Development of Strategies for the Synthesis of Heterocycles and Carbocycles; and Investigation of Chemistry Course Placement on Undergraduate Students

by

Elsa M. Hinds

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Chemistry)
in the University of Michigan
2019

Doctoral Committee:

Professor John P. Wolfe, Chair
Professor John Montgomery
Assistant Professor Ginger V. Shultz
Assistant Professor Matthew B. Soellner

Elsa M. Hinds

hindsels@umich.edu

ORCID iD: 0000-0002-0097-4150

Dedication

This dissertation is dedicated to Mike and Wesley

Table of Contents

List of Figures

List of Tables

List of Schemes

List of Abbreviations

Ac……....acetyl
acac……...acetylacetonate
Bn …… ……benzyl
Boc…… *tert*-butyloxycarbonyl
BrettPhos…….2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
Cbz …….carboxybenzyl
Cy……cyclohexyl
dba……dibenzylideneacetone
DCE……..1,2-dichloroethane
DCM……dichloromethane
DMF……dimethylformamide
dr……diastereomeric ratio
eq……equation
Et……...ethyl
EWG……electron withdrawing group
L or L_n……ligand
Me……..methyl
MeCN……acetonitrile
Mes…….mesitylene
n-Bu……...…*n*-butyl
Ph……..phenyl
PHOX……..phenyl oxazoline
PMP……..*para*-methoxyphenyl
Pn…….....pentyl
R……general functional group
RuPhos.....2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

SPhos.....2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl

t-Bu……....*tert*-butyl

THF……tetrahydrofuran

Tf……triflyl

Y……..O or NR

X……general halide

Abstract

Heterocycles and carbocycles are important motifs in synthetic chemistry as they are present in many natural products and pharmaceuticals and possess biological activities. Among other uses, cyclic and bicyclic urea motifs are found in HIV protease inhibitors, and can be used as chiral auxiliaries in organic synthesis. Indanes and indane derivatives are CNS stimulants and possess, among others, anti-inflammatory, antiviral, and anti-cancer properties.

Chapter 2 of this thesis describes a new method for the synthesis of cyclic and bicyclic ureas via a new ruthenium-catalyzed cross-metathesis/aza-Michael reaction strategy. This method provides access to functionalized bicyclic ureas with stereochemical patterns that are not easily accessible with other methods. The cyclic and bicyclic urea products were synthesized with this method in moderate to good yield and up to >20:1 dr.

In recent years, the Wolfe group has examined the synthesis of carbocycles using palladium-catalyzed alkene difunctionalization reactions. These methods have been developed to synthesize amino-substituted carbocycles, alkoxy-substituted carbocycles, and alkyl-substituted carbocycles using alkene-tethered triflates and exogenous nucleophiles. Chapter 3 of this thesis describes the pursuit of the use of internal alkenes and carbon-based nucleophiles to synthesize alkyl-substituted carbocycles. Carbocycles were synthesized in moderate to good yields and in excellent diastereoselectivity.

The remaining chapters of this thesis describe efforts toward chemical education research examining placement experiences of undergraduate students at the University of Michigan. Chapter 4 examines the factors that students consider when making their decision about which course to take first in the chemistry sequence. Students tend to consider their perceived preparedness and the university recommendation when making their decision.

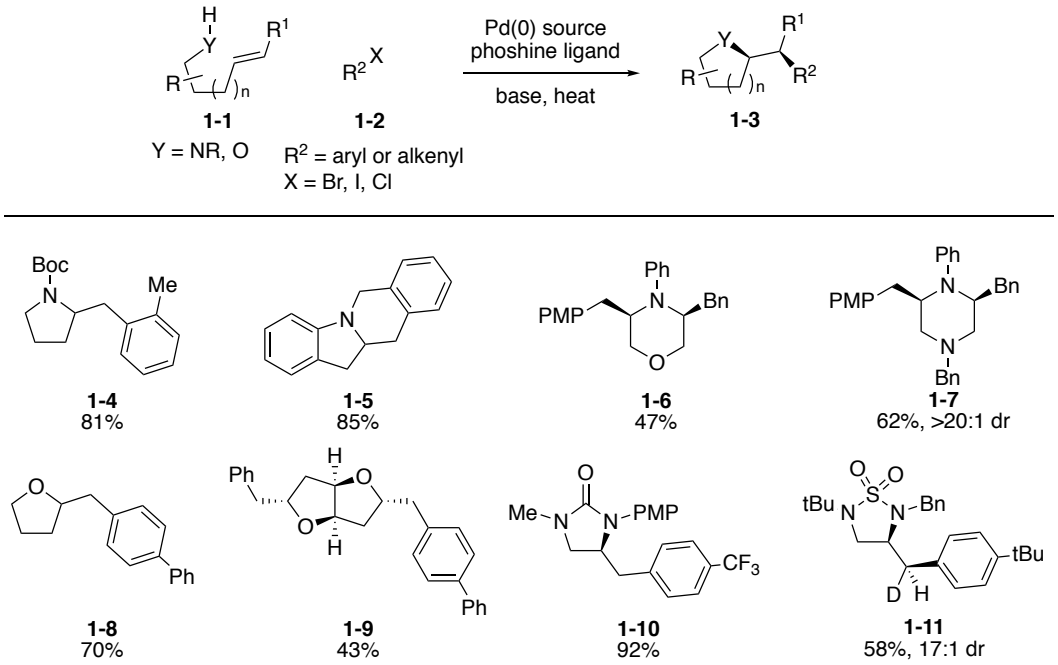
Chapter 5 of this thesis examines the effect of student decision-making on their experience in the subsequent courses. Students were asked about their perceived preparedness for their current chemistry course and also the perceived cost of their decision. Students tend to have felt more prepared for their current course if they were recommended for a course that was above what they enrolled into. Also students felt there were positive and negative consequences of their decision, and although for the most part students felt they made the right decision, but some reflected on effort costs including loss of valued alternatives, emotional cost, and task effort cost.

Chapter 1
Synthetic Interest In and Methods Toward Heterocycles and Carbocycles

1.1 Synthesis of heterocycles via palladium or ruthenium catalysis

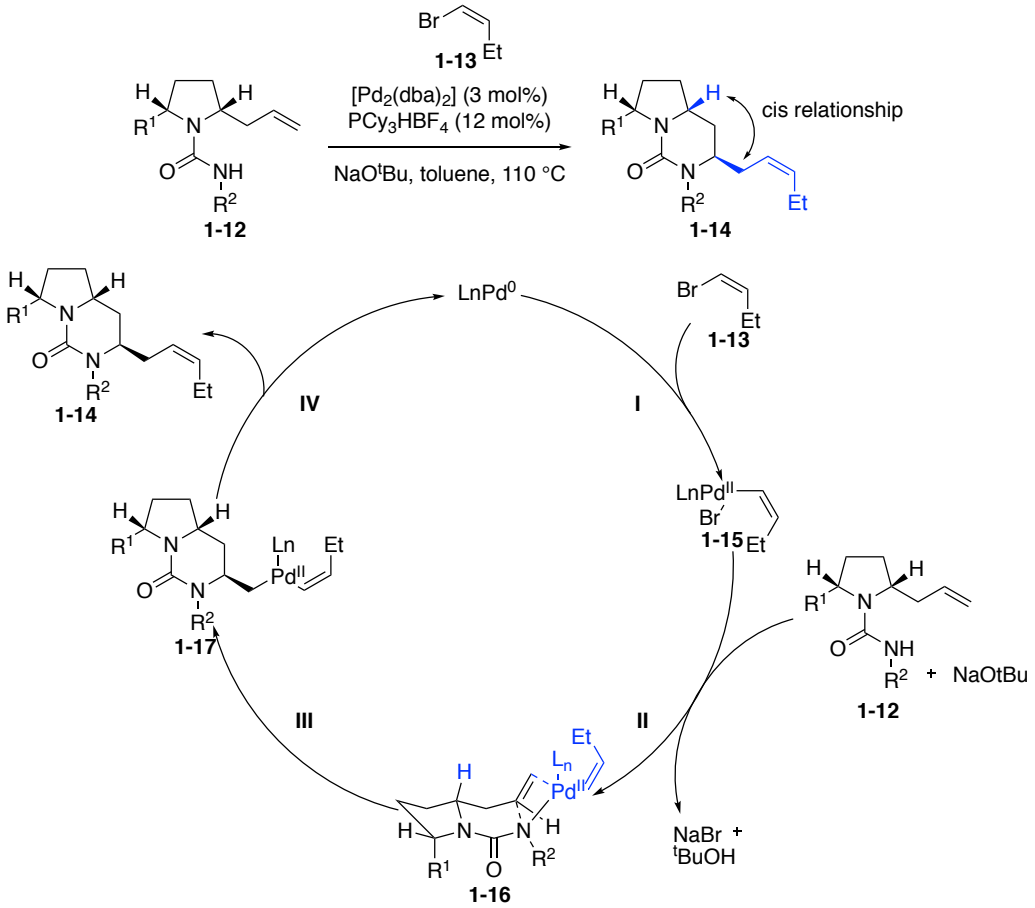
Heterocyclic motifs are desirable synthetic targets because they are found in many pharmaceuticals and natural products. The synthesis of these products is an ongoing challenge for chemists, and a worthwhile objective. Among the most interesting motifs are cyclic and bicyclic ureas, and strategies to access these are of interest to the synthetic community.

Chemistry in the Wolfe group historically has been focused on the synthesis of heterocycles via palladium-catalyzed alkene difunctionalization reactions.[1] These reactions take simple starting materials and build molecular complexity by forming a ring, a C-C, and a C-N or -O bond in one step. These products are formed in high yield and high stereoselectivity. Over the first 10 years our group developed methods to access substituted pyrrolidines,[2] piperazines,[3] morpholines,[4] cyclic sulfamides,[5] tetrahydrofurans,[6] lactams,[7] and cyclic ureas[8] in high yield and with high stereoselectivity (Scheme 1-1). During that time, the group was able to access products resulting from *syn* addition to the alkene, which were formed via *syn*-heteropalladation of the alkene. The stereochemistry is derived from a boat-like transition state in the six-membered ring synthesis.



Scheme 1-1. Examples of palladium-catalyzed carbofunctionalization reactions

The mechanism by which this transformation occurs for the formation of bicyclic ureas is depicted in Scheme 1-2. The *cis*-relationship depicted refers to the relationship of the hydrogen and the R group on the 6-membered ring being on the same side of the ring. The first step (**I**) includes oxidative addition of the palladium into the halogen-carbon bond to form intermediate **1-15**, deprotonation of **1-12** and alkene coordination (step **II**) give intermediate **1-16**, highlighting the *cis*-relationship of the proton and alkyl group off of the six-membered ring. *Syn*-aminopalladation (insertion of the alkene into the palladium-nitrogen bond) (step **III**) follows to form the six-membered ring to yield intermediate **1-17**. Reductive elimination (step **IV**) follows and gives the final product as well as the reduced palladium (0) catalyst to restart the cycle.



Scheme 1-2. Wolfe group bicyclic urea synthesis via palladium-catalyzed alkene difunctionalization

The strategy allowed for the access of natural products: (+) Merobatzelladine B[9] and 9-*epi*-batzelladine K (Figure 1-1).[10] These natural products feature guanidinium cores, and present anti-HIV, anti-malarial, and anti-viral properties and are important targets for total synthesis. (–)-Tylophorine,[11] (+)-Aphanorphine,[12] have also been synthesized using this chemistry.

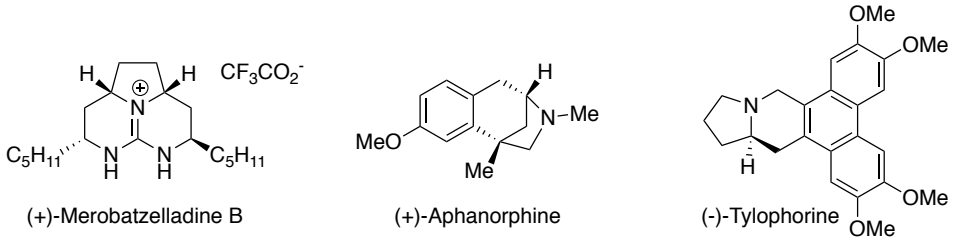
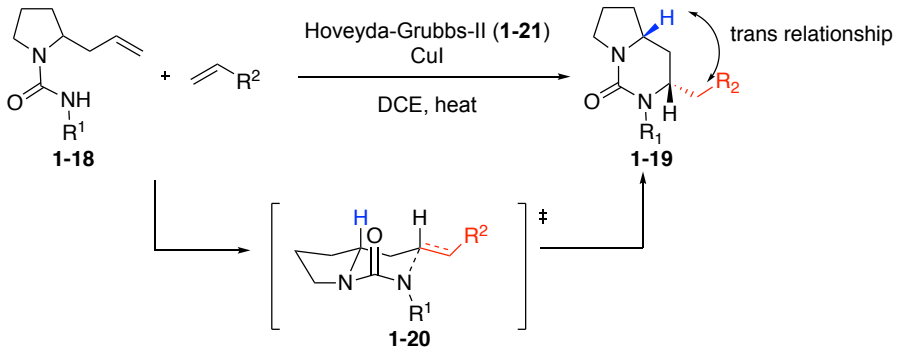


Figure 1-1. Natural products synthesized via Wolfe group palladium-catalyzed alkene difunctionalization reactions

With the benefit of high selectivity for *cis* products, gave one limitation of the approach: the strategy did not allow access to *trans* products. We thought that could be accomplished with the use of a ruthenium-catalyzed cross-metathesis/aza-Michael reaction with ureas. The hypothesis behind this was that the transition state of the aza-Michael reaction from **1-18** to **1-19** would be a chair-like transition state (**1-20**), instead of the boat-like transition state seen in *cis* products (Scheme 1-3). These products would also feature an electrophilic handle that will be functionalizable after, instead of the aryl or alkenyl motifs, which historically were standard in Wolfe group alkene difunctionalization



Scheme 1-3. Cross-metathesis/aza-Michael reaction strategy

The cross-metathesis/aza-Michael reaction strategy has been a useful, albeit limited tool to synthesize cyclic amines and amides. Developed by del Pozo and Fustero, the strategy has been used to synthesize substituted pyrrolidines, piperidines, and lactams (Figure 1-2).[13] The use of chiral organocatalysts and chiral Brønsted acids allowed the synthesis of pyrrolidines enantioselectively.[14]

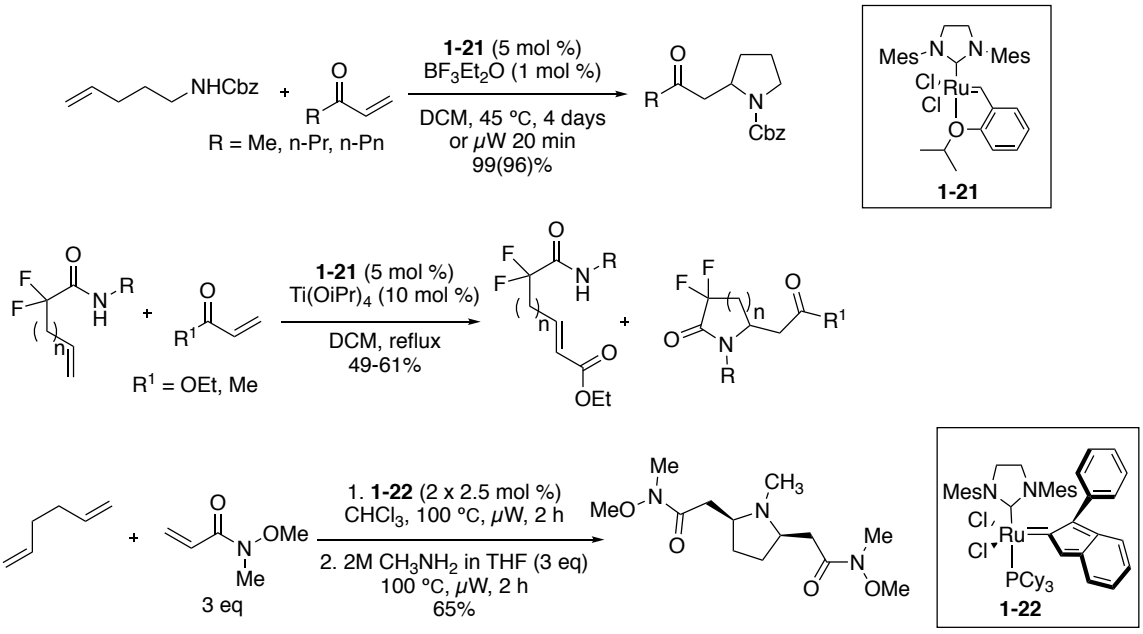
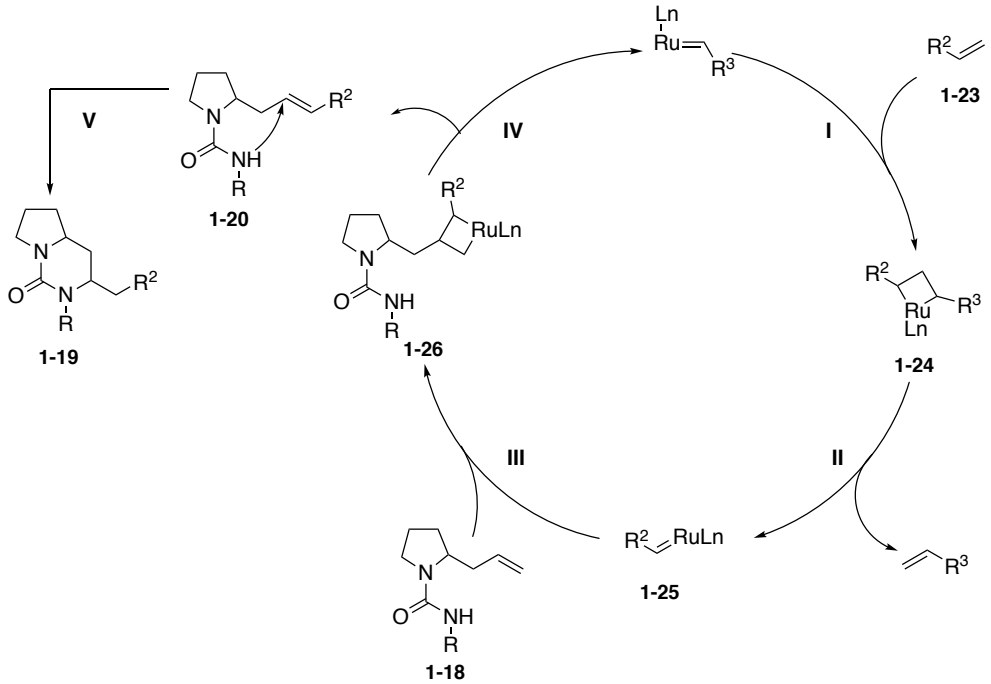


Figure 1-2. Examples of cross-metathesis/aza-Michael reaction

This approach was yet to be applied to ureas for the synthesis of cyclic ureas, and the mechanism by which this happens is depicted in Scheme 1-4. A series of [2+2] (steps **I** and **III**) and retro [2+2] (steps **II** and **IV**) cyclizations yield cross metathesis product **1-20**, and the aza-Michael reaction gives cyclic urea **1-19**.

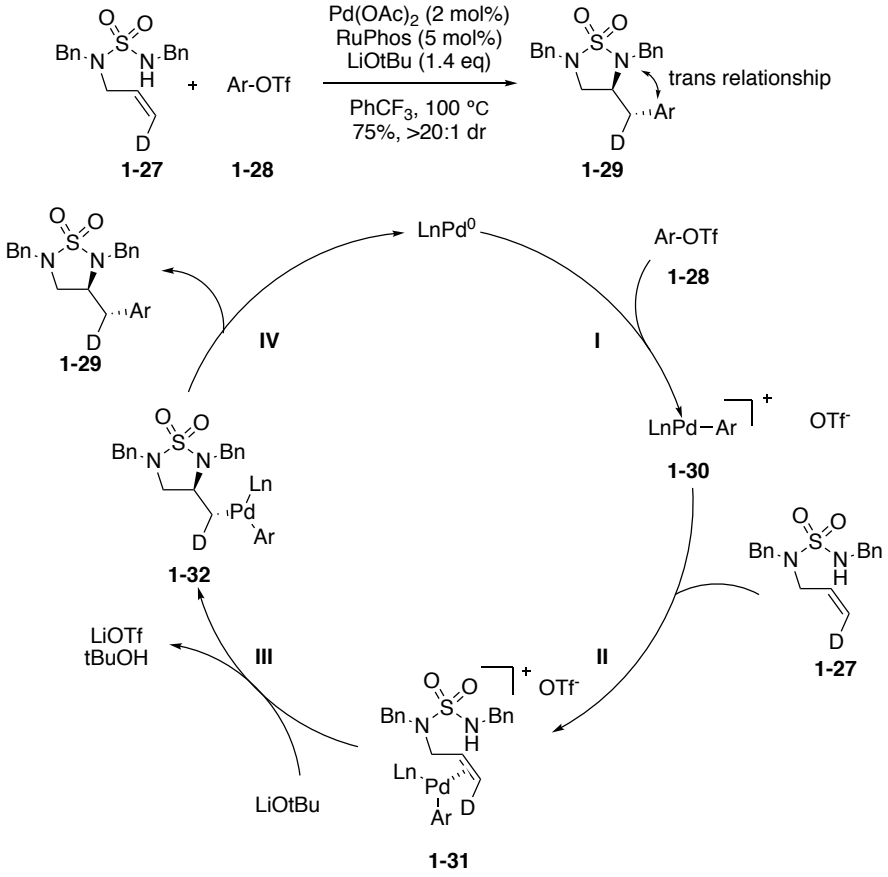


Scheme 1-4. Cross-metathesis/aza-Michael reaction mechanism

This approach was developed to access cyclic and bicyclic ureas via this ruthenium-catalyzed cyclization, to be able to access ureas with the *trans*-stereochemical relationship previously not accessible via other methods. These products would include an electrophilic handle on the formed ring that can be functionalized later. The development of this is described in chapter 2 of this thesis.

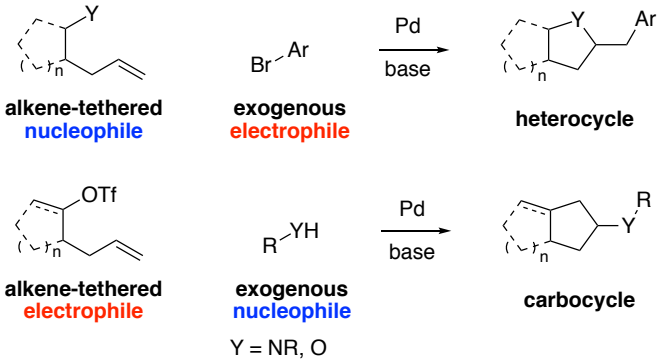
1.2 Synthesis of carbocycles via palladium-catalyzed alkene difunctionalization reaction

In 2014 we published a report of palladium-catalyzed alkene difunctionalization that proceeded through an *anti*-aminopalladation step to yield *trans* products (Scheme 1-5).[5a] We were able to access products with a *trans*-relationship in the substituents shown in **1-29**. We made changes to the *syn* reaction parameters, including: change of counterion from a halide to a triflate, use of a more electron-donating ligand CPhos or RuPhos instead of XPhos or DPEPhos, and changing the solvent to trifluorotoluene from toluene, yielded *trans* products that were not previously accessible. The development of *anti* conditions allowed the access to new products as well as a new mechanistic strategy: it was found that the palladium is not bound to the nucleophile (Scheme 1-5). The reaction mechanism proceeds via oxidative addition of the aryl triflate **1-28** (step **I**), followed by alkene complexation with the palladium (step **II**) to yield intermediate **1-31**. Base-facilitated *anti*-aminopalladation (step **III**) yields intermediate **1-32**, which can reductively eliminate to yield desired heterocycle **1-29**.



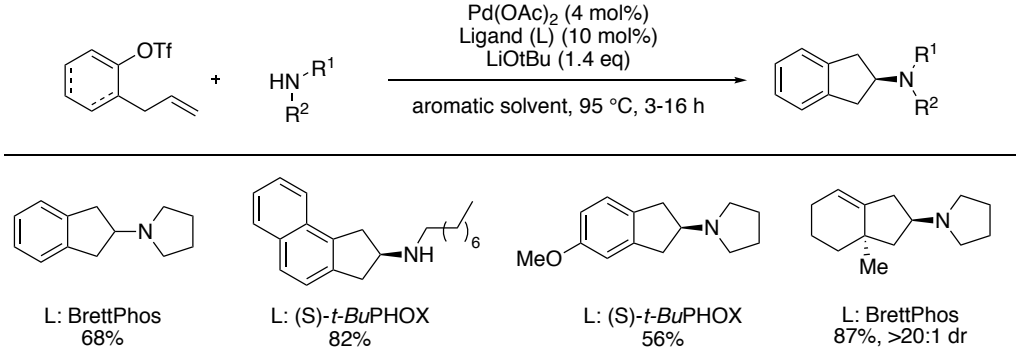
Scheme 1-5. *Anti*-alkene difunctionalization reaction mechanism

This discovery brought up new a new group research question: if the nucleophile does not need to be bound to the palladium, could this strategy use instead an exogenous nucleophile and an alkene-tethered electrophile? This question is depicted in Scheme 1-6, and brought about a new research direction of the Wolfe group. Could the group use alkenyl or aryl triflates that are tethered to an alkene and exogenous nucleophiles to synthesize carbocycles using this chemistry?



Scheme 1-6. Approach to opposite alkene difunctionalization reactions

Throughout Dr. White's thesis work he developed this new alkene difunctionalization reaction strategy. In 2015 the group published the first alkene carboamination reactions using exogenous amine nucleophiles, which yielded 2-aminoindane derivatives,[15] and then in 2017 published an enantioselective synthesis of chiral amino-substituted carbocycles and 2-aminoindanes.[16] These syntheses were accomplished in good yield and in high selectivity (Scheme 1-7). Similar to the old approach described above, these reactions still build significant molecular complexity (a ring, a C-C and C-N or -O bonds) in one step in good stereoselectivity.



L: BrettPhos
68%

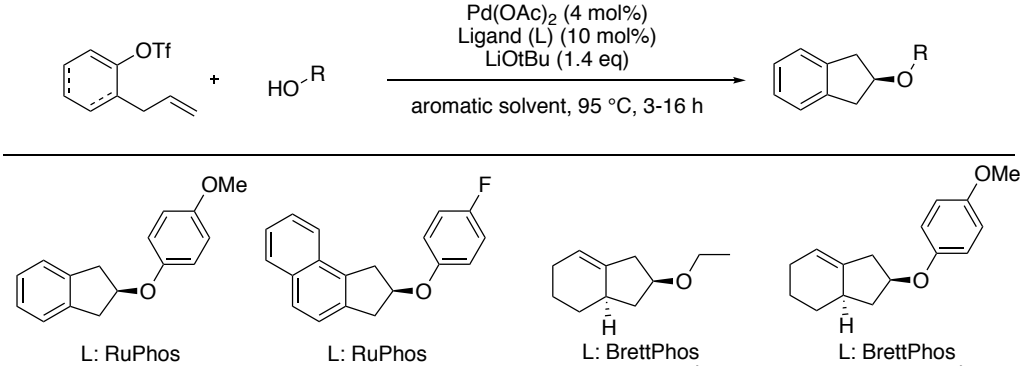
L: (S)-*t-Bu*PHOX
82%

L: (S)-*t-Bu*PHOX
56%

L: BrettPhos
87%, >20:1 dr

Scheme 1-7. Synthesis of amino-substituted carbocycles

After the use of amines as nucleophiles in these reactions, the use of alcohols was explored. In 2017 the group published the synthesis of alkoxy-substituted carbocycles using alcohols and phenols (Scheme 1-8) in high yield and high stereoselectivity.[17] These three strategies demonstrated the use of amine and alcohol nucleophiles for alkene difunctionalization reactions for the synthesis of carbocycles. For the most part, these strategies were used with terminal alkenes, and synthesized between 1 and 2 stereocenters in the reaction.



L: RuPhos
94%

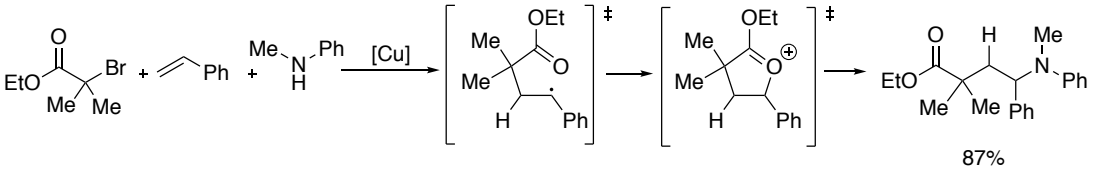
L: RuPhos
97%

L: BrettPhos
28%, >20:1 dr

L: BrettPhos
86%, >20:1 dr

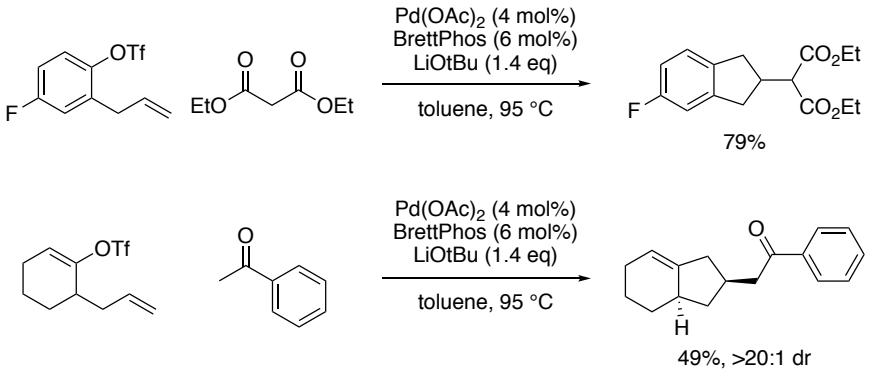
Scheme 1-8. Synthesis of alkoxy-substituted carbocycles

Alkene carboamination with an external amine nucleophile is an area of chemistry of interest outside of the Wolfe group. In 2018, Hull and coworkers reported a copper-catalyzed alkene carboamination strategy to synthesize substituted amines and lactams (Scheme 1-9).[18] Their approach featured a radical-initiated alkene difunctionalization on a styrene derivative, bromo isobutyrates, and an aromatic-substituted amine nucleophile to synthesize their products. The three-component reactions developed methods by which alkene carboamination does not require the tethering that is required for the Wolfe group method. The alkene could be a separate component, thus increasing the scope of carboamination reactions, but not synthesizing a ring.



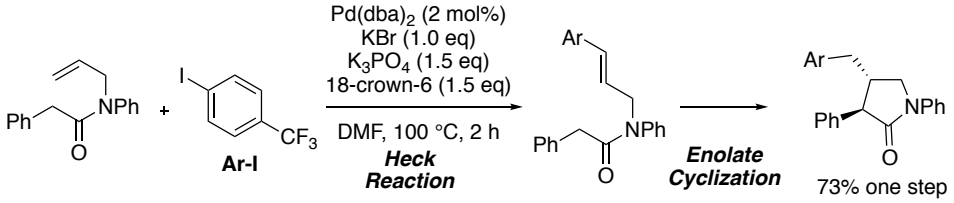
Scheme 1-9. Hull's copper-catalyzed carboamination

Following the use of amine and alcohol nucleophiles in the alkene difunctionalization reactions, the next step was to use carbon-centered, enolate-based nucleophiles. In his thesis, Dr. White began exploring the use of carbon acids (enolate-forming under basic conditions) on terminal alkenes (Scheme 1-10).[19] Malonates, or similarly acidic carbon molecules can be used as nucleophiles in the Aldol or Claisen reaction, and they can also be used as nucleophiles in other C-C bond-forming reactions.



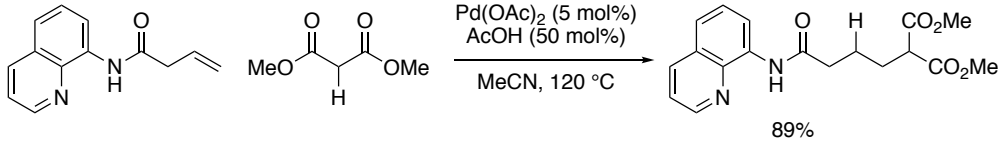
Scheme 1-10. Dr. White's palladium-catalyzed alkene carboalkylation of terminal alkenes

In 2017, Giri and coworkers reported the synthesis of substituted lactams via a palladium-catalyzed alkene difunctionalization that utilizes a tandem heck reaction/enolate cyclization cascade (Scheme 1-11).[20] They use a benzyl-substituted allyl amide, which features an enolizable proton that can react with the Heck reaction product to form the lactams in one step.



Scheme 1-11. Giri's palladium-catalyzaed alkene difunctionalization

Additionally, in 2016, Engle and coworkers reported a palladium-catalyzed hydrocarbofunctionalization of alkenes tethered to a donating group using malonates and other acidic carbon nucleophiles (Scheme 1-12).[21] The synthesis of these products was accomplished in good to high yield and high regiocontrol.



Scheme 1-12. Engle's palladium-catalyzed alkene hydrocarbofunctionalization

The work outlined in the examples above was completed with terminal alkenes, and as such produce between 1-2 stereocenters over the course of the reaction. With the use of internal alkenes, another stereocenter could be produced. This is a natural extension of the terminal alkene approach: whether or not it could be accomplished on internal alkenes. The main goal of chapter 3 of this thesis focuses on the development of carboalkylation of internal alkenes via palladium catalyzed alkene difunctionalization. The carbon acid nucleophiles could be used to synthesize alkylated indane derivatives, which are displayed in many interesting molecules such as neolignan, Pauciflorol F, and Caragasinin A (Figure 1-3).[22]

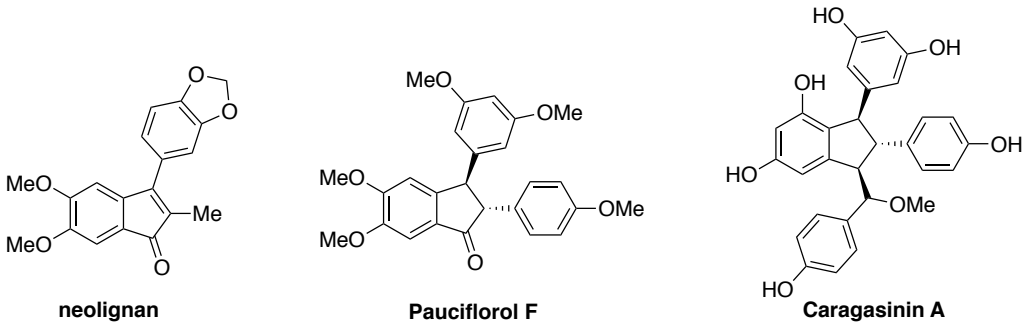


Figure 1-3. Natural products of alkylated indane derivatives

1.3 Conclusion

Research in the Wolfe group is focused on synthesizing interesting heterocycles and carbocycles. Most of this work has been accomplished using palladium catalyzed alkene difunctionalization reactions using either a nucleophile tethered to an alkene and an external electrophile or an electrophile tethered to an alkene, and an external nucleophile. The following chapters describe work that accessed heterocycles via ruthenium catalysis and carbocycles via palladium catalysis, consistent with the goals outlined here.

1.4 References

(1) For a recent review of palladium-catalyzed alkene difunctionalization reactions: Garlets, Z. G.; White, D. R.; & Wolfe, J. P. Recent Developments in Pd(0)-Catalyzed Alkene-Carboheterofunctionalization Reactions. *Asian J. Org. Chem*. **2017**, *6*, 636–653.

(2) Bertrand, M. B. & Wolfe, J. P. Stereoselective synthesis of N-protected pyrrolidines via Pd-catalyzed reactions of γ-(N-acylamino) alkenes and γ-(N-Boc-amino) alkenes with aryl bromides.*Tetrahedron*, **2005**, *61*, 6447–6459.

(3) Nakhla, J. S.; Schultz, D. M.; Wolfe, J. P. Palladium-Catalyzed Alkene Carboamination Reactions for the Synthesis of Substituted Piperazines. *Tetrahedron*, **2009**, *65*, 6549–6570.

(4) Leathen, M. L.;Rosen, B. R.; & Wolfe, J. P. A New Strategy for the Synthesis of Substituted Morpholines. *J. Org. Chem*. **2009,** *74*, 5107-5110.

(5) (a) Fornwald, R. M.; Fritz, J. A.; & Wolfe, J. P. Influence of Catalyst Structure and Reaction Conditions on anti- versus syn-Aminopalladation Pathways in Pd-Catalyzed Alkene Carboamination Reactions of N-Allylsulfamides. *Chem. Eur. J.* **2014**, *20*, 8782–8790. (b) Garlets, Z. J.; Parenti, K. R.; & Wolfe, J. P. Asymmetric Palladium-Catalyzed Alkene Carboamination Reactions for the Synthesis of Cyclic Sulfamides. *Chem. Eur. J.* **2016**, *22*, 5919-5922.

(6) (a) Hay, M. B.; Hardin, A. R.; & Wolfe, J. P. Palladium-Catalyzed Synthesis of Tetrahydrofurans from γ−Hydroxy Terminal Alkenes: Scope, Limitations, and Stereoselectivity*. J. Org. Chem*. **2005**, *70*, 3099-3107. (b) Ward, A. F. & Wolfe, J. P. Synthesis of Fused-Ring and Attached-Ring *bis*-Tetrahydrofurans via Pd-Catalyzed Carboetherification. *Org. Lett*. **2009**, *11*, 2209-2212.

(7) Fritz, J. A. & Wolfe, J. P. Stereoselective Synthesis of Imidazolidin-2-ones via Pd-Catalyzed Alkene Carboamination. Scope and Limitations. *Tetrahedron*, **2008**, *64*, 6838–6852.

(8) Boothe, J. R.; Shen, Y.; & Wolfe, J. P. Synthesis of Substituted γ- and δ-Lactams via Pd-Catalyzed Alkene Carboamination Reactions. *J. Org. Chem.* **2017***, 82*, 2777-2786.

(9) Babij, N. R. & Wolfe, J. P. Asymmetric Total Synthesis of (+)-Merobatzelladine B. *Angew. Chem. Int. Ed.* **2012**, *51*, 4128-4130.

(10) Babij, N. R. & Wolfe, J. P. Desymmetrization of meso-2,5-Diallylpyrrolidinyl Ureas through Asymmetric Palladium-Catalyzed Carboamination: Stereocontrolled Synthesis of Bicyclic Ureas. *Angew. Chem. Int. Ed.* **2013**,*52*, 9247–9250.

(11) Mai, D. N.; Wolfe, J. P. Asymmetric Palladium-Catalyzed Carboamination Reactions for the Synthesis of Enantiomerically Enriched 2-(Arylmethyl)- and 2-(Alkenylmethyl)pyrrolidines. *J. Am. Chem. Soc.* **2010**, *132*, 12157- 12159.

(12) For an asymmetric approach, see: (a) Mai, D. N.; Rosen, B. R.; Wolfe J. P. Asymmetric Palladium-Catalyzed Carboamination Reactions for the Synthesis of Enantiomerically Enriched 2-(Arylmethyl)- and 2-(Alkenylmethyl)pyrrolidines. *Org. Lett*. **2011**, *13*, 2932- 2935. For a racemic synthesis, see: (b) Peterson, L. J.; Wolfe, J. P. Palladium-Catalyzed Alkene Carboamination Reactions of Electron-Poor Nitrogen Nucleophiles. *Adv. Synth. Catal*. **2015**, *357*, 2339- 2344.

(13) (a) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; & del Pozo, C. Microwave-Assisted Tandem Cross Metathesis Intramolecular Aza-Michael Reaction: An Easy Entry to Cyclic β-Amino Carbonyl Derivatives. *J. Am. Chem. Soc*. **2007**, *129*, 6700−6701. (b) Fustero, S.; Báez, C.; Sánchez-Roselló, M.; Asensio, A.; Miro, J.; del Pozo, C. A New Tandem Cross Metathesis-Intramolecular Aza-Michael Reaction for the Synthesis of α,α-Difluorinated Lactams. *Synthesis* **2012**, *44*, 1863−1873. (c) Chou, S. P.; Huang, J.-L. Tandem Cross-Metathesis and Intramolecular aza-Michael Reaction to Synthesize Bicyclic Piperidines and Indolizine 167E. *Tetrahedron Lett*. **2012**, *53*, 5552−5554. (d) Boufroura, H.; Mauduit, M.; Dre ge, E.; Joseph, D. Step- Economical Access to Valuable Weinreb Amide 2,5-Disubstituted Pyrrolidines by a Sequential One-Pot Two-Directional Cross-Metathesis/Cyclizing Aza-Michael Process. *J. Org. Chem*. **2013**, *78*, 2346−2354. (e) Dre ge, E.; Oko, J.; Venot, P.-E.; Gigant, N.; Joseph, D. Microwave-Assisted Telescoped Cross-Metathesis-Ring Closing Aza-Michael Reaction Sequence: Step-Economical Access to Nicotine-Lobeline Hybrid Analogues. *RSC Adv*. **2015**, *5*, 96720−96724. (f) Salih, N.; Adams, H.; Jackson, R. F. W. Synthesis of ω-Oxo

Amino Acids and trans-5-Substituted Proline Derivatives Using Cross-Metathesis of Unsaturated Amino Acids. *J. Org. Chem*. **2016**, *81*, 8386−8393.

(14) (a) Liu, H.; Zheng, C.; Guo, J.; Zhang, M.; & Yu, S. Enantioselective Synthesis of 2-substituted Pyrrolidines via Domino Cross Metathesis/Intramolecular Aza-Michael Addition. *RSC Adv.*, **2013**, *3*, 1666-1668. (b) Cai, Q.; Zheng, C.; & You, S. Enantioselective Intramolecular Aza-Michael Additions of Indoles Catalyzed by Chiral Phosphoric Acids. *Angew. Chem. Int. Ed.* **2010**, *49*, 8666-8669. (c) Chen, L. & Hou, D. Asymmetric Aza-Michael Addition: Synthesis of (-)-Allosedridine and (-)-2-Epi-ethylnorlobelol. *Tetrahredron: Asymmetry*, **2008**, *19*, 715-720.

(15) White, D. R.; Hutt, J. T.; & Wolfe, J. P. Asymmetric Pd-Catalyzed Alkene Carboamination Reactions for the Synthesis of 2-Aminoindane Derivatives. *J. Am. Chem. Soc.* **2015**, *137*, 11246−11249.

(16) White, D. R. & Wolfe, J. P. Stereocontrolled Synthesis of Amino- Substituted Carbocycles by Pd-Catalyzed Alkene Carboamination Reactions *Chem. Eur. J.* **2017**,*23*, 5419 –5423.

(17) White, D. R.; Herman, M. I.; & Wolfe, J. P. Palladium-Catalyzed Alkene Carboalkoxylation Reactions of Phenols and Alcohols for the Synthesis of Carbocycles *Org. Lett.* **2017**, 19, 4311-4314.

(18) Gockel, S. N.; Buchanan, T. L.; Hull, K. L. Cu-Catalyzed Three-Component Carboamination of Alkenes. *J. Am. Chem. Soc*. **2018**, *140*, 58−61.

(19) White D. PhD Dissertation: Palladium Catalyzed Alkene Difunctionalization Reactions for the Synthesis of Polycyclic Nitrogen Heterocycles and Functionalized Carbocycles. University of Michigan, 2017.

(20) Dhungana, R. K.; Shrestha, B.; Thapa-Magar, R.; Basnet, P.; & Giri, R. Pd-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Unactivated Olefins by a Heck Reaction/Enolate Cyclization Cascade *Org. Lett.* **2017**, *19*, 2154−2157.

(21) (a) Yang, K. S.; Gurak, J. A.; Liu, Z.; & Engle, K. M. Catalytic, Regioselective Hydrocarbofunctionalization of Unactivated Alkenes with Diverse C−H Nucleophiles *J. Am. Chem. Soc*, **2016**, *138*, 14705-14712. (b) Liu, Z.; Zeng, T.; Yang, K. S.; & Engle, K.

M. β,γ-Vicinal Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Directed Nucleopalladation. *J. Am. Chem. Soc*. **2016**, *138*, 15122−15125.

