Build/Couple/Pair and Multifunctional Catalysis
Strategies for the Synthesis of Heterocycles from
Simple Starting Materials

Ph.D. Thesis

Erhad Ascic

April 2012

Department of Chemistry
Technical University of Denmark
Build/Couple/Pair and Multifunctional Catalysis Strategies for the Synthesis of Heterocycles from Simple Starting Materials

Ph.D. Thesis by Erhad Ascic
© 2012 by Erhad Asic

All rights reserved
PREFACE

This thesis is submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy from the Department of Chemistry at the Technical University of Denmark. The work presented in this thesis was carried out from May 2009 to April 2012 under supervision of Prof. Thomas E. Nielsen, and financed by the DSF Center for Antimicrobial Research (CAR). During this period, two different projects have been carried out, which are disclosed in two separate chapters, dealing with diversity-oriented synthesis and multifunctional catalysis for the construction of heterocycles.

First and foremost I would like to thank Prof. Thomas E. Nielsen for being a great mentor, who has given me the opportunity of broadening my skills in a stimulating research environment, excellently equipped with all facilities needed for modern organic synthesis. I am also deeply grateful to Thomas for his superb guidance, fruitful collaboration, and for his great ideas, which has led to exciting discoveries and a wonderful working atmosphere.

I would like to express my gratitude to all of my colleagues (Dr. Jacob F. Jensen, Dr. Sebastian T. Le Quement, Dr. Katrine Qvortrup, Dr. Rico Petersen, Tina Gustafsson, Kennedy M. Taveras, Vitaly V. Komnatnyy, Anders Emil Cohrt, Mette R. Hansen, Mette Terp Petersen, Casper L. Hansen, Mette Ishøey, Claus G. Bang, Remi Mikkelsen, and Thomas Flagstad), who made my place in the Nielsen group very enjoyable. Dr. Jacob, F. Jensen, Dr. Sebastian T. Le Quement, Casper L. Hansen, Mette Ishøey, Mathilde Daugaard, and Tina Gustafsson are gratefully acknowledged for their outstanding contributions to the work presented in this thesis, and for great chemistry discussions. Furthermore, Dr. Sebastian T. Le Quement is greatly acknowledged for assisting me with writing the manuscripts, and Mette Ishøey is thanked for preparing a really cool cover for ACS Comb. Sci. on the chemistry described in Chapter 1.
I would like to give special thanks to my lab mate and friend Dr. Rico Petersen to whom I am very grateful for all the great philosophical discussions on anything and everything. Especially I would like to thank Rico for turning bad days into good days through his contagious laughter, good sense of humor, and for a fine selection of music (e.g., medo brundo, baci mi jednu bombu, and øresundsvisan) that streamed out of his computer and/or radio, which made my day. Also I would like to thank Rico for proofreading this thesis.

I would like to thank the rest of the crew in the Department of Chemistry, Building 201, for providing a splendid working atmosphere. I am also deeply thankful to my friend Dr. Toni Rantanen from Queen’s University, Kingston, Canada for taking his time to proofread this thesis.

Finally, where would I be without my family? I would like to express my deepest gratitude to my better half, my dear wife Selma, for her support during the writing of this thesis, but most importantly, for making my life complete. I would also like to thank my parents, Sead and Semka, my sister, Dina, and my brother, Rijad, for always being there for me when needed. My love and efforts put into this work stem from their continued support. This thesis is dedicated to all of them.

________________________________________

Erhad Ascic
Kgs. Lyngby, April 2012
ABSTRACT

Chapter 1. Build/Couple/Pair Strategy Combining the Petasis 3-Component Reaction with Ru-Catalyzed Ring-Closing Metathesis

A “build/couple/pair” strategy for the efficient and concise (2-5 step) synthesis of structurally distinct skeletons is described. A Petasis 3-component reaction is used to synthesize anti-amino alcohols displaying pairwise reactive combinations of alkene moieties. Upon treatment with a ruthenium alkylidene catalyst, these dienes selectively undergo ring-closing metathesis reactions to form skeletally distinct heterocycles. In addition, a ruthenium-catalyzed tandem RCM/isomerization/N-alkyliminium cyclization sequence to hitherto unknown oxazabicyclooctane derivatives is developed which grants an extra element of skeletal diversity. Further skeletal diversification reactions utilizing palladium-catalyzed ring-contraction and intramolecular Diels-Alder reactions are also demonstrated.


A multifunctional catalysis approach, involving a ruthenium-catalyzed tandem ring-closing metathesis/isomerization/N-acyliminium cyclization sequence, is described. Double bonds created during ring-closing metathesis isomerize to generate reactive N-acyliminium intermediates which undergo intramolecular cyclization reactions with
tethered heteroatom and carbon nucleophiles. In the tandem process, two new rings are formed, where a single metal catalyzes two mechanistically distinct reactions in one chemical operation. In this way, a series of interesting indolizidinones are formed in good yields with excellent diastereoselectivities, including a formal total synthesis of the antiparasitic natural product harmicine and the first total synthesis of mescalotam. Furthermore, preliminary asymmetric variants of the tandem process have been identified, affording indolizinioindoles in up to 60% ee.

Finally, a palladium-catalyzed tandem Tsuji-Trost/isomerization/N-alkyliminium cyclization to various tetrahydro-β-carbolines (THBCs) is described. The developed tandem process constitutes a metal-catalyzed alternative to the Pictet-Spengler reaction for the synthesis of THBCs, where a single metal catalyzes two mechanistically distinct reactions in one chemical operation.
Resumé

Kapite 1. En ’’build/couple/pair’’ strategi der kombinerer Petasis 3-komponent reaktionen og Ru-katalysert ringlukningsmetatase


En multifunktionel katalysestrategi, der involverer ruthenium-katalysert tandem ringlukningsmetatase/isomerisering/N-acyliminium cykliseringssekvens, er beskrevet. Dobbeltbindinger dannet under ringlukningsmetatase isomeriseres til reaktive N-acyliminium ioner, der undergår intramolekylære cykliseringsreaktioner i tilstedeværelse af heteroatom- og carbonnukleofiler. To nye ringe dannes i denne
tandem process, hvor et enkelt metal katalyser to mekanistisk forskellige reaktioner i en kemisk operation. På denne måde dannes en række interessante indolizidinoner i gode udbytter med fremragende diastereoselektiviteter, herunder udføres der en formel totalsyntese af det antiparasistic naturprodukt harmicine og den første totalsyntese af mescalotam. Derudover er asymmetriske varianter af tandem-processen blevet undersøgt, og visse indolizinoindoler blev syntetiseret i op til 60% ee.

# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACM</td>
<td>alkyne cross-metathesis</td>
</tr>
<tr>
<td>ADMET</td>
<td>acyclic diene metathesis polymerization</td>
</tr>
<tr>
<td>All</td>
<td>allyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>B/C/P</td>
<td>build/couple/pair</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>bs</td>
<td>broad singlet</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CM</td>
<td>cross-metathesis</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>ddd</td>
<td>doublet of doublet of doublets</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-dimethyl-4-aminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DOS</td>
<td>diversity-oriented synthesis</td>
</tr>
<tr>
<td>DMS</td>
<td>dimethyl sulfide</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1'-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets</td>
</tr>
<tr>
<td>EDC-HCl</td>
<td>N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>e.g.</td>
<td>exempli gratia</td>
</tr>
<tr>
<td>eq</td>
<td>equation</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
</tbody>
</table>
ESI-MS electrospray ionization mass spectrometry
Et ethyl
EYCM enyne cross-metathesis
FT-IR fourier transform infrared spectroscopy
h hour(s)
HFIP hexafluoroisopropanol
HMBC heteronuclear multiple bond correlation
HPK hetero Pauson-Khand
HRMS high-resolution mass spectrometry
HSQC heteronuclear single quantum coherence
HOBT 1-hydroxybenzotriazole
Hz hertz
IMDA intramolecular Diels-Alder
i-Pr iso-propyl
m multiplet
m-CPBA meta-chloroperoxybenzoic acid
Me methyl
Mes mesityl; 2,4,6-trimethylbenzene
MHz megahertz
mp melting point
MS molecular sieves
MTAD 4-methyl-1,2,4-triazoline-3,5-dione
NBS N-bromosuccinimide
NMM N-methylmorpholine
NMR nuclear magnetic resonance
NOE nuclear Overhauser effect
NOESY nuclear Overhauser enhancement spectroscopy
3-CR 3-component reaction
Ph phenyl
PMA phosphomolybdic acid
PMB p-methoxybenzyl
PMP p-methoxyphenyl
ppm parts per million
PyBOP benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
q quartet
RCAM ring-closing alkyne metathesis
RCEYM ring-closing enyne metathesis
viii
RCM  ring-closing metathesis
ROM  ring-opening metathesis
ROMP ring-opening metathesis polymerization
RP-HPLC reversed-phase high-performance liquid chromatography
RRM ring-rearrangement metathesis
rt  room temperature
s  singlet
$S_{\text{NAr}}$ nucleophilic aromatic substitution
TBAF tetrabutylammonium fluoride
TBDMSCl tert-butyldimethylsilyl chloride
$t$-Bu tert-butyl
TFA trifluoroacetic acid
$\text{TF}_2\text{O}$ trifluoromethanesulfonic anhydride
THBC tetrahydro-β-carboline
THF tetrahydrofuran
TLC thin layer chromatography
TMANO trimethylamine $N$-oxide
Ts toluenesulfonyl; tosyl
PUBLICATIONS

Publications Included in Appendix


TABLE OF CONTENTS

PREFACE ...................................................................................................................... i
ABSTRACT ................................................................................................................. iii
RESUMÉ ....................................................................................................................... v
LIST OF ABBREVIATIONS ........................................................................................... vii
PUBLICATIONS .............................................................................................................. x
TABLE OF CONTENTS ............................................................................................... xi

CHAPTER 1. Build/Couple/Pair Strategy Combining the Petasis Reaction with Ru-Catalyzed Ring-Closing Metathesis.............................................................................................. 1

1.1 Introduction .............................................................................................................. 1
  1.1.1 Small Organic Molecules and Their Impact on Life-Science ......................... 1
  1.1.2 Case Studies...................................................................................................... 2
  1.1.3 Planning Organic Synthesis towards Small Organic Molecule Probes and Drugs............................................................................................................................... 5
  1.1.4 Build/Couple/Pair (B/C/P) Strategy ................................................................. 9
  1.1.5 Functional Group Pairing Reactions in a B/C/P Strategy ................................ 10
  1.1.6 Recent Synthesis of Macrocyclic Lactams and Lactones with a B/C/P Strategy ............................................................................................................................ 12
  1.1.7 Synthesis of Macrocyclic Peptidomimetics with a Build/Couple/Pair Strategy ............................................................................................................................ 15
  1.1.8 B/C/P Strategy Combining Enantioselective Mannich Reaction with Various Functional Group Pairing Reactions ................................................................. 16
1.1.9 B/C/P Strategy Combining Metathesis Cascades with Inter- and Intramolecular Diels-Alder Reactions ................................................................. 17
1.2.0 B/C/P Strategy Combining Petasis 3-Component Reaction with Various Functional Group Pairing Reactions ............................................................. 19
1.2.1 Petasis 3-Component Reaction Suitable for the Couple Phase .................. 20
1.2.2 Aim of the Project ......................................................................................... 22
1.2.3 Results and discussion ......................................................................................... 23
1.2.4 Synthesis of Amine Building Block .............................................................. 23
1.2.5 Synthesis of α-Hydroxy Aldehyde Building Block ........................................ 24
1.2.6 Synthesis of Estronylboronic Acid Building Block ....................................... 25
1.2.7 Couple Phase: Petasis 3-Component Reactions of Olefin-Functionalized Building Blocks ....................................................................................................... 25
1.2.8 Pair Phase: Functional Group Pairing of Alkene-Containing Amino Alcohols .................................................................................................................. 27
1.2.9 Proposed Mechanism for the Formation of Oxazabicyclooctane .................. 29
1.3.0 Pair Phase: Selective Formation of Tetrahydroazepines and Oxazabicyclooctanes ............................................................................................... 30
1.3.1 Pair Phase: Two Consecutive Petasis 3-CR and subsequent RCM Reaction in the Construction of a Complex Morpholine Skeleton ......................... 33
1.3.2 Summary ......................................................................................................... 34
1.3.3 Experimental Section ...................................................................................... 35

CHAPTER 2. Multifunctional Catalysis: Synthesis of Heterocycles from Simple Starting Materials .......................................................................................... 69

2.1 Introduction ........................................................................................................ 69
2.1.1 Multifunctional Catalysis ............................................................................... 69
2.1.2 Olefin Metathesis ............................................................................................ 71
2.1.3 Multifunctional Catalysis with Ruthenium Metathesis Catalysts ............. 73
CHAPTER 1

Build/Couple/Pair Strategy Combining the Petasis Reaction with Ru-Catalyzed Ring-Closing Metathesis

1.1 Introduction

1.1.1 Small Organic Molecules and Their Impact on Life-Science

Small organic molecules, such as naturally occurring compounds ranging from simple alcohols to complex opium alkaloids, have been used by mankind for centuries for therapeutic and hallucinogenic purposes. Chemists and biologists have been studying small organic molecules, such as hormones, vitamins, amino acids, in living systems for over a century, to better understand the fundamental processes of life. The most important discovery is perhaps that nucleobases, ribose sugars, and phosphates are joined to form the oligomeric nucleotides, known as DNA and RNA, which contains genetic information essential for life. This discovery has recently culminated in the complete mapping of the human genome. Over the past decade, sequencing of the human genome has provided insight into how genes and cellular pathways underlie various disease processes. For example, systematic and comprehensive studies have led to the identification of over 2,850 genes underlying Mendelian diseases, and over 1,100 loci associated with common diseases. These genes encode amino acid sequences that are translated into essential proteins, such as receptors, signaling proteins, protein constituents of the cytoskeleton (microfilaments, microtubules, and
various motor proteins), and transcription factors. Since the beginning of the 20th century, small organic molecules (typically < 800 Da) have been used as tools that function as specific probes or modulators in biological systems, mainly by interacting with specific macromolecular targets by suppressing or stimulating their function. In this way, the structure and role of a protein can be explored by monitoring phenotypic changes in the particular system. Furthermore, gene(s) encoding a specific protein can be revealed and studied. This can lead to new drug targets and eventually the discovery of small-molecule lead compounds for the development of new drugs. The study of protein functions in biological systems with small molecules is often referred to as chemical genetics. This area of research has posed a dramatic effect on life-science research in recent years, and some selected examples hereof are given below.

1.1.2 Case Studies

Our understanding of the cytoskeleton has been greatly improved by the use of small molecule probes. For example, in studies on the cytoskeleton, natural products such as taxol, vinblastine, vincristine, colchicine, epothilone, eleutherobin, discodermolid, and the synthetic compound nocodazole (Figure 1), were used as tools for the identification tubulin modifications. Tubulin is a subunit of the microtubule which constitutes a major part of the cytoskeletal system in cells. The function hereof is important to maintain the cell structure by providing platforms for vesicular transport and by forming the mitotic spindle network necessary for mitosis (cell division). The small-molecule probes, depicted in Figure 1, have shown to bind and interfere with the microtubule in one way or another, and some of these have in fact been developed into approved drugs. For example, taxol, which is being extracted from the bark of western yew, is used today to treat breast and lung cancer by stimulating the polymerization of microtubules. The vinca alkaloids vinblastine and vincristine were shown to inhibit the polymerization of microtubule structures and thus disrupt the formation of microtubules important for cell division. Another example is the discovery of the synthetic compound monastrol (Figure 1). Monastrol modulates the kinesin protein Eg5, which is a mitotic motor protein important for powering microtubules
responsible for spindle bipolarity during cell division. Monastrol has been identified as a valuable tool for probing the functions of Eg5 during mitosis as it is cell permeable and at the same time displaying a very specific reversible binding to Eg5.

![Chemical structures]

**Figure 1.** Microtubule-modulating small molecules.

Naturally occurring small molecules, such as phalloidin, jasplakinolide, latrunculins, and cytochalasins (Figure 2) modulate the function of actin, a protein subunit of actin filament, which are the thinnest filaments of the cytoskeleton and critically important for cell movement and shape. These small-molecule modulators have been valuable tools for revealing the functions of actin filaments.

![Chemical structures]

**Figure 2.** Actin-modulating small molecules.

For example, phalloidin (Figure 2) was shown to promote actin polymerization by binding to filamentous actin (F-actin), and preventing its depolymerization.
though phalloidin is of limited use in living cells due to cell impermeability, fluorescently labeled phalloidin has been used as a tool to stain actin filaments and thereby investigate their distribution in cultured cells. The macrocyclic polypeptide jasplakinolide (Figure 2), isolated from a marine sponge, is cell permeable and has been used in living cells to investigate actin filament disassembly by binding to F-actin. As a result, a process called protrusion motility, which is involved in wound healing and immune cell activation, can be studied.

Other examples include the use of small-molecules to probe transcription factors. Transcription factors are proteins that bind to specific DNA sequences, thereby regulating transcription of genetic material from DNA to mRNA. The human genome encodes around 2000-3000 transcription factors and this class may represent more than 10% of all genes. The discovery of small molecules that can modulate transcription factors by directly disrupting protein-protein or protein-DNA interactions is important to elucidate the function of these proteins. For example, linoleic acid and nitronapthofuran (Figure 3) bind to a nuclear receptor called HNF4α.

Figure 3. Transcription factor-modulating small molecules.

HNF4α is a transcription factor important in many metabolic pathways (e.g., regulating the hepatic lipid metabolism), which are linked to diseases, such as diabetes. Binding of linoleic acid to HNF4α was shown to occur through reversible interactions that modulate the function of HNF4α. On the other hand, binding of nitronapthofuran to HNF4α proved to be effective for enhancing HNF4α-
mediated gene transcription. Another important transcription factor is the estrogen receptor, which constitutes a group of proteins now validated as targets for the treatment of breast cancer. For example, estrogen receptors function as a transcription factor only after being activated by natural or synthetic estrogen. Once activated by estrogen, the estrogen receptor can bind to the DNA and recruit steroid receptor coactivators that regulate gene transcription. Small molecule modulators, such as 6-alkyl-2,6-diaminopyrimidine, guanylhydrazone, and amphipathic benzene (Figure 3), have been shown to inhibit the interaction between steroid coactivator and the estrogen receptor and thereby block estrogen receptor activity. Small molecules have also been used to modulate signaling proteins, and a recent example is shown below. The small-molecule modulators depicted in Figure 4 are effective in probing protein phosphatases involved in insulin signaling, and are considered as targets for the development of new drugs against diabetes.

**Figure 4.** Selected protein phosphatase inhibitors.

### 1.1.3 Planning Organic Synthesis towards Small Organic Molecule Probes and Drugs

As explained in the previous section, small molecules may be important tools for dissecting biological systems. Small molecules can help us understand biological systems by discovering protein targets and probe cellular pathways, and ultimately define mechanisms of disease processes. This may eventually lead to the rational design of small molecule drug candidates.
It has been estimated that around 10% of the genes in the human genome encode 3051 proteins able to bind small-molecule compounds,28 but only 1000 of these proteins are known to be modulated by small molecules.29 In order to facilitate the discovery of probes for protein targets, it is important that chemical screening libraries (for high-throughput and other screening techniques)30 covers a large chemical space.31 The chemical space is constituted by a given set of “dimensions” defined by a descriptive molecular operator (e.g., molecular weight, solubility, molecular shape, number hereoatoms and rings, and many more).4a,31 Since the number of small molecules in biologically relevant chemical space is huge, planning strategies have been pursued to synthesize compound collections that broadly populate chemical space efficiently.4 Three general planning strategies for small molecule synthesis are often emphasized: target-oriented synthesis (TOC), combinatorial chemistry and diversity-oriented synthesis (DOS), (Figure 5).

Figure 5. Three-dimensional plots illustrating chemical space. A) TOS of a single target structure (illustrated as a blue sphere). B) Combinatorial chemistry in the synthesis of a collection of analogues of a given structure, typically with known properties (illustrated as red spheres) C) DOS of a collection of diverse molecules, typically with unknown properties (illustrated as coloured spheres)

For example, the aim of TOS is to develop a synthetic approach to a particular naturally occurring compound, or to a synthetic compound that possesses biological
activity. TOS therefore covers a specific region of chemical space, and retrosynthetic planning (going from complex to simple) is used as a problem solving technique for devising appropriate pathways (Figure 5A).

Synthesis of libraries of analogues of a given target structure, such as derivatization of a natural product or drug, can be achieved with combinatorial chemistry. As a result, a dense region of chemical space is explored (Figure 5B). For example, the chemical space around a lead compound can be explored by varying appendage sites, which is typically applied in the optimization of a drug candidate. TOS and combinatorial chemistry have led to major advances in chemical genetics by providing access to biologically active small molecules, but the drawback is that the library design is restricted to provide compounds that only cover minor regions of chemical space. These strategies may therefore not deliver libraries with sufficient structural diversity for forward chemical genetics studies. To achieve compound libraries that broadly populate chemical space, a more diversity-oriented synthesis (DOS) approach may instead be applied.

During the past decade, DOS has materialized as a synthetic approach different from TOS which may be considered as an “evolved” embodiment of combinatorial chemistry. In contrast to TOS and combinatorial chemistry, DOS does not aim to construct targets populating a discrete region of chemical space. Retrosynthetic planning is therefore not effective as a problem-solving technique. Instead, diversity-oriented synthesis relies on forward-synthetic planning (going from simple to complex and diverse), for the synthesis of collections of structurally diverse small molecules with unknown properties. As a result, a broad swath of chemical space is covered (Figure 5C). However, in order to be successful in planning DOS, it is important that the library synthesis relies on efficient organic reactions that lead to skeletal and stereochemically diverse compounds. Recent related planning strategies include, synthesis of libraries via biology-oriented synthesis (e.g., libraries focused on diversity based around natural product inspired scaffolds), libraries-from-libraries strategies.
(e.g., solid-phase synthesis of combinatorial libraries linked to chemical transformations to yield new libraries),\textsuperscript{35} and a formalized planning strategy for DOS, referred to as the \textit{Build/Couple/Pair} (B/C/P) strategy.\textsuperscript{36} The main contents of this thesis are related to B/C/P strategies for the synthesis of small molecules which are both skeletally and stereochemically diverse.
1.1.4 Build/Couple/Pair (B/C/P) Strategy

The B/C/P strategy is an innovative 3-6 step approach proposed by Nielsen and Schreiber for the efficient and systematic generation of skeletally and stereochemically diverse small organic molecule libraries suitable for biological screening. The strategy consists of three phases:

1. **Build** phase: Building blocks are generated asymmetrically in few steps from commercially available starting materials. These building blocks are prepared with functional groups appropriately situated for subsequent intermolecular coupling reactions (couple phase). The building blocks should ideally be synthesized in all possible stereoisomeric forms.

2. **Couple** phase: Building blocks are joined together intermolecularly to generate a densely functionalized template appropriately aligning functional groups with well-defined stereochemical orientations for subsequent functional group pairing reactions (pair phase).

3. **Pair** phase: Intramolecular functional group pairing reactions of appropriately positioned functional groups are mediated. This will ideally yield a complete matrix of stereochemically and skeletally diverse compounds. In the pair phase it is important to use effective intramolecular functional group pairing reactions to access a complete matrix of skeletally diverse products.

An ideal system for the generation of diverse small molecules utilizing B/C/P strategy is illustrated below (Figure 5). Building blocks with different functional groups (non-polar and polar functionalities) appropriately situated as chemical handles can be assembled (couple phase) to a densely functionalized template. Subsequent effective functional group pairing reactions (pair phase) can be achieved by polar-polar combinations (e.g., amine/ester to form a lactam); polar-nonpolar combinations (e.g., nitro/alkyne/alkene cyclization reactions enabled by transition metals); or by
nonpolar/nonpolar combinations (e.g., ring-closing metathesis of two alkene units to form cycloalkenes). Furthermore, incorporation of molecular fragments intermolecularly in the pair phase may result in higher and more complex skeletons (e.g., transition metal mediated alkyne/alkene pairing with incorporation of an external CO in a Pauson-Khand reaction).

Figure 5. Build/Couple/Pair (B/C/P) strategy in the construction of small diverse molecules.

1.1.5 Functional Group Pairing Reactions in a B/C/P Strategy

The term functional group pairing was suggested by Porco and co-workers. This refers to functional groups (e.g., polar and nonpolar functional groups) aligned to be “paired” to afford structurally distinct carbon skeletons (Scheme 1). During the couple phase, building blocks, such as β-nitrostyrenes and α-substituted malonates, were coupled together by an asymmetric Michael addition, which was catalyzed by a Cinchona alkaloid derivative 1 to form the enantiomerically pure highly functionalized Michael adducts of type 2. Subsequent selective nitro reduction could pair the polar (NH₂, and ester) functionalities forming lactams 3, 7, and 10. Pairing between non-polar (alkyne, alkene) and polar (nitro) functional groups could be achieved through
nitro activation followed by intramolecular cycloaddition reaction yielding the corresponding isoxazole 4 and isoxazoline 5 adducts. Transition metals, such as Ru, Au, Co were used to selectively pair the non-polar alkene and alkyne functional groups of 2 through ring-closing metathesis (RCM), ring-closing-enzyme metathesis (RCEYM), cycloisomerization, and Pauson-Khand reaction, to form scaffolds 6, 8, 9 and 11. Intermolecular Diels-Alder reaction of 11 with N-phenylmaleimide afforded 12.

Scheme 1. Reagents and conditions: (a) 1 (10 mol%), THF; (b) (i) Zn, AcOH/THF (ii) Na<sub>2</sub>CO<sub>3</sub>; (c) PhNCO, Et<sub>3</sub>N, PhMe, r.t.; (d) Boc<sub>2</sub>O, DMAP, PhMe; (e) Co<sub>2</sub>(CO)<sub>8</sub>, µW, 150 W, 80 °C, CH<sub>2</sub>Cl<sub>2</sub>; (f) Grubbs II catalyst, µw, 150 W, 50 °C, CH<sub>2</sub>Cl<sub>2</sub>; (g) AuCl(PPh<sub>3</sub>), AgOTf, PhMe, 50 °C; (h) Grubbs I catalyst, ethylene, µw, 150 W, 60 °C, CH<sub>2</sub>Cl<sub>2</sub>; (i) N-phenylmaleimide, µw, 300 W, 160 °C, PhMe

11
1.1.6 Recent Synthesis of Macrocyclic Lactams and Lactones with a B/C/P Strategy

Macrocyclic structures are attractive for drug discovery due to their unique functionality, which is suitable for interacting with specific protein targets. Medium- to large-sized ring systems are underrepresented in screening collections due to today’s lacking methods for their synthesis. Therefore the majority of current macrocyclic drugs are isolated from natural sources. Recent advances within the field of diversity-oriented synthesis have shown that B/C/P is a convenient strategy in the synthesis of highly complex natural-like macrocyclic scaffolds. Three recent B/C/P examples are described below.

A B/C/P strategy has been developed by Marcaurelle and co-workers, where different amine and carboxylic acid building blocks were assembled using a straightforward amide coupling reaction (Scheme 2). Subsequent amide reduction rendered a densely functionalized secondary amine template with a complete matrix of 8 possible stereoisomers. This template was further coupled and derivatized to templates 14, 15, and 16. Following functional group pairing reactions of individual templates through nucleophilic aromatic substitution (S_NAr), Huisgen [3+2] cycloaddition and ring-closing metathesis (RCM), formed a diverse collection of macrocyclic skeletons 17-19. The macrocycles varied in size from 8- to 14-membered rings, and were prepared as a complete set of stereoisomers. Scaffolds resulting from RCM pairing reaction 19 were attached to solid support and further diversified yielding a 14400-membered library of type 20. Biological screening of the library led to the discovery of a new class of histone deacetylase inhibitors represented by BRD-4805 (Scheme 2).
Scheme 2. Reagents and conditions: (a) PyBOP, DIPEA, CH$_2$Cl$_2$, 71-96%; (b) BH$_3$-DMS, THF, 10% Na/K tartrate, MeOH; (c) 2-fluoro-5-nitrobenzoyl chloride (n = 0), or 2-fluoro-5-nitrophenyl acetyl chloride (n = 1), Et$_3$N, CH$_2$Cl$_2$; (d) 4-azidobutanoic acid, PyBOP, DIPEA, CH$_2$Cl$_2$, rt; (e) TBAF, THF, 72-93%; (f) propargyl bromide, NaHMDS, THF, DMF, -78°C to r.t.; (g) 5-nitro-2-(pent-4-en-2-yl)oxybenzoyl chloride, DIPEA, CH$_2$Cl$_2$; (h) TBAF, THF, 0 °C; (i) NaH, allyl bromide, DMF; (j) CsF, DMF, 85 °C; (k) [CpRuCl]$_4$, PhMe, 70 °C, PhMe, 55 °C; (l) Hoveyda-Grubbs II (10 mol%)}

Furthermore, in a follow-up paper by Marcaurelle and co-workers,$^{40}$ scaffolds 17 were further diversified on solid-phase yielding a 6488-membered library of type 21. Biological screening resulted in the identification of **BRD-0476**, a novel suppressor of β-cell apoptosis (Scheme 2).
In a conceptually different B/C/P strategy developed by Schreiber and co-workers, a novel gold (I)-catalyzed reaction to generate a variety of skeletally diverse macrocyclic lactones was described (Scheme 3). In the coupling phase different combinations of propargyl propiolate building blocks (with olefin functional groups $R_1^3$ appropriately situated for ring-closing metathesis (RCM) in the pair phase) and various alcohol nucleophiles were assembled to yield a densely functionalized unsaturated ketone template. This transformation is noteworthy as the coupling phase occurred through an unprecedented gold(I)-catalyzed [3,3]-sigmatropic rearrangement, followed by a 6-endo dig cyclization to intermediate. Trapping of this intermediate with alcohol nucleophiles afforded. Subsequent Ru-alkylidene catalyzed RCM as a functional-group-pairing reaction (pair phase) yielded a variety of distinct macrocyclic lactones. The variation in resulting lactone skeletons resulted from different functional group pairing of olefin moieties residing from the building blocks.

Scheme 3. Illustration of B/C/P strategy in the construction of macrocyclic lactones.

Furthermore, when subjecting to a polymer-supported triphenylphosphine followed by addition of various carboxylic acids a densely functionalized 2-pyridone
template 33 could be isolated. Subsequent Ru-alkylidene catalyzed RCM afforded additional diverse macrocyclic lactones 34-36.

1.1.7 Synthesis of Macrocyclic Peptidomimetics with a Build/Couple/Pair Strategy

Spring and co-workers have recently demonstrated a B/C/P strategy toward the synthesis of a library of 14 compounds, based around macrocyclic 1,4-, 1,5-triazoles and diketopiperazine (DKP) scaffolds. In the couple phase, chiral azido-amine 37 and chiral alkyne-acid 38 building blocks were assembled using an amide coupling reaction, and the resulting linear tripeptide 40 was afforded as three stereoisomers in decent yield (Scheme 4). Following Cu or Ru catalyzed regioselective 1,3-dipolar cycloaddition, selectively combined the azide and alkyne functionalities generating macrocyclic 1,4-, and 1,5-disubstituted triazoles 42a-b in good yield. Further scaffold diversification could be achieved by introducing a DKP unit into the macrocyclic framework (see, compounds 43a-b, Scheme 4). This pairing step was done by subjecting 42a-b to AcOH in 2-butanol together with solid supported NMM (morpholinemethyl-polystyrene) followed by microwave heating.

Scheme 4. Reagents and Conditions: (a) EDC-HCl, HOBT, Et3N, CH2Cl2; (b) CuI, DIPEA, THF, reflux, then HCl-MeOH; (c)[Cp*RuCl]4, PhMe, reflux, then HCl-MeOH; (d) AcOH, NMM*, 2-butanol, microwave 150 °C.
Spring and co-workers demonstrated further that by replacing the linear alkyl chain in building block 38 by an aromatic ring in the building block 39, the linear tripeptide 41 could be achieved in 87% yield. During the subsequent pairing phase the macrocyclic peptidomimetic scaffolds 44 and 45 could be made. Thus, demonstrating the versatility of the methodology employed, by varying the building blocks, and at the same time introducing extra rigidity to the macrocycles being formed. Furthermore, in preliminary biological assays they also demonstrated that compound 45 showed significant antibacterial activity against *Staphylococcus aureus*.

1.1.8 B/C/P Strategy Combining Enantioselective Mannich Reaction with Various Functional Group Pairing Reactions

In a recent paper by Schreiber and co-workers, a B/C/P strategy that relies on an organocatalyzed *syn*-diastereoselective Mannich reaction, as the couple phase, is described. In their work several different skeletons can be achieved in 3-4 steps starting from commercially available reagents (Scheme 5). During the *couple* phase, commercially available building blocks are coupled via a Mannich reaction to form *syn*-diastereomeric aminoaldehyde 46. Further couplings of 46 via urea formation afforded 47. Under slightly acidic conditions 47 could be transformed to 48, in which both products 47 and 48 were suitable for intramolecular functional group pairing reactions. The hemiaminal 47 was converted into the bridged bicycle 50 by Weinreb amidation followed by *in situ* cyclization. Compound 48 was under acidic conditions transformed to 51 through Pictet-Spengler cyclization. Acylation of 46 to scaffold 49 and subsequent nitroine derived intramolecular 1,3-cycloaddition reaction afforded 52. Derivatization of the aldehyde functionality in 46 via a Wittig reaction afforded *syn* product 53. Following alkylation reactions yielded densely functionalized templates 54-56, poised for subsequent intramolecular functional group pairing reactions. For example, intramolecular Heck reaction of 54, and 56 to 57, and 59 could be achieved. Functional group pairing of 55 was achieved by Pauson-Khand reaction between the nonpolar alkene/alkyne moieties, to form 58.
Scheme 5. Reagents and conditions: (a) Al₂O₃, CH₂Cl₂; (b) cat. DL-proline, 1,4-dioxane; (c) 3,4-dimethoxyphenethyl isocyanate, 60 °C, 2 d; (d) 10% TFA, 1,4-dioxane; (e) acryloyl chloride, DIPEA, CH₂Cl₂; (f) BnNH₂, AlMe₃, CH₂Cl₂, r.t., 22 h; (g) TFA, CH₂Cl₂; (h) CH₃-NHOH, NaHCO₃, CH₃CN, 80 °C, 19 h; (i) (Ph)₃P=CHCO₂Bn, CH₂Cl₂, rt; (j) 2-iodobenzyl bromide, NaHCO₃, LiI, CH₃CN, 80 °C; (k) propargyl bromide, NaHCO₃, DMF, 70 °C; (l) 2,3-dibromopropene, NaHCO₃, LiI, CH₃CN; (m) Pd(OAc)₂, Ph₃P, K₂CO₃, CH₃CN, reflux; (n) CO₂f(CO)₆, TMANO, THF, r.t.; (o) Pd(OAc)₂, Ph₃P, K₂CO₃, CH₃CN, reflux

1.1.9 B/C/P Strategy Combining Metathesis Cascades with Inter- and Intramolecular Diels-Alder Reactions.

Nelson and co-workers has recently demonstrated a B/C/P strategy based on methathesis cascades followed by inter- and intramolecular Diels-Alder reactions. Their approach yielded a range of unprecedented scaffolds (>30), and some selected examples are demonstrated in Scheme 6. They started by preparing a range of metathesis substrates by coupling two appropriate building blocks together. For example, the hydroxyl acetate 61 was coupled onto a fluorous-tagged safety-catch linker 60, which afforded the fluorous-tagged intermediate 67. Further coupling of 67 with building blocks 64, 65 and 66 afforded the metathesis substrates 68, 69, and 70. Metathesis cascade reactions of 68, 69, and 70 were successfully paired affording...
compounds 71, 72, and 73. Following intermolecular DA cycloaddition reactions of 71 and 72 with PTAD gave after acid-catalyzed cleavage of the fluorous tag, the final products 74 and 75. The metathesis product 73 was further derivatized on both alcohols with mono-methyl fumarate and following IMDA cycloaddition afforded the tricyclic product 76. By coupling hydroxyl acetate 62 and propargylic building block 63 via a Fukuyama-Mitsunobu reaction, followed by an acylation, the metathesis substrate 78 was achieved. This substrate was successfully paired affording the metathesis product 79. Further functional group pairing reactions from 79 to 80 and 81 could be achieved via intramolecular- and intermolecular DA reactions.

Scheme 6. Reagents and conditions: (a) DEAD, PPh₃, THF, 0 °C; (b) NH₃ in MeOH; (c) NBS, CH₂Cl₂, 0 °C to r.t.; (d) acryloyl chloride, iPr₂NEt, CH₂Cl₂, 0 °C; (e) Hoveyda-Grubbs II, CH₂Cl₂; (f) Grubbs I, CH₂Cl₂; (g) HF-pyridine, THF, r.t.; (h) MTAD, CH₂Cl₂, then TFA (3%); (i) mono-methyl fumarate, DCC, DMAP, THF; (j) MeCN, MW; (k) p-xylene, heat
1.2.0 B/C/P Strategy Combining Petasis 3-Component Reaction with Various Functional Group Pairing Reactions

Schreiber and co-workers have couple of years ago reported a B/C/P strategy that enables the synthesis (in only 3-5 steps from readily available building blocks) of a collection of 15 or more diverse polycyclic skeletons, suitable for small-molecule screenings. The reaction relies on a Petasis 3-component reaction as the couple phase, which couples benzyl lactol (masked as α-hydroxy aldehyde), amine, and trans-cyclopropylvinylboronic acid to form aminoalcohol as a single trans-diastereomer. Following propargylation (as a second couple step) afforded a densely functionalized template, suitable for subsequent functional group pairing reactions to give a range of structurally diverse molecules (Scheme 7).

For example, transition metals, such as Pd and Ru were used to selectively pair the non-polar alkene, alkyne or cyclopropane functional groups of through cycloisomerization and enyne metathesis reactions, to form scaffolds. By using reaction conditions involving m-CPBA, gold-catalyzed cycloketalization, and Pauson-Khand reaction, functional group pairing between the non-polar (alkene, alkyne) and the polar (N-oxide, hydroxyl, CO) functional groups could be achieved, affording skeletons. In addition, NaH-mediated lactonization could pair polar (OH, and ester) functionalities of forming, which was further derivatized through new distinct transition metal based functional group pairing reactions to form.

Further functional group pairing reactions involving Diels-Alder cycloaddition reactions of with MTAD yielded compounds. All of these compounds were made in only 3-5 steps from the building blocks.
Scheme 7. Reagents and conditions: (a) EtOH, r.t.; (b) propargyl bromide, NaHCO₃, DMF, 70 °C; (c) [Pd(PPh₃)₂(OAc)₂] 10 mol%, benzene, 80 °C; (d) Hoveyda-Grubbs II 10 mol%, CH₂Cl₂, reflux; (e) [CpRu(CH₃CN)₃PF₆] 10 mol%, acetone, r.t.; (f) NaAuCl₄ 10 mol%, MeOH, rt; (g) [Co(CO)₈], trimethylamine-N-oxide, NH₄Cl; (h) NaH, toluene, rt; (i) mCPBA, THF, -78 °C to 0 °C; (j) 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), CH₂Cl₂, r.t.

