Palladium- and Ruthenium-Catalyzed Decarboxylative Allylations
and Michael Addition-Allylation Reactions. Applications in Nitrogen
Heterocycle Synthesis

By
Chao Wang
B.S. Henan University of Technology, 1999
M.S. Chem. TianJin University, 2002

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Doctor of Philosophy

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Jon A. Tunge, chair

______________________________
Jeffrey Aubé

______________________________
Robert G. Carlson

______________________________
Paul R. Hanson

______________________________
Helena C. Malinakova

______________________________
Date Submitted
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Date approved
Abstract

Chao Wang, Ph.D.

Department of Chemistry, June 2008

University of Kansas

Our group has a long-standing interest in Pd or Ru-catalyzed decarboxylative coupling reactions. It has been shown that allyl β-ketoesters, upon treatment with palladium or ruthenium, generate freely diffusing enolates and π-allyl electrophiles. Consequently, we were curious about whether appropriate reactants (such as Michael acceptors) could be used to intercept these intermediates during the reaction. It has been since shown that a [Cp*RuCl]₄/bipyridyl catalyst effectively induces a regioselective tandem Michael addition-allylation reaction. This protocol works well with a variety of allyl β-ketoesters and Michael acceptors. Interestingly, ruthenium complexes behave as bifunctional catalysts, which activate the electrophilic allyl fragment and catalyze the decarboxylative formation of enolate nucleophiles. In addition, we have shown that cyclic carbamates diastereoselectively produce vinyl azetidines in good yields via a decarboxylative ring contraction. The diastereoselectivity is facilitated by rapid epimerization of the C₅ stereocenter through π-σ-π allyl interconversion. This allows the synthesis of highly diastereoenriched azetidines from diastereomeric mixtures of cyclic allylic carbamates. Furthermore, in
the presence of Michael acceptors, the cyclic carbamates undergo tandem Michael
addition-allylation to produce highly substituted piperidines with good
diastereoselectivity. Moreover, we have demonstrated that vinyl benzoxazinones
undergo decarboxylative allylation to generate a series of dihydroquinoline
derivatives. Once again, reaction in the presence of Michael acceptors led to a formal
decarboxylative [4+2] cycloaddition. The analogous reaction in the presence of
nonracemic palladium catalysts led to a highly enantioselective reaction. Lastly, a
selenium-catalyzed oxidative halogenation of carbonyl compounds was developed.
Interestingly, phenylselenides were found to be efficient and selective catalysts that
enhance the electrophilicity of oxidized halogen sources such as NCS toward
$\alpha$–halogenation of carbonyl containing compounds such as ketones, $\beta$-ketoesters, and
even $\alpha,\beta$-unsaturated ketones. In most cases, monohalogenated products were
generated exclusively.
To my wife, Lisha

and my baby, Gavin
Acknowledgement

Five years of graduate study is not that easy, which were composed with both joys and tears. When I looked back, there are so many peoples I have been worked with, and without their help, I can never stick to my graduate study and summit such a big mountain in my life. So I feel like to say something and express my great appreciation of their companionship.

I want to say “thank you” to my wife, Lisha. You always believe in me and have been supportive during my graduate study. Even though we are different in majors, you are willing to talk about chemistry and apparently chemistry is not your favorite spot. I still remembered those times you had to listen to my practice talks and provide me with valuable feedbacks. In living, I really enjoyed your company, which makes things easier. Though you seldom cook, I must admit that I did enjoy cooking. You are an extremely smart, smart PhD candidate and just need a little bit more focus. My baby-Gavin is really a blessing to us. I just can not imagine you are almost two years old now. To watch you growing up make me happy everyday. Being a daddy is not only changing dippers, feeding, but to spend a lot of time together and have fun. I love you both very much.

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impact my whole life. You do set up a model for me to follow in the future.

I also want to express my gratitude to other committee members, Dr Carlson, Helena, Jeff and Paul. You taught me that there are a lot of funs in chemistry, which made my journey to my PhD degree more pleasant. I really appreciate your mentorship. Dr Carlson, you are my advisor on organic colloquium and taught me the spectroscopy course. I am always impressed at your organization and dedication to your students. Jeff and Paul, your knowledge and provoking points at the problem sets make learning more fun, and I did have a wonderful time at KU. Helena, I sat in your synthesis course and have been working as a GTA with you. Your innovative ways of teaching is awesome. Again, I would like to thank Helena and Paul for being the readers of my dissertation.

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analysis, Todd Williams and Bob Drake for Mass Spectroscopy analysis and Victor Day for X-ray crystallographic analysis.

Finally, I want to share my joy with my family. I have been very lucky to live with them in the past two years. My parents, Wenzhi Wang and Xuejie Zhang, your encouragement and supportiveness hold me up and help me go through the good times and bad times of my graduate study, and here I become the first member of the family with a PhD degree. My parents-in-law, Ruxing Zhang and Ying Du, You are great and I can not imagine to finish my study here at KU without your help. I enjoy playing games together and I love you all.
# Palladium- and Ruthenium-Catalyzed Decarboxylative Tandem Michael Additon-Allylation Reactions and Further Applications in Nitrogen Heterocycles Synthesis

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Abbreviations

- Ac: acetyl
- Ar: aryl
- Bn: benzyl
- Bu: butyl
- Bz: benzoyl
- cat.: catalytic
- COD: cyclooctadiene
- COT: 1,3,5-cyclooctatriene
- COSY: correlation spectroscopy
- Cp: cyclopentadienyl
- dba: dibenzylidene acetone
- de: diastereomeric excess
- DEPT: distortionless enhancement by polarization transfer
- DIEA: diisopropylethylamine
- DMA: dimethylacetamide
- DMAP: 4-(dimethylamino)pyridine
- DMF: N, N-dimethylformamide
- DMSO: dimethylsulfoxide
- dppb: diphenylphosphinobutane
- dppe: diphenylphosphinoethane
- dppp: diphenylphosphinopropane
- dppf: 1,1’-bis(diphenylphosphino)ferrocene
- dr: diastereomeric ratio
- ee: enantiomeric excess
- ent: enantiomer
- Et: ethyl
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<th>Abbreviation</th>
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<td>EWG</td>
<td>electron-withdrawing group</td>
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<tr>
<td>GC</td>
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<tr>
<td>Het</td>
<td>heteroaryl</td>
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<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
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<td>HRMS</td>
<td>high resolution mass spectrometry</td>
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<td>IR</td>
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<td>LAH</td>
<td>lithim aluminum hydride</td>
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<td>LDA</td>
<td>lithim diisopropylamide</td>
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<td>Ln</td>
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<td>Me</td>
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<td>NBS</td>
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<td>n-BuLi</td>
<td>n-butyl lithium</td>
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<td>NMR</td>
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<td>Ns</td>
<td>p-nitrobenzene sulfonyl</td>
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<td>Np</td>
<td>naphthyl</td>
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<td>Nuc</td>
<td>nucleophile</td>
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<td>Pd</td>
<td>palladium</td>
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<tr>
<td>Ph</td>
<td>phenyl</td>
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<td>ppm</td>
<td>part per million</td>
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<tr>
<td>Se</td>
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<td>sec-BuLi</td>
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<td>Succ</td>
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<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
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<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
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<tr>
<td>'Bu</td>
<td>tert-butyl</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>Tf</td>
<td>triflate</td>
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<tr>
<td>TMEDA</td>
<td>tetramethylethylene diamine</td>
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<td>TMG</td>
<td>tetramethylguanidine</td>
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<tr>
<td>TMSCl</td>
<td>trimethylsilyl chloride</td>
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<tr>
<td>tol</td>
<td>toluene</td>
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<tr>
<td>Ts</td>
<td>tosyl</td>
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<tr>
<td>µW</td>
<td>microwave</td>
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Chapter 1

Ruthenium-Catalyzed Decarboxylative Insertion of Michael Acceptors into Allyl Ketoesters
1.1 Overview of Ruthenium-Catalyzed Allylation Reactions

New methodologies for C-C bond formation have been driving progress in synthetic organic chemistry. Transition metals were introduced as reagents and catalysts in this scenario because they often allow reactions to proceed under mild conditions and with high functional group compatibility. Furthermore, transition metal complex-catalyzed reactions are often highly chemoselective, regioselective and stereoselective, so they have found wide applications in modern synthesis.\(^1\) Also of note here is that transition metal functions by either activating the reactants or by stabilizing the high energy transition state and product through coordination.\(^2\)

Palladium and ruthenium-catalyzed allylic alkylations have attracted many research groups’ interest across the world. Possibly one of the most remarkable examples is the Tsuji-Trost allylation reaction,\(^3,4\) which has been extensively explored and generated thousands of references since its discovery in 1965. The general reaction scheme and mechanism are shown in Scheme 1. The reaction starts by coordination of the Pd(0) catalyst to the allylic substrate 1a, followed by nucleophilic displacement of the leaving group to generate a π-allylpalladium complex 1c, which undergoes nucleophilic substitution to generate the allylation product 1f. Trost proposed two different mechanisms, depending on the nature of the nucleophiles.\(^5\) With hard nucleophiles, the reaction was thought to proceed by ligand exchanging
first, followed by reductive elimination to give the product 1h with reversed stereochemistry; while the soft nucleophiles attack the π-allyl unit directly in the sense of $S_N2$ reaction, during which double inversion generates the product 1i with overall retention stereochemistry.

Scheme 1 Tsuji-Trost allylation reaction

Palladium-catalyzed allylic alkylations normally generate linear products as compared to ruthenium catalysts, which afford branched products.\(^5\) Tsuji reported the first ruthenium catalyzed allylic alkylation in 1985 as illustrated in Scheme 2.\(^6\) The combination of $\text{RhH(PPh}_3)_4$ with $n$-butyl phosphine favored the branched product 2d, while the palladium catalyst generated a mixture of linear 2c and branched product 2d in a ratio of 73:27.
Much early work in the field of ruthenium-catalyzed allylic alkylations was done by Watanabe et al. In 1993, Watanabe published their results on different ruthenium complex-catalyzed allylations of β-ketoesters with allylic carbonates (Scheme 3). A Ru(COD)(COT) complex was found to favor the addition of nucleophiles to the more substituted terminus of the Ru-allyl complex as shown in Scheme 3. The addition of ethyl acetoacetate 3a to cinnamyl methyl carbonate 3b is quite regioselective, affording exclusively the branched product. Also included are other ruthenium complexes, such as Ru3(CO)3, RuH2(PPh3)4, RuCl2((PPh3)2 and RuCl3; however those catalysts showed little or no reactivity toward allylation reaction. It was proposed that the regioselectivity depends on the structure of the substrates and ligands that coordinate to the ruthenium catalyst. For instance, the ratio of linear to branched product dropped to 50:50 when dimethyl or diethyl malonate were used as nucleophiles instead of the ketoester.
Scheme 3 Ru(COD)(COT) catalyzed regioselective allylation of β-ketoesters

Along this line, various Ru(II) catalysts were developed in order to incorporate heteroatom nucleophiles rather than carbon nucleophiles. For example, Cp*RuCl(cod) was found to catalyze allylic amination of cinnamyl methyl carbonate 3b, which generated the branched product 4b and linear product 4c in a ratio of 84:16 (Scheme 4).  

Scheme 4 [Cp*RuCl(cod)] catalyzed allylic amination

In 1999, the same Cp*RuCl(cod) catalyst was used for the allylation of thiols, which were generally thought to poison transition metal catalysts due to their strong coordinating ability. This reaction was relatively regioselective and favored the linear allylic thioether (Scheme 5). Interestingly, under mild reaction conditions, two
regioisomers 5a and 5b gave an identical mixture of products 5c and 5d in a ratio of 78:22 and 95% and 77% yield respectively. Thus, it was logically proposed that a \( \pi \)-allylruthenium complex was involved as the reactive intermediate. [CpRu(PPh\(_3\))\(_2\)Cl] was also shown to catalyze allylation of phenols and thiols, however the regioselectivity was only 50:50.\(^{11}\)

**Scheme 5 Regioselective thiol allylation**

In 2002, Trost reported a stereospecific allylic alkylation with [Cp*Ru(NCCH\(_3\))\(_3\)]PF\(_6\).\(^{12}\) This Ru-catalyzed allylation proved to be highly regioselective, favoring the branched product 6a over linear product 6b as illustrated in Scheme 6. The reaction conditions were generally mild, however a general solvent and temperature that was effective for all substrates was not found.

**Scheme 6 [Cp*Ru(NCCH\(_3\))\(_3\)]PF\(_6\)-catalyzed regioselective allylation**
The general reaction mechanism is thought to proceed by formation of ruthenium \( \pi \)-allyl complex 7c, followed by nucleophilic attack at the more substituted allyl terminus to generate 7d. Decomplexation then produces allylic alkylation product 7e and regenerates the catalyst 7a.\(^{13}\)

**Scheme 7 Proposed catalytic cycle**

To investigate the stereochemical course of the Ru-catalyzed allylation, two diastereoisomers 8a and 8b were synthesized and allowed to react with piperidine 8c in the presence of 5 mol\% of [CpRuCl(cod)] and 5 mol\% of NH\(_4\)PF\(_6\).\(^{14}\) The *cis*-carbonate 8a gave primarily *cis*-product 8d; whereas in the case of *trans*-carbonate 8b, *trans*-product 8e was produced predominately over 8d in a ratio of 98:2. This result indicates a double inversion mechanism giving rise to overall retention of stereochemistry, which is consistent with the stereochemical course of
related Pd-catalyzed allylic substitutions.\textsuperscript{15}

**Scheme 8** Stereochemical course of Ru-catalyzed allylation

![Scheme 8 Diagram]

Our research group has been interested in extending the utility of the above transformations to the use of ketone enolates using transition metal-catalyzed decarboxylative allylation. For instance, Erin showed that allyl $\beta$-ketoesters $9a$ combined with a [Cp*Ru(bpy)Cl] catalyst undergo regioselective allylation to form $\gamma\delta$-unsaturated ketones $9b$ under neutral conditions (Scheme 9).\textsuperscript{16} To be noted here is that non-stabilized ketone enolates were formed under extremely mild reaction conditions compared to the traditional methods of generating ketone enolates using strong bases such as lithium diisopropylamide. As expected, Ru-catalyzed allylic alkylation favors the branched products $9b$, and in most cases, the regioselectivity was over 19:1.
**Scheme 9** Synthesis of $\gamma\delta$-unsaturated ketones from allyl $\beta$-ketoesters

\[
\begin{align*}
\text{R}_1\text{O} & \quad \text{R}_2
\end{align*}
\]

\[
\begin{align*}
\text{9a} & \quad \text{10m\% [Cp}^{*}\text{Ru(bpy)Cl]} & \quad \text{CH}_2\text{Cl}_2, \text{rt} & \quad \text{-CO}_2 & \quad \text{9b}
\end{align*}
\]

81-96% yield

1.2 Palladium-Catalyzed Decarboxylative Generation of Enolate Nucleophiles

1.2.1 Palladium-Catalyzed Decarboxylative Generation of Enolate Nucleophiles

The concept of differing reactivity of “hard” and “soft” nucleophiles with palladium $\pi$-allyl complexes was introduced in 1996 by Trost et al.\(^5\) “Soft” nucleophiles refer to those resulting from conjugated acids with a pK\(_a\) less than 25; whereas “hard” nucleophiles are defined as those, whose conjugated acids have a pK\(_a\) that is greater than 25. Those nucleophiles are also called non-stabilized nucleophiles. The two types of nucleophiles react differently with non-stabilized nucleophiles coordinating to the metals before nucleophilic attack, while stabilized nucleophiles attack the $\pi$-allyl species directly.

Allylation of non-stabilized nucleophiles, for example ketone enolates, was traditionally carried out in the presence of a strong base, which limits its synthetic utility if the substrate contains base-labile functional groups or multiple enolizable hydrogens. As such, methodology performed under non-basic conditions would be highly desirable. Interestingly, allyl $\beta$-ketoesters, upon treatment with palladium
generate ketone enolates under extremely mild conditions. Pioneering work in this
development was done by Tsuji and Saegusa.\textsuperscript{17-20}

In 1980, Saegusa reported a facile Pd-catalyzed decarboxylative allylation with
allyl cyclohexanone-2-carboxylate \textit{10a} as shown in Scheme 10.\textsuperscript{17} A Pd(II) enolate
intermediate \textit{10c} was thought to be involved in the course of this reaction.

\textbf{Scheme 10 Pd-catalyzed decarboxylative allylation with cyclic allyl $\beta$-ketoesters}

\begin{equation}
\begin{array}{c}
\text{10a} \\
\xrightarrow{5 \text{ mol\% Pd(PPh}_3)_4} \\
\text{DMF, rt} \\
96\% \\
\end{array}
\end{equation}

Following that, Tsuji further investigated the ligand effects and reported a
Pd-catalyzed decarboxylation-dehydrogenation to produce various $\alpha,\beta$-unsaturated
ektones \textit{11c} (Scheme 11).\textsuperscript{18} A bidentate phosphine ligand, diphenylphosphino
ferrocene (dppf), combined with a Pd catalyst precursor produced mainly enone
products \textit{11c} in refluxing acetonitrile. In contrast, triphenylphosphine ligand gave the
decarboxylative allylation product \textit{11b}. Protonated product \textit{11d} was formed in the
presence of ammonium formate, which further enriched the synthetic utility of allyl
$\beta$-ketoesters. Noteworthy is that solvents also play a key role here and it has been
shown that aprotic solvents such as DMF and acetonitrile favor the formation of
enones. On the other hand, allylation occurred in $t$-butyl alcohol. Interestingly, the
presence of an $\alpha$-substituent R is crucial for the formation of 11c. For example, allylation product 11b was formed in almost equal amount as well as double allylation products when R equals to hydrogen.

**Scheme 11 Pd-catalyzed decarboxylation-dehydrogenation**

Furthermore, acyclic allyl $\beta$-ketoesters 12a have been shown to undergo a regioselective decarboxylative allylation smoothly, producing the $\gamma\delta$-unsaturated ketone products 12e through nucleophilic attack at the less substituted terminus of the Pd-allyl complex 12d (Scheme 12).

Also of note is that regioisomeric reactant, 12b, gave the identical linear olefin products 12e as expected for a reaction involving a $\pi$-allylpalladium intermediate 12d.
In addition to ketoesters, starting materials with other electron-withdrawing groups (EWG), such as ester, nitrile, and nitro were also investigated (Scheme 12), however, malonate and cyanoacetate substrates were somewhat less reactive than the corresponding carbonyl substrates 12a, and consequently higher temperatures were required. For instance, when the EWG was CO\(_2\)Me, decarboxylative allylation was carried out in refluxing dioxane or DMF, affording product 12g in 75% yield.

Scheme 13 Asymmetric allylic alkylation (AAA)
In 2004, Burger and Tunge reported an asymmetric allylic alkylation (AAA) of non-stabilized ketone enolates catalyzed by a combination of 5 mol% Pd$_2$(dba)$_3$ and 10 mol% Trost ligand 13e as illustrated in Scheme 13.\textsuperscript{21} The allylation products 13c and 13d were obtained in excellent enantioselectivity. Also included in this report was a crossover experiment, conducted to investigate whether the decarboxylative allylation occurred intra- or intermolecularly (Scheme 14). Treatment of a mixture of substrates 14a and 14b with the standard reaction conditions afforded almost equal quantities of all four possible products. This result seems to indicate that freely diffusing enolates (or enolate precursors) and π-allylpalladium species 14c were generated during the course of the reaction. This phenomenon was also noted by others, consequently intramolecular trapping of the generated enolates with aldehydes was reported.\textsuperscript{22}

**Scheme 14 Crossover experiment**

1.2.2 Multiple Transformations Via Palladium Enolate Chemistry

Palladium enolates have been postulated as important intermediates in the
decarboxylative allylic alkylation of β-ketoesters (Scheme 15).\textsuperscript{17} In their subsequent study, Tsuji reported the first intramolecular aldol reaction of palladium enolates with aldehydes under non-basic conditions.\textsuperscript{22} Oxidative addition of allyl β-ketoesters \textit{15a} to Pd(0), followed by decarboxylation generated a Pd(II) enolate \textit{15c}, which underwent an intramolecular aldol reaction to smoothly produce \textit{15d}. Aldol products \textit{15b} were obtained in good to excellent yield. The regeneration of the palladium catalyst from intermediate \textit{15d} was unfortunately not addressed by this report.

\textbf{Scheme 15 Intramolecular aldol reaction with allyl β-ketoesters}

![Scheme 15 Intramolecular aldol reaction with allyl β-ketoesters](image)

Various α, β-unsaturated ketones tethered to allyl β-ketoesters were also shown to react with palladium enolates, generated by decarboxylation of allyl β-ketoesters to produce cyclic Michael adducts \textit{16d} (Scheme 16).\textsuperscript{23} Also included in this report was a brief screening of reaction conditions to optimize the yield of Michael adducts \textit{16d}. It was found that treatment of \textit{16a} with catalytic amount of Pd(PPh\textsubscript{3})\textsubscript{4} in CH\textsubscript{3}CN at room temperature generated exclusively the Michael product \textit{16d} by protonation of intermediate \textit{16c}, while the Michael addition/allylation product \textit{16e} and the Michael
addition/β-hydride elimination product 16f were formed as minor products under other conditions. This reaction was proposed to go through a similar pathway as the intramolecular aldol reaction shown in Scheme 15.

**Scheme 16 Intramolecular Michael Addition with allyl β-ketoesters**

Even though those Pd-enolates have been shown to undergo intramolecular nucleophilic additions to aldehydes and enones, the intermolecular version is problematic due to the competitive decarboxylative allylic alkylations. In this regard, a hetero-bimetallic catalyst complex was shown to efficiently catalyze the intermolecular decarboxylative aldol reaction of allyl β-ketoesters with aldehydes as shown in Scheme 17. The incorporation of a metal salt YbCl₃ was thought to promote either the formation of metal enolates or nucleophilic additions by increasing the electrophilicity of aldehydes. Interestingly, it was necessary to adopt two equivalents of allyl β-ketoesters 17a to aldehydes 17b in order to achieve high yield of aldol products. Based on their results, Schaus suggested that the second equivalent
allyl β–ketoester reacted with intermediate 17d to give aldol product 17c and a metal enolate 17e, which undergoes allylation to regenerate the Pd(0) catalyst. This hypothesis was supported by separation of a stoichiometric amount allylic alkylation product 17g.

Scheme 17 Heterobimetallic-catalyzed decarboxylative aldol reaction

In addition, electron-poor olefins were also compatible with the above reaction protocol. It has been shown that electron poor olefins such as benzylidene malononitrile 18c, react with allyl β–ketoester 18a in the presence of Pd(PPh₃)₄ to generate 18d in high yield (Scheme 18). Michael addition of an oxygen-bonded palladium enolate 18d to activated olefin 18c produce an intermediate 18d, which, upon allylation finishes this cascade reaction. However, the substrate scope was not well addressed in this paper, and allyl β–ketoester 18a with an unsubstituted alkene unit was the only one used in their reactions.
Scheme 18 Pd-catalyzed intermolecular Michael addition with activated olefins

In conclusion, transition metal-catalyzed allylic alkylation has proven to be an important and convenient tool for organic synthesis, which is still a “hot” topic, and finds many applications in natural products synthesis.29-33 Yet, despite the significant attention directed toward catalytic allylic alkylation, many challenges still exist.

1.3 Ruthenium-Catalyzed Tandem Michael Addition-Allylation

The desire to rapidly generate complex molecules has driven the search for new catalytic processes that effect multiple transformations in one pot. Notable recent examples include tandem cyclization-arylation,34 allylation/Pauson-Khand,35 and olefin metathesis-hydrogenation.36 All those transformations rely on the ability of a transition metal to catalyze two distinct sequential transformations. On the other hand, a bifunctional catalyst that can simultaneously activate two components of a reaction mixture toward reaction with a third should facilitate multiple concurrent bond-forming reaction with high atomic economy.37

During our investigation on transition metal-catalyzed decarboxylative alkylation
of allyl \( \beta \)-ketoesters, namely the Carroll rearrangement, we and other have shown that transition metals play two functions, catalyzing the decarboxylative formation of enolate nucleophiles and activating the electrophilic allyl fragment toward nucleophilic substitution.\textsuperscript{16, 38, 39} In this regard, a \([\text{Cp}^*\text{Ru(bpy)Cl}]\) complex was shown to catalyze the decarboxylative allylation regioselectively, favoring the branched product (Scheme 9).\textsuperscript{16} A crossover experiment was carried out to elucidate the reaction mechanism. Allyl \( \beta \)-ketoesters \textbf{19a} and \textbf{19b} were prepared and upon treatment with 10 mol\% \([\text{Cp}^*\text{Ru(bpy)Cl}]\), all four possible products were formed in a statistical yield (Scheme 19). This result seems to suggest that allyl \( \beta \)-ketoesters are sources of freely diffusing enolates and allylic cations.

\textbf{Scheme 19 Cross-over experiment}

Consequently, we were curious whether those enolate intermediates could be trapped by appropriate reactant. As mentioned above, the enolates generated by
Pd-catalyzed decarboxylation have been intramolecularly intercepted by aldehydes and Michael acceptors.\textsuperscript{22, 23} However, the intermolecular version seems to be problematic due to the competing allylation. Recent focus has been directed toward this end. To recap, Schaus reported an intermolecular aldol reaction using a hetero-bimetallic catalyst system (Scheme 17)\textsuperscript{25} and Yamamoto found that electron-poor olefins such as benzylidene malononitrile can intercept palladium enolates and undergo intermolecular Michael addition reactions.\textsuperscript{26}

\subsection*{1.3.1 Transition-metal Directed Aldol Reaction}

Based on those precedents with Pd-enolates chemistry, we decided to investigate the tandem Michael addition-allylation of pronucleophiles under the conditions for Ru-catalyzed decarboxylative allylation.\textsuperscript{16} First, different aldehydes were studied since the aldol adducts are synthetically useful. It has been found that $\alpha,\alpha$-disubstitution of the $\beta$-ketoester starting materials slows the Carroll rearrangement and consequently, the rearrangement requires higher temperature.\textsuperscript{40} The hypothesis here is that, if the competing allylic alkylation is slow, then the generated Pd-enolates could be possibly trapped by aldehydes. To test this hypothesis, disubstituted $\beta$-ketoester 20a was prepared and treated with a catalytic amount of Pd(PPh$_3$)$_4$ in the presence of five equivalents of benzaldehyde (Scheme 20). However, neither the decarboxylative allylation product nor the aldol adducts formed.
Instead, the competing elimination product 20b and protonated enolate 20c were formed exclusively.

**Scheme 20 Pd-enolate directed aldol reaction**

```
\[
\begin{array}{c}
\text{Et} & \text{Et} \\
\text{O} & \text{O} & \text{PhCHO} & 10 \text{ mol}\% \text{Pd(PPh} \text{3})_4 \\
20a & 5\text{eq} & \text{C}_6\text{D}_6, 80 \degree \text{C} & \text{Et} & \text{Et} \\
\end{array}
\]

Following that, starting material 19a was synthesized and allowed to react with benzaldehyde in the presence of palladium catalyst. Unfortunately, the linear decarboxylative allylic alkylation product 21b was produced. Similarly, when a ruthenium complex was employed as the catalyst, the branched alkylation product 21c was formed and no aldol reaction products were observed (Scheme 21).

**Scheme 21 Pd-enolate directed aldol reaction**

```
\[
\begin{array}{c}
\text{Et} & \text{Et} & \text{O} & \text{O} & \text{Ph} & \text{PhCHO} & 5\text{eq} \\
\text{Et} & \text{O} & \text{O} & \text{PhCHO} & 2.5 \text{ mol}\% \text{[Cp}^\text{*}\text{RuCl]}_4 \rightarrow \text{Et} & \text{Et} & \text{O} & \text{O} & \text{Et} & \text{Et} \\
19a & 10 \text{ mol}\% \text{Pd(PPh} \text{3})_4 & \text{CD}_2\text{Cl}_2, \text{rt} & \text{21b} & \text{21c} & \text{10 mol}\% \text{bpy, CD}_2\text{Cl}_2, \text{rt} \\
\end{array}
\]

In the light of Schaus’ strategy,25 Lewis acids were also incorporated as a cocatalyst in an attempt to activate aldehydes toward nucleophilic addition. However both ZnCl\textsubscript{2} and YbCl\textsubscript{3}, which were shown to be the most effective Lewis acids by Schaus, failed in our case and only decarboxylative alkylation products, such as 21c,
24a-b were produced as shown in Scheme 22. The possible reason could be either that the Lewis acids were not compatible with the ruthenium catalyst complex or that the Lewis acids did not activate the aldehyde enough to be trapped by the enolate intermediates. Besides, other solvents, such as THF, CH$_3$CN and CH$_2$Cl$_2$ were used, and it was found that solvent effects were negligible. In most case, decarboxylative allylation products were formed as the major products, even though in some cases, trace amounts of aldol adducts were generated. As to substrate 22a, a combination of palladium with different phosphine ligands and Lewis acids were also studied. Surprisingly, no reaction occurred and the starting material stayed intact over the course of the reaction.

**Scheme 22 Attempted use of Lewis acids to facilitate a directed aldol reaction**

Even though standard allyl $\beta$-ketoesters did not undergo intermolecular aldol reactions, silyl $\beta$-ketoester 25a showed interesting reactivity toward benzaldehyde (Scheme23). With the ruthenium complex, only 65% of the starting material 25a underwent decarboxylation after 48 hours and small amount of the aldol product 25b
was formed along with by-products; whereas Pd(PPh$_3$)$_4$ has shown super catalytic activity, the decarboxylation completed in 10 minutes and the aldol adduct 25b was generated cleanly in one hour (95% NMR yield).

**Scheme 23** Pd-enolate directed aldol reaction with silyl β-ketoester

![Scheme 23](image)

The successful aldol reaction can be rationalized as follows. The expected oxidative addition reaction would produce π-allylpalladium complex 26a which undergoes a desilylation reaction to generate 1,3-butadiene and intermediate 26b, which was supported by the formation of a new proton signal at 3.5 ppm in the $^1$H NMR spectrum of the reaction mixture. Aldol reaction generates intermediate 26c, which then undergoes intramolecular silyl transfer, followed by decarboxylation to furnish product 25b as shown in Scheme 24.
1.3.2 Transition Metal-Catalyzed Michael Addition-Allylation Reactions

It has been shown that Michael additions to electron-poor olefins (RCH=CHZ₂) generate stabilized nucleophiles, which are well known to undergo transition metal facilitated allylic alkylation. Thus, we expected that ruthenium would be a competent catalyst for a tandem Michael addition-allylation reaction. Fortunately, benzylidene malononitrile smoothly reacted with the unsubstituted allyl β–ketoesters 22a under the condition of previously developed for catalytic Carroll-type rearrangement, affording the desired product 27a in high yield as shown in Scheme 25.⁴¹ Thus, activated Michael acceptors are ideally set up to undergo tandem enolate addition and allylation. Furthermore, it was envisioned the regiochemistry of allylation could be controlled by the appropriate choice of the transition metal catalyst.¹²,⁴²

Scheme 25 Reaction conditions for decarboxylative olefin insertion
To begin, a range of Michael acceptors were investigated to test their compatibility with the above reaction conditions. Based on the screening results, it was found that the electrophilicity of the Michael acceptors/electrophile is crucial for the successful decarboxylative olefin insertion. The unsuccessful Michael acceptors 28b are shown in Scheme 26. Except for DMAD, a strong \( \pi \)-acid known to deactivating the transition metal catalysts through coordination, all other Michael acceptors did not undergo the tandem Michael addition-allylation reactions and the Carroll rearrangement products 28c were formed exclusively.

**Scheme 26 Unsuccessful Michael acceptors**

After that, our attention was focused on the benzyldene malononitrile derivatives, which have been shown to efficiently trap the Pd-enolates as illustrated previously in Scheme 27. Various \( \beta \)-ketoesters and malononitriles were prepared. Interestingly, the electronics of the malononitrile are crucial to the success of the decarboxylytative insertion. When \( p \)-hydroxybenzylidene malononitrile (electrophilicity, \( E = -10.8 \))

---

24
was employed as the electrophile, Michael addition-allylation product 29a was obtained in <5% yield, in which the decarboxylation-allylation product was formed exclusively (Scheme 27). This issue was addressed by simply acylation of the hydroxyl group and in that case, Michael addition-allylation product 27b was obtained in 97% isolated yield.\textsuperscript{43}

Scheme 27 Effects of the electrophilicity of Michael acceptors

The most successful reactions achieved were those with olefins containing two electron-withdrawing groups, which is consistent with their electrophilicity parameters (18c, Ar=Ph, E= -9.42).\textsuperscript{43} Also shown in Scheme 27 is a Meldrum’s acid derivative 29b that is an effective Michael acceptor, showing that activated diesters are also viable reaction partners. Yamamoto has shown that Michael acceptors with acyclic diesters do not undergo tandem Michael addition-allylation reactions under palladium catalysis, which was attributed to lack of coplanarity of the two esters due to the sterics.\textsuperscript{26} Whereas in the case of Meldrum’s acid derivative 29b, the six-membered ring helps to lock the coplanarity of the ester groups, enhancing the
electrophilicity of the olefin.

Next, we turned our attention to developing the first regioselective tandem Michael addition-allylic alkylation of activated Michael acceptors. It was gratifying to find that treatment of 30a with benzylidene malononitrile, 2.5 mol % [Cp*RuCl]₄, and 10 mol % bipyridine at room temperature in methylene chloride produced 27c in high yield (89%) and over 19:1 regioselectivity (dr = 1.9:1) (Scheme 28). The analogous palladium-catalyzed reaction produced the opposite regioisomer 30b in 80% yield. The regioselectivities for ruthenium and palladium catalysts are consistent with those observed for other allylation reactions.⁵, ¹², ²⁶

Scheme 28 Catalyst-dependent regioselectivity

A variety of allyl β-ketoesters undergo smooth decarboxylative coupling with Michael acceptors (Table 1). Variation of the R¹ group shows that the reaction is typified by regiospecific formation of enolates (Scheme 28). Of note here is that the diastereoselectivity of products 27c and 27i, formed from the unsubstituted allyl partners are generally higher than those synthesized from the other regioisomers. This observation is interesting and deserves further attention. It is noteworthy that
equilibration of the kinetic enolate does not occur even when $R_1^1$ is benzyl and there is a large thermodynamic driving force favoring the formation of the stabilized enolate. In fact, previous attempts to generate the terminal enolate of phenylacetone by deprotonation have failed.$^{44,45}$

**Table 1 Yields of tandem ruthenium-catalyzed Michael addition-allylations**

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$R_4$</th>
<th>Prod.</th>
<th>Time (h)$^a$</th>
<th>% Yield (dr)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>27a</td>
<td>2</td>
<td>84</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>$p$-C$_6$H$_4$OAc</td>
<td>27b</td>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>27c</td>
<td>12</td>
<td>89 (1.9:1)</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>27c</td>
<td>6</td>
<td>85 (3.5:1)</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>27d</td>
<td>4.5</td>
<td>87</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>27e</td>
<td>5.5</td>
<td>64</td>
</tr>
<tr>
<td>Et</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>27f</td>
<td>22</td>
<td>93 (1.8:1)</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>$p$-C$_6$H$_4$OMe</td>
<td>Ph</td>
<td>27g</td>
<td>18</td>
<td>62 (1.6:1)</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>$p$-C$_6$H$_4$OCl</td>
<td>Ph</td>
<td>27h</td>
<td>19</td>
<td>62 (1.8:1)</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>$p$-C$_6$H$_4$OAc</td>
<td>27i</td>
<td>48</td>
<td>92 (2.7:1)</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>$p$-C$_6$H$_4$OAc</td>
<td>27i</td>
<td>16</td>
<td>76 (4.5:1)</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise mentioned, the reaction was carried out with allyl $\beta$-ketoester (0.2 M), Michael acceptor (0.2 M), $[\text{Cp}^*\text{RuCl}]_4$ (0.005 M), and bpy (0.02 M) in CH$_2$Cl$_2$ at room temperature. $^b$ Isolated yield after column chromatography. $^c$ The branched product was formed exclusively, with references to the size of substitutent $R_2$ and $R_3$. 
For the reason of comparison, two allyl β-ketoesters were treated with 10 mol% Pd(PPh₃)₄ in the presence of one equivalent Michael acceptors, affording the opposite regioisomers 30b, 30c in high yield (Table 2).

Table 2 Yields of Pd-catalyzed tandem Michael addition-allylation

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R⁴</th>
<th>Prod.</th>
<th>Time (h)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>30b</td>
<td>13</td>
<td>80</td>
</tr>
<tr>
<td>Et</td>
<td>Ph</td>
<td>Ph</td>
<td>30c</td>
<td>17</td>
<td>88</td>
</tr>
</tbody>
</table>

*a* Unless otherwise mentioned, the reaction was carried out with allyl β-ketoester (0.2 M), Michael acceptor (0.2 M) and Pd(PPh₃)₄ (0.02 M) in CH₂Cl₂ at room temperature. *b* Isolated yield after column chromatography.

One application of the tandem Michael addition-allylation reaction protocol was found in the modification of coumarin derivatives, and product 31b was obtained in 45% yield; however the product was formed cleanly based on ¹H NMR spectrum. This could serve as a rapid way for modifying coumarin, which is the core structure of many biologically active compounds.⁴⁶,⁴⁷ Also shown in Table 3 is a Meldrum’s acid derivative, which functions as efficient Michael acceptors to furnish products 31a and 31c in good yields. Of note here is that the formation of product 31c was catalyzed by Pd(PPh₃)₄; whereas when [Cp*Ru(bpy)Cl] was employed as the catalyst,
the Carroll rearrangement product was produced as the major one. This is possibly due to the steric hindrance of cyclopentene ring but it illustrates the trend that palladium catalysts are generally more active toward tandem Michael addition-allylation than the corresponding ruthenium catalysts. This hypothesis was further supported by the longer reaction times when [Cp*Ru(bpy)Cl] catalyst was adopted as the catalyst, comparing with that of Pd catalyst. For example, product 31c was formed in 12 hours with Pd(PPh₃)₄; while with [Cp*Ru(bpy)Cl] catalyst, the reaction did not go to completion even after 180 hours. It is noteworthy that the diastereoselectivity of addition to the cyclic Michael acceptor is much higher than that observed for benzylidene malononitrile derivatives, in which a less constrained transition state is involved (Table 1).

Table 3 Yields of tandem Michael addition-allylation of other Michael acceptors

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Michael acceptor</th>
<th>Prod.</th>
<th>Time (h)ᵃ</th>
<th>% Yield (dr)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>31a</td>
<td>1.5</td>
<td>51</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>31b</td>
<td>2</td>
<td>45 (12:1)</td>
</tr>
<tr>
<td>Me</td>
<td></td>
<td></td>
<td>Ph</td>
<td>31c</td>
<td>1.5</td>
<td>65 (5.5:1)</td>
</tr>
</tbody>
</table>

ᵃ Unless otherwise mentioned, the reaction was carried out with allyl β-ketoester (0.2 M),
Michael acceptor (0.2 M) and [Cp*RuCl]₄ (0.005 M), and bpy (0.02 M) in CH₂Cl₂ at room temperature. ⁶ Isolated yield after column chromatography. ⁷ using 10 mol% Pd(PPh₃)₄.

Following that, more diesters and β-ketoester derivatives were investigated and the results are summarized in Scheme 29. In the presence of a [Cp*Ru(bpy)Cl] catalyst, allyl β-ketoesters 30a reacted with three equivalents of Meldrum’s acid derivative 29b, affording a mixture of Michael addition-allylation product 32a and Carroll rearrangement product 32b in a ratio of 1.2:1. We propose that the bulky styrene unit accounts for the lower selectivity, similar to cyclopentene derivative mentioned above. Since cyanocoumarin has shown to be effective Michael acceptors, 3-acetyl coumarin 32c was also examined as a partner for decarboxylative olefin insertion; however the Carroll rearrangement products were formed instead.

**Scheme 29 Tandem Michael addition-allylation with lower chemoselectivity**

While we expected that the above reactions involved π-allyl ruthenium intermediates, this was confirmed by the reactions of regioisomeric allyl β-ketoesters 33a and 30a which give the same product 27c (Scheme 30). Thus the reaction
regiospecifically generates enolates followed by regioselective allylation. Interestingly, the less substituted olefin reactant 33a provides product more rapidly. Consistent with this trend, the unsubstituted allyl partners generally react most quickly. This implies that coordination of the alkene to ruthenium may be important prior to, or in, the rate-limiting step.

**Scheme 30 Regioselective allylation**

![Scheme 30](image)

Our group has a long-standing interest in decarboxylative allylation reactions. In 2005, Dinesh reported a decarboxylative allyl-acetylide coupling of 34a to form 1,4-ene product 34b, in which a palladium-allyl-acetylide intermediate 34f was thought to be involved as shown in Scheme 31. Consequently, we were curious whether the Pd-acetylide intermediate can be trapped by Michael acceptors. However, treatment of the propiolate ester 34a with benzylidene malononitrile 18c yielded a mixture of products 34c and 34b in almost 1:1 ratio. Phenyl propiolic acid 34d was also studied in this context, in which palladium acetate was employed as the catalyst to facilitate the generation of a Pd-acetylide intermediate 34g. Surprisingly, reductive
elimination occurred predominantly over insertion reaction, and Pd black was formed along with acetic acid which in turn supported the formation of proposed intermediate 34g. The product structure was tentatively assigned as 34e.

**Scheme 31** Tandem Michael addition-allylation with Pd-acetylide intermediate

To further expand our tandem Michael addition-allylation, a three-component coupling reaction was investigated (Scheme 32). Here toluene was chosen as the solvent because of the need for *in situ* formation of allyl β-ketoester 35b. Interestingly, the linear product 35c was produced with a pair of diastereotopic protons signal at 2.6 and 2.7 ppm, along with unreacted starting material 35b in a ratio of 0.6:1. The reaction was also carried out with Pd(PPh3)4 as the catalyst, in which a messy mixture was generated with recovery of cinnamyl alcohol.
Scheme 32 *Three components coupling reactions*

Finally, to illustrate the utility of the benzylidene diester electrophiles, we performed a simple hydrolysis and decarboxylation of 31a (Scheme 33). Products like the resulting $\gamma\delta$-unsaturated acid 36a, are particularly useful substrates for halolactonizations.\(^{49}\)

Scheme 33 *Utility of the benzylidene Meldrum's derivatives*

Another noteworthy application could be found in the rapid synthesis of polycyclic tropane alkaloid precursor 37d. Michael acceptor 37a bearing a nitro group was prepared and reacted with allyl-$\beta$-ketoester 22a to form the insertion product 37b, which was partially reduced to hydroxyl amine followed by cyclization to generate nitrone product 37c. Upon refluxing in toluene, intramolecular [3+2] cycloaddition afforded the polycyclic ring system.\(^{50,51}\) The efficient ring construction
strategy was not followed up due to time constraints.

**Scheme 34 Tropane alkaloid ring synthesis**

The tandem Michael addition-allylic alkylations involved in all of the above reactions are thought to start by oxidative addition the allylic ester, followed by decarboxylation to generate freely diffusing enolates $\text{38b}$ and $\pi$-allyl species $\text{38c}$ (Scheme 35). The addition enolates to activated Michael acceptors (RCH=C(EWG)$_2$) produces stabilized enolates $\text{38d}$, which are well-known nucleophiles for metal-catalyzed allylic substitution to produce product $\text{38e}$ and regenerate the catalyst.$^5$
In conclusion, we have developed a regioselective, catalytic coupling of enolates, Michael acceptors, and allyl electrophiles. The tandem Michael addition-allylation is made possible by the decarboxylative activation of allyl β-ketoesters to produce enolates and π-allyl metal electrophiles. We are currently exploring similar reactions that exploit our ability to regiospecifically generate enolates from β-keto esters at room temperature under base-free conditions.
1.4 References


31. Sim, S. H.; Park, H. J.; Lee, S. I.; Chung, Y. K., Palladium(0)-catalyzed


Appendix A

Experimental Procedures and Data for Chapter 1
General Experimental

THF was dried over sodium metal. Toluene, methylene chloride and diethyl ether were dried over activated alumina on a solvent system purchased from Innovative Technology, Inc. Acetonitrile and 1,4-dioxane were dried and stored over activated molecular sieves. Commercially available reagents were used without additional purification unless otherwise stated. Products were purified on silica gel from Sorbent Technologies (230x400 mesh, 60 Å porosity, pH 6.5-7.5). Ruthenium and palladium compounds were obtained from Strem. Thin layer chromatography was performed on silica gel 60F_{254} plates (EM-5715-7, EMD chemicals). UV lamp (254 nm) or KMnO_{4} stain were used for monitoring TLC plates.

_{1}H and _{13}C NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer and referenced to residual protio solvent signals. Structural assignments are based on _{1}H, _{13}C, DEPT-135, COSY, and HMQC spectroscopies and X-ray data. High resolution mass spectrometry was performed on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). High resolution mass spectrometry was performed on a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. FTIR spectra were acquired on a Shimadzu FTIR-8400S spectrometer. HPLC analysis was performed on a Shimadzu SCL-10A VP instrument.
**Preparation of Starting Materials**

Generally, allyl β-ketoesters were synthesized by the DMAP catalyzed coupling reaction between commercially available allylic alcohols with diketene, followed by purification via flash column chromatography when $R_1$ equals to methyl group. (SiO$_2$, 7:1 hexane: ethyl acetate).$^2$

![Chemical structure](image)

For silyl allyl β-ketoester 25a, the allylic alcohol was prepared,$^3$ followed by coupling with diketene.$^2$ To a solution of propargyl triethylsilane (500 mg, 4.4 mmol) in 5 mL THF at -78 °C under argon was added n-butyl lithium (4.9 mmol, 1.1 eq.) dropwise, and the reaction mixture was stirred at -78 °C for 0.5 hour before adding paraformaldehyde (4.9 mmol, 1.1 eq.) portion wise. The mixture was warmed to room temperature and kept stirring overnight. The reaction was quenched with sat. NH$_4$Cl solution, extracted with EtOAc. The organic phase was washed with brine, dried over MgSO$_4$ and concentrated to give the crude product, which was taken to the next step without further purification.

To a solution of LAH (340 mg, 8.8 mmol, 2.0 eq.) in 15 mL THF under argon was slowly added a solution of crude alkyne (4.4 mmol) in 5 mL THF via cannulation. The reaction mixture was then heated to reflux for 1hr, followed by quenching with water which was monitored by the release of hydrogen. The resulting mixture was filtered over a celite pad, dried over MgSO$_4$ and the solvent was removed to afford the corresponding allylic alcohol.
To a solution of the allylic alcohol (225 mg, 1.6 mmol) in 10 mL ether under argon was added diketene in one portion (1.8 mmol, 1.1 eq.), followed by DMAP (17.6 mg, 0.16 mmol, 0.1 eq). The reaction mixture was kept stirring until reaction completion indicated by TLC (generally 1.5 hr). The reaction was quenched with sat. NH₄Cl solution, extracted with ether. The organic phase was washed with brine, dried over MgSO₄ and concentrated to give the crude product, which was purified by flash column chromatography (SiO₂, 10:1 hexane: ethyl acetate).

If R¹ is a group other than methyl, then the allyl β-ketoesters were synthesized by the condensation of the corresponding acid chloride with Meldrum’s acid, followed by addition of the appropriate allylic alcohol.

To a solution of the Meldrum’s acid (1.5 g, 10.4 mmol) in 20 mL dichloromethane at 0 °C under argon was added pyridine (26.0 mmol, 2.5 eq.) over 5 mins, followed by propionyl chloride (10.4 mmol, 1.0 eq.) over 20 mins. The resulting orange mixture was kept stirring until reaction completion indicated by TLC (generally 12 hrs). The reaction mixture was poured to a mixture of ice and HCl (2 M/L), extracted with dichloromethane, dried over MgSO₄ and concentrated to give the crude product, which was purified by flash column chromatography (SiO₂, 8:1 hexane: ethyl acetate).
General procedure for ruthenium-catalyzed tandem Michael-allylation:

In a Schlenk tube under argon, \([\text{Cp}^*\text{RuCl}]_4\) (2.5 mol %), bipyridine (10 mol %), allyl \(\beta\)-ketoester (1 mmol) and malonitrile (1 equiv.) were dissolved in 5 mL of methylene chloride. The resulting deep purple solution was stirred at room temperature under Ar. The reaction was monitored by TLC. Following solvent evaporation the crude product was purified via flash chromatography (SiO\(_2\), 6:1 hexane: ethyl acetate), providing the products in > 95% purity as determined by \(^1\)H NMR spectroscopy.

General procedure for the palladium-catalyzed tandem Michael-allylation:

In a Schlenk tube under argon, \([\text{Pd(PPh}_3]_4\) (10 mol %), allyl \(\beta\)-ketoester (1 mmol) and malonitrile (1 equiv.) were dissolved in 5 mL of methylene chloride. The resulting yellow solution was stirred at room temperature under Ar. The reaction was monitored by TLC. Following solvent evaporation the crude product was purified via flash chromatography (SiO\(_2\), 6:1 hexane: ethyl acetate), providing the products in > 95% purity as determined by \(^1\)H NMR spectroscopy.
Spectroscopic Data

\[
\text{(E)-4-\{(trimethylsilyl)but-2-enyl\}3-oxobutanoate}
\]

\[\text{27a (cw1067)} \]

\text{colorless oil}

\[1^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta \text{ppm 12.08 (0.1 H, br. S.: CH(OH)=), 5.85 (1H, ddd, J=15.2, 8.3, 8.2 Hz: TMSCH}_2\text{CH}=), 5.45 (1H, m: CH=), 4.57 (2H, d, J=6.8 Hz: CH}_2\text{CO), 3.46 (s, 2H: C(O)CH}_2\text{), 2.26 (3H, s: C(O)CH}_3\text{), 1.56 (2H, dd, J=8.2, 0.5 Hz: CH}_2\text{TMS), 0.04 (s, 9H: CH}_3\text{(TMS)).}
\]

\[13^1\text{C NMR (100 MHz, CDCl}_3\text{)} \delta \text{ppm 203.95 (C}=O\text{), 167.5 (CO}_2\text{), 135.20 (CH=), 122.05 (TMSCH}_2\text{CH}=), 66.97 (OCH}_2\text{), 50.68 (CH}_2\text{CO), 30.52 (CH}_3\text{CO), 23.49 (TMSCH}_2\text{), -1.86 (CH}_3\text{(TMS)).}
\]

\[
\text{4-phenyl-4-\{(trimethylsilyloxy)butan-2-one}
\]

\[\text{25b (cw1070)} \]

\text{Pd(PPh}_3\text{)_4: 95\% NMR yield}

\[1^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta \text{ppm 7.36 (m, 4H: arom H), 7.28 (m, 1H: arom H), 5.18 (dd, 1H, J=8.8, 4.0 Hz: CHPh), 2.93 (dd, 1H, J=15.2, 8.8 Hz: C(O)CH}_2\text{), 2.61 (dd, 1H, J=15.3, 4.0 Hz: C(O)CH}_2\text{), 2.15 (s, 3H: C(O)CH}_3\text{), 0.03 (s, 9H: CH}_3\text{(TMS)).}
\]

\[
\text{allyl 3-oxobutanoate}
\]

\[\text{22a (cw1083)} \]

\text{colorless oil}

\[1^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta \text{ppm 12.05 (0.1 H, br. S.: CH(OH)=), 5.95 (1H, m: CH=), 5.37 (1H, d, J=17.2 Hz: CH=CH(H)}_\text{H(E), 5.28 (1H, d, J=11.7 Hz: CH=CH(H)}_\text{H(Z), 4.65 (2H, d, J=6.8 Hz: CH}_2\text{O), 3.51 (s, 2H: C(O)CH}_2\text{), 2.27 (3H, s: C(O)CH}_3\text{).}
\]

\[13^1\text{C NMR (100 MHz, CDCl}_3\text{)} \delta \text{ppm 201.0 (C}=O\text{), 167.3 (CO}_2\text{), 132.4 (CH=), 118.8 (=CH}_2\text{), 66.3 (OCH}_2\text{), 50.5 (CH}_2\text{CO), 30.6 (CH}_3\text{CO).}
\]
2-allyl-2-(3-oxo-1-phenylbutyl)malononitrile

\[ \text{27a} \] (cw1110)

colorless oil

[Cp\(^*\)Ru(bpy)Cl]: 84% yield

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44 (m, 5H: arom H), 5.98-5.88 (m, 1H, \(J = 10.1, 6.8, 7.3, 7.1\) Hz: =CH), 5.43 (d, 1H, \(J = 10.1\) Hz: CH=CH(\(H\))\(_2\)), 5.23 (d, 1H, \(J = 6.8\) Hz: CH=CH(\(H\))\(_2\)), 3.78 (dd, 1H, \(J = 10.4, 3.5\) Hz: C(O)CH\(_2\)C\(\text{H}\)Ph), 3.44 (dd, \(J = 10.4, 6.8\) Hz: CH=CH(\(H\))\(_2\)), 3.23 (dd, \(J = 3.5, 17.4\) Hz, 1H: C(O)CH\(_2\)), 2.47(dd, \(J = 7.6, 13.9\) Hz, 1H: CH\(_2\)CH=), 2.39(dd, \(J = 5.8, 13.9\) Hz, 1H: CH\(_2\)CH=), 2.13(s, 3H: C(O)CH\(_3\))

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 203.95 (C=O), 136.15 (Quat.), 129.54 (=CH), 129.54 (Arom. CH), 123.36 (=CH\(_2\)), 115.91 (CN), 46.25 (CHPh), 43.52 (C(CN)\(_2\)), 40.73 (CH\(_2\)CH=), 30.86 (CH\(_3\)).