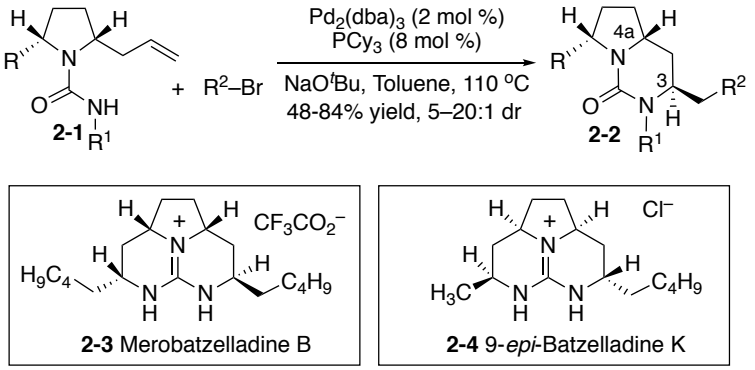
(22) (a) Zhu, M.; Liu, J.; Yu, J.; Chen, L.; Zhang, C.; Wang, L. $AlCl_3$-Promoted Formal [2+3]-Cycloaddition of 1,1-Cyclopropane Diesters with N-Benzylic Sulfonamides to Construct Highly Stereoselective Indane Derivatives. *Org. Lett.* **2014**, *16*, 1856-1859. (b) Ramesh, K. & Satuanarayana, G. An Approach to One-Pot Regioselective Synthesis of Indenones through Palladium-Catalyzed Annulation in Water. *Eur. J. Org. Chem.* **2018**, *30,* 4135-4146. (c) Alpers, S.; Vlietinck, A.; Pieters, L. Lignans and neolignans as lead compounds. *Phytochemistry Reviews*, **2003**, *2*, 201–217. (d) Pereira, G. A. N.; Souza, G. C.; Santos, L. S.; Baratas, L. E. S.; Meneses, C. C. F.; Krettli, A. U.; Daniel-Ribeiro, C. T; & Alves, C. N. Synthesis, antimalarial activity in vitro, and docking studies of novel neolignan derivatives. *Chem Biol Drug Des*. **2017**, *90*, 464–472. (e) Faiz, S.; Yousaf, M.; Zahoor, A. F.; Naqvi, S. A. R.; Irfan, A.; & Zaman, G. Synthetic strategies toward the synthesis of polyphenolic natural products: Pauciflorol F and isopaucifloral F: A review, *Synthetic Communications*, **2017**, *47*, 1121-1135. (f) Jeffrey, J. L. Sarpong, R. Concise Synthesis of Pauciflorol F Using a Larock Annulation. *Org. Lett.* **2009**, *11*, 5450-5453.

Chapter 2
Ruthenium-Catalyzed Tandem Cross-Metathesis Aza-Michael Reaction Strategy for the Synthesis of Cyclic and Bicyclic Ureas

2.1 Introduction

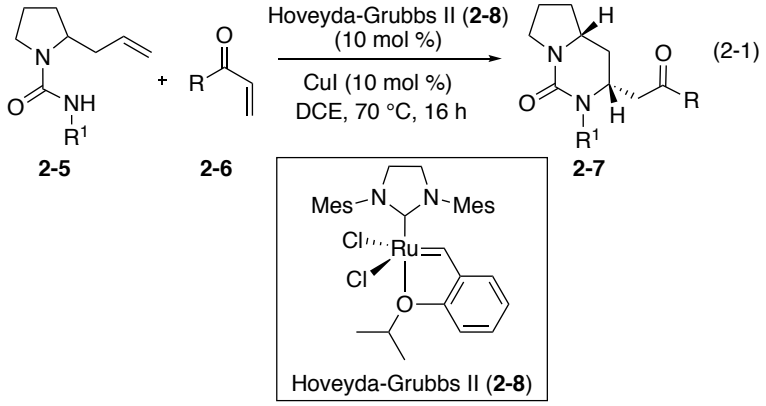
Cyclic and bicyclic ureas are common subunits that are found in many biologically active molecules and natural products, including HIV protease inhibitors,[1] 5-HT_3 receptor antagonists,[2] and NK_1 antagonists.[3] Chiral imidazolidin-2-ones have also been widely utilized as chiral auxiliaries in organic synthesis.[4] In addition, cyclic or bicyclic ureas have been utilized as intermediates in the synthesis of cyclic guanidines,[5] which are also found in a number of biologically active compounds and natural products,[6] including the Batzelladine family of alkaloids. Given the significance of cyclic ureas, many synthetic strategies have been developed to generate these molecules.[7] However, very few of these strategies effect both formation of the ring *and* a carbon-carbon bond in a single one-flask operation.[8]

Our group has previously described a method for the synthesis of cyclic and bicyclic ureas via Pd-catalyzed alkene carboamination reactions[9] between *N*-allylureas **2-1** and aryl/alkenyl halides that effects the formation of both the ring and a C–C bond, and generates products **2-2** with a high level of diastereoselectivity in most cases (Scheme 2-1).[10,11,12] The utility of this method has been demonstrated through its use in the synthesis of (+)-Merobatzelladine B (**2-3**)[11] and 9-*epi*-batzelladine K (**2-4**).[12] However, the stereochemical outcome of these reactions is substrate-controlled, and although bicyclic products with a *cis*-relationship between the angular C4a H-atom and the C3 alkyl group are formed in high dr, we have been unable to access the analogous *trans*-stereoisomers, which could serve as precursors to many other biologically active batzelladine alkaloids,[5] in acceptably high yield and selectivity using the Pd-catalyzed alkene carboamination strategy.[8]



Scheme 2-1 Prior synthesis of bicyclic ureas via Pd-catalyzed alkene carboamination reactions

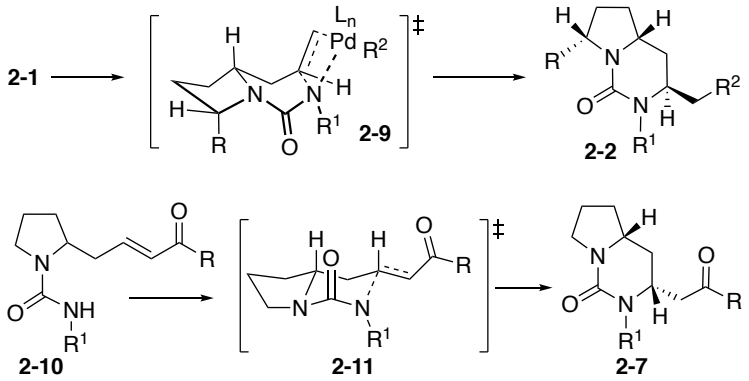
Herein we describe a new method for the synthesis of bicyclic and cyclic ureas, via a cross-metathesis/aza Michael reaction sequence between ureas **2-5** bearing pendant alkenes and a,b-unsaturated carbonyl compounds **2-6**, which provides access to bicyclic urea stereoisomers **2-7** that cannot be prepared via the Pd-catalyzed alkene carboamination strategy (eq 2-1). The reaction generates the ring, a C–N bond, and a C–C bond, and provides urea products bearing functional groups that can be further elaborated using standard chemistry.



2.2 Synthetic Approach and Reaction Optimization

The use of an alkene cross-metathesis/aza-Michael reaction cascade for the construction of heterocycles was first reported by Fustero; unsaturated cbz-protected amines were coupled with α,β-unsaturated ketones to afford N-cbz-pyrrolidine products in good to excellent yield and moderate stereocontrol.[14] Subsequent studies illustrated this approach could also provide access to cyclic amides,[15a] and that a range of a,b-unsaturated carbonyl derivatives were viable substrates.[15] We reasoned this strategy

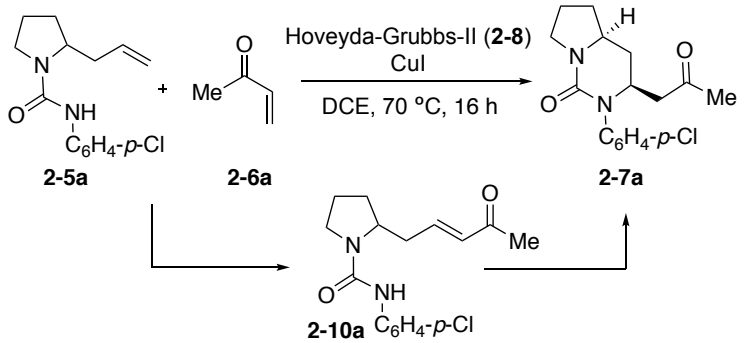
could also be applicable to the construction of cyclic ureas, and that this also may provide access to stereoisomers that were not accessible with the Pd-catalyzed carboamination method. The major stereoisomer in the Pd-chemistry derives from *syn*-aminopalladation of the alkene through a boat-like transition state (**2-1** –> **2-9** –> **2-2**), whereas it seemed the 1,4-addition of the intermediate metathesis product **2-10** would likely proceed through chair-like transition state **2-11** to give **2-7** (Scheme 2-2).



Scheme 2-2. Bicyclic urea stereochemisty

In order to explore the feasibility of this transformation, we examined the reaction of urea **2-5a** with methyl vinyl ketone (MVK) using the Hoveyda-Grubbs II complex **2-8** as the catalyst (Table 2-1), because this catalyst system had provided good results in the previously reported metathesis/Michael cascades. An initial run with 1.5 equiv **2-6a**, 10 mol% of catalyst **2-8**, and 10 mol % of CuI at 50 °C afforded the desired product **2-7a** in 47% yield and 5:1 dr (entry 1).[16] Increasing the temperature to 70 °C, and increasing the amount of **2-6a** to 5 equiv, afforded **2-7a** in 70% yield with excellent (>20:1) diastereoselectivity (entry 2). The CuI co-catalyst was essential, as efforts to carry out the transformation in the absence of CuI led to the formation of a 1:1 mixture of **2-7a**:**2-10a** in low yield, along with several unidentified side products (entry 5). This suggests that the CuI may be acting as a weak Lewis acid in the Michael addition step, although it was originally included to facilitate the alkene metathesis.[17] An attempt to decrease the catalyst loading to 5 mol % **2-8** and 5 mol % CuI also led to a mixture of **2-7a** and **2-10a** (entry 4). Interestingly, use of the Grubbs II catalyst in place of **2-8** produced only **2-10a** (entry 3).

Table 2-1. Optimization studies



entry[a]	equiv **2-6a**	mol % **2-8**	mol % CuI	**2-7a: 2-10a**	yield %[b] (dr)[c]
1	1.5	10	10	>20:1	47 (5:1)[d]
2	5	10	10	>20:1	70 (>20:1)
3	1.5	10[e]	10	<1:20	0[e]
4	5	5	5	10:1	47 (>20:1)
5	5	5	0	1:1	20[e]

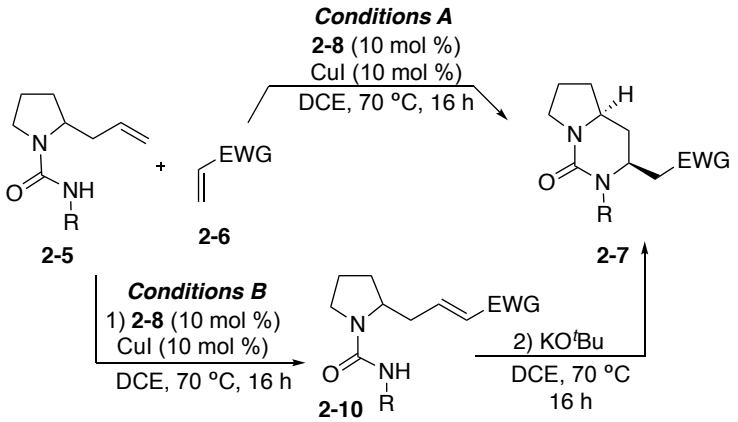
[a]Conditions: 1.0 equiv **2-5a**, 1.5 or 5 equiv **2-6a**, 0–10 mol % CuI, 5–10 mol % **2-8**, DCE, 70 °C, 16 h. [b]Isolated yield (average of two or more experiments). [c]Diastereomeric ratios were determined by ^{1}H NMR analysis. [d]The reaction was conducted at 50 °C. [e]The reaction was conducted with the Grubbs II catalyst in place of **2-8**. Only the metathesis product **2-10a** was observed. [e]Several unidentified side products were also formed. The yield in this case was determined by ^{1}H NMR analysis using phenanthrene as an internal standard.

2.3 Reaction Scope

We then explored the scope of this transformation by varying the substituent on the cyclizing nitrogen atom, along with the electron-deficient alkene coupling partner (Table 2-2). The one-pot cascade metathesis/Michael reactions proceeded smoothly for the coupling of **2-5a-c** with MVK to provide **2-7a**-**c** in good yield with high diastereoselectivity (entries 1-3). However, our initially optimized conditions (Table 2-2, conditions A) did not afford the bicyclic urea product in the reaction between *p*-nitrophenyl urea **2-5d** and MVK. Instead, only the cross-metathesis product **2-10** was generated. However, a two-step sequence (Table 2, conditions B) in which the cross-metathesis product was isolated, and then treated with KO^{t}Bu at 70 °C, led to the formation of **2-7d** in 40% yield, with modest (4:1) diastereoselectivity (entry 4). Use of other reagents to effect the Michael addition step, such as BF_3•OEt_2, Ti(O*i*Pr)$_4$, LiHMDS, or TBAF, failed to provide improved results in this system, although BF_3•OEt_2 was subsequently found to give higher yields in the formation of monocyclic products (see below). Efforts to employ conditions A in reactions of **2-5a-d** with methyl acrylate produced only the cross-metathesis product, but the two-step sequence afforded the

desired products **2-7e-h** in low to moderate yield. Diasteroselectivities in this latter set of reactions were highly dependent on the electronic properties of the N-substituent. Substrates **2-5a-b** bearing PMP or *p*-chlorophenyl groups on the cyclizing nitrogen atom provided **2-7a-b** with >20:1 dr, and the electron-rich PMB-protected substrate **2-5c** was converted to **2-7g** with 8:1 dr. But, in contrast, the *p*-nitrophenyl derivative **2-5d** provided **2-7h** with no selectivity (1:1 dr). In this latter case the lack of selectivity might be due to thermodynamically controlled, rather than kinetically controlled, selectivity in the Michael addition step. The origin of the low yield for the formation of **2-7h** is not entirely clear, as significant amounts of side products were not detected, but the reaction was reproducibly low-yielding. Although the cascade cross-metathesis/Michael reactions were effective with MVK and methyl acrylate, attempts to use other electron deficient alkenes failed to afford the desired product in useful yields. Reactions involving acrylonitrile returned only **2-5** along with the metathesis dimer of acrylonitrile, whereas use of crotonaldehyde or acrolein provided small amounts of products (ca 10–30%) along with complex mixtures of side products, and use of *N*-methoxy-*N*-methylacrylamide gave a complex mixture of products along with some unreacted starting material.

Table 2-2. Synthesis of bicyclic ureas



entry	R (**2-5**)	EWG (**2-6**)	conditions[a]	yield % (**2-7**)[b] (dr)[c]
1	C_6H_4-*p*-Cl (**2-5a**)	C(O)Me (**2-6a**)	A	70 (**2-7a**) (>20:1)
2	PMP (**2-5b**)	C(O)Me	A	65 (**2-7b**) (>20:1)
3	PMB (**2-5c**)	C(O)Me	A	60 (**2-7c**) (8:1)

4	C_6H_4-*p*-NO_2 (**2-5d**)	C(O)Me	B	40 (**2-7d**) (4:1)
5	C_6H_4-*p*-Cl (**2-5a**)	CO_2Me (**2-6b**)	B	38 (**2-7e**) (3:1)
6	PMP (**2-5b**)	CO_2Me	B	24 (**2-7f**) (5:1)
7	PMB (**2-5c**)	CO_2Me	B	43 (**2-7g**) (8:1)
8	C_6H_4-*p*-NO_2 (**2-5d**)	CO_2Me	B	29 (**2-7h**) (1:1)

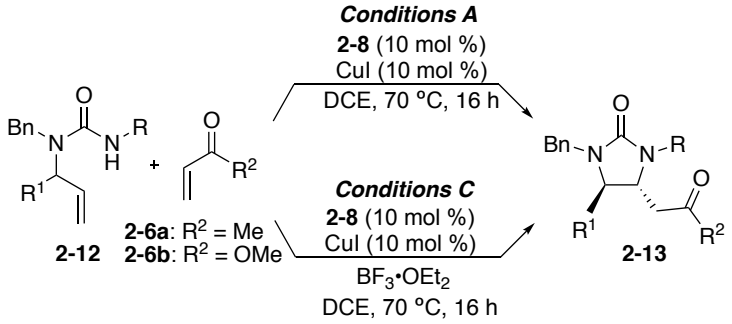
[a]Conditions **A**: 1.0 equiv **2-5**, 5 equiv **2-6**, 10 mol % CuI, 10 mol % **2-8**, DCE, 70 °C, 16 h. [b]Isolated yield (average of two or more experiments). Conditions **B**: (1) 1.0 equiv **2-5**, 5 equiv **2-6**, 10 mol % CuI, 10 mol % **2-8**, DCE, 70 °C, 16 h; (2) KO^{t}Bu (1.5 equiv), DCE, 70 °C, 16 h. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis.

With reaction conditions in hand for the synthesis of bicyclic urea products, we sought to expand the scope of this transformation to the synthesis of monocyclic urea products from acyclic *N*-allylurea substrates **2-12a-e** (Table 2-3). Reactions between unsubstituted substrates **2-12a-c** and MVK provided the desired cyclic urea products **2-13a-c** in moderate yield (entries 1–3). In contrast to the reactions between **2-5d** and MVK, the reaction of nitrophenyl urea substrate **2-12c** afforded the cyclic urea product **2-13c** in one step, without the need for a subsequent base-mediated transformation. Substrates **2-12d-e**, which contain a methyl group in the allylic position, were also converted to cyclic ureas in moderate yield, but diastereoselectivity was poor (2:1 dr; entries 4–5). Efforts to employ a substrate related to **2-12b** that contained a methyl group at the internal alkene carbon failed to afford the desired product. Instead, only unreacted starting material was observed, which is consistent with the fact that more highly substituted alkenes are much less reactive towards alkene metathesis.[18]

As observed with substrates **2-5a-d,** efforts to use the standard protocol (conditions A) for reactions of acyclic ureas **2-12a-b** with methyl acrylate failed to produce acceptable yields of the desired product, and mixtures of cyclic urea and acyclic metathesis products were obtained. Moreover, the two-step procedure used with **2-5a-d**, in which the metathesis product was treated with KO^{t}Bu to effect the Michael addition (conditions B), was also unsuccessful with **2-12a-c**. However, we were pleased to find that a modified version of the original Fustero procedure,[15a] in which the metathesis was conducted in one step with the presence of added BF_3•OEt_2 (conditions

C), provided cyclic ureas **2-13f-g** in moderate yield. In contrast, electron-poor urea **12c** was converted to **2-13h** in one step under the standard conditions A.

Table 2-3. Synthesis of monocyclic ureas



entry	R	R^1	R^2	conditions[a]	yield %[b] (dr)[c]
1	C_6H_4-*p*-Cl (**2-12a**)	H	Me	A	66 (**2-13a**)
2	PMP (**2-12b**)	H	Me	A	57 (**2-13b**)
3	C_6H_4-*p*-NO_2 (**2-12c**)	H	Me	A	61 (**2-13c**)
4	PMP (**2-12d**)	Me	Me	A	52 (**2-13d**) (2:1)
5	C_6H_4-*p*-NO_2 (**2-12e**)	Me	Me	A	47 (**2-13e**) (2:1)
6	C_6H_4-*p*-Cl (**2-12a**)	H	OMe	C	44 (**2-13f**)
7	PMP (**2-12b**)	H	OMe	C	41 (**2-13g**)
8	C_6H_4-*p*-NO_2 (**2-12c**)	H	OMe	A	71 (**2-13h**)

[a]Conditions **A**: 1.0 equiv **2-5**, 5 equiv **2-6**, 10 mol % CuI, 10 mol % **2-8**, DCE, 70 °C, 16 h. [b]Isolated yield (average of two or more experiments). Conditions **C**: (1) 1.0 equiv **2-5**, 5 equiv **2-6**, 1 equiv BF_3•OEt_2, 10 mol % CuI, 10 mol % **2-8** DCE, 70 °C, 16 h, [c]Diastereomeric ratios were determined by ^{1}H NMR analysis.

2.4 Conclusion

We have developed a new cross-metathesis/aza-Michael reaction strategy that effects the transformation of ureas derived from 2-allylpyrrolidine or *N*-allylbenzylamine into bicyclic and monocyclic ureas, respectively, with formation of the ring, a C–N bond, a C–C bond, and introduction of ketone or ester functionality adjacent to the ring. Products in reactions that employ MVK are formed in moderate yield, with moderate to excellent levels of diastereoselectivity, and similar transformations of methyl acrylate provide products in low to moderate yield, with modest diastereoselectivity. The observed high diastereoselectivities likely arise via a kinetically-controlled Michael addition reaction that proceeds through a chair-like transition state, whereas lower

selectivities may result from thermodynamic control in a reversible Michael addition step.

The work described in this chapter was published in *The Journal of Organic Chemistry*. The work in this chapter was adapted with permission from Hinds, E. M.; Wolfe, J. P. A Cross-Metathesis/Aza-Michael Reaction Strategy for the Synthesis of Cyclic and Bicyclic Ureas. *J. Org. Chem.*, **2018**, *83*, 10668–10676. Copyright (2018) American Chemical Society.

2.5 Experimental

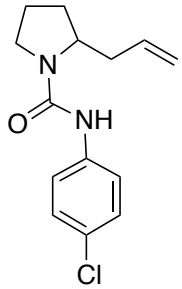
General Considerations: All reactions were carried out under a nitrogen atmosphere in flame- or oven-dried glassware. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. The Hoveyda-Grubbs II catalyst and *N*-Boc-pyrrolidine were purchased from Sigma-Aldrich Chemical Co., and used without further purification. 1,2-dichloroethane (DCE) was purchased from Acros chemicals and was purified via freeze-pump-thaw prior to use. *tert*-Butyl 2-allylpyrrolidine-1-carboxylate,[19] *N*-benzylprop-2-en-1-amine,[10b] and *N*-benzylbut-3-en-2-amine[10b] were prepared according to published procedures. Dichloromethane, toluene, and tetrahydrofuran were purified using a GlassContour solvent purification system. Boron trifluoride diethyl etherate, tetramethylethylenediamine, methyl vinyl ketone, and methyl acrylate were purified by distillation 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 2-2–2-3 are averages of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Tables 2-2–2-3.*

Experimental Procedures and Compound Characterization Data for Substrates

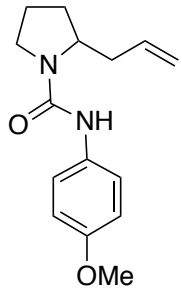
General Procedure 1: Synthesis of Pyrrolidinyl Ureas. A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with *tert*-butyl 2-allylpyrrolidine-1-carboxylate[19] (1 equiv), and dichloromethane (0.2 M). The mixture was cooled to 0 °C and trifluoroacetic acid (1.0 M) was added dropwise. The reaction mixture was warmed to rt and stirred overnight, then was basified to pH > 12 with ammonium hydroxide. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 2-allylpyrrolidine as a volatile oil that was used without purification.

The crude 2-allylpyrrolidine was dissolved in dichloromethane (0.2 M) and the appropriate isocyanate (1.1 equiv) was added. The resulting mixture was stirred at rt

overnight then was concentrated *in vacuo*. The crude urea product was purified via flash chromatography on silica gel using 40% ethyl acetate in hexanes as the eluent to afford the 2-allylpyrrolidinyl urea, which was stored as a 0.2 M solution in 1,2-dichloroethane.

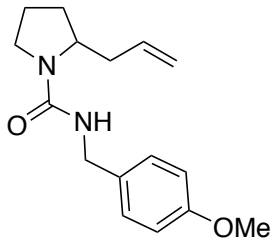


2-Allyl-*N*-(4-chlorophenyl) pyrrolidine-1-carboxamide (**2-5a**). The title compound was prepared from *tert*-butyl 2-allylpyrrolidine-1-carboxylate (1.20 g, 6 mmol) and para-chlorophenyl isocyanate (1.01 g, 6.66 mmol) according to General Procedure 1. This procedure afforded 1.04 g (65%) of the title compound as a yellow solid, mp 69–70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.38–7.31 (m, 2H), 7.26–7.18 (m, 2H), 6.28 (s, 1H), 5.86–5.73 (m, 1H), 5.16–5.05 (m, 2H), 4.08–4.00 (m, 1H), 3.48–3.37 (m, 2H), 2.54 (ddt, *J* = 3.0, 5.8, 13.5 Hz, 1H), 2.17 (dt, *J* = 8.4, 13.6 Hz, 1H), 2.07–1.95 (m, 1H), 1.98–1.88 (m, 2H), 1.81 (ddt, *J* = 2.5, 6.2, 8.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 153.7, 137.8, 135.0, 128.7, 127.6, 120.7, 117.6, 57.3, 46.4, 38.6, 29.6, 23.7. IR (film) 3305.2, 1641.1 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{18}ClN_2O$ 265.1108; Found 265.1106.

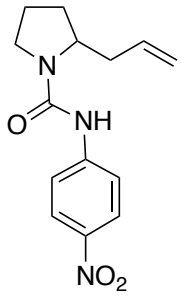


2-Allyl-*N*-(4-methoxyphenyl) pyrrolidine-1-carboxamide (**2-5b**). The title compound was prepared from *tert*-butyl 2-allylpyrrolidine-1-carboxylate (1.28 g, 6.06 mmol) and para-methoxyphenyl isocyanate (0.86 mL, 6.66 mmol) according to General Procedure 1 to afford 1.28 g (81%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.32–7.24 (m, 2H), 6.86–6.78 (m, 2H), 6.17 (s, 1H), 5.86–5.73 (m, 1H), 5.13–5.03 (m, 2H), 4.03 (tt, *J* = 3.5, 7.4 Hz, 1H), 3.76 (s, 3H), 3.44–3.37 (m, 2H), 2.60–2.51

(m, 1H), 2.22–2.11 (m, 1H), 2.04–1.91 (m, 2H), 1.79 (ddt, *J* = 2.6, 6.1, 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 155.6, 154.4, 135.2, 132.2, 121.8, 117.4, 114.0, 57.2, 55.5, 46.3, 38.7, 29.5, 23.8. IR (film) 3291.8, 1635.7 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{21}N_2O_2$ 261.1603; Found 261.1602.



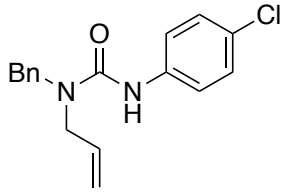
2-Allyl-*N*-(4-methoxybenzyl)pyrrolidine-1-carboxamide (**2-5c**). The title compound was prepared from *tert*-butyl 2-allylpyrrolidine-1-carboxylate (2.01 g, 9.5 mmol) and para-methoxybenzyl isocyanate (1.5 mL, 10.5 mmol) according to General Procedure 1. This procedure afforded 0.324 g (49%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.28–7.21 (m, 2H), 6.90–6.80 (m, 2H), 5.77 (dddd, *J* = 6.5, 7.7, 10.2, 16.9 Hz, 1H), 5.10–4.99 (m, 2H), 4.45 (s, 1H), 4.36 (q, *J* = 14.4 Hz, 2H), 3.97 (tt, *J* = 3.2, 6.9 Hz, 1H), 3.79 (s, 3H), 3.34–3.23 (m, 2H), 2.56–2.47 (m, 1H), 2.13 (dddd, *J* = 1.2, 8.0, 8.9, 13.7 Hz, 1H), 1.99–1.83 (m, 3H), 1.76 (ddt, *J* = 2.6, 6.1, 8.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 158.8, 156.6, 135.3, 131.9, 129.1, 117.2, 113.9, 56.9, 55.3, 46.1, 44.1, 38.8, 29.4, 23.6. IR (film) 3321.8, 1624.3, cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{23}N_2O_2$ 275.1760; Found 275.1758.



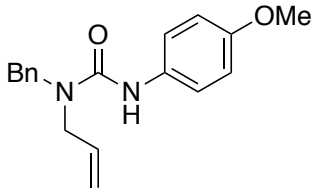
2-Allyl-*N*-(4-nitrophenyl) pyrrolidine-1-carboxamide (**2-5d**). The title compound was prepared from *tert*-butyl 2-allylpyrrolidine-1-carboxylate (0.50 g, 2.4 mmol) and para-nitrophenyl isocyanate (0.43 g, 2.6 mmol) according to General Procedure 1. This procedure afforded 0.324 g (49%) of the title compound as a yellow solid, mp 99–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.16 (d, *J* = 9.1 Hz, 2H), 7.61–7.54 (m, 2H), 6.59 (s, 1H), 5.82 (ddt, *J*= 7.2, 10.3, 17.2 Hz, 1H), 5.18–5.09 (m, 2H), 4.09 (dt, *J* = 5.0, 10.4 Hz,

1H), 3.53–3.46 (m, 2H), 2.56 (dt, *J*= 5.5, 12.2 Hz, 1H), 2.27–2.15 (m, 2H), 2.12–2.01 (m, 1H), 2.04–1.94 (m, 1H), 1.85 (ddq, *J* = 2.8, 3.6, 6.4, 9.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 152.7, 145.3, 142.3, 134.7, 125.1, 118.0, 57.6, 46.5, 38.5, 29.7, 23.7. IR (film) 3325, 1654.9 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ Calcd for $C_{14}H_{18}N_3O_3$ 276.1348; Found 276.1343.

General Procedure 2: Synthesis of *N*-Benzyl-*N*-Allylureas. A flame-dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with the appropriate benzylamine (1 equiv), dichloromethane (1.0 M), and the appropriate isocyanate (1.4 equiv). The resulting mixture was stirred at rt overnight then was concentrated *in vacuo* to yield the crude urea product, which was purified via flash chromatography on silica gel using 20% ethyl acetate in hexanes as the eluent.

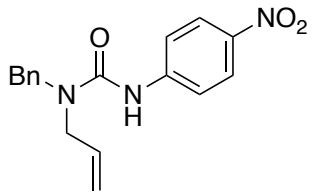


1-Allyl-1-benzyl-3-(4-chlorophenyl)urea (**2-12a**). The title compound was prepared from *N*-benzylprop-2-en-1-amine[10a] (0.997 g, 6.6 mmol) and 4-chlorophenyl isocyanate (1.44 g, 9.4 mmol) using General Procedure 2. This procedure afforded 1.68 g (85%) the title compound as a peach color solid, mp 84–85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.40–7.33 (m, 2H), 7.37–7.27 (m, 3H), 7.27–7.17 (m, 4H), 6.45 (s, 1H), 5.85 (ddt, *J* = 5.4, 10.5, 17.3 Hz, 1H), 5.35–5.26 (m, 2H), 4.58 (s, 2H), 3.97 (dt, *J* = 1.7, 5.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 155.5, 137.7, 137.4, 133.7, 128.9, 128.8, 127.9, 127.8, 127.5, 120.9, 117.6, 50.6, 50.0. IR (film) 3325.6, 1636.6, cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{18}ClN_2O$ 301.1108; Found 301.1114.

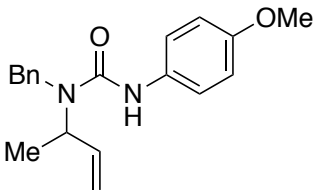


1-Allyl-1-benzyl-3-(4-methoxyphenyl)urea (**2-12b**). The title compound was prepared from *N*-benzylprop-2-en-1-amine[10b] (0.996 g, 6.6 mmol) and 4-methoxyphenyl isocyanate (1.1 mL, 9.3 mmol) using General Procedure 2. This procedure afforded

1.53 g (79%) of the title compound as a white-tan solid, mp 88-90 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.40–7.26 (m, 5H), 7.23–7.17 (m, 2H), 6.84–6.78 (m, 2H), 6.37 (s, 1H), 5.85 (ddt, *J* = 5.4, 10.5, 17.2 Hz, 1H), 5.33–5.23 (m, 2H), 4.57 (s, 2H), 3.96 (dt, *J* = 1.7, 5.5 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 156.1, 155.7, 137.7, 133.8, 132.1, 128.8, 127.6, 127.5, 122.0, 117.4, 114.0, 55.5, 50.5, 49.9. IR (film) 3326.0, 1634.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{21}N_2O_2$ 297.1603; Found 297.1604.

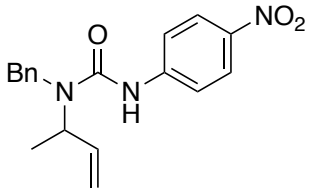


1-Allyl-1-benzyl-3-(4-nitrophenyl)urea (**2-12c**). The title compound was prepared from *N*-benzylprop-2-en-1-amine (1.00 g, 6.6 mmol) and 4-nitrophenyl isocyanate (1.54 g, 9.4 mmol) using General Procedure 2. This procedure afforded 1.51 g (74%) of the title compound as a pale yellow solid, mp 106–108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.14–8.09 (m, 2H), 7.48–7.42 (m, 2H), 7.41–7.34 (m, 3H), 7.32 (dt, *J* = 1.7, 6.1 Hz, 2H), 6.88 (s, 1H), 5.87 (ddt, *J* = 5.4, 10.6, 17.2 Hz, 1H), 5.38–5.30 (m, 2H), 4.60 (s, 2H), 4.00 (dt, *J* = 1.7, 5.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 154.7, 145.3, 142.4, 136.9, 133.4, 129.0, 128.0, 127.5, 125.0, 118.4, 118.0, 50.8, 50.2. IR (film) 3341.3, 1657.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}N_3O_3$ 312.1348; Found 312.1351.



1-Benzyl-1-(but-3-en-2-yl)-3-(4-methoxyphenyl)urea (**2-12d**). The title compound was prepared from *N*-benzylbut-3-en-2-amine (0.302 g, 1.86 mmol) and 4-methoxyphenyl isocyanate (0.34 mL, 2.61 mmol) using General Procedure 2. This procedure afforded 0.512 g (88%) the title compound as an orange-pink solid, mp 87–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.39–7.37 (m, 5H), 7.10–7.03 (m, 2H), 6.81–6.73 (m, 2H), 6.23 (s, 1H), 5.99 (ddd, *J* = 4.4, 10.6, 17.5 Hz, 1H), 5.31–5.20 (m, 2H), 5.00 (dtt, *J* = 2.4, 5.3, 7.3 Hz, 1H), 4.53 (d, *J* = 17.1 Hz, 1H), 4.37 (d, *J* = 17.1 Hz, 1H), 3.74 (s, 3H), 1.33 (d, *J* = 6.9

Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 156.1, 155.7, 139.2, 138.0, 132.1, 129.0, 127.7, 126.9, 121.9, 116.2, 114.0, 55.5, 53.2, 47.4, 16.6. IR (film) 3322.7, 1633.5 cm^{-1} HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ Calcd for $C_{19}H_{23}N_2O_2$ 311.1760; Found 311.1764.



1-Benzyl-1-(but-3-en-2-yl)-3-(4-nitrophenyl)urea (**2-12e**). The title compound was prepared from *N*-benzylbut-3-en-2-amine (0.135 g, 0.84 mmol) and 4-nitrophenyl isocyanate (0.193 g, 1.2 mmol) using General Procedure 2. This procedure afforded 0.088 g (32%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.12–8.05 (d, *J* = 9 Hz, 2H), 7.46–7.39 (m, 2H), 7.39–7.32 (m, 3H), 7.34–7.27 (m, 2H), 6.75 (s, 1H), 6.00 (ddd, *J* = 4.4, 10.4, 17.6 Hz, 1H), 5.35–5.28 (m, 2H), 4.97 (s, 1H), 4.58 (d, *J* = 16.9 Hz, 1H), 4.41 (d, *J* = 16.9 Hz, 1H), 1.37 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 154.8, 145.2, 142.4, 138.7, 137.2, 129.3, 128.2, 126.8, 125.0, 118.2, 117.0, 52.8, 47.8, 16.6. IR (film) 3390.6, 1653.2 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ Calcd for $C_{18}H_{20}N_3O_3$ 326.1505; Found 326.1501.

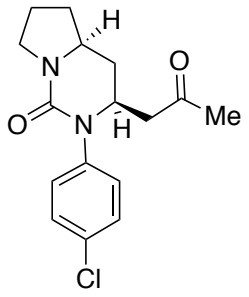
Experimental Procedures and Compound Characterization Data for Products of the Metathesis/Michael Reaction Sequence.

General Procedure 3 (Conditions A). A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the Hoveyda-Grubbs II catalyst (0.02 mmol, 10 mol %), and copper iodide (0.02 mmol, 10 mol %). The flask was purged with nitrogen, charged with the appropriate urea substrate (0.2 mmol) in 1,2-dichloroethane (0.2 M), and the resulting mixture was stirred for 5 minutes at rt. Methyl vinyl ketone or methyl acrylate (1.0 mmol) was added and the reaction mixture was heated to 70 °C with stirring overnight. The reaction mixture was then cooled to rt and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford the desired product.

General Procedure 4 (Conditions B). The reaction was carried out according to General Procedure 3. The cross-metathesis product (**2-10**) was purified by flash chromatography on silica gel, and then transferred as a solution in 1,2-dichloroethane (1

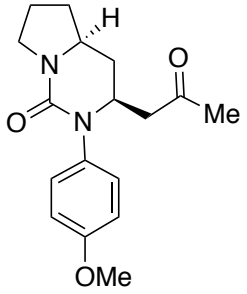
mL) to a nitrogen-filled flame-dried Schlenk tube equipped with a stir bar that had been charged with potassium *tert*-butoxide (1.5 equiv). The mixture was heated to 70 °C with stirring overnight, then was cooled to rt, and quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with dichloromethane (3 x 2 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford the desired product.

General Procedure 5 (Conditions C). A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of nitrogen and charged with the Hoveyda-Grubbs II catalyst (0.02 mmol, 10 mol %), and copper iodide (0.02 mmol, 10 mol %). The flask was purged with nitrogen and the appropriate substrate (0.2 mmol) in 1,2-dichloroethane (0.2 M) was added. The resulting mixture was stirred for 5 min at rt, then methyl acrylate (1.0 mmol) and boron trifluoride diethyl etherate (0.2 mmol) were added. The reaction mixture was heated to 70 °C with stirring overnight, then was cooled to rt and the reaction was quenched with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with dichloromethane (3 x 2 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford the desired product.

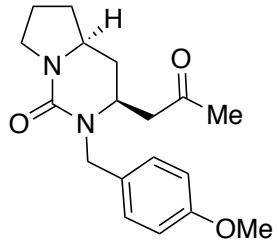


(±)-(3*S,4a*S**)-2-(4-Chlorophenyl)-3-(2-oxopropyl)hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one** (**2-7a**). The title compound was prepared from 2-allyl-*N*-(4-chlorophenyl) pyrrolidine-1-carboxamide (52 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 50% ethyl acetate in hexanes -> 100% ethyl acetate as the eluent). This procedure afforded 52.7 mg (86%) as a brown solid, mp 110–112 °C. The compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major

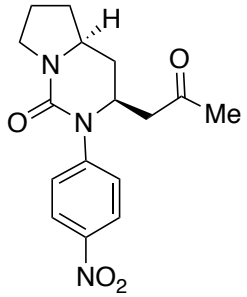
isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.29 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 4.29 (ddt, *J* = 3.8, 8.1, 14.9 Hz, 1H), 3.69–3.57 (m, 1H), 3.48 (dd, *J* = 5.0, 9.4 Hz, 2H), 2.48 (ddt, *J* = 3.2, 12.6, 28.4 Hz, 2H), 2.33 (ddd, *J* = 2.8, 8.6, 17.5 Hz, 1H), 2.23–2.10 (m, 1H), 1.96 (s 3H), 1.79 (dddt, *J* = 3.0, 6.6, 9.6, 12.7 Hz, 2H), 1.56–1.35 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 206.0, 154.3, 139.2, 132.3, 130.5, 129.0, 54.7, 53.0, 48.5, 45.9, 35.7, 33.5, 30.7, 23.1. IR (film) 3425.6, 1712.6, 1631.3 cm^{-1}. HRMS (ESI^{+} TOF) m/z: $[M + H]^{+}$ Calcd for $C_{16}H_{20}ClN_2O_2$ 307.1213; Found 307.1215.



(±)-(3*S,4a*S**)-2-(4-Methoxyphenyl)-3-(2-oxopropyl)hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one** (**2-7b**). The title compound was prepared from 2-allyl-*N*-(4-methoxyphenyl) pyrrolidine-1-carboxamide (52 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 40% ethyl acetate in hexanes -> 100% ethyl acetate as the eluent). This procedure afforded 24.4 mg (75%) of the title compound as a purple solid, mp 103–106 °C. 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, $CDCl_3$) d 7.13 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.27 (ddt, *J* = 4.0, 8.1, 12.0 Hz, 1H), 3.79 (s, 3H), 3.64 (tt, *J* = 4.5, 10.3 Hz, 1H), 3.56–3.47 (m, 2H), 2.57 (dd, *J* = 4.2, 17.4 Hz, 1H), 2.44 (dt, *J* = 3.4, 12.7 Hz, 1H), 2.32 (dd, *J* = 8.4, 17.5 Hz, 1H), 2.20–2.10 (m, 1H), 1.89 (s, 3H), 1.80 (ttd, *J* = 6.6, 9.3, 12.3 Hz, 2H), 1.56–1.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 206.3, 158.2, 133.3, 130.5, 114.2, 55.4, 54.8, 53.4, 48.6, 46.0, 35.7, 33.6, 30.7, 29.7, 23.2. IR (film) 3412.2, 1713.2, 1635.4 cm^{-1}. HRMS (ESI^{+} TOF) m/z: $[M + H]^{+}$ Calcd for $C_{17}H_{23}N_2O_3$ 303.1709; Found 303.1707.



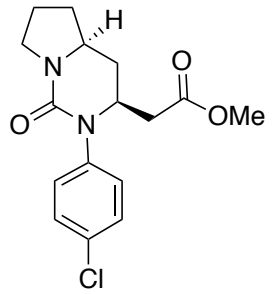
(±)-(3*S,4a*S**)-2-(4-Methoxybenzyl)-3-(2-oxopropyl)hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one** (**2-7c**). The title compound was prepared from 2-allyl-*N*-(4-methoxybenzyl) pyrrolidine-1-carboxamide (55 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 50% ethyl acetate in hexanes -> 100:0 ethyl acetate as the eluent). This procedure afforded 45 mg (71%) of the title compound as a purple solid, mp 109–112 °C. 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 (500 MHz, $CDCl_3$) d 7.27–7.13 (m, 2H), 6.88–6.80 (m, 2H), 4.82 (d, *J* = 15.9 Hz, 1H), 4.29 (d, *J* = 15.9 Hz, 1H), 3.89–3.84 (m, 1H), 3.78 (s, 3H), 3.80–3.71 (m, 1H), 3.65–3.40 (m, 3H), 2.86 (dd, *J* = 4.0, 16.9 Hz, 1H), 2.38–2.25 (m, 2H), 2.14–2.02 (m, 1H), 1.99 (s, 2H), 1.93 (dtt, *J* = 11.8, 7.0, 2.3 Hz, 1H), 1.78 (ttd, *J* = 6.9, 9.3, 12.4 Hz, 1H), 1.45 (tdd, *J* = 7.3, 9.8, 11.9 Hz, 1H), 1.36–1.23 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 206.3, 158.5, 156.3, 131.1, 128.4, 113.9, 55.3, 54.2, 50.7, 47.9, 47.2, 46.1, 35.9, 33.7, 30.8, 23.2. IR (film) 3444.4, 1712.3, 1612.6 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{25}N_2O_3$ 317.1865; Found 317.1855.