1.2.1 Petasis 3-CR Suitable for the Couple Phase.

The Petasis 3-component reaction (Petasis 3-CR) is ideally suited for B/C/P pathways, since skeletal diversity can be readily introduced through careful selection of functional groups in the three building block components. Furthermore, the Petasis 3-CR proceeds in a highly diastereoselective fashion (as shown in Scheme 8), thus offering possibilities for the introduction of stereochemical diversity. This is due to the existing chiral center of the α-hydroxy aldehyde building block, which imparts...
diastereoselectivity from only one face of the electrophilic iminium ion being accessible to the nucleophilic boronate species 102 (formed after coordination to the β-alcohol). This results in the formation of the anti β-amino alcohol 103a (Scheme 8).


Schreiber and co-workers have recently described a catalyst-controlled diastereoselective Petasis 3CR,\textsuperscript{47} that successfully overrides the intrinsic anti diastereoselectivity, hence enabling synthesis of syn β-amino alcohols 103b as single diastereomer. In this way, a full matrix of stereoisomeric (4 possible) amino alcohol templates can in theory be produced, thus opening possibilities to complete stereochemical diversity in the pair phase.
1.2.2 Aim of the Project

The aim of the work presented herein is to develop a B/C/P strategy that entails a pairwise display of alkene moieties around an anti-amino alcohol template. By combining the Petasis 3-CR (in the couple phase), with ring-closing metathesis (in the pair phase), a collection of diverse carbo- and heterocycles of different sizes can be envisioned (Figure 6).

**Figure 6.** A Build/Couple/Pair Strategy Combining the Petasis 3-Component Reaction with Ring-Closing Metathesis

Synthesis and assembly of building blocks to yield olefin-functionalized anti β-amino alcohol templates, and subsequent functional group pairing reactions to give complex heterocycles will be discussed. Furthermore, a recently discovered Ru-alkyldene catalyzed tandem RCM/isomerization/cyclization reaction to introduce an extra element of skeletal diversity in the pair phase will be presented.
1.23 Results and Discussion

1.2.4 Synthesis of Amine Buiding Blocks

The allylamine building blocks 104 and 105 were prepared by alkylationing allylamine with an appropriate alkyl bromide in the presence of base (Scheme 9).\(^4^8\)

\[
\text{NH}_2 \xrightarrow{\text{a or b}} R\text{-NH} - \text{CH}_2
\]

\[
R = \text{Ph (80%)} 104 \quad R = \text{5-bromo-pent-1-ene (53%)} 105
\]

**Scheme 9.** Synthesis of amine building blocks 104 and 105. Reagents and conditions: (a) benzyl bromide, K\(_2\)CO\(_3\), r.t.; (b) 5-bromo-pent-1-ene, K\(_2\)CO\(_3\), r.t.

The allylamine building block 106 was prepared *via* a known procedure.\(^4^9\) Reduction of trimethoxyphenylacetic acid to the corresponding alcohol, followed by Dess-Martin oxidation to give the aldehyde, and finally a reductive amination with allylamine produced 106 (Scheme 10).

\[
\begin{align*}
\text{CO}_2\text{H} & \xrightarrow{\text{a, b, c}} \text{R} & \text{NH} & \text{MeO} \\
\text{MeO} & \text{MeO} & \text{MeO} & \text{OMe}
\end{align*}
\]

\[
\text{25\% 3 steps}
\]

\[
\text{MeO} \quad \text{OMe}
\]

**Scheme 10.** Synthesis of amine building block 106. Reagents and conditions: (a) LiAlH\(_4\), Et\(_2\)O, 0 \text{\degree C}, 72\%; (b) Dess-Martin periodinane, CH\(_2\)Cl\(_2\), r.t., 85%; (c) allylamine, r.t., 30 min, then NaBH\(_3\)CN, CH\(_3\)CN, 41%.
1.2.5 Synthesis of α-Hydroxy Aldehyde Building Block

The two α-hydroxy aldehydes, masked as lactol building blocks 112 and 113, were prepared in 2-3 steps using known procedures from commercially available starting materials (Scheme 11). Indium-mediated allylation of 107 with allyl bromide provided the corresponding glycolic acid 108 in 54% isolated yield. Ketalization with dimethoxypropane and pyridium p-toluenesulfonate provided 110. Subsequent DIBAL-H reduction afforded lactol 112 in 96% yield. Ketalization of commercially available 2-hydroxy-3-phenylpropanoic acid 109 provided ketal 111 in 87% yield, and subsequent DIBAL-H reduction afforded lactol 113 in 95% yield. Ketals 110 and 111 were stable when stored at 0 °C for several months. However, lactols 112 and 113 are unstable over time, even at 0 °C. Freshly prepared masked α-hydroxy aldehydes were consistently applied in the couple phase to ensure reproducible results of anti-amino alcohols.

Scheme 11. Synthesis of lactols 112 and 113. Reagents and conditions: (a) allyl bromide, THF:H₂O (2:1), 0 °C, indium; (b) acetone, 2,2-dimethoxypropane, pyridium p-toluenesulfonate; (c) CH₂Cl₂, DIBAL-H, -78 °C.
1.2.6 Synthesis of Estronylboronic Acid Building Block

Estronylboronic acid building block 114 was prepared from commercially available estrone (Scheme 12). Triflation of estrone,\textsuperscript{53} and subsequent Pd-catalyzed cross-coupling of estronyltriflate with pinacolborane afforded estronylpinacol borane in 68\% isolated yield. Subsequent cleavage of the pinacolboronic ester with NaIO\textsubscript{4} in ammonium acetate-water for 48 h at room temperature afforded the final estronylboronic acid building block 114 (50\% yield over three steps).\textsuperscript{54}

![Scheme 12. Synthesis of estronylboronic acid. Reagents and conditions: (a) Tf\textsubscript{2}O, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 0 \textdegree C 99\%; (b) Et\textsubscript{3}N, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, Pd\textsubscript{2}(dba)\textsubscript{3}-CHCl\textsubscript{3}, 1,4-dioxane, 100 \textdegree C, 68\%; (c) NaIO\textsubscript{4}, NH\textsubscript{4}OAc/H\textsubscript{2}O, acetone, rt, 74\%.](image)

1.2.7 Couple Phase: Petasis 3-Component Reactions of Olefin-Functionalized Building Blocks

Building block components for the Petasis 3-CR, were next matched so that the resulting amino alcohols contained olefin functionalities appropriately aligned as chemical handles for functional group pairing reactions (pair phase) towards diverse skeletons.

The Petasis 3-CRs were mediated in a mixture of CH\textsubscript{2}Cl\textsubscript{2} and hexafluoroisopropanol (HFIP),\textsuperscript{55} affording 16 different olefin functionalized diastereomerically pure anti-amino alcohol products 115-130 in decent to good yields (24-95\%, Scheme 13).
Scheme 13. *Couple* Phase: Petasis 3-Component Reactions of Olefin-Functionalized Building Blocks. Product 123 was obtained as a 1:1 diastereomeric mixture of *anti*-amino alcohols.

Alkene appendage diversification could be achieved by varying the amine, the α-hydroxy aldehyde and the boronic acid components. Alkene moieties were generally introduced in the amine component, except in 125 (see Scheme 13). In many cases the olefin moieties could be introduced via lactol 112, forming compounds 115-123, 125, 129 and 130. The use of *trans*-phenylvinylboronic acid enabled the introduction of an alkene moiety via the boronic acid component (compounds 125, 126, and 130).
Furthermore, the use of 2-furanboronic acid enabled the introduction of a diene (compounds 128 and 129), suitable for intramolecular Diels-Alder reactions.

1.2.8 Pair Phase: Functional-Group Pairing of Alkene-Containing Amino Alcohols

A series of skeletal diversification reactions were next explored. Ring-closing metathesis with Grubbs II catalyst at slightly elevated temperatures (50 °C) proved to be the most optimal reaction conditions for the generation of 5-membered ring systems 131 and 132 in good yields (71-85%, Scheme 14). Ring-closing metathesis of diallylamine 127 to afford pyrrolidine 133 proved to be problematic. Screening of several catalysts (Grubbs-I, Grubbs-II, Hoveyda-Grubbs-I and Hoveyda-Grubbs-II catalysts) in different solvents (CH₂Cl₂ and toluene) and at different temperatures, proved unsuccessful. In all cases a good recovery of starting material was achieved. Previously reported successful RCM protocols of basic and nucleophilic diallylamines in the presence of Ti(i-PrO)₄ gave unsatisfactory results in our hands. Only recovery of starting material was obtained. Ring-closing metathesis of substrate 115 and 116 with Grubbs II at room temperature afforded tetrahydroazepine 135 and 136 in good yield (71-80%, see Scheme 14). The skeletally distinct tetrahydroazepine 138 could be achieved efficiently from 124 at 50 °C with Grubbs II catalyst in 81% isolated yield.

Additional skeletal diversification could be achieved by subjecting tetrahydroazepines 136 and 138 to Pd-catalyzed ring-contraction conditions which afforded two new 5-membered ring systems (embedded in 137, and 139, respectively). Both reactions proceeded in acceptable yield and in a highly diastereoselective manner (>10:1 and >8.1, respectively). The relative stereochemistry of compound 137 was assigned by 2D NOESY (see, experimental section for details). The stereochemistry of the newly formed stereocenter of the major compound of 139 could not be assigned by NMR studies. The N-allyl and furan functional groups in substrate 128 and 129 could upon refluxing in toluene (or upon heating as a neat reaction) undergo an intramolecular Diels-Alder reaction affording polycyclic pyrrolidine 140 and 141, exo-fused to an...
oxanorbornene moiety, both being formed as single diastereomers. $^1$H NMR analysis, including key NOESY studies determined the relative stereochemistry of the compounds (see, experimental section for details).

Scheme 14. Skeletal diversification reactions. Reagents and conditions: (a) Grubbs II (10 mol%), PhMe, 50 °C, 1-3 h; (b) Grubbs II (10 mol%), PhMe, reflux, 1 h; (c) Grubbs II (10 mol%), CH$_2$Cl$_2$, r.t., 18-22 h; (d) [(allyl)PdCl]$_2$ (15 mol%), triethyl phosphite, morpholine, TFA, CH$_2$Cl$_2$, reflux, 16-17 h; (e) PhMe, reflux, 2 h, or neat, 115 °C, 3 h.

Ring-closing metathesis of 140 to 142 with several different Ru-alkylidene catalysts (e.g., Grubbs II, Hoveyda-Grubbs I and Hoveyda-Grubbs II) in different solvents (e.g., CH$_2$Cl$_2$, m-xylene) and at different temperatures (e.g., room temperature, 50 °C, reflux) did not afford any product. In several cases, a complex product mixture was evidenced by TLC analysis. Subjecting 130, which entails 4 alkene moieties, to RCM conditions was attempted. However, two different Ru-alkylidene catalysts (Grubbs II and Hoveyda-Grubbs II) in two different solvents (toluene and CH$_2$Cl$_2$) at room temperature or at reflux, failed to give any product, and only SM was recovered. Use of additives, such as Ti(i-PrO)$_4$ or HCl (1M solution in ether) to deactivate the 28
nucleophilic, basic nitrogen proved unsuccessful. Skeletal diversity could be further expanded through a serendipitous reaction to oxazabicyclooctane \textbf{134}, by simply subjecting \textbf{115} to Grubbs II catalyst at elevated temperatures. These compounds are very interesting, as they contain an epoxy-bridged bicyclic structure, which is also a key element in naturally occurring compounds, such as in complex zoanthamine and ribasine alkaloids\textsuperscript{58, 59} (Figure 7).

Figure 7. Oxazabicyclooctane (highlighted in blue) scaffold in natural products.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{oxazabicyclooctane.png}
\caption{Oxazabicyclooctane (highlighted in blue) scaffold in natural products.}
\end{figure}

\subsection*{1.2.9 Proposed Mechanism for the Formation of Oxazabicyclooctane}

Intrigued by these new results, one might hypothesize that the formation of \textbf{134} occurs through a Ru-catalyzed double bond isomerization of the RCM product \textbf{135} to form an iminium intermediate, which is then being trapped by the tethered \textit{O}-nucleophile (Figure 8).

Carefully purified tetrahydroazepine (from ruthenium byproducts)\textsuperscript{60} \textbf{135} does not convert into \textbf{134} under thermal conditions; whereas the addition of Grubbs-II rapidly effects the isomerization steps (Figure 8). These results suggest that the Ru-alkylidene catalyst plays a nonmetathetic role in the formation of \textbf{134}. Allylamine isomerization processes involving Ru-alkylidene catalyzed double bond isomerization to form enamines and enol ethers are well-known in the literature and will be the subject of Chapter 2. To the best of our knowledge, no Ru-alkylidene catalyzed allylamine
isomerizations to generate synthetically useful iminium intermediates had been reported so far.

![Figure 8](image)

**Figure 8.** Possible mechanism for the formation of oxazabicyclooctane 134.

1.3.0 *Pair Phase: Selective Formation of Tetrahydroazepines and Oxazabicyclooctanes*

The scope of this newly discovered methodology was investigated. A catalyst screening study was carried out on the model substrate 115, to identify the optimal reaction conditions to form tetrahydroazepine 134 and oxazabicyclooctane 135. A range of Ru-alkylidene catalysts, temperatures, solvents and concentrations were screened. Grubbs-II catalyst in CH$_2$Cl$_2$ at room temperature proved to be the most efficient condition in affording the desired tetrahydroazepine 135 (Table 1, entry 2). The formation of oxazabicyclooctane was highly dependent on the temperature. Most probably the catalyst switches its mode of reactivity upon heating, in order to catalyze the isomerization reaction. With regard to the oxazabicyclooctane formation, Hoveyda-Grubbs II catalyst in toluene at reflux (Table 1, entry 7) was found to be the most promising condition, affording 134 cleanly after only 1 h.

(i) this catalyst screening was conducted by PhD student Mette Ishoey

30
Table 1. Catalyst and Reaction Conditions for the Selective Formation of Tetrahydroazepines and Oxazabicyclooctanes

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent (temp)</th>
<th>ratio <strong>115:135:134</strong> (1 h)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>ratio <strong>115:135:134</strong> (24 h)&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs I</td>
<td>CH₂Cl₂ (rt)</td>
<td>-</td>
<td>52:48:0</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs II</td>
<td>CH₂Cl₂ (rt)</td>
<td>-</td>
<td>1:98:1</td>
</tr>
<tr>
<td>3</td>
<td>Hoveyda-Grubbs II</td>
<td>CH₂Cl₂ (rt)</td>
<td>-</td>
<td>17:82:1</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs II</td>
<td>CH₂Cl₂ (reflux)</td>
<td>6:73:20</td>
<td>5:68:27</td>
</tr>
<tr>
<td>5</td>
<td>Grubbs II</td>
<td>toluene (reflux)</td>
<td>3:10:87&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Hoveyda-Grubbs I</td>
<td>toluene (reflux)</td>
<td>1:45:54&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Hoveyda-Grubbs II</td>
<td>toluene (reflux)</td>
<td>1:3:96&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by RP-HPLC (215 nm).<sup>b</sup> Reaction mixtures were generally clean (>85% of **115**, **135** and **134**).<sup>c</sup> Reactions run at 0.03 M concentration. <sup>d</sup> Complex reaction mixture (<70% of **115**, **135** and **134**).

Next, the substrate scope of the present methodology was examined by employing a range of diene containing β-amino alcohols **115-123**. Representative results are summarized in Table 2. Grubbs II catalyst at low temperature (method A) proved efficient in the synthesis of various tetrahydroazepine derivatives **135**, and **143-150**, whereas Hoveyda-Grubbs II at refluxing toluene (method B) displayed excellent selectivity for the synthesis of oxazabicyclooctane **134**, and **151-158**.
Table 2. *Pair* Phase: Selective Formation of Tetrahydroazepines and Oxabicyclooctanes

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>tetrahydroazepine (method A), yield (%)*ab</th>
<th>oxazabicyclooctane (method B), yield (%)*a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>135, 80</td>
<td>134, 82</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>143, 71</td>
<td>151, 41</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>144, 76</td>
<td>152, 37</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>145, 77</td>
<td>153, 58</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>146, 90</td>
<td>154, 68</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>147, 74</td>
<td>155, 78</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>148, 71</td>
<td>156, 85</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>149, 79</td>
<td>157, 64</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>150, 67&lt;sup&gt;c&lt;/sup&gt;</td>
<td>158, 66&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Isolated yield after flash column chromatography.  
  b See supporting information for detailed reaction conditions.  
  c Products 150/158, were obtained both as 1:1 diastereomeric mixtures of *anti*-amino alcohols/ethers.
1.3.1 Pair Phase: Consecutive Petasis 3-CR and subsequent RCM Reactions for Construction of a Complex Bicyclic Morpholine Skeleton.

As the final extension of the methodology, by utilizing two consecutive Petasis 3-CRs (as couple phase), followed by RCM (as pair phase), a densely functionalized bicyclic morpholine heterocycle could be accessed as a single diastereomer in 5 steps. By treating lactol 113 with allylamine and trans-phenylvinylboronic acid, the anti β-amino alcohol 159 could be obtained in good yield. A subsequent Petasis 3CR with glyoxal and phenylboronic acid provided a morpholine adduct 160 as a mixture (2 spots with similar Rf-values on TLC), containing several diastereomers. When 160 was treated with DBU at 60 °C for 22 h an equilibration occurred to afford the more stable diastereomerically pure 2-hydroxymorpholine compound 161 in 77% yield. Following acylation and RCM afforded the bicyclic morpholine 162 (65%, two steps). The stereochemical relationship was assigned by 2D NOESY experiment (Scheme 13). The vicinal coupling revealed that protons H-1 and H-2 had an axial-axial relationship ($J^3 = 8.2$ Hz), and the spatial orientation between protons H-3 and H-4 showed to be in an axial-equatorial relationship ($J^3 = 3.7$ Hz).

![Scheme 15. 5-step synthesis to morpholine 162. Reagents and Conditions: (a) CH$_2$Cl$_2$:HFIP (3:1), rt, 22 h. (b) glyoxal, phenylboronic acid, ethanol, 50 °C, 72 h. (c) PhMe, DBU, 60 °C, 22 h. (d) Et$_3$N, DMAP, CH$_2$Cl$_2$, acetic anhydride. (e) PhMe, Grubbs II, 50-60 °C, 30 min.](image-url)
1.3.2 Summary

In conclusion, a B/C/P pathway has been developed that implements strategically situated olefin moieties, via Petasis-3CR (as the couple phase), for subsequent intramolecular functional group pairing with RCM, Pd-catalyzed ring-contraction, and IMDA reactions (as the pair phase). In addition a Ru-catalyzed tandem RCM/isomerization/cyclization sequence to hitherto unknown oxazabicyclooctane derivatives has been developed. Overall, this new DOS pathway comprises the efficient (2-5 step) synthesis of a collection of 9 structurally distinct skeletons (Figure 4).

Figure 4. A Build/Couple/Pair strategy combining the Petasis 3-component reaction with Ru-catalyzed RCM, Pd-catalyzed ring-contraction, and IMDA functional group pairing reactions..
1.3.3 Experimental section

**General Methods:** With the exception of estrone-derived compounds, all compounds were obtained as racemic mixtures. Unless otherwise stated, all reactions were run under an argon atmosphere. The glassware were dried over a Bunsen flame or dried in an oven prior to contact with any of the reactants or solvents. All flasks were equipped with a rubber septum, through which transport of chemicals, from or to the flask, was performed by use of a syringe equipped with a needle. All reactions were monitored by thin layer chromatography (TLC) or reversed-phase high-performance liquid chromatography (RP-HPLC). All solvents were were dried over molecular sieves. All commercially available reagents were used without further purification.

Typically all new compounds were characterized by $^1$H NMR and $^{13}$C NMR, COSY, IR, TLC, RP-HPLC, ESI-MS, HRMS and melting point. Some compounds were characterized by HSQC, HMBC and/or NOESY. Evaporation of solvents was performed using a rotary evaporator under reduced pressure at various temperatures. Analytical TLC was conducted using Merck aluminium sheets covered with silica (C-60 F$_{254}$). The plates were either visualized under UV-light or stained by dipping in a developing agent followed by heating. KMnO$_4$ (3 g in H$_2$O (300 mL) along with K$_2$CO$_3$ (20 g) and 5% aqueous NaOH (5 mL)) and/or phosphomolybdic acid (PMA) (10 g in 200 mL EtOH) were used as developing agents. Flash column chromatography was performed using a glass column packed with Matrex 60 Å silica gel (35–70 µm particles) as stationary phase.

Analytical HPLC was conducted on a Waters Alliance 2695 RP-HPLC system using a Symmetry® C-18 column (d 2.5 µm, 4.6 x 75 mm, column temp: 25 °C; flow: 1 mL/min) with detection at 215 nm and 254 nm. Eluents A (0.1% TFA in H$_2$O) and B (0.1% TFA in MeCN) were used in a linear gradient (100% A to 100% B) in a total run time of 13 min. For the recording of $^1$H NMR and $^{13}$C NMR either a Varian Mercury-300 spectrometer (operating at 300 MHz for proton and 75 MHz for carbon), or a Varian Unity Inova-500 spectrometer (operating at 500 MHz for $^1$H NMR) were used. HSQC, HMBC and NOESY were also recorded on the Varian Unity Inova-500 spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and the
coupling constants \( (J) \) in Hz. Usually CDCl\(_3\) was used as the solvent and signal positions were measured relative to the signal for CHCl\(_3\) (\( \delta \) 7.26 ppm, for \(^1\)H NMR and \( \delta \) 77.36 ppm for \(^{13}\)C NMR). IR analysis was performed on a Bruker Alpha FT-IR spectrometer and reported in frequency of absorption (cm\(^{-1}\)). Analytical LC/MS (ESI) analysis was performed on a Waters AQUITY RP-UPLC system equipped with a diode array detector using an AQUITY UPLC BEH C-18 column (\( d \) 1.7 \( \mu \)m, 2.1 x 50 mm; column temp: 65 \(^{\circ}\)C; flow: 0.6 mL/min). Eluents A (0.1% HCO\(_2\)H in H\(_2\)O) and B (0.1% HCO\(_2\)H in MeCN) were used in a linear gradient (5% B to 100% B) in a total run time of 2.6 min. Melting points were measured using a Thomas Hoover capillary melting point apparatus.
**Build**: Synthetic Procedures and Spectroscopic Data for Building Blocks

*N-Benzyl allylamine* (104). K$_2$CO$_3$ (4.83 g, 35.1 mmol) was suspended in allylamine (13.4 g, 17.5 mL, 232 mmol) and benzyl bromide (4.96 g, 3.5 mL, 29 mmol) was added dropwise over a period of 45 min. After stirring at room temperature for 24 h, the reaction mixture was filtered through a pad of celite followed by evaporation of excess allylamine *in vacuo*. The residue was distilled at reduced pressure (1.1 mbar, 30 °C) to give the title compound as a colorless oil. Analytical data matches the reported ones$^{ii}$ (3.45 g, 80%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.36-7.22 (m, 5H), 5.94 (m, 1H), 5.15 (m, 2H), 3.80 (s, 2H), 3.28 (m, 2H), 1.33 (bs, 1H).

*N-Allylpent-4-en-1-amine* (105). K$_2$CO$_3$ (4.44 g, 32.1 mmol) was suspended in allylamine (30.5 g, 40 mL, 540 mmol) and 5-bromopent-1-ene (3.2 mL, 27 mmol) was added dropwise. After stirring at room temperature for 24 h, the reaction mixture was filtered through a pad of celite followed by evaporation of excess allylamine *in vacuo*. The residue was distilled at reduced pressure (3.7-4 mbar, 75-100 °C) to give the title product as a colorless oil (1.76 g, 53%). Analytical data matches the reported ones$^{iii}$. $^1$H NMR (300 MHz, CDCl$_3$) δ 5.85 (m, 2H), 5.05 (m, 4H), 3.23 (m, 2H), 2.61 (m, 2H), 2.07 (m, 2H), 1.58 (m, 2H), 1.30 (bs, 1H).

*2-Hydroxypent-4-enoic acid* (108). Glyoxylic acid (11.0 g, 0.12 mol) was suspended in a mixture of allyl bromide (22.6 g, 16.2 mL, 0.18 mol) and THF: H$_2$O (2:1) (400 mL) at 0 °C. Fine flakes of

---


Indium (14.4 g, 0.13 mol) were added under vigorous stirring and the reaction was allowed to reach room temperature. After 19 h, the reaction was quenched with aqueous 1 M HCl (400 mL) and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 400 mL). The combined organic layers were dried over MgSO$_4$. The volatiles were removed in vacuo and the residue was distilled at reduced pressure (2.7 mbar, 120-130 °C), to give the title compound as a colorless oil (7.51 g, 54%), that crystallized upon standing. Analytical data matches the reported ones.\textsuperscript{iv} \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 5.73 (m, 1H), 5.11 (m, 2H), 4.26 (dd, $J = 6.6, 4.6$ Hz, 1H), 2.55 (m 1H), 2.39 (m, 1H).

5-Allyl-2,2-dimethyl-1,3-dioxolan-4-one (110). 2-Hydroxypent-4-enoic acid (8.00 g, 68.9 mmol) was dissolved in acetone (150 mL). 2,2-dimethoxypropane (57.5 g, 68.0 mL, 552 mmol) and pyridinium $p$-toluenesulfonate (8.60 g, 34.5 mmol) were added and the reaction was stirred at reflux for 2.5 h. After cooling to room temperature the resulting suspension was filtered through a pad of celite, which was washed with EtOAc (2 x 100 mL). The filtrate was evaporated in vacuo and the resulting oil was distilled at reduced pressure (3-4 mbar, 80 °C), to give the title compound as colorless oil (9.77 g, 91%). Analytical data matches the reported ones.\textsuperscript{v} \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 5.71 (tdd, $J = 17.1, 10.2, 6.9$ Hz, 1H), 5.10 (m, 2H), 4.36 (dd, $J = 6.8, 4.4$ Hz, 1H), 2.54 (m, 1H), 2.38 (m, 1H), 1.50 (s, 3H), 1.43 (s, 3H).

**Compound: Lactol 112 (rac).** A solution of 5-allyl-2,2-dimethyl-1,3-dioxolan-4-one (500 mg, 3.20 mmol) in toluene (13 mL) was stirred at -78 °C. DIBAL-H (5.13 mL, 5.13 mmol, 1 M in toluene) was added dropwise and after 30 min the reaction was quenched with aqueous 1 M HCl (6.4 mL). The reaction was allowed to reach room temperature and stirred for another 30 min, whereupon the reaction was diluted with H$_2$O (50 mL) and

\textsuperscript{iv} Kaur, P.; Singh, P.; Kumar, S. *Tetrahedron*, 2005, 61, 8231-8240.  
extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, and the volatiles were removed in vacuo to give the title compound as a colorless oil (2:1 diastereomeric mixture, 488 mg, 96%), which was used immediately without further purification. \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 5.83 (m, 1H, 2 diastereomers), 5.30 (dd, \(J = 5.8, 3.2\) Hz, 1H, 1 diastereomer), 5.14 (m, 3H, 2 diastereomers), 4.05 (m, 1H, 2 diastereomers), 3.71 (d, \(J = 3.8\) Hz, 1H, 1 diastereomer), 3.10 (d, \(J = 6.0\) Hz, 1H, 1 diastereomer), 2.46 (m, 2H, 1 diastereomer), 2.38 (m, 2H, 1 diastereomer), 1.53 (s, 3H, 1 diastereomer), 1.51 (s, 3H, 1 diastereomer), 1.43 (s, 3H, 1 diastereomer), 1.34 (s, 3H, 1 diastereomer); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 133.7/133.2 (2 diastereomers), 117.9/117.5 (2 diastereomers), 110.5/109.5 (2 diastereomers), 99.3/95.1 (2 diastereomers), 82.0/79.0 (2 diastereomers), 37.0/33.1 (2 diastereomers), 28.8/27.8 (2 diastereomers), 26.9/25.8 (2 diastereomers); FT-IR (film) \(\nu\) 3428, 2986, 2937, 1642, 1433, 1381, 1244, 1039, 1012, 917, 843 cm\(^{-1}\).

5-Benzyl-2,2-dimethyl-1,3-dioxolan-4-one (111). 2-Hydroxy-3-phenylpropanoic acid (5.00 g, 30.0 mmol) was dissolved in acetone (60 mL), 2,2-dimethoxypropane (29.8 ml, 240 mmol) and pyridinium \(p\)-toluenesulfonate (3.78 g, 15.0 mmol) were added and the reaction was stirred at reflux for 6 h. After cooling to room temperature, the resulting suspension was filtered through a pad of celite. The filtrate was evaporated in vacuo and the resulting oil was purified by flash column chromatography on silica gel (hexanes:EtOAc (4:1)) to give the title compound as a colorless oil (5.39 g, 87%). Analytical data matches the reported ones.\(^{vi}\) \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.31-7.17 (m, 5H), 4.88 (m, 1H), 3.09 (dd, \(J = 14.5, 4.1\) Hz, 1H), 2.92 (dd, \(J = 14.5, 7.0\) Hz, 1H), 1.46 (s, 3H), 1.32 (s, 3H).

**Compound: Lactol 113 (rac).** A solution of 5-benzyl-2,2-dimethyl-1,3-dioxolan-4-one (300 mg, 1.45 mmol) in toluene (5.8 mL) was stirred at -78°C. DIBAL-H (2.33 mL, 2.33 mmol, 1 M in toluene) was added and after 30 min the reaction was quenched with aqueous 1 M HCl (2.9 mL). The reaction was allowed to reach room temperature and stirred for another 30 min, whereupon the reaction was diluted with H2O (30 mL) and extracted with CH2Cl2 (3 x 30 mL). The combined organic layers were dried over MgSO4, filtered and the volatiles were removed in vacuo to give the title compound as a colorless oil (3:2 diastereomeric mixture, 288 mg, 95%), which was used without further purification. Analytical data matches the reported ones.vi 1H NMR (300 MHz, CDCl3) δ 7.29-7.14 (m, 5H, 2 diastereomers), 6.56 (m, J = 5.0 Hz, 1H, 1 diastereomer), 6.38 (d, J = 5.5 Hz, 1H, 1 diastereomer), 5.15 (dd, J = 5.3, 3.7 Hz, 1H, 1 diastereomer), 5.07 (dd, J = 4.9, 3.5 Hz, 1H, 1 diastereomer), 4.11 (m, 1H, 1 diastereomer), 4.01 (m, 1H, 1 diastereomer), 2.90-2.70 (m, 2H, 2 diastereomers), 1.41 (s, 3H, 1 diastereomer), 1.36 (s, 3H, 1 diastereomer), 1.30 (s, 3H, 1 diastereomer), 1.19 (s, 3H, 1 diastereomer).

**Estronyl triflate.** A solution of estrone (2.50 g, 9.26 mmol) and Et3N (2.60 mL, 18.5 mmol) in CH2Cl2 (46 mL) was stirred at 0°C. Trifluoromethanesulfonic anhydride (1.71 mL, 10.2 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 60 min, and quenched with sat. aqueous NaHCO3 (50 ml). The organic layer was separated, and the aqueous phase was extracted with CH2Cl2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na2SO4, and the volatiles were removed in vacuo. The residue was then purified by flash column chromatography on silica gel (hexanes:EtOAc (4:1)) to give the title compound as a colorless oil (7.49 g, 99%). Analytical data matches the reported ones.vii 1H NMR (300 MHz, CDCl3) δ 7.34 (d, J = 8.5 Hz, 1H), 7.04-6.98 (m, 2H), 2.94 (dd, J = 8.7, 4.2 Hz, 1H), 1.97 (s, 3H, 1H, 1 diastereomer).

2H), 2.51 (dd, J = 18.4, 8.4 Hz, 1H), 2.43-1.94 (m, 6H), 1.67-1.42 (m, 6H), 0.91 (s, 3H).

**Estronyl pinacolborane.** To a solution of estronyl triflate (4.0 g, 9.95 mmol), Pd(dppf)Cl$_2$-CH$_2$Cl$_2$ (400 mg, 0.50 mmol) in dioxane (50 ml) under argon were added Et$_3$N (8.2 mL, 60 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.2 mL, 28.9 mmol) and the mixture was heated at 100 °C for 17 h. Upon cooling to room temperature, the volatiles were removed *in vacuo*. The residue was then purified by flash column chromatography on silica gel (hexanes:EtOAc (8:1)) to give the title compound as a colorless solid (2.55 g, 68%). Analytical data matches the reported ones.*°* $^1$H NMR (300 MHz, CDCl$_3$) δ 7.61-7.56 (m, 2H), 7.32 (d, J = 7.7 Hz, 1H), 2.93 (dd, J = 9.4, 4.8 Hz, 2H), 2.55-1.95 (m, 6H), 1.66-1.40 (m, 7H), 1.34 (s, 12H), 0.90 (s, 3H).

**Estronylboronic acid (114).** Estronyl pinacolborane (2.20 g, 5.78 mmol) was dissolved in acetone (80 mL), and into it added a solution of ammonium acetate (1.78 g, 23.1 mmol) and sodium periodate (4.90 g, 23.1 mmol) in H$_2$O (70 mL). The reaction mixture was stirred for 48 h at room temperature, and then filtered. The volatiles were removed *in vacuo* and the remaining aqueous solution was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na$_2$SO$_4$, and the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (4:1)) to give the title compound as a colorless solid (1.27 g, 74%). Analytical data matches the reported ones.*°* $^1$H NMR (300 MHz, CDCl$_3$) δ 7.63 (s, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.03 (d, J = 7.8 Hz, 1H), 7.01 (s, 1H), 6.73 (s, 1H), 2.61 (bs, 2H), 2.25-1.07 (m, 13H), 0.58 (s, 3H).

Couple: Synthetic procedures and spectroscopic data for compounds 115-130 and 159

**Petasis 3-CR product 115 (rac). General procedure A**: A solution of 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (2.39 g, 15.1 mmol), N-benzyl allylamine (2.45 g, 16.6 mmol) and phenylboronic acid (2.03 g, 16.6 mmol) in a mixture of dry CH₂Cl₂ (20 mL) and hexafluoroisopropanol (33.5 mL). The reaction was left for 24 h at r.t., whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (10:1 v/v), Rf = 0.2) to give the title compound as a colorless oil (2.93 g, 63%). ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.25 (m, 10H), 5.91 (m, 2H), 5.17 (m, 4 H), 4.31 (dt, J = 8.0, 3.5 Hz, 1H), 3.85 (d, J = 13.9 Hz, 1H), 3.67 (d, J = 7.7 Hz, 1H), 3.32 (dd, J = 14.4, 4.8 Hz, 1H), 3.20 (d, J = 13.9 Hz, 1H), 2.83 (dd, J = 14.5, 8.0 Hz, 1H), 2.67 (m, 1H), 2.15 (td, J = 15.4, 7.8 Hz, 1H), 1.96 (bs, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 139.6, 135.8, 135.7, 135.3, 129.7, 128.6, 128.3, 128.2, 127.6, 126.9, 117.8, 117.5, 69.7, 68.8, 54.3, 52.9, 38.8; FT-IR (film) ν 3564, 3461, 3082 cm⁻¹; HRMS (ESI) calcd for C₂₁H₂₅NO [M+H]⁺ 308.2009, found 308.2026.

**Petasis 3-CR product 116 (rac).** Following general procedure A, 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (330 mg, 2.08 mmol), 3,4-dichlorophenylboronic acid (416 mg, 2.19 mmol) and N-benzyl allylamine (322 mg, 2.19 mmol) were reacted for 20 h at room temperature to give the title compound as a pale yellow oil (248 mg, 28%) after flash column chromatography on silica gel (hexanes:EtOAc (15:1)). ¹H NMR (300 MHz, CDCl₃) δ 7.45 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.36-7.22 (m, 5H), 7.16 (dd, J = 8.2, 2.0 Hz, 1H), 5.92-5.76 (m, 2H), 5.20-5.09 (m, 4H), 4.22 (dt, J = 8.1, 3.7 Hz, 1H), 3.81 (d, J = 13.9 Hz, 1H), 3.60 (d, J = 7.4 Hz, 1H), 3.29 (m, 1H), 3.18 (d, J = 13.9 Hz, 1H), 2.79 (dd, J = 14.5, 8.0 Hz, 1H), 2.57 (m, 1H), 2.09 (m, 1H), 1.92 (bs, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 139.1, 136.6, 135.3, 134.6, 132.3, 131.4, 42
130.9, 128.9, 128.5, 128.4, 127.1, 118.4, 118.2, 69.3, 67.0, 54.4, 54.0, 38.9; FT-IR (ATR) ν 3456, 1469 cm⁻¹; HRMS (ESI) calcd for C₂₁H₂₃Cl₂NO [M+H]⁺ 376.1229, found 376.1229.

**Petasis 3-CR product 117 (rac).** Following general procedure A, 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (171 mg, 0.99 mmol), 1-napthaleneboronic acid (171 mg, 0.99 mmol) and N-benzyl allylamine (145 mg, 0.99 mmol) were reacted for 22 h at room temperature to give the title compound as a colorless oil (292 mg, 86%) after flash column chromatography on silica gel (hexanes:EtOAc 9:1 v/v). ¹H NMR (300 MHz, CDCl₃) δ 8.13 (bs, 1H), 7.92-7.89 (m, 1H), 7.88-7.80 (m, 2H), 7.58 (d, J = 7.7 Hz, 1H), 7.54-7.49 (m, 2H), 7.35 (d, J = 4.4 Hz, 4H), 7.31-7.25 (m, 1H), 6.04-5.87 (m, 2H), 5.23-5.07 (m, 4H), 4.69 (d, J = 6.7 Hz, 1H), 4.47 (ddd, J = 9.0, 6.7, 3.4 Hz, 1H), 3.85 (d, J = 14.2 Hz, 1H), 3.41-3.35 (m, 2H), 3.01 (dd, J = 14.8, 7.5 Hz, 1H), 2.66 (m, 1H), 2.15 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 139.8, 135.7, 135.5, 133.9, 133.1, 129.0, 128.1, 128.0, 128.2, 128.1, 126.9, 126.3, 125.8, 125.4, 125.0, 123.9, 117.9, 117.4, 70.6, 54.4, 52.9, 38.9; FT-IR (film) ν 3568, 3062, 2813 cm⁻¹; HRMS (ESI) calcd for C₂₅H₂₇NO [M+H]⁺ 358.2165, found 358.2159.