The assignments of the \(^1\)H and \(^{13}\)C were based on DEPT, COSY, and HMQC spectroscopies.

2-[1-[4-(acetyloxy)phenyl]-3-oxobutyl]-2-(2-propen-1-yl)-propanedinitrile

\[ \text{27b} \] (cw1126)

colorless oil

[Cp\(^*\)Ru(bpy)Cl]: 97% yield

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.42 (m, \(J = 8.6, 2\)H: arom H), 7.14 (m, \(J = 8.6, 2\)H: arom H) 5.93-5.83 (m, 1H, \(J = 10.1, 17.4, 7.6, 5.8\) Hz: =CH), 5.43 (d, 1H, \(J = 10.1\) Hz: CH=CH(\(H\))\(_2\)), 5.34 (d, 1H, \(J = 17.4\) Hz: CH=CH(\(H\))\(_2\)), 3.78 (dd, 1H, \(J = 9.8, 17.7\) Hz, 1H: C(O)CH\(_2\)), 3.36 (dd, \(J = 3.5, 17.7\) Hz, 1H: C(O)CH\(_2\)), 2.47(dd, \(J = 7.6, 13.9\) Hz, 1H: CH\(_2\)CH=), 2.39(dd, \(J = 5.8, 13.9\) Hz, 1H: CH\(_2\)CH=), 2.13(s, 3H: C(O)CH\(_3\))

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 203.40 (C=O), 169.27 (OC=O), 151.24 (Quat.), 132.95 (Quat.), 130.05 (Arom. CH), 128.56 (=CH), 123.66 (=CH\(_2\)), 122.53 (Arom. CH), 115.17 (CN), 14.44 (CN), 46.32 (C(O)CH\(_2\)), 45.30 (CHAr), 42.98 (C(CN)\(_2\)), 40.37 (CH\(_2\)CH=), 30.75 (CH\(_3\)), 21.35 (OC(O)CH\(_3\)).
**FTIR** (CDCl$_3$): $\nu_{\text{max}}$ 3062, 2252, 1770, 1724, 1425, 989, 914.

**HRMS** calcd for C$_{18}$H$_{18}$N$_2$O$_3$Na [M+Na] 333.1215, found 333.1208.

```
\begin{center}
\begin{tikzpicture}
\node[circle, fill=black, inner sep=0.2pt] (A) at (0,0) {$\text{O}$};
\node[circle, fill=black, inner sep=0.2pt] (B) at (1,0) {$\text{O}$};
\node[circle, fill=black, inner sep=0.2pt] (C) at (1.5,0) {$\text{Ph}$};
\node[circle, fill=black, inner sep=0.2pt] (D) at (2.5,0) {$\text{cinnamyl 3-oxobutanoate}$};
\node[circle, fill=black, inner sep=0.2pt] (E) at (3,0) {$\text{20a}^7$ (cw1098)};\end{tikzpicture}
\end{center}
```

colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 12.07 (0.1 H, s: CH(OH)=), 7.42 (2H, m: arom H), 7.35 (2H, t, $J$=7.3 Hz: arom H), 7.30 (1H, d, $J$=7.0 Hz: arom H), 6.70 (1H, d, $J$=15.9 Hz: PhCH=), 6.30 (1H, dt, $J$=15.8, 6.7 Hz: CH), 4.83 (2H, d, $J$=6.5 Hz: CH$_2$O), 3.53 (s, 2H: C(O)CH$_2$), 2.31 (3H, s: C(O)CH$_3$).

```
\begin{center}
\begin{tikzpicture}
\node[circle, fill=black, inner sep=0.2pt] (A) at (0,0) {$\text{O}$};
\node[circle, fill=black, inner sep=0.2pt] (B) at (1,0) {$\text{O}$};
\node[circle, fill=black, inner sep=0.2pt] (C) at (1.5,0) {$\text{Ph}$};
\node[circle, fill=black, inner sep=0.2pt] (D) at (2.5,0) {$\text{1-phenylallyl 3-oxobutanoate}$};
\node[circle, fill=black, inner sep=0.2pt] (E) at (3,0) {$\text{33a}$ (cw1133)};\end{tikzpicture}
\end{center}
```

colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.36 (5H, m: arom H), 6.33 (1H, dt, $J$=6.0, 1.2 Hz: PhCH), 6.04 (1H, ddd, $J$=17.0, 10.6, 5.9 Hz: CH=), 5.33 (2H, m: =CH$_2$), 3.53 (2H, s: C(O)CH$_2$), 2.26 (3H, s: C(O)CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 200.8 (C=O), 138.6 (Quat. arom. C), 166.5 (CO$_2$), 136.0 (CH=), 129.0 (Arom. CH), 128.9 (Arom. CH), 128.9 (Arom. CH), 127.6 (Arom. CH), 118.1 (=CH$_2$), 77.7 (OCH), 50.7 (CH$_2$CO), 30.6 (CH$_3$CO).
**2-(3-oxo-1-phenylbutyl)-2-(1-phenylallyl)malononitrile**

**27c** (cw1104)

- Colorless oil
- [Cp*Ru(bpy)Cl]: 89% yield, dr = 1.9

**2-(3-oxo-1-phenylbutyl)-2-(1-phenylallyl)malononitrile**

**27c** (cw1138)

- Colorless oil
- [Cp*Ru(bpy)Cl]: 85% yield, dr = 3.5

**1H NMR** (400 MHz, CDCl₃) Major diastereoisomer: δ 7.50-7.28 (m, 10H: arom H), 6.41-6.32 (m, 1H, J = 16.9 Hz: =CH), 5.53 (d, 1H, J = 10.4 Hz: CH=CH(H₂), 5.23 (d, 1H, J = 16.9 Hz: CH=CH(H)₂), 3.87 (dd, 1H, J = 10.6, 3.3 Hz: C(O)CH₂CH₃), 3.45-3.38 (m, 2H: C(O)CH₂CH₃), 3.22 (dd, J = 17.4, 3.3 Hz, 1H: C(O)CH₂CH₃), 2.09 (s, 3H: C(O)CH₂CH₃).

Minor diastereoisomer: δ 7.50-7.28 (m, 10H: arom H, overlapping minor/major isomers), 6.44-6.30 (m, 1H, overlapping minor/major isomers: =CH), 5.47 (d, 1H, J = 10.1 Hz: CH=CH(H)₂), 5.36-5.26 (d, 1H, overlapping minor/major isomer: CH=CH(H)₂), 3.76 (dd, 1H, J = 10.6, 3.0 Hz: C(O)CH₂CH₃), 3.45-3.38 (m, 2H: overlapping CH₃, C(O)CH₂CH₃), 3.08 (dd, J = 17.2, 3.0 Hz, 1H: C(O)CH₂CH₃), 2.06 (s, 3H: C(O)CH₂CH₃).

**13C NMR** (100 MHz, CDCl₃) Major diastereoisomer: δ 203.76 (C=O), 137.10 (Quat.), 135.52 (Quat.), 132.40 (CH), 129.34 (Arom. CH), 129.35 (Arom. CH), 128.73 (Arom. CH), 122.90 (CH₂), 115.13 (CN), 114.21 (CN), 52.90 (CH₃), 48.65 (C(CN)₂), 46.85 (C(O)CH₂CH₃), 44.68 (C(O)CH₂CH₃), 30.94 (CH₃).

Minor diastereoisomer: δ 203.76 (overlapping C=O), 136.65 (Quat.), 135.20 (Quat.), 133.84 (CH), 129.58-128.91 (overlapping minor/major isomer: Arom. CH), 121.88 (CH₂), 115.09 (CN), 114.63 (CN), 53.09 (overlapping with solvent: CH₃), 48.84 (overlapping minor/major isomer: C(CN)₂), 45.76 (C(O)CH₂CH₃), 44.71 (overlapping minor/major isomer: C(O)CH₂CH₃), 30.85 (overlapping minor/major isomer: CH₃).

**FTIR** (CDCl₃): νmax 3053, 2304, 1724, 1421, 991, 895.
**HRMS** calcd for C$_{22}$H$_{20}$N$_2$O$_2$Na [M+Na] 351.1473, found 351.1468.

Ph\[O\]\[O\]\[\]
\hspace{2cm} \text{allyl 3-oxo-4-phenylbutanoate}
\hspace{2cm} \text{cw1150}
\hspace{2cm} \text{colorless oil}

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 12.06 (0.1H, s: CH(OH)=), 7.36 (2H, q, $J$=7.1 Hz: arom H), 7.32 (1H, d, $J$=7.5 Hz: arom H), 7.23 (2H, d, $J$=7.5 Hz: arom H), 5.92 (1H, m: CH=), 5.35 (1H, d, $J$=17.2 Hz: CH=CH$_2$), 5.28 (1H, d, $J$=10.4 Hz: CH=CH(H)$_2$), 4.63 (2H, d, $J$=7.0 Hz: CH$_2$O), 3.86 (2H, s: PhCH$_2$), 3.51 (2H, s: C(O)CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 200.7 (C=O), 167.2 (CO$_2$), 133.5 (Quat. arom. C), 131.9 (CH=), 130.0 (Arom. CH), 129.3 (Arom. CH), 127.8 (Arom. CH), 119.4 (=CH$_2$), 66.5 (OCH$_2$), 50.5 (PhCH$_2$), 48.6 (CH$_2$CO).

\[\text{Ph} \underset{O}{\begin{array}{c} \text{CN} \\ \text{CN} \end{array}} \underset{\text{CN}}{\text{Ph}}\]
\hspace{2cm} \text{2-allyl-2-(3-oxo-1,4-diphenylbutyl)malononitrile}
\hspace{2cm} \text{27d (cw1153)}
\hspace{2cm} \text{colorless oil}
\hspace{2cm} \text{[Cp*Ru(bpy)Cl]: 87% yield}

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 (m, 8H: arom H), 7.05 (m, 2H: arom H), 5.87 (m, 1H, $J$ = 10.1, 16.9, 7.6, 7.1 Hz: =CH), 5.41 (d, 1H, $J$ = 10.1 Hz: CH=CH(H)$_2$), 5.31 (d, 1H, $J$ = 16.9 Hz: CH=CH(H)$_2$), 3.77 (dd, 1H, $J$=10.4, 3.3 Hz: C(O)CH$_2$CHPh), 3.66 (AB, 2H: PhCH$_2$C(O)), 3.45 (dd, $J$=10.6, 17.4 Hz, 1H: C(O)CH$_2$), 3.22 (dd, $J$=3.5, 17.2 Hz, 1H: C(O)CH$_3$), 2.46(dd, $J$=7.6, 14.1 Hz, 1H: CH$_2$CH=), 2.42(dd, $J$=7.1, 13.9 Hz, 1H: CH$_2$CH=).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 203.68 (C=O), 135.35 (Quat.), 133.17 (Quat.), 129.77-127.78 (Arom. CH; =CH), 123.75 (=CH$_2$), 115.46 (CN), 114.67 (CN), 51.03 (PhCH$_2$C(O)), 46.37 (CHPh), 44.35 (C(O)CH$_2$), 43.23 (C(CN)$_2$), 40.68 (CH$_2$CH=).

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 12251, 1720, 1454, 989.

**HRMS** calcd for C$_{22}$H$_{20}$N$_2$O$_2$Na [M+Na] 351.1473, found 351.1481.
allyl 3-oxo-3-phenylpropanoate

cw1159° (4:1)
colorless oil

^1H NMR (400 MHz, CDCl$_3$) δ ppm 7.97 (2H, d, $J$=8.0 Hz: arom H), 7.62 (1H, t, $J$=7.4 Hz: arom H), 7.51 (2H, t, $J$=7.0 Hz: arom H), 5.92 (1H, m: CH=), 5.33 (1H, d, $J$=17.2 Hz: CH=CH($H_E$)), 5.25 (1H, d, $J$=10.4 Hz: CH=CH($H_Z$)), 4.69 (2H, dd, $J$=5.7, 1.4 Hz: CH$_2$O), 4.06 (2H, d, $J$=1.8 Hz: C(O)CH$_2$).

Enol form: 12.51 (1H, s: O H), 7.80 (2H, d, $J$=6.9 Hz: arom H), 7.45 (2H, m: arom H), 6.02 (1H, m: CH=), 5.74 (1H, d, $J$=1.8 Hz: PhC(OH)=CH), 5.40 (1H, d, $J$=17.2 Hz: CH=CH($H_E$)), 4.74 (2H, dd, $J$=5.7, 1.4 Hz: CH$_2$O).

13C NMR (100 MHz, CDCl$_3$) δ 195.46 (C=O), 136.46 (Quat.), 135.92 (Quat.), 129.57-128.51 (overlapping Arom. CH; =CH), 123.80 (=CH$_2$), 115.69 (CN), 114.92 (CN), 46.53 (CHPh), 43.53 (C(CN)$_2$), 41.66 (C(O)CH$_2$), 40.83 (CH$_2$=).

FTIR (CDCl$_3$): $\nu_{max}$ 3053, 2308, 1689, 1421, 989, 895.

HRMS calcd for C$_{21}$H$_{19}$N$_2$O [M+H] 315.1497, found 315.1493.
Cinnamyl 3-oxopentanoate

**19a** (cw1114)

Colorless oil

**1H NMR** (400 MHz, CDCl₃) δ ppm 12.09 (0.06 H, s: C(H)(OH)=), 7.24 - 7.58 (5H, m: arom H), 6.71 (1H, d, J = 16.0 Hz: PhCH=), 6.33 (1H, m: =CH), 4.81 (2H, m: CH₂O), 3.52 (s, 2H: C(O)CH₂C), 2.60 (2H, q, J = 7.2 Hz: CH₂CH), 1.09 (3H, t, J = 7.3 Hz: CH₃).

2-(3-oxo-1-phenylpentyl)-2-(1-phenylallyl)malononitrile

**27f** (cw1119)

Colorless oil

[C₅Ru(bpy)Cl]: 93% yield, dr = 1.8

**1H NMR** (400 MHz, CDCl₃) Major diastereoisomer: δ 7.50-7.28 (m, 10H: arom H), 6.42-6.33 (m, 1H, J = 16.9, 10.4, Hz: =CH), 5.53 (d, 1H, J = 10.4 Hz: CH=CH(HE)), 5.23 (d, 1H, J = 16.9 Hz: CH=CH(HE)), 3.90 (dd, 1H, J = 10.4, 16.9 Hz: CH=C=CH(HE)), 3.53-3.29 (m, 2H: overlapping CHPh, C(O)CH₂), 2.45 (m, 1H: C(O)CH₂), 2.92 (m, 1H: C(O)CH₂), 0.95 (app. t, 3H: C(O)CH₂CH₃).

Minor diastereoisomer: δ 7.50-7.28 (m, 10H, arom H: overlapping minor/major isomer), 6.34-6.25 (m, 1H, =CH: overlapping minor/major isomer), 5.43 (d, 1H, J = 10.4 Hz: CH=CH(HE)), 5.28 (d, 1H, J = 16.9 Hz: CH=CH(HE)), 3.76 (dd, 1H, J = 10.4, 3.3 Hz: C(O)CH₂CH₃), 3.53-3.29 (m, 2H: overlapping minor/major isomer CHPh, C(O)CH₂), 2.45 (m, 1H: C(O)CH₂), 2.21 (m, 1H: overlapping minor/major isomer C(O)CH₂), 0.95 (app. t, 3H: overlapping minor/major isomer C(O)CH₂CH₃);

**13C NMR** (100 MHz, CDCl₃) Major diastereoisomer: δ 206.84 (C=O), 137.30 (Quat.), 135.61 (Quat.), 132.61 (=CH), 129.51-128.92 (Arom. CH), 123.30 (=CH₂), 115.32 (CN), 114.42 (CN), 53.09 (CHPh), 48.84 (C(CN)₂), 45.85 (C(O)CH₂), 44.94 (C(O)CH₂CHPh), 37.22 (CH₃CH₂), 7.82 (CH₃).

Minor diastereoisomer: δ 206.84 (C=O: overlapping minor/major isomer), 136.22 (Quat.), 135.61 (Quat.), 134.09 (=CH), 129.51-128.92 (Arom. CH), 121.99 (=CH₂), 120.01 (Arom. CH).
114.89(CN), 114.42 (CN), 54.35 (CHPh), 48.35 (C(CN)₂), 45.47 (C(O)CH₂), 44.65 (C(O)CH₂CHPh), 37.29 (CH₃CH₂), 7.77 (CH₃).

**FTIR** (CDCl₃): $\nu_{\text{max}}$ 2252, 1720, 1456, 991.


**MeO**

(E)-3-(4-methoxyphenyl)allyl 3-oxobutanoate
cw1144¹⁰
colorless oil

**¹H NMR** (400 MHz, CDCl₃) δ ppm 7.35 (2H, d, $J$=8.8 Hz: arom H), 6.88 (2H, d, $J$=8.8 Hz: arom H), 6.64 (1H, d, $J$=16.0 Hz: =C=H$_{Ar}$), 6.17 (1H, dt, $J$=15.8, 6.7 Hz: CH=), 4.80 (2H, dd, $J$=6.7, 1.3 Hz: CH$_2$O), 3.83 (2H, s: C(O)CH$_2$), 2.30 (3H, s: CH$_3$).

2-(1-(4-methoxyphenyl)allyl)-2-(3-oxo-1-phenylbutyl) malononitrile

**²H NMR** (400 MHz, CDCl₃) Major diastereoisomer: δ 7.50-7.21 (m, 5H: arom H), 6.94-6.88 (m, 4H: Arom. H), 6.38-6.23 (m, 1H, $J$ = 16.9, 10.1, 9.1 Hz: =CH$_{Ar}$), 5.51 (d, 1H, $J$ = 10.1 Hz: CH=CH($H_E$), 5.23 (d, 1H, $J$ = 16.9 Hz: CH=CH($H_Z$), 3.81 (s, 3H: OCH$_3$), 3.81-3.85(dd, 1H: overlapping C(O)CH$_2$CHPh, OCH$_3$), 3.48-3.31 (m, 2H: overlapping CH$_3$Ar, C(O)CH$_2$), 3.20 (dd, $J$ =17.2, 3.0 Hz, 1H: C(O)CH$_2$), 2.09(s, 3H: C(O)CH$_3$).

Minor diastereoisomer: δ 7.50-7.21 (m, 5H: arom H, overlapping minor/major isomer), 6.94-6.88 (m, 4H: Arom. H, overlapping minor/major isomer), 6.38-6.23 (m, 1H: =CH$_3$, overlapping minor/major isomer), 5.41 (d, 1H, $J$ = 10.1 Hz: CH=CH($H_E$), 5.23 (d, 1H: CH=CH($H_Z$, overlapping minor/major isomer), 3.85 (s, 3H: OCH$_3$), 3.71(dd, 1H, $J$ =10.9, 3.0 Hz: C(O)CH$_2$CHPh), 3.48-3.31 (m, 2H: overlapping
minor/major isomer: CHAr, C(O)CH₂, 3.08 (dd, J =17.2, 3.0 Hz, 1H: C(O)CH₂), 2.05(s, 3H: C(O)CH₃).

**1³C NMR** (100 MHz, CDCl₃) Major diastereoisomer: δ 203.96 (C=O), 160.27 (Quat.), 135.74 (Quat.), 132.79 (=CH), 130.52-129.22 (Arom. CH), 122.67 (=CH₂), 114.82 (Arom. CH), 115.38 (CN), 114.82 (CN), 55.73 (OCH₃), 52.40 (CHA ł), 49.17 (C(CN)₂), 47.01 (C(O)CH₂), 44.74 (CHPh), 31.12 (CH₃).

Minor diastereoisomer: δ 203.96 (C=O, overlapping minor/major isomer), 136.20 (Quat.), 134.26 (=CH), 130.52-129.22 (Arom. CH, overlapping minor/major isomer), 127.41 (Quat.), 121.59 (=CH₂), 114.82 (Arom. CH, overlapping minor/major isomer), 114.94 (CN), 114.50 (CN), 55.67 (OCH₃), 53.61 (CHA ł), 48.58 (C(CN)₂), 46.58 (C(O)CH₂), 44.51 (CHPh), 31.17 (CH₃). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl₃): νmax 2247, 1724, 1253.

**HRMS** calcd for C_{23}H_{22}N_{2}O_{2}Na [M+Na] 381.1579, found 381.1556.

![Chemical Structure](image)

(E)-3-(4-chlorophenyl)allyl 3-oxobutanoate  
19b (cw1145)¹¹  

colorless oil

**¹H NMR** (400 MHz, CDCl₃) δ ppm 12.04 (0.1 H, s: CH(OH)=), 7.32 (4H, m: arom H), 6.63 (3 H, d, J=15.9, 1.1 Hz: =CHAr), 6.27 (5 H, dt, J=15.9, 6.5 Hz: CH=), 4.81 (2H, dd, J=6.4, 1.3 Hz: CH₂O), 3.53 (2H, s: C(O)CH₂), 2.31 (3H, s: CH₃).
2-(1-(4-chlorophenyl)allyl)-2-(3-oxo-1-phenylbutyl)malononitrile

27h (cw1155)
colorless oil

[\text{Cp}^* \text{Ru(bpy)Cl}]: 62\% \text{ yield, } dr = 1.8

$^1$H NMR (400 MHz, CDCl$_3$) Major diastereoisomer: $\delta$ 7.50-7.22 (m, 9H: arom H), 6.31 (m, 1H, $J = 16.7, 10.4, 9.1$ Hz: \(=\text{CH}\)), 5.55 (d, 1H, $J = 10.4$ Hz: \(=\text{CH}(H)_E\)), 5.21 (d, 1H, $J = 16.7$ Hz: \(=\text{CH}(H)_Z\)), 3.88 (dd, $J = 10.4$ Hz: \(=\text{CH}(H)_E\)), 5.21 (d, 1H, $J = 16.7$ Hz: \(=\text{CH}(H)_Z\)), 3.44-3.34 (m, 2H: overlapping CHAr, C(O)CH$_2$), 3.21 (dd, $J =17.4, 3.3$ Hz, 1H: C(O)CH$_2$), 2.10 (s, 3H: C(O)C$_3$).

Minor diastereoisomer: $\delta$ 7.43-7.22 (m, 9H: arom H), 6.24 (m, 1H, $J = 16.7, 10.4, 9.1$ Hz: \(=\text{CH}\)), 5.44 (d, 1H, $J = 10.4$ Hz: \(=\text{CH}(H)_E\)), 5.26 (d, 1H, $J = 16.7$ Hz: \(=\text{CH}(H)_Z\)), 3.69 (dd, $J = 10.4$ Hz: \(=\text{CH}(H)_E\)), 5.26 (d, 1H, $J = 16.7$ Hz: \(=\text{CH}(H)_Z\)), 3.49 (d, 1H, $J = 8.8$ Hz: CHAr), 3.35 (dd, $J =17.2, 10.4$ Hz, 1H: C(O)CH$_2$), 3.10 (dd, $J =16.9, 3.0$ Hz, 1H: C(O)CH$_2$), 2.07 (s, 3H: C(O)C$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) Major diastereoisomer: $\delta$ 203.83 (C=O), 135.86 (Quat.), 135.42 (Quat.), 131.98 (=CH), 130.30 (Arom. CH), 129.54 (Arom. CH), 123.56 (=CH$_2$), 115.06 (CN), 114.25 (CN), 52.29 (CHAr), 48.65 (C(CN)$_2$), 47.17 (C(O)CH$_2$), 44.79 (CHPh), 31.12 (CH$_3$).

Minor diastereoisomer: $\delta$ 203.78 (C=O), 135.91 (Quat.), 135.39 (Quat.), 133.56 (=CH), 130.70-128.22 (Arom. CH), 122.39 (=CH$_2$), 115.14 (CN), 114.63 (CN), 53.57 (CHAr), 48.21 (C(CN)$_2$), 46.62 (C(O)CH$_2$), 44.53 (CHPh), 31.19 (CH$_3$).

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 2253, 1726, 1425, 990, 912.

HRMS calcd for C$_{21}$H$_{20}$NOCl [M+H-HCN] 337.1, found 337.0.
4-(5',5''-dicyano-2-oxo-6-phenyloct-7-en-4-yl)phenyl acetate

27i (cw1111) colorless oil
[Cp*Ru(bpy)Cl]: 92% yield, dr = 2.7

4-(5',5''-dicyano-2-oxo-6-phenyloct-7-en-4-yl)phenyl acetate

27i (cw1139) colorless oil
[Cp*Ru(bpy)Cl]: 76% yield, dr = 4.5

$^1$H NMR (400 MHz, CDCl$_3$) Major diastereoisomer: $\delta$ 7.51-7.09 (10H: arom H), 6.40-6.23 (m, 1H, $J$ = 10.4, 17.4 Hz: $=$CH), 5.53 (d, 1H, $J$ = 10.4 Hz: CH=$=CH(H)_2$), 5.25 (d, 1H, $J$ = 17.4 Hz: CH=$=CH(H)_2$), 3.89 (dd, 1H, $J$ =3.0, 10.4 Hz: C(O)CH$_2$CH), 3.49-3.27 (m, 2H: overlapping CHPh, C(O)CH$_3$), 3.22 (dd, $J$ =3.0, 17.4 Hz, 1H: C(O)CH$_2$), 2.34 (s, 3H: OC(O)CH$_3$), 2.11(s, 3H: C(O)CH$_3$).

Minor diastereoisomer: $\delta$ 7.51-7.09 (10H: arom H, overlapping minor/major isomer), 6.40-6.23 (m, 1H: $=$CH, overlapping minor/major isomer), 5.42 (d, 1H, $J$ = 10.4 Hz: CH=$=CH(H)_2$), 5.25 (d, 1H, $J$ = 17.4 Hz: CH=$=CH(H)_2$, overlapping minor/major isomer), 3.74 (dd, 1H, $J$ =3.0, 10.4 Hz: C(O)CH$_2$CH), 3.49-3.27 (m, 2H: overlapping minor/major isomer CHPh, C(O)CH$_3$), 3.11 (dd, $J$ =3.0, 17.4 Hz, 1H: C(O)CH$_2$), 2.32 (s, 3H: OC(O)CH$_3$), 2.07 (s, 3H: C(O)CH$_3$);

$^{13}$C NMR (100 MHz, CDCl$_3$) Major diastereoisomer: $\delta$ 203.05 (C=O), 169.46 (OC=O), 151.49 (Quat.), 137.12 (Quat.), 132.45 (=CH), 133.11 (Quat.), 129.57-129.91 (Arom. CH), 122.59 (overlapping $=$CH$_2$, Arom. CH), 115.17 (CN), 114.30 (C), 53.07 (CHPh), 48.77 (C(CN)$_2$), 47.16 (C(O)CH$_2$), 44.15 (CHAr), 31.02 (CH$_3$C(O)), 21.62 (OC(O)CH$_3$).
Minor diastereoisomer: δ 203.05 (C=O, overlapping minor/major isomer), 169.46 (OC=O, overlapping minor/major isomer), 135.40 (Quat.), 134.06 (=CH), 133.52 (Quat.), 133.11 (Quat.), 130.63 (Arom. CH, overlapping minor/major isomer), 122.59 (=CH₂, Arom. CH, overlapping minor/major isomer), 115.17/114.30 (CN, overlapping minor/major isomer), 54.27 (CPh), 48.16 (C(CN)₂), 46.87 (C(O)CH₂), 43.82 (CHAr), 31.07 (CH₃C(O)), 21.62 (OC(O)CH₃, overlapping minor/major isomer).

**FTIR** (CDCl₃): ν₂₃₀₅, 1769, 1724, 1421, 1205, 895.

**HRMS** calcd for C₂₄H₂₂N₂O₃Na [M+Na] 409.1528, found 409.1523.

![Chemical Structure](image)

2-cinnamyl-2-(3-oxo-1-phenylbutyl)malononitrile

30b (cw1124)

colorless oil

Pd(PPh₃)₄: 80% yield

**¹H NMR** (400 MHz, CDCl₃) δ 7.48-7.33 (m, 10H: arom H), 6.65 (d, 1H, J = 15.7 Hz: =CHPh), 6.26 (m, 1H, J = 15.7, 7.6, 7.3 Hz: CH₂CH=), 3.85 (dd, 1H, J = 10.4, 3.5 Hz: C(O)CH₂CHPh), 3.48 (dd, J = 17.4, 10.4 Hz, 1H: C(O)CH₂), 3.26 (dd, J = 17.4, 3.5 Hz, 1H: C(O)CH₂), 2.73 (dd, J = 7.6, 13.9 Hz, 1H: CH₂CH=), 2.60 (dd, J = 7.3, 13.9 Hz, 1H: CH₂CH=), 2.15 (s, 3H: C(O)CH₃);

**¹³C NMR** (100 MHz, CDCl₃) δ 203.96 (C=O), 137.99 (=CHPh), 136.19 (Quat.), 136.19 (Quat.), 129.57 (Arom. CH), 129.50 (Arom. CH), 129.46 (Arom. CH), 129.17 (Arom. CH), 128.90 (Arom. CH), 127.14 (Arom. CH), 122.07 (CH₂CH=), 115.78 (CN), 115.00 (CN), 46.35 (CHPh), 46.20 (C(O)CH₂CHPh), 43.88 (C(CN)₂), 40.26 (CH₂CH=), 30.87 (CH₃).

**FTIR** (CDCl₃): ν₂₂₄₈, 1724, 1456, 968.

2-cinnamyl-2-(3-oxo-1-phenylpentyl)malononitrile
\(30c\) (cw1156)
colorless oil

Pd(PPh\(_3\))\(_4\): 88% yield

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44-7.31 (m, 10H: arom H), 6.60 (d, 1H, \(J = 15.7\) Hz: =CHPh), 6.21 (m, 1H, \(J = 15.7, 7.8, 7.3\) Hz: CH=CHPh), 3.86 (dd, 1H, \(J = 10.1, 3.5\) Hz: C(O)CH\(_2\)CHPh), 3.42 (dd, 1H, \(J = 10.1, 17.1\) Hz: EtC(O)CH\(_2\)H), 3.20 (dd, 1H, \(J = 3.5, 17.1\) Hz: EtC(O)CH\(_2\)H), 2.66 (dd, \(J = 13.9, 7.8\) Hz, 1H: CH\(_3\)CH=), 2.58-2.47 (m, 2H: overlapping CH\(_2\)CH=, CH\(_2\)C(O)), 2.31 (q, 1H, \(J = 7.3\) Hz: CH\(_2\)C(O)), 0.95 (t, 3H, \(J = 7.3\) Hz: C(O)CH\(_2\)CH\(_3\)).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 206.77 (C=O), 138.27 (=CHPh), 136.15 (Quat.), 135.82 (Quat.), 129.64-128.87 (Arom. CH), 127.12 (Arom. CH), 119.53 (CH=CHPh), 115.67 (CN), 114.90 (CN), 46.47 (CHPh), 45.30 (EtC(O)CH\(_2\)) 43.68 (C(CN)\(_2\)), 40.22 (CH\(_2\)CH=), 37.20 (CH\(_2\)C(O)), 7.87 (CH\(_3\)).

FTIR (CDCl\(_3\)): \(\nu_{max}\) 2249, 1720, 1456, 968.

HRMS calcd for C\(_{23}\)H\(_{23}\)N\(_2\)O [M+H] 343.1810, found 343.1830.

5-allyl-2',2''-dimethyl-5-(3-oxo-1-phenylbutyl)-1,3-dioxane-4,6-dione
\(31a\) (cw1120)
colorless oil
[\(\text{Cp}^*\text{Ru(bpy)Cl}\): 51% yield

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.31 (m, 3H: arom H), 7.19 (d, \(J = 6.8\) Hz, 2H: arom H), 5.74-5.64 (m, 1H, \(J = 12.9, 5.1, 12.6\) Hz: =CH), 5.25 (d, 1H, \(J = 12.9\) Hz: CH=CH(H)\(_2\)), 5.22 (d, 1H, \(J = 5.1\) Hz: CH=CH(H)\(_3\)), 4.05 (dd, 1H, \(J = 8.8, 5.3\) Hz: C(O)CH\(_2\)CHPh), 3.35 (app t, 2H: C(O)CH\(_2\)), 2.89 (dd, \(J = 7.8, 12.6\) Hz, 1H: CH\(_2\)CH=), 2.77 (dd, \(J = 7.3, 12.6\) Hz, 1H: CH\(_2\)CH=), 2.10 (s, 3H: C(O)CH\(_3\)), 1.52 (s, 3H: CH\(_3\)), 0.71 (s, 3H: CH\(_3\)).
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.01 (C=O), 168.46 (OC=O) 167.80 (OC=O) 139.41 (Quat.), 131.70 (=CH), 129.59 (Arom. CH), 129.38 (Arom. CH), 128.57 (Arom. CH), 121.99 (=CH$_2$), 106.64 (C(CH$_3$)$_2$), 59.89 (C(CO$_2$R)$_2$), 47.89 (CHPh), 43.91 (C(O)CH$_2$), 41.42 (CH$_2$CH=), 30.91/30.82 (overlapping C(O)CH$_3$ with CH$_3$), 28.26 (CH$_3$).

FTIR (CDCl$_3$): $\nu_{max}$ 3063, 1765, 1732, 1456.

HRMS calcd for C$_{19}$H$_{22}$O$_3$Na [M+Na] 353.1365, found 353.1347.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35 (m, 2H: arom H), 7.18 (app. t, 1H: arom H), 7.09 (app. d, 1H: arom H), 5.85 (m, 1H, J = 10.1, 16.9 Hz: =CH), 5.33 (d, 1H, $J$ = 10.1 Hz, CH=CH(H)$_2$), 5.10 (d, 1H, $J$ = 16.9 Hz: CH=CH(H)$_2$), 3.80 (dd, 1H, $J$ = 6.6, 3.0 Hz: CH), 3.16 (dd, 1H, $J$ = 17.9, 2.8 Hz: C(O)CH$_2$), 2.83 (dd, 1H, $J$ = 17.9, 9.6 Hz: C(O)CH$_2$), 2.59 (dd, 1H, $J$ = 6.6, 14.1 Hz, 1H: CH$_2$CH=), 2.38 (dd, 1H, $J$ = 8.1, 13.9 Hz: CH$_2$CH=), 2.11 (3H: C(O)CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.35 (C=O), 162.95 (OC=O), 149.94 (Quat.), 130.31 (Arom. CH), 129.04 (=CH), 126.11 (Arom. CH), 123.16 (=CH$_2$), 121.51 (Quat.), 117.25 (Arom. CH), 116.84 (CN), 49.70 (t-C(CN)(CO$_2$)), 47.03 (C(O)CH$_2$), 38.38 (overlapping CH$_2$CH=, CHCH$_2$CO), 30.83 (CH$_3$).

FTIR (CDCl$_3$): $\nu_{max}$ 2250, 1780, 1726, 912.

HRMS calcd for C$_{16}$H$_{15}$NO$_3$Na [M+Na] 292.0950, found 292.0946.
**5-(cyclopent-2-enyl)-2,2-dimethyl-5-(3-oxo-1-phenylbutyl)-1,3-dioxane-4,6-dione**

{\text{31c (cw1123)}}

colorless oil

$^{1}\text{H NMR}$ (400 MHz, CDCl$_3$) $\delta$ ppm 6.15 (1H, m: OCH$_3$), 5.85 (1H, dd, $J$=3.3, 2.2 Hz: CH=), 5.78 (1H, m: =CHCH$_2$), 3.44 (2H, s: C(O)CH$_2$), 2.53 (1H, m: CH$_2$), 2.33 (4H, m: overlapping CH$_3$, CH$_2$), 1.87 (1H, m: CH$_2$), 1.73 (1H, m: CH$_2$).

$^{13}\text{C NMR}$ (100 MHz, CDCl$_3$) Major diastereoisomer: $\delta$ 206.31 (C=O), 169.40 (OC=O) 167.72 (OC=O), 139.78 (Quat.), 136.36 (=CH: $\delta$=5.97ppm), 130.14 (Arom. CH), 129.46 (Arom. CH), 128.37 (CH$_2$: $\delta$=5.51ppm), 106.27 (C(CH$_3$)$_2$), 62.11 (C(CO$_2$R)$_2$), 55.19 (CHCH=CH), 44.27 (CHPh), 43.87(C(O)CH$_2$), 32.73 (CH$_2$=).
δ = 2.37 ppm), 29.61 (CH₃), 29.37 (CH₃), 29.16 (CH₃), 23.85 (CH₂CHCH=CH: δ = 2.08 ppm).

Minor diastereoisomer: δ 206.31 (C=O, overlapping minor/major isomer), 168.65 (OC=O) 166.77 (OC=O), 140.70 (Quat.), 134.36 (=CH: δ = 5.97 ppm), 130.14, 129.46 (Arom. CH, overlapping minor/major isomer), 128.37 (=CH: δ = 5.51 ppm, overlapping minor/major isomer), 106.51 (C(CH₃)₂), 62.48 (C(O)₂R₂), 55.19 (CHCH=CH, overlapping minor/major isomer), 44.78 (CHPh), 43.69 (C(O)CH₂), 32.09 (CH₂CH=: δ = 2.46 ppm), 29.61, 29.37, 29.16 (CH₃, overlapping minor/major isomer), 27.63 (CH₂CHCH=CH, δ = 2.56 ppm).

**FTIR** (CDCl₃): ν max 3063, 1765, 1732, 1456, 945.


\[
\begin{align*}
\text{(E)-pent-1-en-4-yne-1,5-diyl dibenzene} \\
\text{34b}^{13} \text{(cw1212)} \\
\text{colorless oil} \\
\text{40% yield}
\end{align*}
\]

**¹H NMR** (400 MHz, CDCl₃) δ 7.33-7.51 (m, 5H: arom H), 6.75 (d, 1 H, J=15.7 Hz: =CHPh), 6.29 (dt, 1 H, J=6.0, 16.0 Hz: CHCH₂), 3.41 (d, 2 H, J=4.0 Hz: CH₂).

\[
\begin{align*}
\text{2-cinnamyl-2-(1,3-diphenylprop-2-ynyl)malononitrile} \\
\text{34c (cw1212)} \\
\text{colorless oil} \\
\text{40% yield}
\end{align*}
\]

**¹H NMR** (400 MHz, CDCl₃) δ 7.37-7.66 (m, 10H: arom H), 6.80 (d, 1 H, J=15.7 Hz: =CHPh), 6.29 (ddd, 1 H, J=15.4, 7.6, 7.5 Hz: CHCH₂), 4.39 (s, 1 H: CHPh), 3.14 (t, 1H, J=8.1 Hz: CH₂).
2-allyl-5-oxo-3-phenylhexanoic acid

36a (cw1177)

colorless oil

80% yield, dr = 1.5

$^1$H NMR (400 MHz, CDCl$_3$) Major diastereoisomer: $\delta$ 7.33 (m, 2H: arom H), $\delta$ 7.26 (m, 3H: arom H), $\delta$ 5.70 (m, 1H, $J = 7.3$ Hz: =CH), 4.97 (app s, 1H, CH=CH($H_{(E)}$), 4.94 (d, 1H, $J = 7.3$ Hz: =CH=CH($H_{(Z)}$), 3.33 (td, 1H, $J = 10.4$, $J = 3.8$ Hz: C(O)CH$_2$CHPh), 2.98 (dd, 1H, $J = 10.4$, $J = 16.4$ Hz: C(O)CH$_3$), 2.77 (dd, 1H, $J = 3.8$, $J = 16.4$ Hz: C(O)CH$_2$), 2.67 (td, 1H, $J = 4.1$, 1H, $J = 10.1$ Hz: CHCO$_2$H), 2.10 (m, 1H: overlapping H$_2$O, CH$_2$CH=), 1.97 (3H: overlapping CD$_3$CN, CH$_2$CH=), 1.97 (3H: overlapping CD$_3$CN, C(O)CH$_3$).

Minor diastereoisomer: $\delta$ 7.35-7.23 (m, 5H: arom H, overlapping minor/major isomer), $\delta$ 5.80 (m, 1H, $J = 17.2$, 9.9 Hz: =CH), 5.06 (d, 1H, $J = 17.2$ Hz, CH=CH($H_{(E)}$), 5.04 (d, 1H, $J = 9.9$ Hz: CH=CH($H_{(Z)}$), 3.42 (td, 1H, $J = 9.2$, 4.8 Hz: C(O)CH$_2$CHPh), 3.03-2.88 (m, 1H: C(O)CH$_2$, overlapping minor/major isomer), 2.80-2.65 (m, 2H: overlapping minor/major isomer C(O)CH$_3$, CHCO$_2$H), 2.32 (m, 2H: overlapping H$_2$O, CH$_2$CH=), 1.97 (3H: overlapping minor/major isomer CD$_3$CN, C(O)CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) Major diastereoisomer: $\delta$ 206.26 (C=O), 174.34 (HOC=O), 141.41 (Quat.), 135.03 (=CH), 128.07 (Arom. CH), 126.47 (Arom. CH), 115.82 (=CH$_2$), 50.31 (CHCO$_2$H), 46.96 (C(O)CH$_3$), 42.52 (CHPh), 34.20 (CH$_2$CH=), 29.26 (CH$_3$).

Minor diastereoisomer: $\delta$ 206.85 (C=O), 174.97 (HOC=O), 142.01 (Quat.), 135.59 (=CH), 128.22 (Arom. CH, overlapping minor/major isomer), 126.62 (Arom. CH), 116.24 (=CH$_2$, overlapping minor/major isomer), 50.29 (CHCO$_2$H), 45.98 (C(O)CH$_2$), 42.12 (CHPh), 33.85 (CH$_2$CH=), 29.53 (CH$_3$, overlapping minor/major isomer).

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 1745, 1711.

HRMS calcd for C$_{15}$H$_{18}$O$_3$Na [M+Na] 269.1154, found 269.1154.
2-allyl-2-nitro-5-oxo-3-phenylhexanenitrile

\chem{\text{37b (cw2064)}}
colorless oil
Pd(PPh\textsubscript{3})\textsubscript{4}, 56% yield

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \textit{δ} ppm 7.34 (m, 5H: arom H), 5.78 (m, 1H: =CH), 5.35 (dd, 1H, \textit{J}=5.0, 0.7 Hz: CH=CH(H\textsubscript{2}), 5.35 (dd, 1H, \textit{J}=11.8, 0.9 Hz: CH=CH(H\textsubscript{1})), 4.16 (dd, 1H, \textit{J}=8.9, 4.3 Hz: C(O)CH\textsubscript{2}CHPh), 3.29 (dd, 1H, \textit{J}=17.7, 8.9 Hz: C(O)CH\textsubscript{2}), 3.09 (m, 2H: overlapping CH\textsubscript{2}CH=, C(O)CH\textsubscript{2}), 2.83 (dd, 1H, \textit{J}=14.5, 6.5 Hz: CH\textsubscript{2}CH=), 2.14 (s, 3H: C(O)C\textsubscript{H}\textsubscript{3}).

\textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) \textit{δ} ppm 203.95 (C=O), 136.15 (Quat.), 129.54 (=CH), 129.54 (Arom. CH), 123.36 (=CH\textsubscript{2}), 115.66 (CN), 114.91 (CN), 46.25 (CHPh), 46.10 (C(O)CH\textsubscript{2}), 43.52 (C(CN)\textsubscript{2}), 40.73 (CH\textsubscript{2}CH=), 30.86 (CH\textsubscript{3}).

2-allyl-2-cyano-5-methyl-3-phenyl-3,4-dihydro-2H-pyrrole 1-oxide

\chem{\text{37c (cw2083)}}
colorless oil
79% yield

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \textit{δ} ppm 7.42 (m, 3H: arom H), 7.34 (d, 2H, \textit{J}=8.0 Hz: arom H), 5.76 (m, 1H: =CH), 5.42 (m, 2H: CH\textsubscript{3}=), 3.74 (t, 1H, \textit{J}=8.0 Hz: CH\textsubscript{2}), 3.11 (m, 3H: overlapping CH\textsubscript{2}CH=, CHPh and CH\textsubscript{2}), 2.87 (dd, 1H, \textit{J}=14.2, 8.1 Hz: CH\textsubscript{2}CH=), 2.23 (s, 3H: CH\textsubscript{3}).

\textbf{\textsuperscript{13}C NMR} (101MHz, CDCl\textsubscript{3}) \textit{δ} ppm 145.7 (C=N), 136.2 (Quat. arom C), 129.8 (=CH), 129.6 (Arom. CH), 129.3 (Arom. CH), 128.9 (Arom. CH), 123.3 (=CH\textsubscript{2}), 116.0 (CN), 79.0 (Quat. C), 44.6 (CH\textsubscript{2}), 39.7 (CHPh), 37.9 (CH\textsubscript{2}CH=), 13.8 (CH\textsubscript{3}).
37d (cw2097)
brown solid
35% yield

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.39-7.40 (m, 4H: arom H), 7.33 (ddd, 1H, \(J=4.9, 3.4, 2.4\) Hz: arom H), 4.98 (t, 1H, \(J=4.9\) Hz: OH), 3.57 (dd, 1H, \(J=10.1, 5.6\) Hz: CHPh), 2.73 (m, 2H; overlapping CH\(_2\)CH, CH\(_2\)CHPh), 2.08 (dd, 1H, \(J=14.2, 5.6\) Hz: CH\(_3\)CHPh), 1.97 (m, 2H; overlapping CH\(_3\)C(CN)N, CH\(_2\)CH), 1.64 (d, 1H, \(J=11.9\) Hz: CH\(_2\)C(CN)N), 1.47 (s, 3H: CH\(_3\)).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) ppm 142.8 (Quat. C), 129.3 (Arom. CH), 128.6 (Arom. CH), 128.2 (Arom. CH), 120.7 (CN), 81.0 (OCH), 72.9 (Quat. CN(CN)), 71.5 (Quat. CN(OCH)), 50.5 (CHPh), 49.8 (CH\(_2\)CH), 48.4 (CH\(_2\)C(CN)N), 44.4 (CH\(_2\)CHPh), 28.2 (CH\(_3\)). The assignments of the \(^1\text{H}\) and \(^{13}\text{C}\) were based on DEPT, COSY, HMQC etc.

\textbf{FTIR}\ (CDCl\(_3\)): \(\nu_{\text{max}}\) 3067, 2976, 2241, 1495, 1456, 1292, 883.

References:


Chapter 2

The Synthesis of Nitrogen-Containing Heterocycles via the Palladium-Catalyzed Decarboxylative Allylation
2.1 Importance of Nitrogen Heterocycles in the Pharmaceutical Industry

Heterocycles are structural motifs found in 68% of drugs in the clinical stage or on the market, and seven of the top ten selling drugs are N-heterocycles (Figure 1). These structural components are also found in biologically active natural products. To match the increasing interest in N-containing heterocycles, many methods have been developed for efficient synthesis of those important heterocycles, on gram to ton scale for industrial production.

**Figure 1 Structures of top-selling drugs**

* unit in millions USD
An interesting subclass of $N$-heterocycles is the four-membered azetidine alkaloids, which have not drawn a lot of attention as compared to the analogous aziridine, pyrrolidine and piperidine alkaloids. The reason partially resides in the fact that there are not many natural products reported to include the azetidine ring structure. Nevertheless, azetidine rings do show up as the structural motifs of some pharmaceuticals and agrochemicals due to their interesting biological activities. For example, sphingosine derivatives penaresidin A and B isolated from a marine sponge exhibit potent actomyosin ATPase-activating activity, while penazetidin A is found to be a protein kinase C inhibitor (Figure 2).4-5 All these compounds feature a hydroxyl azetidine ring and their syntheses have been achieved by several synthetic groups.6-11

Figure 2 Sphingosine type azetidine alkaloids isolated from marine sponge

Some other representative examples are shown in Figure 3. Enantiopure $L$-azetidine carboxylic acid ($L$-Aze) 1a was isolated from convallaria majalis plants and serves an potential building block for a variety of molecules.12 Mugineic acid (1b), excreted from the roof of barley, is a typical phytosiderophore, promoting the absorption and transportation of iron in plants.13 Nicotianamine 1c, present in “soy
“sauce” was identified as an inhibitor of angiotensin I-converting enzyme (ACE).\textsuperscript{14} Vioporlide A 1d, isolated from \textit{cystobacter violoceus} displays interesting antifungal activity.\textsuperscript{15} Due to its complex and challenging ring structure, gelsemoxonie 1e has been a synthetic target ever since it was separated from \textit{gelemium elegants}.\textsuperscript{16} Furthermore, gelsemoxonie 1e has shown potent analgesic and antispasmodic activity.\textsuperscript{17} Another interesting family of azetidine alkaloids are the polyxins 2a-2d, which are present in cultures of \textit{streptomyces cacaoi var. asoenisis} and exhibits antifungal activity.\textsuperscript{18}

\textbf{Figure 3} Natural products bearing an azetidine ring

![Natural products bearing an azetidine ring](image)

In addition, azetidine alkaloids could become the target of medicinal chemistry studies in which \textit{N}-heterocycles are frequently studied. For example, a neuronal nicotinic acetylcholine receptor (nAChR) inhibitor ABT-594 was identified in the
SAR study of morphine-related non-opioid drug (-)-epibatidine with similar potency (Figure 4).\textsuperscript{19, 20} More importantly, ABT-594 did not appear to cause opioid-related physical dependence or opioid analgesic activity, which should motivate further studies of azetidine analogs.