(±)-(3*S,4a*S**)-2-(4-Nitrophenyl)-3-(2-oxopropyl)hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one** (**2-7d**). The title compound was prepared from 2-allyl-*N*-(4-nitrophenyl) pyrrolidine-1-carboxamide (55 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 4. The cross-metathesis step afforded 45 mg (71%) of (±)-(*E*)-*N*-(4-nitrophenyl)-2-(4-oxopent-2-en-1-yl)pyrrolidine-1-carboxamide (**2-10d**) as a brown

oil (chromatography was performed using 40% ethyl acetate in hexanes -> 100% ethyl acetate as the eluent). ^{1}H NMR (500 MHz, $CDCl_3$) 8.17 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 6.79 (dt, *J* = 7.3, 15.1 Hz, 1H), 6.56 (s, 1H), 6.13 (d, *J* = 15.8 Hz, 1H), 4.26 (dq, *J* = 4.3, 8.3 Hz, 1H), 3.53 (s, 1H), 3.48 (d, *J* = 7.7 Hz, 1H), 2.76 (dt, *J* = 5.3, 11.9 Hz, 1H), 2.45–2.34 (m, 1H), 2.25 (s, 3H), 2.04 (dtd, *J* = 6.8, 11.7, 13.0, 26.1 Hz, 3H), 1.83–1.75 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$) d 198.28, 152.72, 145.05, 143.86, 143.70, 133.29, 124.89, 118.20, 56.83, 46.46, 37.14, 29.57, 27.15, 24.06. IR (film) 3356.4, 2970.5, 1662.6, 1542.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}N_3O_4$ 318.1454; Found 318.1453.

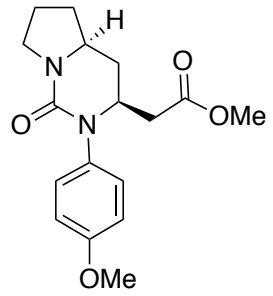
Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 100% ethyl acetate as the eluent) afforded 39 mg (65%; 45% over two steps from **2-5d**) of the title compound as a white-tan solid, mp 143–147 °C. The compound was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.19 (dd, *J* = 7.7, 9.6 Hz, 2H), 7.48–7.41 (d, *J* = 9 Hz, 2H), 4.68 (dq, *J* = 2.6, 3.3, 9.5 Hz, 1H), 3.70–3.56 (m, 2H), 3.55–3.47 (m, 1H), 2.78 (dd, *J* = 9.7, 17.9 Hz, 1H), 2.70–2.61 (m, 1H), 2.28 (ddd, *J* = 2.1, 3.7, 13.5 Hz, 1H), 2.23–2.14 (m, 1H), 2.10–1.93 (m, 4H), 1.92–1.75 (m, 2H), 1.61–1.41 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 205.6, 153.0, 148.0, 144.4, 128.4, 126.4, 124.3, 124.0, 53.1, 46.0, 33.7, 31.5, 30.6, 23.3. IR (film) 2973.4, 1711.9, 1640 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}N_3O_4$ 318.1454; Found 318.1453.



(±)-(3*S,4a*S**)-Methyl 2-(2-(4-chlorophenyl)-1-oxooctahydropyrrolo[1,2-*c*]pyrimidin-3-yl)acetate** (**2-7e**). The title compound was prepared from 2-allyl-*N*-(4-chlorophenyl) pyrrolidine-1-carboxamide (53 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 4. The cross-metathesis step afforded 41 mg

(63%) of (*E*)-4-{1-[(4-chlorophenyl)carbamoyl]pyrrolidin-2-yl]but-2-enoate (**2-10e**) as a purple oil (chromatography was performed using 40% ethyl acetate in hexanes as the eluent). The compound was obtained as a 4:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.38–7.31 (m, 2H), 7.26–7.17 (m, 2H), 6.91 (dt, *J* = 7.5, 15.3 Hz, 1H), 6.26 (s, 1H), 5.88 (dt, *J* = 1.4, 15.6 Hz, 1H), 4.17 (dq, *J* = 3.6, 10.2 Hz, 1H), 3.72 (s, 3H), 3.49–3.36 (m, 2H), 2.73 (dddd, *J* = 1.5, 3.6, 6.9, 14.0 Hz, 1H), 2.44–2.33 (m, 1H), 2.06–1.89 (m, 3H), 1.80–1.71 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 166.7, 153.6, 145.2, 137.6, 128.8, 128.5, 123.3, 120.9, 56.6, 51.5, 46.4, 36.7, 29.5, 24.0. IR (film) 3329.9, 1719.5, 1642.9 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}ClN_2O_3$ 323.1162; Found 323.1161.

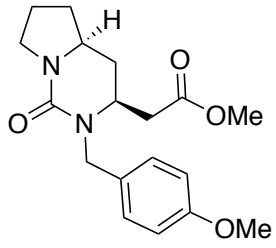
Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 40% ethyl acetate in hexanes -> 100% ethyl acetate as the eluent) afforded 25 mg (63%, 38% over two steps from **2-5a**) of the title compound as a white solid, mp 117–118 °C. The compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.38–7.27 (m, 2H), 7.17 (dd, *J* = 8.6, 1.7 Hz, 2H), 4.23 (ddt, *J* = 4.1, 8.5, 11.2 Hz, 1H), 3.72–3.60 (m, 1H), 3.56 (s, 3H), 3.53–3.45 (m, 2H), 2.57–2.40 (m, 2H), 2.19–2.12 (m, 2H), 2.05–1.92 (m, 1H), 1.82 (ddt, *J* = 15.1, 12.0, 4.5 Hz, 1H), 1.60–1.47 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 171.1, 154.2, 139.0, 130.6, 129.1, 54.6, 54.0, 51.7, 45.9, 39.9, 35.6, 33.8, 31.7, 23.1. IR (film) 1733.2, 1639.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}ClN_2O_3$ 323.1162; Found 323.1163.



(±)-(3*S,4a*S**)-Methyl 2-[2-(4-methoxyphenyl)-1-oxooctahydropyrrolo[1,2-*c*]pyrimidin-3-yl]acetate** (**2-7f**). The title compound was prepared from 2-allyl-*N*-(4-methoxyphenyl) pyrrolidine-1-carboxamide (52 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 4. The cross-metathesis step afforded 54 mg

(85%) of methyl (*E*)-4-{1-[(4-methoxyphenyl)carbamoyl]pyrrolidin-2-yl}but-2-enoate (**10f**) as a brown/tan oil (chromatography was performed using 40% ethyl acetate in hexanes as the eluent). The compound was obtained as a 5:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.31–7.24 (m, 2H), 6.97–6.87 (m, 1H), 6.85–6.78 (m, 2H), 6.13 (s, 1H), 5.98–5.84 (m, 1H), 4.20–4.06 (m, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.47–3.35 (m, 2H), 2.74 (dddd, *J* = 1.6, 3.6, 7.0, 14.1 Hz, 1H), 2.38 (dddd, *J* = 1.4, 8.0, 9.0, 14.2 Hz, 1H), 2.03–1.96 (m, 3H), 1.74 (ddt, *J* = 3.4, 5.4, 12.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 166.8, 155.8, 154.3, 145.5, 131.9, 123.2, 122.1, 114.1, 56.5, 55.5, 51.5, 46.3, 36.9, 29.7, 24.0. IR (film) 3322.7, 2950.0, 1719.1, 1639.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{23}N_2O_4$ 319.1658; Found 319.1656.

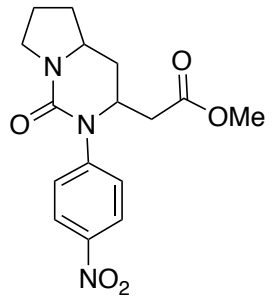
Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 100% ethyl acetate as the eluent) afforded 46 mg (84%, 71% over two steps from **2-5b**) of the title compound as a yellow solid, mp 107–110 °C. The compound was obtained as a 5:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.12 (d, *J* = 8.4 Hz, 2H), 6.90–6.84 (m, 2H), 4.23–4.15 (m, 1H), 3.79 (s, 3H), 3.65 (s, 1H), 3.57 (s, 1H), 3.54 (s, 3H), 3.51 (dd, *J* = 4.9, 9.4 Hz, 2H), 2.45 (td, *J* = 3.7, 13.7, 14.8 Hz, 2H), 2.18 (dt, *J* = 7.4, 14.5 Hz, 2H), 2.00–1.93 (m, 1H), 1.81 (s, 1H), 1.55 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 171.4 158.3, 154.7, 133.2, 130.1, 114.2, 55.4, 54.7, 54.2, 51.6, 46.0, 40.1, 35.6, 33.6, 23.1. IR (film) 1734.2, 1634.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{23}N_2O_4$ 319.1658; Found 319.1661.



(±)-(3*S,4a*S**)-Methyl 2-(2-(4-methoxybenzyl)-1-oxooctahydropyrrolo[1,2-*c*]pyrimidin-3-yl)acetate** (**2-7g**). The title compound was prepared from 2-allyl-*N*-(4-methoxybenzyl) pyrrolidine-1-carboxamide (55 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 4. The cross-metathesis step afforded 48 mg

(72%) of (*E*)-methyl 4-{1-[(4-methoxybenzyl)carbamoyl]pyrrolidin-2-yl}but-2-enoate (**2-10g**) as a pink-purple oil (chromatography was performed using 40% ethyl acetate in hexanes as the eluent). The compound was obtained as a >20:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.31–7.16 (m, 2H), 6.97–6.81 (m, 3H), 5.86 (dt, *J* = 1.5, 15.6 Hz, 1H), 4.44 (s, 1H), 4.41–4.29 (m, 1H), 4.35 (s, 1H), 4.11 (ddd, *J* = 3.1, 5.5, 9.8 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.32–3.19 (m, 2H), 2.70 (dddd, *J* = 1.5, 3.6, 7.0, 14.0 Hz, 1H), 2.42–2.31 (m, 1H), 1.99–1.85 (m, 2H), 1.75–1.66 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 166.8, 158.9, 156.5, 145.7, 131.7, 129.1, 123.1, 114.0, 56.3, 55.3, 51.5, 46.0, 44.1, 37.1, 29.5, 23.9. IR (film) 3333.9, 1719.5, 1626.1 cm^{-1}. HRMS (ESI^{+} TOF) m/z: $[M + H]^{+}$ Calcd for $C_{18}H_{25}N_2O_4$ 333.1814; Found 333.1806.

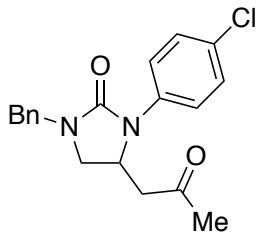
Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 100% ethyl acetate as the eluent) afforded 26 mg (54%, 39% over two steps from **2-5c**) of the title compound as a yellow oil. The compound was obtained as a 8:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.25–7.14 (m, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 5.02 (d, *J* = 15.9 Hz, 1H), 4.21 (d, *J* = 15.9 Hz, 1H), 3.78 (s, 2H), 3.64 (d, *J* = 14.9 Hz, 3H), 3.63–3.40 (m, 3H), 2.77 (dd, *J* = 3.9, 15.2 Hz, 1H), 2.31–2.20 (m, 2H), 2.11 (qd, *J* = 3.8, 7.3 Hz, 1H), 2.05–1.89 (m, 1H), 1.93 (s, 1H), 1.86–1.72 (m, 1H), 1.54–1.35 (m, 2H), 0.39 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 171.3, 158.6, 156.1, 130.8, 128.5, 113.9, 55.2, 54.1, 51.7, 51.3, 46.7, 46.1, 39.0, 35.5, 33.5, 23.2. IR (film) 1734.0, 1614.3 cm^{-1}. HRMS (ESI^{+} TOF) m/z: $[M + H]^{+}$ Calcd for $C_{18}H_{25}N_2O_4$ 333.1814; Found 333.1810.



Methyl 2[(2-(4-nitrophenyl)-1-oxooctahydropyrrolo[1,2-*c*]pyrimidin-3-yl]acetate (**2-7h**). The title compound was prepared from 2-allyl-*N*-(4-nitrophenyl) pyrrolidine-1-carboxamide (55 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General

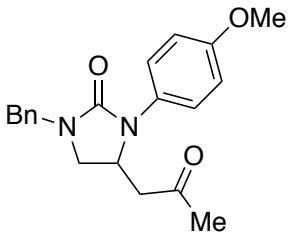
Procedure 4. The cross-metathesis step afforded 36 mg (54%) of (*E*)-methyl 4-{1-[(4-nitrophenyl)carbamoyl]pyrrolidin-2-yl}but-2-enoate (**2-10h**) as a brown oil (chromatography was performed using 40% ethyl acetate in hexanes as the eluent). The compound was obtained as a 4:1 mixture of *E*:*Z* isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.39–7.31 (m, 2H), 7.26–7.18 (m, 2H), 6.91 (dt, *J* = 7.5, 15.3 Hz, 1H), 6.26 (s, 2H), 5.89 (dt, *J* = 1.5, 15.5 Hz, 1H), 4.18 (dq, *J* = 3.7, 10.2 Hz, 1H), 3.72 (s, 3H), 3.49–3.36 (m, 2H), 2.73 (dddd, *J* = 1.4, 3.7, 6.8, 13.7 Hz, 1H), 2.44–2.34 (m, 1H), 2.07–1.95 (m, 2H), 1.75 (tq, *J* = 3.8, 5.0, 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 166.6, 152.7, 145.2, 144.8, 142.4, 125.1, 123.6, 118.2, 56.8, 51.6, 46.5, 36.5, 29.5, 24.0. IR (film) 3357.3, 1718.3, 1654.4 cm^{-1}. HRMS (ESI^{+} TOF) m/z: [M + H]$^{+}$ Calcd for $C_{16}H_{20}N_3O_5$ 334.1403; Found 334.1401.

Treatment of the cross-metathesis product with KO^{t}Bu (chromatography was performed using 100% ethyl acetate as the eluent) afforded 19.4 mg (58%, 31% over two steps from **2-5d**) of the title compound as a yellow solid, mp 99–100 °C. 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 (500 MHz, $CDCl_3$) d 8.24–8.16 (m, 4H), 7.50–7.42 (m, 4H), 4.61 (dtd, *J* = 1.9, 5.1, 10.6 Hz, 1H), 4.39 (ddt, *J* = 4.0, 8.4, 10.7 Hz, 1H), 3.75–3.46 (m, 12H), 2.67–2.43 (m, 4H), 2.34–2.16 (m, 4H), 2.08–1.95 (m, 2H), 1.90–1.79 (m, 3H), 1.67–1.51 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 170.7, 153.3, 152.9, 148.0, 146.7, 145.5, 144.5, 128.7, 126.7, 124.3, 124.0, 54.5, 53.6, 52.8, 51.9, 46.5, 46.0, 39.7, 37.6, 35.6, 33.7, 33.5, 31.6, 23.3, 23.0. IR (film) 1733.7, 1644.3 cm^{-1}. HRMS (ESI^{+} TOF) m/z: [M + H]$^{+}$ Calcd for $C_{16}H_{20}N_3O_5$ 334.1403; Found 334.1403.

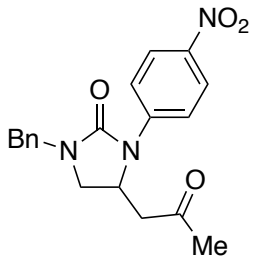


1-Benzyl-3-(4-chlorophenyl)-4-(2-oxopropyl)imidazolidin-2-one (**2-13a**). The title compound was prepared from 1-allyl-1-benzyl-3-(4-chlorophenyl)urea (60 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3

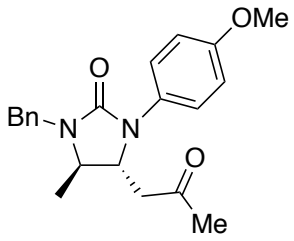
(chromatography was performed using 20% ethyl acetate in hexanes -> 40% ethyl acetate in hexanes as the eluent). This procedure afforded 48 mg (70%) of the title compound as a brown solid, mp 89-92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.42–7.35 (m, 2H), 7.35–7.18 (m, 5H), 4.59 (dddd, *J* = 2.8, 4.7, 8.6, 10.0 Hz, 1H), 4.47–4.36 (m, 2H), 3.64 (t, *J* = 9.1 Hz, 1H), 2.97–2.88 (m, 2H), 2.59 (dd, *J* = 10.1, 18.3 Hz, 1H), 2.37 (s, 1H), 2.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 206.2, 157.3, 137.0, 136.5, 129.1, 128.8, 128.7, 128.3, 127.7, 121.8, 49.1, 48.1, 47.9, 46.1, 30.5. IR (film) 1699.5, 1493.4 cm^{-1}. HRMS (ESI^{+} TOF) m/z: [M + H]$^{+}$ Calcd for $C_{19}H_{20}ClN_2O_2$ 343.1213; Found 343.1212.



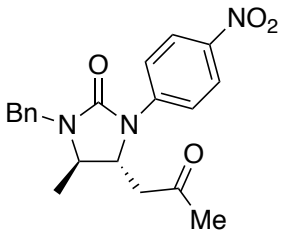
1-Benzyl-3-(4-methoxyphenyl)-4-(2-oxopropyl)imidazolidin-2-one (**2-13b**). The title compound was prepared from 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea (60 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 20% ethyl acetate in hexanes -> 40% ethyl acetate in hexanes as the eluent). This procedure afforded 43 mg (63%) of the title compound as a brown solid, mp 110-111 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.38–7.21 (m, 7H), 6.95–6.86 (m, 2H), 4.55–4.42 (m, 2H), 4.38 (d, *J* = 14.9 Hz, 1H), 3.79 (s, 3H), 3.63 (t, *J* = 9.0 Hz, 1H), 2.94–2.86 (m, 2H), 2.57 (dd, *J* = 10.0, 18.2 Hz, 1H), 2.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 206.4, 158.2, 156.7, 136.8, 131.2, 128.7, 128.3, 127.6, 124.0, 114.4, 55.5, 50.3, 48.3, 48.1, 46.5, 30.5. IR (film) 1694.4, 1511.5 cm^{-1}. HRMS (ESI^{+} TOF) m/z: [M + H]$^{+}$ Calcd for $C_{20}H_{23}N_2O_3$ 339.1709; Found 339.1713.



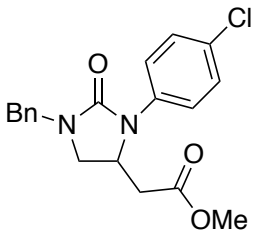
1-Benzyl-3-(4-nitrophenyl)-4-(2-oxopropyl)imidazolidin-2-one (**2-13c**). The title compound was prepared from 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (60 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 20% ethyl acetate in hexanes -> 40% ethyl acetate in hexanes as the eluent) to afford 44 mg (62%) yellow solid, mp 132-135 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.20 (d, *J* = 9.5 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 2H), 7.40–7.25 (m, 5H), 4.76–4.67 (m, 1H), 4.51–4.37 (m, 2H), 3.67 (t, *J* = 9.2 Hz, 1H), 3.04–2.94 (m, 2H), 2.69 (dd, *J* = 10.3, 18.5 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 205.9, 156.2, 144.5, 142.2, 135.9, 128.8, 128.3, 128.0, 125.0, 117.8, 48.7, 47.9, 47.8, 45.7, 30.5. IR (film) 3404.4, 2924.0, 1704.3, 1593.4, 1500.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}N_3O_4$ 354.1454; Found 354.1451.



(4*R,5*R**)-1-Benzyl-3-(4-methoxyphenyl)-5-methyl-4-(2-oxopropyl)imidazolidin-2-one** (**2-13d**). The title compound was prepared from 1-benzyl-1-(but-3-en-2-yl)-3-(4-methoxyphenyl)urea (62 mg, 0.2 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 20% ethyl acetate in hexanes -> 40% ethyl acetate in hexanes as the eluent). This procedure afforded 40 mg (56%) of the title compound as a brown oil. 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, $CDCl_3$) d 7.40–7.19 (m, 5H), 6.89 (dd, *J*= 2.6, 9.2 Hz, 2H), 4.86 (d, *J* = 15.3 Hz, 1H), 4.17 (dt, *J* = 3.5, 9.2 Hz, 1H), 4.05 (d, *J* = 15.3 Hz, 1H), 3.79 (s, 3H), 3.84–3.71 (m, 1H), 3.14 (qd, *J* = 3.8, 6.2 Hz, 1H), 2.82–2.72 (m, 1H), 2.50 (dd, *J* = 9.2, 17.9 Hz, 1H), 1.98 (s, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 206.5, 157.1, 156.4, 137.4, 131.3, 128.6, 128.2, 127.5, 123.5, 114.4, 57.6, 55.5, 54.4, 45.9, 45.0, 30.7, 18.2. IR (film) 3362.5, 2932.6, 1693.8, 1511.5 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{25}N_2O_3$ 353.1865; Found 353.1866.

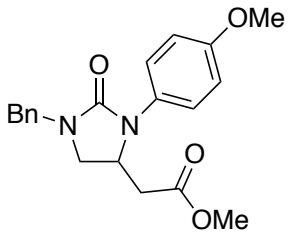


(4*R,5*R**)-1-Benzyl-5-methyl-3-(4-nitrophenyl)-4-(2-oxopropyl)imidazolidin-2-one** (**2-13e**). The title compound was prepared from 1-benzyl-1-(but-3-en-2-yl)-3-(4-nitrophenyl)urea (40 g, 0.12 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 20% ethyl acetate in hexanes -> 25% ethyl acetate in hexanes as the eluent). This procedure afforded 21 mg (48%) of the title compound as a white-tan solid, mp 155-158 °C. 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, $CDCl_3$) d 8.24–8.17 (m, 2H), 7.76–7.68 (m, 2H), 7.36 (dd, *J* = 6.5, 8.0 Hz, 2H), 7.35–7.26 (m, 3H), 4.93 (d, *J* = 15.2 Hz, 1H), 4.37–4.27 (m, 1H), 4.03 (d, *J* = 15.1 Hz, 1H), 3.14 (qd, *J*= 2.0, 6.3 Hz, 1H), 2.86 (dd, *J* = 2.3, 18.5 Hz, 1H), 2.56 (dd, *J* = 10.2, 18.5 Hz, 1H), 2.06 (s, 3H), 1.31 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 205.9, 155.2, 144.9, 142.0, 136.6, 128.9, 128.1, 127.9, 125.1, 117.1, 56.1, 54.2, 45.2, 44.9, 30.6, 18.3. IR (film) 1709.5, 1595.1 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}N_3O_4$ 368.1610; Found 368.1608.

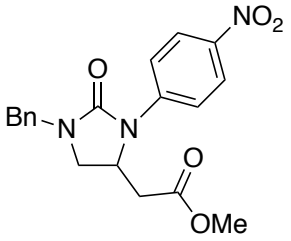


Methyl 2-[1-benzyl-3-(4-chlorophenyl)-2-oxoimidazolidin-4-yl]acetate (**2-13f**). The title compound was prepared from 1-allyl-1-benzyl-3-(4-chlorophenyl)urea (60 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 5 (chromatography was performed using 25% ethyl acetate in hexanes -> 40% ethyl acetate in hexanes as the eluent). This procedure afforded 34 mg (47%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.46–7.14 (m, 9H), 4.61–4.45 (m, 2H), 4.40 (d, *J* = 14.8 Hz, 1H), 3.80–3.56 (m, 3H), 3.10 (dd, *J* = 4.5, 9.5 Hz, 1H), 2.78 (dd, *J* = 3.2, 16.4 Hz, 1H), 2.44 (dd, *J* = 9.9, 16.3 Hz, 1H), 1.46 (s, 1H). ^{13}C NMR

(126 MHz, $CDCl_3$) d 170.8, 136.4, 129.1, 128.7, 128.3, 127.0, 125.1, 122.5, 121.2, 52.0, 50.8, 50.1, 48.0, 47.6, 37.0. IR (film) 1732.7, 1703.0, 1594.2 cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}ClN_2O_3$ 359.1162; Found 359.1161.



Methyl 2-[1-benzyl-3-(4-methoxyphenyl)-2-oxoimidazolidin-4-yl]acetate (**2-13g**). The title compound was prepared from 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea (60 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 5 (chromatography was performed using 25% ethyl acetate in hexanes -> 40% ethyl acetate in hexanes as the eluent). This procedure afforded 35 mg (48%) of the title compound as a white-tan solid, mp 64–67 °C. ^1H NMR (500 MHz, $CDCl_3$) d 7.38–7.23 (m, 7H), 6.96–6.86 (m, 2H), 4.54–4.43 (m, 2H), 4.39 (d, *J* = 14.8 Hz, 1H), 3.79 (d, *J* = 1.3 Hz, 3H), 3.60 (d, *J* = 1.3 Hz, 3H), 3.07 (ddd, *J* = 1.2, 5.4, 9.3 Hz, 1H), 2.75 (dt, *J* = 2.2, 16.3 Hz, 1H), 2.42 (ddd, *J* = 1.2, 9.8, 16.3 Hz, 1H), 1.25 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 171.0, 158.2, 156.8, 136.8, 128.7, 128.3, 127.6, 124.3, 114.4, 55.5, 51.8, 51.2, 48.1, 47.9, 37.4, 29.7. IR (film) 1733.7, 1699.7, cm^{-1}. HRMS (ESI^+ TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2O_4$ 355.1658; Found 355.1657.

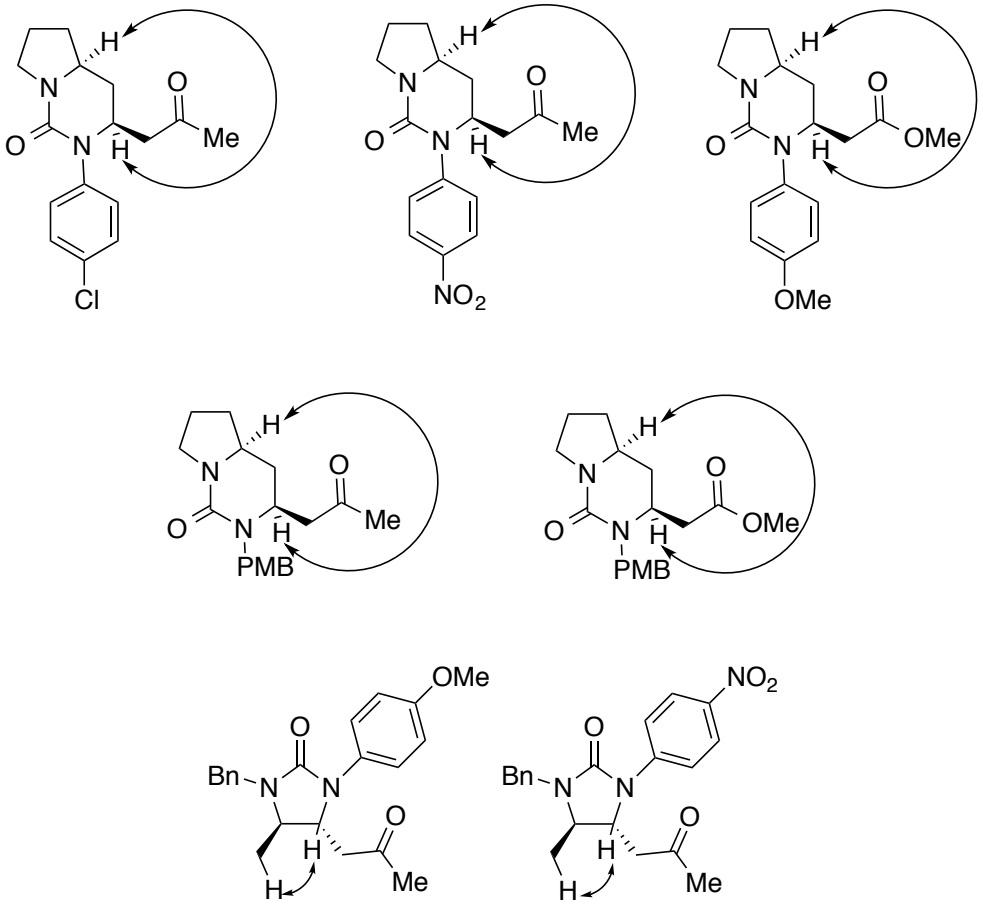


Methyl 2-[1-benzyl-3-(4-nitrophenyl)-2-oxoimidazolidin-4-yl]acetate (**2-13h**). The title compound was prepared from 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (62 mg, 0.2 mmol) and methyl acrylate (0.1 mL, 1 mmol) using General Procedure 3 (chromatography was performed using 25% ethyl acetate in hexanes as the eluent). This procedure afforded 52 mg (70%) of the title compound as a yellow solid, mp 130-132 °C. ^1H NMR (500 MHz, $CDCl_3$) d 8.25–8.18 (m, 2H), 7.77–7.69 (m, 2H), 7.36 (dd, *J* = 6.4, 7.9 Hz, 2H), 7.34–7.26 (m, 3H), 4.72–4.63 (m, 1H), 4.51 (d, *J* = 14.9 Hz,

1H), 4.45 (d, *J* = 14.9 Hz, 1H), 3.67 (s, 3H), 3.64 (t, *J* = 9.0 Hz, 1H), 3.17 (dd, *J* = 3.2, 9.6 Hz, 1H), 2.84 (dd, *J* = 2.7, 16.5 Hz, 1H), 2.53 (dd, *J* = 10.1, 16.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 170.4, 156.2, 144.4, 142.4, 135.8, 128.9, 128.3, 128.0, 125.1, 117.9, 52.2, 49.6, 47.9, 47.3, 36.6. IR (film) 1707.8, 1594.1 cm^{-1}. HRMS (ESI$^+$ TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}N_3O_5$ 370.1403; Found 370.1402.

Assignment of relative stereochemistry

The relative stereochemistry of compounds **2-7a-d**, **2-7g** and **2-13e-f** were assigned by ^{1}H NMR nOe analysis. Key nOe enhancements are shown below. The relative stereochemistry of **2-7e-f** was assigned based on analogy to **2-7a-d**.



2.6 References

(1) (a) De Lucca, G. V.; Lam, P. Y. S. De Novo Design, Discovery, and Development of Cyclic Urea HIV Protease Inhibitors. *Drugs Future* **1998**, *23*, 987–994. (b) Salituro, F. G.; Baker, C. T.; Court, J. J.; Deininger, D. D.; Kim, E. E.; Li, B.; Novak, P. M.; Rao, B. G.; Pazhanisamy, S.; Porter, M. D.; Schairer, W. C.; Tung, R. D. Design and Synthesis of Novel Conformationally Restricted HIV Protease Inhibitors. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3637–3642. (c) Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. L. Novel Inhibitors of HIV Protease: Design, Synthesis, and Biological Evaluation of Picomolar Inhibitors Containing Cyclic P1/P2 Scaffolds. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159–1162. (d) De Clercq, E. New Developments in anti-HIV Chemotherapy. *Biochim. Biophys. Acta* **2002**, *1587*, 258–275. (e) Kazmierski, W. M.; Furfine, E.; Gray-Nunez, Y.; Spaltenstein, A.; Wright, L. Potent Inhibitors of the HIV-1 Protease Incorporating Cyclic Urea P1-P2 Scaffold. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 5685–5687.

(2) Heidempergher, F.; Pillan, A.; Pinciroli, V.; Vaghi, F.; Arrigoni, C.; Bolis, G.; Caccia, C.; Dho, L.; McArthur, R.; Varasi, M. Phenylimidazolidin-2-one Derivatives as Selective 5-HT_3 Receptor Antagonists and Refinement of the Pharmacophore Model for 5-HT_3 Receptor Binding. *J. Med. Chem*. **1997**, *40*, 3369–3380.

(3) (a) Reichard, G. A.; Stengone, C.; Paliwal, S.; Mergelsberg, I.; Majmundar, S.; Wang, C.; Tiberi, R.; McPhail, A. T.; Piwinski, J. J.; Shih, N.-Y. Asymmetric Synthesis of 4,4-Disubstituted-2-Imidazolidinones: Potent NK_1 Antagonists. *Org. Lett*. **2003**, *5*, 4249–4251. (b) Shue, H.-J.; Chen, X.; Shih, N.-Y.; Blythin, D. J.; Paliwal, S.; Lin, L.; Gu, D.; Schwerdt, J. H.; Shah, S.; Reichard, G. A.; Piwinski, J. J.; Duffy, R. A.; Lachowicz, J. E.; Coffin, V. L.; Liu, F.; Nomeir, A. A.; Morgan, C. A.; Varty, G. B. Cyclic Urea Derivatives as Potent NK_1 Selective Antagonists. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 3896–3899. (c) Shue, H.-J.; Chen, X.; Schwerdt, J. H.; Paliwal, S.; Blythin, D. J.; Lin, L.; Gu, D.; Wang, C.; Reichard, G. A.; Wang, H.; Piwinski, J. J.; Duffy, R. A.; Lachowicz, J. E.; Coffin, V. L.; Nomeir, A. A.; Morgan, C. A.; Varty, G. B.; Shih, N.-Y. Cyclic Urea

Derivatives as Potent NK_1 Selective Antagonists. Part II: Effects of Fluoro and Benzylic Methyl Substitutions. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 1065–1069.

(4) (a) Cardillo, G.; D'Amico, A.; Orena, M.; Sandri, S. Diastereoselective Alkylation of 3-Acylimidazolidin-2-Ones: Synthesis of (*R*) and (*S*)-Lavandulol. *J. Org. Chem*. **1988**, *53*, 2354–2356. (b) Sankhavasi, W.; Yamamoto, M.; Kohmoto, S.; Yamada, K. New Chiral Auxiliary; 4,5-Diphenyl-1-methuyl-2-imidazolidinone. Its Utility in Highly Enantioselective Aldol Reaction. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1425–1427. (c) Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. Ephedrine-Derived Imidazolidin-2-ones. Broad Utility Chiral Auxiliaries in Asymmetric Synthesis. *Chem. Ber.* **1993**, *126*, 2663–2673.

(5) For selected examples of bicyclic ureas as intermediates in the synthesis of tricyclic guanidines, see: a) Evans, P. A.; Qin, J.; Robinson, J. E.; Bazin B. Enantioselective Total Synthesis of the Polycyclic Guanidine-Containing Marine Alkaloid (–)-Batzelladine D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7417–7419. b) Aron, Z. D.; Overman, L. E. Total Synthesis and Properties of the Crambescidin Core Zwitterionic Acid and Crambescidin 359. *J. Am. Chem. Soc.* **2005**, *127*, 3380–3390. c) Rama Rao, A. V.; Gurjar, M. K.; Vasudevan, J. An Enantiospecific Synthesis of the Tricyclic Guanidine Segment of the anti-HIV Marine Alkaloid Batzelladine A. *J. Chem. Soc., Chem. Commun.* **1995**, 1369–1370. d) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. Enantioselective Total Synthesis of (–)-Ptilomycalin A. *J. Am. Chem. Soc.* **1995**, *117*, 2657–2658.

(6) (a) Berlinck, R. G. S.; Trindade-Silva, A. E.; Santos, M. F. C. The Chemistry and Biology of Organic Guanidine Derivatives. *Nat. Prod. Rep*. **2012**, *29*, 1382–1406. (b) Berlinck, R. G. S.; Burtoloso, A. C. B.; Trindade-Silva, A. E.; Romminger, S.; Morais, R. P.; Bandeira, K.; Mizuno, C. M. The Chemistry and Biology of Organic Guanidine Derivatives. *Nat. Prod. Rep*. **2010**, *27*, 1871–1907. (c) Berlinck, R. G. S.; Burtoloso, C. B.; Kossuga, M. H. The Chemistry and Biology of Organic Guanidine Derivatives. *Nat. Prod. Rep.* **2008**, *25*, 919–954.

(7) For a review, see: (a) Sartori, G.; Maggi, R. Product Class 8: Acyclic and Cyclic Ureas in *Science of Synthesis (Houben-Weyl Methods of Molecular Transformations)*; Ley, S. V., Knight, J. G., Eds.; Thieme: Stuttgart, 2005; Vol. 18, pp 665–758. For

selected examples of metal-catalyzed reactions that afford cyclic ureas, see: (b) Trost, B. M.; Fandrick, D. R. Dynamic Kinetic Asymmetric Cycloadditions of Isocyanates to Vinylaziridines. *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837. (c) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. Pd(II)-Catalyzed Intermolecular 1,2-Diamination of Conjugated Dienes. *J. Am. Chem. Soc*. **2005**, *127*, 7308–7309. (d) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. Palladium(II)-Catalyzed Intramolecular Diamination of Unfunctionalized Alkenes. *J. Am. Chem. Soc.* **2005**, *127*, 14586–14587. (e) Du, H.; Zhao, B.; Shi, Y. A Facile Pd(0)-Catalyzed Regio- and Stereoselective Diamination of Conjugated Dienes and Trienes. *J. Am. Chem. Soc.* **2007**, *129*, 762–763. (f) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. Expanding the Substrate Scope for C–H Amination Reactions: Oxidative Cyclization of Urea and Guanidine Derivatives. *Org. Lett.* **2006**, *8*, 1073–1076.

(8) (a) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. Urea as the Most Reactive and Versatile Nitrogen Nucleophile for the Palladium(2+)-Catalyzed Cyclization of Unsaturated Amines. *J. Am. Chem. Soc.* **1988**, *110*, 3994–4002. (b) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. Palladium(II)-Catalyzed Intramolecular Aminocarbonylation of *endo*-Carbamates under Wacker Type Conditions. *J. Org. Chem.* **1997**, *62*, 2113–2122.

(9) For recent reviews, see: (a) Garlets, Z. J.; White, D. R.; Wolfe, J. P. Recent Developments in Pd^0-Catalyzed Alkene Carboheterofunctionalization Reactions. *Asian J. Org. Chem*. **2017**, *6*, 636–653. (b) Schultz, D. M.; Wolfe, J. P. Recent Developments in Palladium-Catalyzed Alkene Aminoarylation Reactions for the Synthesis of Nitrogen Heterocycles. *Synthesis* **2012**, 351–361. (c) Wolfe, J. P. Stereoselective Synthesis of Saturated Heterocycles via Palladium-Catalyzed Alkene Carboetherification and Carboamination Reactions. *Synlett* **2008**, 2913–2937.

(10) (a) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. A New Synthesis of Imidazolidin-2-ones via Pd-Catalyzed Carboamination of *N*-Allylureas. *Org. Lett.* **2006**, *8*, 2531–2534. (b) Fritz, J. A.; Wolfe, J. P. Stereoselective Synthesis of Imidazolidin-2-ones via Pd-Catalyzed Alkene Carboamination. Scope and Limitations. *Tetrahedron* **2008**, *64*, 6838–6852. (c) Hopkins, B. A.; Wolfe, J. P. Synthesis of Enantiomerically Enriched

Imidizolidin-2-ones through Asymmetric Palladium-Catalyzed Alkene Carboamination Reactions. *Angew. Chem. Int. Ed.* **2012**, *51*, 9886–9890.

(11) Babij, N. R.; Wolfe, J. P. Asymmetric Total Synthesis of (+)-Merobatzelladine B. *Angew. Chem., Int. Ed.* **2012**, *51*, 4128–4130.

(12) Babij, N. R.; Wolfe, J. P. Desymmetrization of *meso*-2,5-Diallylpyrrolidinyl Ureas through Asymmetric Palladium-Catalyzed Carboamination: Stereocontrolled Synthesis of Bicyclic Ureas. *Angew. Chem., Int. Ed.* **2013**, *52*, 9247–9250.

(13) We have developed a method for the generation of the analogous *trans*-bicyclic sulfamides, but this approach gave unsatisfactory results with ureas. See: Babij, N. R.; McKenna, G. M.; Fornwald, R. M.; Wolfe, J. P. Stereocontrolled Synthesis of Bicyclic Sulfamides via Pd-Catalyzed Alkene Carboamination Reactions. Control of 1,3-Asymmetric Induction by Manipulating Mechanistic Pathways. *Org. Lett.* **2014**, *16*, 3412–3415.

(14) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. Microwave-Assisted Tandem Cross Metathesis Intramolecular Aza-Michael Reaction: An Easy Entry to Cyclic b-Amino Carbonyl Derivatives. *J. Am. Chem. Soc*. **2007**, *129*, 6700–6701.

(15) (a) Chen, L. -J.; Hou, D. -R. Asymmetric Aza-Michael Addition: Synthesis of (–)-Allosedridine and (–)-2-*epi*-Ethylnorlobelol. *Tetrahedron: Asymmetry* **2008**, *19*, 715–720. (b) Fustero, S.; Báez, C.; Sánchez-Roselló, M.; Asensio, A.; Miro, J.; del Pozo, C. A New Tandem Cross Metathesis-Intramolecular Aza-Michael Reaction for the Synthesis of a,a-Difluorinated Lactams. *Synthesis* **2012**, 1863–1873. (c) Chou, S. P.; Huang, J. -L. Tandem Cross-Metathesis and Intramolecular aza-Michael Reaction to Synthesize Bicyclic Piperidines and Indolizine 167E. *Tetrahedron Lett.* **2012**, *53*, 5552–5554. (d) Boufroura, H.; Mauduit, M.; Drège, E.; Joseph, D. Step-Economical Access to Valuable Weinreb Amide 2,5-Disubstituted Pyrrolidines by a Sequential One-Pot Two-Directional Cross-Metathesis/Cyclizing Aza-Michael Process. *J. Org. Chem.* **2013**, *78*, 2346–2354. (e) Drège, E.; Oko, J.; Venot, P. -E.; Gigant, N.; Joseph, D. Microwave-Assisted Telescoped Cross-Metathesis-Ring Closing Aza-Michael Reaction Sequence: Step-Economical Access to Nicotine-Lobeline Hybrid Analogues. *RSC Adv.* **2015**, *5*, 96720–96724. (f) Salih, N.; Adams, H.; Jackson, R. F. W. Synthesis of w-Oxo Amino

Acids and *trans*-5-Substituted Proline Derivatives Using Cross-Metathesis of Unsaturated Amino Acids. *J. Org. Chem.* **2016**, *81*, 8386–8393.

(16) The relative stereochemistry of the cross-metathesis/aza Michael reaction products was assigned by ^{1}H NMR nOe analysis. See the Experimental for complete descriptions of stereochemical assignments.

(17) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. Rate Enhanced Olefin Cross-Metathesis Reactions: The Copper Iodide Effect. *J. Org. Chem.* **2011**, *76*, 4697–4702.

(18) Chatterjee, A. K.; Grubbs, R. H. Synthesis of Trisubstituted Alkenes via Olefin Cross-Metathesis. *Org. Lett.* **1999**, *1*, 1751–1753.

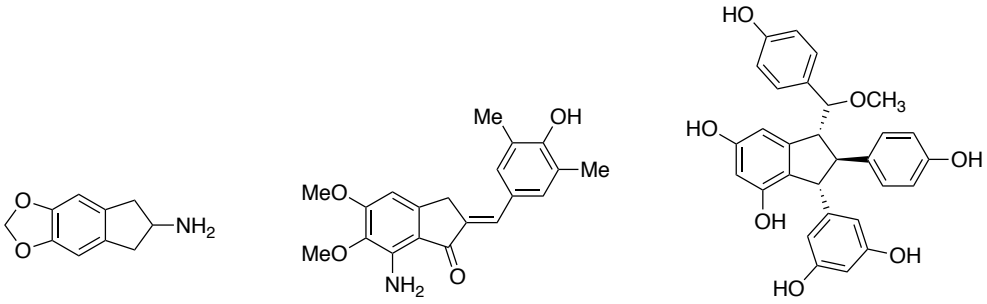
(19) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M; Lu, K.; Watson, R. T. Reactivity and Enantioselectivity in the Reactions of Scalemic Stereogenic a-(*N*-Carbamoyl)alkylcuprates. *J. Org. Chem*. **2004**, *69*, 3076–3086.

