruction, it may be useful to cover more material ahead of time in CHEM 220 (for example, staying an additional lecture ahead may reduce facilitator issues in study group). Alternately, continuing to reinforce facilitators' ability to ask the liaison GSI when confronted with topics from study group with which they are unfamiliar.

Seeking to add our own understanding and conclusions to the rich tapestry of PLSG and PLTL literature, we have been able to show that implementation of a subject matter-based course, viewed through the lens of instruction, seems to allow peer facilitators in peer-led study groups at the University of Michigan a high degree of subject matter fidelity (and therefore instructional coherence), as long as they actively engage with material covered in the companion course. Efforts to continue to understand the nature of facilitator development of content knowledge through the lens of an instructor are currently underway.

5-7 Note from the Author

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5-8 Appendices

Listed Appendices begin on the next page. Bolded strategies were emergent from study groups – standard text strategies were emergent from CHEM 220.

Table 5.6 – Strategy Codes for EZ Stereochemistry

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Assign – E if alkene shaped like a Z	Method of alkene stereochemistry assignment denoted with phrasing specifically or analogous to “alkene shaped like a Z”	2	0	1	0	0
Assign EZ – reqs 2 unique per carbon	To have E/Z assignments, the alkene must have two unique substituents on each carbon	2	2	1	1	0
Assign Z if on same side	If both high priority substituents are on the same side, alkene is Z	9	6	8	7	0
Assign priority to substituents	As with R/S Stereochemistry, Cahn-Ingold-Prelog rules are used to assign substituent priorities for assigning alkene stereochemistry	26	16	19	20	2
Consider branching	Cahn-Ingold-Prelog: involving branching to detetrmine points of divergence	6	3	5	6	0
EZ by entgegen vs zusammen	Derivations of the Germen Entgegen for apart and Zusammen for together	0	0	0	0	0
Epposite and zame meaning	If both highest priority substitutents are on the “Zame” side of the alkene = Z; if both are on “Epposite” sides of the alkene = E	17	11	8	12	0

Table 5.7 – Strategy Codes for Electrophilic Addition

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Acid base rate is faster than EA	Acid-base reactions will be faster than electrophilic addition	3	3	1	3	0
Carbocation stability – substitution	The more substituted carbocations will be more stable (3º > 2º >> 1º)	19	14	11	15	1
Resonance contributes to carbocation stability	Resonance delocalization of positive charge confers a greater stability to carbocations	15	14	6	11	1
Resonance overrides degree of substitution for C+	When confronted with an electrophilic addition reaction wherein the one potential carbocation has a greater substitution, but another has the ability for resonance, the resonance-stabilized carbocation is more stable	3	3	2	2	0
Strong versus weak acid	Understanding of the active acid in solution for alkene addition reactions	11	8	7	9	1

Table 5.8 – Strategy Codes for Newman Projection

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Assign or draw eclipsed	Correct assignment or representation of eclipsed conformations	10	9	5	4	0
Assign or draw staggered	Correct assignment or representation of staggered conformations	8	6	5	5	0
Assign or use anti vs syn arrangement	Correct assignment or representation of substituents as syn or anti	4	3	2	3	0
Assign or use gauche vs periplanar	Correct assignment or representation of substituents as gauche or periplanar	12	8	9	4	1
Conf pref – charge to charge interaction	Understanding whether a conformation that has a charge-charge interaction is greater or less stable due to this interaction	7	3	5	4	1
Conf pref – based on sterics	Understanding that steric interactions are generally minimized in Newman Projections	26	17	17	9	0
Conf pref – H-bonding	Understanding cases when hydrogen-bonding impacts stability of Newman Projections	16	10	10	6	1