**Figure 4** *Synthetic azetidine ABT-594 as analog of natural (-)-epibatidine*

\[
\text{ABT-594} \quad \text{(-)-epibatidine}
\]

### 2.2 Overview of Azetidine Synthesis

#### 2.2.1 Azetidine Ring Syntheses from 1,3–Amino Halides

A traditional way for azetidine ring synthesis is intramolecular cyclization of amines bearing a good leaving group at the γ-position, for example γ–chloroamines \textit{3a}, as shown in Scheme 1.\textsuperscript{21, 22} Other leaving groups were also tested in this context, including: bromo, iodo, tosylate, mesylate and triflate groups. It was found that, due to slow kinetics (unfavorable enthalpy of activation) of four-membered ring closure, those transformations were generally very slow even when treated with a strong base at higher temperatures.\textsuperscript{23} The best combination was shown by Shioiri, in which tosylamide \textit{3c} with a tosylate leaving group was utilized as the reactant.\textsuperscript{24} The intramolecular \textit{S}_\text{N}2 substitution yields the azetidine product \textit{3d} and \textit{3e} in combined 93% yield with the correct stereochemistry.
Scheme 1 Intramolecular Ring closure of 1,3–amino halides

\[
\begin{align*}
3a \xrightarrow{\text{NaOH, acetone, } \Delta} & \quad 3b \\
3c \xrightarrow{\text{NaH, MeOH, RT, 11h}} & \quad 3d, 3e
\end{align*}
\]

2.2.2 Azetidine Ring Syntheses from 1,3–Amino Alcohols

Azetidine rings can also be synthesized from 1,3–amino alcohols under Mitsunobu-type reaction conditions, in which stoichiometric amount of PPh\(_3\) is used in the presence of an oxidant such as DEAD, Br\(_2\) or CBr\(_4\) (Scheme 2).\(^{25, 26}\) Even though the reactions can be carried out under mild conditions, the yields of azetidine products 4b and 4d are moderate.\(^{27, 28}\) Furthermore, in addition to the poor atom economy of these reactions, the phosphine oxide byproducts are notorious for complicating product purification.

Scheme 2 Intramolecular Ring closure of 1,3–amino alcohols

\[
\begin{align*}
4a \xrightarrow{\text{EtO}_2 C\text{-}N=N\text{-CO}_2 \text{Et, PPh}_3} & \quad 4b \\
4c \xrightarrow{\text{PPh}_3, \text{CBr}_4} & \quad 4d
\end{align*}
\]
2.2.3 One Pot Azetidine Ring Syntheses from via 1,3-Dielectrophiles

For the intramolecular azetidine ring closure reactions, secondary amines are used to avoid the byproducts of competitive dialkylation. However, by carefully controlling the reaction conditions, the cyclized azetidine ring product 5c was produced via dialkylation of primary amine 5b in 75% yield as shown in Scheme 3.\textsuperscript{29} One thing to note here is that this transformation could be carried out on kilogram scale. Dibromoelectrophile 5d was also used to synthesize the azetidine product 5f. However the reaction conditions need to be carefully controlled to avoid competing reactions.\textsuperscript{30}

\textbf{Scheme 3 Intramolecular ring closure of 1,3-dielectrophiles with primary amines}

2.2.4 Azetidine Ring Syntheses via Ring Contraction

Lastly, decarboxylative ring contraction of carbamate 6a yielded azetidine 6b in 85% yield at high temperature and pressure (Scheme 4).\textsuperscript{31} Similarly, the four-membered ring product 6d was produced via a metal facilitated ring contraction of urea derivative 6c.
Scheme 4 *Ring synthesis via six-membered ring contractions*

2.3 Pd-Catalyzed Azetidine Synthesis via Decarboxylative Ring Contraction

Our group has shown that cyclohexenyl pyrazoyl carboxylate **7a** undergoes a similar decarboxylative amination to furnish product **7b** in good yield as shown in Scheme 5. It is also known that 6-vinyl-1,3-oxazinanones undergo ring opening and decarboxylation in the presence of palladium catalysts, and the intermediate palladium allyl complexes have been trapped by pendant nucleophiles and CO to yield oxazine **7d** and pyrrolidinone **7f** respectively.
Scheme 5 Nitrogen nucleophiles in Pd-catalyzed allylation reactions

On the basis of this precedent, we hypothesized that vinyl oxazinanones 8 would undergo decarboxylative ring contractions and allow facile generation of vinyl azetidines 13 (Scheme 6).

Scheme 6 Decarboxylative ring contraction

To begin, free allylic carbamates 9a and 9b were allowed to react under our standard conditions as shown in Scheme 7. However, substrate 9a did not react even at 77 °C in toluene. This is possibly due to the steric hinderance of geminal dimethyl substituents or the difficulty of generating an unstabilized amide nucleophile by decarboxylation. That decarboxylation can take place under these conditions is
shown by the formation of butadiene product 9d from exclusive $\beta$-hydride elimination from vinyl oxazinanone 9b. This suggested that the amide anion generated was too basic, which promoted elimination. Also showed here is a scheme for preparing the vinyl oxazinanone 9b.

**Scheme 7** Decarboxylative ring contractions with N-unprotected carbamates

With the goal of reducing the basicity of nitrogen, we turned to the reaction of tosyl-protected carbamates. Thus, 10a was prepared from the corresponding 1,3-amino alcohol by treatment with carbonyl diimidazole.\(^{33, 35}\) Indeed, allowing trans-10a (>19:1 dr) to react in the presence of 5 mol% of Pd(PPh$_3$)$_4$ in CH$_2$Cl$_2$ at 25 °C led to rapid evolution of CO$_2$ and formation of the vinyl azetidine 13a in 74% yield with no observable formation of the tetrahydropyridine 10b (Scheme 8).\(^{36, 37}\)
Scheme 8 Diastereoselective decarboxylative azetidine synthesis

Next, several control experiments were conducted to probe the effect of the palladium catalyst (Scheme 9). No reaction occurred without catalyst and starting material 10a was recovered. Similarly, amino alcohol 11a was treated with our standard reaction conditions, in which azetidiene product 13a was not formed and reactant 11a remained intact. Lastly, treatment of compound 11b with 5 mol% of Pd(PPh₃)₄ afforded a messy polymeric mixture, which further demonstrated that 6-vinyl-1,3-oxazinanones are the best substrates for diastereoselective, decarboxylative ring contractions.

Scheme 9 Control experiments
Turning back to the successful ring contraction, we noted that the ratio of diastereomers in the product azetidine (16:1) was slightly smaller than that of the starting material (>19:1). This suggested that the diastereomers were interconverting on the time scale of the cyclization. To test this hypothesis, cis-10a was prepared and subjected to the same reaction conditions (Scheme 10). Although the rate of the reaction with cis-10b was somewhat slower than that with trans-10a, the product was identical. Thus, epimerization through $\pi$-$\sigma$-$\pi$ allyl interconversion is faster than cyclization (Scheme 10).\(^3\) This is an important observation because it allows the synthesis of highly diastereoenriched azetidines from diastereomixtures of the cyclic allylic carbamates.

\textbf{Scheme 10} \textit{Diastereoselective decarboxylative azetidine synthesis}

As further proof, two diastereoisomers 12a and 12b produced identical vinyl azetidine product 13e in 78\% yield (Scheme 11). More importantly, highly diastereoenriched azetidines 13g and 13h were synthesized from 1:1 diastereomixtures of the cyclic allylic carbamates 12c and 12d.
Rapid formation of the vinyl azetidine can be explained by one of two possible mechanisms (Scheme 12). First, nitrogen may coordinate to palladium to form a five-membered metallacycle A that would give rise to the azetidine upon reductive elimination.$^{39,40}$ Second, a free nitrogen anion might preferentially undergo backside attack at the 4-carbon of \(\pi\)-allyl complex B. The two mechanisms are readily distinguished by the stereochemistry of the cyclization. Reductive elimination from a five-membered metallacycle should give overall inversion of stereochemistry, and backside attack by an amide anion should result in overall retention of stereochemistry.$^{41}$
Scheme 12 Two possible mechanisms of the vinyl azetidines formation

The stereochemical analysis of the ring contraction can only be performed if the substrate does not epimerize. Therefore, substrate $14a$ was chosen for study because the initial stereochemistry of the allyl alcohol cannot be lost by a $\pi$-$\sigma$-$\pi$ epimerization mechanism that is common for terminally unsubstituted $\pi$-allyl complexes. The azetidine formed from $14a$ under our standard reaction conditions was shown to be the trans isomer by nOe experiments, indicating that the reaction proceeds with overall retention of stereochemistry. Thus, the reaction likely proceeds by backside attack of the amide anion on the $\pi$-allyl ligand via B.

Regarding the preferential four-member cyclization, Rutjes and Hiemstra have suggested a stereoelectronic origin for the regioselectivity of related cyclizations of $\beta$-aminoallenes.$^{36}$ Monosubstituted palladium $\pi$-allyl complexes can adopt two conformations, and the syn conformation is thermodynamically favored because it avoids A1,3-strain (Scheme 13). Although the syn conformation can readily give rise
to the vinyl azetidine, the anti conformation is required for formation of the tetrahydropyridine derivative.

**Scheme 13** Stereoelectronic origin for the preferential four-membered cyclization

To probe this mechanistic hypothesis, a 6-phenyl vinyloxazinanone 15a was prepared. Such a substrate should prefer to place the sterically smaller amino alkyl fragment in the anti position and would be expected to preferentially form the tetrahydropyridine isomer (Scheme 14) if the Rutjes mechanism is correct. Indeed, treatment of 15a under standard reaction conditions produced tetrahydropyridine 15b in quantitative yield. Furthermore, scrutiny of the reaction progression by $^1$H NMR spectroscopy showed no evidence for intermediate azetidine formation, indicating that tetrahydropyridine 15b is the kinetic product. A similar 6-methyl-substituted derivative 15c was prepared and allowed to react with 5 mol% of Pd(PPh$_3$)$_4$ in CH$_2$Cl$_2$. In this case, deprotonation is favored, and diene 15d is the only observable product of the reaction. Bicyclic vinyl oxazinanone 15e was also tested, in which
deprotonation occurred exclusively to produce diene product 15f in a quantitative yield.

**Scheme 14** Stereoelectronic effects on the ring cyclizations

Although the above considerations eliminate the possibility of formation of tertiary C-N bonds via decarboxylative ring contraction, other substitution patterns are allowed. For example, both 5-alkyl- and 5-aryl-substituted 1,3-oxazinanones provide good yields and selectivities for trans-1,2-vinyl azetidines (Table 1). The 4-substituted vinyl oxazinanones react similarly, but they provide the syn-1,3-vinyl azetidines with good diastereoselectivity. The stereochemical outcome for either case can be rationalized on the basis of the preference for substituents to occupy the pseudoequatorial positions of the four-membered transition state 16a for cyclization as shown in Scheme 15.
Table 1 Yields and diastereoselectivities for decarboxylative ring contractions

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Product</th>
<th>Yield (dr)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>13a</td>
<td>74 (16:1)</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>13b</td>
<td>62 (&gt;19:1)</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>13c</td>
<td>&lt;1</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>13d</td>
<td>&lt;5</td>
</tr>
<tr>
<td>H</td>
<td>p-ClC₆H₄</td>
<td>H</td>
<td>H</td>
<td>13e</td>
<td>78 (&gt;19:1)</td>
</tr>
<tr>
<td>H</td>
<td>p-MeOC₆H₄</td>
<td>H</td>
<td>H</td>
<td>13f</td>
<td>84 (14:1)</td>
</tr>
<tr>
<td>H</td>
<td>CH₂Ph</td>
<td>H</td>
<td>H</td>
<td>13g</td>
<td>60 (8.5:1)b</td>
</tr>
<tr>
<td>H</td>
<td>CH(CH₃)₂</td>
<td>H</td>
<td>H</td>
<td>13h</td>
<td>93 (&gt;19:1)b</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>13i</td>
<td>92 (&gt;19:1)</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>13j</td>
<td>78 (8:1)</td>
</tr>
</tbody>
</table>

a Yield and dr of isolated product via column chromatography. b Prepared from ca. 1:1 syn/anti-1.

Scheme 15 Transition state for the decarboxylative ring contraction
On the basis of literature reports, the formation of vinyl azetidines is expected to be reversible.\textsuperscript{36, 42-45} In accord, treatment of 17a for 10 min at room temperature provided the vinyl azetidine 13i; however, prolonged standing in the presence of the Pd(0) catalyst resulted in complete conversion to the thermodynamically more stable tetrahydropyridine isomer 17b (Scheme 16). A diastereomixture 17a was treated with the standard reaction conditions. As expected, diastereoenriched azetidine product 13i was formed at comparable rates. Also to be noted here is that lower catalyst loading (0.8 mol\% of Pd(PPh$_3$)$_4$) completely shut the isomerization off and the thermodynamic tetrahydropyridine isomer 17b was not formed even after three days. Thus, the rapid reaction rate and mild conditions of azetidine formation are important because they allow one to avoid isomerization which can be significant at elevated temperatures and/or catalyst loadings.\textsuperscript{36}

**Scheme 16 Isomerization of azetidines to thermodynamically stable pyridines**
2.3.1 Other observations

Unsubstituted vinyl oxazinanone 18a was prepared and treated with 5 mol% of Pd(PPh₃)₄ in CH₂Cl₂ (Scheme 17). In this case a (presumably) polymeric mixture was formed within 10 minutes at room temperature, even though a small amount of twelve-membered dimer 18c was separated via column chromatography (26% yield). This product was confirmed by two triplet double ¹H signal (1:1 ratio) at 5.4 and 5.6 ppm respectively in the ¹H NMR spectrum.

**Scheme 17 Investigation on reaction scope**

Benzoyl-protected substrate 19a was prepared and allowed to react with Pd(PPh₃)₄ in CH₂Cl₂ at room temperature (Scheme 18). Instead of the four-membered azetidine product, a six-membered oxazine 19b was produced as a 1.7:1 diastereomixture in 72% yield. Presumably, a zwitterionic intermediate A was generated upon decarboxylation, which was in resonance with intermediate B. This intermediate is perfectly set up for the oxazine ring closure which is consistent with the related reaction discovered by Cook.³⁴ We were also curious whether the oxazine product isomerizes at higher temperature. In that regard, compound 19b was treated
with 5 mol % of Pd(PPh$_3$)$_4$ in toluene at 80 °C and a diene product 19c was formed cleanly in 96% NMR yield.

**Scheme 18 Substrate with a different N-protection group**

In summary, we have developed a unique ring contraction of cyclic carbamates that diastereoselectively produces vinyl azetidines. Importantly, the reaction proceeds under mild conditions and produces CO$_2$ as the only byproduct.

### 2.4 The Importance of Bioactive Quinolines and Their Derivatives

Other well-known $N$-heterocycles are quinolines and their derivatives such as 1,2-dihydroquinoline, isoquinoline and tetrahydroquinoline. These compounds occur widely in nature and find many applications including their use as building blocks for organic synthesis, and as potential candidates for pharmaceuticals, antioxidants, agrochemicals and dyes.

The 1,2-dihydroquinoline alkaloids are an interesting type of compounds, which
can be converted to quinolines by oxidation and in that regard, two dihydroquinoline
derivatives 20a and 20b have been used in rubber production as antioxidants (Figure
5). Substituted 1,2-dihydroquinoline derivative 20c has shown potent antibacterial
activity and high inhibition of *Escherichia coli* dihydrofolate reductase. In other
cases, reduction or electrophilic addition to the double bond of 1,2-dihydroquinoline
generates 1,2,3,4-tetrahydroquinoline derivatives.

**Figure 5 1,2-Dihydroquinoline alkaloids**

2.5 Overview of 1,2-Dihydroquinoline Synthesis

Even though 1,2-dihydroquinolines have not drawn a lot of attention, possibly
due to their inherent instability and the scarcity of natural products bearing a
1,2-dihydroquinoline structure element, they are a potential building block for
quinoline and tetrahydroquinolin alkaloids. For example, Taguchi recently reported
a convenient synthesis of fluorinated 1,2-dihydroquinolines synthesis from
substituted anilines (Scheme 19). Dihydroquinoline 21a was smoothly converted to
quinoline 21b or tetrahydroquinoline 21c by either air oxidation or reduction
respectively.
2.5.1 Skraup and Skraup/Doebner-Miller procedures starting with aniline derivatives

Quinoline derivative synthesis has drawn a lot of attention due to their biological activities (Chapter 2.4). Traditionally, quinolines were synthesized from the corresponding aniline derivatives via the Skraup procedure shown in Scheme 20. Glycerol was used as the synthetic equivalent of acrolein, which cyclized with aniline to generate a 1,2-dihydroquinoline intermediate 22a, followed by oxidation to give quinoline product 22b. The related Skraup/Doebner-Miller procedure involves a reaction of aniline with α,β-unsaturated aldehydes or ketones in the presence of HCl or Lewis acids. Air oxidation of intermediate 22c produced the quinoline product 22d. However, those transformations require a large amount of sulfuric acid or strong Lewis acid combined with harsh reaction conditions. Thus, the products were generally obtained in low to moderate yields.
A modified Skraup/Doebner-Miller procedure has been adopted for 1,2-dihydroquinoline synthesis, in which disubstituted mesityl oxide derivatives were employed instead (Scheme 21). Compounds 23a and 23b were synthesized by treatment of anilines with mesityl oxide derivatives catalyzed by iodine. As such, the aromatization of the 1,2-dihydroquinolines would require losing one molecule of methane (Riehm quinoline synthesis), which is more difficult than losing a molecule of hydrogen.

The major drawback of this procedure is the low yield of dihydroquinoline product due to the competing polymerization. Recently solvent-free Skraup Doebner-
Miller reactions have been developed with microwave radiation.\textsuperscript{54} For example, a series of dihydroquinoline products were synthesized in moderate yields by treatment of aniline with enones in the presence of silica gel charged with indium trichloride under microwave conditions.

\textit{2.5.2 Transition-metal catalyzed 1,2-dihydroquinoline synthesis}

There are several drawbacks of traditional methods for 1,2-dihydroquinoline or quinoline synthesis. For example most reactions need high temperature in the presence of a strong Bronsted or Lewis acids. Functional group compatibility, decomposition of products, and competing side reactions are always the concerns under those harsh conditions. To potentially alleviate these problems, transition metal catalysts have been introduced into this scenario.

Transition metal-catalyzed heteroannulation reactions have been extensively studied due to the potential biological and pharmaceutical activity of those heterocyclic compounds. For example, substituted 2-iodoanilines have been shown to undergo a Heck reaction with \textit{cis}-dimethyl maleate to generate \textit{trans}-olefin intermediate 24a, which upon cyclization produced quinolone 24b in moderate yields (Scheme 22). Larock reported a similar procedure with allylic alcohols, in which $\beta$-hydride eliminations afforded enol intermediates 24c, followed by intramolecular condensations and oxidations to furnish quinolines 24e.\textsuperscript{55}
Scheme 22 Heck-type coupling reaction

Another procedure involves intramolecular amination of substituted 2-allylanilines 25a and 25c produced dihydroquinoline 25b and indole 25d respectively in the presence of catalytic amount of PdCl$_2$(CH$_3$CN)$_2$ (Scheme 23). Interestingly, different chemoselectivity displayed with simple allyl side chain in which a 5-exo-trig was favored over 6-endo-trig, whereas the dimethyl substituted allylaniline 25a predominantly generated the 6-endo-trig product. The reason possibly resides in the stability of a tertiary carbocation.

Scheme 23 Intramolecular amination of olefines
Gold and silver have been used for the functionalization of alkynes based on their unique Lewis acidity. In 2005, Li reported their results on hydroamination of alkynes with a silver catalyst toward the synthesis of highly substituted 1,2-dihydroquinolines. A possible mechanism was also postulated as shown in Scheme 24. Silver-catalyzed hydroamination generates an enamine intermediate 26c in tautomerization with ketimine 26d, and reaction of ketimine with another molecule of alkynes yields propargylamine 26e, followed by intramolecular cyclization and further addition to give highly functionalized 1,2-dihydroquinoline product 26b.

**Scheme 24 Silver-catalyzed 1,2-dihydroquinoline synthesis**
Gold complexes were also found to catalyze similar transformations. Recently, an efficient synthesis of quinolines and dihydroquinolines catalyzed by Au(I) was disclosed by Che under microwave radiation (Scheme 25).\textsuperscript{57} Product 27e was prepared by a Au-catalyzed tandem hydroamination-hydroarylation of phenyl acetylene in 91\% yield.

**Scheme 25** *Gold-catalyzed 1,2-dihydroquinoline synthesis*

Finally, ring-closing metathesis strategies have also been employed in 1,2-dihydroquinoline synthesis (Scheme 26). For example, 2-vinyl allylamines 28b underwent ring-closing metathesis smoothly in the presence of Grubbs’ catalyst A or B to generate the dihydroquinoline product 28c in high yield.\textsuperscript{58} Dihydroquinolines with acidic sensitive N–protecting groups 28d were subsequently deprotected and air-oxidized to give quinoline product 28e during silica gel chromatography in good to excellent yield.
Evans reported an efficient synthesis of 1,2-dihydroquinoline rings using a regioselective allylic amination combined with ring-closing metathesis in the presence of rhodium catalysts as shown in Scheme 27. Vinyl aniline 29a reacted with enatiopure allylic carbonate 29b to produce the RCM reaction precursor 29c in excellent reigoselectivity (36:1). Upon treatment with Grubbs’s catalyst A, 1,2-dihydroquinoline product 29e was furnished in 92% yield.
Other transition metals such as copper,\textsuperscript{59,60} manganese\textsuperscript{61} and iron\textsuperscript{62} etc have also shown catalytic activity toward the synthesis of dihydroquinolines. However, due to their similarity with the transition metals mentioned above, those catalysts are not covered in this dissertation.

\textbf{2.5.3 1,2-dihydroquinolines synthesis via modification of quinoline rings}

It has been shown that nucleophilic addition to quinoline derivatives furnishes 1,2-dihydroquinoline products, which were then transformed to tetrahydroquinolines through reduction (Scheme 28). For example, treatment of quinoline 30a with n-butyl lithium or ethyl magnesium bromide produces 1,2-dihydroquinolines 30b and 30d in 97\% and 57\% yield respectively.\textsuperscript{48,63,64} Interestingly, activation of quinoline 30a by converting it to iminium salt 30f allowed the nucleophilic attack of weaker nucleophiles, and in fact compound 30g was obtained in 66\% yield.\textsuperscript{65}

\textbf{Scheme 28 Conversion of quinolines to 1,2-dihydroquinolines}
2.6 Decarboxylative Dihydroquinoline Synthesis via Aza-ortho-xylylene Intermediates

Even though there are many reported procedures for 1,2-dihydroquinoline synthesis, the current methods still have some limitations in regard to the cost and availability of substrates, prolonged reaction times at high temperature, strongly acidic conditions and functional group compatibility. As such, a mild and efficient method for dihydroquinoline synthesis is still highly desirable.

We have previously reported that vinyl oxazinanones 31a underwent catalytic diastereoselective decarboxylative ring contraction to form vinyl azetidines under mild conditions in good yield. A zwitterionic π-allyl palladium complex 31b was proposed as the intermediate (Scheme 29). We reasoned that conjugation of the two charges would allow mild catalytic generation of aza-ortho-xylylene intermediates. Such a scenario creates two possibilities. The zwitterionic intermediate can potentially expel Pd(0) to produce a free aza-ortho-xylylene 31e. Alternatively, if Pd remains coordinated, then a polarized aza-ortho-xylylene intermediate 31d will result. Then substituted 1,2-dihydroquinolines could be formed via either a cyclization of the π-allyl intermediate 31d or a electrocyclization of the free aza-ortho-xylylene 31e.
Scheme 29 Zwitterionic π-allyl palladium intermediates

To begin, the parent vinyl benzoazoxinanone 32a was prepared and subjected to Pd(PPh₃)₄ in CH₂Cl₂ at room temperature. In contrast to the saturated analogs which undergo ring contraction to azetidines, 32a produced the hydroquinoline 33a in 65% yield (Scheme 30). Interestingly, conducting the same reaction in toluene solvent produces the 12-membered dimer 34a exclusively. Even though the dimer product 34a was obtained in 36% isolated yield, this compound was formed cleanly as shown by ¹H NMR spectroscopy. Since it is improbable that such a dimer could arise from concerted [6+6] cycloaddition, it seems likely that Pd-polarized aza-o-xylene 32b is the intermediate in these reactions.
Next we turned our attention to investigating the reaction scope. It since has been shown that various vinyl benzoxazinanones undergo smooth intramolecular decarboxylative allylic aminations and the dihydroquinoline products were obtained in good to excellent yield (Table 2).

Table 2 Yields of dihydroquinolines via intramolecular decarboxylative allylations

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield% a</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>33a</td>
<td>65b</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>33b</td>
<td>77</td>
</tr>
<tr>
<td>p-Me</td>
<td>H</td>
<td>33c</td>
<td>50b</td>
</tr>
<tr>
<td>p-Me</td>
<td>Me</td>
<td>33d</td>
<td>94</td>
</tr>
<tr>
<td>p-F</td>
<td>H</td>
<td>33e</td>
<td>51b</td>
</tr>
<tr>
<td>p-F</td>
<td>Me</td>
<td>33f</td>
<td>82</td>
</tr>
<tr>
<td>p-MeO</td>
<td>H</td>
<td>33g</td>
<td>80b</td>
</tr>
<tr>
<td>p-MeO</td>
<td>Me</td>
<td>32h</td>
<td>92</td>
</tr>
</tbody>
</table>

a Yield of isolated product via column chromatography. b The by-products were dimers or polymers, which were somehow suppressed by performing the reaction in dilute solution with lower catalyst loading.
The clean formation of dimer products was also interesting to us and treatment of different vinyl benzoxazinanones with a catalytic amount of Pd(PPh$_3$)$_4$ in toluene gave the 12-membered ring products 34 in good to excellent yield at room temperature as shown in Table 3. The coupling constants of olefins suggested a trans-geometry in compounds 34a, 34b and 34c ($J = 16.2$ Hz); while compound 34d ($J = 9.8$ Hz) was formed with a cis-olefin geometry. At this point, we don’t have a reasonable explanation for this stereoselectivity.

Table 3. Yields of dimer products via intermolecular decarboxylative cycloaddition

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>34a $^a$</td>
<td>36 $^c$</td>
</tr>
<tr>
<td>Me</td>
<td>34b $^a$</td>
<td>87</td>
</tr>
<tr>
<td>OMe</td>
<td>34c $^a$</td>
<td>94</td>
</tr>
<tr>
<td>F</td>
<td>34d $^b$</td>
<td>92 $^d$</td>
</tr>
</tbody>
</table>

$^a$ Dimer products with a trans-olefin geometry. $^b$ Dimer product with a cis-olefin geometry. $^c$ Yield of isolated product via column chromatography and 34a was formed cleanly as shown by $^1$HNMR spectroscopy. $^d$ This reaction was carried out in dichloroethane at 60 °C.

To further shed light on the reaction mechanism, vinyl benzoxazinanone 32a was allowed to react with vinyl butyl ether in the presence of 5 mol% Pd(PPh$_3$)$_4$ in toluene as shown in Scheme 31. If a free aza-orthoxyylene is indeed being formed, then one would predict that it would undergo [4+2] cycloaddition with vinyl butyl ether.
However, the dimer product $34a$ was formed smoothly in the presence of a dienophile and no [4+2] cycloaddition reaction occurred. Interestingly, if the reaction was heated to 100 °C, dimer product $34a$ cleanly isomerized to the thermodynamically more stable dihydroquinoline product $33a$. This reaction was also performed in dichloromethane, in which dihydroquinoline $33a$ was formed along with the dimer $34a$ in a ratio of 4:1. These observations suggest that palladium catalyzes the equilibration of dimers 34 and dihydroquinolines 33. To test this hypothesis, isolated dimer products $34a$ and $34c$ were treated with catalytic amount of Pd(PPh$_3$)$_4$ in toluene at 100 °C; however no equilibration occurred and the reactant kept intact over the course of the reaction. One thing to note here is that palladium black precipitated out the reaction solution at high temperatures.

**Scheme 31 Kinetic vs thermodynamic product**
General observations related to dihydroquinoline synthesis

Vinyl benzoazinanone 35a, with a terminal disubstituted olefin, was prepared and treated with our standard reaction conditions. No reaction occurred and starting material was recovered either at room temperature or 110 °C, which suggests that the coordination between olefin and catalyst must occur first for the reaction to proceed (Scheme 32). Also of note is that dihydroquinolines 35d were produced in high yield with no observation of dimer formation. Actually when we tried to synthesize dimer 35i, the intramolecular cyclization was much faster and dihydroquinoline 33d was generated exclusively.

Scheme 32 Intramolecular vs intermolecular cyclization
An interesting observation was found with substrate 36a with two electron donating groups on the phenyl ring as illustrated in Scheme 33. Treatment of 36a with 5 mol% Pd(PPh₃)₄ in methylene chloride did not generate the dihydroquinoline product 36b, even though decarboxylation did occur and a new product was formed, whose structure is yet to be determined. However this compound was not stable under the reaction conditions and polymeric products were formed if the reaction mixture was allowed to stand overnight. Similarly, the Ts-protection of carbamate 36a was problematic due to the generation of a polymer-like mixture. This result seems to indicate that under basic conditions, carbamate 36a generates a free aza-o-xylylene upon losing CO₂.

**Scheme 33 Problematic reactions**

Vinyl benzoxazinanones with different protecting groups were also prepared and subjected to the decarboxylative allylic amination under our standard reaction conditions (Scheme 34). It was found that benzyl-protected benzoxazinanone 37a was not reactive, as expected considering that the decarboxylation is not favorable since
the pKa of the secondary amine is relatively high. The reaction only afforded a small amount of quinoline product 37b (3% conversion), while most of starting material was recovered. When N-nosyl benzoxazinanone 37c was allowed to react with 5 mol% Pd(PPh₃)₄, dihydroquinoline 37d did form along with large amount of polymer-like byproduct. Benzoyl protected benzoxazinanone 37e was also prepared and treated with the standard condition to generate the oxazine product 37f in 96% NMR yield.

Scheme 34 Vinyl benzoxazinanones with different protecting groups

The formation of dihydroquinoline ring was thought to start by oxidative addition, followed by decarboxylation to generate a palladium-polarized aza-ortho-xylylene intermediate 38b, followed by intramolecular allylic amination to product 38d and regenerate the catalyst (Scheme 35). Due to unfavorable enthalpy of 4-membered ring
closure and bond angles, the 6-membered ring was favored as compared to the decarboxylative ring contraction of unsaturated analogues.

**Scheme 35** *Catalytic cycle for decarboxylative dihydroquinoline synthesis via aza-ortho-xylylene intermediates*

In conclusion, we have developed a unique and efficient way for dihydroquinoline synthesis through palladium-polarized aza-ortho-xylylene intermediates. Interestingly, carrying out the same reactions in less polar solvents such as toluene produced a 12-membered dimer product cleanly, while reactions in more polar dichloromethane selectively produced dihydroquinolines. Importantly, the reactions proceed under mild conditions and produce CO$_2$ as the only byproduct.
2.7 References


63. Goldstein, S. W.; Dambek, P. J., 2-Substituted 1,2,3,4-tetrahydroquinolines from quinoline. *Synthesis-Stuttgart* **1989**, 221-222.


69. Van De Water, R. W.; Pettus, T. R. R., o-Quinone methides: intermediates

Appendix B

Experimental Procedures and Data for Chapter 2
General Experimental

THF was dried over sodium metal. Toluene, methylene chloride and diethyl ether were dried over activated alumina on a solvent system purchased from Innovative Technology, Inc. Acetonitrile and 1,4-dioxane were dried and stored over activated molecular sieves. Commercially available reagents were used without additional purification unless otherwise stated. Products were purified on silica gel from Sorbent Technologies (230x400 mesh, 60 Å porosity, pH 6.5-7.5). Ruthenium and palladium compounds were obtained from Strem. Thin layer chromatography was performed on silica gel 60F\textsubscript{254} plates (EM-5715-7, EMD chemicals). UV lamp (254 nm) or KMnO\textsubscript{4} stain were used for monitoring TLC plates.

\textsuperscript{1}H and \textsuperscript{13}C NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer and referenced to residual protio solvent signals. Structural assignments are based on \textsuperscript{1}H, \textsuperscript{13}C, DEPT-135, COSY, and HMQC spectroscopies and X-ray data. High resolution mass spectrometry was performed on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). High resolution mass spectrometry was performed on a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. FTIR spectra were acquired on a Shimadzu FTIR-8400S spectrometer. HPLC analysis was performed on a Shimadzu SCL-10A VP instrument.
Preparation of Starting Materials

Vinyl oxazinanone 9a, in which $R_1=H$ were prepared from the corresponding amino alcohols, which were synthesized by reduction of $\beta$-hydroxy nitriles with LAH. $^1$ $\beta$-Hydroxy nitriles were prepared by treatment of substituted nitriles with n-butyl lithium, followed by aldol reaction with the aldehydes. To increase the yield of aldol reaction, a modified procedure was used and 1.5 eq. of chloro trimethylsilane was added to trap the generated enolates, followed by methanol quenched. $^2$

To a solution of n-butyl lithium (9.6 mmol, 1.1 eq.) in THF at -78 °C under argon was added benzyl cyanide (1.0 g, 8.7 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 0.5 hour before adding a solution of acrolein (486 mg, 8.7 mmol, 1.0 eq.) in THF via cannulation. The reaction mixture turned pale yellow color upon addition and kept stirring at -78 °C until reaction completion indicated by TLC (generally 0.5 hr-1.5h). The reaction was quenched by chloro trimethylsilane (1.5 g, 13.1 mmol, 1.5 eq.), followed by adding methanol (2.0 ml). The reaction mixture was extracted by ethyl acetate, washed with brine, dried over magnesium sulfate and concentrated to give the crude product, which was purified by flash column chromatography (SiO$_2$, 5:1 Hexane: Ethyl acetate). $^2$

\[
\begin{align*}
\text{NC} \text{Ph} & \xrightarrow{1) \text{n-BuLi, THF, } -78^\circ \text{C, 0.5hr}}  \text{OH} \text{Ph} \\
\text{H} \text{O} & \xrightarrow{2) \text{Acrolein, THF}} \text{NC} \text{Ph} \\
\text{OH} & \xrightarrow{3) \text{TMSCl}} \text{Ts} \text{N} \text{O} \text{R}^1 \text{R}^2 \\
& \xrightarrow{4) \text{MeOH}} 9a
\end{align*}
\]

To a solution of LAH (290 mg, 7.6 mmol, 1.2 eq.) in THF under argon at 0 °C was slowly added a solution of cyano alcohol (1.1 g, 6.4 mmol) in THF via
cannulation. The resulting yellow mixture was kept stirring until reaction completion indicated by TLC (generally 0.5 hr). Because amino alcohols were very polar with a higher solubility in water, a slightly different work-up procedure was used. Small amount of water was added dropwise to the reaction mixture to quench the excess amount of LAH, which was monitored by the release of hydrogen, followed by adding ethyl acetate and filtration over a celite pad, dried over magnesium sulfate and the solvent was removed to afford the crude product which was taken to the next step without further purification. (One thing to note here is that the reduction step is very sensitive to water, and the solvent was dried over sodium metal before use.)

The preparation of carbamates was achieved by treatment of amino alcohols with CDI (carbonyl diimidazole) reagent.\(^3\) The coupling step could also be performed stepwise by reacting with chloroformate, followed by an intramolecular cyclization under basic conditions.\(^4\) To a solution of amino alcohol (1.1g, 5.2 mmol) in THF at room temperature was added carbonyl diimidazole (CDI, 923 mg, 5.7 mmol, 1.1 eq). The mixture was kept stirring at room temperature until reaction completion indicated by TLC (generally 12 hr). Most of the THF was removed, and the residue was taken up with ethyl acetate, washed with dilute hydrochloric acid, brined and dried over magnesium sulfate and concentrated to give the crude product, which was purified by flash column chromatography (SiO\(_2\), 1:2 Hexane: Ethyl acetate).
Finally,  $N$-protected carbamates were prepared according to literature procedure. Sodium hydride and n-butyl lithium were both used for deprotonation, though the latter one gave the product in better yield. To a solution of carbamate (300 mg, 2.1 mmol) in THF at -78 °C under argon was added n-BuLi (2.3 mmol, 1.1 eq.) dropwise, and stirred for 1.5 hr before the addition of TsCl (486 mg, 2.6 mmol, 1.2 eq.) in one portion. The yellow solution turned colorless upon addition of TsCl and monitored by TLC analysis. The reaction was quenched with sat. NH$_4$Cl solution after 0.5 hr, extracted with ethyl acetate. The organic phase was washed with brined, dried over magnesium sulfate and concentrated to give the crude product, which was purified by flash column chromatography (SiO$_2$, 1:5 Hexane: Ethyl acetate).

This method was not successful when $R_2, R_3$ are both aromatic rings, in which 1,4-addition was favored due to steric reasons.
In the case of R¹=Ph, amino alcohol was efficiently synthesized from the corresponding adol adduct by a reductive amination protocol developed by Yamazaki.⁶

\[
\begin{align*}
\text{PhCOCH}_3 & \overset{\text{LDA}}{\rightarrow} \text{PhCOCH}_3
\end{align*}
\]

**General procedure for catalytic decarboxylative ring contraction of vinyl oxazinanoes:**

In a Schlenk tube under argon, Pd(PPh₃)₄ (0.05 mmol) and carbamate (1 mmol) were dissolved in 5 mL of methylene chloride. The resulting yellow solution was stirred at ambient temperature under Ar until reaction completion was indicated by TLC (generally 10 min.-2h). Following solvent evaporation, the crude product was purified via flash chromatography (SiO₂, 7:1 Hexane: Ethyl acetate).

**Spectroscopic Data**

\[
\begin{align*}
\text{Ts} & \quad \text{N} \\
& \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{Ph} \\
5\text{-phenyl-3-tosyl-6-vinyl-1,3-oxazinan-2-one} & \quad \text{10a (cw1293)} \\
\text{Colorless oil}
\end{align*}
\]

^{1}H NMR (400 MHz, CDCl₃) δ ppm 7.90 (d, 2H, J = 8.3 Hz: arom H), 7.31 - 7.43 (m, 4H: arom H), 7.21 (dd, 2H, J=7.7, 1.6 Hz: arom H), 5.62 (ddd, 1H, J=17.1, 10.7, 5.9 Hz: CH=), 5.27 (dt, 1H, J=17.1, 1.1 Hz: CH=CH(H)ₑₑ), 5.19 (dt, 1H, J=10.6, 1.0 Hz: CH=CH(H)ₑₑ), 4.95 (dd, 1H, J=9.4, 5.8 Hz: OCH), 4.28 (dd, 1H, J=12.2, 5.2 Hz: diastereotopic CH₂NTs), 3.98 (dd, 1H, J=12.2, 10.5 Hz: diastereotopic CH₂NTs), 3.12 (td, 1H, J=9.9, 5.2 Hz: PhCH), 2.46 (s, 3H: CH₃).
3-phenyl-1-tosyl-2-vinylazetidine

\[ \text{13a} \text{(cw2028)} \]
White solid
Pd(PPh\(_3\))\(_4\): 74% yield, dr = 16

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 7.81 (d, 2H, \(J = 8.3\) Hz: arom H), 7.43 (d, 2H, \(J = 7.8\) Hz: arom H), 7.22 (m, 3H: arom H), 6.88 (m, 3H: arom H), 6.06 (m, 1H: =CH), 5.35 (d, 1H, \(J = 17.2\) Hz: CH=CH(H)\(_E\)), 5.24 (d, 1H, \(J = 10.4\) Hz: CH=CH(H)\(_Z\)), 4.35 (t, 1H, \(J = 7.6\) Hz: CHNTs), 4.06 (t, 1H, \(J = 7.8\) Hz: CH\(_2\)), 3.77 (t, 1H, \(J = 8.1\) Hz: CH\(_2\)), 3.52 (q, 1H, \(J = 8.3, 16.4\) Hz: PhCH), 2.51 (s, 3H: CH\(_3\)).

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 144.52 (Quat.), 139.33 (Quat.), 136.96 (=CH), 132.92 (Quat.), 130.14 (Arom. CH), 129.05 (Arom. CH), 128.95 (Arom. CH), 127.63 (Arom. CH), 127.38 (Arom. CH), 118.24 (=CH\(_2\)), 72.74 (CHNTs), 54.44 (CH\(_2\)), 41.96 (CHPh), 21.95 (CH\(_3\)). The assignments of the \(^1\text{H}\) and \(^{13}\text{C}\) were based on DEPT, COSY, HMQC etc.

\text{FTIR}\) (CDCl\(_3\)): \(\nu_{\text{max}}\) 3088, 3065, 3032, 1599, 1495, 1346, 1165, 818, 669.

\text{HRMS}\) calcd for C\(_{18}\)H\(_{20}\)NO\(_2\)S [M+H] 314.1215, found 314.1201.

5-phenyl-6-styryl-3-tosyl-1,3-oxazinan-2-one

\[ \text{14a} \text{(cw2117)} \]
Colorless oil

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.92 (d, 1H, \(J = 8.4\) Hz: arom H), 7.34 (m, 6H: arom H), 7.22 (m, 6H: arom H), 6.54 (d, 1H, \(J = 16.0\) Hz: =CHPh), 5.92 (dd, 1H, \(J = 5.2\) Hz: CH=), 5.12 (ddd, 1H, \(J = 9.5, 6.3, 1.2\) Hz: OCH), 4.32 (dd, 1H, \(J = 12.2, 5.2\) Hz: diastereotopic CH\(_2\)NTs), 4.01 (dd, 1H, \(J = 12.2, 10.6\) Hz: diastereotopic CH\(_2\)NTs), 3.21 (td, 1H, \(J = 10.0, 5.1\) Hz: CHPh), 2.46 (s, 3H: CH\(_3\)).
3-phenyl-2-styryl-1-tosylazetidine

13b (cw2121)
White solid
Pd(PPh₃)₄: 62% yield, dr = >19:1

**¹H NMR** (400 MHz, CDCl₃) δ 7.86 (d, 2H, J = 8.3 Hz: arom H), 7.44 (d, 2H, J = 7.8 Hz: arom H), 7.34 (m, 4.6H: arom H), 7.25 (m, 3.4H: arom H), 6.90 (m, 2H: arom H), 6.59 (d, 1H, J = 15.9 Hz: =CHPh), 6.39 (dd, 1H, J = 7.1, 15.9 Hz: =CH), 4.50 (t, 1H, J = 7.3 Hz: CHNTs), 4.12 (t, 1H, J = 8.3 Hz: CH₂), 3.83 (t, 1H, J = 8.3 Hz: CH₂), 3.61 (q, 1H, J = 8.3, 16.2 Hz: PhCH), 2.49 (s, 3H: CH₃).

**¹³C NMR** (100 MHz, CDCl₃) δ 144.74 (Quat.), 139.26 (Quat.), 136.44 (Quat.), 133.31 (=CHPh), 132.61 (Quat.), 130.27-127.19 (overlapping Arom. CH, =CH), 72.94 (CHNTs), 54.37 (CH₂), 42.56 (CHPh), 22.05 (CH₃). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl₃): νmax 3084, 3065, 3032, 1599, 1495, 1346, 1163, 966, 816, 750, 669.

**HRMS** calcd for C₂₄H₂₄NO₂S [M+H] 390.1528, found 390.1547.

5-(4-chlorophenyl)-3-tosyl-6-vinyl-1,3-oxazinan-2-one

12a (cw2098)
Colorless oil

**¹H NMR** (400 MHz, CDCl₃) δ ppm 7.88 (d, 2H, J = 8.3 Hz: arom H), 7.14 (m, 2H: arom H), 5.61 (ddd, 1H, J = 17.0, 10.7, 5.9 Hz: CH=), 5.27 (d, 1H, J = 17.2 Hz: CH=CH(H)₁), 5.22 (d, 1H, J = 10.5 Hz: CH=CH(H)₂), 4.91 (m, 1H: OCH), 4.25 (dd, 1H, J = 12.3, 5.1 Hz: diastereotopic CH₂NTs), 3.95 (m, 1H: diastereotopic CH₂NTs), 3.12 (ddd, 1H, J = 9.5, 4.9, 4.8 Hz: ArCH), 2.47 (s, 3H: CH₃).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 148.5 (NCO$_2$), 145.8 (Quat.), 135.2 (Quat.), 134.6 (Quat.), 133.6 (Quat.), 130.8 (CH=), 129.9 (Arom. CH), 129.8 (Arom. CH), 129.6 (Arom. CH), 129.3 (Arom. CH), 120.5 (=CH$_2$), 81.2 (OCH), 47.8 (CH$_2$NTs), 41.0 (ArCH), 22.2 (CH$_3$).

![Chemical Structure](image)

$^{13}$(4-chlorophenyl)-1-tosyl-2-vinylazetidine

13e (cw2100)

colorless oil

Pd(PPh$_3$)$_4$: 78% yield, dr >19:1

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.78 (d, 2H, $J$ = 8.3 Hz: arom H), 7.44 (d, 2H, $J$ = 8.1 Hz: arom H), 7.20 (d, 2H, $J$ = 8.6Hz: arom H), 6.76 (d, 2H, $J$ = 8.6Hz: arom H), 6.03 (m, 1H: =CH), 5.32 (d, 1H, $J$ = 17.2 Hz: CH=CH($H_2$)), 5.23 (d, 1H, $J$ = 10.4 Hz: CH=CH($H_2$)), 4.25 (t, 1H, $J$ =7.1 Hz: CHNTs), 4.05 (t, 1H, $J$ =8.1 Hz: CH$_2$), 3.69 (t, 1H, $J$ =8.4Hz: CH$_2$), 3.48 (q, 1H, $J$ =8.3, 16.4 Hz: ArCH), 2.52 (s, 3H: CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 144.36 (Quat.), 137.35 (Quat.), 136.24 (=CH), 133.28 (Quat.), 131.97 (Quat.), 129.86-128.37 (Arom. CH), 118.27 (=CH$_2$), 72.47 (CHNTs), 53.97 (CH$_2$), 40.91 (CHAr), 21.68 (CH$_3$). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{\max}$ 3087, 3031, 1600, 1495, 1348, 1165, 1094, 820, 669.

HRMS calcd for C$_{18}$H$_{19}$ClNO$_2$S [M+H] 348.0825, found 348.0820.
5-(4-methoxyphenyl)-3-tosyl-6-vinyl-1,3-oxazinan-2-one

cw2136
White solid

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.91 (d, 1H, J=8.5 Hz: arom H), 7.34 (d, 1H, J=8.1Hz: arom H), 7.12 (d, 1H, J=8.8 Hz: arom H), 6.91 (d, 1H, J=8.7 Hz: arom H), 5.61 (ddd, 1H, J=16.9, 10.7, 5.8 Hz: CH=), 5.27 (d, 1H, J=17.2 Hz: CH=CH$_2$), 5.19 (d, 1H, J=10.6 Hz: CH=CH$_2$), 4.90 (dd, 1H, J=9.5, 5.8 Hz: OCH), 4.25 (dd, 1H, J=12.2, 10.7 Hz: diastereotopic CH$_2$NTs), 3.93 (s, 3H: OC$_3$H$_3$), 3.83 (s, 3H: OC$_3$H$_3$), 3.07 (td, 1H, J=10.0, 5.2 Hz: ArCH), 2.47 (s, 3H: CH$_3$).

3-(4-methoxyphenyl)-1-tosyl-2-vinylazetidine

13f (cw2140)
White solid

Pd(PPh$_3$)$_4$: 84% yield, dr = 14:1

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.81 (d, 2H, J = 8.3 Hz: arom H), 7.42 (d, 2H, J = 8.6 Hz: arom H), 7.22 (m, 3H: arom H), 6.75 (s, 4H: arom H), 6.04 (m, 1H: =CH), 5.26 (dd, 2H, J = 10.4, 16.9 Hz: =CH$_2$), 4.24 (t, 1H, J =7.1 Hz: CHNTs), 4.04 (t, 1H, J =7.8 Hz: CH$_2$), 3.77 (s, 3H: OCH$_3$), 3.68 (t, 1H, J =7.8Hz: CH$_2$), 3.46 (q, 1H: ArCH), 2.52 (s, 3H: CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.25 (Quat.), 144.60 (Quat.), 136.91 (=CH), 132.41 (Quat.), 131.26 (Quat.), 130.22-128.56 (Arom. CH), 118.26 (=CH$_2$), 114.42 (Arom. CH), 73.26 (CHNTs), 55.68 (OCH$_3$), 54.89 (CH$_2$), 41.42 (CHAr), 22.07 (CH$_3$). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{max}$ 3065, 3005, 1516, 1466, 1346, 1250, 1165, 829, 818.
HRMS calcd for C19H22NO2S [M+H] 344.1320, found 344.1315.

\[
\begin{align*}
\text{Ts} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\end{align*}
\]

5-benzyl-3-tosyl-6-vinyl-1,3-oxazinan-2-one

**12c (cw2164)**

White solid, dr = 1:1

**1H NMR** (400 MHz, CDCl\textsubscript{3}) δ ppm 7.90 (t, 4H, J=8.4 Hz: arom H (cis/trans)), 7.34 (m, 10H: arom H (cis/trans)), 7.15 (dd, 4H, J=16.9, 7.0 Hz: arom H (cis/trans)), 5.91 (td, 1H, J=11.3, 5.4 Hz: =CH (cis/trans)), 5.81 (ddd, 1H, J=17.0, 10.8, 5.9 Hz: =CH (cis/trans)), 5.38 (m, 4H: =CH\textsubscript{2} (cis/trans)), 4.61 (t, 1H: OCH (cis/trans)), 4.83 (br. s., 1H: OCH (cis/trans)), 3.88 (dd, 1H, J=12.2, 4.8 Hz: CH\textsubscript{2}NTs (cis/trans)), 3.69 (ddd, 1H, J=11.9, 7.5, 7.4 Hz: CH\textsubscript{2}NTs (cis/trans)), 2.90 (dd, 1H, J=14.0, 5.9 Hz: CH\textsubscript{3}Ph (cis/trans)), 2.78 (d, 1H, J=7.8 Hz: CH\textsubscript{2}Ph (cis/trans)), 2.56 (m, 3H: overlapping CH\textsubscript{2}Ph, BnCH (cis/trans)), 2.47 (s, 3H: CH\textsubscript{3} (cis/trans)), 2.46 (s, 3H: CH\textsubscript{3} (cis/trans)), 2.28 (m, 1H: BnCH (cis/trans)).

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Ts} & \quad \text{O}
\end{align*}
\]

3-benzyl-1-tosyl-2-vinylazetidine

**13g (cw2170)**

White solid

Pd(PPh\textsubscript{3})\textsubscript{4}: 60% yield, dr = 8.5

**1H NMR** (400 MHz, CDCl\textsubscript{3}) δ 7.74 (d, J = 8.3 Hz, 2H: arom H), 7.37 (d, J =8.6 Hz, 2H: arom H), 7.23 (m, 3H: arom H), 7.25 (d, J = 7.1 Hz, 2H: arom H), 5.85 (m, 1H: =CH), 5.14 (dd, J = 9.8, 17.7 Hz, 1H: =CH\textsubscript{2}), 4.04 (t, 1H, J =6.8 Hz: CHNTs), 3.78 (t, J =7.8 Hz, 1H: CH\textsubscript{2}NTs), 3.36 (t, J =7.6Hz, 1H: CH\textsubscript{2}NTs), 2.62 (m, 1H: BnCH), 2.50 (m, 5H: overlapping CH\textsubscript{2}, CH\textsubscript{3}).

**13C NMR** (100 MHz, CDCl\textsubscript{3}) δ 144.42 (Quat.), 138.26 (Quat.), 137.02 (=CH), 132.62 (Quat.), 130.07-126.93 (Arom. CH), 117.74 (=CH\textsubscript{2}), 70.47 (CHNTs), 53.45 (CH\textsubscript{2}NTs), 38.97 (CH\textsubscript{2}Ph), 38.31 (CHBn), 22.08 (CH\textsubscript{3}). The assignments of the **1H** and **13C** were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl\textsubscript{3}): ν\textsubscript{max} 3086, 3065, 3030, 1599, 1497, 1344, 1165, 816, 669.