Chapter 3

Palladium-Catalyzed Alkene Dialkylation Reactions on Internal Alkenes

3.1 Introduction

Substituted carbocycles are useful subunits found in natural products. Indanes and similar products are found in pharmaceuticals and used for materials chemistry because they possess cytotoxic, anti-cancer, anti-oxidant, and pesticidal properties.[1,2] Some indanes also possess antiobesity, antidiabetic, anti-inflammatory, and immunomodulatory properties (Figure 3-1).[3]



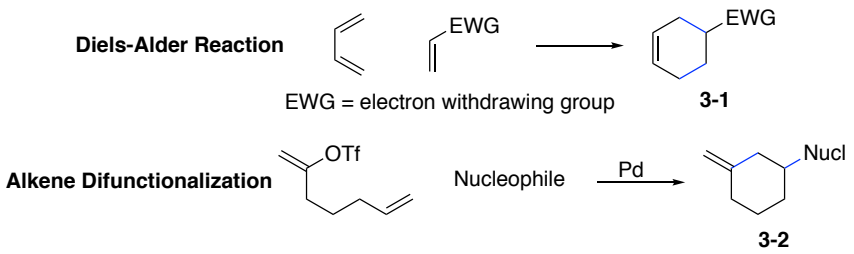
MDAI
CNS stimulant

Indanocine
anti-cancer

Caragasinin A
anti-oxidant

Figure 3-1. Biologically relevant carbocyclic targets

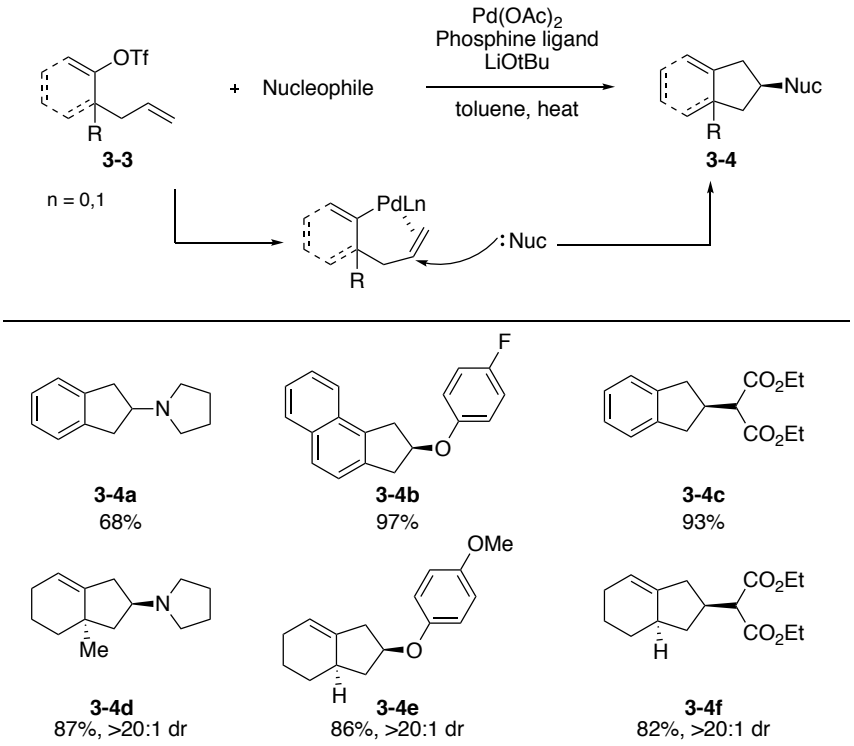
The ability to synthesize carbocycles is also a fundamentally important strategy in organic synthesis. Constructing carbocycles in one step is nontrivial, and methods have been developed in this area.[4] The Diels-Alder reaction synthesizes a cyclohexene in one step, but forms two bonds within the six-membered ring **3-1** (Scheme 3-1).[5] Constructing cyclopentanes and differently-substituted cyclohexanes is still a challenge. This chapter describes our efforts toward the synthesis of substituted carbocycles via palladium-catalyzed alkene dialkylation reactions to synthesize carbocycles similar to **3-2**.



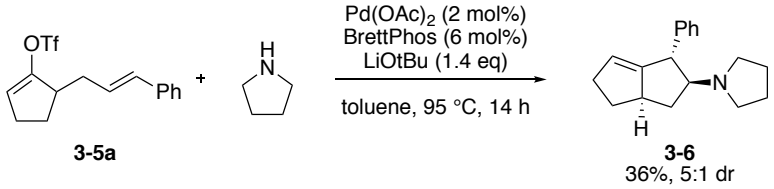
Scheme 3-1. Comparison of cyclohexanes and cyclohexenes synthesized via Diels-Alder vs alkene difunctionalization reactions

In recent years, the Wolfe group has been interested in developing palladium-catalyzed alkene difunctionalization reactions to synthesize carbocycles. We have developed methods to synthesize amino and alkoxy substituted indane derivatives and substituted carbocycles using external amine[6] and alcohol[7] nucleophiles, respectively. A few examples of this are depicted in Table 3-1. A variety of alkenyl and aryl triflates (**3-3**) are used and many amine and alcohol nucleophiles are successful. These are synthesized in good to excellent yield and in excellent diastereoselectivity with respect to the formation of **3-4**. We have also developed a strategy for using carbon-based nucleophiles to give alkene dialkylation products (**3-4c** and **3-4f**).[8] This has been a valuable tool to diastereoselectively synthesize substituted carbocycles efficiently and effectively.

Table 3-1. Examples of palladium-catalyzed alkene carbofunctionalization of terminal alkenes

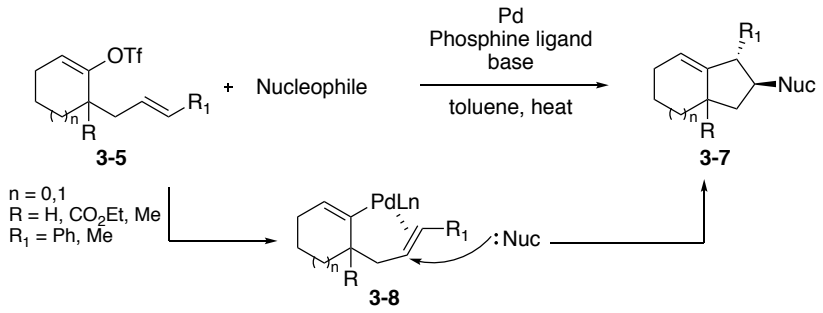


Although we have previously shown the synthesis of substituted carbocycles using terminal alkenes,[6,7] prior efforts to use substrates bearing internal alkenes are limited. We published a proof of concept reaction in our paper describing our work synthesizing amine-substituted carbocycles, and this reaction produced a moderate yield of **3-6** (Scheme 3-2).[6b]



Scheme 3-2. Synthesis of amine-substituted carbocycle using an internal alkene

This project is meant to expand our substrate scope of our alkene difunctionalization to include internal alkenes, which will increase the complexity of the molecules we can synthesize as it increases the amount of stereocenters created during the reaction. We began with substrates similar to **3-5**, yielding products **3-7**, which are created via the intermediate **3-8** (Scheme 3-3).



Scheme 3-3. Palladium-catalyzed internal alkene difunctionalization reactions

A detailed in-depth mechanism by which this transformation occurs on **3-5a** is shown in Figure 3-2. After oxidative addition (step **I**) of **3-5a**, which yields the cationic palladium complex **3-9**, the palladium coordinates to the tethered alkene (step **II**) yielding complex **3-10**. Subsequent deprotonation and addition of the nucleophile (step **III**) gives palladacycle **3-11**, and reductive elimination (step **IV**) then yields the desired carbocycle **3-7a**.

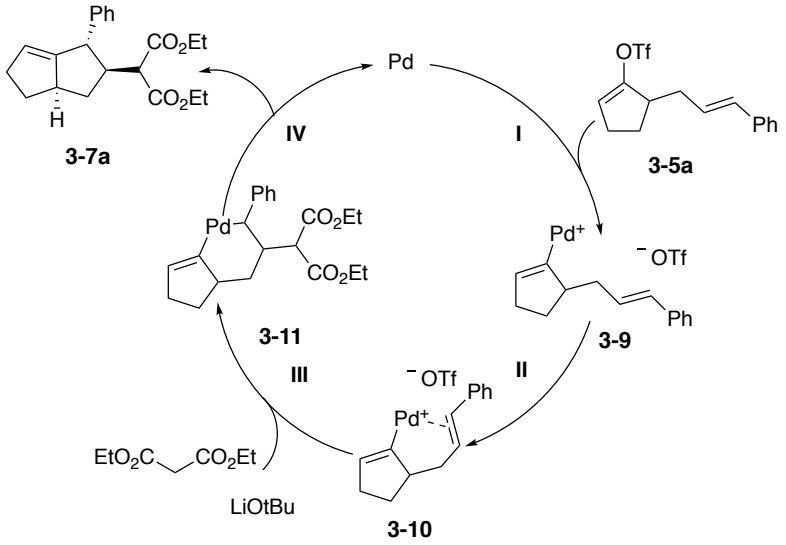
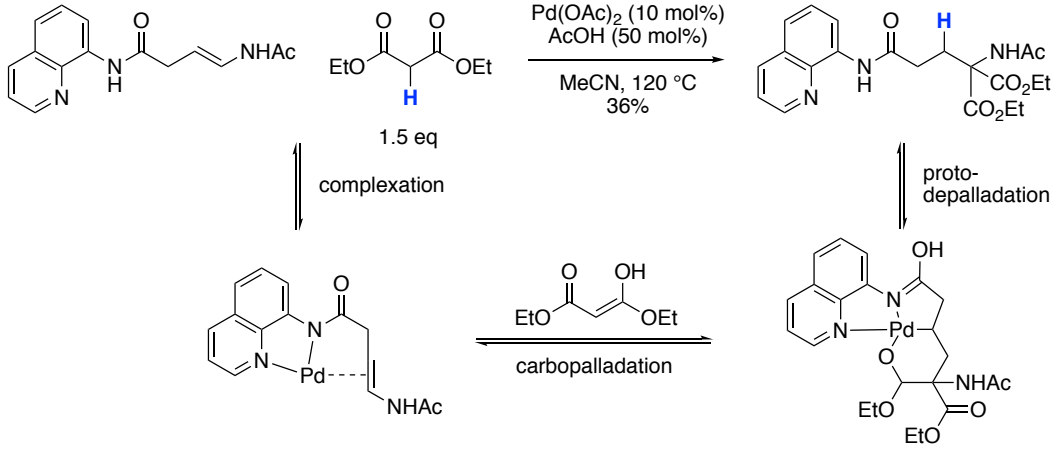


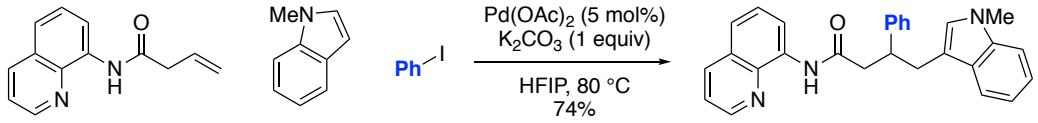
Figure 3-2. Palladium-catalyzed alkene difunctionalization mechanism

Our use of carbon-based nucleophiles utilizes basic conditions to create enolate nucleophiles that attack our palladacycle. Engle recently published the use of acetic acid in a palladium-catalyzed hydrocarbofunctionalization of alkenes with directing groups (Scheme 3-4).[9] They were able to facilitate hydrocarbofunctionalization of alkenes with different carbon acids with terminal alkenes and a few internal alkenes (Scheme 3-4). They have also accomplished a base-mediated dicarbofunctionalization

on the same substrate (Scheme 3-5).[10] In this case their nucleophiles were primarily indoles and a few carbon acids, and their electrophiles were either aryl or alkenyl iodides.



Scheme 3-4. Engle's acid-promoted palladium-catalyzed difunctionalization of alkenes

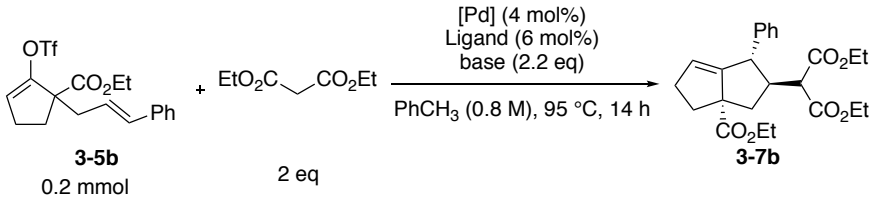


Scheme 3-5. Engle's base-promoted palladium-catalyzed difunctionalization of alkenes

3.2 Synthetic Approach and Reaction Optimization

To develop our internal alkene difunctionalization strategy, we looked at the previously optimized conditions used on terminal alkenes first (palladium acetate, BrettPhos, lithium *tert*-butoxide), and then started to re-optimize by changing the Buchwald ligand. Generally, on parent substrate **3-5b**, electron-rich Buchwald ligands worked better than other ligands, and palladium acetylacetonate worked better than palladium acetate. The most encouraging results are summarized in Table 3-2. The combination of SPhos and palladium acetylacetonate with lithium *tert*-butoxide, in 0.8 M of toluene yielded the best results on the reaction with **3-5b** and diethyl malonate.

Table 3-2. Optimization studies



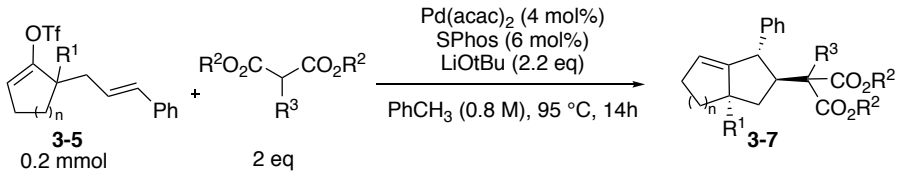
entry	Pd	ligand	yield %[b] (dr)[c]
1	$Pd(OAc)_2$	BrettPhos	22 (>20:1)[d]
2	$Pd(OAc)_2$	CPhos	47 (>20:1)
3	$Pd(OAc)_2$	RuPhos	48 (>20:1)
4	$Pd(OAc)_2$	SPhos	45 (>20:1)
5	$Pd(OAc)_2$	DPEPhos	65 (>20:1)[e]
6	$Pd(acac)_2$	DPEPhos	47 (>20:1)[f]
7	$Pd(acac)_2$	SPhos	79 (>20:1)

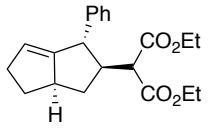
[a]Conditions: 1.0 equiv **3-5b**, 2.0 equiv diethyl malonate, 2 mol% Pd, 4 mol % ligand, 2.2 equiv LiOtBu, 0.8 M toluene, 95 °C, 14 h. [b]Isolated yield (average of two or more experiments). [c]Diastereomeric ratios were determined by ^{1}H NMR analysis. [d]The result of a single experiment. [e]LiHMDS was used as a base instead of LiOtBu. [f]The yield in this case was determined by ^{1}H NMR analysis using phenanthrene as an internal standard.

3.3 Reaction Scope

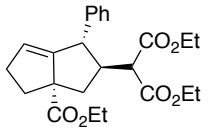
With reaction conditions in hand, we then explored the scope of the reactions with alkenyl triflates with internal alkenes is summarized in Table 3-3. We varied the size of the ring on the alkenyl triflate to include 5- and 6-membered ring alkenyl triflates. Reactions with 6-membered ring triflates (**3-7e-3-7k/l**) generally worked the same or better than the 5-membered ring triflates (**3-7a-3-7d**), likely due to less steric strain in the transition state.

Table 3-3. Scope of alkenyl triflate reactions

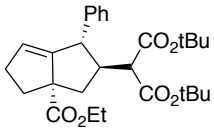




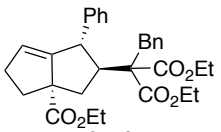
3-7a
21%, >20:1 dr



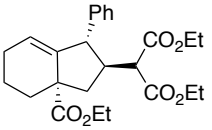
3-7b
79%, >20:1 dr



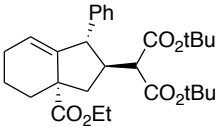
3-7c
55%, >20:1 dr



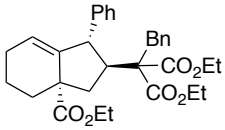
3-7d
42%[a], >20:1 dr



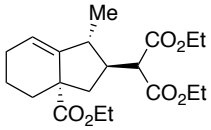
3-7e
62%, >20:1 dr



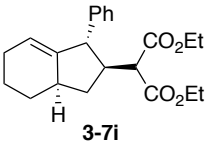
3-7f
53%, >20:1 dr



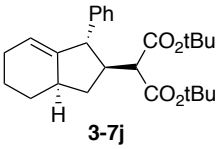
3-7g
45%[a], >20:1 dr



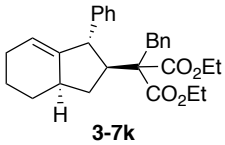
3-7h
43%, >20:1 dr



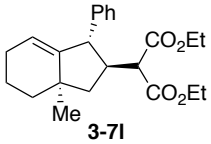
3-7i
71%, >20:1 dr



3-7j
58%, >20:1 dr



3-7k
40%[a], >20:1 dr



3-7l
55%, >20:1 dr

[a] = reactions were run at 110 °C

The ester substituent appeared to be important, particularly with the cyclopentane substrate, as reactions with a hydrogen there instead did not work as well (**3-7a**). This did not hold true with the cyclohexane substrate, as those substrates containing the hydrogen worked as well, or better than, the ester-substituted substrate (**3-7i** & **3-7j**). When there was a methyl substituent on the cyclohexane substrate (**3-7l**), the reactions worked similarly well to the hydrogen- and ester-containing substituents.

We varied the substituent on the end of the alkene to include a cinnamyl- and crotyl-based substrate, and cinnamyl was more successful. Crotyl based substrates only worked with the cyclohexenyl triflate (**3-8h**), as the other substrates (with ester and no ester) were unsuccessful except with this example. With respect to the mass balance in these reactions, reduced triflate **3-12** was sometimes observed in less than 10% in the crude NMR. Other than **3-12**, no other side products or starting material were observed in successful reactions, and the ketone **3-13b** was not observed.

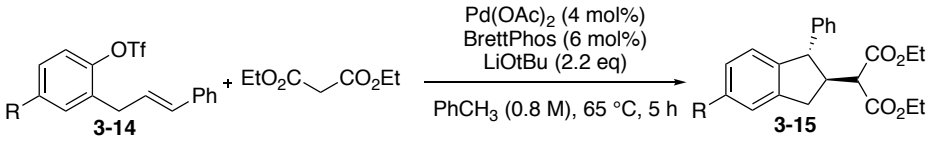
3-12 **3-13b**

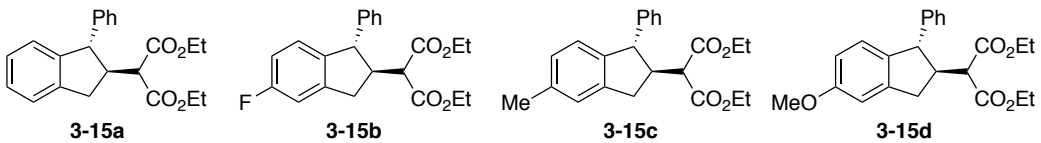
Figure 3-3. Side products from reactions with alkenyl triflates

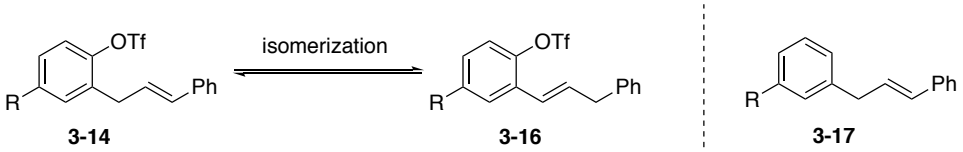
We found that benzyl diethylmalonate required increased reaction temperature, as triflate starting material (**3-5**) was observed at normal conditions (**3-7d**, **3-7g**, **3-7k**). Other enolate nucleophiles such as acetophenone, Meldrum's acid, acetoacetates, acetates, and malononitrile were also attempted, but unfortunately those yielded no product. We varied the nucleophile to include amines and alcohols, and were disappointed to find that benzylamine, pyrrolidine, phenol, and *para*-methoxyphenol were inconsistent in product production or unreactive in this system.

The use of aryl triflates (**3-15**) was pursued to access indane derivatives (Table 3-4). The aryl triflates presented challenges not seen with the alkenyl triflates. We saw isomerization of the internal alkene, likely due to the combination of conjugation with the phenyl group and the possibility of conjugation with the aromatic ring (Scheme 3-6). These reactions were run for less time and at a lower temperature than the alkenyl triflates to decrease the chance of the formation of the isomerization side product **3-16**. We did not see any of reduced triflate similar to what we saw with the alkenyl trilfates (**3-17**). We found that palladium acetate and BrettPhos was a better catalyst system for the aryl triflates, which is consistent with previous results.[5]

Table 3-4. Scope of aryl triflate reactions







Scheme 3-6. Isomerization of aryl triflate **3-14**

3.4 Stereochemistry

The origin of the stereochemistry of the formation of **3-7i**, and the reaction in general is likely due to the chair-like transition state shown in intermediate **3-18** (Figure 3-3). Consistent with our other studies in this area with other substrates, the substituents are aligned to decrease the 1,3-diaxial interactions of the chair. Both hydrogens of the alkene are arranged so they are in the axial position in the chair in **3-18**, instead of the other substituents, as well as the hydrogen in the cyclohexane ring. This results in a lower overall energy of the intermediate, and our final diastereomer that forms almost exclusively.

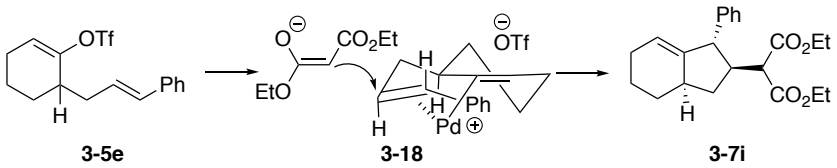
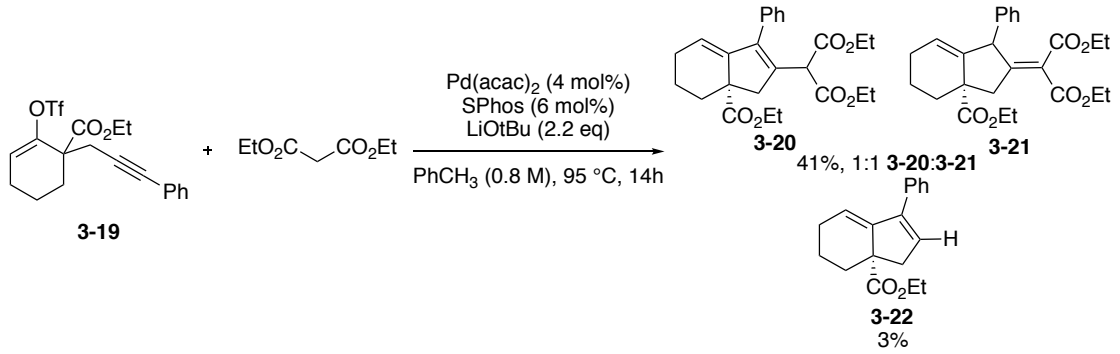


Figure 3-4. Origin of stereochemistry for the formation of **3-7i**

3.5 Alkynyl Substrates

In addition to internal alkenes, internal alkynes have been briefly examined in these reactions. When alkynyl substrate **3-19** is treated with the alkenyl triflate conditions, they produce a product that includes an alkene in the 5-membered ring that would be difficult to install otherwise (Scheme 3-7). An REU student, Chu Thet Ywe, assisted work on this project and the preliminary results were interesting. In the reaction of **3-19** with diethyl malonate at least three products were formed, some expected: **3-20** and **3-21**, and one unexpected: **3-22**. The formation and isolation of **3-22** is a particularly interesting result because it can formally be viewed as a 5-endo[11] reductive Heck reaction, which occurs in the absence of an obvious reducing agent. Further studies will also focus on how to access **3-22** intentionally and if this can be optimized. Future studies will be directed towards examining and optimizing the reactivity of **3-19** and **3-23** to form **3-20** and **3-24**. Aryl triflate **3-23** will hopefully be an easier substrate to

prepare (Scheme 3-8). The nucleophile scope will include a variety of malonates as well as amines and alcohols, because those nucleophiles have not been tried with an alkynyl substrate.



Scheme 3-7. Palladium-catalyzed alkyne difunctionalization on alkenyl triflate **3-19**

Scheme 3-8. Palladium-catalyzed alkyne difunctionalization on aryl triflate **3-23**

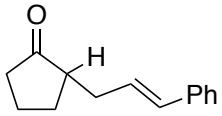
3.6. Conclusions

This chapter described efforts toward the synthesis of carbocycles via palladium-catalyzed alkene dialkylation. The products were synthesized in moderate to good yields, with excellent diastereoselectivity. Despite the relatively limited scope, the products are worthwhile and formed in their diastereomers exclusively. The preliminary results on the alkynyl substrates are encouraging, and further studies will be conducted to optimize these conditions.

3.7 Experimental

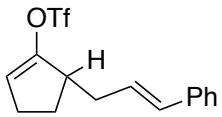
General: All reactions were carried out under nitrogen atmosphere in flame- or oven-dried glassware. All catalysts and reagents were obtained from commercial sources and were used as obtained unless otherwise noted.[12] N-(2-pyridyl)triflamide was synthesized via previously published methods.[13] Dichloromethane, toluene, and tetrahydrofuran were purified using a GlassContour solvent purification system. All substrates were stored at 0 °C freezer under nitrogen. 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 supporting information describe the result of a single experiment, whereas yields reported in Tables 3-2 and 3-3 are averages of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 3-2 and 3-3.

Experimental Procedures and Compound Characterization Data for Substrates

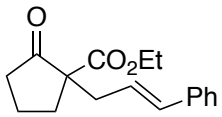


2-Cinnamylcyclopentan-1-one (3-13a). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with palladium allyl chloride dimer (0.146 g, 0.4 mmol, 0.02 equiv), dppf (0.665 g, 1.2 mmol, 0.06 mmol) and methanol (80 mL). The mixture was stirred at rt for 60 min. The orange reaction mixture was charged with cinnamyl alcohol (2.8 mL, 22 mmol, 1.1 equiv), and stirred for 30 min. Cyclopentanone (2.1 mL, 20 mmol, 1 equiv) and pyrrolidine (0.33 mL, 4 mmol, 0.2 mmol) were added then stirred at 45 °C for 16 h. The reaction was quenched with cold saturated aqueous ammonium chloride (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford yellow oil that was purified via column chromatography (2% -> 5% ethyl acetate in hexanes) to yield 3.379 g (83%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.39 – 7.13 (m, 5H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.24 – 6.08 (m, 1H),

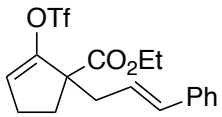
2.65 (d, *J* = 10.0 Hz, 1H), 2.41 – 2.16 (m, 4H), 2.11 (d, *J* = 8.8 Hz, 1H), 2.01 (s, 1H), 1.81 (d, *J* = 20.3 Hz, 1H), 1.63 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 220.4, 137.4, 131.8, 128.5, 127.6, 127.1, 126.0, 49.0, 38.2, 33.1, 29.0, 20.7.IR (film) 3024.8, 2960.7, 2876.1, 1732.7, 1597.2, 1493.6, 1449.2 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H]+ calcd for $C_{14}H_{16}O$ 201.1280; found 201.1274.



5-Cinnamylcyclopent-1-en-1-yl trifluoromethanesulfonate (3-5a). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with THF (20 mL) and diisopropylamine (1.05 mL, 7.5 mmol, 1.5 equiv) was added. The mixture was cooled to 0 °C and *n*-BuLi (2.5 M in hexanes, 3.0 mL, 7.5 mmol, 1.5 equiv) was added dropwise and stirred for 30 min. The mixture was cooled to -78 °C and 2-cinnamylcyclopentan-1-one (**3-13a**, 1.0 g, 5.0 mmol, 1 equiv) in THF (20 mL) were added dropwise over the course of 70 min. The reaction mixture and stirred for 2 h at -78 °C, then N-(2-pyridyl)triflamide (2.61 g, 7.29 mmol, 1.2 equiv) in THF (10 mL) was added and the reaction was warmed to -41 °C then the reaction stirred at rt for 2 h. The reaction was quenched with water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford yellow oil that was purified via column chromatography (0% -> 2% ethyl acetate in hexanes) to yield 0.8675 g (52%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.35 (d, *J* = 18.6 Hz, 4H), 7.26 (s, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.18 (d, *J* = 15.7 Hz, 1H), 5.71 (s, 1H), 3.04 (s, 1H), 2.57 (d, *J* = 19.8 Hz, 1H), 2.35 (d, *J* = 39.0 Hz, 3H), 2.20 (s, 1H), 1.80 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 151.3, 137.3, 132.6, 128.5, 127.2, 126.3, 126.1, 117.4, 43.0, 35.7, 26.7, 26.6. IR (film) 3027.9, 2927.8, 1656.6, 1495.7, 1418.5 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H]+ calcd for $C_{15}H_{15}F_3O_3S$ 333.0772; found 333.0767.

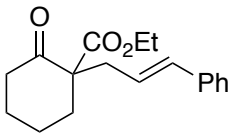


Ethyl 1-cinnamyl-2-oxocyclopentane-1-carboxylate (3-13b). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with sodium hydride (60% in mineral oil, 0.534 g, 13.35 mmol, 0.89 equiv) and THF (6 mL). The mixture was cooled to 0 °C and ethyl-2-oxocyclopentanecarboxylate (1.9 mL, 15 mmol, 1 equiv) in THF (10 mL) as added dropwise over the course of 90 min. The reaction mixture was warmed to rt and stirred for 90 min, then cinnamyl bromide (2.6 mL, 17.25 mmol, 1.15 equiv) in THF (5 mL) was added then stirred at rt for 16 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford yellow oil that was purified via column chromatography (10% ethyl acetate in hexanes) to yield 1.84 g (45%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.30 (d, *J* = 29.8 Hz, 4H), 7.21 (d, *J* = 14.2 Hz, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.16 – 6.01 (m, 1H), 4.25 – 4.10 (m, 2H), 2.89 – 2.73 (m, 1H), 2.59 – 2.37 (m, 3H), 2.31 – 2.16 (m, 1H), 2.04 (d, *J* = 14.0 Hz, 2H), 1.90 (d, *J* = 17.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 214.6, 170.9, 137.0, 134.1, 128.5, 127.4, 126.2, 124.5, 77.3, 77.1, 76.8, 61.5, 38.1, 37.0, 32.3, 19.6, 14.1. IR (film) 2978.0, 1747.5, 1719.9, 1448.4 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H]+ calcd for $C_{17}H_{20}O_3$ 272.1413; found 273.1485.

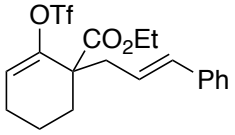


Ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (3-5b). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with THF (10 mL) and diisopropylamine (1.0 mL, 7.29 mmol, 1.7 equiv) was added. The mixture was cooled to 0 °C and n-BuLi (2.5 M in hexanes, 2.9 mL, 7.29 mmol, 1.7 equiv) was added dropwise and stirred for 30 min. The mixture was cooled to -78 °C and ethyl 1-cinnamyl-2-oxocyclopentane-1-carboxylate (**3-13b**, 1.17 g, 4.29 mmol, 1 equiv) in THF (10 mL) were added dropwise over the course of 90 min. The reaction mixture was stirred at -78 °C for 2.5 h, then N-(2-pyridyl)triflamide (2.61 g, 7.29 mmol, 1.7 equiv) in THF (5 mL) was added then stirred at rt for 16 h. The reaction was quenched with water (20 mL). The layers were separated and the aqueous layer

was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford yellow oil that was purified via column chromatography (2% -> 5% ethyl acetate in hexanes) to yield 1.18 g (68%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.42 – 7.14 (m, 5H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.14 – 6.00 (m, 1H), 5.80 (s, 1H), 4.32 – 4.11 (m, 2H), 2.78 (d, *J* = 8.0 Hz, 2H), 2.63 (d, *J* = 14.1 Hz, 1H), 2.48 (d, *J* = 9.3 Hz, 2H), 2.35 (d, *J* = 5.5 Hz, 1H), 2.15 – 1.93 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 172.5, 147.9, 137.0, 134.5, 128.5, 127.5, 126.2, 123.6, 118.3, 77.2, 77.0, 76.7, 61.6, 57.6, 38.0, 31.2, 26.2, 14.0. IR (film) 2954.6, 1728.6, 1602.5, 1422.8 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H]+ calcd for $C_{18}H_{19}F_3O_5S$ 405.0984; found 405.0978.

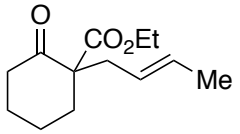


Ethyl 1-cinnamyl-2-oxocyclohexane-1-carboxylate (3-13c). The title compound was synthesized via a similar procedure to ethyl 1-cinnamyl-2-oxocyclopentane-1-carboxylate (**3-13b**), except using ethyl-2-oxocyclohexanecarboxylate (3.2 mL, 20 mmol, 1 equiv), cinnamyl bromide (3.4 mL, 23.0 mmol, 1.15 equiv), and sodium hydride (0.712 g, 17.8 mmol, 0.89 equiv) to yield 3.58 g (63%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.39 – 7.12 (m, 5H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.17 (t, *J* = 15.4 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.74 (d, *J* = 20.1 Hz, 1H), 2.49 (d, *J* = 26.9 Hz, 3H), 2.00 (s, 1H), 1.81 – 1.57 (m, 3H), 1.57 – 1.49 (m, 1H), 1.45 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 207.6, 171.5, 137.2, 133.2, 128.4, 127.2, 126.1, 125.1, 61.3, 41.2, 38.6, 36.1, 27.9, 27.5, 22.5, 14.2. IR (film) 2937.5, 2867.0, 1709.8, 1597.9, 1495.7, 1449.0 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H]+ calcd for $C_{18}H_{22}O_3$ 287.1647; found 287.1642.

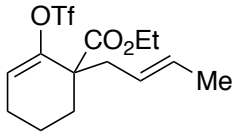


Ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (3-5c). The title compound was synthesized via a similar procedure to ethyl 1-cinnamyl-2-oxocyclopentane-1-carboxylate (**3-5b**), except using ethyl 1-cinnamyl-2-

oxocyclohexane-1-carboxylate (**3-13c**) (1.13 g, 4.0 mmol, 1 equiv), LDA (6.73 mmol, 1.7 equiv), and N-(2-pyridyl)triflamide (2.409 g, 6.73 mmol, 1.7 equiv) to yield 1.06 g (64%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.46 – 7.12 (m, 5H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.12 (t, *J* = 15.4 Hz, 1H), 5.92 (s, 1H), 4.36 – 4.11 (m, 2H), 2.82 – 2.64 (m, 2H), 2.38 – 2.10 (m, 3H), 1.82 – 1.53 (m, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 172.6, 148.1, 137.0, 134.5, 128.5, 127.5, 126.2, 123.8, 120.3, 61.8, 50.5, 38.7, 32.3, 24.4, 18.6, 14.0. IR (film) 2940.6, 1730.3, 1677.1, 1495.3, 1413.4 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H]+ calcd for $C_{19}H_{21}F_3O_5S$ 419.1140; found 419.1135.

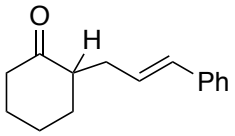


Ethyl 1-cinnamyl-2-oxocyclohexane-1-carboxylate (3-13d). The title compound was synthesized via a similar procedure to ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**3-13d**), except using ethyl-2-oxocyclohexanecarboxylate (3.4 mL, 21.1 mmol, 1 equiv), crotyl bromide (2.5 mL, 24.3 mmol, 1.15 equiv), and sodium hydride (0.75 g, 18.8 mmol, 0.89 equiv) to yield 2.26 g (48%) of a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 5.54 – 5.22 (m, 2H), 4.26 – 4.04 (m, 2H), 2.45 (dd, *J* = 51.3, 14.6 Hz, 4H), 2.22 (d, *J* = 21.4 Hz, 1H), 1.96 (s, 1H), 1.81 – 1.51 (m, 6H), 1.42 (d, *J* = 16.2 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 207.7, 171.6, 128.8, 125.6, 61.1, 41.1, 38.0, 35.7, 27.5, 22.5, 22.4, 17.9, 14.1. IR (film) 2938.6, 2864.7, 1710.4, 1438.04 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H^{+}]+ calcd for $C_{13}H_{20}O_3$ 225.1491; found 225.1485.

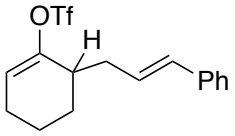


(*E*) Ethyl-1-(but-2-en-1-yl)-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (3-5d). The title compound was synthesized via a similar procedure to ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**3-5c**), except using ethyl 1-cinnamyl-2-oxocyclohexane-1-carboxylate (**3-13d**) (0.98 g, 4.46 mmol, 1 equiv), LDA (7.6 mmol, 1.7 equiv), and N-(2-pyridyl)triflamide (2.66 g, 7.6 mmol, 1.7 equiv) to yield 0.623 g (40%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d

5.86 (s, 1H), 5.57 – 5.45 (m, 1H), 5.28 (d, *J* = 15.0 Hz, 1H), 4.15 (d, *J* = 16.3 Hz, 2H), 2.47 (s, 2H), 2.29 – 2.08 (m, 3H), 1.63 (d, *J* = 15.5 Hz, 6H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 172.8, 148.2, 130.2, 124.5, 120.0, 61.5, 50.3, 38.3, 32.1, 32.0, 31.9, 24.4, 18.7, 13.9. IR (film) 2941.1, 1731.2, 1677.4, 1414.4 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{14}H_{19}F_3O_5S$ 357.0984; found 357.0978.

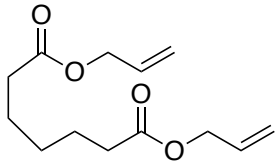


2-Cinnamylcyclohexan-1-one (3-13e). The title compound was synthesized via a similar procedure to 2-cinnamylcyclopentan-1-one (**3-13a**), except using cyclohexanone (2.1 mL, 20 mmol, 1 equiv), cinnamyl alcohol (2.8 mL, 2.2 mmol, 1.1 equiv), palladium allyl chloride dimer (0.146 g, 0.4 mmol, 0.02 equiv), dppf (0.665 g, 1.2 mmol, 0.06 mmol) and pyrrolidine (0.33 mL, 4.0 mmol, 0.2 equiv) to yield 2.74 g (63%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.44 – 7.23 (m, 4H), 7.19 (s, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.20 (t, *J* = 15.2 Hz, 1H), 2.73 – 2.60 (m, 1H), 2.43 (d, *J* = 15.8 Hz, 2H), 2.32 (d, *J* = 19.2 Hz, 1H), 2.25 – 2.00 (m, 3H), 1.88 (s, 1H), 1.67 (s, 2H), 1.41 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 212.4, 137.5, 131.6, 128.5, 128.4, 128.3, 127.0, 126.0, 50.7, 42.1, 33.6, 27.9, 25.0. IR (film) 3024.6, 2931.0, 2858.9, 1705.24, 1597.9, 1494.4, 1447.1 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H]+ calcd for $C_{15}H_{18}O$ 215.1436; found 215.1430.

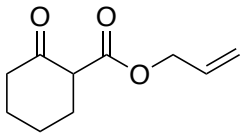


6-Cinnamylcyclohex-1-en-1-yl trifluoromethanesulfonate (3-5e). The title compound was synthesized via a similar procedure to 5-cinnamylcyclopent-1-en-1-yl trifluoromethanesulfonate (**3-5a**), except using 2-cinnamylcyclohexan-1-one (**3-13e**) (0.544 g, 2.54 mmol, 1 equiv), LDA (3.82 mmol, 1.5 equiv), and N-(2-pyridyl)triflamide (1.09 g, 3.05 mmol, 1.2 equiv) to yield 0.660 g (75%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.43 – 7.13 (m, 5H), 6.45 (d, *J* = 15.6 Hz, 1H), 6.23 – 6.04 (m, 1H), 5.83 (s, 1H), 2.62 (d, *J* = 10.1 Hz, 2H), 2.40 – 2.26 (m, 1H), 2.18 (s, 2H), 1.88 (s, 1H), 1.62 (dd, *J* = 49.8, 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 151.7, 137.3, 132.7, 128.5,

127.2, 126.7, 126.1, 119.5, 37.6, 35.1, 27.8, 24.3, 19.0. IR (film) 3027.0, 2934.5, 1680.2, 1494.3, 1412.5 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + NH_4^+]+ calcd for $C_{16}H_{17}F_3O_3S$ 364.1194; found 364.1189.

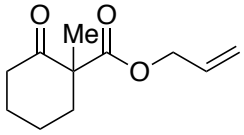


Diallyl heptanedioate (3-25). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with pimelic acid (6.05 g, 37.5 mmol, 1 equiv), toluene (80 mL, 2.0 M). Allyl alcohol (7.6 mL, 112.5 mmol, 3 equiv) and pTsOH□H_2O (0.285 g, 1.5 mmol, 0.04 equiv) were added, and the septum was replaced with a Dean-Stark apparatus and condenser. The reaction was heated to 120 °C and stirred for 16 h. The reaction was cooled to rt, and the mixture was quenched with saturated aqueous sodium bicarbonate (20 mL). The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 20 mL), brine (20 mL) and dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 7.505 g (89%) colorless oil that was used without purification. Spectral data matches previously reported data.[14]

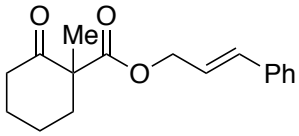


Allyl 2-oxocyclohexane-1-carboxylate (3-26). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with allyl alcohol (0.06 mL, 0.88 mmol, 0.1 equiv), sodium hydride (0.704 g, 17.6 mmol, 2.0 equiv), charged with toluene (30 mL). The suspension stirred at rt and diallyl heptanedioate **(3-25**) (2.00 g, 8.8 mmol, 1 equiv) in 10 mL toluene was added. The reaction was heated to 100 °C and stirred for 16 h. The reaction was cooled to rt, and the mixture was quenched with saturated aqueous ammonium chloride (20 mL) and HCl (1 M, 20 mL). The layers were separated and aqueous layer was extracted with diethyl ether, and the organic layer was washed with brine (20 mL) and dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford a colorless oil, which was purified via flash column chromatography (5% ethyl

acetate in hexanes) to yield 1.404 g (88%) colorless oil. Spectral data matches previously reported data.[14]

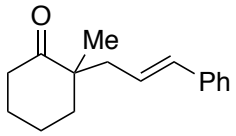


Allyl 1-methyl-2-oxocyclohexane-1-carboxylate (3-27). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with allyl 2-oxocyclohexane-1-carboxylate (**3-26**) (1.069 g, 5.9 mmol, 1.0 equiv), THF (20 mL, 0.3 M). The mixture was cooled to 0 °C, and charged with sodium hydride (60% in mineral oil, 0.26 g, 6.5 mmol, 1.1 equiv) and the mixture stirred for 30 min. Methyl iodide (0.4 mL, 6.5 mmol, 1.1 equiv) was added, and the reaction stirred for 16 h as it gradually warmed to rt. The reaction was quenched with water via syringe, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the organic layer was washed with brine (20 mL) and dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford a colorless oil, which was purified via flash column chromatography (5% ethyl acetate in hexanes) to yield 0.9275 g (80%) colorless oil. Spectral data matches previously reported data.[14]

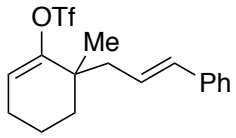


Cinnamyl 1-methyl-2-oxocyclohexane-1-carboxylate (3-28). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with allyl 1-methyl-2-oxocyclohexane-1-carboxylate (**3-27**) (1.169 g, 5.97 mmol, 1 equiv), Grubbs catalyst II (0.203 g, 0.239 mmol, 0.04 equiv), copper iodide (68.1 mg, 0.358 mmol, 0.06 equiv). The flask was evacuated and diethyl ether (30 mL, 0.2 M) and styrene (2.05 mL, 17.9 mmol, 3.0 equiv) were at rt. The septum was replaced with a condenser and the reaction was stirred at 40 °C for 15 h. The reaction was cooled to rt, and concentrated *in vacuo* to yield a purple crude material, which was purified via column chromatography (5% ethyl acetate in hexanes) to yield 0.904 g (63%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.48 – 7.17 (m, 5H), 6.72 – 6.58 (m, 1H), 6.28 (ddt, *J* = 22.4, 15.9, 6.5 Hz, 1H), 4.87 – 4.72 (m, 2H), 2.59 – 2.38 (m, 3H), 2.03 (dtdd, *J* = 19.8, 12.1, 5.9, 3.1

Hz, 1H), 1.83 (dddd, *J* = 16.0, 10.2, 4.8, 3.2 Hz, 1H), 1.76 – 1.58 (m, 2H), 1.58 – 1.41 (m, 2H), 1.32 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 208.2, 172.9, 136.0, 134.8, 134.0, 128.6, 126.7, 123.2, 122.4, 65.8, 65.7, 57.2, 41.4, 40.7, 38.2, 36.2, 35.3, 27.5, 22.6, 21.3. IR (film) 2935.8, 2867.1, 1709.7 (2 peaks), 1495.5, 1449.5 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + Na$^+$]+ calcd for $C_{17}H_{20}O_3Na$ 295.1305; found 295.1305.