Table 5.8, cont. – Strategy Codes for Newman Projections

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Conf pref for staggered	Understanding that staggered conformations are lower energy than eclipsed conformations	10	7	5	2	0
Convert to Newman from chair VIA PLANAR	Using Newman Projections to visualize chair conformations, by first drawing the planar cyclohexane ring, then drawing the Newman Projection	1	0	1	1	0
Convert to Newman from Dash and Wedge	Correct generation of a Newman Projection from a standard dash-and-wedge molecular representation	33	20	18	16	2
Convert to Newman Projections from Chairs	In contrast to VIA PLANAR, this is a direct conversion to a Newman Projection from a chair conformation	5	2	4	4	0
Draw different conformations	Correct rotation about central carbons to represent different Newman Projections of the same molecule	15	15	5	5	0
Energy levels of Newman conformations	Understanding the comparative (not specific) energy levels of various Newman Projections	12	13	7	7	0
Relative Conf – A values	Rationalizing relative conformational energy levels based on substituent A-Values	1	1	1	1	0

Table 5.9 – Strategy Codes for RS Stereochemistry

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
[OLD] Assign –swap atoms and assign opposite RS	An archaic code recently replaced and broken down into two codes: To get lowest priority in back – Swap back atom with lowest priority, Assign – Opposite R-S if atoms were swapped ***and*** any other assign codes used (**While archaic, included for completeness**)	0	0	0	0	0
Assign – clockwise counterclockwise priority	Method of assigning stereochemistry using a clockface description (clockwise is R, counterclockwise is S)	51	27	32	37	8
Assign – Opposite R-S if atoms were swapped	Used with To get lowest priority in back – Swap back atom with lowest priority	5	3	3	3	0
Assign – right sleft hand rule	The Right-Hand Rule method of assignment (point thumb in the direction of priority 4; if fingers curl 1,2,3 then assignment is R, if not assignment is S)	39	33	12	26	1
Assign – steering wheel	Assigning stereochemistry as if driving a car (turn left for S, turn right for R)	3	0	2	1	0
Assign chiral Atom – reqs 4 different subs'ts	In order to be considered chiral, an atom must be bound to four unique substituents	47	30	26	32	4
Priority – consider branching if they're the same	When determining priorities, if two substituents are the same (i.e.; carbon), then all substituents attached to each carbon must be assigned priority, and so on, until a point of divergence is identified	39	29	23	29	5
Priority of substitutents – double bonds count as two identical branches	Following the Cahn-Ingold-Prelog rules for assigning priority in the case of all double (and triple) bonds	17	11	11	14	2

Table 5.9, cont. – Strategy Codes for RS Stereochemistry

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Priority of Substitutents	Cahn-Ingold-Prelog substituent rules properly used	75	48	45	61	8
To get lowest priority in back – change perspective	Used in cases when a student is presenting a problem and describes mentally placing themselves elsewhere in space around the molecule ***without employing any other strategy, such as a Newman Projection, etc.***	5	4	3	4	1
To get lowest priority in back – use a Newman projection	Using a Newman Projection of a bond to perform a rotation and place the lowest priority substituent in back	7	4	3	4	0
To get lowest priority in back – Swap back atom with lowest priority	Used in conjunction with Assign – Opposite R-S if atoms were swapped; describes when a student swaps the back atom with the lowest priority, assigns stereochemistry (as if normal), and then “swaps” back their assignment	5	3	3	3	0
To get lowest priority in back – tripod arm	Using the thumb, index, and middle finger as a tripod of substituents, and the arm as a fourth substituent to visualize bond rotation	1	1	0	1	0
To get lowest priority in back – umbrella	Visualization of chiral atom as an umbrella to perform a bond rotation	2	0	2	1	0
To get lowest priority in back – propeller	Visualization of chiral atom as a propeller to perform a bond rotation	3	3	1	0	0
To get lowest priority in back – model kit	Visualization of chiral atom with a molecular model kit in order to rotate and depict chiral atom with lowest priority in back for stereochemical assignment	2	0	2	2	0