**HRMS** calcd for C19H22NO2S [M+H] 328.1371, found 328.1360.
5-isopropyl-3-tosyl-6-vinyl-1,3-oxazinan-2-one

12d (cw3099)
White solid, dr = 1:1

\[ \text{Ts} \quad \text{N} \quad \text{O} \quad \text{O} \]

\[ \text{5-isopropyl-3-tosyl-6-vinyl-1,3-oxazinan-2-one} \]

\[ \text{12d (cw3099)} \]

\[ \text{White solid, dr = 1:1} \]

\[ \text{1H NMR (400 MHz, CDCl} \text{3) } \delta \text{ ppm 7.93 (t, 4H, J=7.8 Hz: arom H (cis/trans)), 7.35 (d, 4H: arom H (cis/trans)), 5.81 (m, 2H: =CH (cis/trans)), 5.34 (m, 4H: =CH}_2 \text{ (cis/trans)), 4.93 (br. s., 1H: OCH (cis/trans)), 4.72 (t, 1H, J=6.5 Hz: OCH (cis/trans)), 4.12 (ddd, 1H, J=11.7, 5.3, 1.6 Hz: CH}_2 \text{NTs (cis/trans)), 3.93 (m, 1H: CH}_2 \text{NTs (cis/trans)), 3.84 (m, 1H: CH}_2 \text{NTs (cis/trans)), 3.48 (t, 1H, J=11.9 Hz: CH}_2 \text{NTs (cis/trans)), 2.46 (s, 6H: CH}_3 \text{Ts (cis/trans)), 1.91 (m, 2H: overlapping CH(CH}_3)_2, CHCH}_2 \text{NTs (cis/trans)), 1.78 (m, 1H: overlapping CH(CH}_3)_2, CHCH}_2 \text{NTs (cis/trans)), 1.59 (m, 1H: overlapping CH(CH}_3)_2, CHCH}_2 \text{ (cis/trans)), 1.06 (m, 8H: CH}_3 \text{ (cis/trans)), 0.99 (d, 4H, J = 6.8 Hz: CH}_3 \text{ (cis/trans)).} \]

\[ \text{13C NMR (100 MHz, CDCl} \text{3) } \delta \text{ ppm 144.31 (Quat.), 137.99 (=CH), 130.03 (Quat.), 128.75 (Arom. CH), 128.75 (Arom. CH), 117.68 (=CH}_2, 70.12 (CHNTs), 52.51 (CH}_2 \text{NTs), 44.20 (CH), 32.51 (CH(CH}_3)_2, 22.03 (CH}_3 \text{(Ts)), 19.71/19.59 (CH}_3). \]

The assignments of the \textsuperscript{1}H and \textsuperscript{13}C were based on DEPT, COSY, HMQC, NOESY etc.

\[ \text{FTIR (CDCl}_3): \nu_{\text{max}} \text{ 3053, 1599, 1495, 1344, 1163, 818, 671.} \]

\[ \text{HRMS calcd for C}_{15}\text{H}_{21}\text{NO}_2\text{SNa [M+Na] 302.1191, found 302.1191.} \]
4-phenyl-3-tosyl-6-vinyl-1,3-oxazinan-2-one

17a (cw2212)
White solid

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.23 - 7.37 (m, 5H: arom H), 7.15 (d, 2H, $J$=7.8 Hz: arom H), 7.04 (d, 2H, $J$=8.6 Hz: arom H), 5.84 (ddd, 1H, $J$=17.1, 10.8, 5.9 Hz: CH=), 5.47 (m, 2H: overlapping CH=CH($H_E$) and CHPh), 5.32 (d, 1H, $J$=10.6 Hz: CH=CH($H_Z$)), 4.91 (dd, 1H, $J$=11.3, 5.9 Hz: OCH), 2.63 (ddd, 1H, $J$=14.4, 8.1, 1.9 Hz: diastereotopic CH$_2$), 2.36 (s, 3H: CH$_3$), 2.04 (dt, 1H, $J$=14.4, 11.0 Hz: diastereotopic CH$_2$).

2-phenyl-1-tosyl-4-vinylazetidine

13i (cw2221)
Colorless oil
Pd(PPh$_3$)$_4$: 92% yield, dr >19:1

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, $J$ = 8.3 Hz, 2H: arom H), 7.42 (d, $J$ = 7.1 Hz, 2H: arom H), 7.33 (m, 5H: arom H), 6.06 (m, 1H: =CH), 5.38 (d, 1H, $J$ = 17.2 Hz: CH=CH($H_E$)), 5.25 (d, 1H, $J$ = 10.4 Hz: CH=CH($H_Z$)), 4.81 (t, 1H, $J$ =8.3 Hz: PhCH), 4.41 (q, $J$ =8.1, 4.9 Hz, 1H: CHCH=CH$_2$), 2.61 (dt, $J$ =8.3, 10.9 Hz, 1H: CH$_2$), 2.45(s, 3H: CH$_3$), 1.99(dt, $J$ =8.3, 10.9 Hz, 1H: CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 141.05 (Quat.), 141.05 (Quat.), 137.92 (=CH), 133.46 (Quat.), 130.02-126.96 (Arom. CH), 117.71 (=CH$_2$), 62.66 (PhCH), 66.19 (CHCH=CH$_2$), 33.68 (CH$_2$), 22.02 (CH$_3$). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC, NOESY etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3087, 3066, 3031, 1599, 1495, 1346, 1163, 816, 748, 665.

HRMS calcd for C$_{18}$H$_{20}$NO$_2$S [M+H] 314.1215, found 314.1216; C$_{18}$H$_{19}$NO$_2$SNa [M+Na] 336.1034, found 336.1048.
4-methyl-3-tosyl-6-vinyl-1,3-oxazinan-2-one
cw2243
colorless oil

\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta \text{ ppm } 7.99 \text{ (d, 2H, } J=8.7 \text{ Hz: arom H}), 7.33 \text{ (dd, 2H, } J=8.1, 0.6 \text{ Hz: arom H}), 5.84 \text{ (ddd, 1H, } J=17.2, 10.7, 5.6 \text{ Hz: CH=)}, 5.40 \text{ (dd, 1H, } J=17.2, 0.9 \text{ Hz: CH=CH(H)E}), 5.29 \text{ (d, 1H, } J=10.7 \text{ Hz: CH=CH(H)Z}), 4.66 \text{ (m, 2H: overlapping CHCH}_3 \text{ and OCH}), 2.45 \text{ (m, 4H: overlapping CH}_3\text{NTs and diastereotopic CH}_2\text{)}, 1.77 \text{ (dt, 1H, } J=14.1, 9.7 \text{ Hz: diastereotopic CH}_2\text{), 1.49 (s, 3H: CH}_3\text{).} \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta 143.85 \text{ (Quat.), 137.94 (=CH), 132.66 (Quat.), 129.65 (Arom. CH), 128.34 (Arom. CH), 116.91 (=CH}_2\text{), 61.47 (CHNTs), 56.68 (CHCH}_3\text{), 31.68 (CH}_2\text{), 22.56 (CH}_3\text{), 21.61 (CH}_3\text{(Ts))}. \]

FTIR (CDCl3): \( \nu_{\text{max}} \) 3055, 1600, 1495, 1342, 1163, 818.

HRMS calcd for C_{13}H_{18}NO_{2}S [M+H] 252.1058, found 252.1056.
6-phenyl-3-tosyl-6-vinyl-1,3-oxazinan-2-one

15a (cw2223)
White solid

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.80 (dd, 2H, $J$=8.3, 1.5 Hz: arom H), 7.31 (m, 7H: arom H), 6.02 (ddd, 1H, $J$=17.2, 10.8, 1.4 Hz: CH=), 5.26 (dd, 1H, $J$=7.4, 1.4 Hz: CH=CH($H_2$)), 5.24 (dd, 1H, $J$=13.9, 1.3 Hz: CH=CH($H$)$_2$), 3.96 (dddd, 1H, $J$=12.0, 6.8, 5.2, 1.2 Hz: diastereotopic CH$_2$NTs), 3.75 (m, 1H: diastereotopic CH$_2$NTs), 2.47 (m, 5H: overlapping: CH$_3$ and CH$_2$).

4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine

15b (cw2226)
White solid

Pd(PPh$_3$)$_4$: 99% yield

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, $J$ = 8.1 Hz, 2H: arom H), 7.34 (m, 7H: arom H), 5.98 (broad s, 1H: =CH), 3.78 (broad s, 2H: =HCCH$_2$NTs), 3.34 (t, 2H, $J$ =5.6 Hz: TsNCH$_2$), 2.64 (broad s, 2H: CH$_2$), 2.46 (s, 3H: CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 144.10 (Quat.), 140.50 (Quat.), 135.76 (Quat.), 133.42 (Quat.), 130.12-125.40 (Arom. CH), 119.40 (=CH), 45.69 (=HCCH$_2$NTs) 43.45 (CH$_2$NTs), 27.96 (CH$_2$), 21.98 (CH$_3$). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3065, 3033, 1597, 1495, 1342, 1167, 816, 673.

HRMS calcd for C$_{18}$H$_{20}$NO$_2$S [M+H] 314.1215, found 314.1212.
6-methyl-3-tosyl-6-vinyl-1,3-oxazinan-2-one

\(15c\) (cw2189)
colorless oil

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.85 (d, 2H, \(J=8.1\) Hz: arom H), 7.38 (d, 2H, \(J=8.4\) Hz: arom H), 5.82 (ddd, 1H, \(J=17.2, 10.9, 0.8\) Hz: \(\text{CH}\)), 5.21 (d, 1H, \(J=10.9\) Hz: \(\text{CH} = \text{CH}(H)_{\text{arom}}\)), 5.08 (d, 1H, \(J=17.2\) Hz: \(\text{CH} = \text{CH}(H)_{\text{arom}}\)), 4.07 (dt, 1H, \(J=11.9, 4.6\) Hz: diastereotopic \(\text{CH}_2\text{NTs}\)), 3.73 (td, 1H, \(J=11.8, 5.0\) Hz: diastereotopic \(\text{CH}_2\text{NTs}\)), 2.48 (s, 3H: \(\text{CH}_3\text{Ts}\)), 2.07 (m, 2H: \(\text{CH}_2\text{NTs}\)), 1.45 (s, 3H: \(\text{CH}_3\text{Ts}\)).

\(\text{NH}\)

4-methyl-N-(3-methylenepent-4-enyl)benzenesulfonamide

\(15d\) (cw2201)
colorless oil

Pd(PPH\(_3\))\(_4\): 40% yield

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.76 (d, \(J=8.3\) Hz, 2H: arom H), 7.33 (d, \(J=8.5\) Hz, 2H: arom H), 6.29 (dd, 1H, \(J=17.7, 10.8\) Hz: \(\text{CH} = \text{CH}\)), 4.92-5.19 (m, 4H: overlapping \(\text{CH}_2\)), 4.50 (s, 1H: \(\text{NHTs}\)), 3.12 (q, \(J=6.7\) Hz, 2H: \(\text{CH}_2\text{NHTs}\)), 2.45 (s, 3H: \(\text{CH}_3\text{Ts}\)), 2.41 (t, 2H, \(J=6.9\) Hz: \(\text{CH}_2\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 143.85 (Quat.), 142.57 (Quat.), 138.10 (CH=), 137.37 (Quat.), 130.13 (Arom. CH), 127.53 (Arom. CH), 118.57 (overlapping \(\text{CH}_2\)), 114.65 (overlapping \(\text{CH}_2\)), 41.82 (\(\text{CH}_2\text{NHTs}\)), 21.98 (CH\(_3\)), 31.93 (CH\(_2\)).

3-tosyl-1-oxa-3-azaspiro[5.5]undec-7-en-2-one

\(15e\) (cw2122)
colorless oil

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.95 (d, 2H, \(J=8.3\) Hz: arom H), 7.34 (dt, 2H, \(J=8.0, 0.7\) Hz: arom H), 6.02 (ddd, 1H, \(J=10.1, 4.2, 3.2\) Hz: \(\text{CHCH}_2\)), 5.62 (d, 1H, \(J=10.2\) Hz: \(\text{CH}\)), 4.02 (ddd, 2H, \(J=6.8, 6.0, 1.2\) Hz: \(\text{CH}_2\text{NHTs}\)), 2.45 (s, 3H: \(\text{CH}_3\)).
2.05 (m, 5H: overlapping CH₂), 1.87 (m, 1H: overlapping CH₂), 1.67 (m, 2H: overlapping CH₂).

\[
\text{NHTs}
\]

\[
\text{N-(2-(cyclohexa-1,3-dienyl)ethyl)-4-methylbenzenesulfonamide}
\]

\[
\text{15f (cw2129) colorless oil}
\]

\[
Pd(PPh₃)₄: 99% yield
\]

\[
\text{1H NMR (400 MHz, CDCl₃) δ ppm 7.75 (d, 2H, } J=8.3 \text{ Hz: arom H), 7.32 (d, 2H, } J=8.6 \text{ Hz: arom H), 5.82 (m, 1H: =CHCH₂), 5.65 (d, 1H, } J=9.6 \text{ Hz: CH=), 5.47 (br. s., 1H: CH=\text{C(Quat.)}, 4.46 (s, 1H: NHTs), 3.02 (q, 2H, } J=6.1 \text{ Hz: CH₂NHTs), 2.45 (s, 3H, overlapping CH₂), 2.16 (t, 3H, } J=6.7 \text{ Hz: overlapping CH₂), 2.08 (s, 3H: CH₃).}
\]

\[
\text{13C NMR (100 MHz, CDCl₃) δ ppm 143.80 (Quat.), 137.27 (Quat.), 132.00 (Quat.), 130.11 (Arom. CH), 128.52 (CH=), 127.54 (Arom. CH), 126.02 (CH=), 123.89 (CH=), 41.74 (CH₂NHTs), 35.55 (CH₂), 22.62 (CH₂), 22.58 (CH₂), 21.98 (CH₃).}
\]

\[
\text{2-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine}
\]

\[
\text{17b (cw2222) White solid}
\]

\[
Pd(PPh₃)₄: 68% yield
\]

\[
\text{1H NMR (400 MHz, CDCl₃) δ 7.71 (d, } J=7.8, 2\text{H: arom H), 7.38 (d, } J=8.3, 2\text{H: arom H), 7.29 (m, 5H: arom H), 5.81 (m, 1H: PhCHCH₂=CH), 5.61 (m, 1H, =CH), 5.32 (br d, 1H, } J=5.6 \text{ Hz: PhCH), 4.14 (br d, } J=17.7 \text{ Hz, 1H: CH₂NTs), 3.42 (br d, } J=19.7 \text{ Hz, 1H: CH₂NTs), 2.43 (5H: overlapping CH₂CHPh, CH₃).}
\]

\[
\text{13C NMR (100 MHz, CDCl₃) δ 134.51 (Quat.), 139.58 (Quat.), 138.12 (Quat.), 129.95-127.43 (Arom. CH), 124.32 (PhCHCH₂=CH), 124.13 (=CH), 53.21 (PhCH) 41.21 (CH₂NTs), 26.76 (CH₂), 21.95 (CH₃). The assignments of the } ^1\text{H and } ^13\text{C were based on DEPT, COSY, HMQC etc.}
\]

\[
\text{FTIR (CDCl₃): } \nu_{\text{max}} 3065, 3040, 1599, 1494, 1344, 1161, 816, 654.
\]

\[
\text{HRMS calcd for C}_{18}\text{H}_{20}\text{NO}_{2}\text{S [M+H] 314.1215, found 314.1219; C}_{18}\text{H}_{19}\text{NO}_{2}\text{SNa [M+Na] 336.1034, found 336.1038.}
\]
1H NMR (400 MHz, CDCl₃) δ ppm 7.04 (d, 1H, J=8.4 Hz: arom H), 7.36 (d, 1H, J=8.0 Hz: arom H), 5.83 (ddd, 1H, J=17.2, 10.7, 5.3 Hz: CH=), 5.32 (m, 1H: =CH₂), 4.84 (m, 1H: OCH), 4.08 (dt, 1H, J=12.0, 5.3 Hz: CH₂NTs), 3.91 (d, 1H, J=12.0, 9.5, 4.9 Hz: CH₂NTs), 2.46 (s, 3H: CH₃), 2.25 (m, 1H: CH₂), 1.98 (m, 1H: CH₂).

1H NMR (400 MHz, CDCl₃) δ ppm 7.72 (d, 4H, J=8.3 Hz: arom H), 7.72 (d, 4H, J=8.6 Hz: arom H), 5.62 (dt, 1H, J=15.6, 6.8 Hz: CH=), 5.45 (dt, 1H, J=15.4, 5.8 Hz: CH=), 3.58 (d, 4H, J=5.8 Hz: CH₂NTs), 3.20 (m, 4H: CH₂), 2.45 (s, 6H: CH₃), 2.41 (m, 4H: CH₂).

1H NMR (400 MHz, CDCl₃) δ ppm 7.20 - 7.59 (m, 10H: arom H (cis/trans)), 6.10 (m, 1H: =CH (cis/trans)), 5.97 (m, 1H: =CH (cis/trans)), 5.55 (m, 4H: =CH₂ (cis/trans)), 4.95 (br. s., 1H: OCH (cis/trans)), 4.74 (br. s., 1H: OCH (cis/trans)), 3.96 (d, 1H, J=13.3 Hz: CH₂NTs (cis/trans)), 3.88 (ddd, 1H, J=12.8, 5.4, 4.2 Hz: CH₂NTs (cis/trans)), 3.59 (m, 2H: CH₂NTs (cis/trans)), 3.02 (ddd, 1H, J=13.9, 4.5, 4.3 Hz: overlapping CH₂Ph, CHBn (cis/trans)), 2.83 (m, 1H: overlapping CH₂Ph, CHBn
(cis/trans)), 2.66 (m, 3H: overlapping CH$_2$Ph, CHBn (cis/trans)), 2.39 (m, 1H: overlapping CH$_2$Ph, CHBn (cis/trans)).

![Diagram](5-benzyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine 19b (cw2179)

White solid

Pd(PPh$_3$)$_4$: 60% yield, dr = 1.5:1

$^1$H NMR (400 MHz, CDCl$_3$) Major diastereoisomer: δ ppm 8.00 (m, 2 H: arom H, overlapping minor/major isomers), 7.44 (m, 3 H: arom H, overlapping minor/major isomers), 7.33 (m, 2 H: arom H, overlapping minor/major isomers), 7.26 (m, 3 H: arom H, overlapping minor/major isomers), 6.00 (m, 1 H, overlapping minor/major isomer: CH=), 5.40 (m, 2 H: =CH$_2$), 4.60 (t, 1 H, J=5.9 Hz: OCH), 3.59 (dd, 1 H, d, J=16.8, 4.9 Hz: CH$_2$N), 3.37 (td, 1 H, J=16.6, 8.1 Hz: CH$_2$N), 2.94 (dd, 1 H, J=13.6, 6.3 Hz: CH$_2$Ph), 2.58 (m, 1 H: CH$_2$Ph), 2.08 (m, 1 H: CHBn).

Minor diastereoisomer: δ ppm 8.00 (m, 2 H: arom H, overlapping minor/major isomers), 7.44 (m, 3 H: arom H, overlapping minor/major isomers), 7.33 (m, 2 H: arom H, overlapping minor/major isomers), 7.26 (m, 3 H: arom H, overlapping minor/major isomers), 6.00 (m, 1 H, overlapping minor/major isomer: CH=), 5.40 (m, 2 H: =CH$_2$), 4.87 (t, 1 H, J=3.7 Hz: OCH), 3.59 (dd, 1 H, d, J=16.8, 4.9 Hz: CH$_2$N), 3.37 (td, 1 H, J=16.6, 8.1 Hz: CH$_2$N), 2.68 - 2.73 (m, 1 H: CH$_2$Ph), 2.58 (m, 1 H: CH$_2$Ph), 2.43 (m, 1 H: CHBn).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 155.14 (C=N), 139.55 (C=N), 139.40 (Quat.), 136.43 (CH=), 134.15 (Quat.), 133.60 (CH=), 126.81-130.85 (Arom. CH), 118.75 (=CH$_2$), 118.30 (=CH$_2$), 78.94 (OCH), 77.67 (OCH), 46.29 (CH$_2$N), 37.37 (CHBn), 37.26 (CH$_2$Ph), 34.66 (CH$_2$Ph) (1.5:1 diastereomixture). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMOC etc.

FTIR (CDCl$_3$): ν$_{max}$ 3062, 3030, 2926, 1657, 1581, 1495, 1117.

HRMS calcd for C$_{19}$H$_{20}$NO [M+H] 278.1545, found 278.1527.
N-(2-benzylpenta-2,4-dienyl)benzamide

**19c** (cw2182)

colorless oil

Pd(PPh$_3$)$_4$: 96% NMR yield, dr = 1:1:1

$^1$H NMR (400 MHz, CDCl$_3$) Major diastereoisomer: $\delta$ ppm 7.72 (m, 3H: arom H), 7.53 (m, 4H: arom H), 6.98 - 7.19 (m, 3 H: arom H), 6.66 (m, 1H: CH=), 6.01 (d, 1H, $J$=11.1 Hz: BnC=CH), 5.68 (br. s., 1H: NH), 5.15 (m, 2H; =CH$_2$), 3.99 (d, 2H, $J$=5.6 Hz: CH$_2$NH), 3.42 (s, 2H: CH$_2$Ph).

Minor diastereoisomer: $\delta$ ppm 7.72 (m, 3H: arom H), 7.53 (m, 4H: arom H), 6.98 - 7.19 (m, 3 H: arom H), 6.77 (m, 1H: CH=), 6.14 (d, 1H, $J$=11.1 Hz: BnC=CH), 5.68 (br. s., 1H: NH), 5.15 (m, 2H; =CH$_2$), 4.18 (d, 2H, $J$=5.6 Hz: CH$_2$N), 3.99 (s, 2H: CH$_2$Ph).
General procedure for synthesizing starting vinyl benzoxazinanones:

Amino benzaldehydes were synthesized by oxidation of the corresponding amino alcohols except commercially available ones. N-protected carbamates were prepared from amino aldehydes by literature methods, followed by tosylation. $^1$H NMR spectra were referenced to residual protio solvent signals. Structural assignments are based on $^1$H, $^{13}$C, DEPT-135, COSY, HMQC.

Substituted ortho-amino benzyl alcohols were treated with chloroformate to synthesize the corresponding carbamates, which were oxidized to aldehydes with PCC (pyridinium chlorochromate). Grinard Reaction of the aldehydes, followed by intramolecular cyclization upon treatment with potassium carbonate, generated the desired vinyl benzoxazinanones in high yield. Finally, N-tosylation gave the starting material according to literature procedure. One thing to note here is that all the above procedures generate the desired products in high yield and purity. Consequently, the only necessary flash column separation was the tosylation step, just to ensure the high purity of the starting material for Pd-catalyzed decarboxylative dihydroquinoline syntheses and asymmetric cycloadditions.

To a solution of amino alcohol (2.9 g, 23 mmol) in 14 ml 1,4-dioxane, 14 ml saturated NaHCO$_3$ and 5 ml of water at 0 °C, was added dropwise methyl chloroformate (2.2 ml, 1.2 eq.), and the reaction mixture was warmed up slowly to room temperature and stirred overnight. The reaction was quenched by brine, extracted by ethyl acetate, dried over magnesium sulfate and concentrated to give the crude product, which was purified by flash column chromatography (SiO$_2$, 2:1
Hexane: Ethyl acetate. The oxidation was carried out with PCC (pyridinium chlorochromate) preabsorbed on Al₂O₃. To a solution of carbamate (1.0 g, 5.5 mmol) in 30 ml dichloromethane at rt was added PCC/Al₂O₃ (8.3 mmol, 1.2 eq.) in one portion. The reaction mixture was kept stirring until reaction completion indicated by TLC (generally 2 hr). 50 ml of ether was poured in the reaction mixture and the resulting solution was filter through a pad of Florisil. The reaction flask was rinse three times and the organic phase was combined and the solvent was removed to give the amino aldehyde in 94% yield, which is pure enough for the next step reaction. (One thing to note here is that longer oxidation time lowers the yield)

To a solution of amino aldehyde (450 mg, 2.5 mmol) in THF under argon at -78 °C was slowly added Grinard reagent (5.5 mmol, 2.2 eq.). The resulting yellow mixture was kept stirring at -78 °C for 2hrs before quenched with saturated NH₄Cl solution. The crude product was extracted with ethyl acetate three times, dried over magnesium sulfate and the solvent was removed to afford the crude product, which was taken to the next step without further purification. To a solution of allylic alchohol (520 mg, 2.5 mmol) in 7 ml MeOH was added dropwise 10% K₃CO₃ solution (3.3 mmol, 1.3 eq.). The reaction mixture was stirred at rt for 10 hrs until reaction completion indicated by TLC. The reaction was dilute with water, neutralized with 10% HCl solution, followed by extraction with ethyl acetate. The organic phase was washed with dilute hydrochloric acid, brined and dried over
magnesium sulfate and concentrated to give the crude product, which was purified by flash column chromatography (SiO\textsubscript{2}, 4:1 Hexane: Ethyl acetate).

Finally, \(N\)-protected carbamates were prepared according to literature procedure.\textsuperscript{11} Sodium hydride was used as the base for deprotonation. To a solution of carbamate (430 mg, 2.5 mmol) in THF at 0 \(^\circ\)C under argon was added NaH (5.0 mmol, 2.0 eq) in one portion and reaction was stirred for 1hr before TsCl (3.0 mmol, 1.2 eq) was added. The reaction was allowed to warm up to room temperature and kept stirring till reaction completion indicated by TLC (generally 1 hr). The reaction was quenched with sat. NH\textsubscript{4}Cl solution after 0.5 hr, extracted with ethyl acetate. The organic phase was washed with brined, dried over magnesium sulfate and concentrated to give the crude product, which was purified by flash column chromatography (SiO\textsubscript{2}, 5:1 Hexane: Ethyl acetate).

General procedure for catalytic decarboxylative dihydroquinoline synthesis from vinyl benzoazinanones:

In a Schlenk tube under argon, Pd(PPh\textsubscript{3})\textsubscript{4} (0.05 mmol) and vinyl benzoazinanone \textit{1a} (1 mmol) were dissolved in 5 mL of methylene chloride. The resulting yellow solution was stirred at ambient temperature under Ar until the
completion of the reaction was indicated by TLC (generally 1h-4h). Following solvent evaporation under reduced pressure, the crude product was purified via flash chromatography (SiO\(_2\), 7:1 Hexane: Ethyl acetate).

**General procedure for catalytic decarboxylative dimer synthesis from vinyl benzoxazinanones:**

In a Schlenk tube under argon, Pd(PPh\(_3\))\(_4\) (0.05 mmol) and vinyl benzoxazinanone 1 (1 mmol) were dissolved in 5 mL of toluene. The resulting yellow solution was stirred at ambient temperature under Ar until reaction completion was indicated by TLC (ca. 10 min). Following solvent evaporation under reduced pressure, the crude product was purified via flash chromatography (SiO\(_2\), 2:1 Hexane: Ethyl acetate).

![1-tosyl-4-vinyl-1\(H\)-benzo[\(d\)][1,3]oxazin-2(4\(H\))-one 32a (cw3124) White solid](image)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 8.10 (2H, d, \(J=8.3\) Hz: Ar CH), 7.62 (1H, d, \(J=8.2\) Hz: Ar CH), 7.40 (3H, m: Ar CH), 7.24 (3H, m: Ar CH), 6.04 (1H, ddd, \(J=17.0, 10.6, 6.1\) Hz: =CH), 5.64 (1H, d, \(J=6.0\) Hz: CHCH=), 5.46 (1H, dd, \(J=10.5, 0.6\) Hz: CH=CH\((H)\)\(_Z\)), 5.38 (1H, dd, \(J=17.2, 0.6\) Hz: CH=CH\((H)\)\(_E\)), 2.46 (3H, s: CH\(_3\)Ts).
1-tosyl-1,2-dihydroquinoline

38a (cw3154)
White solid
Pd(PPh$_3$)$_4$: 65% yield

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.67 (1H, d, $J$=8.08 Hz: Ar CH), 7.26 (2H, d, $J$=8.08 Hz: Ar CH), 7.23 (1H, dd, $J$=8.08, 1.77 Hz: Ar CH), 7.14 (1H, td, $J$=7.45, 1.26 Hz: Ar CH), 7.04 (2H, d, $J$=8.59 Hz: Ar CH), 6.90 (1H, dd, $J$=7.33, 1.52 Hz: Ar CH), 5.99 (1H, d, $J$=9.60 Hz: =CH), 5.55 (1H, dt, $J$=9.60, 4.17 Hz: =CHCH$_2$), 4.41 (2H, dd, $J$=4.17, 1.64 Hz: CH$_2$), 2.31 (3H, s: CH$_3$Ts).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 143.40 (quat. Ar C), 136.32 (quat. Ar C), 134.97 (quat. Ar C), 129.55 (quat. Ar C), 129.06 (Ar CH), 127.98 (Ar CH), 127.30 (Ar CH), 126.86 (Ar CH), 126.68 (Ar CH), 126.48 (Ar CH), 125.89 (=CH), 123.98 (=CHCH$_2$), 45.4 (CH$_2$), 21.6 (CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMOC etc.

FTIR (CH$_2$Cl$_2$): $\nu_{max}$ 3053, 2986, 1421, 1262, 895

HRMS calcd for C$_{16}$H$_{15}$NO$_2$SNa [M+Na] 308.0721, found 308.0729.

4-(prop-1-en-2-yl)-1-tosyl-1H-benzo[d][1,3]oxazin-2(4H)-one

32a (cw3248)
White solid

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.09 (2H, d, $J$=8.4 Hz: Ar CH), 7.62 (1H, d, $J$=8.1 Hz: Ar CH), 7.39 (3H, m: Ar CH), 7.25 (1H, m: Ar CH), 7.15 (1H, m: Ar CH), 5.59 (1H, s: OCH), 5.17 (1H, s: =CH), 4.97 (1H, s: =CH), 2.46 (3H, s: CH$_3$Ts), 1.78 (3H, s: CH$_3$).
3-methyl-1-tosyl-1,2-dihydroquinoline

38b (cw3261)
White solid

Pd(PPh₃)₄: 77% yield

**¹H NMR** (400 MHz, CDCl₃) δ ppm 7.66 (1H, d, J=7.83 Hz: Ar CH), 7.24 (2H, d, J=8.08 Hz: Ar CH), 7.19 (1H, dd, J=7.83, 1.52 Hz: Ar CH), 7.15 (1H, dd, J=7.45, 1.39 Hz: Ar CH), 7.05 (2H, d, J=8.34 Hz: Ar CH), 6.85 (1H, d, J=7.33 Hz: Ar CH), 5.71 (1 H, s: =CH), 4.24 (2 H, s: CH₂), 2.32 (3H, s: CH₃Ts), 1.64 (3H, s: CH₃).

**¹³C NMR** (100 MHz, CDCl₃) δ ppm 143.43 (quat. Ar C), 135.98 (quat. Ar C), 133.77 (quat. Ar C), 133.6 (=C), 130.6 (quat. Ar C), 128.9 (Ar CH), 126.9 (Ar CH), 126.8 (Ar CH), 125.7 (Ar CH), 120.9 (=CH), 49.4 (CH₂), 21.6 (CH₃Ts), 20.7 (CH₃). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

**FTIR** (CH₂Cl₂): ν max 3053, 2985, 1421, 1261, 895.

**HRMS** calcd for C₁₇H₁₇NO₂SNa [M+Na] 322.0878, found 322.0879.

4-(2-methylprop-1-enyl)-1-tosyl-1H-benzo[d][1,3]oxazin-2(4H)-one

35a (cw3249)
White solid

**¹H NMR** (400 MHz, CDCl₃) δ ppm 7.66 (1H, d, J=7.9 Hz: Ar CH), 7.28 (2H, m: Ar CH), 7.21 (2H, d, J=8.5 Hz: Ar CH), 7.07 (2H, d, J=8.0 Hz: Ar CH), 6.99 (1H, dd, J=7.4, 1.7 Hz: Ar CH), 5.98 (1H, d, J=9.3 Hz: OCH), 5.38 (1H, d, J=9.4 Hz: CH=), 2.35 (3H, s: CH₃Ts), 1.46 (6H, s: CH₃).
6-methyl-1-tosyl-4-vinyl-1H-benzo[d][1,3]oxazin-2(4H)-one

cw3257

colorless oil

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.07 (2H, d, $J$=8.4 Hz: Ar CH), 7.49 (1H, d, $J$=8.3 Hz: Ar CH), 7.37 (2H, d, $J$=8.7 Hz: Ar CH), 7.20 (1H, d, $J$=8.3 Hz: Ar CH), 6.97 (1H, s: Ar CH), 6.02 (1H, ddd, $J$=17.1, 10.5, 6.1 Hz: $=C$H), 5.58 (1H, d, $J$=6.1 Hz: CCH=), 5.44 (1H, dd, $J$=10.4, 0.8 Hz: CH=$=CH(H)_2$), 5.35 (1H, d, $J$=17.2 Hz: CH=$=CH(H)_E$), 2.45 (3H, s: overlapping CH$_3$Ts, CH$_3$), 2.35 (3H, s: overlapping CH$_3$Ts, CH$_3$).

6-methyl-1-tosyl-1.2-dihydroquinoline

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.59 (1 H, d, $J$=8.15 Hz: Ar CH), 7.31 (2 H, d, $J$=8.27 Hz: Ar CH), 7.08 (3 H, d, $J$=8.02 Hz: Ar CH), 6.75 (1 H, s: Ar CH), 5.98 (1 H, d, $J$=9.60 Hz: $=C$H), 5.56 (1 H, dt, $J$=9.60, 4.17 Hz: $=CHCH_2$), 4.41 (2 H, dd, $J$=4.04, 1.64 Hz: CH$_2$), 2.35 (3 H, s: overlapping CH$_3$Ts, CH$_3$), 2.32 (3 H, s: overlapping CH$_3$Ts, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 143.26 (quat. Ar C), 136.46 (quat. Ar C), 136.39 (quat. Ar C), 132.41 (quat. Ar C), 129.31 (quat. Ar C), 129.03 (Ar CH), 128.67 (Ar CH), 127.34 (Ar CH), 126.99 (Ar CH), 126.71 (Ar CH), 125.95 (=CH), 123.84 (=CHCH$_2$), 45.46 (CH$_2$), 21.55 (overlapping CH$_3$, CH$_3$Ts), 21.03 (overlapping CH$_3$, CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CH$_2$Cl$_2$): $\nu_{max}$ 3053, 2986, 1489, 1421, 1271, 1258, 895

HRMS calcd for C$_{17}$H$_{18}$NO$_2$S [M+] 300.1058, found 300.1059.
6-methyl-4-(prop-1-en-2-yl)-1-tosyl-1H-benzo[d][1,3]oxazin-2(4H)-one

35g (cw4204)
White solid

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta \) ppm 8.10 (2H, d, \(J=8.3\) Hz: Ar CH), 7.52 (1H, d, \(J=8.4\) Hz: Ar CH), 7.39 (2H, d, \(J=8.0\) Hz: Ar CH), 7.23 (1H, d, \(J=8.4\) Hz: Ar CH), 6.97 (1H, s: Ar CH), 5.57 (1H, s: OC\(\mathrm{H}\)), 5.18 (1H, s: =CH), 4.99 (1H, s: =CH), 2.48 (3H, s: overlapping CH\(_3\)Ts, CH\(_3\)), 2.38 (3H, s: overlapping CH\(_3\)Ts, CH\(_3\)), 1.80 (3H, s: CH\(_3\)C=).

3,6-dimethyl-1-tosyl-1,2-dihydroquinoline

38d (cw4207)
White solid

Pd(PPh\(_3\))\(_4\): 94% yield

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta \) ppm 7.56 (1 H, d, \(J=8.15\) Hz: Ar CH), 7.26 (2 H, d, \(J=8.21\) Hz: Ar CH), 7.07 (2 H, d, \(J=8.27\) Hz: Ar CH), 7.03 (1 H, dd, \(J=8.08, 1.52\) Hz: Ar CH), 6.68 (1 H, s: Ar CH), 5.67 (1 H, s: =CH), 4.23 (2 H, s: CH\(_2\)), 2.35 (3 H, s: overlapping CH\(_3\)Ts, CH\(_3\)), 2.31 (3 H, s: overlapping CH\(_3\)Ts, CH\(_3\)), 1.63 (3 H, s: =CCH\(_3\)).

\(^13C\) NMR (100 MHz, CDCl\(_3\)) \(\delta \) ppm 143.32 (quat. Ar C), 136.51 (quat. Ar C), 135.98 (quat. Ar C), 133.58 (=C), 131.02 (quat. Ar C), 130.34 (quat. Ar C), 128.96 (Ar CH), 127.67 (Ar CH), 126.88 (Ar CH), 126.64 (Ar CH), 126.22 (Ar CH), 121.00 (=CH), 49.48 (CH\(_2\)), 21.57 (overlapping CH\(_3\)Ts, CH\(_3\)), 21.08 (overlapping CH\(_3\)Ts, CH\(_3\)), 20.78 (=CCH\(_3\)). The assignments of the \(^1H\) and \(^13C\) were based on DEPT, COSY, HMQC etc.

FTIR (CH\(_2\)Cl\(_2\)): \(\nu_{\text{max}}\) 3054, 2926, 1493, 1346, 1271.

HRMS calcd for C\(_{18}\)H\(_{23}\)N\(_2\)O\(_2\)S [M+NH\(_4\)] 331.1480, found 331.1479.
6-fluoro-1-tosyl-4-vinyl-1*H*-benzo[**d**][1,3]oxazin-2(*H*)-one

cw3288
colorless oil

**1H NMR** (400 MHz, CDCl₃) δ ppm 8.08 (2H, d, J=8.4 Hz: Ar CH), 7.60 (1H, dd, J=9.1, 4.5 Hz: Ar CH), 7.39 (2H, dd, J=8.1, 0.6 Hz: Ar CH), 7.13 (1H, td, J=8.5, 2.9 Hz: Ar CH), 6.92 (1H, dd, J=7.7, 2.8 Hz: Ar CH), 6.01 (1H, ddd, J=17.0, 10.6, 6.2 Hz: =CH), 5.60 (1H, d, J=6.2 Hz: CH=), 5.50 (1H, d, J=10.4 Hz: CH=CH(H)₂), 5.40 (1H, d, J=17.6 Hz: CH=CH(H)₃E), 2.47 (3H, s: CH₃Ts).

6-fluoro-1-tosyl-1,2-dihydroquinoline

**38e** (cw3298)
White solid

**Pd(PPh₃)₄**: 51% yield

**1H NMR** (400 MHz, CDCl₃) δ ppm 7.66 (1 H, dd, J=8.72, 5.05 Hz: Ar CH), 7.28 (2 H, d, J=8.34 Hz: Ar CH), 7.08 (2 H, d, J=8.46 Hz: Ar CH), 6.96 (1 H, td, J=8.57, 2.94 Hz: Ar CH), 6.63 (1 H, dd, J=8.59, 2.91 Hz: Ar CH), 5.95 (1 H, d, J=9.66 Hz: =CH), 5.63 (1 H, dt, J=9.19, 4.20 Hz: =CHCH₂), 4.42 (2 H, dd, J=4.11, 1.71 Hz: CH₂), 2.35 (3 H, s: CH₃Ts).

**13C NMR** (100 MHz, CDCl₃) δ ppm 143.6 quat. Ar C), 136.0 (quat. Ar C), 129.1 (Ar CH), 128.9 (quat. Ar C), 128.8 (quat. Ar C), 127.8 (quat. Ar C), 127.3 (Ar CH), 125.5 (=CHCH₂), 125.2 (=CH), 114.4 Ar CH), 112.9 (Ar CH), 112.7 (Ar CH), 45.4 (CH₂), 21.5 (CH₃Ts).

**FTIR** (CH₂Cl₂): νmax 3063, 2926, 1713, 1487, 1352, 1167.

**HRMS** calcd for C₁₆H₁₈FN₂O₂S [M+NH₄] 321.1073, found 321.1074.
6-fluoro-4-(prop-1-en-2-yl)-1-tosyl-1H-benzo[d][1,3]oxazin-2(4H)-one
cw3289
colorless oil

\( ^1H \text{ NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) ppm 8.07 (2H, d, \( J=8.3 \) Hz: Ar CH), 7.60 (1H, dd, \( J=9.0, 4.5 \) Hz: Ar CH), 7.38 (2H, d, \( J=8.0 \) Hz: Ar CH), 7.12 (1H, td, \( J=8.2, 2.5 \) Hz: Ar CH), 6.88 (1H, dd, \( J=7.7, 2.8 \) Hz: Ar CH), 5.56 (1H, s: OCH), 5.20 (1H, s: =CH), 4.99 (1H, s: =CH), 2.47 (3H, s: CH\(_3\)Ts), 1.78 (3H, s: CH\(_3\)).

6-fluoro-3-methyl-1-tosyl-1,2-dihydroquinoline

\( 38f \) (cw3293)
White solid
Pd(PPh\(_3\))\(_4\): 82% yield

\( ^1H \text{ NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) ppm 7.64 (1 H, dd, \( J=8.81, 5.21 \) Hz: Ar CH), 7.25 (2 H, d, \( J=8.3 \) Hz: Ar CH), 7.09 (2 H, d, \( J=8.46 \) Hz: Ar CH), 6.91 (1 H, td, \( J=8.59, 2.91 \) Hz: Ar CH), 6.56 (1 H, dd, \( J=8.75, 2.87 \) Hz: Ar CH), 5.61 (1 H, s: =CH), 4.25 (2 H, s: CH\(_2\)), 2.35 (3 H, s: CH\(_3\)Ts), 1.66 (3 H, s: CH\(_3\)).

\( ^{13}C \text{ NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) ppm 160.01 (quat. Ar C), 143.63 (quat. Ar C), 135.69 (quat. Ar C), 135.53 (quat. Ar C), 132.40 (=C), 129.35 (quat. Ar C), 129.05 (Ar CH), 128.56 (Ar CH), 126.86 (Ar CH), 120.36 (=CH), 113.39 (Ar CH), 111.83 (Ar CH), 49.46 (CH\(_2\)), 21.54 (CH\(_3\)Ts), 20.72 (CH\(_3\)). The assignments of the \(^1H\) and \(^{13}C\) were based on DEPT, COSY, HMQC etc.

\( \text{FTIR (CH}_2\text{Cl}_2): \nu_{\text{max}} 3053, 2986, 1480, 1348, 1166. \)

\( \text{HRMS} \) calcd for C\(_{17}\)H\(_{16}\)FNO\(_2\)S [M+] 317.0886, found 317.0887.
6-methoxy-1-tosyl-4-vinyl-1H-benzo[1,3]oxazin-2(4H)-one

cw4142
White solid

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.06 (2H, d, $J$=8.5 Hz: Ar CH), 7.52 (1H, d, $J$=9.0 Hz: Ar CH), 7.37 (2H, d, $J$=8.5 Hz: Ar CH), 6.93 (1H, dd, $J$=9.0, 2.8 Hz: Ar CH), 6.69 (1H, d, $J$=2.8 Hz: Ar CH), 6.01 (1H, ddd, $J$=17.0, 10.6, 6.1 Hz: =CH), 5.58 (1H, d, $J$=6.0 Hz: CHCH=), 5.45 (1H, d, $J$=11.1 Hz: CH=CH(H)$_2$), 5.37 (1H, d, $J$=17.2 Hz: CH=CH(H)$_2$), 3.81 (3H, s: OCH$_3$), 2.46 (3H, s: CH$_3$Ts).

6-methoxy-1-tosyl-1,2-dihydroquinoline

38g (cw4194)
White solid

Pd(PPh$_3$)$_4$: 80% yield

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.62 (1 H, d, $J$=8.84 Hz: Ar CH), 7.28 (2 H, d, $J$=8.34 Hz: Ar CH), 7.09 (1 H, d, $J$=8.53 Hz: Ar CH), 6.82 (1 H, dd, $J$=8.81, 2.94 Hz: Ar CH), 6.47 (1 H, d, $J$=2.91 Hz: Ar CH), 5.95 (1 H, d, $J$=9.60 Hz: =CH), 5.56 (1 H, dt, $J$=9.60, 4.04 Hz: =CHCH$_2$), 4.40 (2 H, dd, $J$=4.07, 1.67 Hz: CH$_2$), 3.81 (3 H, s: OCH$_3$), 2.35 (3 H, s: CH$_3$Ts).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 158.20 (quat. Ar C), 143.30 (quat. Ar C), 136.14 (quat. Ar C), 130.69 (quat. Ar C), 129.03 (Ar CH), 128.35 (Ar CH), 127.78 (quat. Ar C), 127.39 (Ar CH), 125.84 (=C), 124.60 (=CHCH$_2$), 113.02 (Ar CH), 111.53 (Ar CH), 55.48 (OCH$_3$), 45.54 (CH$_2$), 21.57 (CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CH$_2$Cl$_2$): $\nu$$_{max}$ 3050, 2923, 1491, 1350, 1271.

HRMS calcd for C$_{17}$H$_{17}$NO$_3$SNa [M+Na] 338.0827, found 338.0828.
6-methoxy-4-(prop-1-en-2-yl)-1-tosyl-1H-benzo[d][1,3]oxazin-2(4H)-one
cw4196
White solid

^1H NMR (400 MHz, CDCl₃) δ ppm 8.08 (2H, d, J=8.4 Hz: Ar CH), 7.55 (1H, d, J=9.0 Hz: Ar CH), 7.39 (2H, d, J=8.5 Hz: Ar CH), 6.95 (1H, dd, J=9.0, 2.8 Hz: Ar CH), 6.69 (1H, d, J=2.7 Hz: Ar CH), 5.55 (1H, s: OCH), 5.17 (1H, s: =CH), 4.99 (1H, s: =CH), 3.83 (3H, s: OCH₃), 2.48 (3H, s: CH₃Ts), 1.79 (3H, s: CH₃).

^13C NMR (100 MHz, CDCl₃) δ ppm 157.4 (C ONTS), 149.4 (quat. Ar C), 145.5 (=C), 139.5 (quat. Ar C), 135.8 (quat. Ar C), 129.6 (Ar CH), 129.0 (Ar CH), 127.6 (quat. Ar C), 127.2 (quat. Ar C), 122.2 (Ar CH), 117.2 (Ar CH), 114.0 (Ar CH), 111.2 (=CH), 82.2 (OCH), 55.7 (OCH₃), 21.7 (CH₃Ts), 18.4 (CH₃).

6-methoxy-3-methyl-1-tosyl-1,2-dihydroquinoline
38h (cw4200)
White solid
Pd(PPh₃)₄: 92% yield

^1H NMR (400 MHz, CDCl₃) δ ppm 7.61 (1 H, d, J=8.78 Hz: Ar CH), 7.25 (2 H, d, J=8.27 Hz: Ar CH), 7.09 (2 H, d, J=8.08 Hz: Ar CH), 6.79 (1 H, dd, J=8.78, 2.91 Hz: Ar CH), 6.41 (1 H, d, J=2.84 Hz: Ar CH), 5.66 (1 H, s: =CH), 4.23 (2 H, s: CH₂), 3.81 (3 H, s: OCH₃), 2.36 (3 H, s: CH₃Ts), 1.65 (3 H, s: CH₃).

^13C NMR (100 MHz, CDCl₃) δ ppm 158.28 (quat. Ar C), 143.34 (quat. Ar C), 135.77 (quat. Ar C), 134.41 (=C), 131.76 (quat. Ar C), 128.94 (Ar CH), 128.16 (Ar CH), 126.91 (Ar CH), 126.46 (quat. Ar C), 120.97 (=CH), 111.97 (Ar CH), 110.77 (Ar CH), 55.45 (OCH₃), 49.58 (CH₂), 21.57 (CH₃Ts), 20.78 (CH₃). The assignments of the ^1H and ^13C were based on DEPT, COSY, HMGC etc.

FTIR (CH₂Cl₂): νmax 3052, 2929, 1346, 1259, 1165
HRMS calcd for C₁₈H₁₉NO₅SNa [M+Na] 352.0984, found 352.0982.
6,7-dimethoxy-4-vinyl-1\textit{H}-benzo[\textit{d}][1,3]oxazin-2(4\textit{H})-one

\textit{36a} (cw4060)

White solid

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 7.48 (1H, br. s.: NH), 6.60 (1H, s: Ar CH), 6.35 (1H, s: Ar CH), 6.05 (1H, ddd, \(J=17.0, 10.4, 6.5\) Hz: =CH), 5.74 (1H, d, \(J=6.6\) Hz: CH=), 5.41 (1H, d, \(J=10.4\) Hz: CH=CH\textit{H}\textsubscript{2}), 5.36 (1H, d, \(J=17.4\) Hz: CH=CH\textit{H}\textsubscript{2}), 3.87 (3H, s: OCH\textsubscript{3}), 3.84 (3H, s: OCH\textsubscript{3}).

\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{N} & \quad \text{O} \\
\text{OH} & \\
\text{MeO} & \\
\end{align*}

(7E,15E)-5,13-ditosyl-5,6,13,14-tetrahydrodibenzo[b,h][1,7]diazacyclododecine

\textit{39a} (cw4017)

White solid

Pd(PPh\textsubscript{3})\textsubscript{4}: 36\% yield, dr = 8:1

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 7.83 (4H, d, \(J=8.1\) Hz: Ar CH), 7.50 (2H, d, \(J=16.4\) Hz: =CH), 7.41 (4H, d, \(J=8.6\) Hz: Ar CH), 7.28 (2H, d, \(J=8.7\) Hz: Ar CH), 7.15-7.25 (4H, m: Ar CH), 6.94 (2H, d, \(J=7.8\) Hz: Ar CH), 5.46 (2H, dt, \(J=16.1, 5.9\) Hz: =CHCH\textsubscript{2}), 4.66 (2H, ddd, \(J=13.2, 5.9, 1.3\) Hz: CH\textsubscript{2}), 3.73 (6H, s: CH\textsubscript{3}), 3.62 (2H, dd, \(J=13.2, 5.9\) Hz: CH\textsubscript{2}), 2.47 (6H, s: CH\textsubscript{3}Ts).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 143.9 (quat. Ar C), 139.0 (quat. Ar C), 137.3 (=CH), 136.0 (quat. Ar C), 130.0 (Ar CH), 129.6 (quat. Ar C), 129.0 (Ar CH), 128.5 (Ar CH), 128.4 (Ar CH), 128.2 (Ar CH), 127.0 (Ar CH), 124.6 (=CHCH\textsubscript{2}), 50.9 (CH\textsubscript{2}), 21.7 (CH\textsubscript{3}Ts). The assignments of the \textsuperscript{1}H and \textsuperscript{13}C were based on DEPT, COSY, HMQC etc.

\textbf{FTIR} (CH\textsubscript{2}Cl\textsubscript{2}): \(\nu_{\text{max}}\) 3051, 2926, 1346, 1271, 1161, 760.

\textbf{HRMS} calcld for C\textsubscript{32}H\textsubscript{34}N\textsubscript{3}O\textsubscript{4}S\textsubscript{2} [M+NH\textsubscript{4}] 588.1991, found 588.1990.
(7E,15E)-2,10-dimethyl-5,13-ditosyl-5,6,13,14-tetrahydrodibenzo[b,h][1,7]diazacyclododecine
39b (cw4223)
White solid
Pd(PPh₃)₄: 87% yield, dr = 5.5:1

¹H NMR (400 MHz, CDCl₃) δ ppm 7.83 (4H, d, J=8.2 Hz: Ar CH), 7.42 (6H, m: overlapping Ar CH, =CH), 7.07 (1H, s: Ar CH), 6.97 (2H, d, J=8.3 Hz: Ar CH), 6.81 (2H, d, J=8.1 Hz: Ar CH), 5.44 (2H, dt, J=16.2, 6.0 Hz: =CHCH₂), 4.63 (2H, ddd, J=13.1, 6.0, 1.5 Hz: CH₂), 3.63 (2H, dd, J=13.1, 5.9 Hz: CH₂), 2.48 (6 H, s: CH₃Ts), 2.25 (6 H, s: CH₃).