**Petasis 3-CR product 118 (rac).** Following general procedure A, 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (150 mg, 0.95 mmol), 4-biphenylboronic acid (196 mg, 0.99 mmol) and N-benzyl allylamine (145 mg, 0.99 mmol), were reacted for 23 h at room temperature to give the title compound as a colorless oil (247 mg, 68%) after flash column chromatography on silica gel (hexanes:EtOAc 9:1 v/v, Rₚ = 0.3). ¹H NMR (300 MHz, CDCl₃) δ 7.57-7.12 (m, 14H), 5.82 (m, 2H), 5.09 (m, 4H), 4.24 (dt, J = 8.1, 3.5 Hz, 1H), 3.79 (d, J = 14.0 Hz, 1H), 3.61 (d, J = 7.8 Hz, 1H), 3.25 (m, 1H), 3.15 (d, J = 14.0 Hz, 1H), 2.77 (dd, J = 14.5, 8.0 Hz, 1H), 2.61 (m, 1H), 2.08 (m, 1H), 1.89 (bs, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 140.6, 140.3, 139.6, 135.8, 135.2, 134.8, 130.1, 128.7, 128.6, 128.3, 127.2, 127.0, 126.9, 126.8, 117.8, 117.7, 69.6, 67.5, 54.4,
52.9, 38.8; FT-IR (ATR) ν 3564, 3461, 3062, 2812, 1486, 1450, 695 cm⁻¹; HRMS (ESI) calcd for C_{27}H_{29}NO [M+H]^+ 384.2322, found 384.2319.

**Petasis 3-CR product 119 (rac).** Following general procedure A, 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (260 mg, 1.65 mmol), 2,4-dimethoxyphenylboronic acid (314 mg, 1.72 mmol) and N-benzyl allylamine (253 mg, 1.72 mmol), were reacted for 22 h at room temperature to give the title compound as a colorless oil (510 mg, 84%) after flash column chromatography on silica gel (hexanes:EtoAc (8:1 v/v), Rᵣ = 0.3). ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.20 (m, 6H), 6.56-6.52 (m, 2H), 5.99-5.82 (m, 2H), 5.15-5.07 (m, 4H), 4.25 (dt, J = 8.0, 3.3 Hz, 1H), 4.17 (d, J = 7.6 Hz, 1H), 3.84 (s, 3H), 3.81 (d, J = 14.1 Hz, 1H), 3.79 (s, 3H), 3.29 (d, J = 14.1 Hz, 1H), 3.26 (m, 1H), 2.90 (dd, J = 14.5, 7.6 Hz, 1H), 2.66 (m, 1H), 2.22 (bs, 1H), 2.12 (dd, J = 15.0, 7.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 159.9, 159.5, 140.3, 136.3, 135.9, 131.0, 128.5, 128.0, 126.6, 117.1, 116.9, 116.9, 104.0, 98.5, 70.1, 60.8, 55.2, 55.11, 54.4, 53.1, 38.9; FT-IR (film) ν 3561, 3000, 1762, 1639 cm⁻¹; HRMS (ESI) calcd for C_{23}H_{29}NO_{3} [M+H]^+ 368.2220, found 368.2221.

**Petasis 3-CR product 120 (rac).** Following general procedure A, 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (200 mg, 1.26 mmol), 3,5-dimethyl-4-methoxyphenylboronic acid (239 mg, 1.32 mmol) and N-benzyl allylamine (194 mg, 1.32 mmol), were reacted for 25 h at room temperature to give the title compound as a pale green oil (356 mg, 78%) after flash column chromatography on silica gel (hexanes: EtOAc (8:1 v/v), Rᵣ = 0.3). ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.20 (m, 5H), 6.90 (s, 2H), 5.95-5.78 (m, 2H), 5.17-5.08 (m, 4H), 4.21 (dt, J = 8.2, 3.4 Hz, 1H), 3.78 (d, J = 13.9 Hz, 1H), 3.73 (s, 3H), 3.51 (d, J = 8.0 Hz, 1H), 3.26 (m, 1H), 3.15 (d, J = 13.9 Hz, 1H), 2.78 (dd, J = 14.4, 8.0 Hz, 1H), 2.66 (m, 1H), 2.29 (s, 6H), 2.12 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 156.3, 139.8, 136.0, 135.5, 130.7, 130.4, 130.1, 128.6, 128.2, 126.8, 117.6, 117.4, 69.7, 67.2, 59.6, 54.3, 52.9, 38.7, 16.3; FT-IR (film) ν
3476, 2923, 1484, 1452 cm$^{-1}$; HRMS (ESI) calcd for C$_{24}$H$_{31}$NO$_2$ [M+H]$^{+}$ 366.2428, found 366.2423.

**Petasis 3-CR product 121 (rac).** Following general procedure A, 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (400 mg, 2.53 mmol), 4-acetylphenylboronic acid (434 mg, 2.65 mmol) and N-benzyl allylamine (391 mg, 2.65 mmol) were reacted for 19 h at room temperature to give the title compound as a yellow oil (248 mg, 28%) after flash column chromatography on silica gel (hexanes:EtOAc (4:1), $R_f$ = 0.2). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.98 (d, $J$ = 8.3 Hz, 2H), 7.42 (d, $J$ = 8.3 Hz, 2H), 7.33-7.22 (m, 5H), 5.93-5.79 (m, 2H), 5.20-5.09 (m, 4H), 4.30 (dt, $J$ = 8.1, 3.6 Hz, 1H), 3.83 (d, $J$ = 13.9 Hz, 1H), 3.71 (d, $J$ = 7.5 Hz, 1H), 3.32 (m, 1H, 1H), 3.18 (d, $J$ = 14.0 Hz, 1H), 2.79 (dd, $J$ = 14.4, 8.0 Hz, 1H), 2.65-2.56 (m, 4H), 2.10 (m, 1H), 1.99 (bs, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 197.8, 141.9, 139.2, 136.3, 135.4, 134.8, 129.8, 128.5, 128.4, 128.1, 127.0, 118.2, 118.1, 69.4, 67.5, 54.4, 52.9, 38.9, 26.6; FT-IR (film) $\nu$ 3461, 1678, 1267 cm$^{-1}$; HRMS (ESI) calcd for C$_{23}$H$_{27}$NO$_2$ [M+H]$^{+}$ 350.2115, found 350.2116.

**Petasis 3-CR product 122 (rac).** Following general procedure A, 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (380 mg, 2.40 mmol), 1-benzothiophen-2-ylboronic acid (450 mg, 2.53 mmol) and N-benzyl allylamine (372 mg, 2.53 mmol) were reacted for 19 h at room temperature to give the title compound as a yellow/orange oil (764 mg, 88%) after flash column chromatography on silica gel (hexanes:EtOAc (9:1 v/v), $R_f$ = 0.3). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.86 (d, $J$ = 6.3 Hz, 1H), 7.80 (d, $J$ = 7.5 Hz, 1H), 7.41-7.25 (m, 7H), 7.22 (s, 1H), 5.98-5.83 (m, 2H), 5.29-5.13 (m, 4H), 4.25 (bs, 1H), 4.04 (d, $J$ = 7.3 Hz, 1H), 3.94 (d, $J$ = 13.9 Hz, 1H), 3.41-3.36 (m, 2H), 2.99 (dd, $J$ = 14.4, 8.0 Hz, 1H), 2.69 (m, 1H), 2.25 (td, $J$ = 15.1, 7.7 Hz, 1H), 2.07 (bs, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 139.9, 139.8, 139.3, 139.1, 135.6, 134.7, 128.7, 128.3, 127.0, 124.4, 124.2, 124.1, 123.2, 122.1, 118.0, 117.9, 70.9, 63.9, 54.7, 53.3, 38.6; FT-IR (film) $\nu$
3446, 3063, 2815, 1455 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{23}\)H\(_{25}\)NOS [M+H] \(^{+}\) 364.1730, found 364.1715.

**Petasis 3-CR product 123 (123’ and 123’’).** Following general procedure A. 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (300 mg, 1.89 mmol), estroneboronic acid (594 mg, 1.99 mmol) and N-benzyl allylamine (293 mg, 1.99 mmol) were reacted for 20 h at room temperature to give the title compound as a white solid (1:1 diastereomeric mixture, 684 mg, 75%) after flash column chromatography on silica gel (hexanes:EtOAc (4:1)) \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.34-7.25 (m, 6H), 7.08 (d, \(J = 8.0\) Hz, 1H), 7.01 (s, 1H), 5.98-5.81 (m, 2H), 5.21-5.10 (m, 4H), 4.27 (dt, \(J = 8.2, 3.3\) Hz, 1H), 3.83 (d, \(J = 14.0\) Hz, 1H), 3.58 (d, \(J = 8.0\) Hz, 1H), 3.30 (m, 1H), 3.18 (d, \(J = 13.9\) Hz, 1H), 2.95 (m, 2H), 2.81 (dd, \(J = 14.4, 8.0\) Hz, 1H), 2.70 (m, 1H), 2.57-2.42 (m, 2H), 2.33 (m, 1H), 2.22-1.97 (m, 5H), 1.68-1.45 (m, 7H), 0.94 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 221.1, 140.0, 139.7, 136.5, 136.4, 135.7, 133.1, 130.7 (diastereomer), 130.5 (diastereomer), 128.9, 128.5, 127.3 (diastereomer), 127.2 (diastereomer), 125.4, 117.9, 117.8, 69.9, 67.7 (diastereomer) 67.6 (diastereomer), 54.7, 53.2, 50.8, 48.2, 44.6, 39.1, 38.3, 36.1, 31.8, 29.8, 26.8, 25.8, 21.8, 14.3; mp 62-65 °C; FT-IR (film) \(\nu\) 3468, 2929, 1736 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{33}\)H\(_{41}\)NO\(_2\) [M+H] \(^{+}\) 484.3210, found 484.3210.

**Petasis 3-CR product 124 (rac).** Following general procedure A, 5-benzyl-2,2-dimethyl-1,3-dioxolan-4-ol (500 mg, 2.40 mmol), 3,4-dichloro-phenylboronic acid (477 mg, 2.52 mmol) and N-allylpent-4-en-1-amine (281 mg, 2.52 mmol) were reacted for 20 h at room temperature to give the title compound as a light green oil (200 mg, 21%) after flash column chromatography on silica gel (hexanes:EtOAc (8:1 v/v)). \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.04 (m, 8H), 5.80-5.62 (m, 2H), 5.11 (m,
2H), 4.90 (m, 2H), 4.24 (ddd, J = 9.0, 6.4, 3.8 Hz, 1H), 3.49 (d, J = 6.4 Hz, 1H), 3.20 (m, 1H), 2.86-2.78 (m, 2H), 2.53-2.34 (m, 2H), 2.25 (td, J = 13.4, 6.8 Hz, 1H), 1.95 (m, 2H), 1.48 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 138.5, 138.2, 137.2, 135.5, 132.1, 131.5, 129.9, 129.2, 129.0, 128.5, 126.4, 117.6, 114.8, 71.2, 53.1, 49.5, 40.8, 31.3, 26.1; FT-IR (film) ν 3458, 3076, 2836, 1453 cm⁻¹; HRMS (ESI) calcd for C23H27Cl2NO [M+H]⁺ 404.1542, found 404.1544.

**Petasis 3-CR product 125 (rac).** Following general procedure A, 5-allyl-2,2-dimethyl-1,3-dioxolan-4-ol (330 mg, 2.00 mmol), trans-2-phenylvinylboronic acid (310 mg, 2.10 mmol) and dibenzylamine (414 mg, 404 µL, 2.10 mmol) were reacted for 24 h at room temperature to give the title compound as a colorless oil (801 mg, >95%) after flash column chromatography on silica gel (hexanes:EtOAc (9:1 v/v), Rf = 0.3). ¹H NMR (300 MHz, CDCl3) δ 7.48-7.25 (m, 15H), 6.52 (d, J = 15.9 Hz, 1H), 6.34 (dd, J = 15.9, 9.6 Hz, 1H), 5.79 (m, 1H), 5.12 (m, 2H), 4.10 (m, 1H), 3.92 (d, J = 13.9 Hz, 2H), 3.54 (d, J = 13.7 Hz, 2H), 3.17 (dd, J = 9.5, 7.1 Hz, 1H), 2.69 (m, 1H), 2.17 (m, 1H), 2.05 (bs, 1H); ¹³C NMR (75 MHz, CDCl3) δ 139.6, 136.4, 136.2, 135.0, 128.8, 128.5, 128.3, 127.7, 126.9, 126.5, 124.6, 117.7, 70.8, 66.4, 55.1, 38.6; FT-IR (film) ν 3563, 3437, 3081, 3061, 1639 cm⁻¹; HRMS (ESI) calcd for C27H29NO [M+H]⁺ 384.2322, found 384.2333.

**Petasis 3-CR product 126 (rac).** Following general procedure A, 5-benzyl-2,2-dimethyl-1,3-dioxolan-4-ol (500 mg, 2.40 mmol), trans-2-phenylvinylboronic acid (390 mg, 2.64 mmol) and N-benzyl allylamine (389 mg, 2.64 mmol) were reacted for 24 h at room temperature to give the title compound as a colorless oil (767 mg, 84%) after flash column chromatography on silica gel (hexanes:EtOAc (8:1 v/v), Rf = 0.2). ¹H NMR (300 MHz, CDCl3) δ 7.53-7.28 (m, 15H), 6.62 (d, J = 15.9 Hz, 1H), 6.40 (dd, J = 15.9, 9.5 Hz, 1H), 5.98 (m, 1H), 5.28 (m, 2H), 4.19 (m, 1H), 4.03 (d, J = 13.9 Hz, 1H), 3.63 (d, J = 13.9 Hz, 1H), 3.46 (dd, J = 14.5, 5.4 Hz, 1H), 3.33 (dd, J = 9.5, 6.1 Hz, 1H), 3.24-
3.17 (m, 2H), 2.72 (dd, \(J = 13.9, 8.9\) Hz, 1H), 2.44, (bs, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 139.7, 139.0, 136.5, 135.8, 135.5, 129.2, 128.6, 128.5, 128.3, 128.2, 127.6, 126.8, 126.4, 126.1, 125.0, 117.5, 72.4, 67.0, 54.7, 53.5, 40.5; FT-IR (film) \(\nu\) 3563, 3443, 3082, 3061, 1659 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{27}\)H\(_{29}\)NO [M+H] \(+\) 384.2322, found 384.2335.

Petasis 3-CR product 127 (rac). Following general procedure A, 5-benzyl-2,2-dimethyl-1,3-dioxolan-4-ol (119 mg, 0.57 mmol), phenylboronic acid (76.7 mg, 0.629 mmol) and diallylamine (61.1 mg, 77.7 \(\mu\)L, 0.629 mmol) were reacted for 22 h at room temperature to give the title compound as a colorless oil (125 mg, 72%) after flash column chromatography on silica gel (hexanes:EtOAc (9:1 v/v)). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.11 (m, 10H), 5.81-5.68 (m, 2H), 5.14-5.03 (m, 4H), 4.34 (m, 1H), 3.61 (d, \(J = 6.3\) Hz, 1H), 3.29 (dd, \(J = 14.4, 4.9\) Hz, 2H), 2.91-2.76 (m, 3H), 2.42 (dd, \(J = 13.9, 8.6\) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 139.2, 135.6, 135.0, 129.9, 129.2, 128.2, 128.1, 127.7, 126.1, 118.1, 71.3, 68.2, 53.0, 40.7; FT-IR (film) \(\nu\) 3561, 3457,3062, 3027, 2976,2920, 2814, 1640, 1602 cm\(^{-1}\); MS (ESI) calcd for C\(_{27}\)H\(_{29}\)NO [M+H] \(+\) 308.2, found 308.2.

Petasis 3-CR product 128 (rac). Following general procedure A, 5-benzyl-2,2-dimethyl-1,3-dioxolan-4-ol (700 mg, 3.36 mmol), 2-furanboronic acid (376 mg, 3.36 mmol) and diallylamine (413 \(\mu\)l, 3.36 mmol) and the reaction was stirred at room temperature for 1 h. The volatiles were removed and following purification by flash chromatography (hexanes:EtOAc (12:1 v/v), \(R_f = 0.2\)) afforded the titled product in 240 mg (24%) as an colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.34 (dd, \(J = 0.7\) Hz, 1H), 7.25-7.11 (m, 5H), 6.30 (dd, \(J = 3.2, 1.8\) Hz, 1H), 6.17 (dd, \(J = 3.2, 0.7\) Hz, 1H), 5.72 (m, 2H), 5.09 (m, 4H), 4.22 (m, 1H) 3.70 (d, \(J = 7.9\) Hz, 1H), 3.27 (m, 2H), 3.17 (dd, \(J = 14.0, 3.3\) Hz, 1H), 2.72 (dd, \(J = 14.4, 7.7\) Hz, 2H), 2.53 (dd, \(J = 14.0, 9.0\) Hz, 1H), 1.91 (bs, 1H).
1H, OH); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.9, 141.9, 139.2, 136.2, 129.4, 128.3, 126.2, 117.2, 109.9, 109.7, 71.9, 61.6, 54.0, 40.7.

**Petasis 3-CR product 129 (rac).**

To a solution of allyl-2.2-dimethyl-1,3-dioxolan-4-ol (240 mg, 1.52 mmol) CH$_2$Cl$_2$ (13 ml) was added 2-furanylboronic acid (173.5 mg, 1.55 mmol) and diallylamine (192 µl, 1.55 mmol) and the reaction was stirred at room temperature for 2.5 h. Then 1 more equivalent of 2-furanylboronic acid and diallylamine was added. After 20 h of reaction time at room temperature, the volatiles were removed and following purification by flash chromatography (hexanes:EtOAc (10:1 v/v), $R_f$ = 0.2) afforded the titled product in 134 mg (38%) as an colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.42 (s, 1H), 6.36 (dd, $J$ = 3.0, 2.0 Hz, 1H), 6.23 (d, $J$ = 3.2Hz, 1H), 5.89 (m, 1H), 5.76 (m, 2H), 5.15 (m, 6H), 4.15 (dt, $J$ = 8.0, 3.6 Hz, 1H), 3.73 (d, $J$ = 8.0Hz, 1H), 3.30 (m, 2H), 2.76 (dd, $J$ = 14.7, 8.1 Hz, 2H), 2.59 (m, 1H), 2.21 (td, $J$ = 15.3, 7.7 Hz, 1H), 2.02 (bs, 1H, OH); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.9, 142.0, 136.2, 134.9, 117.7, 117.2, 109.9, 109.7, 69.7, 61.3, 53.9, 38.6.

**Petasis 3-CR product 130 (rac).** Following general procedure A,

5-allyl-2.2-dimethyl-1,3-dioxolan-4-ol (240 mg, 1.52 mmol), trans-phenylvinylboronic acid (229 mg, 1.55 mmol) and diallylamine (192 µl, 1.55 mmol) were reacted at room temperature for 22 h. The volatiles were removed and following purification by flash chromatography (hexanes:EtOAc (6:1 v/v), $R_f$ = 0.2) afforded the titled product in 256 mg (63%) as an colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.35-7.14 (m, 5H), 6.43 (d, $J$ = 16.0Hz, 1H), 6.15 (dd, $J$ = 16.0, 9.6 Hz, 1H), 5.87-5.68 (m, 3H), 5.13-4.99 (m, 6H), 3.83 (td, $J$ = 8.1, 4.9 Hz, 1H), 3.27 (dd, $J$ = 14.5, 5.6 Hz, 2H), 3.12 (dd, $J$ = 9.6, 5.3 Hz, 1H), 3.03 (dd, $J$ = 14.6, 7.1Hz, 2H), 2.58 (bs, 1H, OH), 2.29 (m, 2H., 2.15, (td, $J$=15.0, 7.6 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 136.6, 135.8, 135.0, 135.0, 128.5, 127.6, 126.4, 125.3, 117.3, 70.1, 67.1, 53.4, 38.4; LC-MS (ESI$^+$) M/z: 284.3 [M+H]$^+$. 

49
Rac3-(allylamino)-1,5-diphenylpent-4-en-2-ol 159 (rac). Following general procedure A, 5-benzyl-2,2-dimethyl-1,3-dioxolan-4-ol (400 mg, 1.92 mmol), trans-2-phenylvinylboronic acid (297 mg, 2.01 mmol) and allylamine (115.2 mg, 151 µL, 2.01 mmol) were reacted for 22 h at room temperature to give the title compound as a yellow oil (475 mg, 84%) after flash column chromatography on silica gel (gradient elution: EtOAc to CH$_2$Cl$_2$:MeOH (9:1 v/v)). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.47-7.23 (m, 10H), 6.54 (d, $J$ = 16.0 Hz, 1H), 6.25 (dd, $J$ = 16.0, 8.9 Hz, 1H), 5.87 (tdd, $J$ = 16.3, 10.2, 6.0 Hz, 1H), 5.15 (m, 2H), 4.04 (ddd, $J$ = 7.5, 6.1, 3.1 Hz, 1H), 3.31-3.13 (m, 3H), 2.78 (m, 2H), 2.57 (bs, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.6, 136.6, 136.3, 134.0, 129.2, 128.5, 128.3, 127.6, 126.9, 126.4, 126.2, 116.2, 73.7, 64.0, 49.3, 39.9; FT-IR (ATR) ν 3226, 3020, 2839 cm$^{-1}$; HRMS (ESI) calcd for C$_{20}$H$_{23}$NO [M+H]$^+$ 294.1852, found 294.1853.
**Pair: Synthetic Procedures and Spectroscopic Data for Compounds**

**Oxazabicyclooctane 134 (rac).** A stirred solution of 115 (150 mg, 0.448 mmol) in dry toluene (19 mL) was added the Hoveyda-Grubbs II catalyst (31.0 mg, 0.0448 mmol). The reaction was refluxed for 1 h whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (10:1 v/v), \( R_f = 0.3 \)) to give the title compound as a pale green oil (111 mg, 82%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.53-7.15 (m, 10H), 4.70 (s, 1H), 4.60 (m, 1H), 4.25 (d, \( J = 6.1 \) Hz, 1H), 3.92 (d, \( J = 13.6 \) Hz, 1H), 3.79 (d, \( J = 13.6 \) Hz, 1H), 1.76 (m, 1H), 1.81-1.06 (m, 6H); \(^1\)\(^3\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 140.2, 138.6, 128.4, 128.3, 127.0, 126.9, 126.5, 93.2, 78.7, 71.6, 60.5, 32.2, 25.4, 15.9; FT-IR (film) \( \nu \) 3084, 3060, 2940, 2817, 1602 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{19}\)H\(_{21}\)NO \([\text{M+H}]^+\) 280.1696, found 280.1701.

**Oxazabicyclooctane 151 (rac).** A stirred solution of 116 (80 mg, 0.213 mmol) in dry toluene (4.3 mL) was added the Hoveyda-Grubbs II catalyst (13.3 mg, 0.0213 mmol). The reaction was refluxed for 1 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (9:1 v/v), \( R_f = 0.2 \)) to give the title compound as an orange oil (30 mg, 41%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.64 (s, 1H), 7.37-7.17 (m, 7H), 4.71 (bs, 1H), 4.59 (m, 1H), 4.17 (d, \( J = 6.2 \) Hz, 1H), 3.87 (d, \( J = 13.5 \) Hz, 1H), 3.81 (d, \( J = 13.5 \) Hz, 1H), 1.68-1.06 (m, 6H); \(^1\)\(^3\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 139.5, 139.2, 132.4, 130.4, 130.3, 129.0, 128.4, 127.2, 126.4, 93.4, 78.4, 70.8, 60.6, 31.9, 25.3, 15.8; FT-IR (film) \( \nu \) 2946, 1467 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{19}\)H\(_{19}\)Cl\(_2\)NO \([\text{M+H}]^+\) 348.0916, found 348.0915.
Oxazabicyclooctane 152 (rac). A stirred solution of 117 (50 mg, 0.140 mmol) in dry toluene (5.6 mL) was added the Hoveyda-Grubbs II catalyst (8.9 mg, 0.0140 mmol). The reaction was heated to 100-105 °C for 1 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (16:1 v/v), R_f = 0.2) to give the title compound as a pale green oil (17 mg, 37%). ^1H NMR (300 MHz, CDCl_3) δ 8.45 (dd, J = 7.2, 0.9 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.82 (m, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.49-7.41 (m, 5H), 7.30 (t, J = 7.6 Hz, 2H), 7.20 (m, 1H), 5.00 (bt, J = 4.8 Hz, 1H), 4.80-4.78 (m, 2H), 3.94 (d, J = 13.5 Hz, 1H), 3.86 (d, J = 13.5 Hz, 1H), 2.02 (m, 1H), 1.66-1.50 (m, 2H), 1.41 (m, 1H), 1.18 (m, 1H), 0.77 (m, 1H); ^13C NMR (75 MHz, CDCl_3) δ 140.4, 134.2, 133.8, 131.8, 129.2, 128.7, 128.6, 127.8, 127.2, 126.2, 125.8, 125.6, 125.0, 123.2, 92.5, 78.3, 70.7, 60.6, 32.3, 25.6, 15.9; FT-IR (film) ν 2936, 905, 781, 703 cm^{-1}; HRMS (ESI) calcd for C_{23}H_{23}NO [M+H]^+ 330.1852, found 330.1854.

Oxazabicyclooctane 153 (rac). A stirred solution of 118 (90 mg, 0.23 mmol) in dry toluene (4.6 mL) was added the Hoveyda-Grubbs II catalyst (14.5 mg, 0.023 mmol) and the reaction was refluxed for 1 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (9:1 v/v), R_f = 0.2) to give the title compound as a pale green oil (48 mg, 58%). ^1H NMR (300 MHz, CDCl_3) δ 7.59-7.50 (m, 6H), 7.44-7.14 (m, 8H), 4.72 (bs, 1H), 4.64 (bs, 1H), 4.29 (d, J = 6.2 Hz, 1H), 3.95 (d, J = 13.6 Hz, 1H), 3.82 (d, J = 13.7 Hz, 1H), 1.79 (tdd, J = 18.4, 12.1, 5.9 Hz, 1H), 1.67-1.51 (m, 2H), 1.34 (dd, J = 11.9, 5.6 Hz, 1H), 1.25-1.13 (m, 2H); ^13C NMR (75 MHz, CDCl_3) δ 140.8, 140.1, 139.4, 137.8, 128.7, 128.4, 128.3, 127.4, 127.1, 127.1, 127.0, 126.9, 93.3, 78.7, 71.5, 60.5, 32.2, 25.5, 15.9; FT-IR (film) ν 2940, 1486 cm^{-1}; HRMS (ESI) calcd for C_{25}H_{25}NO [M+H]^+ 356.2009 found, 356.1990.
Oxazabicyclooctane 154 (rac). A stirred solution of 119 (70 mg, 0.190 mmol) in dry toluene (3.8 mL) was added the Hoveyda-Grubbs II catalyst (11.9 mg, 0.0190 mmol). The reaction was refluxed for 1 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (8:1 v/v), R_f = 0.2) to give the title compound as a pale green oil (44 mg, 68%). ^1H NMR (300 MHz, CDCl_3) δ 8.04 (dd, J = 8.4, 0.9 Hz, 1H), 7.50 (d, J = 7.2 Hz, 2H), 7.37 (m, 2H), 7.26 (m, 1H), 6.57 (dd, J = 8.4, 2.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 4.87 (m, 1H), 4.75 (bs, 1H), 4.25 (d, J = 5.8 Hz, 1H), 3.94 (d, J = 13.8 Hz, 1H), 3.87 (d, J = 14.0 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 1.87 (ddt, J = 18.4, 12.4, 6.0Hz, 1H), 1.71-1.58 (m, 2H), 1.41 (m, 1H), 1.28 (m, 1H), 1.08 (bddd, J = 13.6, 5.7, 1H); ^13C NMR (75 MHz, CDCl_3) δ 159.7, 157.9, 140.5, 128.5, 128.3, 128.2, 126.8, 119.3, 103.3, 98.1, 92.1, 77.3, 68.3, 60.4, 55.2, 55.0, 32.2, 25.7, 15.9; FT-IR (film) ν 2934, 2835, 1611, 1585, 1499 cm^{-1}; HRMS (ESI) calcd for C_{21}H_{25}NO_3 [M+H]^+ 340.1907, found 340.1906.

Oxazabicyclooctane 155 (rac). A stirred solution of 120 (100 mg, 0.275 mmol) in dry toluene (5.4 mL) was added the Hoveyda-Grubbs II catalyst (17.2 mg, 0.0275 mmol). The reaction was refluxed for 1 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography (hexanes:EtOAc (19:1 v/v), R_f = 0.2) to give the title compound as a green oil (71 mg, 78%). ^1H NMR (300 MHz, CDCl_3) δ 7.41 (d, J = 7.2 Hz, 2H), 7.31-7.25 (m, 2H), 7.21-7.13 (m, 3H), 4.67 (bs, 1H), 4.55 (m, 1H), 4.14 (d, J = 6.1 Hz, 1H), 3.91 (d, J = 13.5 Hz, 1H), 3.76 (d, J = 13.7 Hz, 1H), 3.66 (s, 3H), 2.24 (s, 6H), 1.78 (m, 1H), 1.63-1.49 (m, 2H), 1.31 (dd, J = 12.9, 5.2 Hz, 1H), 1.23-1.12 (m, 2H); ^13C NMR (75 MHz, CDCl_3) δ 140.3, 133.6, 130.5, 128.4, 128.3, 127.2, 126.9, 93.1, 78.7, 71.2, 60.5, 59.6, 32.2, 25.4, 16.3, 15.9; FT-IR (film) ν 2938, 1484 cm^{-1}; HRMS (ESI) calcd for C_{22}H_{27}NO_2 [M+H]^+ 338.2115, found 338.2137.
Oxazabicyclooctane 156 (rac). A stirred solution of 121 (100 mg, 0.286 mmol) in dry toluene (5.7 mL) was added the Hoveyda-Grubbs II catalyst (18.0 mg, 0.0286 mmol). The reaction was refluxed for 1 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (8:1 v/v), R_f = 0.2) to give the title compound as a green oil (78 mg, 85%). \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.89 (d, \(J = 8.4\) Hz, 2H), 7.61 (d, \(J = 7.9\) Hz, 2H), 7.40 (d, \(J = 7.2\) Hz, 2H), 7.29-7.18 (m, 3H), 4.72 (bs, 1H), 4.65 (m, 1H), 4.28 (d, \(J = 6.2\) Hz, 1H), 3.90 (d, \(J = 13.6\) Hz, 1H), 3.82 (d, \(J = 13.6\) Hz, 1H), 2.53 (s, 3H), 1.73-1.50 (m, 3H), 1.34 (m, 1H), 1.19 (m, 1H), 1.05 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 197.7, 144.4, 139.7, 135.7, 128.5, 128.4, 128.3, 127.1, 127.0, 93.3, 78.5, 71.6, 60.6, 31.9, 26.5, 25.4, 15.8; FT-IR (film) \(\nu\) 2944, 1679 cm\(^{-1}\); HRMS (ESI) calcd for C\textsubscript{21}H\textsubscript{23}NO\textsubscript{2} [M+H]\(^+\) 322.1802 found, 322.1803.

Oxazabicyclooctane 157 (rac). A stirred solution of 122 (100 mg, 0.275 mmol) in dry toluene (5.5 mL) was added the Hoveyda-Grubbs II catalyst (17.3 mg, 0.0275 mmol). The reaction was refluxed for 2 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (10:1 v/v), R_f = 0.2) to give the title compound as an orange oil (59 mg, 64%). \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.75 (m, 1H), 7.64 (m, 1H), 7.44 (d, \(J = 7.5\) Hz, 2H), 7.30-7.15 (m, 6H), 4.67 (bs, 1H), 4.57 (m, 1H), 4.45 (d, \(J = 6.1\) Hz, 1H), 4.08 (d, \(J = 13.4\) Hz, 1H), 3.81 (d, \(J = 13.4\) Hz, 1H), 2.15 (m, 1H), 1.72-1.51 (m, 2H), 1.42 (dd, \(J = 6.2, 14.1\) Hz, 1H), 1.32-1.25 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 144.5, 140.2, 139.7, 139.1, 128.5, 128.3, 127.1, 124.0, 123.6, 122.9, 122.2, 120.3, 93.2, 78.5, 68.5, 60.5, 31.9, 25.4, 16.1; FT-IR (film) \(\nu\) 2957, 1455, 1341 cm\(^{-1}\); HRMS (ESI) calcd for C\textsubscript{21}H\textsubscript{21}NOS [M+H]\(^+\) 336.1417 found, 336.1418.
Oxazabicyclooctane 158 (158’ and 158’’). A stirred solution of 123 (100 mg, 0.210 mmol) in dry toluene (4.2 mL) was added the Hoveyda-Grubbs II catalyst (13.5 mg, 0.0210 mmol). The reaction was refluxed for 40 min, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (9:1 v/v), R_f = 0.2) to give the title compound as a pale green oil that solidified as a sticky solid (1:1 diastereomeric mixture, 63 mg, 66%). 1H NMR (300 MHz, CDCl3) δ 7.49 (d, J = 7.5 Hz, 2H), 7.36-7.25 (m, 6H), 4.76 (bs, 1H), 4.66 (bs, 1H), 4.27 (d, J = 6.1 Hz, 1H), 3.99 (d, J = 13.6 Hz, 1H), 3.85 (d, J = 13.6 Hz, 1H), 2.95 (m, 2H), 2.51 (dd, J = 18.9, 8.7 Hz, 1H), 2.44 (m, 1H), 2.33 (m, 1H), 2.18-2.01 (m, 3H), 1.97 (m, 1H), 1.85 (m, 1H), 1.68-1.21 (m, 13H), 0.93 (s, 3H), 13C NMR (75 MHz, CDCl3) δ 220.8, 140.29/140.28 (diastereomers), 137.95/137.92 (diastereomers), 136.34/136.32 (diastereomers), 136.08/136.06 (diastereomers), 128.4, 128.3, 127.5, 127.4, 126.9, 125.2, 124.4, 124.3, 124.3, 93.1, 78.64/78.62 (diastereomers), 71.3, 60.4, 50.4, 47.9, 44.34/44.32 (diastereomers), 38.1, 35.8, 32.2, 31.5, 29.57/29.53 (diastereomers), 26.5, 25.6, 25.4, 21.5, 15.9, 13.8; FT-IR (film) ν 2931, 1736 cm⁻¹; HRMS (ESI) calcd for C₃₁H₃₇NO₂ [M+H]⁺ 456.2897, found 456.2894.

Tetrahydroazepine 135 (rac). A stirred solution of 115 (123 mg, 0.40 mmol) in dry CH₂Cl₂ (16 mL) was added the Grubbs II catalyst (34 mg, 0.040 mmol). The reaction was stirred at room temperature for 22 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (4:1 v/v)) to give the title compound as a brown oil (89 mg, 80%). 1H NMR (300 MHz, CDCl3) δ 7.38-7.125 (m, 10H), 5.63 (m, 2H), 4.02 (ddd, J = 7.6, 5.2, 2.3 Hz, 1H), 3.78 (d, J = 5.2 Hz, 1H), 3.53 (d, J = 14.0 Hz, 1H), 3.39 (d, J = 14.0 Hz, 1H), 3.31 (m, 1H), 3.11 (m, 1H), 2.66-2.43 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 140.7, 139.4, 130.4, 128.5, 128.4, 128.3,
Tetrahydroazepine 143 (rac). A stirred solution of 116 (64 mg, 0.17 mmol) in dry CH₂Cl₂ (3.5 mL) was added the Grubbs II catalyst (14.5 mg, 0.017 mmol). The reaction was stirred at room temperature for 18 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (8:1 v/v), (Rf = 0.2) to give the title compound as a brown oil (42 mg, 71%). ¹H NMR (300 MHz, CDCl₃) δ 7.47 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.24-7.12 (m, 6H), 5.64-5.55 (m, 2H), 3.96 (bs, 1H), 3.72 (d, J = 5.3 Hz, 1H), 3.54 (d, J = 13.9 Hz, 1H), 3.41 (d, J = 13.9 Hz, 1H), 3.29 (m, 1H), 3.12 (m, 1H), 2.51 (m, 2H), 2.29 (bs, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 141.7, 138.8, 132.5, 131.2, 130.4, 130.3, 130.1, 128.4, 128.3, 127.6, 127.0, 125.7, 73.6, 73.3, 59.7, 49.5, 33.3; FT-IR (film) ν 3380, 3023, 1464 cm⁻¹; HRMS (ESI) calcd for C₁₉H₂₂NO [M+H]⁺ 280.2, found 208.3.

Tetrahydroazepine 144 (rac). A stirred solution of 117 (98 mg, 0.27 mmol) in dry CH₂Cl₂ (27 mL) at 0°C was added the Grubbs II catalyst (23.3 mg, 0.027 mmol). The reaction was allowed to reach room temperature and stirred for 19 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (8:1 v/v), Rf = 0.2) to give the title compound as a white solid (68 mg, 76%). ¹H NMR (300 MHz, CDCl₃) δ 8.24 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 7.1 Hz, 1HH), 7.78 (dd, J = 8.0, 1.5 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.49-7.35 (m, 3H), 7.18-7.05 (m, 5H), 5.73 (m, 1H), 5.61 (m, 1H), 4.56 (d, J = 3.5 Hz, 1H), 4.12 (bs, 1H), 3.6 (d, J = 14.3 Hz, 1H), 3.37-3.22 (m, 3H), 2.79 (m, 1H), 2.35-2.25 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 139.4, 137.4, 134.1, 131.7, 131.3, 128.9, 128.2, 128.1, 127.8, 126.6, 126.1, 125.9, 125.5, 125.4, 124.5, 123.3, 72.2, 71.8, 58.8, 50.4, 31.8; FT-
IR (film) ν 3226, 3029, 1452 cm$^{-1}$; mp 107-109 $^\circ$C; HRMS (ESI) calcd for C$_{23}$H$_{23}$NO [M+H]$^+$ 330.1852, found 330.1859.

**Tetrahydroazepine 145 (rac).** A stirred solution of 118 (52 mg, 0.13 mmol) in dry CH$_2$Cl$_2$ (2.8 mL) was added the Grubbs II catalyst (11.9 mg, 0.013 mmol). The reaction was stirred at room temperature for 22 h, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (9:1 v/v), $R_f = 0.2$) to give the title compound as a yellow oil (36 mg, 77%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.53-7.13 (m, 14H), 5.64 (m, 2H), 4.06 (ddd, $J = 7.5, 5.4, 2.3$ Hz, 1H), 3.83 (d, $J = 5.2$ Hz, 1H), 3.58 (d, $J = 14.0$ Hz, 1H), 3.44 (d, $J = 14.0$ Hz, 1H), 3.34 (bd, $J = 16.1$ Hz, 1H), 3.14 (bd, $J = 16.2$ Hz, 1H), 2.58 (m, 2H), 2.44 (bs, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.6, 140.3, 139.7, 139.4, 130.4, 128.9, 128.7, 128.4, 128.2, 127.3, 127.2, 127.0, 126.8, 126.1, 74.7, 73.3, 59.7, 50.1, 33.2; FT-IR (film) ν 3405, 3025, 2913, 1485 cm$^{-1}$; HRMS (ESI) calcd for C$_{25}$H$_{25}$NO [M+H]$^+$ 356.2009, found 356.2034.