Table 5.10 – Strategy Codes for Rings

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Assign Cis or Trans by moving your point of reference	Using Newman Projections, new chair orientations, or other frame-of-reference switching tools to re-orient one's point of reference in order to visualize how to assign cis or trans	1	1	0	0	1
Assign Cis or Trans from wedges and dashes	If both substituents are dashes or wedges, cis; if one is dashed, one wedged; trans	5	4	2	4	0
Assign Cis or Trans if on same/different face of ring	When dealing with a planar ring, substituents that are both dashes or both wedges are cis, while mixed dash/wedge substituents are trans	4	4	3	2	0
Assigning equatorial or axial from bulkiness of subs't	Comparative use of substituent sterics to understand whether a substituent prefers equatorial or axial conformation (e.g., "*tert*-butyl is bigger than chloride, so if I need on to be equatorial, I'll choose the biggest: *tert*-butyl")	6	2	5	2	0
Axial or equatorial by Parallels	When drawing a chair, understanding the sets of parallels needed to correctly draw the chair's substituent orientations	4	1	3	2	1
Chair Flips – Axial and Equatorial orientations change	When performing a chair flip (i.e. interconverting between two chair conformations), understanding that all axial substituents become equatorial, and all equatorial substituents become axial	18	9	11	10	4
Chair Flips – Up stays up, down stays down	When performing a chair flip, knowing that all substituents that were pointed 'up' above the plane of the ring will still be pointed 'up'; same for 'down'	9	5	4	6	0

Table 5.10, cont. – Strategy Codes for Rings

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Chair flips by drawing both chairs	Drawing both chairs (left-leaning and right-leaning) and visualizing substituent orientation change in this manner)	13	5	8	8	4
Chair flips by rotating around the ring	Drawing the same chair (e.g. just the right-leaning chair) and rotating the substitutents around the ring to perform a chair-flip	8	8	2	4	1
Check chair flips by drawing planar version	Verifying an accurate chair flip was performed by drawing the dash-wesge planar version of the chair	2	1	1	0	0
[Gesture] Visualization of Substituents during flip with fingers	A gesture made in some study group(s) involving pointer and middle finger maintaining the same orientations, but by flicking the wrist, a student watches substituents maintain orientations while still 'flipping'	1	0	1	1	0
ID Conformers by difference in axial and equatorial for a subs't	Determining that two molecules are conformers based on the idea that a chair flip (change in conformation) will result in two conformers, and extrapolating that to changes in axial/equatorial substituents	1	1	0	0	0
Preference between chairs – H Bond	Understanding how hydrogen-bond ability may impact which is the preferred chair conformation	3	2	3	3	0
Preference between chairs – Newman	Using Newman Projections to visualize the preferred chair conformation	2	1	1	0	0

Table 5.10, cont. – Strategy Codes for Rings

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Pref. between chairs by substituent orientation	Understanding how relative substituent orientation affects which chair is the preferred conformation	13	8	8	11	1
Preference between chairs by A-values	Understanding how substituent A-Values help determine which chair is the preferred conformation	6	6	0	0	0
Relative Keq	Knowing which direction the equilibrium lies in equilibrium between two chairs	15	9	11	12	2
To draw – Number the Carbons	Numbers carbons when converting to or from a chair in order to preserve consistency and minimize mistakes (book-keeping)	13	8	8	7	0
To Draw planar from chair, up wedges down dashes	When drawing a planar (dash-and-wedge) cyclohexane from a chair and visualizing from the top looking down on the chair, remembering that all ‘up’ substitutents are wedges, all ‘down’ substitutents are dashes	7	5	5	6	1
To draw ring from planar, wedges up dashes down	When drawing a chair from a (dash-and-wedge) cyclohexane and visualizing from the top looking down on the chair, remembering that all ‘up’ substitutents were wedges, all ‘down’ substituents were dashes	17	9	9	11	2