¹³C NMR (126 MHz, CDCl₃) δ ppm 138.8 (quat. Ar C), 143.8 (quat. Ar C), 138.6 (quat. Ar C), 137.4 (=CH), 136.1 (quat. Ar C), 134.7 (quat. Ar C), 129.9 (Ar CH), 129.3 (Ar CH), 128.2 (Ar CH), 128.1 (Ar CH), 127.6 (Ar CH), 124.3 (=CHCH₂), 50.8 (CH₂), 21.7 (CH₃Ts), 21.2 (CH₃). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

FTIR (CH₂Cl₂): νmax 2924, 1599, 1491, 1346, 1163.

HRMS calcd for C₃₄H₃₈N₃O₄S₂ [NH₄] 616.2304, found 616.2302.

(7E,15E)-2,10-dimethoxy-5,13-ditosyl-5,6,13,14-tetrahydrodibenzo[b,h][1,7]diazacyclododecine
39c (cw4205)
White solid
Pd(PPh₃)₄: 94% yield, dr = 6.7:1

¹H NMR (400 MHz, CDCl₃) δ ppm 7.81 (4 H, d, J=8.21 Hz: Ar CH), 7.35 - 7.54 (6 H, m: overlapping Ar CH, =CH), 6.82 (2 H, d, J=8.72 Hz: Ar CH), 6.76 (2 H, d, J=2.91 Hz: Ar CH), 6.69 (2 H, dd, J=8.72, 2.84 Hz: Ar CH), 5.46 (2 H, dt, J=16.14, 5.89 Hz: =CHCH₂), 4.66 (2 H, ddd, J=13.17, 5.87, 1.29 Hz: CH₂), 3.73 (6 H, s: CH₃), 3.62 (2 H, dd, J=13.17, 5.91 Hz: CH₂), 2.47 (6 H, s: CH₃Ts).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 159.5 (quat. Ar C), 143.8 quat. Ar C), 140.1 (quat. Ar C), 137.2 (=CH), 136.1 (quat. Ar C), 129.9 (Ar CH), 129.4 (Ar CH), 128.1 (Ar CH), 124.9 (=CHCH$_2$), 114.1 (Ar CH), 111.7 (Ar CH), 55.4 (OCH$_3$), 50.8 (CH$_2$), 21.7 (CH$_3$Ts); Note: onequat. Ar carbon is not found. The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CH$_2$Cl$_2$): $\nu_{\text{max}}$ 3065, 2926, 1599, 1570, 1493, 1258, 1161.

HRMS calcd for C$_{34}$H$_{34}$N$_2$O$_6$S$_2$Na [M+Na] 653.1756, found 653.1762.

(7Z,15Z)-2,10-difluoro-5,13-ditosyl-5,6,13,14-tetrahydrodibenzo[b,h][1,7]diazacyclododecine 39d (cw4210)
Colorless oil
Pd(PPh$_3$)$_4$: 92% yield

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.53 (2 H, d, $J$=8.15 Hz: Ar CH), 7.33 (4 H, d, $J$=8.21 Hz: Ar CH), 7.19 - 7.26 (2 H, m: Ar CH), 7.11 (4 H, d, $J$=7.89 Hz: Ar CH), 6.91 (2 H, t, $J$=8.75 Hz: Ar CH), 6.29 (2 H, d, $J$=9.73 Hz: =CH), 5.67 (2 H, dt, $J$=9.79, 4.26 Hz: =CHCH$_2$), 4.46 (4 H, dd, $J$=3.73, 1.39 Hz: CH$_2$), 2.36 (6 H, s: CH$_3$Ts),

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 158.80 (quat. Ar C), 156.82 (quat. Ar C), 143.78 (quat. Ar C), 136.15 (quat. Ar C), 129.25 (Ar CH), 128.20 (Ar CH), 127.23 (Ar CH), 124.33 (=CH), 122.33 (Ar CH), 118.55 (=CHCH$_2$), 117.84 (quat. Ar C), 113.03 (Ar CH), 45.14 (CH$_2$), 21.59 (CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CH$_2$Cl$_2$): $\nu_{\text{max}}$ 3065, 2926, 1612, 1472, 1263, 1167, 750.

HRMS calcd for C$_{32}$H$_{28}$F$_2$N$_2$O$_4$S$_2$Na [M+Na] 629.1356, found 629.1359.
1-benzoyl-4-vinyl-1H-benzo[d][1,3]oxazin-2(4H)-one

37e (cw3159)

Colorless oil

1H NMR (400 MHz, CDCl3) δ ppm 7.90 (2H, d, J=8.1 Hz: Ar CH), 7.62 (1H, t, J=7.5 Hz: Ar CH), 7.55 (1H, d, J=8.1 Hz: Ar CH), 7.49 (2H, t, J=7.8 Hz: Ar CH), 7.36 (1H, m: Ar CH), 7.26 (2H, d, J=15.2 Hz: Ar CH), 6.27 (1H, td, J=11.2, 5.2 Hz: =CH), 5.93 (1H, d, J=5.6 Hz: CHCH=), 5.59 (1H, dd, J=10.4, 0.6 Hz: CH=CH(H)Z), 5.46 (6H, d, J=17.2 Hz: CH=CH(H)E)).

2-phenyl-4-vinyl-4H-benzo[d][1,3]oxazine

42f (cw3164)

White solid

Pd(PPh3)4: 96% NMR yield

1H NMR (400 MHz, CDCl3) δ ppm 8.17 (2H, dd, J=8.3, 1.4 Hz: Ar CH), 7.68 (4H, m: Ar CH), 7.33 (3H, m: Ar CH), 6.11 (1H, m: =CH), 5.88 (1H, d, J=6.3 Hz: OCH), 5.33 (2H, m: =CH2).

1-benzyl-4-vinyl-1H-benzo[d][1,3]oxazin-2(4H)-one

37a (cw3191)

colorless oil

1H NMR (400 MHz, CDCl3) δ ppm 7.37 (5H, m: Ar CH), 7.28 (1H, dd, J=15.6, 1.7 Hz: Ar CH), 7.19 (1H, d, J=6.4 Hz: Ar CH), 7.14 (1H, d, J=7.4 Hz: Ar CH), 6.92 (1H, d, J=8.2 Hz: Ar CH), 6.18 (1H, ddd, J=17.1, 10.4, 5.9 Hz: =CH), 5.85 (1H, d, J=6.0
Hz: \( CHCH= \), 5.51 (1H, d, \( J=10.4 \) Hz: \( CH=CHH_2 \)), 5.42 (1H, d, \( J=17.1 \) Hz: \( CH=CHH_E \)), 5.24 (2H, m: \( CH_2Ph \)).

\[
\begin{array}{c}
\text{Ts} \\
\text{1-tosyl-1H-benzo[d][1,3]oxazin-2(4H)-one} \\
\text{cw4161} \\
\text{colorless oil}
\end{array}
\]

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 8.14 (2H, d, \( J=8.4 \) Hz: Ar \( CH \)), 7.60 (1H, d, \( J=8.4 \) Hz: Ar \( CH \)), 7.40 (3H, d, \( J=8.1 \) Hz: Ar \( CH \)), 7.24 (2H, d, \( J=6.4 \) Hz: Ar \( CH \)), 5.13 (2H, s: \( CH_2 \)), 2.47 (3H, s: \( CH_3Ts \)).
Reference:


Chapter 3

Palladium-catalyzed Decarboxylative Cycloaddition Reactions
3.1 Introduction

Substituted piperidines are frequently encountered structural motifs of alkaloids that are abundant in nature and have attracted much attention due to their significant biological activities.\textsuperscript{1,2} Statistics indicate that more than 12,000 piperidine derivatives have been claimed to be in clinical or preclinical studies.\textsuperscript{3}

The industrial preparation of piperidines has largely relied on nickel-catalyzed hydrogenation of pyridine. The routine synthesis of piperdine in the laboratory is also achieved with resort to the reduction of the corresponding pyridines. For example, sodium in alcohol solvent has been employed to reduce pyridines. Transition metal-catalyzed hydrogenation is also used due to the mild reaction conditions and functional group compatibility. For instance, piperdine 1d was prepared by selective reduction by resorting to different transition metals as shown in Scheme 1.\textsuperscript{4}

**Scheme 1** Piperidines synthesis via transition metal-catalyzed reduction of pyridines

Intramolecular \(N\)-cyclizations have also been widely used for piperidine ring preparation from precursors such as 1,5-amino halides, 1,5-diamino alcohols, 1,5-diamines and 1,5-dihalides.\textsuperscript{5} For example, piperidines 2b and 2d were synthesized from the corresponding 1,5-aminohalides in good yields (Scheme 2).\textsuperscript{6,7}
However, secondary amines with an electron withdrawing group were used to avoid competing side reactions such as dialkylation and intermolecular \( N \)-alkylation.

**Scheme 2 Piperidine synthesized from 1,5-aminohalides**

Intramolecular ring closure of 1,5-amino alcohols is another classical way for piperidine preparation (Scheme 3). In the late 1940’s, Woods reported the synthesis of piperidine 3d from a free 1,5-amino alcohol 3b.\(^8\) Conversion of 3b to its sulfate salt 3c was achieved by treatment with sulfuric acid and piperidine 3d was formed by refluxing with hydrobromide acid. Similarly, piperidines 3g and 3j were prepared from their corresponding 1,5-aminoalcohols.\(^9,10\)
Scheme 3 Piperidine synthesized from 1,5-aminoalcohols

Pseudoconhydrine 4c isolated along with coniine from Poison Hemlock, *coniun maculatum* was synthesized via an intramolecular reductive amination of intermediate 4b (Scheme 4).<sup>9</sup> Alkaloid solenopsine 4h, a subcategory of ant venoms, displays potent antifungal, insecticide and repellent activity.<sup>14,15</sup> The synthesis featured an intermolecular double condensations of (-)-phenylglycinol 4d and glutaraldehyde 4e to form an iminium intermediate 4f, which was trapped by KCN to furnish cyanopiperidine 4g. Further elaborations provided the alkaloid product 4h.<sup>10</sup>
Transition metal-mediated piperidine synthesis has drawn a lot of attention. In 2000, Trost reported a ruthenium-catalyzed piperidine synthesis from allene 5a and enone 5b (Scheme 5). A ruthenacycle 5d was thought to be involved, and subsequent intramolecular nucleophilic attack to furnish the piperidine product 5c in 53% yield.

Ring closing methathesis (RCM) has also been applied in piperidine synthesis as shown in Scheme 6. Tetrahydropyridine 6b was prepared by treatment of compound 6a with 10 mol% Grubbs’ catalyst A, and (R)-coniine 6c was obtained upon further
elaboration. Coniine 6c is a poisonous alkaloid, which is found in poison hemlock and the yellow pitcher plant.\textsuperscript{12}

**Scheme 6** *Piperidines synthesis via Ring closing methathesis (RCM)*

![Scheme 6](image)

An intramolecular aminomercuration protocol was developed by Harding and applied in the synthesis of alkaloid (±)-Pseudoconhydrine 7d (Scheme 7).\textsuperscript{13, 14} Aziridine 7c was formed from iodo compound 7b upon treatment of hydrobromide in acetic acid. Electrophilic ring opening followed by hydrolysis yield the alkaloid product 7d in 50% yield.

**Scheme 7** *Piperidines synthesis via intramolecular aminomercuration*

![Scheme 7](image)

Palladium catalysts have also been used for the synthesis of piperidine alkaloids (Scheme 8). For example, Hirai reported an efficient Pd-catalyzed intramolecular
$N$-alkylation to yield a mixture of diastereoisomers $8b$ and $8c$ in a ratio of 8:1.\textsuperscript{15} In 2005, Harrity reported a stepwise [3+3] cycloaddition for constructing the piperidine ring system.\textsuperscript{16} Aziridine $8d$ was allowed to react with allylic alcohol $8e$ under strong basic conditions to yield the corresponding amine product $8f$, which, upon intramolecular cyclization generated piperidine alkaloid $8g$ in the presence of Pd(OAc)$_2$ and a cocatalytic Ti(O$i$Pr)$_4$. A Pd $\pi$-allyl intermediate was generated during the course of this reaction, and ring closure of carbamates with free allylic alcohols has been catalyzed by Pd(II) catalysts.\textsuperscript{17}

**Scheme 8** Piperidines synthesis from Pd-catalyzed intramolecular $N$-annulations

Even though there are many synthetic methods for piperidine ring preparation, the substrates availability, harsh reaction conditions and functional group tolerance are some limitations of the current methods. Therefore, the need for a novel and efficient method for substituted piperidine synthesis, especially highly-substituted piperidines still exists.
3.2 Synthesis of Highly-substituted Piperidines

In 2002, Yamamoto reported an efficient synthesis of pyrrolidine derivative 9b via Pd-catalyzed ring expansion of vinyl azetidine 9a in the presence of electron-poor olefin; however, the pyrrolidine product was formed in very low diastereoselectivity (dr = 1.2). The reaction was thought to proceed by forming a zwitterionic π-allyl palladium intermediate 9c from vinyl azetidine in the presence of Pd catalyst.\(^{18}\)

**Scheme 9 Nitrogen nucleophiles in Pd-catalyzed allylation reactions**

We have previously shown that vinyl oxazinanones 10a underwent catalytic diastereoselective decarboxylative ring contraction to form vinyl azetidines 10b under mild conditions in good yield (Scheme 11).\(^{19}\) In addition to the decarboxylative ring contractions, it was envisioned that performing the decarboxylation in the presence of Michael acceptors would result in decarboxylative olefin insertion to provide highly-substituted vinyl piperidines 11a.
Upon Pd-facilitated decarboxylation, zwitterionic π-allyl intermediates 12c should lend themselves to decarboxylative olefin insertion if the intermediate amide anion could be intercepted by a suitably electrophilic Michael acceptor (Scheme 11). The resulting stabilized carbanion 12d could undergo addition to the π-allyl palladium fragment which would give rise to 4-vinyl piperidines. Indeed, treatment of rac-12a with benzylidene malononitrile and Pd(PPh₃)₄ produced the vinyl piperidine 13a as a single diastereoisomer in excellent yield. The reaction is rapid, and vinyl azetidines are not observed as intermediates when the reaction is monitored by ¹H NMR spectroscopy. Once again, cis-12a provides the same product as trans-12a, indicating that π-allyl epimerization is faster than cyclization.
Other Michael acceptors were also tried with our standard reaction conditions as shown in Scheme 12. It turned out that the electronics of the Michael acceptors are crucial to the success of the decarboxylative cycloaddition reactions. The same phenomenon has been observed in the Ru-catalyzed tandem Michael addition-allylation reactions. Not surprisingly, when Michael acceptor such as 14a or dipolarphile 14c was employed, no cycloaddition product was observed and the decarboxylative ring contraction product was formed exclusively. In the case of ethyl cyanobutenoate 14d, azetidine 14b was generated first and later transformed to a messy polymeric mixture. Of note here is that when p-hydroxybenzylidene malononitrile was employed as the electrophile, the \(O\)-allylation product 14g was formed exclusively in 90% NMR yield, which in turn supported that a zwitterionic \(\pi\)-allyl intermediate was formed first then subsequently quenched by the nucleophile present.
Interesting chemoselectivity was observed when a sterically-hindered Michael acceptor 15a was used (Scheme 13). Treatment of vinyl oxazinanone 12a with 5 mol% Pd(PPh₃)₄ in the presence of 15a at rt yielded the unexpected tetrahydropyridine ring product 15b exclusively in 10 mins. Interestingly, the scale-up reaction gave a 1:1 mixture of products 15b and cycloaddition adduct 15f in 99% combined yield. This chemoselectivity was interesting since it has been shown that, in the absence of benzylidenedemalononitrile, the four-membered vinyl azetidine product is favored over the tetrahydropyridine due to stereoelectronic effects. We reasoned that cycloaddition could be favored if the substrate was less sterically demanding so the unsubstituted vinyl oxazinanone 12b was prepared in that regard. Treatment of
12b under our standard reaction conditions produced the six-membered cycloaddition product in 38% isolated yield with no observation of piperidine product. The lower yield was attributed to the formation of a polymer-type byproduct, which has been observed when the decarboxylative ring contraction was performed with vinyl oxazinanone 12b in the absence of Michael acceptor. As expected, this chemoselectivity was switched back when vinyl oxazinanone 12c was used, and the six-membered ring product 15e was generated exclusively in 80% NMR yield.

Scheme 13 Interesting chemoselectivity

Ultimately, if the Michael acceptors are properly chosen, a variety of vinyl oxazinanones undergo smooth decarboxylative cycloaddition reactions (Table 1). Although the stereocontrol is good when the vinyl oxazinanone is substituted at C₄, C₅, or C₆, the stereocontrol is not high when the vinyl oxazinanone is unsubstituted
(i.e., 13j,k trans/cis~3:1, Table 1) or with a small substituent (i.e., 13l,m trans/cis=2:1, Table 1).

**Table 1 Yields and diastereoselectivities of decarboxylative olefin insertions**

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Productᵃ</th>
<th>Yield (dr)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>13a</td>
<td>94 (&gt;19:1)ᶜ</td>
</tr>
<tr>
<td>p-MeOC₆H₄</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>13b</td>
<td>88 (&gt;19:1)</td>
</tr>
<tr>
<td>p-MeOC₆H₄</td>
<td>H</td>
<td>H</td>
<td>p-AcOC₆H₄</td>
<td>13c</td>
<td>81 (&gt;19:1)</td>
</tr>
<tr>
<td>p-ClC₆H₄</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>13d</td>
<td>87 (&gt;19:1)</td>
</tr>
<tr>
<td>p-ClC₆H₄</td>
<td>H</td>
<td>H</td>
<td>p-AcOC₆H₄</td>
<td>13e</td>
<td>96 (&gt;19:1)</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>p-AcOC₆H₄</td>
<td>13f</td>
<td>76 (&gt;19:1)</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>13g</td>
<td>54 (10:1)</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>p-AcOC₆H₄</td>
<td>13h</td>
<td>53 (&gt;19:1)</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>13i</td>
<td>66 (8.3:1)</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>13j</td>
<td>85 (1:3)</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>p-AcOC₆H₄</td>
<td>13k</td>
<td>99 (1.2:8)</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>Ph</td>
<td>13l</td>
<td>99 (1:2)</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>p-AcOC₆H₄</td>
<td>13m</td>
<td>92 (1:2)</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>13n</td>
<td>87 (1:19)</td>
</tr>
</tbody>
</table>

ᵃ Unless otherwise mentioned, the reaction was carried out with vinyl oxazinanone (1 mmol), Michael acceptor (1 mmol), Pd(PPh₃)₄ (0.05 mmol) in CH₂Cl₂ at room temperature. ᵇ Yield and syn/anti ratio of isolated product. ᵈ >19:1 indicates that the minor diastereomer was not detected by ¹H NMR spectroscopy.
Although the preference for formation of 2,4-trans products, as determined by nOe experiments, from unsubstituted vinyl oxazinanones is difficult to explain, the diastereoselectivity of the substituted derivatives is straightforward. In these cases, the product is the result of cyclization through a conformation A or B that places the larger groups in equatorial positions as shown in Scheme 14. Such an interpretation requires that the Michael addition is reversible, allowing the diastereoselectivity to be controlled by the relative barriers for cyclization.

**Scheme 14 Preferred six-membered transition state**

![Preferred six-membered transition state](image)

Furthermore, the above cycloaddition can be applied to an annulation of cyanocoumarins, which are frequently encountered structural motifs of many biologically active compounds (Table 2). Although product 16a was isolated in lower yield than other substrates, investigation of the reaction by $^1$H NMR spectroscopy shows clean formation of 16a. Furthermore, the annulation sets three contiguous stereocenters with high diastereoselectivity for syn addition to the coumarin. Unlike entry 1 and 2, when $R^2$ equals to a phenyl group, decarboxylative cycloaddition product 16c was produced along with the four-membered azetidine
product in a ratio of 2.5:1. The reason was partially attributed to the sterically bulkier vinyloxazinanone, which slows down the intermolecular cycloaddition reaction. For example, the reaction with unsubstituted vinyl oxazinanone took less than 10 minutes, whereas substituted ones need days to complete as shown in Table 2.

Table 2 Yields and diastereoselectivities with cyanocoumarin Michael acceptor

<table>
<thead>
<tr>
<th>entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Michael acceptor</th>
<th>Product</th>
<th>time</th>
<th>Yield (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td></td>
<td>16a</td>
<td>10min</td>
<td>49 (&gt;19:1)$^b$</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CH$_3$</td>
<td></td>
<td>16b</td>
<td>36 hr</td>
<td>88 (1:1)</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>H</td>
<td></td>
<td>16c</td>
<td>3 days</td>
<td>71 (&gt;19:1)$^c$</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise mentioned, the reaction was carried out with vinyl oxazinanone (1 mmol), Michael acceptor (1 mmol), Pd(PPh$_3$)$_4$ (0.05 mmol) in CH$_2$Cl$_2$ at room temperature. $^b$ $^1$H NMR yield are very high. $^c$ $^1$H NMR yield and the reaction time is 3 days.

Spiro vinyl oxazinanone 17a was treated with 5 mol% Pd(PPh$_3$)$_4$ in the presence of one equivalent of Michael acceptor; however, cycloaddition did not occur and $\beta$-hydride elimination product 17b was formed exclusively (Scheme 15). Interestingly, decarboxylative ring contraction product 17d was yielded when cis-oxazinanone 17c was employed under our standard reaction conditions. Noteworthy here is that the four-membered azetidine 17d did not isomerize to the thermodynamically more stable tetrahydropyridine, which occurred smoothly without benzylidene malononitrile.
present. We have no reasonable explanation for why cycloaddition reaction did not occur with compound 17c; however it may reside in steric effects brought by the cis-geometry of 4,6-substituents.

**Scheme 15 Substrates with no reactivity toward cycloadditions**

While 17c is an extreme example, the decarboxylative ring contractions often competed with the cycloaddition reaction pathway as shown in Table 3. The lower yields of vinyl piperidines 13g and 13h were due to the formation of azetidine products (Table 1). In addition, a 1:1 mixture of 13o and 18b was formed with a bulky isopropyl substituted oxazinanone (entry 3).
Table 3 Lower chemoselectivity with sterically hindered vinyl oxazinanones

![Chemistry Diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>$R^4$</th>
<th>Product</th>
<th>ratio</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>13g:18a</td>
<td>2.3:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>$p$-AcOC$_2$H$_5$</td>
<td>13h:18a</td>
<td>1.7:1</td>
</tr>
<tr>
<td>3</td>
<td>CH(CH$_3$)$_2$</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>13n:18b</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>13n:19a$^b$</td>
<td>7.5:1$^c$</td>
</tr>
</tbody>
</table>

$^a$ Except for 3o, 2,4-cis vinylpiperidine was the major diastereoisomer. $^b$ 6-membered decarboxylative ring product 9a was formed as the by-product. $^c$ the product ratio of scale-up reaction, while $^d$HNMR reaction ratio was 2.5:1.

A benzoyl protected vinyl oxazinanone 20a (1:1 cis/trans) was also employed in the decarboxylative cycloaddition reaction, which produced a mixture of cycloaddition product 20b and decarboxylative allylation product 20c (~1:1 ratio) as illustrated in Scheme 16. However, when compound 20c was treated with a palladium catalyst in toluene at 80 °C in the presence of a Michael acceptor, $\beta$-hydride elimination product 20d was generated formed without the formation of cycloaddition product 20b.
Scheme 16 Cycloaddition with Bz-protected vinyl oxazinanone

As a further extension of the above decarboxylative cycloadditions, we would like to develop an asymmetric version of this reaction protocol. Toward that end, vinyl oxazinanone 12a was allowed to react with isocyanate 21a and carbodiimide 21c in the presence of 5 mol% Pd(PPh₃)₄ in dichloromethane at room temperature, in which cycloaddition product 21b and ring contraction product 14b were produced respectively as shown in Scheme 17. Other oxazinanones were also used and cycloaddtion products 21e and 21g were obtained in 72% and 70% yield respectively. Of note here is that the reactions with isocyanate were very sensitive to water and the solvent needed to be dried over basic anhydrous alumina to ensure the clean formation of cycloaddition products.
Scheme 17 Cycloadditions of heterocumulenes

The decarboxylative cycloadditions were also carried out in the presence of 5 mol% Pd$_2$(dba)$_3$ combined with 10 mol% of the Trost ligand (Scheme 18). With the Trost ligand, cycloaddition reactions were generally faster and cleaner than those catalyzed by Pd(PPh$_3$)$_4$. However, we had a hard time in separating compound 21e and 21g on chiral stationary phase HPLC (Diacel Chiralpak AD-H and OD-H) and the stereoselectivity of these reactions deserve further attention.
Finally, to investigate the utility of the malonitrile-containing products, we performed a hydrolysis and decarboxylation of 13j to the mono cyano-substituted piperidine product as shown in Scheme 19. Acidic condition gave a mixture of starting material along with an unidentified new product; however the reaction did not go to completion, even at high temperature.\textsuperscript{26, 27} An analogue, 1,1-cyclohexane dicarbonitrile 22b, was then prepared and used as the standard substance for comparison. Treatment of 22b with concentrated sodium hydroxide solution afforded the corresponding carboxylic acid 22c, which upon decarboxylation gave 22d in quantitative yield.\textsuperscript{23} However, a messy mixture formed when 13j was treated under the same reaction conditions.
Scheme 19: Acid and base hydrolysis of nitriles

Platinum complexes A and B have been shown to catalyze the partial hydrolysis of nitriles to amides. Treatment of 1,1-cyclohexanedicarbonitrile 22b with 0.5 mol% catalyst A and B provided the amide product 23d (Scheme 20). According to literature report, complex B was catalytically more active than A; however only one of the nitrile function group was selectively hydrolyzed in both cases to generate the corresponding cyanoamide product 23d, which was further hydrolyzed to the dicarboxylacid 22c.
Scheme 20 Platinium complexes catalyzed nitriles hydrolysis

\[
\text{K}_2\text{PtCl}_4 + 4 \text{PPh}_3 + 2 \text{KOH} \quad \text{C}_2\text{H}_5\text{OH} \quad 62\% \quad \text{Pt(PPPh}_3\text{)}_4 + \text{MeHMe} \quad \text{O} \quad \text{P} \quad \text{O} \quad \text{Pt} \quad \text{O} \quad \text{P} \quad \text{H} \quad \text{H} \quad \text{OH}
\]

Piperdine derivatives 24a and 24c were also subjected to the Pt-catalyzed nitrile hydrolysis, in which amide products 24b and 24d were formed smoothly as shown in Scheme 21. It is worthy to note that in both cases, a diastereoisomeric mixture was obtained cleanly.

Scheme 21 Pt- catalyzed nitriles hydrolysis with piperdine derivatives

A radical process has previously been used to decyanate germinal dinitriles (Scheme 22).\textsuperscript{25} Interestingly, treatment of piperdine 25a with AIBN and t-butyl tin hydride generated the deacetylated product 25b while the cyano groups remained
intact. Strong bases such as $n$-butyl lithium induced a $\beta$-elimination reaction to form diene product 25d along with another product, whose structure was temporarily signed to be 25e.

**Scheme 22 Other reaction conditions**

In summary, we have reported that decarboxylation of the vinyl oxazinanones in the presence of Michael acceptors results in cycloaddition to form highly substituted piperidines with good diastereoselectivity. Importantly, those reactions proceed under mild conditions and produce CO$_2$ as the only byproduct. We further demonstrated that the resulting geminal dinitriles can be transformed to the corresponding amides with resort to Pt-catalyzed nitrile hydrolysis.
3.3 Palladium-Catalyzed Asymmetric, Diastereoselective Cycloadditions in Hydroquinoline Synthesis

3.3.1 Methods for generating aza-ortho-xylylenes and applications in synthesis

Aza-ortho-xylylenes like 26a are highly reactive intermediates that have been used to construct nitrogen heterocycles ever since Smolinsky proposed the structure of aza-ortho-xylylene for the first time in 1961.\textsuperscript{31, 32} Other xylylene analogues, such as the oxy- and thio-xylyenes are also known and have found many applications in heterocyclic ring syntheses (Scheme 23).\textsuperscript{26, 27} Aza-o-xyylene 26a could isomerize to benzoazetidine 26b, during which the driving force is the rearomatization; however theoretical calculations at the MP2 level showed that isomer 26a is more stable.\textsuperscript{28}

Scheme 23 Aza-ortho-xyylene and its analogues

![Scheme 23](image)

Preparation of aza-ortho-xyylene 27c was achieved by treatment of benzoazetine 27b with either thermal or photochemical conditions, followed by intermolecular Diels-Alder reaction with N-phenylmaleimide (NPMI) or 1,4-naphthoquinone (NQ) to give quinoline products 27d and 27f respectively as illustrated in Scheme 24.\textsuperscript{29, 30}
Another convenient strategy for generating aza-ortho-xylylenes is 1,4-elimination reactions of various 1,4-amino benzyl derivatives as illustrated in Scheme 27. Upon losing one molecule of ethanol and CO\textsubscript{2}, aza-ortho-xylylene 30b was formed from 1,4-amino benzyl carbonate 30a, followed by an intramolecular 6π electrocyclization reaction to furnish a benzoxazine derivative 30c in 58% yield. In the presence of a dienophile, Diels-Alder adduct 30d was obtained, albeit in low yield. In 1986, Saegusa showed that a TMS-protected ammonium salt 30e reacted with cesium fluoride to generate xylyene intermediate 30f under mild reaction conditions, during which one molecule of trimethylamine was extruded. Cycloaddition with diethyl maleate generated the quinoline products 30g and 30h in combined 50% yield. 1,4-Elimination of HCl from o-(chloromethyl)aniline derivatives has also been used for generating xylyenes. For instance, treatment of 30i and 30j with cesium carbonate produced aza-ortho-xylylenes intermediates, which then underwent cycloadditions.
with vinyl ethyl ether to give quinoline products \(30k\) and \(30l\) in good yields.\(^{40,41}\)

**Scheme 27** Aza-ortho-xylylenes preparation via 1,4-elimination reactions

Benzosultams have also served as the precursor to aza-ortho-xylylenes upon losing one molecule of SO\(_2\) as shown in Scheme 25. For instance, intermediate \(28b\) reacted with a dienophile NPMI to produce the corresponding [4+2] cycloaddition product \(28c\), while a dimeric eight-membered diazocine \(28f\) was formed through a formal [4+4] cycloaddition in the absence of dienophiles.\(^{33-35}\) The intramolecular Diels-Alder reactions of xyylene intermediates \(28h\) and \(28k\) were also investigated, in which the corresponding tetrahydroquinolines were synthesized in good yields.
Finally, and most relevant to this chapter, thermal decarboxylation of benzoxazinanones 29a also results in the formation of aza-ortho-xylylenes such as 29b; the aza-o-xyylene was trapped with different dienophiles to give the related Diels-Alder adducts 29c and 29e in moderate yields (Scheme 26). Similarly, treatment of benzoxazinanones 29f with flash vacuum pyrolysis (FVP) at 180 °C produced aza-ortho-xylylene intermediates 29g, which underwent an intramolecular [4+2] cycloaddition to produce quinoline derivatives 29h in moderate to low yield.36
Scheme 26 Reactions of Aza-ortho-xylylenes prepared from benzoxazinanones

\[ \text{Scheme 26: Reactions of Aza-ortho-xylylenes prepared from benzoxazinanones} \]

3.3.2 Palladium-facilitated aza-ortho-xylylene generation and its application in hydroquinoline synthesis

Recently, we have shown that catalytic decarboxylative cycloadditions of aza-ortho-xylylenes occurs under mild conditions via zwitterionic $\pi$-allyl palladium intermediates (Scheme 28). This was discussed in chapter 2.\textsuperscript{19} Two possible intermediates \textbf{31d} and \textbf{31e} were proposed to form from the decarboxylation of \textbf{31a} and our experimental results supported that palladium-polarized aza-o-xylylenes \textbf{31d} are likely the intermediates, considering the formation of dimer product \textbf{31c}. Next we wanted to develop a diastereoselective, asymmetric [4+2] cycloaddition of palladium-polarized aza-o-xylylenes with electron deficient olefins.
If zwitterionic Pd-allyl intermediates are indeed being formed, then one would also predict that they would undergo [4+2] cycloadditions with electron deficient olefins as shown in Scheme 29. Indeed, upon treatment of the benzoxazinanone 31a with Pd(PPh₃)₄ in the presence of one equivalent of benzylidene malononitrile 32a, cycloaddition occurs to produce the highly substituted dihydroquinoline 33a with good diastereoselectivity. This reaction was also carried out in non-polar solvents such as toluene and cycloaddition adduct 33a was afforded smoothly with no observation of the dimer formation.

**Scheme 29 [4+2] cycloaddition with electron deficient olefin**
To exclude the possibility that the free aza-o-xylene intermediate is involved in the above [4+2] cycloaddition, different dienophiles 34a and 34c were allowed to react with vinyl benzoxazinanone 31a catalyzed by 5 mol% Pd(PPh₃)₄ in either methylene chloride or toluene as shown in Scheme 30. Either of these electrophiles would be expected to react with a free aza-o-xylene intermediate. The cycloaddition adducts such as 34b were not formed in those reactions, which further confirmed that palladium-polarized aza-o-xylenes are likely the relevant intermediates.

**Scheme 30 Other dienophiles do not undergo [4+2] cycloadditions**

Next, we turned our attention toward the development of an asymmetric version of this cycloaddition. Standard ligand screening quickly revealed that the Trost-ligands are superior ligands for the asymmetric cycloaddition (Table 4).³⁸ While the diphenyldiamine-based ligand 35e provided the highest enantioselectivity, the ligand based on the anthracenyl diamine 35g provided high enantioselectivity as well.
as superior diastereoselectivity. A single recrystallization of the product derived from 35g provided an 87% yield of highly enantio- and diastereoenriched hydroquinoline (97% ee, 50:1 dr).

**Table 4 Ligand and solvent screening results**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Sovlen</th>
<th>33a:31b</th>
<th>ee 33a</th>
<th>dr</th>
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<tbody>
<tr>
<td>35a</td>
<td>CD2Cl2</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>35b</td>
<td>CD2Cl2</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>35c</td>
<td>CD2Cl2</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>35d</td>
<td>CD2Cl2</td>
<td>&gt;19:1</td>
<td>78</td>
<td>7:1</td>
</tr>
<tr>
<td>35e</td>
<td>CD2Cl2</td>
<td>&gt;19:1</td>
<td>92</td>
<td>9:1</td>
</tr>
<tr>
<td>35f</td>
<td>C6D6</td>
<td>1.7:1</td>
<td>78</td>
<td>9.4:1</td>
</tr>
<tr>
<td>35f</td>
<td>CH2Cl2</td>
<td>0.85:1</td>
<td>69</td>
<td>6:1</td>
</tr>
<tr>
<td>35f</td>
<td>THF</td>
<td>5.5:1</td>
<td>69</td>
<td>&gt;19:1</td>
</tr>
<tr>
<td>35g</td>
<td>C6D6</td>
<td>10.6:1</td>
<td>88</td>
<td>15:1</td>
</tr>
<tr>
<td>35g</td>
<td>CH2Cl2</td>
<td>&gt;19:1</td>
<td>89&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19:1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>35g</td>
<td>THF</td>
<td>&gt;19:1</td>
<td>89</td>
<td>32:1</td>
</tr>
<tr>
<td>35g</td>
<td>dioxane</td>
<td>&gt;19:1</td>
<td>87</td>
<td>21:1</td>
</tr>
</tbody>
</table>

*<sup>a</sup> 97% ee and 50:1 dr after a single recrystallization.*

Using these as standard reaction conditions, we briefly explored the effect of electronics on the reaction. If the benzylidene malononitrile was too electron rich [i.e. $\text{p-MeOC}_6\text{H}_4\text{CHC(CN)}_2$] then the intermolecular cycloaddition did not compete with the intramolecular cyclization to form dihydroquinolines.<sup>39, 40</sup> However, if the olefin was sufficiently electron deficient, then the cycloaddition proceeded with both high
enantioselectivity and diastereoselectivity; the ee’s and dr’s of the product dihydroquinolines before recrystallization are shown in Table 5. Highly electron-deficient olefins slowed the reaction substantially, presumably due to favorable binding to the Pd(0) catalyst.\textsuperscript{41} For example, in contrast to most reactions which were facile at room temperature, the nitro-containing benzylidene malononitrile (33b-33d, Table 5) required 80 °C for the reaction to proceed. It is noteworthy that the reaction selectivity was largely unaffected by the increased reaction temperature.

**Table 5 Asymmetric decarboxylative cycloaddition of vinyl oxazinanones.\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Product</th>
<th>X</th>
<th>Y</th>
<th>Yield</th>
<th>ee</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>33b\textsuperscript{b}</td>
<td>p-OMe</td>
<td>p-NO₂</td>
<td>91</td>
<td>99</td>
<td>25:1</td>
</tr>
<tr>
<td>33c\textsuperscript{b}</td>
<td>p-Me</td>
<td>p-NO₂</td>
<td>90</td>
<td>99</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>33d\textsuperscript{c}</td>
<td>H</td>
<td>p-NO₂</td>
<td>78</td>
<td>96</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>33e</td>
<td>p-OMe</td>
<td>p-CO₂Me</td>
<td>99</td>
<td>92</td>
<td>25:1</td>
</tr>
<tr>
<td>33f</td>
<td>p-Me</td>
<td>p-CO₂Me</td>
<td>97</td>
<td>98</td>
<td>37:1</td>
</tr>
<tr>
<td>33g</td>
<td>H</td>
<td>p-CO₂Me</td>
<td>76</td>
<td>96</td>
<td>25:1</td>
</tr>
<tr>
<td>33h</td>
<td>p-OMe</td>
<td>o-CF₃</td>
<td>97</td>
<td>86</td>
<td>29:1</td>
</tr>
<tr>
<td>33i</td>
<td>p-Me</td>
<td>o-CF₃</td>
<td>85</td>
<td>98</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>33j</td>
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<td>o-CF₃</td>
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<td>89</td>
<td>36:1</td>
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<td>33k</td>
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<td>p-CF₃</td>
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<td>84</td>
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<td>p-CF₃</td>
<td>88</td>
<td>86</td>
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</tr>
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<td>90</td>
<td>91</td>
<td>45:1</td>
</tr>
<tr>
<td>33n</td>
<td>p-OMe</td>
<td>p-OAc</td>
<td>90</td>
<td>80</td>
<td>50:1</td>
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<td>33o</td>
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<td>p-OAc</td>
<td>73</td>
<td>90</td>
<td>70:1</td>
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<td>33p</td>
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<td>p-OAc</td>
<td>52</td>
<td>91</td>
<td>92:1</td>
</tr>
<tr>
<td>33q</td>
<td>p-F</td>
<td>p-OAc</td>
<td>60</td>
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<td>&gt;99:1</td>
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<td>33r</td>
<td>p-OMe</td>
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<td>92</td>
<td>86</td>
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<tr>
<td>33s</td>
<td>p-Me</td>
<td>H</td>
<td>77</td>
<td>92</td>
<td>&gt;99:1</td>
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<tr>
<td>33t</td>
<td>p-F</td>
<td>H</td>
<td>75</td>
<td>87</td>
<td>87:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 1.0 mmol substrate was treated with Pd\textsubscript{2}(dba)\textsubscript{3} (0.025 mmol) and 35g (0.055 mmol) in CH\textsubscript{2}Cl\textsubscript{2} at room temperature. \textsuperscript{b} run in CH\textsubscript{2}Cl\textsubscript{2} at 40 °C for 25 h. \textsuperscript{c} run in toluene at 80 °C for 6 h.
The origin of the stereoselectivity in this reaction is not known, however the reaction likely proceeds through aza-Michael addition of intermediate 36a to the activated olefin (Scheme 31). The resulting stabilized carbanionic intermediate can then undergo intramolecular cyclization. The two potential stereochemistry-determining steps in such a transformation are 1) the aza-Michael addition or 2) the cyclization. Since it is difficult to imagine that the chirality of the ligands could effect a highly enantioselective aza-Michael addition, our working hypothesis is that reversible conjugate addition is followed by stereochemistry-determining cyclization. This hypothesis is consistent with the pKa values for malononitrile (11.2) and the arylsulfonamide (9-10).42

Scheme 31 The origin of the reaction’s stereoselectivity

Curtin-Hammett analysis of the resulting kinetic scenario indicates that the major product of the reaction will result from the most favorable cyclization.43 Elegant studies have allowed Lloyd-Jones to develop a model for the binding of Trost ligands
These studies suggest that Trost ligand binds to produce a complex of C1-symmetry where the ligand bulk is concentrated in the upper right-hand and lower left-hand quadrants. Superimposing our intermediate onto Lloyd-Jones’ model gives four potential transition states for cyclization; three are shown in Scheme 32. The favored transition state results from placing the benzylidene malononitrile fragment in the least hindered quadrant and the phenyl group is directed away from the bulky ligand in back. Such a prediction is confirmed by an X-ray crystal structure of the product that is of sufficient quality to allow determination of the relative and absolute configuration of the product.

**Scheme 32 Possible transition states for cyclizations**

Other electron deficient olefins were also tested to check their compatibility. Meldrum’s acid derivative 37a has been shown to be a suitable reactant for both
Ru-catalyzed tandem Michael addition-allylic alkylations and Pd-catalyzed decarboxylative olefin insertions with vinyl oxazinanones.\textsuperscript{19, 20} Interestingly, when compound 37a was allowed to react with different vinyl benzoxazinanones, a mixture of six- and eight-membered ring products was generated in different ratios (Scheme 33). Of note here is that Meldrum’s acid derivative 37a is very reactive and those reactions were done in less than 10 minutes without observing any dihydroquinoline formation. However cycloaddition reactions became much slower with Pd\textsubscript{2}(dba)\textsubscript{3} and anthracenyl diamine Trost ligand and a polymer-like product was generated. Since the asymmetric decarboxylative cycloaddition reactions were only realized during the formation of terminal olefins, that research was not further carried on.

**Scheme 33** Six-membered vs eight-membered cycloaddition products
In addition, the above cycloadditions can be applied to the annulation of cyanocoumarins, which are frequently encountered structural motifs of many biologically active compounds.\textsuperscript{21,22} For example, vinyl benzoxazinanone 31\textsuperscript{a} reacted with three equivalents of cyanocourmarin 38\textsuperscript{a} in the presence of Pd(PPh\textsubscript{3})\textsubscript{4} to yield a mixture of cycloadducts and dihydroquinolines in a ratio of 1.5:1, which can be improved to 7:1 by carrying out the reaction at higher concentration as shown in Scheme 34. Varying the electronics of the benzoxazinanones did not produce significant beneficial effects plus polymer-like byproducts were always formed along with dihydroquinolines. The optimization of those reaction conditions was not performed but could warrant further attention.

**Scheme 34 [4+2] cycloadditions with cyanocoumarin**
Regarding to the substrate scope, electron deficient olefin 39b was allowed the react with benzoazinanone 39a (Scheme 35). Even though racemic cycloaddition products were formed smoothly in two hours at room temperature, dihydroquinolines along with polymer byproducts were formed when the same reaction were catalyzed by Pd$_2$(dba)$_3$ and different Trost ligands in a much slower rate. Even though we are not exactly sure about the reason, it could reside in two factors. First, it is known that phenylsulfonyl group is bulkier than the corresponding cyano group and thus slow down the cycloaddition step. Secondly, phenylsulfonyl has been shown to function as a ligand for palladium catalysts. Consequently, the competition of ligand binding between Trost ligands and 39b may favor the intramolecular cyclization.\textsuperscript{45,46}

**Scheme 35** [4+2] cycloadditions with other electron deficient olefins

Vinyl benzoazinanones 40a with a methyl substituent on the olefin were allowed to react with electron deficient olefins, generating a mixture of cycloaddition product 40b and dihydroquinoline 31b with poor chemoselectivity, even though
generally those reactions were clean with no occurrence of dimer by-products (Scheme 36). Vinyl benoxazinanones 40d yielded dihydroquinoline 40e exclusively, while compound 40h was obtained as the major product from 40f.

Scheme 36 [4+2] cycloadditions with substitute vinyl benoxazinanones

Cycloadditions of vinyl benoxazinanones with different N-protecting groups were also performed (Scheme 37). For example, nosyl-protected substrate formed product 41b smoothly at the cost of requiring excess of olefin 32a. The analogous [4+2] cycloadditions of benzoyl-protected benoxazinanone 41b did not afford the corresponding cycloadducts and intramolecular cyclization occurred to give product 41d.
Scheme 37 Vinyl benzoxazinanones with different N-protecting groups

![Scheme 37 Diagram]

The generation of aza-ortho-xylylene intermediate was proven to be very difficult with substrate 42a, which remained intact in most cases (Scheme 38). Interestingly, when benzoxazinanone 42a was allowed to react with benzylidene malononitrile under microwave irradiation in DMF at 180 °C, a diamine product 42b was generated in high yield with or without the palladium catalyst. Other solvents would have been planned but the Microwave reactor broke down. Trapping the aza-o-xylylene intermediates with amines was also tried and starting material was recovered.
Trapping aza-o-xylene intermediates with good nucleophiles has been reported.\textsuperscript{47-49} Similarly, secondary amines have been used in our experiments as shown in Scheme 39. The secondary amines 43a and 43d turned out to be so reactive that those reactions were finished in less than 10 minutes and a control experiment without palladium catalyst was also performed to generate product 43e in less than an hour. Such reactivity was later proven to be problematic when benzoxazinanone 31a was allowed to react with piperidine 43d in the presence of Pd\(_2\)(dba)\(_3\) and Trost ligand 35e, which produced product 43e as a racemic mixture. Interestingly, those reactions displayed different regioselectivity from traditional Pd-catalyzed allylic alkylation.

In our case, the terminal olefins 43b and 43e were formed exclusively, and at higher
temperature, terminal olefin product 43b isomerized to the more thermodynamically stable product 43c.

**Scheme 39 Allylic aminations via Aza-o-xylene intermediates**

Aniline derivatives were allowed to reacted with benzoxazinanone 31a in the presence of Pd(PPh₃)₄ and addition products 44b and 44d were obtained in less than 20 minutes (Scheme 40); however the products were not stable and transformed into polymer-like by-products upon standing overnight. This reaction did not occur without palladium catalyst and was very sluggish in toluene.

**Scheme 40 Allylic aminations via Aza-o-xylene intermediates**
A racemic diamine product 45b was prepared by treatment of benzylamine with benzoazinanone 31a in the presence of 5 mol% Pd(PPh₃)₄ as shown in Scheme 41. With anthracenyl diamine Trost ligand 35g, enantioenriched product 45b was obtained (55% and 50% ee at 0 °C and 25 °C respectively), while the ee of aniline derivative 45d was very low. We reasoned that electron-poor amines such as cyanopyrrole could potentially give a better enantioselectivity because of its lower nucleophilicity, which deserves further attention.

**Scheme 41 Asymmetric allylic aminations**

To further expand the scope of asymmetric [4+2] cycloadditions, tosyl isocyanate was allowed to react with treated vinyl benzoazinanone 31a as shown in Scheme 42. Even though racemic mixture 46b was formed cleanly in 55% isolated yield, the asymmetric reaction gave the cycloaddition product in 24% ee at higher temperature.
Other Trost ligands combined with Pd$_2$(dba)$_3$ generated a messy mixture of dihydroquinoline and polymer byproducts.

**Scheme 42 [4+2] cycloadditions with tosyl isocyanate**

In conclusion, we have developed an asymmetric decarboxylative cycloaddition that proceeds through intermediates that may be viewed as palladium-polarized aza-ortho-xylylenes. Formal [4+2] cycloaddition of these intermediates produces enantioenriched hydroquinolines with high diastereoselectivity. The implied stabilization of aza-ortho-xylylenes by palladium is expected to translate to other reactive intermediates.
3.4 References


33. Wojciechowski, K., Synthesis of 1,2,3,4-tetrahydroquinoline-2,3-dicarboxylic acid derivatives. *Synlett* 1991, 571-572.


Appendix C

Experimental Procedures and Data for Chapter 3
General Experimental

THF was dried over sodium metal. Toluene, methylene chloride and diethyl ether were dried over activated alumina on a solvent system purchased from Innovative Technology, Inc.\textsuperscript{1} Acetonitrile and 1,4-dioxane were dried and stored over activated molecular sieves. Commercially available reagents were used without additional purification unless otherwise stated. Products were purified on silica gel from Sorbent Technologies (230x400 mesh, 60 Å porosity, pH 6.5-7.5). Ruthenium and palladium compounds were obtained from Strem. Thin layer chromatography was performed on silica gel 60F\textsubscript{254} plates (EM-5715-7, EMD chemicals). UV lamp (254 nm) or KMnO\textsubscript{4} stain were used for monitoring TLC plates.

\textsuperscript{1}H and \textsuperscript{13}C NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer and referenced to residual protio solvent signals. Structural assignments are based on \textsuperscript{1}H, \textsuperscript{13}C, DEPT-135, COSY, and HMQC spectroscopies and X-ray data. High resolution mass spectrometry was performed on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). High resolution mass spectrometry was performed on a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. FTIR spectra were acquired on a Shimadzu FTIR-8400S spectrometer. HPLC analysis was performed on a Shimadzu SCL-10A VP instrument.

Preparation of Starting Materials

Vinyl oxazinanones were prepared as reported in Chapter 2 of this thesis.
General procedure for catalytic decarboxylative olefin insertions:

In a Schlenk tube under argon, Pd(PPh$_3$)$_4$ (0.05 mmol) and carbamate I (1 mmol), and different Michael acceptors (1 mmol) were dissolved in 5 mL of methylene chloride. The resulting yellow solution was stirred at ambient temperature under Ar until reaction completion was indicated by TLC. Following solvent evaporation, the crude product was purified via flash chromatography (SiO$_2$, 5:1 Hexane: Ethyl acetate).

Spectroscopic Data

\[
\text{2,5-diphenyl-1-tosyl-4-vinylpiperidine-3,3-dicarbonitrile} \quad 13\text{a(cw2027)}}
\]

colorless oil

Pd(PPh$_3$)$_4$: 94% yield, dr >19:1

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.47 (m, 3H: arom H), 7.38 (m, 7H: arom H), 7.18 (d, 2H, J = 6.8 Hz: arom H), 7.06 (d, 2H, J = 8.6 Hz: arom H), 5.93 (s, 1H: PhCHNTs), 5.62 (m, 1H: CH$_2$=CH), 5.20 (dd, 2H, J = 10.4, 16.9 Hz: =CH$_2$), 3.99 (dd, 1H, J = 4.5, 13.4 Hz: CH$_2$NTs), 3.39 (m, 1H: CH$_2$NTs), 3.25 (m, 2H: overlapping PhCH, CHCH=CH$_2$), 2.35 (s, 3H: CH$_3$Ts).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 144.36 (Quat.), 137.84 (Quat), 135.27 (Quat.), 133.91 (Quat.), 132.12 (=CH), 130.26-127.81 (Arom.CH), 124.47 (=CH$_2$), 113.79 (CN), 113.31 (CN), 61.54 (PhCHNTs), 47.51 (CH$_2$), 45.80/43.83 (overlapping PhCH, CHCH=CH$_2$), 45.07 (CCN$_2$), 21.91 (CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3090, 3065, 3034, 2251, 1599, 1497, 1354, 1167, 806, 758, 663.