**Tetrahydroazepine 146 (rac).** A stirred solution of 119 (83 mg, 0.22 mmol) in dry toluene (4.4 mL) was added the Grubbs II catalyst (38.4 mg, 0.044 mmol). The reaction was heated to 40 $^\circ$C for 20 min, whereupon the volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (3:1 v/v)) to give the title compound as a brown oil (67 mg, 90%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.51 (m, 1H), 7.29-7.17 (m, 5H), 6.52-6.48 (m, 2H), 5.73-5.62 (m, 2H), 4.34 (d, $J = 4.7$ Hz, 1H), 4.05 (bs, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.65 (d, $J = 14.1$ Hz, 1H), 3.50 (d, $J = 14.1$ Hz, 1H), 3.34 (m, 1H), 3.19 (m, 1H), 2.70 (m, 1H), 2.52-2.44 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.7, 158.5, 139.9, 130.5, 128.4, 128.2, 128.0, 126.5, 125.9, 121.6, 104.0, 98.5, 72.6, 67.1, 59.5, 55.3, 55.2, 49.8, 32.6; FT-IR (film) ν 3406, 2930, 1607 cm$^{-1}$; HRMS (ESI) calcd for C$_{21}$H$_{25}$NO$_3$ [M+H]$^+$ 340.1907, found 340.1907.
Tetrahydroazepine 147 (rac). A solution of 120 (100 mg, 0.27 mmol) in dry toluene (5.4 mL) was added the Grubbs II catalyst (23.3 mg, 0.027 mmol). The reaction was heated to 40 °C for 45 min, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (5:1 v/v), Rf = 0.2) to give the title compound as a brown oil (67 mg, 74%). 1H NMR (300 MHz, CDCl3) δ 7.34-7.19 (m, 5H), 7.04 (s, 2H), 5.71-5.68 (m, 2H), 4.06 (m, 1H), 3.77-3.69 (m, 4H), 3.60 (d, J = 13.9 Hz), 3.45 (d, J = 13.9 Hz, 1H), 3.37 (m, 1H), 3.13 (m, 1H), 2.62 (m, 2H), 2.28 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 156.1, 139.6, 135.8, 130.7, 130.4, 128.8, 128.4, 128.1, 126.7, 126.3, 74.8, 73.1, 59.6, 59.5, 49.8, 33.3, 16.2; FT-IR (film) ν 3437, 2921, 1483 cm⁻¹; HRMS (ESI) calcd for C22H27NO2 [M+H]+ 338.2115, found 338.2115.

Tetrahydroazepine 148 (rac). A stirred solution of 121 (80 mg, 0.22 mmol) in dry CH2Cl2 (4.6 mL) was added the Grubbs II catalyst (19.4 mg, 0.022 mmol). The reaction was stirred at room temperature for 18 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (4:1 v/v)) to give the title compound as a brown oil (47 mg, 71%). 1H NMR (300 MHz, CDCl3) δ 7.88 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.26-7.12 (m, 5H), 5.67-5.57 (m, 2H), 4.03 (bs, 1H), 3.84 (d, J = 5.1 Hz, 1H), 3.53 (d, J = 14.0 Hz, 1H), 3.41 (d, J = 14.0 Hz, 1H), 3.31 (m, 1H), 3.14 (m, 1H), 2.64-2.37 (m, 6H); 13C NMR (75 MHz, CDCl3) δ 197.7, 147.0, 139.0, 136.2, 130.4, 128.6, 128.5, 128.4, 128.3, 126.9, 125.7, 74.7, 73.3, 59.7, 49.8, 33.1, 26.5; FT-IR (film) ν 3437, 2921, 1483 cm⁻¹; HRMS (ESI) calcd for C21H23NO2 [M+H]+ 322.1802, found 322.1802.

Tetrahydroazepine 149 (rac). A stirred solution of 122 (100 mg, 0.275 mmol) in dry CH2Cl2 (5.5 mL) was added the Grubbs II catalyst (23.4 mg, 0.0275 mmol). The reaction was stirred at room
temperature for 20 h whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (4:1 v/v) Rf = 0.3) to give the title compound as a brown oil (73 mg, 79%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.73 (m, 1H), 7.64 (m, 1H), 7.30-7.13 (m, 8H), 5.64 (m, 1H), 5.53 (m, 1H), 4.13-4.07 (m, 2H), 3.71 (m, 2H), 3.46 (m, 1H), 3.06 (dd, $J = 17.7, 5.2$ Hz, 1H), 2.67-2.49 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 145.4, 139.6, 139.5, 139.1, 129.8, 128.6, 128.3, 127.1, 126.1, 124.1, 124.0, 123.2, 122.4, 122.1, 74.1, 69.7, 59.8, 48.7, 34.7; FT-IR (film) ν 3376, 3022, 1434 cm$^{-1}$; HRMS (ESI) calcd for C$_{21}$H$_{21}$NOS [M+H]$^+$ 336.1417, found 336.1415.

**Tetrahydroazepine 150 (150' and 150'**) A stirred solution of 123 (100 mg, 0.21 mmol) in dry toluene (4.2 mL) was added the Grubbs II catalyst (27.0 mg, 0.032 mmol). The reaction was stirred at 50 °C for 40 min, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (4:1 v/v)) to give the title compound as a white solid (1:1 diastereomeric mixture, 66 mg, 67%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31-7.21 (m, 7H), 7.15 (bd, $J = 5.3$ Hz, 1H), 5.72 (m, 2H), 4.11 (m, 1H), 3.80 (d, $J = 5.4$ Hz, 1H), 3.63 (dd, $J = 13.9, 3.5$ Hz, 1H), 3.49 (d, $J = 13.9$ Hz, 1H), 3.40 (bd, $J = 16.8$ Hz, 1H), 3.18 (bd, $J = 16.5$ Hz, 1H), 2.94 (m, 2H), 2.71 (bd, $J = 16.9$ Hz, 1H), 2.62-2.43 (m, 3H), 2.32 (m, 1H), 2.20-1.97 (m, 4H), 1.67-1.45 (m, 7H), 0.94 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 220.8, 139.6/139.5 (diastereomers), 138.8, 138.0/137.9 (diastereomers), 136.6/136.5 (diastereomers), 130.46/130.41 (diastereomers), 129.2, 129.1, 128.42/128.40 (diastereomers), 128.1, 126.7, 126.25/126.23 (diastereomers), 125.9, 125.7, 125.4, 74.82/74.80 (diastereomers), 73.17/73.13 (diastereomers), 59.67/59.64 (diastereomers), 50.4, 49.9, 47.9, 44.3, 38.0, 35.7, 33.3/33.2 (diastereomers), 31.5, 29.5, 26.4, 25.59/25.57 (diastereomers), 21.5, 13.8; FT-IR (film) ν 3434, 2926, 1734 cm$^{-1}$; HRMS (ESI) calcd for C$_{31}$H$_{37}$NO$_2$ [M+H]$^+$ 456.2897, found 456.2900.
Rac-2-(dibenzylamino)cyclopent-3-enol (131). A stirred solution of 125 (100 mg, 0.260 mmol) in dry toluene (5.2 mL) was added the Grubbs II catalyst (11.0 mg, 0.013 mmol). The reaction was heated to 50 °C for 1 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (9:1 v/v), R_f = 0.2) to give the title compound as a brown/red oil (51 mg, 71%). 1H NMR (300 MHz, CDCl_3) δ 7.36-7.22 (m, 10H), 5.91 (m, 1H), 5.81 (bs, 1H), 4.43 (bs, 1H), 4.09 (bs, 1H), 3.89 (m, 1H), 3.84 (d, J = 14.0 Hz, 2H), 3.61 (d, J = 14.0 Hz, 2H), 2.61 (m, 1H), 2.35 (m, 1H), 13C NMR (75 MHz, CDCl_3) δ 138.8, 132.5, 128.6, 128.4, 127.5, 127.1, 68.7, 68.2, 56.0, 40.9; FT-IR (film) ν 3371, 3059, 3027, 2925, 2840 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{19}\)H\(_{21}\)NO [M+H]\(^+\) 280.1696, found 280.1692.

Rac-1-Benzyl-2,5-dihydro-1H-pyrrol-2-yl)-2-phenylethanol (132). A stirred solution of 126 (100 mg, 0.26 mmol) in dry toluene (5.2 mL) was added the Grubbs II catalyst (11.0 mg, 0.013 mmol). The reaction was heated to 50 °C for 3 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (2:1 v/v), R_f = 0.2) to give the title compound as a dark brown oil (62 mg, 85%). 1H NMR (300 MHz, CDCl_3) δ 7.36-7.21 (m, 10H), 5.93-5.84 (m, 2H), 4.03 (d, J = 13.1 Hz, 1H), 3.86 (m, 1H, 3), 3.77-3.71 (m, 2H), 3.58 (d, J = 13.1 Hz, 1H), 3.49 (bs, 1H), 3.28 (m, 1H), 2.98 (dd, J = 13.7, 8.1 Hz, 1H), 2.78 (dd, J = 13.7, 5.7 Hz, 1H); 13C NMR (75 MHz, CDCl_3) δ 138.7, 129.4, 129.0, 128.4, 128.4, 128.3, 127.0, 126.2, 125.8, 73.9, 70.9, 60.1, 58.1, 39.9; FT-IR (film) ν 3445, 3059, 3027, 2925, 2840 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{19}\)H\(_{21}\)NO [M+H]\(^+\) 280.1696, found 280.1708.
**Rac-(2S,3R,5S)-1-benzyl-2-(3,4-dichlorophenyl)-5-vinylpyrrolidin-3-ol (137).** A solution of allyl palladium chloride dimer (15.8 mg, 0.04 mmol), triethyl phosphite (28.8 mg, 29.7 µL, 0.17 mmol) and morpholine (18.9 mg, 18.8 µL, 0.21 mmol) in dry CH₂Cl₂ (2.5 mL) was stirred at room temperature for 5 min. Then, a solution of 136 (100 mg, 0.28 mmol) in dry CH₂Cl₂ (0.3 mL) and TFA (41.5 mg, 27.9 µL, 0.28 mmol) were added. The reaction was refluxed for 17 h and then cooled to room temperature. The reaction mixture was directly purified by flash column chromatography on silica gel (hexanes:EtOAc (4:1 v/v)) to give the title compound as a green oil (dry > 10:1, 65 mg, 65%).

**1H NMR** (500 MHz, CDCl₃) δ 7.38 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.20-7.07 (m, 4H), 6.96-6.93 (m, 2H), 5.70 (ddd, J = 8.1, 10.0, 17.3 Hz, 1H), 5.20 (m, 1H), 5.07 (m, 1H), 3.84 (bs, 1H), 3.60 (s, 2H), 3.44 (dd, J = 16.1, 8.1 Hz, 1H), 3.37 (d, J = 4.5 Hz, 1H), 1.87 (ddd, J = 13.3, 8.6, 7.2, 1H), 1.75 (ddd, J = 13.3, 7.4, 3.8 Hz, 1H), 1.67 (d, J = 2.2 Hz, 1H); **13C NMR** (75 MHz, CDCl₃) δ 142.4, 140.4, 136.2, 132.4, 130.7, 130.2, 129.8, 129.2, 128.3, 127.8, 126.9, 126.8, 116.5, 78.4, 74.3, 63.7, 53.8, 40.0; **FT-IR (film)** ν 3338, 2923, 1463 cm⁻¹; **HRMS (ESI)** calcd for C₁₉H₁₉Cl₂NO [M+H]⁺ 348.0916, found 348.0917.

**Rac-1-(3,4-dichlorophenyl)-3-phenyl-1-(2,3,4,7-tetrahydro-1H-azepin-1-yl)propan-2-ol (138).** A stirred solution of 124 (125 mg, 0.31 mmol) in dry toluene (6.2 mL) was added the Grubbs II catalyst (26.3 mg, 0.031 mmol). The reaction was heated to 50 °C for 30 min, whereupon the volatiles were removed in vacuo. The residue was purifid by flash column chromatography on silica gel (hexanes:EtOAc (4:1 v/v), Rf = 0.2) to give the title compound as a brown oil (94 mg, 81%).

**1H NMR** (300 MHz, CDCl₃) δ 7.36-7.33 (m, 2H), 7.24-7.06 (m, 6H), 5.87 (td, J = 11.2, 5.7 Hz, 1H), 5.47 (td, J = 10.9, 5.5 Hz, 1H), 4.27 (td, J = 8.6, 4.3 Hz, 1H), 3.54 (d, J = 4.4 Hz, 1H), 3.27 (dd, J = 16.0, 5.6 Hz, 1H), 3.12 (dd, J = 16.0, 5.4 Hz, 1H), 2.96 (m, 1H), 2.82 (m, 1H), 2.69 (bs, 1H), 2.45 (dd, J = 4.2, 14.0 Hz, 1H), 2.29 (dd, J = 14.0, 8.4 Hz, 1H), 2.19 (m, 2H), 1.51 (m, 2H); **13C NMR** (75 MHz,
CDCl$_3$ $\delta$ 138.4, 137.6, 134.4, 132.1, 131.6, 131.5, 129.9, 129.1, 128.4, 128.4, 126.4, 70.2, 67.2, 55.0, 50.5, 40.5, 28.1, 23.6; FT-IR (film) $\nu$ 3454, 2834, 1512, 1233 cm$^{-1}$; HRMS (ESI) calcd for C$_{21}$H$_{23}$Cl$_2$NO $\left[\text{M+H}\right]^+$ 376.1229, found 376.1225.

**Rac-1-(3,4-dichlorophenyl)-3-phenyl-1-(2-vinylpyrrolidin-1-yl)propan-2-ol (139).** A solution of allyl palladium chloride dimer (9.5 mg, 0.026 mmol), triethyl phosphite (16.7 mg, 17.2 $\mu$L, 0.10 mmol) and morpholine (11.4 mg, 11.3 $\mu$L, 0.12 mmol) in dry CH$_2$Cl$_2$ (1.5 mL) was stirred at room temperature for 5 min. Then, a solution of 138 (65 mg, 0.17 mmol) in dry CH$_2$Cl$_2$ (0.3 mL) and TFA (20.1 mg, 13.5 $\mu$L, 0.17 mmol) were added. The reaction was refluxed for 16 h and then cooled to room temperature. The reaction mixture was directly purified by flash column chromatography on silica gel (hexanes:EtOAc (4:1)) to give the title compound as a yellow oil ($dr$ > 8:1, 23 mg, 35 %). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.44-7.11 (m, 8H), 5.80 (ddd, $J$ = 17.0, 10.2, 8.6 Hz, 1H), 5.15-5.11 (m, 2H), 4.31 (m, 1H), 3.59 (d, $J$ = 6.6 Hz, 1H), 3.00-2.91 (m, 2H), 2.82 (m, 1H), 2.46 (m, 1H), 2.36 (m, 1H), 2.09 (bs, 1H), 1.88-1.73 (m, 2H), 1.65-1.52 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 140.8, 138.7, 136.6, 131.9, 131.6, 131.1, 129.3, 129.2, 128.4, 126.3, 116.3, 72.1, 67.6, 64.1, 48.3, 40.5, 31.1, 22.5; FT-IR (film) $\nu$ 3462, 2964, 1467 cm$^{-1}$; HRMS (ESI) calcd for C$_{21}$H$_{23}$Cl$_2$NO $\left[\text{M+H}\right]^+$ 376.1229, found 376.1227.

**Diels-Alder Product 140 (rac).** Compound 108 (34 mg, 0.136 mmol) was heated to 115 °C for 2.5-3 h and the residue was purified by flash chromatography (R$_f$ = 0.2 n-hexane-EtOAc 1:2 v/v) to give the titled product 140 in 26 mg (75%) as an green oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.73 (d, $J$ = 5.8 Hz, 1H), 6.21 (dd, $J$ = 5.8, 1.3 Hz, 1H), 5.93-5.82 (m, 2H), 5.20-5.09 (m, 4H), 4.95 (dd, $J$ = 4.3, 1.3 Hz, 1H), 3.89 (ddd, $J$ = 8.0, 5.8, 1.9 Hz, 1H), 3.45 (dd, $J$ = 13.7, 5.2 Hz, 1H), 3.30 (dd, $J$ = 8.4, 7.0 Hz, 1H), 3.04 (dd, $J$ = 13.7, 7.7 Hz, 1H), 2.92 (bs, 1H, OH), 2.76 (d, 1H, $J$ = 1.7Hz, 1H), 2.64 (d, 1H, $J$ = 7.7 Hz, 1H),
2.58 (td, $J = 15.2, 7.7$ Hz, 1H), 2.38 (m, 1H), 2.13 (dd, $J = 10.4, 8.9$ Hz, 1H), 1.86 (m, 1H), 1.63 (m, 1H), 1.30 (dd, $J = 11.4, 7.7$ Hz, 1H); LC-MS (ESI⁺) M/z: 248.2 [M+H]⁺.

### Diels-Alder Product 141 (rac).

A solution of 128 (144 mg, 0.48 mmol) in toluene (1 ml) was heated to reflux for 2 h. The volatiles were evaporated and the residue flash chromatographed ($R_f = 0.2$ n-hexane-EtOAc 1:2 v/v) to give the titled product 141 in 136 mg (95%) as an colorless oil. $^1$H NMR (500 MHz, CDCl₃) $\delta$ 7.30-7.18 (m, 5H), 6.86 (d, $J = 6.0$ Hz, 1H), 6.26 (d, $J = 5.7$ Hz, 1H), 5.80 (m, 1H), 5.09 (d, $J = 17.1$ Hz, 1H), 5.05 (d, $J = 10.1$ Hz, 1H), 4.98 (d, $J = 3.8$ Hz, 1H), 4.05 (t, $J = 7.0$ Hz, 1H), 3.34 (dd, $J = 13.7, 5.1$ Hz, 1H), 3.28 (m, 1H), 3.11 (dd, $J = 13.8, 8.0$ Hz, 1H), 2.97-2.90 (m, 3H), 2.75 (bs, 1H), 2.10 (m, 1H), 1.98 (m, 1H), 1.63 (td, $J = 11.3, 3.7$ Hz, 1H), 1.32 (dd, $J = 11.3, 7.7$ Hz, 1H); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 138.8, 136.2, 135.3, 133.9, 129.3, 128.3, 126.2, 117.1, 97.5, 78.8, 71.3, 68.0, 57.9, 56.5, 43.0, 38.7, 29.5; HRMS Calcd for C₁₉H₂₃NO₂ [M+H]⁺ 298.1802, found 298.1806.

### Rac-4-allyl-6-benzyl-3-phenyl-5-((E)-styryl)morpholin-2-ol (161).

A solution of 159 (197 mg, 0.67 mmol), phenylboronic acid (327 mg, 2.7 mmol) and glyoxal (53.7 mg, 0.70 mmol) in ethanol (5 mL) was stirred at 50 °C for 72 h. The volatiles were removed in vacuo and the residue was purified by flash column chromatography on silica gel (hexanes:EtOAc 4:1 v/v), to give a mixture of diastereomers of 160 (122 mg, 45 %). The product was dissolved in toluene (1.2 mL), and DBU (111 µL, 0.742 mmol) was added. The reaction was stirred at 60 °C for 22 h, and directly purified by flash column chromatography on silica gel (hexanes:EtOAc 4:1 v/v)) to give the title compound 161 as a pale green oil ($dr >19:1$, 93 mg, 77 %). $^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.43 (m, 2H), 7.32-7.12 (m, 13H), 6.62 (dd, $J = 16.1, 10.0$ Hz, 1H), 6.38 (d, $J = 16.1$ Hz, 1H), 5.53 (m, 1H), 4.93 (m, 2H), 4.64 (dd, $J = 7.5, 3.6$ Hz, 1H), 4.19 (dd, $J = 8.1, 5.8, 2.3$ Hz, 1H), 3.50 (d, $J = 7.6$ Hz, 1H), 3.31 (dd, $J = 10.1, 2.3$ Hz, 1H), 2.94 (d, $J = 4.1$ Hz, 1H), 2.80-2.73 (m, 3H), 2.63 (dd, $J = 14.2, 5.8$ Hz, 1H); $^{13}$C NMR (75 MHz,
Rac-4-allyl-6-benzyl-3-phenyl-5-((E)-styryl)morpholin-2-yl acetate. A stirred solution of 161 (160 mg, 0.389 mmol), Et$_3$N (272 µL, 1.94 mmol), and DMAP (9.50 mg, 0.078 mmol) in CH$_2$Cl$_2$ (2.0 mL) was added acetic anhydride (147 µL, 1.55 mmol) dropwise. The reaction was then stirred at room temperature for 2 h, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (9:1 v/v)) to give the title compound as a colorless solid (152 mg, 86 %). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.53 (m, 2H), 7.41 (m, 4H), 7.33-7.22 (m, 9H), 6.70 (dd, $J$ = 16.1, 10.1 Hz, 1H), 6.46 (d, $J$ = 16.1 Hz, 1H), 5.79 (d, $J$ = 8.2 Hz, 1H), 5.62 (dddd, $J$ = 14.2, 9.5, 7.6, 4.7 Hz, 1H), 5.03 (m, 2H), 4.43 (dt, $J$ = 7.0, 2.3 Hz, 1H), 3.79 (d, $J$ = 8.2 Hz, 1H), 3.40 (dd, $J$ = 10.1, 2.3 Hz, 1H), 3.00-2.89 (m, 3H), 2.74 (dd, $J$ = 14.4, 7.0 Hz, 1H), 1.91 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.5, 137.7, 137.5, 137.1, 136.6, 135.7, 129.1, 128.6, 128.4, 128.3, 128.0, 127.8, 126.5, 126.3, 121.2, 117.0, 96.1, 78.6, 64.1, 59.8, 52.2, 38.4, 20.7; mp 150-152 °C; FT-IR (film) ν 1747, 1221 cm$^{-1}$; HRMS (ESI) calcd for C$_{30}$H$_{31}$NO$_3$ [M+H]$^+$ 454.2377, found 454.2377.

Rac-1-benzyl-4-phenyl-3,4,6,8a-tetrahydro-1H-pyrrolo[2,1-c][1,4]oxazin-3-yl acetate (162). A stirred solution of (2S,3S,5S,6R)-4-allyl-6-benzyl-3-phenyl-5-((E)-styryl)morpholin-2-yl acetate (97.0 mg, 0.214 mmol) in dry toluene (4.3 mL) was added the Grubbs II catalyst (18.2 mg, 0.021 mmol). The reaction was stirred at 50-60 °C for 30 min, whereupon the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc (8:1 v/v)) to give the title compound 132 as a white solid (57 mg, 76 %). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.41 (d,
$J = 6.9$ Hz, 2H), 7.31-7.21 (m, 8H), 6.17 (m, 1H), 6.08 (bs, 1H), 5.66 (d, $J = 8.2$ Hz, 1H), 4.50 (dt, $J = 7.0$, 3.7 Hz, 1H), 3.67 (m, 1H), 3.43 (d, $J = 8.1$ Hz, 1H), 3.34 (bd, $J = 15.5$ Hz, 1H), 3.25 (dd, $J = 14.2$, 7.1 Hz, 1H), 3.19 (bd, $J = 15.6$ Hz, 1H), 2.99 (dd, $J = 14.2$, 7.1 Hz, 1H), 1.87 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.5, 138.3, 137.2, 131.4, 129.1, 129.0, 128.4, 128.1, 127.8, 127.3, 126.5, 94.8, 75.2, 66.0, 63.6, 58.8, 38.9, 20.6; mp 86-89 °C; FT-IR (film) $\nu$ 2921, 2822, 1754, 1220 cm$^{-1}$; HRMS (ESI) calcd for C$_{22}$H$_{23}$NO$_3$ [M+H]$^+$ 350.1751, found 350.1762.
Table 3. Comparison of $^1$H-$^1$H 2D NOESY characteristics of 108 and 109$^a$

<table>
<thead>
<tr>
<th>atom assignment</th>
<th>compound 140 NOEs</th>
<th>compound 141 NOEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H^1$</td>
<td>$H^2$, $H^6$ (weak)</td>
<td>$H^2$, $H^6$ (weak)</td>
</tr>
<tr>
<td>$H^2$</td>
<td>$H^1$, $H^3$, $H^4$</td>
<td>$H^1$, $H^3$, $H^4$</td>
</tr>
<tr>
<td>$H^3$</td>
<td>$H^2$, $H^4$, $H^5$</td>
<td>$H^2$, $H^4$, $H^5$</td>
</tr>
<tr>
<td></td>
<td>$H^4$, $H^6$ (weak), $H^3$</td>
<td>$H^4$, $H^6$, $H^3$ (weak)</td>
</tr>
<tr>
<td></td>
<td>(weak)</td>
<td></td>
</tr>
<tr>
<td>$H^4'$</td>
<td>$H^4$, $H^5$, $H^3$</td>
<td>$H^3$, $H^6$ (weak), $H^5$, $H^3$ (weak)</td>
</tr>
<tr>
<td>$H^5$</td>
<td>$H^5$, $H^6$</td>
<td>$H^5$, $H^6$</td>
</tr>
<tr>
<td>$H^5'$</td>
<td>$H^4$, $H^7$ (weak), $H^5$</td>
<td>$H^4$, $H^7$, $H^5$</td>
</tr>
<tr>
<td>$H^6$</td>
<td>$H^1$ (weak), $H^4$ (weak),</td>
<td>$H^1$ (weak), $H^4$, $H^5$</td>
</tr>
<tr>
<td></td>
<td>$H^4$, $H^5$</td>
<td></td>
</tr>
<tr>
<td>$H^7$</td>
<td>$H^5$</td>
<td>$H^5$</td>
</tr>
</tbody>
</table>

$^a$ The 2D NOESY spectra of both 140 and 141 showed no characteristic NOEs between $H$-6 and $H$-7), but strong NOE could be observed between $H$-7 and $H$-5, indicative for a *trans*-relationship between $H$-7 and $H$-5. Furthermore, strong NOEs could be observed between $H$-6 and $H$-5 and $H$-6 and $H$-4. These results altogether demonstrates an IMDA reaction resulting in a pyrrolidine ring that is *exo*-fused to the oxanorbornene moiety.
Table 4. $^1$H-$^1$H 2D NOESY characteristics of 137$^a$

<table>
<thead>
<tr>
<th>atom assignment</th>
<th>compound 137 NOEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H^1$</td>
<td>$H^2$, $H^3$</td>
</tr>
<tr>
<td>$H^2$</td>
<td>$H^1$</td>
</tr>
<tr>
<td>$H^{2'}$</td>
<td>$H^3$</td>
</tr>
<tr>
<td>$H^3$</td>
<td>$H^5$ (weak), $H^{4'}$ (strong), $H^{2'}$, $H^4$</td>
</tr>
<tr>
<td>$H^4$</td>
<td>$H^3$ (strong), $H^5$ (weak),</td>
</tr>
<tr>
<td>$H^{4'}$</td>
<td>$H^3$ (weak), $H^5$ (strong)</td>
</tr>
<tr>
<td>$H^5$</td>
<td>$H^6$ (weak), $H^4$ (strong), $H^{4'}$ (weak), OH</td>
</tr>
<tr>
<td>$H^6$</td>
<td>$H^5$ (weak), $H^{4'}$, OH</td>
</tr>
<tr>
<td>OH</td>
<td>$H^5$, $H^6$</td>
</tr>
</tbody>
</table>

$^a$ The 2D NOESY spectra showed that out of the two geminal protons $H^4$ and $H^{4'}$, $H^4$ had strong NOE with $H^5$, whereas $H^{4'}$ had strong NOE with $H^3$. No NOEs were observed between $H^5$ and $H^3$. Furthermore, the protons on OH, had NOE with both $H^{4'}$ and $H^6$. Also NOE could be observed between $H^6$ and $H^{4'}$, but no NOE between $H^6$ and $H^4$ could be found.
Chapter 2

Multifunctional Catalysis: Synthesis of Heterocycles from Simple Starting Materials

2.1 Introduction

2.1.1 Multifunctional Catalysis

As described in Chapter 1 the ability to provide bioactive small molecules by organic synthesis is essential in the hunt for improved small molecule probes and drugs. Chemical processes have therefore been developed that are high-yielding and highly chemo-, regio-, and stereoselective, albeit often hampered by excessive use of reagents and unwanted side-products and waste. Consequently there is a huge demand for environmentally benign, also referred to as green and sustainable, chemical processes\(^6^2\) which not only consider high yield and selectivity, but also atom economy\(^6^3\) associated with the overall reaction efficiency. To address these modern-day challenges in chemistry, effective catalysts that can promote several distinct chemical transformations in a single chemical operation, would be valuable.

To date, a plethora of catalysts have been developed, that are highly selective for one specific chemical transformation. In this respect, the field of transition-metal based catalysis has revolutionized chemical synthesis throughout the years. Most notable are perhaps the Nobel Prize-winning metal based asymmetric hydrogenations/oxidations (awarded jointly to William S. Knowles, Ryoji Nyori, and K. Barry Sharpless in 2001),\(^6^4\) metal catalyzed olefin metathesis (awarded jointly to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock in 2005),\(^6^5\) and metal based cross-coupling

In a promising new direction for research in metal catalysis researchers are taking advantage of metal catalysts with *multiple modes of action*. The concept of *multifunctional catalysis* has received an increasing amount of attention, where a single metal catalyst is able to mediate several mechanistically distinct chemical transformations in a single reaction vessel. This approach is less laborious and minimizes the use of additional material, produces less waste, and lower the yield losses associated with the reaction (as normally encountered during purification of intermediates), and represents a unique opportunity for the development of new tandem processes. However, to be successful in multifunctional catalysis, the catalyst needs to be able to change its mode of reactivity under certain reaction conditions without decomposing. In the ideal catalytic system, simple alteration of the reaction conditions (e.g., temperature variation, use of additives, alteration of associated ligands on the metal, solvent polarity, *etc*), can be used to make the catalyst switch its mode of reactivity (e.g., from mode 1 to mode 2, see Figure 9). In this way, multiple new chemical bond-forming reactions can be achieved in a one-pot fashion.

![Figure 9](image_url)  
*Figure 9.* Illustration of a tandem process with a multifunctional catalyst displaying two distinct modes of reactivity.
2.1.2 Olefin Metathesis

Olefin metathesis\(^{69}\) (“metathesis” from Greek meaning “change of position, transposition”) is a unique chemical process, which redistributes the carbon atoms of two olefins to form two new olefins,\(^{70}\) in the presence of a suitable metal catalyst. The development of olefin metathesis over the past 15 years has rendered it one of the most powerful and general methods for carbon-carbon double bond formation in organic synthesis, a fact evidenced by the announcement of the Nobel Prize in 2005.\(^{65}\) The success of olefin metathesis is largely attributed to the development of stable well-defined metal alkylidene catalysts, which display unique reactivity and selectivity in a range of metathetic transformations. For example, carbon-carbon double bond can be formed by joining two alkene moieties intramolecularly (diene metathesis), referred to as ring-closing metathesis\(^{71}\) (RCM), in the synthesis of small to large rings. Furthermore, cross-metathesis\(^{72}\) (CM), ring opening metathesis polymerization (ROMP), and acyclic diene metathesis polymerization\(^{73}\) (ADMET) in the synthesis of polymer materials (Figure 10), can be carried out with pendant functional groups. In addition, enyne metathesis (of an alkene/alkyne), such as ring-closing enyne metathesis (RCEYM) and enyne cross-metathesis (EYCM), is maturing to also become important for the synthesis of complex molecular architectures.\(^{74}\)

---

**Figure 10.** Three olefin metathesis categories are described: diene, enyne and diyne metathesis.
Furthermore, diyne metathesis, such as ring-closing alkyne metathesis (RCAM) and alkyne cross metathesis (ACM), holds great potential for the synthesis of complex structures.\textsuperscript{75} Recently, an increasing number of tandem or domino processes combining sequences of two or more predisposed olefin metathesis processes (e.g., RCM-ROM-RCM or CR-ROM-RCM), also known as ring-rearrangement metathesis (RRM), has emerged as a powerful tool for the rapid construction of complex molecules.\textsuperscript{76}

The generally accepted mechanism for olefin metathesis (sometimes referred to as ‘Chauvin mechanism’) was first proposed by Chauvin and Hérisson in the early 1970s.\textsuperscript{77} According to this mechanism, the process proceeds through a sequence of reversible and alternating [2+2] cycloaddition and cycloreversion reactions, involving alkenes, metal carbenes (e.g., Ru-5, Ru-11 and 163) and metallacyclobutane intermediates (Figure 11).

![Simplified catalytic cycle of RCM together with three commonly used alkene metathesis catalysts.](image)

**Figure 11.** Simplified catalytic cycle of RCM together with three commonly used alkene metathesis catalysts.
It should be mentioned that the individual steps of the catalytic cycle in principle are reversible and that the equilibrium towards the productive metathesis pathway can be facilitated in many ways. For example, in RCM the forward process produces two molecules (cycloalkene and volatile alkene) and is therefore entropically driven, whereas the driving force for ROM and ROMP is release of ring strain.

2.1.3 Multifunctional Catalysis with Ruthenium Metathesis Catalysts

Studies on olefin metathesis have over the years led to the discovery of unexpected non-metathetic side reactions. Although these reactions typically are highly substrate and reaction condition dependent, and possibly caused by ill-defined metal-catalytic species, they represent a promising area of research for multifunctional metal-catalyzed tandem processes.

The research described in this chapter employs the concept of multifunctional catalysis featuring ruthenium alkylidene catalysts, which can mediate one or more distinct reactions in addition to a highly predictable metathesis reaction, e.g. RCM followed by an unconventional non-metathetic ruthenium-catalyzed reaction, in a single chemical operation. In this way, unprecedented rapid conversion of simple starting materials to complex molecular architectures can be achieved.
2.1.4 Tandem Ruthenium-Catalyzed RCM/Kharasch cyclization

Snapper and co-workers\(^{79}\) have demonstrated an effective multifunctional catalysis approach utilizing the Grubbs I catalyst. By treating halogenated acyclic dienes of type 164 with Grubbs I in toluene at elevated temperatures, the expected RCM reaction occurred, followed by a ruthenium-catalyzed atom transfer radical cyclization (Kharasch reaction) to provide bicycles of type 165a-g (Scheme 16) in a single reaction vessel. Furthermore, by combining intra- and intermolecular Kharasch addition reactions with RCM, the ruthenium catalyst could affect three new carbon-carbon and two new carbon-halogen bonds with four new stereocenters formed. For example, when 164 was subjected to Grubbs I in \(m\)-xylene, RCM was accompanied by an intramolecular Kharasch reaction. Subsequent addition of styrene promoted an intermolecular Kharasch reaction to give 166a-b in good yield (52-76\%) in a one pot operation.

![Scheme 16. Tandem ruthenium-catalyzed RCM/Kharasch reaction towards polyfunctionalized bicycles. Reagents and conditions: Grubbs I (5 mol\%), \(m\)-xylene, reflux, 2 h, then styrene (5 equiv) addition, reflux 5 h.](image-url)
2.1.5 Tandem Ruthenium-Catalyzed RCM/Transfer Dehydrogenation

Grubbs and co-workers have demonstrated an interesting sequential tandem approach incorporating three distinct chemical transformations catalyzed by a single-component ruthenium catalyst in a single reaction vessel (Scheme 17). In their work, the diene 167 was ring-closed with Grubbs II affording 168. Addition of NaOH and 3-pentenone initiated a ruthenium-catalyzed transfer dehydrogenation reaction yielding intermediate 169. Subsequent addition of H₂ afforded an effective ruthenium hydrogenation catalyst, which reduced the double bond to afford the naturally occurring muscone 170 in 56% isolated yield over 3 steps.

Scheme 17. Reagents and conditions: (a) Grubbs II, mesitylene/CH₂Cl₂, 50 °C, 12 h. (b) Addition of NaOH, 3-pentanone, reflux, 1 day. (c) Reaction transferred to Parr bomb, 800 psi, H₂, 80 °C, 1 day.

It is interesting to see how simple alteration of the reaction conditions (addition of additives) can switch the reactivity of the catalyst in such a way that three distinct chemical transformations are mediated in one-pot without poisoning the catalyst.
2.1.6 Tandem Ruthenium-Catalyzed RCM/Dihydroxylation

Blechert and co-workers\textsuperscript{81} have shown how a ruthenium alkylidene catalyst can function as a pre-catalyst for dihydroxylation reactions. This sequential tandem process relies on Grubbs I-catalyzed RCM followed by a subsequent \textit{in situ} oxidation of the ruthenium source with NaIO\textsubscript{4}/YbCl\textsubscript{3}·6H\textsubscript{2}O to provide an active dihydroxylation catalyst. This catalyst was used for a \textit{cis}-dihydroxylation of the newly formed double bond to give various cyclic compounds 171a-i (Scheme 18).

Scheme 18. Reagents and conditions: Grubbs I (1-2 mol%), CH\textsubscript{2}Cl\textsubscript{2}, reflux, 1h. (b) NaIO\textsubscript{4}, YbCl\textsubscript{3}·6H\textsubscript{2}O, MeCN/EtOAc/H\textsubscript{2}O, 0 °C

The advantage of this process is that two distinct transformations can be catalyzed by the same Ru source in a sequential tandem fashion. In addition, a variety of functional groups could be tolerated. The disadvantage is that the dihydroxylation step is highly dependent on the solvent. Therefore, dichloromethane has to be removed after RCM \textit{in vacuo}, before addition of the crude residue to a mixture of MeCN/EtOAc/H\textsubscript{2}O, and YbCl\textsubscript{3}·6H\textsubscript{2}O and NaIO\textsubscript{4}. 

76
A similar tandem RCM/dihydroxylation process has also been demonstrated by Snapper and co-workers.\textsuperscript{82} By overcoming the need to change the solvent to set on the second mode of catalytic activity, this process (Scheme 19) seems somewhat more practical than the Blechert approach (Scheme 18). For example, RCM of \textbf{172} and \textbf{174} with Grubbs II catalyst in EtOAc afforded the corresponding ring-closed products. The dihydroxylated products \textbf{173a-c} and \textbf{175a-b} were obtained by transferring the metathesis products in EtOAc to a preformed Ce(IV)-periodato complex in MeCN/H\textsubscript{2}O (6:1), which was prepared from NaIO\textsubscript{4} and CeCl\textsubscript{3}·7H\textsubscript{2}O.

![Scheme 19](image)

**Scheme 19.** Reagents and conditions: (a) Grubbs II (5 mol%), rt, EtOAc. (b) NaIO\textsubscript{4}, CeCl\textsubscript{3}·7H\textsubscript{2}O, MeCN/H\textsubscript{2}O (6:1).

More noteworthy, the Grubbs II catalyst can be modified in \textit{situ} to catalyze a ketohydroxylation (instead of dihydroxylation) reaction after the RCM reaction,\textsuperscript{49} by simply changing the additives from NaIO\textsubscript{4} and CeCl\textsubscript{3}·7H\textsubscript{2}O to oxone and NaHCO\textsubscript{3}. In this way a range of α-hydroxy ketones \textbf{176a-g} could be formed in good yields (Scheme 20).

![Scheme 20](image)

**Scheme 20.** Reagents and conditions: (a) Grubbs II (5-10 mol%), r.t., EtOAc. (b) NaHCO\textsubscript{3}, Oxone, MeCN/H\textsubscript{2}O (6:1).
2.1.7 Tandem Ruthenium-Catalyzed RCM/Hetero-Pauson-Khand Reaction

The group of Snapper\textsuperscript{83} has also described a ruthenium-catalyzed tandem RCM/hetero-Pauson-Khand cycloaddition reaction. The reaction was carried out using acyclic diene substrates 177, 179, 181, and 183 which underwent RCM with Grubbs II catalyst. Subsequent addition of CO and NaOMe to the reaction mixture modified the Ru species \textit{in situ} to catalyze a hetero-Pauson-Khand (HPK) cycloaddition reaction, generating polycyclic heterocycles of type 178a-c, 180, 182, and 184 in good yields (Scheme 21). The role of the pyridine group in the substrate was shown to be critical during the tandem process, which is attributed to the role of pyridyl as a ligand during the HPK cycloaddition process.