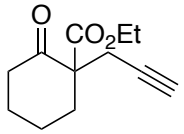


2-Cinnamyl-2-methylcyclohexan-1-one (3-13f). A flame-dried Shlenk flask equipped with a stir bar was cooled under a stream of nitrogen and charged with Palladium acetate (27.8 mg g, 0.124 mmol, 0.10 equiv), triphenylphosphine (0.812 g, 3.10 mmol, 2.5 equiv). The flask was evacuated and tetrahydrofuran (25 mL, 0.1 M) and cinnamyl 1-methyl-2-oxocyclohexane-1-carboxylate **(3-27)** (0.337 g, 1.24 mmol, 1.0 equiv) were at rt. The septum was replaced with a condenser and the reaction was stirred at 30 °C for 15 h. The reaction was cooled to rt, diluted with diethyl ether and filtered through a pad of silica and concentrated *in vacuo* to yield a yellow oil, which was purified via column chromatography (2% -> 5% ethyl acetate in hexanes) to yield 33.9 mg (12%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.36 – 7.25 (m, 5H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.18 – 6.06 (m, 1H), 2.47 (d, *J* = 15.0 Hz, 4H), 1.91 – 1.68 (m, 4H), 1.68 – 1.56 (m, 1H), 1.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 215.4, 137.4, 133.6, 133.0, 128.5, 128.4, 127.1, 126.1, 125.7, 48.9, 38.8, 27.4, 22.9, 21.1. IR (film) 3026.3, 2931.9, 2863.5, 1704.1, 1598.2, 1495.1 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{16}H_{21}O$ 229.1587; found 229.1586.

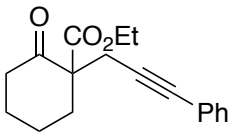


6-Cinnamyl-6-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (3-5f). The title compound was synthesized via a similar procedure to ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**3-5c**), except using 2-cinnamyl-2-methylcyclohexan-1-one (**3-13f**) (1.13 g, 4.0 mmol, 1 equiv), LDA (6.73 mmol, 1.7 equiv), and N-(2-pyridyl)triflamide (2.409 g, 6.73 mmol, 1.7 equiv) to yield

1.06 g (64%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.45 – 7.13 (m, 5H), 6.43 (d, *J* = 15.7 Hz, 1H), 6.21 – 6.05 (m, 1H), 5.76 (d, *J* = 4.1 Hz, 1H), 2.46 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.31 (ddd, *J* = 13.8, 8.1, 1.2 Hz, 1H), 2.17 (d, *J* = 5.7 Hz, 2H), 1.87 – 1.78 (m, 1H), 1.73 – 1.58 (m, 2H), 1.58 – 1.48 (m, 2H), 1.20 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 154.8, 137.3, 133.6, 128.5, 127.2, 126.1, 125.1, 117.3, 42.0, 38.7, 35.4, 24.7, 24.5, 18.2. IR (film) 3027.8, 2938.4, 1495.6, 1457.0, 1410.0 cm^{-1}. HRMS (Electron Ionization Impact TOF) m/z: [M]+ calcd for $C_{17}H_{19}F_3O_3S$ 360.1007; found 360.1024.

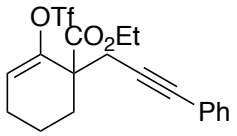


Ethyl 2-oxo-1-(prop-2-yn-1-yl)cyclohexane-1-carboxylate (3-29). A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with ethyl-2-oxocyclohexanecarboxylate (1.6 mL, 10 mmol, 1.0 equiv), acetone/tetrahydrofuran (0.4 M). Cesium carbonate (4.89 g, 15 mmol, 1.5 equiv) and propargyl bromide (80% wt in toluene, 2.3 mL, 20 mmol, 2.0 equiv) were added and the reaction stirred at rt for 15 h. The reaction mixture was filtered through a pad of celite, eluting with ethyl acetate. The filtrate was concentrated *in vacuo* to yield a colorless oil, which was purified via column chromatography (5% -> 10% ethyl acetate in hexanes) to yield 1.212 g (58%) colorless oil. Spectral data matches previously reported data.[15]

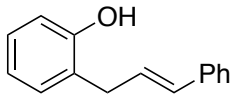


Ethyl 2-oxo-1-(3-phenylprop-2-yn-1-yl)cyclohexane-1-carboxylate (3-30). A flame-dried Shlenk flask equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd(PPh_3)_2Cl_2$ (0.151 g, 3.6 mmol, 0.09 equiv), copper iodide (82 mg, 0.432 mmol, 0.18 equiv), tetrahydrofuran (0.25 M). Triethylamine (0.50 mL, 3.6 mmol, 1.5 equiv), ethyl 2-oxo-1-(prop-2-yn-1-yl)cyclohexane-1-carboxylate (**3-29**) (0.5 g, 2.4 mmol, 1.0 equiv) and iodobenzene (toluene, 0.40 mL, 3.6 mmol, 1.5 equiv) were added and the reaction stirred at 40 °C for 14 h. The reaction mixture was filtered through a pad of celite, eluting with ethyl acetate. The filtrate was concentrated *in vacuo* to yield a orange oil, which was purified via column chromatography (5% -> 10% ethyl acetate in

hexanes) to yield 0.417 g (61%) colorless oil. Spectral data matches previously reported data.[15]

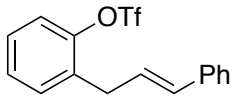


Ethyl 1-(3-phenylprop-2-yn-1-yl)-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (3-19). The title compound was synthesized via a similar procedure to ethyl 2-oxo-1-(3-phenylprop-2-yn-1-yl)cyclohexane-1-carboxylate (**3-5c**), except using ethyl 2-oxo-1-(3-phenylprop-2-yn-1-yl)cyclohexane-1-carboxylate (**3-30**) (0.42 g, 1.47 mmol, 1 equiv), LDA (2.50 mmol, 1.7 equiv), and N-(2-pyridyl)triflamide (0.895 g, 2.50 mmol, 1.7 equiv) to yield 0.135 g (22%) of a colorless oil. ^{1}H NMR (500 MHz, Benzene-d_6) d 7.41 (d, *J* = 7.9 Hz, 2H), 6.94 (s, 3H), 5.73 (s, 1H), 3.96 (d, *J* = 23.0 Hz, 2H), 2.99 – 2.73 (m, 2H), 2.16 (d, *J* = 18.4 Hz, 1H), 1.77 – 1.65 (m, 1H), 1.55 (s, 2H), 1.42 (s, 1H), 1.24 (s, 1H), 0.96 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Benzene-d_6) d 171.0, 147.2, 131.6, 128.2, 127.6, 127.4, 123.5, 120.7, 84.6, 84.0, 61.6, 50.1, 32.6, 26.4, 23.9, 18.4, 13.5. IR (film) 2939.3, 1733.3, 1680.7, 1598.7, 1491.3, 1443.6, 1415.2 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{19}H_{20}F_3O_5S$ 417.0978; found 417.0977.

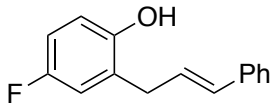


2-cinnamylphenol (3-31a). A flame-dried 2-neck flask equipped with a stir bar and a condenser was cooled under a stream of nitrogen and charged with phenol (2.0 g, 21.2 mmol, 1.0 equiv) and diethyl ether (22 mL, 0.1 M). Sodium hydride (60% in mineral oil, 1.7 g, 42.4 mmol, 2.0 equiv) was added, and the reaction stirred at rt for 30 min. Cinnamyl chloride was added and the reaction stirred at 37 °C for 6 h. The reaction was cooled to rt, and the mixture was transferred to an Erlenmeyer containing HCl (0.1 M, 75 mL). The mixture was stirred briefly and the layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a yellow oil that was purified via column chromatography (5% -> 10% ethyl acetate in hexanes) to yield 2.52 g (57%) of a yellow semisolid. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.28 (d, *J* = 18.1 Hz, 4H), 7.25 – 7.11 (m, 3H), 6.91 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H),

6.44 – 6.34 (m, 1H), 4.89 (s, 1H), 3.58 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 154.0, 131.5, 130.5, 128.5, 127.9, 127.3, 126.2, 121.0, 115.8, 34.1. IR (film) 3531.5, 3025.4, 1591.7, 1493.9, 14.53.4 cm^{-1}. HRMS (ESI- TOF) m/z: [M - H^+]+ calcd for $C_{15}H_{14}O$ 209.0966; found 209.0972.

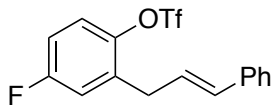


2-Cinnamylphenyl trifluoromethanesulfonate (3-14a). A flame-dried flask equipped with a stir bar and was cooled under a stream of nitrogen and charged with 2-cinnamylphenol (**3-31a**) (0.934 g, 4.45 mmol, 1.0 equiv) and dichloromethane (20 mL, 0.2 M). Pyridine (0.72 mL, 8.9 mmol, 2.0 equiv) was added, and the reaction was cooled to 0 °C. Trifluoromethanesulfonic anhydride (1.5 mL, 8.9 mmol, 2.0 equiv) was added, and ice bath was removed and the reaction stirred for 15 h as the reaction warmed to rt. The purple mixture was filtered through a pad of celite, eluting with ethyl acetate. The purple filtrate was concentrated *in vacuo* to yield a purple oil, which was purified via column chromatography to yield 1.18 g (78%) colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.46 – 7.13 (m, 9H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.35 – 6.22 (m, 1H), 3.65 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 147.9, 137.0, 133.1, 132.7, 131.4, 128.5, 128.2, 127.4, 126.2, 126.1, 121.4, 33.2. IR (film) 3029.2, 2922.6, 1595.3, 1578.6, 1487.4, 1418.4 cm^{-1}. HRMS (Electron Impact Ionization TOF) m/z: [M + H^+]+ calcd for $C_{16}H_{13}F_3O_3S$ 342.0538; found 342.0538.

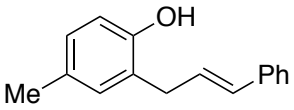


2-Cinnamyl-4-fluorophenol (3-31b). The title compound was synthesized via a similar procedure to 2-cinnamylphenol (**3-31a**), except using 4-fluorophenol (2.9 g, 17.86 mmol, 1.0 equiv), cinnamyl chloride (2.5 mL, 17.86 mmol, 1.0 equiv), and sodium hydride (1.428 g, 35.7 mmol, 2.0 equiv) to yield 2.617 g (64%) of a yellow solid. mp: 51-52 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.41 – 7.16 (m, 5H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.83 (d, *J* = 13.6 Hz, 1H), 6.75 (d, *J* = 13.4 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 4.78 (s, 1H), 3.54 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 158.1, 156.2, 149.9, 136.9, 132.0, 128.6, 127.4, 127.0, 126.2, 116.5, 114.0, 113.8, 34.0. IR (film)

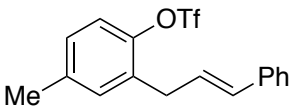
3411.7, 3026.4, 1619.3, 1598.1, 1494.3, 1437.5 cm^{-1}. HRMS (ESI- TOF) m/z: [M - H^+]+ calcd for $C_{15}H_{13}FO$ 227.0872; found 227.0878.



2-Cinnamyl-4-fluorophenyl trifluoromethanesulfonate (3-14b). The title compound was synthesized via a similar procedure to 2-cinnamylphenyl trifluoromethanesulfonate (**3-14b**), except using 2-cinnamyl-4-fluorophenol (**3-31b**) (0.79 g, 3.47 mmol, 1.0 equiv), Trifluoromethanesulfonic anhydride (1.16 mL, 6.94 mmol, 2.0 equiv), and pyridine (0.56 mL, 6.94 mmol, 2.0 equiv) to yield 0.8474 g (68%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.52 – 7.22 (m, 6H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.04 (s, 1H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.31 (d, *J* = 22.7 Hz, 1H), 3.69 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 162.6, 160.6, 143.5, 136.8, 135.9, 133.5, 127.7, 126.3, 125.1, 118.0, 117.8, 115.1, 114.9, 33.3. IR (film) 3010.5, 1592.3, 1485.4, 1420.0 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H^+]+ calcd for $C_{16}H_{12}F_4O_3S$ 361.0522; found 361.0516.

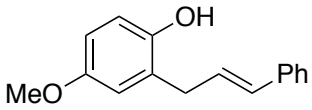


2-Cinnamyl-4-methylphenol (3-31c). The title compound was synthesized via a similar procedure to 2-cinnamylphenol (**3-31a**), except using 4-methylphenol (2.3 mL, 22.0 mmol, 1.0 equiv), cinnamyl chloride (3.0 mL, 22.0 mmol, 1.0 equiv), and sodium hydride (1.80 g, 44.0 mmol, 2.0 equiv) to yield 2.684 g (54%) of a yellow semisolid. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.44 – 7.14 (m, 5H), 6.96 (d, *J* = 20.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.39 (d, *J* = 28.9 Hz, 1H), 4.75 (s, 1H), 3.54 (d, *J* = 6.5 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 151.7, 137.1, 131.4, 131.0, 130.2, 128.2, 128.1, 127.3, 126.2, 115.6, 34.1, 20.5. IR (film) 3214.4, 2750.3, 1495.7, 1405.2, 1275.7 cm^{-1}. HRMS (Electron Impact Ionization TOF) m/z: [M + H^+]+ calcd for $C_{16}H_{16}O$ 224.1201; found 224.1201.

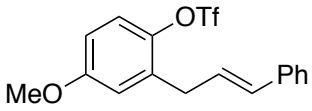


2-Cinnamyl-4-methylphenyl trifluoromethanesulfonate (3-14c). The title compound was synthesized via a similar procedure to 2-cinnamylphenyl trifluoromethanesulfonate

(**3-14a**), except using 2-cinnamyl-4-methylphenol (**3-31c**) (1.02 g, 4.46 mmol, 1.0 equiv), Trifluoromethanesulfonic anhydride (1.5 mL, 8.93 mmol, 2.0 equiv), and pyridine (0.72 mL, 8.93 mmol, 2.0 equiv) to yield 1.20 g (76%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.38 (d, *J* = 7.5 Hz, 2H), 7.32 (s, 2H), 7.24 (s, 1H), 7.16 (s, 2H), 7.11 (s, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.35 – 6.21 (m, 1H), 3.61 (d, *J* = 6.9 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 145.8, 138.5, 137.1, 132.6, 132.5, 131.9, 128.7, 128.5, 128.4, 127.4, 126.3, 121.1, 33.2, 20.9. IR (film) 3028.5, 2924.4, 1599.3, 1490.7, 1417.7 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + NH_4^+]+ calcd for $C_{17}H_{15}F_3O_3S$ 374.1038; found 374.1032.



2-Cinnamyl-4-methoxyphenol (3-31d). The title compound was synthesized via a similar procedure to 2-cinnamylphenol (**3-31a**), except using 4-methoxyphenol (1.9 g, 14.4 mmol, 1.0 equiv), cinnamyl chloride (2.0 mL, 14.4 mmol, 1.0 equiv), and sodium hydride (1.15 g, 28.8 mmol, 2.0 equiv) to yield 1.516 g (44%) of a orange solid. mp: 74-76 °C. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.46 – 7.10 (m, 5H), 6.83 – 6.61 (m, 3H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 4.59 (s, 1H), 3.76 (s, 3H), 3.54 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 153.8, 147.9, 137.0, 131.6, 128.6, 127.7, 126.8, 126.2, 116.5, 116.0, 112.6, 55.7, 34.3. IR (film) 3384.8, 3025.5, 2936.8, 2832.9, 1598.5, 1495.7, 1430.9 cm^{-1}. HRMS (ESI- TOF) m/z: [M - H^+]+ calcd for $C_{16}H_{16}O_2$ 239.1072; found 239.1078.

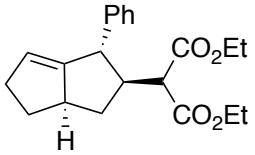


2-Cinnamyl-4-methoxyphenyl trifluoromethanesulfonate (3-14d). The title compound was synthesized via a similar procedure to 2-cinnamylphenyl trifluoromethanesulfonate (**3-14a**), except using 2-cinnamyl-4-methoxyphenol (**3-31d**) (1.0 g, 4.17 mmol, 1.0 equiv), Trifluoromethanesulfonic anhydride (1.4 mL, 8.33 mmol, 2.0 equiv), and pyridine (0.67 mL, 8.33 mmol, 2.0 equiv) to yield 1.18 g (76%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.44 – 7.13 (m, 6H), 6.87 (s, 1H), 6.79 (d, *J* = 9.0 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.34 – 6.18 (m, 1H), 3.80 (s, 3H), 3.60 (d, *J* = 6.9

Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) d 159.0, 141.3, 137.0, 134.4, 132.8, 128.5, 127.4, 126.2, 126.0, 122.4, 116.3, 112.8, 55.7, 33.5. IR (film) 3028.7, 1587.1, 1489.5, 1465.2, 1415.8 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + NH_4^+]+ calcd for $C_{17}H_{15}F_3O_4S$ 390.0987; found 390.0981.

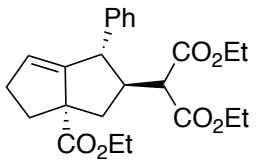
Experimental Procedures and Compound Characterization Data for Products.

General Procedure for Palladium-catalyzed reactions on alkenyl triflates A. A flame-dried 4 mL vial equipped with a stir bar and was cooled under a stream of nitrogen and charged with the appropriate triflate (0.2 mmol, 1.0 equiv), palladium (II) acetylacetonate (0.008 mmol, 0.04 equiv), SPhos (0.012 mmol, 0.06 equiv), lithium *tert*-butoxide (0.44 mmol, 2.2 equiv). The vial was purged with nitrogen and charged with toluene (0.8 M) and the appropriate malonate (0.6 mmol, 3.6 equiv). The vial was capped and placed in a stir plate and heated to 95 °C for 14 h. The mixture was cooled to rt, charged with phenanthrene (1 equiv), and diluted with dichloromethane (1 mL), and quenched with saturated ammonium chloride (1 mL). The aqueous layer was extracted with dichloromethane (3 x 1 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford the desired product.

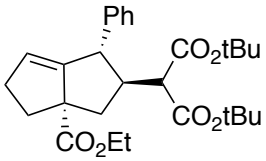


(1*R*,2*S*,3a*R)*-Diethyl 2-(1-phenyl-1,2,3,3a,4,5-hexahydropentalen-2-yl)malonate (3-7a). The title compound was prepared from 5-cinnamylcyclopent-1-en-1-yl trifluoromethanesulfonate (**3-5a**) (62.4 mg, 0.19 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure A. This procedure afforded 18.8 mg (30%) of the title compound as a colorless 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 (500 MHz, $CDCl_3$) d 7.26 (d, *J* = 15.0 Hz, 3H), 7.17 (dd, *J* = 14.6, 7.3 Hz, 2H), 5.25 (s, 1H), 4.23 – 4.05 (m, 2H), 3.92 (d, *J* = 10.8 Hz, 1H), 3.77 (d, *J* = 17.9 Hz, 1H), 3.55 – 3.38 (m, 2H), 3.20 (s, 1H), 3.05 (d, *J* = 17.1 Hz, 1H), 2.59 (s, 1H), 2.49 (s, 1H), 2.29 (d, *J* = 18.0 Hz, 1H), 2.15 (d, *J* = 12.1 Hz, 1H), 1.56 (s, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.05 (t,

J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 168.4, 155.7, 144.6, 128.3, 127.6, 126.2, 120.2, 61.2, 55.7, 52.3, 51.5, 47.2, 37.2, 36.7, 32.1, 14.1. IR (film) 2932.7, 2849.4, 1730.9, 1600.8, 1495.7, 1452.3 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{21}H_{26}O_4$ 343.1909; found 343.1904.

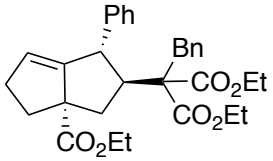


(1*S*,2*S*,3a*S*)-Diethyl 2-[3a-(Ethoxycarbonyl)-1-phenyl-1,2,3,3a,4,5-hexahydropentalen-2-yl] malonate (3-7b). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (**3-5b**) (70.9 mg, 0.18 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure A. This procedure afforded 53.8 mg (72%) 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 (500 MHz, $CDCl_3$) d 7.32 – 7.08 (m, 4H), 5.58 (s, 1H), 4.27 – 4.01 (m, 4H), 3.95 (d, *J* = 14.3 Hz, 1H), 3.82 (d, *J* = 17.9 Hz, 1H), 3.62 (d, *J* = 5.8 Hz, 1H), 3.48 (d, *J* = 7.3 Hz, 1H), 3.24 (s, 1H), 2.93 (s, 1H), 2.77 (d, *J* = 12.0 Hz, 1H), 2.52 (d, *J* = 24.2 Hz, 1H), 2.33 (d, *J* = 6.4 Hz, 1H), 1.93 – 1.78 (m, 1H), 1.45 (s, 1H), 1.34 – 1.15 (m, 8H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 175.8, 168.2, 166.6, 153.3, 142.8, 128.3, 127.7, 126.3, 125.9, 64.9, 61.4, 60.7, 55.1, 54.3, 50.2, 47.1, 41.7, 39.5, 39.3, 37.1, 14.1. IR (film) 2981.1, 2936.2, 1725.0 (2 peaks), 1597.5, 1495.8, 1446.8 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{24}H_{30}O_6$ 415.2121; found 415.2115.

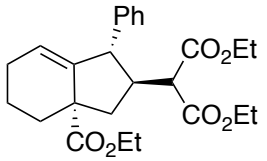


(1*S*,2*S*,3a*S*)-Di-*tert*-butyl 2-[3a-(ethoxycarbonyl)-1-phenyl-1,2,3,3a,4,5-hexahydropentalen-2-yl]malonate (3-7c). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (**3-5b**) (80.8 mg, 0.2 mmol) and ditert-butyl malonate (0.1 mL, 0.4 mmol) using General Procedure A. This procedure afforded 54.5 mg (58%) of the title compound as a pale yellow oil. The

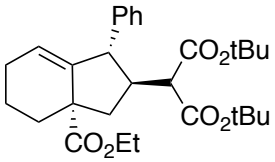
compound was obtained as a 20:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.23 (d, *J* = 5.5 Hz, 4H), 7.15 (d, *J* = 2.8 Hz, 1H), 5.59 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.64 (d, *J* = 8.3 Hz, 1H), 3.32 (d, *J* = 6.8 Hz, 1H), 3.14 (t, *J* = 16.4 Hz, 1H), 2.93 (d, *J* = 8.2 Hz, 1H), 2.84 – 2.72 (m, 1H), 2.52 (d, *J* = 18.6 Hz, 1H), 2.35 (d, *J* = 19.0 Hz, 1H), 1.93 – 1.81 (m, 1H), 1.46 (s, 11H), 1.31 (s, 8H), 1.15 (d, *J* = 15.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 175.8, 167.7, 153.3, 143.0, 128.3, 127.7, 126.2, 125.7, 81.5, 64.8, 60.6, 56.9, 49.9, 47.0, 39.1, 37.1, 28.0, 27.7, 14.1. IR (film) 2977.8, 2933.2, 1721.1 (2 peaks), 1596.3, 1497.0, 1454.5 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{28}H_{38}O_6$ 471.2747; found 471.2741.



(1*S*,2*S*,3a*S*)-Diethyl 2-benzyl-2-[3a-(ethoxycarbonyl)-1-phenyl-1,2,3,3a,4,5-hexahydro pentalen-2-yl]malonate (3-7d). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-ene-1-carboxylate (**3-5b**) (89.2 mg, 0.22 mmol) and benzyl diethyl malonate (0.1 mL, 0.43 mmol) using General Procedure A, except that the reaction was run in xylenes at 110 °C. This procedure afforded 45.4 mg (41%) of the title compound as a colorless 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 (500 MHz, $CDCl_3$) d 7.10 (d, *J* = 6.5 Hz, 10H), 5.54 (s, 1H), 4.05 (dd, *J* = 28.0, 3.6 Hz, 3H), 3.98 – 3.82 (m, 3H), 3.68 (d, *J* = 14.3 Hz, 1H), 3.57 – 3.46 (m, 1H), 3.19 (s, 2H), 3.02 – 2.81 (m, 2H), 2.57 – 2.43 (m, 1H), 2.30 (d, *J* = 19.4 Hz, 1H), 1.91 – 1.75 (m, 1H), 1.62 – 1.49 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 176.2, 170.3, 153.8, 143.7, 136.6, 130.2, 128.2, 127.9, 127.5, 126.7, 125.9, 124.4, 64.0, 61.0, 60.8, 52.4, 46.0, 40.6, 39.6, 37.9, 37.2, 14.0, 13.5. IR (film) 2980.3, 1719.6, 1602.1, 1495.9, 1454.1 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{31}H_{36}O_6$ 505.2590; found 505.2585.

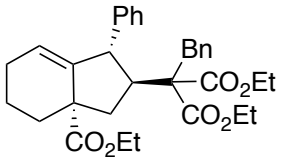


(1*S*,2*S*,3a*S*)-Diethyl 2-[3a-(ethoxycarbonyl)-1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl] malonate (3-7e). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**3-5c**) (83.0 mg, 0.20 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure A. This procedure afforded 62.5 mg (73%) of the title compound as a colorless 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 (500 MHz, Benzene-d_6) d 7.64 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 29.3 Hz, 2H), 7.02 (s, 1H), 5.33 (s, 1H), 4.06 – 3.78 (m, 4H), 3.59 (d, *J* = 7.2 Hz, 1H), 3.49 (d, *J* = 6.9 Hz, 1H), 3.44 (d, *J* = 17.9 Hz, 1H), 3.04 (t, *J* = 17.0 Hz, 2H), 2.37 (d, *J* = 12.5 Hz, 1H), 1.89 (d, *J* = 11.9 Hz, 1H), 1.75 (s, 1H), 1.61 – 1.38 (m, 3H), 1.31 (s, 1H), 1.12 (s, 1H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H), 0.70 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Benzene-d_6) d 175.1, 167.9, 167.6, 144.5, 143.3, 129.4, 127.5, 126.3, 123.8, 60.6, 54.2, 53.5, 44.6, 41.9, 33.0, 24.5, 19.2, 13.9, 13.7, 13.3. IR (film) 2983.1, (2254.8?), 1724.1, 1605.6, 1446.6 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{25}H_{32}O_6$ 429.2277; found 429.2272.

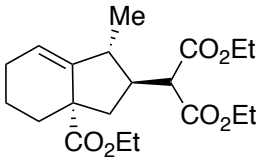


(1*S*,2*S*,3a*S*)-Di-*tert*-butyl 2-[3a-(ethoxycarbonyl)-1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl]malonate (3-7f). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**3-5c**) (83.6 mg, 0.20 mmol) and ditert-butyl malonate (0.1 mL, 0.4 mmol) using General Procedure A. This procedure afforded 64.1 mg (66%) of the title compound as a colorless 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 (500 MHz, $CDCl_3$) d 7.39 (d, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.18 (s, 1H), 5.44 (s, 1H), 4.20 (d, *J* = 7.1 Hz, 2H), 3.52 (d, *J* = 12.9 Hz, 1H), 3.20 (d, *J* = 5.8 Hz, 1H), 2.66 (d, *J* = 12.2 Hz, 1H), 2.57 (s,

1H), 2.34 (d, *J* = 12.5 Hz, 1H), 2.12 (d, *J* = 18.6 Hz, 1H), 2.03 (s, 1H), 1.66 (d, *J* = 46.4 Hz, 2H), 1.47 (s, 9H), 1.28-1.25 (m, 14H). ^{13}C NMR (126 MHz, $CDCl_3$) d 176.0, 167.8, 144.4, 143.2, 128.9, 128.2, 126.3, 123.8, 81.5, 60.8, 55.1, 53.4, 52.9, 44.2, 40.8, 33.3, 28.0, 27.7, 24.5, 19.1, 14.3. IR (film) 2977.9, 2934.0, 1722.4 (2 peaks), 1496.0, 1453.7 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{29}H_{40}O_6$ 485.2903; found 485.2898.

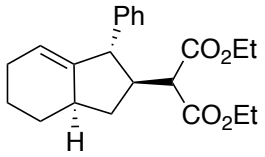


(1*S*,2*S*,3a*S*)-Diethyl 2-benzyl-2-[3a-(ethoxycarbonyl-1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl]malonate (3-7g). The title compound was prepared from ethyl 1-cinnamyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**3-5c**) (85.4 mg, 0.20 mmol) and benzyl diethyl malonate (0.1 mL, 0.43 mmol) using General Procedure A, except that the reaction was run in xylenes at 110 °C. This procedure afforded 53.3 mg (51%) of the title compound as a colorless 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 (500 MHz, $CDCl_3$) d 7.38 – 7.21 (m, 4H), 7.16 – 7.08 (m, 3H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.43 (s, 1H), 4.28 – 4.03 (m, 2H), 4.03 – 3.84 (m, 2H), 3.71 (d, *J* = 18.7 Hz, 2H), 3.10 (d, *J* = 13.9 Hz, 1H), 3.01 (d, *J* = 14.1 Hz, 1H), 2.84 (d, *J* = 12.6 Hz, 1H), 2.27 (d, *J* = 15.8 Hz, 1H), 2.01 (d, *J* = 55.5 Hz, 2H), 1.61 (d, *J* = 46.6 Hz, 2H), 1.25 (dt, *J* = 14.2, 8.3 Hz, 5H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 175.9, 170.0, 144.9, 144.5, 137.0, 130.2, 128.6, 128.0, 127.8, 126.6, 123.4, 62.2, 60.9, 52.4, 51.8, 48.2, 40.9, 40.4, 33.6, 31.6, 24.5, 22.6, 18.9, 14.1, 13.9. IR (film) 2979.9, 2935.7, 1720.8, 1601.5, 1495.7, 1453.5 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{32}H_{38}O_6$ 519.2747; found 519.2741.

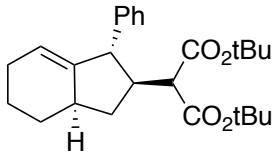


(1*R*,2*S*,3a*S*)-Diethyl 2-[3a-(ethoxycarbonyl)-1-methyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl]malonate (3-17). The title compound was prepared from ethyl (*E*)-1-(but-2-

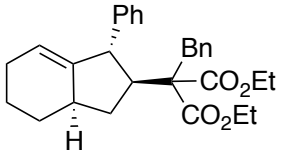
en-1-yl)-2-{[(trifluoromethyl)sulfonyl]oxy}cyclohex-2-ene-1-carboxylate (**3-5d**) (73.5 mg, 0.21 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure A. This procedure afforded 40.1 mg (52%) of the title compound as a colorless oil. The compound was obtained as a 3.5:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 5.54 (s, 1H), 4.17 (d, *J* = 7.1 Hz, 6H), 3.34 (s, 1H), 3.26 (d, *J* = 6.0 Hz, 1H), 2.44 – 2.31 (m, 2H), 2.29 – 2.18 (m, 1H), 2.14 (d, *J* = 21.0 Hz, 1H), 1.99 (s, 2H), 1.65 (d, *J* = 29.8 Hz, 2H), 1.53 (dddq, *J* = 14.0, 10.7, 7.3, 3.4 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 9H), 1.12 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 175.5, 169.0, 168.4, 141.8, 114.4, 61.3, 61.1, 60.6, 54.8, 51.0, 49.7, 37.9, 31.7, 24.2, 19.6, 16.3, 14.1. IR (film) 2980.4, 2935.8, 1725.2 (2 peaks), 1446.7, cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{20}H_{30}O_6$ 367.2121; found 367.2115.



(1*R*,2*S*,3a*R*)-Diethyl 2-(1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (3-7i). The title compound was prepared from 6-cinnamylcyclohex-1-en-1-yl trifluoromethanesulfonate (**3-5e**) (69.0 mg, 0.20 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure A. This procedure afforded 54.1 mg (76%) of the title compound as a colorless 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 (500 MHz, $CDCl_3$) d 7.25 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 7.1 Hz, 3H), 5.23 (s, 1H), 4.24 – 4.05 (m, 2H), 3.82 (d, *J* = 17.9 Hz, 1H), 3.63 (d, *J* = 10.8 Hz, 1H), 3.40 (d, *J* = 9.4 Hz, 1H), 3.34 (d, *J* = 8.1 Hz, 1H), 2.78 – 2.66 (m, 1H), 2.51 (s, 1H), 2.31 (d, *J* = 11.6 Hz, 1H), 2.00 (d, *J* = 32.0 Hz, 3H), 1.79 (d, *J* = 13.2 Hz, 1H), 1.47 (s, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.16 – 0.95 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) d 168.6, 147.6, 145.2, 128.2, 126.1, 120.3, 61.2, 55.5, 53.1, 46.4, 41.3, 37.5, 28.8, 25.1, 22.2, 14.1, 13.7. IR (film) 2979.6, 2927.6, 2857.3, 1730.9, 1601.5, 1451.8 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{22}H_{28}O_4$ 357.2066; found 357.2060.

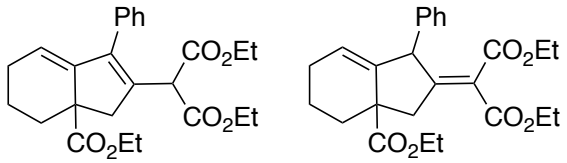


(1*R*,2*S*,3a*R*)-Di-*tert*-butyl 2-(1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (3-7j). The title compound was prepared from 6-cinnamylcyclohex-1-en-1-yl trifluoromethanesulfonate (**3-5e**) (73.1 mg, 0.21 mmol) and ditert-butyl malonate (0.1 mL, 0.4 mmol) using General Procedure A. This procedure afforded 53.9 mg (62%) of the title compound as a white solid. mp: 79-81 °C. 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, $CDCl_3$) d 7.32 – 7.10 (m, 5H), 5.25 (s, 1H), 3.43 (d, *J* = 9.1 Hz, 1H), 3.19 (d, *J* = 7.0 Hz, 1H), 2.69 – 2.56 (m, 1H), 2.50 (s, 1H), 2.36 – 2.24 (m, 1H), 2.01 (d, *J* = 20.2 Hz, 3H), 1.78 (d, *J* = 16.4 Hz, 1H), 1.46 (s, 9H), 1.26 (s, 9H), 1.16 (s, 2H), 1.08 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 168.0, 147.7, 145.5, 128.3, 126.0, 120.0, 81.4, 81.2, 56.8, 53.1, 46.1, 41.1, 36.8, 29.0, 28.0, 25.1, 22.3. IR (film) 2977.9, 2929.2, 1720.2 (2), 1601.8, 1477.5, 1452.7 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]+$ calcd for $C_{26}H_{36}O_4$ 413.2692; found 413.2686.

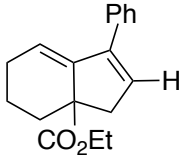


(1*R*,2*S*,3a*R*)-Diethyl 2-benzyl-2-(1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (3-7k). The title compound was prepared from 6-cinnamylcyclohex-1-en-1-yl trifluoromethanesulfonate (**3-5e**) (57.6 mg, 0.17 mmol) and benzyl diethyl malonate (0.1 mL, 0.43 mmol) using General Procedure A, except that the reaction was run in xylenes at 110 °C. This procedure afforded 39.0 mg (51%) of the title compound as a colorless 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 (500 MHz, $CDCl_3$) d 7.41 – 7.06 (m, 10H), 6.96 (s, 2H), 5.27 (s, 1H), 4.13 (dd, *J* = 31.9, 14.0 Hz, 2H), 4.04 – 3.87 (m, 3H), 3.82 (d, *J* = 17.9 Hz, 1H), 3.65 (d, *J* = 7.1 Hz, 1H), 3.17 (d, *J* = 13.9 Hz, 1H), 3.09 (d, *J* = 13.9 Hz, 1H), 2.94 (d, *J* = 10.6 Hz, 1H), 2.54 (s, 1H), 2.40 (d, *J* = 12.3 Hz, 1H), 2.04 (d, *J* = 17.2 Hz, 1H), 1.93 (s, 2H), 1.74 (d, *J* = 15.9 Hz, 1H), 1.40 (s, 4H), 1.22 (s, 2H), 1.09 (t, *J* = 7.1 Hz, 4H), 1.01 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz,

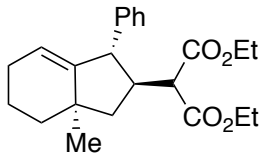
$CDCl_3$) d 170.4, 148.1, 147.5, 136.9, 130.2, 128.3, 127.8, 126.5, 119.2, 62.8, 60.8, 54.7, 51.9, 50.3, 40.5, 39.9, 36.0, 34.6, 29.2, 25.08, 22.1, 13.9. IR (film) 3027.9, 2979.3, 2929.1, 2854.1, 1725.4, 1602.4, 1495.3 cm^{-1}. HRMS (ESI+ TOF) m/z: $[M + H^+]+$ calcd for $C_{29}H_{35}O_4$ 447.2530; found 447.2530.



Diethyl-2-[7a-(ethoxycarbonyl)-3-phenyl-5,6,7,7a-tetrahydro-1*H*-inden-2-yl]malonate (3-20) and **diethyl 2-(3a-(ethoxycarbonyl)-1-phenyl-1,3,3a,4,5,6-hexahydro-2*H*-inden-2-ylidene)malonate (3-21).** The title compound was prepared from diethyl-2-(7a-(ethoxycarbonyl)-3-phenyl-5,6,7,7a-tetrahydro-1*H*-inden-2-yl)malonate (**3-19**) (62.4 mg, 0.19 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure A. This procedure afforded 18.8 mg (30%) of the title compound as a colorless oil. The compound was obtained as a 1:1 mixture of isomers as judged by ^{1}H NMR analysis. Data are for the major isomer. ^{1}H NMR (500 MHz, Benzene-d_6) d 7.80 (d, *J* = 7.3 Hz, 2H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 5H), 7.01 (d, *J* = 17.8 Hz, 3H), 5.80 (s, 1H), 5.27 (s, 1H), 5.07 (s, 1H), 4.79 (s, 1H), 4.57 (s, 1H), 4.19 – 3.67 (m, 14H), 3.57 (d, *J* = 16.1 Hz, 1H), 3.12 (d, *J* = 14.3 Hz, 1H), 2.97 (d, *J* = 14.5 Hz, 1H), 2.70 (d, *J* = 14.5 Hz, 1H), 2.57 (dd, *J* = 15.3, 11.7 Hz, 1H), 2.49 (d, *J* = 14.4 Hz, 1H), 2.41 (d, *J* = 12.0 Hz, 1H), 2.33 (d, *J* = 12.3 Hz, 1H), 2.01 (d, *J* = 26.7 Hz, 2H), 1.78 (d, *J* = 19.4 Hz, 2H), 1.49 (d, *J* = 74.5 Hz, 7H), 1.28 (d, *J* = 28.2 Hz, 6H), 1.03 (d, *J* = 7.4 Hz, 4H), 0.99 – 0.66 (m, 17H). ^{13}C NMR (126 MHz, Benzene-d_6) d 174.2, 173.8, 168.2, 167.6, 167.5, 143.1, 143.0, 140.8, 140.7, 139.7, 138.2, 129.4, 129.1, 128.8, 128.7, 128.4, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 126.9, 123.5, 119.9, 118.1, 61.0, 60.3, 60.3, 60.2, 56.5, 56.4, 53.1, 52.3, 50.2, 49.8, 44.8, 42.1, 41.5, 31.5, 29.8, 29.5, 24.3, 24.0, 19.9, 19.5, 14.0, 13.9, 13.9, 13.8, 13.6, 13.5. IR (film) 2981.6, 2934.4, 1727.3, 1493.9, 1444.6 cm^{-1}.



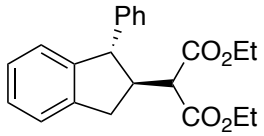
Ethyl 1-phenyl-3,4,5,6-tetrahydro-3a*H*-indene-3a-carboxylate (3-22). ^{1}H NMR (500 MHz, Benzene-d_6) d 7.12 (s, 16H), 6.98 (s, 2H), 6.42 (s, 1H), 5.54 (s, 1H), 3.88 (d, *J* = 15.5 Hz, 2H), 3.21 (d, *J* = 14.7 Hz, 1H), 2.72 (d, *J* = 16.9 Hz, 1H), 2.41 (d, *J* = 12.0 Hz, 2H), 2.09 (d, *J* = 19.8 Hz, 2H), 1.88 (d, *J* = 14.3 Hz, 2H), 1.73 (d, *J* = 17.2 Hz, 2H), 1.59 (s, 3H), 1.40 – 1.05 (m, 16H), 1.03 – 0.72 (m, 9H). ^{13}C NMR (126 MHz, Benzene-d_6) d 128.4, 126.3, 117.3, 116.5, 60.2, 43.0, 30.1, 29.8, 24.0, 19.8, 13.8. IR (film) 2918.3, 2848.8, 1724.1, 1449.1 cm^{-1}.



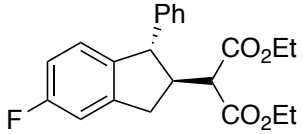
(1*R*,2*S*,3a*R*)-Diethyl 2-(3a-methyl-1-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)malonate (3-7l) The title compound was prepared from 6-cinnamyl-6-methyl cyclohex-1-en-1-yl trifluoromethanesulfonate (**3-5f**) (44.6 mg, 0.12 mmol) and benzyl diethyl malonate (0.1 mL, 0.43 mmol) using General Procedure A. This procedure afforded 28.4 mg (62%) of the title compound as a colorless 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 (500 MHz, $CDCl_3$) d 7.29 – 7.11 (m, 5H), 5.20 (s, 1H), 4.24 – 4.07 (m, 2H), 3.77 (d, *J* = 17.9 Hz, 1H), 3.58 (d, *J* = 17.9 Hz, 1H), 3.47 (d, *J* = 10.1 Hz, 1H), 3.35 (d, *J* = 8.1 Hz, 1H), 3.04 – 2.92 (m, 1H), 2.11 – 1.90 (m, 3H), 1.82 – 1.60 (m, 3H), 1.38 – 1.15 (m, 5H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 154.8, 137.3, 133.6, 128.5, 127.2, 126.1, 125.1, 117.3, 42.0, 38.7, 35.4, 24.7, 24.5, 18.2. IR (film) 2977.3, 2933.5, 1731.4, 1492.9, 1452.0 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{23}H_{31}O_4$ 371.2217; found 371.2217.

General Procedure for Palladium-catalyzed reactions on aryl triflates B. A flame-dried 4 mL vial equipped with a stir bar and was cooled under a stream of nitrogen and charged with the appropriate triflate (0.2 mmol, 1.0 equiv), palladium acetate (0.008 mmol, 0.04 equiv), BrettPhos (0.012 mmol, 0.06 equiv), lithium *tert*-butoxide (0.44 mmol, 2.2 equiv). The vial was purged with nitrogen and charged with toluene (0.8 M) and the appropriate malonate (0.6 mmol, 3.6 equiv). The vial was capped and placed in a stir plate and heated to 65 °C for 5 h. The mixture was cooled to rt, charged with

phenanthrene (1 equiv), and diluted with dichloromethane (1 mL), and quenched with saturated ammonium chloride (1 mL). The aqueous layer was extracted with dichloromethane (3 x 1 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford the desired product.

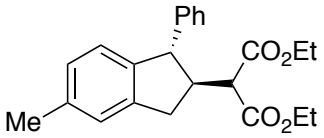


(1*S*,2*S*)-Diethyl 2-(1-phenyl-2,3-dihydro-1*H*-inden-2-yl)malonate (3-15a). The title compound was prepared from 2-cinnamylphenyl trifluoromethanesulfonate (**3-14a**) (75.2 mg, 0.22 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure B. This procedure afforded 39.8 mg (51%) of the title compound as a colorless 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 (500 MHz, Benzene-d_6) d 7.22 – 6.97 (m, 7H), 6.93 (s, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 4.27 (d, *J* = 9.0 Hz, 1H), 3.86 (d, *J* = 23.6 Hz, 2H), 3.73 – 3.52 (m, 3H), 3.45 (d, *J* = 23.6 Hz, 1H), 3.29 (d, *J* = 24.5 Hz, 1H), 3.03 – 2.90 (m, 1H), 0.83 (t, *J* = 7.1 Hz, 3H), 0.73 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Benzene-d_6) d 168.1, 145.9, 143.4, 142.0, 128.9, 127.8, 127.7, 127.6, 127.5, 126.6, 124.9, 124.2, 60.7, 55.0, 48.9, 36.0, 13.7. IR (film) 2981.7, 2927.1, 1730.5, 1601.2, 1493.8, 1454.3 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{22}H_{24}O_4$ 353.1753; found 353.1747.