HRMS calcd for C$_{28}$H$_{26}$N$_3$O$_2$S [M+H] 468.1746, found 468.1737.
5-(4-methoxyphenyl)-2-phenyl-1-tosyl-4-vinylpiperidine-3,3-dicarbonitrile

13b (cw2139)
colorless oil
Pd(PPh₃)₄: 88% yield, dr >19:1

^1H NMR (400 MHz, CDCl₃) δ 7.45 (m, 4H: arom H), 7.38 (t, 4H, J = 8.3 Hz: arom H), 7.09 (m, 4H: arom H), 6.90 (d, 2H, J = 8.6 Hz: arom H), 5.92 (s, 1H: PhCHNTs), 5.61 (m, 1H: CH₂=CH), 5.21 (dd, 2H, J = 10.4, 17.2 Hz: =CH₂), 3.97 (dd, 1H, J = 4.5, 12.6 Hz: CH₂NTs), 3.82 (s, 3H: OCH₃), 3.35 (dd, 1H, J = 5.8, 12.9 Hz: CH₂NTs), 3.19 (m, 2H: overlapping ArCH, CHCH=CH₂), 2.35 (s, 3H: CH₃Ts).

^13C NMR (75 MHz, CDCl₃) δ 159.71 (Quat.), 144.32 (Quat.), 135.26 (Quat.), 132.93 (Quat.), 132.26 (=CH), 130.24-127.81 (Arom.CH), 124.38 (=CH₂), 114.94 (Arom.CH), 113.81 (CN), 113.34 (CN), 61.53 (PhCHNTs), 55.72 (OCH₃), 47.66 (CH₂), 45.96/43.00 (overlapping ArCH, CHCH=CH₂), 45.12 (CCN₂), 21.91 (CH₃Ts). The assignments of the ^1H and ^13C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl₃): v_max 3092, 3061, 3035, 2253, 1514, 1456, 1354, 1167, 814, 762, 660.

HRMS caled for C₂₉H₂₇N₃O₃SNa [M+Na] 520.1671, found 520.1652.

4-(3,3-dicyano-5-(4-methoxyphenyl)-1-tosyl-4-vinylpiperidin-2-yl)phenyl acetate
13c (cw2143)
colorless oil
Pd(PPh₃)₄: 81% yield, dr >19:1

^1H NMR (400 MHz, CDCl₃) δ 7.44 (d, 2H, J = 8.6 Hz: arom H), 7.37 (d, 2H, J = 6.8 Hz: arom H), 7.10 (m, 6H: arom H), 6.91 (d, 2H, J = 8.6 Hz: arom H), 5.92 (s, 1H: PhCHNTs), 5.60 (m, 1H: CH₂=CH), 5.22 (dd, 2H, J = 10.4, 16.9 Hz: =CH₂), 3.96 (dd, 1H, J = 4.3, 12.6 Hz: CH₂NTs), 3.82 (s, 3H: OCH₃), 3.20 (m, 3H: overlapping CH₂NTs, ArCH, CHCH=CH₂), 2.36 (s, 6H: overlapping CH₃Ts, OCOCH₃).
$^{13}\text{C NMR}$ (75 MHz, CDCl$_3$) δ 169.14 (OCOCH$_3$), δ 159.72 (Quat.), 152.04 (Quat.), 144.59 (Quat.), 135.03 (Quat.), 132.12 (–CH), 131.22-127.72 (Arom.CH), 124.49 (=CH$_2$), 122.76 (Arom.CH), 114.94 (Arom.CH), 113.68 (CN), 113.29 (CN), 60.89 (PhCHNTs), 55.72 ((OCH$_3$), 47.62 (CH$_2$), 45.85/42.95 (overlapping PhCH, CHCH=CH$_2$), 45.10 (CCN$_2$), 21.90/21.61 (overlapping CH$_3$Ts, OCOCH$_3$). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl$_3$): $v_{\text{max}}$ 3089, 3034, 2251, 1769, 1610, 1514, 1354, 1167, 833, 660.

**HRMS** calcd for C$_{31}$H$_{29}$N$_3$O$_5$SNa [M+Na] 578.1726, found 578.1730.

5-(4-chlorophenyl)-2-phenyl-1-tosyl-4-vinylpiperidine-3,3-dicarbonitrile

13d(cw2091)

colorless oil

Pd(PPh$_3$)$_4$: 87% yield, dr >19:1

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.45-7.35 (m, 9H: arom H), 7.13-7.06 (m, 4H: arom H), 5.93 (s, 1H: PhCHNTs), 5.60 (m, 1H: CH$_2$=CH), 5.27 (d, 1H, $J$=10.4 Hz: =CH$_2$), 5.16 (d, 1H, $J$=16.9 Hz: =CH$_2$), 3.97 (dd, 1H, $J$ = 4.3, 12.9 Hz: CH$_2$NTs), 3.24 (m, 3H: overlapping CH$_2$NTs, ArCH, CHCH=CH$_2$), 2.35 (s, 3H: CH$_3$(Ts)).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 144.47 (Quat.), 136.32 (Quat.), 135.20 (Quat.), 134.50 (Quat.), 133.77 (Quat.), 131.84 (–CH), 130.31-127.78 (Arom.CH), 124.78 (=CH$_2$), 113.67 (CN), 113.15 (CN), 61.48 (PhCHNTs), 47.36 (CH$_2$), 45.85 (CHCH=CH$_2$), 44.99 (CCN$_2$), 43.30 (ArCH), 21.92 (CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl$_3$): $v_{\text{max}}$ 3091, 3062, 3035, 2255, 1599, 1493, 1354, 1167, 1092, 831, 663.

**HRMS** calcd for C$_{28}$H$_{24}$ClN$_3$O$_2$SNa [M+Na] 524.1175, found 524.1163.
4-(5-(4-chlorophenyl)-3,3-dicyano-1-tosyl-4-vinylpiperidin-2-yl)phenyl acetate

\[ 13e(cw2099) \]

**colorless oil**

\[ \text{Pd(PPh}_3\text{)}_4: \text{96\% yield, dr >19:1} \]

\[ ^1H\text{ NMR} \ (400 \text{ MHz, CDCl}_3) \delta \ 7.36 \ (d, 2H, J = 8.2 \text{ Hz: arom H}), \ 7.28 \ (t, 4H, J = 8.5 \text{ Hz: arom H}), \ 7.02 \ (m, 6H: arom H), \ 5.84 \ (s, 1H: PhCHNTs), \ 5.50 \ (m, 1H: CH$_2$=CH$_2$), \ 5.18 \ (d, 1H, J = 10.4 \text{ Hz: =CH$_2$}), \ 5.08 \ (d, 1H, J = 17.0 \text{ Hz: =CH$_2$}), \ 3.89 \ (dd, 1H, J = 4.4, 12.9 \text{ Hz: CH$_2$NTs}), \ 3.15 \ (m, 2H: overlapping CH$_2$NTs, ArCH), \ 3.02 \ (t, 1H, J = 9.1 \text{ Hz: CHCH=CH$_2$}), \ 2.27/2.26 \ (s, 6H: overlapping CH$_3$(Ts), OCOCH$_3$).**

\[ ^13C\text{ NMR} \ (75 \text{ MHz, CDCl}_3) \delta \ 168.67 \text{ (OCOCH$_3$)}, \ 151.70 \text{ (Quat.)}, \ 144.32 \text{ (Quat.)}, \ 144.59 \text{ (Quat.)}, \ 135.81/134.70/134.18 \text{ (Quat.)}, \ 131.30 \text{ (=CH), 130.71-127.34 (Arom.CH), 124.46 (=CH$_2$), 122.40 (Arom.CH)}, \ 113.12 \text{ (CN), 112.71 (CN), 60.45 (PhCHNTs), 46.93 (CH$_2$), 45.42 (CHCH=CH$_2$), 44.54 (CCN$_2$), 42.87 (ArCH), 21.49/21.17 (overlapping CH$_3$Ts, OCOCH$_3$).**

The assignments of the $^1H$ and $^{13}C$ were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl$_3$): $\nu_{\max}$ 3090, 3032, 2253, 1751, 1601, 1495, 1348, 1163, 1092, 813.

**HRMS** caled for C$_{30}$H$_{26}$N$_3$O$_4$SClNa [M+Na] 582.1230, found 582.1223.

\[ \text{Pd(PPh}_3\text{)}_4: \text{76\% yield, dr >19:1} \]

4-(3,3-dicyano-5-phenyl-1-tosyl-4-vinylpiperidin-2-yl)phenyl acetate

\[ 13f(cw2033) \]

**colorless oil**

\[ \text{Pd(PPh}_3\text{)}_4: \text{76\% yield, dr >19:1} \]

\[ ^1H\text{ NMR} \ (400 \text{ MHz, CDCl}_3) \delta \ 7.48 \ (d, 2H, J = 8.8 \text{ Hz: arom H}), \ 7.40 \ (m, 5H: arom H), \ 7.18 \ (d, 2H, J = 8.1 \text{ Hz: arom H}), \ 7.13 \ (m, 5H: arom H), \ 5.94 \ (s, 1H: PhCHNTs), \ 5.61 \ (m, 1H: CH$_2$=CH$_2$), \ 5.22 \ (dd, 2H, J = 10.4, 16.7 \text{ Hz: =CH$_2$}), \ 3.99 \ (dd, 1H, J = 4.3, 12.9 \text{ Hz: CH$_2$NTs}), \ 3.31 \ (dd, 1H, J = 11.4, 24.2 \text{ Hz: CH$_2$NTs}), \ 3.20 \ (m, 2H: overlapping PhCH, CHCH=CH$_2$), \ 2.36/2.35 \ (s, 6H: overlapping CH$_3$(Ts), OCOCH$_3$).**
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.09 (OCOCH\(_3\)), \(\delta\) 152.07 (Quat.), 144.61 (Quat), 137.74 (Quat.), 135.11 (Quat.), 131.98 (=CH), 131.22-127.74 (Arom.CH), 124.55 (=CH\(_2\)), 122.76 (Arom.CH), 113.65 (CN), 113.25 (CN), 60.91 (PhCHNTs), 47.71 (CH\(_2\)), 45.71/43.78 (overlapping PhCH, CHCH=CH\(_2\)), 45.04 (CCN\(_2\)), 21.88/21.58 (overlapping CH\(_3\)Ts, OCOCH\(_3\)). The assignments of the \(^1\)H and \(^{13}\)C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl\(_3\)): \(\nu_{\text{max}}\) 3090, 3065, 3034, 2251, 1767, 1599, 1497, 1354, 1167, 814, 660.

HRMS calcd for C\(_{30}\)H\(_{27}\)N\(_3\)O\(_4\)Na [M+Na] 548.1620, found 548.1620.

\[
\begin{align*}
\text{2,5-diphenyl-4-styryl-1-tosylpiperidine-3,3-dicarbonitrile} \\
\text{13g (cw2124)} \\
\text{colorless oil}
\end{align*}
\]

Pd(PPh\(_3\))\(_4\): 54% yield, dr = 10:1

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.52-7.08 (19H: arom H), 6.44 (d, 1H, \(J=15.7\) Hz: =CHPh), 5.96 (s, 1H: CHAr), 5.92 (dd, 1H, \(J=8.6, 15.7\) Hz: =CH), 4.03 (m, 1H: CH\(_2\)NTs), 3.38 (3H: overlapping CH\(_2\)NTs, PhCH, CHCH=CH), 2.37 (s, 3H: CH\(_3\)(Ts)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.38 (Quat.), 138.74 (=CHPh), 137.85 (Quat.), 135.80 (Quat.), 135.30 (Quat.), 133.98 (Quat.), 130.28-127.10 (Arom.CH), 122.95 (=CH), 113.95 (CN), 113.34 (CN), 61.66 (PhCHNTs), 47.61 (CH\(_2\)), 45.52 (CCN\(_2\)), 45.38 (CHCH=CH\(_2\)), 44.28 (CHPh), 21.93 (CH\(_3\)(Ts)). The assignments of the \(^1\)H and \(^{13}\)C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl\(_3\)): \(\nu_{\text{max}}\) 3067, 3032, 2253, 1769, 1599, 1497, 1354, 1165, 974, 814, 758, 663.

HRMS calcd for C\(_{34}\)H\(_{29}\)N\(_3\)O\(_2\)Na [M+Na] 566.1878, found 566.1874.
4-(3,3-dicyano-5-phenyl-4-styryl-1-tosylpiperidin-2-yl)phenyl acetate

13h (cw2152)
colorless oil

Pd(PPh₃)₄: 53% yield, dr > 19:1

1H NMR (400 MHz, CDCl₃) δ 7.52 (d, 2H, J = 8.8 Hz: arom H), 7.39 (d, 2H, J = 8.3 Hz: arom H), 7.36 (d, 2H, J = 7.6 Hz: arom H), 7.30-7.19 (m, 8H: arom H), 7.14 (t, 4H: arom H), 6.47 (d, 1H, J = 15.9 Hz: =CPh), 5.98 (s, 1H: CHAr), 5.91 (dd, 1H, J = 8.3, 15.7 Hz: =CH), 4.06 (dd, 1H, J = 3.8, 12.6 Hz: CH₂NTs), 3.36 (m, 3H: overlapping CH₂NTs, PhCH, CHCH = CH), 2.37 (s, 6H: overlapping CH₃Ts, OCOCH₃).

13C NMR (75 MHz, CDCl₃) δ 169.15 (OCOCH₃), δ 152.08 (Quat.), 144.65 (Quat), 138.84 (=CHPh), 137.73 (Quat.), 135.76 (Quat.), 135.08 (Quat.), 131.27-127.12 (Arom.CH), 122.82 (=CH), 113.83 (CN), 113.29 (CN), 61.03 (ArCHNTs), 47.59 (CH₂), 45.52 (CHCH = CH₂), 45.27 (CCN), 44.22 (CHPh), 21.92/21.63 (overlapping CH₃Ts, OCOCH₃). The assignments of the 1H and 13C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl₃): ν max 3084, 3061, 3032, 2255, 1769, 1599, 1508, 1354, 1271, 1167, 976, 816, 762, 694.


5-benzyl-2-phenyl-1-tosyl-4-vinylpiperidine-3,3-dicarbonitrile

13i (cw2178)
colorless oil

Pd(PPh₃)₄: 66% yield, dr = 8.3:1

1H NMR (400 MHz, CDCl₃) δ 7.31 (m, 10H: arom H), 7.08 (m, 4H: arom H), 5.82 (m, 2H: overlapping PhCHNTs, CH₂ = CH), 5.58 (dd, 2H, J = 10.4, 16.9 Hz: =CH₂), 3.57 (dd, 1H, J = 5.1, 13.9 Hz: CH₂NTs), 2.98 (m, 2H: overlapping CH₂NTs, CH₂Ph),

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2.83 (t, 1H, $J = 9.1$ Hz: CHCH=CH$_2$), 2.38 (m, 4H: overlapping CH$_3$Ts, CH$_2$NTs), 2.12 (m, 1H: CHBn).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 144.28 (Quat.), 137.17 (Quat.), 135.19 (Quat.), 133.88 (Quat.), 132.03 (=CH), 130.06-127.45 (Arom.CH), 125.16 (=CH$_2$), 113.98 (CN), 113.47 (CN), 61.22 (PhCHNTs), 46.78/44.63 (overlapping CHCH=CH$_2$, CCN$_2$), 44.68 (CH$_3$NTs), 37.42/37.26 (overlapping PhCH$_2$, BnCH), 21.95 (CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3055, 3030, 2252, 1599, 1495, 1354, 1169, 814, 762, 663.

HRMS calcd for C$_{28}$H$_{26}$N$_3$O$_2$S $[$M+NH$_4$] 499.2168, found 499.2163.

$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (m, 5H: arom H), $\delta$ 7.31 (d, 2H, $J = 7.6$ Hz: arom H), 7.07 (d, 2H, $J = 8.1$ Hz: arom H), 5.86 (m, 1H: CH$_2$=CH), 5.80 (s, 1H: PhCH), 5.41 (d, 1H, $J = 10.4$ Hz: CH=CH(H)$_2$), 5.35 (d, 1H, $J = 16.9$ Hz: CH=CH(H)$_2$), 3.94 (m, 1H: CH$_2$NTs), 3.40 (m, 1H: CH$_2$NTs), 3.02 (m, 1H: CHCH=CH$_2$), 2.35 (s, 3H: CH$_3$Ts), 2.03 (m, 1H: CH$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 144.35 (Quat.), 135.26 (Quat.), 133.96 (Quat.), 133.79 (=CH), 130.15-127.82 (Arom.CH), 122.24 (=CH$_2$), 113.59 (CN), 113.43 (CN), 61.55 (CHPh), 44.40 (CCN$_2$), 40.99 (CH$_2$NTs), 40.42 (CHCH=CH$_2$), 26.55 (CH$_2$), 21.91 (CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3059, 3036, 2254, 1599, 1495, 1350, 1169, 814, 760, 663.

HRMS calcd for C$_{22}$H$_{21}$N$_3$O$_2$SNa $[$M+Na$]$ 414.1252, found 414.1246.
The assignments of the 

\[ \text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta 7.38 \ (m, 5H: \text{arom } H), \delta 7.30 \ (d, 2H, J = 6.8 \text{ Hz: arom } H), \ 7.20 \ (d, 2H, J = 8.1 \text{ Hz: arom } H), \ 5.88 \ (m, 1H: \text{CH}_2=\text{CH}), \ 5.45 \ (d, 1H, J = 10.1 \text{ Hz: CH}=\text{CH}(H)_2), \ 5.41 \ (d, 1H, J = 16.7 \text{ Hz: CH}=\text{CH}(H)_2), \ 4.73 \ (s, 1H: \text{PhCH}), \ 4.03 \ (m, 1H: \text{CH}_2\text{NTs}), \ 3.48 \ (m, 1H: \text{CH}_2\text{NTs}), \ 2.68 \ (m, 1H: \text{CHCH}=\text{CH}_2), \ 2.43 \ (s, 3H: \text{CH}_3\text{Ts}), \ 2.23 \ (m, 1H: \text{CH}_2), \ 2.01 \ (m, 1H: \text{CH}_2). \]

\[ \text{C NMR} \ (75 \text{ MHz, CDCl}_3) \delta 144.72 \ (\text{Quat.}), \ 135.71 \ (\text{Arom.CH}), \ 133.76 \ (\text{Quat.}), \ 133.32 \ (=\text{CH}), \ 130.27-127.99 \ (\text{Arom.CH}), \ 122.27 \ (=\text{CH}_2), \ 114.18 \ (\text{CN}), \ 112.56 \ (\text{CN}), \ 66.19 \ (\text{CHPh}), \ 47.08 \ (\text{CHCH}=\text{CH}_2), \ 46.42 \ (\text{CCN}_2), \ 44.20 \ (\text{CH}_2\text{NTs}), \ 26.47 \ (\text{CH}_2), \ 21.98 \ (\text{CH}_3\text{Ts}). \]

The assignments of the \(^1\text{H}\) and \(^{13}\text{C}\) were based on DEPT, COSY, HMOC etc.

\[ \text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta 7.37 \ (m, 4H: \text{arom } H), \delta 7.23 \ (d, 2H, J = 8.3 \text{ Hz: arom } H), \ 7.01 \ (d, 2H, J = 8.8 \text{ Hz: arom } H), \ 5.86 \ (m, 1H: \text{CH}_2=\text{CH}), \ 5.44(d, 1H, J = 9.3 \text{ Hz: CH}=\text{CH}(H)_2), \ 5.42 \ (d, 1H, J = 16.2 \text{ Hz: CH}=\text{CH}(H)_2), \ 4.71 \ (s, 1H: \text{ArCH}), \ 4.06 \ (m, 1H: \text{CH}_2\text{NTs}), \ 3.47 \ (m, 1H: \text{CH}_2\text{NTs}), \ 2.70 \ (m, 1H: \text{CHCH}=\text{CH}_2), \ 2.42 \ (s, 3H: \text{CH}_3\text{Ts}), \ 2.33 \ (s, 3H: \text{CH}_3\text{CO}_2), \ 2.23 \ (m, 1H: \text{CH}_2), \ 2.02 \ (m, 1H: \text{CH}_2). \]

\[ \text{C NMR} \ (75 \text{ MHz, CDCl}_3) \delta 169.13 \ (\text{OCOCH}_3), \delta 152.13 \ (\text{Quat}), \ 144.84 \ (\text{Quat}), \ 135.79 \ (\text{Quat}), \ 133.26 \ (=\text{CH}), \ 130.90-127.92 \ (\text{Arom.CH}), \ 122.35 \ (=\text{CH}_2), \ 121.94 \ (\text{Arom. CH}), \ 113.99 \ (\text{CN}), \ 112.48 \ (\text{CN}), \ 65.81 \ (\text{CHAr}), \ 47.22 \ (\text{CHCH}=\text{CH}_2), \ 46.40 \ (\text{CCN}_2), \ 44.28 \ (\text{CH}_2\text{NTs}), \ 26.55 \ (\text{CH}_2), \ 21.63 \ (\text{overlapping CH}_3\text{Ts, CH}_3\text{CO}_2). \]

The assignments of the \(^1\text{H}\) and \(^{13}\text{C}\) were based on DEPT, COSY, HMOC etc.
FTIR (CDCl₃): νₘₚ 3063, 2253, 1762, 1597, 1508, 1354, 1169, 816.


![Chemical structure](image)

4-(3,3-dicyano-1-tosyl-4-vinylpiperidin-2-yl)phenyl acetate

**13k (cw2163)**

colorless oil

Pd(PPh₃)₄: 99% yield, dr =1:2.8

**¹H NMR** (400 MHz, CDCl₃) δ 7.42 (d, 2H, J =8.1 Hz: arom H), δ 7.39 (d, 2H, J =8.8 Hz: arom H), 7.13 (d, 2H, J =8.3 Hz: arom H), 7.06 (d, 2H, J =8.6 Hz: arom H), 5.85 (m, 1H: CH₂=CH), 5.82 (s, 1H: ArCH), 5.42 (d, 1H, J = 10.4 Hz: CH=CH(H)₂), 5.39 (d, 1H, J = 16.9 Hz: CH=CH(CH₃)), 3.95 (q, 1H, J = 7.6, 16.2 Hz: CHCH=CH₂), 2.95 (q, 3H: CH₃Ts), 2.32 (s, 3H: CH₃CO₂), 2.02 (m, 1H: CH₂).

**¹³C NMR** (75 MHz, CDCl₃) δ 169.14 (OCOCH₃), δ 151.98 (Quat.), 144.60 (Quat.), 135.08 (Quat.), 133.64 (=CH), 131.31-127.78 (Arom.CH), 122.60 (Arom. CH), 122.35 (=CH₂), 113.42 (CN), 113.36 (CN), 60.90 (CHAr), 44.43 (CCN₂), 40.90 (CH₂NTs), 40.43 (CHCH=CH₂), 26.54 (CH₂), 21.90/21.58 (overlapping CH₃Ts, CH₃CO₂). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl₃): νₘₚ 3062, 2253, 1769, 1599, 1508, 1350, 1165, 816.


209
HRMS calcd for C_{23}H_{24}N_{3}O_{2}S [M+H] 406.1598, found 406.1563.
(m, 1H: CH₃NTs), 2.40 (s, 3H: CH₃Ts), 2.31 (s, 3H: CH₃CO₂), 2.29 (m, 1H: CH₂), 2.03 (m, 1H: CH₂), 1.42 (s, 3H: CH₃).

**¹³C NMR** (75 MHz, CDCl₃) δ 169.10 (OCOCH₃), δ 151.92 (Quat.), 144.44 (Quat), 133.18 (=CH), 136.55 (Quat.), 130.75 (Arom.CH), 130.01 (Arom.CH), 127.69(Arom.CH),130.01 (Arom.CH), 120.24 (=CH₂), 113.78 (CN), 113.38 (CN), 62.03 (CHar), 50.75 (CCN₂), 43.42 (Quat.), 41.55 (CH₂NTs), 31.71 (CH₂), 25.35 (CH₂Ts), 21.95, 21.61 (overlapping CH₃, CH₃CO₂). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl₃): ν max 3056, 2252, 1763, 1599, 1510, 1369, 1163, 814, 760.

**HRMS** calcd for C_{25}H_{29}N₄O₄S [M+NH₄] 481.1909, found 481.1890.

2,4-diphenyl-1-tosyl-4-vinylpiperidine-3,3-dicarbonitrile

**13n** (cw2227)
White solid

Pd(PPh₃)₄: 87% yield, dr = 1:19

**¹H NMR** (400 MHz, CDCl₃) δ 7.62-7.12 (m, 14H: arom H), 6.45 (dd, J =11.1, 17.4 Hz, 1H: CH₂=CH), 5.72 (dd, 1H, J =3.0, 11.1 Hz: =CH₂), 5.39 (dd, 1H, J =2.8, 17.4 Hz: =CH₂), 4.67 (s, 1H: PhCH), 4.26 (m, 1H: CH₂NTs), 3.61 (m, 1H: CH₂NTs), 3.01 (app t, 1H: CH₂), 2.58 (app d, 1H: CH₂), 2.42 (s, 3H: CH₃Ts).

**¹³C NMR** (75 MHz, CDCl₃) δ 144.33 (Quat.), 140.58 (Quat), 136.65 (=CH), 136.17 (Quat.), 132.49 (Quat.), 130.90-127.97 (Arom.CH), 121.89 (=CH₂), 113.56 (CN), 113.26 (CN), 65.18 (PhCHNTs), 52.41/50.56 (overlapping CCN₂, CH(Ph)CH=CH₂), 43.44 (CH₂NTs), 30.70 (CH₂), 21.98 (CH₃(Ts)). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl₃): ν max 3094, 3065, 3038, 2253, 1597, 1495, 1350, 1161, 814, 777, 660.

**HRMS** calcd for C_{28}H_{25}N₃O₂SNa [M+Na] 490.1565, found 490.1560.
(E)-N-(5-(4-(2,2-dicyanovinyl)phenoxy)-2-phenylpent-3-enyl)-4-methylbenzenesulfonamide

14g (cw2031)
colorless oil
Pd(PPh₃)₄: 90% NMR yield, dr: 1:1

$^1$H NMR (400 MHz, CDCl₃) δ ppm 7.03-7.95 (m, 26H: arom H), 5.97 (m, 2H: =CH), 5.75 (td, 1H, $J$=15.7, 5.3 Hz: =CHCH₂), 5.53 (m, 1H: =CH), 5.36 (d, 2H, $J$=5.6 Hz: OCH₂), 4.62 (d, 2H, $J$=5.6 Hz: OCH₂), 3.87 (m, 2H: CHPh), 3.51 (br. s., 2H: NHTs), 3.28 (m, 2H: CH₂NHTs), 3.12 (m, 2H: CH₂NHTs), 2.46 (s, 3H: CH₃Ts), 2.43 (s, 3H: CH₃Ts).

3-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine

15b (cw2048)
White solid
Pd(PPh₃)₄: 99% combined yield(15b/15f)

$^1$H NMR (400 MHz, CDCl₃) δ ppm 7.70 (d, 2H, $J$=8.1 Hz: arom H), 7.21 - 7.34 (m, 5H: arom H), 7.04 (d, 2H, $J$=8.1 Hz: arom H), 5.68 (m, 1H: =CHCH₂), 5.41 (m, 1H: CH=), 4.68 (m, 1H: TsNCH₂), 3.40 (m, 1H: CH₂CH=), 3.20 (dt, 1H, $J$=12.6, 6.9 Hz: TsNCH₂), 3.08 (m, 1H: CH₂CH=), 2.63 (td, 1H, $J$=13.3, 8.3 Hz: CHPh), 2.44 (s, 3H: CH₃).
(rac)-3,3-dimethyl-7-phenyl-8-tosyl-11-vinyl-2,4-dioxa-8-azaspiro[5.5]undecane-1,5-dione

15c (cw2176)
White solid
Pd(PPh₃)₄: 38% combined yield(15c/15d), dr: 2:1

1H NMR (400 MHz, CDCl₃) δ ppm 7.46 (d, 2H, J=8.2 Hz: arom H), 7.20 - 7.30 (m, 7H: arom H), 5.50 (m, 1H: CH=), 5.12 (dd, 2H, J=17.1 Hz: CH₂=), 4.80 (s, 1H: CHPh), 4.39 (m, 1H: diastereotopic CH₂NTs), 3.19 (m, 1H: diastereotopic CH₂NTs), 2.72 (m, 1H: CH), 2.44 (s, 3H: CH₃), 2.35 (m, 1H: diastereotopic CH₂), 1.81 (ddd, 1H, J=13.8, 5.1, 1.7 Hz: diastereotopic CH₂), 1.50 (s, 3H: CH₃), 0.71 (s, 3H: CH₃).

13C NMR (100 MHz, CDCl₃) δ ppm 168.6 (OC=O), 163.5 (OC=O), 144.2 (Quat. Arom. C), 136.3 (Quat. Arom. C), 135.2 (=CH), 134.9 (Quat. Arom. C), 130.3 (Arom. CH), 129.9 (Arom. CH), 129.3 (Arom. CH), 128.6 (Arom. CH), 128.4 (Arom. CH), 120.9 (=CH₂), 106.8 (C(CH₃)₂), 66.3 (CHPh), 61.2 (C(CO₂R)₂), 48.9 (CH), 46.4 (CH₂NTs), 30.1 (CH₃), 29.1 (CH₃), 25.8 (CH₂), 22.0 (CH₃(Ts)). The assignments of the 1H and 13C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl₃): νmax 3053, 2988, 1780, 1749, 1359, 1164, 941.

HRMS calcd for C_{25}H_{27}NO₆SNa [M+Na] 492.1457, found 492.1451.

(rac)-3,3-dimethyl-7-phenyl-8-tosyl-11-vinyl-2,4-dioxa-8-azaspiro[5.5]undecane-1,5-dione

15d (cw2176)
White solid

1H NMR (400 MHz, CDCl₃) δ ppm 7.33 (m, 5H: arom H), 7.25 (m, 2H: arom H), 7.05 (d, 2H, J=8.0 Hz: arom H), 5.68 (dt, 1H, J=10.2, 8.6 Hz: CH=), 5.59 (s, 1H: CHPh), 5.27 (dd, 1H, J=17.2, 0.8 Hz: CH₂=CH(E)), 5.19 (dd, 1H, J=10.3, 0.9 Hz: CH₂=CH(Z)), 3.83 (dd, 1H, J=5.7 Hz: diastereotopic CH₂NTs), 3.63 (m, 1H: CH), 3.40 (td, 1H, J=13.3, 3.7 Hz: diastereotopic CH₂NTs), 2.33 (s, 3H: CH₃Ts), 2.72 (m,
1H: diastereotopic CH₂, 1.90 (s, 3H: CH₃), 1.83 (m, 1H: diastereotopic CH₂), 1.66 (s, 3H: CH₃).

\(^{13}\text{C NMR}\) (100 MHz, CDCl₃) δ ppm 165.1 (OC=O), 164.6 (OC=O), 143.2 (Quat. Arom.C), 136.3 (=CH), 135.8 (Quat. Arom.C), 134.9 (Quat. Arom.C), 129.9 (Arom.CH), 129.5 (Arom.CH), 129.1 (Arom.CH), 128.6 (Arom.CH), 127.4 (Arom.CH), 120.5 (=CH₂), 105.7 (C(CH₃)₂), 61.4 (CHPh), 58.5 (C(CO₂R)₂), 39.9 (CH₂NTs), 38.3 (CH), 30.7 (CH₃), 28.4 (CH₃), 25.7 (CH₂), 21.5 (CH₃(Ts)). The assignments of the \(^1\text{H}\) and \(^{13}\text{C}\) were based on DEPT, COSY, HMQC etc.

\textbf{FTIR} (CDCl₃): \(\nu_{\text{max}}\) 3053, 2988, 1780, 1749, 1359, 1164.

\textbf{HRMS} calcd for C\(_{25}\)H\(_{27}\)NO\(_6\)SNa [M+Na] 492.1457, found 492.1451.

\[\text{TS} \quad \begin{array}{c}
\begin{array}{c}
\text{Ts} \\
\text{N} \\
\text{O} \\
\text{Me}
\end{array}
\end{array}
\]

3-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydropyridine
\textbf{15e} (cw2141)

Colorless oil
Pd(PPh\(_3\))\(_4\): 80\% combined yield

\textbf{\(^1\text{H NMR}\)} (400 MHz, CDCl₃) δ ppm 7.70 (d, 2H, \(J=8.1\) Hz: arom H), 7.35 (d, 2H, \(J=7.6\) Hz: arom H), 7.09 (d, 2H, \(J=7.6\) Hz: arom H), 6.98 (d, 2H, \(J=8.3\) Hz: arom H), 5.65 (dd, 1H, \(J=15.8, 8.0\) Hz: =CHCH₂), 5.04 (dd, 1H, \(J=8.6, 1.8\) Hz: CH=), 4.64 (m, 1H: TsNCH₂), 3.79 (s, 3H: OCH₃), 3.34 (m, 1H: CH₃CH=), 3.15 (dd, 1H, \(J=12.8, 6.2\) Hz: TsNCH₂), 3.10 (m, 1H: CH₂CH=), 2.68 (m, 1H: CHPh), 2.47 (s, 3H: CH₃).

\[\begin{array}{c}
\text{TS} \quad \begin{array}{c}
\begin{array}{c}
\text{Ts} \\
\text{N} \\
\text{O} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{Ph}
\end{array}
\end{array}
\end{array}
\]

(rac)-3,3-dimethyl-7,10-diphenyl-8-tosyl-11-vinyl-2,4-dioxap-8-azaspiro[5.5]undecane-1,5-dione
\textbf{15f} (cw2048)

White solid
Pd(PPh\(_3\))\(_4\): 99\% combined yield(15b/15f)

\textbf{\(^1\text{H NMR}\)} (400 MHz, CDCl₃) δ ppm 7.46 (dd, 2H, \(J=7.3, 1.0\) Hz: arom H), 7.26 (d, 2H, \(J=8.1\) Hz: arom H), 7.34 (m, 8H: arom H), 7.00 (ddd, 2H, \(J=7.9, 1.4, 0.7\) Hz: arom H), 5.68 (s, 1H: CHPh(NTs)), 5.53 (m, 1H: CH=), 5.02 (m, 2H: CH₂=), 4.09
(m, 1H: CHPh), 3.90 (m, 2H: overlapping diastereotopic CH₂NTs and CHCH=), 3.38 (t, 1H, J=13.0 Hz: diastereotopic CH₂NTs), 2.30 (s, 3H: CH₃Ts), 1.92 (s, 3H: CH₃), 1.67 (s, 3H: CH₃).

**1³C NMR** (100 MHz, CDCl₃) δ ppm 165.5 (OC=O), 165.2 (OC=O), 143.6 (Quat. Arom.C), 140.4 (Quat. Arom.C), 136.2 (Quat. Arom.C), 135.2 (CH), 135.1 (Quat. Arom.C), 130.0 (Arom.CH), 129.7 (Arom.CH), 129.6 (Arom.CH), 129.3 (Arom.CH), 129.2 (Arom.CH), 128.7 (Arom.CH), 127.9 (Arom.CH), 127.6 (Arom.CH), 123.1 (CH₂), 106.3 (C(CH₃)₂), 62.1 (CHPh(TsNTs)), 60.1 (C(CO₂R)₂), 46.6 (CH₂), 44.0 (CHCH=), 42.4 (CHPh), 31.2 (CH₃), 28.8 (CH₃), 21.8 (CH₃(Ts)). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

![Structure](image)

5-oxo-1-tosyl-4-vinyl-2,3,4,5,10b-hexahydro-1H-chromeno[4,3-b]pyridine-4-a-carbonitrile

**16a (cw2169)**

colorless oil

Pd(PPh₃)₄: 49% yield, dr = >19:1

**¹H NMR** (400 MHz, CDCl₃) δ 7.98 (d, J = 8.3, 2H: arom H), 7.61 (d, J = 7.8, 1H: arom H), 7.39 (m, 4H: arom H), 7.16 (d, J =8.1, 1H: arom H), 6.12 (s, 1H, J =8.3 Hz: TsNCH), 5.76 (m, 1H: =CH), 5.25(d, 1H, J = 10.1 Hz: CH=CH(H)₂), 5.12 (d, 1H, J = 16.9 Hz: CH=CH(H)₂), 3.62 (broad d, 1H, J =13.6 Hz: CH₂NTs), 3.10 (td, 1H, J =3.8, 13.6 Hz: CH₂NTs), 2.48 (m, 4H: overlapping CHCH=CH₂, CH₃), 1.63 (m, 2H: CH₂).

**¹³C NMR** (75 MHz, CDCl₃) δ 161.3 (OCOCH₃), 149.6 (Quat.), 145.1 (Quat.), 136.3 (Quat.), 133.8 (=CH), 131.4-126.9 (Arom. CH), 121.0 (=CH₂), 117.7 (Arom. CH), 115.5 (CN), 55.8 (TsNCH), 51.5 (CCN), 40.7 (CHCH=CH₂), 39.7 (TsNCH₂), 27.8 (CH₂), 22.1 (CH₃). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC, NOESY etc. The absolute configuration was assigned, based on the X-ray structure.

**FTIR** (CDCl₃): v max 3086, 2252, 1772, 1589, 1487, 1354, 1194, 816.

**HRMS** calcd for C₂₂H₂₀N₂O₄SNa [M+Na] 431.1041, found 431.1032.
HRMS calcd for C_{23}H_{26}N_{3}O_{4}S [M+NH4] 440.1644, found 440.1643.

FTIR (CDCl3): $\nu_{\text{max}}$ 3092, 3061, 2253, 1761, 1591, 1489, 1331, 1161, 816.

Pd(PPh₃)$_4$: 89% NMR yield

$^1$H NMR (400 MHz, CDCl₃) δ ppm 7.75 (d, 2 H, $J$=8.3 Hz: arom H), 7.32 (d, 2 H, $J$=8.6 Hz: arom H), 5.82 (m, 1 H: =CHCH$_2$), 5.65 (d, 1 H, $J$=9.6 Hz: CH=), 5.47 (br. s., 1 H: CH=C(Quat.)), 4.46 (s, 1 H: NHTs), 3.02 (q, 2 H, $J$=6.1 Hz: CH$_2$NHTs), 2.45 (s, 3 H, overlapping CH$_2$), 2.16 (t, 3 H, $J$=6.7 Hz: overlapping CH$_2$), 2.08 (s, 3 H: CH$_3$).
2-phenyl-1-tosyl-4-vinylazetidine

17d (cw2219)
colorless oil

Pd(PPh₃)₄: 92% NMR yield yield

1H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 8.3 Hz, 2H: arom H), 7.42 (d, J = 7.1 Hz, 2H: arom H) 7.33 (m, 5H: arom H), 6.06 (m, 1H: =CH), 5.38 (d, 1H, J = 17.2 Hz: CH=CH(H)b), 5.25 (d, 1H, J = 10.4 Hz: CH=CH(H)z), 4.81 (t, 1H, J = 8.3 Hz: PhCH), 4.41 (q, J = 8.1, 4.9 Hz, 1H: CHCH=CH₂), 2.61 (d, t, J = 8.3, 10.9 Hz, 1H: CH₂), 2.45 (s, 3H: CH₃), 1.99 (d, t, J = 8.3, 10.9 Hz, 1H: CH₂). More information about this compound is available in Chapter 2 of this thesis.

1-benzoyl-5-benzyl-2-phenyl-4-vinylpiperidine-3,3-dicarbonitrile

20b (cw2179)
White solid

Pd(PPh₃)₄: 36% yield, dr 3:9:1

1H NMR (400 MHz, CDCl₃) δ ppm 7.49 (m, 10H: arom H), 7.18 (t, 3H, J=3.1 Hz: arom H), 6.80 (m, 2H, m: arom H), 6.07 (dt, 1H, J=16.7, 10.0 Hz: CH₂=CH), 5.92 (s, 1H: PhCHNBz), 5.70 (d, 1H, J=10.2 Hz: CH=CH(E)), 5.61 (d, 1H, J=16.7 Hz: CH=CH(Z)), 4.03 (dd, 1H, J=14.6, 2.9 Hz: CH₂NTs), 3.59 (dd, 1H, J=14.7, 5.1 Hz: CH₂NTs), 3.38 (dd, 1H, J=9.7, 5.7 Hz: CHCH=CH₂), 2.79 (d, 1H, J=13.4 Hz: diastereotopic CH₂Ph), 2.53 (m, 2H: overlapping CHBn, diastereotopic CH₂Ph).

13C NMR (100 MHz, CDCl₃) δ ppm 172.9 (CO), 138.9 (Quat. Arom.C), 134.6 (Quat. Arom.C), 131.4 (Quat. Arom.C), 130.4 (=CH), 129.9 (Arom.CH), 129.7 (Arom.CH), 129.4 (Arom.CH), 129.3 (Arom.CH), 129.0 (Arom.CH), 128.1 (Arom.CH), 127.7 (Arom.CH), 127.0 (Arom.CH), 126.9 (Arom.CH), 125.7 (=CH₂), 114.9 (CN), 114.2 (CN), 58.9 (PhCHNTs), 48.4 (CHCH=CH₂), 44.1 (CH₂NTs), 43.0 (CCN₂), 39.1 (BnCH), 35.8 (CH₂Ph). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.
5-benzyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine

20c (cw2179)
White solid
Pd(PPh₃)$_4$: 39% yield, dr 2.2:1

$^1$H NMR (400 MHz, CDCl₃) Major diastereoisomer: δ ppm 8.00 (m, 2 H: arom H, overlapping minor/major isomers), 7.44 (m, 3 H: arom H, overlapping minor/major isomers), 7.33 (m, 2 H: arom H, overlapping minor/major isomers), 7.26 (m, 3 H: arom H, overlapping minor/major isomers), 6.00 (m, 1 H, overlapping minor/major isomer: CH=), 5.40 (m, 2 H: =CH₂), 4.60 (t, 1 H, $J$=5.9 Hz: OCH), 3.59 (dd, 1 H, d, $J$=16.8, 4.9 Hz: CH$_2$N), 3.37 (td, 1 H, $J$=16.6, 8.1 Hz: CH$_2$N), 2.94 (dd, 1 H, $J$=13.6, 6.3 Hz: CH$_2$Ph), 2.58 (m, 1 H: CH$_2$Ph), 2.08 (m, 1 H: CHBn).

Minor diastereoisomer: δ ppm 8.00 (m, 2 H: arom H, overlapping minor/major isomers), 7.44 (m, 3 H: arom H, overlapping minor/major isomers), 7.33 (m, 2 H: arom H, overlapping minor/major isomers), 7.26 (m, 3 H: arom H, overlapping minor/major isomers), 6.00 (m, 1 H, overlapping minor/major isomer: CH=), 5.40 (m, 2 H: =CH₂), 4.87 (t, 1 H, $J$=3.7 Hz: OCH), 3.59 (dd, 1 H, d, $J$=16.8, 4.9 Hz: CH$_2$N), 3.37 (td, 1 H, $J$=16.6, 8.1 Hz: CH$_2$N), 2.68 - 2.73 (m, 1 H: CH$_2$Ph), 2.58 (m, 1 H: CH$_2$Ph), 2.43 (m, 1 H: CHBn).

$^1$H NMR (400 MHz, CDCl₃) Major diastereoisomer: δ ppm 7.72 (m, 3H: arom H), 7.53 (m, 4H: arom H), 6.98 - 7.19 (m, 3 H: arom H), 6.66 (m, 1H: CH=), 6.01 (d, 1H, $J$=11.1 Hz: BnC=CH), 5.68 (br. s., 1H: NH), 5.15 (m, 2H; =CH$_2$), 3.99 (d, 2H, $J$=5.6 Hz: CH$_2$NH), 3.42 (s, 2H: CH$_2$Ph).

Minor diastereoisomer: δ ppm 7.72 (m, 3H: arom H), 7.53 (m, 4H: arom H), 6.98 - 7.19 (m, 3 H: arom H), 6.77 (m, 1H: CH=), 6.14 (d, 1H, $J$=11.1 Hz: BnC=CH), 5.68
(br. s., 1H: NH), 5.15 (m, 2 H; =CH₂), 4.18 (d, 2H, J=5.6 Hz: CH₂N), 3.99 (s, 2H: CH₂Ph).

![Diagram of 5-phenyl-1,3-ditosyl-4-vinyldihydro-2(1H)-one]

5-phenyl-1,3-ditosyl-4-vinyldihydro-2(1H)-one

21b (cw2104)
colorless oil
Pd(PPh₃)₄: 98% yield, dr =3.1:1

\(^1\text{H} \text{ NMR}\) (400 MHz, CDCl₃) δ ppm 7.85 (dd, 2H, J=8.4, 2.0 Hz: arom H), 7.77 (d, 2H, J=8.3 Hz: arom H), 7.36 (dd, 4H, J=8.6, 0.6 Hz: arom H), 7.20 (dd, 4H, J=7.6, 0.7 Hz: arom H), 7.12 (d, 2H, J=5.0 Hz: arom H), 5.68 (m, 1H: CH=CH), 5.40 (dd, 2H, J=10.6, 1.8 Hz: CH=CH(H)₂), 5.31 (m, 1H: CHNTs), 5.18 (dd, 1H, J=17.1, 1.9 Hz: CH=CH(H)₁), 4.35 (dt, 1H, J=12.7, 1.9 Hz: diastereotopic CH₂NTs), 4.07 (dd, 1H, J=12.7, 5.3 Hz: diastereotopic CH₂NTs), 3.53 (m, 1H: PhCH.), 2.49 (s, 3H: CH₃Ts), 2.41 (s, 3H: CH₃Ts).

![Diagram of 4-methyl-1,3-ditosyl-4-vinyldihydro-2(1H)-one]

4-methyl-1,3-ditosyl-4-vinyldihydro-2(1H)-one

21e (cw2270)
colorless oil
Pd(PPh₃)₄: 72% yield

\(^1\text{H} \text{ NMR}\) (400 MHz, CDCl₃) δ ppm 7.79 (dd, 4H, J=14.0, 8.3 Hz: arom H), 7.23 (t, 4H, J=9.0 Hz: arom H), 6.13 (dd, 1H, J=17.4, 10.8 Hz: CH₂=CH), 5.32 (d, 1H, J=10.6 Hz: CH=CH(H)₂), 5.24 (d, 1H, J=17.4 Hz: CH=CH(H)₁), 3.89 (dd, 2H, J=7.1, 3.9 Hz: CH₂NTs), 3.83 (d, 2H, J=7.8, 4.0 Hz: CH₂NTs), 2.44 (s, 3H: CH₃Ts), 2.43 (s, 3H: CH₃Ts), 2.03 (m, 2H: CH₂), 1.91 (s, 3H: CH₃).
1,3-di-tosyl-4-vinyltetrahydroimidin-2(1H)-one

21g (cw2266/267) colorless oil

Pd(PPh₃)₄: 70% NMR yield

Pd₂(dbạ)₃/Trost ligand: 85% NMR yield

¹H NMR (400 MHz, CDCl₃) δ ppm 7.83 (m, 4H: arom H), 7.27 (dd, 4H, J=5.2, 2.8 Hz: arom H), 5.29 (dd, 1H, J=10.5, 1.5 Hz: CH=CH(H)₂), 5.25 (m, 1H: CH), 5.01 (dd, 1H, J=17.1, 1.7 Hz: CH=CH(H)₂), 4.03 (m, 1H: diastereotopic CH₂NTs), 3.69 (m, 1H: diastereotopic CH₂NTs), 2.44 (s, 6H: CH₃Ts), 2.15 (m, 2H: CH₂).

¹³C NMR (125 MHz, CDCl₃) δ ppm 157.0 (CO), 144.9 (Quat. Arom.C), 135.6 (Quat. Arom.C), 134.1 (=CH), 129.2 (Arom.CH), 129.1 (Arom.CH), 118.6 (=CH₂), 56.2 (CHCH=CH₂), 42.3 (CH₂NTs), 26.8 (CH₂), 22.7 (CH₂NTs).

1-cyanocyclohexanecarboxamide

23d (cw3030) White solid

¹H NMR (400 MHz, CDCl₃) δ ppm 6.42 (br. s., 2H: CONH₂), 2.03 (m, 2H: CH₂), 1.82 (m, 5H: CH₂), 1.62 (m, 2H: CH₂), 1.26 (m, 1H: CH₂).

¹³C NMR (100 MHz, CDCl₃) δ ppm 171.1 (CONH₂), 121.1 (CN), 46.2 (Quat. C), 33.0 (CH₂), 24.6 (CH₂), 22.6 (CH₂).
2-benzyl-3-cyano-1-tosyl-4-vinylpiperidine-3-carboxamide

24d (cw3052)
White solid
Cat. B: 95% yield, dr = 2.5:1

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.85 (m, 7H: arom H), 7.20 (m, 3H: arom H), 7.10 (d, 2H, $J$=8.1 Hz: arom H), 7.02 (d, 2H, $J$=8.0 Hz: arom H), 6.38 (br. s., 1H: CONH$_2$), 5.77 (m, 1H: =CH), 5.63 (s, 1H: PhCHNTs), 5.44 (m, 2H: =CH$_2$), 3.52 (dd, 1H, $J$=13.3, 5.1 Hz: diastereotopic CH$_2$NTs), 3.24 (dd, 1H, $J$=11.7, 8.7 Hz: diastereotopic CH$_2$NTs), 3.11 (dd, 1H, $J$=14.0, 3.4 Hz: diastereotopic CH$_2$Ph), 3.00 (t, 1H, $J$=12.6 Hz: CHCH=CH$_2$), 2.42 (m, 1H: diastereotopic CH$_2$Ph), 2.35 (3, 3H: CH$_3$Ts), 2.17 (m, 1H: CHBn).
General procedure for synthesizing starting vinyl benzoxazinanones:

Vinyl benzoxazinanones were prepared as reported in Chapter 2 of this thesis.

General procedure for asymmetric cycloadditions:

In a Schlenk tube under argon, Pd$_2$(dba)$_3$ (0.05 mmol), Trost ligand (0.11 mmol), vinyl benzoxazinanone 1 (1 mmol) and the benzyldiene malononitrile (1 mmol) were dissolved in 5 mL of methylene chloride. The resulting yellow solution was stirred at ambient temperature under Ar until the reaction completion was indicated by TLC (generally 4-6 hrs). Following solvent evaporation under reduced pressure, the crude product was purified via flash chromatography (SiO$_2$, 5:1 Hexane: Ethyl acetate).

\[
\text{(2S,4S)-2-phenyl-1-tosyl-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile) 33a (cw3194)}
\]

white solid

Pd(PPh$_3$)$_4$: 98% yield, dr = 8.9:1
Pd/Trost ligand: 97% yield, 89% ee (S,S), dr = 19:1
87% yield, 97% ee (S,S), dr = 50:1 after a single recrystallization

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.89 (1 H, dd, $J$=8.0, 1.0 Hz: Ar CH), 7.51 - 7.67 (4 H, m: Ar CH), 7.39 - 7.51 (5 H, m: Ar CH), 7.29 (2 H, d, $J$=7.8 Hz: Ar CH), 7.17 (1 H, d, $J$=7.7 Hz: Ar CH), 5.91 (1 H, dt, $J$=16.8, 9.8 Hz: CH=CH$_2$), 5.77 (1 H, s: CHPh), 5.61 (1 H, dd, $J$=10.1, 1.0 Hz: CH=CH(H)$_{cis}$), 5.09 (1 H, d, $J$=16.8 Hz: CH=CH(H)$_{trans}$), 2.56 (1 H, d, $J$=9.7 Hz: CHCH=), 2.47 (3 H, s: CH$_3$Ts).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 145.1 (quat. Ar C), 136.7 (quat. Ar C), 135.1 (quat. Ar C), 134.5 (quat. Ar C), 131.6 (quat. Ar C), 130.2 (Ar CH), 130.0 (Ar CH), 129.6 (Ar CH), 129.3 (CH=CH$_2$), 129.2 (Ar CH), 128.6 (Ar CH), 128.2 (Ar CH), 127.3 (Ar CH), 127.0 (Ar CH), 126.8 (Ar CH), 125.0 (=CH$_2$), 113.9 (CN), 111.2
(CN), 65.8 (CHPh), 50.0 (CCN₂), 49.1 (CHCH=), 21.6 (CH₃Ts). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl₃): νₓₓımₚ 3053, 2986, 2305, 1597, 1483, 1421, 1262, 895.