Table 5.11 – Strategy Codes for Stereoisomer Relationships

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Assign achiral – EZ or cis trans only source of stereochemistry	Understanding that unsymmetrical alkenes without a chiral atom present are achiral molecules that still possess stereochemical labels	11	8	8	3	0
Assign Achiral Diastereomer – No RS Stereocenters	When determining whether a molecule has an achiral diastereomer: cases when there are no chiral atoms present in the molecule	14	11	7	6	0
Assign Chiral – Has RS stereocenters but isn't meso	Molecules that contain chiral atoms that are ***not*** meso compounds are themselves chiral molecules	30	26	14	16	2
Assign constitutional (structural) isomer if same formula different connectivity	Assigning a molecule as a constitutional (structural) isomer if the same atoms are present, but in a different arrangement	12	8	7	7	1
Assign diastereomer – change EZ	Whenever changing alkene stereochemistry, labeling the new stereoisomer as a diastereomer of the original	25	18	13	13	0
Assign diastereomer – change less than all RS stereocenters	In cases when any R/S stereocenters are changed (but not all of them); assigning the new stereoisomer as a diastereomer	49	40	23	29	1
Assign diastereomer – ring cis vs trans	Assigning ring cis/trans partners as diastereomers of one another	8	6	2	4	0
Assign different conformation if same molecule but sigma bond rotated	In cases when the relationship between two molecules is assigned, understanding a conformational shift as opposed to two different molecules	14	12	5	3	0
Assign different molecule if new molecule is enantiomer or diastereomer of another	Understanding that stereoisomers are different molecules, including enantiomers and diastereomers	7	8	3	2	0

Table 5.11, cont. – Strategy Codes for Stereoisomer Relationships

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Assign enantiomer – change all RS but not EZ	Understanding that enantiomers have all R/S stereocenters changed ***and*** none of the E/Z stereocenters changed	49	35	25	32	5
Assign enantiomer – mirror image is new compound	When taking the mirror image of a compound, understanding that the original and mirror image are enantiomers	14	8	10	5	0
Assign meso – mirror image is new compound	If, when taking the mirror image of a compound: the original and mirror image are the same: correctly assigning the molecule as meso	12	11	4	7	1
Assign meso – two opposite SCs with same substituents and internal molecular symmetry	When a compound contains two stereocenters with identical substituents (i.e. there is internal molecular symmetry) and the stereocenters have opposite assignment, assigning the compound as meso	47	36	19	35	3
Assign Optically Active – if compound is chiral	Properly demonstrating understanding that all chiral compounds are optically active	17	13	7	7	1
Assign Optical Activity from Enat Diast or Conf relationship to known compound	When presented a known optical activity value for a compound, understanding the ability to (a) assign optical activity to the enantiomer, (b) know that the optical activity cannot be assigned to diastereomers from an experimental value, and (c) assign optical activity if the same molecule	4	4	1	0	0
Assign same molecule if only perspective changes	In cases when two depictions of the same molecule have been used, and students are asked to compare them, assigning that they are the same molecule (i.e. stereoisomerism is preserved)	2	1	1	1	0
Chart Visualization Technique	A chart used to show the relationships between stereoisomers, from lecture	3	0	3	1	0

Table 5.11, cont. – Strategy Codes for Stereoisomer Relationships

Strategy	Description	Total Use	Facilitator Use	Member Use	Correct	Incorrect
Draw Diastereomer – change EZ or cis trans	When asked to draw a diastereomer of a compound, changing E/Z ***or*** cis/trans	4	3	1	2	0
Draw Diastereomer – flip two substituents of less than all chiral C	When asked to draw a diastereomer of a compound, changing any number of R/S stereocenters ***except*** for all R/S stereocenters	3	1	2	2	0
Draw Enantiomer – Mirror Image	In order to produce the enantiomer of a compound, draw the mirror image	4	4	1	2	0
Draw enantiomer – change all RS stereocenters but not EZ	In order to produce the enantiomer of a compound, change all R/S stereocenters but not E/Z alkene isomerism	7	6	1	8	2
Draw Meso – Correct Internal Molecular Symmetry	When asked to draw a meso compound, correctly showing the internal molecular symmetry present	1	1	1	0	0
Meso – convert all dashes and wedges to get the same molecule	When determining whether a compound is meso, if you convert all dashes to wedges (and wedges to dashes), thereby changing all R/S stereocenters, you end up with the same compound (due to the compound being meso)	9	6	5	8	1
No. of stereoisomers is 2^n stereocenters unless meso	The classic 2^n rule from lecture regarding the number of stereoisomers represented by a given connectivity	15	9	9	9	1
Optically active – has RS stereocenters but not meso	Assigning any chiral compounds as optically active from the presence of R/S stereocenters (no meso compounds)	39	25	20	23	2
Without stereocenters – cannot be meso have enantiomer and is not optically active	A collective code where a compound without stereocenters cannot possess any of the qualities listed in the code	2	2	1	1	0

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