Scheme 21. Reagents and conditions: Grubbs II (10 mol%), PhMe, 100 °C, then (b) NaOMe (20 mol%), CO (7 atm), 180 °C, 36 h.
### 2.1.8 Tandem Ruthenium-Catalyzed RCM/Isomerization

Olefin isomerization was reported by Grubbs and co-workers in 1996 as a side reaction occurring during the synthesis of macrocyclic compounds. Since then, ruthenium alkylidenes have been used as precatalysts for olefin isomerization reactions of unsaturated oxygen- and nitrogen-containing compounds (e.g., in the deprotection of allylic amine- and ether-derivatives, and isomerization of terminal olefins into their internal counterparts.

This kind of diverse reactivity of ruthenium catalysts has been exploited in tandem processes combining RCM with subsequent isomerization in the synthesis of various cyclic compounds. In this context, Snapper and co-workers have demonstrated a ruthenium-catalyzed tandem RCM/isomerization sequence that yields diverse five- and seven-membered cyclic enol ethers and in one instance a cyclic six-membered enamine (see Scheme 22). The authors suggest that the isomerization-active catalyst is a ruthenium hydride species, as a dilute hydrogen atmosphere (95:5 N\textsubscript{2}:H\textsubscript{2} gas mixture) is needed to affect the isomerization. Interestingly, formation of trisubstituted enol ethers was never obtained, indicating that the isomerization is sensitive towards steric.

![Scheme 22](image)

**Scheme 22.** Reagents and conditions: (a) Grubbs II (10-15 mol%), CH\textsubscript{2}Cl\textsubscript{2}, rt, 1h, then 95:5 N\textsubscript{2}:H\textsubscript{2}, 45-70 °C, 8-12 h.

A conceptually similar ruthenium catalyzed tandem RCM/isomerization sequence has been developed by Schmidt and co-workers in the synthesis of five-, six- and seven-membered enol ethers (Scheme 23). They demonstrated that additives other
than H₂, including ethyl vinyl ether, NaBH₄, NaH, or 2-propanol together with NaOH, can convert the metathesis-active ruthenium catalyst to an isomerization-active ruthenium-hydride species in situ.

**Scheme 23.** Reagents and conditions: (a) Grubbs I catalyst (5 mol%), PhMe, rt, then (b) addition of EtOCH=CH₂, or NaBH₄ (50 mol%), or NaH (50 mol%) or 2-propanol (30% v/v) and NaOH (50 mol%), 110 °C

In addition, Fustero and co-workers has reported a tandem RCM/isomerization process useful for the preparation of fluorinated unsaturated lactam derivatives without the need for additives to promote the isomerization. Comparable, to our findings regarding the selective synthesis of tetrahydroazepines and oxazabicyclooctanes (cf., Chapter 1), Fustero and co-workers note that the temperature is crucial for the isomerization to occur (see, Scheme 24). At low temperatures, only RCM products 188a-d were obtained, whereas at refluxing toluene the isomerized enamides 189a-d were obtained exclusively.

**Scheme 24.** Reagents and conditions: (a) Grubbs II (5-10 mol%), PhMe, reflux, 1-2 h. (b) Grubbs I (5-10 mol%), CH₂Cl₂, reflux 5-6 h
2.1.9 Aim of the Project

The examples discussed in the introduction illustrate how ruthenium alkylidene catalysts can serve as multifunctional catalysts for a variety of useful non-metathetic transformations. To the best of my knowledge there are no prior examples of tandem processes involving ruthenium catalyzed RCM followed by isomerization into useful \(N\)-alkyliminium- or \(N\)-acyliminium intermediates.

Inspired by the results described in Chapter 1 (ruthenium-catalyzed RCM/isomerization/\(N\)-alkyliminium cyclization to oxazabicyclooctanes) and other reported works on RCM followed by isomerization, we speculated if enamides generated in the event of a RCM/isomerization sequence could be further isomerized into highly electrophilic \(N\)-acyliminium intermediates. The presence of a suitably tethered nucleophile would then bring about a second cyclization (Figure 12).

**Figure 12.** Tandem RCM/isomerization/\(N\)-acyliminium cyclization.

In the following sections the screening of a variety of ruthenium alkylidene catalysts to find best multifunctional catalyst for RCM/isomerization/\(N\)-acyliminium cyclization will be described. The optimized reaction conditions are then used in the synthesis of novel and biologically interesting indolizidinone derivatives. Further experiments to better understand the mechanism will also be discussed. Finally, multifunctional catalysis incorporating a Pd-catalyzed tandem Tsuji-Trost/isomerization/\(N\)-alkyliminium cyclization sequence to tetrahydro-\(\beta\)-carboline scaffolds will be described.
2.2.0 Results and Discussion

2.2.1 Synthesis of Substrates.
All substrates necessary for the tandem process were prepared in 2-3 steps using straightforward procedures.\textsuperscript{ix} For example, commercial or readily synthesized substrates 190-197 were allylated with allyl bromide in the presence of base affording allylated products 198-205 in moderate yields (Table 5).

Table 5. Allylation of amines 190-197 to products 198-205

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>product, yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>190</td>
<td>3-indole</td>
<td>CO\textsubscript{2}Me</td>
<td>198, 46</td>
</tr>
<tr>
<td>2</td>
<td>191</td>
<td>3-benzothiophene</td>
<td>CO\textsubscript{2}Me</td>
<td>199, 63</td>
</tr>
<tr>
<td>3</td>
<td>192</td>
<td>(2,3-MeO)\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>CO\textsubscript{2}Me</td>
<td>200, 60</td>
</tr>
<tr>
<td>4</td>
<td>193</td>
<td>2-furan</td>
<td>CO\textsubscript{2}Me</td>
<td>201, 53</td>
</tr>
<tr>
<td>5</td>
<td>194</td>
<td>3-thiophene</td>
<td>CO\textsubscript{2}Me</td>
<td>202, 78</td>
</tr>
<tr>
<td>6</td>
<td>195</td>
<td>CH\textsubscript{2}OH</td>
<td>Ph</td>
<td>203, 24\textsuperscript{b}</td>
</tr>
<tr>
<td>7</td>
<td>196</td>
<td>OH</td>
<td>i-Pr</td>
<td>204, 39\textsuperscript{b}</td>
</tr>
<tr>
<td>8</td>
<td>197</td>
<td>OH</td>
<td>Ph</td>
<td>205, 46\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yield after flash column chromatography. \textsuperscript{b} Reagents and conditions: allyl bromide, Et\textsubscript{3}N, THF, rt, overnight.

Substrates 190-194 were prepared from the corresponding commercially available amino acids using AcCl/MeOH.\textsuperscript{93} Substrate 195 was obtained by reducing commercially available 3-amino-3-phenylpropanoic acid with LiAlH\textsubscript{4} (Scheme 25).

(ix) The author thanks Dr. Jacob F. Jensen for assistance with the synthesis of substrates.

82
Scheme 25. Reagents and conditions: (a) AcCl/MeOH, 0 °C, then reflux; (b) THF, LiAlH₄, 0 °C then refluxed, 2 h

Compounds 207-215 necessary for the tandem RCM/isomerization/cyclization were prepared by acylating substrates 106, 198-204, and 206 with acryloyl chloride in the presence of triethylamine in dichloromethane at low temperatures (see Table 6).

Table 6. Acylation of amines 106, 198-204, 206 to dienes 207-215

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R¹</th>
<th>R²</th>
<th>product, yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>206</td>
<td>3-indole</td>
<td>H</td>
<td>207, 59</td>
</tr>
<tr>
<td>2</td>
<td>198</td>
<td>3-indole</td>
<td>CO₂Me</td>
<td>208, 83</td>
</tr>
<tr>
<td>3</td>
<td>199</td>
<td>3-benzothiophene</td>
<td>CO₂Me</td>
<td>209, 96</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>2,3-(MeO)₂C₆H₃</td>
<td>CO₂Me</td>
<td>210, 86</td>
</tr>
<tr>
<td>5</td>
<td>201</td>
<td>2-furan</td>
<td>CO₂Me</td>
<td>211, 61</td>
</tr>
<tr>
<td>6</td>
<td>202</td>
<td>3-thiophene</td>
<td>CO₂Me</td>
<td>212, 82</td>
</tr>
<tr>
<td>7</td>
<td>106</td>
<td>2,3,4-(MeO)₃C₆H₂</td>
<td>H</td>
<td>213, 74</td>
</tr>
<tr>
<td>8</td>
<td>203</td>
<td>CH₂OH</td>
<td>Ph</td>
<td>214, 25</td>
</tr>
<tr>
<td>9</td>
<td>204</td>
<td>OH</td>
<td>i-Pr</td>
<td>215, 26</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield after flash column chromatography.
Acylation of 203 and 204 (entries 8 and 9, Table 2) proved to be problematic. This is due to concurrent acylation of both the hydroxyl and nitrogen moieties, affording products 214-215 in low yield (25-26%). This problem could be circumvented by protecting the hydroxyl group of substrate 205 prior to the acylation (Scheme 26). Compound 205 was TBDMS-protected and N-acylated with acryloyl chloride, before a final removal of the TBDMS group afforded 216 in 56% isolated yield over 3 steps (Scheme 26).

Scheme 26. Preparation of substrate 216. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, 60 °C, 2h, 80%; (b) CH₂Cl₂, acryloyl chloride, 0 °C to r.t., 23h, 86%; (c) THF, TBAF, 0 °C to r.t., 30 min, 81%.

To introduce a methyl group at the iminium centre, a regioselective palladium-catalyzed allylic amination of benzylamine, followed by acylation with acryloyl chloride was conducted, affording diene 217 in 56% overall yield (Scheme 27).

Scheme 27. Preparation of substrate 217. Reagents and conditions: (a) [(allyl)PdCl]₂, Cy₂P(o-biphenyl), DBU, THF, 65%; (b) acryloyl chloride, Et₃N, CH₂Cl₂, 87%.
2.2.2 Ruthenium Alkylidene Catalyst Screening

A catalyst screen employed compound 207 as model substrate, which contains an indole moiety as the reactive \( \pi \)-nucleophile. The resulting product 218b (see Table 7) has a tetracyclic indolizinoindole ring system which is a key structural element in a range of pharmacologically interesting compounds, such as receptor antagonists, and antibacterial, and antiparasitic agents. Access to indolizinoindole derivatives has therefore been widely pursued in the literature.

Several ruthenium alkylidene catalysts Ru-1-11 (see, Figure 9) in refluxing toluene or \( m \)-xylene were screened (see Table 7). Changing solvent from refluxing toluene to refluxing \( m \)-xylene had an effect on the isomerization, indicating that higher temperatures were required to achieve complete conversion. Notably, with 15% of catalyst in refluxing \( m \)-xylene, several catalysts brought about a full conversion into the desired product 218b (entries 3, 6, 11, 14, and 19), and the reactions were generally very clean as indicated by RP-HPLC, except for entry 17 which showed other unidentified peaks. By lowering the amount of catalyst to 5%, the Hoveyda-Grubbs catalyst Ru-2 gave the cleanest product and highest conversion (95%) of 207 to 218b (see Table 13, entry 4).

Figure 13. Ruthenium alkylidine catalysts.
Table 7. Screening of catalysts Ru-1-11 for RCM/isomerization/N-acyliminium cyclization

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>product distribution 207:218a:218b&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru-1</td>
<td>toluene</td>
<td>100:0:0</td>
</tr>
<tr>
<td>2</td>
<td>Ru-2</td>
<td>toluene</td>
<td>0:2:98</td>
</tr>
<tr>
<td>3</td>
<td>Ru-2</td>
<td>m-xylene</td>
<td>0:0:100</td>
</tr>
<tr>
<td>4</td>
<td>Ru-2</td>
<td>m-xylene</td>
<td>0:5:95&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Ru-3</td>
<td>toluene</td>
<td>0:26:74</td>
</tr>
<tr>
<td>6</td>
<td>Ru-3</td>
<td>m-xylene</td>
<td>0:0:100</td>
</tr>
<tr>
<td>7</td>
<td>Ru-3</td>
<td>m-xylene</td>
<td>0:10:90&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Ru-4</td>
<td>toluene</td>
<td>83:3:14</td>
</tr>
<tr>
<td>9</td>
<td>Ru-5</td>
<td>toluene</td>
<td>54:6:40</td>
</tr>
<tr>
<td>10</td>
<td>Ru-6</td>
<td>toluene</td>
<td>36:0:64</td>
</tr>
<tr>
<td>11</td>
<td>Ru-6</td>
<td>m-xylene</td>
<td>0:0:100</td>
</tr>
<tr>
<td>12</td>
<td>Ru-6</td>
<td>m-xylene</td>
<td>38:0:62&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>Ru-7</td>
<td>toluene</td>
<td>0:12:88</td>
</tr>
<tr>
<td>14</td>
<td>Ru-7</td>
<td>m-xylene</td>
<td>0:0:100</td>
</tr>
<tr>
<td>15</td>
<td>Ru-7</td>
<td>m-xylene</td>
<td>0:5:95&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>16</td>
<td>Ru-8</td>
<td>toluene</td>
<td>61:4:35</td>
</tr>
<tr>
<td>17</td>
<td>Ru-9</td>
<td>toluene</td>
<td>25:38:37</td>
</tr>
<tr>
<td>18</td>
<td>Ru-10</td>
<td>toluene</td>
<td>3:14:83</td>
</tr>
<tr>
<td>19</td>
<td>Ru-10</td>
<td>m-xylene</td>
<td>0:0:100</td>
</tr>
<tr>
<td>20</td>
<td>Ru-10</td>
<td>m-xylene</td>
<td>7:13:80&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>21</td>
<td>Ru-11</td>
<td>toluene</td>
<td>0:70:30</td>
</tr>
</tbody>
</table>

<sup>a</sup> With the exception of entry 17, product mixtures were generally clean (>85% of 207:218a:218b) in the reaction mixture as indicated by RP-HPLC).  
<sup>b</sup> The reaction was carried out with 5% of catalyst.
2.2.3 Investigation of Ru-2 Catalyst on the Isomerization

By raising the catalyst loading of Ru-2 to 6 mol%, the reaction was complete within 17 h, affording 218b in 82% isolated yield (Scheme 28, right side). By this method two new carbon-carbon bonds are being formed, and a 4-step formal total synthesis of the antiparasitic natural product harmicine\textsuperscript{64,65b} 223 could be accomplished.

![Scheme 28 Optimized reaction conditions and investigation of 218a under various conditions.](image)

By subjecting 207 to Ru-2 in m-xylene at lower temperature (60 °C), metathesis product 218a could be isolated in 75% yield (Scheme 28, left side). The following conversion of 218a to 218b was investigated under various conditions. For example, when subjecting 218a to catalyst Ru-2, the desired product 218b was formed quantitatively in less than 5h. The same experiment without catalyst led to a 1:1 mixture of 218a and 218b, unambiguously demonstrating the beneficial effect of added catalyst to the non-metathetic part of the tandem sequence. Further investigation showed that addition of TFA (1 equiv), converts 218a to 218b, in less than 10 min. The homologues substrates 219 and 220 did not convert to 221 and 222 under the optimized reaction conditions, only RCM products were obtained (Scheme 29)

![Scheme 29. RCM/isomerization/cyclization on the homologous substrates 219 and 220.](image)
Chierici and co-workers has proposed a plausible mechanism for the formation of \( N \)-acyliminium ion from \( \alpha,\beta \)-unsaturated \( \gamma \)-lactam 224 involving several acid mediated keto-enol tautomerizations (Scheme 30).\(^9\)

\[
\begin{align*}
&\text{HN} \quad \text{O} \\
&\xrightarrow{+H^+} \\
&\text{HN} \quad \text{O} \\
&\xleftarrow{+H^+} \\
&\text{HN} \quad \text{O} \\
&\xrightarrow{+H^+} \\
&\text{HN} \quad \text{O} \\
&\xleftarrow{\text{1,2-hydride shift}} \\
&\text{HN} \quad \text{O}
\end{align*}
\]

\textbf{Scheme 30.} Proposed mechanism from Chierici and co-workers.

Based on their results, and the fact that the homologous substrates 219 and 220 did not convert into the tetracycles 221 and 222, and that TFA rapidly converts 218a to 218b, a non-metathetic role of ruthenium, not necessarily involving intermediacy of ruthenium hydride species, was suggested. We think that the ruthenium catalyst promotes favorable tautomerization events by acting as a Lewis acid.\(^1\)

Furthermore, the conversion of 207 to 218b can be mediated cleanly in one operation with \textbf{Ru-2} in the presence of 1-2% TFA or BF\(_3\)·Et\(_2\)O in refluxing \( m \)-xylene, shortening reaction times to 1 h but with slightly lower yields (56-76\%, see entries 1,2, 8-10, Table 8). Higher loading of TFA or BF\(_3\)·Et\(_2\)O resulted in incomplete RCM to 218a (entries 3, 4, 11). Acetic acid did not have any beneficial influence on the reaction, indicating that stronger acid is preferred for the isomerization step.
Table 8. Screening of TFA, BF$_3$·Et$_2$O and acetic acid for RCM/isomerization/N-acyliminium cyclization

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>equivalents</th>
<th>product distribution</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA</td>
<td>0.01</td>
<td>6:0:94</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>0.05</td>
<td>7:0:93</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>TFA</td>
<td>0.20</td>
<td>15:0:85</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>1</td>
<td>78:0:22</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>acetic acid</td>
<td>0.05</td>
<td>11:44:45</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>acetic acid</td>
<td>0.20</td>
<td>10:40:50</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>acetic acid</td>
<td>1</td>
<td>39:39:22</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>BF$_3$·Et$_2$O</td>
<td>0.02</td>
<td>0:95:5</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>BF$_3$·Et$_2$O</td>
<td>0.05</td>
<td>0:0:100</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>BF$_3$·Et$_2$O</td>
<td>0.20</td>
<td>0:0:100</td>
<td>56</td>
</tr>
<tr>
<td>11</td>
<td>BF$_3$·Et$_2$O</td>
<td>1</td>
<td>33:0:67</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Reaction profiles in entries 1, 8, and 9 were generally clean (>85% of 207:218a:218b) in the reaction mixture as indicated by RP-HPLC). $^b$ isolated yield after flash column chromatography.

In further experiments, substrate 225 was subjected to Grubbs II catalyst followed by addition of pyrrolidine and TFA, which resulted in the formation of unexpected product 226 in 81% isolated yield. This result suggests that the keto-enol tautomerizations are involved as intermediates where the enol 227 acts as a nucleophile (Scheme 31). This methodology could also be applied to substrate 228 resulting in bicycle of type 229, although in low yield (around 10-16%). These results are preliminary and future work will investigate the scope of the reaction.
Scheme 31. A dual Ru/pyrrolidine catalyzed tandem RCM/isomerization/cyclization. Reagents and conditions: (a) Grubbs II (10-20 mol%), 50 °C, 20-45 min; (b) pyrrolidine (2 equiv), TFA (1 equiv), 1h, 50 °C.

This methodology offers unique opportunities for exploring tandem processes where the same reaction centre can be used either as an electrophilic or nucleophilic entity, depending on the nature of the tethered functionality and the reaction conditions. In this way a dual reactivity or umpolung of the centre is useful for the synthesis of interesting heterocycles.

2.2.4 Investigation of Asymmetric Tandem Catalysis

As described above, the formation of N-acyliminium ions from α,β-unsaturated γ-lactams may be greatly accelerated by addition of acid. For these reasons, a chiral Brønsted acid catalyst could in theory function as a proton source and constitute an asymmetric environment during the reaction. For example, chiral BINOL-derived phosphoric acids\textsuperscript{101} are suitable as Brønsted acids to deliver a proton to the α,β-unsaturated γ-lactam \textsuperscript{218}a. The resulting chiral conjugate base of that phosphoric acid could then ion pair with the cyclic N-acyliminium ion being formed.\textsuperscript{102} If the enol type N-acyliminium intermediate is present, hydrogen bonding would be feasible between the hydroxyl group and phosphoric acid. This could lead to face differentiation in the proposed reaction transition-state A (see Table 9), and the presence of an indole nucleophile would bring about a cyclization from one of the two differentiated faces.

Initial enantioselective tandem RCM/isomerization/cyclization sequences were examined with a range of phosphoric acids \textsuperscript{230}a-e, having different substituents at the 3 and 3’ positions (Table 5). These were added together with Grubbs II catalyst Ru-11...
in the beginning of the reaction and brought to reflux in \textit{m}-xylene or \ce{CH2Cl2}. Pleasingly, all of the screened organocatalysts afforded \textit{218b} cleanly within 1 h at 110 °C in \textit{m}-xylene, without inhibition of the RCM reaction, whereas 24 h was required to fully convert \textit{207} to \textit{218b} in refluxing \ce{CH2Cl2} (entry 11, Table 9). At rt, (entry 7), a mixture of \textit{218a} and \textit{218b} was obtained after 24 h, whereas at -23 °C only starting material was recovered (entry 8). Several acid catalysts induced enantioselectivity, and the best was obtained when \textit{207} at a concentration of 1-4 mM was subjected to \textit{230e} in \textit{m}-xylene at 110 °C (entries 9 and 10, 60% \textit{ee}).

\textit{Table 9}. Optimization of asymmetric reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>organocatalyst, R</th>
<th>[\textit{207}] (mM)</th>
<th>temperature (°C)</th>
<th>solvent</th>
<th>time</th>
<th>\textit{ee} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\textit{230a}, H</td>
<td>25</td>
<td>110</td>
<td>\textit{m}-xylene</td>
<td>1 h</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>\textit{230b}, 9-anthracene</td>
<td>25</td>
<td>110</td>
<td>\textit{m}-xylene</td>
<td>1 h</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>\textit{230c}, 3,5-(\textit{CF3})2\textit{C6H3}</td>
<td>25</td>
<td>110</td>
<td>\textit{m}-xylene</td>
<td>1 h</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>\textit{230d}, 2,4,6-(\textit{i}-Pr)3\textit{C6H2}</td>
<td>25</td>
<td>110</td>
<td>\textit{m}-xylene</td>
<td>1 h</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>\textit{230e}, \textit{SiPh3}</td>
<td>25</td>
<td>110</td>
<td>\textit{m}-xylene</td>
<td>1 h</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>\textit{230e}, \textit{SiPh3}</td>
<td>100</td>
<td>110</td>
<td>\textit{m}-xylene</td>
<td>1 h</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>\textit{230e}, \textit{SiPh3}</td>
<td>100</td>
<td>r.t.</td>
<td>\textit{m}-xylene</td>
<td>24 h</td>
<td>50\textsuperscript{a}</td>
</tr>
<tr>
<td>8</td>
<td>\textit{230e}, \textit{SiPh3}</td>
<td>100</td>
<td>-23</td>
<td>\textit{m}-xylene</td>
<td>24 h</td>
<td>\textsuperscript{b}</td>
</tr>
<tr>
<td>9</td>
<td>\textit{230e}, \textit{SiPh3}</td>
<td>4</td>
<td>110 °C</td>
<td>\textit{m}-xylene</td>
<td>1 h</td>
<td>60 \textsuperscript{a}</td>
</tr>
<tr>
<td>10</td>
<td>\textit{230e}, \textit{SiPh3}</td>
<td>1</td>
<td>110 °C</td>
<td>\textit{m}-xylene</td>
<td>2 h</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>\textit{230e}, \textit{SiPh3}</td>
<td>4</td>
<td>45 °C</td>
<td>\ce{CH2Cl2}</td>
<td>24 h</td>
<td>46</td>
</tr>
</tbody>
</table>

\textsuperscript{a} \textit{207} was recovered in 1:1 ratio with product \textit{218b}. \textsuperscript{b} Only \textit{207} was observed.
2.2.5 Substrate Scope
With suitable reaction conditions in hand, the substrate scope of the ruthenium-catalyzed tandem RCM/isomerization/cyclization sequence was examined. The substrates contained a variety of tethered nucleophiles. For example, with N-methylated indole 231, the yield increased to 86% (see eq 1). Trimethoxybenzene substrate 213 also underwent the tandem sequence to give a tetrahydroisoquinoline derivative 233 in good yield (64%, see eq 2). This method represents the first synthesis of mescalotam,\textsuperscript{103} a naturally occurring plant alkaloid isolated from cactus \textit{Peyote}, which is known to exhibit medicinal and hallucinogenic properties.\textsuperscript{104}

\[ \text{eq 1} \quad m\text{-xylene, reflux, 24 h} \]

\[ \text{eq 2} \quad m\text{-xylene, reflux, 5 h} \]

\[ \text{eq 3} \quad m\text{-xylene, reflux, 22 h} \]

\[ \text{eq 4} \quad m\text{-xylene, reflux, 21 h} \]
The introduction of a methylester substituent, as present in tryptophan 208 and benzothienylalanine 209 derivatives (eqs 3 and 4) effectively directed the formation of the new stereocenter with excellent trans-diastereoselectivity at the ring junction. The reaction can be characterized as a Pictet-Spengler type cyclization105 (Scheme 32, pathways A and B) with a mechanism that involves attack of the indole C-3 at the N-acyliminium ion to form a spiroindolenine intermediate 208a or 208b. Following rearrangement to 208c-d and elimination of a proton affords, either trans or the cis-products 234 and 234a can be formed.

Scheme 32. Proposed mechanistical steps in pathways A and B: (a) formation of spiroindolenine 208a-b; (b) rearrangement to 208c-d; (c) elimination of proton.

The observed trans-diastereoselectivity can be explained by steric involving from considerable allylic strain.106 For example, the allylic strain present in substrate 208 in pathway B, where the methylester group is in the plane of the carbonyl oxygen, is sterically disfavored, whereas in pathway A, the hydrogen α to methylester is instead in the plane of the carbonyl oxygen. Therefore pathway A is favored, resulting in the observed trans-diastereoselectivity of the reaction. This observation complements earlier findings of Nielsen and Meldal on trans-diastereoselective N-acyliminium Pictet-Spengler cyclizations.98a
The extension of the methodology to oxygen nucleophiles was also examined for substrates 214-216 and, rewardingly, bicycles 236-238 were formed in decent yields, with excellent diastereoselectivity (eq 5).

![Image of chemical structures and equations]

The nucleophilicity of the aromatic ring is highly important for the tandem process, as evident from the reactions in eq 6-8. These compounds were not converted to the corresponding tricycles under the conditions described in equations 1-5. Ring-closing metathesis occurred smoothly for these substrates but further conversion had to be mediated by the subsequent addition of 1-4 equiv of TFA to the reaction mixture. In this way, tricyclic compounds 239-241 were obtained in good to excellent yields and diastereoselectivities (eq 6-8).
The methodology was also extended to an intermolecular variant, where indole and phenethylethanol acted as external nucleophiles in the reaction with the \( N \)-acyliminium intermediates derived from 242 and 243 affording products 244 and 245, respectively, in good yields (82-84\%, eq 11). When 217 were subjected to the same conditions, the quaternary centre-containing 246 was obtained in 88\% yield, (eq 12).

![Chemical structures and reactions]

When subjecting substrate 242 to Grubbs II catalyst Ru-11, followed by addition of indole, and phosphoric acid 230a-d, a mixture of regioisomers 244 and 247, were obtained (Table 10). Formation of 247 is highly dependent on the substituents at the 3 and 3′ positions of phosphoric acid (Table 10, entries 1-4). When using organocatalyst 130d the \( N \)-alkylated product could be obtained in 24\% isolated yield and 60 \% \( ee \) (Table 10, entry 4).
Table 10. Optimization of the reaction conditions.

These preliminary results were not investigated any further, because a novel enantioselective N-H functionalization of various indoles 249 with α,β-unsaturated γ-lactam 248, catalyzed by phosphoric acid 230d, affording various N-alkylated products 250 in good yield and enantioselectivities (Scheme 17), was reported by Huang and co-workers.107

<table>
<thead>
<tr>
<th>entry</th>
<th>organocatalyst</th>
<th>R</th>
<th>product distribution 244:247</th>
<th>ee of 247 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>230a</td>
<td>H</td>
<td>100:0</td>
<td>_b</td>
</tr>
<tr>
<td>2</td>
<td>230c</td>
<td>3,5-(CF₃)₂C₆H₃</td>
<td>70:30</td>
<td>_b</td>
</tr>
<tr>
<td>3</td>
<td>230b</td>
<td>9-anthracene</td>
<td>37:63</td>
<td>_b</td>
</tr>
<tr>
<td>4</td>
<td>230d</td>
<td>2,4,6-(i-Pr)₃C₆H₂</td>
<td>32:68</td>
<td>60</td>
</tr>
</tbody>
</table>

* ee for 244 was not assigned.  
  
* ee for 247 was not assigned

Scheme 17. Enantioselective N-functionalization of indoles with α,β-unsaturated γ-lactam reported by Huang and co-workers.
2.2.6 Multifunctional Catalysis in the Synthesis of THBCs

During studies on the development of new ruthenium alkylidene-catalyzed isomerization reactions, the substrate \( N \)-benzyl-\( N \)-allyltryptamine \( 252 \), in the presence of Grubbs II catalyst \( \text{Ru-11} \) in refluxing \( m \)-xylene, proved to be a convenient precursor for the formation of tetrahydro-\( \beta \)-carboline (THBC) \( 253 \) (73 % isolated yield, Scheme 33A). Substrate \( 252 \) was prepared in 2 steps from tryptamine \( 251 \) and benzaldehyde via reductive amination followed by alkylation with allyl bromide and base.

Scheme 33. A) Reagents and conditions: (a) tryptamine, benzaldehyde, MeOH, 3Å MS, r.t. 24 h, then \( \text{NaBH}_4 \), 95%; (b) allylbromide, \( \text{K}_2\text{CO}_3 \), DMF, r.t., 94%; (c) \( \text{Ru-11} \) (10 mol%), \( m \)-xylene, reflux, 1h, 73%. B) Selected pharmacologically important THBC alkaloids.

The tricyclic THBC ring system is a key structural element in a range of biologically and pharmacologically important alkaloids (see, Scheme 33B), and they are traditionally synthesized via the Pictet-Spengler reaction incorporating tryptamines and aldehydes under acidic reaction conditions. This method relies on a Ru-alkylidene mediated isomerization of allylic amines to form reactive \( N \)-alkyliminium intermediates which are being trapped by a tethered indole nucleophile to form THBCs. The concurrent isomerization into synthetically useful iminium intermediates remains virtually unexplored in the literature. The only example to date, was demonstrated by Terada and co-workers, who reported a dual ruthenium
hydride/Brønsted acid-catalyzed tandem process, where allylamines are isomerized to iminium intermediates that undergo Friedel-Crafts type reactions with electron-rich aromatics. Next, a variety of transition-metal sources was investigated in the reaction. All catalysts in amounts of 15 mol% were shown to mediate a complete transformation of 252 to 253 within 2 h (Table 11). Several catalysts brought about a clean conversion to 253, within 23 h, when catalyst loading was decreased to 1 mol% (entries 1, 2, 5, 8 and 9). When the catalyst loading was reduced to 0.1 mol%, Wilkinson’s catalyst and Ru alkylidene Ru-8 (entries 1, and 8) proved to be the most efficient for the isomerization.

**Table 11. Screening of transition metal catalysts for the synthesis of THBC 253**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conversion (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 h&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>Rh(PPh&lt;sub&gt;3&lt;/sub&gt;)Cl</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>RuHCl(CO)PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Pd(Pr-Bu&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Grubbs II (Ru-11)</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>Hoveyda-Grubbs I (Ru-2)</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>Hoveyda-Grubbs II (Ru-3)</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>Ru-8</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>Ru-9</td>
<td>100</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by RP-HPLC (215 nm).<br><sup>b</sup> Product mixtures were generally very clean (>85% of 252 and 253 in the reaction mixture).<br><sup>c</sup> Reaction carried out with 15 mol% catalyst.<br><sup>d</sup> Reaction in brackets was carried out with 0.1 mol% catalyst.

(x) this catalyst optimization was carried out by PhD student Casper L. Hansen.
As demonstrated in Table 11 several different metal catalysts were shown to mediate the isomerization, and the strategy thus opens up possibilities for developing multifunctional catalysts for new tandem processes. For example, a tandem Tsuji-Trost/isomerization/iminium cyclization approach was achieved, where a range of readily available tryptamines 254-259 could be efficiently converted to THBCs 253, and 260-264 (48-86%) when reacted with allylmethylcarbonate and Pd(PPh₃)₄ in refluxing toluene (see Table 12).

The tandem process provides a metal-catalyzed variant of the Pictet-Spengler reaction for the synthesis of THBCs, where a single metal catalyzes two mechanistically distinct chemical reactions in one operation. At this stage, the Pd catalyst loading is high and further experiments with other catalysts to decrease the catalyst loading in the tandem process will be the subject of future research.

**Table 12** Synthesis of THBCs via a Pd-catalyzed Tsuji-Trost/isomerization/iminium cyclization sequence

<table>
<thead>
<tr>
<th>entry</th>
<th>substrates</th>
<th>R²</th>
<th>R1</th>
<th>product, yield [a] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>254</td>
<td>Bn</td>
<td>H</td>
<td>253, 85</td>
</tr>
<tr>
<td>2</td>
<td>255</td>
<td>(4-NO₂)C₆H₄CH₂</td>
<td>H</td>
<td>260, 86</td>
</tr>
<tr>
<td>3</td>
<td>256</td>
<td>(3,4-OMe)₂C₆H₅CH₂</td>
<td>H</td>
<td>261, 81</td>
</tr>
<tr>
<td>4</td>
<td>257</td>
<td>CyCH₂</td>
<td>H</td>
<td>262, 67</td>
</tr>
<tr>
<td>5</td>
<td>258</td>
<td>n-Hept</td>
<td>H</td>
<td>263, 48</td>
</tr>
<tr>
<td>6</td>
<td>259</td>
<td>Bn</td>
<td>6-OMe</td>
<td>264, 67</td>
</tr>
</tbody>
</table>

[a] Isolated yield after flash column chromatography.
2.2.7 Summary
In summary, a multifunctional catalysis approach, via a ruthenium-catalyzed tandem ring-closing metathesis/isomerization/N-acyliminium cyclization sequence has been developed. In the tandem process two new rings are formed in a single synthetic operation, which proceeds through a metathesis reaction and attack of tethered carbon and heteroatom nucleophiles on N-acyliminium intermediates. The resulting products are generally formed in good to very good yield with excellent diastereoselectivities. Furthermore, asymmetric version of the tandem process has been pursued affording indolizinoindoles in up to 60% ee.

In addition, a novel Pd-catalyzed tandem Tsuji-Trost/isomerization/N-alkyliminium cyclization has been developed. In this tandem process various THBC ring systems have been formed in good yields from readily available tryptamines.
2.2.8 Experimental section

**General Methods:** Cf. section 1.1.6 for general methods.

**(S)-Methyl 2-amino-3-(benzo[b]thiophen-3-yl)propanoate (191).**

Under a N₂ atmosphere acetyl chloride (1.06 g, 13.56 mmol) was added drop wise to stirred and cooled (0 °C) methanol (10 mL). After complete addition the solution was stirred for additional 5 min. and then treated with (S)-2-amino-3-(benzo[b]thiophen-3-yl)propanoic acid (1.00 g, 4.52 mmol). The reaction mixture was heated to reflux and maintained for 2 h., followed by cooling to r.t., and quenching with aqueous sat. NaHCO₃ (50 mL). Extraction with CH₂Cl₂ (3 x 50 mL), drying over Na₂SO₄ filtration and conc. in **vacuo** afforded the crude oil 960 mg (90%), which was used without further purification in the following step. ¹H NMR (300 MHz, CDCl₃) δ 7.87 (m, 1H), 7.80 (m, 1H), 7.38 (m, 2H), 7.24 (s, 1H), 3.88 (dd, J = 8.2, 5.0 Hz, 1H), 3.71 (s, 3H), 3.37 (ddd, J = 15.1, 5.0, 0.9 Hz, 1H), 3.10 (ddd, J = 14.2, 8.1, 0.6 Hz, 1H) 1.60 (br s, 2H, NH₂); ¹³C NMR (75 MHz, CDCl₃) δ 175.3, 140.4, 138.7, 131.8, 124.3, 124.0, 123.7, 122.9, 121.6, 54.4, 52.1, 34.0; LC-MS (ESI⁺) m/z: 236.2 (M+H)⁺.

**(S)-methyl 2-(allylamino)-3-(thiophen-3-yl)propanoate (194).**

Similar to procedure as described above, acetylchloride (1.1 ml, 1.3 equiv) was added dropwise to methanol (10 ml) at 0 °C under a N₂ atmosphere. After 5 min. (S)-2-amino-3-(thiophen-3-yl)propanoic acid (1.0 g, 5.84 mol) was added in one portion. The final solution was heated to reflux for 2 h. Saturated NaHCO₃ (50 ml) was added and the product was extracted with CH₂Cl₂ (3x100 ml). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in **vacuo** to give 950 mg (88%) of the title product which was used without further purification. ¹H NMR (300 MHz, CDCl₃) δ 7.40 (m, 1H), 7.16 (s, 1H), 6.94 (d, J = 4.9 Hz, 1H), 3.56 (m, 5H), 2.84 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 175.3, 130.4, 128.7, 125.6, 122.2, 55.0, 51.4, 35.1; LC-MS (ESI⁺) m/z: 186.1 (M+H)⁺.
Rac-3-Amino-3-phenylpropan-1-ol (195).

Under a N₂ atmosphere LiAlH₄ (3.20 g, 0.084 mol) was added in portions to a stirred and cooled (0 °C) solution of 3-amino-3-phenylpropanoic acid (4.00 g, 0.0242 mol) and THF (80 mL). After complete addition the suspension was heated to reflux and maintained for 2 h. The cooled suspension was quenched with water and then treated with sat. NaHCO₃ (aq) (30 mL) and further diluted with EtOAc (200 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 200 mL), and the combined organic phase was dried over Na₂SO₄, and conc. in vacuo to afford a yellow oil. The crude oil was purified by flash chromatography (eluent gradient of 100% EtOAc to EtOAc:MeOH (4:1 v/v)) to give 1.82 g (50%) of 3-amino-3-phenylpropan-1-ol as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.21 (m, 5H), 4.11 (dd, J = 7.9, 5.3 Hz, 1H), 3.78 (dd, J = 5.3, 0.6 Hz, 1H), 3.75 (s, 1H, OH), 2.90 (br s, 2H, NH₂), 1.88 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 145.9, 128.6, 127.1, 125.7, 61.7, 56.1, 29.6; LC-MS (ESI⁺) m/z: 152.2 (M+H)⁺.

(S)-Methyl 2-(allylamino)-3-(1H-indol-3-yl)propanoate (198).

**General procedure A:** A solution of (S)-methyl 2-amino-3-(1H-indol-3-yl) propanoate⁵⁹a (3.30 g, 0.0162 mol) in dry THF (20 mL) and dry DMF (20mL) was treated at r.t., with allyl bromide (2.06 g, 0.017 mol), Cs₂CO₃ (5.28 g, 0.0162 mol) and molecular sieves (4Å, 1.0 g). The final suspension was stirred overnight and then filtered through celite together with EtOAc (100 mL) and water (50 mL). The organic phase was separated and washed with brine (100 mL), dried over Na₂SO₄, filtered and conc. in vacuo. The crude oil was purified by flash chromatography (eluent gradient 10 to 20% EtOAc in n-hexanes v/v) to give 1.96 g (46%) of the title product as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 8.33 (br s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.15 (m, 2H), 7.10 (s, 1H), 5.82 (m, 1H), 5.12 (ddd, J = 17.2, 1.4 Hz, 1H), 5.06 (ddd, J = 17.2, 1 Hz, 1H), 3.54 (m, 1H) 3.65 (s, 3H), 3.35-3.10 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 145.9, 128.6, 127.1, 125.7, 61.7, 56.1, 29.6;
MHz, CDCl$_3$ $\delta$ 175.2, 136.1, 135.9, 127.3, 122.9, 121.9, 119.3, 118.6, 116.4, 111.1, 110.7, 61.1, 51.7, 50.6, 29.2; LC-MS (ESI$^+$) m/z: 259.3 (M+H)$^+$. 

(S)-Methyl 2-(allylamino)-3-(benzo[b]thiophen-3-yl)propanoate (199).

From (S)-methyl 2-amino-3-(benzo[b]thiophen-3-yl)propanoate (880 mg, 3.74 mmol) and applying the above described procedure A, the title product was obtained as a light yellow oil after purification by flash chromatography, using 20% Et$_2$O in $n$-hexane as eluent. Yield 649 mg (63%). [$\alpha$]$^\text{20}$$^D +17.0$ ($c$ 0.375, EtOH); IR (film) v 2924, 1734; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.85 (m, 1H), 7.77 (m, 1H), 7.37 (m, 2H), 7.23 (s, 1H), 5.82 (m, 1H), 5.10 (m, 2H), 3.72 (t, $J$ = 7.0 Hz, 1H), 3.60 (s, 3H), 3.25 (m, 4H), 2.75 (br s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.9, 140.3, 138.7, 135.8, 131.7, 124.2, 124.0, 123.6, 122.8, 121.5, 116.6, 60.4, 51.8, 50.6, 32.4; HRMS Calcd for C$_{15}$H$_{17}$NO$_2$S. 276.105 [M+H$^+$], found 276.105.

(S)-Methyl 2-(allylamino)-3-(3,4-dimethoxyphenyl)propanoate (200).

From (S)-methyl 2-amino-3-(3,4-dimethoxyphenyl) propanoate (1.70 g, 7.10 mmol) and applying the above described procedure A, the title product was obtained as a light yellow oil after purification by flash chromatography, using an eluent gradient of $n$-hexane and Et$_2$O. Yield 1.18 g (60%). [$\alpha$]$^\text{20}$$^D +15.5$ ($c$ 1.0, EtOH); IR (film) v 2950, 1731, 1514; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.80-6.55 (m, 3H), 5.76 (m, 1H), 5.04 (m, 2H), 3.78 (s, 6H), 3.65 (m, 1H), 3.60 (s, 3H), 3.47 (t, $J$ = 6.8 Hz, 1H), 3.20 (m, 1H), 3.07 (m, 1H), 2.84 (d, $J$ = 6.8 Hz, 1H), 1.70 (br s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.7, 148.5, 147.5, 135.8, 129.3, 120.9, 116.1, 112.0, 110.8, 61.8, 55.5 (2C), 51.4, 50.4, 39.0; HRMS Calcd for C$_{15}$H$_{21}$NO$_4$. 280.1543 [M+H$^+$], found 280.1548.
(S)-Methyl 2-(allylamino)-3-(furan-2-yl)propanoate (201).

From (S)-methyl 2-amino-3-(furan-2-yl)propanoate (432.0 mg, 2.56 mmol) and applying the above described procedure A, the title product was obtained as a clear oil after purification by flash chromatography, using a gradient of n-hexane and Et₂O. Yield 282 mg (53%). \([\alpha]^{20}_D +8.8\ (c\ 1.3,\ EtOH);\) IR (film) \(\nu\ 1736;\) \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\ 7.29\ (dd,\ J = 2.1, < 1.0\ Hz,\ 1H),\ 6.25\ (dd,\ J = 3.2,\ 2.1\ Hz,\ 1H),\ 6.06\ (dd,\ J = 3.2, < 1.0\ Hz,\ 1H),\ 5.81\ (m,\ 1H),\ 5.08\ (m,\ 2H),\ 3.66\ (s,\ 3H),\ 3.57\ (t,\ J = 6.5\ Hz,\ 1H),\ 3.26\ (dddd,\ J = 8.8, 5.9, 1.5\ Hz,\ 1H),\ 3.11\ (ddddd,\ J = 8.8, 5.9, 1.5\ Hz,\ 1H),\ 2.98\ (d,\ J = 6.4\ Hz,\ 2H),\ 1.65\ (br\ s,\ 1H);\) \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\ 174.4,\ 151.2,\ 141.6,\ 135.9,\ 116.4,\ 110.1,\ 107.2,\ 59.4,\ 51.7,\ 50.4,\ 32.0;\) HRMS Calcd for C\(_{11}\)H\(_{15}\)NO\(_3\). 210.1125 [M+H\(^+\)], found 210.1133.

(S)-Methyl 2-(allylamino)-3-(thiophen-3-yl)propanoate (202).

From (S)-methyl 2-amino-3-(thiophen-3-yl)propanoate 200 mg, 1.08 mmol) and applying the above described procedure A, the title product was obtained as a colourless oil after purification by flash chromatography, using n-Hexane/EtOAc (4:1, v/v) as eluent. Yield 189 mg (78%). \([\alpha]^{20}_D +8.4\ (c\ 0.190,\ EtOH);\) IR (film) \(\nu\ 3339,\ 3078,\ 3000,\ 2950,\ 2841,\ 1730;\) \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\ 7.24\ (dd,\ J = 3.0, 4.9\ Hz,\ 1H),\ 7.01\ (bs,\ 1\ H),\ 6.92\ (dd,\ J = 4.9, 1.3\ Hz,\ 1H),\ 5.81\ (tdd,\ 1H,\ J = 17.1,\ 10.2,\ 6.0\ Hz,\ 1H),\ 5.10\ (m,\ 2H),\ 3.66\ (s,\ 3H),\ 3.53\ (t,\ J = 6.6\ Hz,\ 1H),\ 3.27\ (m,\ 1H),\ 3.11\ (m,\ 1H),\ 2.99\ (d,\ J = 6.6\ Hz,\ 2H),\ 1.60\ (bs,\ 1H,\ NH);\) \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\ 174.8,\ 137.2,\ 136.0,\ 128.3,\ 125.5,\ 122.2,\ 116.3,\ 61.2,\ 51.7,\ 50.5,\ 33.9;\) HRMS Calcd for C\(_{11}\)H\(_{15}\)NO\(_3\)S 226.0896 [M+H\(^+\)], found 226.0908.
Rac-3-(Allylamino)-3-phenylpropan-1-ol (203).

**General procedure B:** From 3-amino-3-phenylpropan-1-ol (1.50 g, 0.010 mol) was dissolved in dry THF (10 mL) and then subsequently treated drop wise with Et$_3$N (1.06 g, 0.0105 mol) and allyl bromide (1.213 g, 0.010 mol). After stirring overnight the suspension was diluted with CH$_2$Cl$_2$ (50 mL), filtered through celite and concentrated in vacuo. The crude oil was purified by flash chromatography (eluent gradient of 50 to 100 % EtOAc in n-hexane) to yield the title product in 465 mg (24%) as clear oil. IR (film) ν 3260, 3067, 2848, 1046; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.32-7.25 (m, 2H), 7.23-7.14 (m, 3H), 5.79 (m, 1H), 5.08-5.97 (m, 2H), 3.81-3.67 (m, 3H), 3.20 (br s, 1H, OH), 3.01 (m, 2H), 1.90 (m, 1H), 1.74 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 142.9, 136.1, 128.6 (2C), 127.3, 126.5 (2C), 116.3, 63.1, 62.7, 49.5, 38.5; HRMS Calcd for C$_{12}$H$_{17}$NO 192.1383 [M+H$^+$], found 192.1388.

(S)-2-(Allylamino)-3-methylbutan-1-ol (204).

From (S)-vanilol (2.0 g, 0.0193 mol) and applying the above described procedure B, the title product was obtained as clear oil after purification by flash chromatography using an eluent gradient of 50% to 100% EtOAc in heptane. Yield 1.07 g (39%). Analytical data matches the reported ones:$^{xi}$ $^1$H NMR (300 MHz, CDCl$_3$) δ 5.90 (m, 1H), 5.17 (m, 1H), 5.08 (m, 1H), 3.58 (dd, $J = 10.6, 4.3$ Hz, 1H), 3.31 (dd, $J = 10.6, 7.0$ Hz, 1H), 3.25 (m, 1H), 2.40 (m, 1H), 1.80 (q, $J = 6.8$ Hz 1H), 0.95 (d, $J = 6.8$ Hz, 1H), 0.88 (d, $J = 6.8$ Hz, 1H); LC-MS (ESI$^+$ m/z): 144.2 (M+H$^+$).

---

(S)-2-(Allylamino)-2-phenylethanol (205).

Allyl bromide (890 mg, 472 µl, 7.36 mmol) was added drop wise to a solution of (S)-(+-)-2-phenylglycinol (1.0 g, 7.29 mmol) and triethylamine (760 mg, 1.05 ml, 7.50 mmol) in anhydrous THF (3.6 ml) and the reaction was stirred at room temperature for 20 h. The white precipitate was filtered, washed with ethyl acetate. The filtrate was concentrated in vacuo and the crude oil was purified by flash chromatography n-Hexane/EtOAc (1:8, v/v) to afford 519 mg (46%) of the title product as colorless oil. Analytical data matches the reported ones.\textsuperscript{xii} \([\alpha]^{20}_D +58.5\) (c 0.71, EtOH) (lit.: \([\alpha]^{20}_D -74.4\) (c 1, CH\textsubscript{2}Cl\textsubscript{2}); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.15-7.30 (m, 5H); 5.78 (m, 1H), 5.01 (m, 2H), 3.71 (dd, \(J = 4.3, 8.6\) Hz, 1H), 3.61 (dd, \(J = 4.4, 10.8\) Hz, 1H), 3.47 (dd, \(J = 8.6, 10.8\) Hz, 1H), 2.97 (tdd, \(J = 1.3, 6.4, 14.0\) Hz, 1H), 3.11 (m, 1H), 2.49 (s, 2H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 140.3, 136.4, 128.6, 127.6, 127.2, 116.2, 66.5, 63.7, 49.7.

(2S)-2-(Allylamino)-2-phenylethanol 55 (542 mg, 3.06 mmol), TBDMSCl (600 mg, 3.98 mmol, 1.3 equiv), and imidazole (521 mg, 7.65 mmol, 2.5 equiv) were dissolved in anhydrous DMF (2.5 ml) at rt.. The reaction mixture was stirred at 60 °C for 2 h and then purified by flash chromatography n-Hexane/EtOAc (9:1, v/v) to afford 718 mg (80%) of the title product as a colorless oil. \([\alpha]^{20}_D +30.2\) (c 1.13, EtOH); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.35-7.19 (m, 5H), 5.86 (dddd, \(J =17.0, 10.3, 6.6, 5.1\) Hz, 1H), 5.09 (m, 2H), 3.80 (dd, \(J = 8.9, 4.0\) Hz, 1H), 3.65 (dd, \(J = 9.9, 4.0\) Hz, 1H), 3.53 (dd, \(J = 9.9, 9.0\) Hz, 1H), 3.00 (m, 1H), 3.15 (m, 1H), 2.03 (bs, 1H), 0.87 (s, 9H), \(\delta\) 0.00 (s, 6H), \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 140.8, 137.1, 128.3, 127.7, 127.3, 115.3, 68.4, 64.2, 49.9, 25.9, 18.3, -5.4, -5.5; HRMS Calcd for C\textsubscript{17}H\textsubscript{29}NOSi 292.2091 [M+H\textsuperscript{+}], found 292.2096.

\textsuperscript{xii} Vasse, J. L.; Joosten, A.; Denhez, C.; Szymoniak, J. Org Lett. 2005, 7, 4887-4889
**N-(2-(1H-indol-3-yl)ethyl)prop-2-en-1-amine (206).**

3-(2-Bromoethyl)indole (5.0 g, 0.0223 mol) was dissolved in allylamine (25.5 g, 0.446 mol) and then treated with K$_2$CO$_3$ (3.70 g, 0.0270 mol). After stirring overnight at room temperature, the suspension was filtered and excess allylamine was removed under reduced pressure. The crude oil was purified by flash chromatography on silica (eluient gradient 100% CH$_2$Cl$_2$ to CH$_2$Cl$_2$:MeOH:Et$_3$N 89:10:1) to give 3.78 g (85%) of *N-(2-(1H-indol-3-yl)ethyl)prop-2-en-1-amine* as a yellow brown oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.44 (br s, 1H), 7.64 (dd, $J$ = 7.8, 0.7 Hz, 1H), 7.36 (dd, $J$ = 8.0 Hz, 1H), 7.24-7.10 (m, 2H), 7.03 (s, 1H, NH), 5.91 (m, 1H), 5.17 (m, 1H), 5.11 (m, 1H), (ddd, $J$ = 6.1, 1.5, 1.5 Hz, 2H), 3.02 (m, 4H), 2.64 (br s, 1H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 136.3, 135.8, 127.3, 122.1, 121.9, 119.1, 118.8, 116.6, 113.3, 111.2, 52.0, 49.0, 25.4.; LC-MS (ESI+) m/z: 201.2 (M+H)$^+$. 

**Rac-N-benzylbut-3-en-2-amine.**

In a dry round-bottom flask were placed [Pd($\eta^3$-C$_3$H$_5$)Cl]$_2$ (96 mg, 0.26 mmol, 10 mol%), (2-biphenyl)dicyclohexylphosphine (368 mg, 1.05 mmol) and dry THF (2.0 ml). DBU (400 µl, 2.68 mmol), crotylacetate (300 mg, 2.63 mmol) and benzylamine (293 µl, 2.68 mmol) were added via syringe and the solution was stirred under argon atmosphere for 4 h. Water (50 ml) was added, the organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 30 ml). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated *in vacuo* and the residue was purified by flash chromatography *n*-Hexane/EtOAc (3:1, v/v) to afford the title product in 273 mg (65%) as a yellow oil. Analytical data matches the reported one.$^{94}$ $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35-7.20 (m, 5H), 5.72 (ddd, $J$ = 17.3, 10.1, 7.6 Hz, 1H), 5.15-5.06 (m, 2H), 3.81 (d, $J$ = 13.0 Hz, 1H), 3.68 (d, $J$ = 13.0 Hz, 1H), 3.30-3.15 (m, 1H), 1.18 (d, $J$ = 6.5 Hz, 3H).
4-(allylamino)butan-2-one.

Allylamine (2.6 ml, 25 mmol), was dissolved in CH₂Cl₂ (175 ml) and methyl vinyl ketone (2.6 ml, 32 mmol) was added and the reaction was stirred at room temperature for 80 min. The contents were concentrated in vacuo and following purification by flash chromatography CH₂Cl₂/MeOH (95:5, v/v) afforded 1.94 g (49%) of the titled product as orange oil. **¹H NMR (300 MHz, CDCl₃) δ 5.82 (tdd, J = 17.1, 10.2, 5.9 Hz, 1H), 5.17-4.99 (m, 2H), 3.18 (td, J = 6.0, 1.43 Hz, 2H), 2.79-2.74 (m, 2H), 2.65-2.55 (m, 2H), 2.10 (s, 3H), 1.68 (bs, 1H, NH). **¹³C NMR (75 MHz, CDCl₃) δ 208.3, 136.4, 115.8, 52.3, 43.5, 43.4, 30.0.

5-(allylamino)pentan-1-ol.

Allylamine (13 ml, 30 equiv) was added to K₂CO₃ (1.0 g, 7.2 mmol, 1.2 equiv) and 5-bromo-1-pentanol (1.0 g, 6.0 mmol) was added dropwise under vigorous stirring at room temperature. After stirring overnight at room temperature, the suspension was filtered and excess allylamine was removed under reduced pressure. The crude oil was purified by distillation on kugelrör (150 °C, 1.7 mbar), which afforded 600 mg (70%) of the title product as yellow/orange oil. **¹H NMR (300 MHz, CDCl₃) δ 5.93-5.79 (m, 1H), 5.16-5.04 (m, 2H), 3.59-3.55 (m, 2H), 3.22-3.19 (m, 2H), 2.61-2.56 (m, 2H), 2.21 (bs, 2H), 1.58-1.34 (m, 6H); **¹³C NMR (75 MHz, CDCl₃) δ 136.4, 116.0, 62.1, 52.3, 49.0, 32.4, 29.4, 23.3.

N-(3,4,5-Trimethoxyphenethyl)prop-2-en-1-amine (106).

To a solution of 2-(3,4,5-trimethoxyphenyl)acetaldehyde (300 mg, 1.43 mmol) in absolute CH₃CN (2 ml) was added prop-2-en-1-amine (320 µl, 4.30 mmol, 3 equiv) and the (xiii) prepared according to Pelphrey, P. M.; Popov, V. M.; Joska, T. M.; Bierlein, J. M.; Bolstad, E. S. D.; Fillingham, Y. A.; Wright, D. L.; Anderson, A. C. J. Med. Chem. 2007, 50, 940-950.
resulting solution was stirred at room temperature under nitrogen atmosphere for 30 min. NaBH₄CN (135 mg, 2.14 mmol, 1.5 equiv) was added and after additional 30 min. stirring, acetic acid (163 µl, 2 equiv) was added. The final reaction mixture was then stirred for further 20 min and then worked up by dilution with CH₂Cl₂ (30 ml) and washing with 1N NaOH (aq) (2x15ml). The water phase was extracted with CH₂Cl₂ (25 ml) and the combined organic phase was dried over Na₂SO₄, concentrated in vacuo and following purification by flash chromatography CH₂Cl₂/MeOH (95:5, v/v) afforded 147 mg (41%) of the title product as a clear oil. IR (film) ν 3075, 2996, 2936, 1587, 1506, 1455, 1122; ¹H NMR (300 MHz, CDCl₃) δ 6.40 (s, 2H), 5.87 (tdd, J = 17.1, 10.2, 6.1 Hz, 1H), 5.11 (m, 2H), 3.81 (s, 6 H), 3.79 (s, 3H), 3.26 (td, J = 6.1, 1.4 Hz, 2H), 2.86 (m, 2H) ppm 2.75 (m, 2H), 2.15 (bs, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 153.1, 136.1, 135.4, 116.3, 105.4, 60.7, 55.9, 52.1, 50.2, 36.4; HRMS Calcd for C₁₄H₂₁NO₃ 252.1594 [M+H⁺], found 252.1598.

**N-(2-(1H-Indol-3-yl)ethyl)-N-allylacrylamide (207).**

**General procedure C:** Under a nitrogen atmosphere N-(2-(1H-indol-3-yl)ethyl)prop-2-en-1-amine (3.34 g, 0.0167 mol) was dissolved in CH₂Cl₂ (50 mL) and then cooled to 0 °C in an ice bath. With stirring the solution was subsequently treated drop wise with Et₃N (2.02 g, 0.020 mol) followed by acryloyl chloride (1.81 g, 0.020 mmol). The final solution was slowly warmed to r.t., overnight and then quenched with water (50 mL). CH₂Cl₂ (100 mL) was added and the organic phase was separated. The organic phase was washed with brine (150 mL), dried over Na₂SO₄ and conc. in vacuo. The crude oil was purified by flash chromatography (eluent gradient 20 to 50% EtOAc in heptane) to give 2.51 g (59%) of title product as clear oil. IR (film) ν 3269, 1643/1605 (rotamers) 1455; ¹H NMR (300 MHz, CDCl₃) δ 8.78 (br s, 1H, 1 rotamer), 8.63 (br s, 1H, 1 rotamer), 7.62 (d, J = 7.6 Hz, 1H, 1 rotamer), 7.57 (d, J = 7.6 Hz, 1H, rotamer), 7.37 (dd, J = 6.4 Hz, 1H, both rotamers), 7.30-7.08 (m, 2H), 7.00 (s, 1H, rotamer), 6.95 (s, 1H, rotamer), 6.56-6.30 (m, 2H), 5.79 (m, 1H), 5.73 (dd, J = 9.5, 3.0 Hz, 1H, rotamer), 5.50 (dd, J = 13.0, 1.4 Hz, 2H, NO₂, 1H, rotamer), 5.43 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 5.00 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 4.75 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 4.70 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 4.65 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 4.55 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 4.35 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 4.25 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 4.15 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 4.05 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.95 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.85 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.75 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.65 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.55 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.45 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.35 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.25 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.15 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 3.05 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.95 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.85 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.75 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.65 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.55 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.45 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.35 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.25 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.15 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 2.05 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.95 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.85 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.75 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.65 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.55 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.45 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.35 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.25 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.15 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 1.05 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.95 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.85 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.75 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.65 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.55 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.45 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.35 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.25 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.15 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer), 0.05 (dd, J = 13.0, 10.3 Hz, 2H, NO₂, 1H, rotamer).
5.59 (dd, J = 10.0, 2.3 Hz, 1H, rotamer), 5.23-5.08 (m, 2H), 4.08 (d, J = 5.9 Hz, 1H), 3.89 (m, 1H), 3.73 (t, J = 7.5 Hz, 1H), 3.64 (t, J = 7.1 Hz, 1H), 3.06 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 166.6/166.3 (rotamers), 136.3/136.2 (rotamers), 133.2/133.0 (rotamers), 128.0, 127.9/127.3 (rotamers) 127.2/126.9 (rotamers), 122.4/122.1 (rotamers), 121.9/121.7 (rotamers), 119.3/119.1 (rotamers), 118.6/118.0 (rotamers), 117.2/116.7 (rotamers), 112.7/111.5 (rotamers), 111.5/111.2 (rotamers), 50.8/48.8 (rotamers), 47.9/47.7 (rotamers), 25.2/23.6 (rotamers); LC-MS (ESI+) m/z: 255.3 (M+H)+, 277.3 (M+Na)+; HRMS Calcd for C_{16}H_{18}N_{2}O 255.1492 [M+H]+, found 255.1499.

(S)-Methyl 2-(N-allylacrylamido)-3-(1H-indol-3-yl)propanoate (208).

From (S)- Methyl 2-(allylamino)-3-(1H-indol-3-yl)propanoate (1.00 g, 3.87 mmol) and applying the above described procedure C, (S)-methyl 2-(N-allylacrylamido)-3-(1H-indol-3-yl)propanoate was obtained as a clear oil after purification by flash chromatography using an eluent gradient of 20 to 50 % EtOAc in heptane. Yield 1.01 g (83%). [α]$_D^{20}$ -229.4 (c 0.51, EtOH); IR (film) ν 3387, 3307, 1738, 1644, 1609, 1457, 1434; 1H NMR (300 MHz, D$_6$-acetone) δ 10.10 (br s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 7.0 Hz, 1H), 7.16-6.95 (m, 3H), 6.53 (dd, J = 16.7, 10.3 Hz, 1H), 6.27 (dd, J = 16.7, 2.5 Hz, 1H) 5.68-5.55 (m, 2H), 5.12 (m, 1H), 4.99 (m, 1H), 4.79 (dd, J = 9.0, 6.1 Hz, 1H) 3.97 (m, 1H), 3.53 (m, 2H), 3.52 (s, 3H), 3.45 (m, 2H); 13C NMR (75 MHz, D$_6$-acetone) δ; 172.8, 167.7, 138.5, 136.3, 130.4, 129.5, 129.1, 125.2, 123.1, 120.5, 120.1, 117.9, 113.2, 112.9, 61.6, 53.1, 52.0, 26.6; LC-MS (ESI+) m/z: 313.3 (M+H)+, 335.3 (M+Na)+; HRMS Calcd for C_{16}H_{20}N_{2}O_{3} 313.1547 [M+H]+, found 313.1548.
(S)-Methyl 2-(N-allylacrylamido)-3-(benzo[b]thiophen-3-yl)propanoate (209).

From (S)-methyl 2-(allylamino)-3-(benzo[b]thiophen-3-yl)propanoate (660 mg, 2.24 mmol) and applying the above described procedure C, (S)-methyl 2-(N-allylacrylamido)-3-(benzo[b]thiophen-3-yl)propanoate was obtained as a light yellow oil after purification by flash chromatography using an eluent gradient of 100% heptane to 20% Et₂O in heptane. Yield 710 mg (96%). \([\alpha]^{20}_D -197\ (c\ 1.0,\ EtOH);\ IR (film) \nu\ 2949,\ 1736,\ 1648,\ 1613,\ 1459;\ ^1H\ NMR (300 MHz, CDCl₃) \delta\ 7.85 (m, 1H),\ 7.76 (m, 1H),\ 7.36 (m, 2H),\ 7.18 (s, 1H),\ 6.41 (s, 1H),\ 6.39 (d, \(J = 2.1\) Hz, 1H),\ 5.70 (dd, \(J = 7.3,\ 5.1\) Hz, 1H),\ 5.46 (m, 1H),\ 5.97 (m, 1H),\ 4.60 (dd, \(J = 8.5,\ 6.7\) Hz, 2H),\ 3.83 (m, 1H),\ 3.73 (m, 3H),\ 3.57 (m, 2H),\ 3.39 (m, 1H); \(^{13}C\ NMR (75 MHz, CDCl₃) \delta\ 170.7,\ 166.7,\ 140.2,\ 138.6,\ 132.8,\ 132.1,\ 129.0,\ 127.6,\ 124.3,\ 124.1,\ 123.6,\ 122.9,\ 121.4,\ 117.5,\ 59.1,\ 52.3,\ 50.7,\ 27.8;\ LC-MS (ESI⁺) \(m/z\): 330.3(M+H)⁺; HRMS Calcd for C₁₈H₁₉NO₅S 330.1158 [M+H⁺], found 330.1171.

(S)-Methyl 2-(N-allylacrylamido)-3-(3,4-dimethoxyphenyl)propanoate (210).

From (S)-methyl 2-(allylamino)-3-(3,4-dimethoxyphenyl)propanoate (430.0 mg, 1.54 mmol) and applying the above described procedure C, the title product was obtained as a white solid after purification by flash chromatography using an eluent gradient of 100% heptane to 50% Et₂O in heptane. Yield 441 mg (86%). Mp = 94-95 °C; \([\alpha]^{20}_D -237\ (c\ 1.0,\ EtOH);\ IR (film) \nu\ 2951,\ 1738,\ 1650,\ 1613,\ 1516;\ ^1H NMR (300 MHz, CDCl₃) \delta\ 6.78-6.69 (m, 3H),\ 6.38 (m, 2H),\ 5.67 (dd, \(J = 8.4,\ 4.0\) Hz, 1H),\ 5.56 (m, 1H),\ 5.12 (m, 2H), 4.53 (dd, \(J = 9.5,\ 6.0\) Hz, 1H), 3.87 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 3.44 (m, 1H), 3.24 (m, 1H); \(^{13}C\ NMR (75 MHz, CDCl₃) \delta\ 170.9,\ 166.6,\ 148.7,\ 147.6,\ 133.3,\ 130.1,\ 128.8,\ 127.6,\ 121.1,\ 117.4,\ 112.2,\ 111.0,\ 60.8,\ 55.7 (2C),\ 52.2,\ 50.8,\ 34.4;\ HRMS Calcd for C₁₈H₂₃NO₅ 334.1649 [M+H⁺], found 334.1656.
(S)-Methyl 2-(N-allylacrylamido)-3-(furan-2-yl)propanoate (211).

From (S)-methyl 2-(allylamino)-3-(furan-2-yl)propanoate (225.0 mg, 1.08 mmol) and applying the above described **procedure C**, the title product was obtained as a clear oil after purification by flash chromatography using an eluent gradient of 100% heptane to 30% Et<sub>2</sub>O in heptane. Yield 175 mg (61%). [α]<sup>20</sup>D -194 (c 1.1, EtOH); IR (film) ν 1738, 1650/1614 (rotamers); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.31 (dd, J = 2.1, 1.0 Hz, 1H), 6.38 (m, 1H), 6.36 (m, 1H), 6.26 (dd, J = 3.1, 2.0 Hz, 1H), 6.06 (dd, J = 3.1, <1.0 Hz, 1H), 5.68 (dd, J = 9.5, 6.5 Hz, 1H), 5.60 (m, 1H), 5.20 (m, 1H), 5.14 (m, 1H), 4.50 (t, J = 7.5 Hz, 1H), 3.94 (m, 1H), 3.72 (s, 3H), 3.52 (m, 1H), 3.36 (d, J = 7.5 Hz, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.5, 166.6, 151.7, 141.4, 133.1, 128.9, 127.5, 117.6, 110.5, 107.5, 59.0, 52.3, 51.1, 27.6; HRMS Calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> 263.1158, found 264.1236 [M+H<sup>+</sup>].

(S)-Methyl 2-(N-allylacrylamido)-3-(thiophen-3-yl)propanoate (212).

From (S)-methyl 2-(allylamino)-3-(thiophen-3-yl)propanoate (364 mg, 1.62 mmol) and applying the above described **procedure C**, (S)-methyl 2-(N-allylacrylamido)-3-(thiophen-3-yl)propanoate was obtained after purification by flash chromatography using n-Hexane/EtOAc (4:1, v/v). Yield 371 mg (82%). [α]<sup>20</sup>D -159 (c 0.560, EtOH); IR (film) ν 1736, 1648, 1613; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.24 (dd, J = 4.9, 2.9 Hz, 1H), 7.00 (bs, 1H), 6.92 (dd, J = 4.9, 1.1 Hz, 1H), 6.39 (m, 2H), 5.69 (dd, J = 8.9, 3.5 Hz, 1H), 5.58 (m, 1H), 5.12 (m, 2H), 4.68 (dd, J = 9.5, 5.9 Hz, 1H), 3.94 (d, J = 19.3 Hz, 1H), 3.70 (s, 3H) ppm 3.55 (dd, J = 17.7, 5.3Hz, 1H), 3.32 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.8, 166.7, 137.8, 133.3, 128.9, 128.3, 127.6, 125.6, 122.2, 117.4, 59.7, 52.2, 50.4, 29.4; HRMS Calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub>S 280.1002 [M+H<sup>+</sup>], found 280.0997.
**N-Allyl-N-(3,4,5-trimethoxyphenethyl)acrylamide (213).**

From **N-(3,4,5-trimethoxyphenethyl)prop-2-en-1-amine** (147 mg, 0.58 mmol) and applying the above described **procedure C**, **N-allyl-N-(3,4,5-trimethoxyphenethyl)acrylamide** was obtained as a clear oil after purification by flash chromatography using *n*-Hexane/EtOAc (2:1, v/v). Yield 131 mg (74%). IR (film) ν 2938, 2838, 1647, 1610, 1454, 1123 \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 6.50-6.29 (m, 4H), 5.70 (m, 2H), 5.13 (m, 2H), 4.01 (m, 1H), 3.83 (m, 2H), 3.81 (s, 6H), 3.78 (s, 3H), 3.55 (m, 2H), 2.79 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ 166.4/165.9 (rotamers), 153.3/153.1 (rotamers), 136.8/136.2 (rotamers), 134.8/133.7 (rotamers), 133.2/132.9 (rotamers), 128.0, 127.6/127.1 (rotamers), 117.2/116.6 (rotamers), 105.6/105.5 (rotamers), 60.8/60.7 (rotamers), 56.0/55.9 (rotamers), 50.8/48.7 (rotamers), 48.9/48.6 (rotamers), 35.9/34.4 (rotamers); HRMS Calcd for C\(_{17}\)H\(_{23}\)NO\(_4\) 306.1700 [M+H\(^+\)], found 306.1714.

**Rac-N-Allyl-N-(3-hydroxy-1-phenylpropyl)acrylamide (214).**

**General procedure D:** Under a N\(_2\) atmosphere 3-(allylamino)-3-phenylpropan-1-ol (303 mg, 1.58 mmol) was dissolved in CH\(_2\)Cl\(_2\) (20 mL) and cooled to 0 °C in an ice bath. With stirring Et\(_3\)N (2.2 equiv., 354 mg, 3.48 mmol) and acryloyl chloride (2.0 equiv., 331 mg, 3.16 mmol) was added drop wise. The reaction flask was removed from the icebath, and the final solution was stirred overnight at rt. and then diluted with CH\(_2\)Cl\(_2\) (100 mL). The organic phase was subsequently washed with water (50 mL) and brine (50 mL), dried over Na\(_2\)SO\(_4\) and conc. in vacuo. The crude oil was dissolved in THF (20 mL)/water (3 mL) and treated with LiOH•H\(_2\)O (60 mg, 1.58 mmol). The final solution was stirred overnight at rt. and then diluted with brine (50 mL) and CH\(_2\)Cl\(_2\) (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was dried over Na\(_2\)SO\(_4\), and conc. in vacuo to afford yellow oil. The crude oil was purified by flash chromatography (eluent 30% EtOAc in heptane) to give 97 mg (25%) of **N-allyl-N-(3-hydroxy-1-phenylpropyl)acrylamide**. IR
(film) ν 3410, 2945, 1639/1602 (rotamers), 1424; ^1^H NMR (300 MHz, CDCl$_3$) δ 7.37-7.25 (m, 5H), 6.51 (m, 2H), 6.10 (dd, $J = 12.0$, 3.5 Hz, 1H), 5.76 (dd, $J = 8.4$, 3.9 Hz, 1H), 5.35 (m, 1H), 4.95 (m, 2H), 4.90-3.49 (m, 5H), 2.25-1.80 (m, 2H); ^1^C NMR (75 MHz, CDCl$_3$) δ 168.2, 138.7, 134.2, 129.6, 128.6, 127.9, 127.7, 117.2, 77.4, 77.0, 76.6, 58.3, 53.0, 46.0, 32.6; HRMS Calcd for C$_{15}$H$_{19}$NO$_2$ 246.1489 [M+H$^+$], found 246.1483.

(S)-N- Allyl-N-(1-hydroxy-3-methylbutan-2-yl)acrylamide (215).

From (S)-2-(allylamino)-3-methylbutan-1-ol (355.0 mg, 2.47 mmol) and applying the above described procedure D, (S)-N-allyl-N-(1-hydroxy-3-methylbutan-2-yl)acrylamide was obtained as a clear oil after purification by flash chromatography using an eluent gradient of 50% to 100% EtOAc in heptane. Yield 129 mg (26%). [α]$_{20}^D$ -24 (c 1.0, EtOH); IR (film) ν 3392, 2963, 1639, 1602, 1430; ^1^H NMR (300 MHz, CDCl$_3$) δ 6.62 (dd, $J = 16.8$, 10.6 Hz, 1H, rotamer), 6.49 (dd, $J = 16.7$, 10.2 Hz, 1H, rotamer), 6.31 (dd, $J = 16.7$, 2.1 Hz, 1H, rotamer), 6.21 (dd, $J = 16.8$, 2.0 Hz, 1H, rotamer), 6.04 (m, 1H, rotamer), 6.84 (m, 1H, rotamer), 5.67 (dd, $J = 10.2$, 2.1 Hz, 1H, rotamer), 5.60 (dd, $J = 10.6$, 2.0 Hz, 1H, rotamer), 5.20 (m, 2H, overlap of rotamers), 4.25-3.45 (m, 5H), 3.25 (br s, 1H, OH), 2.25 (m, 1H, rotamer), 1.80 (m, 1H, rotamer), 0.9 (m, 6H, overlap of rotamers); ^1^C NMR (75 MHz, CDCl$_3$) δ 168.5/168.3 (rotamers), 134.8/134.0 (rotamers), 129.0/127.0 (rotamers), 128.4, 117.5/116.8 (rotamers), 66.8/66.3 (rotamers), 62.8/61.0 (rotamers), 50.7/45.5 (rotamers), 28.0/26.2 (rotamers), 20.2/20.0 (rotamers); LC-MS (ESI$^+$ m/z): 198.3 (M+H$^+$), 220.3 (M+Na$^+$); HRMS Calcd for C$_{11}$H$_{19}$NO$_2$ 198.1489 [M+H$^+$], found 198.1493.
(S)-N-Allyl-N-(2-(tert-butyldimethylsilyloxy)-1-phenylethyl)acrylamide.

(S)-N-(2-(tert-butyldimethylsilyloxy)-1-phenylethyl)prop-2-en-1-amine (637 mg, 2.19 mmol) was dissolved in CH₂Cl₂ (21 ml) and Et₃N (443 mg, 618 µl, 4.38 mmol) was added. Then acryloyl chloride (207 mg, 185 µl, 2.29 mmol) was added drop wise at 0 °C. The reaction was allowed to warm up to room temperature and then stirred for additional 23 h. The volatiles were removed in vacuo and the following purification by flash chromatography n-Hexane/EtOAc (2:1, v/v) afforded 647 mg (86%) of the title product as colorless oil. IR (film) ν 2953, 2928, 2856, 1650, 1613, 1460, 1416; ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.18 (m, 5H), 6.76-6.25 (m, 2H), 5.72-5.53 (m, 3H), 5.13-4.89 (m, 2H), 4.10-3.82 (m, 4H), 0.81 (s, 9H), 0.00 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.1, 138.2, 135.0, 128.6, 128.5, 128.2, 128.1, 127.4, 116. 62.4, 58.7, 47.7, 25.7, 18.1, -5.5; HRMS Calcd for C₂₀H₃₁NO₂Si 346.2197 [M+H⁺], found 346.2202.

(S)-N-Allyl-N-(2-hydroxy-1-phenylethyl)acrylamide (216).

(S)-N-Allyl-N-(2-(tert-butyldimethylsilyloxy)-1-phenylethyl)acrylamide (600 mg, 1.76 mmol) was dissolved in anhydrous THF (7 ml), and TBAF (3.48 ml, 1M in THF) was added drop wise at 0 °C. After complete addition the reaction mixture was warmed to room temperature and stirred for additional 30 min. Evaporation of the solvent and purification by flash chromatography n-Hexane/EtOAc (1:1, v/v) afforded 322 mg (81%) the title product as clear oil. IR (film) ν 3381, 3085, 3063, 2929, 1639, 1601, 1451, 1417, 1322, 1226: ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.20 (m, 5H), 6.54-6.37 (m, 2H), 5.72-5.57 (m, 3H), 5.13-5.07 (m, 2H), 4.09 (m, 2H), 3.80 (m, 2H), 3.40 (bs, 1H, OH); ¹³C NMR (75 MHz, CDCl₃) δ 168.3, 137.0, 134.1, 128.9, 128.6, 128.3, 128.1, 127.8, 116.8, 62.6, 60.4, 47.7; HRMS Calcd for C₁₄H₁₇NO₂ 232.1332 [M+H⁺], found 232.1341.
N-Allyl-N-(2-(1-methyl-1H-indol-3-yl)ethyl)acrylamide (231).

Under a nitrogen atmosphere N-(2-(1H-indol-3-yl)ethyl)-N-allylacrylamide (306 mg, 1.20 mmol) was dissolved in dry DMF (10 mL) and then cooled to 0 °C in an ice bath. With stirring, the solution was treated with NaH (in mineral oil 69 mg, 1.56 mmol). After 15 min. stirring at 0 °C the suspension was treated drop wise with methyl iodide (255 mg, 1.80 mmol). The final solution was slowly warmed to r.t., overnight and then quenched with water (5 mL). The product was extracted with EtOAc (3 x 30 mL), dried over Na₂SO₄ and conc. in vacuo. The crude oil was purified by flash chromatography (eluent gradient of 100% CH₂Cl₂ to 100% Et₂O) to give 170 g (53%) of the title product as clear oil. IR (film) υ 3055, 2931, 1648/1611 (rotamers), 1470, 1425; ¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, J = 7.9 Hz, 1H, rotamer), 7.55 (d, J = 7.8 Hz, 1H, rotamer), 7.33-7.06 (m, 3H), 6.91 (s, 1H, rotamer), 6.85 (s, 1H, rotamer), 6.55-6.29 (m, 2H), 5.79 (m, 1H), 5.70 (dd, J = 9.5, 2.7 Hz, 1H, rotamer), 5.60 (dd, J = 10.1, 2.3 Hz, 1H, rotamer), 5.15 (m, 2H), 4.08 (d, J = 5.9 Hz, 1H), 3.90 (m, 1H), 3.75 (s, 3H), 3.66 (m, 2H), 3.04 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 166.5/166.1 (rotamers), 136.9, 133.4/133.1 (rotamers), 127.9, 127.8/127.4 (rotamers) 126.9/126.7 (rotamers), 121.8, 121.5, 118.9, 118.8/118.3 (rotamers), 117.2/116.6 (rotamers), 111.7/110.5 (rotamers), 109.4/109.1 (rotamers), 50.8/48.8 (rotamers), 48.0/47.9 (rotamers), 32.6, 25.2/23.6 (rotamers); HRMS Calcd for C₁₇H₂₀N₂O 269.1648 [M+H⁺], found 269.1663.

N-Allyl-N-(naphthalen-2-ylmethyl)acrylamide (242).

From N-(Naphthalen-2-ylmethyl)prop-2-en-1-amine (400 mg, 2.03 mmol) and applying the above described procedure C, the title product was obtained as a colorless oil after purification by flash chromatography using n-Hexane/EtOAc (9:1, v/v) as eluent. Yield 422 mg (83%). IR (film) υ 1647/1611 (rotamers), 1461, 1427, 1416, 1368, 1328; ¹H NMR (300 MHz, CDCl₃) δ 7.61 (m, 7H + rotamer), 6.54 (m, 2H + rotamer), 5.78 (m, 2H + 116
rotamer), 5.18 (m, 2H + rotamer), 4.83 (s, 2H), 4.73 (s, 2H, rotamer), 4.14 (d, J = 6.0 Hz, 2H, rotamer), 3.92 (d, J = 4.7 Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\) \(\delta\) 166.8/166.7 (rotamers), 134.8/134.1 (rotamers), 133.3, 133.2, 132.7/132.6 (rotamers), 129.9/128.6 (rotamers), 128.7/128.4 (rotamers), 127.6, 127.5, 126.9, 126.5/126.3 (rotamers), 126.1/126.0 (rotamers), 125.8, 124.9/124.3 (rotamers), 117.8/116.9 (rotamers), 50.1/48.9 (rotamers), 48.8/48.4 (rotamers); HRMS Calcd for C\(_{17}\)H\(_{17}\)NO 252.1383 [M+H\(^+\)], found 252.1394.

**Rac-N-benzyl-N-(but-3-en-2-yl)acrylamide (217).**

![Ph](image.png) ![Me](image.png) 217

From N-benzylbut-3-en-2-amine (100 mg, 0.62 mmol) and applying the above described **procedure C**, the title product was obtained as colorless oil after purification by flash chromatography using \(n\)-hexane/EtOAc (4:1, v/v) as eluent. Yield 116 mg (87%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.32-7.19 (m, 5H + rotamer), 6.70-6.28 (m, 2H + rotamer), 5.90-5.58 (m, 2H + rotamer) 5.42-5.34 (m, 1H), 5.18-5.09 (m, 2H), 4.58-4.31 (m, 2H + rotamer), 1.26-1.16 (m, 3H + rotamer).

**5,6,11,11b-Tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (218b).**

![image.png] 218b

**General procedure E:** N-(2-(1H-indol-3-yl)ethyl)-N-allylacrylamide (111 mg, 0.44 mmol) was dissolved in anhydrous \(m\)-xylene (17 ml) and Grubbs-Hoveyda 1\(^{st}\) generation catalyst (15.9 mg, 6 mol%) was added under nitrogen atmosphere and the reaction was brought to reflux and left to react for 17 h or until full conversion occurred, as indicated by TLC. The contents were transferred to a silica column and eluted with EtOAc to yield 80.2 mg (82%) of the title product as a colorless solid. mp 241-244 °C IR (film) ν 3246, 1657, 1419, 1309; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 11.01 (s, 1H, NH), 7.37 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 4.88 (t, J = 7.4 Hz, 1H), 4.24 (dd, J = 12.9, 5.6 Hz, 1H), 2.95 (dt, J = 12.2, 4.9 Hz, 1H), 2.25 (m, 1H), 2.58 (m, 4H), \(\delta\) 1.76 (m, 1H), \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\)
118.2, 136.0, 134.5, 126.3, 120.9, 118.5, 117.8, 111.1, 105.8, 53.6, 36.8, 30.9, 25.4, 20.7; HRMS Calcd for C_{14}H_{14}N_{2}O 227.1179 [M+H]^+; found 227.1188.

In a dry round-bottom flask, under argon atmosphere, was added N-(2-(1H-indol-3-yl)ethyl)-N-allylacrylamide (20.0 mg, 0.08 mmol), m-xylene (20 ml), followed by addition of Grubbs II (6.6 mg, 10 mol%) and 69d (6.8 mg, 10 mol%) and the solution was heated to 110 °C for 1 h. The contents were transferred to a silica column and eluted with EtOAc to yield the product (11.4 mg, 61%, 60% ee) as a colorless solid. The enantiomeric excess was determined by Chiralcel OD-H (0.46 cm x 25 cm), mobile phase: hexane/IPA 87/13, flow: 1.23 ml/min, λ = 254 nm.

11-Methyl-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (232).

From N-allyl-N-[2-(1-methyl-1H-indol-3-yl)ethyl]acrylamide (120 mg, 0.45 mmol) and applying general procedure E by using 6 mol% Grubbs-Hoveyda 1st generation catalyst and 24 h of reaction time, the title product was obtained as a light brown solid after purification by flash chromatography on silica using EtOAc as eluent. Yield 93 mg (86%). Mp 151-153 °C; IR (film) ν 3046, 2967, 2904, 2850, 1681; ¹H NMR (300 MHz, DMSO-d$_6$) δ 7.39 (dd, J = 8.0, 4.3 Hz, 2H); 6.99 (t, J = 7.0 Hz, 1H), 7.11 (m, 1H), 4.98 (dd, J = 8.7, 7.1 Hz, 1H), 4.27 (dd, J = 12.8, 5.3 Hz, 1H), 3.65 (s, 3H), 2.86 (dt, J = 12.2, 4.4 Hz, 1H), 2.60 (m, 4H), 2.28 (ddd, J = 16.4, 9.4, 1.4 Hz, 1H), 1.75 (m, 1H); ¹³C NMR (75 MHz, DMSO-d$_6$) δ 171.9, 136.7, 135.5, 125.9, 121.0, 118.7, 117.9, 109.2, 106.1, 53.3, 36.8, 118
Mescalotam (233).

From N-allyl-N-[2-(3,4,5-trimethoxyphenyl)ethyl]acrylamide (50 mg, 0.16 mmol) and applying general procedure E by using 6 mol% Grubbs-Hoveyda 1st generation catalyst and 5 h of reaction time, the title product was obtained as a light brown oil after purification by flash chromatography on silica using n-hexane/EtOAc (1:4, v/v) as eluent. Yield 29 mg (64%). IR (film) ν 3457, 2936, 1672, 1408, 1119; 1H NMR (300 MHz, CDCl3) δ 6.29 (s, 1H), 4.65 (dd, J = 9.4, 6.6 Hz, 1H), 4.25 (d, J = 8.3 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.72 (s, 3H), 2.72 (m, 3H), 2.47 (m, 2H), 2.29 (ddd, J = 16.6, 9.4, 1.5 Hz, 1H), 1.59 (m, 1H); 13C NMR (75 MHz, CDCl3) δ 173.3, 152.4, 150.6, 140.3, 129.3, 123.1, 107.4, 60.7, 60.5, 55.9, 54.9, 36.7, 31.7, 29.2, 28.5; HRMS Calcd for C15H16N2O 241.1335 [M+H+], found 241.1339.


From (R)-methyl 2-(N-allylacrylamido)-3-(1H-indol-3-yl)propanoate (308 mg, 0.99 mmol) and applying general procedure E by using 6 mol% Grubbs-Hoveyda 1st generation catalyst and 22 h of reaction time, the title product was obtained as a clear oil and as a mixture of two diastereomers, with the ratio 9:91 cis/trans, after the normal purification by flash chromatography on silica using EtOAc as eluent. Yield 171 mg (61%). Analytical data matches the reported ones.xiv [α]20D +63.4 (c 0.205, EtOH) (lit.7 [α]20D +150 (c 1.50, CHCl3); 1H NMR (300 MHz, CDCl3) δ 9.38 (bs, 1H, NH), 7.45 (d, J = 7.2 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.12 (m, 1H), 7.06 (m, 1H), 5.31 (d, J = 6.7 Hz, 1H), 5.17 (dd, J = 8.9, 7.0 Hz, 1H), 3.61 (s, 3H, 3.40 (td, J = 15.8,

1.2 Hz, 1H), 3.09 (ddd, J = 5.8, 7.4, 2.2 Hz, 1H), 2.71-2.42 (m, 3H), 1.88 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 173.7, 171.0, 136.3, 132.7, 126.4, 121.8, 119.3, 119.1, 111.0, 104.6, 52.4, 52.2, 49.2, 31.4, 26.3, 23.5; HRMS Calcd for C\(_{16}\)H\(_{16}\)N\(_2\)O\(_3\) 285.1234 [M+H\(^+\)], found 285.1234.

**Methyl (5S,11bR)-3-oxo-1,2,3,5,6,11b-hexahydro[1]benzothieno[3,2-g]indolizine-5-carboxylate (235).**

From methyl N-acryloyl-N-allyl-3-(1-benzothiophen-3-yl)-L-alaninate (100 mg, 0.30 mmol) and applying **general procedure E** by using 6 mol% Grubbs-Hoveyda 1\(^{st}\) generation catalyst and 21 h of reaction time, the title product was obtained as a green solid after purification by flash chromatography on silica using n-hexane/EtOAc (1:1, v/v) as eluent. Yield 66 mg (73%). Mp 158-161 °C; \([\alpha]^{20}\)\(_D\) +138 (c 0.250, EtOH); IR (film) \(\nu\) 3060, 2999, 2942, 1733, 1692, 1402; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.80 (d, \(J = 7.2\) Hz, 1H), 7.63 (d, \(J = 8.3\) Hz, 1H), 7.36 (m, 2H), 5.37 (d, \(J = 7.2\) Hz, 1H), 5.20 (m, 1H), 3.68 (s, 3H), 3.51 (m, 1H), 3.11 (ddd, \(J = 16.5, 7.8, 2.6\) Hz, 1H), 2.75-2.47 (m, 3H), 1.97 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 173.7, 170.6, 138.5, 138.1, 136.3, 125.0, 124.6, 124.4, 122.6, 121.1, 53.6, 52.6, 48.2, 31.3, 27.9, 25.8; HRMS Calcd for C\(_{16}\)H\(_{15}\)NO\(_3\)S 302.084 [M+H\(^+\)], found 302.086.

**Rac-4-Phenyltetrahydro-2H-pyrrolo[2,1-b][1,3]oxazin-6(7H)-one (236).**

From N-allyl-N-(3-hydroxy-1-phenylpropyl)acrylamide (71 mg, 0.28 mmol) and applying **general procedure E** by using 6 mol% Grubbs-Hoveyda 1\(^{st}\) generation catalyst and 21 h of reaction time, the title product was obtained as a brown oil after purification by flash chromatography on silica using n-hexane/EtOAc (1:1, v/v) as eluent. Yield 33 mg (53%). IR (film) \(\nu\) 2962, 2931, 2859, 1688; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.32-7.16 (m, 5H), 5.44 (d, \(J = 5.9\) Hz, 1H), 4.97 (dd, \(J = 6.7, 2.4\) Hz, 1H), 3.89 (m, 1H), 3.69 (dt, \(J = 12.1, 2.6\) Hz, 1H), 2.47 (m, 2H), 2.22 (m, 2H), 2.08 (qd, \(J = 14.2, 2.2\) Hz, 1H), 1.88 (dddd, \(J = 14.0, 120
10.3, 5.1, 2.4 Hz, 1 H), $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.4, 138.2, 128.7, 127.1, 126.6, 84.9, 63.3, 48.9, 28.7, 27.7, 24.8 HRMS Calcd for C$_{13}$H$_{15}$NO$_2$ 218.1176 [M+H$^+$]. Found 218.1172.

(3S,7aR)-3-Isopropyltetrahydropyrrolo[2,1-b]oxazol-5(6H)-one (237).

From (S)-N-Allyl-N-(1-hydroxy-3-methylbutan-2-yl)acroloylamide (44 mg, 0.22 mmol) and applying general procedure E, by using 6 mol% Grubbs-Hoveyda 1$^{\text{st}}$ generation catalyst and 21 h of reaction time, the title product was obtained as colorless oil after purification by flash chromatography on silica using $n$-hexane/EtOAc (2:1, v/v). Yield 23 mg (62%). Analytical data matches the reported ones.$^{xvi}$ $[^{1}]$$\alpha$$_D^2$ +61.2 (c 1.06, EtOH) (lit.$^{xvi}$: $[^{1}]$$\alpha$$_D^2$ +70.0 (c 1.44, CHCl$_3$)); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.05 (dd, $J$ = 6.2, 2.3 Hz, 1H), 4.15 (dd, $J$ = 8.2, 6.9 Hz, 1H), 3.69 (td, $J$ = 8.0, 6.8 Hz, 1H), 3.61 (dd, $J$ = 8.3, 6.8 Hz, 1H), 2.64 (ddd, $J$ = 17.5, 10.5, 7.0 Hz, 1H), 2.49 (ddd, $J$ = 17.5, 10.4, 4.4 Hz, 1H), 2.35 (m, 1H), 2.03 (dddd, $J$ = 14.2, 7.0, 10.5, 2.3 Hz, 1H), 1.65 (tdd, $J$ = 13.4, 8.2, 6.7 Hz, 1H), 0.99 (d, $J$ = 6.7 Hz, 3H), 0.89 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 179.9, 92.1, 70.9, 61.1, 32.0, 31.4, 24.1, 19.7, 18.4;; LC-MS (ESI$^+$) m/z: 170.2 (M+H$^+$).

(3S,7aR)-3-phenyltetrahydropyrrolo[2,1-b]oxazol-5(6H)-one (238).

From (S)-N-allyl-N-(3-hydroxy-2-phenylpropyl)acrylamide (100 mg, 0.44 mmol) and applying general procedure E by using 6 mol% Grubbs-Hoveyda 1$^{\text{st}}$ generation catalyst and 18 h of reaction time, the title product was obtained as a colorless solid after purification by flash chromatography on silica using $n$-hexane/EtOAc (1:1, v/v) as eluent. Yield 64 mg (72%). Analytical data matches the reported ones.$^{xv}$ Mp 63-67 $^\circ$C; $[^{1}]$$\alpha$$_D^2$ +168 (c 0.665, EtOH) (lit.$^{xv}$: $[^{1}]$$\alpha$$_D^2$ +154 (c 1.29, EtOH)); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.39-7.26 (m, 5H), 5.21 (dd, $J$ = 6.2, 2.6 Hz, 1H), 5.03 (t, $J$ = 7.5 Hz, 1H), 4.49 (dd, $J$ = 8.7, 2.3 Hz, 1H).

---

7.8 Hz, 1H), 3.74 (dd, J = 8.7, 7.2 Hz, 1H), 2.67 (ddd, J = 17.8, 10.4, 7.5 Hz, 1H),
2.43 (m, 2H), 2.06 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 179.6, 139.6, 128.7, 127.5,
125.7, 92.8, 74.6, 57.9, 31.5, 24.4; LC-MS (ESI$^+$) m/z: 204.12 (M+H)$^+$. (5S,10bR)-methyl 8,9-dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline-5-carboxylate (239).

**General procedure F:** (2S)-Methyl 3-allyl-2-(3,4-dimethoxybenzyl)-4-oxohex-5-enoate (100 mg, 0.30 mmol) was dissolved in dry m-xylene (6 ml), and Grubbs-Hoveyda 1$^\text{st}$ generation catalyst (10.8 mg, 6 mol%) was added under nitrogen atmosphere and the reaction was heated to reflux until full conversion to ring-closed product, as indicated by TLC (1 h needed for full conversion in this case). The solution was then cooled to room temperature and TFA (34.2 mg, 0.30 mmol, 1 equiv) was added and the reaction was heated to 80 °C for 2 h or until full conversion to the title product, indicated by TLC. The content was transferred to a silica column and eluted with EtOAc to yield 89.8 mg (98%) of the titled compound as green oil. [$\alpha$]$^{20}_{D} +49$ (c 0.240, EtOH); IR (film) ν 2952, 2836, 1738, 1683, 1514, 1407, 1349, 1256, 1201, 1118, 1023; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.61 (s, 1H), 6.55 (s, 1H), 5.14 (dd, J = 6.8, 2.5 Hz, 1H), 4.96 (dd, J = 9.1, 6.7 Hz, 1H), 3.86 (s, 6H), 3.15 (m, 2H), 2.67 (m, 2H), 2.49 (m, 1H), 1.83 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.7, 170.9, 148.3, 147.9, 128.1, 122.5, 111.4, 107.4, 55.9, 55.8, 54.4, 52.5, 48.9, 31.5, 29.9, 28.1; HRMS Calcd for C$_{16}$H$_{19}$NO$_3$ 306.1336 [M+H$^+$], found 306.1338.

(5S,9aR)-methyl 7-oxo-4,5,7,8,9,9a-hexahydrofuro[2,3-g]indolizine-5-carboxylate (240).

From (S)-methyl 2-(N-allylacrylamido)-3-(furan-2-yl)propanoate (76.5 mg, 0.290 mmol) and applying general procedure F by using 6 mol% Grubbs-Hoveyda 1$^\text{st}$ generation catalyst and TFA (4 equiv), the title product was obtained an orange oil after purification by flash chromatography on silica using n-hexane/EtOAc (1:1, v/v) as eluent. Yield 40.0 mg (59%). [$\alpha$]$^{20}_{D}$ 122
(5S,9aR)-methyl 7-oxo-4,5,7,8,9,9a-hexahydrothieno[3,2-g]indolizine-5-carboxylate (241).

From (S)-methyl 2-((N-allylacrylamido)-3-(thiophen-3-yl)propanoate (100 mg, 0.36 mmol) and applying general procedure F by using 6 mol% Grubbs-Hoveyda 1st generation catalyst and TFA (3 equiv), the title product was obtained as a light green oil after purification by flash chromatography on silica using n-hexane/EtOAc (1:2, v/v) as eluent. Yield 76 mg (85%). $[\alpha]_{20}^{20} +64.3$ (c 0.370, EtOH); IR (film) ν 1737, 1685, 1433, 1404, 1180; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.17 (d, J = 5.0 Hz, 1H), 6.76 (d, J = 5.1 Hz, 1H), 5.22 (bd, J = 7.5 Hz, 1H), 5.08 (m, 1H), 3.67 (s, 3H), 3.29 (d, J = 15.7 Hz, 1H), 2.98 (dd, J = 6.7, 5.5 Hz, 1H), 2.70-2.43 (m, 3H), 1.87 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.5, 170.6, 135.1, 130.5, 126.8, 123.7, 53.6, 52.5, 48.5, 31.3, 28.3, 27.2; HRMS Calcd for C$_{12}$H$_{13}$NO$_3$S 252.0689 [M+H$^+$], found 252.0679.

1-methyl-2H-pyrrolizin-5(3H)-one (226).

$N$-allyl-$N$-(3-oxobutyl)acrylamide 225 (50 mg, 0.27 mmol) was dissolved in toluene (2.7 ml) and Grubbs II catalyst (46 mg, 20 mol%) was added. The reaction was heated to 50 °C for 20 min and pyrrolidine (44 µl, 0.54 mmol, 2 equiv) was added followed by addition of TFA (21 µl, 0.27 mmol, 1 equiv). The reaction was reacted at 50 °C for 1 h. The solution was cooled to room temperature and the content was transferred to a silica column and eluted with EtOAc to yield 30 mg (81%) of the title compound as brown oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.96 (d, m, J = 5.59 Hz, 1H), 6.30 (d, J = 5.59 Hz, 1H), 3.85-3.69 (m, 2H), 123
3.09-3.03 (m, 2H), 1.99 (t, J = 1.93 Hz, 3H), $^{13}$C NMR (75 MHz, CDCl$_3$) δ 165.5, 140.9, 131.2, 126.6, 124.7, 40.2, 39.5, 13.3; LC-MS (ESI+) m/z: 136.1 (M+H)$^+$. 

5,6,7,8-tetrahydro-3H-pyrrolo[1,2-a]azepin-3-one (229).

$\text{N-allyl-N-(5-oxopentyl)acrylamide 228}$ (50 mg, 0.25 mmol) was dissolved in toluene (2.5 ml) and Grubbs II catalyst (21 mg, 10 mol%) was added. The reaction was heated to 50 °C for 45 min and pyrrolidine (36 µl, 0.50 mmol, 2 equiv) was added followed by addition of TFA (19 µl, 0.25 mmol, 1 equiv). The reaction was reacted at 50 °C for 1 h. The solution was cooled to room temperature and the content was transferred to a silica column and eluted with EtOAc to yield 6 mg (16%) of the title compound as brown oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.85 (d, J = 5.62 Hz, 1H), 6.07 (dd, J = 5.62, 0.75 Hz, 1H), 5.42 (t, J = 5.21 Hz, 1H), 3.69-3.65 (m, 2H), 2.55-2.41 (m, 2H), 1.82-1.76 (m, 4H); LC-MS (ESI+) m/z: 150.2 (M+H)$^+$. 

5-(1H-Indol-3-yl)-1-(naphthalen-2-ylmethyl)pyrrolidin-2-one (244).

$\text{N-allyl-N-(naphthalen-2-ylmethyl)acrylamide}$ (50 mg, 0.20 mmol) was dissolved in dry $m$-xylene (2 ml), and Grubbs-Hoveyda 1$^{st}$ generation catalyst (7.2 mg, 6 mol%) was added under nitrogen atmosphere followed by indole (94 mg, 0.8 mmol, 4 equiv) and the reaction was brought to reflux and left to react for 17 h. The contents were transferred to a silica column and eluted with n-Hexane/EtOAc (1:1, v/v) to yield the title product in 39 mg (57%) as brown oil. If applying general procedure F and 6% of Grubbs-Hoveyda I catalyst, TFA (1 eq), and indole (1.1 equiv) the product was obtained in 84% isolated yield. IR (film) ν 3408, 3247, 3054, 2926, 1652, 1454, 1416, 1370, 1340; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.61 (bs, 1H, NH), 7.75 (m, 3H), 7.45 (m, 5H), 7.25 (m, 2H), 7.11 (dd, J = 8.0, 7.1, 1.0 Hz, 1H), 7.00 (d, J = 2.5 Hz, 1H), 5.24 (d, J = 14.6 Hz, 1H), 4.78 (dd, J = 7.9, 6.5 Hz, 1H), 3.74 (d, J = 14.6 Hz, 1H), 2.68 (m, 2H), 2.39 (m, 1H), 2.22 (dd, J = 13.0, 9.8, 7.7, 6.4 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.1, 136.9, 134.3, 133.1, 132.7, 128.3, 127.6, 127.5, 127.1, 126.3, 126.1, 124
125.8, 125.3, 122.9, 122.5, 119.9, 118.9, 144.8, 111.6, 54.8, 44.3, 30.8, 26.7; HRMS Calcd for C_{23}H_{20}N_2O 341.164 [M+H]^+, found 341.165.

1-Benzyl-5-phenethoxypyrrolidin-2-one (245).

From N-allyl-N-benzylacrylamide (20 mg, 0.1 mmol) and applying general procedure F by using 10 mol% Grubbs II generation catalyst, TFA (1 equiv), and phenethylethanol (1.1 equiv) the title product was obtained as an brown oil after purification by flash chromatography on silica using n-hexane/EtOAc (4/1) as eluent. Yield 23 mg (82%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.29-6.97 (m, 10 H), 4.77, (d, \(J = 14.7\) Hz, 1H), 4.63 (dd, \(J = 6.3, 1.6\) Hz, 1H), 3.73 (d, \(J = 14.7\) Hz, 1H), 3.54-3.34 (m, 2H), 2.75 (t, \(J = 6.7\) Hz, 2H), 2.48 (m, 1H), 2.27 (m, 1H), 2.02-1.77 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 174.7, 138.7, 136.4, 128.9, 128.5, 128.3, 127.4, 126.4, 88.2, 66.8, 43.6, 36.2, 28.9, 24.3; LC-MS (ESI+) m/z: 296.4 (M+H)^+.

1-Benzyl-5-(1H-indol-3-yl)-5-methylpyrrolidin-2-one (246).

From N-benzyl-N-(but-3-en-2-yl)acrylamide (20.1 mg, 0.09 mmol), and applying general procedure F by using 10 mol% Grubbs II generation catalyst, TFA (1 equiv), and indole (1.1 equiv) the title product was obtained as an brown oil after purification by flash chromatography on silica using n-hexane/EtOAc (1:1, v/v) as eluent. Yield 25.0 mg (88%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.49 (bs, 1H, NH), 7.37 (dd, \(J = 14.1, 8.1\) Hz, 2H), 7.17-6.99 (m, 7H), 6.93 (s, 1H), 4.87 (d, \(J = 15.2\) Hz, 1H), 3.59 (d, \(J = 15.2\) Hz, 1H), 2.73-2.39 (m, 3H), 2.14-1.88 (m, 1H), 1.39 (s, 3H).

5-(1H-indol-1-yl)-1-(naphthalen-2-ylmethyl)pyrrolidin-2-one (247).

\(N\)-allyl-N-(naphthalen-2-ylmethyl)acrylamide (20.0 mg, 0.08 mmol) was dissolved in dry \(m\)-xylene (0.8 ml), and Grubbs II catalyst (4.0 mg, 6 mol%) was added under nitrogen atmosphere followed by indole (10.3 mg, 0.09 mmol, 1.1 equiv) and 69d (12.0
mg, 20 mol%). Then, the reaction was brought to reflux and left to react for 2 h. The contents were transferred to a silica column and eluted with n-Hexane/EtOAc (1:2, v/v) to yield the titled product in 7 mg (26%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.82-7.69 (m, 2H), 7.63-7.57 (m, 2H), 7.43-7.39 (m, 2H), 7.28 (s, 1H), 7.20-7.16 (m, 1H), 7.12-7.07 (m, 2H), 7.00-6.95 (m, 2H), 6.55 (d, $J = 3.29$ Hz, 1H), 4.71 (dd, $J = 7.8, 4.1$ Hz, 1H), 3.38 (d, $J = 14.5$ Hz, 1H), 3.06 (t, $J = 7.1$ Hz, 2 H), 2.84-2.73 (m, 1H), 2.64-2.42 (m, 2H), 2.21-2.11 (m, 1H).

1-(2-(1H-Indol-3-yl)ethyl)-1H-pyrrol-2(5H)-one (218a).

$N$-(2-(1H-Indol-3-yl)ethyl)-$N$-allylacrylamide (100 mg, 0.39 mmol) was dissolved in anhydrous $m$-xylene (16 ml) and Grubbs-Hoveyda 1$^\text{st}$ generation catalyst (23.6 mg, 10 mol%) was added under nitrogen atmosphere and the reaction was heated to 60 °C for 4 h. The contents were transferred to a silica column and eluted with EtOAc to yield the title product (66 mg, 75%) as a brown oil. IR (film) $\nu$ 3266, 1654, 1454, 1338; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.66 (s, 1H), 7.36 (m, 1H), 7.59 (d, $J = 7.8$Hz, 1H), 7.10 (m, 1H), 7.18 (m, 1H), 6.99 (d, $J = 2.2$ Hz, 1H), 6.16 (td, $J = 6.0, 1.8$ Hz, 1 H), 6.94 (td, $J = 6.0, 1.7$ Hz, 1 H), 3.80 (m, 4H), 3.06 (t, $J = 7.1$ Hz, 2 H), $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.5, 142.8, 136.7, 127.9, 127.2, 122.1, 121.8, 119.1, 118.4, 112.3, 111.3, 53.3, 42.5, 24.5; HRMS Calcd for C$_{14}$H$_{14}$N$_2$O 227.1179 [M+H$^+$], found 227.1179.

1-(2-(1H-indol-3-yl)ethyl)-1,6-dihydropyridin-2(3H)-one (221).

$N$-(2-(1H-indol-3-yl)ethyl)-$N$-allylbut-3-enamide (50 mg, 0.18 mmol) was dissolved in anhydrous $m$-xylene (7.5 ml) and Grubbs-Hoveyda 1$^\text{st}$ generation catalyst (6.72 mg, 6 mol%) was added under nitrogen atmosphere and the reaction was heated to reflux for 18 h. The contents were transferred to a silica column and eluted with EtOAc to yield the title product (30.4 mg, 68%) as a brown oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.32 (bs, 1H, NH), 7.67 (d, $J = 8.0$ Hz, 1H), 7.37 (dd, $J = 7.92, 1.0$ Hz, 1H), 7.21-7.09 (m, 2H), 7.04 (d, $J = 2.31$ Hz, 1H).
Hz, 1H), 5.82-5.69 (m, 1H), 5.67-5.54 (m, 1H), 3.86-3.80 (m, 2H), 3.76-3.70 (m, 2H), 3.15-3.04 (m, 2H), 3.02-2.96 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 167.0, 136.2, 127.3, 122.5, 122.0, 121.9, 120.8, 119.2, 118.6, 112.9, 111.1, 49.5, 47.7, 32.2, 22.8; LC-MS (ESI+) m/z: 241.2 (M+H)+.

**N-benzyl-2-(1H-indol-3-yl)ethanamine.**

In a round-bottomed flask fitted with a magnetic stirring bar, tryptamine (2.50 g, 15.6 mmol) and benzaldehyde (1.66 g, 1.59 mL, 15.6 mmol) were dissolved in MeOH (63 mL). The reaction mixture was added molecular sieves (3Å) and stirred at rt. The reaction was monitored by TLC, and upon full conversion of benzaldehyde (24 h), solid NaBH₄ (590 mg, 15.6 mmol) was added. After further 16 h of stirring, the reaction mixture was filtered through a pad of celite, which was washed with MeOH (2 x 50 mL). The filtrate was evaporated in vacuo. The residue was taken up in sat. NaHCO₃ (50 mL), H₂O (50 mL) and EtOAc (100 mL) and transferred to a separatory funnel. The organic layer was separated and washed with H₂O (50 mL) and brine (50 mL). The organic layer was dried over Na₂SO₄ and evaporated in vacuo to give the title compound as a brown oil (3.89g, >95%). The compound was used in the next step without further purification; 1H NMR (300 MHz, DMSO-d₆) δ 10.79 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.37-7.25 (m, 5H), 7.24-7.16 (m, 1H), 7.12 (d, J = 2.3 Hz, 1H), 7.09-7.01 (m, 1H), 6.99-6.90 (m, 1H), 3.87 (s, 2H), 2.91-2.74 (m, 4H); 13C NMR (75 MHz, DMSO-d₆) δ 140.8, 136.2, 128.0, 127.9, 127.2, 126.4, 122.5, 120.8, 118.2, 118.0, 112.5, 111.3, 52.8, 49.5, 25.4; LC-MS (ESI+) m/z: 251.3 (M+H)+.

**N-(2-(1H-indol-3-yl)ethyl)-N-benzylprop-2-en-1-amine (252).**

In a round-bottomed flask fitted with a magnetic stirring bar, allyl bromide (1.55 g, 1.11 mL, 12.8 mmol) was added to a stirred suspension of N-benzyl-2-(1H-indol-3-yl)ethanamine (1.6 g, 6.4 mmol) and K₂CO₃ (2.85 g, 19.8 mmol) in DMF (20 mL). The reaction was stirred at
r.t., and was monitored by TLC. Upon full conversion of the starting material (30 min), the reaction mixture was evaporated in vacuo. The residue was taken up in CH$_2$Cl$_2$ (100 mL) and water (80 mL) and transferred to a separatory funnel. The organic layer was separated and the aqueous phase was further extracted with CH$_2$Cl$_2$ (1 x 100 mL). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (Et$_3$N:MeOH:CH$_2$Cl$_2$; 1:2:97), to give the titled compound as a brown/yellow oil (1.76 g, 94%); IR (film) ν 3417, 3058, 2972, 2801, 1454, 735; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.75 (s, 1H), 7.41-7.18 (m, 7H), 7.10-6.98 (m, 2H), 6.95-6.85 (m, 1H), 5.91 (ddt, $J$ = 16.4, 10.2, 6.3 Hz, 1H), 5.24 (dd, $J$ = 17.2, 2.0 Hz, 1H), 5.15 (dd, $J$ = 10.2, 2.1 Hz, 1H), 3.66 (s, 2H), 3.16 (d, $J$ = 6.3 Hz, 2H), 2.85 (dd, $J$ = 9.8, 5.8 Hz, 2H), 2.68 (dd, $J$ = 9.7, 5.7 Hz, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 139.5, 136.1, 136.0, 128.5, 128.0, 127.1, 126.7, 122.3, 120.7, 118.1, 118.0, 117.1, 112.4, 111.2, 57.3, 56.1, 53.6, 22.3; HRMS Calcd for C$_{20}$H$_{23}$N$_2$ 291.1861 [M+H$^+$], found 291.1855.

2-benzyl-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (253).

**General procedure G:** In a round-bottom flask fitted with a magnetic stirring bar and a reflux condenser, $N$-benzyltryptamine 254 (48 mg, 0.19 mmol) was dissolved in toluene (1.6 ml). Allylmethylcarbonate (18.6 mg, 18.2 µl, 0.16 mmol) was added, followed by Pd(PPh$_3$)$_4$ (28.0 mg, 15 mol%). The reaction was stirred at reflux and was followed by TLC. After 4 h, the reaction was cooled to room temperature and transferred to column chromatography for purification on silica gel (EtOAc:n-hexanes 1:3, v/v), to yield the title compound (in 40 mg, 85%); IR (film) ν 3408, 3082, 3027, 2929, 2841, 1449, 1227; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.66 (s, 1H), 7.38-7.26. (m, 7H), δ 7.02 (t, $J$ = 7.3 Hz, 1H), 6.94 (t, $J$ = 7.2 Hz, 1H), 3.79 (d, J = 13.5 Hz, 1H), 3.64 (d, J = 13.6 Hz, 1H), 3.54 (s, 1H), 3.19-2.98 (m, 1H), 2.85-2.67 (m, 2H), 2.52 (s, 1H), 1.91-1.71 (m, 2H), 0.88 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 139.8, 135.8, 135.6, 128.6, 128.1, 126.8, 126.7, 120.3, 118.1, 117.4, 110.8, 106.2, 57.7, 56.7, 44.9, 26.0, 18.0, 10.3; HRMS Calcd for C$_{20}$H$_{23}$N$_2$ 291.1861 [M+H$^+$], found 291.1854.
1-ethyl-2-(4-nitrobenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (260).

Following general procedure H, the reaction of N-(4-nitro)benzyltryptamine 255 (61.0 mg, 0.20 mmol), allylcarbonate (20 mg, 19.6 µl, 0.17 mmol), and Pd(PPh₃)₄ (59 mg, 30 mol%), gave after purification by flash column chromatography on silica gel (EtOAc:hexanes 1:6, v/v), the title compound (49 mg, 86%). IR (film) ν 3402, 2931, 1559, 1513, 1340; ¹H NMR (300 MHz, DMSO-d₆) δ 10.67 (s, 1H), 8.22 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.02 (t, J = 6.9 Hz, 1H), 6.94 (t, J = 7.1 Hz, 1H), 3.92 (d, J = 14.8 Hz, 1H, 3.80 (d, J = 14.7 Hz, 1H), 3.58-3.47 (m, 1H), 3.14-2.98 (m, 1H, 2.83-2.78 (m, 2H), 2.76-7.25 (m, 2H), 2.57-2.52 (m, 1H), 1.93-1.73 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, DMSO-d₆) δ 148.5, 146.4, 135.8, 135.3, 129.4, 126.7, 123.3, 120.3, 118.1, 117.4, 110.8, 106.1, 58.3, 56.0, 45.0, 26.0, 18.0, 10.3; HRMS Calcd for C₂₀H₂₂N₃O₂ 336.1712 [M+H⁺], found 336.1710.

2-(3,4-dimethoxybenzyl)-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (261).

Following general procedure H, the reaction of N-(3,4-dimethoxy)benzyltryptamine 256 (64.0 mg, 0.20 mmol), allylcarbonate (20 mg, 19.6 µl, 0.17 mmol), and Pd(PPh₃)₄ (59 mg, 30 mol%), gave after purification by flash column chromatography on silica gel (EtOAc:hexanes 1:1, v/v), the title compound (49 mg, 81%). IR (film) ν 3366, 2932, 2835, 1511, 1462, 1451, 1257, 1257, 1229, 1135, 1024; ¹H NMR (300 MHz, DMSO-d₆) δ 10.63 (s, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.05-6.79 (m, 5H), 3.73 (s, 6H), 3.70-3.46 (m, 3H), 3.16-3.07 (m, 1H), 2.89-2.67 (m, 2H), 2.58-2.42 (m, 1H), 1.79 (ddq, J = 28.4, 14.2, 7.2 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, DMSO-d₆) δ 148.5, 147.6, 135.8, 135.7, 132.1, 126.8, 120.5, 120.2, 118.0, 117.4, 112.1, 111.3, 110.7, 106.0, 57.1, 56.3, 55.4, 55.2, 44.9, 26.2, 18.0, 10.5; HRMS Calcd for C₂₂H₂₇N₂O₂ 351.2073 [M+H⁺], found 351.2067.
2-(cyclohexylmethyl)-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (260).

Following general procedure H, the reaction of N-cyclohexylmethyltryptamine 257 (53.0 mg, 0.20 mmol), allylcarbonate (20 mg, 19.6 µl, 0.17 mmol), and Pd(PPh₃)₄ (59 mg, 30 mol%), gave after purification by flash column chromatography on silica gel (EtOAc:hexanes 1:8, v/v), the title compound (34 mg , 67%). IR (film) ν 3407, 2918, 2846, 1464, 1446; ¹H NMR (300 MHz, CDCl₃) δ 7.53 (s, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.23-7.18 (m, 1H), 7.09-6.96 (m, 2H), 3.43-3.34 (m, 1H), 3.18-3.03 (m, 1H), 2.82-2.62 (m, 2H), 2.45 (dt, J = 10.5, 4.7 Hz, 1H), 2.28 (qd, J = 12.6, 7.0 Hz, 2H), 1.86-1.53 (m, 7H), 1.51-1.34 (m, 1H), 1.25-1.05 (m, 4H), 0.92 (t, J = 7.3 Hz, 3H), 0.88-0.72 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 136.2, 136.0, 127.7, 121.4, 119.4, 118.3, 110.9, 108.6, 60.7, 59.8, 45.9, 36.8, 32.3, 32.0, 27.5, 27.3, 26.7, 18.5, 11.0; HRMS Calcd for C₂₀H₂₉N₂ 297.2331 [M+H⁺], found 297.2326.

1-ethyl-2-heptyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (263).

Following general procedure H, the reaction of N-heptyltryptamine 258 (53.3 mg, 0.20 mmol), allylcarbonate (20 mg, 19.6 µl, 0.17 mmol), and Pd(PPh₃)₄ (59 mg, 30 mol%), gave after purification by flash column chromatography on silica gel (EtOAc:hexanes 1:2, v/v), the title compound (24.6 mg, 48%). IR (film) ν 3408, 2925, 2854, 1464, 1452; ¹H NMR (300 MHz, DMSO-d₆) δ 10.62 (s, J = 24.5 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 6.99 (dt, J = 8.1, 1.2 Hz, 1H), 6.92 (dt, J = 7.2, 0.9 Hz, 1H), 3.51 (dd, J = 7.0, 4.1 Hz, 1H), 3.08 (ddd, J = 14.0, 8.8, 4.9 Hz, 1H), 2.72 (ddd, J = 22.5, 8.5, 4.6 Hz, 2H), 2.60-2.40 (m, 2H), 1.94-1.59 (m, 2H), 1.53-1.45 (m, 2H), 1.39-1.22 (m, 8H), 0.96-0.73 (m, 6H); ¹³C NMR (75 MHz, DMSO-d₆) δ 136.7, 136.5, 127.4, 120.9, 118.7, 118.0, 111.5, 107.1, 58.9, 53.2, 45.9, 32.1, 29.4, 28.3, 27.5, 26.6, 22.8, 18.9, 14.7, 11.1; HRMS Calcd for C₂₀H₃₁N₂ 299.2487 [M+H⁺], found 299.2482.
2-benzyl-1-ethyl-7-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (264).

Following general procedure H, the reaction of N-benzyl-(6-methoxy)tryptamine 259 (56.0 mg, 0.20 mmol), allylcarbonate (20 mg, 19.6 µl, 0.17 mmol), and Pd(PPh₃)₄ (29.0 mg, 15 mol%), gave after purification by flash column chromatography on silica gel (EtOAc:hexanes 1:6, v/v), the title compound (36.5 mg, 67%). IR (film) ν 3368, 1687, 1458, 1200, 1158, 1048, 1003; ¹H NMR (300 MHz, CDCl₃) δ 7.44 (s, 1H), 7.37-7.10 (m, 6H), 6.75 (d, J = 2.2 Hz, 1H), 6.70 (dd, J = 8.5, 2.3 Hz, 1H), 3.75 (s, 3H), 3.70 (d, J = 2.7 Hz, 1H), 3.61 (d, J = 13.5 Hz, 1H), 3.44 (t, J = 6.3 Hz, 1H), 3.12 (ddd, J = 14.9, 9.5, 5.0 Hz, 1H), 2.76 (ddt, J = 7.5, 5.2, 4.4 Hz, 2H), 2.46 (dt, J = 8.5, 4.7 Hz, 1H), 1.78-1.65 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 156.3, 140.3, 136.8, 134.5, 129.2, 128.5, 127.2, 122.2, 118.8, 108.9, 108.2, 95.4, 58.4, 57.6, 56.2, 45.4, 27.5, 18.6, 11.0; LC-MS (ESI+) m/z: 321.5 (M+H)⁺.
References


(2) For excellent review of the impact of the sequencing of the human genome, see: Lander, E. S.; *Nature*, 2011, 470, 187-197.


(23) For review on estrogen receptors, see: (a) Dahlman-Wright, K.; Cavailles, S. A.; Fuqua S. A.; Jordan, C.; Katzenellenbogen, J. A.; Korach, K. S.; Maggi, A.;


(55) HFIP has been demonstrated in the literature to accelerate Petasis-3CRs, see: Nanda, K. K.; Trotter, W. B.; *Tetrahedron Lett.* **2005**, *46*, 2025-2028.


(70) Olefin metathesis as a result of metal-catalyzed redistribution of carbon-carbon double bonds was first described by Calderon and co-workers, see: (a) Calderon, N.; Chem, H. Y.; Scott, K. W. Tetrahedron Lett. 1967, 34, 3327-3329. (b) Calderon, N. Acc. Chem. Res. 1972, 5, 127


(72) For specific review on CM, see: Chatterjee, A. K.; Choi, L.-T.; Sanders, D. P.; Grubbs, R. H. J. Am. Chem. Soc. 2003, 125, 11360-11370.

(73) For specific review on ROMP and ADMET reactions, see: Buchmeiser, M. R. Chem. Rev. 2000, 100, 1565-1604


(76) For specific review on RRM reactions, see: Holub, N.; Blechert, S. Chem. Asian. J. 2007, 2, 1064-1082.


(97) Kam, T.-S.; Sim, K.-M. Phytochemistry 1998, 47, 145-147.

Org. Lett. 2008, 10, 1577-1580;  


(103) Kapadia, G. Chem. Commun. 1968, 1688-1689


(106) For review on allylic strain in six-membered rings, see: Johnson, F. Chem. Rev. 1968, 68, 375-413


Appendix – Publications

1. "A Build/Couple/Pair Strategy Combining The Petasis Reaction with Ru-Catalyzed Ring-Closing Metathesis and Isomerization" Erhad Ascic, Sebastian T. Le Quement, Mette Ishøey, Mathilde Daugaard, and Thomas, E. Nielsen. ACS. Comb. Sci. 2012, 14, 253-257. [Front cover included, prepared by PhD student Mette Ishøey]


Build/Couple/Pair Strategy Combining the Petasis 3-Component Reaction with Ru-Catalyzed Ring-Closing Metathesis and Isomerization

Erhad Ascic, Sebastian T. Le Quement, Mette Ishoey, Mathilde Daugaard, and Thomas E. Nielsen*

Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

Supporting Information

ABSTRACT: A “build/couple/pair” pathway for the systematic synthesis of structurally diverse small molecules is presented. The Petasis 3-component reaction was used to synthesize anti-amino alcohols displaying pairwise reactive combinations of alkene moieties. Upon treatment with a ruthenium alkylidene-catalyst, these dienes selectively underwent ring-closing metathesis reactions to form 5- and 7-membered heterocycles and cyclic aminals via a tandem isomerization/N-alkyliminium cyclization sequence.

KEYWORDS: Petasis 3-component reaction, ring-closing metathesis, isomerization, build/couple/pair

In the wake of recent years’ discoveries in human genomics, the hunt for small molecule probes with unique biological properties has been intensified in academic laboratories. Affordable screening technologies relying, at least in part, on commercial compound collections now enable life science researchers to rapidly and routinely identify small molecule leads for biological investigation. However, to advance biological probe discovery, it is becoming increasingly accepted that screening collections should include more novel, synthetically tractable molecules of sufficient structural diversity. In this context, innovative synthetic strategies have been proposed for the systematic generation of compound libraries. To more effectively facilitate hit-to-lead processes, such as those encountered during early stage probe development, synthetic concepts that prioritize molecular optimizability more stringently are needed. By emphasizing the access to all stereochemical variants of structurally complex small molecule scaffolds as an optimal coherent design principle and a prerequisite for the development of effective stereostructure activity relations, the recently proposed “build/couple/pair” (B/C/P) strategy has gained some attention. In the first phase (build phase), building blocks incorporating defined stereogenic units and tailored reactive functionalities are generated asymmetrically. The building blocks are then assembled (couple phase) through intermolecular bond-forming processes to yield a complete matrix of stereoisomers of the main carbon framework, prior to intramolecular joining of strategically positioned functional groups (pair phase).

We herein report our progress toward a B/C/P pathway that entails the combinatorial pairwise display of alkene moieties around an amino alcohol template (Figure 1). The combination of the Petasis 3-component reaction (Petasis 3-CR) (couple) and Ru alkylidene-catalyzed ring-closing metathesis (RCM) (pair) would then result in a collection of carbo- and heterocycles of different sizes and appendage modifications. This strategy also opens for the application of a recently discovered Ru alkylidene-catalyzed tandem RCM/isomerization/cyclization reaction to introduce an extra element of skeletal diversity in the pair phase (Figure 2).

All desired olefin-containing components (boronic acid, α-hydroxy aldehyde, and amine) were readily synthesized in few
Components for the Petasis 3-CR were then matched so that the resulting amino alcohols contained two olefin functionalities aligned to undergo Ru-catalyzed ring-closing metathesis and form small rings. The Petasis 3-CRs were mediated in a mixture of CH2Cl2 and hexafluoroisopropanol (HFIP) (Scheme 1; couple phase) as solvent,12 generally giving the diastereomerically pure anti-amino alcohol products in decent to good yields (>60%). These synthetic transformations were conveniently demonstrated with racemic α-hydroxy aldehydes masked as the corresponding lactols, but most enantiopure aldehyde components would be accessible from readily available α-hydroxy carboxylic acid derivatives.13a For example, the metal-catalyzed asymmetric allylation of glyoxylic acid derivatives could be an important step (build) in the generation of a stereochemically complete assembly of

![Scheme 1. Couple Phase: Petasis 3-Component Reactions of Olefin-Functionalized Building Blocks](image)

![Scheme 2. Pair Phase: Functional-Group Pairing of Alkene-Containing Amino Alcohols](image)

![Figure 2. Mechanism for the Formation of Oxazabicyclooctane 2a](image)

### Table 1. Catalyst and Reaction Conditions for the Selective Formation of Tetrahydroazepines (Selected Results)\textsuperscript{a,b,c}

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent (temp)</th>
<th>ratio \textit{1a}:\textit{3a}:\textit{2a} (1 h)\textsuperscript{d,e}</th>
<th>ratio \textit{1a}:\textit{3a}:\textit{2a} (24 h)\textsuperscript{d,e}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs I</td>
<td>CH\textsubscript{2}Cl\textsubscript{2} (rt)</td>
<td>NA\textsuperscript{d}</td>
<td>52:48:0</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs II</td>
<td>CH\textsubscript{2}Cl\textsubscript{2} (rt)</td>
<td>NA</td>
<td>1:98:1</td>
</tr>
<tr>
<td>3</td>
<td>Hoveyda–Grubbs II</td>
<td>CH\textsubscript{2}Cl\textsubscript{2} (rt)</td>
<td>NA</td>
<td>17:82:1</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs II</td>
<td>CH\textsubscript{2}Cl\textsubscript{2} (reflux)</td>
<td>6:73:20</td>
<td>5:68:27</td>
</tr>
<tr>
<td>5</td>
<td>Grubbs II</td>
<td>toluene (reflux)</td>
<td>3:10:87\textsuperscript{f}</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>Hoveyda–Grubbs I</td>
<td>toluene (reflux)</td>
<td>1:45:54\textsuperscript{g}</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>Hoveyda–Grubbs II</td>
<td>toluene (reflux)</td>
<td>1:3:96\textsuperscript{h}</td>
<td>NA</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Consult the Supporting Information for a full account on all catalyst optimization experiments. \textsuperscript{b}Determined by RP-HPLC (215 nm). \textsuperscript{c}Reaction mixtures were generally clean (>85% of \textit{1a}, \textit{3a}, and \textit{2a}). \textsuperscript{d}NA: Not available. \textsuperscript{e}Reactions run at 0.03 M concentration. \textsuperscript{f}Complex reaction mixture (<70% of \textit{1a}, \textit{3a}, and \textit{2a}).
alkylidene-catalysis (Scheme 2; 5-membered ring systems) with Grubbs II catalyst (Figure 2). Disappointingly, diallylamine was not transformed into the desired 5-membered pyrrolidine. Even the addition of catalytic amounts of Ti(IV)-arylboronic acids (Scheme 2) proved unsuccessful. 

Products resulting from the reaction of electron-deficient alkene-containing building blocks. Notably, the use of trans-phenylvinylboronic acid enabled the introduction of an alkene moiety via the boronic acid component (compounds 1k−l). Products resulting from the reaction of electron-deficient arylboronic acids (1b, 1g, and 1j) were not surprisingly obtained in lower yields.

Amino alcohols 1a−b and 1j−m were then subjected to Ru alkylidene-catalysis (Scheme 2; pair phase). The 5-membered ring systems 5 and 6, were smoothly obtained (71% and 85%, respectively) in the presence of Grubbs’ second generation catalyst (Grubbs II). Disappointingly, diallylamine 1m could not be transformed into the desired 5-membered pyrrolidine 7. Even the addition of catalytic amounts of Ti(i-PrO)₄, previously reported to enable the RCM reaction of diallylamines, proved unsuccessful. 

Substrate 1j was transformed into the 7-membered RCM product 4 with Grubbs II at slightly elevated temperature (50 °C), whereas tetrahydroazepines 3a−b could be efficiently obtained using the same catalyst at room temperature. An additional mode of skeletal diversification was demonstrated by subjecting RCM products 3b and 4 to Pd-catalyzed ring-contraction reactions, which afforded two new 5-membered rings (8 and 9, respectively) in acceptable yields and in a highly diastereoselective fashion (>10:1 and >8:1, respectively).

We have previously described the Ru alkylidene-mediated formation of 8-oxa-6-azabicyclo[3.2.1]octane (oxazabicyclooctane) 2a from substrate 1a at elevated temperature (Scheme 2). We speculated that the formation of 2a was the result of a metal-assisted double bond isomerization of the RCM product 3a to an iminium intermediate, subsequently trapped by the tethered 0-nucleophile (Figure 2). Although processes involving tandem RCM/isomerization have been reported, the concomitant isomerization to synthetically useful iminium ions has only been marginally explored.

To provide synthetically useful protocols for the selective formation of tetrahydroazepine and oxazabicyclooctane ring systems, an extensive optimization study was carried out (Table 1, selected results), the challenge being to identify reaction conditions that provide minimal or maximal postmetathesis olefin isomerization.

To this end, a range of ruthenium catalysts, temperatures, and reactant stoichiometries were thoroughly examined. When running the reactions at room temperature (entries 1−3), the Grubbs II catalyst was sufficiently efficient for the RCM reaction, while still keeping formation of the oxazabicyclooctane at satisfyingly low levels (entry 2). The results clearly revealed the superiority of the Hoveyda–Grubbs II catalyst (entry 7) and the necessity of elevated temperatures (entries 4−7) for the initiation of oxazabicyclooctane formation.

In general, the developed protocols proved highly efficient when applied to a range of diene-containing amino alcohols (1a−i), as evidenced by the formation of tetrahydroazepines and oxazabicyclooctanes in good to excellent yields (Table 2). Compared to our previous findings, the conversion of 1a into oxazabicyclooctane 2a was improved from 63% to 82% when using method B (Table 2, entry 1). In a few instances, substrates only reluctantly underwent RCM reaction, necessitating the use of higher reaction temperatures.

In a final stage toward more complex structures, an approach taking advantage of two consecutive Petasis 3-CRs of a parent amine was investigated. Allylamine was treated with lactol and reactant stoichiometries were thoroughly examined. When running the reactions at room temperature (entries 3), the Grubbs II catalyst was sufficiently efficient for the RCM reaction, while still keeping formation of the oxazabicyclooctane at satisfyingly low levels (entry 2). The results clearly revealed the superiority of the Hoveyda–Grubbs II catalyst (entry 7) and the necessity of elevated temperatures (entries 4−7) for the initiation of oxazabicyclooctane formation.

In general, the developed protocols proved highly efficient when applied to a range of diene-containing amino alcohols (1a−i), as evidenced by the formation of tetrahydroazepines and oxazabicyclooctanes in good to excellent yields (Table 2).

In a final stage toward more complex structures, an approach taking advantage of two consecutive Petasis 3-CRs of a parent amine was investigated. Allylamine was treated with lactol and reactant stoichiometries were thoroughly examined. When running the reactions at room temperature (entries 3), the Grubbs II catalyst was sufficiently efficient for the RCM reaction, while still keeping formation of the oxazabicyclooctane at satisfyingly low levels (entry 2). The results clearly revealed the superiority of the Hoveyda–Grubbs II catalyst (entry 7) and the necessity of elevated temperatures (entries 4−7) for the initiation of oxazabicyclooctane formation.

In general, the developed protocols proved highly efficient when applied to a range of diene-containing amino alcohols (1a−i), as evidenced by the formation of tetrahydroazepines and oxazabicyclooctanes in good to excellent yields (Table 2). Compared to our previous findings, the conversion of 1a into oxazabicyclooctane 2a was improved from 63% to 82% when using method B (Table 2, entry 1). In a few instances, substrates only reluctantly underwent RCM reaction, necessitating the use of higher reaction temperatures.

In a final stage toward more complex structures, an approach taking advantage of two consecutive Petasis 3-CRs of a parent amine was investigated. Allylamine was treated with lactol and reactant stoichiometries were thoroughly examined. When running the reactions at room temperature (entries 3), the Grubbs II catalyst was sufficiently efficient for the RCM reaction, while still keeping formation of the oxazabicyclooctane at satisfyingly low levels (entry 2). The results clearly revealed the superiority of the Hoveyda–Grubbs II catalyst (entry 7) and the necessity of elevated temperatures (entries 4−7) for the initiation of oxazabicyclooctane formation.

In general, the developed protocols proved highly efficient when applied to a range of diene-containing amino alcohols (1a−i), as evidenced by the formation of tetrahydroazepines and oxazabicyclooctanes in good to excellent yields (Table 2). Compared to our previous findings, the conversion of 1a into oxazabicyclooctane 2a was improved from 63% to 82% when using method B (Table 2, entry 1). In a few instances, substrates only reluctantly underwent RCM reaction, necessitating the use of higher reaction temperatures.

Table 2. Pair Phase: Selective Formation of Tetrahydroazepines and Oxazabicyclooctanes

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>tetrahydroazepine (method A), yield (%)</th>
<th>oxazabicyclooctane (method B), yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>3a, 80</td>
<td>2a, 82</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>3b, 71</td>
<td>2b, 41</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>3c, 76</td>
<td>2c, 37</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>3d, 77</td>
<td>2d, 58</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>3e, 90</td>
<td>2e, 68</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>3f, 74</td>
<td>2f, 78</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>3g, 71</td>
<td>2g, 85</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>3h, 79</td>
<td>2h, 64</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>3i, 67</td>
<td>2i, 66</td>
</tr>
</tbody>
</table>

*Isolated yield after flash column chromatography. See Supporting Information for detailed reaction conditions. Products 3i/2a were obtained as 1:1 diastereomeric mixtures of anti-amino alcohols/ethers.
In conclusion, important steps toward a B/C/P strategy relying on the strategic positioning of olefin moieties around an amino alcohol template, effectively combining the Petasis 3CR (couple) with Ru-catalyzed RCM and isomerization reactions (pair), have been taken. By mix-matching combinations of olefin-containing components, this modular strategy rapidly gains access to skeletal diversely molecules. To provide an element of skeletal diversification control, catalysts and reaction conditions for the selective formation of tetrahydrozepines and azacyclooctanes have been developed. In the future, we hope to bring syn-selective Petasis reactions into the scope of the present methodology and thereby provide a more complete B/C/P pathway.

**ASSOCIATED CONTENT**

3 Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

**AUTHOR INFORMATION**

*E-mail: ten@kemi.dtu.dk.*

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

This work was supported by the Technical University of Denmark, Danish Council for Strategic Research, Danish Council for Independent Research, Lundbeck Foundation, Carlsberg Foundation and Torkil Holm Foundation.

**REFERENCES**


(9) We note here that the present work does not aim to apply compound filters frequently used in medicinal chemistry efforts, such as Lipinski’s Rule of 5, but merely seeks to demonstrate proof-of-concept from a synthetic chemistry point-of-view. For large scale library production, it is understood that building blocks would be matched to ensure optimal molecular properties (solubility, lipophilicity, metabolic vulnerability, etc.) of the resulting screening entities.


(11) Consult the Supporting Information for a full account on the synthesis of building blocks.


Olefin metathesis is an extremely powerful and general method for carbon–carbon bond formation in organic synthesis.[1] For example, ruthenium alkylidene catalyzed metathesis has been widely used to construct a variety of alkenes for applications in chemistry, materials science, and chemical biology. A key asset of the metathesis process is the unique olefin functional group selectivity mediated by robust and well-defined catalytic systems.

Over the years, however, unexpected non-metathetic reactions have been observed under metathesis conditions.[2] Although these reactions typically are highly substrate dependent, associated with specific reaction conditions, and possibly caused by ill-defined metal-catalytic species, they represent a unique opportunity for the development of tandem processes.[3] It is well recognized that tandem reactions offer major advantages in the synthesis of valuable target compounds. In this context, metathesis mediated by ruthenium alkylidene catalysts 1e and 1k (Grubbs first- and second-generation catalysts; Figure 1) has successfully been coupled to nonmetathetic transformations, such as double-bond isomerization,[4–6] hydrogenation,[7–9] cyclopropanation,[10] dihydroxylation,[11,12] keto-hydroxylation,[12] and Kharasch addition reactions.[13]

Only a few reports have dealt with the tandem ring-closing metathesis (RCM)/double-bond isomerization. Notable works by the groups of Snapper[4] and Schmidt[5] have independently shown how cyclic allyl ethers can isomerize into 2,3-dihydropyrans. Schmidt and co-workers have also shown the beneficial effect of added hydride to favor the isomerization step. Inspired by the work of Fustero et al. (RCM/isomerization),[14] and Pérez-Castells and co-workers (RCM/isomerization/cyclopropanation),[15] we speculated that enamides generated in the event of a RCM/isomerization sequence could be further isomerized into reactive N-acyliminium intermediates (Scheme 1).[16] The presence of a suitably tethered nucleophile could then bring about a second cyclization step.

Initial investigations were focused on substrate 2 (see Table 1), which contains an indole moiety as a potentially reactive π nucleophile. The resulting product has a tetracyclic indolizinoindole core that is present in a range of pharmacologically interesting compounds, such as GPCR antagonists,[17] antibacterial,[18] and antiparasitic agents.[19] Access to enantiopure indolizinoindole derivatives has also been widely pursued in recent efforts in asymmetric catalysis.[20] We started out by screening ruthenium catalysts 1a–k (Figure 1), in toluene at reflux (Table 1). The reactions were generally very clean, as indicated by UPLC-MS and 1H NMR spec-
Table 1: Screening of catalysts for RCM/isomerization/N-acyliminium cyclization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>2/3a/3b [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>toluene</td>
<td>100:0:0</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>toluene</td>
<td>0:2.98</td>
</tr>
<tr>
<td>3</td>
<td>1b m-xylene</td>
<td>0:0:100</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1b m-xylene</td>
<td>0:0:100</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>toluene</td>
<td>26:74</td>
</tr>
<tr>
<td>6</td>
<td>1c m-xylene</td>
<td>0:0:100</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1d</td>
<td>toluene</td>
<td>83:3:14</td>
</tr>
<tr>
<td>8</td>
<td>1e</td>
<td>toluene</td>
<td>54:64:0</td>
</tr>
<tr>
<td>9</td>
<td>1f</td>
<td>toluene</td>
<td>36:0:64</td>
</tr>
<tr>
<td>10</td>
<td>1f m-xylene</td>
<td>38:0:62</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1f m-xylene</td>
<td>38:0:62</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1g</td>
<td>m-xylene</td>
<td>0:0:12:28</td>
</tr>
<tr>
<td>13</td>
<td>1g m-xylene</td>
<td>0:0:12:28</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1g</td>
<td>m-xylene</td>
<td>0:0:100</td>
</tr>
<tr>
<td>15</td>
<td>1g m-xylene</td>
<td>0:0:100</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1h</td>
<td>toluene</td>
<td>61:4:35</td>
</tr>
<tr>
<td>17</td>
<td>1i</td>
<td>toluene</td>
<td>25:38:37</td>
</tr>
<tr>
<td>18</td>
<td>1j</td>
<td>toluene</td>
<td>3:14:83</td>
</tr>
<tr>
<td>19</td>
<td>1j m-xylene</td>
<td>0:0:100</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1j m-xylene</td>
<td>0:0:100</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>1k</td>
<td>toluene</td>
<td>70:30</td>
</tr>
</tbody>
</table>

[a] With the exception of entry 17, product mixtures were generally clean (> 85% of 2/3a/3b in the reaction mixture as indicated by RP-HPLC analysis). [b] The reaction was carried out with 5 mol% of catalyst.

troscopy, and the proposed enamide intermediate was never detected.\(^{[21]}\) Notably, with 15 mol% of catalyst in m-xylene at reflux, several catalysts brought about clean conversion into the desired product 3b (entries 3, 6, 11, 14, and 19). When the amount of catalyst was lowered to 5 mol%, the Hoveyda–Grubbs catalyst 1b gave the cleanest and highest conversion (95%) of 2 into 3b (entry 4). When the catalyst loading was raised to 6 mol%, the reaction was complete in 17 hours (Scheme 2a), and gave 3b in 81% yield. When 2 was subjected to the same reaction conditions at lower temperature (60 °C), the metathesis product 3a could be isolated in 75% yield. After careful removal of trace amounts of ruthenium,\(^{[22]}\) the conversion of 3a into 3b was investigated under various reaction conditions. When 3a was treated with catalyst 1b, the desired product formed quantitatively in less than 5 hours. The same experiment without catalyst led to a 1:1 mixture of 3a and 3b, thus indicating a thermal background reaction, but also unambiguously demonstrating the beneficial effect of the catalyst in the nonmetathetic part of the tandem sequence. The synthesis of 3b represents a formal total synthesis of the antiparasitic natural product harmicine\(^{[19,20]}\). The homologous substrates 4 and 5 were not converted into the tetracycles 4b and 5b under the optimized conditions (although they still underwent RCM reactions) and TFA rapidly converted 3a into 3b (Scheme 2a); together these findings suggest to us that the nonmetathetic role of the ruthenium does not necessarily involve a ruthenium hydride intermediate, but somehow promotes favorable tautomerization events during the isomerization (Scheme 2b). In additional experiments, we also noted that the conversion of 2 into 3b can be catalyzed cleanly with 1b in the presence of 1–2% TFA or BF₃·Et₂O (added at the beginning of the reaction) in m-xylene heated at reflux, thus shortening the reaction times to less than 1 hour but giving slightly lower yields (70–75%; Scheme 2a).

The reaction using the N-methylated indole 6 gave an increased yield of 86% (Scheme 3). The introduction of a substituent, as present in the tryptophan (8) and benzothiophenylalanine (10) derivatives, effectively directed the formation of the new stereocenter with excellent trans diastereoselectivity at the ring junction. The trimethoxybenzene derivative 12 also underwent the tandem reaction sequence to give the tetrahydroisoquinoline derivative 13 in good yield (64%). The methodology was also extended to an intermolecular variant, wherein indole acted as the nucleophile in the reaction with the N-acyliminium intermediate that was derived from 14, in good yield (57%). Under these reaction conditions, however, the reaction required the addition of 4 equivalents of indole. If 14 was instead treated with 1b at reflux for 1 hour, followed by the addition of indole (1 equiv) and TFA (1 equiv) and additionally reacted for 1 hour, then 15 could be isolated in 84% yield. The nucleophilicity of the aromatic ring is highly important, as evident for substrates 16, 18, and 20 (Scheme 4), which were not converted into the corresponding tricycles under reaction conditions similar to those used in Scheme 3. Ring-closing metathesis occurred smoothly for these substrates but further conversion was better mediated by the subsequent addition of 1–4 equiva-
lents of TFA to the reaction mixture. In this way, tricyclic compounds 17, 19 and 21 were obtained in good to excellent yields.

Furthermore, the extension of the methodology to heteroatom nucleophiles was briefly examined by using substrates 22a–c, and, rewardingly, hemiaminals 23a–c were formed in good yield and with excellent diastereoselectivity (Scheme 5).

The tandem methodology presented herein, presumably involves the generation of an N-acyliminium species. Therefore, it was natural to also investigate whether N-alkyliminium ions could be formed during a similar tandem process. In a preliminary study on amino alcohol 24, treatment with 10 mol % of the Grubbs second-generation catalyst 1k resulted in a tandem metathesis/isomerization/cyclization sequence to give the bicyclic product 26 in good yield (Scheme 6). Notably, carefully purified cyclic alkene 25 does not convert into 26 under thermal conditions whereas the addition of 1k rapidly effects the isomerization steps.

In summary, an efficient ruthenium-catalyzed tandem ring-closing metathesis/isomerization/N-acyliminium cyclization sequence has been developed. In this tandem process, two new rings are formed in a single synthetic operation, which proceeds through a metathesis reaction and attack of tethered carbon and heteroatom nucleophiles on iminium intermediates. The resulting bi-, tri-, and tetracyclic ring systems are generally formed in good to excellent yields with excellent diastereoselectivities. We believe that our findings point in a promising direction for future metathesis research.

Received: January 18, 2011
Published online: April 21, 2011

Keywords: cyclization · isomerization · metathesis · ruthenium · tandem reactions


Synthesis of tetrahydro-β-carbolines via isomerization of N-allyltryptamines: a metal-catalyzed variation on the Pictet–Spengler theme†

Erhad Ascic,‡ Casper L. Hansen,‡ Sebastian T. Le Quement and Thomas E. Nielsen*

Received 8th December 2011, Accepted 7th February 2012
DOI: 10.1039/c2cc17704h

An efficient and broadly applicable alternative to the classical Pictet–Spengler synthesis of tetrahydro-β-carbolines is presented. The method relies on metal-catalyzed isomerization of allylic amines to form reactive iminium intermediates which can be trapped by a tethered indole nucleophile.

The tricyclic 1,2,3,4-tetrahydro-β-carboline (THBC) ring system is a key structural element in a range of biologically and pharmacologically important alkaloids isolated from a variety of natural sources (Fig. 1).1 THBCs are traditionally synthesized via the Pictet–Spengler reaction, where tryptamines are condensed with aldehydes under acidic reaction conditions.2 We herein wish to report an alternative route to THBCs, which relies on metal-catalyzed isomerization of N-allyltryptamines (Fig. 2).

Metal-catalyzed double-bond isomerization of allylic amines to enamines has found widespread applications in organic synthesis.3–6 Surprisingly, the concurrent isomerization into synthetically useful iminium intermediates remains virtually unexplored. Along these lines, Sorimachi and Terada have reported a dual ruthenium hydride/Brønsted acid-catalyzed tandem process, where allylamines are isomerized to iminium intermediates that undergo Friedel–Crafts type reactions with electron-rich aromatics.7a Similarly, we have recently demonstrated how cyclic allylic amines isomerize under the influence of Ru alkylidene catalysts to generate cyclic N-acyliminium intermediates useful for the synthesis of heterocyclic compounds.7b These findings now lead us to propose allylic amines as convenient precursors for the metal-catalyzed formation of iminium ions which are commonly utilized intermediates in the synthesis of heterocyclic compounds, such as the present variation on the Pictet–Spengler theme.8

Initial investigations focused on the conversion of allylic amine 1a to THBC 2a (Table 1), where a range of Rh-, Pd-, and Ru-based catalysts was examined. Several catalysts in amounts of 1 mol% were shown to mediate a complete transformation within 23 h (Table 1, entries 1, 2, 8, and 9).

Table 1 Transition metal catalysts for the synthesis of THBC 2a (selected results)ab

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversionc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(PPh₃)₃Cl</td>
<td>76 (100 33)²⁷</td>
</tr>
<tr>
<td>2</td>
<td>RuHCl(CO)(PPh₃)₃</td>
<td>68 (100 14)²⁷</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₄</td>
<td>58 (66)</td>
</tr>
<tr>
<td>4</td>
<td>Pd(Pr-Bu₃)₂</td>
<td>5 (14)</td>
</tr>
<tr>
<td>5</td>
<td>Grubbs II</td>
<td>95 (95 7)²⁷</td>
</tr>
<tr>
<td>6</td>
<td>Hoveyda–Grubbs I</td>
<td>60 (10)</td>
</tr>
<tr>
<td>7</td>
<td>Hoveyda–Grubbs II</td>
<td>30 (47)</td>
</tr>
<tr>
<td>8</td>
<td>Ru(PC₅)₃(MPi)(PM)Cl₂</td>
<td>95 (100 42)²⁷</td>
</tr>
<tr>
<td>9</td>
<td>Ru(MPi)(i-PROPM)Cl₂</td>
<td>100 (100 5)²⁷</td>
</tr>
</tbody>
</table>

a See the ESI for a full account on reaction optimization. b Abbreviations: MPI, 1,3-bis(2-methylphenyl)-2-imidazolidinyldiene; PM, phenylmethylene; PRO, propoxy. c Determined by RP-HPLC (215 nm). d Product mixtures were generally very clean (>85% of 1a and 2a in the reaction mixture). e Reaction carried out with 0.1 mol% catalyst.

Department of Chemistry, Technical University of Denmark,
DK-2800 Kgs. Lyngby, Denmark. E-mail: ten@kemi.dtu.dk; Fax: +45 4593 3968; Tel: +45 4525 2134
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data for all substrates and products. See DOI: 10.1039/c2cc17704h
‡ These authors contributed equally.
Table 2  Rh-catalyzed synthesis of THBCs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>R&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Product, yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2a, 90</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>(4-NO&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2b, 86</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>(3,4-(OMe)&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2c, 77</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>CyCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2d, 86</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>Heptyl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2e, 69</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>Allyl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2f, 71</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2g, 49&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2h, 75</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>5-OMe</td>
<td>2i, 94</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>6-OMe</td>
<td>2j, 76</td>
</tr>
<tr>
<td>11</td>
<td>1k</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>7-Me</td>
<td>2k, 80</td>
</tr>
<tr>
<td>12</td>
<td>1l</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>5-Me</td>
<td>2l, 81</td>
</tr>
<tr>
<td>13</td>
<td>1m</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>5-F</td>
<td>2m, 42</td>
</tr>
<tr>
<td>14</td>
<td>1n</td>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>5-Br</td>
<td>2n, 68</td>
</tr>
<tr>
<td>15</td>
<td>1o</td>
<td>Bn</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>2o, 26&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>16</td>
<td>1p</td>
<td>Bn</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>2p, 71&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>17</td>
<td>1q</td>
<td>Bn</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>2q, 65</td>
</tr>
<tr>
<td>18</td>
<td>1r</td>
<td>Bn</td>
<td>H</td>
<td>(4-NO&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>H</td>
<td>2r, 43&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>19</td>
<td>1s</td>
<td>Bn</td>
<td>H</td>
<td>(4-OMe)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>H</td>
<td>2s, 59&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after flash column chromatography.  
<sup>b</sup> Reaction carried out with 15 mol% catalyst.  
<sup>c</sup> 51% yield, when using 30 mol% catalyst and 60 mol% n-BuLi.

A reduction of the loading to 0.1 mol% clearly identified Wilkinson’s catalyst (Table 1, entry 1) and Ru alkylidene catalyst Ru(PCy<sub>3</sub>)(MPI)(PM)Cl<sub>2</sub> (Table 1, entry 8) as most efficient. In control experiments with catalytic amounts of acid, such as TFA, and absence of catalyst, no conversion of starting material could be detected, which points to a unique role of the metal catalyst. When applied to a range of readily available N-alkyl-N-allyltryptamines, Wilkinson’s catalyst proved to be highly efficient (Table 2). THBCs 2a-s were obtained in 26–94% yield. Variation of R<sup>1</sup> and the indole substitution pattern did not significantly affect the reaction (Table 2, entries 1–14). On the other hand, the N-allylic substituent pattern greatly influenced reactivity (Table 2, entries 15–19), and some substrates (1g, 1o–p and 1r–s) needed up to 15 mol% of catalyst to achieve high substrate conversion and isolated product yields.

The successful metal-catalyzed double bond isomerization reactions may stimulate the development of asymmetric variants. Much recent work has indeed been dedicated to asymmetric Pictet–Spengler-type reactions. To this end, we briefly investigated Ru-catalysis with chiral ligands, and cooperative catalysis of metals and chiral Brønsted acid for the reaction (see ESI†). Unfortunately, these preliminary experiments did not reveal any signs of asymmetric induction. The classical Pictet–Spengler reaction of tryptophan esters with aldehydes typically proceeds with limited diastereocntrol in the synthesis of 1,3-disubstituted tetrahydro-β-carbolines. The stereochemical outcome is highly dependent on both reaction conditions and the stereoelectronic nature of the reactive amine and aldehyde components. It was therefore interesting to examine if the action of Wilkinson’s catalyst in the event of iminium ion formation could influence the diastereoselectivity of the cyclization step. Unfortunately, the methyl ester of N-benzyl-N-allyltryptophan did not undergo any significant conversion under the reaction conditions shown in Table 2, and only traces of the THBC product were detected by LC/MS analysis. Evidently, the action of this catalyst may be sensitive to the steric congestion posed by the ester moiety, and/or the reduced nucleophilicity of the intermediate iminium nitrogen atom.

The methodology was also extended to a sequential reaction process (Scheme 1), where secondary tryptamine 3a was allylated before adding Wilkinson’s catalyst, ultimately providing THBC 2a in good yield.

Finally, to provide a one-pot sequence analogous to the Pictet–Spengler reaction, a tandem Tsuji–Trost/isomerization/iminium cyclization approach was demonstrated (Table 3). A range of readily available secondary tryptamines (3a–e and 3j) were obtained in 26–94% yield. Variation of R<sup>1</sup> and the indole substitution pattern did not significantly affect the reaction (Table 2, entries 1–14). On the other hand, the N-allylic substituent pattern greatly influenced reactivity (Table 2, entries 15–19), and some substrates (1g, 1o–p and 1r–s) needed up to 15 mol% of catalyst to achieve high substrate conversion and isolated product yields.

Scheme 1 Synthesis of THBC 2a via a one-pot allylation/isomerization/cyclization sequence.

Table 3 Synthesis of THBCs via a Pd-catalyzed Tsuji–Trost/isomerization/iminium cyclization sequence

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Product, yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Bn</td>
<td>H</td>
<td>2a, 85</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>(4-NO&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>2b, 86</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>(3,4-(OMe)&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>2c, 81</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>CyCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>2d, 67</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>Heptyl</td>
<td>H</td>
<td>2e, 48</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>Bn</td>
<td>6-OMe</td>
<td>2j, 67</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after flash column chromatography.
could be efficiently converted to THBCs (48–86%) when reacted with allylmethylcarbonate and Pd(PPh₃)₄ in refluxing toluene.

In summary, we have shown that metal-catalyzed tandem isomerization/cyclization of N-allyltryptamines constitutes an efficient alternative to the Pictet–Spengler reaction for the synthesis of THBCs. Several metal catalysts were shown to facilitate isomerization/cyclization of N-alkyliminium cyclization, thus providing a metal-catalyzed variant of the Pictet–Spengler reaction.

Notes and references