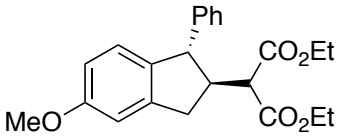


(1*S*,2*S*)-Diethyl 2-(5-fluoro-1-phenyl-2,3-dihydro-1*H*-inden-2-yl)malonate (3-15b). The title compound was prepared from 2-cinnamyl 4-fluorophenyl trifluoromethanesulfonate (**3-14b**) (64.7 mg, 0.18 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure B. This procedure afforded 31.0 mg (47%) of the title compound as a colorless 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 (500 MHz, Benzene-d_6) d 7.16 – 6.94 (m, 5H), 6.69 (d, *J* = 10.3 Hz, 1H), 6.60 (t, *J* = 8.7

Hz, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 4.13 (d, *J* = 8.4 Hz, 1H), 3.95 – 3.76 (m, 2H), 3.54 (d, *J* = 20.2 Hz, 3H), 3.21 (d, *J* = 30.2 Hz, 2H), 2.86 – 2.72 (m, 1H(t, *J* = 7.1 Hz, 3H), 0.73 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Benzene-d_6) d 168.0, 163.5, 161.5, 144.2, 144.1, 143.1, 128.8, 127.9, 126.7, 126.0, 113.6, 111.2, 60.8, 54.5, 49.2, 35.8, 13.7. IR (film) 2981.8, 1728.0, 1600.2, 1483.7 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{22}H_{23}FO_4$ 371.1659; found 371.1653.



(1*S*,2*S*)-Diethyl 2-(5-methyl-1-phenyl-2,3-dihydro-1*H*-inden-2-yl)malonate (3-15c). The title compound was prepared from 2-cinnamyl 4-methylphenyl trifluoromethanesulfonate (**3-14c**) (81.6 mg, 0.23 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure B. This procedure afforded 29.2 mg (35%) of the title compound as a colorless 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 (500 MHz, Benzene-d_6) d 7.17 (d, *J* = 7.2 Hz, 2H), 7.09 (s, 2H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.87 (s, 1H), 6.77 (s, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 4.28 (d, *J* = 8.7 Hz, 1H), 3.96 – 3.78 (m, 2H), 3.73 – 3.53 (m, 3H), 3.50 – 3.37 (m, 1H), 3.37 – 3.25 (m, 1H), 2.97 (d, *J* = 24.3 Hz, 1H), 2.11 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (126 MHz, Benzene-d_6) d 168.2, 143.7, 142.9, 142.1, 136.2, 128.9, 127.5, 126.5, 124.9, 124.7, 60.7, 54.8, 49.2, 35.9, 20.9, 13.6. IR (film) 2980.6, 1728.9, 1602.0, 1493.5, 1453.4 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H$^+$]+ calcd for $C_{23}H_{26}O_4$ 367.1909; found 367.1904.

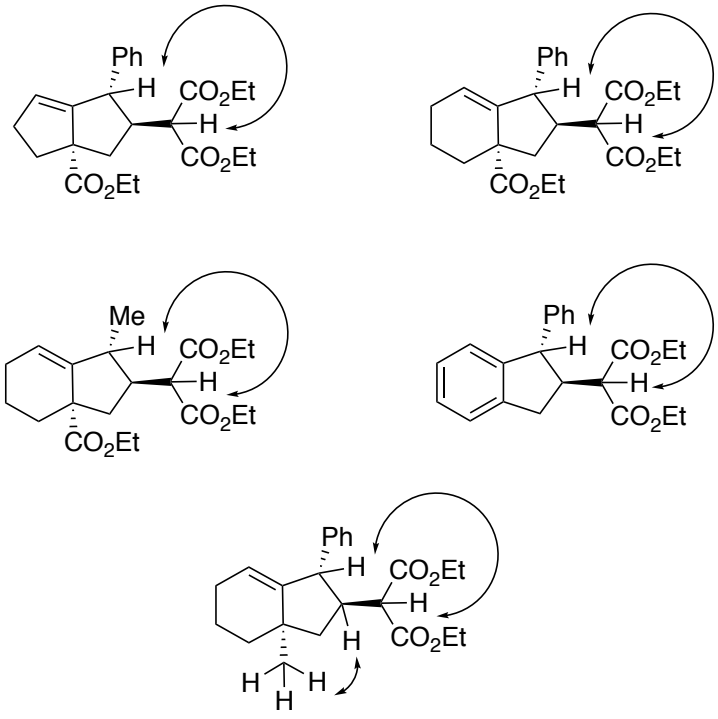


(1*S*,2*S*)-Diethyl 2-(5-methoxy-1-phenyl-2,3-dihydro-1*H*-inden-2-yl)malonate (3-15d). The title compound was prepared from 2-cinnamyl 4-methoxyphenyl trifluoromethanesulfonate (**3-14d**) (81.6 mg, 0.23 mmol) and diethyl malonate (0.1 mL, 0.6 mmol) using General Procedure B. This procedure afforded 29.2 mg (35%) of the title compound as a colorless 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 (500 MHz, Benzene-d_6) d 7.19 (d, *J* = 7.2 Hz, 2H), 7.10 (s, 3H), 7.01 (s, 1H), 6.69 (d, *J* = 19.9 Hz, 2H), 6.61 (d, *J* = 10.3 Hz, 1H), 4.26 (d, *J* = 8.5 Hz, 1H), 3.97 – 3.78 (m, 2H), 3.76 – 3.53 (m, 3H), 3.49 – 3.36 (m, 1H), 3.30 (s, 3H), 3.04 – 2.87 (m, 1H), 0.85 (s, 3H), 0.74 (s, 3H). ^{13}C NMR (126 MHz, Benzene-d_6) d 168.2, 159.5, 143.9, 143.4, 137.8, 128.8, 128.3, 127.9, 126.5, 125.6, 113.0, 109.5, 60.7, 54.8, 54.6, 54.3, 49.4, 36.1, 13.7. IR (film) 2980.7, 1727.7, 1608.5, 1588.8, 1491.4 cm^{-1}. HRMS (ESI+ TOF) m/z: [M + H^{+}]+ calcd for $C_{23}H_{26}O_5$ 383.1859; found 383.1853.

Stereochemical Determinations

Determination of relative stereochemistry by nOe:



3.8 References

(1) a) Zhu, M.; Liu, J.; Yu, J.; Chen, L.; Zhang, C.; & Wang, L. $AlCl_3$-Promoted Formal [2+3]-Cycloaddition of 1,1-Cyclopropane Diesters with *N*-Benzylic Sulfonamides to Construct Highly Stereoselective Indane Derivatives. *Org. Lett.*, **2014**, *16*, 1856-1859. b) Yao, S.; Lopes, V. H. C.; Fernandez, F.; Garcia-Mera, X.; Morales, M.; Rodriguez-Borges, J. E.; & Cordiero, M. N. D. S. Synthesis and QSAR Study of the Anticancer Activity of Some Novel Indane Carbocyclic Nucleosides. *Bioorganic & Medicinal Chemistry*, **2003**, *11*, 4999–5006.

(2) Tithi, N. S., Hossan, M. & Bachar, S. C. Synthesis and Biological Activity Evaluation of Indan-1-Carboxylic Acid-3-Semicarbazone and Indan-1-Acetic Acid-3-Semicarbazone. *Lat. Am. J. Pharm*. **2015**, *34*, 116-123.

(3) a) Bristol-Myers Squibb Company; Preparation of indanes as modulaters of glucocorticoid receptor, Ap-1, or NF-κ B activity for se as antiobesity, antidiabetic, anti-inflammatory, or immunomodulating agents. WO 2007073503 A2, June 28, 2007. b) Minatti, A.; Zheng, X.; Buchwald, S. L. Synthesis of Chiral 3-Substituted Inadnones via an Enantioselective Reductive-Heck Reaction. *J. Org. Chem.* **2007**, *72*, 9253-9258.

(4) a) Mukai, C.; Kuroda, N.; Ukon, R.; & Itoh, R. Preparation of Carbocycles via Base-Catalyzed Endo-Mode Cyclization of Allenes, *J. Org. Chem.* **2005**, *70*, 6282-6290. b) McGarraugh, P. G.; & Brenner, S. E. A New Organocatalyzed Michael-Michael Cascade Reaction Generates Highly Substitues Fused Carbocycles. *Org. Lett.*, **2009**, *11*, 5654-5657.

(5) (a) Nicolaou, K.; Snyder, S.; Montagnon, T.; Vassilikogiannakis, G. The Diels–Alder Reaction in Total Synthesis. *Angew. Chem. Int. Ed.* **2002** , *41* , 1668-1698. (b) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. Organic Chemistry; Oxford University Press Inc.: New York City, NY, 2012; pp 879-896.

(6) a) White, D. R.; Hutt, J. T.; & Wolfe, J. P. Asymmetric Pd-Catalyzed Alkene Carboamination Reactions for the Synthesis of 2-Aminoindane Derivatives. *J. Am. Chem. Soc.* **2015**, *137*, 11246−11249. b) White, D. R. & Wolfe, J. P. Stereocontrolled Synthesis of Amino- Substituted Carbocycles by Pd-Catalyzed Alkene Carboamination Reactions *Chem. Eur. J.* **2017**,*23*, 5419 –5423.

(7) White, D. R.; Herman, M. I.; & Wolfe, J. P. Palladium-Catalyzed Alkene Carboalkoxylation Reactions of Phenols and Alcohols for the Synthesis of Carbocycles *Org. Lett.* **2017**, 19, 4311-4314.

(8) White D. PhD Dissertation: Palladium Catalyzed Alkene Difunctionalization Reactions for the Synthesis of Polycyclic Nitrogen Heterocycles and Functionalized Carbocycles. University of Michigan, 2017.

(9) Yang, K. S.; Gurak, J. A.; Liu, Z.; & Engle, K. M. Catalytic, Regioselective Hydrocarbofunctionalization of Unactivated Alkenes with Diverse C-H Nucleophiles. *J. Am. Chem. Soc.,* **2016**, *138*, 14705-14712.

(10) Liu, Z.; Zeng, T.; Yang, K. S., & Engle, K. M. β,γ-Vicinal Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Directed Nucleopalladation. *J. Am. Chem. Soc.,* **2016**, *138*, 15122-15125.

(11) Overhand, Mark; Hecht, Sidney M. "A Concise Synthesis of the Antifungal Agent (+)-Preussin". *J. Org. Chem*. **1994**, *59,* 4721–4722.

(12) Dieter, R. K.; Chandupatla, K. R.; Topping, C. M; Lu, K.; Watson, R. T. Reactivity and Enantioselectivity in the Reactions of Scalemic Stereogenic α-(*N*-Carbamoyl)alkylcuprates. *J. Org. Chem*. **2004**, *69*, 3076-3086.

(13) Comins, D. L.; Dehghani, A. Pyridine-derived triflating reagents: An improved preparation of vinyl triflates from metallo enolates. *Tetrahedron Lett.* **1992**, *33*, 6299-6302.

(14) Mohr, J. T.; Krout, M. R. Stoltz, B. M. Preparation of (*S*)-2-Allyl-2-Methylcyclohexanone. *Organic Syntheses*, **2009**, *86*, 194-211.

(15) Zhu, S.; Zhang, Q.; Chen, K.; Jiang, H. Synergistic Catalysis: Metal/Proton-Catalyzed Cyclization of Alkynones Toward Bicyclo[3.*n*.1]alkanones. *Angew. Chem. Int. Ed*., **2015**, *54*, 9414-9418.

Chapter 4
Factors that Influence Undergraduate Student Chemistry Course Selection

4.1 Introduction

The first year of college represents a critical juncture in science, technology, engineering and math (STEM) education because retention is strongly influenced by students' experiences in their first college courses.[1] In light of the potency of a students' first year, the choice about which introductory chemistry course to take first may impact the persistence of students and their performance in subsequent courses.[2] Studies have shown that female and male students have different reasons for choosing science courses and for career choices in general.[3] Dick and coworkers have demonstrated that, while parents and teachers were perceived to be influential on high school student career choices in the sciences and engineering, potential pay was a more important factor for the male students and interest was an important factor in rejecting science.[4] Palmer and coworkers reported several factors that impact high school students' decisions to reject or accept science courses, including attitudes and enjoyment, interest and engagement, ability and self-efficacy, and gender.[5] These studies showed differences between the effects of extrinsic and intrinsic motivators on students' attitudes toward science. For example, it was found that advice from peers was generally less important than other factors for students deciding whether to continue studying science. Findings also indicated that high school students enjoy science when it is engaging and relevant, especially if they feel competent and have self-efficacy.

In addition to the aforementioned factors governing students' dispositions toward science, there is a great deal of interest in the methods used to predict how students will perform in introductory chemistry courses. Performance on standardized tests[6], high school GPA[7], and other demographic information[8] have all been examined as predictors of students' performance in chemistry courses.[9] While these approaches have

predictive utility,[10] studies conducted on the use of placement tests to determine student readiness for general chemistry found that 20-30% of students were misplaced when the placement test score was the only factor that mediated student enrollment.[6] Further, though tests may be used to inform student placement in introductory courses, we know very little about how students select introductory chemistry courses when they are given the choice. This information is important for chemistry departments and advisors who recommend courses for students because they need to be informed about how students receive their recommendations and how students ultimately make academic decisions that involve chemistry course selection.

This work follows a quantitative analysis of the impact of students' first chemistry course on their grade performance and their likelihood of enrolling in later chemistry courses.[2] Importantly, it was shown that male students benefited more from taking general chemistry than did female students, though they were similarly prepared. This chapter expands on these findings by examining the factors that impact students decisions about which course to take first and how those factors predict their likelihood of deviating from recommendation provided by a placement test. In particular, we examined how students navigate course choice and how those factors influence their compliance or deviation from their recommendation.

4.2 Research Questions

Our study focused on learning how students make their decision about which chemistry course to enroll in first and whether or not those factors influence the students' likelihood to deviate from their placement. We used two guiding questions for our study:

1. What factors influence students' decisions about which introductory chemistry course to take first?
2. How do these factors influence students' likelihood to deviate from their placement recommendation?

4.3 Theoretical Framework

The study of student placement experience was framed by the theory of socialization described by Eccles,[11] who described an expectancy-value model that

conceptualizes students' motivations for academic decision-making (Figure 4-1). Eccles found that students participate in high achievement activities if they find value in these activities (*task value*) and if they feel they have an *expectation for success*. Many factors influence these feelings, including family influences (e.g., how much parents value school), social factors (e.g., gender/ethnicity training and socialization), and current competence level.

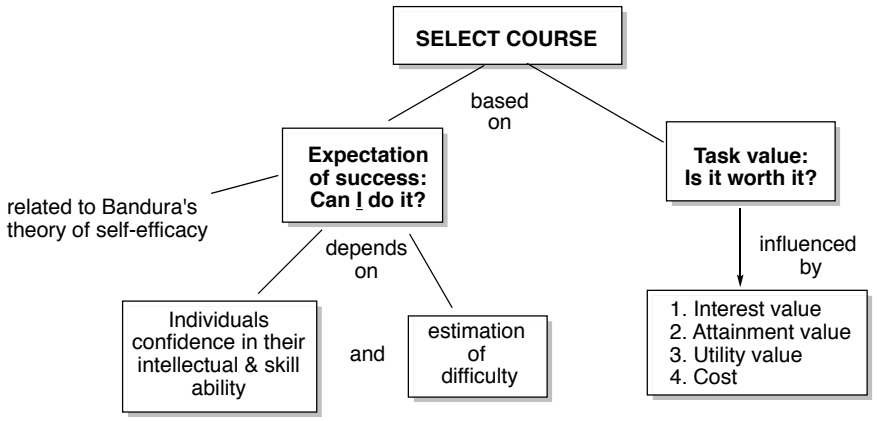


Figure 4-1. Eccles' model of socialization

As depicted in Figure 4-1, Eccles' model provides a framework for understanding students' motivations for pursuing science.[11] This model provides an explanation for the importance of *expectation for success* as it is compared with the importance of high *task value*. The *expectation for success* comes from self-confidence, the estimation of difficulty, usually stemming from advice from peers, family, or academic advisors, among other factors. The *task value* includes, among other factors, interest and requirements for an academic program. These factors were used to help pinpoint differences in different groups of students, and therefore give educators more information to help them create opportunities for students to choose their courses appropriately.

Prior studies have also shown that self-efficacy plays a role in achievement-related decisions.[3] The theory of self-efficacy, as described by Bandura,[12] proposed four sources of self-efficacy that we considered in this context: enactive mastery experiences, vicarious experiences, verbal persuasion, and physiological and affective states. For example, gains in self-efficacy can be attributed to an enactive mastery

experience in which students are successful in a difficult task. Drawing on this model, we aimed to understand how the chemistry placement experience either contributes to or detracts from a students' self-efficacy.

4.4 Methods

This study relied on phenomenography to understand how students make their decision about which course to take first.[13] The key assumption is that there are qualitatively distinct ways in which students experience academic decisions regarding which courses to take and when. To study this phenomenon we used a mixed-methods approach including a survey of students in three courses and interviews with a subset of the participants.

4.5 Study Context

At the University of Michigan, the chemistry curriculum follows a 1:2:1 sequence where one semester of general chemistry (*Macroscopic Investigations and Reaction Principles*), is followed by two of organic chemistry (*Structure and Reactivity I and II*), and ends with a semester of introductory physical/inorganic chemistry (*Physical Chemistry Principles*). Physical Chemical Principles is an introductory physical chemistry course, which may serve as a second semester of general chemistry. As depicted in Figure 4-2, when students arrive at the University, they can choose to enroll in general chemistry or begin organic chemistry (there are no prerequisites for organic chemistry).[14] To help them make this decision, incoming students take a chemistry placement test, which assesses their general chemistry competency, and a math placement test. The chemistry exam is an ACS chemistry exam (ACS NSTA Cooperative Examination for High School Chemistry, Form 1975, Part 1) and the math exam is focused on pre-calculus and was developed in-house. The results of both tests provide an advising recommendation for which course is best suited for them. High achievers on both of the placement tests are recommended to enroll in organic chemistry; as such, many students enroll in this course during the first semester of their first year of college.

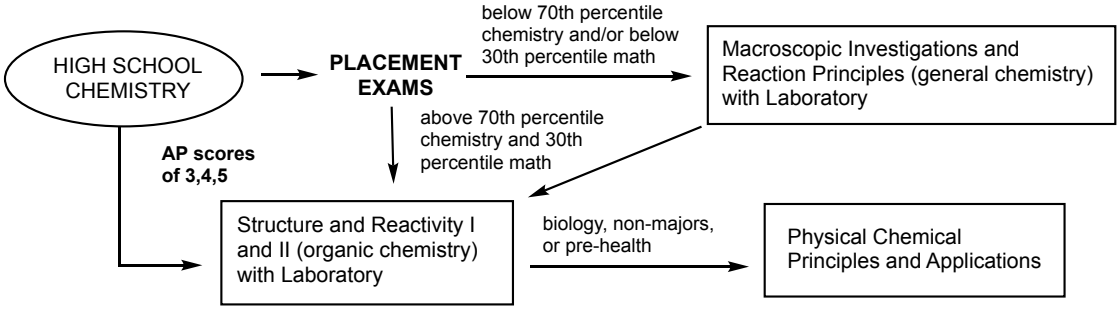


Figure 4-2. Chemistry placement sequence at the University of Michigan (UM)

4.6 Data Collection

In order to understand how students select chemistry courses, we employed a parallel mixed methods research approach.[15] Data came from three primary sources: (1) a survey administered at the beginning of the semester to gauge students' experience with the placement process and in the relevant introductory courses, (2) focus group interviews that were conducted with a subset of survey respondents (N=50), and (3) a survey administered at the end of the semester to gauge student confidence in continuing STEM coursework, which is not included in this analysis. Note that survey data from students who did not complete both surveys were omitted from the analysis. All students enrolled in the three courses (general, organic, and physical chemistry) were invited to participate in the study and a total of 2,020 completed surveys at the beginning and end of the Fall 2015 semester (response rate 71%). These three courses were selected because they represent progressive points along the introductory sequence described above (Figure 4-2). The first survey included questions regarding student demographic information, confidence about their retention in their choice of major, what course they were recommended to take and what they eventually took, their motivation for taking the course they are currently enrolled in, and a question that asked them to rank factors that influenced their course decision. Students were also provided an open text field in which to write in additional factors that influenced their decision. Cognitive interviews were conducted to evaluate whether the survey questions were interpreted by students as intended.[16] Registrar data was collected to confirm students advising recommendation and course selection in order to establish whether students had deviated from their placement recommendation. Eight percent of study participants did not receive a placement recommendation and were omitted from

the analysis. Students consented to participate in both surveys and interviews and IRB approval was obtained prior to data collection. Students received participation points in their respective courses for completion of the surveys. Interview participation was voluntary.

The focus group interviews and expanded written responses included questions that were intended to contextualize the survey data, the details of which are provided in the Experimental section of this chapter. A stratified sampling strategy was used to help ensure breadth in our interview sample (ref *15*, p 144). Students who responded in their survey indicating they were willing to be interviewed were organized by reported ethnicity, gender, and current course of enrollment and from this set randomly selected. The random selection was conducted using the randomization tool in the statistical program SPSS (Version 24), which was used to weigh the sample more heavily toward students from underrepresented groups to ensure that they were represented in the interviews. Students from the randomized list were invited to participate and were arranged into focus group interview sessions (ranging 1 to 10 participants) based on their scheduling availability and course they were enrolled in. Field notes taken during the interviews were analyzed and after 15 focus groups (N=50 participants) no new themes emerged were noted indicating that saturation was reached. In total fifteen focus group sessions were conducted. At the start of the focus group interviews, students completed pre-interview writing, which asked them to describe their placement experience and to indicate which factors were important to them in making their course decision. These factors included the ones offered in the survey, in addition to factors that were written in the open field from the survey. The pre-interview writing also prompted students to identify any factors that they would remove from or add to the list, and why, and is included in the Experimental section of this chapter.

4.7 Data Analysis

The survey data was first analyzed for descriptive statistics using SPSS (Table 4-1).[17] The primary focus of the analysis was the question “Please indicate to what degree the following factors impacted your decision about which course to take first”. We completed an exploratory factor analysis on this question to reduce the data, and identified two components that account for 45% of the variance.[18] The number of

meaningful components was determined by evaluating a scree plot and by comparison of the orthogonally rotated matrices produced for 2, 3, 4, and 5 components. The two-component set produced the strongest loading (>0.5) of factors in each component and was the only set with no cross-loading of factors (factors loading strongly on more than one component). From the analysis, factors were grouped together based on their similarity to create similar components.[18] The two components were named 1) *personal factors* and 2) *institutional factors* based on the factors that loaded more than 0.5 in the component matrix. Using these components, and other demographic information, we completed a binary logistic regression to identify which of the components predict whether or not students deviate from their placement recommendation. Survey results were analyzed for two groups (A) all students and (B) non-engineers, because engineering students may make different course decisions based on the requirements of their academic program compared to non-engineering students.[19] Demographic information for the participants, including their course selection decision, is included in the Experimental section of this chapter.

Table 4-1. Descriptive Statistics for the Question of of the Survey for Total Data Set, Data Set A

Factor[b]	N	Mean[c]	SE	SD
Academic plans	2019	4.29	0.016	0.704
Course load	2019	3.86	0.020	0.918
Discussion with advisor	2018	3.80	0.020	0.904
Confidence about preparation	2018	3.79	0.022	0.971
Placement test recommendation	2020	3.78	0.021	0.951
Advice from friends	2017	2.88	0.025	1.118
Rumors about the course	2018	2.81	0.025	1.102
Advice from family	2018	2.70	0.026	1.179
Non-academic obligations	2013	2.53	0.026	1.156
Other	1212	2.32	0.033	1.162
Family concerns	2019	2.02	0.026	1.151
Financial concerns	2017	1.93	0.025	1.120

[a]Non-engineer data set (data set B) yielded similar results and is included in the Experimental section of this chapter. [b]Students were asked “Please indicate the degree to which the following factors were important to you in making your decision about which course to take first.” [c]The scale for responses ranges from “Not at all important” = 1, to “Extremely important” = 5.

Interview recordings were transcribed verbatim and examined using the constant comparative method (ref *15*, pp 434–440). We coded the interviews using open coding and iteratively added and adjusted codes through out the initial analysis. Coding was

conducted using the program NVivo (version 11) and the resultant codes were compiled in a dictionary (available in the Experimental section of this chapter). A colleague, who was experienced with qualitative analysis, was provided with the dictionary and coded a subset (20%) of the interviews. Differences in coding were discussed between coders and the dictionary was refined. An inter-rater reliability of 0.876 (Krippendorff's alpha) among the coders of the interviews was obtained. The codes in our dictionary were used when someone described why they chose their first class and specifically the factors that led them to their decision. We used open coding and the constant comparison method to complete preliminary coding and produced a preliminary dictionary. Inter rater agreement was completed: an additional rater received three interviews (one from each course) and the preliminary dictionary. There was a 0.32 preliminary agreement according to Krippendorff's alpha. We had two meetings where we discussed the coding and refined the dictionary to include more details and become the below dictionary. The first refinement of the dictionary led us to a 0.76 agreement according to Krippendorff's alpha, followed by a second refinement, which led us to 0.88 agreement according to Krippendorff's alpha. We used the new dictionary to recode all of the focus group interviews, which led us to the frequencies used in the paper. When it came to coding the interviews, we looked for when a student specifically mentioned "XX" as being a reason why they chose the course as their first course. When it came to negative coding (i.e. students mentioning reasons they did not use when they made their decision), we did not code the ones not mentioned (and assumed they were in the positive). We did not code any codes mentioned in the negative – we only ascribed codes to passages in which students mention a factor having an effect on their decision in the positive. The code frequencies were used to contextualize survey findings based on the assumption that the factors that were important for students would come up more often during the interviews.

4.8. Results

Question 1: In the introductory chemistry sequence, what factors influence students' decisions about which course to take first?

Quantitative analysis focusing on a single survey question was used to investigate the reasons behind students' decision of which course to take first.

Participants ranked eleven items on a five-point scale to indicate their relative importance (not at all important to extremely important). The descriptive statistics of those factors are summarized in Table 4-1. Highly rated factors (those above a mean of 3.5) included: confidence about preparation, academic plans, course load, discussion with advisor, and placement test recommendation. Results in both groups (all students – Data Set A and non engineer students – Data Set B) were comparable in magnitude and significance. We also obtained demographic and advising information for each student for use in a predictive model. From this data it was determined that engineering student course selection differed from other students; for Data Set A (all students), 80.5% of students comply with their placement recommendation, and in Data Set B (engineers removed), 83.7% of students comply with their recommendations. This is consistent with the course requirements of some engineering majors who take the placement test, but do not require organic chemistry for their particular major.

We next applied a *factor analysis* data reduction method, which assembles correlated variables into a few interpretable underlying components (please see Supporting Information).[4,18,21] This approach revealed similarities between factors based on student answers to the survey question. Two components emerged from the analysis (Table 2) and account for 45% of the variance of the data (in both Data Sets A and B). The first component, which we have labeled *personal,* is a combination of family and financial concerns, rumors about the course, advice from family and friends, and non-academic obligations. The second component, which we have labeled *institutional,* includes confidence about preparation in chemistry, academic plans (usually meaning major or plans for after college), course load, discussion with advisor, and placement test recommendation. These components map well with the Eccles model.[11] Where factors loading with the *personal* components are related to students' "*expectation for success*" and factors loading with *institutional* are related to students' consideration of "is it worth it?" and the *task value*. These components were used to predict whether or not students would deviate from their advising recommendation for their first course.

Table 4-2. Table of Components from Factor Analysis and their loading for total data set, Data Set A

Factor	Component 1 *personal*[b]	Component 2 *institutional*[b]

Family concerns	**0.789**	-0.113
Financial concerns	**0.727**	-0.186
Rumors about the course	**0.590**	0.117
Advice from family	**0.743**	0.061
Advice from friends	**0.717**	0.147
Non-academic obligations	**0.644**	0.041
Confidence about preparation	0.097	**0.597**
Academic plans	-0.022	**0.600**
Course load	0.262	**0.513**
Discussion with advisor	-0.014	**0.600**
Placement test recommendation	-0.141	**0.682**

[a]Non-engineer Data Set (Data Set B) yielded similar results and is included in the Experimental. [b]Factors that load >|0.5| are included in the component

Using the components generated in the factor analysis, we completed a *binary logistic regression analysis* to determine the extent to which the components and demographics predict the likelihood that students will deviate from the placement recommendation (Table 4-3).[4,22] Registrar data was used to create a variable to represent whether participating students deviated from placement advice. A binary logistic regression model was then used to predict participants' likelihood of deviating based on a variety of variables, including the two components generated by factor analysis. Binary logistic regression can be interpreted where, Exp(B) < 1 indicates that students are less likely to deviate if they rated that factor highly; Exp(B) = 1 indicates that students are no more or less likely to deviate if they rated that factor highly; and Exp(B) > 1 indicates that students are more likely to deviate. For both data sets students who place importance on *institutional factors* are *less likely* to deviate in their course choice, whereas students who place importance on *personal factors* are *more likely* to deviate from their course recommendation. All of these findings were statistically significant.

Participant demographics were also included in the binary logistic regression model. A statistically significant difference between male and female students was observed when all students were included and female students, who rated key factors highly, are 2.6x more likely to deviate than male students in Data Set A. When engineers are removed from the model (Data Set B) gender is still statistically significant but female students are only 1.6x more likely to deviate than male students. We also investigated ethnicity and estimated parental income as factors, which were not

statistically significant and could not be ruled out. Further information on this can be found in the Experimental section of this chapter.

Table 4-3. Results of Binary Logistic Regression Used to identify factors that predict student course selection decisions

Factor	Exp(B) Data Set A All students	Exp (B) Data Set B Engineers removed
Component 1: *personal*	1.227[c]	1.298[d]
Component 2: *institutional*	0.643[b]	0.743[c]
Gender	2.520[b]	1.608[d]
Ethnicity (Asian)		
Ethnicity (White)	0.736	0.93
Ethnicity (Other	0.891	1.310

[a] = $p<0.0001$ [c] = $p<0.005$, [d] = $p<0.05$. [b] missing parental income data (20%) skewed the data enough that we did not include it on our analysis.

Question 2: How do these factors influence students' likelihood to deviate from their placement recommendation?

Interviews were conducted in order to elucidate the reasoning behind students' decision making and to contextualize survey responses. Interview transcripts were analyzed inductively to identify factors, which were then compared to factors included in the survey. The frequencies of the most common factors that students discussed in the context of their placement decision are shown in Table 4-4. Most of these codes correspond to the *institutional factors* component from our factor analysis (Table 4-2).

Table 4-4. Code frequency for more common student-described factors relating to their decision about which course to take first

Code	Brief example	Frequency, Number Coded[a,b]	
		Interviews	Times
Discussion with advisor	210 m2: "I talked to my advisor. I trusted him, and he said that it was a good choice and that I should go for it, so I just had to do to do it."	15	36
Placement test results and placement test recommendation	230 f1: "Mostly I focused on the placement exam as guiding me."	15	32
Academic plans and required	210 m2 "I put well academic plans, cause I thought I was going to be a chemE or material science major, so that influence my decision."	14	37
Confidence	130 f3: "I marked off confidence about preparation in chemistry, and that just goes back to a bad high school experience."	14	34

Time since last chemistry course	130 m3: “Time since my last chemistry course, cause I took it in junior year, so I just like during the exam I felt like I didn't really remember a lot of the stuff.”	7	12
Rumors about the course	210 m6: “I had heard from family members who had taken organic chemistry before this is the class that's kind of a weed-out class that's gonna be hard.”	6	10
Course rigor and load	210 m1: “Course rigor and rumors about the course, because orgo has quite a uh infamous representation.”	6	9
Family concerns	130 f3: “I checked off advice from my family. Um I talked to my parents, cause my parents are doctors, … they both told me that um or recommended that especially if I didn't feel really comfortable with the general chemistry topics that it was probably better just even if I like if it ended up being review just to solidify the foundation um and then move on until orgo.”	6	7
Advice from friends	210 f3: “I didn't hear it was hard don't take it. I heard it was hard.”	3	6
Interest	210 m1: “Interest um I mean I'm majoring in chemistry. So I obviously enjoy chem.”	3	3
Scheduling	230 m1: “It was a little rough for me, because I have practice, so I run track for Michigan, and … that's why I didn't I couldn't take it freshman year.”	2	3
Health and stress levels	210 m1: “I think the health and stress levels kind of plays into a lot of these other factors”	2	2
Financial concerns	230 f3: “Not financial aid that the school gives you, but I know that personally I don't wanna take more than 4 years if I don't have to.”	1	1

[a]130 = Macroscopic Investigations and Reaction Principles; 210 = Structure and Reactivity I; 230 = Physical Chemistry Principles. [b]There were 15 focus group interviews conducted and each focus group contained between 1-10 students

Confidence was frequently discussed during the interviews – it was the fourth-most frequently described factor by individual participants and across interviews (Table 4-4). This finding is consistent with the survey, in which confidence in preparation in chemistry was rated highly. “Confidence about preparation” from the survey was included in the *institutional* component in factor analysis, which was statistically significant in predicting compliance with the placement recommendation. Personal confidence was also the most common “other” text entries students provided in the survey. One physical general chemistry student described their own confidence about their preparation:

> “I guess for me the two themes that kind of arose were one my own confidence in my ability and then on the other hand my preparation or did I feel adequately prepared. I think that a lot of the factors that I chose fell into one of those two categories.”

This finding is consistent both with the *expectancy for success* component of the Eccles model and with the self-efficacy model from Bandura, where students' self-efficacy is important for decision-making.

Interview results also support that *personal factors* (family and financial concerns, advice from friends and family, and nonacademic obligations) are also important in students' decisions to take a course. A student from general chemistry said the following about her family's concerns about her going into organic chemistry:

> "I checked off advice from my family. I talked to my parents, cause my parents are doctors. They both told me that or recommended that especially if I didn't feel really comfortable with the general chemistry topics that it was probably better just even if I like, if it ended up being review, just to solidify the foundation and then move on until orgo."

However, some students claimed that for themselves, *institutional factors* outweighed their *personal* concerns. For example, one student said the following, which indicates that for her the *institutional* component outweighs the *personal* component in the decision:

> "Like my dad when he said you know this is known to be a difficult weeder class he said you should still just defer to what Michigan tells you to do, though. Because he's like it could be different at different colleges, so if the exam is telling you that you're ready, then you should do it if you feel comfortable."

This discussion also aligns well with the Eccles model because the student referred to both her own comfort level with chemistry as well as deferring to UM's recommendation.

During the interviews many participants indicated that they were happy with their decision. However some students expressed regret in their decision. A third physical general chemistry student expressed regret about when she took a class:

> "I think I would just change when I took it. So I went straight into orgo, but I think I would've chosen not to take it my first semester of college, cause I just was not prepared for my workload or how to really study for it. So I think if I'd like given myself that semester to actually like adjust to it."

Students also expressed a desire to know more about what they can expect from organic chemistry before making their decision. According to students who we interviewed, some pre-major advisors are unaware of the organic chemistry curricula

and the structure of the course. Furthermore, although many students were aware of rumors related to organic chemistry and its notoriety as a "weeder" course, many said the rumors did not significantly impact their decision.

4.9 Discussion

The factors that influence students' decision about which chemistry course to take first were investigated. *Institutional factors* were predominant in predicting students' course selection decision. Although the other two factors (component 1 – *personal factors*) do weigh into students' decision, most students follow the University's recommendation and advice (*institutional factors*) when choosing their first chemistry course. The frequency with which students discussed academic plans, placement test results, and discussion with their advisor during interviews corroborates this finding. Component 2 (*institutional factors*) predicted that students were more likely to comply with the recommendation, and during the interviews the five factors that contribute to component 2 were among the most frequent codes, supporting their importance in student decision-making. In other words, if students have a need for the course, are recommended to take it, and feel confident in their preparation, they are likely to comply with their recommendation. This is consistent with our theoretical model of socialization theory by Eccles, who indicated that high *task value* and high *expectation for success* are important for academic decision-making (Figure 4-1).[11]

One factor that was frequently discussed during the interviews was confidence, which was part of Component 2 (*institutional factors*). In particular, students cited previous experience which made them feel confident about going into organic chemistry, or the reverse where a poor experience caused them to feel like they should begin with general chemistry. This finding aligns with Bandura's self-efficacy studies, where, if a student has an enactive mastery experience (doing well in a previous chemistry class for example),[12] it positively impacts their self-efficacy and may motivate them to take the course that they perceive to be more difficult. Furthermore, if a student performs well on the placement test and receives a high score, it may also positively impact their self-efficacy such that the test itself is an enactive mastery experience. If this experience is followed by a discussion with an advisor, the students' self-efficacy could be impacted by verbal persuasion. This finding is consistent with other studies of

academic decision-making. For example, when studying identity of high school physics students, Hazari and colleagues found students' previous performance was important for developing student self-efficacy.[23]

In addition to analysis of student deviation from their placement recommendation, we obtained data about the students' estimated parental income, the students' gender, and ethnic identity. Estimated parental income and ethnic identity were not statistically significant and thus could not be ruled out as factors that do or do not contribute to placement decisions. The significance of gender is consistent with findings reported by Moakler and Kim, who found that gender was a meaningful contributor to students' choice of STEM major in college.[24]

4.10 Limitations

One limitation of the study was sample size. Only a small percentage of students who deviated from their placement recommendation and of these only two were interviewed. Furthermore, some variables in the regression analysis were not statistically significant and may also be attributed to our overall sample size (please see the Experimental section for student demographics). For example, estimated parental income and ethnic identity could not be ruled out as important in student academic decisions. The study was conducted during the "on cycle" term and thus it is possible that not all student perspectives were represented as students who enroll in the "off cycle" may have different experiences as compared to the "on cycle" students. Finally, these findings are not necessarily generalizable to other institutional contexts as the investigation took place at a single selective institution where the introductory course sequence is atypical. However, the findings should be of interest to any chemistry department using AP scores or placement tests to guide student placement as they underscore the need for appropriately validated placement tests and well-informed advisors.

4.11 Implications

Our findings suggest that most students will follow the recommendation offered by a placement test and the advice that university advisors provide them, provided they feel confident in their abilities. Some students expressed that they did not feel very

confident until they met with an advisor and received their placement test score, which supports the need for the exam to be well-vetted and accurate and for advisors to be well-versed in the coursework they are advising students about. Multiple students expressed a wish that they knew the format of organic chemistry, the differences between general chemistry and organic chemistry, and that their advisor were more informed about the differences between the two. If students rely heavily on institutional advice, as was the case in this study, this underscores the importance of accurate tests that are well vetted and appropriate for the student population.

Many factors influence students' decisions about which course to take first in the introductory chemistry sequence. Based on the surveys and interviews conducted herein, confidence, academic plans, and placement test recommendation were common factors for influencing students' decisions. These factors were found to be statistically significant in our binary logistic regression and were among the most commonly discussed factors in our focus group interviews. Additional factors, such as advice from family and friends and rumors about the course, were less frequently discussed in our interviews but were found to be statistically significant in predicting whether students deviate from their placement recommendation.

The work described in this chapter was published in the *Journal of Chemical Education*. This chapter was adapted with permission from Hinds, E. M.; Shultz, G. V. Investigation of the Factors That Influence Undergraduate Student Chemistry Course Selection, *J. Chem. Educ.,* **2018**, *95*, 913–919.

4.12 Experimental

I. Course Descriptions

The content in all three courses remained consistent over the course of the study and all courses operated using a traditional lecture format.

The **CHEM 130 - Macroscopic Investigations and Reaction Principles** (first semester general chemistry) course is intended as a stand-alone course that fulfills the general chemistry requirement for some disciplines, for instance many engineering majors, or that serves to strengthen the chemistry background of students who did not meet the standard of preparation for organic chemistry. Around 2000 students take general chemistry each year. Faculty instructors rotate into the course, however, the content and structure of the course were maintained by a single course coordinator over the duration of the study. The course meets for three 50-minute lectures each week for a 15-week semester. Each week students also meet for 50-minute discussion lead by a graduate student teaching assistant. The average lecture section is comprised of 400 students and discussion sections average 20 students. The course primarily utilizes exams (two midterms and one final exam) to assess student performance. All students in all sections of the course take the same exams. The exams are multiple choice and account for 70% of the final grade. The remainder of the grade comes from weekly discussion quizzes, homework, and class participation through clickers. The course includes traditional general chemistry topics including: atomic structure, balancing chemical equations, stoichiometry, moles, reactions (precipitations, acid/base, redox), gas laws, enthalpy, quantum numbers, electron configurations, Lewis structures, molecular geometry, phase changes, intermolecular forces, and an introduction to equilibrium and acid-base chemistry.

The first term **CHEM 210 - Structure and Reactivity** (Organic Chemistry) course enrollment is comparable to general chemistry also enrolling around 2000 students yearly, of which roughly 20% are students with freshman status. Faculty instructors also rotate into this course, but as in the other courses included in this study the course syllabus and a set of master lecture notes remained constant over the duration of the study. The course meets for three 50 minute lectures each week for a 15 week semester. Each week students also meet for a single 50 minute discussion lead by a

graduate student teaching assistant. The average lecture section is 400 students and discussion sections average 25 students. The course utilizes exams (three midterms and one final exam) to assess student performance. The exams in organic chemistry are distinct from both General Chemistry and Chemical Physical Principles exams in that they are composed of literature-based questions that require students to respond by writing or drawing. All students in all sections of the course take common exams. Course topics are designed for student mastery with little prior knowledge. They include Lewis structures, bonding, resonance, isomers, intermolecular forces, atomic and molecular orbitals including double and triple bonds, organic acids and bases and acid-base equilibria, organic reactions between electrophiles and nucleophiles, alkanes (NMR, conformation, nomenclature), organic molecule shapes and stereochemistry, nucleophilic substitution and elimination, leaving groups, alkenes (electrophilic addition, carbocations), alkynes (structure, isomerism, nomenclature, acidity, addition, and reduction) and electrophilic aromatic substitution.

CHEM 230 - Physical Chemical Principles is intended as a fourth term in chemistry for non-chemistry science majors and students completing the two-year chemistry sequence required by medical or dental graduate programs. Chemistry majors typically enroll in a separate calculus based course. Approximately 700 students (mostly juniors and seniors who have previously completed both semesters of organic chemistry) take the course per year. The course has the same meeting structure as both general chemistry and the first semester organic chemistry course. It meets for three 50 minutes lectures each week for a 15 week semester. Each week students also meet for a single 50 minutes discussion lead by a graduate student teaching assistant. Topics mirror those typically found in a second semester general chemistry course with an in-depth emphasis on thermodynamic principles to explain why physical and chemical 3 processes take place. Topics include: ideal and real gases; work; enthalpy; entropy; Gibbs free energy; equilibrium as applied to chemical reactions, physical change, and solutions; acid-base equilibria including titrations and buffers; solubility; electrochemistry; an introduction to kinetics; and nuclear chemistry.

II. Interview Protocol

Interview Protocol (goal 30-45 mins)

Interview script:

A. YOU SAY: “The chemistry department has recently initiated a study to investigate how students are affected by enrolling, or not enrolling, in CHEM 130 (general chemistry) during their academic career. You have agreed to participate in an interview as part of this study. There are several reasons for asking you to participate, including:

To find out how you were impacted by your decision to enroll in your first chemistry class after learning your placement test results.

To learn how you were affected by your placement, and what you might change about the process.

This interview is confidential. Transcripts from the recordings of the discussions and the documents produced from the analysis will not include names or any identifying information about the participants, other than summary information - for example, how many people enrolled in CHEM 130 instead of CHEM 210, when they were recommended for the latter.

Are there any questions before we begin?”

[Signed consent obtained here]

B. **Pre-interview writing: (FOCUS GROUP)**

YOU SAY: “To begin we would like you to do a little bit of writing about your experience. This is intended to help surface your memories about chemistry placement. Take your time and let me know if you have any questions.”[They do writing]

[discuss writing prompt]

Q1 YOU SAY “The first question asks you to describe what you remember about your experience with chemistry placement. Please describe your experience including when you took the placement test, what the test was like and what your conversation with your advisor was like”

Q2. “The next question asks you to consider a list of factors that might be important in make a decision about what course to take first. Please describe the factors that you decided were important and explain why they were important to you.”

Q3 “Finally, would you add or remove anything from the list? If so, why?”

Follow ups:

What do you think makes general chemistry different from orgo?

Why do you think orgo might have a reputation for being hard?

What is your experience in Chemistry 130 (210, 230) like right now? Or

OR (210, 230 only) How was your experience in 130 when you took it?

C. **FOCUS GROUP Interview Questions:**

230 AND 210 ONLY: If they took 130, did it help them in 210 or 230 (respectively)? Why or why not? (OR didn't take 130, did it impact in 210 or 230)

Would you make the same placement decision again or recommend other students to do the same? - make open ended not y/n?

What do you wish you knew that would help you make a better decision?

Is there anything else that you might want to add?

III. Prewriting document

We asked interview participants to answer the following 2 questions.

1. At UM, students receive a recommendation about whether to start with general chemistry or organic chemistry based on their performance on a chemistry placement exam or if they have AP Chemistry credit. This is usually a process that happens during orientation. Please describe what you remember about your experience with chemistry placement.

2. Below you will find a list of factors that may be important to UM students when deciding whether to take general chemistry or organic chemistry first. Please read over the list and put and "X" next to any items that you consider to be important to you.

- Family concerns
- Financial aid
- Confidence about preparation in chemistry
- Time since last chemistry course
- Academic plans
- Applicability/major

- Graduation requirements
- Course rigor
- Course load (number of courses you need to take first)
- Rumors about the course
- Advice from family
- Advice from friends
- Discussion with and academic advisor
- Advising recommendation based on placement test
- Nonacademic obligations (work study, sports, etc)
- Personal confidence
- Interest
- Health/Stress levels
- Scheduling

a. Please explain why you selected those items you marked with an "X"

b. Would you add or remove anything from this list? If so, what and why?

IV. Survey Frequencies

Table 4-5. Table of Demographic Frequencies of all Courses

Entry	Demographic	Data set A (everyone) N = 2,020	Data set B (engineers removed) N = 1,363
	Gender		
1	Male	953 (47.2%)	515 (37.8%)
2	Female	1,067 (52.8%)	849 (62.2%)
3	Missing	0 (0%)	0 (0%)
	Ethnicity		
4	Ethnicity: Asian	368 (18.2%)	271 (19.9%)
5	Ethnicity: White	1,198 (59.3%)	810 (59.4%)
6	Ethnicity: Other	454 (22.5%)	283 (20.7%)
7	Other: Black/African American	59 (2.9%)	41 (3.0%)
8	Other: Two or more races	85 (4.2%)	66 (4.8%)
9	Other: Not indicated	120 (5.9%)	76 (5.6%)
10	Other: Non-resident alien	73 (3.6%)	29 (2.1%)
11	Other: Hispanic/Latino	112 (5.5%)	68 (5.0%)
12	Other: American Indian/Alaskan Native	5 (0.2%)	3 (0.2%)
13	Other: Native Hawaiian	0 (0.0%)	0 (0.0%)
14	Other: Missing	0 (0.0%)	0 (0.0%)
	Course Decision		
15	Complied with recommendation	1,627 (80.5%)	1,141 (83.7%)
16	Deviated (gen chem ➔ orgo)	41 (2.0%)	40 (2.9%)

17	Deviated (orgo ➔ gen chem)	235 (11.6%)	74 (5.4%)
18	Missing	117 (5.8%)	109 (8.0%)
	Estimated Parent Income		
19	Parent income (< 25 K)	90 (4.5%)	69 (5.1%)
20	Parent income (25 – 50 K)	119 (5.9%)	66 (4.8%)
21	Parent income (50 – 75 K)	160 (7.9%)	112 (8.2%)
22	Parent income (75 – 100 K)	183 (9.1%)	123 (9.0%)
23	Parent income (100 – 200 K)	553 (27.4%)	381 (27.9%)
24	Parent income (> 200 K)	509 (25.2%)	344 (25.2%)
25	Missing	406 (20.1%)	269 (19.7%)

V. Non-Engineer Descriptive Statistics

Table 4-6. Nonengineer Descriptive Statistics

Entry	Factor	N	Mean	SE	SD
1	Academic plans	1363	4.31	0.018	0.671
2	Course load	1363	3.91	0.024	0.882
3	Confidence about preparation	1363	3.87	0.025	0.906
4	Placement test recommendation	1364	3.79	0.025	0.930
5	Discussion with advisor	1362	3.75	0.025	0.909
6	Advice from friends	1362	2.98	0.030	1.102
7	Rumors about course	1363	2.93	0.029	1.083
8	Advice from family	1362	2.80	0.032	1.186
9	Non-academic obligations	1358	2.58	0.032	1.178
10	Family concerns	1363	2.11	0.032	1.198
11	Financial concerns	1362	1.99	0.031	1.156
12	Other	729	2.36	0.044	1.181

VI. Factor Analysis for all students (Data Set A)

Table 4-7. Factor Analysis Variance for All Students (Data Set A)

Total Variance Explained

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings[a]
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total
1	3.353	30.480	30.480	3.353	30.480	30.480	3.202
2	1.659	15.077	45.557	1.659	15.077	45.557	2.068
3	1.120	10.180	55.737				
4	1.017	9.244	64.981				
5	.796	7.234	72.215				
6	.688	6.258	78.473				
7	.620	5.635	84.108				
8	.572	5.200	89.308				
9	.529	4.807	94.116				
10	.353	3.207	97.323				
11	.295	2.677	100.000				

Extraction Method: Principal Component Analysis.

a. When components are correlated, sums of squared loadings cannot be added to obtain a total variance.

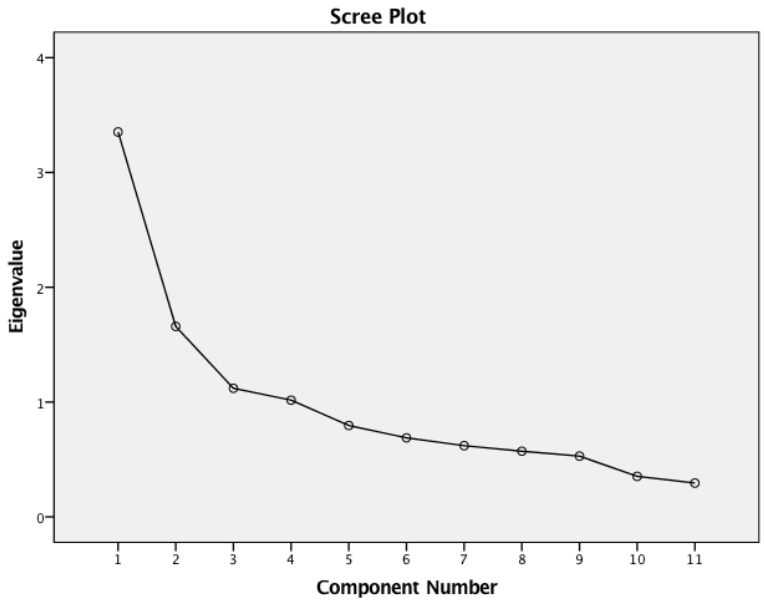


Figure 4-3. Scree Plot for Data Set A

VII. Non-Engineer Factor Analysis (Data Set B)

Table 4-8. Nonengineer Variance Factor Analysis (Data Set B)

Total Variance Explained

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings[a]
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total
1	3.334	30.309	30.309	3.334	30.309	30.309	3.157
2	1.711	15.554	45.862	1.711	15.554	45.862	2.151
3	1.070	9.726	55.588				
4	1.021	9.284	64.872				
5	.802	7.292	72.163				
6	.697	6.338	78.502				
7	.612	5.562	84.064				
8	.563	5.118	89.182				
9	.524	4.760	93.942				
10	.356	3.235	97.177				
11	.311	2.823	100.000				

Extraction Method: Principal Component Analysis.
a. When components are correlated, sums of squared loadings cannot be added to obtain a total variance.

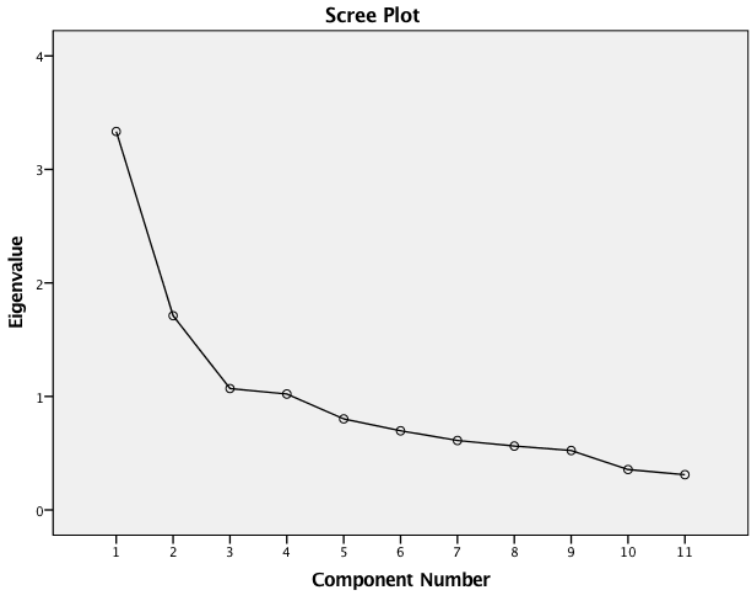


Figure 4-4. Scree Plot for Nonengineer Data Set (Data Set B)

Table 4-9. Nonengineer Data Set (B) Factor Analysis

Entry	Factor	Component 1	Component 2
1	Family concerns	0.810	-0.144
2	Financial concerns	0.751	-0.229
3	Confidence about preparation	0.057	0.610
4	Academic plans	-0.064	0.620
5	Course load	0.256	0.537
6	Rumors about course	0.540	0.198
7	Advice from family	0.736	0.067
8	Advice from friends	0.689	0.178
9	Discussion with advisor	0.042	0.577
10	Placement test recommendation	-0.116	0.667
11	Non-academic obligation	0.641	0.053

XIV. Code Dictionary

Table 4-10. Code dictionary

Code	Definition	Example
Academic plans/required	students said this was important when making their decision, primarily major or intended career field, as well as graduation requirements	130 Oct 12 f2 08:34.06: "I think the biggest ones are probably confidence at preparation in chemistry and then the time since I last took a chemistry class and then my academic plans, because um so I'm studying engineering, and then I have to take a chemistry course, but if I wanna do chemical engineering, then I gotta take more, so I want to make sure I had a strong background, and then I was also hoping by taking general chemistry I might get like more of an idea if that is something I wanna

		pursue."
Advice from friends	students said this was important when making their decision, such as "my friends said…"	210 Oct 29 f2 39:06.10: "I checked off advice from friends, but it was more like what I heard like not like the rumors side where people are like oh it's hard don't take it, but more like when people explain to you like well it was hard because you know I had a lot of work to do but I got it done. Like that kind of advice factored in. But not like the rumor advice, because I don't really like to listen to that because usually it's just people that like didn't work hard and failed."
Confidence	students said this was important when making their decision, includes confidence in preparation, personal confidence	130 Oct 19 m3 03:51.27: "Okay so confidence like I was pretty confident, cause I took AP chem and I was like sure like gen chem shouldn't be like really hard, but like I was just concerned because at Michigan everything's harder here"
Course rigor and course load	students said this was important when making their decision, specifically they list this as a reason they chose their first course or thinking about the course load involved	130 Oct 19 m1 05:32.17:" And course rigor um I've heard that general chem is a lot of busy work, so um uh it was just it sounded like it was more time-consuming than anything else. Um and then also the course load. I was uh um I'm taking the general like electives for or like the general classes for um for engineering for Michigan engineering classes. And so I knew that um general chem would be as much work as like the design um based engineering courses."
Discussion with advisor	students said this was important when making their decision, primarily discussing their conversation with their orientation advisor	230 Oct 16 FG1 f2 06:58.27: "discussion with an academic advisor after she was very like adament about you should definitely not take general chemistry"
Family concerns and advice from family	students said this was important when making their decision, includes parental/sibling worries/hesitations about their courses	130 Oct 9 f3 08:26.23: "I checked off advice from my family. Um I talked to my parents, cause my parents are doctors, um so I was like yeah I just asked them like you know is it worth it to go straight into orgo or can I just spend a semester in gen chem? And um they both told me that um or recommended uh that um especially if I didn't feel really comfortable with the general chemistry topics that it was probably better just even if I like if it ended up being review just to solidify the foundation um and then move on until orgo."

Financial concerns	students said this was important when making their decision, such as financial aid worries	230 Oct 16 FG1 f3 15:13.13: "I would maybe say like financial concerns. Like not financial aid that the school gives you, but I know that personally I don't wanna take more than 4 years if I don't have to. And I wanna fit everything into semesters cause you know if like fulltime students, it's the same price 12-18 credits, so like if I can take as many credits as I can to get them out of the way, I'll do that so I don't have to pay more money and take another semester".
Health and stress levels	students said this was important when making their decision, such as being stressed out and wanting to avoid that	130 Oct 12 f1 07:59.13: "I also put one next to stress and health levels, and so if I wasn't doing well, it would just cause me to be more stressed out, which isn't gonna help me at all, and it will probably make me perform worse, cause I can't focus when I'm stressed."
Interest	students said this was important when making their decision, usually specifically being interested in chemistry	130 Oct 19 m3 03:51.27: "I'm pretty interested in chem but like I don't wanna pursue it all the way, so that's why I take orgo."
Placement test results and recommendation	students said this was important when making their decision, including using their score and recommendation produced by the score as a guide for what course to take	230 Oct 16 FG1 f2 06:58.27: "advising based on the placement test. That too. I don't know what my score was, but it was pretty high. And then academic obligations."
Rumors about the course	students said general course rumors were an important factor when making their decision, such as it is a weeder course (if they say "my friends said…" This goes under advice from friends code, even if the advice is a rumor – depending on what they say it might go under both)	130 Oct 14 f1 03:24.18: "I didn't hear very much like coming in, but once I was here, I heard that it was pretty awful. Um I had my roommate freshman year had been placed into organic chemistry, and I think she failed it, so I think that scared me a lot, so..."
Scheduling and nonacademic obligations	students said this was important when making their decision, such as having issues fitting in the courses (lab and lecture) into their schedule, or when discussing nonacademic obligations	230 Oct 20 m1 03:31.18: "also like kind of scheduling. It was a little rough for me, because I have practice, so I run track for Michigan, and so like practice takes up a lot of time. Um so like that's why I didn't I couldn't take it freshman year."
Time since last chem course	students said this was important when making their decision, usually discussing how long it has been since they took high school chemistry	210 Oct 28 f2 09:50.00: "the last time I took a chemistry course was a couple years ago,"

4.13 References

(1) Chen, X. STEM Attrition: College Students' Paths Into and Out of STEM Fields (NCES 2014-001). National Center for Education Statistics, Institute of Education Sciences, U.S. Department of Education, Washington, DC. **2013**; Available at: http://nces.ed.gov/pubs2014/2014001rev.pdf (accessed Mar 2018).

(2) Shultz, G. V.; Gottfried, A. C.; Winschel, G. A. Impact of General Chemistry on Student Achievement and Progression to Subsequent Chemistry Courses: A Regression Discontinuity Analysis. *J. Chem. Ed.* **2015***, 92*, 1449-1455.

(3) For reviews on factors influencing students' choices to continue with science: a) Ainley, J.; Kos, J.; Nicholas, M. *Participation in science, mathematics and technology in Australian education*. **2008**, Melbourne: ACER Research Monograph. b) Henriksen, E. K. Introduction: Participation in science, technology, engineering and mathematics (STEM) education: Presenting the challenge and introducing Project IRIS. In E. K. Henriksen, J. Dillon, & J. Ryder (Eds.), *Understanding Student Participation and Choice in Science and Technology Education* (pp. 1-14). **2015**. Dordrecht: Spinger. c) Lyons, T.; Quinn, F. Choosing Science. Understanding the Declines in Senior High School Science Enrolments. Armindale, NSW: University of New England. **2010**. Retrived from http://simerr.une.edu.au/pages/projects/131choosingscience.pdf. d) Regan, E.; Dewitt, J. Attitude, interest and factors influencing STEM enrollment behavior: A review of relevant literature. In E. K. Henriksen, J. Dillon, & J. Ryder (Eds.), *Understanding Student Participation and Choice in Science and Technology Education* (pp. 63-88). **2015**. Dordrecht: Spinger.

(4) Dick, T. P.; Rallis, S. F. Factors and Influences on High School Students' Career Choices. *Journal for Research in Mathematics Education*, **1991**, *22*, 281-292.

(5) Palmer, T.; Burke, P. F.; Aubusson, P. Why School Students Choose and Reject Science: A Study of the Factors that Students Consider When Selecting Subjects. *International Journal of Science Education*, **2017**, *39*, 645-662.

(6) McFate, C.; Olmstead, J. Assessing Student Preparation through Placement Tests. *J. Chem. Educ.* **1999**, *76*, 562-565.

(7) Sadler, P. M.; Tai, R. H. Advanced Placement Exam Scores as a Predictor of Performance in Introductory College Biology, Chemistry, and Physics Courses. *Sci. Educ*. **2007**, *16*, 1-19.

(8) a) Tai, R. H.; Sadler, P. M. High School Chemistry Instructional Practices and Their Association with College Chemistry Grades. *J. Chem. Educ*. **2007**, *84*, 1040-1046. b) Tai, R. H.; Sadler, P. M.; Loehr, J. F. Factors Influencing Success in Introductory College Chemistry. *J. Res. Sci. Teach*. **2005**, *42*, 987-1012.

(9) a) Wagner, E. P.; Sasser, H.; DiBiase. Predicting Students at Risk in General chemistry Using Pre-semester Assessments and Demographic Information. *J. Chem. Educ*. **2002**, *79*, 749-755. b) Easter, D.C. Factors Influencing Student Prerequisite Preparation for and Subsequent Performance in College Chemistry Two: A Statistical Investigation. *J. Chem. Educ*. **2010**, *87*, 535-540.

(10) a) Chan, J. Y. K.; Bauer, C. F. Identifying At-Risk Students in General Chemistry via Cluster Analysis of Affective Characteristics. *J. Chem. Educ*. **2014**, *91*, 1417-1425. b) Bunce, D. M.; Hutchinson, K.D. The Use of GALT (Group Assessment of Logical Thinking) as a Predictor of Academic Success in College Chemistry. *J. Chem. Educ*. **1993**, *70*, 183-187. c) Leopold, D. G.; Edgar, B. Degree of Mathematics Fluency and Success in Second-Semester Introductory Chemistry. *J. Chem. Educ*. **2008**, *85*, 724-731. d) Carter, C. S.; LaRussa, M. A.; Bodner, G. M. A Study of Two Measures of Spatial Ability as Predictors of Success in Different Levels of General Chemistry. *J. Res. Sci. Teach*. **1987**, *24*, 645-657. e) Creech, L.R.; Sweeder, R.D. Analysis of Student Performance in Large-Enrollment Life Science Courses. *CBE-Life Sci. Educ*. **2012**, *11*, 386-391.

(11) Eccles, J. S. Families, Schools, and Developing Achievement-Related Motivations and Engagement. In *Handbook of Socialization Theory and Research,* Grusec, J. E., Hastings, P. D., Eds.; Guilford Press: New York, **2007**; pp 665–691.

(12) Bandura, A. *Self-efficacy – the Exercise of Control*; W. H. Freeman and Company: New York, USA, **1997**; pp 79-115.

(13) Richardson, J. T. E. The Concepts and Methods of Phenomenographic Research. *Review of Educational Research*, **1999**, *69*, pp 53-82.

(14) a) Ege, S. N.; Coppola, B. P.; Lawton, R. G. The University of Michigan Undergraduate Chemistry Curriculum 1. Philosophy, Curriculum, and the Nature of Change. *J. Chem. Educ.* **1997***, 74*, 74-83. b) Coppola, B. P.; Ege, S. N.; Lawton, R. G. The University of Michigan Undergraduate Chemistry Curriculum 2. Instructional Strategies and Assessment. *J. Chem. Educ.* **1997***, 74*, 84-94.

(15) Creswell, J. W. *Educational Research – Planning, Conducting, and Evaluating Quantitative and Qualitative Research,* 4 ed.; Pearson: Boston, **2012**; pp. 534-575.

(16) Willis, G. B. Cognitive Interviewing – A "How To" Guide. *Reducing Survey Error through Research on the Cogntitive and Decision Processes in Surveys* **1999**, American Statistical Association meeting. Available online: http://www.dea.univr.it/documenti/OccorrenzaIns/matdid/matdid823948.pdf (accessed Mar 2018).

(17) Hinton, P. R.; Brownlow, C.; McMurray, I.; Cozens, B. SPSS Explained. Routledge, London and New York, **2004**, pp. 313-337.

(18) DiStefano, C.; Zhu, M.; Mindrila, D. Understanding and Using Factor Scores: Considerations for the Applied Research. *Practical Assessment, Research & Evaluation*, **2009**, *14*, 20. Available online: http://pareonline.net/getvn.asp?v=14&n=20 (accessed Mar 2018).

(19) ABET accreditation UM engineering department uses: http://www.abet.org/accreditation/ (accessed Mar 2018).

(20) a) Orthogonal and oblique rotations: Yong, A. G.; Pearce, S. A Beginner's Guide to Factor Analysis: Focusing on Exploratory Factor Analysis. *Tutorials in Quantitative Methods for Psychology*, **2013**, *9*, 79-94. b) Oblique rotations: Costello, A. B.; Osborne, J. W. Best Practices in Exploratory Factor Analysis: Four Recommendations for Getting the Most From Your Analysis. *Practical Assessment Research & Evaluation*, **2005**, *10(7)*, 1-9.

(21) Sakar, E.; Keskin, S.; Unver, H. Using Factor Analysis Scores in Multiple Linear Regression Model for Prediction of Kernel Weight in Ankara Walnuts, *The Journal of Animal & Plant Science*, **2011**, *21*, 182-185.

(22) Binary regression: Tranmer, M.; Elliot, M. Binary Logistic Regression. Cathie Marsh Center for Census and Survey Research. Available at: http://hummedia.manchester.ac.uk/institutes/cmist/archive-publications/working-papers/2008/2008-20-binary-logistic-regression.pdf (accessed Mar 2018).

(23) Hazari, Z.; Sonnert, G.; Sadler, P. M.; Shanahan, M. Connecting High School Physics Experiences, Outcome Expectations, Physics Identity, and Physics Career Choice: A Gender Study, *Journal of Research in Science Teaching,* **2010**, *47*, 978-1003.

(24) Moakler, M. J. & Kim, M. M. College Major Choice in STEM: Revisiting Confidence and Demographic Factors. *The Career Development Quarterly*, **2014**, *62*, pp 128-142.

Chapter 5
Chemistry Students' Reflections on the Impact of their Course Selection Decisions

5.1 Introduction

To address student retention in STEM, it is important to improve the experiences of all students. Students are differentially impacted by their experiences in introductory STEM courses. For example, male and female students experience STEM courses differently and this has consequences on their retention and representation in STEM fields and careers.[1,2] Students from underrepresented groups (gender, ethnicity, socioeconomic status) also have different experiences in STEM courses and historically have been less likely to choose STEM as a field of study.[1]

Studies of students' decisions to choose or reject science have revealed what is important to students when making decisions about their academic future.[1,2,3] Palmer and colleagues found that student enjoyment, interest, ability, and perceived need are important factors for choosing or rejecting science courses.[4] Studies have shown that female and male students have different reasons for choosing or rejecting science, and that female students are more likely to leave science at the secondary and post-secondary level.[2,4] Female students are more likely to leave science due to lack of positive attitudes, interest, and self-efficacy in science.[2,4] Dick and coworkers found that lack of interest was key in students (male and female) rejecting science.[5] Importantly, students' experiences in these courses also impact whether or not they will leave the sciences.[1,3] Students decisions about which STEM courses to take first may have an outsized impact on their experiences and their persistence in STEM. Chapter 4 reported that students tend to select their first chemistry course based on perceived value and potential for success.[6] This decision is highly impacted by their university recommendation, when there is one.

The study reported here follows an investigation of the factors that influence student course selection when they are given a choice in their first introductory chemistry course (Chapter 4 of this thesis) and a study on the effect of student deviation from their placement recommendation on their performance in subsequent courses.[7]

5.2 Research Questions

The aim of the current study was to better understand the result of students' decisions on their experiences in their current chemistry course and their perception of how prepared they were for that course. The study was guided by the following research questions:

1. Did students feel adequately prepared for their current chemistry course?
2. How do they reflect on their experience in the chemistry sequence?
3. What did they perceive to be the cost of their decision?

By answering these research questions, this study adds to the current understanding about the consequences of students course planning decisions related to the introductory chemistry sequence.

5.3 Expectancy, Value, and Cost

Similar to our study in Chapter 4, this study was guided by Eccles' theory of socialization and expectancy-value, as expanded by Flake, to address the cost aspect of decision-making (Figure 5-1).[8,9] The expectancy-value (EV) model indicates that student participation in activities is based on student expectation for success and the perceived task value of the activity.[8] Expectation for success refers to whether or not students feel they possess sufficient ability to complete the activity successfully, which is related to student self-efficacy as framed by Bandura.[10] Task value refers to whether or not students feel there is worth for them in participating in the activity.

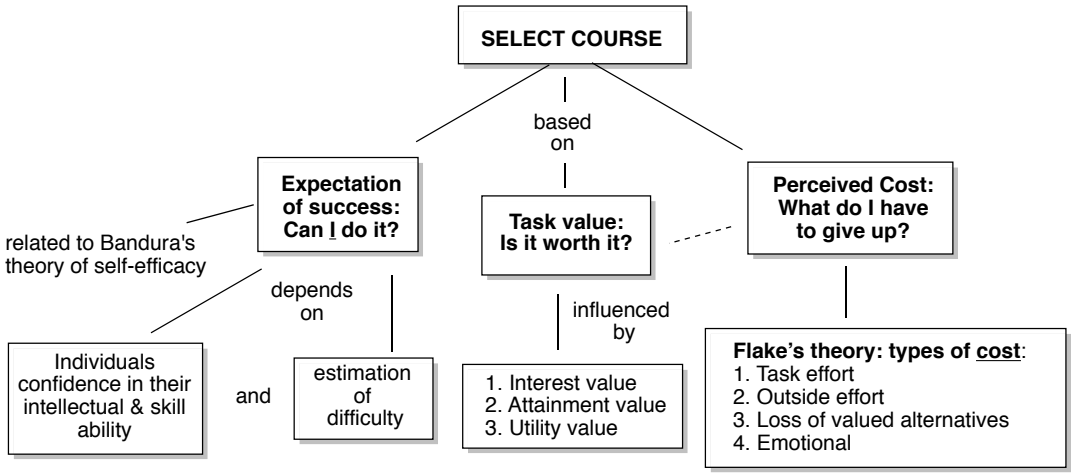


Figure 5-1. Map of the theoretical framework: Expectancy, value, and cost

Flake further developed the EV model by focusing on the components of cost for participation in activities.[9] Flake describes cost as a separate and measureable component of the EV model because cost is related to both task value and expectation of success. As in the Eccles' model, expectation of success is tied to self-efficacy, which is informed by Bandura's theory.[10] To derive the expanded cost model Flake studied college student motivation using interviews and factor analysis, and identified four salient components of cost that someone considers when choosing to participate in an activity: 1) task effort (there is too much effort required to participate); 2) outside effort (there is too much else in my life requiring my attention at this moment); 3) loss of valued alternatives (there is too much effort required and it takes away from participating in a different activity); 4) and emotional cost (the stress level in this activity is too high).[9] With respect to the Eccles' model, outside effort is related to expectation of success and task value, whereas the other types of effort are primarily more aligned with task value. This complexity demonstrates why cost should be its own component in the model.

Although Figure 5-1 shows the components of this EV model as separate, cost is related to both expectation of success and task value. This theoretical framework informs the analysis of students' reflections on how their decision about which chemistry course to take first impacted them moving forward. It is assumed that cost as described by Flake could apply to this study in a few ways. For example, time spent taking a course a student did not need could reflect both task effort and loss of valued

alternatives costs. Whereas, taking a course that was too challenging for them could reflect emotional, loss of valued alternatives, or task effort cost. Specifically, the goal of this study was to understand whether or not students felt adequately prepared for the course they did end up taking and the perceived cost of their decision.

5.4 Methods

This study used phenomenography to examine how students were impacted by their decision about which course to take first.[11] The phenomenon examined was the lived-experience of students when they chose their first chemistry course and their experience in those courses. Similar to our other studies in this area, this study sought to understand how different groups of students are impacted by their decisions and their experiences in the introductory course sequence. A convergent parallel mixed method approach was used to capture a richer understanding of this phenomenon that included quantitative analysis survey results, which were contextualized with qualitative interview data.[12]

5.5 Study Context

Similar to in Chapter 4, this study was conducted at the University of Michigan (UM), where the chemistry sequence follows at 1:2:1 order (Figure 5-2).[13] The four-course sequence begins with general chemistry, followed by two semesters of organic chemistry, and a semester of introductory physical chemistry/general chemistry II. Incoming students take two placement tests at orientation: a general chemistry exam (ACS NSTA Cooperative Examination for High School Chemistry, Form 1975, Part 1) and a pre-calculus test that was developed in house. From these results students are recommended to take either Macroscopic Investigations and Reaction Principles (General Chemistry) or Structure and Reactivity I (Organic Chemistry I). As a consequence many first year students are recommended to enroll in organic chemistry I in their first semester in college. Regardless of their recommendation, students can take General or Organic Chemistry first, as there are no prerequisite requirements for either course.

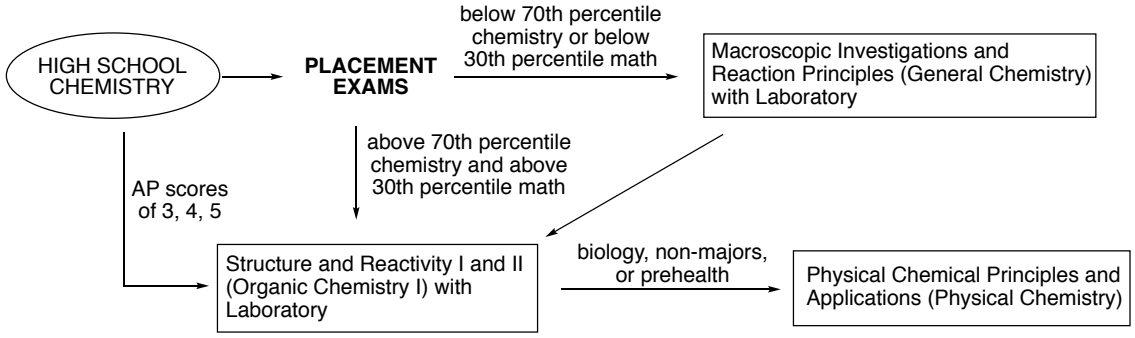


Figure 5-2. Introductory chemistry sequence at the University of Michigan (UM)

5.6 Data Collection

This study was conducted using a convergent parallel mixed-methods approach to investigate student experiences in the introductory course sequence as a result of their decision about which course to take first.[12] Students in the three courses described above: General Chemistry, Organic Chemistry I, and Physical Chemical Principles and Applications (Physical Chemistry) in the Fall 2015 semester at UM were the subjects of this study. The primary data sources were: 1) a survey given at the beginning of the semester including questions about course decision and their perspectives on their experience; 2) an end of term survey including questions about their experience in their current course and their perceived preparedness; and 3) focus group interviews to gather deeper information about the students' specific experiences. The interview protocol is included in the supporting information of this article. Only students who completed both pre and post surveys were included in the analysis where N=1,646 (response rate 71%). Cognitive interviews were used to determine whether survey questions were interpreted as intended as described in our prior report.[14] IRB approval was obtained and students consented to participate before research began.

The study also included focus group interviews to contextualize the quantitative findings. The sampling strategy had two stages. First, students were asked during the initial survey whether they were willing to be interviewed. Second, data about participants from this pool were inputted into statistical program SPSS (Version 24) to randomly draw students using a stratified sampling strategy (ref 12, p 144). Using the SPSS tool, participants were randomized so there would be more weight on students from underrepresented groups in order to capture a breadth of student group

experiences. Students from the final pool were then invited by email to participate in a focus group interview. The focus group interviews were organized based on the participants' current course. N = 50 students were interviewed in focus groups that ranged from 1 to 10 participants, depending on their scheduling availability. At the start of the focus group students completed pre-interview writing about their placement experience to help refresh their memory prior to group discussion. Details regarding the specific questions are provided in the supporting information.

5.7 Data Analysis

Statistical analysis of survey questions was carried out using SPSS. In order to investigate different groups of students, a set of course-based data sets were created for students from each of the three courses (Figure 5-2). Eight data sets were created by first splitting the data set into two sets 1) total/all students and 2) non-engineer students. Engineering students have different course requirements than other students and this first separation allowed us to examine that difference.[15] In each of these two sets, the data was split again four ways based on participating students current enrollment: 1) all courses, 2) General Chemistry, 3) Organic Chemistry, and 4) Physical General Chemistry, to obtain 8 data sets in all (Table 5-1). There were no discernable trends when individual courses were examined by regression; full regression results are presented in the Experimental section of this chapter (Tables 5-7 and 5-8). Three new categorical variables were created from the registrar data to indicate whether a student complied with their recommendation about which course to take first. The first variable is "Placement Decision", which refers to all student enrollment/recommendation relationships (what the students were recommended for in relation to what they took). The other two variables were made based off of the "Placement Decision" variable. "Deviated UP" indicates the student was recommended to take General Chemistry, but enrolled in Organic Chemistry first (0 = no, 1 = yes), and "Deviated DOWN" indicates that the student was recommended to take Organic Chemistry but enrolled in General Chemistry (0 = no, 1 = yes). The other factors (gender, ethnicity, estimated parental income, HS GPA, placement score) used in the regression analysis were provided from the survey or the registrar data.

Table 5-1. Data sets created for statistical analysis

Data Set	College	Course
1	All Students	All Courses
2		General Chemistry
3		Organic Chemistry
4		Physical General Chemistry
5	Non-engineering	All Courses
6		General Chemistry
7		Organic Chemistry
8		Physical General Chemistry

The quantitative analysis focused on two questions from the survey instrument reported in Chapter 4. To learn more about their experience, we also asked students to what degree they agreed with the following statements in the exit survey: “The chemistry knowledge I had when I began the course was sufficient to be successful on assignments and exams” and “I did not feel adequately prepared for this course” using a five point Likert scale. These responses were combined with demographic information and registration information before performing the linear regression analysis.[16,17] The dependent variables in these analyses were the answers to those above questions and the independent variables were “Placement Decision”, “Deviated UP”, and “Deviated DOWN”. Other factors including gender, ethnicity, estimated parental income, HS GPA, and placement score were included in the model to account for other observable student characteristics that may be correlated with the outcome variable.

Interview recordings were transcribed verbatim and examined using the constant comparative method (ref 12, pp 434–440). The focus group interviews were analyzed to answer the question “How did [the students’] decision impact them moving forward?” and the coding included reflections on their experience and recommendations for other students. We first read through the interviews to become familiar with the data and to see whether they relayed information about how students’ decision impacted them, whether students would make the same decision again, and the perceived cost of their decision. The interviews were then open coded using NVivo (version 11) by me and an initial code dictionary was created. A colleague, who was familiar with the data set and had prior experience coding interview data, was provided with the dictionary and a subset of the interviews (one from each of the three courses) to code. Initial inter-rater agreement was 0.43 (Krippendorf’s alpha). Codes were discussed and the dictionary

was refined until a value of 0.91 (Krippendorf alpha value) was obtained. The fifteen interviews were then re-coded with the finalized dictionary (please see the Experimental section).

5.8 Results and Discussion

Question 1: Did students feel adequately prepared?

In the post-term survey students were asked to indicate whether or not they felt prepared for the course they were currently enrolled in, to determine whether or not they felt their decision was the right one. Students indicated their agreement with the following two statements with Likert-style responses: *The chemistry knowledge I had when I began the course was sufficient to be successful on assignments and exams*, and *I did not feel adequately prepared for this course.* These statements provided a proxy for expectation of success from the EV model, where students reflected on their potential for success in introductory chemistry. These statements essentially negate one another and inverse answers were expected with respect to the other, which also provided a measure of validity for our results.[18] Table 5-2 shows that students were generally neutral or agreed with the statement that the chemistry knowledge they had when they began their chemistry course was sufficient, as the means for all courses were above 2.80, and as high as 3.15 for Physical Chemistry. Furthermore, students on average disagreed with the second (negatively-framed) question. It is intuitive that students who persisted to the fourth chemistry course in a sequence would indicate a higher preparedness than those in earlier courses. Thus, it is possible that some subset of students who struggled in earlier courses did not make it all the way to the final course and the students in the final course are more mature and confident and likely to have felt prepared.

Table 5-2. Descriptive statistics for the preparedness questions

Question	Course	Subset (N)	Mean (Std. Dev)
The chemistry knowledge I had when I began the course was sufficient to be successful on assignments and exams.	All Courses	All Students (1646)	2.92 (1.147)
		Non-engineers (1127)	2.91 (1.142)
	General Chemistry	All Students (810)	2.85 (1.190)
		Non-engineers (444)	2.80 (1.184)
	Organic Chemistry	All Students (622)	2.92 (1.066)
		Non-engineers (480)	2.90 (1.070)
	Physical Chemistry	All Students (184)	3.15 (1.167)
		Non-engineers (179)	3.14 (1.170)
I did not feel adequately	All Courses	All Students (1641)	2.65 (1.013)

prepared for this course.		Non-engineers (1122)	2.72 (1.021)
	General Chemistry	All Students (806)	2.61 (1.030)
		Non-engineers (440)	2.72 (1.046)
	Organic Chemistry	All Students (621)	2.75 (0.956)
		Non-engineers (479)	2.79 (0.956)
	Physical Chemistry	All Students (184)	2.47 (1.050)
		Non-engineers (179)	2.47 (1.051)

The scale for responses ranges from “Strongly disagree” = 1, to “Strongly agree” = 5.

Linear regression was performed to examine whether or not compliance with the recommendation about which course to take first was related to students’ perception of their preparedness for the introductory chemistry courses.[16] Whether or not students deviated from their placement recommendation was examined - specifically whether or not students enrolled in Organic Chemistry when recommended to take General Chemistry or enrolled in General Chemistry when recommended to take Organic Chemistry - because one could expect that students who took a course “above” what they were recommended for would feel differently about their preparedness than a student who took the course “below” the course they were recommended for. Demographic factors, including gender, ethnicity, estimated parental income, and placement exam score, were also included in the model.[16,17]

Table 5-3 shows the linear regression results from the first survey question. Standard coefficient beta values |>0.1| were interpreted as meaningful and a positive standard coefficient beta value as indicating that the factor positively predicts their answer to the survey question, whereas a negative standard coefficient beta value indicates that the factor negatively predicts their answer. Values were considered statistically significant where $p < 0.05$. Both the “Placement Decision” and “Deviated DOWN” variables as well as placement score were statistically significant, meaningful predictors of their response. “Deviated UP” was not statistically significant and could not be ruled out as a factor related to students’ perceived level of preparedness. Fewer students “Deviated UP” or took Organic Chemistry when they were recommended to take General Chemistry, which may account for this result.

Table 5-3. Linear Regression for all courses for survey question: The chemistry knowledge I had when I began the course was sufficient to be successful on assignments and exams

Subset	Demographic	Standard Coeff Beta
All students	Placement Decision	-0.187[b]
	Deviated UP	0.023

	Deviated DOWN	0.193[a]
	Placement Score	0.249[a]
	Gender	-0.036
	Ethnicity	0.001
	Parental Income	0.037
	HS GPA	0.023
Non-engineers	Placement Decision	-0.140[c]
	Deviated UP	0.031
	Deviated DOWN	0.155[b]
	Placement Score	0.175[b]
	Gender	-0.084[c]
	Ethnicity	0.001
	Parental Income	0.057
	HS GPA	0.043

a = $p<0.0001$b = $p<0.005$,c = $p<0.05$

The coefficient for "Placement Decision" was meaningful and significant, which generally indicates that their placement decision was correlated to their perceived preparation, but does not distinguish between the specific decision type. Placement Score was positive and significant; indicating that the greater the placement score was the more prepared a student felt. The "Deviated DOWN" coefficient was positive indicating that students who took General Chemistry first, though they were recommended to take Organic Chemistry first, felt more prepared. This is unsurprising; because, if a student takes a course that they have been told they do not need, they are more likely to have been more prepared for the course than someone who was advised to take it. They may also feel more confident, based on their own experience with chemistry or based on the results of the placement test that contributed to an enactive mastery or validating experience from the recommendation process itself. A discussion with advisor, which usually includes a recommendation, may have served as a form of verbal persuasion, also contributing to a students' self-efficacy. All are related to Bandura's theory as potential contributors to self-efficacy.[10] Students' placement scores were correlated with their self-perceived preparedness as well as their actual preparedness, as measured by test performance in our previously published study.[7] In the non-engineering data set, gender was statistically significant, but the standard coefficient beta value was below $|<0.1|$. It was also statistically significant in a few individual course data sets (represented in Tables 5-7 and 5-8 in the Experimental section of this chapter), but was inconsistent so deemed not useful for this analysis.

Table 5-4 shows the results for the second survey question: *I did not feel adequately prepared for this course*. As expected, the results for this question are the

inverse of the previous question. Both the “Placement Decision”, “Deviated Down”, and “Placement Score” variables were statistically significant, meaningful predictors of their response. The Beta Coefficient for each was similar in magnitude, but opposite in direction from the first statement. Corroborating that students who “Deviated DOWN” were more likely to feel prepared relative to other students. Again, “Deviated UP” was not statistically significant and the null hypothesis, that students who take Organic Chemistry when recommended to take General Chemistry first would not feel differently prepared than other students, could not be ruled out. Gender did not appear to have the same impact as with question 1, further confirming the analysis of these results.

Table 5-4. Statistically significant results from the linear regression analysis for the survey question: I did not feel adequately prepared for this course

Course	Subset	Demographic	Standard Coeff Beta
All courses	All students	Placement Decision	-0.295[a]
		Deviated UP	0.001
		Deviated DOWN	-0.254[a]
		Placement Score	-0.299[a]
		Gender	0.036
		Ethnicity	-0.017
		Parental Income	-0.031
		HS GPA	-0.011
	Non-engineers	Placement Decision	0.208[b]
		Deviated UP	-0.004
		Deviated DOWN	-0.148[b]
		Placement Score	-0.241[a]
		Gender	0.035
		Ethnicity	0.011
		Parental Income	-0.006
		HS GPA	0.011

a = $p<0.0001$, b = $p<0.005$, c = $p<0.05$

Question 2: How do students reflect on their experience?

Focus group interviews were thematically analyzed and indicated that students regarded relative maturity and the development of academic skill-fullness as important factors in their experiences in the first chemistry courses. Of the fifty students interviewed, twenty-six said they would make the same decision again given the information they had at the time of the interview. One student said:

> “Yes, I would make the same decision again. I think having a good basis or that General Chemistry gives you in a college environment is crucial.”

Four Organic Chemistry students and five Physical Chemistry students expressed some regret, which included a combination of 1) what course they took first,

2) when they took it, or some other variable. One student said the following when reflecting on her experience:

> "I think I would just change when I took it. So I went straight into Orgo, but I think I would've chosen not to take it my first semester of college, cause I just was not prepared for my workload or how to really study for it. So I think if I'd like given myself that semester to actually like adjust to it. I don't think that I really forgot many of the concepts from AP Chem, so I don't think taking Gen Chem that semester would've really helped, but I do think that if I had held off on taking Orgo, it would've been better."

This and other students recognized that their maturity and academic skillfulness was developing during the first semester of their freshman year. They describe how General Chemistry course would not have been helpful, but rather just taking Organic Chemistry at a later term would have been better than as a first semester first year student. This perspective suggests that students do not necessarily need to take General Chemistry prior to Organic Chemistry, but that taking Organic Chemistry later in their college careers would increase their likelihood for success. Therefore, in addition to deciding whether to take General Chemistry or Organic Chemistry first, students should also carefully consider when to take their first chemistry course.

This view was conveyed by several other students during the interviews. Some Organic Chemistry and Physical Chemistry students described how they either were, or would have been more prepared for Organic Chemistry as a second-semester first year student or as a sophomore. One said the following:

> "I agree that I definitely would've done better in orgo 1 probably if I had taken it my sophomore year, because I took it my freshman year first semester… I think I would've done better if I had taken it after I had already adjusted to college".

Likewise, seven students, who took General Chemistry first, reflected that they felt they were more prepared for Organic Chemistry as a sophomore or a second semester first year student. One student reflecting on her experience said:

> "If I had taken Orgo freshman year, I don't know if I would've done as well as I did when I took it sophomore year, because I had already had that freshman like adjustment to college".

On the other hand, other students who took organic chemistry first indicated satisfaction with their decision. One Organic Chemistry student in particular said the following about feeling prepared when asked if they would make the same decision again:

> "I would definitely [take Organic Chemistry first] again. Feel pretty comfortable. I think I'll probably be one of those graduates from my high school that goes back and tells everybody you'll be okay. Like you're being prepared."

These exemplars illustrate the range of responses provided by students: some expressed regret or discomfort with taking organic chemistry first while others were satisfied with their decision to take organic chemistry first. Both are linked to students' perspectives of their general preparedness and maturity rather than difficulty of the content.

Many students expressed positive and negative course reflections, but these experiences are not necessarily related to their course planning decisions, but rather may occur as a function of the specific structure of the course. For example, many students discussed how the course they were taking was difficult due to format of the course, or because of the material. Students in Organic Chemistry discussed how the difficulties of Organic Chemistry lie not in the material, but rather how the class is run:

> "Yeah, they don't guide us. There's no like no homework or anything to like keep us on track. And you can't learn everything from lectures, so you're basically looking up stuff yourself. I mean there's all the resources too but like the I've been to the after-school tutoring, and since there's so many people, you can't really get much taught.",

Another student discussed differences between Organic and General Chemistry, and how they perceived General Chemistry as a weeder course:

> "Because Orgo at least was kind of interesting. I mean you knew that it was gonna be a challenge and you like geared up for it. Gen Chem I feel like kind of hurt my ego, because I went in going you know this is literally the most basic level of chemistry taught at the university level. And it just like hits you in the face, because all of the sudden, you're just like, surprise, it's sort of like a weeder."

These examples illustrate how students have negative reflections on both General and Organic Chemistry courses that were independent of their placement decisions, and again more related to their perceived lack of maturity when they took their respective

courses. For example, the student reflecting on Organic Chemistry described challenges related to the lack of structure and requirement of independence on the part of the student. Similarly, the General Chemistry student described the relative intensity of the course as challenging. Indicating that both courses may require a greater degree of maturity on the part of the student.

Question 3: What did students perceive to be the cost of their decision?

Qualitative analysis of focus group interviews was used to examine what students perceived to be the cost of their decision about which course to take first. Students described costs including emotional, task effort, and loss of valued alternatives as costs described by the Flake adapted EV model.[9] With respect to emotional costs, students discussed course regrets and negative personal reflections on their experience in either general or organic chemistry. For example, a Physical Chemistry student recalled her experience with failing Organic Chemistry the first time around:

> "I actually failed Orgo. I took it my first semester. I mean there is like a lot of reasons, and I like take complete responsibility for that…I didn't take it with anyone I knew, which was like problem número uno, because like coursepack you don't get answers so like and I mean I was an outgoing person, but it's a huge class I didn't like my discussion [instructor]. I didn't think he was helpful at all."

This exemplar conveys an emotional cost of a student's decision and their perception of its impact on them. First, it was inferred that failing Organic Chemistry would take an emotional toll on the student. The cost described by this student also includes both *loss of valued alternatives* and *task effort* because the student had to take the course again, which cost them time and credits spent on a second attempt at Organic Chemistry later in their college career.

Cost in the form of *loss of valued alternatives* was specifically discussed with relation to course planning concerns, such as having to take other courses and trying to fit all their desired courses into their time in college. A General Chemistry student described struggling to fit in all the classes they wanted to take:

> "I just I wanted to take French, but I couldn't, because I couldn't schedule it and because there's so much chemistry in my schedule."

In this case, the cost of their course decision was that they needed to sacrifice time in other courses, take a course later than they wanted to, or not at all.

Many students indicated that they wish they knew more about the course structure and the nature of Organic Chemistry when they were making their decision. Specifically, students had a sense of General Chemistry based on high school experiences, whereas the nature of Organic Chemistry as a subject was a mystery. An Organic Chemistry student, who took General Chemistry first, said:

> "I wish I had a more realistic idea of what Orgo was about because I probably would've picked it first. Or well not done Gen Chem at all then. Cause I didn't need it for my major, and I'm kinda like I took this class for no reason."

This also reflected both *task effort* and *loss of valued alternatives* costs on the part of the student. Additionally a General Chemistry student said:

> "I kind of wish I knew how the sort of like the lab discussion and lecture thing kind of worked because that was I mean if anything that was kind of hard to schedule around, and also it's a lot of chemistry, so that's like that's one thing I definitely didn't expect to take this much chem my first semester of college."

These reflections may be particularly useful for faculty or advisors who are guiding students through their course selection. Many students indicated this as a critical piece of information they wish they had when they made their decision.

In summary, we sought to better understand how prepared students felt for the chemistry course that they were enrolled in at the time of the study in light of their placement decision. Students generally reported feeling prepared for the course they took (or feeling neutral about it). If a student deviated down in their enrollment, they tended to report being more prepared. The second research question was concerned how students reflected on their experience and the third question on their perceptions about the cost of their decision. The latter is particularly relevant to Flake's work, wherein the importance of cost was included as a salient component of Eccles' EV model.[8,9] Students held a variety conceptions about their experience including *emotional, task effort*, and *loss of valued alternatives* types of costs. Students reflected about what they wish they knew when they were making their decision and many

indicated that they knew more about course structure and about the nature of Organic Chemistry was when they made their decision.

5.9 Limitations

One limitation of this study is that data was collected only over one semester in our three courses. A longitudinal study would give a richer understanding of the students' experience over time, but was beyond the scope of our study. Relatedly, this data was only collected during the "on" cycle, so perspectives of some students who elected to not take introductory chemistry that semester could be missing. Lastly, our findings are specific to the context of the study, because UM allows students the freedom to take courses in an order that suits them with guidance. However, these results are transferrable to other departments where AP credit or other mechanisms are used for placement or recommendations or where alternative curriculum models are used because these departments may want to learn more about students' perspectives on their placement and chemistry experience, as well as their perceived preparedness.

5.10 Implications

This study added to present understanding about whether students' placement decision is related to their perception of their preparedness for chemistry coursework and the costs incurred by students as a result of their decision. These results are particularly relevant for institutions and chemistry departments that use placement tests to guide students' course planning decisions. Findings revealed that students generally felt prepared for the course they took, but that there costs associated with their decision.[9] Likewise, chemistry advisors may be provided with a greater understanding about student perspectives that can aid them in guiding students. Specifically, a primary finding was that students recognized the maturity that develops as they navigate college-level chemistry, and that students should not only be concerned with which class to take first, but also when to their first course. Further, while students have a better idea about what to expect from college level General Chemistry, Organic Chemistry is more nebulous. Thus, helping them to understand the differences between the two courses better aid them in their course planning decisions.

The work summarized in this chapter is in preparation for submission to *Chemistry Education Research and Practice*.

5.11 Experimental

I. Course Descriptions

The content in all three courses remained consistent over the course of the study and all courses operated using a traditional lecture format.

The **CHEM 130 - Macroscopic Investigations and Reaction Principles** (first semester General Chemistry) course is intended as a stand-alone course that fulfills the general chemistry requirement for some disciplines, for instance many engineering majors, or that serves to strengthen the chemistry background of students who did not meet the standard of preparation for organic chemistry. Around 2000 students take general chemistry each year. Faculty instructors rotate into the course, however, the content and structure of the course were maintained by a single course coordinator over the duration of the study. The course meets for three 50-minute lectures each week for a 15-week semester. Each week students also meet for 50-minute discussion lead by a graduate student teaching assistant. The average lecture section is comprised of 400 students and discussion sections average 20 students. The course primarily utilizes exams (two midterms and one final exam) to assess student performance. All students in all sections of the course take the same exams. The exams are multiple choice and account for 70% of the final grade. The remainder of the grade comes from weekly discussion quizzes, homework, and class participation through clickers. The course includes traditional general chemistry topics including: atomic structure, balancing chemical equations, stoichiometry, moles, reactions (precipitations, acid/base, redox), gas laws, enthalpy, quantum numbers, electron configurations, Lewis structures, molecular geometry, phase changes, intermolecular forces, and an introduction to equilibrium and acid-base chemistry.

The first term **CHEM 210 - Structure and Reactivity** (Organic Chemistry) course enrollment is comparable to general chemistry also enrolling around 2000 students yearly, of which roughly 20% are students with freshman status. Faculty instructors also rotate into this course, but as in the other courses included in this study the course syllabus and a set of master lecture notes remained constant over the duration of the study. The course meets for three 50 minute lectures each week for a 15 week semester. Each week students also meet for a single 50 minute discussion lead by a

graduate student teaching assistant. The average lecture section is 400 students and discussion sections average 25 students. The course utilizes exams (three midterms and one final exam) to assess student performance. The exams in organic chemistry are distinct from both General Chemistry and Chemical Physical Principles exams in that they are composed of literature-based questions that require students to respond by writing or drawing. All students in all sections of the course take common exams. Course topics are designed for student mastery with little prior knowledge. They include Lewis structures, bonding, resonance, isomers, intermolecular forces, atomic and molecular orbitals including double and triple bonds, organic acids and bases and acid-base equilibria, organic reactions between electrophiles and nucleophiles, alkanes (NMR, conformation, nomenclature), organic molecule shapes and stereochemistry, nucleophilic substitution and elimination, leaving groups, alkenes (electrophilic addition, carbocations), alkynes (structure, isomerism, nomenclature, acidity, addition, and reduction) and electrophilic aromatic substitution.

CHEM 230 - Physical Chemical Principles (Physical Chemistry) is intended as a fourth term in chemistry for non-chemistry science majors and students completing the two-year chemistry sequence required by medical or dental graduate programs. Chemistry majors typically enroll in a separate calculus based course. Approximately 700 students (mostly juniors and seniors who have previously completed both semesters of organic chemistry) take the course per year. The course has the same meeting structure as both general chemistry and the first semester organic chemistry course. It meets for three 50 minutes lectures each week for a 15 week semester. Each week students also meet for a single 50 minutes discussion lead by a graduate student teaching assistant. Topics mirror those typically found in a second semester general chemistry course with an in-depth emphasis on thermodynamic principles to explain why physical and chemical 3 processes take place. Topics include: ideal and real gases; work; enthalpy; entropy; Gibbs free energy; equilibrium as applied to chemical reactions, physical change, and solutions; acid-base equilibria including titrations and buffers; solubility; electrochemistry; an introduction to kinetics; and nuclear chemistry.

II. Interview Protocol

Interview Protocol (goal 30-45 mins)

Interview script:

INTERVIEWER: “The chemistry department has recently initiated a study to investigate how students are affected by enrolling, or not enrolling, in CHEM 130 (general chemistry) during their academic career. You have agreed to participate in an interview as part of this study. There are several reasons for asking you to participate, including:

To find out how you were impacted by your decision to enroll in your first chemistry class after learning your placement test results.

To learn how you were affected by your placement, and what you might change about the process.

This interview is confidential. Transcripts from the recordings of the discussions and the documents produced from the analysis will not include names or any identifying information about the participants, other than summary information - for example, how many people enrolled in CHEM 130 instead of CHEM 210, when they were recommended for the latter.

Are there any questions before we begin?”

[Signed consent obtained here]

INTERVIEWER: “To begin we would like you to do a little bit of writing about your experience. This is intended to help surface your memories about chemistry placement. Take your time and let me know if you have any questions.”[They do writing]

[discuss writing prompt]

Q1 “The first question asks you to describe what you remember about your experience with chemistry placement. Please describe your experience including when you took the placement test, what the test was like and what your conversation with your advisor was like”

Q2. “The next question asks you to consider a list of factors that might be important in make a decision about what course to take first. Please describe the factors that you decided were important and explain why they were important to you.”

Q3 “Finally, would you add or remove anything from the list? If so, why?”

Probing Questions:

What do you think makes general chemistry different from organic?

Why do you think organic might have a reputation for being hard?
What is your experience in Chemistry 130 (210, 230) like right now? Or
OR (210, 230 only) How was your experience in 130 when you took it?
230 AND 210 ONLY: If they took 130, did it help them in 210 or 230 (respectively)? Why or why not? (OR didn't take 130, did it impact in 210 or 230)
Would you make the same placement decision again or recommend other students to do the same? - make open ended not y/n?
What do you wish you knew that would help you make a better decision?
Is there anything else that you might want to add?

III. Prewriting document

We asked interview participants to answer the following 2 questions.

1. Students receive a recommendation about whether to start with general chemistry or organic chemistry based on their performance on a chemistry placement exam or if they have AP Chemistry credit. This is usually a process that happens during orientation. Please describe what you remember about your experience with chemistry placement.

2. Below you will find a list of factors that may be important to students when deciding whether to take general chemistry or organic chemistry first. Please read over the list and put and "X" next to any items that you consider to be important to you.

- Family concerns
- Financial aid
- Confidence about preparation in chemistry
- Time since last chemistry course
- Academic plans
- Applicability/major
- Graduation requirements
- Course rigor
- Course load (number of courses you need to take first)
- Rumors about the course
- Advice from family
- Advice from friends

- Discussion with and academic advisor
- Advising recommendation based on placement test
- Nonacademic obligations (work study, sports, etc)
- Personal confidence
- Interest
- Health/Stress levels
- Scheduling

a. Please explain why you selected those items you marked with an "X"

b. Would you add or remove anything from this list? If so, what and why?

IV. Survey Frequencies

Table 5-5. Table of frequencies for all courses

Entry	Demographic	Data set (N)							
		A (2,020)	**B (1,363)**	**C (923)**	**D (498)**	**E (842)**	**F (627)**	**G (209)**	**H (204)**
				Gender					
1	Male	953 (47.2%)	515 (37.8%)	476 (51.6%)	175 (35.1%)	380 (45.1%)	252 (40.2%)	77 (36.8%)	76 (37.3%)
2	Female	1,067 (52.8%)	849 (62.2%)	447 (48.4%)	323 (64.9%)	462 (54.9%)	375 (59.8%)	132 (63.2%)	128 (62.7%)
3	Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
				Ethnicity					
4	Ethnicity: Asian	368 (18.2%)	271 (19.9%)	125 (13.5%)	71 (14.3%)	179 (21.3%)	140 (22.3%)	57 (27.3%)	55 (27.0%)
5	Ethnicity: White	1,198 (59.3%)	810 (59.4%)	569 (61.6%)	313 (62.9%)	496 (58.9%)	372 (59.3%)	109 (52.2%)	106 (52.0%)
6	Ethnicity: Other	454 (22.5%)	283 (20.7%)	229 (24.8%)	114 (22.9%)	167 (19.8%)	115 (18.3%)	43 (20.6%)	43 (21.1%)
7	Other: Black/African American	59 (2.9%)	41 (3.0%)	32 (3.5%)	16 (3.2%)	16 (1.9%)	14 (2.2%)	7 (3.3%)	7 (3.4%)
8	Other: Two or more races	85 (4.2%)	66 (4.8%)	43 (4.7%)	29 (5.8%)	35 (4.2%)	30 (4.8%)	6 (2.9%)	6 (2.9%)
9	Other: Not indicated	120 (5.9%)	76 (5.6%)	53 (5.7%)	26 (5.2%)	42 (5.0%)	26 (4.1%)	21 (10.0%)	21 (10.3%)
10	Other: Non-resident alien	73 (3.6%)	29 (2.1%)	40 (4.3%)	14 (2.8%)	27 (3.2%)	12 (1.9%)	3 (1.4%)	3 (1.5%)
11	Other: Hispanic/Latino	112 (5.5%)	68 (5.0%)	59 (6.4%)	27 (5.4%)	44 (5.2%)	32 (5.1%)	6 (2.9%)	6 (2.9%)
12	Other: American Indian/Alaskan Native	5 (0.2%)	3 (0.2%)	2 (0.2%)	2 (0.4%)	3 (0.4%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
13	Other: Native Hawaiian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
14	Other: Missing	0	0	0	0	0	0	0	0

		(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)
		Course Decision							
15	Complied with recommendation	1,627 (80.5%)	1,141 (83.7%)	672 (72.8%)	403 (80.9%)	731 (86.8%)	527 (84.0%)	184 (88.0%)	179 (87.7%)
16	Deviated (gen chem ➔ orgo)	41 (2.0%)	40 (2.9%)	-	-	30 (3.6%)	29 (4.6%)	10 (4.8%)	10 (4.9%)
17	Deviated (orgo ➔ gen chem)	235 (11.6%)	74 (5.4%)	201 (21.8%)	47 (90.4%)	25 (3.0%)	21 (3.3%)	5 (2.4%)	5 (2.5%)
18	Missing	117 (5.8%)	109 (8.0%)	50 (5.4%)	48 (9.6%)	56 (6.7%)	50 (8.0%)	10 (4.8%)	10 (4.9%)
		Estimated Parent Income							
19	Parent income (< 25 K)	90 (4.5%)	69 (5.1%)	42 (4.6%)	26 (5.2%)	34 (4.0%)	29 (4.6%)	10 (4.8%)	10 (4.9%)
20	Parent income (25 – 50 K)	119 (5.9%)	66 (4.8%)	68 (7.4%)	30 (6.0%)	41 (4.9%)	26 (4.1%)	9 (4.3%)	9 (4.4%)
21	Parent income (50 – 75 K)	160 (7.9%)	112 (8.2%)	65 (7.0%	36 (7.2%)	73 (8.7%)	56 (8.9%)	17 (8.1%)	17 (8.3%)
22	Parent income (75 – 100 K)	183 (9.1%)	123 (9.0%)	91 (9.9%)	45 (9.0%)	70 (8.3%)	56 (8.9%)	21 (10.0%)	21 (10.3%)
23	Parent income (100 – 200 K)	553 (27.4%)	381 (27.9%)	243 (26.3)	138 (27.7%)	242 (28.7%)	183 (29.2%)	57 (27.3%)	54 (26.5%)
24	Parent income (> 200 K)	509 (25.2%)	344 (25.2%)	226 (79.6%)	118 (23.7%)	207 (24.6%)	155 (24.7%)	62 (29.7%)	60 (29.4%)
25	Missing	406 (20.1%)	269 (19.7%)	188 (20.4%)	105 (21.1%)	175 (20.8%)	122 (19.5%)	33 (15.8%)	33 (16.2%)

Data set key: A= Total Students - all courses, B = Nonengineers - all courses, C = Total Students - General Chemistry, D = Nonengineers - General Chemistry, E = Total Students - Organic chemistry I, F = Nonengineers - Organic chemistry I, G = Total Students - Physical Chemistry Principles, H = Nonengineers - Physical Chemistry Principles

V. Coding Method

The codes in our dictionary were used when someone described why they chose their first class and specifically the factors that led them to their decision. The first author used open coding and the constant comparison method to complete preliminary coding and produced a preliminary dictionary. Inter rater agreement was completed: an additional rater received three interviews (one from each course) and the preliminary dictionary. There was a 0.43 preliminary agreement according to Krippendorff's alpha. We had two meetings where we discussed the coding and refined the dictionary to include more details and become the below dictionary. The first refinement of the dictionary led us to a 0.79 agreement according to Krippendorff's alpha, followed by a second refinement, which led us to 0.91 agreement according to Krippendorff's alpha. The first author used the new dictionary to recode all of the focus group interviews, which led us to the frequencies used in the paper. When it came to coding the interviews, we looked for when a student specifically mentioned "XX" as being a reason

why they chose the course as their first course. When it came to negative coding (i.e. students mentioning reasons they did not use when they made their decision), we did not code the ones not mentioned (and assumed they were in the positive). We did not code any codes mentioned in the negative – we only ascribed codes to passages in which students mention a factor having an effect on their decision in the positive.

VI. Code Dictionary

Guiding Questions for open coding: How did their decision impact them moving forward? What are their reflections on their decision and chemistry sequence experience?

Table 5-6. Code dictionary

Code #	Code	Definition	Example
		General Reflections	
1	Course regrets	Students describe regret about the choice they made - specifically related to the order they took the course in, or when they took the course	210 Oct 28 [00:13:47.05] f2: Uhh I think if I knew what I knew now, I wouldn't have taken gen chem.
2	Registration concerns	Students discuss fitting in all classes they are interested in and fulfilling requirements for major or other academic plans (also discussing how much time they have in college to fit in all their classes) - specifically this is a consideration they took when choosing their classes, or an effect of the course they did choose (for them or for others)	230 Oct 16 2 [00:22:02.02] m4: It may be not directly related to the placement, but I would tell them like there's definitely trade-offs, so I value going through gen chem. I actually didn't I hated it at the time, actually. But like now I'm thinking it was a good start for me, and that transition to orgo, I think would be really tough for a first-semester freshman, but I would also tell them that like it's a big time trade-off um cause you take gen chem first semester usually and then I've like the advice I've got was take orgo in one year, so I took that second semester off from the chemistry class, and now it's like it's a real big time crunch for me to fit all um my pre-med stuff especially with the like a non-traditional major and stuff um so that that's a big thing to let them be aware of at least. 230 Oct 16 2 [00:03:40.10] m1: I didn't, but I wish I had. Um because now I'm like having to go back and find a course that I can do that'll fulfill that requirement, because a lot of pharmacy schools don't take AP credit at all, so you have to have a different gen chem that's not that
3	Made the right decision and would make the same	Students said they made the right decision and would make the	210 Oct 29 [00:42:01.10] f2: Umm yes I would have still done the same decision.

	decision again	same decision again, knowing what they know now	
4	AP chemistry or high school chemistry helped	Students mention how AP chem (or other high school components (including teachers)) helped them in their experience at UM (not related to actual placement)	210 Oct 29 FG [00:13:11.03] f3: I would agree, because I think that orgo is a completely yeah it's still chemistry, but I think it's a completely different subject, and I mean, a lot of my high school came here, and we always talk about how our AP bio and our AP chem teachers were wonderful. They prepared us amazingly.
5	Learning new material	Students discuss how they are learning new stuff in whatever class they're taking	210 Oct 29 [00:18:15.25] m1: Kind of contrary to what he was saying was that I feel like as far as material that I've learned in organic chemistry so far um I'm like very unfamiliar with it. Like I don't have very much experience with any of it, and it's a lot of it is just like going into lecture, and I don't have the book. I don't read the book. But going into lecture, it's like all learning, reading, or all learning in class, which is interesting. Uh it's worked out very well for me so far, but it's definitely like you go to lecture and from beginning to end I'm like learning new things or reviewing things that I've learned in this class.
6	Mostly review	Students discuss how the material they saw in their UM chemistry classes were mostly review for them	130 Oct 12 [00:12:04.12] f3: Um well I think that as I kind of go through I...it's sort of like the whole course for me kind of jogs my memory like every day I like remember how to do something, and then I'll be able to do it and practice it a few times, so that's nice.
		Gen Chem reflections	
7	Positive gen chem reflections	Students describe enjoying gen chem (gen chem course, specifically) - personal and general	130 Oct 12 [00:20:16.04] f2: I actually enjoy the class.
8	130 prepared them well	Students say that 130 prepared them for later coursework (does not include predictions for 130 students) (gen chem course, specifically)	130 Oct 14 [00:04:17.10] f1: So I've actually taken both orgos, and I did very well in them, and I think gen chem did a very good job of preparing me for it.
9	Gen chem helped with basic stuff	Students report gen chem helping with basic orgo stuff (gen chem course, specifically)	210 Oct 29 [00:40:23.06] f3: I think it helped with like the basic stuff like we had said.
10	Gen chem is easier than orgo	Students describe gen chem being easier than orgo (gen chem course or material)	210 Oct 27 [00:20:52.22] f3: I think material-wise, gen chem is easier than orgo just personally. And I personally work better when there's a lot of numbers, which was the nature of gen chem.

11	Valued going through gen chem	Students report valuing taking gen chem, or not regretting taking it (gen chem course, specifically)	230 Oct 16 2 [00:22:02.02] m4: It may be not directly related to the placement, but I would tell them like there's definitely trade-offs, so I value going through gen chem. I actually didn't I hated it at the time, actually.
12	Negative gen chem reflections	Students describe not enjoying gen chem, or discusses gen chem being a weeder course (gen chem course, specifically) - personal and general	130 Oct 12 [00:19:37.21] f3: Yeah, I definitely agree. It makes it I don't know if less enjoyable is the word, but it definitely sort of is ... I'm just like uh I don't really wanna go to chem today, but...It is what it is. If you have to take it, you have to take it.
13	Do not regret not taking gen chem	Students describe not regretting their choice to take orgo first, or mention how gen chem material is not necessary	230 Oct 21 [00:08:45.06] m1: But I still think that overall it's not detrimental that I skipped 125 and 130.
14	Gen chem content didn't help with orgo	Students report gen chem not helping with orgo, or not being necessary for orgo - no negative or positive impact	210 Oct 28 [00:21:25.04] m1: I don't think you need it to do well in orgo. I haven't...we haven't really done anything gen chem in orgo.
15	Gen chem hurt their ego/was difficult	Students report feeling less confident after taking gen chem - thought they would do super well in gen chem and didn't (gen chem course, specifically)	230 Oct 21 [00:11:50.16] f2: ... Gen chem I feel like kind of hurt my ego, because I went in going you know this is literally the most basic level of chemistry taught at the university level. And it just like hits you in the face, because all of the sudden, you're just like, surprise, it's sort of like a weeder.
16	Taking gen chem would have probably been helpful	Students say taking 130 might have been helpful in general (can be said by any student)	230 Oct 22 [00:27:39.23] f1: ...I don't know if my AP chemistry was the same like course content that would be in 130, but if so, then I think yeah it would be helpful.
		Orgo Reflections	
17	Positive orgo reflections	Students describe enjoying orgo (orgo course, specifically)	210 Oct 26 [00:15:08.06] m4: I agree with that a lot. Like I actually enjoy this course much more than I liked gen chem. …
18	Orgo was easier/better than gen chem	Students reported orgo being easier than gen chem (course or material)	210 Oct 27 [00:20:07.19] m3:… Something like this, and then the exams were only calculations that were tricky. This one doesn't have calculations, and so it's based on concepts, and it's a lot easier.
19	Negative orgo reflections (general)	Students describe how orgo is a difficult course/material; includes discussion of orgo being a weeder class - (can be based on someone else's experience)	210 Oct 29 [00:18:15.25] m1: Kind of contrary to what he was saying was that I feel like as far as material that I've learned in organic chemistry so far um I'm like very unfamiliar with it. …

20	Negative orgo reflections (personal)	Students describe not enjoying orgo, specifically struggling or having a hard time, or being unfamiliar with the material, orgo was hard for **me** always includes 19 as well)	210 Oct 29 18:53.29] m1: So not a lot of previous knowledge is really helping me I would say, so I and I'm not very familiar with the things that were that are being brought up. I hadn't even heard of really resonance structures like I didn't know what that was, and that's like the one of the biggest basis things of like the first test was just like resonance and learning all that. So I had to learn it all from scratch, which was a little difficult
21	Teaching methods/course structure for orgo make it tougher/something to get used to	Students discuss how orgo is a tough class because of the way the course is set up (always inlcudes 19 as well) - usually based on exams being the only source of scores, lack of answers to coursepack, teaching up until the test	210 Oct 27 [00:20:30.00] f2: Um well I think that the material itself is of equivalent difficulty between gen chem and orgo. However, I feel that it is a lot harder to do well in class because of the teaching mechanism that they have in place.
22	Failed orgo (1)	Student reported failing orgo	230 Oct 20 [00:08:48.12] f1: I was the exact opposite. I actually failed orgo. Um so I took it my first semester. I mean there is like a lot of reasons, and I like take complete responsibility for that. …
23	Would have been more prepared for orgo/done better if they didn't take it first semester (reflection)	Students describe feeling that they would have been more prepared for orgo if they took it as a sophomore (or second semester first year) (reflection from students who did not do it)	230 Oct 16 FG1 [00:25:31.24] f3: I agree that I definitely would've done better in orgo 1 probably if I had taken it my sophmore year, because I took it my freshman year first semester and I also was taking calc 2 at the time.
24	Was more prepared for orgo as a sophomore/second semester first year (reflection)	Students describe feeling that they were more prepared for orgo when they took it as a sophomore (or second semester first year) (reflection from students who did it)	210 Oct 28 [00:12:55.20] f1: I mean it's a huge transition coming from high school to Michigan. Like...it's a lot more work, you're more dependent on yourselves, I wasn't exactly you know prepared for how the classes were gonna go. And this like this year I knew what to expect so I guess in that way it's better too.
	neutral orgo reflections		
25	Orgo and gen chem differences	Students discussed differences between orgo and gen chem (material or course)	210 Oct 29 [00:14:52.27] f3: I felt like gen chem was a lot more equations, which are easier to grasp. Just like logic and mathematically, whereas orgo is way more in depth and you have to draw, and you have to change... it's like we don't use equations.

26	Science = orgo	Students discuss how most students who are interested in science should take orgo first	210 Oct 28 [00:20:32.19] m1: ... If you're gonna go into science though I'd expect you to kind of place out of it. Like the gen chem, I guess. Cause you should. I don't know. If you're interested in science...
		230 Reflections	
27	Positive pchem reflections	Students describe enjoying pchem, in some cases more than orgo	230 Oct 16 2 [00:16:54.25] m1: I definitely like the structure a lot more. I think that the material is probably on par in terms of difficulty, but I feel like I understand it a lot more because I'm forced to do something with it twice a week. Um for the online homeworks and then the clicker in class is a lot. It helps me realize okay here's what I actually understand, and it forces me to actually think in class instead of just mindlessly taking notes, which I felt orgo was, because it was just you have to just keep writing, keep writing, keep writing, because he was going so fast. So...
28	Negative pchem reflections	Students describe not enjoying pchem	230 Oct 22 [00:15:17.15] f2: Uhh I don't know. I feel a little less confident with my chemistry abilities, actually.
29	Would have done better in 230 if they took 130	Students reflect on how they would have done better in 230 if they had taken 130 - (specific code of 17 - always coded together)	230 Oct 16 1 [00:18:10.07] f2: Umm...yeah kind of going off what you said. Not taking 130 I feel like is not necessarily put me behind but made me struggle more in 230. I know I'm kind of having a hard time with it right now. Um just because it's been so long since I learned it. ...
30	Pchem before orgo?	Students discuss how they might have preferred to take 230 before 210 (shortly after gen chem/ap chem) to retain info better	230 Oct 16 1 [00:05:40.12] f3: I don't think I really did. I think actually thinking about it might've been smarter for me to take P Chem before orgo, even though like that that's you know PChem's probably a harder class, but I feel like it builds more off of what I learned in high school. Or what would've been in general chem, so I feel like if I maybe switched the two, I wouldn't've had this, because now it's been I'm a junior so it's been like 4 or 5 years since I took like what I consider to be like the chem class where I learned all this stuff in high school, so I feel like if I had taken it closer to then, I wouldn't've had so much trouble remembering everything. ...
		Wish they knew	
31	Wish they knew what orgo was before deciding	Students reflect on their placement experience and mention how knowing what orgo was (how it's different from gen/pchem) would have helped them make a more informedd ecision	130 Oct 12 [00:15:13.18] f3: Maybe a sense of what organic chemistry was. (they were asked what they wish they knew before they made their decision)

32	Wish they knew about course structure (any course) before deciding	Students wish they knew how different courses were structured before making their decision	130 Oct 12 [00:15:21.16] f3: I kind of wish I knew how the sort of like the lab discussion and lecture thing kind of worked because that was I mean if anything that was kind of hard to schedule around, and also it's a lot of chemistry, so that's like that's one thing I definitely didn't expect to take this much chem my first semester of college.
	Recommendations	recommendations are indicated by vocabulary such as: I would tell others/recommend/I would tell someone else, etc..	
33	Recommend going where comfortable	Students recommend to future students taking the class where they are comfortable, includes comments about "if they think they're ready" and related wording	130 Oct 12 [00:17:40.07] f3: I think it depends on the individual too, like I think if you get placed into gen chem, but you feel like you are capable of taking orgo, then like that's I think that's a personal decision, but I think the way that it's set up right now where you have sort of all these like steps that you have to go through first to really make sure that you're taking the right class I think that's really efficient.
34	Recommend taking lab and lecture together	Students recommend taking the lab and lecture together	130 Oct 12 [00:18:19.07] f1: I would advise to just do it in one go and get it over with. If you don't have to take that much chemistry, that way it's not dragged out or anything, so some people are taking 130 now, and they're gonna take the lab later on, but I was just like I'm gonna get it over with, and then later on I'll be able to take my french and...
35	Would recommend following placement test	Students recommend following the placement test recommendation	230 Oct 16 1 [00:32:17.17] f2: Well yeah I would trust the placement test, but I think if like going off the placement test and advising... trust your confidence I would say.
36	Would recommend others take gen chem	Students recommend taking gen chem first	130 Oct 19 [00:11:35.23] m1: I would definitely recommend it.
37	Would recommend others take orgo	Students recommend taking orgo first	210 Oct 26 [00:20:27.25] m6: Don't be scared of orgo.
38	Would recommend not taking orgo with other hard classes	Students recommend taking orgo with a balance of less strenuous courses (not calc 2, bio, other hard sciences, etc)	230 Oct 16 FG1 [08:47.09] f1: Um, I have a lot of the same ones that you marked, but in addition, I also said like the course load, course rigor, and your scheduling, because obviously chemistry is a pretty intensive course. It's very difficult. It's termed a weeder class. And so I feel like if you have a lot of other requirements to do, I don't recommend taking it with a lot of other harder classes, because otherwise you're not probably gonna do that well in it because it does take so much time. Umm...and so I actually used those probably more so when I'm thinking about what classes to take is how hard they're gonna be versus...you know. What they're used for.

39	Don't take orgo first semester (recommendation)	Students recommend not taking orgo in a students first semester or they discussed regret taking it at a first semester first year	230 Oct 20 [00:12:14.26] f1: I personally um so I'm a peer advisor for UROP too, so I kind of like have incoming freshman that I recommend things. I personally say do not take Orgo when you're in your first semester. Like I don't think they should have to take gen chem if they tested out, cause I still think I knew my stuff from gen chem, but like orgo is pretty different from the concepts of gen chem. ...
40	Would recommend taking orgo with friends/use study groups	Students specifically recommend taking the course with friends, and using study groups	230 Oct 16 FG1: [00:32:56.14] f1: I'd also recommend if it's possible taking it with friends or at least making a really solid group of people right from the start.

[a]125 = Macroscopic Investigations and Reaction Principles; 210 = Structure and Reactivity I; 230 = Physical Chemistry Principles. Please see Supporting Information for all codes and their frequencies.

VII. Linear Regression Results

Table 5-7. Linear regression results for survey question: The chemistry knowledge I had when I began the course was sufficient to be successful on assignments and exams for all data set

Course	Subset	Demographic	Standard Coeff Beta
All courses	All students	Placement Decision	-0.187[b]
		Deviated UP	0.023
		Deviated DOWN	0.193[a]
		Placement Score	0.249[a]
		Gender	-0.036
		Ethnicity	0.001
		Parental Income	0.037
		HS GPA	0.023
All courses	Nonengineers	Placement Decision	-0.140[c]
		Deviated UP	0.031
		Deviated DOWN	0.155[b]
		Placement Score	0.175[b]
		Gender	-0.084[c]
		Ethnicity	0.001
		Parental Income	0.057
		HS GPA	0.043
CHEM 130	All Students	DeviateDOWN	0.262[a]
		Placement Score	-0.106[c]
		Gender	-0.036
		Ethnicity	0.001
		Parental Income	0.037
		HS GPA	0.023
CHEM 130	Nonengineers	DeviateDOWN	0.016
		Placement Score	0.300[a]
		Gender	-0.033
		Ethnicity	-0.055
		Parental Income	0.025
		HS GPA	0.064
CHEM 210	All Students	Placement Decision	-0.142

		DeviateUP	0.002
		DeviateDOWN	0.116[c]
		Placement Score	-0.008
		Gender	-0.159[b]
		Ethnicity	0.003
		Parental Income	0.006
		HS GPA	0.044
CHEM 210	Nonenegineers	Placement Decision	-0.077
		DeviateUP	0.004
		DeviateDOWN	0.078
		Placement Score	-0.008
		Gender	-0.158[b]
		Ethnicity	0.003
		Parental Income	0.006
		HS GPA	0.044
CHEM 230	All Students	Placement Decision	-0.069
		Deviated UP	0.053
		Deviated DOWN	0.079
		Placement Score	0.087
		Gender	-0.055
		Ethnicity	0.034
		Parental Income	0.284[b]
		HS GPA	0.143
CHEM 230	Nonengineers	Placement Decision	-0.049
		Deviated UP	0.055
		Deviated DOWN	0.078
		Placement Score	0.061
		Gender	-0.046
		Ethnicity	0.039
		Parental Income	0.284[b]
		HS GPA	0.141

[a] = p<0.0001[b] = p<0.005,[c] = p<0.05

Table 5-8. Results from the linear regression analysis for the survey question: I did not feel adequately prepared for this course for all data sets

Course	Subset	Demographic	Standard Coeff Beta
All courses	All students	Placement Decision	-0.295[a]
		Deviated UP	0.001
		Deviated DOWN	-0.254[a]
		Placement Score	-0.299[a]
		Gender	0.036
		Ethnicity	-0.017
		Parental Income	-0.031
		HS GPA	-0.011
All courses	Nonengineers	Placement Decision	0.208[b]
		Deviated UP	-0.004
		Deviated DOWN	-0.148[b]
		Placement Score	-0.241[a]
		Gender	0.035
		Ethnicity	0.011
		Parental Income	-0.006
		HS GPA	0.011
CHEM 130	All Students	Placement Decision	-0.265[a]

		Placement Score	0.155[b]
		Gender	0.057
		Ethnicity	0.030
		Parental Income	0.027
		HS GPA	-0.048
CHEM 130	Nonengineers	Deviated DOWN	0.027
		Placement Score	-0.263[a]
		Gender	0.003
		Ethnicity	0.081
		Parental Income	0.088
		HS GPA	-0.031
CHEM 210	All Students	Placement Decision	0.278
		Deviated UP	0.058
		Deviated DOWN	-0.097
		Placement Score	-0.257[b]
		Gender	0.035
		Ethnicity	-0.064
		Parental Income	-0.117[c]
		HS GPA	-0.002
CHEM 210	Nonenegineers	Placement Decision	0.208[c]
		Deviated UP	0.058
		Deviated DOWN	-0.066
		Placement Score	-0.143
		Gender	0.038
		Ethnicity	-0.035
		Parental Income	-0.077
		HS GPA	0.040
CHEM 230	All Students	Deviate	-0.095
		Deviated UP	-0.097
		Deviated DOWN	-0.039
		Placement Score	-0.190
		Gender	0.089
		Ethnicity	-0.065
		Parental Income	-0.043
		HS GPA	-0.067
CHEM 230	Nonengineers	Deviate	-0.100
		Deviated UP	-0.099
		Deviated DOWN	-0.041
		Placement Score	-0.174
		Gender	0.083
		Ethnicity	-0.057
		Parental Income	-0.038
		HS GPA	-0.052

[a] = $p<0.0001$ [b] = $p<0.005$, [c] = $p<0.05$

5.12 References

(1) Henriksen, E. K. Introduction: Participation in science, technology, engineering and mathematics (STEM) education: Presenting the challenge and introducing Project IRIS. In E. K. Henriksen, J. Dillon, & J. Ryder (Eds.), Understanding Student Participation and Choice in Science and Technology Education (pp. 1-14). 2015. Dordrecht: Spinger.

(2) Hazari, Z.; Sonnert, G.; Sadler, P. M.; Shanahan, M. Connecting High School Physics Experiences, Outcome Expectations, Physics Identity, and Physics Career Choice: A Gender Study, *Journal of Research in Science Teaching,* **2010**, *47*, 978-1003.

(3) For reviews on factors influencing students' choices to continue with science: a) Ainley, J.; Kos, J.; Nicholas, M. Participation in science, mathematics and technology in Australian education. 2008, Melbourne: ACER Research Monograph. b) Lyons, T.; Quinn, F. Choosing Science. Understanding the Declines in Senior High School Science Enrolments. Armindale, NSW: University of New England. **2010**. Retrieved from http://simerr.une.edu.au/pages/projects/131choosingscience.pdf. c) Regan, E.; Dewitt, J. Attitude, interest and factors influencing STEM enrollment behavior: A review of relevant literature. In E. K. Henriksen, J. Dillon, & J. Ryder (Eds.), *Understanding Student Participation and Choice in Science and Technology Education* (pp. 63-88). **2015**. Dordrecht: Spinger. d) Moakler, M. J. & Kim, M. M. College Major Choice in STEM: Revisiting Confidence and Demographic Factors. *The Career Development Quarterly*, **2014**, *62*, pp 128-142.

(4) Palmer, T.; Burke, P. F.; Aubusson, P. Why School Students Choose and Reject Science: A Study of the Factors that Students Consider When Selecting Subjects. *International Journal of Science Education*, **2017**, *39*, 645-662.

(5) Dick, T. P.; Rallis, S. F. Factors and Influences on High School Students' Career Choices. *Journal for Research in Mathematics Education*, **1991**, *22*, 281-292.

(6) Hinds, E. M.; Shultz, G. V. Investigation of the Factors That Influence Undergraduate Student Chemistry Course Selection. *J. Chem. Educ.* **2018***, 95*, 913−919.

(7) Shultz, G. V.; Gottfried, A. C.; Winschel, G. A. Impact of General Chemistry on Student Achievement and Progression to Subsequent Chemistry Courses: A Regression Discontinuity Analysis. *J. Chem. Ed.* **2015***, 92*, 1449-1455.

(8) Eccles, J. S. Families, Schools, and Developing Achievement-Related Motivations and Engagement. In *Handbook of Socialization Theory and Research,* Grusec, J. E., Hastings, P. D., Eds.; Guilford Press: New York, **2007**; pp 665–691.

(9) Flake, J. K.; Barron, K. E.; Hulleman, C.; McCoach, B. D. Measuring Cost: The Forgotten Component of the Expectancy-Value Theory, *Contemporary Educational Psychology*, **2015**, *41*, 232-244.

(10) Bandura, A. *Self-efficacy – the Exercise of Control*; W. H. Freeman and Company: New York, USA, **1997**; pp 79-115.

(11) Richardson, J. T. E. The Concepts and Methods of Phenomenographic Research. *Review of Educational Research*, **1999**, *69*, pp 53-82.

(12) Creswell, J. W. Educational Research – Planning, Conducting, and Evaluating Quantitative and Qualitative Research, 4 ed.; Pearson: Boston, **2012**; pp. 541.

(13) a) Ege, S. N.; Coppola, B. P.; Lawton, R. G. The University of Michigan Undergraduate Chemistry Curriculum 1. Philosophy, Curriculum, and the Nature of Change. *J. Chem. Educ.* **1997***, 74*, 74-83. b) Coppola, B. P.; Ege, S. N.; Lawton, R. G. The University of Michigan Undergraduate Chemistry Curriculum 2. Instructional Strategies and Assessment. *J. Chem. Educ.* **1997***, 74*, 84-94.

(14) Willis, G. B. Cognitive Interviewing – A "How To" Guide. *Reducing Survey Error through Research on the Cogntitive and Decision Processes in Surveys* **1999**, American Statistical Association meeting. Available online: http://www.dea.univr.it/documenti/OccorrenzaIns/matdid/matdid823948.pdf (accessed Mar 2018).

(15) ABET accreditation UM engineering department uses: http://www.abet.org/accreditation/ (accessed Mar 2018).

(16) Hinton, P. R.; Brownlow, C.; McMurray, I.; Cozens, B. SPSS Explained. Routledge, London and New York, **2004**, pp. 295-320.

(17) Theobald, R.; Freeman, S. Is It the Intervention or the Students? Using Linear Regression to Control for Student Characteristics in Undergraduate STEM Education Research. *CBE – Life Sciences Education,* **2014**, *13*, 41-48.

(18) Arjoon, J. A.; Xu, X.; Lewis, J. E. Understanding the State of the Art for Measurement in Chemistry Education Research: Examining the Psychometric Evidence*. J. Chem. Educ*. **2013**, *90*, 536−545.