**HRMS** calcd for C₂₆H₂₁N₃O₂SNa [M+Na] 462.1252, found 462.1251.

Separated enantiomers on a Diacel Chiralpak AD-H HPLC column (96% Hexane/IPA, 1.0 mL/min), tr (major) = 22.8 min, tr (minor) = 32.1 min.

![Structure of 33b](image)

(2S,4S)-6-methoxy-2-(4-nitrophenyl)-1-tosyl-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile 33b (cw4155)

Pd/Trost ligand: 91% yield, 99% ee (S,S), dr = 25:1

¹H NMR (400 MHz, CDCl₃) δ ppm 7.89 (1 H, dd, J=8.0, 1.0 Hz: Ar CH), 7.51 - 7.67 (4 H, m: Ar CH), 7.39 - 7.51 (5 H, m: Ar CH), 7.29 (2 H, d, J=7.8 Hz: Ar CH), 7.17 (1 H, d, J=7.7 Hz: Ar CH), 5.91 (1 H, dt, J=16.8, 9.8 Hz: CH=CH₂), 5.77 (1 H, s: CHPh), 5.61 (1 H, dd, J=10.1, 1.0 Hz: CH=CH(H)ₜᵢₛ), 5.09 (1 H, d, J=16.8 Hz: CH=CH(H)ₜᵢₛ), 2.56 (1 H, d, J=9.7 Hz: CHCH=), 2.47 (3 H, s: CH₃Ts).

¹³C NMR (75 MHz, CDCl₃) δ ppm 159.5 (quat. Ar C), 148.5 (quat. Ar C), 145.5 (quat. Ar C), 143.5 (quat. Ar C), 133.7 (quat. Ar C), 132.8 (quat. Ar C), 130.2 (Ar CH), 128.7 (CH=), 128.3 (Ar CH), 127.4 (Ar CH), 126.6 (Ar CH), 125.6 (=CH₂), 124.4 (Ar CH), 114.7 (Ar CH), 113.4 (CN), 113.2 (Ar CH), 110.8 (CN), 65.1 (CHAr), 55.7 (OCH₃), 49.1 (CHCH=), 48.9 (CCN₂), 21.7 (CH₃Ts). The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl₃): νₓₓımₚ 3053, 2927, 2303, 1608, 1529, 1350, 1263, 1169, 893.

**HRMS** calcd for C₂₇H₂₂N₄O₅SNa [M+Na] 537.1209, found 537.1207.

Separated enantiomers on Diacel Chiralpak OD-H HPLC column (90% Hexane/IPA, 1.0 mL/min), tr (minor) = 24.9 min, tr (major) = 28.5 min.
(2S,4S)-6-methyl-2-(4-nitrophenyl)-1-tosyl-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile 33c (cw4165)

white solid

Pd/Trost ligand: 90% yield, 99% ee (S,S), dr >99:1

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.31 (2 H, d, $J$=8.7 Hz: Ar $CH$), 7.69 - 7.85 (3 H, m: Ar $CH$), 7.36 - 7.49 (3 H, m: Ar $CH$), 7.29 - 7.36 (2 H, m, $J$=8.0 Hz: Ar $CH$), 6.94 (1 H, s: Ar $CH$), 5.86 (1 H, dt, $J$=16.8, 9.8 Hz: $CH=CH$), 5.76 (1 H, s: CHAr), 5.61 (1 H, d, $J$=10.0 Hz: $CH=CH(H)_{cis}$), 5.06 (1 H, d, $J$=16.7 Hz: $CH=CH(H)_{trans}$), 2.47 (3 H, s: $CH_3$Ts), 2.38 - 2.45 (4 H, m: overlapping $CH_3$Ts, $CH=CH$).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 148.4 (quat. Ar $C$), 145.4 (quat. Ar $C$), 143.5 (quat. Ar $C$), 138.9 (quat. Ar $C$), 133.8 (quat. Ar $C$), 131.6 (quat. Ar $C$), 131.1 (Ar $CH$), 130.8 (quat. Ar $C$), 130.1 (Ar $CH$), 128.9 ($CH=CH_2$), 128.3 (Ar $CH$), 128.2 (Ar $CH$), 127.3 (Ar $CH$), 127.2 (Ar $CH$), 125.3 ($CH_2$), 124.4 (Ar $CH$), 113.4 (CN), 110.8 (CN), 65.0 (CHAr), 49.1 ($CCN_2$), 49.0 ($CHCH=$), 21.6 ($CH_3$Ts), 21.4 ($CH_3$).
The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{max}$ 3053, 2986, 2305, 1528, 1352, 1269, 1259, 895, 818.

HRMS calcld for C$_{27}$H$_{22}$N$_4$O$_4$SNa [M+Na] 521.1259, found 521.1262.

Separated enantiomers on Diacel Chiralpak OD-H HPLC column (90% Hexane/IPA, 1.0 mL/min), tr (minor) = 16.6 min, tr (major) = 20.1 min.
\[ \text{(2S,4S)-2-(4-nitrophenyl)-1-tosyl-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dcarbonitrile} \]

33d (cw4116)
white solid

Pd/Trost ligand: 78% yield, 96% ee (S,S), dr >99:1

\[ ^1H \text{ NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \ \delta \text{ ppm} \ 8.32 (2 \text{ H, d, } J=7.5 \text{ Hz: Ar CH}), 7.92 (1 \text{ H, d, } J=8.0 \text{ Hz: Ar CH}), 7.75 (2 \text{ H, d, } J=7.5 \text{ Hz: Ar CH}), 7.60 (1 \text{ H, t, } J=7.7 \text{ Hz), 7.42 - 7.47 (1 \text{ H, m: Ar CH}), 7.40 (2 \text{ H, d, } J=7.9 \text{ Hz: Ar CH}), 7.31 (2 \text{ H, d, } J=7.6 \text{ Hz: Ar CH}), 7.17 (1 \text{ H, d, } J=7.6 \text{ Hz: Ar CH}), 5.87 (1 \text{ H, ddd, } J=17.0, 10.0, 9.8 \text{ Hz: CH=}), 5.78 (1 \text{ H, s: CHAr}), 5.63 (1 \text{ H, d, } J=10.0 \text{ Hz: CH=CH}_\text{cis}), 5.09 (1 \text{ H, d, } J=16.7 \text{ Hz: CH=CH}_\text{trans}), 2.47 (4 \text{ H, s: overlapping CH}_3\text{Ts, CHCH=}). \]

\[ ^{13}C \text{ NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \text{ ppm} \ 148.6 \text{ (quat. Ar C), 145.6 \ (quat. Ar C), 143.4 \ (quat. Ar C), 134.4 \ (quat. Ar C), 133.8 \ (quat. Ar C), 131.1 \ (quat. Ar C), 130.6 \ (Ar CH), 130.2 \ (Ar CH), 128.8 \ (=CH), 128.7 \ (Ar CH), 128.6 \ (Ar CH), 128.3 \ (Ar CH), 127.3 \ (Ar CH), 126.9 \ (Ar CH), 125.5 \ (=CH_2), 124.5 \ (Ar CH), 113.4 \ (CN), 110.8 \ (CN), 65.1 \ (CHAr), 49.2 \ (C(CN)_2), 49.1 \ (CHCH=), 21.7 \ (CH_3\text{Ts}).} \]

The assignments of the \(^1\text{H}\) and \(^{13}\text{C}\) were based on DEPT, COSY, HMQC etc.

\[ \text{FTIR (CDCl}_3): \nu_{\text{max}} \ 3053, 2952, 2854, 2337, 1529, 1350, 1327, 1171, 910. \]

\[ \text{HRMS calcd for } C_{26}H_{20}N_4O_4Sn [M+Na] 507.1103, \text{ found } 507.1097. \]

Separated enantiomers on Diacel Chiralpak OD-H HPLC column (90% Hexane/IPA, 1.0 mL/min), tr (minor) = 20.6 min, tr (major) = 25.0 min.
methyl 4-((2S,4S)-3,3-dicyano-6-methoxy-1-tosyl-4-vinyl-1,2,3,4-tetrahydroquinolin-2-yl)benzoate

**33e** (cw4187)
white solid

Pd/Trost ligand: 99% yield, 92% ee (S,S), dr =25:1

**1H NMR** (400 MHz, CDCl₃) δ ppm 8.11 (2 H, d, J=8.3 Hz: Ar CH), 7.80 (1 H, d, J=8.8 Hz: Ar CH), 7.62 (2 H, d, J=8.4 Hz: Ar CH), 7.41 (2 H, d, J=8.2 Hz: Ar CH), 7.28 - 7.38 (2 H, m, J=8.2 Hz: Ar CH), 7.06 (1 H, dd, J=8.8, 2.7 Hz: Ar CH), 6.64 (1 H, d, J=2.5 Hz: Ar CH), 5.83 (1 H, dt, J=16.8, 9.8 Hz: CH=CH₂), 5.74 (1 H, s: CHAr), 5.58 (1 H, d, J=10.1 Hz: CH=CH(H)ₗ), 5.01 (1 H, d, J=16.8 Hz: CH=CH(H)ₜ), 3.93 (3 H, s: CO₂CH₃), 3.85 (3 H, s: OCH₃), 2.46 (3 H, s: CH₃Ts), 2.36 (1 H, d, J=9.6 Hz: CHCH=). The assignments of the **1H** and **13C** were based on DEPT, COSY, HMQC etc.

**13C NMR** (75 MHz, CDCl₃) δ ppm 166.3 (CO₂CH₃), 159.4 (quat. Ar C), 145.2 (quat. Ar C), 141.4 (quat. Ar C), 134.1 (quat. Ar C), 133.1 (quat. Ar C), 131.3 (quat. Ar C), 130.5 (Ar CH), 130.2 (Ar CH), 130.1 (Ar CH), 128.9 (CH=CH₂), 127.4 (Ar CH), 127.1 (Ar CH), 127.0 (quat. Ar C), 125.4 (=CH₂), 114.6 (Ar CH), 113.7 (CN), 113.1 (Ar CH), 111.0 (CN), 65.4 (CHAr), 55.7 (OCH₃), 52.3 (CO₂CH₃), 49.3 (CCN₂), 49.1 (CHCH=), 21.6 (CH₃Ts). The assignments of the **1H** and **13C** were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl₃): νmax 3055, 2953, 2928, 2305, 1725, 1593, 1495, 1360, 1169, 916.


Separated enantiomers on Diacel Chiralpak AD-H HPLC column (90% Hexane/IPA, 1.0 mL/min), tr (major) = 31.0 min, tr (minor) = 54.0 min.
methyl 4-((2S,4S)-3,3-dicyano-6-methyl-1-tosyl-4-vinyl-1,2,3,4-tetrahydroquinolin-2-y)benzoate

33f (cw4099)
white solid
Pd/Trost ligand: 97% yield, 98% ee (S,S), dr = 37:1

^1H NMR (400 MHz, CDCl₃) δ ppm 8.10 (2 H, d, J=8.4 Hz: Ar CH), 7.74 (1 H, d, J=8.1 Hz: Ar CH), 7.60 (2 H, d, J=8.4 Hz: Ar CH), 7.40 (2 H, d, J=8.3 Hz: Ar CH), 7.35 (1 H, d, J=8.1 Hz: Ar CH), 7.28 (2 H, d, J=8.4 Hz: Ar CH), 7.09 (2 H, d, J=8.4 Hz: Ar CH), 7.04 (1 H, d, J=16.7 Hz: CH=CH(H)trans), 6.92 (1 H, s: Ar CH), 5.86 (1 H, dt, J=16.8, 9.8 Hz: CH₂CH₂), 5.75 (1 H, s: CHAr), 5.58 (1 H, d, J=10.0 Hz: CH=CH(H)cis), 5.04 (1 H, d, J=16.7 Hz: CH=CH(H)trans), 3.91 (3 H, s: CO₂CH₃), 2.44 (4 H, s: overlapping CH₃Ts, CHCH=), 2.39 (3 H, s: CH₃).

^13C NMR (75 MHz, CDCl₃) δ ppm 166.3 (CO₂CH₃), 145.2 (quat. Ar C), 141.5 (quat. Ar C), 138.7 (quat. Ar C), 134.2 (quat. Ar C), 132.0 (quat. Ar C), 131.3 (quat. Ar C), 131.1 (quat. Ar C), 131.0 (Ar CH), 130.5 (Ar CH), 130.1 (Ar CH), 129.9 (Ar CH), 129.2 (CH=CH₂), 128.4 (Ar CH), 127.3 (Ar CH), 127.1 (Ar CH), 125.1 (=CH₂), 113.8 (CN), 111.1 (CN), 65.4 (CHAr), 52.4 (CO₂CH₃), 49.5 (CCN₂), 49.1 (CHCH=), 21.6 (CH₃Ts), 21.4 (CH₃). The assignments of the ^1H and ^13C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl₃): νmax 3053, 2955, 2359, 1722, 1493, 1437, 1366, 1283, 1171, 918


Separated enantiomers on Diacel Chiralpak AD-H HPLC column (90% Hexane/IPA, 1.0 mL/min), tr (major) = 26.5 min, tr (minor) = 38.5 min.
methyl 4-((2S,4S)-3,3-dicyano-1-tosyl-4-vinyl-1,2,3,4-tetrahydroquinolin-2-yl)benzoate

33g (cw4090)
white solid
Pd/Trost ligand: 76% yield, 96% ee (S,S), dr =25:1

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.10 (2 H, d, $J$=8.46 Hz: Ar CH), 7.89 (1 H, d, $J$=7.96 Hz: Ar CH), 7.61 (2 H, d, $J$=8.40 Hz: Ar CH), 7.56 (1 H, t, $J$=7.77 Hz: Ar CH), 7.35 - 7.51 (3 H, m: Ar CH), 7.27 (2 H, d, $J$=7.64 Hz: Ar CH), 7.14 (1 H, d, $J$=7.64 Hz: Ar CH), 5.86 (1 H, dt, $J$=16.75, 9.84 Hz: CH=CH$_2$), 5.77 (1 H, s: CHAr), 5.59 (1 H, d, $J$=10.04 Hz: CH=CH(H)$_{cis}$), 5.07 (1 H, d, $J$=16.74 Hz: CH=CH(H)$_{trans}$), 3.91 (3 H, s: OC$_3$H$_3$), 2.50 (1 H, d, $J$=9.60 Hz: C=CH), 2.43 (3 H, s: CH$_3$Ts).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 166.3 (CO$_2$Me), 145.3 (quat. Ar), 141.3 (quat. Ar), 134.8 (quat. Ar C), 134.1 (quat. Ar C), 131.4 (quat. Ar C), 131.3 (quat. Ar C), 130.5 (Ar CH), 130.4 (Ar CH), 130.1 (Ar CH), 129.1 (CH=CH$_2$), 128.6 (Ar CH), 128.4 (Ar CH), 127.3 (Ar CH), 127.2 (Ar CH), 126.8 (Ar CH), 125.3 (=CH$_2$), 113.7 (CN), 111.0 (CN), 65.4 (CHPh), 52.4 (OC$_3$H$_3$), 49.5 (CCN$_2$), 49.1 (CHCH=), 21.6 (CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3065, 2953, 2928, 2350, 1724, 1367, 1283, 862.

HRMS calcd for C$_{28}$H$_{23}$N$_3$O$_4$SNa [M+Na] 520.1307, found 520.1307.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (96% Hexane/IPA, 1.0 mL/min), tr (major) = 67.0 min, tr (minor) = 123.6 min.
Pd/Trost ligand: 97% yield, 86% ee (S,S), dr = 29:1

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.76 (2 H, dd, $J$=14.0, 8.2 Hz: Ar CH), 7.52 - 7.64 (2 H, m: Ar CH), 7.42 - 7.52 (3 H, m: Ar CH), 7.35 (2 H, d, $J$=7.8 Hz: Ar CH), 7.10 (1 H, dd, $J$=8.8, 2.8 Hz: Ar CH), 6.72 (1 H, s: Ar CH), 6.30 (1 H, s: CH=), 5.90 (1 H, ddd, $J$=17.0, 9.8, 9.6 Hz: CH=CH$_2$), 5.61 (1 H, dd, $J$=10.0, 0.6 Hz: CH=CH(H)$_{cis}$), 4.99 (1 H, d, $J$=16.7 Hz: CH=CH(H)$_{trans}$), 3.89 (3 H, s: OCH$_3$), 2.49 (3 H, s: CH$_3$Ts), 2.30 (1 H, d, $J$=9.5 Hz: CH=).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 159.5 (quat. Ar C), 145.2 (quat. Ar C), 135.3 (quat. Ar C), 134.3 (quat. Ar C), 132.9 (quat. Ar C), 132.3 (Ar CH), 130.5 (Ar CH), 130.3 (Ar CH), 129.8 (Ar CH), 128.9 (CH=CH$_2$), 128.0 (quat. Ar C), 127.9 (quat. Ar C), 127.7 (Ar CH), 127.3 (Ar CH), 127.2 (Ar CH), 125.5 (=CH$_2$), 114.8 (Ar CH), 113.0 (Ar CH), 112.6 (CN), 111.6 (CN), 111.6 (CN), 59.8 (CHAr), 55.7 (OCH$_3$), 49.9 (CH=), 49.2 (CCN$_2$), 21.6 (CH$_3$Ts). (Note: CF$_3$ carbon is not found). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3053, 2986, 2300, 1495, 1421, 1311, 1271, 895.

HRMS calcd for C$_{28}$H$_{22}$F$_3$N$_3$O$_3$SNa [M+Na] 560.1232, found 560.1232.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (96% Hexane/IPA, 1.0 mL/min), tr (major) = 16.4 min, tr (minor) = 26.4 min.
(2S,4S)-6-methyl-1-tosyl-2-(2-(trifluoromethyl)phenyl)-4-vinyl-1,2-
dihydroquinoline-3,3(4H)-dicarbonitrile

33i (cw4098)

white solid
Pd/Trost ligand: 85% yield, 98% ee (S,S), dr >99:1

\[ \text{Me} \]
\[ \text{CN} \]
\[ \text{CN} \]
\[ \text{Ts} \]
\[ \text{F}_3\text{C} \]

\[ \begin{align*}
\text{H NMR} & \quad (400 \text{ MHz}, \text{CDCl}_3) \delta \text{ ppm} \quad 7.75 (1 \text{ H, d, } J=8.1 \text{ Hz: Ar} \text{CH}), \ 7.68 (1 \text{ H, d, } J=8.1 \text{ Hz: Ar} \text{CH}), \ 7.49 - 7.59 (2 \text{ H, m: Ar} \text{CH}), \ 7.41 - 7.47 (3 \text{ H, m: Ar} \text{CH}), \ 7.38 (1 \text{ H, d, } J=8.1 \text{ Hz: Ar} \text{CH}), \ 7.32 (2 \text{ H, d, } J=8.5 \text{ Hz: Ar} \text{CH}), \ 6.99 (1 \text{ H, s: Ar} \text{CH}), \ 6.30 (1 \text{ H, s: CHAr}), \ 5.91 (1 \text{ H, dt, } J=16.8, 9.8 \text{ Hz: } \text{CH} = \text{CH}_2), \ 5.59 (1 \text{ H, d, } J=10.1 \text{ Hz: CH} = \text{CH(H)cis}), \ 5.00 (1 \text{ H, d, } J=16.8 \text{ Hz: CH} = \text{CH(H)trans}), \ 2.47 (3 \text{ H, s: CH}_3 \text{Ts}), \ 2.44 (3 \text{ H, s: CH}_3), \ 2.35 (1 \text{ H, d, } J=9.6 \text{ Hz: CHCH=}).
\end{align*} \]

\[ \text{C NMR} & \quad (75 \text{ MHz}, \text{CDCl}_3) \delta \text{ ppm} \quad 145.1 \text{ (quat. Ar C)}, \ 138.8 \text{ (quat. Ar C)}, \ 135.3 \text{ (quat. Ar C)}, \ 134.5 \text{ (quat. Ar C)}, \ 133.0 \text{ (quat. Ar C)}, \ 132.3 \text{ (Ar CH)}, \ 131.1 \text{ (quat. Ar C)}, \ 131.0 \text{ (Ar CH)}, \ 130.5 \text{ (Ar CH)}, \ 130.2 \text{ (Ar CH)}, \ 129.7 \text{ (Ar CH)}, \ 129.2 \text{ (CH=CH)}, \ 128.8 \text{ (Ar CH)}, \ 128.0 \text{ (Ar CH)}, \ 127.4 \text{ (Ar CH)}, \ 127.2 \text{ (Ar CH)}, \ 125.6 \text{ (quat. Ar C)}, \ 125.2 \text{ (CH}_2), \ 112.6 \text{ (CN)}, \ 111.7 \text{ (CN)}, \ 59.8 \text{ (CHAr)}, \ 49.8 \text{ (CHCH=)}, \ 49.4 \text{ (CCN}_2), \ 21.6 \text{ (CH}_3 \text{Ts}), \ 21.5 \text{ (CH}_3). \text{ (Note: CF}_3\text{ carbon is not found). The assignments of the } ^{1}\text{H and } ^{13}\text{C were based on DEPT, COSY, HMQC etc.}
\]

\[ \text{FTIR (CDCl}_3\text{): } \nu_{\text{max}} \text{ ppm 3053, 2925, 2350, 1493, 1310, 1175, 912.}\]

\[ \text{HRMS calcld for C}_{28}\text{H}_{26}\text{F}_3\text{N}_4\text{O}_2\text{S [M+NH}_4\text{] 539.1729, found 539.1719.}\]

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (98% Hexane/IPA, 1.0 mL/min), tr (major) = 15.3 min, tr (minor) = 20.9 min.
(2S,4S)-1-tosyl-2-(2-(trifluoromethyl)phenyl)-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile

**33j (cw4097)**

white solid

Pd/Trost ligand: 78% yield, 89% ee (S,S), dr =36:1

**1H NMR** (400 MHz, CDCl₃) δ ppm 7.81 (1 H, dd, J=8.1, 1.0 Hz: Ar CH), 7.76 (1 H, d, J=7.1 Hz: Ar CH), 7.51 - 7.68 (3 H, m: Ar CH), 7.43 (4 H, dd, J=10.3, 8.0 Hz: Ar CH), 7.32 (2 H, d, J=8.3 Hz: Ar CH), 7.20 (1 H, d, J=7.7 Hz: Ar CH), 6.31 (1 H, s: CHAr), 5.91 (1 H, dt, J=16.8, 9.8 Hz: CH=), 5.59 (1 H, d, J=10.0 Hz: CH=CHeis), 5.02 (1 H, d, J=16.8 Hz: CH=CHtrans), 2.46 (3 H, s: CH₃Ts), 2.41 (1 H, d, J=9.6 Hz: CHCH=).

**13C NMR** (75 MHz, CDCl₃) δ ppm 145.3 (quat. Ar C), 135.7 (quat. Ar C), 135.2 (quat. Ar C), 134.4 (quat. Ar C), 132.3 (Ar CH), 131.4 (quat. Ar C), 130.5 (Ar CH), 130.4 (Ar CH), 130.2 (Ar CH), 129.8 (Ar CH), 129.0 (=CH), 128.5 (Ar CH), 127.8 (Ar CH), 127.3 (Ar CH), 127.2 (Ar CH), 127.1 (quat. Ar C), 126.9 (Ar CH), 125.4 (=CH₂), 112.5 (CN), 111.6 (CN), 59.8 (CHAr), 49.9 (CHCH=), 49.4 (C(CN)₂), 21.6 (CH₃Ts). (Note: CF₃ carbon is not found). The assignments of the 1H and 13C were based on DEPT, COSY, HMHC etc.

**FTIR** (CDCl₃): νmax 3053, 2926, 2338, 1599, 1485, 1371, 1312, 1175, 1132, 818.

**HRMS** calcd for C₂₇H₂₀F₃N₃O₂SNa [M+Na] 530.1126, found 530.1132.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (96% Hexane/IPA, 1.0 mL/min), tr (major) = 13.7 min, tr (minor) = 16.9 min.
(2S,4S)-6-methoxy-1-tosyl-2-(4-(trifluoromethyl)phenyl)-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile

33k (cw4188)
white solid
Pd/Trost ligand: 93% yield, 84% ee (S,S), dr = 37:1

\[^1\text{H NMR}\] (400 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 7.82 (2 H, d, \(J=8.8\) Hz: Ar CH), 7.72 (3 H, t, \(J=8.0\) Hz: Ar CH), 7.42 (2 H, d, \(J=8.3\) Hz: Ar CH), 7.30 - 7.39 (2 H, m: Ar CH), 7.08 (1 H, dd, \(J=8.8, 2.8\) Hz: Ar CH), 6.67 (1 H, s: Ar CH), 5.86 (1 H, dt, \(J=16.7, 9.8\) Hz: CH=CH\textsubscript{2}), 5.74 (1 H, s: CHAr), 5.61 (1 H, d, \(J=10.0\) Hz: CH=CH(H)\textsubscript{cis}), 5.04 (1 H, d, \(J=16.8\) Hz: CH=CH(H)\textsubscript{trans}), 3.87 (3 H, s: OCH\textsubscript{3}), 2.48 (3 H, s: CH\textsubscript{3}Ts), 2.39 (1 H, d, \(J=9.2\) Hz: CHCH=).

\[^{13}\text{C NMR}\] (75 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 159.4 (quat. Ar C), 145.3 (quat. Ar C), 140.6 (quat. Ar C), 133.9 (quat. Ar C), 133.0 (quat. Ar C), 131.5 (quat. Ar C), 130.1 (Ar CH), 128.9 (CH=CH\textsubscript{2}), 127.6 (Ar CH), 127.4 (Ar CH), 126.9 (quat. Ar C), 126.3 (Ar CH), 126.2 (Ar CH), 125.4 (=CH\textsubscript{2}), 114.6 (Ar CH), 113.6 (CN), 113.2 (Ar CH), 110.9 (CN), 65.3 (CHAr), 55.7 (OCH\textsubscript{3}), 49.2 (CCN\textsubscript{2}), 49.1 (CHCH=), 21.6 (CH\textsubscript{3}Ts).

Note: CF\textsubscript{3} carbon is not found. The assignments of the \(^1\text{H}\) and \(^{13}\text{C}\) were based on DEPT, COSY, HMBC etc.

\[\text{FTIR}\] (CDCl\textsubscript{3}): \(\nu_{\text{max}}\) 3055, 2962, 2928, 2330, 1607, 1495, 1325, 1271, 1171, 914.

\[\text{HRMS}\] calcd for C\textsubscript{28}H\textsubscript{22}F\textsubscript{3}N\textsubscript{3}O\textsubscript{3}SNa [M+Na] 560.1232, found 560.1231.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (90% Hexane/IPA, 1.0 mL/min), \(t_r\) (major) = 10.0 min, \(t_r\) (minor) = 18.9 min.
(2S,4S)-6-methyl-1-tosyl-2-(4-(trifluoromethyl)phenyl)-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile

331 (cw4199)

white solid

Pd/Trost ligand: 88% yield, 86% ee (S,S), dr =56:1

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.75 (1 H, d, $J$=8.1 Hz: Ar CH), 7.60 - 7.73 (4 H, m: Ar CH), 7.40 (2 H, d, $J$=8.3 Hz: Ar CH), 7.36 (1 H, dd, $J$=7.8, 0.9 Hz: Ar CH), 7.29 (2 H, d, $J$=8.0 Hz: Ar CH), 6.93 (1 H, s: Ar CH), 5.87 (1 H, dt, $J$=16.8, 9.8 Hz: CH=CH$_2$), 5.73 (1 H, s: C$_2$H), 5.60 (1 H, d, $J$=10.1 Hz: CH=C=H$_{\text{cis}}$), 5.05 (1 H, d, $J$=16.8 Hz: CH=C=H$_{\text{trans}}$), 2.43 - 2.53 (4 H, m: overlapping CH$_2$Ts, CHCH=), 2.40 (3 H, s: CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 145.3 (quat. Ar C), 140.7 (quat. Ar C), 140.6 (quat. Ar C), 138.8 (quat. Ar C), 134.1 (quat. Ar C), 131.9 (quat. Ar C), 131.1 (Ar C), 129.8 (quat. Ar C), 129.2 (CH=CH$_2$), 128.4 (Ar CH), 127.6 (Ar CH), 127.4 (Ar CH), 127.3 (Ar CH), 126.2 (Ar CH), 125.2 (=CH$_2$), 113.7 (CN), 111.0 (CN), 65.3 (CHAr), 49.4 (CCN$_2$), 49.1 (CHCH=), 21.6 (CH$_3$Ts), 21.4 (CH$_3$).

(Note: CF$_3$ carbon is not found). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3053, 2925, 2305, 1597, 1493, 1325, 1171, 1132.

HRMS calcd for C$_{28}$H$_{22}$N$_3$O$_2$SNa [M+Na] 544.1283, found 544.1286.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (96% Hexane/IPA, 1.0 mL/min), tr (major) = 13.3 min, tr (minor) = 23.3 min.
(2S,4S)-1-tosyl-2-(4-(trifluoromethyl)phenyl)-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile

33m (cw4111)
white solid
Pd/Trost ligand: 90% yield, 91% ee (S,S), dr =45:1

^1H NMR (400 MHz, CDCl₃) δ ppm 7.91 (1 H, dd, J=8.0, 0.9 Hz: Ar CH), 7.70 (4 H, q, J=8.5 Hz: Ar CH), 7.58 (1 H, t, J=7.8 Hz: Ar CH), 7.37 - 7.50 (3 H, m: Ar CH), 7.29 (2 H, d, J=8.0 Hz: Ar CH), 7.17 (1 H, d, J=7.7 Hz: Ar CH), 5.89 (1 H, dt, J=16.8, 9.8 Hz: CH=), 5.76 (1 H, s: CHAr), 5.62 (1 H, d, J=10.0 Hz: CH=CH₂cis), 5.10 (1 H, d, J=16.8 Hz: CH=CH₂trans), 2.52 (1 H, d, J=9.6 Hz: CHCH=), 2.45 (3 H, s: CH₃Ts).

^13C NMR (75 MHz, CDCl₃) δ ppm 145.4 (quat. Ar C), 140.5 (quat. Ar C), 134.7 (quat. Ar C), 134.0 (quat. Ar C), 131.3 (quat. Ar C), 130.4 (Ar CH), 130.1 (Ar CH), 129.0 (=CH), 128.5 (Ar CH), 128.5 (Ar CH), 127.7 (Ar CH), 127.3 (Ar CH), 126.8 (overlapping Ar CH, quat. Ar C), 126.3 (Ar CH), 125.3(=CH₂), 113.5 (CN), 110.9 (CN), 65.3 (CHAr), 49.4 (C(CN)₂), 49.2 (CHCH=), 21.6 (CH₃Ts). (Note: CF₃ carbon is not found). The assignments of the ^1H and ^13C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl₃): νmax 3053, 2927, 2337, 1367, 1327, 1170, 1132, 852.

HRMS calcd for C_{27}H_{24}F_{3}N_{4}O_{2}S [M+NH₄] 525.1572, found 525.1586.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (98% Hexane/IPA, 1.0 mL/min), tr (major) = 19.6 min, tr (minor) = 24.2 min.
4-((2S,4S)-3,3-dicyano-6-methoxy-1-tosyl-4-vinyl-1,2,3,4-tetrahydroquinolin-2-y)phenyl acetate

33n (cw4185)

white solid

Pd/Trost ligand: 90% yield, 80% ee (S,S), dr = 50:1

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.75 (1 H, d, $J$=8.8 Hz: Ar CH), 7.53 (2 H, d, $J$=8.5 Hz: Ar CH), 7.40 (2 H, d, $J$=8.0 Hz: Ar CH), 7.30 (2 H, d, $J$=8.0 Hz: Ar CH), 7.18 (2 H, d, $J$=8.5 Hz: Ar CH), 7.04 (1 H, dd, $J$=8.7, 2.7 Hz: Ar CH), 6.65 (1 H, br. s.: Ar CH), 5.85 (1 H, dt, $J$=16.8, 9.7 Hz: CH=CH$_2$), 5.71 (1 H, s: CHAr), 2.39 (1 H, d, $J$=9.5 Hz: CHCH=), 2.30 (3 H, s: OCOCH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 168.9 (OOC), 159.3 (quat. Ar C), 151.5 (quat. Ar C), 145.1 (quat. Ar C), 134.2 (quat. Ar C), 134.1 (quat. Ar C), 133.3 (quat. Ar C), 130.2 (Ar CH), 130.0 (Ar CH), 129.1 (CH=CH$_2$), 128.2 (Ar CH), 127.4 (Ar CH), 127.1 (quat. Ar C), 125.2 (=CH$_2$), 122.3 (Ar CH), 114.5 (Ar CH), 113.9 (CN), 113.1 (Ar CH), 111.1 (CN), 65.3 (CHAr), 55.7 (OCH$_3$), 49.6 (CCN$_2$), 49.1 (CH($CH_3$)), 21.6 (CH$_3$Ts), 21.2 (OCOCH$_3$). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMOC etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3053, 2928, 2303, 1767, 1607, 1495, 1367, 1263, 1169, 912.

HRMS calcd for C$_{29}$H$_{29}$N$_4$O$_5$S [M+NH$_4$] 545.1859, found 545.1860.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (90% Hexane/IPA, 1.0 mL/min), tr (major) = 18.8 min, tr (minor) = 35.6 min.
4-((2S,4S)-3,3-dicyano-6-methyl-1-tosyl-4-vinyl-1,2,3,4-tetrahydroquinolin-2-yl)phenyl acetate

Pd/Trost ligand: 73% yield, 90% ee (S,S), dr = 70:1

**1H NMR** (400 MHz, CDCl₃) δ ppm 7.68 (1 H, d, J=8.1 Hz: Ar CH), 7.50 (2 H, d, J=8.7 Hz: Ar CH), 7.38 (2 H, d, J=8.3 Hz: Ar CH), 7.32 (1 H, d, J=8.1 Hz: Ar CH), 7.26 (2 H, d, J=8.5 Hz: Ar CH), 7.15 (2 H, d, J=8.6 Hz: Ar CH), 6.91 (1 H, s: Ar CH), 5.86 (1 H, dt, J=16.8, 9.9 Hz: C=CH₂), 5.71 (1 H, s: C=CH₂), 5.56 (1 H, d, J=10.0 Hz: CH=CH(H)trans), 5.04 (1 H, d, J=16.8 Hz: CH=CH(H)cis), 2.48 (1 H, d, J=9.7 Hz: CHCH=), 2.43 (3 H, s: CH₃Ts), 2.38 (3 H, s: CH₃), 2.28 (3 H, s: OCOCH₃).

**13C NMR** (75 MHz, CDCl₃) δ ppm 168.9 (OCOCH₃), 151.5 (quat. Ar C), 145.1 (quat. Ar C), 138.6 (quat. Ar C), 134.4 (quat. Ar C), 134.1 (quat. Ar C), 132.2 (quat. Ar C), 131.3 (quat. Ar C), 130.9 (Ar CH), 130.0 (Ar CH), 129.4 (CH=CH₂), 128.4 (Ar CH), 128.3 (Ar CH), 127.4 (Ar CH), 124.9 (=CH₂), 123.0 (Ar CH), 122.3 (Ar CH), 113.9 (CN), 111.2 (CN), 65.2 (CHAr), 49.8 (CCN₂), 49.1 (CHCH=), 21.6 (CH₃Ts), 21.4 (CH₃), 21.2 (OCOCH₃). The assignments of the 1H and 13C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl₃): νmax 3053, 2986, 2305, 1769, 1597, 1506, 1493, 1369, 1203, 1171, 914.

**HRMS** calcd for C₂₉H₂₅N₃O₄SNa [M+Na] 534.1463, found 534.1458.

Separated enantiomers on Diacet Chiralpak AD-H HPLC column (96% Hexane/IPA, 1.0 mL/min), tr (major) = 28.5 min, tr (minor) = 51.4 min.
4-((2S,4S)-3,3-dicyano-1-tosyl-4-vinyl-1,2,3,4-tetrahydroquinolin-2-yl)phenyl acetate

**33p** (cw3268)
white solid
Pd/Trost ligand: 52% yield, 91% ee (S,S), dr =92:1

**1H NMR** (400 MHz, CDCl$_3$) δ ppm 7.52 (1 H, d, J=7.8 Hz: Ar CH), 7.52 (2 H, d, J=8.6 Hz: Ar CH), 7.38 - 7.41 (3 H, m: Ar CH), 7.28 (2 H, d, J=6.1 Hz: Ar CH), 7.18 (2 H, d, J=8.8 Hz: Ar CH), 7.15 (1 H, d, J=7.8 Hz: Ar CH), 5.87 (1 H, dt, J=16.8, 9.8 Hz: CH=CH$_2$), 5.74 (1 H, s: CHAr), 5.58 (1 H, d, J=10.0 Hz: CH=CH(H)$_{cis}$), 5.07 (1 H, d, J=16.7 Hz: CH=CH(H)$_{trans}$), 2.55 (1 H, d, J=9.6 Hz: CHCH=), 2.42 (3 H, s: CH$_3$Ts), 2.28 (3 H, s: CH$_3$).

**13C NMR** (75 MHz, CDCl$_3$) δ ppm 168.8 (OCMe), 151.5 (quat. Ar C), 145.2 (quat. Ar C, s), 134.9 (quat. Ar C), 134.4 (quat. Ar C), 134.0 (quat. Ar C), 131.6 (quat. Ar C), 130.2 (Ar CH), 130.0 (Ar CH), 129.2 (CH=CH$_2$), 128.6 (Ar CH), 128.5 (Ar CH), 128.3 (Ar CH), 127.3 (Ar CH), 126.8 (Ar CH), 125.1 (CH$_2$), 122.3 (Ar CH), 113.8 (CN), 111.1 (CN), 65.3 (CHPh), 49.9 (CCN$_2$), 49.1 (CHCH=), 21.6 (CH$_3$Ts), 21.2 (CH$_3$). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl$_3$): $\nu_{\text{max}}$ 3053, 2350, 1769, 1597, 1369, 1204, 1171, 914.

**HRMS** calcd for C$_{28}$H$_{27}$N$_4$O$_4$S [M+NH$_4$] 515.1753, found 515.1752.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (96% Hexane/IPA, 1.0 mL/min), tr (major) = 35.4 min, tr (minor) = 76.4 min.
4-((S,S)-3,3-dicyano-6-fluoro-1-tosyl-4-vinyl-1,2,3,4-tetrahydroquinolinol-2-yl)phenyl acetate

33q (cw4003)
white solid
Pd/Trost ligand: 60% yield, 87% ee (S,S), dr >99:1

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.74 (1 H, dd, $J$=8.8, 4.8 Hz: Ar CH), 7.42 (2 H, d, $J$=8.8 Hz: Ar CH), 7.32 (2 H, d, $J$=8.1 Hz: Ar CH), 7.22 (2 H, d, $J$=8.3 Hz: Ar CH), 7.14 (3 H, m: Ar CH), 6.80 (1 H, dd, $J$=8.3, 2.8 Hz: Ar CH), 5.82 (1 H, dt, $J$=16.8, 9.8 Hz: CH=CH$_2$), 5.73 (1 H, s: CHAr), 5.61 (1 H, d, $J$=10.1 Hz: CH=CH(H)$_{\text{cis}}$), 5.08 (1 H, d, $J$=16.8 Hz: CH=CH(H)$_{\text{trans}}$), 2.50 (1 H, d, $J$=9.5 Hz: CHCH=), 2.44 (3 H, s: CH$_3$Ts), 2.29 (3 H, s: OCOCH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 168.9 (OCOCH$_3$), 165.7 (quat. Ar C), 155.3 (quat. Ar C), 151.6 (quat. Ar C), 145.5 (quat. Ar C), 134.1 (quat. Ar C), 133.7 (quat. Ar C), 132.4 (Ar CH), 130.8 (quat. Ar C), 130.2 (Ar CH), 128.5 (CH=CH$_2$), 128.2 (Ar CH), 127.4 (Ar CH), 125.8 (=CH$_2$), 122.4 (Ar CH), 117.1 (Ar CH), 114.2 (Ar CH), 113.5 (CN), 110.9 (CN), 65.3 (CHAr), 49.6 (CCN$_2$), 48.9 (CHCH=), 21.6 (CH$_3$Ts), 21.2 (OCOCH$_3$). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{\text{max}}$ 3062, 2926, 2359, 1713 1487, 1352, 1167, 874.

HRMS calcd for C$_{28}$H$_{22}$FN$_3$O$_4$S [M+] 515.1315, found 515.1340.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (96% Hexane/IPA, 1.0 mL/min), tr (major) = 46.3 min, tr (minor) = 99.7 min.
(2S,4S)-6-methoxy-2-phenyl-1-tosyl-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile

33r (cw4184)
white solid
Pd/Trost ligand: 92% yield, 86% ee (S,S), dr = 54:1

1H NMR (400 MHz, CDCl₃) δ ppm 7.79 (1 H, d, J=8.8 Hz: Ar CH), 7.54 (2 H, d, J=7.1 Hz: Ar CH), 7.42 (5 H, d, J=5.3 Hz: Ar CH), 7.30 (1 H, d, J=8.2 Hz: Ar CH), 7.05 (1 H, dd, J=8.8, 2.8 Hz: Ar CH), 6.65 (1 H, d, J=2.7 Hz: Ar CH), 5.85 (1 H, dt, J=16.9, 9.8 Hz: CH=CH₂), 5.73 (1 H, s: CHAr), 5.57 (1 H, d, J=10.1 Hz: CH=CH(H)ₜ₉), 5.01 (1 H, d, J=16.8 Hz: CH=CH(H)ₜ₉), 3.84 (3 H, s: OCH₃), 2.46 (3 H, s: CH₂Ts), 2.38 (1 H, dd, J=9.5 Hz: CHCH=).

13C NMR (75 MHz, CDCl₃) δ ppm 159.3 (quat. Ar C), 145.0 (quat. Ar C), 136.8 (quat. Ar C), 134.3 (quat. Ar C), 133.3 (quat. Ar C), 130.2 (Ar CH), 130.0 (Ar CH), 129.6 (Ar CH), 129.2 (overlapping CH=CH₂, Ar CH), 127.4 (Ar CH), 127.3 (quat. Ar C), 127.0 (Ar CH), 125.1 (=CH₂), 114.5 (Ar CH), 114.0 (CN), 113.0 (Ar CH), 111.2 (CN), 65.7 (CHAr), 55.7 (OCH₃), 49.7 (CCN₂), 49.1 (CHCH=), 21.6 (CH₃Ts). The assignments of the 1H and 13C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl₃): νmax 3053, 2927, 2320, 1599, 1495, 1364, 1271, 1169, 914.

HRMS caled for C₂₇H₂₃N₃O₃SNa [M+Na] 492.1358, found 492.1357.

Separated enantiomers on Diacet Chiralpak AD-H HPLC column (90% Hexane/IPA, 1.0 mL/min), tr (major) = 13.6 min, tr (minor) = 32.3 min.
(2S,4S)-6-methyl-2-phenyl-1-tosyl-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile

33s (cw3265)

white solid

Pd/Trost ligand: 77% yield, 92% ee (S,S), dr >99:1

**1H NMR** (400 MHz, CDCl₃) δ ppm 7.75 (1 H, d, J=8.1 Hz: Ar CH), 7.53 (2 H, dd, J=7.7, 1.6 Hz: Ar CH), 7.39 - 7.48 (4 H, m: Ar CH), 7.35 (1 H, d, J=8.0 Hz: Ar CH), 7.28 (2 H, d, J=8.0 Hz: Ar CH), 6.94 (1 H, s: Ar CH), 5.89 (1 H, dt, J=16.8, 9.9 Hz: CH=CH₂), 5.75 (1 H, s: CHPh), 5.58 (1 H, dd, J=10.1, 0.9 Hz: CH=CH(H)ₜᵣᵢₙs), 5.05 (1 H, d, J=16.8 Hz: CH=CH(H)ₜᵣᵢₙs), 2.48 (1 H, d, J=9.7 Hz: CHCH=), 2.45 (3 H, s: CH₃Ts), 2.40 (3 H, s: CH₃).

**13C NMR** (75 MHz, CDCl₃) δ ppm 145.0 (quat. Ar C), 138.5 (quat. Ar C), 136.8 (quat. Ar C), 134.6 (quat. Ar C), 132.4 (quat. Ar C), 131.3 (quat. Ar C), 130.9 (Ar CH), 130.0 (Ar CH), 129.6 (Ar CH), 129.4 (CH=CH₂), 129.2 (Ar CH), 128.5 (Ar CH), 127.3 (Ar CH), 127.3 (Ar CH), 127.0 (Ar CH), 124.8 (=CH₂), 114.0 (CN), 111.3 (CN), 65.7 (CHAr), 50.0 (CN₂), 49.1 (CHCH=), 21.6 (CH₃Ts), 21.4 (CH₃).

The assignments of the ¹H and ¹³C were based on DEPT, COSY, HMQC etc.

**FTIR** (CDCl₃): νmax 3053, 2920, 2302, 1597, 1493, 1366, 1171.

**HRMS** caled for C₂₇H₂₃N₃O₂SNa [M+Na] 476.1409, found 476.1408.

Separated enantiomers on Diacet Chiralpak AD-H HPLC column (96% Hexane/IPA, 1.0 mL/min), tr (major) = 19.6 min, tr (minor) = 30.3 min.
(2S,4S)-6-fluoro-2-phenyl-1-tosyl-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile

33t (cw3299)

white solid

Pd/Trost ligand: 75% yield, 87% ee (S,S), dr = 87:1

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.78 (1 H, dd, $J$=8.8, 4.9 Hz: Ar CH), 7.42 (2 H, dd, $J$=7.8, 1.8 Hz: Ar CH), 7.37 (5 H, m: Ar CH), 7.23 (2 H, d, $J$=8.1 Hz: Ar CH), 7.15 - 7.20 (1 H, m: Ar CH), 6.87 (1 H, dd, $J$=8.4, 2.8 Hz: Ar CH), 5.83 (1 H, dt, $J$=16.8, 9.8 Hz: CH=CH$_2$), 5.74 (1 H, s: CHPh), 5.61 (1 H, d, $J$=10.1 Hz: CH=CH(H)$_{cis}$), 5.06 (1 H, d, $J$=16.8 Hz: CH=CH(H)$_{trans}$), 2.40 - 2.60 (4 H, m: overlapping CH$_3$Ts, CHCH=).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 160.5 (quat. Ar C), 145.3 (quat. Ar C), 136.4 (quat. Ar C), 134.3 (quat. Ar C), 131.0 (quat. Ar C), 131.0 (quat. Ar C), 130.1 (Ar CH), 129.7 (Ar CH), 129.2 (Ar CH), 128.6 (CH=), 127.8 (Ar CH), 127.3 (Ar CH), 126.9 (Ar CH), 125.7 (CH$_2$), 117.1 (Ar CH), 114.4 (Ar CH), 113.7 (CN), 111.0 (CN), 65.8 (CHAr), 49.7 (CCN$_2$), 49.0 (CHCH=), 21.6 (CH$_3$Ts). The assignments of the $^1$H and $^{13}$C were based on DEPT, COSY, HMQC etc.

FTIR (CDCl$_3$): $\nu_{max}$ 3053, 2986, 2305, 1489, 1367, 1271, 914.

HRMS calcd for C$_{26}$H$_{24}$FN$_4$O$_2$S [M+NH$_4$] 475.1604, found 475.1600.

Separated enantiomers on Diacel Chiralpak AD-H HPLC column (90% Hexane/IPA, 1.0 mL/min), tr (major) = 14.0 min, tr (minor) = 29.5 min.
2,2-dimethyl-2'-phenyl-1'-tosyl-4'-vinyl-2',4'-dihydro-1'H-spiro[1,3]dioxane-5,3'-quinoline]-4,6-dione

\[
\text{37b (cW3267)}
\]

\[\text{Pd(PPh}_3\text{)}_4; \text{63\% combined yield}\]

\[\begin{align*}
\text{37b:} & \text{37c=1.5:1} \\
\text{37b:} & \text{37c=4:1(NMR reaction)}
\end{align*}\]

\[\begin{align*}
\text{(Z)-2',2'-dimethyl-2-phenyl-1-tosyl-2,4-dihydro-1H-spiro[benzo[b]azocine-3,5'-[1,3]dioxane]-4',6'-dione} \\
\text{2,2-dimethyl-2'-phenyl-1'-tosyl-4'-vinyl-2',4'-dihydro-1'H-spiro[1,3]dioxane-5,3'-quinoline]-4,6-dione}
\end{align*}\]

\[\text{37b (cW3267)}\]

\[\text{Pd(PPh}_3\text{)}_4; \text{63\% combined yield}\]

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{) compound 37b:} & \text{δ ppm 7.00-7.48 (overlapping Ar CH),} \\
& \text{6.53 (s, 1H: CHPh), 6.21 (d, 1H, J=15.7 Hz: =CH2), 5.72 (dt, 1H, J=15.6, 7.8 Hz:} \\
& \text{=CHCH}_2\text{), 2.65 (d, 2H, J=7.6 Hz: CH}_2\text{), 2.26 (s, 3H: CH}_3\text{Ts), 1.65 (s, 3H: CH}_3, \text{1.43} \\
& \text{(s, 3H: CH}_3\text{).}
\end{align*}\]

\[\text{Compound 37c:} \text{7.00-7.48 (overlapping Ar CH), 6.06 (s, 1H: CHPh), 5.44 (m, 1H:} \\
\text{CH=CH}_2\text{), 4.69 (d, 1H, J=15.9 Hz: CH=CH(H)}_\text{trans}.\]

\[\begin{align*}
\text{37e:} & \text{37f= 6.3:1} \\
\text{37e (cW3276)} \\
\text{Pd(PPh}_3\text{)}_4; \text{85\% NMR yield}\]

\[\begin{align*}
\text{(Z)-2',2',8-trimethyl-2-phenyl-1-tosyl-2,4-dihydro-1H-spiro[benzo[b]azocine-3,5'-[1,3]dioxane]-4',6'-dione} \\
\text{2,2,6'-trimethyl-2'-phenyl-1'-tosyl-4'-vinyl-2',4'-dihydro-1'H-spiro[1,3]dioxane-5,3'-quinoline]-4,6-dione}
\end{align*}\]

\[\text{37e (cW3276)}\]

\[\text{Pd(PPh}_3\text{)}_4; \text{85\% NMR yield}\]

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{) compound 37e:} & \text{δ ppm 7.03-7.57 (overlapping Ar CH),} \\
& \text{6.56 (s, 1H: CHPh), 6.33 (d, 1H, J=15.6 Hz: =CH2), 5.85 (dt, 1H, J=15.6, 7.8 Hz:} \\
& \text{=CHCH}_2\text{), 2.77 (dd, 2H, J=7.6, 1.1 Hz: CH}_2\text{), 2.40 (s, 3H: CH}_3\text{Ts), 2.28 (s, 3H: CH}_3, \text{1.80} \\
& \text{(s, 3H: CH}_3, \text{1.58 (s, 3H: CH}_3\text{).}
\end{align*}\]

\[\text{Compound 37f:} \text{7.03-7.57 (overlapping Ar CH), 6.19 (s, 1H: CHPh), 5.59 (dt, 1H,} \\
\text{J=16.9, 10.1 Hz: CH=CH}_2\text{), 4.81 (d, 1H, J=17.7 Hz: CH=CH(H)}_\text{trans}.\]

\[\text{242}\]
(Z)-8-fluoro-2',2'-dimethyl-2-phenyl-1-tosyl-2,4-dihydro-1H-spiro[benzo[b]azocine-3,5'-[1,3]dioxane]-4',6'-dione
6'-fluoro-2,2-dimethyl-2-phenyl-1'-tosyl-4'-vinyl-2',4'-dihydro-1'H-spiro[1,3]dioxane-5,3'-quinoline-4,6-dione

$^{3}$H NMR $^{(400 \text{ MHz, CDCl}_{3})}$ compound $^{37h}$: $\delta$ ppm 7.06-7.49 (overlapping Ar CH), 6.72 (s, 1H: CHPh), 6.34 (d, 1H, $J$=15.6 Hz: =CH), 5.88 (t, 1H, $J$=15.7, 7.5 Hz: =CHCH$_2$), 2.76 (d, 2H, $J$=7.8 Hz: CH$_2$), 2.42 (s, 3H: CH$_3$Ts), 1.80 (s, 3H: CH$_3$), 1.60 (s, 3H: CH$_3$).

Compound $^{37i}$: $\delta$ ppm 7.06-7.49 (overlapping Ar CH), 6.19 (s, 1H: CHPh), 5.53 (dt, 1H, $J$=16.8, 10.1 Hz: CH=CH$_2$), 5.38 (d, 1H, $J$=10.0 Hz: CH=CH(H)$_{cis}$), 4.84 (d, 1H, $J$=16.8 Hz: CH=CH(H)$_{trans}$), 2.66 (s, 3H: CH$_3$), 2.43 (s, 3H: CH$_3$Ts), 1.51 (s, 3H: CH$_3$).

$^{1}$H NMR $^{(400 \text{ MHz, CDCl}_{3})}$ compound $^{38b}$: $\delta$ ppm 7.04-7.34 (overlapping Ar CH), 6.34 (s, 1H: CHNTs), 5.23 (m, 1H: CH=CH$_2$), 5.16 (d, 1H, $J$=9.8 Hz: CH=CH(H)$_{cis}$), 5.05 (d, 1H, $J$=16.4 Hz: CH=CH(H)$_{trans}$), 3.47 (d, 1H, $J$=8.8 Hz: CHCH=), 2.43 (s, 3H: CH$_3$Ts).

Compound $^{38c}$: $\delta$ ppm 7.04-7.34 (overlapping Ar CH), 6.04 (d, 1H, $J$=9.4 Hz: CH=), 5.61 (dt, 1H, $J$=9.5, 4.2 Hz: =CHCH$_2$), 5.38 (d, 1H, $J$=10.0 Hz: CH=CH(H)$_{cis}$), 4.84 (d, 1H, $J$=16.8 Hz: CH=CH(H)$_{trans}$), 4.43 (dd, 2H, $J$=4.1, 1.7 Hz: CH$_2$NTs), 2.35 (s, 3H: CH$_3$Ts).
9-methyl-6-oxo-12-tosyl-7-vinyl-6a,7,12,12a-tetrahydro-6H-chromeno[4,3-b]quinoline-6a-carbonitrile
6-methyl-1-tosyl-1,2-dihydroquinoline

38d (cw3275)
Pd(PPh₃)₄: 80% NMR yield

^1H NMR (400 MHz, CDCl₃) compound 38d: δ ppm 6.98-7.34 (overlapping Ar CH), 6.28 (s, 1H: CHNTs), 5.28 (dd, 1H, J=16.4, 9.5 Hz: CH=CH₂), 5.17 (d, 1H, J=9.9 Hz: CH=CH(H)cis), 5.03 (d, 1H, J=15.9 Hz: CH=CH(H)trans), 3.36 (d, 1H, J=9.2 Hz: CHCH=), 2.43 (s, 3H: CH₃Ts), 2.24 (s, 3H: CH₃).

Compound 38e: δ ppm 6.98-7.34 (overlapping Ar CH), 5.99 (1H, d, J=9.3 Hz: =CH), 5.57 (1H, dt, J=9.6, 4.17 Hz: =CHCH₂), 4.39 (2H, dd, J=4.0, 1.6 Hz: CH₂), 2.35 (3H, s: overlapping CH₃Ts, CH₃), 2.31 (3H, s: overlapping CH₃Ts, CH₃).

2-phenyl-3-(phenylsulfonyl)-1-tosyl-4-vinyl-1,2,3,4-tetrahydroquinoline-3-carbonitrile

39e (cw4046)
white solid
Pd(PPh₃)₄: 80% NMR yield, dr >19:1

^1H NMR (400 MHz, CDCl₃) δ ppm 6.06-7.76 (overlapping Ar CH), 6.07 (s, 1H: CHPh), 5.92 (1H, ddd, J=17.0, 10.0, 9.7 Hz: CH=CH₂), 5.38 (d, 1H, J=10.2 Hz: CH=CH(H)cis), 4.86(1H, d, J=17.2 Hz: CH=CH(H)trans), 3.18 (1H, d, J=9.3 Hz: CHCH=), 2.43 (3H, s: CH₃Ts).
6-methyl-2-phenyl-3-(phenylsulfonyl)-1-tosyl-4-vinyl-1,2,3,4-tetrahydroquinoline-3-carbonitrile

39d (cw4047)
white solid
Pd(PPh₃)₄: 75% yield, dr >19:1

1H NMR (400 MHz, CDCl₃) δ ppm 7.99 (2H, d, J=8.5 Hz: Ar CH), 7.74 (1H, t, J=7.5 Hz: Ar CH), 7.55 (4H, m: Ar CH), 7.46 (1H, d, J=8.0 Hz: Ar CH), 7.23 (3H, m: Ar CH), 7.15 (1H, t, J=7.4 Hz: Ar CH), 6.99 (3H, d, J=7.7 Hz: Ar CH), 6.50 (2H, d, J=8.1 Hz: Ar CH), 5.98 (3H, m: overlapping CH=CH₂, CHPh), 5.38 (dd, 1H, J=10.1, 1.4 Hz: CH=CH(H)₃C₆H), 4.79 (1H, d, J=16.8 Hz: CH=CH(H)₃C₆H₃), 3.12 (1H, d, J=9.3 Hz: CHCH=), 2.42 (3H, s: overlapping CH₃, CH₃Ts), 2.39 (3H, s: overlapping CH₃, CH₃Ts). The assignments of the 1H was based on COSY.

2-phenyl-4-(prop-1-en-2-yl)-1-tosyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile

40b (cw3270)
Pd(PPh₃)₄: 55% NMR yield

1H NMR (400 MHz, CDCl₃) δ ppm 7.12-7.49 (overlapping Ar CH), 5.62 (1H, s: Ar CH), 5.36 (1H, s: =CH₂), 5.34 (1H, s: =CH₂), 2.43 (3H, s: CH₃Ts), 1.74 (3H, s: CH₃).

4-(3,3-dicyano-4-(prop-1-en-2-yl)-1-tosyl-1,2,3,4-tetrahydroquinolin-2-yl)phenyl acetate

40c (cw3255)
Pd(PPh₃)₄: 67% NMR yield
$^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.12-7.42 (overlapping Ar CH), 5.62 (1H, s: Ar CH), 5.36 (1H, s: =CH$_2$), 5.34 (1H, s: =CH$_2$), 2.35 (6H: overlapping CH$_3$Ts and CH$_3$OAc), 1.66 (3H, s: CH$_3$).

![Chemical structure](image)

1-(4-nitrophenylsulfonyl)-2-phenyl-4-vinyl-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile

41b (cw4055)
Pd(PPh$_3$)$_4$: 92% NMR yield

$^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ ppm 6.97-8.26 (overlapping Ar CH), 5.95 (1H, ddd, $J$=16.6, 10.0, 9.8 Hz: CH=CH$_2$), 5.86 (1H, s: CHPh), 5.69 (1H, d, $J$=10.2 Hz: CH=C=H)$_{cis}$, 5.33 (1H, d, $J$=16.80 Hz: CH=C=H)$_{trans}$, 3.02 (1H, d, $J$=9.5 Hz: CH=H$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 143.34 (quat. C), 138.00 (quat. Ar C), 129.5 (Ar CH), 129.5 (Ar CH), 128.5 (Ar CH), 127.4 (quat. Ar C), 126.8 (Ar CH), 124.0 (Ar CH), 121.3 (Ar CH), 63.0 (CH$_2$), 44.5 (CH$_3$), 21.6 (CH$_3$Ts).

$^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.68 (2H, m d, $J$=8.3 Hz: Ar CH (Ts)), 7.54 (1H, d, $J$=7.5 Hz: Ar CH), 7.20 - 7.33 (3H, m: overlapping Ar CH), 6.98 (2H, dddd, $J$=14.3, 7.5, 6.7, 0.7 Hz: Ar CH), 3.12 (2H, s: CH$_2$), 2.39 (3H, s: CH$_3$Ts), 2.19 (6H, s: CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 143.34 (quat. Ar C), 138.00 (quat. Ar C), 129.5 (Ar CH), 129.5 (Ar CH), 128.5 (Ar CH), 127.4 (quat. Ar C), 126.8 (Ar CH), 124.0 (Ar CH), 121.3 (Ar CH), 63.0 (CH$_2$), 44.5 (CH$_3$), 21.6 (CH$_3$Ts).
$\text{4-methyl-}\text{N-}(2-(1-\text{pyrrolidin-1-yl})\text{allyl})\text{phenyl} \text{benzenesulfonamide}$

43b (cw3204)

White solid

Pd(PPh$_3$)$_4$: 97% yield

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 11.89 (1H, br. s.: NH$_2$Ts), 7.85 (2H, d, $J$=8.1 Hz: arom H), 7.58 (1H, d, $J$=8.1 Hz: arom H), 7.32 (2H, d, $J$=8.0 Hz: arom H), 7.23 (1H, t, $J$=7.7 Hz: arom H), 7.04 (1H, m: arom H), 6.99 (1H, d, $J$=7.3 Hz: arom H), 5.88 (1H, dt, $J$=16.9, 9.5 Hz: CHCH=CH$_2$), 5.14 (1H, d, $J$=16.9 Hz: CH=CH(H)$_{\text{trans}}$), 5.02 (1H, d, $J$=10.0 Hz: CH=CH(H)$_{\text{cis}}$), 3.75 (1H, d, $J$=8.9 Hz: CHCH=CH$_2$), 2.61 (2H, m: NCH$_2$), 2.49 (2H, m: NCH$_2$), 2.45 (3H, s: CH$_3$Ts), 1.91 (4H, m: CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 143.4 (quat. Ar C), 137.8 (quat. Ar C), 137.1 (quat. Ar C), 136.5 (CH=CH$_2$), 129.5 (Ar CH), 128.8 (Ar CH), 128.7 (quat. Ar C), 128.2 (Ar CH), 127.0 (Ar CH), 123.1 (Ar CH), 118.1 (Ar CH), 117.2 (=CH$_2$), 74.3 (CHCH=CH$_2$), 51.8 (CH$_2$N), 23.6 (CH$_2$), 21.5 (CH$_3$Ts).

$\text{4-methyl-}\text{N-}(2-(1-\text{piperidin-1-yl})\text{allyl})\text{phenyl} \text{benzenesulfonamide}$

43b (cw3167)

Colorless oil

Pd(PPh$_3$)$_4$: 36% yield, 99% NMR yield

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 12.11 (1H, br. s.: NH$_2$Ts), 7.72 (2H, d, $J$=8.3 Hz: arom H), 7.42 (1H, dd, $J$=8.1, 1.2 Hz: arom H), 7.21 (2H, d, $J$=8.0 Hz: arom H), 7.13 (1H, td, $J$=7.5, 2.0 Hz: arom H), 6.92 (2H, m: arom H), 5.71 (1H, dt, $J$=16.9, 9.9 Hz: CHCH=CH$_2$), 5.05 (1H, dd, $J$=10.1, 1.6 Hz: CH=CH(H)$_{\text{cis}}$), 5.00 (1H, dd, $J$=16.9, 1.5 Hz: CH=CH(H)$_{\text{trans}}$), 3.57 (1H, d, $J$=9.7 Hz: CHCH=CH$_2$), 2.40 (3H, s: CH$_2$), 2.35 (3H, s: CH$_3$Ts), 1.62 (5H, br. s.: CH$_2$), 1.45 (2H, br. s.: CH$_2$).
1H NMR (400 MHz, CDCl₃) δ ppm 7.46 (2H, d, J=8.3 Hz: arom H), 7.38 (1H, d, J=8.2 Hz: arom H), 7.18 (8H, m: arom H), 6.85 (2H, m: arom H), 5.64 (1H, ddd, J=17.2, 10.1, 7.4 Hz: CH=CH₂), 4.90 (2H, m: =CH₂), 4.00 (1H, d, J=7.6 Hz: CHCH=CH₂), 3.69 (2H, s: NH), 3.52 (2H, m: CH₂), 2.21 (3H, s: CH₃Ts).

1,3-ditosyl-4-vinyl-3,4-dihydroquinazolin-2(1H)-one

5c (cw3227)
Colorless oil
Pd(PPh₃)₄: 95% NMR yield
White solid
Pd(PPh₃)₄: 55% yield
Pd/Trost ligand: 24% ee

1H NMR (400 MHz, CDCl₃) δ ppm 8.07 (2H, d, J=8.4 Hz: Ar CH), 7.94 (2H, d, J=8.4 Hz: Ar CH), 7.28 (8H, m: Ar CH), 5.95 (1H, d, J=5.6 Hz: CHCH=), 5.83 (1H, td, J=11.0, 5.1 Hz: CH=CH₂), 5.18 (1H, dd, J=10.3, 1.4 Hz: CH=CH(H)cis), 5.08 (1H, dd, J=16.9, 1.5 Hz: CH=CH(H)trans), 2.46 (6H, s: CH₃Ts).
X-ray Crystallography Data for 16a

16a was synthesized by the standard decarboxylative olefin insertion reaction from vinyl oxazinonone. The colorless crystal was formed in a solvent mixture of dichloromethane and hexane.

Crystal Structure Data:
**Comments**  The asymmetric unit contains one crystallographically-independent \( \text{C}_{22}\text{H}_{20}\text{N}_{2}\text{O}_{4}\text{S} \) molecule. All thermal vibration ellipsoids are drawn at the 50% probability level.

**Brief Experimental Description to be Included as Text or as a Footnote at Time of Publication**

Colorless crystals of \( \text{C}_{22}\text{H}_{20}\text{N}_{2}\text{O}_{4}\text{S} \) are, at 100(2) K, triclinic, space group \( \overline{1}(\text{C}_{i}-\text{No. 2}) \) with \( a = 7.7457(6) \) Å, \( b = 8.3807(6) \) Å, \( c = 15.163(1) \) Å, \( \alpha = 85.166(2)^\circ \), \( \beta = 89.549(2)^\circ \), \( \gamma = 74.976(1)^\circ \), \( V = 947.2(1) \) Å\(^3\) and \( Z = 2 \) molecules \{\( d_{\text{calcd}} = 1.432 \) g/cm\(^3\); \( \mu_{\alpha}(\text{MoK}\alpha) = 0.204 \text{mm}^{-1} \). A full hemisphere of diffracted intensities (1850 10-second frames with an \( \omega \) scan width of 0.30\(^\circ\)) was measured for a single-domain specimen using graphite-monochromated MoK\(_\alpha\) radiation (\( \lambda = 0.71073 \) Å) on a
Bruker SMART APEX CCD Single Crystal Diffraction System. X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 5305 reflections. A total of 11612 integrated reflection intensities having 2θ((MoKα)< 61.00° were produced using the Bruker program SAINT; 5684 of these were unique and gave R_{int} = 0.046 with a coverage which was 98.5% complete. The data were corrected for variable absorption effects using Gaussian face-indexed absorption corrections; the transmission factors ranged from 0.932 to 0.983. The Bruker software package SHELXTL Version 6.10 was used to solve the structure using “direct methods” techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL software package. All hydrogen atoms were located from difference Fourier syntheses and included in the structural model as individual isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles.

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. A total of 342 parameters were refined using no restraints, 5684 data and weights of w = 1/[σ^2(F^2) + (0.0790 P)^2], where P = [F_o^2 + 2F_c^2] / 3. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.046 for 4539 independent absorption-corrected reflections having 2θ(MoKα)< 61.00° and 1>2σ(I); R_1(unweighted, based on F) = 0.058 and wR_2(weighted, based on F^2) = 0.126 for all 5684 independent absorption-corrected reflections having 2θ(MoKα)< 61.00°. The largest shift/s.u. was 0.001 in the final refinement cycle. The final difference map had maxima and minima of 0.79 and -0.51 e/Å^3, respectively.

Acknowledgment

The authors thank the National Science Foundation (grant CHE-0079282) and the University of Kansas for funds to purchase the X-ray instrument and computers.

Table 1. Crystal data and structure refinement for C_{22}H_{20}N_{2}O_{4}S.
Empirical formula

C\textsubscript{22}H\textsubscript{20}N\textsubscript{2}O\textsubscript{4}S

Formula weight

408.46

Temperature

100(2) K

Wavelength

0.71073 Å

Crystal system

Triclinic

Space group

\text{\overline{1}}(C\textsubscript{i} – No. 2)

Unit cell dimensions

\begin{align*}
a &= 7.7457(6) \text{ Å} \\
b &= 8.3807(6) \text{ Å} \\
c &= 15.163(1) \text{ Å}
\end{align*}

\begin{align*}
\alpha &= 85.166(2)^{\circ} \\
\beta &= 89.549(2)^{\circ} \\
\gamma &= 74.976
\end{align*}

Volume

947.2(1) \text{ Å}^3

Z

2

Density (calculated)

1.432 Mg/m\textsuperscript{3}

Absorption coefficient

0.204 mm\textsuperscript{-1}

F(000)

428

Crystal size

0.45 x 0.24 x 0.10 mm\textsuperscript{3}

Theta range for data collection

2.53° to 30.50°.

Index ranges

-11 \leq h \leq 11, -11 \leq k \leq 11, -21 \leq l \leq 21

Reflections collected

11612

Independent reflections

5684 [R\text{int} = 0.046]

Completeness to theta = 30.50°

98.5 %

Absorption correction

Integration

Max. and min. transmission

0.983 and 0.932

Refinement method

Full-matrix least-squares on F\textsuperscript{2}

Data / restraints / parameters

5684 / 0 / 342

Goodness-of-fit on F\textsuperscript{2}

1.037

Final R indices [I>2sigma(I)]

R\textsubscript{1} = 0.046, wR\textsubscript{2} = 0.119

R indices (all data)

R\textsubscript{1} = 0.058, wR\textsubscript{2} = 0.126

Largest diff. peak and hole

0.79 and -0.51 e.Å\textsuperscript{-3}

\begin{align*}
R\textsubscript{1} &= S \frac{||F_o|| - ||F_c||}{||F_o||} / S ||F_o|| \\
wR\textsubscript{2} &= \left\{ S \frac{w(F_o^2 - F_c^2)^2}{S[w(F_o^2)^2]} \right\}^{1/2}
\end{align*}
Table 2. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters (Å$^2$ x $10^3$) for C$_2$H$_{20}$N$_2$O$_4$S. U (eq) is defined as one third of the trace of the orthogonalized U$_{ij}$ tensor.

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### Table 4. Bond angles [°] for C$_{22}$H$_{20}$N$_{2}$O$_{4}$S.

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Table 5. Anisotropic displacement parameters ($\AA^2 \times 10^3$) for C$_{22}$H$_{20}$N$_2$O$_4$S. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^* U_{11} + ... + 2hk a^* b^* U_{12} ]$

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Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C_{22}H_{20}N_2O_4S.

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Table 7. Torsion angles [°] for $\text{C}_{22}\text{H}_{20}\text{N}_{2}\text{O}_{4}\text{S}$.

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13n was synthesized by the standard decarboxylative olefin insertion reaction from vinyl oxazinanone. The colorless crystal was formed in a solvent mixture of dichloromethane and hexane.

Crystal Structure Data:
Comments
The asymmetric unit contains one crystallographically-independent C_{28}H_{25}N_{3}O_{2}S molecule. All thermal vibration ellipsoids are drawn at the 50% probability level.
Brief Experimental Description to be Included as Text or as a Footnote at Time of Publication

Colorless crystals of C_{28}H_{25}N_{3}O_{2}S are, at 100(2) K, monoclinic, space group P2_1/c – C_{2h}^5 (No. 14)^2 with \( a = 12.781(1) \, \text{Å} \), \( b = 14.997(1) \, \text{Å} \), \( c = 13.507(1) \, \text{Å} \), \( \beta = 114.749(1)^\circ \), \( V = 2351.1(2) \, \text{Å}^3 \) and \( Z = 4 \) molecules \{ \text{d}_{\text{calc}} = 1.321 \, \text{g/cm}^3; \mu_{\text{a}(\text{MoK}\alpha)} = 0.169 \, \text{mm}^{-1} \}. A full hemisphere of diffracted intensities (1850 10-second frames with an \( \omega \) scan width of 0.30°) was measured for a single-domain specimen using graphite-monochromated MoK\_ radiation (\( \lambda = 0.71073 \, \text{Å} \)) on a Bruker SMART APEX CCD Single Crystal Diffraction System.\(^3\) X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 3098 reflections. A total of 28640 integrated reflection intensities having \( 2\theta((\text{MoK}\alpha)< 61.07^\circ \) were produced using the Bruker program SAINT;\(^4\) 7181 of these were unique and gave \( R_{\text{int}} = 0.069 \) with a coverage which was 99.8% complete. The data were corrected empirically for variable absorption effects using 893 equivalent reflections; the relative transmission factors ranged from 0.951 to 1.000. The Bruker software package SHELXTL Version 6.10 was used to solve the structure using “direct methods” techniques. All stages of weighted full-matrix least-squares refinement were conducted using \( F_0^2 \) data with the SHELXTL software package.\(^5\) All hydrogen atoms were located from difference Fourier syntheses and included in the structural model as individual isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles.

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. A total of 407 parameters were refined using no restraints, 7181 data and weights of \( w = 1/[\sigma^2(F^2) + (0.0302 \, P)^2] \), where \( P = [F_0^2 + 2F_C^2] / 3 \). Final agreement factors at convergence are: \( R_1(\text{unweighted}, \text{based on } F) = 0.049 \) for 4498 independent absorption-corrected reflections having \( 2\theta(\text{MoK}\alpha)< 61.07^\circ \) and \( I>2\sigma(I); R_1(\text{unweighted}, \text{based on } F) = 0.086 \) and \( wR_2(\text{weighted}, \text{based on } F^2) = 0.091 \) for all 7181 independent absorption-corrected reflections having \( 2\theta(\text{MoK}\alpha)< 61.07^\circ \). The
largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.46 and -0.46 e/Å³, respectively.

Table 1. Crystal Data and Structure Refinement for C₂₈H₂₅N₃O₂S.

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<th>Value</th>
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<tr>
<td>Volume</td>
<td>2351.1(2) Å</td>
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<tr>
<td>Z</td>
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<td>Crystal size</td>
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<td>Empirical</td>
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<td>Max. and min. transmission</td>
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<td>Data / restraints / parameters</td>
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<tr>
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<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R₁ = 0.049, wR₂ = 0.083</td>
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<tr>
<td>R indices (all data)</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.459 and -0.464 e/Å³</td>
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\[ R_1 = \frac{|F_o| - |F_c|}{|F_o|} \]
\[ wR_2 = \left( \frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2} \right)^{1/2} \]

Table 2. Atomic coordinates (x \(10^4\)) and equivalent isotropic displacement parameters (Å\(^2\) x \(10^3\)) for C\(_{28}\)H\(_{25}\)N\(_3\)O\(_2\)S. U (eq) is defined as one third of the trace of the orthogonalized U\(_{ij}\) tensor.

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Table 5. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) for C_{28}H_{25}N_3O_2S. The anisotropic displacement factor exponent takes the form: 

$$-2\pi^2 [h^2 a^* U_{11} + \ldots + 2hk a^* b^* U_{12}]$$

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Table 6. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for C$_{28}$H$_{25}$N$_3$O$_2$S.
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Table 7. Torsion angles [°] for C_{28}H_{33}N_{3}O_{2}S.

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33a was synthesized by the standard asymmetric decarboxylative cycloaddition reaction from benzoxazinonone. The colorless crystal was formed in ethanol.

Crystal Structure Data:
The asymmetric unit contains one C_{26}H_{21}N_{3}O_{2}S molecule. All displacement ellipsoids are drawn at the 50% probability level.

**Brief Experimental Description to be Included as Text or as a Footnote at Time of Publication**

Colorless crystals of C_{26}H_{21}N_{3}O_{2}S are, at 100(2) K, orthorhombic, space group P2_12_1 D_2^4 (No. 19) with a = 8.4257(6) Å, b = 8.7925(6) Å, c = 30.075(2) Å, V = 2228.1(3) Å^3 and Z = 4 molecules \{d_{calc} = 1.310 \text{ g/cm}^3; \mu_a(\text{MoK}\alpha) = 0.174 \text{ mm}^{-1}\}. A full hemisphere of diffracted intensities (1850 10-second frames with a \(\omega\) scan width of 0.30°) was measured for a single-domain specimen using graphite-monochromated MoK\(\alpha\) radiation (\(\lambda = 0.71073\) Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System. X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 9106 reflections. A total of 26648 integrated reflection intensities having 2\(\theta\)((MoK\alpha) < 60.07° were produced using the Bruker program SAINT; 6483 of these were unique and gave R_{int} = 0.044 with a coverage which was 99.8% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission...
factors ranged from 0.902 to 1.000. The Bruker software package SHELXTL was used to solve the structure using “direct methods” techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_0^2 data with the SHELXTL Version 6.10 software package.

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were located in a difference Fourier and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. A total of 373 parameters were refined using no restraints, 6483 data and weights of w = 1/ [σ^2 (F^2) + (0.0545 P)^2], where P = [F_0^2 + 2F_C^2] / 3. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.042 for 6087 independent absorption-corrected “observed” reflections having 2θ(MoKα) < 60.07° and I>2σ(I); R_1(unweighted, based on F) = 0.045 and wR_2(weighted, based on F^2) = 0.094 for all 6483 independent absorption-corrected reflections having 2θ(MoKα) < 60.07°. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.47 and -0.25 e/Å^3, respectively. The absolute configuration for the C_{26}H_{21}N_{3}O_{2}S molecule was reliably determined experimentally using anomalous dispersion of the x-rays; the “Flack” absolute structure parameter refined to a final value of 0.02(5).
Acknowledgment

The authors thank the National Science Foundation (grant CHE-0079282) and the University of Kansas for funds to purchase the x-ray instrument and computers.

Table 1. Crystal data and structure refinement for C_{26}H_{21}N_{3}O_{2}S.

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<td>Absorption correction</td>
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<td>Max. and min. transmission</td>
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<td>R indices (all data)</td>
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<td>Largest diff. peak and hole</td>
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\[ R_1 = \sum \frac{|F_o| - |F_c|}{|F_o|} / \sum |F_o| \]
\[ wR_2 = \left( \sum \frac{w(F_o^2 - F_c^2)}{\sum w(F_o^2)} \right)^{1/2} \]

Table 2. Atomic coordinates (x \(10^4\)) and equivalent isotropic displacement parameters (\(\text{Å}^2 \times 10^3\)) for \(\text{C}_{26}\text{H}_{21}\text{N}_3\text{O}_2\text{S}\). \(U\) (eq) is defined as one third of the trace of the orthogonalized \(U_{ij}\) tensor.

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Table 3. Bond lengths [Å] for $C_{26}H_{21}N_3O_2S$.  

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C(20)-C(25) 1.399(2)  C(24)-C(25) 1.384(2)
C(21)-C(22) 1.394(2)  C(24)-H(24) 1.00(2)
C(21)-H(21) 0.93(2)   C(25)-H(25) 0.90(2)
C(22)-C(23) 1.390(2)  C(26)-H(26A) 0.94(3)
C(22)-H(22) 0.96(2)   C(26)-H(26B) 0.88(3)
C(23)-C(24) 1.400(2)  C(26)-H(26C) 0.93(3)

Table 4. Bond angles [°] for C$_{26}$H$_{21}$N$_3$O$_2$S.

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Table 5. Anisotropic displacement parameters (Å² x 10^3) for C_{26}H_{21}N_{3}O_{2}S. The anisotropic displacement factor exponent takes the form: \(-2\pi^2 \left[ h^2 a^* a^* U_{11} + ... + 2 h k a^* b^* U_{12} \right] \)

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Table 6. Hydrogen coordinates ($10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for C\textsubscript{26}H\textsubscript{21}N\textsubscript{3}O\textsubscript{2}S.

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Table 7. Torsion angles [°] for C_{28}H_{21}N_{3}O_{2}S.

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Chapter 4

Selenocatalytic $\alpha$-Halogenation
4.1 Importance of Catalytic $\alpha$-Halogenation of Carbonyl Compounds

Halogenation reactions have drawn a lot of attention and been extensively studied. The reason partially resides in the fact that a large amount of halogenated natural products, isolated from terrestrial and marine organisms displayed interesting biological and pharmaceutical activities as shown in Scheme 1. For instance, thyrsiferyl acetate $1a$ is known to inhibit protein phosphatase and halomon $1b$ displays antitumor and cytotoxic activities.$^{1-3}$ Mailione $1c$ showed interesting anthelminthic properties and furanones $1d$ exhibits anti-fouling properties.$^{4-6}$ Cyclized sesquiterpenes $1e$, $1f$ and acetogenins $1g$ display broad spectrum antimicrobial and antiviral activity.$^7$ Halogens are known to be the bioisosteres of a wide variety of atoms such as hydrogen and carbon.$^8$ Introducing halogens into the drug candidate can potentially enhance both the activity and bioavailability, for example chlorination improves the lipophilicity of the medicine.

Scheme 1 Halogenated marine natural products
Secondly, halogenated products are important synthetic intermediates for further manipulations, and this trend has been further magnified by those discoveries of transition metal-catalyzed coupling reactions such as Suzuki, Stille, Heck, Sonogashira etc.\textsuperscript{9-12} Traditionally, $\alpha$-halogenation of carbonyl compounds uses reagents such as HOX or X$_2$, which often exhibit poor chemoselectivity and competing side reactions such as dihalogenation.\textsuperscript{13, 14} Catalytic $\alpha$-halogenation has been introduced into this scenario to address such a problem and received much attention lately due to the importance of the products as synthetic precursors and pharmaceuticals.\textsuperscript{15} The majority of these methods focus on the catalytic activation of the carbonyl substrate by formation of enolates as shown in Scheme 2. $\alpha$-Halogenations of $\beta$-ketoesters 2a with N-halosuccinimide were carried out under mild conditions in the presence of a Lewis acid catalyst Mg(ClO$_4$)$_2$.\textsuperscript{16} Enantiomerically enriched products 2f were produced in 62-90\% ee by treatment of $\beta$-ketoesters 2d with a fluorination reagent 2d catalyzed by a chiral Lewis acid complex 2g.\textsuperscript{17} Lectka \textit{et al.} reported a novel catalyst system for asymmetric chlorination and bromination. A chiral benzoylquinine catalyst functioned as a nucleophile to react with ketenes 2i to give acylammonium enolates, which were then halogenated to generate products 2k in decent yield and excellent enantioselectivities.\textsuperscript{18} However, those transformations have drawbacks in terms of
substrate scope and reaction yield. For example, in the first two cases, the α-substituents of β-ketoesters 2a and 2d are necessary in order to avoid the formation of dihalogenated products. The yields of the third reaction were hampered by a homodimerization side reaction.

**Scheme 2** Catalytic α-halogenation via enolate intermediates

Catalytic activation of the carbonyl substrate by formation of enamines is shown in Scheme 3. Enantiopure amines 3d and 3h were used to catalyze the formation of enamine intermediates, followed by chlorination to generate products 3c and 3g in good enantioselectivities.\textsuperscript{8, 19} Alternatively, the catalytic formation of X₂ (X = Cl, Br, I) from H₂O₂/NaX,\textsuperscript{20} or N-halosuccinimides has been a successful approach.\textsuperscript{21} However,
in order to control the selectivity of halogenation, one would like to utilize a catalyst that halogenates ketones through reagent-bound halogens rather than freely diffusing oxidized halogen species.

**Scheme 3 Catalytic α-halogenation via enamine intermediates**

![Scheme 3](image)

### 4.2 Selenium-Catalyzed Halogenation of Carbonyl Compounds

Recently, we described the use of phenylselenium chloride as a catalyst for allylic halogenation of olefins with N-chlorosuccinimide (NCS) 4b as shown in Scheme 4.\(^{22}\) In the course of these studies we noted that the reaction was inhibited by NCS. To explain the observed inhibition we postulated that the phenylselenyl chloride catalyst was in equilibrium with the oxidized PhSe(succinimide)Cl\(_2\) 4d.\(^ {23}\) While PhSe(succinimide)Cl\(_2\) 4d was less active for allylic halogenation, it is known that the related PhSeCl\(_3\) α-halogenates ketones.\(^ {24}\) Therefore we thought that 4d might be a useful catalyst for the α-halogenation of ketones with NCS.
**Scheme 4** *Selenocatalytic allylic chlorinations*

In order to test whether arylselenides can activate NCS toward nucleophilic attack, 2-carboxethoxycyclohexanone 5a was treated with 5 mol% PhSeCl and 1.1 equiv. NCS in CH$_3$CN (Scheme 5). Analysis of the reaction mixture after 10 min. at room temperature showed complete conversion to the α-chloro product 6a. A control reaction run in the absence of PhSeCl showed < 1% reaction.

**Scheme 5** *Catalytic α–chlorination of a β-ketoester*

We envisioned several possible mechanisms for product formation as shown in Scheme 6. First, the β-ketoester could be α-selenylated by PhSeCl to afford 7a.$^{25,26}$ Oxidation of 7a by NCS would give 7b which could reductively eliminate the halogenated product (Mechanism A)$^{27}$ Alternatively, the β-ketoester can be α-selenylated by the Se(IV) reagent 4d, providing 7c, which could liberate 6a upon
reductive elimination (Mechanism B). Finally, selenation at oxygen would form 7d, which could undergo intramolecular nucleophilic attack at the chlorine (Mechanism C). While mechanisms A and B differ by the oxidation state of the selenylating agent, the latter two mechanisms differ only by whether the α-carbon is electrophilically selenylated or chlorinated.

**Scheme 6 Three possible mechanisms for catalytic α–halogenation of β-ketoesters**

In order to gain some mechanistic insight several reactions utilizing stoichiometric PhSeCl were run. First, 5a was treated with PhSeCl in CH₃CN. After stirring overnight, the selenylated product 7a was isolated and purified by chromatography. Treatment of 7a with NCS in CD₃CN at room temperature did provide halogenated product 6a, however after standing 2.5 hours, the reaction was not complete ($t_{1/2} \sim 150$ min.). Therefore, pathway A is not kinetically competent with
the observed catalysis ($t_{1/2} < 10$ min.). Next, product $7a$ was treated with $\text{SO}_2\text{Cl}_2$ in $\text{CD}_3\text{CN}$, which should provide intermediate $7c$. Doing so led cleanly to one product, tentatively identified as $7c$ based on $^1\text{H}$ NMR spectroscopy. This compound was stable for several hours at room temperature, but slowly decomposed overnight to give $6a$ (67 % conversion after 28 h). Once again, this indicates that intermediate $7c$ is not a kinetically competent intermediate. Therefore, it appears that the mechanism of catalysis is electrophilic chlorination rather than selenylation. *This is important because it shows that selenium can be used to enhance the electrophilicity of oxidized halogen sources such as NCS.*

With this knowledge in hand, we set out to explore the scope of the catalysis and the results are shown in Table 1. Halogenation of $\beta$-ketoesters provided monohalo adducts exclusively. Importantly, the halogenation could be conducted in the presence of olefins (substrate $5g$), without competing allylic halogenation. $2\text{I}$ Cyclohexanone $5h$ was readily $\alpha$-halogenated, showing that the $\beta$-keto activating group is not required. However, a qualitative correlation between the rate of the reaction and the rate of enolization is noteworthy. Unfortunately, cyclohexanone $5h$ was not as selective for monochlorination, and a 4:1 mixture of $\alpha$-chlorocyclohexanone: $\alpha,\alpha'$-dichlorocyclohexane was obtained.
Table 1 *PhSeCl* catalyzed α-chlorination of ketones in CH$_3$CN

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Structure</th>
<th>Time</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td><img src="image" alt="Structure" /></td>
<td>10 min</td>
<td>6a</td>
<td>86</td>
</tr>
<tr>
<td>5b</td>
<td><img src="image" alt="Structure" /></td>
<td>10 min</td>
<td>6b</td>
<td>81</td>
</tr>
<tr>
<td>5c</td>
<td><img src="image" alt="Structure" /></td>
<td>18 hr</td>
<td>6c</td>
<td>63</td>
</tr>
<tr>
<td>5d</td>
<td><img src="image" alt="Structure" /></td>
<td>30 min</td>
<td>6d</td>
<td>74</td>
</tr>
<tr>
<td>5e</td>
<td><img src="image" alt="Structure" /></td>
<td>10 min</td>
<td>6e</td>
<td>68</td>
</tr>
<tr>
<td>5f</td>
<td><img src="image" alt="Structure" /></td>
<td>48 hr</td>
<td>6f</td>
<td>95</td>
</tr>
<tr>
<td>5g</td>
<td><img src="image" alt="Structure" /></td>
<td>16 hr</td>
<td>6g</td>
<td>87</td>
</tr>
<tr>
<td>5h</td>
<td><img src="image" alt="Structure" /></td>
<td>18 hr</td>
<td>6h</td>
<td>61$^a$</td>
</tr>
<tr>
<td>5i</td>
<td><img src="image" alt="Structure" /></td>
<td>7 hr</td>
<td>6i</td>
<td>79$^b$</td>
</tr>
</tbody>
</table>

$^a$ isolated yield of monochlorocyclohexanone $^b$ product is vinyl chloride.

We reasoned that the selectivity for monochlorination could be increased if the monochlorointermediate was trapped by solvent as a hemiacetal or an acetal (Scheme 7). Investigating the reaction in methanol showed that cyclohexanone was chlorinated by NCS in < 1 h at room temperature and $^1$H and $^{13}$C NMR spectroscopies of the reaction mixture showed the presence of 8a with no evidence for dichlorinated product. α-Chlorocyclohexanone was liberated in good yield (72 %) upon passage through silica gel. Once again, no reaction occurred in the control without PhSeCl. Aside from the faster reaction kinetics in methanol, the reaction progress was
conveniently monitored by the dissolution of the relatively insoluble NCS.

**Scheme 7 Trapping monochlorocyclohexanone in methanol**

![Scheme 7 Diagram]

Importantly, cyclohexanone was also $\alpha$-brominated to provide $\alpha$-bromocyclohexanone in 86 % yield when NBS replaced NCS. No reaction was observed in the absence of PhSeBr.

Finally, we investigated the chlorination of an $\alpha,\beta$-unsaturated ketone, mesityl oxide 5i (Scheme 8). Interestingly, treatment of mesityl oxide with NCS and 5 mol % PhSeCl in CH$_3$CN provided good yield of vinyl halide 6i,\(^{28}\) however, switching the solvent to MeOH completely reversed the selectivity and only the product of methyl halogenation 9i was observed.

**Scheme 8 Regiochemical solvent effect**

![Scheme 8 Diagram]

In conclusion, we have demonstrated that phenylselenides are efficient and selective catalysts for $\alpha$-chlorination of ketones. Experiments suggest that the
mechanism of the reaction involves oxidative addition of NCS to selenium which activates the “chloronium” toward nucleophilic attack by enols/enolates. This represents the first example of such an activation of oxidized halogen reagents.
4.3 References

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Appendix D

Experimental Procedures and Data for Chapter 4
**General Experimental**

THF was dried over sodium metal and distilled under vacuum. Toluene, methylene chloride and diethyl ether were dried over activated alumina on a solvent system purchased from Innovative Technology, Inc.\(^1\) Acetonitrile and 1,4-dioxane were dried and stored over activated molecular sieves. Commercially available reagents were used without additional purification unless otherwise stated. Products were purified on silica gel from Sorbent Technologies (230x400 mesh, 60 Å porosity, pH 6.5-7.5). Ruthenium and palladium compounds were obtained from Strem. Thin layer chromatography was performed on silica gel 60F\(_{254}\) plates (EM-5715-7, EMD chemicals). UV lamp (254 nm) or KMnO\(_4\) stain were used for monitoring TLC plates.

\(^1\)H and \(^{13}\)C NMR spectra were obtained on a Bruker Avance 400 or Bruker Avance 500 DRX spectrometer and referenced to residual protio solvent signals. Structural assignments are based on \(^1\)H, \(^{13}\)C, DEPT-135, COSY, and HMQC spectroscopies and X-ray data. High resolution mass spectrometry was performed on an AUTOSPEC-Q tandem hybrid mass spectrometer (VG Analytical Ltd, Manchester, UK). High resolution mass spectrometry was performed on a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. FTIR spectra were acquired on a Shimadzu FTIR-8400S spectrometer. HPLC analysis was performed on a Shimadzu SCL-10A VP instrument.
**Preparation of Starting Materials**

Allyl β-ketoesters were synthesized by the DMAP catalyzed coupling reaction between commercially available allylic alcohols with diketene, followed by purification via flash column chromatography when $R^1$ equals to methyl group. (SiO$_2$, 7:1 Hexane: Ethyl acetate).$^2$

\[
\begin{align*}
\text{O} & \quad \text{R}^2 \quad \text{C} & \quad \text{O} & \quad \text{R}^1 \quad \text{Et}_2\text{O, rt} \\
\text{R}^3 & \quad \text{OH} & \quad \text{R}^3 & \quad \text{O} & \quad \text{R}^2
\end{align*}
\]

To a solution of the allylic alcohol (225 mg, 1.6 mmol) in 10 ml ether under argon was added diketene in one portion (1.8 mmol, 1.1 eq.), followed by DMAP (17.6 mg, 0.16 mmol, 0.1 eq). The reaction mixture was kept stirring until reaction completion indicated by TLC (generally 1.5 hr). The reaction was quenched with sat. NH$_4$Cl solution, extracted with ether. The organic phase was washed with brined, dried over magnesium sulfate and concentrated to give the crude product, which was purified by flash column chromatography (SiO$_2$, 10:1 Hexane: Ethyl acetate). All other β-ketoesters are commercially available and used without further purification.

**General procedure for Selenocatalytic α-Halogenation:**

In a Schlenk tube under argon, PhSeCl (5 mol%, 0.13 mmol) was dissolved in 3 mL CH$_3$CN. To this orange color solution at room temperature was added β-ketoesters (2.51 mmol, 1.0 eq.), followed by $N$-chlorosuccinimide (2.51 mmol, 1.0 eq.). The addition resulted in an immediate color change from orange to yellow (normally in 10 mins) which indicates the reaction completion. In the mean time, the
reaction was also monitored by TLC. Following solvent evaporation the crude product was purified via flash chromatography (SiO$_2$, 15:1 Hexane: Ethyl acetate).

**Spectroscopic Data**

![Structure of ethyl 1-chloro-2-oxocyclohexancarboxylate](image)

**6a** (cw1008)$^3$

- Colorless oil
- 86% yield

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.30 (q, $J = 7.1$ Hz, 2H: OCH$_2$), 2.83 (m, 2H: ClCCH$_2$), 2.45 (m, 1H: CH$_2$), 2.14 (m, 1H: CH$_2$), 2.01-1.82 (m, 3H: CH$_2$), 1.75(m, 1H: CH$_2$), 1.31(t, $J = 7.1$ Hz, 3H: CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.67 (C=O), 167.22 (OC=O), 73.47 (ClC), 66.82 (OCH$_2$), 39.60 (C=OCH$_2$), 38.82 (2.83) (CH$_2$), 26.67 (ambiguous CH$_2$), 22.14 (ambiguous CH$_2$), 13.87(CH$_3$).

![Structure of ethyl 2-chloro-3-oxobutanoate](image)

**6b** (cw1005)$^4$

- Colorless oil
- 81% yield

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.76 (s, 1H: CICH), 4.30 (q, $J = 7.1$ Hz, 2H: OCH$_2$), 2.39 (s, 3H: CH$_3$C=O), 1.32 (t, $J = 7.1$ Hz, 3H: CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.61 (C=O), 164.92 (OC=O), 63.14 (ClC), 61.31 (OCH$_2$), 26.21 (O=CCH$_3$), 13.89 (CH$_3$).
ethyl 2-chloro-2-methyl-3-oxobutanoate

6c (cw1016)\(^5\)
colorless oil
63% yield

\[^1\text{H}\text{ NMR}\ (400 \text{ MHz}, \text{CDCl}_3) \delta 4.27 \ (q, \ J = 7.1 \text{ Hz, } 2\text{H: OCH}_2), 2.37 \ (s, \ 3\text{H: CH}_3\text{C}=\text{O}), 1.82 \ (s, \ 3\text{H: CH}_2\text{CCl}), 1.30 \ (t, \ J = 7.1 \text{ Hz, } 3\text{H: CH}_3).\]

\[^{13}\text{C NMR}\ (75 \text{ MHz, CDCl}_3) \delta 198.80 \ (\text{C}=\text{O}), 168.03 \ (\text{OC}=\text{O}), 70.72 \ (\text{Cl}), 63.04 \ (\text{OCH}_2), 25.25 \ (\text{ambiguous CH}_3), 24.22 \ (\text{ambiguous CH}_3), 13.89 \ (1.30) \ (\text{CH}_3).\]

ethyl 2-chloro-3-oxopentanoate

\(\text{7.5:1}\)

(E)-ethyl 2-chloro-3-hydroxypent-2-enoate

6d (cw1030)\(^6\)
colorless oil
74% yield

\[^1\text{H}\text{ NMR}\ (400 \text{ MHz, CDCl}_3) \delta 5.29 \ (s, \ 1\text{H: ClCH}), 4.41 \ (q, \ J = 7.1 \text{ Hz, } 2\text{H: OCH}_2 \text{ of the enol isomer}), 4.28 \ (q, \ J = 7.1 \text{ Hz, } 2\text{H: OCH}_2), 2.91 \ (q, \ J = 7.1 \text{ Hz, } 2\text{H: CH}_2\text{C}=\text{O} \text{ of the enol isomer}), 2.79 \ (q, \ J = 7.1 \text{ Hz, } 2\text{H: CH}_2\text{C}=\text{O}), 1.28 \ (t, \ J = 7.1 \text{ Hz, } 3\text{H: ambiguous CH}_3), 1.07 \ (t, \ J = 7.1 \text{ Hz, } 3\text{H: ambiguous CH}_3).\]

\[^{13}\text{C NMR}\ (75 \text{ MHz, CDCl}_3) \delta 200.87 \ (\text{C}=\text{O}), 166.97 \ (\text{OC}=\text{O}), 64.38 \ (\text{Cl}), 62.79 \ (\text{OCH}_2), 34.25 \ (2.79) \ (\text{CH}_2), 15.18 \ (\text{ambiguous CH}_3), 8.90 \ (\text{ambiguous CH}_3).\]
methyl 2-chloro-3-oxobutanoate \( \rightleftharpoons \) (E)-methyl 2-chloro-3-hydroxybut-2-enoate

6e (cw1031)

\[ \text{colorless oil} \]

\[ \text{68\% yield} \]

\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 12.24 (1H: OH), 4.78 (s, 1H: CHCl), 3.85 (s, 3H, ambiguous OCH}_3), 3.84 (s, 3H, ambiguous OCH}_3), 2.34 (s, 3H: CH}_3C=O), 2.18 (s, 3H: CH}_3COH). \]

\[ ^13C \text{ NMR} (75 \text{ MHz, CDCl}_3) \delta 196.58 (C=O), 172.21 (ambiguous, OC=O), 169.64 (ambiguous, OC=O), 165.42 (HOC=), 96.74 (=CCI), 61.06 (CCI), 53.76 (ambiguous OCH}_3), 52.69 (ambiguous OCH}_3), 26.27 (2.34) (CH}_3), 19.73 (2.18) (CH}_3). \]

ethyl 2-benzyl-2-chloro-3-oxobutanoate

6f (cw1032)

\[ \text{colorless oil} \]

\[ \text{95\% yield} \]

\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 7.25-7.30 (m, 3H: arom H), 7.21 (m, 2H: arom H), 4.22 (m, 2H: OCH}_2), 3.53 (dd, J = 14.4, 21.5 Hz, 1H: diastereotopic CH}_2Ph), 3.44 (dd, J = 14.4, 21.5 Hz, 1H: diastereotopic CH}_2Ph), 2.24 (app. d, J = 3.8 Hz, 3H: CH}_3C=O), 1.24 (app. t, J = 7.1 Hz, 3H: CH}_3). \]

\[ ^13C \text{ NMR} (75 \text{ MHz, CDCl}_3) \delta 198.90 (C=O), 167.02 (OC=O), 133.92 (arom. C), 130.58 (arom. C), 128.18 (arom. C), 127.48 (arom. C), 75.24 (ClC), 63.04 (OCH}_2), 42.15 (2.48) (CH}_2Ph), 26.50 (2.24) (CH}_3), 13.80 (1.24) (CH}_3). \]
cinnamyl 2-chloro-3-oxobutanoate $\rightleftharpoons$ (E)-cinnamyl 2-chloro-3-hydroxybut-2-enoate

$6g$ (cw1013)$^9$

colorless oil
87% yield

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.28 (1H: OH), 7.40 (m, 5H: arom H), 7.32 (m, 5H: arom H), 6.72 (dd, 2H: ambiguous CH=), 6.31 (m, 2H: ambiguous CH=), 4.89 (app. t, J = 4.57 Hz, 4H: ambiguous CH$_2$O), 4.81 (s, 1H: ClCH), 2.40 (s, 3H: CH$_3$CO), 2.20 (s, 3H: CH$_3$COH).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 207.36 (C=O), 143.35 (arom. C), 137.49 (arom. C), 132.76 (CH=), 130.39 (CH=), 129.13 (arom. CH), 128.91 (arom. CH), 128.06 (arom. CH), 127.75 (arom. CH), 127.12 (arom. CH), 126.65 (arom. CH), 49.82 (CH$_2$), 44.36 (CH), 31.20 (CH$_3$).

2-chlorocyclohexanone

$6h$ (cw2056)$^{10}$

colorless oil
61% yield

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.37 (q, J = 5.2 Hz, 1H: ClCH), 2.78 (m, 1H: diastereotopic ClCCCH$_2$), 2.30-2.43 (m, 2H: CH$_2$C=O), 1.97-2.12 (m, 2H: ambiguous CH$_2$), 1.88-1.95 (m, 1H: ambiguous CH$_2$), 1.79-1.87 (m, 1H: ambiguous CH$_2$), 1.68-1.77 (m, 1H: ambiguous CH$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 203.41 (C=O), 62.87 (ClC), 39.41 (C=OCH$_2$), 37.40 (2.78) (CH$_2$), 27.02 (ambiguous CH$_2$), 22.90 (ambiguous CH$_2$).

3-chloro-4-methylpent-3-en-2-one

$6i$$^{11}$

1-chloro-4-methylpent-3-en-2-one

$9i$$^{12}$
References:


