DEVELOPMENT OF STEREOSELECTIVE IRIDIUM-CATALYZED
ALLYLIC ALKYLATION METHODS

Thesis by
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To my dad
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ABSTRACT

The Stoltz group, and moreover the synthetic community at large, has long been interested in the development of methods for the synthesis of enantioenriched all-carbon quaternary stereocenters. Historically, our group’s interest has centered on palladium-catalyzed allylic alkylation, though recently effort has moved to include the study of iridium catalysts. This thesis presents four related projects, all unified by the use of enantioselective iridium-catalyzed allylic alkylation to construct highly-congested C–C bonds.

First, the development of the first diastereo-, enantio-, and regioselective iridium-catalyzed allylic alkylation reaction of prochiral enolates to form vicinal tertiary and all-carbon quaternary stereodyads with alkyl-substituted allylic electrophiles is described. Next, the first enantioselective iridium-catalyzed allylic alkylation reaction of a masked acyl cyanide (MAC) nucleophile is presented, representing a rare example of umpolung strategy in iridium-catalyzed allylic alkylation. Additionally, the application of a MAC reagent in the first highly enantioselective iridium-catalyzed allylic alkylation to provide access to products bearing an allylic all-carbon quaternary stereocenter is detailed. The use of the MAC nucleophile enables the one-pot preparation of α-quaternary carboxylic acids, esters, and amides with a high degree of enantioselectivity. Finally, the first enantioselective transition metal-catalyzed allylic alkylation providing access to acyclic products bearing vicinal all-carbon quaternary centers is presented.

   S.E.S participated in designing second generation synthetic routes, experimental work, data acquisition and analysis, and manuscript preparation.


   S.E.S. participated in reaction optimization, experimental work, data acquisition and analysis, and manuscript preparation.


   S.E.S. led the writing of the review manuscript.


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<td>[α]D</td>
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Et  ethyl
EtOAc ethyl acetate
EWG electron withdrawing group
FAB fast atom bombardment
g gram(s)
GC gas chromatography
gCOSY gradient-selected correlation spectroscopy
h hour(s)
HG-II Hoveyda-Grubbs catalyst 2nd generation
HMBC heteronuclear multiple bond correlation
HMDS 1,1,1,3,3,3-hexamethyldisilazane
HMPA hexamethylphosphoramide
HPLC high-performance liquid chromatography
HRMS high-resolution mass spectroscopy
HSQC heteronuclear single quantum correlation
Hz hertz
hv light
i-Pr isopropyl
i.e. that is (Latin id est)
IBX 2-iodoxybenzoic acid
IPA isopropanol, 2-propanol
Ipc diisopinocampheyl
IR infrared (spectroscopy)
\( J \) coupling constant
K Kelvin(s) (absolute temperature)
kcal kilocalorie
KHMDS potassium hexamethyldisilazide
L liter; ligand
L* chiral ligand
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$o$ ortho

$p$ para

Pd/C palladium on carbon

Ph phenyl

pH hydrogen ion concentration in aqueous solution

PHOX phosphinooxazoline ligand

Pin 2,3-dimethylbutane-2,3-diol (pinacol)

Piv trimethylacetyl, pivaloyl

$pKa$ $pK$ for association of an acid

pMBz 4-methoxy-benzoyl

pmdba bis(4-methoxybenzylidene)acetone

ppm parts per million

PPTS pyridinium $p$-toluenesulfonate

Pr propyl

Proton sponge 1,8-bis(dimethylamino)naphthalene

Py pyridine

$q$ quartet

R generic for any atom or functional group

RCM ring-closing metathesis

Red-Al sodium bis(2-methoxyethoxy)aluminium hydride

Ref. reference

$R_f$ retention factor

$s$ singlet or strong or selectivity factor

sat. saturated

SFC supercritical fluid chromatography

$t$ triplet

$t$-Bu $t$ert-butyl

TBAF tetrabutylammonium fluoride

TBAI tetrabutylammonium iodide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tr>
<td>TBAT</td>
<td>tetrabutylammonium difluorotriphenylsilicate</td>
</tr>
<tr>
<td>TBD</td>
<td>1,3,4-triazabicyclo[4.4.0]dec-5-ene</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butyl hydroperoxide</td>
</tr>
<tr>
<td>TBME</td>
<td>tert-butyl methyl ether</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl (triflyl)</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
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<td>trifluoroacetic anhydride</td>
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<tr>
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<td>2,2,2-trifluoroethanol</td>
</tr>
<tr>
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<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
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<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>$N,N,N',N'$-tetramethylethylenediamine</td>
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<tr>
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<td>tolyl</td>
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<tr>
<td>$t_R$</td>
<td>retention time</td>
</tr>
<tr>
<td>Ts</td>
<td>$p$-toluenesulfonyl (tosyl)</td>
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<tr>
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<td>anionic ligand or halide</td>
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<td>micro</td>
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Chapter 1 – Stereoselective Iridium-Catalyzed Allylic Alkylation Reactions with Crotyl Chloride

CHAPTER 1

Stereoselective Iridium-Catalyzed Allylic Alkylation Reactions with Crotyl Chloride†

1.1 INTRODUCTION

The synthesis of singular all-carbon quaternary stereocenters has been a longstanding challenge in the synthetic community.¹ Significant progress in this area over the past few decades has recently shifted the forefront of investigation toward the more difficult task of constructing vicinal stereodyads bearing at least one quaternary stereocenter. This nascent field is beset with difficulties not only arising from the increased steric in the bond-forming event, but also the additional requirement of diastereocontrol. Among the available methodologies tailored for this challenge,²,³ iridium-catalyzed allylic alkylations represent some of the most selective strategies, yet remain underdeveloped.⁴

† This work was performed in collaboration with Dr. J. Caleb Hethcox. Portions of this chapter have been reproduced with permission from Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. Angew. Chem. Int. Ed. 2016, 55, 16092–16095 © 2016 Wiley-VCH and Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. ACS Catal. 2016, 6, 6207–6213 © 2016 American Chemical Society.
The first diastereo-, enantio-, and regioselective iridium-catalyzed allylic alkylation was disclosed by Takemoto in 2003 and remained the sole report of such a transformation for a decade.\(^5\) Of the eleven published accounts of enantio- and diastereoselective iridium-catalyzed allylic alkylation since,\(^6,7,8\) only five reports provide access to vicinal tertiary and all-carbon quaternary stereocenters.\(^6\) However, none of these protocols tolerate the use of alkyl-substituted electrophiles (Figure 1.1a). Conversely, the four singular examples employing alkyl-substituted electrophiles in two published papers fail to enable construction of all-carbon quaternary stereocenters (Figure 1.1b).\(^7\) While these protocols provide access to valuable chiral synthons, a wide variety of synthetic targets require the installation of alkyl-substituted stereodyads between neighboring tertiary and quaternary carbon atoms (Figure 1.2). To the best of our knowledge, no transition metal-catalyzed process allows for the preparation of this
desired motif. Herein, we describe the first method for the iridium-catalyzed synthesis of alkyl-substituted vicinal tertiary and all-carbon quaternary stereocenters via allylic alkylation of prochiral enolates (Figure 1.1c).

**Figure 1.2** Select natural products bearing alkyl-substituted vicinal tertiary and quaternary stereocenters.

![Natural Products](image)

**ligularone (1)**
**crinipellin B (2)**
**elisabethin A (3)**

1.2 BACKGROUND TO DIASTEREO-, ENANTIO-, AND REGIOSELECTIVE IRIDIUM-CATALYZED ALLYLIC ALKYLATION WITH PROCHIRAL ENOLATES

A more detailed description of the twelve diastereo-, enantio-, and regioselective iridium-catalyzed allylic alkylation methods\(^5\) previously disclosed at the time we began this investigation is discussed vide infra.

1.2.1 IRIDIUM CATALYST-CONTROLLED PROCESSES

1.2.1.1 Acyclic Nucleophiles

Takemoto reported the first diastereo-, enantio-, and regioselective iridium-catalyzed allylic alkylation reaction, wherein an iridium complex of bidentate chiral phosphite L1 and [Ir(cod)Cl]₂ catalyzes the reaction of glycinate nucleophile 4 and aryl-substituted allylic phosphates 6 (Scheme 1.1).\(^5\) The corresponding branched products 7
and 9 bearing vicinal tertiary and trisubstituted stereocenters are afforded in moderate to excellent yields with good to excellent enantioselectivities, albeit with moderate diastereoselectivities. Takemoto also found that simply by employing either KOH or LiHMDS, the diastereomeric ratio can be inverted in order to preferentially access either diastereomer (7 versus 9); this synthetically useful phenomenon has yet to be reported again.

**Scheme 1.1** First report of diastereo- and enantioselective iridium-catalyzed allylic alkylation

The different behavior of the bases is believed to be the result of contrasting enolate geometry; the hypothesis being that KOH predominately gives the E-enolate 5 and LiHMDS instead forms the Z-enolate 8. This observation illuminates the additional challenge that acyclic, prochiral nucleophiles present in contrast to cyclic nucleophiles in diastereo- and enantioselective allylic alkylation chemistry. In acyclic cases, the enolate geometry must be selectively controlled in addition to the facial approach of the
nucleophile. This combination of challenges has resulted in significantly fewer reports of acyclic, prochiral enolate nucleophiles as compared to cyclic, prochiral nucleophiles.

A decade after Takemoto’s report, our group disclosed the second report of an iridium-catalyzed allylic alkylation of acyclic enolates in 2013 (Scheme 1.2).\textsuperscript{6a} Like Takemoto, we found chelation of the enolate with a metal cation, specifically lithium, to be crucial to the diastereoselectivity as bases lacking a chelating metal cation (i.e., DABCO) provide significantly lower selectivity. By deprotonating ketoesters 10 with LiO\textsubscript{t}-Bu prior to introduction of the electrophile, products 12 bearing vicinal tertiary and all-carbon quaternary stereocenters can be obtained in moderate to excellent selectivities with the use of a catalyst derived from [Ir(cod)Cl\textsubscript{2}] and Me-THQphos (L\textsubscript{2}). While a majority of the cinnamyl carbonates 11 proceed with a high degree of regioselectivity (>90:10), we found that the use of electron-deficient aryl-substituted electrophiles 11 (e.g., R = C\textsubscript{6}H\textsubscript{5}NO\textsubscript{2} or C\textsubscript{6}H\textsubscript{5}CF\textsubscript{3}) lead to a decrease in selectivity (50:50–86:14).

\textit{Scheme 1.2 Allylic alkylation of acyclic β-ketoesters by Stoltz}

\[
\begin{align*}
\text{Ar} & \quad \text{O} & \quad \text{O} & \quad \text{Et} \\
\text{R}^{1} & \quad \text{O} & \quad \text{CO}_{2}\text{Me} \\
10 & & & \\
\text{R}^{1} = \text{alkyl, benzyl, propargyl, F, Cl} \\
\end{align*}
\]

\[
\text{Ar} & \quad \text{O} & \quad \text{R}^{2} \\
\text{R}^{1} & \quad \text{CO}_{2}\text{Et} \\
12 & & & \\
\text{R}^{1} & \quad \text{all} & \quad \text{carbon quaternary stereocenters} \\
\]

\[
\begin{align*}
\text{[Ir(cod)Cl\textsubscript{2}] (2 mol %)} & \\
(R,R_{a})-L\textsubscript{2} (4 mol %) & \\
\text{LiO\textsubscript{t}-Bu (200 mol %)} & \\
\text{TBD (10 mol %)} & \\
\text{THF, 25 °C} & \\
\text{Ar} & \quad \text{O} & \quad \text{R}^{2} \\
\text{R}^{1} & \quad \text{CO}_{2}\text{Et} \\
12 & & & \\
\text{21 examples} & \quad \text{78–95\% yield} & \quad \text{50:50–95:5 branched/linear} & \quad 6:1–20:1 \text{ dr} & \quad 91–99\% \text{ ee} \\
\text{(R,R_{a})-L\textsubscript{2}} & \quad \text{TBD} & \\
\end{align*}
\]
In 2016, Hartwig found that acyclic α-alkoxy ketones 13 undergo selective allylic alkylation reactions with allyl carbonates 14 in the presence of preformed metallacyclic iridium complex 15, LiHMDS, and CuBr (Scheme 1.3). In these reactions, the geometry of the acyclic enolate, formed by deprotonation with the lithium base, is controlled by chelation to a copper(I) salt. Interestingly, the identity of the cation associated with the base is also found to play an integral role in achieving high diastereoselectivities, with KHMDS providing much lower selectivities than LiHMDS. The exact nature of this cation dependence is unknown. It is also worth noting that the scope of this reaction permits the use of crotyl carbonates, albeit in lower diastereoselectivities (ca. 7:1 dr). This is one of only two reports of alkyl-substituted electrophiles in a diastereoselective iridium-catalyzed allylic alkylation.

**Scheme 1.3** Allylic alkylation with acyclic α-alkoxy ketones by Hartwig

```
13 \[\text{Ar} \ O\ R^1\]
R^1 = aryl, heteroaryl
R^2 = Me, MOM, MEM, PMB
15 \[\text{Ir} \ N\ Ar \ P\ Ar \ Me\]
14 \[\text{R}^3\ \text{OCO}_2\text{Me}\]
16 \[\text{R}^1\ \text{R}^2\ \text{R}^3\]
THF, 5 °C
LiHMDS (200 mol %)
CuBr (200 mol %)
23 examples
71–99% yield
6:1–20:1 dr
88–99% ee
```

1.2.1.2 Cyclic Nucleophiles

In 2013, Hartwig published the first example of a diastereoselective iridium-catalyzed allylic alkylation of cyclic, prochiral nucleophiles (Scheme 1.4). In this report, vicinal tertiary and tetra-substituted stereodyads are created via the allylic alkylation of azlactones 18 with aryl- and alkenyl-substituted allylic carbonates 11 in the
presence of catalytic amounts of achiral silver phosphate 17, 3 Å molecular sieves, and an iridium catalyst generated in situ from [Ir(cod)Cl]₂ and ligand L₃. Through a series of control experiments, the authors were able to determine that both the phosphate and methyl carbonate anions, but not the silver cation, are key to the high reaction diastereoselectivity (up to >20:1 dr). The counteranions are presumed to deprotonate and control the facial attack of the nucleophile while the silver cation is believed to sequester chloride and promote the formation of the active metallacyclic iridium catalyst.

Scheme 1.4 Counterion-assisted iridium-catalyzed allylic alkylation of azlactones by Hartwig

This counterion strategy did not prove fruitful in the iridium-catalyzed allylic alkylation of substituted 5H-oxazol-4-ones 20 or 5H-thiazol-4-ones 24 (Scheme 1.5). Application of the previously developed conditions to the reaction of 5H-oxazol-4-ones 20 with cinnamyl carbonates failed to yield desired allylic alkylation products 23 (Scheme 1.5a). The yields were improved by examining a number of organic and inorganic bases in combination with silver phosphate 17. However, it was not until a substoichiometric amount of diethyl zinc, allylic acetate 21, and preformed catalyst 22
were used in place of the silver phosphate that good diastereoselectivities were achieved (up to 18:1 dr). The authors propose that the addition of diethyl zinc leads to the formation of zinc enolate aggregates ranging from dimers to tetramers, which in turn impart facial selectivity to the prochiral nucleophile.

Scheme 1.5 Cation control of diastereoselectivity in iridium-catalyzed allylic alkylation of a) 5H-oxazol-4-ones 20 and b) 5H-thiazol-4-ones 24 by Hartwig

Application of the optimal conditions developed for 5H-oxazol-4-ones 20 using diethyl zinc does not afford a diastereoselective reaction (1.3:1 dr) with substituted 5H-thiazol-4-ones 24 (Scheme 1.5b). Instead, the authors achieved diastereoselectivity using a magnesium enolate formed from magnesium bis(diisopropyl)amide. The aggregation states of magnesium enolates, which are generally thought to be higher order aggregates than that of the corresponding zinc enolates, are believed to be responsible for the difference in diastereoselectivity. The authors also found that tert-butyl carbonate electrophiles 25 further improve the diastereoselectivities (up to 13:1 dr) for this nucleophile class.
In 2013, our group pioneered the discovery of diastereo- and enantioselective iridium-catalyzed allylic alkylation chemistry of cyclic enolates for the formation of vicinal tertiary and all-carbon quaternary stereocenters (Scheme 1.6).\textsuperscript{6b} Initial investigations involving tetralone 27 revealed that a wide variety of aryl- and heteroaryl-substituted allylic carbonates 28 react to provide products 29 with high yields and stereoselectivities (Scheme 1.6a). The use of Me-THQphos (L\textsubscript{2}) as the chiral ligand and LiBr as a stoichiometric additive were found to be critical in attaining high selectivity. We postulate that LiBr results in lithium enolate aggregates, similar to those proposed by Hartwig.\textsuperscript{8b} In further investigations, we found that reactions involving various monocyclic substrates 30 afford the corresponding products 31 with similarly high yields and selectivities to those of the tetralone-based nucleophiles (Scheme 1.6b). Of note, the use of electron-deficient aryl-substituted electrophiles leads to an erosion in regioselectivity (50:50 to 71:29 branched/linear) in reactions of bicyclic nucleophiles.

**Scheme 1.6** Allylic alkylation of a) bicyclic $\beta$-ketoesters 27 and b) monocyclic $\beta$-ketoesters 30 by Stoltz
Studies toward substrate scope expansion of this reaction led to the successful allylic alkylation of extended enolates derived from unsaturated β-ketoester 33 (Scheme 1.7). Though the yields and selectivities were generally found to be lower than the corresponding saturated analogs (vide supra), allylic alkylation at the α-carbon atom of the extended enolate was achieved to provide products 35 bearing an additional olefin for further functionalization of the molecule.

Scheme 1.7 Allylic alkylation of extended enolates by Stoltz

In 2013, Hartwig found that non-stabilized enolates 36 undergo selective iridium-catalyzed allylic alkylation reactions to form vicinal tertiary and all-carbon quaternary stereocenters using preformed iridium complex 22 and BaOt-Bu (Scheme 1.8). In all cases, products 37 are afforded with excellent enantioenrichment (>98% ee), and even simple cyclohexanone derivatives provide good selectivity for allylic alkylation of the corresponding thermodynamic enolate. This protocol is currently the only reported set of conditions for cyclic nucleophiles that is not limited to softer enolate equivalents (e.g., malonates and β-ketoesters).
Scheme 1.8 Allylic alkylation of non-stabilized enolates by Hartwig

\[
\begin{align*}
&\text{R}^1 = \text{alkyl, aryl, benzyl, OMe} & \text{R}^2 = \text{aryl or alkenyl}
\end{align*}
\]

Scheme 1.9 Dual catalyst-promoted allylic alkylation of aldehydes by Carreira

1.2.2 DUAL CATALYST-CONTROLLED PROCESSES

Methodology that allows for the selective synthesis of all four branched stereoisomers from one set of starting materials is highly sought after in the field of allylic alkylation. However, controlling the facial selectivity of both the nucleophile and the electrophile is a daunting task for a single catalyst. Thus, the use of two catalysts has been required to achieve stereodivergence.

In 2013, Carreira disclosed the first dual catalytic allylic alkylation to construct vicinal tertiary and all-carbon quaternary stereocenters via the use of cinchona alkaloid-derived primary amine \textbf{L}4 and phosphoramidite ligand \textbf{L}5 (Scheme 1.9). With the
appropriate combination of enantiomers of ligand \( L_5 \) and pseudo-enantiomers of \( L_4 \), functionalized aldehyde 40, or any of the three other corresponding stereoisomers, can be obtained with little erosion of selectivity due to mismatched catalysts from aldehyde 38 and branched alcohol 39. The authors propose that the lack of an apparent mismatched pair of catalysts likely arises from a high degree of planarity between the two chiral intermediates in the carbon–carbon bond-forming event. During the course of reaction optimization, the authors discovered that an acid co-catalyst is extremely important for high stereoselectivity, with trichloroacetic acid being optimal. This pioneering study set the foundation for future work using the powerful combination of enamine and iridium catalysis.

Scheme 1.10 Proline-derived dual catalysis by Carreira

In a second-generation protocol, Carreira utilized proline-derived amine \( L_6 \) for the formation of vicinal tertiary stereocenters (Scheme 1.10).\(^8c\) While seemingly simpler from a steric perspective, this transformation in fact produces a number of additional challenges; specifically, both the starting material and allylic alkylation products are potential electrophiles for aldol processes, and the products are susceptible to
epimerization. Nevertheless, the authors found that the appropriate selection of the enantiomers of L5 and L6 allows for the full complement of stereoisomers to be accessed with good to excellent selectivity. Unlike with the cinchona alkaloid-derived catalyst L4 (Scheme 1.9), a significant mismatched pair of catalysts is observed (7:1 dr mismatched versus 20:1 dr matched). In this work, the authors found dimethyl hydrogen phosphate to be the optimal acid co-catalyst (42, R = alkyl). In a follow-up study, the authors reported that this method tolerates α-heteroatoms (42, R = NPhth or OBn) in similarly high yields and selectivities, though trichloroacetic acid is required as the co-catalyst. 8d

Scheme 1.11 Diastereoablative allylic alkylation of 46 by Stoltz

Our group has developed a two-step procedure for the divergent synthesis of various stereoisomers of cyclohexanone derivatives (Scheme 1.11). 6b Trimethylsilyl ethyl ester 46 is readily accessible via the aforementioned iridium-catalyzed allylic alkylation (Scheme 1.6). The use of the two pseudo-enantiomeric phosphinooxazoline (PHOX) ligands L7 and L8 allows for a fluoride-triggered diastereoablative palladium-catalyzed allylic alkylation, delivering either 45 or 47 selectively. While there is a significant difference in selectivities between the two pathways (8:1 dr mismatched versus 18:1 dr
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matched), both palladium-catalyzed allylic alkylation products are obtained in good yields with no loss in enantioselectivity.

Finally, in 2016, Zhang developed a bimetallic dual catalysis strategy for the stereodivergent allylic alkylation of α-hydroxyketones 49 using a chiral iridium complex derived from phosphoramidite L9 and a chiral zinc–ProPhenol (L10) species.7b This method does not require the use of an exogenous base and a range of α-hydroxyl-γ,δ-unsaturated ketones 48/51 containing vicinal stereocenters can be accessed in good yields and stereoselectivities utilizing this protocol. Moreover, with the appropriate combination of L9 and L10 enantiomers, any stereoisomer of product can be constructed with the dual catalytic strategy; however, a significant mismatched pair of catalysts is observed (15:1 dr matched versus 6:1 dr mismatched).

Scheme 1.12 Bimetallic dual catalytic allylic alkylation by Zhang
1.3 REACTION OPTIMIZATION

Based on the precedent from the aforementioned reports of diastereo-, enantio-, and regioselective iridium-catalyzed allylic alkylation, our studies commenced with an exploration of the efficacy of additives, leaving groups, bases, and ligands on the selectivity of the reaction between α-carboxymethyl tetralone (52) and crotyl electrophile 53. Using our previously reported conditions for iridium-catalyzed allylic alkylations with cinnamyl-derived electrophiles as a starting point, the reactivity of tetralone 52 was first investigated with crotyl carbonate in the presence of catalytic phosphoramidite L2·½[Ir(cod)Cl]2 and either LiBr (Table 1.1, entry 1), LiO\textsubscript{t}-Bu (entry 2), or a combination of LiBr and LiO\textsubscript{t}-Bu (entry 3). Unfortunately, while these conditions resulted in excellent conversion and good diastereoselectivity, low levels of regioselectivity were observed. As our earlier work on cinnamyl-derived electrophiles revealed that the regioselectivity improved as carbocation stability increased (i.e., increasingly electron-rich aromatic cinnamyl derivatives), we reasoned that the poor regioselectivity in this case was likely due to the minimal stabilization of the carbocation afforded by the methyl substituent of 53. Specifically, we hypothesized that the attenuated carbocation stability could be effecting slow equilibration between diastereomers of the iridium π-allyl complex, translating into diminished regioselectivity. Previous reports have proposed that LiCl may facilitate the equilibration leading to increased regio- and enantioselectivity, but we noted little improvement in selectivity with the use of LiCl as compared to LiBr (entry 4).

We subsequently turned our attention to the nature of the leaving group on the electrophile. We envisioned that switching from crotyl methyl carbonate to crotyl
chloride would render the anions in solution congruent and perhaps make the effect of the chloride anions more pronounced. To our delight, regioselectivity is dramatically improved with the use of crotyl chloride, albeit with diminished diastereoselectivity (entry 5).

### Table 1.1 Optimization of reaction parameters

| Entry | L Base (200 mol %) | Additive (mol %) | LG | 52:53 | Yield 54-55 (%)<sup>a</sup> | 54:55<sup>b</sup> | dr of 54<sup>c</sup> | ee of 54<sup>d</sup> (%)<sup>e</sup> |
|-------|-------------------|-----------------|----|------|------------------|---------------|-------------|----------------|---------------|
| 1     | L2 – LiBr (100)   | OCO<sub>2</sub>Me | 2:1| 100  | 55:45            | 6.4:1         | –           | –             |
| 2     | L2 LiO<sub>t</sub>-Bu – | OCO<sub>2</sub>Me | 2:1| 85   | 34:66            | 5.3:1         | –           | –             |
| 3     | L2 LiO<sub>t</sub>-Bu LiBr (100) | OCO<sub>2</sub>Me | 2:1| 100  | 45:55            | 6.8:1         | –           | –             |
| 4     | L2 LiO<sub>t</sub>-Bu LiCl (100) | OCO<sub>2</sub>Me | 2:1| 69   | 50:50            | 7.2:1         | –           | –             |
| 5     | L2 LiO<sub>t</sub>-Bu LiCl (100) | Cl             | 2:1| 94   | 86:14            | 4.8:1         | –           | –             |
| 6     | L2 proton sponge LiCl (100) | Cl             | 2:1| 100  | 93:7             | 7.9:1         | 66          | –             |
| 7     | L9 proton sponge LiCl (100) | Cl             | 2:1| 79   | 69:31            | 2.4:1         | –           | –             |
| 8     | L5 proton sponge LiCl (100) | Cl             | 2:1| 91   | 52:48            | 1.5:1         | –           | –             |
| 9     | L11 proton sponge LiCl (100) | Cl             | 2:1| 46   | 95:5             | 6.0:1         | 96          | –             |
| 10    | L11 proton sponge – | Cl             | 2:1| trace| –                | –             | –           | –             |
| 11    | L11 proton sponge LiCl (400) | Cl             | 2:1| 70   | 94:6             | 6.7:1         | 97          | –             |
| 12    | L11 proton sponge LiCl (400) | Cl             | 1:1| 55   | 95:5             | 5.3:1         | 98          | –             |
| 13    | L11 proton sponge LiCl (400) | Cl             | 1:2| 76   | >95:5            | 5.3:1         | 85          | –             |

[a] Reactions performed on 0.1 mmol scale. [b] <sup>1</sup>H NMR yield based on internal standard of the mixture of diastereomers. [c] Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. [d] Determined by chiral SFC analysis. [e] TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene, proton sponge = 1,8-bis(dimethylamino)napthalene.

Previous work demonstrating the marked effect of bases on regio- and diastereoselectivity in iridium-catalyzed allylic alkylations prompted an extensive
We found that the use of proton sponge in place of LiOt-Bu afforded the desired branched product 54 with high regioselectivity (93:7, 54:55) and diastereoselectivity (7.9:1 dr), though in a modest 66% enantiomeric excess (entry 6). A brief study of ligand frameworks (entries 7–9) revealed 3,3’-diphenyl-phosphoramidite L11 to be optimal. Using L11, allylic alkylation product 54 is obtained in excellent enantioselectivity (96% ee) with comparable regio- and diastereoselectivities to L2, though in considerably lower yield (46%, entry 9). Efforts to increase the yield revealed super-stoichiometric levels of LiCl to be both essential and correlative to the conversion (entries 10 and 11). Ultimately, we found that the combination of catalytic phosphoramidite L11·½ [Ir(cod)Cl]2, 200 mol % proton sponge, and 400 mol % LiCl deliver product 54 in 78% yield (entry 11) with an exceptional branched to linear ratio (94:6, 54:55), diastereoselectivity (6.7:1 dr), and enantioselectivity (97% ee). Finally, it should be noted that we observed optimal conversion and selectivity using a 2:1 nucleophile to electrophile ratio; however, the nucleophile and electrophile stoichiometry can be varied (1:1 or 1:2) without dramatically affecting reaction conversion or selectivity, rendering the reaction synthetically practical (entries 12 and 13). Moreover, the excess equivalent of nucleophile can be re-isolated during purification.

1.4 SUBSTRATE SCOPE EXPLORATION

With the optimized conditions identified, we explored the substrate scope of this diastereo-, enantio-, and regioselective allylic alkylation reaction (Table 1.2). Generally, the process is tolerant of a wide range of substituents and functionality on both the arene
and ester groups. We found that increasing the size of the ester moiety (–CO₂Me, –CO₂Et, –CO₂i-Pr) results in formation of the corresponding products 54, 58a, and 58b in increasingly improved regio- and diastereoselectivity but moderately diminished yields. As a balance between yield and selectivity, we moved forward in our investigation using α-carboxyethyl tetralone derivatives. Moreover, we were pleased to find that a (2-trimethylsilyl)ethyl substrate undergoes allylic alkylation to provide 58c with good selectivity, albeit in modest yield. Alkylation product 58c may undergo subsequent fluoride-triggered allylic alkylation mediated by palladium to provide either diastereomer of the bis-alkylation product with catalyst control.12

We sought to further examine the scope of the reaction by exploring the diversity of substitution permitted on the tetralone aromatic ring. Gratifyingly, a wide variety of both electron-donating and withdrawing groups are tolerated at varying positions, though an electronic effect was noted on enantioselectivity. We observed that substrates bearing electron-donating groups (MeO–, Me₂N–) at the 6-position give products 58d and 58e with slightly diminished enantioselectivity (84–86% ee). Conversely, substrates with electron-withdrawing groups (7-MeO–, 7-NO₂–, 6-Br–) afford the corresponding products 58f, 58g, and 58h in excellent enantioselectivity (94–98% ee). Additionally, 5,7-dimethyl-substituted tetralone 58i is furnished in comparable selectivity to unsubstituted α-carboxyethyl tetralone 58a. In all examples, good regio- and diastereoselectivity is observed. Furthermore, during the course of our investigations we found that the β-ketoester moiety is crucial to the reaction. Substrates with this functionality replaced with either a nitrile or ketone provide the corresponding products 58j and 58k in decreased selectivities.
A broader investigation of the substrate scope reveals additional limitations of the catalytic system (Table 1.3). Foremost, no allylic alkylation is observed with alkyl-substituted allicy chloride derivatives other than crotyl chloride (57). With respect to limitations on the nucleophile substrate scope, altering the saturated ring size (e.g., a benzosuberone-derived nucleophile) or employing a 2-tetralone-derived nucleophile...
leads to products 60a and 60b in significantly diminished diastereo- and regioselectivities. Additionally, bicyclic nucleophiles containing fused heterocycles give products 60c and 60d in decreased yields. Use of a chromanone-based nucleophile affords allylic alkylation product 60e with no diastereocontrol. Furthermore, we observed that monocyclic nucleophiles, including lactones, lactams, and piperidones, afford the corresponding products 60f, 60g, 60h, 60i, and 60j in only modest yields. Moreover, with respect to linear nucleophiles, we noted minimal or no conversion to product when a quaternary stereocenter is formed in the allylic alkylation reaction (e.g., 60k, 60l, and 60m), and in the case of propargyl 60m, we hypothesize that the alkyne functionality leads to catalyst poisoning. However, we did observe excellent reactivity for α-halogenated linear nucleophiles, which reacted to give products 60n and 60o in high yield and regioselectivity, though inconsistent diastereo- and enantioselectivities. Finally, we were interested to find that in contrast to the case with a tetralone-derived nucleophile, exchanging the β-ketoester moiety for a nitrile on a linear nucleophile gave product 60p in excellent yields and selectivities.
Table 1.3 Substrate scope limitations

<table>
<thead>
<tr>
<th>Substrate</th>
<th>EWG</th>
<th>Nucleophile/electrophile</th>
<th>Reaction Conditions</th>
<th>THF (0.1 M), 25 °C, 18 h</th>
<th>Combined Isolated Yield</th>
<th>B:l</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>60a</td>
<td>O</td>
<td>+</td>
<td>[Ir(cod)Cl]₂ (2 mol %)</td>
<td>(S,S₉)-L11 (4 mol %)</td>
<td>59a–p</td>
<td>60a</td>
<td>90% yield 97:3 b:l 1.5:1 dr</td>
<td>0% ee</td>
</tr>
<tr>
<td>60b</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60b</td>
<td>90% yield 67:33 b:l 2:1 dr</td>
<td>0% ee</td>
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<tr>
<td>60c</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60c</td>
<td>trace yield</td>
<td>0% ee</td>
</tr>
<tr>
<td>60d</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60d</td>
<td>50% yield &gt;95:5 b:l 1.4:1 dr</td>
<td>0% ee</td>
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<tr>
<td>60e</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60e</td>
<td>trace yield 86:14 b:l 1.2:1 dr</td>
<td>0% ee</td>
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<tr>
<td>60f</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60f</td>
<td>90% yield 67:33 b:l 2:1 dr</td>
<td>0% ee</td>
</tr>
<tr>
<td>60g</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60g</td>
<td>50% yield 86:14 b:l 2:1 dr</td>
<td>0% ee</td>
</tr>
<tr>
<td>60h</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60h</td>
<td>50% yield 86:14 b:l 2:1 dr</td>
<td>0% ee</td>
</tr>
<tr>
<td>60i</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60i</td>
<td>50% yield 86:14 b:l 2:1 dr</td>
<td>0% ee</td>
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<tr>
<td>60j</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60j</td>
<td>50% yield 86:14 b:l 2:1 dr</td>
<td>0% ee</td>
</tr>
<tr>
<td>60k</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60k</td>
<td>no reaction</td>
<td>0% ee</td>
</tr>
<tr>
<td>60l</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60l</td>
<td>50% yield 86:14 b:l 2:1 dr</td>
<td>0% ee</td>
</tr>
<tr>
<td>60m</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60m</td>
<td>50% yield 86:14 b:l 2:1 dr</td>
<td>0% ee</td>
</tr>
<tr>
<td>60n</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60n</td>
<td>50% yield 86:14 b:l 2:1 dr</td>
<td>0% ee</td>
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<tr>
<td>60o</td>
<td>O</td>
<td>+</td>
<td>TBD (10 mol %), LiCl (400 mol %) proton sponge (200 mol %)</td>
<td>THF (0.1 M), 25 °C, 18 h</td>
<td>59a–p</td>
<td>60o</td>
<td>50% yield 86:14 b:l 2:1 dr</td>
<td>0% ee</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.2 mmol scale with 2:1 nucleophile/electrophile. [b] Reaction performed with (S,S₉)-L2. [c] ¹H NMR yield based on internal standard of the mixture of diastereomers; combined isolated yield of branched and linear products given in parentheses. [d] Determined by ¹H NMR analysis of the crude reaction mixture. [e] Reaction performed with 1:1.1 nucleophile/electrophile, 400 mol % proton sponge, and 0.5 M THF. [f] Determined by chiral SFC or HPLC analysis.
1.5 PRODUCT TRANSFORMATIONS

To demonstrate the synthetic utility of this method, we carried out a number of transformations on allylic alkylation products 54 and 58a (Figure 1.3). We found that the addition of allylmagnesium chloride proceeds smoothly to furnish alcohol 61 in 71% yield as a single diastereomer. In a two-step protocol, addition of allyl Grignard with subsequent ring-closing metathesis allows rapid access to tricycle 62 bearing three contiguous stereocenters in 58% yield over two steps. The resultant cyclohexene moiety undergoes diastereoselective dihydroxylation to provide triol 63 bearing five contiguous stereocenters in 59% yield. Both the ester and the ketone functionalities of 58a can be reduced to provide 1,3-diol 64 in 43% yield. Dihydroxylation of the pendant olefin of 58a proceeds with concomitant lactonization to provide highly functionalized γ-butyrolactone 65 in 65% yield. Functionalized γ-butyrolactone moieties are highly prevalent and estimated to be present in about 10% of all natural products. Additionally, Corey–Chaykovsky epoxidation proceeds smoothly, furnishing 66 in 82% yield. Notably, all six of these derivatizations proceed with excellent diastereoselectivity to facilitate the synthesis of at least three contiguous stereocenters, demonstrating the ease with which complexity can be added to these high-value products.
**Figure 1.3** Product transformations of allylic alkylation products 54 and 58a


1.6 CONCLUSIONS

In summary, we have developed the first enantioselective transition-metal-catalyzed allylic alkylation reaction forming vicinal tertiary and all-carbon quaternary stereocenters between prochiral enolates and an alkyl-substituted electrophile. Critical to the success of this new reaction is the identity and ubiquity of the chloride counterion in addition to the use of proton sponge, the combination of which affords excellent regio- and enantioselectivities along with good yields and diastereoselectivities. Additionally, a number of transformations were carried out on the alkylation products to demonstrate the value of this method in rapidly accessing highly functionalized, stereochemically rich polycyclic scaffolds.
1.7 EXPERIMENTAL SECTION

1.7.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Commercially obtained reagents were used as received. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Oakwood Chemicals and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) and preparatory TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, KMnO$_4$, or p-anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. Preparatory HPLC was performed with an Agilent 1200 Series HPLC equipped with two Agilent Zorbax RX-sil silica columns (9.4 x 250 mm) in series. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD-H column (4.6 mm x 25 cm) in series with a Chiralpak AD column (4.6 mm x 25 cm) or a Chiralpak IC column (4.6 mm x 25 cm), all obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Analytical SFC was performed with a Mettler SFC supercritical CO$_2$ analytical chromatography system utilizing a Chiralpak IC column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. $^1$H NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CHCl$_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer.
and are reported relative to residual CDCl$_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of benzene (δ 7.36 ppm), water (δ 1.56 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm$^{-1}$). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell, and are reported as: [α]$_D^T$ (concentration in g/100 mL, solvent).

1.7.1.1 Preparation of Known Compounds

Previously reported methods were used to prepare ligands (S$_a$)-L$_2$,$^{11a,14}$ (S$_a$)-L$_{11}$,$^{11a,14}$ and (S$_a$)-L$_9$,$^{15}$ as well as starting materials 52,$^{16}$ 56a,$^{16}$ 56f,$^{17}$ 56d,$^{18}$ 56i,$^{19}$ and 56j.$^{20}$
1.7.2 Experimental Procedures and Spectroscopic Data

1.7.2.1 Experimental Procedures and Spectroscopic Data for the Synthesis of Tetralone Substrates

Isopropyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (56b). A solution of methyl ester 52\textsuperscript{16} (0.75 g, 3.7 mmol, 1 equiv), Bu\textsubscript{2}SnO (0.091 g, 0.37 mmol, 0.1 equiv), and IPA (15 mL) was heated under reflux for 72 h then concentrated onto silica and purified by silica gel flash column chromatography (3% Et\textsubscript{2}O/hexanes) to give isopropyl ester 56b (1:1 mixture of enol/keto isomers) as a colorless oil (0.62 g, 72% yield): \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 12.56 (s, 0.5H), 8.05 (ddd, \(J = 7.8, 1.5, 0.6\) Hz, 0.5H), 7.81 – 7.77 (m, 0.5H), 7.49 (td, \(J = 7.8, 1.5\) Hz, 0.5H), 7.35 – 7.23 (m, 2H), 7.20 – 7.14 (m, 0.5H), 5.14 (dp, \(J = 17.1, 6.2\) Hz, 1H), 3.56 (dd, \(J = 10.5, 4.7\) Hz, 0.5H), 3.13 – 2.93 (m, 1H), 2.81 (dd, \(J = 8.6, 6.9\) Hz, 1H), 2.60 – 2.52 (m, 1H), 2.53 – 2.43 (m, 0.5H), 2.35 (ddt, \(J = 13.5, 5.7, 4.7\) Hz, 0.5H), 1.32 (d, \(J = 6.3\) Hz, 3H), 1.28 (dd, \(J = 6.3, 2.8\) Hz, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 193.6, 172.5, 170.0, 165.0, 143.8, 139.5, 133.9, 132.0, 130.5, 130.3, 128.9, 127.8, 127.5, 127.0, 126.7, 124.4, 97.5, 69.0, 68.2, 54.9, 27.9, 27.8, 26.5, 22.2 (2C), 21.9, 21.9, 20.7; IR (Neat Film, NaCl) 3070, 3027, 2980, 2937, 2847, 1736, 1687, 1644, 1618, 1571, 1454, 1384, 1322, 121, 1214, 1106, 1084, 949, 831, 770, 744 cm\textsuperscript{-1}; HRMS (MM: ESI-APCI+) \textit{m/z} calc’d for C\textsubscript{14}H\textsubscript{17}O\textsubscript{3} [M+H]\textsuperscript{+}: 233.1172, found 233.1174.
2-(Trimethylsilyl)ethyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (56c). A solution of LiHMDS (1.83 g, 10.9 mmol, 2 equiv) in THF (20 mL) was added dropwise to a solution of 1-tetralone (0.804 g, 5.50 mmol, 1 equiv) in THF (20 mL) via cannula at −78 °C. After 1.5 h at −78 °C, a solution of 2-(trimethylsilyl)ethyl 1H-imidazole-1-carboxylate (1.39 g, 6.55 mmol, 1.2 equiv) in THF (5 mL) was then added. The resulting reaction mixture was allowed to warm to ambient temperature and stirred for 18 h. The reaction was quenched with the addition of saturated NH₄Cl aqueous solution (40 mL) and the aqueous layer was then extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by CombiFlash EZ Prep (12 g silica, 1→5% Et₂O/hexanes, 30 min) to provide ester 56c (3:1 mixture of enol/keto isomers) as a colorless oil (0.40 g, 25%): ¹H NMR (400 MHz, CDCl₃) δ 12.57 (s, 0.75H), 8.08 (dd, J = 7.8, 1.4 Hz, 0.25H), 7.83 (dd, J = 7.8, 1.4 Hz, 0.75H), 7.52 (td, J = 7.8, 1.4 Hz, 0.25H), 7.39 – 7.24 (m, 2H), 7.23 – 7.16 (m, 0.75H), 4.41 – 4.14 (m, 2H), 3.61 (dd, J = 10.3, 4.7 Hz, 0.25H), 3.14 – 2.97 (m, 0.5H), 2.83 (dd, J = 8.9, 6.6 Hz, 1.5H), 2.64 – 2.57 (m, 1.5H), 2.56 – 2.47 (m, 0.25H), 2.38 (m, 0.25H), 1.24 – 0.99 (m, 2H), 0.10 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 193.4, 173.1, 170.5, 165.1, 155.5, 143.8, 139.5, 134.0, 131.9, 131.0, 130.2, 128.9, 127.9, 127.5, 127.0, 126.7, 124.4, 97.2, 66.2, 63.8, 62.9, 54.8, 27.9, 27.8, 26.5, 20.7, 17.7, 17.5, 17.5, −1.3, −1.39, −1.41; IR (Neat Film, NaCl) 3071, 3028, 2954, 2898, 2846, 1739, 1689, 1644, 1620, 1571, 1454, 1394, 1355, 1325, 1270, 1212,
1175, 1133, 1084, 859, 837, 769 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₆H₂₃O₃Si [M+H]^+: 291.1417, found 291.1421.

Ethyl 6-(dimethylamino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (56e).

To a suspension of NaH (0.98 g, 29 mmol, 3.7 equiv, 60 wt %) in THF (10 mL) was added diethyl carbonate (1.9 mL, 16 mmol, 2 equiv). The reaction mixture was brought to reflux at which point a solution of 6-(dimethylamino)-3,4-dihydronaphthalene-1(2H)-one (1.5 g, 7.9 mmol, 1 equiv) in THF (10 mL) was added dropwise via addition funnel over 15 min. The reaction mixture was heated to reflux for an additional 18 h then allowed to cool to ambient temperature, whereupon it was quenched with conc. AcOH (10 mL) and diluted with Et₂O (30 mL). The organic layer was washed with brine (5 x 10 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by CombiFlash EZ Prep (12 g silica, 10→20% EtOAc/hexanes, 30 min) to provide dimethylamine 56e (keto isomer) as a tan solid (1.36 g, 66%): ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 9.0 Hz, 1H), 6.60 (dd, J = 9.0, 2.6 Hz, 1H), 6.36 (d, J = 2.6 Hz, 1H), 4.32 - 4.12 (m, 2H), 3.52 (dd, J = 10.2, 4.7 Hz, 1H), 3.06 (s, 6H), 2.99 - 2.83 (m, 2H), 2.44 (m, 1H), 2.29 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 191.4, 171.2, 153.8, 145.9, 130.1, 128.5, 120.8, 110.6, 109.3, 61.2, 54.5, 40.2, 28.6, 26.8, 14.4; IR (Neat Film, NaCl) 2935, 1735, 1660, 1593, 1521, 1449, 1372, 1308, 1197, 1121, 1084, 923 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₅H₂₀NΟ₃ [M+H]^+: 262.1443, found 262.1473.
**Ethyl 7-nitro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (56g).** A solution of LiHMDS (1.8 g, 11 mmol, 2.1 equiv) in THF (20 mL) was added dropwise to a solution of 7-nitro-3,4-dihydronaphthalene-1(2H)-one (1.0 g, 5.2 mmol, 1 equiv) in THF (20 mL) via cannula at −78 °C. The reaction was stirred for 1.5 h at −78 °C, whereupon ethyl cyanoformate (0.61 g, 6.2 mmol, 1.2 equiv) was added. The resulting reaction mixture was allowed to warm to ambient temperature and was stirred for 18 h. The reaction was quenched with the addition of saturated NH₄Cl aqueous solution (40 mL) and the aqueous layer was then extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (8% EtOAc/hexanes) to provide nitroarene 56g (enol isomer) as a colorless solid (114 mg, 8%): ¹H NMR (400 MHz, CDCl₃) δ 12.45 (s, 1H), 8.65 (d, J = 2.4 Hz, 1H), 8.20 (dd, J = 8.3, 2.4 Hz, 1H), 7.37 (dt, J = 8.3, 1.0 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.95 (t, J = 7.8 Hz, 2H), 2.66 (dd, J = 8.8, 6.9 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 172.4, 162.5, 147.3, 146.3, 131.6, 128.5, 125.0, 119.6, 98.9, 61.2, 28.0, 20.2, 14.4; IR (Neat Film, NaCl) 2996, 2962, 2907, 2858, 1755, 1648, 1514, 1401, 1344, 1270, 1252, 1216, 1068, 1027, 907, 806, 745 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₃H₁₄NO₅ [M+H]⁺: 264.0872, found 264.0871. Please note that a minor amount of keto isomer is present in the spectra, which does not impact the characterization.
Ethyl 6-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (56h). A solution of LiHMDS (1.8 g, 11 mmol, 2.1 equiv) in THF (20 mL) was added dropwise to a solution of 6-bromo-3,4-dihydronaphthalene-1(2H)-one \(^{16}\) (1.2 g, 5.2 mmol, 1 equiv) in THF (20 mL) via cannula at \(-78 \, ^\circ\text{C}\). The reaction was stirred for 1.5 h at \(-78 \, ^\circ\text{C}\), whereupon ethyl cyanoformate (0.61 g, 6.2 mmol, 1.2 equiv) was added. The resulting reaction mixture was allowed to warm to ambient temperature and was stirred for 18 h. The reaction was quenched with the addition of saturated NH\(_4\)Cl aqueous solution (40 mL) and the aqueous layer was then extracted with Et\(_2\)O (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude residue was purified by CombiFlash EZ Prep (12 g silica, 5\(\rightarrow\)20\% EtOAc/hexanes, 30 min) to provide bromide 56h (4:1 mixture of enol/keto isomers) as a tan solid (0.63 g, 41\%): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 12.44 (s, 0.8H), 7.90 (d, \(J = 8.3 \, \text{Hz}\), 0.2H), 7.64 (d, \(J = 8.3 \, \text{Hz}\), 0.8H), 7.46 – 7.38 (m, 1.2H), 7.33 (dd, \(J = 2.0\), 1.0 Hz, 0.8H), 4.27 (p, \(J = 7.0 \, \text{Hz}\), 2H), 3.58 (dd, \(J = 10.0\), 4.7 Hz, 0.2H), 3.09 – 2.90 (m, 0.4H), 2.78 (dd, \(J = 8.9\), 6.7 Hz, 1.6H), 2.62 – 2.52 (m, 1.6H), 2.53 – 2.27 (m, 0.4H), 1.34 (t, \(J = 7.1 \, \text{Hz}\), 2.4H), 1.29 (t, \(J = 7.1 \, \text{Hz}\), 0.6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 192.5, 172.7, 170.0, 164.2, 145.4, 141.4, 131.8, 130.7, 130.6, 130.0 129.9, 129.6, 129.3, 129.1, 126.0, 124.9, 97.4, 61.6, 60.8, 54.4, 27.7, 27.5, 26.3, 20.5, 14.4, 14.3; IR (Neat Film, NaCl) 2979, 2958, 2902, 2848, 1740, 1689, 1645, 1616, 1588, 1558, 1479, 1406, 1377, 1267, 1214, 1195, 1096, 1025, 845, 829, 758 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{13}\)H\(_{14}\)BrO\(_3\) [M+H]\(^+\): 297.0126, found 297.0134.
2-Acetyl-3,4-dihyronaphthalen-1(2H)-one (56k). To a suspension of NaH (0.49 g, 21 mmol, 2 equiv, 60 wt %) in EtOAc (2 mL) cooled to 0 °C, a solution of 1-tetralone (1.5 g, 10 mmol, 1 equiv) in toluene (0.5 mL) was added dropwise. After H₂ evolution ceased, the resulting solution was heated to 40 °C for 3 h. The reaction mixture was then allowed to cool to ambient temperature, whereupon it was quenched with MeOH (5 mL), poured onto H₂O (20 mL), neutralized with conc. HCl, and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to give ketone 56k (enol isomer) as a pale yellow solid (0.51 g, 26%): ¹H NMR (400 MHz, CDCl₃) δ 7.94 (dd, J = 7.7, 1.4 Hz, 1H), 7.40 (td, J = 7.7, 1.4 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.20 (dq, J = 7.7, 0.7 Hz, 1H), 2.87 (dd, J = 8.5, 6.3 Hz, 2H), 2.68 – 2.59 (m, 2H), 2.24 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 194.0, 177.0, 140.9, 132.0, 131.2, 127.7, 127.0, 126.0, 106.1, 28.4, 24.1, 22.9; IR (Neat Film, NaCl) 3061, 2940, 2893, 2838, 1598, 1567, 1414, 1354, 1294, 1213, 1156, 1079, 1033, 974, 902, 788, 737, 548 cm⁻¹; HRMS (MM: ESI-APCI⁺) m/z calc’d for C₁₂H₁₃O₂ [M+H]⁺: 189.0910, found 189.0908. Please note that the exchangeable enol proton was not observed in the ¹H NMR spectrum.
1.7.2.2 Additional Optimization of Reaction Parameters

**Table 1.4** Additional optimization of reaction parameters

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[a] Reactions performed with 0.1 mmol of 53, 0.2 mmol of 52, 0.2 mmol of base, and 0.4 mmol of additive. [b] Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. [c] Trace conversion.
1.7.2.3 General Procedure for Optimization Reactions (Table 1.1 & 1.4)

In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]₂ (1.3 mg, 0.0020 mmol, 2 mol %), ligand L (0.0040 mmol, 4 mol %), TBD (1.4 mg, 0.010 mmol, 10 mol %), and THF (0.5 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with base, additive, tetralone 52 (0.20 mmol), and THF (0.25 mL). The pre-formed catalyst solution (vial A) was then transferred to vial B followed by 0.25 mL of a solution of crotyl electrophile 53 (0.2 M in THF). The vial was sealed and stirred at 25 °C. After 18 h, the vial was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc. The crude mixture was concentrated and dimethyl maleate (0.050 mmol in 0.5 mL CDCl₃) was added. The NMR yield (measured in reference to dimethyl maleate δ 6.28 ppm (s, 2H)), regioselectivity (branched product to linear product: 54:55), and diastereoselectivity were determined by ¹H NMR analysis of the crude mixture. The residue was purified by preparatory TLC (10% Et₂O/hexanes) to afford the combined branched (54/epi-54) and linear (55) products as an inseparable mixture. The major diastereomer (54) was isolated by preparatory HPLC (2% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; λ = 254 nm) and analyzed by chiral SFC (3% MeOH, 3.5 mL/min, Chiralpak AD-H column, λ = 254 nm).

1.7.2.4 General Procedure for the Iridium-Catalyzed Allylic Alkylation

Please note that the absolute configuration was determined only for compound 58f via x-ray crystallographic analysis. The absolute configuration for all other products
has been inferred by analogy. For respective HPLC and SFC conditions, please refer to Table 1.5.

**Methyl \((S)-2-((S)-\text{but-3-en-2-yl})-1-\text{oxo}-1,2,3,4-\text{tetrahydronaphthalene}-2-\text{carboxylate (54).}** In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added \([\text{Ir(cod)Cl}]_2\) (2.7 mg, 0.0040 mmol, 2 mol %), ligand \((S,S)\text{-L11 (4.9 mg, 0.0080 mmol, 4 mol %), TBD (2.8 mg, 0.020 mmol, 10 mol %), and THF (1 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with proton sponge (86 mg, 0.40 mmol, 200 mol %), tetralone 52 (82 mg, 0.40 mmol, 200 mol %), LiCl (34 mg, 0.80 mmol, 400 mol %), and THF (0.5 mL). The pre-formed catalyst solution (vial A) was then transferred to vial B followed by a solution of crotyl chloride 57 (18 mg, 0.20 mmol, 100 mol %) in THF (0.5 mL). The vial was sealed and stirred at 25 °C. After 18 h, the vial was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc. The crude mixture was concentrated and dimethyl maleate (0.10 mmol in 0.5 mL CDCl₃) was added. The NMR yield (74%, measured in reference to dimethyl maleate 𝛿 6.28 ppm (s, 2H)), regioselectivity (branched product to linear product, b:l = 93:7), and diastereoselectivity (dr = 6:1) were determined by ¹H NMR analysis of the crude mixture. The residue was purified by preparatory TLC (10% Et₂O/hexanes) to give the isolated yield of the branched and linear products (38.0 mg, 74% combined yield). The diastereomers were separated by preparatory HPLC (2% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; 𝜆 = 254 nm).
Major diastereomer 54 was isolated as a colorless oil: 96% ee; \([\alpha]_D^{25} – 48.5 (c 0.8,\text{ CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.05\ (\text{dd}, J = 7.9, 1.5, 0.5\ Hz, 1\text{H}), 7.45\ (\text{td}, J = 7.4, 1.5\ Hz, 1\text{H}), 7.30\ (\text{ddt}, J = 7.3, 6.9, 1.1\ Hz, 1\text{H}), 7.20\ (\text{dtt}, J = 7.6, 1.3, 0.7\ Hz, 1\text{H}), 5.82\ (\text{ddd}, J = 17.0, 10.2, 8.9\ Hz, 1\text{H}), 5.12 – 4.97\ (\text{m}, 2\text{H}), 3.64\ (\text{s}, 3\text{H}), 3.28 – 3.09\ (\text{m}, 2\text{H}), 2.90\ (\text{ddd}, J = 17.4, 4.9, 3.0\ Hz, 1\text{H}), 2.43\ (\text{ddd}, J = 13.7, 4.7, 3.0\ Hz, 1\text{H}), 2.22\ (\text{ddd}, J = 13.7, 12.3, 4.9\ Hz, 1\text{H}), 1.15\ (\text{d}, J = 6.9\ Hz, 3\text{H});\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 194.3, 171.2, 143.4, 139.1, 133.6, 132.7, 128.9, 128.2, 126.8, 116.6, 61.2, 52.5, 43.5, 27.8, 26.3, 16.6;\ IR (Neat Film, NaCl) 3073, 2951, 2850, 1732, 1688, 1454, 1434, 1290, 1241, 1220, 993, 917, 746 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc’d for C\(_{16}\)H\(_{19}\)O\(_3\) [M+H]\(^+\): 259.1329, found 259.1329; SFC conditions: 3% MeOH, 3.5 mL/min, Chiralpak AD-H column, \(\lambda = 254\ \text{nm}, t_R\) (min): major = 5.170, minor = 5.968.

Minor diastereomer epi-54 (which was inseparable from major diastereomer 54) was isolated as a colorless oil: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.05\ (\text{dd}, J = 7.9, 1.4\ Hz, 1\text{H}), 7.46\ (\text{td}, J = 7.5, 1.5\ Hz, 1\text{H}), 7.34 – 7.27\ (\text{m}, 1\text{H}), 7.23 – 7.16\ (\text{m}, 1\text{H}), 5.98\ (\text{ddd}, J = 17.2, 10.3, 7.8\ Hz, 1\text{H}), 5.12 – 5.00\ (\text{m}, 2\text{H}), 3.65\ (\text{s}, 3\text{H}), 3.27 – 3.05\ (\text{m}, 2\text{H}), 2.97 – 2.85\ (\text{m}, 1\text{H}), 2.45\ (\text{ddd}, J = 19.3, 13.7, 4.7, 3.2\ Hz, 1\text{H}), 2.17 – 2.10\ (\text{m}, 1\text{H}), 1.10\ (\text{d}, J = 7.0\ Hz, 3\text{H});\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 194.5, 171.3, 143.3, 139.9, 133.6, 132.7, 128.8, 128.2, 126.8, 116.2, 61.2, 52.5, 42.5, 28.5, 26.3, 15.0;\ IR (Neat Film, NaCl) 3072,
Chapter 1 – Stereoselective Iridium-Catalyzed Allylic Alkylation Reactions with Crotly Chloride

2951, 1734, 1686, 1601, 1453, 1438, 1289, 1240, 1219, 1000, 917, 808, 746 cm$^{-1}$. HRMS (MM: ESI-APCI+) $m/z$ calc’d for C$_{16}$H$_{19}$O$_3$ [M+H]$^+$: 259.1329, found 259.1332. Please note that the provided spectra for epi-54 reflect the inseparable mixture of epi-54 and 54, while the tabulated NMR data is for only epi-54.

Linear isomer 55 was isolated as a colorless oil: 23% ee; $[\alpha]_D^{25} -5.2$ (c 0.7, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.14 – 8.06 (m, 1H), 7.60 – 7.47 (m, 1H), 7.36 (tdd, $J = 7.8, 1.3, 0.6$ Hz, 1H), 7.29 – 7.23 (m, 1H), 5.68 – 5.56 (m, 1H), 5.56 – 5.40 (m, 1H), 3.73 (s, 3H), 3.19 – 3.08 (m, 1H), 2.97 (dt, $J = 17.3, 4.9$ Hz, 1H), 2.71 (ddt, $J = 7.2, 2.5, 1.2$ Hz, 2H), 2.57 (dt, $J = 13.8, 4.9$ Hz, 1H), 2.26 – 2.13 (m, 1H), 1.71 (dq, $J = 6.4, 1.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.3, 172.3, 143.5, 133.6, 132.1, 129.8, 128.9, 128.2, 126.9, 125.7, 57.8, 52.6, 37.7, 30.5, 26.0, 18.2; IR (Neat Film, NaCl) 2918, 2850, 1732, 1689, 1601, 1434, 1263, 1236, 1086, 973, 944, 802, 743 cm$^{-1}$. HRMS (MM: ESI-APCI+) $m/z$ calc’d for C$_{16}$H$_{19}$O$_3$ [M+H]$^+$: 259.1329, found 259.1324; HPLC conditions: 1% IPA, 1 mL/min, Chiralpak IC column, $\lambda = 254$ nm, $t_R$ (min): major = 19.785, minor = 24.041.

1.7.2.5 Spectroscopic Data for the Iridium-Catalyzed Allylic Alkylation Products

Ethyl (S)-2-(((S)-but-3-en-2-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (58a). Product 58a was prepared according to the general procedure and isolated by
preparatory TLC (10% Et₂O/hexanes) to give the isolated yield of the branched and linear products (30.3 mg, 56% combined yield). The major diastereomer was isolated as a colorless oil by preparatory HPLC (2% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; λ = 254 nm): 96% ee; \([\alpha]_D^{25} = -44.3\) (c 0.1, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) δ 8.04 (dd, \(J = 7.5, 1.5\) Hz, 1H), 7.44 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.31 – 7.26 (m, 1H), 7.19 (d, \(J = 7.5\) Hz, 1H), 5.84 (ddd, \(J = 17.0, 10.2, 8.8\) Hz, 1H), 5.20 – 4.96 (m, 2H), 4.24 – 3.95 (m, 2H), 3.26 – 3.08 (m, 2H), 2.89 (ddd, \(J = 17.4, 4.7, 3.0\) Hz, 1H), 2.41 (ddd, \(J = 13.7, 4.7, 3.0\) Hz, 1H), 2.21 (ddd, \(J = 13.7, 12.3, 4.7\) Hz, 1H), 1.19 – 1.09 (m, 6H); \(^13\)C NMR (101 MHz, CDCl₃) δ 194.4, 170.7, 143.2, 139.1, 133.5, 132.9, 128.8, 128.1, 126.7, 116.5, 61.4, 60.8, 43.4, 28.1, 26.3, 16.6, 14.2; IR (Neat Film, NaCl) 3073, 2978, 2938, 1729, 1693, 1639, 1600, 1454, 1290, 1237, 1220, 1019, 909, 746, 652 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \(m/z\) calc’d for C\(_{17}\)H\(_{21}\)O\(_3\) [M+H]\(^+\): 273.1485, found 273.1493; SFC conditions: 3% MeOH, 3.5 mL/min, Chiralpak AD-H column, λ = 254 nm, \(t_R\) (min): major = 4.539, minor = 5.113.

Isopropyl \((S)-2-((S)-but-3-en-2-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate\) (58b). Product 58b was prepared according to the general procedure and isolated by preparatory TLC (8% EtOAc/hexanes) to give the isolated yield of the branched and linear products (31.3 mg, 55% combined yield). The major diastereomer was isolated as a colorless oil by preparatory HPLC (2% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; λ = 254 nm): 96% ee;
[α]D<sup>25</sup> –61.5 (c 0.6, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.02 (dd, J = 7.9, 1.4 Hz, 1H), 7.43 (td, J = 7.5, 1.5 Hz, 1H), 7.37 – 7.22 (m, 1H), 7.18 (d, J = 7.7 Hz, 1H), 5.86 (ddd, J = 17.1, 10.2, 8.8 Hz, 1H), 5.12 – 4.92 (m, 3H), 3.23 – 3.11 (m, 1H), 3.11 – 2.98 (m, 1H), 2.89 (ddd, J = 17.5, 5.1, 2.9 Hz, 1H), 2.39 (ddd, J = 13.7, 4.8, 2.9 Hz, 1H), 2.20 (ddd, J = 13.7, 12.2, 5.0 Hz, 1H), 1.18 (dd, J = 6.6, 5.3 Hz, 6H), 1.02 (d, J = 6.2 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 194.6, 170.4, 143.0, 139.2, 133.3, 133.2, 128.7, 128.0, 126.7, 116.5, 69.0, 60.6, 43.4, 28.5, 26.3, 21.8, 21.6, 16.7; IR (Neat Film, NaCl) 3073, 2979, 2936, 1724, 1694, 16001, 1456, 1374, 1288, 1244, 1220, 1179, 1144, 1105, 915, 744 cm<sup>-1</sup>; HRMS (MM: ESI-APCI+) m/z calc’d for C<sub>18</sub>H<sub>23</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 287.1642, found 287.1650; HPLC conditions: 1% EtOH/hexanes, 1 mL/min, Chiralpak AD then AD-H column, λ = 254 nm, t<sub>R</sub> (min): major = 10.378, minor = 11.179.

2-(Trimethylsilyl)ethyl (S)-2-((S)-but-3-en-2-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (58c). Product 58c was prepared according to the general procedure and isolated by preparatory TLC (5% Et<sub>2</sub>O/hexanes) to give the isolated yield of the branched and linear products (18.3 mg, 27% combined yield). The major diastereomer was isolated as a colorless oil by preparatory HPLC (1% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; λ = 254 nm): 89% ee; [α]D<sup>25</sup> –46.0 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.04 (dd, J = 8.0, 1.5 Hz, 1H), 7.44 (td, J = 8.0, 1.5 Hz, 1H), 7.29 (t, J = 8.0, 1H), 7.19 (d, J = 8.0, 1H), 5.84 (ddd, J = 17.0, 10.2, 8.8 Hz, 1H), 5.15 – 5.00 (m, 2H), 4.23 – 4.03
(m, 2H), 3.26 – 3.02 (m, 2H), 2.88 (ddd, J = 17.4, 4.9, 2.9 Hz, 1H), 2.40 (ddd, J = 13.7, 4.7, 2.9 Hz, 1H), 2.21 (ddd, J = 13.6, 12.3, 4.9 Hz, 1H), 1.16 (d, J = 6.8 Hz, 3H), 0.89 (dd, J = 9.3, 8.1 Hz, 2H), –0.03 (s, 9H); \(^{13}\text{C}\) NMR (101 MHz, \(\text{CDCl}_3\)) \(\delta\) 194.4, 171.0, 143.3, 139.2, 133.5, 133.0, 128.8, 128.2, 126.7, 116.5, 63.9, 60.8, 43.5, 28.2, 26.3, 17.4, 16.6, –1.5 (3C); IR (Neat Film, \(\text{NaCl}\)) 3074, 2955, 2899, 1727, 1693, 1601, 1454, 1289, 1251, 1220, 1141, 1041, 918, 860, 837, 746, 695 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for \(\text{C}_{20}\text{H}_{28}\text{O}_3\text{SiNa [M+Na]}^+\): 367.1706, found 367.1720; HPLC conditions: 1% EtOH/hexanes, 1 mL/min, Chiralpak AD then AD-H column, \(\lambda\) = 254 nm, \(t_R\) (min): major = 9.018, minor = 9.737.

**Ethyl (\(S\))-2-((\(S\))-but-3-en-2-yl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (58d).** Product 58d was prepared according to the general procedure and isolated by preparatory TLC (8% \(\text{Et}_2\text{O}/\text{hexanes}\)) to give the isolated yield of the branched and linear products (33.0 mg, 55% combined yield). The major diastereomer was isolated as a colorless oil by preparatory HPLC (7% \(\text{EtOAc}/\text{hexanes}\), two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; \(\lambda = 254\) nm): 84% ee; \([\alpha]_D^{25}\) = \(-12.3\) (c 0.5, \(\text{CHCl}_3\)); \(^1\text{H}\) NMR (400 MHz, \(\text{CDCl}_3\)) \(\delta\) 8.02 (d, \(J = 8.8\) Hz, 1H), 6.81 (ddd, \(J = 8.8, 2.6, 0.7\) Hz, 1H), 6.63 (d, \(J = 2.6\) Hz, 1H), 5.82 (ddd, \(J = 17.1, 10.2, 8.8\) Hz, 1H), 5.12 – 4.97 (m, 2H), 4.20 – 3.99 (m, 2H), 3.84 (s, 3H), 3.26 – 3.08 (m, 2H), 2.84 (ddd, \(J = 17.4, 4.9, 3.0\) Hz, 1H), 2.39 (ddd, \(J = 13.6, 4.7, 2.9\) Hz, 1H), 2.17 (ddd, \(J = 13.7, 12.4, 4.9\) Hz, 1H), 1.16 (t, \(J = 7.1\) Hz, 3H), 1.12 (d, \(J = 6.9\) Hz, 3H); \(^{13}\text{C}\) NMR (101 MHz, \(\text{CDCl}_3\)) \(\delta\) 193.0,
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170.8, 163.7, 145.9, 139.2, 130.7, 126.5, 116.4, 113.5, 112.3, 61.4, 60.6, 55.6, 43.3, 27.7, 26.7, 16.5, 14.3; IR (Neat Film, NaCl) 3075, 2964, 2935, 2849, 1727, 1681, 1600, 1494, 1446, 1354, 1253, 1217, 1094, 917, 854, 824 cm⁻¹; HRMS (MM: ESI-APCI+) m/z calc’d for C₁₈H₂₃O₄ [M+H]⁺: 303.1591, found 303.1583; HPLC conditions: 1% EtOH/hexanes, 1 mL/min, Chiralpak AD then AD-H column, λ = 254 nm, tᵣ (min): major = 23.903, minor = 29.498.

**Ethyl (S)-2-((S)-but-3-en-2-yl)-6-(dimethylamino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (58e).** Product 58e was prepared according to the general procedure and isolated by preparatory TLC (10% EtOAc/hexanes) to give the isolated yield of the branched and linear products (29.0 mg, 46% combined yield). The major diastereomer was isolated as a colorless solid by preparatory HPLC (10% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; λ = 254 nm): 86% ee; [α]D²⁵ +8.5 (c 0.9, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, J = 8.9 Hz, 1H), 6.59 (dd, J = 9.0, 2.6 Hz, 1H), 6.31 (d, J = 2.5 Hz, 1H), 5.82 (ddd, J = 17.1, 10.2, 8.7 Hz, 1H), 5.15 – 4.96 (m, 2H), 4.10 (ddq, J = 41.7, 10.8, 7.1 Hz, 2H), 3.31 – 3.12 (m, 2H), 3.04 (s, 6H), 2.78 (ddd, J = 17.1, 4.8, 3.0 Hz, 1H), 2.36 (ddd, J = 13.4, 4.6, 3.0 Hz, 1H), 2.13 (ddd, J = 13.4, 12.5, 4.8 Hz, 1H), 1.18 (t, J = 7.1 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 192.1, 171.2, 153.6, 145.5, 139.5, 130.5, 121.9, 116.1, 110.5, 109.2, 61.2, 60.5, 43.2, 40.2 (2C), 27.4, 26.9, 16.4, 14.3; IR (Neat Film, NaCl) 3078, 2935, 1725, 1666, 1595, 1520, 1446, 1370, 1293, 1221,
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1196, 1125, 1025, 912, 813 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc’d for C$_{19}$H$_{26}$NO$_3$ [M+H]$^+$: 316.1907, found 316.1912; HPLC conditions: 3% EtOH/hexanes, 1 mL/min, Chiralpak AD then AD-H column, $\lambda = 254$ nm, $t_R$ (min): major = 24.809, minor = 33.026.

**Ethyl (S)-2-((S)-but-3-en-2-yl)-7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (58f).** Product 58f was prepared according to the general procedure and isolated by preparatory TLC (8% Et$_2$O/hexanes) to give the isolated yield of the branched and linear products (41.0 mg, 68% combined yield). The major diastereomer was isolated as a colorless oil by preparatory HPLC (2% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; $\lambda = 254$ nm): 94% ee; $[\alpha]_D^{25}$ –76.8 (c 0.8, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52 (d, $J = 2.8$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.03 (dd, $J = 8.4$, 2.8 Hz, 1H), 5.84 (ddd, $J = 17.0$, 10.2, 8.9 Hz, 1H), 5.12 – 4.95 (m, 2H), 4.20 – 4.02 (m, 2H), 3.83 (s, 3H), 3.17 – 3.04 (m, 2H), 2.83 (ddd, $J = 17.2$, 5.0, 2.9 Hz, 1H), 2.39 (ddd, $J = 13.6$, 4.6, 2.9 Hz, 1H), 2.19 (ddd, $J = 13.7$, 12.2, 5.0 Hz, 1H), 1.22 – 1.09 (m, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 194.4, 170.7, 158.3, 139.0, 135.7, 133.6, 129.9, 122.0, 116.4, 109.6, 61.3, 60.5, 55.5, 43.4, 28.4, 25.4, 16.6, 14.1; IR (Neat Film, NaCl) 3075, 2963, 2936, 2838, 1728, 1688, 1609, 1497, 1463, 1419, 1329, 1279, 1232, 1175, 1143, 1034, 920, 881, 819 cm$^{-1}$; HRMS (MM: ESI-APCI+) $m/z$ calc’d for C$_{18}$H$_{23}$O$_4$ [M+H]$^+$: 303.1591, found 303.1583; HPLC conditions: 1% EtOH/hexanes, 1
mL/min, Chiralpak AD then AD-H column, λ = 254 nm, t<sub>R</sub> (min): major = 17.216, minor = 14.519.

**Ethyl (S)-2-((S)-but-3-en-2-yl)-7-nitro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (58g).** Product 58g was prepared according to the general procedure and isolated by preparatory TLC (20% EtOAc/hexanes) to give the isolated yield of inseparable branched and linear products (52.0 mg, 82% combined yield): 93% ee; [α]<sup>25</sup> = 53.5 (c 1.4, CHCl₃); <sup>1</sup>H NMR (400 MHz, CDCl₃, major diastereomer) δ 8.86 (d, J = 2.5 Hz, 1H), 8.27 (dd, J = 8.4, 2.5 Hz, 1H), 7.39 (dt, J = 8.7, 0.9 Hz, 1H), 5.81 (ddd, J = 17.1, 10.2, 8.9 Hz, 1H), 5.23 – 4.99 (m, 2H), 4.25 – 3.97 (m, 2H), 3.24 (dddd, J = 18.1, 12.3, 4.8, 1.1 Hz, 1H), 3.13 – 2.96 (m, 2H), 2.46 (ddd, J = 13.9, 4.8, 2.7 Hz, 1H), 2.24 (ddd, J = 13.9, 12.4, 4.9 Hz, 1H), 1.21 – 1.12 (m, 6H); <sup>13</sup>C NMR (101 MHz, CDCl₃, major diastereomer) δ 192.4, 170.2, 149.7, 147.2, 138.5, 133.8, 130.3, 127.2, 123.4, 117.2, 61.8, 60.8, 43.6, 27.9, 26.7, 16.6, 14.2; IR (Neat Film, NaCl) 3079, 2979, 2938, 1727, 1698, 1612, 1526, 1421, 1347, 1218, 1181, 1018, 931, 740 cm⁻¹; HRMS (FAB+) m/z calc’d for \( \text{C}_{17}\text{H}_{20}\text{NO}_5 \) [M+H]<sup>+</sup>: 318.1341, found 318.1333; HPLC conditions: 5% EtOH/hexanes, 1 mL/min, Chiralpak AD then AD-H column, λ = 254 nm, t<sub>R</sub> (min): major = 14.901, minor = 13.808.
Ethyl (S)-6-bromo-2-((S)-but-3-en-2-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (58h). Product 58h was prepared according to the general procedure and isolated by silica gel flash column chromatography (5% Et₂O/hexanes) to give the isolated yield of the branched and linear products (44.0 mg, 63% combined yield). The major diastereomer was isolated as a colorless oil by preparatory HPLC (0.8% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; λ = 254 nm): 98% ee; [α]D^25 = −32.7 (c 2.3, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 8.4 Hz, 1H), 7.42 (ddd, J = 8.4, 2.0, 0.8 Hz, 1H), 7.40 – 7.35 (m, 1H), 5.81 (ddd, J = 17.1, 10.2, 8.9 Hz, 1H), 5.11 – 4.98 (m, 2H), 4.20 – 3.99 (m, 2H), 3.25 – 3.02 (m, 2H), 2.85 (ddd, J = 17.6, 4.9, 2.8 Hz, 1H), 2.40 (ddd, J = 13.7, 4.8, 2.9 Hz, 1H), 2.19 (ddd, J = 13.8, 12.3, 4.9 Hz, 1H), 1.20 – 1.12 (m, 6H); ^13C NMR (101 MHz, CDCl₃) δ 193.6, 170.5, 144.9, 138.9, 131.8, 131.7, 130.2, 129.8, 128.7, 116.8, 61.6, 60.7, 43.5, 28.0, 26.1, 16.6, 14.3; IR (Neat Film, NaCl) 3074, 2977, 2936, 1728, 1690, 1587, 1444, 1353, 1279, 1235, 1218, 1182, 1144, 1018, 910, 838, 670 cm⁻¹; HRMS (EI+) m/z calc’d for C₁₇H₁₉O₃Br [M]^+: 350.0518, found 350.0491; SFC conditions: 3% MeOH/hexanes, 3.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 9.330, minor = 8.616.
Ethyl (S)-2-((S)-but-3-en-2-yl)-6,8-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (58i). Product 58i was prepared according to the general procedure and isolated by preparatory TLC (9% EtOAc/hexanes) to give the isolated yield of the branched and linear products (31.0 mg, 52% combined yield). The major diastereomer was isolated as a colorless oil by preparatory HPLC (1.5% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; \( \lambda = 254 \) nm): 96% ee; \([\alpha]_D^{25} = -35.1 \) (c 0.3, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.72 (d, \( J = 2.0 \) Hz, 1H), 7.22 – 7.08 (m, 1H), 5.85 (ddd, \( J = 17.0, 10.2, 8.9 \) Hz, 1H), 5.18 – 4.94 (m, 2H), 4.20 – 3.86 (m, 2H), 3.18 – 3.08 (m, 1H), 2.92 (ddd, \( J = 16.9, 11.6, 5.0 \) Hz, 1H), 2.81 (ddd, \( J = 17.7, 5.6, 3.0 \) Hz, 1H), 2.45 (ddd, \( J = 13.8, 4.9, 3.0 \) Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 2.15 (ddd, \( J = 13.8, 11.5, 5.5 \) Hz, 1H), 1.17 – 1.10 (m, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 194.9, 170.7, 139.2, 138.7, 136.4, 136.0, 135.8, 132.9, 126.0, 116.4, 61.3, 60.2, 42.9, 27.1, 23.3, 21.0, 19.3, 16.5, 14.2; IR (Neat Film, NaCl) 3075, 2976, 2935, 1730, 1688, 1611, 1477, 1445, 1375, 1286, 1236, 1222, 1163, 1139, 1020, 919, 884 cm\(^{-1}\); HRMS (MM: ESI-APCI+) \( m/z \) calc’d for C\(_{19}\)H\(_{25}\)O\(_3\) [M+H]\(^+\): 301.1798, found 301.1801; HPLC conditions: 1% IPA/hexanes, 1 mL/min, Chiralpak IC column, \( \lambda = 254 \) nm, \( t_R \) (min): major = 9.599, minor = 10.926.
(R)-2-((S)-but-3-en-2-yl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbonitrile (58j). Product 58j was prepared according to the general procedure and isolated by preparatory TLC (17% EtOAc/hexanes) to give the isolated yield of the branched and linear products (43.0 mg, 95% combined yield). The major diastereomer was isolated as a colorless oil by preparatory HPLC (4% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; λ = 254 nm): 52% ee; [α]D25 +11.4 (c 0.4, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.03 (dd, J = 8.0, 1.4 Hz, 1H), 7.54 (td, J = 7.5, 1.5 Hz, 1H), 7.45 – 7.32 (m, 1H), 7.29 – 7.25 (m, 1H), 5.91 (ddd, J = 17.0, 10.3, 8.0 Hz, 1H), 5.17 (dt, J = 10.3, 1.1 Hz, 1H), 5.05 (dt, J = 17.1, 1.2 Hz, 1H), 3.27 – 2.89 (m, 3H), 2.43 (ddd, J = 7.1, 5.3, 3.4 Hz, 2H), 1.22 (d, J = 6.8 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 190.3, 142.4, 137.1, 134.6, 130.7, 129.0, 128.9, 127.6, 118.5, 118.1, 53.0, 39.8, 28.5, 25.2, 15.3; IR (Neat Film, NaCl) 2975, 2930, 1693, 1600, 1454, 1292, 1223, 1158, 1096, 992, 927, 904, 788, 741 cm⁻¹; HRMS (FAB+) m/z calc’d for C15H16ON [M+H]+: 226.1232, found 226.1240; HPLC conditions: 2% EtOH/hexanes, 1 mL/min, Chiralpak AD then AD-H column, λ = 254 nm, tR (min): major = 24.027, minor = 26.658.

(R)-2-acetyl-2-((S)-but-3-en-2-yl)-3,4-dihydonaphthalene-1(2H)-one (58k). Product 10k was prepared according to the general procedure and isolated by preparatory TLC (9% EtOAc/hexanes) to give the isolated yield of the branched and linear products (11.0
mg, 23% combined yield). The major diastereomer was isolated as a colorless oil by preparatory HPLC (4% EtOAc/hexanes, two Agilent Zorbax RX-sil silica columns in series; flow rate = 15 mL/min; \( \lambda = 254 \) nm): 65% ee; \([\alpha]_D^{25} -43.3 \) (c 0.2, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.05 (dt, \( J = 8.0, 0.9 \) Hz, 1H), 7.47 (td, \( J = 7.5, 1.5 \) Hz, 1H), 7.33 – 7.27 (m, 1H), 7.19 (dtt, \( J = 7.7, 1.2, 0.6 \) Hz, 1H), 5.64 (ddd, \( J = 17.0, 10.2, 8.8 \) Hz, 1H), 5.27 – 4.94 (m, 2H), 3.46 – 3.32 (m, 1H), 3.16 (dddt, \( J = 17.4, 12.6, 4.7, 1.1 \) Hz, 1H), 2.84 (ddd, \( J = 17.4, 5.0, 2.7 \) Hz, 1H), 2.47 (ddd, \( J = 13.5, 4.7, 2.7 \) Hz, 1H), 2.12 – 2.06 (m, 1H), 2.09 (s, 3H), 1.06 (d, \( J = 6.8 \) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 204.7, 196.8, 144.2, 138.3, 134.1, 132.8, 129.0, 128.0, 126.7, 116.5, 68.4, 42.6, 26.9, 25.9, 24.7, 16.3; IR (Neat Film, NaCl) 3076, 2971, 2937, 1708, 1674, 1599, 1464, 1359, 1295, 1231, 1208, 1120, 995, 912, 781, 754, 737 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{16}\)H\(_{19}\)O\(_2\) [M+H]: 243.1385, found 243.1381; HPLC conditions: 1% EtOH/hexanes, 1 mL/min, Chiralpak AD then AD-H column, \( \lambda = 254 \) nm, \( t_R \) (min): major = 11.271, minor = 11.944.

1.7.2.6 Experimental Procedures and Spectroscopic Data for the Transformations of Allylic Alkyl-Lation Products

Ethyl (1\(R\),2\(S\))-1-allyl-2-((S)-but-3-en-2-yl)-1-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (61). Allylmagnesium chloride (0.065 mL, 0.11 mmol, 1.1 equiv, 1.7 M in THF) was added dropwise to a solution of ethyl ester 58a (27 mg, 1.0 mmol, 1 equiv) in THF (0.5 mL) at \(-78 \) °C. The mixture was stirred at \(-78 \) °C for
4 h, whereupon the reaction was quenched with a saturated NH₄Cl aqueous solution (1 mL). The aqueous layer was then extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (9% Et₂O/hexanes) to give alcohol 61 as a colorless oil (31 mg, 71% yield): [α]D⁺²⁵ +27.3 (c 0.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.50 (m, 1H), 7.20 – 7.14 (m, 2H), 7.10 – 7.02 (m, 1H), 5.99 (dd, J = 17.1, 10.2, 8.5 Hz, 1H), 5.65 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 4.98 – 4.85 (m, 2H), 4.85 – 4.76 (m, 1H), 4.68 (dd, J = 17.1, 1.9, 1.0 Hz, 1H), 4.33 – 4.19 (m, 2H), 4.01 (s, 1H), 2.94 – 2.86 (m, 2H), 2.72 (ddt, J = 8.6, 7.0, 0.8 Hz, 1H), 2.52 – 2.30 (m, 3H), 2.21 – 2.12 (m, 1H), 1.35 (t, J = 7.1 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.9, 142.0, 140.7, 134.1, 133.7, 127.9, 126.7, 126.3, 125.5, 117.5, 114.7, 76.6, 61.1, 56.4, 47.2, 41.2, 25.2, 23.3, 16.7, 14.4; IR (Neat Film, NaCl) 3492, 3075, 2978, 2930, 2853, 1732, 1694, 1640, 1455, 1376, 1267, 1213, 1026, 914, 766, 732, 665 cm⁻¹; HRMS (FAB+) m/z calc’d for C₂₀H₂₇O₃ [M+H]⁺: 315.1960, found 315.1954.

Ethyl (4bR,8S,8aS)-4b-hydroxy-8-methyl-5,8,9,10-tetrahydrophenanthrene-8a(4bH)-carboxylate (62). A solution of bis-olefin 61 (4.0 mg, 0.013 mmol, 1 equiv), Hoveyda-Grubbs Catalyst-II (1.4 mg, 2.6 µmol, 0.2 equiv), and CH₂Cl₂ (0.5 mL) was stirred at ambient temperature for 18 h, whereupon the reaction mixture was concentrated under reduced pressure. The crude residue was purified by preparatory TLC (9%
EtOAc/hexanes) to give tricycle 62 as a colorless oil (3.0 mg, 81% yield): \([\alpha]_D^{25} +7.9\) (c 0.2, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.55 – 7.46 (m, 1H), 7.22 – 7.16 (m, 2H), 7.13 – 7.06 (m, 1H), 5.82 (ddt, \(J = 10.1, 5.1, 2.6\) Hz, 1H), 5.56 (ddt, \(J = 10.1, 2.6, 1.8\) Hz, 1H), 3.96 (qd, \(J = 7.1, 1.0\) Hz, 2H), 3.36 (ddt, \(J = 18.0, 3.8, 2.6\) Hz, 1H), 3.09 – 2.96 (m, 1H), 2.96 – 2.78 (m, 2H), 2.70 – 2.57 (m, 1H), 2.49 – 2.38 (m, 1H), 2.28 – 2.11 (m, 1H), 1.12 (d, \(J = 7.6\) Hz, 3H), 1.07 (t, \(J = 7.1\) Hz, 3H); \(^13\)C NMR (101 MHz, CDCl₃) \(\delta\) 172.2, 140.0, 136.0, 130.6, 129.6, 127.9, 126.3, 125.1, 124.1, 70.5, 60.0, 52.2, 36.8, 36.4, 26.4, 25.5, 16.2, 14.2; IR (Neat Film, NaCl) 3488, 3019, 2972, 2934, 1727, 1715, 1451, 1453, 1368, 1293, 1251, 1177, 1027, 887, 761, 694 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{18}\)H\(_{23}\)O\(_3\) [M+H]\(^+\): 287.1647, found 287.1637. Please note that the exchangeable hydroxy proton was not observed in the \(^1\)H NMR spectrum.

![Diagram](image)

**Ethyl (4bR,6R,7S,8R,8aS)-4b,6,7-trihydroxy-8-methyl-5,6,7,8,9,10-hexahydrophenanthrene-8a(4bH)-carboxylate (63).** A solution of olefin 62 (18 mg, 0.058 mmol, 1 equiv), K\(_2\)OsO₄ (1.0 mg, 2.8 \(\mu\)mol, 0.05 equiv), \(N\)-methylmorpholine \(N\)-oxide (11 mg, 0.093 mmol, 1.6 equiv), and THF/H\(_2\)O (3:1, 0.2 mL) was stirred at ambient temperature for 18 h, whereupon the reaction was quenched with saturated Na\(_2\)S\(_2\)O\(_3\) aqueous solution (1 mL). The aqueous layer was then extracted with EtOAc (5 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (17% EtOAc/hexanes) to give triol 63 as a colorless oil (11 mg, 59% yield): \([\alpha]_D^{25} +3.8\) (c
0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.34 (dd, J = 7.8, 1.5 Hz, 1H), 7.19 (td, J = 7.4, 1.5 Hz, 1H), 7.16 – 7.05 (m, 2H), 4.26 (q, J = 3.3 Hz, 1H), 3.82 (q, J = 7.1 Hz, 2H), 3.74 (dd, J = 11.0, 3.5 Hz, 1H), 3.70 – 3.56 (m, 1H), 3.06 – 2.92 (m, 3H), 2.78 (dd, J = 14.6, 3.0 Hz, 1H), 2.61 – 2.44 (m, 1H), 2.24 – 2.05 (m, 2H), 1.10 (d, J = 6.8 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 172.9, 139.4, 136.9, 129.6, 128.4, 125.8, 123.8, 73.0, 72.7, 70.5, 60.4, 56.1, 37.3, 35.3, 25.9, 25.1, 13.9, 12.3; IR (Neat Film, NaCl) 3284, 2970, 2928, 1723, 1452, 1382, 1259, 1234, 1189, 1103, 1054, 1020, 867, 834, 763, 722 cm⁻¹; HRMS (MM: ESI-APCI–) m/z calc’d for C₁₈H₂₄O₃Cl [M+Cl]⁻: 355.1318, found 355.1326. Please note that two of the exchangeable hydroxy protons were not observed in the ¹H NMR spectrum.

![structure](image)

(1R,2R)-2-((S)-But-3-en-2-yl)-2-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (64). DIBAL (0.071 mL, 0.40 mmol, 4 equiv) was added dropwise to a solution of ethyl ester 58a (27 mg, 1.0 mmol, 1 equiv) in THF (0.6 mL) at −78 °C. The mixture was stirred at −78 °C for 6 h, whereupon the reaction was quenched with a saturated Rochelle’s salt aqueous solution (1 mL) and stirred for 18 h at ambient temperature. The aqueous layer was then extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (20% EtOAc/hexanes) to give diol 64 as a colorless oil (10 mg, 43% yield): [α]D²⁵ +105.7 (c 0.7, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.49 – 7.44 (m, 1H), 7.24 – 7.18 (m, 2H), 7.11 (ddd, J = 5.5, 2.4, 1.2 Hz, 1H),
6.30 (ddd, \( J = 17.2, 10.1, 9.1 \) Hz, 1H), 4.99 (ddd, \( J = 10.1, 2.1, 0.6 \) Hz, 1H), 4.90 (ddd, \( J = 17.3, 2.1, 0.9 \) Hz, 1H), 4.80 (d, \( J = 7.3 \) Hz, 1H), 3.81 (dd, \( J = 11.3, 5.5 \) Hz, 1H), 3.59 (dd, \( J = 11.4, 3.7 \) Hz, 1H), 2.91 – 2.66 (m, 2H), 2.65 – 2.57 (m, 2H), 2.19 (bs, 1H), 1.75 (ddd, \( J = 13.8, 7.2, 6.5 \) Hz, 1H), 1.64 – 1.50 (m, 1H), 1.04 (d, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 144.5, 138.9, 135.9, 128.4, 127.3, 127.0, 126.5, 115.1, 75.3, 67.3, 43.7, 39.8, 25.8, 25.7, 15.5; IR (Neat Film, NaCl) 3404, 3069, 3020, 2932, 1634, 1602, 1455, 1417, 1374, 1268, 1217, 1191, 1045, 991, 913, 774, 741, 641 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{15}\)H\(_{19}\)O\(_2\) [(M+H)–H\(_2\)]\(^+\): 231.1385, found 231.1385. Please note that a minor amount of epimeric product is present in the \(^1\)H NMR spectrum.

![Chemical Structure](image)

**(3S,4R)-5-(Hydroxymethyl)-4-methyl-3',4,4',5-tetrahydro-1'H,2'H-spiro[furan-3,2'-naphthalene]-1',2-dione (65).** A solution of methyl ester 54 (20.0 mg, 0.077 mmol, 1 equiv), K\(_2\)OsO\(_4\) (3.0 mg, 0.0081 mmol, 0.11 equiv), N-methylmorpholine N-oxide (15 mg, 0.12 mmol, 1.6 equiv), and THF/H\(_2\)O (3:1, 0.4 mL) was stirred at ambient temperature for 12 h, whereupon a second addition of K\(_2\)OsO\(_4\) and N-methylmorpholine N-oxide was added and the reaction was stirred for an additional 24 h. The reaction was quenched with saturated Na\(_2\)S\(_2\)O\(_3\) aqueous solution (1 mL). The aqueous layer was then extracted with EtOAc (5 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (33% EtOAc/hexanes) to give lactone 65 as a colorless oil (13 mg, 65% yield): \([\alpha]_D^{25}\) +7.0 (c 0.2, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\))
δ 8.07 (dd, J = 7.9, 1.4 Hz, 1H), 7.52 (td, J = 7.5, 1.5 Hz, 1H), 7.38 – 7.31 (m, 1H), 4.26 (ddd, J = 10.5, 5.6, 2.4 Hz, 1H), 4.01 (ddd, J = 12.8, 7.0, 2.5 Hz, 1H), 3.82 (dt, J = 12.4, 6.0 Hz, 1H), 3.59 (dq, J = 10.5, 7.0 Hz, 1H), 3.47 – 3.34 (m, 1H), 2.98 (dt, J = 17.0, 3.8 Hz, 1H), 2.32 – 2.25 (m, 2H), 1.94 (t, J = 6.7 Hz, 1H), 1.03 (d, J = 7.0 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 192.6, 173.5, 144.0, 134.4, 131.8, 129.0, 128.8, 127.2, 84.3, 62.9, 57.7, 36.1, 25.6, 25.3, 10.8; IR (Neat Film, NaCl) 3444, 2928, 2851, 1760, 1682, 1599, 1455, 1308, 1239, 1217, 1166, 1094, 1056, 1021, 914, 759, 733, 656 cm⁻¹; HRMS (FAB+) m/z calc’d for C15H17O4 [M+H]+: 261.1127, found 261.1129.

NOE correlation:

Ethyl (1R,2S)-2-((S)-but-3-en-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,2’-oxirane]-2-carboxylate (66). (CH3)3SOI (35 mg, 0.17 mmol, 1.7 equiv) and NaH (5.0 mg, 0.15 mmol, 1.5 equiv, 60 wt %) were dissolved in DMSO (1.5 mL). The mixture was stirred for 20 min at ambient temperature, whereupon a solution of ketone 58a (27 mg, 0.10 mmol, 1 equiv) in DMSO (1.0 mL) was added. The resulting solution was stirred for an additional 18 h. H2O (2.0 mL) was then added to the reaction mixture and the aqueous layer was extractd with EtOAc (3 x 5 mL). The organic layer was washed with H2O (5.0 mL) and brine (5.0 mL), dried over Na2SO4, and concentrated under reduced pressure.
The crude residue was purified by preparatory TLC (3% Et₂O/hexanes) to give epoxide 66 as a colorless oil (23 mg, 82% yield): \([\alpha]_D^{25} +10.4 (c \ 0.1, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.23 – 7.15 (m, 3H), 7.15 – 7.07 (m, 1H), 6.07 (ddd, \(J = 17.1, 10.3, 8.1\) Hz, 1H), 4.93 (ddd, \(J = 10.2, 1.9, 0.8\) Hz, 1H), 4.74 (ddd, \(J = 17.1, 2.0, 1.1\) Hz, 1H), 4.29 – 4.06 (m, 2H), 3.01 – 2.94 (m, 1H), 2.98 (d, \(J = 5.1\) Hz, 1H), 2.93 – 2.82 (m, 1H), 2.82 – 2.71 (m, 1H), 2.62 (d, \(J = 5.1\) Hz, 1H), 2.35 (ddd, \(J = 14.0, 8.2, 5.7\) Hz, 1H), 2.09 (ddd, \(J = 14.2, 6.9, 5.5\) Hz, 1H), 1.29 (t, \(J = 7.1\) Hz, 3H), 0.99 (d, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\); 173.4, 140.9, 138.2, 136.4, 127.8, 127.4, 126.8, 123.4, 115.1, 61.0, 59.1, 56.5, 51.9, 40.2, 28.0, 26.2, 15.8, 14.4; IR (Neat Film, NaCl) 3073, 2977, 2938, 1723, 1489, 1456, 1368, 1296, 1255, 1233, 1213, 1134, 1096, 1025, 915, 760 cm\(^{-1}\); HRMS (FAB+) m/z calc’d for C\(_{18}\)H\(_{21}\)O\(_3\) [(M+H) – H\(_2\)]\(^+\): 285.1491, found 285.1487. Please note that the relative stereochemistry of 16 has been assigned via analogy to 11 and 14.

1.7.2.7 Determination of Enantiomeric Excess

Please note racemic products (rac-54, rac-58) were synthesized as follows: in a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added [Rh(CO)\(_2\)Cl\(_2\)] (10 mol %) and but-3-en-2-yl methyl carbonate (140 mol %) in THF. Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with tetralone 52, 56a–k (100 mol %), NaH (110 mol %), and THF. The pre-formed catalyst solution (vial A) was then transferred to vial B and the vial was sealed and stirred at 25 °C. After 18 h, the vial was removed from the glove box and filtered through celite,
rinsing with EtOAc to give the crude racemic product. The residue was purified as in the general procedure for the Ir-catalyzed allylic alkylation.

**Table 1.5 Determination of enantiomeric excess**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Assay Conditions</th>
<th>Retention time of major isomer (min)</th>
<th>Retention time of minor isomer (min)</th>
<th>%ee</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>SFC Chiralpak AD-H 3% MeOH isocratic, 3.5 mL/min</td>
<td>5.170</td>
<td>5.968</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min</td>
<td>19.785</td>
<td>24.041</td>
<td>23%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>SFC Chiralpak AD-H 3% MeOH isocratic, 3.5 mL/min</td>
<td>4.539</td>
<td>5.113</td>
<td>96%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>HPLC Chiralpak AD then AD-H 1% EtOH/hexanes isocratic, 1 mL/min</td>
<td>10.378</td>
<td>11.179</td>
<td>96%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>HPLC Chiralpak AD then AD-H 1% EtOH/hexanes isocratic, 1 mL/min</td>
<td>9.018</td>
<td>9.737</td>
<td>89%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Image" /></td>
<td>HPLC Chiralpak AD then AD-H 1% EtOH/hexanes isocratic, 1 mL/min</td>
<td>23.903</td>
<td>29.498</td>
<td>84%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Image" /></td>
<td>HPLC Chiralpak AD then AD-H 3% EtOH/hexanes isocratic, 1 mL/min</td>
<td>24.809</td>
<td>33.026</td>
<td>86%</td>
</tr>
<tr>
<td>Entry</td>
<td>Product</td>
<td>Assay Conditions</td>
<td>Retention time of major isomer (min)</td>
<td>Retention time of minor isomer (min)</td>
<td>%ee</td>
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<tr>
<td>8</td>
<td><img src="image1" alt="Image" /></td>
<td>HPLC Chiralpak AD then AD-H 1% EtOH/hexanes isocratic, 1 mL/min</td>
<td>17.216</td>
<td>14.519</td>
<td>94%</td>
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<tr>
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<td><img src="image2" alt="Image" /></td>
<td>HPLC Chiralpak AD then AD-H 5% EtOH/hexanes isocratic, 1 mL/min</td>
<td>14.901</td>
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<td>93%</td>
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<td>SFC Chiralpak AD-H 3% MeOH isocratic, 3.5 mL/min</td>
<td>9.330</td>
<td>8.616</td>
<td>98%</td>
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<td>11</td>
<td><img src="image4" alt="Image" /></td>
<td>HPLC Chiralpak AD-I 1% IPA/hexanes isocratic, 1 mL/min</td>
<td>9.599</td>
<td>10.926</td>
<td>96%</td>
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<td><img src="image5" alt="Image" /></td>
<td>HPLC Chiralpak AD then AD-H 2% EtOH/hexanes isocratic, 1 mL/min</td>
<td>24.027</td>
<td>26.658</td>
<td>52%</td>
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<tr>
<td>13</td>
<td><img src="image6" alt="Image" /></td>
<td>HPLC Chiralpak AD then AD-H 1% EtOH/hexanes isocratic, 1 mL/min</td>
<td>11.271</td>
<td>11.944</td>
<td>65%</td>
</tr>
</tbody>
</table>

1.8 REFERENCES AND NOTES


Chapter 1 – Stereoselective Iridium-Catalyzed Allylic Alkylation Reactions with Crotyl Chloride


APPENDIX 1

Spectra Relevant to Chapter 1:

Stereoselective Iridium-Catalyzed Allylic Alkylation

Reactions with Crotyl Chloride
Figure A1.1: $^1$H NMR (400 MHz, CDCl$_3$) of compound 54
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.2 Infrared spectrum (Thin Film, NaCl) of compound 54

Figure A1.3 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 54
Figure A1.4 $^1$H NMR (400 MHz, CDCl$_3$) of compound epi-54
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.5 Infrared spectrum (Thin Film, NaCl) of compound epi-54

Figure A1.6 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound epi-54
Figure A1.7 $^1$H NMR (400 MHz, CDCl$_3$) of compound 55
Figure A1.8 Infrared spectrum (Thin Film, NaCl) of compound 55

Figure A1.9 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 55
Figure A1.10 $^1$H NMR (400 MHz, CDCl$_3$) of compound 56b
Figure A1.11 Infrared spectrum (Thin Film, NaCl) of compound 56b

Figure A1.12 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 56b
Figure A1.13 $^1$H NMR (400 MHz, CDCl$_3$) of compound 56c
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.14 Infrared spectrum (Thin Film, NaCl) of compound 56c

Figure A1.15 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 56c
Figure A1.16 $^1$H NMR (400 MHz, CDCl$_3$) of compound 56e
Figure A1.17 Infrared spectrum (Thin Film, NaCl) of compound 56e

Figure A1.18 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 56e
Figure A1.19 $^1$H NMR (400 MHz, CDCl$_3$) of compound 56g
Figure A1.20 Infrared spectrum (Thin Film, NaCl) of compound 56g

Figure A1.21 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 56g
Figure A1.22 $^1$H NMR (400 MHz, CDCl$_3$) of compound 56h
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.23 Infrared spectrum (Thin Film, NaCl) of compound 56h

Figure A1.24 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 56h
Figure A1.25 $^1$H NMR (400 MHz, CDCl$_3$) of compound 56k
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.26 Infrared spectrum (Thin Film, NaCl) of compound 56k

Figure A1.27 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 56k
Figure A1.28 $^1$H NMR (400 MHz, CDCl$_3$) of compound 58a
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.29 Infrared spectrum (Thin Film, NaCl) of compound 58a

Figure A1.30 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 58a
Figure A1.31: $^{1}H$ NMR (400 MHz, CDCl$_3$) of compound 58b
Figure A1.32 Infrared spectrum (Thin Film, NaCl) of compound 58b

Figure A1.33 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 58b
Figure A1.34 $^1$H NMR (400 MHz, CDCl$_3$) of compound 58c
Appendix 1 – Spectra Relevant to Chapter 1

**Figure A1.35** Infrared spectrum (Thin Film, NaCl) of compound $58c$

**Figure A1.36** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound $58c$
Figure A1.37: $^1$H NMR (400 MHz, CDCl$_3$) of compound 58d.
Figure A1.38 Infrared spectrum (Thin Film, NaCl) of compound 58d

Figure A1.39 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 58d
Figure A1.40 $^1$H NMR (400 MHz, CDCl$_3$) of compound 58e
Figure A1.41 Infrared spectrum (Thin Film, NaCl) of compound 58e

Figure A1.42 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 58e
Figure A1.43 $^1$H NMR (400 MHz, CDCl$_3$) of compound 58f
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.44 Infrared spectrum (Thin Film, NaCl) of compound 58f

Figure A1.45 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 58f
Figure A1.46: $^1$H NMR (400 MHz, CDCl$_3$) of compound 58g
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.47 Infrared spectrum (Thin Film, NaCl) of compound 58g

Figure A1.48 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 58g
Figure A1.49: $^1$H NMR (400 MHz, CDCl$_3$) of compound 58h
Appendix 1 – Spectra Relevant to Chapter 1

**Figure A1.50** Infrared spectrum (Thin Film, NaCl) of compound 58h

**Figure A1.51** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 58h
Figure A1.52 $^1$H NMR (400 MHz, CDCl$_3$) of compound 58i
Figure A1.53 Infrared spectrum (Thin Film, NaCl) of compound 58i

Figure A1.54 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 58i
Figure A1.55 $^1H$ NMR (400 MHz, CDCl$_3$) of compound 58j
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.56 Infrared spectrum (Thin Film, NaCl) of compound 58j

Figure A1.57 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 58j
Figure A1.58 $^1$H NMR (400 MHz, CDCl$_3$) of compound 58k
Figure A1.59 Infrared spectrum (Thin Film, NaCl) of compound $58k$

Figure A1.60 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound $58k$
Figure A1.61: $^1$H NMR (400 MHz, CDCl$_3$) of compound 61.
Figure A1.62 Infrared spectrum (Thin Film, NaCl) of compound 61

Figure A1.63 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 61
Figure A1.64 \( ^1H \) NMR (400 MHz, CDCl\(_3\)) of compound 62
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.65 Infrared spectrum (Thin Film, NaCl) of compound 62

Figure A1.66 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 62
Figure A1.67: $^1$H NMR (400 MHz, CDCl$_3$) of compound 63.
Appendix 1 – Spectra Relevant to Chapter 1

Figure A1.68 Infrared spectrum (Thin Film, NaCl) of compound 63

Figure A1.69 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 63
Figure A1.70 $^1$H NMR (400 MHz, CDCl$_3$) of compound 64
Figure A1.71 Infrared spectrum (Thin Film, NaCl) of compound 64

Figure A1.72 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 64
Figure A1.73: $^1$H NMR (400 MHz, CDCl$_3$) of compound 65
Appendix 1 – Spectra Relevant to Chapter 1

**Figure A1.74** Infrared spectrum (Thin Film, NaCl) of compound 65

**Figure A1.75** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 65
Figure A1.76. NOESY (400 MHz, CDCl₃) of compound 65.
Figure A1.77 $^1$H NMR (400 MHz, CDCl$_3$) of compound 66
Figure A1.78 Infrared spectrum (Thin Film, NaCl) of compound 66

Figure A1.79 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 66
APPENDIX 2

X-Ray Crystallography Reports Relevant to Chapter 1:

Stereoselective Iridium-Catalyzed Allylic Alkylation Reactions

with Crotyl Chloride
A2.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker D8 Venture Kappa Duo Photon 100 CMOS diffractometer.

A2.1.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF ALLYLIC ALKYLATION PRODUCT 58e

![X-ray crystal structure of allylic alkylation product 58e](image)

The alkylation product 58e (86% ee) was recrystallized by slow evaporation of hexanes to provide crystals suitable for X-ray analysis, m.p. = 67 – 69 °C.

**Figure A2.1** X-ray crystal structure of allylic alkylation product 58e

| Table A2.1 Crystal data and structure refinement for allylic alkylation product 58e |
|---------------------------------|---------------------------------|
| Empirical formula              | C19 H25 N O3                    |
| Formula weight                 | 315.40                          |
| Temperature                    | 100(2) K                        |
| Wavelength                     | 1.54178 Å                       |
Appendix 2 – X-Ray Crystallography Reports Relevant to Chapter 1

Crystal system
Monoclinic

Space group
P2₁

Unit cell dimensions

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<th>b</th>
<th>c</th>
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Volume
850.2(2) Å³

Z
2

Density (calculated)
1.232 Mg/m³

Absorption coefficient
0.661 mm⁻¹

F(000)
340

Crystal size
0.240 x 0.230 x 0.080 mm³

Theta range for data collection
2.422 to 79.330°.

Index ranges
-9<=h<=8, -7<=k<=7, -23<=l<=23

Reflections collected
26025

Independent reflections
3636 [R(int) = 0.0411]

Completeness to theta = 67.679°
99.6%

Absorption correction
Semi-empirical from equivalents

Refinement method
Full-matrix least-squares on F²

Data / restraints / parameters
3636 / 1 / 212

Goodness-of-fit on F²
1.094

Final R indices [I>2sigma(I)]
R₁ = 0.0271, wR₂ = 0.0727

R indices (all data)
R₁ = 0.0274, wR₂ = 0.0730

Absolute structure parameter
0.07(3)

Extinction coefficient
n/a

Largest diff. peak and hole
0.132 and -0.164 e.Å⁻³

Table A2.2 Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å² x 10⁴) for 58e. U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

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Table A2.3 Bond lengths [Å] and angles [°] for 58e

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Appendix 2 – X-Ray Crystallography Reports Relevant to Chapter 1

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C(4)-H(4A) 0.9900
C(4)-H(4B) 0.9900
C(5)-C(6) 1.388(2)
C(5)-C(10) 1.4074(19)
C(6)-C(7) 1.4096(19)
C(6)-H(6) 0.9500
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C(8)-C(9) 1.376(2)
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C(11)-H(11B) 0.9800
C(11)-H(11C) 0.9800
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C(12)-H(12C) 0.9800
C(14)-C(15) 1.505(2)
C(14)-H(14A) 0.9900
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C(7)-N(1)-C(11) 119.66(12)
Appendix 2 – X-Ray Crystallography Reports Relevant to Chapter 1

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C(13)-C(2)-C(1)  108.76(11)
C(3)-C(2)-C(16)  111.84(12)
C(13)-C(2)-C(16)  106.93(11)
C(1)-C(2)-C(16)  110.60(11)
C(4)-C(3)-C(2)  112.21(12)
C(4)-C(3)-H(3A)  109.2
C(2)-C(3)-H(3A)  109.2
C(4)-C(3)-H(3B)  109.2
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H(3A)-C(3)-H(3B)  107.9
C(5)-C(4)-C(3)  112.26(11)
C(5)-C(4)-H(4A)  109.2
C(3)-C(4)-H(4A)  109.2
C(5)-C(4)-H(4B)  109.2
C(3)-C(4)-H(4B)  109.2
H(4A)-C(4)-H(4B)  107.9
C(6)-C(5)-C(10)  120.11(13)
C(6)-C(5)-C(4)  119.48(12)
C(10)-C(5)-C(4)  120.38(12)
C(5)-C(6)-C(7)  121.95(12)
C(5)-C(6)-H(6)  119.0
C(7)-C(6)-H(6)  119.0
N(1)-C(7)-C(6)  121.49(12)
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C(9)-C(8)-C(7)  120.20(13)
C(9)-C(8)-H(8)  119.9
C(7)-C(8)-H(8)  119.9
C(8)-C(9)-C(10)  122.17(13)
C(8)-C(9)-H(9)  118.9
C(10)-C(9)-H(9)  118.9
C(9)-C(10)-C(5)  118.13(13)
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O(3)-C(13)-C(2)  124.53(13)
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O(2)-C(14)-C(15)  110.68(13)
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Table A2.4 Anisotropic displacement parameters (Å² x 10³) for 58e. The anisotropic displacement factor exponent takes the form: -2π² | h² a*² U₁₁ + ... + 2 h k a* b* U₁₂ |

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**Appendix 2 – X-Ray Crystallography Reports Relevant to Chapter 1**

**A2.1.2 X-RAY CRYSTAL STRUCTURE ANALYSIS OF TRIOL 63**

Triol 63 was recrystallized by slow evaporation of benzene to provide crystals suitable for X-ray analysis, m.p. = 111 – 115 °C.

*Figure A2.2 X-ray crystal structure of triol 63*

![X-ray crystal structure of triol 63](image)

*Table A2.6 Crystal data and structure refinement for triol 63*

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<td>Wavelength</td>
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<tr>
<td></td>
<td>b = 21.3194(5) Å</td>
</tr>
<tr>
<td></td>
<td>c = 18.6055(6) Å</td>
</tr>
<tr>
<td></td>
<td>a = 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 90°.</td>
</tr>
<tr>
<td></td>
<td>g = 120°.</td>
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Volume: \(7323.6(4) \text{ Å}^3\)
Z: 12
Density (calculated): 1.305 Mg/m\(^3\)
Absorption coefficient: 0.695 mm\(^{-1}\)
\(F(000)\): 3108
Crystal size: \(.2 \times .1 \times .1 \text{ mm}^3\)
Theta range for data collection: 2.393 to 58.098°
Index ranges: \(-22 \leq h \leq 20, -22 \leq k \leq 22, -20 \leq l \leq 20\)
Reflections collected: 60463
Independent reflections: 3412 \([R(\text{int}) = 0.0731]\)
Completeness to theta = 67.679°: 78.2 %
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 0.7514 and 0.6563
Refinement method: Full-matrix least-squares on \(F^2\)
Data / restraints / parameters: 3412 / 1 / 283
Goodness-of-fit on \(F^2\): 1.110
Final R indices \([I > 2\sigma(I)]\): \(R1 = 0.0803, wR2 = 0.1889\)
R indices (all data): \(R1 = 0.1100, wR2 = 0.2084\)
Absolute structure parameter: 0.03(8)
Extinction coefficient: n/a
Largest diff. peak and hole: 0.290 and -0.263 e.Å\(^{-3}\)

Table A2.7 Atomic coordinates \((x 10^4)\) and equivalent isotropic displacement parameters \((\text{Å}^2 x 10^3)\) for 63. \(U(\text{eq})\) is defined as one third of the trace of the orthogonalized \(U_{ij}\) tensor.

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### Appendix 2 – X-Ray Crystallography Reports Relevant to Chapter 1

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Table A2.9 Anisotropic displacement parameters (Å² x 10³) for 63. The anisotropic displacement factor exponent takes the form: -2π² [ h² a² U₁¹ + ... + 2 h k a* b* U₁₂ ]

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### Table A2.10

Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\AA^2 \times 10^3$) for $\text{C}(\text{Rays})$

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<tr>
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<th>z</th>
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This table provides the hydrogen coordinates and isotropic displacement parameters for the crystallographic analysis of the C layers in the context of the ray crystallography reports relevant to Chapter 1.
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A2.1.3  X-RAY CRYSTAL STRUCTURE ANALYSIS OF DIOL 64

![Diagram of diol 64](image)

Diol 64 was recrystallized in boiling heptane to provide crystals suitable for X-ray analysis, m.p. = 97 – 99 °C.

Figure A2.3 X-ray crystal structure of diol 64

Table A2.11 Crystal data and structure refinement for diol 64

<table>
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<th>Property</th>
<th>Value</th>
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<tr>
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<td>100(2) K</td>
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<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
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<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
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<tr>
<td>Space group</td>
<td>P2₁</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.0972(3) Å  a = 90°.</td>
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</tbody>
</table>
b = 6.3583(2) Å   b = 105.4260(10)°.
c = 12.5999(4) Å   g = 90°.

Volume
625.33(4) Å³

Z
2

Density (calculated)
1.234 Mg/m³

Absorption coefficient
0.630 mm⁻¹

F(000)
252

Crystal size
.1 x .1 x .1 mm³

Theta range for data collection
3.639 to 79.259°.

Index ranges
-10<=h<=10, -8<=k<=8, -15<=l<=16

Reflections collected
20029

Independent reflections
2647 [R(int) = 0.0449]

Completeness to theta = 67.679°
100.0 %

Absorption correction
Semi-empirical from equivalents

Refinement method
Full-matrix least-squares on F²

Data / restraints / parameters
2647 / 3 / 163

Goodness-of-fit on F²
1.085

Final R indices [I>2sigma(I)]
R1 = 0.0296, wR2 = 0.0677

R indices (all data)
R1 = 0.0312, wR2 = 0.0687

Absolute structure parameter
0.04(8)

Extinction coefficient
n/a

Largest diff. peak and hole
0.144 and -0.158 e.Å⁻³
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**Table A2.12** Atomic coordinates (x $10^{-4}$) and equivalent isotropic displacement parameters ($\approx \AA x 10^3$) for 64. $U(eq)$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

<table>
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**Table A2.13** Bond lengths [Å] and angles [°] for 64

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C(4)-H(4B) 0.9900
C(5)-C(6) 1.396(2)
C(5)-C(10) 1.400(2)
C(6)-C(7) 1.385(3)
C(6)-H(6) 0.9500
C(7)-C(8) 1.389(3)
C(7)-H(7) 0.9500
C(8)-C(9) 1.384(3)
C(8)-H(8) 0.9500
C(9)-C(10) 1.395(2)
C(9)-H(9) 0.9500
O(1)-H(1O) 0.93(2)
O(2)-C(11) 1.432(2)
O(2)-H(2O) 0.91(2)
C(11)-H(11A) 0.9900
C(11)-H(11B) 0.9900
C(12)-C(14) 1.508(2)
C(12)-C(13) 1.537(3)
C(12)-H(12) 1.0000
C(13)-H(13A) 0.9800
C(13)-H(13B) 0.9800
C(13)-H(13C) 0.9800
C(14)-C(15) 1.322(3)
C(14)-H(14) 0.9500
C(15)-H(15A) 0.9500
C(15)-H(15B) 0.9500
O(1)-C(1)-C(10) 110.31(13)
O(1)-C(1)-C(2) 110.47(13)
C(10)-C(1)-C(2) 115.37(14)
O(1)-C(1)-H(1) 106.7
C(10)-C(1)-H(1) 106.7
C(2)-C(1)-H(1) 106.7
C(3)-C(2)-C(1) 107.46(13)
C(3)-C(2)-C(11) 108.58(14)
C(1)-C(2)-C(11) 107.34(13)
C(3)-C(2)-C(12) 114.66(14)
C(1)-C(2)-C(12) 113.27(15)
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C(11)-C(2)-C(12)  105.21(13)
C(4)-C(3)-C(2)    114.18(14)
C(4)-C(3)-H(3A)   108.7
C(2)-C(3)-H(3A)   108.7
C(4)-C(3)-H(3B)   108.7
C(2)-C(3)-H(3B)   108.7
H(3A)-C(3)-H(3B)  107.6
C(5)-C(4)-C(3)    112.78(14)
C(5)-C(4)-H(4A)   109.0
C(3)-C(4)-H(4A)   109.0
C(5)-C(4)-H(4B)   109.0
C(3)-C(4)-H(4B)   109.0
H(4A)-C(4)-H(4B)  107.8
C(6)-C(5)-C(10)   118.84(16)
C(6)-C(5)-C(4)    119.89(15)
C(10)-C(5)-C(4)   121.27(15)
C(7)-C(6)-C(5)    121.68(17)
C(7)-C(6)-H(6)    119.2
C(5)-C(6)-H(6)    119.2
C(6)-C(7)-C(8)    119.20(17)
C(6)-C(7)-H(7)    120.4
C(8)-C(7)-H(7)    120.4
C(9)-C(8)-C(7)    119.79(18)
C(9)-C(8)-H(8)    120.1
C(7)-C(8)-H(8)    120.1
C(8)-C(9)-C(10)   121.30(17)
C(8)-C(9)-H(9)    119.3
C(10)-C(9)-H(9)   119.3
C(9)-C(10)-C(5)   119.13(16)
C(9)-C(10)-C(1)   118.63(15)
C(5)-C(10)-C(1)   122.16(15)
C(1)-O(1)-H(1O)   107.5(19)
C(11)-O(2)-H(2O)  115.1(17)
O(2)-C(11)-C(2)   112.54(14)
O(2)-C(11)-H(11A) 109.1
C(2)-C(11)-H(11A) 109.1
O(2)-C(11)-H(11B) 109.1
C(2)-C(11)-H(11B) 109.1
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**Table A2.14** Anisotropic displacement parameters \((\text{Å}^2 \times 10^3)\) for 14. The anisotropic displacement factor exponent takes the form: \(-2\pi^2 \left\{ h^2 a^* U^1 + ... + 2 h k a^* b^* U^{12} \right\}\)

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H(11A)-C(11)-H(11B) 107.8
C(14)-C(12)-C(13) 108.99(15)
C(14)-C(12)-C(2) 111.98(15)
C(13)-C(12)-C(2) 116.67(15)
C(14)-C(12)-H(12) 106.2
C(13)-C(12)-H(12) 106.2
C(2)-C(12)-H(12) 106.2
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H(13A)-C(13)-H(13B) 109.5
C(12)-C(13)-H(13C) 109.5
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H(13B)-C(13)-H(13C) 109.5
C(15)-C(14)-C(12) 125.79(17)
C(15)-C(14)-H(14) 117.1
C(12)-C(14)-H(14) 117.1
C(14)-C(15)-H(15A) 120.0
C(14)-C(15)-H(15B) 120.0
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Appendix 2 – X-Ray Crystallography Reports Relevant to Chapter 1

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Table A2.15 Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for 64

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CHAPTER 2

Enantioselective Iridium-Catalyzed Allylic Alkylation Reactions of Masked Acyl Cyanide Equivalents

2.1 INTRODUCTION AND BACKGROUND

Since the first report of an asymmetric iridium-catalyzed allylic alkylation in 1997, the technology has been widely developed for normal reactivity patterns between electrophilic π-allyl species and nucleophilic enolate equivalents, organometallic reagents, or heteroatoms (Figure 2.1a, left). However, the application of an umpolung strategy to stitch together a formally electrophilic group and a π-allyl cation via enantioselective iridium-catalyzed allylic alkylation remains underexplored (Figure 2.1a, right). To date, only two examples of reverse-polarity nucleophiles in iridium-catalyzed allylic alkylation have been reported (Figure 2.1b). In 2008, Helmchen showed that the extensively explored malononitrile nucleophile can operate as a methoxy carbonyl synthon with the

† This work was performed in collaboration with Dr. J. Caleb Hethcox. Portions of this chapter have been reproduced with permission from Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. Org. Lett. 2017, 19, 1527–1529 © 2017 American Chemical Society.
subsequent application of an oxidative degradation process (Figure 2.1b, left). More recently, Carreira disclosed the use of formaldehyde \(N,N\)-dialkylhydrazone as a formyl anion equivalent in iridium-catalyzed allylic alkylation reactions (Figure 2.1b, right).

Herein, we describe the first use of an acyl cyanide equivalent in asymmetric iridium-catalyzed allylic alkylation, which formally serves as the addition of carbon monoxide (Figure 2.1c, left).

**Figure 2.1** Iridium-catalyzed allylic alkylation strategies

*a) Iridium-Catalyzed Allylic Alkylation Strategies*

![Diagram](image)

Standard (>60 reports)

Umpolung (2 reports)

*b) Prior Art: Umpolung Strategy Iridium-Catalyzed Allylic Alkylation*

![Diagram](image)

Helmchen\(^4\)

Carreira\(^5\)

*c) This Research: Use of an Umpoled Masked Acyl Cyanide (MAC) Reagent*

![Diagram](image)

As part of our ongoing research program to develop iridium-catalyzed allylic alkylation methods,\(^6\) we became interested in exploring the reactivity of masked acyl cyanide (MAC) reagents as reverse-polarity nucleophiles with \(\pi\)-allyl electrophiles. Following reaction with an electrophile, these umpoled synthons, developed by
Chapter 2 – Enantioselective Iridium-Catalyzed Allylic Alkylation Reactions of Masked Acyl Cyanide Equivalents

Yamamoto and Nemoto,\(^7\) can be unmasked to reveal a transient acyl cyanide intermediate, which can be further transformed into a carboxylic acid, amide, or ester.\(^7,8\) We envisioned that the novel application of MAC reagents to iridium-catalyzed allylic alkylation chemistry could provide access to highly desirable, enantioenriched vinylated \(\alpha\)-aryl carbonyl derivatives, which are otherwise difficult to prepare (Figure 1c, right).\(^9\)

\section*{2.2 REACTION OPTIMIZATION}

Preliminary studies focused on the identification of a suitable protecting group for MAC nucleophile \(67\) in order to achieve the allylic alkylation reaction. Using our previously reported conditions for iridium-catalyzed allylic alkylations with cinnamyl-derived electrophiles as a starting point,\(^6a\) we found that the reaction of either silyl ether \(67a\) or acetate \(67b\) with cinnamyl carbonate (68) furnishes desired products \(69a\) and \(69b\), respectively, albeit in low yields (Table 2.1, entries 1 and 2). However, the use of methoxymethyl ether \(67c\) provides allylic alkylation product \(69c\) in 64\% yield (entry 3). Moreover, we were pleased to find that product \(69c\) can be obtained with excellent enantioselectivity (95\% ee), obviating the need for further optimization beyond that of conversion. Of note, as in our prior investigations on iridium-catalyzed allylic alkylation,\(^6a\) LiBr was found to improve the regioselectivity of the allylic alkylation reaction – the use of 200 mol \% (in comparison to 100 mol \% as utilized in our previous report\(^6a\)) provides consistently higher yields of desired branched product \(69\).

Efforts to increase the reaction conversion revealed that altering the nucleophile to electrophile ratio from 1:2 to 2:1 improves the yield to 77\% with no erosion of enantioselectivity (entries 4 and 5). We observed that extending the reaction time from 18...
to 48 hours provides product 69c in a now synthetically useful 85% yield and 97% ee (entry 6). Ultimately, we found that treatment of a mixture (2:1) of nucleophile 67c to electrophile 68 with a combination of catalytic Ir(cod)Cl·L2 (4 mol %) and LiBr (200 mol %) at 60 °C delivers allylic alkylation product 69c in a high 86% yield with an exceptional 96% enantioselectivity in only 18 hours (entry 7).

Table 2.1 Optimization of reaction parameters

<table>
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<th>Temp (°C)</th>
<th>Yield (%)b</th>
<th>ee (%)c</th>
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[a] Reactions performed on 0.1 mmol scale. [b] 1H NMR yield based on internal standard. [c] Determined by chiral HPLC analysis. [d] Reaction run for 48 h. [e] TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene.

### 2.3 SUBSTRATE SCOPE EXPLORATION

With the optimized conditions identified, the substrate scope of the enantioselective umpolung reaction was explored (Table 2.2). Our investigation began by probing the effects of electronics on reaction yield and selectivity. Gratifyingly, we observed that para-substituted aryl electrophiles bearing both electron-withdrawing (–Br, –CF3, –F) and electron-donating (–OMe) groups furnish products 71a–d with consistently excellent enantioselectivities (>95% ee). While products 71a (–Br) and 71d (–OMe) are obtained in high yield (>94% yield), diminished yields (58% and 69% yield,
respectively) are observed for the more electron-poor products 71b (–CF₃) and 71c (–F).

Further examination of electrophile electronics revealed that meta-Cl-substituted 71e, as well as poly-alkoxylated 71f and 71g, are each furnished in good yields (>81%) and high enantioselectivities (92–98% ee), despite varying electronics. Studies involving sterically demanding substrates showed that products 71h ( –2-Np) and 71i ( –ortho-Me) can be provided with good selectivities (92% and 89% ee, respectively), albeit in moderate yields (41% and 65%, respectively). Additionally, we were pleased to discover that pyridine 71j, furan 71k, and thiophene 71l are each afforded with excellent enantioselectivities (90–96% ee) and in moderate to high yields (73–94%).

Table 2.2 Electrophile substrate scope

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<td>58</td>
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<td>71l</td>
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[a] Reactions performed on 0.2 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC or SFC analysis. [d] Reaction run for 36 h at 50 °C.
A broader investigation of the substrate scope revealed limitations of the developed catalytic system (Table 2.3). Foremost, alkenyl substitution is not tolerated on allylic electrophile 70 and leads to significantly diminished yields and enantioselectivities, as is observed in the formation of iso-propenyl 71m, cyclohexyl 71n, and propenyl 71o. Additionally, a propargyl-substituted electrophile does not give desired product 71q in the allylic alkylation reaction, likely due to catalyst poisoning by binding of the alkyne to the metal source. Finally, the optimized reaction conditions fail to provide synthetically useful yields or high regioselectivities when alkyl-substituted allylic electrophiles are employed (e.g., 71q–u).

Table 2.3 Electrophilic substrate scope limitations

<table>
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<tr>
<td></td>
<td>71u</td>
<td>no reaction</td>
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[a] Reactions performed on 0.2 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC or SFC analysis. [d] ^1H NMR yield based on internal standard.
Chapter 2 – Enantioselective Iridium-Catalyzed Allylic Alkylation Reactions of Masked Acyl Cyanide Equivalents

To demonstrate the synthetic utility of this method, a preparatory scale (4 mmol) reaction was performed (Scheme 2.1). Using cinnamyl carbonate (68), both the yield and enantioselectivity of the reaction are unchanged from those obtained at 0.1 mmol scale.

**Scheme 2.1 Preparatory scale reaction**

![Scheme 2.1 Preparatory scale reaction](image)

2.4 **CONCLUSIONS**

In summary, we have developed the first enantioselective iridium-catalyzed allylic alkylation reaction of masked acyl cyanide (MAC) reagents. The umpolung strategy showcased in this reaction diverges from the normal reactivity patterns employed in all but two of the previously reported iridium-catalyzed allylic alkylations and is the first report of a carbon monoxide synthon in iridium-catalyzed allylic alkylation. Critical to the success of this new reaction is the identity of the methoxymethyl protecting group on the MAC reagent. The developed methodology proceeds with moderate to excellent yields (up to 95%) and high levels of enantioselectivity (up to 98% ee) on up to gram scale for a wide range of aryl- and heteroaryl-substituted allylic electrophiles. Furthermore, MAC adducts bearing resemblance to compound 4c have been transformed into acids, amides, and esters by unmasking the alkoxy malononitrile moiety.\(^7,^8\) Thus, this methodology serves as an entry to enantioenriched vinylated \(\alpha\)-aryl carbonyl derivatives.
2.5 EXPERIMENTAL SECTION

2.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Commercially obtained reagents were used as received. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Oakwood Chemicals and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) and preparatory TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, KMnO4 or p-anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak IC column (4.6 mm x 25 cm) or a Chiralpak AD column (4.6 mm x 25 cm), both obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. Analytical SFC was performed with a Mettler SFC supercritical CO2 analytical chromatography system utilizing a Chiralpak IC-3 column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. 1H NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CHCl3 (δ 7.26 ppm). 13C NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CDCl3 (δ 77.16 ppm). Data for 1H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet.
Data for $^{13}$C NMR are reported in terms of chemical shifts ($\delta$ ppm). Some reported spectra include minor solvent impurities of benzene ($\delta$ 7.36 ppm), water ($\delta$ 1.56 ppm), ethyl acetate ($\delta$ 4.12, 2.05, 1.26 ppm), methylene chloride ($\delta$ 5.30 ppm), grease ($\delta$ 1.26, 0.86 ppm), and/or silicon grease ($\delta$ 0.07 ppm), which do not impact product assignments. IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm$^{-1}$). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell, and are reported as: $\left[\alpha\right]_D^T$ (concentration in g/100 mL, solvent).

### 2.5.1.1 Preparation of Known Compounds

Previously reported methods were used to prepare ligand $\left(S,S_a\right)$-L$^2$ as well as starting materials 67a–c, 68, 70a, 70b, 70c, 70d, 70h, 70i, 70j, 70k, 70l.
**2.5.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA**

**2.5.2.1 General Procedure for the Synthesis of Electrophiles**

![Image of (E)-3-(3-Chlorophenyl)allyl methyl carbonate (70e)]

(E)-3-(3-Chlorophenyl)allyl methyl carbonate (70e). To a solution of methyl (E)-3-(3-chlorophenyl)prop-2-enoate\(^{17}\) (1.4 g, 7.0 mmol, 1 equiv) in Et\(_2\)O (28 mL) at −78 °C was added DIBAL (3.0 g, 21 mmol, 3 equiv) dropwise. The resulting reaction mixture was stirred at −78 °C for 2.5 h, whereupon the reaction was quenched with a saturated aqueous Rochelle’s salt solution (10 mL). The cooling bath was then removed and the reaction was stirred for 18 h at ambient temperature. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure.

The crude material was then dissolved in CH\(_2\)Cl\(_2\) (10 mL) and cooled to 0 °C. Pyridine (1.7 mL, 21 mmol, 3 equiv) was added followed by methyl chloroformate (0.81 mL, 11 mmol, 1.5 equiv) dropwise. The resulting solution was allowed to warm to ambient temperature and stirred for 18 h. The reaction was quenched with the addition of 1 M HCl (10 mL) and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (5% EtOAc/hexanes) to give carbonate 70e as a colorless oil (1.0 g, 63% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.43 – 7.37 (m, 1H), 7.30 – 7.23 (m, 3H), 6.69 – 6.60 (m, 1H), 6.32 (dt, \(J = 15.9, 6.3\) Hz, 1H), 4.81 (dd, \(J = 6.3, 1.4\) Hz, 2H), 3.84 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.7, 138.0, 134.7, 133.2, 130.0, 128.3,
126.7, 125.0, 124.2, 68.1, 55.1; IR (Neat Film, NaCl) 3010, 2956, 2856, 1748, 1594, 1567, 1442, 1377, 1261, 1091, 1078, 962, 791, 777, 682 cm\(^{-1}\); HRMS (MM: FAB+) \(m/z\) calc’d for C\(_{11}\)H\(_{11}\)ClO\(_3\) [M]+: 226.0397, found 226.0398.

### 2.5.2.2 Spectroscopic Data for the Synthesis of Electrophiles

#### (E)-3-(Benzo[d][1,3]dioxol-5-yl)allyl methyl carbonate (70f).
Carbonate 70f was prepared from methyl (2\(E\))-3-(1,3-benzodioxol-5-yl)acrylate\(^\text{18}\) according to the general procedure and isolated by silica gel flash column chromatography (5\% EtOAc/hexanes) as a colorless solid (0.79 g, 48\% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.93 (d, \(J = 1.6\) Hz, 1H), 6.83 (ddd, \(J = 7.9, 1.6, 0.5\) Hz, 1H), 6.79 – 6.73 (m, 1H), 6.60 (dt, \(J = 15.7, 1.3\) Hz, 1H), 6.12 (dt, \(J = 15.7, 6.6\) Hz, 1H), 5.96 (s, 2H), 4.76 (dd, \(J = 6.6, 1.3\) Hz, 2H), 3.80 (s, 3H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.8, 148.2, 147.9, 134.9, 130.6, 121.8, 120.7, 108.4, 106.0, 101.3, 68.7, 55.0; IR (Neat Film, NaCl) 3003, 2956, 2895, 2781, 1747, 1504, 1491, 1446, 1384, 1355, 1252, 1194, 1126, 1039, 933, 863, 791 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{12}\)H\(_{12}\)O\(_5\) [M]+: 236.0685, found 236.0674.

#### (E)-Methyl (3-(3,4,5-trimethoxyphenyl)allyl) carbonate (70g).
Carbonate 70g was prepared from methyl 3,4,5-trimethoxycinnamate\(^\text{19}\) according to the general procedure and isolated by silica gel flash column chromatography (5\% EtOAc/hexanes) as a
colorless oil (1.2 g, 65% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.65 – 6.56 (m, 3H), 6.21 (dt, \(J = 15.8, 6.5\) Hz, 1H), 4.78 (dd, \(J = 6.5, 1.3\) Hz, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 3.81 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.8, 153.4, 138.4, 135.0, 131.8, 122.0, 103.9, 68.5, 61.1, 56.2, 55.0; IR (Neat Film, NaCl) 2999, 2956, 2840, 1748, 1583, 1508, 1452, 1420, 1339, 1265, 1128, 1010, 941, 850, 792 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{14}\)H\(_{18}\)O\(_6\) [M]: 282.1103, found 282.1114.

2.5.2.3 General Procedure for Optimization Reactions (Table 2.1)

In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added \([\text{Ir(cod)Cl}]_2\) (1.3 mg, 0.0020 mmol, 2 mol %), ligand \((S,S_a)-\text{L}2\) (1.8 mg, 0.0040 mmol, 4 mol %), TBD (1.4 mg, 0.010 mmol, 10 mol%), and THF (0.5 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with LiBr (17 mg, 0.20 mmol, 200 mol %), MAC nucleophile 67 (0.20 mmol), and THF (0.25 mL). The pre-formed catalyst solution (vial A) was then transferred to vial B followed by 0.25 mL of a solution of cinnamyl carbonate 68 (0.4 M in THF). The vial was sealed and stirred at the specified temperature. After 18 or 48 h, the vial was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc. The crude mixture was concentrated and 1,2,4,5-tetrachloro-3-nitrobenzene (0.10 mmol in 0.5 mL CDCl\(_3\)) was added. The NMR yield (measured in reference to 1,2,4,5-tetrachloro-3-nitrobenzene \(\delta\) 7.74 ppm (s, 1H)) was determined by \(^1\)H NMR analysis of the crude mixture. The residue was purified by preparatory TLC (15% EtOAc/hexanes) to afford product 69, which was analyzed by chiral HPLC (1% IPA, 1.0 mL/min, Chiralpak IC column, \(\lambda = 210\) nm).
2.5.2.4 General Procedure for the Iridium-Catalyzed Allylic Alkylation

Please note that the absolute configuration of product 69c was assigned by conversion to (R)-2-phenylbutanoic acid. All other products (71a–l) were assigned by analogy. For respective HPLC and SFC conditions, please refer to Table 2.4.

(R)-2-(Methoxymethoxy)-2-(1-phenylallyl)malononitrile (69c). In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]₂ (2.7 mg, 0.0040 mmol, 2 mol %), ligand (S,S₂)-L₂ (3.7 mg, 0.0080 mmol, 4 mol %), TBD (2.8 mg, 0.020 mmol, 10 mol %), and THF (1 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with LiBr (35 mg, 0.40 mmol, 200 mol %), MAC nucleophile 67c (50 mg, 0.40 mmol, 200 mol %), and THF (0.5 mL). The pre-formed catalyst solution (vial A) was then transferred to vial B followed by a solution of cinnamyl carbonate 68 (38 mg, 0.20 mmol, 100 mol %) in THF (0.5 mL). The vial was sealed and stirred at 60 °C. After 18 h, the vial was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc. The crude mixture was concentrated and the resulting residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to give the product 69c as a colorless oil (41 mg, 85% yield): 95% ee; [α]D²⁵ = −41.3 (c 2.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.47 − 7.32 (m, 5H), 6.29 (ddd, J = 16.9, 10.3, 8.6 Hz, 1H), 5.53 − 5.38 (m, 2H), 5.06 − 4.94 (m, 2H), 3.97 − 3.91 (m, 1H), 3.44 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 134.4, 131.5, 129.6, 129.1, 128.9,
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IR (Neat Film, NaCl) 3065, 3033, 2961, 2904, 2851, 2244, 1750, 1496, 1455, 1420, 1267, 1217, 1164, 1109, 1053, 1033, 967, 940, 791, 732, 700 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{14}\)H\(_{15}\)N\(_2\)O\(_2\) [M+H]\(^+\): 243.1131, found 243.1134; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, \(\lambda = 210\) nm, \(t_R\) (min): major = 12.831, minor = 17.466.

2.5.2.5 Procedure for the Preparatory Scale Reaction

(R)-2-(Methoxymethoxy)-2-(1-phenylallyl)malononitrile (69c). In a nitrogen-filled glove box, a solution of \([\text{Ir(cod)}\text{Cl}]_2\) (106 mg, 0.16 mmol, 2 mol %), ligand (S,S\(_a\))-L2 (145 mg, 0.32 mmol, 4 mol %), TBD (110 mg, 0.79 mmol, 10 mol %) in THF (20 mL) was stirred at 25 °C. After 10 minutes, the catalyst mixture was added to a mixture of LiBr (0.69 g, 7.9 mmol, 200 mol %), MAC nucleophile 67c (1 g, 7.9 mmol, 200 mol %), and THF (20 mL) followed by cinnamyl carbonate 68 (0.76 g, 4.0 mmol, 100 mol %). The flask was removed from the glove box and stirred at 60 °C. After 18 h, the crude reaction mixture was concentrated and the resulting residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to give the product 69c as a colorless oil (0.82 g, 86% yield): 95% ee, spectroscopic data vide supra.
2.5.2.6 Spectroscopic Data for the Iridium-Catalyzed Allylic Alkylation Products

\[
\begin{align*}
\text{(R)-2-(1-(4-Bromophenyl)allyl)-2-(methoxymethoxy)malononitrile (71a).} \\
\text{Product 71a was prepared according to the general procedure and isolated by silica gel flash column} \\
\text{chromatography (10% EtOAc/hexanes) to give a colorless oil (60 mg, 94% yield): 96\% ee; [}\alpha\text{]}_D^{25} \approx -44.3 (c 3.2, CHCl}_3; ^1\text{H NMR (400 MHz, CDCl}_3) \delta 7.56 - 7.50 (m, 2H), 7.32 - 7.28 (m, 2H), 6.23 (dd, J = 16.9, 10.3, 8.6 Hz, 1H), 5.55 - 5.38 (m, 2H), 5.05 - 4.96 (m, 2H), 3.92 (d, J = 8.6 Hz, 1H), 3.44 (s, 3H); ^13\text{C NMR (101 MHz, CDCl}_3) \delta 133.4, 132.1, 131.3, 130.9, 123.4, 123.2, 112.6, 112.5, 96.6, 69.5, 57.8, 57.5; IR (Neat Film, NaCl) 3013, 2934, 2242, 1488, 1404, 1274, 1216, 1163, 1108, 1034, 1010, 967, 939, 826, 762 cm}^{-1}; \text{HRMS (FAB+)} m/z \text{calc'd for C}_{14}\text{H}_{13}\text{BrO}_2\text{N}_2 [M]^+; 320.0160, \text{found 320.0155; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, }\lambda = 210 \text{ nm, } t_R \text{ (min): major} = 15.852, \text{minor} = 11.623. \\
\end{align*}
\]

\[
\begin{align*}
\text{(R)-2-(Methoxymethoxy)-2-(1-(4-(trifluoromethyl)phenyl)allyl)malononitrile (71b).} \\
\text{Product 71b was prepared according to the general procedure and isolated by preparatory} \\
\text{TLC (5% EtOAc/hexanes, plate eluted three times) to give a pale yellow oil (36 mg, 58\%)
\end{align*}
\]
yield: 96% ee; [\alpha]_D^{25} = -25.2 (c 1.5, CHCl_3); \textsuperscript{1}H NMR (400 MHz, CDCl_3) \delta 7.66 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 6.27 (ddd, J = 16.9, 10.3, 8.7 Hz, 1H), 5.57 – 5.41 (m, 2H), 5.09 – 4.96 (m, 2H), 4.02 (d, J = 8.7 Hz, 1H), 3.44 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl_3) \delta 138.4, 131.5, 131.1, 130.6, 130.2, 125.9 (q, J = 3.9 Hz), 125.3, 123.6, 122.6, 112.5, 112.4, 96.7, 69.4, 58.0, 57.6; IR (Neat Film, NaCl) 2962, 2906, 2835, 2245, 1751, 1618, 1445, 1417, 1445, 1417, 1327, 1269, 1218, 1166, 1127, 1069, 943, 840, 792 cm\textsuperscript{-1}; HRMS (MM: FAB+) \textit{m/z} calc’d for C\textsubscript{15}H\textsubscript{12}F\textsubscript{3}N\textsubscript{2}O\textsubscript{2} [\textit{M+H} – H\textsubscript{2}]\textsuperscript{+}: 309.0851, found 309.0849; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, \lambda = 210 nm, t\textsubscript{R} (min): major = 10.681, minor = 8.223.

\textbf{(R)-2-(1-(4-Fluorophenyl)allyl)-2-(methoxymethoxy)malononitrile (71c).} Product 71c was prepared according to the general procedure and isolated by preparatory TLC (9% EtOAc/hexanes, plate eluted two times) to give a colorless oil (37 mg, 69% yield): 96% ee; [\alpha]_D^{25} = -35.9 (c 1.9, CHCl_3); \textsuperscript{1}H NMR (400 MHz, CDCl_3) \delta 7.47 – 7.32 (m, 2H), 7.15 – 7.02 (m, 2H), 6.25 (ddd, J = 16.9, 10.3, 8.5 Hz, 1H), 5.57 – 5.35 (m, 2H), 5.11 – 4.94 (m, 2H), 3.95 (d, J = 8.5 Hz, 1H), 3.44 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl_3) \delta 164.3, 161.9, 131.5, 131.4, 131.2, 130.2 (d, J = 3.5 Hz), 122.9, 116.1, 115.9, 112.7, 112.6, 96.6, 69.8 (d, J = 1.6 Hz), 57.5 (d, J = 9.2 Hz); IR (Neat Film, NaCl) 3085, 2964, 2847, 2242, 1606, 1511, 1415, 1281, 1230, 1164, 1108, 1053, 968, 940, 798, 766 cm\textsuperscript{-1}; HRMS (ESI+) \textit{m/z} calc’d for C\textsubscript{14}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+}: 261.1039, found 261.1033; HPLC conditions: 1%
IPA, 1 mL/min, Chiralpak IC column, $\lambda = 210$ nm, $t_R$ (min): major = 11.712, minor = 8.971.

(R)-2-(Methoxymethoxy)-2-(1-(4-methoxyphenyl)allyl)malononitrile (71d). Product 71d was prepared according to the general procedure and isolated by silica gel flash column chromatography (5–10% EtOAc/hexanes) to give a colorless oil (52 mg, 95% yield): 95% ee; $[\alpha]_D^{25} -51.8$ (c 2.7, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.31 (m, 2H), 6.92 (d, $J = 8.8$ Hz, 2H), 6.26 (ddd, $J = 16.9$, 10.3, 8.5 Hz, 1H), 5.61 – 5.34 (m, 2H), 5.08 – 4.94 (m, 2H), 3.91 (d, $J = 8.5$ Hz, 1H), 3.82 (s, 3H), 3.45 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 160.1, 131.7, 130.8, 126.3, 122.3, 114.3, 112.82, 112.78, 96.5, 70.1, 57.6, 57.4, 55.4; IR (Neat Film, NaCl) 3005, 2962, 2939, 2905, 2838, 2244, 2052, 1890, 1610, 1584, 15112, 1459, 1305, 1252, 1216, 1182, 1162, 1107, 1031, 937, 834, 783, 765, 625 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{15}$H$_{17}$N$_2$O$_3$ [M+H]$^+$: 273.1239, found 273.1227; SFC conditions: 3% IPA, 3.5 mL/min, Chiralpak IC-3 column, $\lambda = 210$ nm, $t_R$ (min): major = 6.831, minor = 5.267.
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(R)-2-(1-(3-Chlorophenyl)allyl)-2-(methoxymethoxy)malononitrile (71e). Product 71e was prepared according to the general procedure and isolated by silica gel flash column chromatography (10% EtOAc/hexanes) to give a colorless oil (47 mg, 85% yield): 92% ee; [α]D^25 = -38.5 (c 2.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.28 (m, 4H), 6.23 (ddd, J = 16.9, 10.3, 8.7 Hz, 1H), 5.57 – 5.40 (m, 2H), 5.08 – 4.97 (m, 2H), 3.92 (d, J = 8.7 Hz, 1H), 3.45 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 136.4, 134.7, 130.8, 130.2, 129.9, 129.3, 127.8, 123.3, 112.6, 112.4, 96.6, 69.5, 57.9, 57.5; IR (Neat Film, NaCl) 3069, 2962, 2849, 2832, 2244, 1751, 1596, 1576, 1478, 1436, 1418, 1277, 1217, 1164, 1109, 111055, 1032, 967, 940, 884, 797, 760, 730, 713, 690 cm⁻¹; HRMS (ESI+) m/z calc’d for C₁₄H₁₄N₂O₂Cl [M+H]^+: 277.0744, found 277.0715; SFC conditions: 3% IPA, 3.5 mL/min, Chiralpak IC-3 column, λ = 210 nm, t_R (min): major = 3.846, minor = 3.428.

(R)-2-(1-(Benzo[d][1,3]dioxol-5-yl)allyl)-2-(methoxymethoxy)malononitrile (71f). Product 71f was prepared according to the general procedure and isolated by silica gel flash column chromatography (5–10% EtOAc/hexanes) to give a colorless oil (51 mg, 90% yield): 96% ee; [α]D^25 = -40.6 (c 3.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.91 – 6.78 (m, 3H), 6.20 (ddd, J = 16.9, 10.3, 8.5 Hz, 1H), 5.99 (s, 2H), 5.51 – 5.37 (m, 2H),
5.03 (d, J = 1.4 Hz, 2H), 3.86 (d, J = 8.5 Hz, 1H), 3.47 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 148.2, 148.1, 131.5, 127.9, 123.5, 122.5, 112.7, 109.7, 108.7, 101.5, 96.6, 70.0, 58.1, 57.5; IR (Neat Film, NaCl) 3081, 2972, 2902, 2352, 1505, 1488, 1446, 1368, 1251, 1238, 1164, 1108, 1039, 967, 934, 864, 817, 800, 763 cm$^{-1}$; HRMS (ESI+) m/z calc’d for C$_{15}$H$_{15}$N$_2$O$_4$ [M+H]$^+$: 287.1032, found 287.1039; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, $\lambda = 210$ nm, $t_R$ (min): major = 24.142, minor = 19.686.

(R)-2-(Methoxymethoxy)-2-(1-(3,4,5-trimethoxyphenyl)allyl)malononitrile (71g).

Product 71g was prepared according to the general procedure and isolated by silica gel flash column chromatography (20% EtOAc/hexanes) to give a colorless oil (54 mg, 81% yield): 98% ee; $[\alpha]_D^{25}$ = $-28.2$ (c 3.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.63 (s, 2H), 6.23 (ddd, $J = 16.8, 10.3, 8.5$ Hz, 1H), 5.55 – 5.35 (m, 2H), 5.11 – 4.94 (m, 2H), 3.87 (m, 7H), 3.85 (s, 3H), 3.46 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 153.4, 138.5, 131.3, 129.7, 122.6, 112.8, 112.7, 106.6, 96.5, 69.9, 61.0, 58.5, 57.5, 56.3; IR (Neat Film, NaCl) 2941, 2840, 244, 1591, 1509, 1463, 1418, 1333, 1245, 1163, 1127, 1034, 1007, 950, 925, 840, 771, 719 cm$^{-1}$; HRMS (ESI+) m/z calc’d for C$_{17}$H$_{21}$N$_2$O$_5$ [M+H]$^+$: 333.1450, found 333.1450; HPLC conditions: 7% IPA, 1.0 mL/min, Chiralpak AD column, $\lambda = 210$ nm, $t_R$ (min): major = 17.062, minor = 12.809.
(R)-2-(Methoxymethoxy)-2-(1-(naphthalen-1-yl)allyl)malononitrile (71h). Product 71h was prepared according to the general procedure and isolated by preparatory TLC (9% Et₂O/hexanes, plate eluted two times) to give a colorless oil (24 mg, 41% yield): 92% ee; [α]D²⁵ –30.9 (c 1.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.11 (dt, J = 8.5, 1.0 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.81 (dd, J = 7.4, 1.2 Hz, 1H), 7.60 (ddd, J = 8.6, 6.8, 1.5 Hz, 1H), 7.57 – 7.49 (m, 2H), 6.38 (ddd, J = 16.7, 10.3, 8.2 Hz, 1H), 5.57 – 5.43 (m, 2H), 5.05 – 4.92 (m, 3H), 3.40 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 134.1, 132.2, 132.1, 130.8, 129.6, 129.3, 126.9, 126.6, 126.1, 125.3, 122.8, 122.7, 113.10, 112.72, 96.5, 70.1, 57.5, 51.6; IR (Neat Film, NaCl) 3051, 2960, 2926, 2851, 2244, 1708, 1398, 1215, 1162, 1106, 1030, 960, 925, 783 cm⁻¹; HRMS (ESI+) m/z calc’d for C₁₈H₁₇N₂O₂ [M+H]⁺: 293.1290, found 293.1263; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, tᵣ (min): major = 15.134, minor = 10.197.

(R)-2-(Methoxymethoxy)-2-(1-(o-tolyl)allyl)malononitrile (71i). Product 71i was prepared according to the general procedure and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) to give a colorless oil (33 mg, 65% yield): 89% ee; [α]D²⁵ –68.7 (c 1.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.58 – 7.48 (m, 1H), 7.28 –
7.19 (m, 3H), 6.22 (ddd, \( J = 16.9, 10.2, 8.2 \) Hz, 1H), 5.50 – 5.35 (m, 2H), 5.06 – 4.98 (m, 2H), 4.34 (dd, \( J = 8.2, 1.0 \) Hz, 1H), 3.45 (s, 3H), 2.43 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta 137.4, 133.1, 132.0, 131.2, 128.6, 128.1, 126.6, 122.5, 113.0, 112.8, 96.5, 69.8, 57.5, 53.0, 20.3; \) IR (Neat Film, NaCl) 3023, 2958, 2360, 2243, 1748, 1640, 1603, 1489, 1445, 1382, 1264, 1164, 1109, 1034, 943, 846, 792, 748, 654 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{15}\)H\(_{17}\)N\(_2\)O\(_2\) [M+H]\(^+\): 257.1290, found 257.1280; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, \( \lambda = 210 \) nm, \( t_R \) (min): major = 16.719, minor = 9.761.

\[(R)-2-(\text{Methoxymethoxy})-2-(1-(\text{pyridin-3-yl})\text{allyl})\text{malononitrile (71j).} \]

Product 71j was prepared according to the general procedure and isolated by silica gel flash column chromatography (25% acetone/hexanes) to give a pale yellow oil (36 mg, 74% yield): 90% ee; \([\alpha]_D^{25} -30.8 \) (c 2.1, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 8.63 \) (dd, \( J = 4.7, 1.7 \) Hz, 2H), 7.78 (ddddd, \( J = 8.0, 2.3, 1.6, 0.5 \) Hz, 1H), 7.35 (dd, \( J = 7.9, 4.8, 0.8 \) Hz, 1H), 6.27 (dd, \( J = 16.9, 10.3, 8.7 \) Hz, 1H), 5.63 – 5.39 (m, 2H), 5.06 – 4.97 (m, 2H), 4.00 (d, \( J = 8.7 \) Hz, 1H), 3.42 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta 151.1, 150.4, 136.7, 130.4, 130.3, 123.8, 123.7, 112.5, 112.3, 96.7, 69.4, 57.5, 56.0; \) IR (Neat Film, NaCl) 2963, 2943, 2905, 2833, 2244, 1751, 1718, 1590, 1577, 1480, 1419, 1430, 1271, 1217, 1164, 1109, 1028, 970, 941, 848, 817, 756, 714 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{13}\)H\(_{14}\)N\(_3\)O\(_2\) [M+H]\(^+\): 244.1086, found 244.1083; HPLC conditions: 20% IPA, 1.0 mL/min, Chiralpak IC column, \( \lambda = 210 \) nm, \( t_R \) (min): major = 13.161, minor = 23.457.
(R)-2-(1-(Furan-2-yl)allyl)-2-(methoxymethoxy)malononitrile (71k). Product 71k was prepared according to the general procedure and isolated by silica gel flash column chromatography (10% EtOAc/hexanes) to give a colorless oil (34 mg, 73% yield): 96% ee; [α]_D^25 = -44.9 (c 1.5, CHCl₃); _1H NMR (400 MHz, CDCl₃) δ 7.47 (s, 1H), 6.53 – 6.34 (m, 2H), 6.14 (dddd, _J_ = 16.9, 10.2, 8.5, 0.8 Hz, 1H), 5.58 – 5.43 (m, 2H), 5.10 – 4.94 (m, 2H), 4.16 (d, _J_ = 8.5 Hz, 1H), 3.48 (d, _J_ = 8.5 Hz, 3H); _13C NMR (101 MHz, CDCl₃) δ 147.4, 143.5, 129.1, 123.5, 112.4, 112.3, 111.0, 110.4, 96.6, 68.9, 57.5, 52.4; IR (Neat Film, NaCl) 3125, 2091, 2964, 2942, 2905, 2833, 2245, 1499, 1444, 1422, 1270, 1217, 1164, 1109, 1030, 922, 797, 743 cm⁻¹; HRMS (ESI+) _m/z_ calc’d for C_{12}H_{13}N_{2}O_{3} [M+H]^+: 233.0926, found 233.0948; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, _t_R (min): major = 13.297, minor = 10.761.

(S)-2-(Methoxymethoxy)-2-(1-(thiophen-2-yl)allyl)malononitrile (71l). Product 71l was prepared according to the general procedure and isolated by silica gel flash column chromatography (10% EtOAc/hexanes) to give a colorless oil (49 mg, 98% yield): 93% ee; [α]_D^25 = -40.3 (c 2.5, CHCl₃); _1H NMR (400 MHz, CDCl₃) δ 7.20 (ddd, _J_ = 3.6, 1.2, 0.7 Hz, 1H), 7.08 (dd, _J_ = 5.2, 3.6 Hz, 1H), 6.21 (ddd, _J_ = 16.8, 10.2, 8.6 Hz, 1H), 5.58 – 5.48 (m, 2H), 5.09 (d, _J_ = 1.7 Hz, 2H), 4.31 (dd, _J_ = 8.6,
0.8 Hz, 1H), 3.52 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 135.7, 131.3, 128.3, 127.1, 126.9, 123.0, 112.5, 112.4, 96.7, 69.8, 57.6, 54.0; IR (Neat Film, NaCl) 3090, 2963, 2904, 2245, 2079, 1639, 1433k 1365, 1270, 1238, 1216, 1162, 1108, 1029, 922, 856, 839, 704 cm$^{-1}$; HRMS (ESI+) m/z calc’d for C$_{12}$H$_{13}$N$_2$O$_2$S [M+H]$^+$: 249.0698, found 249.0703; SFC conditions: 3% IPA, 3.5 mL/min, Chiralpak IC-3 column, $\lambda = 210$ nm, $t_R$ (min): major = 5.289, minor = 4.010.

2.5.2.7 Determination of Enantiomeric Excess

Please note racemic products were synthesized using racemic 1.2.

Table 2.4 Determination of enantiomeric excess

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Assay Conditions</th>
<th>Retention time of major isomer (min)</th>
<th>Retention time of minor isomer (min)</th>
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<td><img src="image1.png" alt="Product 1" /></td>
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<tr>
<td>2</td>
<td><img src="image2.png" alt="Product 2" /></td>
<td>HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min</td>
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<td>11.623</td>
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<tr>
<td>3</td>
<td><img src="image3.png" alt="Product 3" /></td>
<td>HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min</td>
<td>10.681</td>
<td>8.223</td>
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</tr>
<tr>
<td>Entry</td>
<td>Product</td>
<td>Assay Conditions</td>
<td>Retention time of major isomer (min)</td>
<td>Retention time of minor isomer (min)</td>
<td>%ee</td>
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<tr>
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<td>------------------</td>
<td>-------------------------------------</td>
<td>--------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Image" /></td>
<td>HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min</td>
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<td>6</td>
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<td>SFC Chiralpak IC-3 3% IPA isocratic, 3.5 mL/min</td>
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<td>3.428</td>
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<tr>
<td>7</td>
<td><img src="image4.png" alt="Image" /></td>
<td>HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min</td>
<td>24.142</td>
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<tr>
<td>8</td>
<td><img src="image5.png" alt="Image" /></td>
<td>HPLC Chiralpak AD 7% IPA isocratic, 1 mL/min</td>
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<td>98</td>
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<tr>
<td>9</td>
<td><img src="image6.png" alt="Image" /></td>
<td>HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min</td>
<td>15.134</td>
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<tr>
<td>10</td>
<td><img src="image7.png" alt="Image" /></td>
<td>HPLC Chiralpak IC 1% IPA isocratic, 1 mL/min</td>
<td>16.719</td>
<td>9.761</td>
<td>89</td>
</tr>
</tbody>
</table>
2.6 REFERENCES AND NOTES


(3) Nucleophilic additions of methylene imines to iridium π-allyl complexes have been accomplished via an umpoled strategy. However, the reactions deliver products


Chapter 2 – Enantioselective Iridium-Catalyzed Allylic Alkylation Reactions of Masked Acyl Cyanide Equivalents


APPENDIX 3

Spectra Relevant to Chapter 2:

Enantioselective Iridium-Catalyzed Allylic Alkylation Reactions of Masked Acyl Cyanide Equivalents
Figure A3.1 $^1$H NMR (400 MHz, CDCl$_3$) of compound 69c
Figure A3.2 Infrared spectrum (Thin Film, NaCl) of compound 69c

Figure A3.3 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 69c
Figure A3.4 $^1$H NMR (400 MHz, CDCl$_3$) of compound 70e
Appendix 3 – Spectra Relevant to Chapter 2

Figure A3.5 Infrared spectrum (Thin Film, NaCl) of compound 70e

Figure A3.6 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 70e
Figure A3.7: $^1$H NMR (400 MHz, CDCl$_3$) of compound $70f$. 

Appendix 3 – Spectra Relevant to Chapter 2
Appendix 3 – Spectra Relevant to Chapter 2

Figure A3.8 Infrared spectrum (Thin Film, NaCl) of compound 70f

Figure A3.9 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 70f
Figure A3.10 $^1$H NMR (400 MHz, CDCl$_3$) of compound 70g
Figure A3.11  Infrared spectrum (Thin Film, NaCl) of compound 70g

Figure A3.12  $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 70g
Figure A3.13 $^1$H NMR (400 MHz, CDCl$_3$) of compound 71a
Figure A3.14 Infrared spectrum (Thin Film, NaCl) of compound 71a

Figure A3.15 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71a
Figure A3.16 $^1$H NMR (400 MHz, CDCl$_3$) of compound 71b
Figure A3.17 Infrared spectrum (Thin Film, NaCl) of compound 71b

Figure A3.18 $^{13}$C NMR (101 MHz, CDCl₃) of compound 71b
Figure A3.19 $^1$H NMR (400 MHz, CDCl$_3$) of compound 71c.
Figure A3.20 Infrared spectrum (Thin Film, NaCl) of compound 71c

Figure A3.21 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71c
Figure A3.22 $^1$H NMR (400 MHz, CDCl$_3$) of compound 71d
Appendix 3 – Spectra Relevant to Chapter 2

Figure A3.23 Infrared spectrum (Thin Film, NaCl) of compound 71d

Figure A3.24 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71d
Figure A3.25 $^1$H NMR (400 MHz, CDCl$_3$) of compound 71e
Appendix 3 – Spectra Relevant to Chapter 2

Figure A3.26 Infrared spectrum (Thin Film, NaCl) of compound 71e

Figure A3.27 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71e
Figure A3.28 $^1$H NMR (400 MHz, CDCl$_3$) of compound 71f
Appendix 3 – Spectra Relevant to Chapter 2

Figure A3.29 Infrared spectrum (Thin Film, NaCl) of compound 71f

Figure A3.30 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71f
Figure A3.31: $^1$H NMR (400 MHz, CDCl$_3$) of compound 71g

Appendix 3 – Spectra Relevant to Chapter 2
Figure A3.32 Infrared spectrum (Thin Film, NaCl) of compound 71g

Figure A3.33 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71g
Appendix 3 – Spectra Relevant to Chapter 2

Figure A3.34: $^1$H NMR (400 MHz, CDCl$_3$) of compound 71h
Figure A3.35 Infrared spectrum (Thin Film, NaCl) of compound 71h

Figure A3.36 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71h
Figure A3.38 Infrared spectrum (Thin Film, NaCl) of compound 71i

Figure A3.39 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71i
Figure A3.40 $^1$H NMR (400 MHz, CDCl$_3$) of compound 71j
Figure A3.41 Infrared spectrum (Thin Film, NaCl) of compound 71j

Figure A3.42 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71j
Figure A3.43  $^1$H NMR (400 MHz, CDCl$_3$) of compound 71k
Figure A3.44 Infrared spectrum (Thin Film, NaCl) of compound 71k

Figure A3.45 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 71k
Figure A3.46 $^1$H NMR (400 MHz, CDCl$_3$) of compound 71
Figure A3.47 Infrared spectrum (Thin Film, NaCl) of compound 711

Figure A3.48 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 711
INTRODUCTION AND BACKGROUND

The field of enantioselective iridium-catalyzed allylic alkylation has flourished in the twenty years since the seminal report by Helmchen. Over these two decades, the substrate scope with respect to the nucleophile has expanded significantly to encompass a vast array of both carbon and heteroatom nucleophiles. Conversely, the scope of the electrophiles has remained largely unchanged, being limited to those that produce products bearing a tertiary allylic stereocenter (Figure 3.1a, left). Despite the synthetic community’s longstanding interest in the synthesis of enantioenriched quaternary stereocenters as well as the development of other transition metal-catalyzed processes to access all-carbon quaternary allylic stereocenters, iridium-catalyzed allylic alkylation

† This work was performed in collaboration with Dr. J. Caleb Hethcox. Portions of this chapter have been reproduced with permission from Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. Angew. Chem. Int. Ed. 2017, 56, 11545–11548 © 2017 Wiley-VCH.
Chapter 3 – Enantioselective Synthesis of Acyclic α-Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation

reactions that furnish products possessing such a stereocenter remain conspicuously absent from the literature (Figure 3.1a, right).

**Figure 3.1** Synthesis of allylic all-carbon quaternary stereocenters via enantioselective iridium-catalyzed allylic alkylation

As part of our ongoing program in developing iridium-catalyzed allylic alkylation technology and our continued interest in the catalytic, asymmetric synthesis of quaternary stereocenters, we were attracted to this unmet challenge. Moreover, we imagined that an umpolung strategy iridium-catalyzed allylic alkylation reaction of a trisubstituted allylic electrophile with a masked acyl cyanide (MAC) nucleophile would not only give rise to products containing an enantioenriched allylic all-carbon quaternary stereocenter, but also provide access to highly valuable acyclic α-quaternary carboxylic acid derivatives (i.e., acids, esters, amides) upon unmasking of the MAC functionality (Figure 3.1b). However, success of this strategy hinged upon the implementation of a trisubstituted allylic electrophile, which was predicted to be unreactive in an enantioselective iridium-catalyzed allylic alkylation reaction. It is known that the reaction rates of these processes decrease with increasing substitution on the olefin of the electrophile. Herein, we
discuss the unlocking of this heretofore unreactive class of electrophiles to achieve the first example of an enantioselective iridium-catalyzed allylic alkylation reaction forming a quaternary stereocenter at the allylic position.

3.2 REACTION OPTIMIZATION

Preliminary studies focused on identifying a combination of ligand and additive to promote the reaction of MAC 67c and trisubstituted allylic electrophile 72 (Table 3.1). Application of our standard conditions for iridium-catalyzed allylic alkylation reactions of \([\text{Ir(cod)Cl}]_2\), L2, and LiBr return only starting material (Table 3.1, entry 1).\(^9\) A brief ligand screen revealed that while ligand L9 also results in no reaction (entry 2), the phosphoramidite L5 developed by Carreira provides desired product 73 in 13% yield with a moderate 79% ee (entry 3).\(^3\) Attempts to further increase yield and selectivity via an extensive evaluation of additives known to promote iridium-catalyzed allylic alkylations proved ineffective.\(^2-4,9\) As we hypothesized that the oxidative addition process is slow for trisubstituted allylic electrophiles, we reasoned that the inclusion of a strong Lewis acid would facilitate the ionization of the carbonate during the insertion event, leading to improved reactivity of these recalcitrant electrophiles. Toward this end, we substituted LiBr for triethylborane and were pleased to find that the yield nearly triples and the enantioselectivity rises to 93% ee (entry 4).\(^13\) Upon varying the stoichiometry of nucleophile 67c to electrophile 72, we observed a dramatic increase in yield to 74% with no erosion of enantioselectivity (entry 5). Ultimately, we discovered that exposure of a mixture (1:2) of MAC 67c and trisubstituted allylic electrophile 72 affords MAC adduct 73 in nearly quantitative yield and in 94% ee (entry 6). Of note, excess electrophile 72 is
Chapter 3 – Enantioselective Synthesis of Acyclic α-Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation

not consumed and can be recovered following the iridium-catalyzed allylic alkylation reaction.

**Table 3.1 Optimization of reaction parameters**

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>1:2</th>
<th>Additive (200 mol %)</th>
<th>Yield (%)b</th>
<th>ee (%)c</th>
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<tbody>
<tr>
<td>1</td>
<td>L2</td>
<td>2:1</td>
<td>LiBr</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>L9</td>
<td>2:1</td>
<td>LiBr</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>L5</td>
<td>2:1</td>
<td>LiBr</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>L5</td>
<td>2:1</td>
<td>LiBr</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>1:1.2</td>
<td>LiBr</td>
<td>34</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>L5</td>
<td>1:2</td>
<td>LiBr</td>
<td>99</td>
<td>94</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.1 mmol scale. [b] 'H NMR yield based on internal standard. [c] Determined by chiral HPLC analysis. [d] TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene.

### 3.3 MECHANISTIC INSIGHTS

During the course of our optimization studies, we discovered both the surprising necessity of the guanidine base TBD as well as the importance of electrophile stereochemistry in our newly developed reaction. Though previously reported conditions for the use of L5 in iridium-catalyzed allylic alkylations do not require a base additive,14 we found the inclusion of TBD during the catalyst prestir to be critical to the success of the reaction. TBD is included with ligands L2 and L9 to form an active iridicycle catalyst; however, Carreira has demonstrated that ligand L5 does not form an iridicycle.14
Thus, we hypothesize that TBD may be serving as either a placeholder ligand to prevent the formation of an inactive catalyst or as a base to promote the formation of an active, novel iridicycle.\textsuperscript{2a,c} Additionally, we noted that use of the \textit{E}-trisubstituted allylic electrophile was required, as \textit{Z}-olefin isomer 74 led to markedly decreased yield and selectivity (Table 3.2). We rationalize this difference in reactivity via the preferred conformation of the reactants. Whereas 72 may exist in a planar conformation, the phenyl group of 74 likely prefers to rotate out of plane to alleviate A\textsubscript{1,3} strain (Table 3.2, bottom). In adopting this perpendicular conformation, the phenyl ring has now increased the stercics above and below the olefin as well as become σ-withdrawing rather than π-donating. Finally, neither a kinetic nor a dynamic kinetic resolution occurs under the reaction conditions with the use of terminal olefin \textit{rac}-75 (Table 3.2).

\textbf{Table 3.2} \textit{Electrophile isomers}\textsuperscript{a}

\begin{tabular}{|c|c|c|}
\hline
\textbf{Electrophile} & \textbf{S\textsubscript{a}}-L5 (4.2 mol \%) & TBD (10 mol \%) \\
\hline
\textbf{67c} & \textbf{72}, \textbf{74}, or \textbf{75} & THF (0.1 M), 60 °C, 18 h \\
\hline
\textbf{72} & Ph & \textbf{OMOM} \\
\textbf{74} & \textbf{NC} - \textbf{OCO\textsubscript{2}Me} & \textbf{Ph} \\
\textbf{75} & \textbf{OMOM} & Ph \\
\hline
\textbf{99\% yield}\textsuperscript{b} & \textbf{94\% ee}\textsuperscript{c} & \textbf{18\% yield} \\
\textbf{16\% ee} & \textbf{1\% ee} & \textbf{99\% yield} \\
\hline
\end{tabular}

\textsuperscript{a} Reactions performed with 67c (0.1 mmol) and 72, 74, or 75 (0.2 mmol). \textsuperscript{b} \textsuperscript{1}H NMR yield based on internal standard. \textsuperscript{c} Determined by chiral HPLC analysis.
3.4 SUBSTRATE SCOPE EXPLORATION

Before substrate scope exploration commenced, we identified an additional opportunity for innovation. We imagined that hydrolysis of the MAC functionality of product 73 could be performed in the same reaction vessel as the iridium-catalyzed allylic alkylation reaction to provide direct access to the corresponding carboxylic acid in a one-pot, two-step procedure.\textsuperscript{10} Moreover, we envisioned that these carboxylic acid products would be amenable to purification by a simple acid/base extraction. To this end, we subjected the crude allylic alkylation mixture to hydrolysis with 6M HCl at 80 °C and were pleased to find that pure carboxylic acid 77a is obtained after an aqueous work-up with no need for column chromatography (Table 3.3).

With the optimized protocol in hand, we first explored the effect of substitution on the aryl moiety of electrophile 76 (Table 3.3). We were pleased to find that para-substitution was well tolerated to provide acids 77b–f in consistently high enantioselectivities, though electron-rich substrates provide decreased yields. Meta-substituted products 77g and 77h are obtained in similarly high enantioselectivities (92% and 87% ee, respectively), and bulky naphthyl-substituted acid 77i is furnished in 92% ee, albeit in a moderate 66% yield. Further exploration of steric effects using methyl-substituted derivatives demonstrates that while a single meta-substituent is tolerated to access 77j in 68% yield with 93% ee, the bis-meta-substituted derivative 77k is afforded in a drastically lower 32% yield but with good enantioselectivity (85% ee). Finally, we discovered that ortho-substitution is not tolerated and only starting material is recovered from the reaction.
Table 3.3 Aryl substituent substrate scope

<table>
<thead>
<tr>
<th>Aryl Substituent</th>
<th>Product Structure</th>
<th>Yield</th>
<th>ee</th>
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<tr>
<td>Cl</td>
<td>77a</td>
<td>77%</td>
<td>95% ee</td>
</tr>
<tr>
<td>F</td>
<td>77b</td>
<td>80%</td>
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</tr>
<tr>
<td>n-C4H9</td>
<td>77c</td>
<td>90%</td>
<td>90% ee</td>
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<tr>
<td>6-Me</td>
<td>77d</td>
<td>83%</td>
<td>92% ee</td>
</tr>
<tr>
<td>6-Cl</td>
<td>77e</td>
<td>65%</td>
<td>94% ee</td>
</tr>
<tr>
<td>(2-Me)_2C</td>
<td>77f</td>
<td>51%</td>
<td>95% ee</td>
</tr>
<tr>
<td>6-Br</td>
<td>77g</td>
<td>69%</td>
<td>92% ee</td>
</tr>
<tr>
<td>6-NO2</td>
<td>77h</td>
<td>66%</td>
<td>87% ee</td>
</tr>
<tr>
<td>6-OMe</td>
<td>77i</td>
<td>68%</td>
<td>93% ee</td>
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<tr>
<td>6-OF</td>
<td>77j</td>
<td>68%</td>
<td>83% ee</td>
</tr>
<tr>
<td>6-OSiMe</td>
<td>77k</td>
<td>32%</td>
<td>85% ee</td>
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<tr>
<td></td>
<td>77l</td>
<td>0%</td>
<td>0% ee</td>
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</table>

[a] Reactions performed on 0.2 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC or SFC analysis. [d] Electrophile 76f used as the bis-carbonate which was deprotected during hydrolysis. [e] Reaction run for 48 h. [f] Absolute stereochemistry determined via single crystal X-ray analysis, the absolute stereochemistry of all other compounds has been assigned by analogy. [g] Reaction performed with double catalyst loading.

With the general trends in reactivity corresponding to aryl substitution elucidated, we next turned our attention to the scope of the reaction with respect to the alkyl moiety of the electrophile (Table 3.4). We found that extension of the alkyl chain leads to decreased yields with ethyl-substituted 79a and n-butyl-substituted 79b able to be isolated in 61% and 14% yield, respectively, though both are obtained in similarly excellent enantioselectivities. Furthermore, branched-substituted electrophiles are unreactive and only starting material is recovered in attempts to prepare isopropyl-substituted 79c.
Table 3.4 Non-aryl substituent substrate scope

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>79a</td>
<td>61%</td>
<td>92% ee</td>
</tr>
<tr>
<td>79b</td>
<td>14%</td>
<td>95% ee</td>
</tr>
<tr>
<td>79c</td>
<td>0%</td>
<td>--% ee</td>
</tr>
<tr>
<td>79d/e</td>
<td>trace</td>
<td>--% ee</td>
</tr>
<tr>
<td>79f</td>
<td>32%</td>
<td>3% ee</td>
</tr>
<tr>
<td>79g</td>
<td>63%</td>
<td>63% yield</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.2 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC or SFC analysis.

We then moved to explore the necessity of the aryl functionality. We hypothesized that cyclohexyl- and cyclohexenyl-substituted electrophiles 78d and 78e would mimic the steric bulk of the phenyl moiety of 76a when interacting with the chiral catalyst, but we found that only trace products 79d and 79e are observed under our reaction conditions (Table 3.4). Use of bis-n-alkyl-substituted electrophile 78f provides the corresponding acid 79f in moderate yield, though no enantioselectivity is observed. Finally, we were pleased to find that prenyl methyl carbonate (78g) is a competent electrophile furnishing acid 79g in 63% yield.

A wider exploration into the scope of this novel transformation revealed additional limitations of the catalytic system (Table 3.5). Foremost, while furan- and thiophene-substituted allylic electrophiles are well tolerated in the iridium-catalyzed allylic alkylation reaction, the heteroaromatic functionality on the allylic alkylation product is not amenable to the hydrolysis conditions and thus trace 81a and 81b are recovered. Moreover, alkenyl substitution is not permitted on allylic electrophile 80,
likely due to its ability to bind to the iridium catalyst, and no conversion to propargyl-derived \(81c\) is observed. Additionally, only trace conversion to hydroxymethyl \(81d\) is noted when corresponding TBS-protected allylic electrophile \(80d\) is employed. A trifluoromethyl group in place of the methyl substituent on the electrophile shuts down the allylic alkylation reaction entirely, as does the use of a bulky branched geranyl-derived electrophile, resulting in no isolation of \(81e\) and \(81f\), respectively. Also, use of a tethered allylic electrophile (e.g., tetralone \(80g\)) does not afford corresponding bicyclic product \(81g\). Finally, we found that a tetrasubstituted allylic electrophile was able to yield allylic alkylation product \(81h\), albeit in a modest 11% yield.

\[\text{\textit{Table 3.5} Substrate scope limitations}^a\]

\[
\begin{array}{c}
\text{67c} \quad \text{+} \quad 80 \\
\text{81a} \quad \text{decomposition} \\
\text{81b} \quad \text{decomposition} \\
\text{81c} \quad \text{no reaction} \\
\text{81d} \quad \text{trace yield} \\
\text{81e} \quad \text{no reaction} \\
\text{81f} \quad \text{no reaction} \\
\text{81g} \quad \text{no reaction} \\
\text{81h} \quad 11\% \text{ yield}^b
\end{array}
\]

\[\text{[a] Reactions performed on 0.2 mmol scale. [b] } ^1\text{H NMR yield based on internal standard.}\]
3.5 PRODUCT TRANSFORMATIONS

As MAC adducts can be transformed to essentially any carboxylic acid derivative,\textsuperscript{10} we endeavored to develop additional one-pot transformations to access both \(\alpha\)-quaternary esters and amides. Gratifyingly, we found that alkanolysis of the crude MAC alkylation product with either methanol or allyl alcohol provides methyl ester \textsuperscript{82} and allyl ester \textsuperscript{83} in 88\% and 74\% yield, respectively (Figure 3.2). Similarly, aminolysis provides access to both tertiary amide \textsuperscript{84} in 61\% yield and secondary amide \textsuperscript{85} in 63\% yield.

Figure 3.2 One-pot transformations to \(\alpha\)-quaternary carboxylic acid derivatives\textsuperscript{9}

In order to demonstrate the synthetic utility of the enantioenriched \(\alpha\)-quaternary carboxylic acid derivatives, a series of transformations were performed to access a diverse array of chiral building blocks starting from ester derivative \textsuperscript{82} (Figure 3.3). Hydrogenation of olefin \textsuperscript{82} delivers ethyl-substituted \textsuperscript{86} in 97\% yield. Alcohol \textsuperscript{87} is accessed via reduction of the ester moiety in 73\% yield. Dihydroxylation of the pendant

\[\text{\textsuperscript{82} } \rightarrow \text{\textsuperscript{83} } \rightarrow \text{\textsuperscript{84} } \rightarrow \text{\textsuperscript{85}}\]
olefin proceeds with concomitant lactonization to furnish \( \gamma \)-butyrolactone 88 in 82% yield as a mixture (1:1) of diastereomers. Finally, ozonolysis furnishes aldehyde 89 in moderate yield.

**Figure 3.3** Product transformations of \( \alpha \)-quaternary ester 82

\[
\begin{align*}
86 & \quad \text{a} \quad 87 \\
82 & \quad \text{b} \quad 88 \\
89 & \quad \text{c} \quad 89
\end{align*}
\]

[a] Pd/C, H\(_2\) (balloon), EtOAc, 23 °C, 18 h, 97% yield; [b] Dibal, Et\(_2\)O, 0 °C, 2 h, 73% yield; [c] K\(_2\)OsO\(_4\), NMO, THF/H\(_2\)O (4:1), 23 °C, 18 h, 82% yield (1:1 dr); [d] i. O\(_3\), NaHCO\(_3\), MeOH/CH\(_2\)Cl\(_2\) (1:5), –78 °C, 0.5 h, ii. DMS, –78 °C → 23 °C, 18 h, 50% yield.

### 3.6 CONCLUSIONS

In conclusion, we have developed the first synthesis of all-carbon quaternary allylic stereocenters via enantioselective iridium-catalyzed allylic alkylation. The unprecedented combination of triethylborane and a catalyst prepared from \([\text{Ir}({\text{cod}})\text{Cl}])_2\), \(\text{L}5\), and TBD was used to coerce reactivity from a once poorly reactive class of trisubstituted allylic electrophiles. Furthermore, the use of a single masked acyl cyanide nucleophile facilitates the one-pot syntheses of enantioenriched \( \alpha \)-quaternary acids, esters, and amides. The protocol is tolerant of a wide range of substitution on the aryl moiety to provide the corresponding products in good yields and excellent enantioselectivities. This methodology is critical in laying the groundwork for the future development of
technology to access vicinal quaternary centers via iridium-catalyzed allylic alkylation of prochiral nucleophiles.

3.7 EXPERIMENTAL SECTION

3.7.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Commercially obtained reagents were used as received. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Oakwood Chemicals and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) and preparatory TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, KMnO₄, or p-anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak IC column (4.6 mm x 25 cm) or a Chiralpak AD-H column (4.6 mm x 25 cm), both obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. Analytical SFC was performed with a Mettler SFC supercritical CO₂ analytical chromatography system utilizing a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. Preparatory HPLC was performed with an Agilent 1200 Series HPLC equipped with a Viridis SFC 2-Ethylpyridine 5 μm column (4.6 x 250 mm). ¹H
NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CHCl₃ (δ 7.26 ppm). ¹³C NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CDCl₃ (δ 77.16 ppm). Data for ¹H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ¹³C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of benzene (δ 7.36 ppm), water (δ 1.56 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm⁻¹). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell, and are reported as [α]₀D (concentration in g/100 mL, solvent).
3.7.1.1 Preparation of Known Compounds

Previously reported methods were used to prepare ligands (S,S<sub>a</sub>)-L<sub>2</sub><sup>2c,15</sup> and (S<sub>a</sub>)-L<sub>5</sub><sup>16</sup> as well as starting materials 67<sup>c</sup>,<sup>10b,17</sup> 72<sup>18</sup>, 75<sup>18</sup>, 76<sup>a</sup>,<sup>19</sup> 76<sup>b</sup>,<sup>20</sup> 76<sup>d</sup>,<sup>18</sup> 76<sup>e</sup>,<sup>18</sup> 76<sup>j</sup>,<sup>18</sup> 76<sup>l</sup>,<sup>18</sup> 78<sup>a</sup>,<sup>18</sup> 78<sup>d</sup>,<sup>18</sup> and 78<sup>f</sup><sup>18</sup>.

3.7.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

3.7.2.1 Representative Procedures for the Synthesis of Electrophiles

3.7.2.1.1 Representative Procedure #1: Oxidative Heck Reaction<sup>21</sup>

![Methyl (E)-3-(4-formylphenyl)but-2-enoate (90).](image)

Methyl (E)-3-(4-formylphenyl)but-2-enoate (90). To a solution of (4-formylphenyl)boronic acid (0.75 g, 5.0 mmol, 1 equiv), Pd(OAc)<sub>2</sub> (23 mg, 0.10 mmol, 0.02 equiv), dppp (62 mg, 0.15 mmol, 0.03 equiv) in acetone (8 mL) was added methyl crotonate (1.1 mL, 10.0 mmol, 2 equiv) followed by trifluoroacetic acid (0.12 mL, 1.5 mmol, 0.3 equiv). The resulting slurry was heated under reflux for 48 h, whereupon the reaction was cooled to ambient temperature and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (5% EtOAc/hexanes) to give carbonate 90 as a colorless oil (0.17 g, 17% yield): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.06 (s, 1H), 7.97 – 7.78 (m, 2H), 7.74 – 7.58 (m, 2H), 6.22 (q, J = 1.3 Hz, 1H), 3.80 (s, 3H), 2.62 (d, J = 1.4 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 191.8, 167.0, 154.4, 148.2, 136.5, 130.1, 127.1, 119.0, 51.5, 18.1; IR (Neat Film, NaCl) 2950,
Chapter 3 – Enantioselective Synthesis of Acyclic α-Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation

2839, 1704, 1631, 1434, 1349, 1273, 1214, 1171, 1036, 828 cm\(^{-1}\); HRMS (FAB\(^{+}\)) \(m/z\) calc’d for C\(_{12}\)H\(_{13}\)O\(_3\) [M+H]\(^{+}\): 205.0865, found 205.0860.

3.7.2.1.2 Representative Procedure #2: Reduction & Acylation

\((E)-3-(4-Fluorophenyl)but-2-en-1-yl methyl carbonate (76c).\) To a solution of methyl \((E)-3-(4-fluorophenyl)but-2-enoate\)\(^{22}\) (0.30 g, 1.6 mmol, 1 equiv) in THF (3.1 mL) at –78 °C was added DIBAL (0.85 mL, 4.8 mmol, 3 equiv) dropwise. The resulting reaction mixture was stirred at –78 °C for 2.5 h, whereupon the reaction was quenched with a saturated aqueous Rochelle’s salt solution (5 mL). The cooling bath was then removed and the reaction was stirred for 18 h at ambient temperature. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure.

The crude material was then dissolved in CH\(_2\)Cl\(_2\) (6.4 mL) and cooled to 0 °C. Pyridine (1.1 mL, 13 mmol, 8.3 equiv) was added followed by methyl chloroformate (0.28 mL, 3.7 mmol, 2.3 equiv) dropwise. The resulting solution was allowed to warm to ambient temperature and stirred for 18 h. The reaction was quenched with the addition of 1 M HCl (5 mL) and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (5% EtOAc/hexanes) to give carbonate 76c as a colorless solid (0.14 g, 38% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\) \(\delta\) 7.40 – 7.33 (m, 2H), 7.05 – 6.96 (m,
Chapter 3 – Enantioselective Synthesis of Acyclic α-Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation

2H), 5.87 (tq, J = 7.0, 1.4 Hz, 1H), 4.84 (dd, J = 7.1, 0.8 Hz, 2H), 3.80 (s, 3H), 2.11 (dd, J = 1.4, 0.7 Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 163.7, 161.3, 156.0, 140.2, 138.6 (d, J = 3.3 Hz), 127.6 (d, J = 8.0 Hz), 120.7 (d, J = 1.3 Hz), 115.4, 115.1, 65.0, 55.0, 16.5; IR (Neat Film, NaCl) 2961, 1896, 1742, 1649, 1589, 1468, 1442, 1379, 1334, 1252, 1110, 994, 960, 945, 825, 794 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{12}\)H\(_{13}\)FO\(_3\) [M]\(^+\): 224.0849, found 224.0850.

3.7.2.2 Spectroscopic Data for the Synthesis of Electrophiles

(Z)-methyl (3-phenylbut-2-en-1-yl) carbonate (74). Carbonate 74 was prepared from ethyl (Z)-3-phenylbut-2-enoate\(^{23}\) according to Representative Procedure #2 and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) as a colorless oil (0.18 g, 49% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.41 – 7.18 (m, 5H), 5.76 – 5.68 (m, 1H), 4.58 (dd, J = 7.2, 1.1 Hz, 2H), 3.79 (s, 3H), 2.13 (q, J = 1.2 Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.8, 143.8, 140.3, 128.4, 127.8, 127.6, 120.5, 65.8, 54.8, 25.6; IR (Neat Film, NaCl) 3023, 2956, 1748, 1494, 1441, 1382, 1350, 1263, 1024, 944, 792, 765, 702 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{12}\)H\(_{15}\)O\(_3\) [M+H]\(^+\): 207.1021, found 207.1011.

(E)-3-(4-(((Methoxycarbonyl)oxy)methyl)phenyl)but-2-en-1-yl methyl carbonate (76f). Carbonate 76f was prepared from 90 according to Representative Procedure #2 and
isolated by silica gel flash column chromatography (5% EtOAc/hexanes) as a colorless solid (0.11 g, 46% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44 – 7.31 (m, 4H), 5.98 – 5.88 (m, 1H), 5.15 (s, 2H), 4.85 (dd, \(J = 7.0, 0.9\) Hz, 2H), 3.802 (s, 3H), 3.795 (s, 3H), 2.13 – 2.10 (m, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 156.0, 155.9, 142.8, 140.6, 134.7, 128.5, 126.3, 121.2, 69.4, 65.0, 55.1, 55.0, 16.4; IR (Neat Film, NaCl) 2959, 1754, 1443, 1385, 1333, 1288, 958, 909, 794, 731 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{15}\)H\(_{18}\)O\(_6\) [M]\(^+\): 294.1103, found 294.1098.

\[
\begin{align*}
\text{OMe} \\
\text{Br}
\end{align*}
\]

**Methyl (E)-3-(3-bromophenyl)but-2-enoate (91).** Ester 91 was prepared from (3-bromophenyl)boronic acid according to Representative Procedure #1 and isolated by silica gel flash column chromatography (3% EtOAc/hexanes) as a colorless oil (0.54 g, 42% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.65 – 7.59 (m, 1H), 7.51 (ddd, \(J = 7.9, 2.0, 1.0\) Hz, 1H), 7.45 – 7.37 (m, 1H), 7.31 – 7.26 (m, 1H), 6.14 (q, \(J = 1.3\) Hz, 1H), 3.78 (d, \(J = 1.2\) Hz, 3H), 2.57 (d, \(J = 1.4\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.1, 154.3, 144.4, 132.1, 130.2, 129.6, 125.1, 122.8, 117.9, 51.4, 18.1; IR (Neat Film, NaCl) 3062, 2948, 1719, 1631, 1558, 1435, 1346, 1274, 1191, 1168, 1037, 869, 785, 688 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{11}\)H\(_{12}\)O\(_2\)Br [M+H]\(^+\): 255.0021, found 255.0020.
(E)-3-(3-Bromophenyl)but-2-en-1-yl methyl carbonate (76g). Carbonate 76g was prepared from 91 according to Representative Procedure #2 and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) as a colorless oil (0.47 g, 78% yield): \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.54 (t, \( J = 1.8 \) Hz, 1H), 7.40 (ddd, \( J = 7.9, 1.9, 1.0 \) Hz, 1H), 7.32 (ddd, \( J = 7.8, 1.8, 1.0 \) Hz, 1H), 7.22 – 7.14 (m, 1H), 5.96 – 5.88 (m, 1H), 4.88 – 4.76 (m, 2H), 3.81 (s, 3H), 2.12 – 2.08 (m, 3H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 155.93, 144.65, 139.74, 130.68, 129.96, 129.18, 124.64, 122.65, 122.08, 64.84, 55.02, 16.38; IR (Neat Film, NaCl) 2955, 1748, 1590, 1558, 1442, 1376, 1332, 1263, 946, 789, 690 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{12}\)H\(_{13}\)O\(_3\)Br [M]+: 284.0048, found 284.0073.

(\( E \))-Methyl (3-(3-nitrophenyl)but-2-en-1-yl) carbonate (76h). Carbonate 76h was prepared from methyl (\( E \))-3-(3-nitrophenyl)but-2-enoate\(^{20}\) according to Representative Procedure #2 and isolated by silica gel flash column chromatography (10% EtOAc/hexanes) as a colorless oil (0.47 g, 78% yield): \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.26 (t, \( J = 2.0 \) Hz, 1H), 8.14 (ddd, \( J = 8.2, 2.3, 1.0 \) Hz, 1H), 7.73 (ddd, \( J = 7.8, 1.8, 1.1 \) Hz, 1H), 7.51 (t, \( J = 8.0 \) Hz, 1H), 6.10 – 5.91 (m, 1H), 4.88 (dt, \( J = 6.9, 0.8 \) Hz, 2H), 3.82 (s, 3H), 2.18 (dd, \( J = 1.4, 0.7 \) Hz, 3H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 155.9, 148.5, 144.1, 138.7, 131.9, 129.4, 123.6, 122.5, 121.0, 64.7, 55.1, 16.4; IR (Neat Film, NaCl)
3108, 3026, 2969, 2868, 1750, 1530, 1443, 1384, 1353, 1279, 1096, 994, 949, 930, 876, 788, 736, 682 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₂H₁₄O₅N [M+H]⁺: 252.0872, found 252.0884.

**(E)-methyl (3-(Naphthalen-2-yl)but-2-en-1-yl) carbonate (76i).** Carbonate **76i** was prepared from methyl (E)-3-(naphthalen-2-yl)but-2-enoate²⁴ according to Representative Procedure #2 and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) as a colorless oil (0.26 g, 51% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.86 – 7.77 (m, 4H), 7.58 (dd, J = 8.6, 1.9 Hz, 1H), 7.52 – 7.42 (m, 2H), 6.12 – 6.05 (m, 1H), 4.92 (dq, J = 7.0, 0.7 Hz, 2H), 3.82 (s, 3H), 2.29 – 2.22 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 156.0, 140.9, 139.7, 133.4, 133.0, 128.3, 128.0, 127.7, 126.4, 126.1, 124.9, 124.3, 121.3, 65.2, 55.0, 16.5; IR (Neat Film, NaCl) 3057, 2952, 1752, 1740, 1596, 1467, 1442, 1382, 1248, 997, 941, 818, 794, 740 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₆H₁₆O₃ [M⁺]: 256.1100, found 256.1095.

**(E)-3-(3,5-Dimethylphenyl)but-2-en-1-yl methyl carbonate (76k).** Carbonate **76k** was prepared from methyl (E)-3-(3,5-dimethylphenyl)but-2-enoate²⁵ according to Representative Procedure #2 and isolated by silica gel flash column chromatography (5%
EtOAc/hexanes) as a colorless oil (0.32 g, 86% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.02 (dt, $J = 1.6$, 0.8 Hz, 2H), 6.93 (td, $J = 1.6$, 0.8 Hz, 1H), 5.96 – 5.82 (m, 1H), 4.84 (dd, $J = 7.0$, 0.8 Hz, 2H), 3.80 (s, 3H), 2.31 (d, $J = 0.7$ Hz, 6H), 2.15 – 2.06 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 156.0, 142.6, 141.5, 137.9, 129.4, 123.9, 120.4, 65.1, 54.9, 21.5, 16.5; IR (Neat Film, NaCl) 2956, 2918, 2862, 1748, 1601, 1443, 1376, 1335, 1262, 944, 905, 849, 792, 699 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{14}$H$_{18}$O$_3$ [M]$^+$: 234.1256, found 234.1252.

\[ \text{(E)-Methyl (3-phenylhept-2-en-1-yl) carbonate (78b). Carbonate 78b was prepared from ethyl (E)-3-phenylhept-2-enoate}\]

\[ \text{according to Representative Procedure \#2 and isolated by silica gel flash column chromatography (5\% EtOAc/hexanes) as a colorless oil (0.31 g, 58\% yield):} \]

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 – 7.27 (m, 5H), 5.89 – 5.71 (m, 1H), 4.84 (d, $J = 7.0$ Hz, 2H), 3.80 (s, 3H), 2.73 – 2.46 (m, 2H), 1.41 – 1.24 (m, 4H), 1.06 – 0.73 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 156.0, 146.6, 142.0, 128.4, 127.6, 126.6, 121.1, 65.0, 55.0, 31.2, 30.2, 22.7, 14.0; IR (Neat Film, NaCl) 3034, 2957, 2872, 1748, 1644, 1599, 1493, 1444, 1378, 1344, 1262, 1129, 941, 792, 766, 698 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{15}$H$_{20}$O$_3$ [M]$^+$: 248.1412, found 248.1424.
(E)-Methyl (4-methyl-3-phenylpent-2-en-1-yl) carbonate (78c). Carbonate 78c was prepared from ethyl (E)-4-methyl-3-phenylpent-2-enoate\(^{27}\) according to Representative Procedure #2 and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) as a colorless oil (0.17 g, 17% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.37 – 7.27 (m, 3H), 7.11 – 7.02 (m, 2H), 5.61 (td, \(J = 7.0, 1.3\) Hz, 1H), 4.46 (dd, \(J = 7.0, 0.8\) Hz, 2H), 3.75 (s, 3H), 2.66 – 2.54 (m, 1H), 1.03 (d, \(J = 6.8\) Hz, 6H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.8, 154.0, 139.7, 128.5, 128.2, 127.3, 117.8, 66.1, 54.8, 36.0, 21.5; IR (Neat Film, NaCl) 2961, 2872, 1749, 1492, 1442, 1263, 942, 792, 771, 703 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{14}\)H\(_{19}\)O\(_3\) \([\text{M+H}]^+\): 235.1334, found 235.1344.

(E)-3-(Cyclohex-1-en-1-yl)but-2-en-1-yl methyl carbonate (78e). Carbonate 78e was prepared from ethyl (E)-3-(cyclohex-1-en-1-yl)but-2-enoate\(^{28}\) according to Representative Procedure #2 and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) as a colorless oil (0.25 g, 73% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.00 – 5.92 (m, 1H), 5.68 – 5.55 (m, 1H), 4.79 (d, \(J = 7.0\) Hz, 2H), 3.78 (s, 3H), 2.16 (ddd, \(J = 12.0, 5.9, 3.7\) Hz, 4H), 1.85 (d, \(J = 1.1\) Hz, 3H), 1.73 – 1.49 (m, 4H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 156.0, 141.2, 137.0, 126.0, 116.8, 65.5, 54.9, 26.1, 25.8, 23.0, 22.3, 14.1; IR (Neat Film, NaCl) 2929, 2859, 1749, 1638, 1443, 1263, 1119, 940, 792 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{12}\)H\(_{18}\)O\(_3\) \([\text{M}]^+\): 210.1256, found 210.1252.
3.7.2.3 General Procedure for Optimization Reactions (Table 3.1)

(S)-2-(Methoxymethoxy)-2-(2-phenylbut-3-en-2-yl)malononitrile (73). In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added \([\text{Ir(cod)Cl}_2] \) (1.3 mg, 0.0020 mmol, 2 mol %), ligand \((S)_a-L_5\) (2.5 mg, 0.0042 mmol, 4.2 mol %), TBD (1.4 mg, 0.010 mmol, 10 mol %), and THF (0.5 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with MAC nucleophile 67c (0.10 mmol or 0.20 mmol, as specified), THF (0.5 mL), and the Lewis acid additive (200 mol %). The pre-formed catalyst solution (vial A) was then transferred to vial B followed immediately by carbonate 72 (0.20 mmol, 0.10 mmol, or 0.12 mmol, as specified). The vial was sealed and stirred at 60 °C. After 18 h, the vial was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc. The crude mixture was concentrated and 1,2,4,5-tetrachloro-3-nitrobenzene (0.10 mmol in 0.5 mL CDCl₃) was added. The NMR yield (measured in reference to 1,2,4,5-tetrachloro-3-nitrobenzene \(\delta 7.74\ \text{ppm (s, 1H)}\)) was determined by \(^1\text{H}\) NMR analysis of the crude mixture. The residue was purified by preparatory TLC (15% EtOAc/hexanes) to afford MAC adduct product 73 as a colorless oil. For the purposes of characterization, product 73 was further purified by preparatory HPLC (20% EtOAc/hexanes, Viridis SFC 2-Ethylpyridine 5 \(\mu\)m column, flow rate = 1.5 mL/min; \(\lambda = 230\ \text{nm}\): 94% ee (entry 9); \([\alpha]_D^{25} +11.7\ (c 0.07, \text{CHCl}_3)\) (entry 9); \(^1\text{H}\) NMR (400 MHz, CDCl₃) \(\delta 7.61 – 7.54\ (m, 2H), 7.42 – 7.32\ (m, 3H), 6.51\ (dd, \(J = 17.4, 11.0\ \text{Hz}\), 1H), 5.59 – 5.34\ (m, 2H), 5.02\ (s, 2H), 3.42\ (s, 3H), 1.84\ (s, 3H);
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\( ^{13} \text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 138.3, 137.6, 129.0, 128.57, 238.55, 128.3, 125.2, 119.2, 112.8, 112.7, 96.7, 73.9, 57.5, 52.8, 20.9; IR (Neat Film, NaCl) 3062, 2957, 2896, 2242, 2189, 1750, 1492, 1445, 1358, 1268, 1161, 1108, 1030, 930, 751, 698 cm\(^{-1}\); HRMS (ESI+) \( m/z \) calc’d for C\(_{15}\)H\(_{17}\)N\(_2\)O\(_2\) [M+H]\(^+\): 257.1290, found 257.1313; HPLC conditions: 1% IPA, 1.0 mL/min, Chiralpak IC column, \( \lambda = 210 \text{ nm} \), \( t_R \) (min): major = 13.303, minor = 17.243.

3.7.2.4 General Procedure for the Enantioenriched Carboxylic Acid Synthesis

Please note that the absolute configuration was determined only for compound 77h via x-ray crystallographic analysis. The absolute configuration for all other products has been inferred by analogy. For respective HPLC and SFC conditions, please refer to Table 3.6.

(S)-2-Methyl-2-phenylbut-3-enoic acid (77a). In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]\(_2\) (2.7 mg, 0.0040 mmol, 2 mol %), ligand \( (\text{S}_\text{a})-\text{L5} \) (4.9 mg, 0.0084 mmol, 4.2 mol %), TBD (2.8 mg, 0.020 mmol, 10 mol %), and THF (1 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with MAC nucleophile 67c (25 mg, 0.20 mmol, 100 mol %), THF (1 mL), and B\(_3\)Et\(_3\) (400 \( \mu \)L, 1M in hexanes). The pre-formed catalyst solution (vial A) was then transferred to vial B followed immediately by carbonate 72 (83 mg, 0.40 mmol, 200 mol %). The vial was sealed and stirred at 60 °C. After 18 h or 48 h,
the vial was removed from the glove box, transferred to a 20 mL vial with CH₂Cl₂, and concentrated. The crude material was heated at 80 °C in 6M HCl (4 mL) for 18 h. Whereupon, the reaction mixture was cooled to 0 °C and basified with 6M NaOH (4.5 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 8 mL). The combined organic layers were washed with 2M NaOH (8 mL). The combined aqueous layers were acidified with concentrated HCl, extracted with CH₂Cl₂ (4 x 8 mL), dried over Na₂SO₄, and concentrated under reduced pressure at 0 °C to give the product 77a as a colorless solid (27 mg, 77% yield): 95% ee; [α]D²⁵ +13.5 (c 1.3, CHCl₃); HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, λ = 210 nm, tᵣ (min): major = 12.198, minor = 11.426. Characterization data match those reported in the literature.²⁹ Please note Compounds 77i, 77j, 77k, and 79a–g were prepared at the same concentration with double catalyst loadings.

### 3.7.2.5 Spectroscopic Data for the Enantioenriched Carboxylic Acids

![Product Structure](image)

**[(S)-2-(4-Chlorophenyl)-2-methylbut-3-ENOIC ACID (77b)]**. Product 77b was prepared according to the general procedure to give a pale yellow oil (33 mg, 80% yield): 93% ee; [α]D²⁵ +8.1 (c 1.8, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.24 (m, 4H), 6.38 (dd, J = 17.5, 10.7 Hz, 1H), 5.44 – 5.16 (m, 2H), 1.66 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 180.4, 141.1, 140.1, 133.3, 128.7, 128.3, 116.1, 53.3, 23.3; IR (Neat Film, NaCl) 3089, 2987, 2645, 2539, 1705, 1493, 1400, 1282, 1097, 1014, 928, 826, 755 cm⁻¹; HRMS
(FAB+) \textit{m/z} calc'd for C_{11}H_{12}O_2Cl [M+H]^+: 211.0526, found 211.0528; HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, \( \lambda = 210 \text{ nm} \), \( t_R \) (min): major = 15.642, minor = 14.104.

\begin{center}
\includegraphics[width=0.2\textwidth]{structure_77c.png}
\end{center}

\textbf{(S)-2-(4-Fluorophenyl)-2-methylbut-3-enoic acid (77c).} Product 77c was prepared according to the general procedure to give a pale yellow oil (35 mg, 90% yield): 90% ee; \( \left[ \alpha \right]_D^{25} = +3.4 \) (c 1.5, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 7.46 - 7.19 \) (m, 2H), 7.05 (t, \( J = 8.7 \text{ Hz}, 2H \)), 6.39 (dd, \( J = 17.5, 10.7 \text{ Hz}, 1H \)), 5.42 - 5.14 (m, 2H), 1.67 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta 180.6, 163.2, 160.7, 140.4, 138.3 \) (d, \( J = 3.4 \text{ Hz} \)), 128.5 (d, \( J = 8.1 \text{ Hz} \)), 115.9, 115.5, 115.3, 53.2, 23.5; IR (Neat Film, NaCl) 3088, 2987, 2924, 2642, 1704, 1603, 1510, 1462, 1412, 1277, 1234, 1165, 928, 833, 816, 735 cm\(^{-1}\); HRMS (FAB+) \textit{m/z} calc’d for C\(_{11}\)H\(_{12}\)FO\(_2\) [M+H]^+: 195.0833, found 195.0841; HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, \( \lambda = 210 \text{ nm} \), \( t_R \) (min): major = 15.499, minor = 13.811.

\begin{center}
\includegraphics[width=0.2\textwidth]{structure_77d.png}
\end{center}

\textbf{(S)-2-Methyl-2-(4-(trifluoromethyl)phenyl)but-3-enoic acid (77d).} Product 77d was prepared according to the general procedure to give a pale yellow oil (41 mg, 83% yield):
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92% ee; $[\alpha]_{D}^{25} -2.2$ ($c$ 2.3, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.60 (dt, $J = 8.1$, 0.8 Hz, 2H), 7.45 (dt, $J = 8.3$, 0.8 Hz, 2H), 6.38 (dd, $J = 17.5$, 10.7 Hz, 1H), 5.48 – 5.09 (m, 2H), 1.68 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 179.0, 146.6, 139.7, 129.6, 130.0, 129.5, 127.2, 125.6 (q, $J = 3.7$ Hz), 122.8, 116.6, 53.7, 29.9, 23.4; IR (Neat Film, NaCl) 2926, 2649, 1707, 1618, 1413, 1277, 1167, 1126, 1081, 1016, 930, 940 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{12}$H$_{12}$O$_2$F$_3$ [M+H]$^+$: 245.0789, found 245.0794; SFC conditions: 2% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): major = 13.592, minor = 15.745.

(S)-2-Methyl-2-(p-tolyl)but-3-enoic acid (77e). Product 77e was prepared according to the general procedure to give a pale yellow oil (24 mg, 63% yield): 94% ee; $[\alpha]_{D}^{25} +4.6$ ($c$ 0.8, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 – 7.01 (m, 4H), 6.40 (dd, $J = 17.5$, 10.7 Hz, 1H), 5.59 – 5.08 (m, 2H), 2.34 (s, 3H), 1.64 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 181.0, 140.7, 139.8, 137.0, 129.3, 126.6, 115.4, 53.3, 23.3, 21.1; IR (Neat Film, NaCl) 2986, 1702, 1636, 1512, 1457, 1412, 1276, 1191, 1132, 1077, 1020, 925, 815, 730 cm$^{-1}$; HRMS (ESI-) $m/z$ calc’d for C$_{12}$H$_{13}$O$_2$ [M-H]: 189.0916, found 189.0903; HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): major = 15.393, minor = 14.288.
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(S)-2-(4-(Hydroxymethyl)phenyl)-2-methylbut-3-enolic acid (77f). Product 77f was prepared according to the general procedure and isolated by preparatory TLC (30% acetone/hexanes) to give a colorless solid (21 mg, 51% yield): 95% ee; [α]D\textsuperscript{25} +3.4 (c 0.5, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.33 (q, J = 8.2 Hz, 4H), 6.37 (dd, J = 17.5, 10.7 Hz, 1H), 5.39 – 5.10 (m, 2H), 4.57 (s, 2H), 1.63 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 180.1, 143.2, 140.4, 136.4, 128.8, 127.2, 115.8, 53.6, 45.9, 23.4; IR (Neat Film, NaCl) 2985, 2927, 2642, 1703, 1636, 1152, 1268, 1182, 1076, 926, 836, 731, 683 cm\textsuperscript{-1}; HRMS (FAB+) m/z calc’d for C\textsubscript{12}H\textsubscript{15}O\textsubscript{3} [M+H]\textsuperscript{+}: 207.1021, found 207.1025; HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, λ = 210 nm, t\textsubscript{R} (min): major = 15.258, minor = 14.667.

(S)-2-(3-Bromophenyl)-2-methylbut-3-enolic acid (77g). Product 77g was prepared according to the general procedure to give a pale yellow oil (35 mg, 69% yield): 92% ee; [α]D\textsuperscript{25} −2.6 (c 1.8, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.47 (t, J = 1.9 Hz, 1H), 7.41 (ddd, J = 7.6, 1.9, 1.2 Hz, 1H), 7.29 – 7.18 (m, 1H), 6.35 (dd, J = 17.5, 10.7 Hz, 1H), 5.42 – 5.09 (m, 2H), 1.65 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 179.7, 145.0, 139.8,
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130.5, 130.2, 129.9, 125.5, 122.8, 116.4, 53.5, 23.3; IR (Neat Film, NaCl) 2987, 2644, 1705, 1593, 1566, 1475, 1413, 1280, 1129, 1070, 997, 928, 785, 760, 700 cm⁻¹; HRMS (ESI-) m/z calc’d for C₁₁H₁₀O₂Br [M-H]⁻: 252.9864, found 252.9864; HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, λ = 210 nm, tᵣ (min): major = 15.217, minor = 14.439.

![Chemical Structure](image)

(S)-2-Methyl-2-(3-nitrophenyl)but-3-enoic acid (77h). Product 77h was prepared according to the general procedure to give a colorless solid (41 mg, 93% yield): 87% ee; [α]D 25° +94.5 (c 3.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.22 (t, J = 2.0 Hz, 1H), 8.15 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.69 (ddd, J = 7.9, 1.9, 1.1 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 6.38 (dd, J = 17.5, 10.7 Hz, 1H), 5.59 – 5.11 (m, 2H), 1.72 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 179.6, 148.5, 144.7, 139.2, 133.3, 129.6, 122.5, 122.1, 117.2, 53.7, 23.4; IR (Neat Film, NaCl) 3089, 2988, 2924, 2641, 1707, 1530, 1351, 1276, 1106, 929, 808, 738, 688 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₁H₁₂O₄N [M+H]+: 222.0766, found 222.0769; HPLC conditions: 3% IPA, 1.0 mL/min, Chiralpak AD-H column, λ = 210 nm, tᵣ (min): major = 24.060, minor = 20.907.
(S)-2-Methyl-2-(naphthalen-2-yl)but-3-enoic acid (77i). Product 77i was prepared according to the general procedure to give a pale yellow oil (30 mg, 66% yield): 92% ee; $[\alpha]_D^{25} +7.8$ (c 0.6, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.91 – 7.72 (m, 4H), 7.55 – 7.39 (m, 3H), 6.52 (dd, $J = 17.5, 10.7$ Hz, 1H), 5.57 – 5.11 (m, 2H), 1.77 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 180.9, 140.5, 140.0, 133.3, 132.5, 128.3, 128.2, 127.6, 126.3, 126.2, 125.3, 125.2, 116.0, 53.9, 23.4; IR (Neat Film, NaCl) 3057, 2984, 1701, 1506, 1458, 1411, 1274, 1182, 1128, 1102, 925, 856, 816, 747 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{15}$H$_{14}$O$_2$ [M]$^+$: 226.0994, found 226.0992; HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): major = 28.272, minor = 24.870.

(S)-2-Methyl-2-(m-tolyl)but-3-enoic acid (77j). Product 77j was prepared according to the general procedure to give a pale yellow oil (26 mg, 68% yield): 93% ee; $[\alpha]_D^{25} +5.2$ (c 1.6, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.25 – 7.04 (m, 4H), 6.40 (dd, $J = 17.5, 10.7$ Hz, 1H), 5.45 – 5.08 (m, 2H), 2.44 – 2.20 (m, 3H), 1.65 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 180.2, 142.7, 140.6, 138.3, 128.5, 128.1, 127.3, 123.7, 115.6, 53.6, 23.3, 21.7; IR (Neat Film, NaCl) 2984, 2923, 2648, 1703, 1606, 1459, 1411, 1275, 1178, 1127, 1002, 926, 785, 703 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{12}$H$_{15}$O$_2$ [M+H]$^+$: 191.1072,
found 191.1074; HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 13.800, minor = 12.388.

**((S))-2-(3,5-Dimethylphenyl)-2-methylbut-3-enoic acid (77k).** Product 77k was prepared according to the general procedure and isolated by preparatory TLC (30% acetone/hexanes) to give a colorless oil (13 mg, 32% yield): 85% ee; [α]_D^{25} –40.6 (c 0.1, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ 6.94 (d, J = 8.5 Hz, 3H), 6.42 (dd, J = 17.4, 10.6 Hz, 1H), 5.45 – 5.08 (m, 2H), 2.33 (s, 6H), 1.65 (s, 3H); ^13C NMR (101 MHz, CDCl₃) δ 180.5, 142.8, 140.8, 138.1, 129.0, 124.4, 115.3, 53.6, 23.3, 21.6; IR (Neat Film, NaCl) 2983, 2919, 2639, 1700, 1602, 1411, 1279, 1125, 923, 848, 708 cm⁻¹; HRMS (FAB+) m/z calc’d for C_{13}H_{17}O₂ [M+H]^+: 205.1229, found 205.1233; HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 11.107, minor = 10.064. Please note an HMBC has been included due to the low intensity of the carbonyl ^13C shift at δ 180.5.

**((S))-2-Ethyl-2-phenylbut-3-enoic acid (79a).** Product 79a was prepared according to the general procedure and isolated by preparatory TLC (30% acetone/hexanes) to give a
colorless oil (23 mg, 61% yield): 92% ee; \([\alpha]_D^{25} +17.4 \) (c 0.4, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.38 – 7.22 \) (m, 5H), 6.36 (dd, \(J = 17.7, 10.9 \) Hz, 1H), 5.35 (d, \(J = 10.7 \) Hz, 1H), 5.09 (d, \(J = 17.6 \) Hz, 1H), 2.36 – 2.00 (m, 2H), 0.87 (t, \(J = 7.2 \) Hz, 3H).; \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 180.1, 141.3, 139.1, 128.4, 127.6, 127.2, 116.9, 58.0, 29.4, 9.4\); IR (Neat Film, NaCl) 3060, 2970, 2928, 2636, 1702, 1495, 1448, 1407, 1381, 1261, 1083, 924, 761, 700 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{12}\)H\(_{15}\)O\(_2\) [M+H]+: 191.1072, found 191.1071; HPLC conditions: 1.5% IPA, 1.0 mL/min, two Chiralpak AD-H columns in series, \(\lambda = 210 \) nm, \(t_R \) (min): major = 46.253, minor = 47.271.

\[(S)-2\text{-Phenyl-2-vinylhexanoic acid (79b).}\] Product 79b was prepared according to the general procedure and isolated by preparatory TLC (30% acetone/hexanes) to give a colorless oil (6 mg, 14% yield): 95% ee; \([\alpha]_D^{25} -106.0 \) (c 0.07, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.40 – 7.29 \) (m, 5H), 6.38 (dd, \(J = 17.6, 10.9 \) Hz, 1H), 5.32 (dd, \(J = 10.9, 0.9 \) Hz, 1H), 5.06 (dd, \(J = 17.6, 0.9 \) Hz, 1H), 2.28 – 1.98 (m, 2H), 1.44 – 1.14 (m, 4H), 0.87 (t, \(J = 7.2 \) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 178.4, 141.6, 139.7, 128.4, 127.5, 127.1, 116.6, 57.5, 36.5, 27.0, 23.4, 14.1\); IR (Neat Film, NaCl) 2956, 2928, 2636, 1702, 1495, 1448, 1407, 1381, 1261, 1083, 924, 761, 700 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{14}\)H\(_{19}\)O\(_2\) [M+H]+: 219.1385, found 219.1291; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, \(\lambda = 210 \) nm, \(t_R \) (min): major = 10.646, minor = 11.952.
(R)-2-Methyl-2-phenethylbut-3-enoic acid (79f). Product 79f was prepared according to the general procedure and isolated by preparatory TLC (33% acetone/hexanes) to give a colorless oil (13 mg, 32% yield): 3% ee; $[\alpha]_D^{25} -12.1$ (c 0.7, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44 – 7.04 (m, 5H), 6.10 (dd, $J = 17.6, 10.7$ Hz, 1H), 5.21 (dd, $J = 14.0, 3.3$ Hz, 2H), 2.60 (dt, $J = 11.0, 4.9$ Hz, 2H), 2.33 – 1.79 (m, 2H), 1.40 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 182.0, 142.0, 140.9, 128.54, 128.49, 126.1, 114.7, 48.7, 41.1, 31.2, 20.7; IR (Neat Film, NaCl) 3026, 2927, 1702, 1496, 1454, 1380, 1264, 1147, 1097, 925, 748, 700 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{13}$H$_{17}$O$_2$ [M+H]$^+$: 267.1385, found 267.1376; HPLC conditions: 2% IPA, 1.0 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): major = 18.485, minor = 14.652. *Please note* an HMBC has been included due to the low intensity of the carbonyl $^{13}$C shift at $\delta$ 182.0.

2,2-Dimethylbut-3-enoic acid (79g). Product 79g was prepared according to the general procedure to give a colorless oil (15 mg, 63% yield). Characterization data match those reported in the literature.$^{30}$
3.7.2.6 Experimental Procedures and Spectroscopic Data for the One-pot Syntheses of Carboxylic Acid Derivatives

Methyl (S)-2-(4-chlorophenyl)-2-methylbut-3-enoate (82). In a nitrogen-filled glove box, to a scintillation vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]$_2$ (13 mg, 0.02 mmol, 2 mol %), ligand ($S_a$)-L$_5$ (25 mg, 0.042 mmol, 4.2 mol %), TBD (14 mg, 0.10 mmol, 10 mol %), and THF (5 mL). Vial A was stirred at 25 °C (ca. 10 min) while another scintillation vial (vial B) was charged with MAC nucleophile 67c (126 mg, 1.0 mmol, 100 mol %), THF (5 mL), and BEt$_3$ (2.0 mL, 1M in hexanes). The pre-formed catalyst solution (vial A) was then transferred to vial B followed immediately by carbonate 76b (480 mg, 2.0 mmol, 200 mol %). The vial was sealed and stirred at 60 °C. After 18 h, the vial was removed from the glove box and the reaction mixture was concentrated under reduced pressure.

To the vial of crude MAC adduct equipped with a stir bar and septum cap was added 1:1 AcOH/DME (2 mL, 0.5 M) and CSA (0.26 g, 1.1 mmol, 1.1 equiv) under a nitrogen atmosphere. The reaction was heated to 60 °C for 6 h, whereupon the reaction mixture was cooled to ambient temperature, diluted with anhydrous MeOH (2.8 mL), and cooled to –40 °C. A solution of 1:1 MeOH/Et$_3$N (5.6 mL, 20.1 equiv of Et$_3$N) was added dropwise over 10 min. The reaction mixture was allowed to warm to ambient temperature over 18 h, whereupon the reaction was slowly quenched with saturated NH$_4$Cl aqueous solution (5 mL). The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the
combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure at 0 °C. The crude residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to give methyl ester 82 as a colorless oil (0.20 g, 88% yield): [α]D²⁵ +1.5 (c 0.8, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 6.99 (m, 4H), 6.35 (dd, J = 17.5, 10.7 Hz, 1H), 5.48 – 5.00 (m, 2H), 3.70 (s, 3H), 1.62 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.0, 142.0, 140.6, 132.9, 128.7, 128.1, 115.6, 53.5, 52.7, 23.7; IR (Neat Film, NaCl) 2986, 2952, 1734, 1637, 1493, 1459, 1246, 1181, 1123, 1098, 1014, 926, 828, 757 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₂H₁₃ClO₂ [M+]⁺: 224.0604, found 224.0621.

Allyl (S)-2-(4-chlorophenyl)-2-methylbut-3-enoate (83). In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]₂ (2.7 mg, 0.0040 mmol, 2 mol %), ligand (S₆)-L₅ (4.9 mg, 0.0084 mmol, 4.2 mol %), TBD (2.8 mg, 0.020 mmol, 10 mol %), and THF (1 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with MAC nucleophile 67c (25 mg, 0.20 mmol, 100 mol %), THF (1 mL), and BEt₃ (400 µL, 1M in hexanes). The pre-formed catalyst solution (vial A) was then transferred to vial B followed immediately by carbonate 76b (96 mg, 0.40 mmol, 200 mol %). The vial was sealed and stirred at 60 °C. After 18 h, the vial was removed from the glove box, transferred to a 20 mL vial with CH₂Cl₂, and concentrated.
To the vial of crude MAC adduct equipped with a stir bar and septum cap was added 1:1 AcOH/DME (0.4 mL, 0.5 M) and CSA (51 mg, 0.22 mmol, 1.1 equiv) under a nitrogen atmosphere. The reaction was heated to 60 °C for 6 h, whereupon the reaction mixture was cooled to ambient temperature, diluted with allyl alcohol (0.4 mL), and cooled to 0 °C. A solution of 1:1 Et₃N/allyl alcohol (1.1 mL, 20.4 equiv of Et₃N) was added dropwise over 10 min. The reaction mixture was allowed to warm to ambient temperature over 18 h, whereupon the reaction was slowly quenched with saturated NH₄Cl aqueous solution (5 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure at 0 °C. The crude residue was purified by preparatory TLC (8% EtOAc/hexanes) to give allyl ester 83 as a colorless oil (37 mg, 74% yield): [α]D²⁵ +0.4 (c 2.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.12 (m, 4H), 6.36 (dd, J = 17.5, 10.7 Hz, 1H), 5.85 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.38 – 5.02 (m, 4H), 4.61 (dt, J = 5.6, 1.4 Hz, 2H), 1.63 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 174.1, 142.0, 140.6, 132.9, 131.9, 128.6, 128.1, 118.5, 115.6, 65.9, 53.5, 23.6; IR (Neat Film, NaCl) 3089, 2985, 2930, 2857, 1900, 1734, 1638, 1493, 1236, 1177, 1122, 1097, 1014, 926, 828, 756 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₄H₁₆O₂Cl [M+H]+: 251.0839, found 251.0842.
(S)-2-(4-Chlorophenyl)-2-methyl-1-(pyrrolidin-1-yl)but-3-en-1-one (84). In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]₂ (2.7 mg, 0.0040 mmol, 2 mol %), ligand (Sₐ)-L₅ (4.9 mg, 0.0084 mmol, 4.2 mol %), TBD (2.8 mg, 0.020 mmol, 10 mol %), and THF (1 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with MAC nucleophile 67c (25 mg, 0.20 mmol, 100 mol %), THF (1 mL), and BEt₃ (400 µL, 1M in hexanes). The pre-formed catalyst solution (vial A) was then transferred to vial B followed immediately by carbonate 76b (96 mg, 0.40 mmol, 200 mol %). The vial was sealed and stirred at 60 °C. After 18 h, the vial was removed from the glove box, transferred to a 20 mL vial with CH₂Cl₂ and concentrated.

To the vial of crude MAC adduct equipped with a stir bar and septum cap was added 1:1 AcOH/DME (0.4 mL, 0.5 M) and CSA (51 mg, 0.22 mmol, 1.1 equiv) under a nitrogen atmosphere. The reaction was heated to 60 °C for 6 h, whereupon the reaction mixture was cooled to ambient temperature, diluted with CH₂Cl₂ (0.4 mL), and cooled to −40 °C. A solution of 1:1 pyrrolidine/CH₂Cl₂ (0.67 mL, 20.4 equiv of pyrrolidine) was added dropwise over 10 min then Et₃N (0.57 mL, 4.1 mmol, 20.4 equiv). The reaction mixture was allowed to warm to ambient temperature over 18 h, whereupon the reaction was slowly quenched with saturated NH₄Cl aqueous solution (5 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure.
at 0 °C. The crude residue was purified by preparatory TLC (30% acetone/hexanes) to give amide 84 as a colorless oil (32 mg, 61% yield): [α]D 25 – 49.5 (c 1.7, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.28 (m, 2H), 7.21 – 7.14 (m, 2H), 6.45 (dd, J = 17.4, 10.7 Hz, 1H), 5.27 (dd, J = 10.7, 0.8 Hz, 1H), 5.10 (dd, J = 17.4, 0.8 Hz, 1H), 3.63 – 3.47 (m, 2H), 2.98 (dt, J = 10.6, 6.3 Hz, 1H), 2.52 (dt, J = 10.6, 6.7 Hz, 1H), 1.78 – 1.62 (m, 2H), 1.64 – 1.55 (m, 5H); ¹³C NMR (101 MHz, CDCl₃) δ 172.1, 143.2, 139.7, 132.5, 129.0, 127.6, 115.5, 54.3, 47.52, 47.44, 28.4, 26.5, 23.5; IR (Neat Film, NaCl) 2928, 2873, 1742, 1627, 1491, 1396, 1228, 1185, 1096, 1012, 921, 829, 723 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₅H₁₉ClNO [M+H]⁺: 264.1155, found 264.1154.

\( \text{(S)-N-allyl-2-(4-chlorophenyl)-2-methylbut-3-enamide (85).} \) In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]₂ (2.7 mg, 0.0040 mmol, 2 mol %), ligand \( (S_\alpha)-L5 \) (4.9 mg, 0.0084 mmol, 4.2 mol %), TBD (2.8 mg, 0.020 mmol, 10 mol %), and THF (1 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with MAC nucleophile 67c (25 mg, 0.20 mmol, 100 mol %), THF (1 mL), and BEt₃ (400 µL, 1M in hexanes). The pre-formed catalyst solution (vial A) was then transferred to vial B followed immediately by carbonate 76b (96 mg, 0.40 mmol, 200 mol %). The vial was sealed and stirred at 60 °C. After 18 h, the vial was removed from the glove box, transferred to a 20 mL vial with CH₂Cl₂ and concentrated.
Chapter 3 – Enantioselective Synthesis of Acyclic α-Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation

To the vial of crude MAC adduct equipped with a stir bar and septum cap was added 1:1 AcOH/DME (0.4 mL, 0.5 M) and CSA (51 mg, 0.22 mmol, 1.1 equiv) under a nitrogen atmosphere. The reaction was heated to 60 °C for 6 h, whereupon the reaction mixture was cooled to ambient temperature, diluted with allyl amine (0.4 mL), and cooled to 0 °C. A solution of 1:1 Et₃N/allyl amine (1.1 mL, 20.4 equiv of Et₃N) was added dropwise over 10 min. The reaction mixture was allowed to warm to ambient temperature over 18 h, whereupon the reaction was slowly quenched with saturated NH₄Cl aqueous solution (5 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure at 0 °C. The crude residue was purified by preparatory TLC (30% EtOAc/hexanes) to give allyl amide 85 as a colorless oil (31 mg, 63% yield): [α]D₂⁵ +10.2 (c 1.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.17 (m, 4H), 6.29 (dd, J = 17.4, 10.6 Hz, 1H), 5.90 – 5.75 (m, 1H), 5.64 (s, 1H), 5.33 (dd, J = 10.6, 0.8 Hz, 1H), 5.20 – 5.03 (m, 3H), 3.96 – 3.82 (m, 2H), 1.67 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 174.1, 142.0, 141.8, 134.1, 133.1, 128.9, 128.8, 116.6, 116.5, 54.3, 42.3, 24.6; IR (Neat Film, NaCl) 3341, 3085, 2983, 2931, 1739, 1658, 1520, 1493, 1414, 1270, 1096, 1014, 922, 827, 725, 657 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₄H₁₇NOCl [M+H]⁺: 250.0999, found 250.0991.
3.7.2.7 Experimental Procedures and Spectroscopic Data for the Product Transformations of α-Quaternary Ester 82

**Methyl (S)-2-(4-chlorophenyl)-2-methylbutanoate (86).** To a solution of olefin 82 (13 mg, 0.056 mmol, 1 equiv) in EtOAc (1 mL) was added Pd/C (2.5 mg, 20% w/w). The reaction mixture was sparged with a hydrogen gas (balloon) for 5 minutes and then stirred under a hydrogen atmosphere for 18 h, whereupon the reaction was filtered through celite with EtOAc (5 mL) and concentrated under reduced pressure at 0 °C to give alkyl 86 as a colorless oil (12 mg, 97% yield): \([\alpha]_D^{25} +3.6 (c 1.2, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.41 – 7.15 (m, 4H), 3.67 (s, 3H), 2.31 – 1.80 (m, 2H), 1.53 (s, 3H), 0.83 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 176.5, 142.4, 132.6, 128.6, 127.7, 52.3, 50.4, 32.0, 22.2, 9.2\); IR (Neat Film, NaCl) 2970, 2880, 1731, 1493, 1457, 1383, 1307, 1238, 1147, 1096, 1012, 824, 756, 720 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{12}\)H\(_{16}\)O\(_2\)Cl [M+H]\(^+\): 227.0839, found 227.0840.

![Methyl (S)-2-(4-chlorophenyl)-2-methylbutanoate (86)](image)

**HO**

(S)-2-(4-Chlorophenyl)-2-methylbut-3-en-1-ol (87). DIBAL (0.029 mL, 0.16 mmol, 3 equiv) was added dropwise to a solution of methyl ester 82 (13 mg, 0.056 mmol, 1 equiv) in Et\(_2\)O (1.0 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h, whereupon the reaction was quenched with a saturated Rochelle’s salt aqueous solution (1 mL) and stirred for 18
h at ambient temperature. The aqueous layer was then extracted with CH₂Cl₂ (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure at 0 °C. The crude residue was purified by preparatory TLC (25% acetone/hexanes) to give alcohol 87 as a colorless oil (8 mg, 73% yield): [α]D²⁵ +11.0 (c 0.4, CHCl₃). Characterization data match those reported in the literature.³¹

(3S)-3-(4-Chlorophenyl)-4-hydroxy-3-methylidihydrofuran-2(3H)-one (88). To a solution of olefin 82 (24 mg, 0.10 mmol, 1 equiv) in THF/H₂O (4:1, 1 mL) was added K₂OsO₄ (4.0 mg, 0.010 mmol, 0.1 equiv) and N-methylmorpholine N-oxide (19 mg, 0.16 mmol, 1.6 equiv). The reaction mixture was stirred for 18 h, whereupon the reaction was quenched with sodium sulfite (10 mg, 0.079 mmol, 0.79 equiv) and diluted with water (0.5 mL). The aqueous layer was then extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure at 0 °C. The crude residue was purified by preparatory TLC (30% acetone/hexanes) to give lactone 88 as a colorless oil (19 mg, 82% yield, 1:1 dr): [α]D²⁵ −115.6 (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.26 (m, 4H), 4.58 (dd, J = 4.4, 2.8 Hz, 0.5H), 4.54 (dd, J = 10.2, 4.5 Hz, 0.5H), 4.35 – 4.31 (m, 0.5H), 4.28 – 4.20 (m, 1H), 4.16 (dd, J = 10.1, 2.8 Hz, 0.5H), 1.66 (s, 1.5H), 1.57 (s, 1.5H); ¹³C NMR (101 MHz, CDCl₃) δ 178.4, 178.1, 138.4, 134.4, 134.0, 133.9, 129.6, 129.4, 129.3, 127.8, 76.5, 76.2, 71.8, 71.6, 53.2, 52.8, 22.3, 18.5; IR (Neat Film,
Methyl \((R)-2-(4\text{-chlorophenyl})-2\text{-methyl}-3\text{-oxopropanoate (89)}\). A solution of olefin 82 (10 mg, 0.045 mmol, 1 equiv) and NaHCO\(_3\) (1.0 mg, 0.011 mmol, 0.25 equiv) in MeOH/ CH\(_2\)Cl\(_2\) (1:5, 2.6 mL) was cooled to \(-78 \, ^\circ\text{C}\). Ozone was bubbled through the reaction mixture for 0.5 h, whereupon the reaction mixture was sparged with N\(_2\) and dimethyl sulfide (0.10 mL, 0.14 mmol, 3 equiv) was added. The cooling bath was then removed and the reaction was stirred for 18 h at ambient temperature. The reaction mixture was concentrated under reduced pressure at 0 \, ^\circ\text{C}\) and the crude residue was purified by preparatory TLC (17\% Et\(_2\)O/hexanes) to afford aldehyde 89 as a colorless oil (5.0 mg, 50\% yield): \([\alpha]_D^{25}+9.1\) (c 0.07, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.83 (s, 1H), 7.41 – 7.33 (m, 2H), 7.22 – 7.13 (m, 2H), 3.81 (s, 3H), 1.69 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 196.2, 171.8, 134.8, 134.5, 129.5, 128.5, 61.7, 53.1, 18.0; IR (Neat Film, NaCl) 2992, 2954, 2845, 2726, 1721, 1596, 1494, 1455, 1252, 1122, 1096, 1013, 911, 823, 758, 718 cm\(^{-1}\); HRMS (FAB+) m/z calc’d for C\(_{11}\)H\(_{12}\)ClO\(_3\) [M+H]\(^+\): 227.0475, found 227.0479.
3.7.2.8 Determination of Enantiomeric Excess

Please note racemic products were synthesized using racemic L5.

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<th>Entry</th>
<th>Product</th>
<th>Assay Conditions</th>
<th>Retention time of major isomer (min)</th>
<th>Retention time of minor isomer (min)</th>
<th>%ee</th>
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<td>93%</td>
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<td>Product</td>
<td>Assay Conditions</td>
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<td>Retention time of minor isomer (min)</td>
<td>%ee</td>
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<td><img src="image1.png" alt="Product" /></td>
<td>HPLC Chiralpak AD–H 2% IPA isocratic, 1 mL/min</td>
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<td>92%</td>
</tr>
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Table 3.8: Entry Product Assay Conditions Retention time of major isomer (min) Retention time of minor isomer (min) %ee

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<th>Assay Conditions</th>
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<td>14.652</td>
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### 3.8 REFERENCES AND NOTES


Chapter 3 – Enantioselective Synthesis of Acyclic $\alpha$-Quaternary Carboxylic Acid Derivatives
via Iridium-Catalyzed Allylic Alkylation


Chapter 3 – Enantioselective Synthesis of Acyclic α-Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation


APPENDIX 4

Spectra Relevant to Chapter 3:

Enantioselective Synthesis of Acyclic $\alpha$-Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation
Figure A4.1: \(^1\text{H} \text{ NMR (400 MHz, CDCl}_3\) of compound 73
Figure A4.2 Infrared spectrum (Thin Film, NaCl) of compound 73

Figure A4.3 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 73
Figure A4.4 $^1$H NMR (400 MHz, CDCl$_3$) of compound 74
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.5 Infrared spectrum (Thin Film, NaCl) of compound 74

Figure A4.6 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 74
Figure A4.7 $^1$H NMR (400 MHz, CDCl$_3$) of compound 76c
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.8 Infrared spectrum (Thin Film, NaCl) of compound 76c

Figure A4.9 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 76c
Figure A4.10 $^1$H NMR (400 MHz, CDCl$_3$) of compound 76f
Figure A4.11 Infrared spectrum (Thin Film, NaCl) of compound 76f

Figure A4.12 $^{13}$C NMR (101 MHz, CDCl₃) of compound 76f
Figure A4.13 $^1$H NMR (400 MHz, CDCl$_3$) of compound 76g
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.14 Infrared spectrum (Thin Film, NaCl) of compound 76g

Figure A4.15 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 76g
Figure A4.16: $^1H$ NMR (400 MHz, CDCl$_3$) of compound 76h
Figure A4.17 Infrared spectrum (Thin Film, NaCl) of compound 76h

Figure A4.18 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 76h
Figure A4.19: $^1$H NMR (400 MHz, CDCl$_3$) of compound 76i.
Figure A4.20 Infrared spectrum (Thin Film, NaCl) of compound 76i

Figure A4.21 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 76i
Figure A4.22: $^1$H NMR (400 MHz, CDCl$_3$) of compound 76k
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.23 Infrared spectrum (Thin Film, NaCl) of compound 76k

Figure A4.24 $^{13}$C NMR (101 MHz, CDCl₃) of compound 76k
Figure A4.25 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77b
Figure A4.26 Infrared spectrum (Thin Film, NaCl) of compound 77b

Figure A4.27 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 77b
Figure A4.28 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77c
Figure A4.29 Infrared spectrum (Thin Film, NaCl) of compound 77c

Figure A4.30 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 77c
Figure A4.31 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77d
**Figure A4.32** Infrared spectrum (Thin Film, NaCl) of compound 77d

**Figure A4.33** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 77d
Figure A4.34 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77e
Appendix 4 – Spectra Relevant to Chapter 3

**Figure A4.35** Infrared spectrum (Thin Film, NaCl) of compound 77e

**Figure A4.36** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 77e
Figure A4.37 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77f
Figure A4.38 Infrared spectrum (Thin Film, NaCl) of compound 77f

Figure A4.39 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 77f
Figure A4.40 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77g
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.41 Infrared spectrum (Thin Film, NaCl) of compound 77g

Figure A4.42 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 77g
Figure A4.43 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77h
**Figure A4.44** Infrared spectrum (Thin Film, NaCl) of compound 77h

**Figure A4.45** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 77h
Figure A4.46 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77i
Figure A4.47 Infrared spectrum (Thin Film, NaCl) of compound 77i

Figure A4.48 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 77i
Figure A4.49 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77j
Figure A4.50 Infrared spectrum (Thin Film, NaCl) of compound 77j

Figure A4.51 $^1$C NMR (101 MHz, CDCl$_3$) of compound 77j
Figure A4.52 $^1$H NMR (400 MHz, CDCl$_3$) of compound 77k
Figure A4.53 Infrared spectrum (Thin Film, NaCl) of compound 77k

Figure A4.54 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 77k
Figure A4.55  HMBC (400 MHz, CDCl₃) of compound 77k
Figure A4.56: $^1$H NMR (400 MHz, CDCl$_3$) of compound 78b
Figure A4.57 Infrared spectrum (Thin Film, NaCl) of compound 78b

Figure A4.58 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 78b
Figure A4.59: $^1$H NMR (400 MHz, CDCl$_3$) of compound 78c
Figure A4.60 Infrared spectrum (Thin Film, NaCl) of compound 78c

Figure A4.61 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 78c
Figure A4.62 $^1$H NMR (400 MHz, CDCl$_3$) of compound 78e
Figure A4.63 13C NMR (101 MHz, CDCl₃) of compound 78e

Figure A4.64 1H NMR (101 MHz, CDCl₃) of compound 78e
Figure A4.65 $^1$H NMR (400 MHz, CDCl$_3$) of compound 79a
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.66 Infrared spectrum (Thin Film, NaCl) of compound 79a

Figure A4.67 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 79a
Figure A4.68 $^1$H NMR (400 MHz, CDCl$_3$) of compound 79b
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.69 Infrared spectrum (Thin Film, NaCl) of compound 79b

Figure A4.70 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 79b
Figure A4.71 $^1$H NMR (400 MHz, CDCl$_3$) of compound 79f
Appendix 4 – Spectra Relevant to Chapter 3

**Figure A4.72** Infrared spectrum (Thin Film, NaCl) of compound 79f

**Figure A4.73** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 79f
Figure A4.74 (HMBC, 400 MHz, CDCl₃) of compound 79f
Figure A4.75 $^1$H NMR (400 MHz, CDCl$_3$) of compound 82
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.76 Infrared spectrum (Thin Film, NaCl) of compound 82

Figure A4.77 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 82
Figure A4.78 $^1$H NMR (400 MHz, CDCl$_3$) of compound 83
Figure A4.79 Infrared spectrum (Thin Film, NaCl) of compound 83

Figure A4.80 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 83
Figure A4.81 ¹H NMR (400 MHz, CDCl₃) of compound 84
Figure A4.82 Infrared spectrum (Thin Film, NaCl) of compound 84

Figure A4.83 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 84
Figure A4.84 $^1$H NMR (400 MHz, CDCl$_3$) of compound 85
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.85 Infrared spectrum (Thin Film, NaCl) of compound 85

Figure A4.86 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 85
Figure A4.87: $^1$H NMR (400 MHz, CDCl$_3$) of compound 86
Figure A4.88 Infrared spectrum (Thin Film, NaCl) of compound 86

Figure A4.89 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 86
Appendix 4 – Spectra Relevant to Chapter 3

Figure A4.90 $^1$H NMR (400 MHz, CDCl$_3$) of compound 88
Figure A4.91 Infrared spectrum (Thin Film, NaCl) of compound 88

Figure A4.92 $^{1}^3$C NMR (101 MHz, CDCl$_3$) of compound 88
Figure A4.93 $^1$H NMR (400 MHz, CDCl$_3$) of compound 89
**Figure A4.94** Infrared spectrum (Thin Film, NaCl) of compound 89

**Figure A4.95** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 89
Figure A4.96 $^1$H NMR (400 MHz, CDCl$_3$) of compound 90
Figure A4.97 Infrared spectrum (Thin Film, NaCl) of compound 90

Figure A4.98 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 90
Figure A4.99: $^1$H NMR (400 MHz, CDCl$_3$) of compound 91
Figure A4.100 Infrared spectrum (Thin Film, NaCl) of compound 91

Figure A4.101 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 91
APPENDIX 5

X-Ray Crystallography Reports Relevant to Chapter 3:

Enantioselective Synthesis of Acyclic α-Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation
A5.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker D8 Venture Kappa Duo Photon 100 CMOS diffractometer.

A5.1.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF CARBOXYLIC ACID 77h

Carboxylic acid 77h (87% ee) was recrystallized by slow evaporation of CH₂Cl₂ to provide crystals suitable for X-ray analysis.

Figure A5.1 X-ray crystal structure of carboxylic acid 77h

<table>
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<th>Table A5.1 Crystal data and structure refinement for carboxylic acid 77h</th>
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<td>Temperature</td>
</tr>
<tr>
<td>Wavelength</td>
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Crystal system: Monoclinic
Space group: P2₁
Unit cell dimensions:
- a = 7.3561(3) Å, a = 90°
- b = 6.7600(3) Å, b = 94.5940(10)°
- c = 10.9461(5) Å, g = 90°
Volume: 542.57(4) Å³
Z: 2
Density (calculated): 1.354 Mg/m³
Absorption coefficient: 0.879 mm⁻¹
F(000): 232
Theta range for data collection: 4.051 to 72.406°.
Index ranges: -9 ≤ h ≤ 9, -8 ≤ k ≤ 8, -13 ≤ l ≤ 13
Reflections collected: 24109
Independent reflections: 2132 [R(int) = 0.0427]
Completeness to theta = 67.679°: 100.0 %
Absorption correction: Semi-empirical from equivalents
Refinement method: Full-matrix least-squares on F²
Data / restraints / parameters: 2132 / 1 / 146
Goodness-of-fit on F²: 1.315
Final R indices [I>2σ(I)]: R1 = 0.0495, wR2 = 0.1336
R indices (all data): R1 = 0.0497, wR2 = 0.1346
Absolute structure parameter: 0.08(5)
Extinction coefficient: n/a
Largest diff. peak and hole: 0.312 and -0.539 e.Å⁻³
Table A5.2 Atomic coordinates \((x \times 10^4)\) and equivalent isotropic displacement parameters \((\AA^2 \times 10^3)\) for 77h. \(U(eq)\) is defined as one third of the trace of the orthogonalized \(Uij\) tensor.

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Table A5.3 Bond lengths [Å] and angles [°] for 77h

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Appendix 5 – X-Ray Crystallography Reports Relevant to Chapter 3

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C(7)-C(11) 1.527(2)
C(7)-C(8) 1.539(3)
C(9)-C(10) 1.318(4)
C(11)-O(2) 1.210(2)
C(11)-O(1) 1.321(3)
N(1)-O(3) 1.210(3)
N(1)-O(4) 1.214(3)
C(6)-C(1)-C(2) 123.08(18)
C(6)-C(1)-N(1) 118.68(17)
C(2)-C(1)-N(1) 118.25(17)
C(3)-C(2)-C(1) 119.26(16)
C(2)-C(3)-C(4) 118.74(16)
C(2)-C(3)-C(7) 120.38(14)
C(4)-C(3)-C(7) 120.72(15)
C(5)-C(4)-C(3) 121.17(17)
C(6)-C(5)-C(4) 120.45(17)
C(1)-C(6)-C(5) 117.31(17)
C(9)-C(7)-C(11) 106.08(18)
C(9)-C(7)-C(3) 110.51(16)
C(11)-C(7)-C(3) 109.42(14)
C(9)-C(7)-C(8) 114.1(2)
C(11)-C(7)-C(8) 109.22(15)
C(3)-C(7)-C(8) 107.45(17)
C(10)-C(9)-C(7) 125.3(4)
O(2)-C(11)-O(1) 122.7(2)
O(2)-C(11)-C(7) 124.49(19)
O(1)-C(11)-C(7) 112.85(17)
O(3)-N(1)-O(4) 122.26(19)
O(3)-N(1)-C(1) 118.91(17)
O(4)-N(1)-C(1) 118.82(19)
Table A5.4 Anisotropic displacement parameters \( (\AA^2 \times 10^3) \) for 77h. The anisotropic displacement factor exponent takes the form: \(-2p^2|ih^2 a^* U^{11} + ... + 2hk a^* b^* U^{12} |\)

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Table A5.5 Hydrogen coordinates \( (x \times 10^4) \) and isotropic displacement parameters \( (\AA^2 \times 10^3) \) for 77h

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<td>H(8B)</td>
<td>8145</td>
<td>7730</td>
<td>9284</td>
<td>78</td>
</tr>
<tr>
<td>H(8C)</td>
<td>6333</td>
<td>8135</td>
<td>8410</td>
<td>78</td>
</tr>
<tr>
<td>H(9)</td>
<td>9363</td>
<td>3012</td>
<td>7967</td>
<td>62</td>
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<tr>
<td>H(10A)</td>
<td>10911</td>
<td>6525</td>
<td>8877</td>
<td>103</td>
</tr>
<tr>
<td>H(10B)</td>
<td>11978</td>
<td>4427</td>
<td>8671</td>
<td>103</td>
</tr>
<tr>
<td>H(1)</td>
<td>5466</td>
<td>1842</td>
<td>9160</td>
<td>69</td>
</tr>
</tbody>
</table>
CHAPTER 4

Enantioselective Synthesis Vicinal All-Carbon Quaternary Centers via Iridium-Catalyzed Allylic Alkylation†

4.1 INTRODUCTION AND BACKGROUND

The enantioselective preparation of singular all-carbon quaternary stereocenters has been a persistent challenge in the synthetic community and a topic of great interest to our research group. However, due to significant progress in this area over recent decades, the more formidable challenge of constructing vicinal all-carbon quaternary centers has become the forefront of investigation. A limited number of organic and transition metal-catalyzed methods for the enantioselective preparation of vicinal all-carbon quaternary stereocenters have been reported, with enantioselective transition metal-catalyzed allylic alkylation strategies remaining underexplored.

† This work was performed in collaboration with Dr. J. Caleb Hethcox. Portions of this chapter have been reproduced with permission from Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. Angew. Chem. Int. Ed. 2018, doi: 10.1002/anie.201804820 © 2018 Wiley-VCH.
In 2011, Trost reported an enantioselective palladium-catalyzed allylic alkylation of oxindoles to provide reverse prenylated products containing a homoallylic quaternary stereocenter vicinal to an all-carbon quaternary center (Figure 4.1a). In 2014, Ooi and Zhang each disclosed examples of enantio- and diastereoselective palladium-catalyzed allylic alkylation reactions to form cyclic products bearing vicinal all-carbon quaternary stereocenters (Figure 4.1b). To date, these three methods represent the only enantioselective transition metal-catalyzed allylic alkylation protocols for the synthesis of vicinal all-carbon quaternary centers – none of these reports provide access to acyclic products.

**Figure 4.1** State-of-the-art in the enantioselective synthesis of vicinal all-carbon quaternary centers via transition metal-catalyzed allylic alkylation

**a) Previous Report: Enantioselective Synthesis of Vicinal Quaternary Centers**

Trost (2011)

\[
\begin{align*}
\text{R}^1 & + \text{BocO} & \text{PdL}^* & \text{up to 90% yield} & \text{up to >99% ee} \\
\text{R}^2 & & & \\
\end{align*}
\]

**b) Previous Reports: Enantio- and Diastereoselective Synthesis of Vicinal Quaternary Stereocenters**

Ooi (2014)

\[
\begin{align*}
\text{Ar} & + \text{O} & \text{PdL}^* & \text{up to 99% yield} & \text{up to >20:1 dr} & \text{up to 99% ee} \\
\text{CN} & & & \\
\end{align*}
\]

Zhang (2014)

\[
\begin{align*}
\text{Ar} & + \text{O} & \text{PdL}^* & \text{up to 98% yield} & \text{up to 11:1 dr} & \text{up to 98% ee} \\
\text{CN} & & & \\
\end{align*}
\]

**c) This Research: Enantioselective Synthesis of Vicinal Quaternary Centers with Prochiral Electrophile**

\[
\begin{align*}
\text{R}^1 & + \text{RCO}_2\text{Me} & \text{IrL}^* & \text{up to >99% yield} & \\
\text{CN} & & & \\
\end{align*}
\]
Recently, our group reported the first iridium-catalyzed allylic alkylation method to allow for the synthesis of highly enantioenriched allylic quaternary stereocenters.\textsuperscript{9} Given that iridium-catalyzed allylic alkylation is well known to facilitate the synthesis of vicinal stereocenters (3°/3° and 3°/4°),\textsuperscript{10} we hypothesized that we could utilize our newly developed technology to prepare vicinal all-carbon quaternary centers, with the use of appropriately designed nucleophiles.\textsuperscript{11} Herein, we discuss the first enantioselective transition metal-catalyzed allylic alkylation to form acyclic products bearing vicinal all-carbon quaternary centers (Figure 4.1c).

\section*{4.2 REACTION OPTIMIZATION}

Preliminary studies focused on identifying a suitable catalyst system to promote the reaction of nucleophile 92 and trisubstituted allylic electrophile 72 (Table 4.1). In designing our optimal nucleophile for the allylic alkylation reaction, we imagined that methylmalononitrile (92) would mimic both the acidity and steric bulk of the previously utilized masked acyl cyanide (MAC) nucleophile\textsuperscript{9} (Figure 1C, $R^1 = \text{OMOM}$) as well as provide versatile functional handles for derivatizations of product 93. We were pleased to find that our hypothesis was valid, and when utilizing our optimized conditions for the iridium-catalyzed allylic alkylation of MAC reagents\textsuperscript{9} with nucleophile 92, product 93 is obtained in nearly quantitative yield, though in only a moderate 73% ee (Table 4.1, entry 1). In an effort to improve the enantioselectivity of the transformation we investigated a range of basic additives, as bases have been reported to have a pronounced effect on selectivity in allylic alkylation reactions.\textsuperscript{12} While addition of LiOr-Bu provided only a slight enhancement in enantioselectivity to 81% ee (entry 2), we were delighted to find
that the amine base DABCO affords product 93 in 92% yield and an excellent 95% ee (entry 3). At this time, the specific role of DABCO remains unknown; however, due to the additive’s drastic effect on enantioselectivity, we hypothesize that DABCO allows for increased equilibration between diastereomers of an iridium π-allyl complex by slowing the rate of nucleophilic attack.13,14 Moreover, while we observed the highest yield for the allylic alkylation reaction using a 1:2 nucleophile to electrophile ratio, the nucleophile and electrophile stoichiometry can be varied (1:1 or 2:1) without affecting reaction selectivity, though yields are diminished (entries 4 and 5). Of note, excess electrophile 72 is unable to be quantitatively recovered as a competing elimination reaction takes place to form a diene byproduct.

Table 4.1 Optimization of reaction parameters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nuc:Elec</th>
<th>Base</th>
<th>Yield (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:2</td>
<td>–</td>
<td>&gt;99</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>1:2</td>
<td>LiOt-Bu</td>
<td>&gt;99</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>DABCO</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>1:1</td>
<td>DABCO</td>
<td>67</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>2:1</td>
<td>DABCO</td>
<td>41</td>
<td>94</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.1 mmol scale. [b] 1H NMR yield based on internal standard. [c] Determined by chiral SFC analysis. [d] TBD = 1,3,4-triazabicyclo[4.4.0]dec-5-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane.
4.3 SUBSTRATE SCOPE EXPLORATION

With the optimal conditions identified (Table 4.1, entry 3), we explored the substrate scope for this new transformation. With respect to nucleophile 94, the process is tolerant of a wide variety of substituted malononitrile derivatives (Table 4.2). Specifically, we were pleased to find that increasing the steric bulk on the nucleophile results in formation of the corresponding ethyl-substituted 95a and benzyl-substituted 95b products in only slightly decreased yields (76% and 69%, respectively) and no significant loss in enantioselectivity. Interestingly, phenyl-substituted nucleophile 94c gives full conversion to the linear product (105, Section 4.6.2.5) in the allylic alkylation reaction rather than branched product 95c. Additionally, olefinic substituents on the nucleophile are tolerated under the reaction conditions provided the olefin is at least di-substituted; allyl-substituted 94d returns only starting material in the allylic alkylation reaction while methallyl-substituted product 95e can be prepared in 33% yield with 92% ee and prenyl-substituted product 95f can be constructed in an excellent 92% yield with 96% ee. We reason that increased olefin substitution decreases the affinity of the olefin to bind to the catalyst,15 thus leading to increased yields. Furthermore, we were delighted to discover that carbonyl-containing product 95g can be obtained in a moderate 52% yield with an excellent 96% ee. Finally, fluorinated product 95h can be accessed in a moderate 50% yield with 91% ee.
Table 4.2 Nucleophile substrate scope

<table>
<thead>
<tr>
<th>R</th>
<th>NC</th>
<th>NC + OCO2Me</th>
<th>DABCO (200 mol %)</th>
<th>BEt3 (200 mol %)</th>
<th>[Ir(cod)Cl]2 (2 mol %)</th>
<th>(S,S)-L5 (4 mol %), TBD (10 mol %)</th>
<th>THF (0.1 M), 60 °C, 18 h</th>
<th>R</th>
<th>NC</th>
<th>NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>92, 94a–g</td>
<td>72</td>
<td>93, 95a–g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>R</th>
<th>NC</th>
<th>NC</th>
<th>93</th>
<th>89% yield b</th>
<th>95% ee c</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>95a</td>
<td>76% yield</td>
<td>95% ee</td>
</tr>
<tr>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>95b</td>
<td>69% yield</td>
<td>93% ee</td>
</tr>
<tr>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>95c</td>
<td>0% yield d</td>
<td>~% ee</td>
</tr>
<tr>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>95d</td>
<td>0% yield</td>
<td>~% ee</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R</th>
<th>NC</th>
<th>NC</th>
<th>95e</th>
<th>33% yield</th>
<th>92% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>95f</td>
<td>92% yield</td>
<td>96% ee</td>
</tr>
<tr>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>95g</td>
<td>52% yield</td>
<td>96% ee</td>
</tr>
<tr>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>95h</td>
<td>50% yield</td>
<td>91% ee</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.2 mmol scale. [b] Isolated yield. [c] Determined by chiral SFC. [d] 99% conversion by 1H NMR to linear product 105.

Pleased to find the reaction amenable to a range of nucleophilic substrates, we sought to further examine the scope of the transformation by exploring the diversity of substitution permitted on trisubstituted allylic electrophile 96 (Table 4.3). Gratifyingly, we observed that a series of para-substituted allylic electrophiles bearing both electron-donating (–p-Me, –p-OMe) and withdrawing groups (–p-Ph, –p-F) on the aromatic ring furnish the corresponding products 97a–d in consistently excellent enantioselectivities (>94% ee) when subjected to the reaction conditions utilizing methylmalononitrile (92) as the nucleophile. In evaluating the effect of meta-substitution, we found that products 97e–h (–m-Me, –m-Cl, –m-NO2, 2-Np) can be obtained with similarly high enantiocontrol (>93% ee). Generally, we noted that electron-rich electrophiles (i.e., 96a,
96b, 96e) provide the corresponding allylic alkylation products in slightly diminished yields (67–80% versus 84–99%) as compared to electron-poor electrophiles (i.e., 96c, 96d, 96f, 96g). At this time, ortho-substitution (i.e., –o-Me) is not tolerated under the reaction conditions and no conversion to product 97i is observed. However, we were pleased to discover that the reaction is amenable to bis-alkyl-substitution on the allylic electrophile allowing for access to product 97j in 65% yield and 84% ee as an inseparable mixture (1:1.5) of branched and linear isomers. Additionally, reverse prenylation can be effected to produce achiral product 97k in 61% yield. Finally, extension of the alkyl chain on the allylic electrophile to an ethyl group leads to a decreased yield with 97l isolated in 50% yield but with no loss in selectivity (96% ee).

Table 4.3 Electrophile substrate scope

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>ee</th>
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</thead>
<tbody>
<tr>
<td>97a</td>
<td>80%</td>
<td>96%</td>
</tr>
<tr>
<td>97b</td>
<td>70%</td>
<td>96%</td>
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<tr>
<td>97c</td>
<td>&gt;99%</td>
<td>95%</td>
</tr>
<tr>
<td>97d</td>
<td>99%</td>
<td>94%</td>
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<tr>
<td>97e</td>
<td>67%</td>
<td>95%</td>
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<tr>
<td>97f</td>
<td>99%</td>
<td>99%</td>
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<tr>
<td>97g</td>
<td>84%</td>
<td>93%</td>
</tr>
<tr>
<td>97h</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>97i</td>
<td>0%</td>
<td>–%</td>
</tr>
<tr>
<td>97j</td>
<td>65%</td>
<td>84%</td>
</tr>
<tr>
<td>97k</td>
<td>61%</td>
<td>–%</td>
</tr>
<tr>
<td>97l</td>
<td>50%</td>
<td>96%</td>
</tr>
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</table>

[a] Reactions performed on 0.2 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC or SFC. [d] Absolute stereochemistry determined by single-crystal X-ray analysis; the absolute stereochemistry of all other compounds was assigned by analogy. [e] Isolated as an inseparable mixture (1:1.5) of linear to branched product.
A deeper investigation into the scope of this novel transformation revealed the limits of the catalytic system (Table 4.4). Foremost, Lewis basic functionalities are not tolerated on nucleophile 98 or electrophile 99, thus low yields or no reactivity was observed in the formation of thiophene 100a, furan 100b, ketone 100d, alkyne 100f, pyridine 100k, and thiophene 100l. Moreover, branched substitution on the nucleophile is not permitted in the allylic alkylation reaction as isopropyl-substituted 98 (R1 = i-Pr) returns only starting material. Additionally, drastically altering the pKa of nucleophile 98 shuts down the reaction, as seen with ester-functionalized 100e (R1 = CO2Et). Also, adding significant steric bulk to nucleophile 98 leads to low to no conversion to product (e.g., 100g, 100h). Furthermore, to date, only functionalized-malononitrile nucleophiles have been successful utilized in the reported allylic alkylation reaction, despite studies into other bis-electron-withdrawing group-functionalized nucleophiles (e.g., 1,3-diketone 100j) and unfunctionalized malononitrile (100i). Of note, para-trifluoromethyl-substituted allylic alkylation product 100m can be isolated in a good 75% yield, however the enantiomeric excess could not be determined due to inseparable enantiomers by HPLC and SFC; though we hypothesize that the value would be consistently high as with other electrophile substrates (Table 4.3). With respect to substitution on the electrophile, replacement of the aryl moiety with an alkyl group leads to minimal to no yield of allylic alkylation products 100n, and 100o. Use of a cyclic allylic electrophile does not afford corresponding bicyclic product 100p. Finally, despite the interest and value in the corresponding products (100q and 100r), due to difficulty of substrate preparation, a trifluoromethyl-substitute malononitrile nucleophile and halogen-substituted malononitriles were not explored in the newly developed allylic alkylation reaction.
**Table 4.4 Substrate scope limitations***

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>100a</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>100b</td>
<td>48%</td>
<td>89%</td>
</tr>
<tr>
<td>100c</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>100d</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>100e</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>100f</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>100g</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>100h</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>100i</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>100j</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>100k</td>
<td>trace yield</td>
<td></td>
</tr>
<tr>
<td>100l</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>100m</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>100n</td>
<td>trace yield</td>
<td></td>
</tr>
<tr>
<td>100o</td>
<td>trace yield</td>
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</tr>
<tr>
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<td>100q</td>
<td>not studied</td>
<td></td>
</tr>
<tr>
<td>100r</td>
<td>not studied</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.2 mmol scale. [b] ^1H NMR yield based on internal standard. [c] Determined by chiral HPLC or SFC. [d] Isolated yield.
4.4 PRODUCT TRANSFORMATIONS

With the general reactivity trends for the allylic alkylation reaction explored, we sought to demonstrate the utility of these sterically congested products (Figure 4.2). Though hydrogenation of the olefin in allylic alkylation product 93 using palladium catalysis proved problematic due to competing reduction of the nitrile groups, we found that treatment of 93 with Wilkinson’s catalyst under a hydrogen atmosphere chemoselectively reduces the olefin to furnish 101 in 92% yield. Additionally, ozonolysis of olefin 93 proceeds smoothly to give enantioenriched aldehyde 102 in 93% yield, wherein the aldehyde moiety can serve as a valuable functional handle for further manipulation (e.g., reductive aminations, allylations, and olefinations). Allylic alkylation product 95f was subjected to a two-step ozonolysis/aldol condensation process to deliver a densely functionalized, enantioenriched cyclopentene (106, Section 4.6.2.6) in 43% yield, which can then undergo diastereoselective hydration of the bis-nitrile functionality to provide amide 103 in 1:11 dr. Chiral cyclopentenes have been demonstrated to be key building blocks in a number of complex molecule total syntheses. Finally, enantioenriched lactone 104 bearing vicinal all-carbon quaternary stereocenters can be accessed in 65% yield and 1:2.5 dr from allylic alkylation product 93 via ozonolysis followed by reductive quenching. The transformations forming products 103 and 104 showcase that the diastereotopic nitrile functionalities of the allylic alkylation products are amenable to diastereoselective differentiation to afford vicinal all-carbon quaternary stereocenters, which are otherwise difficult to prepare.
Chapter 4 – Enantioselective Synthesis of Vicinal All-Carbon Quaternary Centers via Iridium-Catalyzed Allylic Alkylation

**Figure 4.2** Product transformations of allylic alkylation products

![Diagram showing product transformations](image)

[a] RhCl(PPh$_3$)$_3$, H$_2$ (balloon), benzene, 23 °C, 18 h, 92% yield; [b] O$_3$, pyridine, CH$_2$Cl$_2$, –78 °C, 4 min, 93% yield; [c] i. O$_3$, pyridine, CH$_2$Cl$_2$, –78 °C, 4 min, ii. p-TsOH, benzene, reflux, 18 h, 47% yield; [d] NaOH, EtOH/H$_2$O (1:1), 60 °C, 18 h, 38% yield, 1:11 dr; [e] i. O$_3$, MeOH, –78 °C, 0.5 h, ii. NaBH$_4$, 0 °C, 3 h, 63% yield, 1:2.5 dr.

### 4.5 CONCLUSIONS

In conclusion, we have developed the first enantioselective transition metal-catalyzed allylic alkylation reaction for the preparation of acyclic products bearing vicinal all-carbon quaternary centers. Key to the success of this new reaction is the use of DABCO in combination with triethylborane and our unique catalyst prepared from [Ir(cod)Cl]$_2$, (S$_3$)-L$_5$, and TBD. The developed method proceeds with moderate to excellent yields and high levels of enantioselectivity for a wide range of substitution on both the malononitrile-derived nucleophile and the trisubstituted allylic electrophile. Furthermore, the allylic alkylation products can be transformed by chemo- and diastereoselective methods to a number of highly valuable, densely functionalized building blocks, including those containing vicinal all-carbon quaternary stereocenters.
4.6 EXPERIMENTAL SECTION

4.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Oakwood Chemicals and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) and preparatory TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, KMnO₄, or p-anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak OJ column (4.6 mm x 25 cm) or a Chiralpak AD-H column (4.6 mm x 25 cm), both obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. Analytical SFC was performed with a Mettler SFC supercritical CO₂ analytical chromatography system utilizing a Chiralpak OJ–H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. ^1H NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CHCl₃ (δ 7.26 ppm). ^13C NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CDCl₃ (δ 77.16 ppm). Data for ^1H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ^13C NMR are reported in terms of chemical shifts (δ ppm).
Some reported spectra include minor solvent impurities of water (δ 1.56 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), acetone (δ 2.17 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm⁻¹). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell, and are reported as: [α]D T (concentration in g/100 mL, solvent).

4.6.1.1 Key Considerations

All synthesized reagents (i.e., (S)-L5, 92, 72, 94, and 96) were dried over P₂O₅ and drierite in a vacuum desiccator under vacuum overnight before use in the iridium-catalyzed allylic alkylation reaction. THF was taken directly from an activated alumina column under argon and used immediately to eliminate the possibility of peroxides. Mesitylene or 1,2,4,5-tetrachloro-3-nitrobenzene were used as the internal standard for determining ¹H NMR yields. Prolonged storage of electrophiles 72 and 96 at room temperature under an air atmosphere results in the formation of an unidentified impurity; storage in a –30 °C freezer allows for prolonged storage.
4.6.1.2 Preparation of Known Compounds

Previously reported methods were used to prepare ligand \((S_{n})-L5\)\(^\text{18}\) as well as starting materials \(92, \text{ 72, 94a, 94b, 94c, 94d, 94e, 94f, 94g, 94h, 96a, 96d, 96e, 96f, 96g, 96h, 96i, 96j, 96k, 96l}\) and \(96m\).

4.6.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

4.6.2.1 Representative Procedures for the Synthesis of Electrophiles

\((E)-3-(4-Methoxyphenyl)but-2-en-1-yl methyl carbonate (96b)\). To a solution of methyl \((E)-3-(4-methoxyphenyl)but-2-enoate\)\(^\text{29}\) (0.21 g, 1.0 mmol, 1 equiv) in THF (6.0 mL) at \(-78 \, ^\circ C\) was added DIBAL (0.62 mL, 3.0 mmol, 3.5 equiv) dropwise. The resulting reaction mixture was stirred at \(-78 \, ^\circ C\) for 2.5 h, whereupon the reaction was quenched with a saturated aqueous Rochelle’s salt solution (10 mL). The cooling bath was then removed and the reaction was stirred for 18 h at ambient temperature. The aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (3 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried over \(\text{Na}_2\text{SO}_4\), and concentrated under reduced pressure.

The crude material was dissolved in \(\text{CH}_2\text{Cl}_2\) (4.0 mL) and cooled to 0 \, ^\circ C. Pyridine (0.64 mL, 8.3 mmol, 8.3 equiv) was added followed by methyl chloroformate (0.20 mL, 2.3 mmol, 2.3 equiv) dropwise. The resulting solution was allowed to warm to ambient temperature and was stirred for 18 h. The reaction was quenched with the addition of 1 M HCl (5 mL) and the aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (3 x 20
mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (5% EtOAc/hexanes) to give carbonate 96b as a colorless solid (0.13 g, 53% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.92 – 5.82 (m, 1H), 4.84 (dd, J = 7.2, 0.8 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2.16 – 2.05 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 159.4, 156.0, 140.7, 134.9, 127.1, 119.1, 113.8, 65.2, 55.4, 54.9, 16.4; IR (Neat Film, NaCl) 2958, 2832, 1753, 1740, 1440, 1381, 1336, 1249, 1028, 942, 819, 798 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₃H₁₆O₃ [M]⁺: 236.1049, found 236.1053.

4.6.2.2 Spectroscopic Data for the Synthesis of Electrophiles

(E)-3-([1,1'-Biphenyl]-4-yl)but-2-en-1-yl methyl carbonate (96c). Carbonate 96c was prepared from methyl (E)-3-([1,1'-biphenyl]-4-yl)but-2-enoate according to the representative procedure and isolated by silica gel flash column chromatography (5% EtOAc/hexanes) as a colorless oil (0.17 g, 52% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 19.6 Hz, 4H), 7.51 – 7.41 (m, 4H), 7.35 (t, J = 7.3 Hz, 1H), 6.00 (td, J = 7.0, 1.4 Hz, 1H), 4.88 (dq, J = 7.0, 0.8 Hz, 2H), 3.81 (s, 3H), 2.17 (dt, J = 1.3, 0.7 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 156.0, 141.4, 140.7, 140.7, 140.6, 128.9, 127.5, 127.1, 126.4, 120.8, 65.1, 55.0, 16.4; IR (Neat Film, NaCl) 3032, 2968, 1750, 1740, 1441, 1408, 1340, 1245, 992, 943, 827, 794, 759, 689 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₈H₁₆O₃ [M]⁺: 282.1256, found 282.1253.
\((E)-3-(3\text{-Chlorophenyl})\text{but-2-en-1-yl methyl carbonate (96f).}\) Carbonate 96f was prepared from methyl \((E)-3-(3\text{-chlorophenyl})\text{but-2-enoate}^{31}\) according to the representative procedure and isolated by silica gel flash column chromatography (10% EtOAc/hexanes) as a colorless oil (0.43 g, 88% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.38 (q, \(J = 1.5\) Hz, 1H), 7.30 – 7.22 (m, 3H), 5.92 (ddt, \(J = 6.9, 5.6, 1.4\) Hz, 1H), 4.84 (dq, \(J = 7.0, 0.8\) Hz, 2H), 3.81 (s, 3H), 2.10 (dt, \(J = 1.4, 0.7\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.9, 144.4, 139.8, 134.4, 129.7, 127.9, 126.3, 124.2, 122.0, 64.9, 55.0, 16.4; IR (Neat Film, NaCl) 2957, 1748, 1594, 1564, 1443, 1377, 1333, 1268, 1172, 1102, 997, 948, 906, 884, 782, 691 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{12}\)H\(_{13}\)ClO\(_3\) [M]\(^{+}\): 240.0553, found 240.0564.

### 4.6.2.3 General Procedure for Optimization Reactions (Table 4.1)

\((S)-2\text{-Methyl-2-(2-phenylbut-3-en-2-yl)malononitrile (93).}\) In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added \([\text{Ir(cod)Cl}]_2\) (1.3 mg, 0.0020 mmol, 2 mol %), ligand \((S_d)-\text{L5}\) (2.0 mg, 0.004 mmol, 4 mol %), TBD (1.4 mg, 0.010 mmol, 10 mol %), and THF (0.5 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with nucleophile 92 (0.10 mmol or 0.20 mmol, as specified), THF (0.5 mL), and the base additive (0 or 200 mol %). The pre-formed catalyst solution (vial A) was then transferred to vial B followed immediately by
carbonate 72 (0.20 mmol, 0.10 mmol, or 0.20 mmol, as specified). The vial was sealed and stirred at 60 °C. After 18 h, the vial was removed from the glove box concentrated under reduced pressure. To the crude reaction mixture was added 1,2,4,5-tetrachloro-3-nitrobenzene (0.10 mmol in 0.5 mL CDCl₃). The NMR yield (measured in reference to 1,2,4,5-tetrachloro-3-nitrobenzene δ 7.74 ppm (s, 1H)) was determined by ¹H NMR analysis of the crude mixture. The residue was purified by preparatory TLC (15% Et₂O/hexanes, eluted twice) to afford allylic alkylation product 3 as a pale yellow oil.

4.6.2.4 General Procedure for the Iridium-Catalyzed Allylic Alkylation

Please note that the absolute configuration was determined only for compound 97c via X-ray crystallographic analysis. The absolute configuration for all other products has been inferred by analogy. For respective HPLC and SFC conditions, please refer to Table S1.

(S)-2-Methyl-2-(2-phenylbut-3-en-2-yl)malononitrile (93). In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]₂ (2.7 mg, 0.0040 mmol, 2 mol %), ligand (S₆)-L₅ (4.0 mg, 0.008 mmol, 4 mol %), TBD (2.8 mg, 0.020 mmol, 10 mol %), and THF (1 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with nucleophile 92 (18 mg, 0.20 mmol, 100 mol %), THF (1 mL), DABCO (45 mg, 0.40 mmol, 200 mol %), and BEt₃ (400 µL, 1M in hexanes). The pre-formed catalyst solution (vial A) was then transferred to vial B followed immediately by carbonate 72 (83 mg, 0.40 mmol, 200 mol %). The vial was
sealed and stirred at 60 °C. After 18 h, the vial was removed from the glove box, transferred to a 20 mL vial with CH₂Cl₂ and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (15% Et₂O/hexanes, eluted twice) to afford allylic alkylation product 93 as a pale yellow oil (37 mg, 89% yield): 95% ee; [α]D²⁵ +32.9 (c 1.9, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.52 (m, 2H), 7.44 – 7.33 (m, 3H), 6.49 (dd, J = 17.3, 11.0 Hz, 1H), 5.63 – 5.31 (m, 2H), 1.80 (s, 3H), 1.66 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 139.2, 138.3, 128.7, 128.6, 128.1, 119.0, 116.1, 116.0, 49.4, 41.9, 21.8, 21.5; IR (Neat Film, NaCl) 3095, 3062, 2992, 2951, 2247, 1749, 1639, 1600, 1496, 1447, 1417, 1386, 1270, 1217, 1165, 1102, 1074, 1031, 1003, 937, 802, 751, cm⁻¹; HRMS (ESI+) m/z calc’d for C₁₄H₁₄N₂ [M]+: 210.1157, found 210.1156; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ–H column, λ = 210 nm, tR (min): major = 3.832, minor = 4.594.

4.6.2.5 Spectroscopic Data for the Iridium-Catalyzed Allylic Alkylation Products

(S)-2-Ethyl-2-(2-phenylbut-3-en-2-y1)malononitrile (95a). Allylic alkylation product 95a was prepared according to the general procedure and isolated by preparatory TLC (100% toluene, eluted twice) to give a pale yellow oil (34 mg, 76% yield): 95% ee; [α]D²⁵ +19.0 (c 0.87, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.63 – 7.51 (m, 2H), 7.45 – 7.31 (m, 3H), 6.51 (dd, J = 17.3, 11.0 Hz, 1H), 5.52 (d, J = 11.0 Hz, 1H), 5.40 (d, J = 17.3 Hz, 1H), 1.90 – 1.72 (m, 5H), 1.27 (t, J = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 139.6,
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138.7, 128.6, 128.5, 128.2, 118.7, 115.2, 115.1, 49.9, 49.7, 27.7, 22.0, 10.7; IR (Neat Film, NaCl) 3094, 3061, 2959, 2931, 2874, 2244, 1730, 1640, 1600, 1496, 1461, 1446, 1416, 1382, 1271, 1175, 1074, 1002, 937, 793, 750, 701 cm$^{-1}$; HRMS (ESI+) $m/z$ calc’d for C$_{15}$H$_{17}$N$_2$ [M+H]$^+$: 225.1392, found 225.1395; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ–H column, $\lambda = 210$ nm, $t_R$ (min): major = 3.378, minor = 4.088.

(S)-2-Benzyl-2-(2-phenylbut-3-en-2-yl)malononitrile (95b). Allylic alkylation product 95b was prepared according to the general procedure and isolated by preparatory TLC (15% Et$_2$O/hexanes, eluted twice) to give a pale yellow oil (39 mg, 69% yield): 93% ee; [$\alpha$]$_D^{25}$ +11.0 (c 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.68 – 7.62 (m, 2H), 7.51 – 7.29 (m, 8H), 6.64 (dd, $J = 17.3$, 11.0 Hz, 1H), 5.60 (d, $J = 11.0$ Hz, 1H), 5.47 (d, $J = 17.2$ Hz, 1H), 3.07 – 2.90 (m, 2H), 1.93 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 139.4, 138.5, 132.6, 130.5, 128.9, 128.7, 128.7, 128.6, 128.3, 119.1, 114.9, 114.7, 50.6, 50.3, 39.6, 22.1; IR (Neat Film, NaCl) 3092, 3063, 3034, 2990, 2927, 2245, 1957, 1884, 1810, 1748, 1602, 1498, 1456, 1446, 1416, 1383, 1270, 1212, 1159, 1110, 1080, 1032, 1004, 938, 766, 749 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{20}$H$_{19}$N$_2$ [M+H]$^+$: 287.1548, found 287.1553; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ–H column, $\lambda = 210$ nm, $t_R$ (min): major = 10.960, minor = 11.727.
(E)-2-Phenyl-2-(3-phenylbut-2-en-1-yl)malononitrile (105). Linear allylic alkylation product SI-1 was prepared according to the general procedure in 99% conversion by $^1$H NMR yield but was inseparable from unreacted electrophile 72. 105 was prepared via an alternate route for verification and characterization. In a nitrogen-filled glove box, to a 1 dram vial equipped with a stir bar was added Pd(PPh$_3$)$_4$ (11 mg, 0.01 mmol, 0.1 mol %), nucleophile 94c (21 mg, 0.15 mmol, 1.5 equiv), electrophile 72 (21 mg, 0.10 mmol, 1.0 equiv), and THF (1 mL). The reaction was stirred for 18 h whereupon the vial was removed from the glove box, transferred to a 20 mL vial with CH$_2$Cl$_2$, and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (20% EtO/hexanes, eluted twice) to afford 105 as a colorless crystalline solid (23 mg, 43% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67 – 7.28 (m, 10H), 5.75 (td, $J = 7.8, 1.5$ Hz, 1H), 3.23 – 3.01 (m, 2H), 1.95 (d, $J = 1.4$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 143.8, 142.6, 131.7, 130.1, 129.8, 128.5, 128.0, 126.1, 126.1, 117.2, 115.0, 42.5, 42.0, 16.6; IR (Neat Film, NaCl) 3062, 3032, 2983, 2930, 2246, 1599, 1494, 1451, 1383, 1277, 1027, 861, 756, 692 cm$^{-1}$; HRMS (FAB+) m/z calc’d for C$_{19}$H$_{17}$N$_2$ [M+H]$^+$: 273.1292, found 273.1387.

(S)-2-(2-methylallyl)-2-(2-phenylbut-3-en-2-yl)malononitrile (95d). Allylic alkylation product 95d was prepared according to the general procedure and isolated by preparatory
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TLC (100% toluene, eluted twice) to give a pale yellow oil (17 mg, 33% yield): 92% ee; $\left[\alpha\right]_D^{25} +26.0$ (c 0.94, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 – 7.56 (m, 2H), 7.45 – 7.32 (m, 3H), 6.54 (dd, $J = 17.3, 11.0$ Hz, 1H), 5.55 (d, $J = 11.0$ Hz, 1H), 5.41 (d, $J = 17.3$ Hz, 1H), 5.11 (t, $J = 1.4$ Hz, 1H), 5.01 (p, $J = 1.0$ Hz, 1H), 2.50 – 2.35 (m, 2H), 1.91 (dd, $J = 1.6, 0.8$ Hz, 3H), 1.84 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 139.4, 138.5, 137.9, 128.7, 128.6, 128.3, 119.1, 118.7, 115.4, 115.2, 50.4, 47.6, 41.5, 23.2, 22.0; IR (Neat Film, NaCl) 3085, 2988, 2242, 1747, 1650, 1496, 1445, 1416, 1381, 1264, 1072, 1004, 910, 792, 750, 698 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{17}$H$_{19}$N$_2$ [M+H]$^+$: 251.1548, found 251.1539; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ–H column, $\lambda = 210$ nm, $t_R$ (min): major = 3.138, minor = 3.923.

(S)-2-(3-Methylbut-2-en-1-yl)-2-(2-phenylbut-3-en-2-yl)malononitrile (95e). Allylic alkylation product 95e was prepared according to the general procedure and isolated by preparatory TLC (5% Et$_2$O/hexanes, eluted twice) to give a colorless oil (49 mg, 92% yield): 96% ee; $\left[\alpha\right]_D^{25} +7.87$ (c 6.3, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 – 7.56 (m, 2H), 7.47 – 7.31 (m, 3H), 6.54 (dd, $J = 17.3, 11.0$ Hz, 1H), 5.54 (d, $J = 11.0$ Hz, 1H), 5.41 (d, $J = 17.3$ Hz, 1H), 5.34 – 5.24 (m, 1H), 2.46 (qd, $J = 14.1, 7.6$ Hz, 2H), 1.84 (s, 3H), 1.78 (d, $J = 1.4$ Hz, 3H), 1.60 (d, $J = 1.4$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 140.4, 139.6, 138.7, 128.6, 128.5, 128.1, 118.7, 115.3, 115.2, 49.6, 48.9, 32.7, 26.1, 21.9, 18.4; IR (Neat Film, NaCl) 3089, 2987, 2926, 2242, 1497, 1446, 1416, 1383,
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1004, 935, 838, 750, 700 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{18}\)H\(_{21}\)N\(_2\) [M+H]\(^+\): 265.1705, found 265.1709; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ–H column, \(\lambda = 210\) nm, \(t_R\) (min): major = 3.095, minor = 4.061.

(S)-2-(3-oxobutyl)-2-(2-phenylbut-3-en-2-yl)malononitrile (95f). Allylic alkylation product 95f was prepared according to the general procedure and isolated by preparatory TLC (20% Et\(_2\)O/hexanes, eluted twice) to give a colorless oil (28 mg, 52% yield): 96% ee; \([\alpha]_D^{25}\) +16.8 (c 1.6, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.62 – 7.53 (m, 2H), 7.46 – 7.30 (m, 3H), 6.50 (dd, \(J = 17.2, 10.9\) Hz, 1H), 5.54 (d, \(J = 11.0\) Hz, 1H), 5.41 (d, \(J = 17.2\) Hz, 1H), 2.86 – 2.75 (m, 2H), 2.19 (s, 3H), 2.17 – 1.97 (m, 2H), 1.82 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 205.1, 139.2, 138.2, 128.7, 128.6, 128.1, 119.1, 115.0, 114.9, 49.8, 47.7, 40.0, 30.2, 27.8, 21.8; IR (Neat Film, NaCl) 3094, 3061, 2991, 2957, 2246, 1721, 1640, 1601, 1582, 1496, 1446, 1418, 1370, 1288, 1215, 1170, 1118, 1080, 1032, 1002, 938, 754, 702 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{17}\)H\(_{19}\)N\(_2\)O [M+H]\(^+\): 267.1497, found 267.1499; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ–H column, \(\lambda = 210\) nm, \(t_R\) (min): major = 5.022, minor = 7.267.
(S)-2-(2-Phenylbut-3-en-2-yl)-2-(3,3,3-trifluoropropyl)malononitrile (95g). Allylic alkylation product 95g was prepared according to the general procedure and isolated by preparatory TLC (100% toluene, eluted twice) to give a colorless oil (29 mg, 50% yield): 91% ee; [α]$_D^{25}$ +16.6 (c 1.8, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.61 – 7.32 (m, 5H), 6.50 (dd, $J$ = 17.2, 10.9 Hz, 1H), 5.59 (d, $J$ = 11.0 Hz, 1H), 5.44 (d, $J$ = 17.2 Hz, 1H), 2.57 – 2.39 (m, 2H), 2.12 – 1.93 (m, 2H), 1.84 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.8, 137.7, 128.87, 128.86, 127.9, 125.7 (q, $J$ = 276.4 Hz), 119.5, 114.3, 114.1, 49.9, 47.5, 31.7, 31.3 (q, $J$ = 30.3 Hz), 27.1 (q, $J$ = 3.4 Hz); IR (Neat Film, NaCl) 3096, 3063, 2992, 2928, 2242, 1496, 1447, 1400, 1318, 1257, 1157, 1089, 1046, 845, 752, 701, 624 cm$^{-1}$; HRMS (ESI+) m/z calc’d for C$_{16}$H$_{15}$F$_2$N$_2$ [M]$^{+}$: 292.1187, found 292.1173; SFC conditions: 1% IPA, 3.0 mL/min, Chiralpak OJ–H column, λ = 210 nm, t$_R$ (min): major = 1.651, minor = 1.868.

(S)-2-Methyl-2-(2-(p-tolyl)but-3-en-2-yl)malononitrile (97a). Allylic alkylation product 97a was prepared according to the general procedure and isolated by preparatory TLC (15% Et$_2$O/hexanes, eluted twice) to give a pale yellow oil (36 mg, 80% yield): 96% ee; [α]$_D^{25}$ +48.7 (c 1.1, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.47 – 7.39 (m, 2H), 7.23 – 7.16 (m, 2H), 6.48 (dd, $J$ = 17.3, 11.0 Hz, 1H), 5.52 (d, $J$ = 11.0 Hz, 1H), 5.40 (d, $J$ =
17.3 Hz, 1H), 2.35 (s, 3H), 1.77 (s, 3H), 1.66 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.44, 138.42, 136.2, 129.3, 128.0, 118.8, 116.2, 116.1, 49.2, 42.0, 21.8, 21.5, 21.1; IR (Neat Film, NaCl) 3094, 2992, 2953, 2925, 2247, 1748, 1682, 1639, 1614, 1515, 1454, 1416, 1383, 1268, 1198, 1102, 1074, 1019, 937, 825, 804, 774 cm$^{-1}$; HRMS (ESI+) m/z calc’d for C$_{15}$H$_{16}$N$_2$ [M]$^+$: 224.1314, found 224.1306; SFC conditions: 1% IPA, 3.0 mL/min, Chiralpak OJ–H column, $\lambda = 210$ nm, $t_R$ (min): major = 3.658, minor = 4.375.

(S)-2-(2-(4-Methoxyphenyl)but-3-en-2-yl)-2-methylmalononitrile (97b). Allylic alkylation product 97b was prepared according to the general procedure and isolated by preparatory TLC (20% Et$_2$O/hexanes, eluted twice) to give a pale yellow oil (34 mg, 70% yield): 96% ee; $[\alpha]_D^{25} +25.4$ (c 2.1, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.42 (m, 2H), 6.95 – 6.88 (m, 2H), 6.47 (dd, $J = 17.3$, 11.0 Hz, 1H), 5.52 (d, $J = 11.0$ Hz, 1H), 5.39 (d, $J = 17.3$ Hz, 1H), 3.82 (s, 3H), 1.77 (s, 3H), 1.65 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.5, 138.5, 131.0, 129.4, 118.7, 116.2, 116.1, 113.9, 55.4, 49.0, 42.1, 21.7, 21.6; IR (Neat Film, NaCl) 2998, 2934, 2832, 2242, 1609, 1514, 1458, 1298, 1257, 1188, 1029, 932, 832, 808, 774 cm$^{-1}$; HRMS (FAB+) m/z calc’d for C$_{15}$H$_{15}$ON$_2$ [(M+H–H$_2$)$^+$: 239.1184, found 239.1198; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ–H column, $\lambda = 210$ nm, $t_R$ (min): major = 5.019, minor = 5.890.
(S)-2-(2-((1,1'-Biphenyl)-4-yl)but-3-en-2-yl)-2-methylmalononitrile (97c). Allylic alkylation product 97c was prepared according to the general procedure and isolated by preparatory TLC (20% Et₂O/hexanes, eluted twice) to give a colorless crystalline solid (58 mg, 99% yield): 95% ee; [α]²⁵⁺42.3 (c 1.9, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.32 (m, 9H), 6.53 (dd, J = 17.3, 10.9 Hz, 1H), 5.58 (d, J = 10.9 Hz, 1H), 5.46 (d, J = 17.3 Hz, 1H), 1.84 (s, 3H), 1.71 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 141.3, 140.1, 138.2, 138.1, 129.0, 128.5, 127.8, 127.24, 127.21, 119.1, 116.1, 116.0, 49.3, 41.9, 21.8, 21.5; IR (Neat Film, NaCl) 3059, 3032, 2992, 2952, 2247, 1749, 1488, 1450, 1416, 1267, 1214, 1168, 1102, 1076, 1007, 937, 842, 766, 749, 698 cm⁻¹; HRMS (FAB+) m/z calc’d for C₂₀H₁₈N₂ [M]+: 286.1470, found 286.1466; SFC conditions: 1% IPA, 2.5 mL/min, Chiralpak OJ–H column, λ = 210 nm, tᵣ (min) major = 43.531, minor = 40.798.

(S)-2-(2-(4-fluorophenyl)but-3-en-2-yl)-2-methylmalononitrile (97d). Allylic alkylation product 97d was prepared according to the general procedure and isolated by preparatory TLC (15% Et₂O/hexanes, eluted twice) to give a colorless oil (45 mg, 99% yield): 94% ee; [α]²⁵⁺23.5 (c 3.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.54 (dd, J = 9.0, 5.1 Hz, 2H), 7.09 (dd, J = 9.1, 8.3 Hz, 2H), 6.46 (dd, J = 17.3, 11.0 Hz, 1H), 5.55 (d,
$J = 11.0$ Hz, 1H), 5.41 (d, $J = 17.3$ Hz, 1H), 1.78 (s, 3H), 1.67 (s, 3H); $^{13}$C NMR (101 MHz, CDC$_3$) $\delta$ 162.6 (d, $J = 249.0$ Hz), 138.1, 135.1 (d, $J = 3.3$ Hz), 130.1, 130.0, 119.3, 115.9 (d, $J = 10.2$ Hz), 115.6 (d, $J = 21.4$ Hz), 49.1, 42.0, 21.7, 21.7; IR (Neat Film, NaCl) 3074, 2993, 2247, 1752, 16001, 1509, 1453, 1416, 1386, 1239, 1170, 1097, 1014, 936, 838, 820, 782, 643 cm$^{-1}$; HRMS (ESI+) $m/z$ calc’d for C$_{14}$H$_{13}$FN$_2$ [M]$^+$: 228.1063, found 228.1036; HPLC conditions: 3% IPA, 1 mL/min, Chiralpak OJ column, $\lambda = 210$ nm, $t_R$ (min): major = 22.493, minor = 29.003.

**(S)-2-Methyl-2-((2-(m-tolyl)but-3-en-2-yl)malononitrile (97e).** Allylic alkylation product 97e was prepared according to the general procedure and isolated by preparatory TLC (15% Et$_2$O/hexanes, eluted twice) to give a colorless oil (30 mg, 67% yield): 95% ee; $[\alpha]_D^{25} +29.8$ (c 1.8, CHCl$_3$); $^1$H NMR (400 MHz, CDC$_3$) $\delta$ 7.39 – 7.33 (m, 2H), 7.32 – 7.22 (m, 1H), 7.17 (ddt, $J = 7.4$, 1.4, 0.7 Hz, 1H), 6.48 (dd, $J = 17.3$, 11.0 Hz, 1H), 5.53 (d, $J = 11.0$ Hz, 1H), 5.42 (d, $J = 17.3$ Hz, 1H), 2.38 (d, $J = 0.8$ Hz, 3H), 1.78 (s, 3H), 1.66 (s, 3H); $^{13}$C NMR (101 MHz, CDC$_3$) $\delta$ 139.1, 138.4, 138.3, 129.2, 128.7, 128.5, 125.1, 118.8, 116.1, 116.0, 49.2, 41.8, 21.8, 21.8, 21.4; IR (Neat Film, NaCl) 3092, 2992, 2951, 2924, 2246, 1638, 1606, 1588, 1492, 1454, 1417, 1384, 1250, 1162, 1106, 1042, 1002, 937, 794, 766, 705 cm$^{-1}$; HRMS (ESI+) $m/z$ calc’d for C$_{15}$H$_{17}$N$_2$ [M+H]$^+$: 225.1392, found 225.1387; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda = 210$ nm, $t_R$ (min): major = 2.897, minor = 3.290.
**Chapter 4 – Enantioselective Synthesis of Vicinal All-Carbon Quaternary Centers via Iridium-Catalyzed Allylic Alkylation**

(S)-2-(2-(3-Chlorophenyl)but-3-en-2-yl)-2-methylmalononitrile (97f). Allylic alkylation product 97f was prepared according to the general procedure and isolated by preparatory TLC (15% Et$_2$O/hexanes, eluted twice) to give a pale yellow oil (48 mg, 99% yield): 99% ee; $\left[\alpha\right]_{D}^{25}$ +3.2 (c 3.2, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55 – 7.43 (m, 2H), 7.40 – 7.30 (m, 2H), 6.43 (dd, $J$ = 17.3, 10.9 Hz, 1H), 5.58 (d, $J$ = 11.0 Hz, 1H), 5.43 (d, $J$ = 17.3 Hz, 1H), 1.78 (s, 3H), 1.68 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.4, 137.6, 134.7, 129.9, 128.8, 128.5, 126.2, 119.6, 115.8, 115.7, 49.3, 41.7, 21.7, 21.4; IR (Neat Film, NaCl) 3071, 2992, 2957, 2247, 1880, 1752, 1637, 1594, 1571, 1478, 1458, 1458, 1414, 1261, 1217, 1168, 1094, 999, 938, 885, 811, 739, 695 cm$^{-1}$; HRMS (ESI+) m/z calc’d for C$_{14}$H$_{13}$ClN$_2$ [M]$^+$: 244.0767, found 244.0773; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ–H column, $\lambda$ = 210 nm, $t_R$ (min): major = 3.255, minor = 4.955.

(S)-2-Methyl-2-(2-(3-nitrophenyl)but-3-en-2-yl)malononitrile (97g). Allylic alkylation product 97g was prepared according to the general procedure and isolated by preparatory TLC (25% Et$_2$O/hexanes) to give a pale yellow solid (43 mg, 84% yield): 93% ee; $\left[\alpha\right]_{D}^{25}$ +38.6 (c 2.2, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.41 (t, $J$ = 2.1 Hz, 1H), 8.25 (ddd, $J$
(S)-2-Methyl-2-(2-(naphthalen-2-yl)but-3-en-2-yl)malononitrile (97h). Allylic alkylation product 97h was prepared according to the general procedure and isolated by preparatory TLC (15% Et₂O/hexanes, eluted twice) to give a colorless oil (48 mg, 93% yield): 95% ee; [α]D²⁵ +57.9 (c 3.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, J = 2.2 Hz, 1H), 7.93 – 7.80 (m, 3H), 7.70 (dd, J = 8.8, 2.1 Hz, 1H), 7.57 – 7.49 (m, 2H), 6.60 (dd, J = 17.3, 10.9 Hz, 1H), 5.60 (d, J = 11.0 Hz, 1H), 5.46 (d, J = 17.3 Hz, 1H), 1.91 (s, 3H), 1.70 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 138.4, 136.5, 132.9, 132.8, 128.6, 128.3, 127.8, 127.5, 127.0, 126.7, 125.4, 119.2, 116.1, 116.0, 49.6, 41.8, 21.8 (2C); IR (Neat Film, NaCl) 3060, 2992, 2950, 2246, 1748, 1637, 1598, 1507, 1453, 1416, 1386, 1277, 1194, 1164, 1130, 1103, 999, 937, 902, 859, 819, 779, 747, 666 cm⁻¹; HRMS (ESI+) m/z calc’d for C₁₈H₁₇N₂ [M+H]⁺: 261.1392, found 261.1378; SFC conditions: 4%
IPA, 2.5 mL/min, Chiralpak OJ–H column, λ = 210 nm, t<sub>R</sub> (min): major = 11.637, minor = 13.691.

(R)-2-Methyl-2-(3-methyl-5-phenylpent-1-en-3-yl)malononitrile (97j). Allylic alkylation product 97j was prepared according to the general procedure and isolated by preparatory TLC (20% Et<sub>2</sub>O/hexanes, eluted twice) to give a pale yellow oil (31 mg, 65% yield as a 1:1.5 mixture of linear to branched products): 84% ee; [α]<sub>D</sub><sup>25</sup> +17.0 (c 1.9, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.28 – 7.06 (m, 13.5H), 5.80 (dd, J = 17.3, 10.8 Hz, 1.5H), 5.48 (dd, J = 10.8, 0.5 Hz, 1.5H), 5.30 (dd, J = 17.4, 0.6 Hz, 1.5H), 5.19 – 5.11 (m, 1H), 2.70 (dd, J = 8.9, 6.7 Hz, 2.5H), 2.57 (dq, J = 7.7, 0.7 Hz, 2H), 2.54 – 2.40 (m, 3H), 2.34 (ddd, J = 8.6, 6.4, 1.1 Hz, 2H), 1.94 (ddd, J = 10.3, 6.8, 5.6 Hz, 3H), 1.71 – 1.67 (m, 3H), 1.64 (s, 4.5H), 1.55 (s, 3H), 1.30 (s, 4.5H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 143.7, 141.4, 141.1, 137.0, 128.7, 128.5, 128.4, 126.4, 126.1, 120.5, 116.3, 115.8, 115.7, 115.3, 46.2, 41.8, 41.5, 38.7, 37.4, 34.2, 31.8, 30.9, 23.8, 20.5, 17.1, 16.9; IR (Neat Film, NaCl) 3087, 3064, 3028, 2989, 2930, 2864, 2247, 1949, 1871, 1812, 1638, 1604, 1497, 1453, 1418, 1385, 1277, 1179, 1104, 1074, 1030, 1002, 936, 751, 714, 699, 624 cm<sup>-1</sup>; HRMS (ESI+) m/z calc’d for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 239.1548, found 239.1530; SFC conditions: 0.1% IPA, 2.5 mL/min, Chiralpak OJ–H column, λ = 210 nm, t<sub>R</sub> (min): major = 7.621, minor = 7.163.
2-Methyl-2-(2-methylbut-3-en-2-yl)malononitrile (97k). Allylic alkylation product 97k was prepared according to the general procedure and isolated by preparatory TLC (20% Et₂O/hexanes, eluted twice) to give a colorless oil (18 mg, 61% yield): ¹H NMR (400 MHz, CDCl₃) δ 5.92 (dd, J = 17.2, 10.8 Hz, 1H), 5.45 – 5.04 (m, 2H), 1.68 (s, 3H), 1.35 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 138.8, 118.2, 115.8, 42.9, 41.2, 22.9, 20.6; IR (Neat Film, NaCl) 3095, 2981, 2941, 2885, 2248, 1643, 1459, 1419, 1383, 1176, 1155, 1112, 998, 934, 735, 688 cm⁻¹; HRMS (ESI+) m/z calc’d for C₉H₁₁N₂ [(M+H)⁻H₂]⁺: 147.0922, found 147.0945.

(S)-2-Methyl-2-(3-phenylpent-1-en-3-yl)malononitrile (97l). Allylic alkylation product 97l was prepared according to the general procedure and isolated by preparatory TLC (15% Et₂O/hexanes, eluted twice) to give a colorless oil (23 mg, 50% yield): 96% ee; [α]D²⁵ +30.4 (c 1.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.46 (m, 2H), 7.46 – 7.29 (m, 3H), 6.19 (ddd, J = 17.6, 11.3, 0.7 Hz, 1H), 5.69 (d, J = 11.3 Hz, 1H), 5.42 (d, J = 17.6 Hz, 1H), 2.50 (dqd, J = 14.3, 7.2, 0.7 Hz, 1H), 2.15 (dq, J = 14.4, 7.2 Hz, 1H), 1.60 (s, 3H), 0.87 (t, J = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 134.8, 134.7, 129.8, 128.58, 128.57, 121.2, 116.3, 116.1, 54.4, 42.6, 26.4, 21.9, 9.1; IR (Neat Film, NaCl) 3094, 3061, 2981, 2944, 2884, 2246, 1638, 1601, 1496, 1448, 1414, 1382, 1180, 1161, 1083, 1002, 940, 751, 704 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₅H₁₇N₂ [M+H]⁺:
225.1392, found 225.1377; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak OJ–H column, λ = 210 nm, \( t_R \) (min): major = 3.270, minor = 4.727.

### 4.6.2.6 Experimental Procedures and Spectroscopic Data for the Product Transformations of Allylic Alkylation Products

(S)-2-Methyl-2-(2-phenylbutan-2-yl)malononitrile (101). In a nitrogen-filled glove box, to a 1 dram vial equipped with a stir bar was added olefin 93 (25 mg, 0.12 mmol, 1 equiv), RhCl(PPh\(_3\))\(_3\) (11 mg, 0.012 mmol, 10 mol %) and benzene (1.2 mL). The reaction mixture was removed from the glove box, sparged with hydrogen (balloon) for 5 minutes, and stirred under a hydrogen atmosphere for 18 h, whereupon the reaction was concentrated under reduced pressure. The crude residue was purified by preparatory TLC (20% EtOAc/hexanes) to give alkyl 101 as a colorless oil (23 mg, 92% yield): \( [\alpha]_D^{25} \) +16.6 (c 1.2, CHCl\(_3\)); \(^1H\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.49 – 7.31 (m, 5H), 2.58 – 2.46 (m, 1H), 1.94 (dq, \( J = 13.6 \), 7.2 Hz, 1H), 1.65 (d, \( J = 0.9 \) Hz, 3H), 1.56 (s, 3H), 0.83 (t, \( J = 7.3 \) Hz, 3H); \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 136.9, 128.7, 128.3 (2C), 116.3, 116.3, 47.3, 43.3, 29.5, 21.2, 20.5, 8.8; IR (Neat Film, NaCl) 3059, 2979, 2943, 2885, 2245, 1602, 15001, 1451, 1391, 1192, 1164, 1098, 1030, 806, 774, 741, 702, 662 cm\(^{-1}\); HRMS (ESI+) \( m/z \) calc’d for C\(_{14}\)H\(_{16}\)N\(_2\) [M]\(^+\): 212.1314, found 212.1291.
(S)-2-Methyl-2-(1-oxo-2-phenylpropan-2-yl)malononitrile (102). A solution of olefin 93 (40.0 mg, 0.19 mmol, 1 equiv) and pyridine (0.038 mL, 0.48 mmol, 2.5 equiv) in CH$_2$Cl$_2$ (2.0 mL) was cooled to −78 °C. Ozone was bubbled through the resulting solution for 4 min, whereupon the reaction mixture was sparged with O$_2$, warmed to ambient temperature, and diluted with CH$_2$Cl$_2$ (5.0 mL). The reaction mixture was washed with saturated aqueous NaHCO$_3$ (5 mL) and the aqueous layer was further extracted with CH$_2$Cl$_2$ (2 x 5 mL). The combined organic layers were washed with 1 M HCl (5 mL), brine (5 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give aldehyde 102 as a colorless solid (37 mg, 93% yield): [α]$_D^{25}$ −46.9 (c 2.1, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.45 (s, 1H), 7.55 – 7.45 (m, 3H), 7.41 – 7.30 (m, 2H), 1.88 (s, 3H), 1.70 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 194.9, 131.1, 130.2, 129.6, 128.9, 115.3, 115.2, 58.3, 37.4, 21.4, 16.3; IR (Neat Film, NaCl) 3033, 3063, 2985, 2954, 2832, 2720, 2249, 1726, 1498, 1448, 1395, 1376, 1262, 1190, 1172, 1080, 923, 869, 764, 703 cm$^{-1}$; HRMS (ESI+) m/z calc’d for C$_{13}$H$_{12}$N$_2$O [M]$^+$: 212.0950, found 212.0948.

(S)-4-Acetyl-2-methyl-2-phenylcyclopent-3-ene-1,1-dicarbonitrile (106). A solution of olefin 95f (42 mg, 0.16 mmol, 1 equiv) and pyridine (0.031 mL, 0.39 mmol, 2.5 equiv) in CH$_2$Cl$_2$ (2.0 mL) was cooled to −78 °C. Ozone was bubbled through the resulting solution for 4 min, whereupon the reaction mixture was sparged with O$_2$, warmed to
ambient temperature, and diluted with CH₂Cl₂ (5.0 mL). The reaction mixture was washed with saturated aqueous NaHCO₃ (5 mL) and the aqueous layer was further extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were washed with 1 M HCl (5 mL), brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure.

The crude material was dissolved in benzene (10 mL) and p-toluenesulfonic acid (30.0 mg, 0.16 mmol, 1 equiv) was added. The resulting solution was stirred at ambient temperature for 0.5 h and then heated under reflux for 18 h, whereupon the reaction mixture was cooled to ambient temperature and diluted with Et₂O (10 mL). Saturated aqueous NaHCO₃ (10 mL) was added to the resulting solution and allowed to stir for 5 min. The organic layer was then separated and washed further with saturated aqueous NaHCO₃ (10 mL), brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (33% acetone/hexanes) to give enone 106 as a colorless oil (19 mg, 47% yield over two steps): [α]D²⁵ 27.3 (c 1.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.36 (m, 5H), 6.91 (dd, J = 2.2, 1.2 Hz, 1H), 3.56 (dd, J = 16.7, 1.2 Hz, 1H), 3.39 (dd, J = 16.7, 2.1 Hz, 1H), 2.48 (s, 3H), 1.82 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 194.6, 145.4, 140.5, 138.8, 129.5 (d, J = 2.6 Hz), 126.3, 114.7, 114.4, 61.4, 45.7, 42.2, 26.8, 23.6; IR (Neat Film, NaCl) 3063, 2978, 2934, 2249, 1676, 1629, 1499, 1446, 1371, 1335, 1267, 1098, 1026, 953, 896, 764, 699 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₆H₁₅ON₂ [M+H]⁺: 251.1184, found 251.1197.
(1S,2S)-4-acetyl-1-cyano-2-methyl-2-phenylcyclopent-3-ene-1-carboxamide (103). A solution of bis-nitrile 106 (19 mg, 0.074 mmol, 1 equiv), NaOH (10 mg, 0.25 mmol, 3.4 equiv) in EtOH/H₂O (1:1, 1.0 mL) was heated to 60 °C for 18 h, whereupon the resulting mixture was cooled to ambient temperature and diluted with EtOAc (5 mL). The solution was washed with brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by preparatory TLC (50% acetone/hexanes) to give amide 103 as a colorless oil (7.5 mg, 38% yield, 1:11 dr): [α]D²⁵ +4.4 (c 1.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.38 (m, 5H), 6.65 (dd, J = 2.3, 1.1 Hz, 1H), 5.76 (s, 2H), 3.71 (dd, J = 17.0, 2.3 Hz, 1H), 3.22 (dd, J = 17.0, 1.1 Hz, 1H), 2.44 (s, 3H), 1.58 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 195.4, 165.9, 146.5, 141.9, 129.8, 129.0, 127.4, 124.9, 120.6, 60.5, 59.0, 39.2, 26.9, 21.4; IR (Neat Film, NaCl) 3338, 3201, 3062, 2980, 2929, 2854, 2242, 1732, 1694, 1673, 1604, 1498, 1446, 1371, 1338, 1259, 1102, 1046, 913, 767, 734, 702 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₆H₁₇O₂N₂ [M+H]⁺: 269.1290, found 269.1282. Please note that the NMR data listed is for the major diastereomer, though both diastereomers can be seen in the NMR spectra in a 1:11 ratio.
Chapter 4 – Enantioselective Synthesis of Vicinal All-Carbon Quaternary Centers via Iridium-Catalyzed Allylic Alkylation

Stereochemical Assignment:

\[ (3R,4S)-3,4\text{-dimethyl-2-oxo-4-phenyltetrahydrofuran-3-carbonitrile} \text{ (104).} \]

A solution of olefin 93 (100.0 mg, 0.48 mmol, 1 equiv) in MeOH (5.0 mL) was cooled to \(-78 \degree C\). Ozone was bubbled through the reaction mixture for 0.5 h, whereupon the resulting solution was sparged with O\(_2\) and NaBH\(_4\) (0.80 mg, 2.1 mmol, 4.4 equiv) was added. The reaction was then warmed to 0 \degree C and stirred for 3 h. The reaction mixture was quenched with the addition of 1 M HCl (5 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20\% acetone/hexanes) to give lactone 104 as a colorless solid (66 mg, 65\% yield, 1:2.5 dr): \([\alpha]_D^{25} +21.3 \text{ (c 3.0, CHCl}_3\text{); } ^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 7.47 – 7.33 \text{ (m, 3H), 7.26 – 7.23 \text{ (m, 2H), 4.78 \text{ (dt, J = 9.1, 0.8 Hz, 1H),}} 4.50 \text{ (d, J = 9.1 Hz, 1H), 1.74 \text{ (d, J = 0.8 Hz, 3H), 1.33 \text{ (s, 3H); }} ^13\text{C NMR (101 MHz,} \text{)}}}
CDCl$_3$ $\delta$ 171.7, 138.7, 129.6, 128.5, 125.6, 117.7, 74.6, 49.6, 49.0, 27.1, 18.9; IR (Neat Film, NaCl) 2979, 2930, 2355, 2242, 1783, 1498, 1445, 1381, 1279, 1172, 1092, 1012, 764, 699 cm$^{-1}$; HRMS (ESI+) m/z calc’d for C$_{13}$H$_{13}$NO$_2$ [M]$^+$: 215.0946, found 215.0966. Please note that the NMR data listed is for the major diastereomer.

NOE correlation:
### 4.6.2.7 Determination of Enantiomeric Excess

*Please note* racemic products were synthesized using racemic L5.

**Table 4.5 Determination of enantiomeric excess**

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<th>Entry</th>
<th>Product</th>
<th>Assay Conditions</th>
<th>Retention time of major isomer (min)</th>
<th>Retention time of minor isomer (min)</th>
<th>%ee</th>
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<td>4.594</td>
<td>95%</td>
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<tr>
<td>2</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>SFC Chiralpak OJ–H 3% IPA isocratic, 2.5 mL/min</td>
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<td>95%</td>
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<tr>
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<td>11.727</td>
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<td>SFC Chiralpak OJ–H 1% IPA isocratic, 3.0 mL/min</td>
<td>1.651</td>
<td>1.868</td>
<td>91%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image2" alt="Product" /></td>
<td>SFC Chiralpak OJ–H 1% IPA isocratic, 3.0 mL/min</td>
<td>3.658</td>
<td>4.375</td>
<td>96%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image3" alt="Product" /></td>
<td>SFC Chiralpak OJ–H 3% IPA isocratic, 2.5 mL/min</td>
<td>5.019</td>
<td>5.890</td>
<td>96%</td>
</tr>
<tr>
<td>10</td>
<td><img src="image4" alt="Product" /></td>
<td>SFC Chiralpak OJ–H 1% IPA isocratic, 2.5 mL/min</td>
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<td>40.798</td>
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<tr>
<td>11</td>
<td><img src="image5" alt="Product" /></td>
<td>HPLC Chiralpak OJ 3% IPA isocratic, 1 mL/min</td>
<td>22.493</td>
<td>29.003</td>
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<td>3.290</td>
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<tr>
<td>13</td>
<td><img src="image7" alt="Product" /></td>
<td>SFC Chiralpak OJ–H 3% IPA isocratic, 2.5 mL/min</td>
<td>3.255</td>
<td>4.955</td>
<td>99%</td>
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4.7 REFERENCES AND NOTES


Chapter 4 – Enantioselective Synthesis of Vicinal All-Carbon Quaternary Centers via Iridium-Catalyzed Allylic Alkylation


(13) DABCO has been previously utilized in iridium-catalyzed allylic alkylation leading to higher yields but slower rates of reaction, see: Bondzic, B. P.; Farwick, A.; Liebich, J.; Eilbracht, P. Org. Biomol. Chem. 2008, 6, 3723–3731.


APPENDIX 6

Spectra Relevant to Chapter 4:

Enantioselective Synthesis of Vicinal All-Carbon Quaternary Centers

via Iridium-Catalyzed Allylic Alkylation
Figure A6.1 $^1$H NMR (400 MHz, CDCl$_3$) of compound 93
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.2 Infrared spectrum (Thin Film, NaCl) of compound 93

Figure A6.3 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 93
Figure A6.4 $^1$H NMR (400 MHz, CDCl$_3$) of compound 95a
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.5 Infrared spectrum (Thin Film, NaCl) of compound 95a

Figure A6.6 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 95a
Figure A6.7 $^1$H NMR (400 MHz, CDCl$_3$) of compound 95b
Figure A6.8 Infrared spectrum (Thin Film, NaCl) of compound 95b

Figure A6.9 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 95b
Figure A6.10 $^1$H NMR (400 MHz, CDCl$_3$) of compound 95d
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.11 Infrared spectrum (Thin Film, NaCl) of compound 95d

Figure A6.12 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 95d
Figure A6.13 $^1$H NMR (400 MHz, CDCl$_3$) of compound 95e
Appendix 6 – Spectra Relevant to Chapter 4

**Figure A6.14** Infrared spectrum (Thin Film, NaCl) of compound 95e

**Figure A6.15** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 95e
Figure A6.16 $^1$H NMR (400 MHz, CDCl$_3$) of compound 95f
Figure A6.17 Infrared spectrum (Thin Film, NaCl) of compound 95f

Figure A6.18 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 95f
Figure A6.19 $^1$H NMR (400 MHz, CDCl$_3$) of compound 95g
Figure A6.20 Infrared spectrum (Thin Film, NaCl) of compound 95g

Figure A6.21 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 95g
Figure A6.22 $^1$H NMR (400 MHz, CDCl$_3$) of compound 96b
Figure A6.23 Infrared spectrum (Thin Film, NaCl) of compound 96b

Figure A6.24 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 96b
Figure A6.25 $^1$H NMR (400 MHz, CDCl$_3$) of compound 96c
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.26 Infrared spectrum (Thin Film, NaCl) of compound 96c

Figure A6.27 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 96c
Figure A6.28 $^1$H NMR (400 MHz, CDCl$_3$) of compound 96f
Appendix 6 – Spectra Relevant to Chapter 4

**Figure A6.29** Infrared spectrum (Thin Film, NaCl) of compound 96f

**Figure A6.30** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 96f
Figure A6.31 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97a
Figure A6.32 Infrared spectrum (Thin Film, NaCl) of compound 97a

Figure A6.33 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97a
Figure A6.34 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97b
Figure A6.35 Infrared spectrum (Thin Film, NaCl) of compound 97b

Figure A6.36 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97b
Figure A6.37 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97c
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.38 Infrared spectrum (Thin Film, NaCl) of compound 97c

Figure A6.39 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97c
Figure A6.40 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97d
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.41 Infrared spectrum (Thin Film, NaCl) of compound 97d

Figure A6.42 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97d
Figure A6.43 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97e
Figure A6.44 Infrared spectrum (Thin Film, NaCl) of compound 97e

Figure A6.45 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97e
Figure A6.46 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97f
Figure A6.47 Infrared spectrum (Thin Film, NaCl) of compound 97f

Figure A6.48 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97f
Figure A6.49 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97g
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.50 Infrared spectrum (Thin Film, NaCl) of compound 97g

Figure A6.51 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97g
Figure A6.52 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97h
Figure A6.53 Infrared spectrum (Thin Film, NaCl) of compound 97h

Figure A6.54 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97h
Figure A6.55: $^1H$ NMR (400 MHz, CDCl$_3$) of compound 97j.
Figure A6.56 Infrared spectrum (Thin Film, NaCl) of compound 97j

Figure A6.57 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97j
Figure A6.58 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97k
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.59 Infrared spectrum (Thin Film, NaCl) of compound 97k

Figure A6.60 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97k
Figure A6.61 $^1$H NMR (400 MHz, CDCl$_3$) of compound 97I
Figure A6.62 Infrared spectrum (Thin Film, NaCl) of compound 97l

Figure A6.63 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 97l
Figure A6.64 $^1$H NMR (400 MHz, CDCl$_3$) of compound 101
Figure A6.65 Infrared spectrum (Thin Film, NaCl) of compound 101

Figure A6.66 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 101
Figure A6.67 $^1$H NMR (400 MHz, CDCl$_3$) of compound 102
Figure A6.68 Infrared spectrum (Thin Film, NaCl) of compound 102

Figure A6.69 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 102
Figure A6.70 $^1H$ NMR (400 MHz, CDCl$_3$) of compound 103
Figure A6.71 Infrared spectrum (Thin Film, NaCl) of compound 103

Figure A6.72 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 103
Figure A6.73 HSQC (400 MHz, CDCl₃) of compound 103
Figure A6.74 HMBC (400 MHz, CDCl$_3$) of compound 103
Figure A6.75: NOESY (400 MHz, CDCl₃) of compound 103
Figure A6.76 $^1$H NMR (400 MHz, CDCl$_3$) of compound 104
Figure A6.77 Infrared spectrum (Thin Film, NaCl) of compound 104

Figure A6.78 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 104
Figure A6.79 NOESY (400 MHz, CDCl₃) of compound 104
Figure A6.80 $^1$H NMR (400 MHz, CDCl$_3$) of compound 105
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.81 Infrared spectrum (Thin Film, NaCl) of compound 105

Figure A6.82 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 105
Figure A6.83 NOESY (400 MHz, CDCl₃) of compound 105
Figure A6.84 $^1$H NMR (400 MHz, CDCl$_3$) of compound 106
Appendix 6 – Spectra Relevant to Chapter 4

Figure A6.85 Infrared spectrum (Thin Film, NaCl) of compound 106

Figure A6.86 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 106
APPENDIX 7

X-Ray Crystallography Reports Relevant to Chapter 4:

*Enantioselective Synthesis of Vicinal All-Carbon Quaternary Centers via Iridium-Catalyzed Allylic Alkylation*
A7.1 GENERAL EXPERIMENTAL

Low-temperature diffraction data (φ-and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Cu Kα radiation (λ = 1.54178 Å) from an IµS micro-source for the structure of compound 97c. The structure was solved by direct methods using SHELXS¹ and refined against $F^2$ on all data by full-matrix least squares with SHELXL-2016² using established refinement techniques.³ All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups). All disordered atoms were refined with the help of similarity restraints on the 1,2- and 1,3-distances and displacement parameters as well as enhanced rigid bond restraints for anisotropic displacement parameters.

Compound 97c crystallizes in the tetragonal space group I4₁ with half a molecule in the asymmetric unit. The molecule is located near a crystallographic 2-fold rotation axis and is disordered by the rotation. The phenyl moiety was disordered over four positions, two of which are pairwise related to the other two by the 2-fold rotation. This requires a number of SADI restraints during refinement. We note that a Bayesian analysis of the Friedel pairs (performed using the "Bijvoet-Pair Analysis" routine of PLATON) confirms the absolute stereochemical assignment based on the Flack x. The output of this analysis gives:
A7.1.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF BIS-NITRILE 97c

Bis-nitrile 97c (95% ee) was recrystallized from boiling hexane to provide crystals suitable for X-ray analysis.

Figure A7.1 X-ray crystal structure of bis-nitrile 97c
**Table A7.1 Crystal data and structure refinement for bis-nitri le 97c**

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<th>Property</th>
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<td>Space group</td>
<td>I41</td>
</tr>
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<td>Unit cell dimensions</td>
<td>a = 10.0971(4) Å, b = 10.0971(4) Å, c = 15.5215(7) Å</td>
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<tr>
<td>Volume</td>
<td>1582.44(14) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
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<td>Density (calculated)</td>
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</tr>
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<td>Independent reflections</td>
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Table A7.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 97c. U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

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Table A7.3 Bond lengths [Å] and angles [°] for 97c

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Appendix 7 – X-Ray Crystallography Reports Relevant to Chapter 4

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C(3)-H(3A)  0.9500
C(3)-H(3B)  0.9500
C(4)-H(4A)  0.9800
C(4)-H(4B)  0.9800
C(4)-H(4C)  0.9800
C(5)-C(8)  1.482(7)
C(5)-C(6)  1.501(13)
C(5)-C(7)  1.503(15)
C(6)-H(6A)  0.9800
C(6)-H(6B)  0.9800
C(6)-H(6C)  0.9800
C(7)-N(1)  1.091(15)
C(8)-N(2)  1.141(9)
C(12)-C(11)-C(16)  116.9(3)
C(12)-C(11)-C(1)  122.6(4)
C(16)-C(11)-C(1)  120.5(4)
C(11)-C(12)-C(13)  122.5(8)
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C(13)-C(12)-H(12)  118.8
C(14)-C(13)-C(12)  120.7(9)
C(14)-C(13)-H(13)  119.7
C(12)-C(13)-H(13)  119.7
C(13)-C(14)-C(15)  116.0(5)
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C(15)-C(14)-C(21)  115.9(18)
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C(14)-C(15)-H(15)  118.1
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C(15)-C(16)-H(16)  119.9
C(11)-C(16)-H(16)  119.9
C(26)-C(21)-C(22)  116.1(14)
C(26)-C(21)-C(14)  126(2)
C(22)-C(21)-C(14)  118(2)
C(23)-C(22)-C(21)  123.3(16)
Appendix 7 – X-Ray Crystallography Reports Relevant to Chapter 4

C(23)-C(22)-H(22)  118.3
C(21)-C(22)-H(22)  118.3
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C(24)-C(25)-C(26)  120.0(15)
C(24)-C(25)-H(25)  120.0
C(26)-C(25)-H(25)  120.0
C(21)-C(26)-C(25)  121.3(13)
C(21)-C(26)-H(26)  119.3
C(25)-C(26)-H(26)  119.3
C(22A)-C(21A)-C(26A)  119.6(19)
C(21A)-C(22A)-C(23A)  119.1(16)
C(21A)-C(22A)-H(22A)  120.5
C(23A)-C(22A)-H(22A)  120.5
C(24A)-C(23A)-C(22A)  121.7(17)
C(24A)-C(23A)-H(23A)  119.1
C(22A)-C(23A)-H(23A)  119.1
C(25A)-C(24A)-C(23A)  118(2)
C(25A)-C(24A)-H(24A)  120.8
C(23A)-C(24A)-H(24A)  120.8
C(24A)-C(25A)-C(26A)  121(2)
C(24A)-C(25A)-H(25A)  119.5
C(26A)-C(25A)-H(25A)  119.5
C(21A)-C(26A)-C(25A)  119.8(18)
C(21A)-C(26A)-H(26A)  120.1
C(25A)-C(26A)-H(26A)  120.1
C(4)-C(1)-C(11)  110.4(8)
C(4)-C(1)-C(2)  113.5(9)
C(11)-C(1)-C(2)  109.7(6)
C(4)-C(1)-C(5)  107.7(7)
C(11)-C(1)-C(5)  109.2(3)
C(2)-C(1)-C(5)  106.2(5)
C(3)-C(2)-C(1)  125.7(8)
C(3)-C(2)-H(2)  117.1
Table A7.4 Anisotropic displacement parameters (Å²x 10³) for 97c. The anisotropic displacement factor exponent takes the form: -2π² [ h² a*² U¹¹ + ... + 2 h k a* b* U¹² ]

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### Table A7.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 97c

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### Table A7.6 Torsion angles [°] for 97c

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### A7.2 REFERENCES AND NOTES


5.1 INTRODUCTION

To enable our ongoing research program focused on the synthesis of complex natural products, we became intested in developing robust methods for the synthesis of stereochemically rich building blocks containing quaternary stereocenters. As a result, our group has developed a range of technologies for the enantioselective preparation of all-carbon quaternary stereocenters.\(^1\) Perhaps most notably, we reported a general asymmetric palladium-catalyzed allylic alkylation method to provide access to a wide variety of products 109 bearing a homoallylic quaternary stereocenter (Figure 5.1, top).\(^2\) Over the past decade, we have expanded this methodology to a broad array of substrates 107\(^3\) and applied this chemistry to facilitate expedient total syntheses of a variety of

\(^†\) Portions of this chapter have been reproduced from Shockley, S. E.;\(^†\) Hethcox, J. C.;\(^†\) Stoltz, B. M. Manuscript submitted.
natural products, including \((-\)-cyanthiwigin F (110),\(^4\) \((+)-dichroanone (111),\(^5\) and \((+)-sibirinine (112, Figure 5.1, bottom).\(^6\)

**Figure 5.1** Stoltz group contributions to palladium-catalyzed allylic alkylation methodology and application in natural product total synthesis

Despite its extensive substrate tolerance, our palladium-catalyzed allylic alkylation technology is limited to the synthesis of isolated stereocenters. Thus, to date, this methodology is not amenable to the direct preparation of vicinal stereocenters, which are found in a variety of synthetic targets such as ligularone (1), crinipellin B (2), and elisabethin A (3, Figure 5.2, top). Inspired by these diverse and numerous stereodyad-containing natural products, we sought to expand our stereoselective allylic alkylation research program to include iridium-catalyzed processes that do enable the construction of such vicinal stereocenters 114 (Figure 5.2, bottom).
While the aforementioned palladium-catalyzed allylic alkylation has been under exploration since the 1960s, iridium-catalyzed allylic alkylation is a relatively new area of research. Takeuchi reported the first example of iridium-catalyzed allylic alkylation in 1997 using malonate nucleophiles, demonstrating that iridium catalysts can provide high branched selectivity (branched to linear ratio, b:l) in contrast to palladium catalysts that favor the synthesis of linear products (Figure 5.3a). Shortly thereafter, Helmchen reported that the reaction could be rendered enantioselective with the inclusion of chiral phosphinooxazoline ligand. In 2003, Takemoto disclosed the first report of a diastereoselective iridium-catalyzed allylic alkylation reaction, wherein prochiral nucleophiles were utilized to form vicinal trisubstituted and tertiary stereocenters (Figure 5.3c, top). It was then a decade later before the next report of diastereoselective iridium-catalyzed allylic alkylation was disclosed, which this time
enabled the preparation of vicinal tertiary and tetra-substituted stereocenters 125 (Figure 5.3c, bottom).\textsuperscript{12}

\textit{Figure 5.3} Timeline for the development of iridium-catalyzed allylic alkylation prior to the Stoltz group’s entry into the field


\[
\text{NaCH(CO}_2\text{Me)}_2 + \text{R} = \text{CO}_2\text{Me} \xrightarrow{[\text{Ir(cod)Cl}_2 \text{ (2 mol %)}] \text{P(OPh)}_3 \text{ (4 mol %)}} \text{THF, reflux} \rightarrow \text{MeO}_2\text{C} = \text{CO}_2\text{Me}
\]

115 116 117

Regioselective

\text{70–100\% yield 93:7–100:0 b:l}

b) \textit{First Enantioselective Iridium-Catalyzed Allylic Alkylation} Helmchen (1997)

\[
\text{NaCH(CO}_2\text{Me)}_2 + \text{Ar} = \text{CO}_2\text{Me} \xrightarrow{[\text{Ir(cod)Cl}_2 \text{ (2 mol %)}] \text{(S)-L12} \text{ (4 mol %)}} \text{THF, reflux} \rightarrow \text{MeO}_2\text{C} = \text{CO}_2\text{Me}
\]

115 118 119

Enantioselective

\text{93–100\% yield 62:38–99:1 b:l 78–95\% ee}

c) \textit{First Diastereoselective Iridium-Catalyzed Allylic Alkylations} Takemoto (2003)

\[
\text{Ph} = \text{CO}_2\text{Bu} + \text{Ar} = \text{OPO(OEt)}_2 \xrightarrow{[\text{Ir(cod)Cl}_2 \text{ (10 mol %)}] \text{(Ra)-L1} \text{ (20 mol %)}} \text{KOH (aq), THF, 0 °C} \rightarrow \text{tt} = \text{O}_2\text{C}
\]

120 121 122

Diastereoselective

\text{63–97\% yield 100:1 b:l 94–97\% ee 2:1–4:1 dr}

Hartwig (2013)

\[
\text{Ph} = \text{CO}_2\text{Bu} + \text{Ar} = \text{OPO(OEt)}_2 \xrightarrow{[\text{Ir(cod)Cl}_2 \text{ (2 mol %)}] \text{(R,R,Ra)-L3} \text{ (4 mol %)}} \text{3 Å MS, PhMe, 23 °C} \rightarrow \text{tt} = \text{O}_2\text{C}
\]

123 124 125

Diastereoselective

\text{69–93\% yield 94–99\% ee 7:1–20:1 dr}

Despite these seminal reports, when our group entered the field in 2013, there were no examples of an iridium-catalyzed allylic alkylation reaction to form a single all-
carbon quaternary stereocenter, let alone a stereodyad containing an all-carbon quaternary stereocenter.\textsuperscript{13} Therefore, we were highly intrigued by the possibility of developing new iridium-catalyzed allylic alkylation technology that would allow for the preparation of sterically congested enantioenriched quaternary stereocenters, and thus potentially open the door to the synthesis of a range of new natural product targets (Figure 5.2, top).

### 5.2 SYNTHESIS OF VICINAL TERTIARY AND ALL-CARBON QUATERNARY STEREOCENTERS VIA ENANTIO- AND DIASTEREOSELECTIVE IRIDIUM-CATALYZED ALYLLIC ALKYLATION

#### 5.2.1 CYCLIC NUCLEOPHILES\textsuperscript{14,15}

In our quest to develop the first iridium-catalyzed allylic alkylation reaction to form vicinal tertiary and all-carbon quaternary stereocenters, we initially selected cyclic prochiral enolates as our nucleophiles in order to obviate the need to control enolate geometry during the allylic alkylation reaction.\textsuperscript{1,16} Thus, our preliminary exploration into this research area commenced with tetralone \textsuperscript{27}. We rapidly found that the standard phosphoramidite ligands \textbf{L13} and \textbf{L9}, which were at the time typically utilized in iridium-catalyzed allylic alkylation with enolate equivalents, were not amenable to the synthesis of a quaternary stereocenter, as neither provided high levels of diastereoselectivity (Table 5.1, entries 1 and 2). Inspired by the work of the You group on the allylic alkylation of heterocycles,\textsuperscript{17} we evaluated the effect of MeTHQPhos (\textbf{L2}) as the ligand and found that it provided product \textbf{127} with a high degree of regio-, diastero-, and enantioselectivity (entry 3).
Chapter 5 – Stereoselective Iridium-Catalyzed Allylic Alkylation in the Stoltz Laboratory: A Summary

Table 5.1 Development of conditions for the iridium-catalyzed allylic alkylation reaction of cyclic nucleophiles forming vicinal tertiary and all-carbon quaternary stereocenters

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</tr>
<tr>
<td>2</td>
<td>L9</td>
<td>NaH (200)</td>
<td>&gt;95:5</td>
<td>1:2</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>L2</td>
<td>NaH (200)</td>
<td>95:5</td>
<td>&gt;20:1</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>L2</td>
<td>–</td>
<td>80:20</td>
<td>11:1</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>L2</td>
<td>LiCl (100)</td>
<td>88:12</td>
<td>14:1</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>L2</td>
<td>LiBr (100)</td>
<td>95:5</td>
<td>&gt;20:1</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

[a] Reactions performed with 0.1 mmol of 126, 0.2 mmol of 27 in THF (0.1M) and allowed to proceed to complete consumption of 126. [b] Determined by $^1$H NMR and UHPLC-MS analysis of the crude mixture. [c] Determined by chiral HPLC analysis of the major diastereomer. [d] TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene.

At this point in our optimization efforts, we realized that the reaction conditions could be simplified if the exogenous base was removed and the carbonate leaving group was instead relied on as the stoichiometric base required for enolate formation. Toward this end, sodium hydride was excluded from the reaction, but we observed diminished selectivity (Table 5.1, entry 4). Previous literature reports documented the beneficial effects of halide salts on selectivity in iridium-catalyzed allylic alkylation reactions. When this strategy was explored in our reaction conditions, LiCl provided only minor enhancement in selectivity (entry 5). However, LiBr led to a pronounced enhancement in
both conversion and selectivity, providing us with our optimized reaction conditions (entry 6).

Upon investigating the substrate scope of the developed transformation, we found the reaction amenable to a wide variety of substitution on both the allylic electrophile and the nucleophile (Scheme 5.1). Though, as a general trend, branched regioselectivity increases with greater carbocation stability on the allylic electrophile, thus electron-rich aromatics 129 (R² = EDG–Ar) provide higher branched to linear ratios. Additionally, the reaction is not limited to aryl substitution on the allylic electrophile, as both heteroaryl and alkenyl substitution provide the corresponding products in good yields and selectivities (e.g., 131a). A key limitation to this initial report is that alkyl-substituted allylic electrophiles are not tolerated and instead proceed with poor conversions and selectivities. With respect to nucleophile 128, we found that the aryl ring of tetralone 27, used as the optimization substrate, could be removed without diminishing reactivity or stereoselectivity of the reaction (e.g., as seen in products 131b and 131c). Finally, we observed that unsaturated nucleophiles 128 are tolerated, allowing for access to products bearing a 1,5-diene (e.g., 131d) for subsequent functionalization, though the addition of LiBr was not required in these reactions.
Scheme 5.1  Enantio- and diastereoselective iridium-catalyzed allylic alkylation of cyclic nucleophiles

Upon further optimization, we found that the reactions of unsaturated nucleophiles (e.g., 132) progressed with a higher degree of selectivity when LiO\textsubscript{t}-Bu was utilized as a base additive in place of LiBr.\textsuperscript{15} These allylic alkylation conditions followed by a subsequent thermal Cope rearrangement, allow unsaturated compounds 132 to formally undergo allylic alkylation at the γ-position to produce compounds such as 35 with a high degree of enantioselectivity (Scheme 5.2).

Scheme 5.2  Iridium-catalyzed allylic alkylation/Cope rearrangement sequence
5.2.2 ACYCLIC NUCLEOPHILES

In looking to expand our iridium-catalyzed allylic alkylation reaction from cyclic enolate nucleophiles to acyclic variants, we fortuitously discovered that our conditions for cyclic nucleophiles provide satisfactory reactivity and selectivity for acyclic nucleophile 134 (Scheme 5.3). With further optimization though, we ultimately found LiOt-Bu to be the optimal additive as it led to shorter reaction times. With respect to the substrate scope of this transformation, we again observed that reaction regioselectivity is directly affected by the electronics of the aryl functionality on allylic electrophile 135, however, enantio- and diastereoselectivities remain consistently excellent. Moreover, heteroaryl-substituted allylic electrophiles are tolerated, as are various substituents at the α-position of acyclic β-ketoester nucleophile 134. However, in contrast to the cyclic variants, we noted pronounced decreases in the diastereomeric ratio of product 136 when ketone 134 was not an aryl ketone (e.g., 136a versus 136d).

Scheme 5.3 Enantio- and diastereoselective iridium-catalyzed allylic alkylation of acyclic nucleophiles 134

<table>
<thead>
<tr>
<th>Select examples</th>
<th>136a</th>
<th>136b</th>
<th>136c</th>
<th>136d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>85% yield</td>
<td>98% yield</td>
<td>99% yield</td>
<td>92% yield</td>
</tr>
<tr>
<td></td>
<td>&gt;20:1 dr</td>
<td>19:1 dr</td>
<td>13:1 dr</td>
<td>4:1 dr</td>
</tr>
<tr>
<td></td>
<td>99% ee</td>
<td>99% ee</td>
<td>99% ee</td>
<td>96% ee</td>
</tr>
</tbody>
</table>
After disclosing methods for the synthesis of vicinal tertiary and all-carbon quaternary stereocenters using cyclic, acyclic, and extended enolate nucleophiles in iridium-catalyzed allylic alkylation, we noted that none of these protocols tolerated the use of alkyl-substituted electrophiles. In fact, at the time, no transition metal-catalyzed process enabled the construction of an alkyl-substituted stereodyad between neighboring tertiary and quaternary carbon atoms. Realizing that many synthetic targets require the installation of this specific stereodyad, we became intrigued with the possibility of further developing our enantio- and diastereoselective iridium-catalyzed allylic alkylation chemistry to allow for the use of allylic electrophiles bearing an sp³-hybridized substituent.

Based on our prior efforts in optimizing iridium-catalyzed allylic alkylation reactions, we anticipated that we would need to explore new combinations of additives and ligands in order to effect selectivity in the reaction between tetralone nucleophile 52, utilized in our seminal report (Table 5.1), and alkyl-substituted electrophile 53 (Table 5.2). Indeed, when we employed our previously reported conditions for cyclic or acyclic nucleophiles, we observed excellent yields and good diastereoselectivities but poor branched to linear ratios (Table 5.2, entries 1 and 2). Given the trends established in our earlier work where regioselectivity increases with increasing carbocation stability of the iridium π-allyl cation, these findings were not surprising as the methyl group is less stabilizing than an aryl substituent. We hypothesized that decreasing carbocation stability results in slow equilibration between iridium π-allyl diastereomers. Thus, we sought to employ LiCl as an additive, which has been proposed to facilitate iridium π-allyl
equilibration and therefore improve regio- and enantioselectivity in iridium-catalyzed allylic alkylation reactions.\textsuperscript{18} While we did not see a marked effect by adding LiCl alone (entry 3), we postulated that by rendering all anions in solution congruent, the effect of the chloride additive would be more pronounced. This hypothesis led us to replace the methyl carbonate leaving group of crotly electrophile \textit{53} with chloride, and in doing so we noted a significant increase in reaction regioselectivity, though the diastereoselectivity was now only moderate (entry 4).

\begin{table}[h]
\centering
\caption{Optimization of iridium-catalyzed allylic alkylation reaction of alkyl-substituted electrophile \textit{53}\textsuperscript{a}}
\begin{tabular}{ccccccccc}
\hline
Entry & \(L\) & Base & Additive & LG & Yield & \(b/c\) & \(d/c\) & ee \\
\hline
1 & L2 & – & LiBr (100) & OCO\textsubscript{2}Me & 100 & 55:45 & 6:4:1 & – \\
2 & L2 & LiO\textsubscript{t}-Bu & – & OCO\textsubscript{2}Me & 85 & 34:66 & 5:3:1 & – \\
3 & L2 & LiO\textsubscript{t}-Bu & LiCl (100) & OCO\textsubscript{2}Me & 69 & 50:50 & 7:2:1 & – \\
4 & L2 & LiO\textsubscript{t}-Bu & LiCl (100) & Cl & 94 & 86:14 & 4:8:1 & – \\
5 & L2 & proton sponge & LiCl (100) & Cl & 100 & 93:7 & 7:9:1 & 66 \\
6 & L11 & proton sponge & LiCl (100) & Cl & 46 & 95:5 & 6:0:1 & 96 \\
7 & L11 & proton sponge & LiCl (400) & Cl & 78 & 94:6 & 6:7:1 & 97 \\
\hline
\end{tabular}
\begin{flushleft}
[a] Reactions performed on 0.1 mmol of \textit{53}, 0.2 mmol of \textit{52} in THF (0.1 M) for 18 h. [b] \textsuperscript{1}H NMR yield of the mixture of diastereomers based on internal standard. [c] Determined by \textsuperscript{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral SFC analysis. [e] Proton sponge = 1,8-bis(dimethylamino)naphthalene.
\end{flushleft}
\end{table}

We next sought to improve the diastereoselectivity of the reaction by investigating additional bases other than LiO\textsubscript{t}-Bu, as we had found in our prior work that bases had a significant effect on selectivity.\textsuperscript{14,15,19} After an extensive screen of bases, we
identified that the bulky amine base, proton sponge, allowed our transformation to proceed in good yield, regio- and diastereoselectivity, but poor enantioselectivity (entry 5). In order to increase the enantioselectivity of our desired reaction, we moved to employ bulkier phosphoramidite ligand \( \text{L11} \), which led to excellent enantioselectivity, though at the expense of yield (entry 6). Ultimately, we discovered that we could improve the reaction yield, with no effect on selectivity, by increasing the amount of the inexpensive \( \text{LiCl} \) additive to 400 mol % (entry 7). This extensive fine-tuning of reaction parameters is included here as an illustrative example of how altering one reaction partner (e.g., the substituent on the electrophile) in an iridium-catalyzed allylic alkylation reaction necessitates complete reoptimization of the system.

The optimized conditions allow for a wide range of substituted tetralone nucleophiles \( \text{56} \) to undergo a highly selective iridium-catalyzed allylic alkylation reaction with crotol chloride (\( \text{57, Scheme 5.4} \)). However, at this time, the nucleophile scope is limited to \( \beta \)-ketoester-based tetralones. We postulate that this limitation is due to both pKa restrictions of the nucleophile that prevent the use of tetralones bearing other \( \alpha \)-electron withdrawing groups (e.g., nitrile, ketone; \( \text{58j} \) versus \( \text{54} \)) as well as the necessity of \( \text{sp}^2 \)-hybridized bulk at the carbonyl \( \alpha' \) position to induce selectivity. With respect to the electrophile, longer chain alkyl-substituted electrophiles result in diminished yields and selectivities, likely due to increased steric. Limitations aside, this transformation represents the first transition metal-catalyzed allylic alkylation reaction forming vicinal tertiary and all-carbon quaternary stereocenters between prochiral enolates and an alkyl-substituted electrophile. \( \text{20} \) We envision that with further exploration of new catalytic
systems that the substrate scope of this transformation can be expanded to additional alkyl-substituted electrophiles in the future.

**Scheme 5.4** Enantio- and diastereoselective iridium-catalyzed allylic alkylation reactions with crotyl chloride (57)

In order to demonstrate the synthetic utility of our enantio- and diastereoselective iridium-catalyzed allylic alkylation methodology, we carried out series of product transformations on allylic alkylation products 137 (Figure 5.4). Notably, all of these derivatizations proceed with excellent diastereoselectivity to facilitate the synthesis of complex building blocks, demonstrating the ease with which complexity can be added to these high-value products.
Figure 5.4 Select examples of diverse product transformations of enantio- and diastereoselective iridium-catalyzed allylic alkylation products 137

[a] pyrrolidine, AcOH, t-BuOMe, reflux, 95% yield; [b] Co₂(CO)₈, CH₂Cl₂, then Me₃NO⋅2H₂O, >20:1 dr, 99% yield; [c] HG-II (10 mol %), CH₂Cl₂, 40 °C, 96% yield; [d] i allylmagnesium chloride, THF, –78 °C, 71% yield, ii) HG-II, CH₂Cl₂, 81% yield, iii) K₂OsO₄, NMO, THF/H₂O, 59% yield; [e] Me₅S(O)I, NaH, DMSO, 82% yield; [f] K₂OsO₄, NMO, THF/H₂O, 65% yield.

5.3 UMPOLED IRI DIUM-CATALYZED AL LY LIC ALKY LATION REAC TIONS

After four years of expanding the limits of enantio- and diastereoselective iridium-catalyzed allylic alkylation, we became aware of another limitation in the field. Specifically, we noted that over the past two decades of iridium-catalyzed allylic alkylation research since the seminal report,⁸ the technology had been widely developed for standard reactivity patterns between electrophilic π-allyl species and nucleophilic enolate equivalents (141), carbanion equivalents (142), or heteroatoms (143, Figure
However, the application of an umpolung strategy in iridium-catalyzed allylic alkylation to stitch together two formally electrophilic species remained underexplored (144, Figure 5.5b, left). At the time, only two examples of reverse-polarity nucleophiles had been reported for this chemistry, though neither were in the carboxylic acid oxidation state which would allow for direct access to either enantioenriched amides, esters, or carboxylic acids.

Figure 5.5 Iridium-catalyzed allylic alkylation strategies

**a) Standard Iridium-Catalyzed Allylic Alkylation**

![Standard Iridium-Catalyzed Allylic Alkylation](image1)

**b) Umpolung Strategy Iridium-Catalyzed Allylic Alkylation via MAC Reagent**

![Umpolung Strategy Iridium-Catalyzed Allylic Alkylation via MAC Reagent](image2)

5.3.1 TERTIARY ALLYLIC STEREOCENTERS

With this gap in the literature noted we set forth to develop an iridium-catalyzed allylic alkylation method for accessing carboxylic acid derivatives and we identified masked acyl cyanide (MAC) reagents 67 as potential nucleophiles (Figure 5.5b, left). These MAC reagents which were developed by Nemoto and Yamamoto, and popularized by Rawal, can expel an equivalent of cyanide when exposed to acid therefore allowing them to function as acyl cyanide nucleophiles (145, Figure 5.5b, right). As acyl cyanides are highly electrophilic, the MAC reagent truly functions as a carbon monoxide
synthon (146). Thus, we envisioned that if the MAC reagent could react with an iridium-\(\pi\) allyl species to generate an alkylation product, we could use extensive literature precedent to unmask the MAC adduct and further transform the transient acyl cyanide to carboxylic acid derivatives 144 upon treatment with heteroatom nucleophiles (e.g., \(\text{H}_2\text{O}\), \(\text{RNH}_2\), \(\text{ROH}\)).\(^{24,25}\) As a result, the MAC reagent would function as each an amide, ester, and carboxylic acid synthon.

Employing our previously disclosed conditions for the iridium-catalyzed allylic alkylation of cyclic nucleophiles to form vicinal tertiary and all-carbon quaternary stereocenters,\(^{14}\) we were able to rapidly establish that the MAC reagent was a competent nucleophile in the iridium-catalyzed reaction given the judicious choice of protecting group on the hydroxyl moiety. Specifically, we found that a methoxymethyl (MOM) group (67c) was required in order to access products 71 in high yields (Scheme 5.5). We hypothesize that this protecting group is optimal due to its small steric profile as well as its potential to coordinate and be activated by the LiBr additive. Using these optimized conditions, we discovered that a range of cinnamyl-derived electrophiles, including heteroaryl-substituted allylic electrophiles, react in high yields and excellent enantioselectivities in up to gram scale to provide allylic alkylation products 71, which are amenable to the synthesis of highly desirable, enantioenriched vinylated \(\alpha\)-aryl carboxylic acid derivatives.\(^{23}\)
5.3.2 QUATERNARY ALLYLIC STEREOCENTERS\textsuperscript{26}

After having developed the iridium-catalyzed allylic alkylation chemistry for MAC nucleophile \textit{67c},\textsuperscript{23} we sought to further leverage the utility of the MAC reagents to access an even more challenging class of compounds – acyclic \(\alpha\)-quaternary carbonyl derivatives. However, our proposed allylic alkylation strategy had one major caveat, namely, enantioenriched quaternary allylic stereocenters had never been synthesized via iridium-catalyzed allylic alkylation reactions (Figure 5.6).\textsuperscript{27}

\textit{Figure 5.6} Limitations in enantioselective iridium-catalyzed allylic alkylation prior to 2017

\begin{center}
\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Nu} & \textbf{R} & \textbf{X} \\
\hline
\textit{149} & \textit{all reports} & \textit{zero reports} \\
\hline
\end{tabular}
\end{table}
\end{center}
Over the past twenty years, enantioselective iridium-catalyzed allylic alkylation reactions have been exclusively limited to those synthesizing tertiary allylic stereocenters (Figure 5.6, left). In contrast, use of a 1,1-disubstituted π-allyl to forge quaternary allylic stereocenters was unreported (Figure 5.6, right). In order to access such a geminal-disubstituted π-allyl species, a trisubstituted allylic electrophile would need to be utilized; however, this class of electrophile was predicted to be unreactive in iridium-catalyzed allylic alkylation chemistry. Literature reports have demonstrated that the reaction rates of these processes decrease with increasing substitution on the olefin of the electrophile. Therefore, we anticipated that our preliminary experiments into this research area would focus on identifying a method in which to unlock reactivity from a heretofore unreactive trisubstituted allylic electrophile (Table 5.3).

As we anticipated, application of our standard conditions for the iridium-catalyzed allylic alkylation of cyclic nucleophiles failed to invoke reactivity from trisubstituted allylic electrophile, instead returning starting material (Table 5.3, entry 1). We rationalized that we would need to explore other phosphoramidite ligand frameworks in order to identify a more reactive catalyst (entries 2 and 3). Ultimately, we identified that phosphoramidite L5, developed by Carreira, was uniquely effective in providing desired product, though in only modest yield (entry 3). In an effort to increase the yield and selectivity of the transformation, we performed an extensive investigation into alternative additives that have proven successful in promoting iridium-catalyzed allylic alkylation reactions. However, it was not until we identified the necessity of a strong Lewis acid co-catalyst to promote oxidative addition via facilitating the ionization of the carbonate leaving group from allylic electrophile that we saw
improved reactivity. Specifically, we discovered that the addition of Lewis acidic triethylborane to the reaction provided access to desired product 73 in nearly triple the conversion and excellent enantioselectivity (entry 4). Finally, we found that we could further improve reaction yield by altering the nucleophile to electrophile stoichiometry such that an excess of electrophile is present (entry 5). Of note, the \( E \)-olefin isomer of allylic electrophile 72 is required, as the \( Z \)-trisubstituted allylic electrophile gave significantly decreased yields and selectivities.

**Table 5.3 Optimization of the enantioselective synthesis of products 73 bearing allylic quaternary stereocenters**

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>67c:72</th>
<th>Additive (200 mol %)</th>
<th>Yield(^b)</th>
<th>ee (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L2</td>
<td>2:1</td>
<td>LiBr</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>L9</td>
<td>2:1</td>
<td>LiBr</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>L5</td>
<td>2:1</td>
<td>LiBr</td>
<td>12</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>L5</td>
<td>2:1</td>
<td>BEt(_3)</td>
<td>34</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>1:2</td>
<td>BEt(_3)</td>
<td>99</td>
<td>94</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.1 mmol scale. [b] \(^{1}\)H NMR yield based on internal standard. [c] Determined by chiral HPLC analysis.

While optimizing the reaction parameters for this novel transformation, we noted the importance of the guanidine base, \( 1,3,5 \)-triazabicyclo[4.4.0]dec-5-ene (TBD), on reactivity. Typically, TBD is utilized as a substoichiometric base additive to promote the
formation of an active iridicycle catalyst. However, Carreira has reported that phosphoramidite L5 does not form an iridicycle and thus a base additive is not required when employing this ligand in iridium-catalyzed allylic alkylation reactions. We postulate that in the case of our developed reaction, TBD may be serving as a labile placeholder ligand to prevent the formation of an inactive catalyst or as a base to promote the formation of a novel active iridicycle.

In looking to how this new reaction could be even further improved, we envisioned that hydrolysis of the MAC functionality of allylic alkylation product could be carried out in the same reaction vessel as the iridium-catalyzed reaction to provide direct access to the corresponding carboxylic acid in a one-pot, two-step procedure (Scheme 5.6). Moreover, we hypothesized that carboxylic acid products could be isolated in high purity after a simple acid/base work up alone, with no need for column chromatography. We were pleased to find that our hypothesis was valid and with our optimized conditions a range of acyclic α-quaternary carboxylic acids were prepared with varying substitution at the α-position. Specifically, both electron withdrawing and donating groups are well tolerated at the para and meta positions of the aryl substituent on electrophile, though diminished yields are observed for bis-meta-substituted arenes and no reactivity is observed with ortho-substituted aryl groups. With respect to the alkyl substituent (R), lengthening the n-alkyl group beyond an ethyl moiety results in poor yields, as does the use of branched alkyl substituents. Also of note, bis-alkyl-substituted allylic electrophiles do not currently fare well in this chemistry (cf., 79f).
As MAC adducts can be transformed into essentially any carboxylic acid derivative, we sought to develop additional one-pot methods to access α-quaternary esters and amides. Toward this end, we were pleased to find that MAC adduct 154 could be advanced in a one-pot fashion to a variety of esters (e.g., 82), as well as amides (e.g., 84) in moderate to high yields following cleavage of the MOM group and interception of the transient acyl cyanide by the appropriate nucleophile (Figure 5.7).
Figure 5.7 Enantioselective synthesis of acyclic α-quaternary esters 82 and amides 84

5.4 SYNTHESIS OF VICINAL ALL-CARBON QUATERNARY CENTERS VIA ENANTIOSELECTIVE IRIDIUM-CATALYZED ALLYLIC ALKYLMATION

Noting that our preparation of enantioenriched α-quaternary carboxylic acid derivatives progresses through intermediate 152, bearing vicinal tetra-substituted and quaternary centers, led us to imagine that we could utilize this iridium-catalyzed allylic alkylation methodology to synthesize highly congested vicinal all-carbon quaternary centers. In designing a nucleophile for this desired reaction, we postulated that the most facile reaction development would be achieved if the malononitrile functionality of the previously utilized MAC nucleophile 67c was kept intact and the α-substitution were not more sterically demanding than the MOM group. Indeed, our previously reported conditions for the synthesis of α-quaternary carboxylic acid derivatives using MAC reagent 67c translated directly to the reaction of methylmalononitrile (155, R^1 = Me) with trisubstituted allylic electrophile 156, though the enantioselectivity was low (Scheme 5.7). As our early work demonstrated that basic additives have pronounced effects on
selectivity, we explored the effect of base on our current reaction. Ultimately, DABCO was revealed to be uniquely effective for this transformation, providing products 157 bearing vicinal all-carbon quaternary centers in moderate to good yields and excellent enantioselectivities for a variety of substituted malononitrile nucleophiles 155 and trisubstituted allylic electrophiles 156. At this time, we believe that the DABCO increases the enantioselectivity of the transformation by allowing for increased equilibration between diastereomers of an iridium π-allyl complex by slowing the rate of nucleophilic attack.\textsuperscript{18,33}

\textbf{Scheme 5.7} Synthesis of vicinal all-carbon quaternary centers 157 via enantioselective iridium-catalyzed allylic alkylation

As we are inspired and driven by the application of our methods in complex molecule synthesis, we sought to demonstrate the feasibility of chemoselective manipulation of allylic alkylation product 157 (Figure 5.8). The olefin functionality of
157 can either be chemoselectively reduced or oxidized via ozonolysis. Furthermore, multistep procedures can be utilized to prepare densely-functionalized compounds bearing two contiguous all-carbon quaternary stereocenters, such as 103 and 104.

**Figure 5.8** Product derivatizations of iridium-catalyzed allylic alkylation products 157 bearing vicinal all-carbon quaternary centers

- **a** RhCl(PPh₃)₃, H₂ (balloon), benzene, 23 °C, 18 h, 92% yield; **b** O₃, pyridine, CH₂Cl₂, −78 °C, 4 min, 93% yield; **c** i. O₃, pyridine, CH₂Cl₂, −78 °C, 4 min, ii. p-TsOH, benzene, reflux, 18 h, 47% yield; **d** NaOH, EtOH/H₂O (1:1), 60 °C, 18 h, 38% yield, 1:11 dr; **e** i. O₃, MeOH, −78 °C, 0.5 h, ii. NaBH₄, 0 °C, 3 h, 65% yield, 1:2.5 dr.

### 5.5 CONCLUSIONS AND FUTURE OUTLOOK

Building on our group’s longstanding interest in the synthesis of enantioenriched quaternary stereocenters, we have sought to expand the limits of iridium-catalyzed allylic alkylation chemistry to encompass the synthesis of sterically congested all-carbon quaternary stereocenters. Initially, we focused on the development of enantio- and diastereoselective iridium-catalyzed allylic alkylation technology for the construction of vicinal tertiary and all-carbon quaternary stereocenters. Our work has enabled the use of both cyclic and acyclic nucleophiles, as well as alkyl-substituted allylic electrophiles in this methodology. We then shifted our attention to umpolung strategy iridium-catalyzed allylic alkylation chemistry and developed MAC reagents as nucleophiles. Continued
study of the umpolung chemistry led to the synthesis of allylic quaternary stereocenters via the use of trisubstituted allylic electrophiles in conjunction with a Lewis acid co-catalyst. Most recently, we have discovered iridium-catalyzed allylic alkylation technology that provides access to vicinal all-carbon quaternary centers.

Despite these advances by our group, as well as beautiful work from other groups in the area,\textsuperscript{13,21} this emerging field is not without limitations. While there have been extensive advances to widen the substrate scope with respect to the nucleophile partner, the allylic electrophile remains largely limited to aryl- and alkenyl-substitution, aside from our reported method for the use of crotol chloride as an electrophile.\textsuperscript{20} Most importantly though, no general method for iridium-catalyzed allylic alkylation exists. As demonstrated vide supra, even minor changes to either the nucleophile or electrophile partner necessitate complete reoptimization of the reaction parameters. Ideally, a single catalyst system will be developed in the future which enables highly selective iridium-catalyzed allylic alkylation reactions for any combination of nucleophile and electrophile.

In looking forward, we envision that the field will shift its attention to the development of enantio- and diastereoselective iridium-catalyzed allylic alkylation for the synthesis of vicinal all-carbon quaternary stereocenters; a highly challenging motif to access that has also become a holy grail for many other areas of synthetic methodology. We hope that our recent work on the synthesis of vicinal quaternary centers will inspire and enable these studies. Ultimately, we look forward to a time when the broader synthetic community embraces iridium-catalyzed allylic alkylation as an enabling and reliable technology for the synthesis of complex targets.
5.6 REFERENCES AND NOTES


Chapter 5 – Stereoselective Iridium-Catalyzed Allylic Alkylation in the Stoltz Laboratory: A Summary


(33) DABCO has been previously utilized in iridium-catalyzed allylic alkylation leading to higher yields but slower rates of reaction, see: B. P. Bondzic, A. Farwick, J. Liebich, P. Eilbracht, Org. Biomol. Chem. 2008, 6, 3723–3731.
A8.1 INTRODUCTION

First isolated in 1995, the taiwaniaquinoid natural products are a family of tricyclic diterpenoids with a unique \([6,5,6]-\)abeo-abietane skeleton (158–164, Figure A8.1).\(^1\) Since their isolation, the taiwaniaquinoids have attracted significant attention from the synthetic community, resulting in a multitude of total and formal syntheses.\(^2\) Interest in these compounds stems from their reported biological activity,\(^3\) in addition to their unique architecture containing a benzylic quaternary stereocenter. Due to the limited number of methodologies capable of installing benzylic quaternary stereocenters, only four catalytic, enantioselective syntheses of taiwaniaquinoids have been published to date.\(^2e,m,q,t\)

\(^{\dagger}\) This work was performed in collaboration with Dr. Jeffrey C. Holder. Portions of this chapter have been reproduced with permission from Shockley, S. E.;\(^2\) Holder, J. C.;\(^1\) Stoltz, B. M. Org. Lett. 2014, 16, 6362–6365 © 2014 American Chemical Society and Shockley, S. E.; Holder, J. C.; Stoltz, B. M. Org. Process Res. Dev. 2015, 19, 974–981 © 2015 American Chemical Society.
Our laboratory has a longstanding interest in the development of methods for the enantioselective synthesis of quaternary stereocenters and the application of these technologies to the synthesis of natural product targets. In 2006, our group reported the first catalytic, enantioselective total synthesis of (+)-dichroanone (159) via enantioselective palladium-catalyzed allylic alkylation (Scheme A8.1). This work featured a linear synthetic sequence, elaborating palladium-catalyzed allylic alkylation product 166 to bicyclic enone 165 by Wacker oxidation and subsequent aldol condensation. The final ring was appended by another aldol condensation, and a novel series of oxidations provided the natural product in only 11 steps.
In 2011, the Stoltz group disclosed the first enantioselective palladium-catalyzed conjugate addition methodology to form quaternary stereocenters in high yields and enantioselectivities (Figure A8.2, top). Following this report, we recognized that the β-aryl ketone motif found in these conjugate addition products mapped onto the scaffold of the taiwaniaquinoid terpene natural products, and we envisioned that a more convergent synthesis of these natural products could be achieved by employing β-aryl ketone as the key intermediate (Figure A8.2, bottom). This modified retrosynthetic analysis facilitates a highly convergent, catalytic, enantioselective key step that brings together 13 of the 19 carbon atoms of the taiwaniaquinoid tricyclic core, including the quaternary stereocenter, in a single chemical transformation. Herein, we discuss the rational design of high-yielding and highly enantioselective conjugate addition reactions of arylboronic acids that facilitate the catalytic, enantioselective formal synthesis of (+)-taiwaniaquinone H (158) and (+)-dichroanone (159) in >99% ee.

Figure A8.2 Stoltz group conjugate addition chemistry as inspiration for revised retrosynthetic analysis of (+)-taiwaniaquinone H (158) and (+)-dichroanone (159)
A8.2 BACKGROUND TO THE STOLTZ GROUP’S ENANTIOSELECTIVE PALLADIUM-CATALYZED CONJUGATE ADDITION CHEMISTRY

A8.2.1 INTRODUCTION TO ENANTIOSELECTIVE TRANSITION METAL-CATALYZED CONJUGATE ADDITION CHEMISTRY

Enantioselective conjugate addition has become a powerful synthetic tool for the assembly of structurally complex molecules. Recently, new developments in this transformation have served as solutions to the persistent challenge of the catalytic, enantioselective synthesis of all-carbon quaternary stereocenters (Scheme A8.2). To date, copper catalysis has dominated the field of enantioselective conjugate addition, however, these copper-catalyzed methods require the use of highly reactive organometallic reagents (e.g., diorganozinc, triorganoaluminum, and organomagnesium reagents). Thus, these reactions typically necessitate rigorously anhydrous reaction conditions and often operate at cryogenic temperatures. Alternatively, chiral rhodium catalysts in combination with air-stable, easily handled organoboron reagents have been shown to produce a wide array of conjugate addition adducts in very high yield and enantiomeric excess. Although extremely effective, these rhodium catalysts are expensive, air-sensitive, and many of the most widely used precatalysts are not commercially available. Additionally, rhodium-catalyzed conjugate additions to form quaternary stereocenters require boroxine or tetraarylborate reagents rather than widely available arylboronic acids. Furthermore, large excesses of the boron reagents are necessary to drive the reactions to completion. These factors diminish the appeal of such rhodium-catalyzed methods in complex molecule synthesis where custom aromatic units are often desired and thus the arene material is of high value.
Palladium-catalyzed conjugate addition reactions are less developed than those using copper and rhodium but offer significant advantages. For example, palladium-catalyzed conjugate addition reactions utilize commercially available, air-stable, and functional group-tolerant boron nucleophiles. Furthermore, the reactions are typically not sensitive to water or oxygen. Together, these features comprise an operationally simple and robust transformation. At the time the Stoltz group began our work in this area, there were only examples of the enantioselective synthesis of tertiary stereocenters in the palladium literature and a single report of the synthesis of quaternary stereocenters, albeit as a racemate. It was not until our report in 2011 that a palladium-derived catalyst was employed to construct an enantioenriched quaternary stereocenter via conjugate addition methodology. Subsequent to our studies, similar palladium-catalyzed conjugate additions to forge quaternary stereocenters were reported by Minnaard and de Vries as well as Stanley.

### INITIAL DISCOVERIES

Our initial studies involved the enantioselective conjugate addition of arylboronic acids to β-substituted carbocyclic enones to generate benzylic all-carbon quaternary stereocenters. We began these efforts by investigating the reaction of 3-
Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichoanone and (+)-Taiwaniaquinone H

methylcyclohexen-2-one (167) with phenylboronic acid (174, Scheme A8.3). Building on the precedent for bidentate, dinitrogen ligands in conjugate addition chemistry,\(^ {15,18}\) we found that a catalyst formed in situ from the combination of Pd(OOCOCF\(_3\))\(_2\) and the chiral pyridinoxazoline ligand, (S)-t-BuPyOx (L14),\(^ {19}\) proved effective in forming β-quaternary ketone product 175 in high yield and enantioselectivity. Many other ligands were examined in the course of our studies but none provided the high selectivities observed with t-BuPyOx (L14). Further optimization revealed that polar, coordinating solvents hindered the reaction while non-polar solvents provided higher conversions and superior enantioinduction. Ultimately, we found that 1,2-dichloroethane allowed for the fastest reaction times (12–24 h) with minimization of side product formation. Furthermore, we were pleased to find that the amount of phenylboronic acid could be reduced to 1.1 equivalents with no detrimental effect on the reactivity other than increased reaction times.

**Scheme A8.3** Initial Stoltz group enantioselective palladium-catalyzed conjugate addition with (S)-t-BuPyOx (L14)

\[
\begin{align*}
\text{L3} (6 \text{ mol } \%) & \quad \text{Pd(OOCOCF}_3\text{)}_2 (5 \text{ mol } \\ & \quad \text{CICH}_2\text{CH}_2\text{Cl} \\ & \quad 60 \degree \text{C, 12 h} \\ & \quad (99\% \text{ yield, 93\% ee})
\end{align*}
\]

Based on control studies, we found the reaction to be insensitive to adventitious moisture and air atmosphere as neither the high yield nor enantioselectivity were impacted upon addition of water (up to 10 equivalents) and no improvements were noted under inert gas atmospheres. Therefore, the reactions may be conducted under ambient
Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H

air in screw-top vials without the need for purification or distillation of any commercially obtained materials. Moreover, the optimal chiral ligand, (S)-t-BuPyOx (L14), can be expediently prepared on relatively large scale in two steps from readily available starting materials.20

Gratifyingly, a wide range of arylboronic acids and enones undergo highly enantioselective reactions under the developed conditions (Table A8.1). With respect to the nucleophile scope, para-substituted arylboronic acids are well tolerated. Alkyl-substituted arylboronic acids react with good yields and enantioselectivities to give products such as 4-methyl- and 4-ethyl-substituted ketones 177a and 177b. However, we noted a distinct electronic trend on selectivity, wherein electron-rich nucleophiles tend to furnish more modest yields and enantioselectivities (177c, 177d, and 177h). Conversely, arylboronic acids bearing electron-withdrawing substituents produce ketone products in excellent enantioselectivities. Specifically, the electron-poor substitution can include carbonyl (177e), trifluoromethyl (177f) or halide (177g) functional groups. Additionally, reactions involving meta-substituted nucleophiles fare well with alkyl (177i), ester (177j), halide (177k), or even nitro groups (177l) on the arylboronic acid. Notably, substituents at the 2-position of the arylboronic acid result in slower reactions and furnish diminished yields of the ketone products in low enantioselectivity (e.g., 2-methylphenylboronic acid results in 13% of its corresponding product in 22% ee). These ortho-arylboroncic acid substrates react with higher yields and enantioselectivities in the palladium-catalyzed conjugate addition manifold described by Minnaard and de Vries.16b
Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H

Table A8.1 Scope of arylboronic acid and enone conjugate acceptors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>177a</td>
<td>99%</td>
<td>87%</td>
</tr>
<tr>
<td>177b</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>177c</td>
<td>96%</td>
<td>74%</td>
</tr>
<tr>
<td>177d</td>
<td>58%</td>
<td>69%</td>
</tr>
<tr>
<td>177e</td>
<td>99%</td>
<td>96%</td>
</tr>
<tr>
<td>177f</td>
<td>99%</td>
<td>96%</td>
</tr>
<tr>
<td>177g</td>
<td>91%</td>
<td>96%</td>
</tr>
<tr>
<td>177h</td>
<td>99%</td>
<td>96%</td>
</tr>
<tr>
<td>177i</td>
<td>52%</td>
<td>82%</td>
</tr>
<tr>
<td>177j</td>
<td>91%</td>
<td>96%</td>
</tr>
<tr>
<td>177k</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>177l</td>
<td>84%</td>
<td>92%</td>
</tr>
<tr>
<td>177m</td>
<td>84%</td>
<td>92%</td>
</tr>
<tr>
<td>177n</td>
<td>85%</td>
<td>93%</td>
</tr>
<tr>
<td>177o</td>
<td>96%</td>
<td>91%</td>
</tr>
<tr>
<td>177p</td>
<td>95%</td>
<td>91%</td>
</tr>
<tr>
<td>177q</td>
<td>74%</td>
<td>91%</td>
</tr>
<tr>
<td>177r</td>
<td>86%</td>
<td>79%</td>
</tr>
<tr>
<td>177s</td>
<td>68%</td>
<td>88%</td>
</tr>
<tr>
<td>177t</td>
<td>65%</td>
<td>91%</td>
</tr>
</tbody>
</table>

[a] Reactions performed with arylboronic acid (0.50 mmol), cycloalkenone (0.25 mmol), Pd(OCOCF₃)₂ (5 mol %), and L14 (6 mol %) in ClCH₂CH₂Cl (1 mL) at 60 °C for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC.

Cyclic enones of different ring sizes, and with a range of β-substitution, react to afford enantioenriched β-quaternary ketone products (Table A8.1). Cyclohexanone products bearing both linear (177o–q) and branched β-substituents (177r and 177s) as
well as functionalized side chains (177t) are formed in good to excellent yields and selectivity from their corresponding substituted Michael acceptors. Moreover, altering the ring size has no deleterious effect on reactivity and furnishes products with five- (177m) or seven-membered (177n) cycloalkanones in high yields and enantioselectivity. To the best of our knowledge, this represents the first example of a single catalyst system that successfully constructs quaternary stereocenters via enantioselective conjugate addition to 5-, 6-, and 7-membered enones.

**A8.2.3 FURTHER REACTION DEVELOPMENT**

Following our initial communication of the construction of quaternary stereocenters by enantioselective palladium-catalyzed conjugate addition,\textsuperscript{4a} we sought to further generalize the substrate scope, reduce the catalyst loading, and lower the reaction temperature.\textsuperscript{4b} While we noted that the addition of water had no deleterious effect in our initial report, we did not consider adventitious water to be a crucial component. Thus, it came as a surprise when attempts to perform the reaction on large scale failed to fully convert enone 167 to product ketone 175. We rationalized that, on small scale, the moisture in the air and on the glassware provided sufficient water to drive the reaction to completion, however, on larger scale this trace moisture was insufficient. Analysis of the balanced equation for the overall transformation indicated that the addition of water is necessary to achieve catalyst turnover (Scheme A8.4). Thus, we found that the addition of 5 equivalents of water to the reaction mixture restored the reactivity when performing reactions on multi-gram scale. To date, reactions as large as 35 mmol scale have been successfully conducted.
Examination of deuterium incorporation in the product ketone supported our hypothesis of water’s role in catalyst turnover. In reactions performed with deuterium oxide in place of water, we found significant deuterium incorporation at the α-methylene position of the carbonyl. This observation was true in reactions run to low conversion as well. These experiments, in combination with the scalability problems encountered without water as an additive, suggested that water is the reagent assisting turnover, rather than the boron nucleophile (Scheme A8.4).

Based on literature reports detailing palladium-catalyzed conjugate addition employing cationic or dicationic precatalysts possessing weakly coordinating anions (PF$_6^-$, SbF$_6^-$, BF$_4^-$, etc.),$^{14}$ we sought to evaluate the effect of salt additives on the reaction rate with the hope of achieving milder reaction conditions (Table A8.2). At 40 °C, with no additives, the addition of phenylboronic acid to 3-methylocyclohexenone (167) is very slow and rarely goes to full conversion before the catalyst decomposes. At this same temperature, we observed that the addition of strongly coordinating anions (e.g., chloride, entry 1) shutdown the reaction while sodium salts with weakly coordinating anions greatly enhanced the reaction rate, albeit with diminished enantioselectivity (e.g., NaPF$_6$, entry 2). Other additives required extended reaction times (e.g., (n-Bu)$_4$NPF$_6$, entry 3). A larger examination of salt additives containing weakly
coordinating counterions revealed that NH₄PF₆ gave the optimal combination of short reaction time with minimized loss of enantioselectivity (entry 4). We posit that these additives alter the catalyst resting state and result in a larger percentage of dissolved palladium species in the catalytic cycle.

**Table A8.2 Effect of additives on reaction rate, yield, and enantioselectivity**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaCl</td>
<td>24</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>NaPF₆</td>
<td>6</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>(n-Bu)₄NPF₆</td>
<td>24</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>NH₄PF₆</td>
<td>12</td>
<td>96</td>
<td>91</td>
</tr>
</tbody>
</table>

[a] Reactions performed with phenylboronic acid (0.5 mmol), 167 (0.25 mmol), NH₄PF₆ (30 mol %), water (5 equiv), Pd(OCOCF₃)₂ (5 mol %), and L14 (6 mol %) in ClCH₂CH₂Cl (1 mL) at 40 °C. [b] GC yield utilizing tridecane standard. [c] Determined by chiral HPLC.

Incorporation of the optimized additives (5 equivalents water, 30 mol % NH₄PF₆) into the reaction conditions allowed for reactions to be conducted at decreased temperatures (23–40 °C) and significantly broadened the substrate scope. Many of the previously studied substrates that contained temperature-sensitive functionalities (e.g., silyl ethers) or groups that may react with trace palladium(0) formed by off-cycle pathways (e.g., arylbromides) afforded higher desired product yields under the modified conditions. For example, ketones 177k, 181a, 177l, and 181b were obtained in nearly double the yield under the new conditions (Table A8.3). Furthermore, at 40 °C the combination of additives allowed catalyst loadings of only 2.5 mol % of palladium and 3 mol % of ligand for most reactions. Moreover, the additives facilitated the reactions of
two new substrate classes: (1) β-acyl cyclic enones and (2) arylboronic acids containing nitrogen substituents. We were pleased to note that β-acyl enone substrates provided access to enantioenriched 1,4-dicarbonyl compounds, with only the olefin insertion process forming the quaternary stereocenter observed (181c–f), as opposed to the isomeric insertion products that would afford tertiary stereocenters. We also observed that aniline-derived boronic acid substrates protected with a trifluoroacetyl group did not poison the catalyst and allowed for the synthesis of heteroatom-substituted products (181e, 181g–j).
Table A8.3 Expanding substrate scope with improved reaction conditions

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>-</td>
<td>55%</td>
<td>97%</td>
</tr>
<tr>
<td>Br</td>
<td>-</td>
<td>44%</td>
<td>86%</td>
</tr>
<tr>
<td>NO2</td>
<td>-</td>
<td>40%</td>
<td>92%</td>
</tr>
<tr>
<td>F</td>
<td>-</td>
<td>32%</td>
<td>77%</td>
</tr>
<tr>
<td>Cl</td>
<td>-</td>
<td>85%</td>
<td>96%</td>
</tr>
<tr>
<td>-</td>
<td>Cl</td>
<td>66%</td>
<td>94%</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>73%</td>
<td>91%</td>
</tr>
<tr>
<td>-</td>
<td>F</td>
<td>72%</td>
<td>93%</td>
</tr>
<tr>
<td>-</td>
<td>F3C</td>
<td>75%</td>
<td>88%</td>
</tr>
<tr>
<td>OMe</td>
<td>-</td>
<td>60%</td>
<td>92%</td>
</tr>
</tbody>
</table>

[a] Blue font: reported yield and ee of the product in the absence of NH4PF6 and water, with reactions performed at 60 °C. Red font: yield and ee of the product with additives. Conditions: reactions were performed with arylboronic acid (1.0 mmol), cycloalkenone (0.5 mmol), NH4PF6 (30 mol %), water (5 equiv), Pd(OOCOCF3)2 (5 mol %), and L14 (6 mol %) in ClCH2CH2Cl (2 mL) at 40–60 °C, 12 h.

A8.2.4 MECHANISTIC HYPOTHESIS

Studies have been conducted to elucidate the catalytic cycle active in our enantioselective conjugate addition chemistry. A range of Lewis and π-acidic metal salts were substituted for palladium with no product observed, signifying that palladium-catalyzed conjugate addition is not a Lewis acid-catalyzed process. The reaction proceeds...
in the presence of mercury drops, which would poison a heterogeneous catalyst, indicating that a soluble complex likely catalyzes the reaction. Furthermore, a nonlinear effect study supported the action of a single, monomeric ML-type catalyst as the kinetically relevant species (Figure A8.3). The linear relationship between catalyst ee and product ee argues against the kinetic relevance of palladium/ligand dimers in solution, as opposed to some catalysts that are known to aggregate in reservoirs.\(^\text{15,22}\)

**Figure A8.3 Linear relationship of catalyst ee to product ee**

Density functional theory (DFT) calculations, performed in collaboration with the Houk laboratory, support the cationic catalytic cycle shown in Figure A8.4.\(^\text{4b,23}\) We postulate that the active catalyst is a cationic palladium(II) hydroxide species, which are known to undergo rapid transmetalation with arylboronic acids without added base.\(^\text{24}\) We envision that arylpalladium 183 forms by transmetalation of the arylboronic acid with cationic catalyst 182. Substrate association via the carbonyl yields an equilibrating mixture of carbonyl-bound complex 184 and olefin-bound complex 185. C-bound enolate 188 is the initial product of alkene insertion into the aryl C–Pd bond. Notably, this
insertion is calculated to be both the enantiodetermining and turnover-limiting step of the catalytic cycle. Subsequent isomerization to $O$-bound tautomer 187 followed by protonation affords the product ketone and regenerates the catalyst (182). This proposed mechanism was experimentally substantiated by a recent collaboration with the Zare laboratory in which arylpalladium cation 183 and enone complex 184/185 were identified by DESI-MS monitoring of the reaction mixture. No intermediates occurring after the predicted turnover-limiting step were observed. The observation of enone-arylpalladium complex 184 for a variety of aryloboronic acid substrates led us to hypothesize that complex 184 may be the resting state. The enantiodetermining alkene insertion step involves a four-membered cyclic transition state, with the lowest energy diastereomer calculated to be transition state 186a, which leads to the observed $(R)$-product. Diastereomer 186a is the most stable as the bulky $t$-Bu group on the ligand points away from the substrate. Analysis of the effects of substituents on the ligand at the 4-position of the oxazoline revealed that replacing the $t$-Bu functionality with smaller groups, such as $i$-Pr, $i$-Bu, or Ph, significantly reduced the selectivity. If instead the oxazoline is substituted at the 5-position practically no enantioselectivity is afforded. Electronic perturbation of the pyridine moiety of the ligand did not erode enantioselectivity, though rates were greatly changed. Therefore, enantioselectivity is primarily attributed to the ligand/substrate steric interactions.
Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H

**Figure A8.4** Proposed catalytic cycle for the enantioselective conjugate addition of arylboronic acids to cyclic enones catalyzed by the combination of Pd(OCOCF$_3$)$_2$ and (S)-t-BuPyOx (L14)

Transition state calculations suggested that stereocontrol predominantly arises from the repulsion of the $\alpha'$-methylene hydrogens on the cyclohexenone substrate with the ligand (Figure A8.5). In the disfavored diastereomeric transition state (186b), these atoms are only 2.3 Å apart and thus incur a significant energetic penalty. Consequently, replacing the CH$_2$ group with an oxygen atom (e.g., lactone 189, Figure A8.5) decreases the energy difference between the two diastereomeric transition states and leads to an observed decrease in enantioselectivity from 93% ee to 57% ee. Of note, $\alpha,\beta$-unsaturated lactone substrates afford high enantioselectivity in the enantioselective palladium-catalyzed conjugate addition described by Minnaard and de Vries.$^{16a}$
**A8.2.5 HETEROCYCLIC ACCEPTORS**

We wished to extend our conjugate addition methodology to the synthesis of stereochemically complex heterocyclic molecules. We found that the palladium-catalyzed conjugate addition of arylboronic acids to chromones and 4-quinolones delivered tertiary stereocenters in high yield and enantioselectivities across multiple heterocyclic scaffolds with a wide range of arylboronic acids (Table A8.4). While chromones\textsuperscript{27,28} and 4-quinolones\textsuperscript{29} have been successfully employed in rhodium-catalyzed conjugate addition, to our knowledge, these are the first examples of enantioselective transition metal-catalyzed conjugate additions to chromones and 4-quinolones using either palladium catalysis or arylboronic acid nucleophiles.\textsuperscript{30}

Overall, a total of 38 adducts were prepared in moderate to excellent yield and high enantioselectivity. Furthermore, the stability of the reaction components to air and moisture affords unprecedented functional group tolerance. Thus, heterocyclic products
bearing heterocyclic substitution (192c), free phenolic groups (192d), and N-substituted arenes (192b and 192f) could be obtained via the conjugate addition methodology.

**Table A8.4** Enantioselective conjugate addition of arylboronic acids to heterocyclic conjugate acceptors

![Chemical Structures]

---

[a] Reactions performed with arylboronic acid (0.50 mmol), heterocyclic acceptor (0.25 mmol), NH₄PF₆ (30 mol %), water (5 equiv), Pd(OOCOCF₃)₂ (5 mol %), and L₁⁴ (6 mol %) in ClCH₂CH₂Cl (1 mL) at 60 °C for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC.

**A8.3 RETROSYNTHETIC ANALYSIS**

The formal synthesis of (+)-taiwaniaquinone H (158) and (+)-dichroanone (159) provided an optimal forum for demonstrating the breadth and generality of our aforementioned palladium-catalyzed conjugate addition chemistry. Our preliminary
strategic disconnections of (+)-taiwaniaquinone H (158) and (+)-dichroanone (159) involved late stage introduction of the gem-dimethyl functionality and oxidation of the C-ring of enone 193 to the quinone (Figure A8.6).\textsuperscript{31,2f} In turn, the B-ring of tricycle 193 was envisioned to be established through ortho-formylation of phenol 194 and subsequent aldol condensation. Finally, we anticipated that the all-carbon quaternary stereocenter could be constructed by enantioselective palladium-catalyzed conjugate addition of 3-methyl-2-cyclohexenone (167) with an appropriate arylboronic acid 195.\textsuperscript{4}

Figure A8.6 Planned retrosynthesis of (+)-taiwaniaquinone H (158) and (+)-dichroanone (159)

\begin{equation}
\begin{array}{c}
\text{R}^2 = \text{Me, (+)-taiwaniaquinone (158)} \\
\text{R}^2 = \text{H, (+)-dichroanone (159)}
\end{array}
\end{equation}

A8.4 FIRST GENERATION ROUTE

We first selected para-acetylyphenylboronic acid 199 (Scheme A8.5) as our conjugate addition substrate. In our previous work we noted that electron-withdrawing substituents at the para-position of the arylboronic acid often afforded highly enantioenriched β-quaternary ketone products.\textsuperscript{4} A plot of the enantiomeric ratio versus the Hammett value (\(\sigma_p\)) for a variety of para-substituted phenylboronic acids demonstrates a strong positive linear correlation, \(R^2 = 0.92\) (Figure A8.7).\textsuperscript{32} The positive value of \(\rho\)
(0.81) suggests that the difference in energy between the diastereomeric transition states leading to the enantiomeric \((S)\) and \((R)\) products increases as the boronic acid becomes increasingly electron deficient. Thus, the best selectivity in the conjugate addition reaction is achieved with electron-withdrawing substituents in the \(para\)-position. Therefore, we chose to mask the isopropyl group as a methyl ketone to achieve a selective conjugate addition reaction.

**Figure A8.7** Hammett plot of \(\log_{10}(er)\) vs \(\sigma_p\) for select boronic acids in the palladium-catalyzed conjugate addition reaction

Access to \(para\)-acetylphenylboronic acid 199 began with acylation of 2,6-dihydroxyacetophenone (196) with pivaloyl chloride to provide arene 197 (Scheme A8.5). Installation of the boryl substituent was accomplished through an iridium-catalyzed C–H borylation. This reaction provided pinacol boronate ester 198 as the exclusive product in 89% yield. Empirically, we identified that protecting the \(meta\)-hydroxyl substituents with pivalate groups allowed for the highest yields in this borylation chemistry. After exhaustive exploration of deprotection conditions, we found
that treatment with diethanolamine and subsequent acid-catalyzed hydrolysis of the transesterified intermediate afforded arylboronic acid 199 in 92% yield.\textsuperscript{34} Boronic acid 199 was treated with 3-methyl-2-cyclohexenone (167) in the presence of Pd(OOCF\textsubscript{3})\textsubscript{2}, (S)-t-BuPyOx (L14), and NH\textsubscript{4}PF\textsubscript{6} at 50° C to afford enantioenriched ketone 169b in 93% yield and 94% ee.\textsuperscript{4b}

\textit{Scheme A8.5 Synthesis of acetyl conjugate addition product 169b}

With ketone 169b in hand, we turned our attention to the installation of the final carbon of the tricyclic core and completion of the B-ring. Regrettably, attempts to formylate arene 169b were unsuccessful. We rationalized that the sterically congested environment surrounding the arene C–H bonds prohibited installation of a functional group handle. Moreover, deprotection of the hydroxyl groups of ketone 169b was not facile, and required treatment with LiSEt to cleanly remove both pivaloyl groups and afford what we predicted to be resorcinol 200 (Scheme A8.6). Though HRMS data matched the molecular formula of desired resorcinol 200, the \textsuperscript{1}H NMR spectra did not
match that of a typical β-quaternary ketone conjugate addition product. We suspected that an unproductive cyclization may have occurred and sought to crystallize derivatives of ketone 202 to confirm the new structure by single crystal X-ray diffraction. Bromination and methylation of compound 202 provided bromoarene 203 as a white crystalline solid. As we suspected, a cyclization had occurred and the structure proved to be [3.2.1]bicycle 203. Thus, we were able to properly assign the structures of cyclization product 202 and arene bromination adduct 203. This X-ray structure also confirms the absolute stereochemistry imparted in enantioselective conjugate addition reactions of arylboronic acids to cyclic conjugate acceptors facilitated by the catalyst derived from the combination of (S)-t-BuPyOx (L14) and Pd(OCOCF3)2.

Scheme A8.6  Unexpected cyclization of phenolic intermediate

Cyclizations of β-aryl ketones to form [3.2.1] bicycles are rare; the few other reports of this transformation require treatment with strong Lewis\textsuperscript{35} or Brønsted acids\textsuperscript{36} at elevated temperatures. These reactions presumably operate via an electrophilic aromatic substitution mechanism. While it is possible that our noted cyclization proceeds through a
similar mechanism, we did not observe cyclization with substrates bearing protected phenols, which suggests that the hydroxyl group or phenoxide may be involved in the cyclization mechanism. This observation led us to propose that this unexpected cyclization may instead occur through a carbonyl ene or lithium phenoxide aldol reaction pathway.

A8.5 SECOND GENERATION ROUTE

As we were unable to functionalize ketone 169b without causing the undesired cyclization, we decided to redesign the arylboronic acid substrate and began examining alternative conjugate addition reactions. Removing the acetyl group would obviate the need to differentiate the benzylic carbonyl from the cyclic ketone while installing the requisite isopropyl group in the first-generation conjugate addition product 169b. We envisioned that a para-halogenated arylboronic acid derivative would allow for facile installation of the isopropyl group via cross-coupling chemistry. Additionally, based on our Hammett plot analysis, we posited that the para-halide would serve as a necessary para-electron-withdrawing group to impart high enantioselectivity in the palladium/L14 conjugate addition chemistry (Figure A8.7).\textsuperscript{4} Gratifyingly, we found that use of these boronic acids furnished products bearing para-iodo (169c), para-bromo (169d), and para-chloro (169e) arenes in high enantioselectivity and moderate to high yields (Table A8.5).
Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H

Table A8.5 Identification of a suitable conjugate addition system

<table>
<thead>
<tr>
<th>Reactions performed with boronic acid (1.5 equiv), 167 (1 equiv), NH$_4$PF$_6$ (30 mol %), water (5 equiv), Pd(OCOCF$_3$)$<em>2$ (5 mol %), and L$</em>{14}$ (6 mol %) in ClCH$_2$CH$_2$Cl at 50 °C for 12 h.</th>
<th>Isolated yield.</th>
<th>Determined by chiral HPLC or SFC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trace product</td>
<td>93% yield</td>
<td>92% ee</td>
</tr>
<tr>
<td>98% yield</td>
<td>&gt;99% ee</td>
<td></td>
</tr>
<tr>
<td>94% yield</td>
<td>&gt;99% ee</td>
<td></td>
</tr>
<tr>
<td>85% yield</td>
<td>85% ee</td>
<td></td>
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</tbody>
</table>

We consequently pursued a revised approach to the natural products via bromoarene 169d, selected both for its superior reactivity in palladium-catalyzed conjugate addition chemistry and facile cross-coupling ability. To access this intermediate, 2-bromoresorcinol 204 was converted to para-bromophenyl boronic acid derivative 207 in 73% yield over four steps (Scheme A8.7). Subsequent catalytic, enantioselective conjugate addition furnished ketone 169d in 98% yield and >99% ee.
Having installed the quaternary stereocenter, we next sought to append the isopropyl group. Attempts to directly cross-couple an isopropyl zinc reagent with bromide 169d gave an inseparable mixture of iso- and n-propyl products. The steric hindrance of the nearby pivaloyl groups thwarted our attempts to cross couple 169d with isopropenyl organometallic regents, but we ultimately achieved success using Molander’s protocol for Suzuki-Miyaura couplings of potassium isopropenyltrifluoroborane salts. Our optimized conditions (170 °C, 1 h, microwave) gave a crude mixture of both cross coupled product and mono-deprotected cross coupled product that could be stirred with tetrabutylammonium hydroxide to furnish isopropenyl phenol 208 in 70% yield (Scheme A8.8).
With a route to mono-deprotected arene 208 established, we turned our efforts once more toward the formation of the B-ring. However, despite the successful removal of one pivaloyl group, the system proved resistant to a number of metal and non-metal mediated ortho-formylations, directed ortho-metalations, and halogenations, regardless of protection of the ketone. We speculate that the failure of these efforts may again be attributed to the formidable steric environment of the arene C–H bonds.

Recognizing that significant steric hindrance would prevent the formation of the B-ring, we sought to diminish the steric environment of the arene by reductive removal of the free phenol. Activation of phenol 208 by exposure to excess perfluorobutanesulfonyl fluoride led to the generation of nonaflate 209 in 80% yield (Scheme A8.9). Subsequent hydrogenation with Pd/C simultaneously cleaved the nonaflate and reduced the isopropenyl functionality to afford isopropyl arene 210 in 72% yield. Finally, the pivaloyl group was replaced with a methyl group by one pot deprotection and methylation with LiSEt and Me₂SO₄ to provide ketone 169f in 83% yield. With the less substituted arene 169f in hand, we believed that the necessary tricycle could now be readily formed by ortho-formylation.
Concurrent with our synthetic efforts, Qin and coworkers reported a formal total synthesis of (+)-taiwaniaquinone H (158) and (+)-dichroanone (159) via enantioselective conjugate addition of (4-isopropyl-3-methyloxyphenyl)boronic acid to 3-methyl-2-cyclohexenone (167) in 85% yield and 85% ee (169f, Table A8.5) using the catalyst developed in our laboratory.\textsuperscript{2t,4a} However, Qin was unable to optimize the conjugate addition substrates to achieve yields or enantioselectivities over 85%. This result aligns well with our Hammett plot analysis; the determined linear relationship predicts an enantioselectivity of 88% for the electron-donating isopropyl group (Figure A8.7). Moreover, this study demonstrated that our common intermediate 169f could be further transformed into the taiwaniaquinoid tricyclic skeleton by ortho-formylation followed by aldol condensation. Therefore, our synthesis of ketone 169f in $>99\%$ ee constitutes a formal synthesis of (+)-taiwaniaquinone H (158) and (+)-dichroanone (159) in the highest reported enantioselectivity to date.
A8.6 CONCLUSIONS

In summary, we have completed the formal catalytic, enantioselective total syntheses of (+)-taiwaniaquinone H (158) and (+)-dichroanone (159) in 35% overall yield, starting from commercially available 2-bromoresorcinol (204). Investigation of electronic effects of arylboronic acid substituents on enantioselectivity enabled the rational design of a highly enantioselective reaction that furnished established intermediate 169f in exceptionally high yield and enantioselectivity. Additionally, an unexpected cyclization to form a [3.2.1] bicycle permitted the unambiguous determination of the absolute stereochemistry of the quaternary stereocenter installed by the palladium/L14-catalyzed conjugate addition reaction by X-ray diffraction analysis.

A8.7 EXPERIMENTAL SECTION

A8.7.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Triethylamine was distilled over CaH2 prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence.
quenching or p-anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. $^1$H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer or a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CHCl$_3$ ($\delta$ 7.26 ppm) or (CH$_3$)$_2$SO ($\delta$ 2.50 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual CDCl$_3$ ($\delta$ 77.16 ppm), (CD$_3$)$_2$SO ($\delta$ 39.52 ppm) or (CD$_3$)$_2$CO ($\delta$ 29.84 ppm). Data for $^1$H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, app = apparent. Data for $^{13}$C NMR are reported in terms of chemical shifts ($\delta$ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm$^{-1}$). High resolution mass spectra (HRMS) were obtained from an Agilent 6200 Series TOF with Agilent G1978A Multimode source in mixed ionization mode (MultiMode ESI/APCI) or from a JEOL JMS-600H in fast atom bombardment (FAB+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell, and are reported as $[\alpha]_D^T$ (concentration in g/100 mL, solvent).

**A8.7.1.1 Preparation of Known Compounds**

Previously reported methods were used to prepare ligand (S)-t-BuPyOx (L14).
A8.7.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

A8.7.2.1 General Procedure and Spectroscopic Data for the Synthesis of Resorcinol Pivaloyl Esters

2-Acetyl-1,3-phenylene bis(2,2-dimethylpropanoate) (197). An oven-dried 1 L round-bottom flask was charged with a magnetic stir bar, 2,6-dihydroxyacetophenone (10 g, 65.7 mmol, 1 equiv) and DMAP (800 mg, 6.57 mmol, 10 mol %). The flask was evacuated under vacuum and back-filled three times with argon. The solids were suspended in CH$_2$Cl$_2$ (450 mL), and NEt$_3$ (23 mL, 165 mmol, 2.5 equiv) was added, at which time the solution became homogenous and a transparent, pale yellow color was observed. The reaction solution was cooled to 0 °C in an ice/water bath and pivaloyl chloride (17 mL, 138 mmol, 2.1 equiv) was added via mechanical syringe pump addition over the course of 2 h. Slow addition is essential to maintain an internal temperature of less than 5 °C and minimize formation of side products. Upon complete addition, the ice/water bath was removed and the reaction mixture was allowed to warm to ambient temperature. After 1 h, the starting material was consumed by TLC analysis (30% acetone/hexanes, stain p-anisaldehyde), and the reaction mixture was quenched with sat. NH$_4$Cl (aq, 300 mL). The mixture was diluted with CH$_2$Cl$_2$ (400 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 100 mL) and the combined organic extracts were washed with 1M HCl (3 x 100 mL) and brine (1 x 100 mL), dried over Mg$_2$SO$_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (150 g silica gel, eluent: 20%
acetone/hexanes) to afford pivaloyl 197 as a white, crystalline solid (19.73 g, 94% yield):

\[ ^1H \text{NMR (500 MHz, CDCl}_3 \delta 7.40 \ (t, \ J = 8.3 \text{ Hz, 1H}), 6.99 \ (d, \ J = 8.2 \text{ Hz, 2H}), 2.45 \ (s, \ 3H), 1.32 \ (s, 18H); \ ^{13}C \text{NMR (125 MHz, CDCl}_3 \delta 198.7, 176.4, 147.9, 130.4, 128.6, 120.1, 39.2, 31.7, 27.1; IR (Neat Film, NaCl): 3487, 3395, 2976, 2936, 2874, 1755, 1705, 1611, 1576, 1478, 1457, 1397, 1368, 1274, 1251, 1233, 1117, 1101 cm}^{-1}; \] 

HRMS (MultiMode ESI/APCI-) \( m/z \) calc’d for C\(_{18}\)H\(_{23}\)O\(_5\) [M-H]: 319.1551, found 319.1542.

\[ \text{2-Bromo-1,3-phenylene bis(2,2-dimethylpropanoate) (205).} \] 

White, crystalline solid (3.77 g, 95% yield): \( ^1H \text{NMR (500 MHz, CDCl}_3 \delta 7.33 \ (t, \ J = 8.2 \text{ Hz, 1H}), 7.00 \ (d, \ J = 8.2 \text{ Hz, 2H}), 1.40 \ (s, 18H); \ ^{13}C \text{NMR (125 MHz, CDCl}_3 \delta 175.8, 149.9, 128.0, 120.9, 111.4, 39.6, 27.4; IR (Neat Film, NaCl): 2971, 2934, 2972, 1762, 1586, 1479, 1460, 1396, 1365, 1274, 1254, 1233, 1093, 1031, 884 cm}^{-1}; \] 

HRMS (MultiMode ESI/APCI+) \( m/z \) calc’d for C\(_{16}\)H\(_{25}\)BrNO\(_4\) [M+NH\(_4\)]\(^+\): 374.0961, found 374.0960.

\[ \text{2-Chloro-1,3-phenylene bis(2,2-dimethylpropanoate) (211).} \] 

White, crystalline solid (7.57 g, 98% yield): \( ^1H \text{NMR (500 MHz, CDCl}_3 \delta 7.28 \ (t, \ J = 8.2 \text{ Hz, 1H}), 7.03 \ (d, \ J = 8.2 \text{ Hz, 2H}), 1.40 \ (s, 18H); \ ^{13}C \text{NMR (125 MHz, CDCl}_3 \delta 175.8, 148.4, 127.0, 121.0, 121.0, 39.3, 27.1; IR (Neat Film, NaCl): 2970, 2935, 2874, 1765, 1749, 1583, 1478,} \]
Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H

1463, 14552, 1397, 1368, 1273, 1259, 1235, 1112, 1033 cm\(^{-1}\); HRMS (MultiMode ESI/APCI+) \(m/z\) calc’d for C\(_{16}H_{25}ClNO_4\) [M+NH\(_4\)]\(^+\): 330.1467, found 330.1472.

\[
\begin{align*}
\text{2-Iodo-1,3-phenylene bis(2,2-dimethylpropanoate) (212). White, crystalline solid (14.0 g, 96% yield): } & & \\
\text{1H NMR (500 MHz, CDCl}_3) \delta 7.35 (t, J = 8.1 Hz, 1H), 6.95 (d, J = 8.1 Hz, 2H), 1.42 (s, 18H); } & & \\
\text{13C NMR (125 MHz, CDCl}_3) \delta 175.9, 152.9, 129.5, 120.0, 88.0, 39.5, 27.5; } & & \\
\text{IR (Neat Film, NaCl): 2972, 2873, 1755, 1583, 1479, 1451, 1396, 1367, 1274, } & & \\
\text{1244, 1218, 1095, 1029, 967, 941, 886 cm}^{-1}\); & & \\
\text{HRMS (MultiMode ESI/APCI-) } m/z\text{ calc’d for } & & \\
\text{C}_{16}H_{20}IO_4\text{ [M-H]}^{-}: 403.0412, \text{found 403.0413.} & & 
\end{align*}
\]

A8.7.2.2 General Procedure and Spectroscopic Data for the Synthesis of Borylated Arenes

\[
\begin{align*}
\text{2-Acetyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-phenylene bis(2,2-} & & \\
\text{dimethylpropanoate) (198). In a nitrogen-filled glove box, a 500 mL round-bottom flask } & & \\
\text{with a Kontes valve was charged with a stir bar, arene 197 (16.02 g, 50.0 mmol, 1.0 } & & \\
\text{equiv), B}_2\text{Pin}_2\text{ (9.5 g, 37.5 mmol, 0.75 equiv), [Ir(cod)(OMe)]}_2\text{ (33 mg, 0.05 mmol, 0.1 } & & \\
\text{mol %), and tetramethylphenanthroline (24 mg, 0.10 mmol, 0.2 mol %). The solids were} & & 
\end{align*}
\]
suspended in THF (50 mL), and the flask was sealed and removed from the glove box. The reaction mixture was stirred in an oil bath heated at 60 °C for 45 h, at which time the reaction was complete by TLC analysis (20% acetone/hexanes, p-anisaldehyde stain). The reaction mixture was cooled to ambient temperature and filtered through a silica gel plug (50 g silica gel, eluent: acetone), and concentrated under reduced pressure. The crude reaction mixture was further purified by silica gel flash chromatography (200 g silica gel, eluent: 20% acetone/hexanes) to afford borylated 198 as an amorphous off-white solid (19.85 g, 89% yield): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38 (s, 2H), 2.43 (s, 3H), 1.33 (s, 12H), 1.32 (s, 18H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 198.8, 176.5, 147.3, 131.0, 126.0, 120.1, 84.6, 39.2, 31.5, 27.2, 25.0; IR (Neat Film, NaCl): 3509, 2981, 2935, 1766, 1707, 1482, 1459, 1405, 1396, 1354, 1331, 1259, 1212, 1147 cm$^{-1}$; HRMS (MultiMode ESI/APCI+) $m/z$ calc’d for C$_{24}$H$_{39}$BNO$_7$ [M+NH$_4$]$^+$: 463.2850, found 463.2852.

[Diagram of 2-Bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-phenylene bis(2,2-dimethylpropanoate) (206).] Amorphous off-white solid (2.04 g, 96% yield): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38 (s, 2H), 1.39 (s, 18H), 1.32 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.8, 149.5, 129.8, 126.6, 114.9, 84.6, 39.5, 27.4, 25.0; IR (Neat Film, NaCl): 2977, 1764, 1600, 1479, 1397, 1389, 1364, 1329, 1274, 1211, 1141, 1094, 1036 cm$^{-1}$;
Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H

HRMS (MultiMode ESI/APCI+) \( m/z \) calc’d for \( C_{22}H_{36}BBrNO_6 [M+NH_4]^+ \): 499.1850, found 499.1834.

![Structural diagram]

**2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-phenylene bis(2,2-dimethylpropanoate)** (213). Amorphous off-white solid (9.01 g, 99% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.41 (s, 2H), 1.38 (s, 18H), 1.33 (s, 12H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 175.9, 148.1, 128.6, 126.8, 124.1, 84.6, 39.4, 27.3, 23.0; IR (Neat Film, NaCl): 2977, 2935, 2873, 1763, 1605, 1480, 1404, 1365, 1326, 1270, 1213, 1145, 1121, 1094, 1036 cm\(^{-1}\); HRMS (MultiMode ESI/APCI+) \( m/z \) calc’d for \( C_{22}H_{36}BClNO_6 [M+NH_4]^+ \): 455.2355, found 455.2358.

![Structural diagram]

**2-Iodo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-phenylene bis(2,2-dimethylpropanoate)** (214). Amorphous off-white solid (12.5 g, 95% yield): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.30 (s, 2H), 1.41 (s, 18H), 1.32 (s, 12H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 175.9, 152.6, 131.2, 125.7, 92.3, 84.6, 39.5, 27.5, 25.0; IR (Neat Film, NaCl): 2974, 2935, 2873, 1761, 1598, 1549, 1480, 1463, 1395, 1360, 1330, 1274, 1209, 1142,
1094, 1034, 965, 900, 848 cm$^{-1}$; HRMS (MultiMode ESI/APCI) $m/z$ calc’d for C$_{22}$H$_{32}$BFIO$_6$ [M+F]: 549.1321, found 549.1337.

A8.7.2.3 General Procedure and Spectroscopic Data for the Synthesis of Boronic Acid Analogues

(4-Acetyl-3,5-bis(pivaloyloxy)phenyl)boronic acid (199). A 250 mL round-bottom flask was charged with a stir bar and pinacol boronate ester 198 (8.65 g, 19.27 mmol, 1.0 equiv). The solid was dissolved in EtOAc (250 mL), and diethanolamine (2.35 mL, 24.10 mmol, 1.25 equiv) was added with vigorous stirring. (Note: a glass pipette was cut to have a wide bore, and this wide-bored pipet was used to add the viscous diethanolamine.) Upon addition of diethanolamine, a white precipitate formed. This suspension was stirred vigorously for a further 4 h at ambient temperature, at which time the mixture was concentrated under reduced pressure. The crude white semi-solid reaction residue was suspended in Et$_2$O (300 mL) and stirred vigorously for 30 min. The suspension was then cooled to $-20$ °C in a freezer overnight. The white solid was collected by vacuum filtration, and the compound was washed with additional portions of Et$_2$O (3 x 50 mL). The collected white solid (7.38 g) was suspended in 0.5 M HCl (200 mL) and stirred vigorously. CH$_2$Cl$_2$ (ca. 50 mL) was added until the solid fully dissolved. The biphasic mixture was stirred for 12 h with extreme vigor. The mixture was then subjected to continuous extraction with boiling CH$_2$Cl$_2$ (300 mL) for 6 h. The combined organic
extracts were concentrated in vacuo and dried under high vacuum to afford boronic acid 199 as an off-white, flaky solid (6.45 g, 92% yield over two steps): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35 (s, 2H), 2.19 (s, 3H), 1.08 (s, 18H); $^{13}$C NMR (125 MHz, acetone-d$_6$) $\delta$ 198.5, 176.7, 148.1, 138.0, 131.2, 126.2, 39.5, 31.7, 27.2; IR (Neat Film, NaCl): 3446, 2975, 2359, 1751, 1700, 1653, 1635, 1558, 1540, 1480, 1456, 1407, 1340, 1247, 1100, 1038 cm$^{-1}$; HRMS (MultiMode ESI/APCI+) m/z calc’ed for C$_{18}$H$_{29}$BNO$_7$ [M+NH$_4$]$^+$: 381.2068, found 381.2061.

(4-Bromo-3,5-bis(pivaloyloxy)phenyl)boronic acid (207). Please note 2 M H$_2$SO$_4$ and THF were used in place of 0.5 M HCl and CH$_2$Cl$_2$, a continuous extraction was not required. Off-white, flaky solid (11.0 g, 82% yield over two steps): $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 7.50 (s, 2H), 1.40 (s, 18H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) $\delta$ 175.3, 148.6, 135.6, 126.3, 112.8, 38.8, 26.8; IR (Neat Film, NaCl): 3454, 3364, 2976, 2937, 2874, 1755, 1733, 1736, 1480, 1454, 1426, 1365, 1342, 1271, 1218, 1137, 1108, 1038 cm$^{-1}$; HRMS (MultiMode ESI/APCI-) m/z calc’ed for C$_{16}$H$_{22}$BBr$_2$O$_6$ [M+Br]$^-$: 477.9918, found 477.9923.
(4-Chloro-3,5-bis(pivaloyloxy)phenyl)boronic acid (215). Please note 2 M H₂SO₄ and THF were used in place of 0.5 M HCl and CH₂Cl₂, a continuous extraction was not required. Off-white, flaky solid (3.50 g, 86% yield over two steps): ¹H NMR (400 MHz, DMSO-d₆) δ 7.53 (s, 2H), 1.34 (s, 18H); ¹³C NMR (100 MHz, DMSO-d₆) δ 175.3, 147.2, 134.8, 126.3, 121.5, 38.8, 26.7; IR (Neat Film, NaCl): 3377, 2980, 1753, 1735, 1639, 1480, 1463, 1428, 1366, 1342, 1280, 1139, 1113, 1089 cm⁻¹; HRMS (MultiMode ESI/APCI-) m/z calc’d for C₁₆H₂₂BCl₂O₆ [M+Cl]⁻: 390.0928, found 390.0936.

(4-Iodo-3,5-bis(pivaloyloxy)phenyl)boronic acid (216). Please note 2 M H₂SO₄ and THF were used in place of 0.5 M HCl and CH₂Cl₂, a continuous extraction was not required. Off-white, flaky solid (4.82 g, 94% yield over two steps): ¹H NMR (500 MHz, DMSO-d₆) δ 7.37 (s, 2H), 1.37 (s, 18H); ¹³C NMR (125 MHz, DMSO-d₆) δ 175.4, 152.0, 136.5, 125.2, 92.0, 38.8, 27.0; IR (Neat Film, NaCl): 3369, 2975, 1759, 1735, 1395, 1360, 1277, 1095, 1034, 904 cm⁻¹; HRMS (MultiMode ESI/APCI-) m/z calc’d for C₁₆H₂₂BClIO₆ [M+Cl]⁻: 482.0284, found 482.0296.
A8.7.2.4 General Procedure and Spectroscopic Data for the Enantioselective Palladium-Catalyzed Conjugate Addition of Arylboronic Acids

**(R)-2-Acetyl-5-(1-methyl-3-oxocyclohexyl)-1,3-phenylene bis(2,2-dimethylpropanoate) (169b).** A 20 mL screw-top vial was charged with a stir bar, Pd(OOCF$_3$)$_2$ (25 mg, 0.075 mmol, 2.5 mol %), (S)-t-BuPyOx (18 mg, 0.099 mmol, 3 mol %), NH$_4$PF$_6$ (145 mg, 0.99 mmol, 30 mol %), and the solids were dissolved in 1,2-dichloroethane (2 mL) and stirred at ambient temperature for 5 min. Not all solids dissolved at this time. A 100 mL round bottom flask was charged with a stir bar, boronic acid 19 (1.20 g, 3.30 mmol, 1.1 equiv), and 1,2-dichloroethane (10 mL), and stirred at ambient temperature. The catalyst solution was filtered through a pipet plugged with a Kimwipe and added to the suspension of boronic acid in one portion. 3-methylcyclohexen-2-one (340 µL, 3.00 mmol, 1.0 equiv) and water (270 µL, 15 mmol, 5 equiv) were added by syringe and the flask was stirred in an oil bath heated to 50 °C for 72 h. When the starting material was consumed as determined by TLC analysis (10% acetone/hexanes, p-anisaldehyde stain), the mixture was cooled to ambient temperature and filtered through a plug of silica gel (eluent: CH$_2$Cl$_2$) and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (200 g silica gel, eluent gradient: 5% acetone/hexanes to 10% acetone/hexanes) to afford conjugate addition product 169b as a colorless oil (1.19 g, 93% yield): 94% ee; $[\alpha]_{D}^{25} = -36.1^\circ$ (c 1.85, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.91 (s, 2H), 2.77 (d, $J = 14.1$ Hz, 1H), 2.42 (s, 4H), 2.33 (t, $J = 6.8$ Hz, 2H), 2.12 (s, 1H), 1.99 – 1.84 (m, 2H), 1.82 – 1.71 (m,
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1H), 1.32 (s, 21H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 210.4, 198.5, 176.4, 151.3, 148.0, 126.5, 117.5, 52.8, 43.0, 40.8, 39.2, 37.6, 31.5, 28.9, 27.2, 27.1, 27.1, 22.0; IR (Neat Film, NaCl): 3404, 2973, 2937, 2874, 1758, 1708, 1620, 1562, 1480, 1408, 1397, 1257, 1095 cm$^{-1}$; HRMS (MultiMode ESI/APCI+) $m/z$ calc’d for C$_{25}$H$_{34}$NaO$_6$ [M+Na]$^+$: 453.2248, found 453.2234; HPLC conditions: 5% IPA, 1.0 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, $t_R$ (min): major = 6.454, minor = 6.227.

![Chemical Structure Image]

(R)-2-Bromo-5-(1-methyl-3-oxocyclohexyl)-1,3-phenylene bis(2,2-dimethylpropanoate) (169d). Please note 1.5 equiv of boronic acid were employed. Colorless solid (4.57 g, 98% yield): >99% ee; $[\alpha]^{25}_D$ $-34.5^\circ$ (c 1.41, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.93 (s, 2H), 2.76 (d, $J = 14.1$ Hz, 1H), 2.44 (d, 14.1 Hz, 1H), 2.33 (t, $J = 6.7$ Hz, 2H), 2.19 – 2.06 (m, 1H), 1.98 – 1.85 (m, 2H), 1.80 – 1.74 (m, 1H), 1.40 (s, 18H), 1.30 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 210.2, 175.8, 149.8, 149.0, 118.4, 108.9, 53.0, 42.8, 40.8, 39.6, 37.7, 28.8, 27.4, 22.1; IR (Neat Film, NaCl): 2973, 2936, 2874, 1763, 1713, 1601, 1571, 1480, 1463, 1408, 1397, 1365, 1272, 1227, 1096, 1037, 894 cm$^{-1}$; HRMS (MultiMode ESI/APCI+) $m/z$ calc’d for C$_{23}$H$_{35}$BrNO$_5$ [M+NH$_4$]$^+$: 484.1693, found 484.1693; HPLC conditions: 20% IPA, 1.0 mL/min, Chiralpak IC column, $\lambda$ = 210 nm, $t_R$ (min): major = 5.795, minor = 6.232.
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\[(R)-2\text{-Chloro-5-(1-methyl-3-oxocyclohexyl)-1,3-phenylene bis(2,2-dimethylpropanoate}}\) (169e). Please note 1.5 equiv of boronic acid were employed. Colorless solid (0.74 g, 94% yield): >99% ee; \([\alpha]^{25}\text{D} = -38.9^\circ \text{ (c } 2.59, \text{ CHCl}_3\text{)}; \text{ }^1\text{H NMR (500 MHz, CDCl}_3\text{) }\delta \text{ 6.95 (s, 2H), 2.76 (d, } J = 14.1 \text{ Hz, 1H), 2.43 (d, } J = 14.1 \text{ Hz, 1H), 2.32 (t, } J = 6.7 \text{ Hz, 2H), 2.15 – 2.06 (m, 1H), 1.98 – 1.84 (m, 2H), 1.82 – 1.71 (m, 1H), 1.38 (s, 18H), 1.30 (s, 3H); }^{13}\text{C NMR (125 MHz, CDCl}_3\text{) }\delta \text{ 210.3, 175.7, 148.2, 147.8, 118.4, 118.3, 52.8, 42.6, 40.6, 39.3, 37.5, 28.7, 27.2, 21.9; IR (Neat Film, NaCl): 2972, 2936, 2874, 2256, 1763, 1713, 1607, 1574, 1479, 1413, 1397, 1352, 1316, 1272, 1227, 1050, 1038, 895, 734 \text{ cm}^{-1}; HRMS (MultiMode ESI/APCI+) }m/z \text{ calc’d for C}_{23}\text{H}_{35}\text{ClNO}_5 [\text{M+NH}_4]^+: 440.2198, \text{ found 440.2197; SFC conditions: 3}\% \text{ IPA, 2.5 mL/min, Chiralpak AS-H column, }\lambda = 210 \text{ nm, } t_R \text{ (min): major } = 5.393, \text{ minor } = 6.285.\]

\[(R)-2\text{-Iodo-5-(1-methyl-3-oxocyclohexyl)-1,3-phenylene bis(2,2-dimethylpropanoate}}\) (169c). Please note 1.5 equiv of boronic acid were employed. Colorless solid (0.40 g, 42% yield): 92% ee; \([\alpha]^{25}\text{D} = -29.2^\circ \text{ (c } 4.47, \text{ CHCl}_3\text{)}; \text{ }^1\text{H NMR (500 MHz, CDCl}_3\text{) }\delta \text{ 6.87 (s, 2H), 2.75 (d, } J = 14.1 \text{ Hz, 1H), 2.42 (d, } J = 14.1 \text{ Hz, 1H), 2.30 (t, } J = 6.8 \text{ Hz, 2H), 2.12 – 2.06 (m, 1H), 1.92 – 1.85 (m, 2H), 1.77 – 1.72 (m, 1H), 1.40 (s, 18H), 1.28 (s, 3H); }^{13}\text{C...}
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NMR (125 MHz, CDCl₃) δ 210.4, 175.9, 152.7, 150.4, 117.6, 85.0, 52.8, 42.7, 40.7, 39.4, 37.5, 28.7, 27.4, 22.0; IR (Neat Film, NaCl): 2972, 2936, 2873, 1759, 1711, 1598, 1560, 1480, 1461, 1396, 1368, 1314, 1271, 1226, 1098, 1036, 914, 894, 754, 733 cm⁻¹; HRMS (MultiMode ESI/APCI+) m/z calc’d for C₂₃H₃₅INO₅ [M+NH₄]⁺: 532.1554, found 532.1567; HPLC conditions: 20% IPA, 1.0 mL/min, Chiralpak IC column, λ = 210 nm, tᵣ (min): major = 6.130, minor = 7.008.

A8.7.2.5 Procedures and Spectroscopic Data for Synthetic Intermediates

(R)-1-(1,3,9-Trihydroxy-5-methyl-6,7,8,9-tetrahydro-5H-5,9-methanobenzo[7]annulen-2-yl)ethanone (202). A 250 mL round-bottom flask was charged with a stir bar, flame-dried under vacuum, back-filled with argon, and charged with THF (25 mL). The solution was cooled to 0 °C in an ice/water bath and ethanethiol (0.890 mL, 12.5 mmol, 2.7 equiv) was added via syringe. n-BuLi (2.5 M solution in hexanes, 5.5 mL, 13.75 mmol, 2.97 equiv) was added dropwise, and a white precipitate was observed at the completion of the addition. DMF (25 mL) was added until the solution became homogenous and clear. The solution was allowed to stir at 0 °C for 30 min. A flame-dried, 25 mL conical flask was charged with ketone 169b (1.99 g, 4.62 mmol, 1 equiv) and DMF (10 mL). The ketone solution was transferred via cannula to the cooled, freshly-prepared solution of LiSEt dropwise over 10 min. The ice/water bath was removed and the reaction was allowed to stir and warm to ambient temperature over 30
min, at which time the starting material was consumed as determined by TLC analysis (20% EtOAc/hexanes, p-anisaldehyde stain). The reaction was quenched by addition of sat. NH₄Cl solution (aq, 50 mL), diluted with CH₂Cl₂ (200 mL) and water (200 mL) and transferred to a separatory funnel. 1M HCl (aq) was added until the aqueous layer was pH 2–4. The aqueous layer was extracted with CH₂Cl₂ (5 x 50 mL) and the combined organic extracts were washed with water (7 x 50 mL), brine (1 x 50 mL), dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography (90 g silica gel, eluent gradient: 10% EtOAc/hexanes to 20% EtOAc/hexanes) to afford tricycle 202 as a pale yellow oil (1.15 g, 95% yield): [α]²⁵_D – 19.0° (c 0.26, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 13.30 (s, 1H), 8.30 (s, 1H), 6.23 (d, J = 1.9 Hz, 1H), 2.71 (s, 3H), 2.58 (bs, 1H), 2.12 (ddd, J = 9.5, 2.9, 2.2 Hz, 1H), 2.01–1.89 (m, 1H), 1.76 – 1.59 (m, 3H), 1.48 – 1.32 (m, 2H), 1.31 (s, 3H), 1.03 – 0.81 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 204.9, 165.8, 156.1, 154.4, 118.8, 109.1, 102.4, 82.3, 59.0, 45.7, 35.4, 34.5, 33.2, 22.9, 21.4; IR (Neat Film, NaCl): 3338, 2934, 2867, 1641, 1588, 1435, 1375, 1324, 1270, 1243, 1124, 1055, 1027, 973, 839 cm⁻¹; HRMS (MultiMode ESI/APCI+) m/z calc’d for C₁₅H₁₉O₄ [M+H]⁺: 263.1278, found 263.1272.

(R)-1-(4-Bromo-1,3,9-trihydroxy-5-methyl-6,7,8,9-tetrahydro-5H-5,9-methanobenzo[7]annulen-2-yl)ethanone (217). A 50 mL, flame-dried, round-bottom flask was charged with a stir bar, tricycle 202 (110 mg, 0.419 mmol, 1 equiv) and
dibromodimethylhydantoin (151 mg, 0.461 mmol, 1.1 equiv). The flask was evacuated under vacuum and back-filled with argon, and the solids were dissolved in CH$_2$Cl$_2$ (5 mL) and stirred at ambient temperature. After 30 min, an aliquot was partitioned between EtOAc (1 mL) and sat. Na$_2$S$_2$O$_3$ (aq, 1 mL), and the organic layer was subjected to LCMS analysis, where no starting material was observed. The red-colored reaction was quenched by the addition of 20% Na$_2$S$_2$O$_3$ solution (aq, 20 mL) and stirred vigorously for 3 h, until the orange/red color was no longer observed. The mixture was partitioned between CH$_2$Cl$_2$ (20 mL) and water (20 mL) and transferred to a separatory funnel. 1M HCl was added until the aqueous layer was pH 3. The aqueous layer was extracted with CH$_2$Cl$_2$ (5 x 25 mL) and the combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (12 g silica gel, eluent gradient: 10% EtOAc/hexanes to 25% EtOAc/hexanes) to afford bromo arene **217** as a yellow, semi-crystalline solid (92 mg, 66% yield): $[\alpha]_{D}^{25} -20.8^\circ$ (c 1.26, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 13.37 (s, 1H), 9.10 (s, 1H), 2.74 (s, 3H), 2.55 (s, 1H), 2.22 (ddd, $J = 9.7, 3.0, 2.2$ Hz, 1H), 1.93 (ddd, $J = 11.2, 6.2, 3.0$ Hz, 1H), 1.75 – 1.64 (m, 4H), 1.61 (s, 3H), 1.35 (td, $J = 13.0, 5.5$ Hz, 1H), 0.96 – 0.80 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 204.5, 154.3, 151.9, 120.2, 110.2, 109.9, 97.9, 81.4, 59.1, 48.8, 34.4, 33.1, 33.0, 24.6, 21.6; IR (Neat Film, NaCl): 3381, 2936, 2852, 1631, 1566, 1415, 1373, 1326, 1274, 1233 cm$^{-1}$; HRMS (MultiMode ESI/APCI-) $m/z$ calc’d for C$_{15}$H$_{16}$BrO$_4$ [M-H]$^-$: 339.0237, found 339.0230.
(R)-1-(4-Bromo-9-hydroxy-1,3-dimethoxy-5-methyl-6,7,8,9-tetrahydro-5H-5,9-methanobenzo[7]annulen-2-yl)ethanone (203). A flame-dried 20 mL vial was charged with a stir bar, bromo-diphenol 217 (92 mg, 0.270 mmol, 1 equiv), Cs$_2$CO$_3$ (194 mg, 0.595 mmol, 2.2 equiv), and acetone (5 mL). The vial was stirred under argon atmosphere at ambient temperature, and methyl iodide (0.037 mL, 0.595 mmol, 2.2 equiv) was added in one portion. The yellow reaction slurry was stirred for 40 h at ambient temperature, at which time the color had faded to a white slurry and the starting material was consumed as determined by TLC analysis (20% EtOAc/hexanes, p-anisaldehyde stain). The reaction was quenched with sat. NH$_4$Cl solution (aq, 5 mL) and stirred for 12 h at ambient temperature. The reaction was diluted with EtOAc (10 mL) and water (10 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over MgSO$_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (12 g silica gel, eluent gradient 10% EtOAc/hexanes to 20% EtOAc/hexanes) to afford 203 as a clear oil that solidified to an amorphous white solid upon standing (62 mg, 63% yield): $[\alpha]^{25}_D$ $–5.8^\circ$ \( (c \ 0.73, \text{CHCl}_3) \); $^1$H NMR (500 MHz, CDCl$_3$) δ 3.81 (s, 3H), 3.80 (s, 3H), 2.56 (s, 3H), 2.24 (dt, $J = 10.1, 2.5$ Hz, 1H), 1.84 – 1.71 (m, 2H), 1.71 – 1.61 (m, 4H), 1.60 (s, 3H), 1.35 (td, $J = 12.9, 5.8$ Hz, 1H), 0.81 – 0.67 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.8, 153.9, 151.0, 148.1, 135.9, 130.5,
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108.9, 79.7, 63.9, 63.1, 58.6, 48.0, 36.7, 33.2, 32.6, 25.1, 21.6; IR (Neat Film, NaCl):
3429, 2938, 2853, 1704, 1642, 1590, 1450, 1382, 1323, 1237, 1120, 1077 cm\(^{-1}\); HRMS (MultiMode ESI/APCI+) \(m/z\) calc’d for C\(_{17}\)H\(_{22}\)BrO\(_4\) [M+H]\(^+\): 369.0696, found 369.0690.

\[(R)-3\text{-Hydroxy-5-(1-methyl-3-oxocyclohexyl)-2-(prop-1-en-2-yl)phenyl pivalate}\] (208). Four 20 mL microwave vials were each charged with a stir bar, ketone 169d (0.594 g, 1.27 mmol, 1 equiv), potassium isopropenyltrifluoroborate (281 mg, 1.91 mmol, 1.25 equiv), \(K_2\text{CO}_3\) (263 g, 1.91 mmol, 1.5 equiv), PPh\(_3\) (33 mg, 0.127 mmol, 10 mol %), and Pd(OAc)\(_2\) (14 mg, 0.0635 mmol, 5 mol %), and capped with a microwave septum top. The vials were evacuated with vacuum and back-filled with argon three times. The solids were suspended in degassed dioxane/H\(_2\)O (9:1 ratio, 20 mL) before the reaction was stirred in the microwave reactor for 1 h at 170 °C on very high absorbance mode. The mixture was cooled to ambient temperature and filtered through a plug of silica gel (eluent: EtOAc) and concentrated under reduced pressure to afford a brown oil.

A 100 mL round-bottom flask was charged with the combined crude reaction residues, a stir bar, Bu\(_4\)NOH (4.7 mL, 7.15 mmol, 2.4 equiv), and dioxane/H\(_2\)O (9:1 ratio, 50 mL). The reaction was stirred at ambient temperature for 10 h, at which point the starting material was consumed as determined by TLC analysis (20% EtOAc/hexanes, \(p\)-anisaldehyde stain). The reaction was quenched with sat. NH\(_4\)Cl (aq, 25 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 x 100
mL), and the combined organic extracts were washed with brine (1 x 100 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (50 g silica gel, eluent gradient: 10% EtOAc/hexanes to 20% EtOAc/hexanes) to afford isopropenyl 208 as a yellow oil (1.23 g, 70% yield over 2 steps): [α]²⁵ D −37.4° (c 1.26, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.79 (d, J = 1.8 Hz, 1H), 6.53 (d, J = 1.8 Hz, 1H), 5.52 (s, 1H), 5.43 (s, 1H), 5.04 (s, 1H), 2.79 (d, J = 14.1 Hz, 1H), 2.41 (d, J = 14.1 Hz, 1H), 2.32 (t, J = 6.7 Hz, 2H), 2.14 – 2.08 (m, 1H), 2.00 (s, 3H), 1.91 – 1.84 (m, 2H), 1.83 – 1.73 (m, 1H), 1.31 (s, 9H), 1.29 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 211.0, 176.8, 152.9, 149.1, 148.7, 138.1, 121.3, 119.3, 111.9, 110.3, 53.2, 42.8, 40.9, 39.2, 37.8, 29.0, 27.3, 23.6, 22.2; IR (Neat Film, NaCl): 3418, 3083, 2970, 2874, 1712, 1620, 1480, 1414, 1368, 1316, 1278, 1230, 1122, 1073, 1035, 1017, 943, 901, 758 cm⁻¹; HRMS (MultiMode ESI/APCI-) m/z calc’d for C₂₁H₂₇O₄ [M-H]⁺: 343.1915, found 343.1926.

(R)-5-(1-Methyl-3-oxocyclohexyl)-3-(perfluorobutoxy)-2-(prop-1-en-2-yl)phenyl pivalate (209). A 15 mL, flame-dried, round-bottom flask was charged with a stir bar, phenol 208 (165 mg, 0.479 mmol, 1 equiv) and DMAP (3 mg, 0.024 mmol, 5 mol%). The flask was evacuated under vacuum and back-filled with argon three times. The solids were dissolved in CH₂Cl₂ (5 mL), and NEt₃ (1.34 mL, 9.58 mmol, 20 equiv) was added. Perfluorobutanesulfonyl fluoride (1.72 mL, 9.58 mmol, 20 equiv) was then added
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dropwise and the resulting solution was stirred at ambient temperature for 18 h, at which time the starting material was consumed as determined by TLC analysis (30% EtOAc/hexanes, p-anisaldehyde stain). The mixture was washed with water (10 mL) and brine (10 mL), and the organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9 g silica gel, gradient: 10% EtOAc/hexanes) to afford nonaflate 209 as a colorless oil (0.2694 g, 80% yield): $[\alpha]^{25}_D$ –22.1° (c 1.31, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.12 (d, $J = 1.8$ Hz, 1H), 7.00 (d, $J = 1.9$ Hz, 1H), 5.39 (t, $J = 1.2$ Hz, 1H), 5.00 (t, $J = 1.2$ Hz, 1H), 2.76 (d, $J = 14.0$ Hz, 1H), 2.47 (d, $J = 14.0$ Hz, 1H), 2.35 (t, $J = 6.8$ Hz, 2H), 2.19 – 2.05 (m, 1H), 2.00 (s, 3H), 1.99 – 1.87 (m, 2H), 1.86 – 1.74 (m, 1H), 1.32 (s, 9H), 1.31 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.1, 176.7, 149.5, 149.5, 147.3, 135.1, 129.6, 120.3, 120.3, 117.0, 116.4, 114.3, 109.9, 108.0, 52.9, 42.9, 40.8, 39.2, 37.6, 28.8, 27.2, 23.1, 22.0; $^{19}$F (376 MHz, CDCl$_3$) δ -80.94 (t, $J = 9.9$ Hz, 3F), -109.86 (t, $J = 14.0$ Hz, 2F), -121.04 – -120.86 (m, 2F), -126.04 (dt, $J = 13.9$, 13.5, 4.9 Hz, 2F). IR (Neat Film, NaCl): 2971, 2877, 1759, 1720, 1649, 1623, 1553, 1482, 1427, 1353, 1240, 1200, 1145, 1107, 1032, 1011, 985, 944, 922 cm$^{-1}$. HRMS (FAB+) m/z calc’d for C$_{25}$H$_{28}$F$_9$O$_6$S [M+H]$^+$: 627.1457, found 627.2216.

(R)-2-Isopropyl-5-(1-methyl-3-oxocyclohexyl)phenyl pivalate (210). A 25 mL Schlenk flask was charged with a stir bar, nonaflate 209 (62.1 mg, 0.110 mmol, 1 equiv), 10%
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Pd/C (62.1 mg, equal weight to that of the nonaflate), Et₃N (38 µL, 0.276 mmol, 2.5 equiv), and MeOH (5 mL). The reaction mixture was degassed then back-filled with H₂ gas (1 atm) using Schlenk technique. The flask was sealed and stirred in an oil bath heated to 65 °C for 11 h. The mixture was cooled to ambient temperature, filtered through a silica gel plug (10 g silica gel, eluent: EtOAc) and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (9 g silica gel, eluent: 5% EtOAc/hexanes) to afford pivaloyl 209 as a colorless oil (26.4 mg, 72% yield): [α]²⁵_D −41.4° (c 1.30, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.2, 2.1 Hz, 1H), 6.90 (d, J = 2.1 Hz, 1H), 3.13 (p, J = 6.9 Hz, 1H), 2.84 (d, J = 14.1 Hz, 1H), 2.45 (d, J = 14.2 Hz, 1H), 2.33 (t, J = 6.7 Hz, 2H), 2.19 – 2.12 (m, 1H), 1.99 – 1.84 (m, 2H), 1.84 – 1.70 (m, 1H), 1.41 (s, 9H), 1.32 (s, 3H), 1.21 (d, J = 6.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 211.4, 177.2, 148.6, 146.5, 138.0, 126.5, 123.3, 119.5, 53.2, 42.6, 40.9, 39.3, 37.9, 29.3, 27.4, 27.1, 23.0, 22.9, 22.2; IR (Neat Film, NaCl): 2963, 2872, 1750, 1714, 1619, 1504, 1462, 1410, 1365, 1276, 1229, 1160, 1120, 1055, 1030, 932, 904 cm⁻¹; HRMS (MultiMode ESI/APCI+) m/z calc’d for C₂₁H₃₄NO₃ [M+NH₄]⁺: 348.2533, found 348.2518.

(R)-3-(4-Isopropyl-3-methoxyphenyl)-3-methylocyclohexane-1-one (169f). A 25 mL round bottom flask was charged with a stir bar, flame-dried under vacuum, back-filled with argon, and charged with THF (2 mL). The solution was cooled to 0 °C in an
ice/water bath and ethanethiol (57 µL, 0.787 mmol, 10 equiv) was added via syringe. n-BuLi (2.5 M solution in hexanes, 322 µL, 0.802 mmol, 10.2 equiv) was added dropwise, and a white precipitate was observed at the completion of the addition. The solution was allowed to stir at 0 °C for 1 h. A flame-dried 15 mL conical flask was charged with pivaloyl 210 (26.0 mg, 0.079 mmol, 1 equiv) and DMF (1 mL). The ketone solution was transferred via cannula to the cooled, freshly-prepared solution of LiSEt dropwise over 5 min. The ice/water bath was removed and the reaction was stirred in an oil bath heated to 45 °C for 6 h, at which time the starting material was consumed as determined by TLC analysis (30% EtOAc/hexanes, p-anisaldehyde stain). Me$_2$SO$_4$ (112 µL, 1.185 mmol, 15 equiv) was added to the reaction mixture and stirred at 45 °C for an additional 15 min, at which time the reaction was complete as determined by TLC analysis (30% EtOAc/hexanes, p-anisaldehyde stain). The reaction was quenched with NH$_4$OH (aq, 5 mL) and stirred at 45 °C for another 15 min then diluted with H$_2$O (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL), dried with MgSO$_4$ and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography (9 g silica gel, eluent: 2.5% EtOAc/hexanes) to afford key intermediate 169f as a colorless oil (17.0 mg, 83 % yield): $[\alpha]^{25}_D$ –60.4$^\circ$ (c 1.49, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.14 (d, $J$ = 8.0 Hz, 1H), 6.86 (dd, $J$ = 8.0, 1.9 Hz, 1H), 6.78 (d, $J$ = 1.9 Hz, 1H) 3.82 (s, 3H), 3.26 (p, $J$ = 6.9 Hz, 1H), 2.87 (d, $J$ = 14.2 Hz, 1H), 2.43 (d, $J$ = 14.1 Hz, 1H), 2.31 (t, $J$ = 6.8 Hz, 2H), 2.20 – 2.14 (m, 1H), 1.93 – 1.82 (m, 2H), 1.72 – 1.62 (m, 1H), 1.33 (s, 3H), 1.19 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 211.8, 156.8, 146.1, 134.9, 126.1, 117.8, 108.3, 55.5, 53.4, 43.0, 41.0, 38.3, 30.1, 26.6, 22.8, 22.2; IR (Neat Film, NaCl): 2958, 2869, 1713, 1611, 1573, 1504, 1462, 1409, 1350, 1305, 1254, 1240, 1164,
1092, 1038, 920 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for C\(_{17}H_{24}O_2\) [M]: 260.1776, found 260.1782.

### A8.7.2.6 Determination of Enantiomeric Excess

*Please note* racemic products were synthesized using racemic i-Pr-PyOx.

**Table A8.6 Determination of enantiomeric excess**

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<tr>
<th>Entry</th>
<th>Product</th>
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<th>Retention time of major isomer (min)</th>
<th>Retention time of minor isomer (min)</th>
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<td>1</td>
<td><img src="structure1.png" alt="Structure" /></td>
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<td><img src="structure2.png" alt="Structure" /></td>
<td>HPLC Chiralpak IC 20% IPA in hexanes isocratic, 1.0 mL/min</td>
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<td>3</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>SFC Chiralpak AS-H 3% IPA in hexanes isocratic, 2.5 mL/min</td>
<td>5.393</td>
<td>6.285</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>HPLC Chiralpak IC 20% IPA in hexanes isocratic, 1.0 mL/min</td>
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## Hammett Plot Data\textsuperscript{a,b}

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<th>er</th>
<th>$\log_{10}(er)$</th>
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<tr>
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### REFERENCES AND NOTES


Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H

Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H


Appendix 8 – A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone and (+)-Taiwaniaquinone H


(13) A paper describing the use of Rh-OlefOX (olefin-oxazoline) complex provided a single example of a phenylboronic acid addition to 3-methylcyclohexen-2-one (e.g., $167 + 174 \rightarrow 175$). However, ketone 175 was isolated in only 36% yield and 85% ee, see: Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew Chem. Int. Ed.* **2010**, *49*, 1143–1146.


(23) All calculations were performed with Gaussian 03. Frisch, M. J.; et al. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.


(25) Our initial hypothesis concerning the reaction mechanism was well informed by the seminal work of Miyaura, see: Nishitaka, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317–4324.


(32) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195. Red crosses in Figure A8.7 are interpolated from the linear least square regression using the known Hammett values (σp) for para-Br and para-iPr.


APPENDIX 9

Spectra Relevant to Appendix 8:

A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone

and (+)-Taiwaniaquinone H
Figure A9.1 ¹H NMR (500 MHz, CDCl₃) of compound 169b
Figure A9.2 Infrared spectrum (Thin Film, NaCl) of compound 169b

Figure A9.3 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 169b
Figure A9.4 $^1$H NMR (500 MHz, $CDCl_3$) of compound 169c
Figure A9.5 Infrared spectrum (Thin Film, NaCl) of compound 169c

Figure A9.6 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 169c
Figure A9.7 $^1$H NMR (500 MHz, CDCl$_3$) of compound 169d
Figure A9.8 Infrared spectrum (Thin Film, NaCl) of compound 169d

Figure A9.9 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 169d
Figure A9.10 $^1$H NMR (500 MHz, CDCl$_3$) of compound 169e
Figure A9.11 Infrared spectrum (Thin Film, NaCl) of compound 169e

Figure A9.12 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 169e
Figure A9.13 $^1$H NMR (500 MHz, CDCl$_3$) of compound 169f
Figure A9.14 Infrared spectrum (Thin Film, NaCl) of compound 169f

Figure A9.15 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 169f
Figure A9.16: $^1$H NMR (500 MHz, CDCl$_3$) of compound 197
Figure A9.17 Infrared spectrum (Thin Film, NaCl) of compound 197

Figure A9.18 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 197
Figure A9.19 \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) of compound 198
Figure A9.20 Infrared spectrum (Thin Film, NaCl) of compound 198

Figure A9.21 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 198
Figure A9.22 $^1$H NMR (500 MHz, CDCl$_3$) of compound 199
Figure A9.23 Infrared spectrum (Thin Film, NaCl) of compound 199

Figure A9.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 199
Figure A9.25 $^1$H NMR (500 MHz, CDCl$_3$) of compound 202
Figure A9.26 Infrared spectrum (Thin Film, NaCl) of compound 202

Figure A9.27 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 202
Figure A9.28 $^1$H NMR (500 MHz, CDCl$_3$) of compound 203
Figure A9.29 Infrared spectrum (Thin Film, NaCl) of compound 203

Figure A9.30 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 203
Figure A9.31 $^1$H NMR (500 MHz, CDCl$_3$) of compound 205
Figure A9.32 Infrared spectrum (Thin Film, NaCl) of compound 205

Figure A9.33 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 205
Figure A9.34 $^1$H NMR (500 MHz, CDCl$_3$) of compound 206

$\text{Pi}O$  \[ \text{Br} \]
$\text{O}\text{Piv}$
Figure A9.35 Infrared spectrum (Thin Film, NaCl) of compound 206

Figure A9.36 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 206
Figure A9.37 $^1$H NMR (500 MHz, CDCl$_3$) of compound 207
Figure A9.38 Infrared spectrum (Thin Film, NaCl) of compound 207

Figure A9.39 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 207
Figure A9.40 $^1$H NMR (500 MHz, CDCl$_3$) of compound 208
**Figure A9.41** Infrared spectrum (Thin Film, NaCl) of compound 208

**Figure A9.42** $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 208
Figure A9.43  $^1$H NMR (500 MHz, CDCl$_3$) of compound 209
Figure A9.44 Infrared spectrum (Thin Film, NaCl) of compound 209

Figure A9.45 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 209
Figure A9.46 $^{19}$F vs $^{13}$C HSQC NMR (376 MHz, CDCl$_3$) of compound 209
Figure A9.47 $^1$H NMR (500 MHz, CDCl$_3$) of compound 210
Figure A9.48 Infrared spectrum (Thin Film, NaCl) of compound 210

Figure A9.49 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 210
Figure A9.50 $^1$H NMR (500 MHz, CDCl$_3$) of compound 211
Appendix 9 – Spectra Relevant Appendix 8

**Figure A9.51** Infrared spectrum (Thin Film, NaCl) of compound 211

**Figure A9.52** $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 211
Figure A9.53 $^1$H NMR (500 MHz, CDCl$_3$) of compound 212
Figure A9.54 Infrared spectrum (Thin Film, NaCl) of compound 212

Figure A9.55 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 212
Figure A9.56 $^1$H NMR (500 MHz, CDCl$_3$) of compound 213
Figure A9.57 Infrared spectrum (Thin Film, NaCl) of compound 213

Figure A9.58 $^{13}$C NMR (125 MHz, CDCl₃) of compound 213
Figure A9.59 $^1$H NMR (500 MHz, CDCl$_3$) of compound 214
Figure A9.60 Infrared spectrum (Thin Film, NaCl) of compound 214

Figure A9.61 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 214
Figure A9.62 $^1$H NMR (500 MHz, CDCl$_3$) of compound 215
Figure A9.63 Infrared spectrum (Thin Film, NaCl) of compound 215

Figure A9.64 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 215
Figure A9.65 $^1$H NMR (500 MHz, CDCl$_3$) of compound 216
**Figure A9.66** Infrared spectrum (Thin Film, NaCl) of compound 216

**Figure A9.67** $^{13}$C NMR (125 MHz, CDCl₃) of compound 216
Figure A9.68 $^1$H NMR (500 MHz, CDCl$_3$) of compound 217
Figure A9.69 Infrared spectrum (Thin Film, NaCl) of compound 217

Figure A9.70 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 217
APPENDIX 10

X-Ray Crystallography Reports Relevant to Appendix 8:

A Catalytic, Enantioselective Formal Synthesis of (+)-Dichroanone

and (+)-Taiwaniaquinone
A10.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker D8 Venture Kappa Duo Photon 100 CMOS diffractometer.

A10.1.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF UNDESIRED TRICYCLE 203

Undesired tricycle 203 was recrystallized by slow evaporation of CH₂Cl₂ and hexanes to provide crystals suitable for X-ray analysis.

Figure A10.1 X-ray crystal structure of undesired tricycle 203

Table A10.1 Crystal data and structure refinement for undesired tricycle 203

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Crystal system

Monoclinic

Space group

C 1 2 1

Unit cell dimensions

a = 18.8295(9) Å  
a = 90°.
b = 7.8451(4) Å  
b = 95.208(2)°.
c = 11.4443(5) Å  
g = 90°.

Volume

1683.56(14) Å³

Z

4

Density (calculated)

1.528 Mg/m³

Absorption coefficient

2.464 mm⁻¹

F(000)

800

Crystal size

0.43 x 0.42 x 0.29 mm³

Theta range for data collection

1.787 to 48.826°.

Index ranges

-39≤h≤39, -16≤k≤16, -22≤l≤24

Reflections collected

78240

Independent reflections

16574 [R(int) = 0.0370]

Completeness to theta = 25.000°

99.8 %

Absorption correction

Semi-empirical from equivalents

Max. and min. transmission

0.5777 and 0.4462

Refinement method

Full-matrix least-squares on F²

Data / restraints / parameters

16574 / 1 / 299

Goodness-of-fit on F²

0.966

Final R indices [I>2sigma(I)]

R1 = 0.0256, wR2 = 0.0521

R indices (all data)

R1 = 0.0344, wR2 = 0.0538

Absolute structure parameter

0.0289(17)

Extinction coefficient

n/a

Largest diff. peak and hole

0.653 and -0.707 e.Å⁻³
Table A10.2 Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for 203. $U(eq)$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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### Table A10.3 Bond lengths [Å] and angles [°] for 203

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C(7)-C(8)-H(8B) 100.8(11)
H(8A)-C(8)-H(8B) 108.1(15)
C(9)-C(8)-C(7) 112.54(7)
C(9)-C(8)-H(8A) 111.3(9)
C(9)-C(8)-H(8B) 113.4(11)
C(8)-C(9)-H(9A) 112.7(10)
C(8)-C(9)-H(9B) 107.0(11)
H(9A)-C(9)-H(9B) 102.1(15)
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C(10)-C(9)-H(9A) 107.8(11)
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C(7)-C(12)-H(12A) 110.7(10)
C(7)-C(12)-H(12B) 108.1(9)
C(11)-C(12)-H(12A) 111.6(10)
C(11)-C(12)-H(12B) 112.1(9)
H(12A)-C(12)-H(12B) 111.5(14)
O(1)-C(13)-H(13A) 108.7(14)
O(1)-C(13)-H(13B) 112.7(11)
O(1)-C(13)-H(13C) 109.0(12)
H(13A)-C(13)-H(13B) 105.4(18)
H(13A)-C(13)-H(13C) 106.8(17)
H(13B)-C(13)-H(13C) 113.8(16)
O(2)-C(14)-C(4) 120.71(9)
O(2)-C(14)-C(15) 122.24(9)
Appendix 10 – X-Ray Crystallography Reports Relevant to Appendix 8

C(15)-C(14)-C(4)  117.05(8)
C(14)-C(15)-H(15A)  106.0(16)
C(14)-C(15)-H(15B)  108.4(13)
C(14)-C(15)-H(15C)  110.2(13)
H(15A)-C(15)-H(15B)  102(2)
H(15A)-C(15)-H(15C)  120(2)
H(15B)-C(15)-H(15C)  109.7(18)
O(3)-C(16)-H(16A)  112.2(11)
O(3)-C(16)-H(16B)  110.1(12)
O(3)-C(16)-H(16C)  102.7(17)
H(16A)-C(16)-H(16B)  111.1(18)
H(16A)-C(16)-H(16C)  110(2)
H(16B)-C(16)-H(16C)  110.8(19)
C(11)-C(17)-H(17A)  113.8(12)
C(11)-C(17)-H(17B)  105.1(16)
C(11)-C(17)-H(17C)  114.3(10)
H(17A)-C(17)-H(17B)  103.5(19)
H(17A)-C(17)-H(17C)  102.8(16)
H(17B)-C(17)-H(17C)  117.1(19)
H(5A)-O(5)-H(5B)  108(5)

Table A10.4 Anisotropic displacement parameters (Å² x 10³) for 203. The anisotropic displacement factor exponent takes the form: -2π² [h² a*²U¹¹ + ... + 2hka*b*U¹²]
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Table A10.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 203
## Table A10.6 Torsion angles [°] for 203

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Table A10.7 Hydrogen bonds for 203 [Å and °]

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</tr>
<tr>
<td>C(16)-H(16B)...O(4)</td>
<td>0.97(2)</td>
<td>2.54(2)</td>
<td>3.1572(13)</td>
<td>121.7(15)</td>
</tr>
<tr>
<td>O(5)-H(5A)...O(2)</td>
<td>0.83(4)</td>
<td>2.18(4)</td>
<td>2.8176(15)</td>
<td>133(3)</td>
</tr>
<tr>
<td>O(5)-H(5B)...O(5)#3</td>
<td>0.93(8)</td>
<td>1.80(7)</td>
<td>2.678(3)</td>
<td>155(8)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,y-1/2,-z+1  #2 x-1/2,y+1/2,z  #3 -x+1,y,-z+1
APPENDIX 11

Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy†

A11.1 INTRODUCTION AND BACKGROUND

The widespread prevalence of spirocycles in biologically active molecules has inspired the development of many methods for the synthesis1 and, more recently, the enantioselective synthesis2 of this motif. During the course of our ongoing efforts in natural product synthesis, the preparation of an enantioenriched spirocyclic cyclohexenone derivative bearing both an all-carbon quaternary stereogenic spirocenter as well as a 1,4-dicarbonyl moiety spanning the spirocenter was required. This goal was challenging not only due to the difficulties in constructing 1,4-dicarboxyls,3 but also due to the inherent challenges of enantioselectively synthesizing an all-carbon quaternary stereocenter.4 As the enantioselective synthesis of all-carbon quaternary stereocenters via

† This work was performed in collaboration with Dr. J. Caleb Hethcox. Portions of this chapter have been reproduced with permission from Shockley, S. E.;† Hethcox, J. C.;† Stoltz, B. M. Tetrahedron Lett. 2017, 58, 3341–3343 © 2017 Elsevier Ltd.
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

palladium-catalyzed allylic alkylation has been developed extensively by our group, we envisioned that rapid entry to the spirocyclic cyclohexenone framework could be achieved if the olefin was disconnected via a ring-closing metathesis reaction (RCM) and the resultant α-quaternary carbonyl derivative could be synthesized asymmetrically via our allylic alkylation methodology (Figure A11.1a). In addition to the application to our own synthetic endeavor, we imagined that this strategy would be amenable to the synthesis of a wide array of all-carbon quaternary spirocyclic compounds, such as acorenone, laurencenone B, and α-chamigrene (Figure A11.1b). However, this plan hinged on the challenging use of bromomethyl vinyl ketone as an alkylation reagent.

Nucleophilic addition to bromomethyl vinyl ketone can be problematic due to the three electrophilic positions on the molecule, which include positions for Michael addition, 1,2-addition, and S_N2 displacement (Figure A11.1c, left). As a solution to this issue, Funk has developed the use of 6-(bromomethyl)-4H-1,3-dioxin as a bromomethyl vinyl ketone surrogate (Figure A11.1c, left). Following alkylation, the dioxin functionality of this reagent can be unmasked under thermal conditions to release formaldehyde and reveal the latent enone. Therefore, we envisioned that we could obviate the challenges of using bromomethyl vinyl ketone by utilizing Funk’s dioxin reagent in our planned strategy (Figure A11.1c, right). However, the use of a substrate bearing such a bulky substituent with Lewis basic oxygens had not yet been explored in our palladium-catalyzed allylic alkylation chemistry.
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Figure A11.1. Strategy and inspiration for the catalytic enantioselective synthesis of all-carbon quaternary spirocycles

A11.2 REACTION DEVELOPMENT

We fortuitously discovered that the standard conditions developed by our group for palladium-catalyzed allylic alkylation reactions were adaptable to this new substrate class (Table A11.1). The use of a catalyst prepared from Pd₂(pmdba)₃ and (S)-(CF₃)₃-t-Bu-PHOX (L15) provided access to a variety of dioxin-substituted allylic alkylation products in consistently high yields and enantioselectivities. Cyclohexanone 219a was obtained in 91% yield and 83% ee. Moreover, tetralone 219b was afforded in similarly
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

high yield and selectivity, and we were pleased to find that lactam 219c could be accessed in an excellent 95% yield and 99% ee. Based on these results in combination with the previously established trends in our palladium-catalyzed allylic alkylation methodology, we infer that the masked methyl vinyl ketone substituent should be broadly applicable to all of the ring systems tolerated in this chemistry.

Table A11.1 Enantioselective palladium-catalyzed allylic alkylation with substrates bearing a masked methyl vinyl ketone

<table>
<thead>
<tr>
<th>L15 (12.5 mol %)</th>
<th>Pd2(pmdba)3 (5 mol %)</th>
<th>solvent (0.1 M), 18 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Reaction Scheme" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>218a-c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>219a-b</td>
<td>91%</td>
<td>83% ee</td>
</tr>
<tr>
<td>219b-c</td>
<td>91%</td>
<td>82% ee</td>
</tr>
<tr>
<td>219c</td>
<td>95%</td>
<td>99% ee</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.2 mmol scale. [b] Performed using THF at 23 °C. [c] Performed using toluene at 40 °C. [d] Isolated yield. [e] Determined by chiral HPLC or SFC.

With the feasibility of utilizing substrates bearing a masked methyl vinyl ketone functionality in our allylic alkylation chemistry established, we moved to demonstrate the ease with which this strategy can provide access to the desired spirocyclic compounds. Though the masked methyl vinyl ketone synthon has been shown to provide access to bridged and fused bicyclic systems, to the best of our knowledge, the utility of this reagent for the synthesis of spirocycles has yet to be demonstrated. We were pleased to
find that the planned thermal unmasking/RCM sequence proceeded smoothly in a single
reaction vessel (Table A11.2). In this procedure, dioxin 219 is unmasked via heating in
toluene at 180 °C for one hour, whereupon the reaction is cooled to 60 °C and a solution
of Hoveyda-Grubbs second-generation catalyst is introduced to complete the annulation.
Using this newly developed protocol, spirocyclic cyclohexenones 220a, 220b, and 220c
were obtained in good to excellent yields, thus demonstrating the viability of this strategy
for the synthesis of enantioenriched spirocycles.

**Table A11.2 One-pot synthesis of spirocyclic compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>220a</td>
<td>93%</td>
</tr>
<tr>
<td>220b</td>
<td>77%</td>
</tr>
<tr>
<td>220c</td>
<td>53%</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.1 mmol scale. [b] Isolated yield.

**A11.3 CONCLUSIONS**

In summary, we have demonstrated that substrates bearing a bulky, highly
oxygenated methyl vinyl ketone surrogate can be utilized in an enantioselective
catalyst-catalyzed allylic alkylation reaction. The resulting allylic alkylation products
are obtained in high yields and selectivities with neither the increased steric hindrance nor the
added Lewis basic oxygen atoms adversely affecting reactivity. Furthermore, we
developed a one-pot unmasking/RCM procedure showcasing that these allylic alkylation products can be easily advanced to enantioenriched spirocycles bearing both an all-carbon quaternary stereogenic spirocenter as well as a 1,4-dicarbonyl functionality spanning the spirocenter. This simple two-step strategy is amenable to the synthesis of a range of enantioenriched spirocyclic natural products.

A11.4 EXPERIMENTAL SECTION

A11.4.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Commercially obtained reagents were used as received. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Oakwood Chemicals and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) and preparatory TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, KMnO₄, or p-anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak IC column (4.6 mm x 25 cm) or Chiralpak AD-H column (4.6 mm x 25 cm), both obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. Analytical SFC was performed with a
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

Mettler SFC supercritical CO₂ analytical chromatography system utilizing a Chiralpak OJ-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. ¹H NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CHCl₃ (δ 7.26 ppm). ¹³C NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer and are reported relative to residual CDCl₃ (δ 77.16 ppm). Data for ¹H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ¹³C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of benzene (δ 7.36 ppm), water (δ 1.56 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm⁻¹). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm pathlength cell, and are reported as: [α]D (concentration in g/100 mL, solvent).
A11.4.1.1 Preparation of Known Compounds

Previously reported methods were used to prepare ligand (S)-L15 and 6-(bromomethyl)-4H-1,3-dioxin.

A11.4.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

A11.4.2.1 Experimental Procedures and Spectroscopic Data for the Synthesis of Allylic Alkylation Substrates

**Allyl 1-((4H-1,3-dioxin-6-yl)methyl)-2-oxocyclohexane-1-carboxylate (218a).** Allyl 2-oxocyclohexane-1-carboxylate (0.20 g, 1.1 mmol, 1 equiv), K$_2$CO$_3$ (0.76 g, 5.5 mmol, 5 equiv), and 6-(bromomethyl)-4H-1,3-dioxin (0.30 g, 1.7 mmol, 1.5 equiv) were dissolved in acetone (5 mL). The resulting reaction mixture was heated under reflux for 18 h, whereupon the reaction was cooled to ambient temperature, filtered through celite with acetone (10 mL), and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (15% EtOAc/hexanes) to give ester 218a as a colorless oil (0.26 g, 84% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.83 (ddt, $J =$ 17.2, 10.4, 5.9 Hz, 1H), 5.31 – 5.12 (m, 2H), 4.89 – 4.80 (m, 2H), 4.66 (t, $J =$ 2.6 Hz, 1H), 4.57 – 4.48 (m, 2H), 4.14 – 4.09 (m, 2H), 2.76 (dt, $J =$ 15.0, 1.6 Hz, 1H), 2.56 (dt, $J =$ 13.9, 3.2 Hz, 1H), 2.43 – 2.25 (m, 2H), 2.24 – 2.16 (m, 1H), 2.01 – 1.89 (m, 1H), 1.82 – 1.63 (m, 2H), 1.56 (dddd, $J =$ 17.0, 12.4, 8.4, 4.4 Hz, 1H), 1.36 (ddd, $J =$ 13.9, 12.2, 4.7 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 206.4, 170.4, 150.3, 131.6, 118.8, 100.8, 90.3, 65.9, 63.7, 59.8, 40.9, 38.8, 35.7, 27.5, 22.3; IR (Neat Film, NaCl) 3083, 2944, 2867,
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

2796, 1715, 1682, 1648, 1451, 1372, 1314, 1175, 1092, 990, 927, 847, 761 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₅H₁₉O₅ [M+H]–H₂: 279.1232, found 279.1224.

Allyl 2-((4H-1,3-dioxin-6-yl)methyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (218b). Allyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate⁹ (0.60 g, 2.8 mmol, 1 equiv), Cs₂CO₃ (1.6 g, 5.0 mmol, 1.8 equiv), and 6-(bromomethyl)-4H-1,3-dioxin⁷ (0.55 g, 3.1 mmol, 1.1 equiv) were dissolved in DMF (19 mL). The resulting reaction mixture was heated to 70 °C for 18 h, whereupon the reaction was cooled to ambient temperature, poured into H₂O (40 mL), and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organics were washed with brine (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to give ester 218b as a pale yellow oil (0.65 g, 71% yield): ¹H NMR (400 MHz, CDCl₃) δ 8.04 (dd, J = 7.9, 1.4 Hz, 1H), 7.47 (td, J = 7.5, 1.5 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.21 (dd, J = 7.6, 1.2 Hz, 1H), 5.80 (ddt, J = 17.2, 10.5, 5.5 Hz, 1H), 5.27 – 5.06 (m, 2H), 4.93 (s, 2H), 4.83 (t, J = 2.6 Hz, 1H), 4.56 (dq, J = 5.6, 1.6 Hz, 2H), 4.20 (dt, J = 2.6, 1.3 Hz, 2H), 3.22 – 3.07 (m, 1H), 3.01 – 2.73 (m, 3H), 2.64 (dt, J = 13.9, 4.6 Hz, 1H), 2.23 – 2.11 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 194.2, 170.8, 150.5, 143.3, 133.6, 132.0, 131.6, 128.9, 128.3, 126.8, 118.3, 101.4, 90.5, 66.0, 64.0, 56.8, 38.4, 30.5, 26.1; IR (Neat Film, NaCl) 2929, 2852,
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

1730, 1688, 1600, 1453, 1371, 1313, 1294, 1232, 1172, 1093, 987, 950, 846, 744 cm⁻¹;

HRMS (FAB+) m/z calc’d for C₁₉H₁₉O₅ [M+H–H₂]: 327.1232, found 3267.1223.

Allyl 3-((4H-1,3-dioxin-6-yl)methyl)-1-benzoyl-2-oxopiperidine-3-carboxylate (218c).

Allyl 1-benzoyl-2-oxopiperidine-3-carboxylate⁵e (0.20 g, 0.70 mmol, 1 equiv), Cs₂CO₃ (0.41 g, 1.3 mmol, 1.8 equiv), and 6-(bromomethyl)-4H-1,3-dioxin⁷ (0.14 g, 0.77 mmol, 1.1 equiv) were dissolved in DMF (5 mL). The resulting reaction mixture was heated to 70 °C for 18 h, whereupon the reaction was cooled to ambient temperature, poured into H₂O (40 mL), and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (25% EtOAc/hexanes) to give ester 218c as a pale yellow oil (0.13 g, 49% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.73 – 7.66 (m, 2H), 7.53 – 7.42 (m, 1H), 7.42 – 7.33 (m, 2H), 5.99 (ddt, J = 17.2, 10.4, 6.0 Hz, 1H), 5.49 – 5.28 (m, 2H), 5.05 – 4.93 (m, 2H), 4.78 (dt, J = 3.0, 1.5 Hz, 1H), 4.72 (ddt, J = 6.0, 1.7, 0.8 Hz, 2H), 4.20 (dq, J = 2.7, 1.2 Hz, 2H), 3.94 – 3.66 (m, 2H), 2.98 – 2.87 (m, 1H), 2.74 – 2.62 (m, 1H), 2.50 – 2.33 (m, 1H), 2.14 – 1.92 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.1, 171.4, 171.3, 150.0, 135.9, 131.9, 131.5, 128.3, 128.1, 119.8, 101.7, 90.7, 66.9, 64.0, 55.3, 46.5, 39.3, 30.3, 20.6; IR (Neat Film, NaCl) 2934, 2856, 1732, 1678, 1448, 1371, 1272, 1231,
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

1170, 1145, 1090, 985, 939, 845, 721, 694, 647 cm⁻¹; HRMS (FAB+) m/z calc’d for C₂₁H₂₄O₆N [M+H]⁺: 386.1604, found 386.1619.

A11.4.2.2 General Procedure for the Asymmetric Palladium-Catalyzed Allylic Alkylation

(S)-2-((4H-1,3-Dioxin-6-yl)methyl)-2-allylcyclohexan-1-one (219a). In a nitrogen-filled glove box, to a 1 dram vial equipped with a stir bar was added Pd₂(pmdba)₃ (11 mg, 0.01 mmol, 5 mol %), ligand (S)-L₁ (13 mg, 0.025 mmol, 12.5 mol %), and THF (2 mL). The resulting mixture was stirred at 25 °C for 30 min, whereupon substrate 218a (56 mg, 0.20 mmol, 1 equiv) was added. The vial was sealed, removed from the glove box, and stirred at 25 °C. After 18 h, the reaction mixture was concentrated under reduced pressure and the crude product was purified by preparatory TLC (10% EtOAc/hexanes) to give allyl 219a as a colorless oil (43 mg, 91% yield): 83% ee; [α]D²⁵ –13.1 (c 1.9, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.66 (ddt, J = 16.5, 10.6, 7.3 Hz, 1H), 5.09 – 4.99 (m, 2H), 4.95 (d, J = 5.4 Hz, 1H), 4.88 (d, J = 5.4 Hz, 1H), 4.68 (t, J = 2.6 Hz, 1H), 4.26 – 4.11 (m, 2H), 2.58 – 2.45 (m, 2H), 2.39 – 2.28 (m, 3H), 2.18 (d, J = 14.5 Hz, 1H), 1.84 (tdd, J = 6.7, 3.4, 1.6 Hz, 1H), 1.79 – 1.69 (m, 5H); ¹³C NMR (101 MHz, CDCl₃) δ 213.9, 151.5, 134.0, 118.4, 100.7, 90.4, 63.9, 51.0, 39.5, 39.4, 39.0, 36.8, 27.3, 21.0; IR (Neat Film, NaCl) 3391, 3074, 2924, 2854, 2795, 1705, 1681, 1638, 1445, 1372, 1311, 1196, 1172, 1124, 1093, 1021, 990, 911, 847, 755, 640 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₄H₁₉O₃
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[M+H]–H$_2$: 235.1334, found 235.1341; HPLC conditions: 3% IPA, 1.0 mL/min, Chiralpak AD–H column, $\lambda$ = 210 nm, $t_R$ (min): major = 7.066, minor = 7.722.

A11.4.2.3 Spectroscopic Data for the Asymmetric Palladium-Catalyzed Allylic Alkylation Products

Please note that the absolute configurations of 219a–c were determined by analogy.$^{5e,8}$ For respective HPLC conditions, please refer to Table A11.3.

(S)-2-((4H-1,3-Dioxin-6-yl)methyl)-2-allyl-3,4-dihydronaphalen-1(2H)-one (219b).

Product 219b was prepared according to the general procedure to give a colorless oil (52 mg, 91% yield): 82% ee; $[\alpha]_D^{25}$ +0.254 (c 2.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.05 (dd, $J$ = 7.8, 1.4 Hz, 1H), 7.47 (td, $J$ = 7.5, 1.5 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.27 – 7.19 (m, 1H), 5.79 (dddd, $J$ = 17.0, 10.3, 7.8, 7.0 Hz, 1H), 5.17 – 5.00 (m, 2H), 5.00 – 4.88 (m, 2H), 4.74 (t, $J$ = 2.6 Hz, 1H), 4.21 (dt, $J$ = 2.5, 1.2 Hz, 2H), 3.02 (dd, $J$ = 7.2, 5.5 Hz, 2H), 2.69 (dq, $J$ = 14.3, 1.3 Hz, 1H), 2.55 (ddt, $J$ = 14.1, 7.0, 1.3 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.27 – 2.21 (m, 1H), 2.11 (ddt, $J$ = 6.0, 4.8, 3.2 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 200.5, 151.5, 143.2, 133.9, 133.2, 132.0, 128.8, 128.2, 126.7, 118.7, 100.8, 90.4, 64.0, 47.8, 39.6, 38.8, 30.4, 25.3; IR (Neat Film, NaCl) 3072, 3004, 2929, 2859, 2794, 1677, 1600, 1454, 1432, 1371, 1289, 1225, 1193, 1172, 1093, 1023, 989, 918, 847, 742 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{18}$H$_{19}$O$_3$ [M+H]–H$_2$: 283.1334, found
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

283.1338; HPLC conditions: 4% IPA, 1.0 mL/min, Chiralpak IC column, $\lambda = 210$ nm, $t_R$ (min): major = 29.702, minor = 23.387.

(S)-3-((4H-1,3-Dioxin-6-yl)methyl)-3-allyl-1-benzoylpiperidin-2-one (219c). Product 219c was prepared according to the general procedure (toluene used in place of THF, reaction mixture heated to 40 °C) to give a pale yellow oil (66 mg, 95% yield): 99% ee; $[\alpha]_D^{25} +11.4$ (c 3.3, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 – 7.31 (m, 5H), 5.76 (ddddd, $J = 17.1$, 10.3, 7.7, 6.9 Hz, 1H), 5.21 – 5.09 (m, 2H), 5.06 – 4.98 (m, 2H), 4.74 (td, $J = 2.7$, 0.8 Hz, 1H), 4.23 (ddd, $J = 2.6$, 1.7, 0.8 Hz, 2H), 3.91 – 3.67 (m, 2H), 2.76 (dddt, $J = 14.3$, 1.7, 0.9 Hz, 1H), 2.59 (dddt, $J = 13.8$, 6.9, 1.3 Hz, 1H), 2.31 (dddt, $J = 13.8$, 7.7, 1.1 Hz, 1H), 2.15 – 2.09 (m, 1H), 2.04 – 1.95 (m, 3H), 1.93 – 1.83 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.1, 175.6, 151.2, 136.7, 133.3, 131.5, 128.2, 127.8, 119.6, 101.2, 90.6, 64.1, 47.0 (2C), 43.5, 41.7, 30.0, 20.0; IR (Neat Film, NaCl) 3346, 3072, 2945, 2868, 2795, 1678, 1600, 1477, 1449, 1386, 1372, 1286, 1150, 1172, 1092, 1023, 990, 919, 846, 792, 725, 696 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{20}$H$_{24}$NO$_4$ [M+H]$^+$: 342.1705, found 342.1714; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak OJ-H column, $\lambda = 210$ nm, $t_R$ (min): major = 11.165, minor = 10.427.
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

A11.4.2.4 General Procedure for Spirocyclic Formation

(3)-Spiro[5,5]undec-9-ene-1,8-dione (220a). To a sealed Biotage microwave vial, allyl 219a (24 mg, 0.10 mmol, 1 equiv) and toluene (0.7 mL) were added. The reaction mixture was heated to 180 °C for 1 h, whereupon the reaction was cooled to 60 °C and a solution of Hoveyda-Grubbs 2nd generation catalyst (6.3 mg, 0.010 mmol, 0.10 equiv) in toluene (0.3 mL) was added. The reaction mixture was then stirred an additional 18 h at 60 °C, cooled to ambient temperature, and directly purified by preparatory TLC (15% EtOAc/hexanes) to give spirocycle 220a as a colorless oil (17 mg, 93% yield): \([\alpha]_D^{25} – 1.4\) (c 1.1, CHCl3); 1H NMR (400 MHz, CDCl3) \(\delta 6.81 (dt, J = 10.1, 4.1 Hz, 1H), 5.99 (dt, J = 10.0, 2.1 Hz, 1H), 2.84 (ddt, J = 18.8, 4.4, 1.4 Hz, 1H), 2.80 – 2.71 (m, 1H), 2.47 – 2.32 (m, 4H), 1.95 – 1.73 (m, 6H); 13C NMR (101 MHz, CDCl3) \(\delta 212.3, 197.4, 146.0, 129.5, 51.5, 45.7, 38.2, 38.1, 33.7, 27.7, 20.8; IR (Neat Film, NaCl) 3037, 2936, 2865, 1705, 1678, 1446, 1424, 1387, 1252, 1135, 736 cm\(^{-1}\); HRMS (FAB+) m/z calc’d for C11H15O2 [M+H]\(^+\): 179.1072, found 179.1078.

A11.4.2.5 Spectroscopic Data for Spirocyclic Compounds

(3)-3',4'-dihydro-1'H-spirocyclohexane-1,2'-naphthalen-3-ene-1',5-dione (220b). Product 220b was prepared according to the general procedure to give a colorless oil (18 mg, 77% yield) after preparatory TLC (15% EtOAc/hexanes): \([\alpha]_D^{25} – 1.5\) (c 1.2, CHCl3);
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (dd, $J =$ 7.8, 1.4 Hz, 1H), 7.50 (td, $J =$ 7.5, 1.5 Hz, 1H), 7.40 – 7.30 (m, 1H), 7.26 – 7.20 (m, 1H), 6.91 – 6.77 (m, 1H), 6.10 (dt, $J =$ 10.3, 2.1 Hz, 1H), 3.09 – 2.89 (m, 3H), 2.82 (d, $J =$ 16.2 Hz, 1H), 2.50 – 2.38 (m, 2H), 2.27 – 2.02 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 199.2, 197.4, 145.6, 142.7, 133.9, 130.8, 129.5, 128.9, 128.5, 127.2, 47.7, 44.6, 32.5, 32.3, 25.0; IR (Neat Film, NaCl) 3034, 2926, 2858, 1683, 1601, 1455, 1388, 1250, 1224, 1157, 946, 750 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{15}$H$_{15}$O$_2$ [M+H]$^+$: 227.1072, found 227.1074.

(S)-2-benzoyl-2-azaspiro[5.5]undec-9-ene-1,8-dione (220c). Product 220c was prepared according to the general procedure to give a colorless oil (15 mg, 53% yield) after preparatory TLC (40% EtOAc/hexanes): $[\alpha]_D^{25}$ +29.7 (c 0.9, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.54 – 7.32 (m, 5H), 6.87 (ddd, $J =$ 10.2, 5.0, 3.3 Hz, 1H), 6.06 (dt, $J =$ 10.1, 2.1 Hz, 1H), 3.91 – 3.74 (m, 2H), 3.09 (dt, $J =$ 18.9, 3.0 Hz, 1H), 2.96 (d, $J =$ 16.1 Hz, 1H), 2.59 (dd, $J =$ 16.2, 1.3 Hz, 1H), 2.49 (ddt, $J =$ 18.9, 5.0, 1.6 Hz, 1H), 2.09 – 1.95 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 196.4, 177.0, 175.1, 145.8, 135.8, 131.9, 129.2, 128.5, 127.6, 47.1, 47.0, 46.4, 34.8, 32.5, 19.3; IR (Neat Film, NaCl) 2949, 1679, 1449, 1388, 1281, 1151, 919, 729, 694, 665 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{17}$H$_{18}$O$_3$N [M+H]$^+$: 284.1287, found 284.1277.
Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy

A11.4.2.6 Determination of Enantiomeric Excess

*Please note* racemic products were synthesized using Pd(PPh₃)₄ in place of Pd₂(pmdba)₃ and (S)-L15.

**Table A11.3** Determination of enantiomeric excess

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Assay Conditions</th>
<th>Retention time of major isomer (min)</th>
<th>Retention time of minor isomer (min)</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image]</td>
<td>HPLC Chiralpak AD-H 3% IPA isocratic, 1 mL/min</td>
<td>7.066</td>
<td>7.722</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>![Image]</td>
<td>HPLC Chiralpak IC 4% IPA isocratic, 1 mL/min</td>
<td>29.702</td>
<td>23.387</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>![Image]</td>
<td>SFC Chiralpak OJ-H 5% IPA isocratic, 2.5 mL/min</td>
<td>11.165</td>
<td>10.427</td>
<td>99</td>
</tr>
</tbody>
</table>

A11.5 REFERENCES AND NOTES

Appendix 11 – Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via an Enantioselective Allylic Alkylation Strategy


APPENDIX 12

Spectra Relevant to Appendix 11:

Asymmetric Synthesis of All-Carbon Quaternary Spirocycles

via an Enantioselective Allylic Alkylation Strategy
Figure A12.1 $^1$H NMR (400 MHz, CDCl$_3$) of compound 218a
Figure A12.2 Infrared spectrum (Thin Film, NaCl) of compound 218a

Figure A12.3 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 218a
Figure A12.4 $^1$H NMR (400 MHz, CDCl$_3$) of compound 218b
**Figure A12.5** Infrared spectrum (Thin Film, NaCl) of compound 218b

**Figure A12.6** $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 218b
Figure A12.7 $^1$H NMR (400 MHz, CDCl₃) of compound 218c
Appendix 12 – Spectra Relevant Appendix 11

Figure A12.8 Infrared spectrum (Thin Film, NaCl) of compound 218c

Figure A12.9 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 218c
Figure A12.10 ¹H NMR (400 MHz, CDCl₃) of compound 219a
Figure A12.11 Infrared spectrum (Thin Film, NaCl) of compound 219a

Figure A12.12 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 219a
Figure A12.13 $^1$H NMR (400 MHz, CDCl$_3$) of compound 219b
Figure A12.14 Infrared spectrum (Thin Film, NaCl) of compound 219b

Figure A12.15 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 219b
Figure A12.16 $^1$H NMR (400 MHz, CDCl$_3$) of compound 219c
Figure A12.17 Infrared spectrum (Thin Film, NaCl) of compound 219c

Figure A12.18 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 219c
Figure A12.19 $^1$H NMR (400 MHz, CDCl$_3$) of compound 220a
Figure A12.20 Infrared spectrum (Thin Film, NaCl) of compound 220a

Figure A12.21 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 220a
Figure A12.22 $^1$H NMR (400 MHz, CDCl$_3$) of compound 220b
Figure A12.23 Infrared spectrum (Thin Film, NaCl) of compound 220b

Figure A12.24 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 220b
Figure A12.25 $^1$H NMR (400 MHz, CDCl$_3$) of compound 220c
Figure A12.26 Infrared spectrum (Thin Film, NaCl) of compound 220c

Figure A12.27 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 220c
APPENDIX 13

Progress Toward the Synthesis of (+)-Isopalhinine A†

A13.1 INTRODUCTION AND BACKGROUND

The *Lycopodium* alkaloids are family of complex, polycyclic, bioactive molecules that have been the subject of intense synthetic efforts over the past fifty years. In 2013, a novel *Lycopodium* alkaloid, (+)-isopalhinine A (221, Scheme A13.1), was isolated containing an unprecedented (5/6/6/6/7) pentacyclic scaffold comprised of a densely functionalized isotwistane core containing vicinal all-carbon quaternary stereocenters appended to a 1-azabicyclo[4.3.1]decane moiety. The complex architecture of (+)-isopalhinine A (221) has piqued the interest of the synthetic community, however, despite one report toward the isotwistane core, the natural product has yet to succumb to total synthesis. Herein, we detail our progress toward (+)-isopalhinine A (221) via a series of evolving strategies unified by the late-stage synthesis of the isotwistane core and the early construction of the functionalized nitrogen-containing heterocycle.

† Portions of this work were performed in collaboration with Dr. J. Caleb Hethcox.
A13.2 IRIDIUM-CATALYZED ALLYLIC ALKYULATION ROUTE

Our initial retrosynthetic analysis of (+)-isopalhinine A (221) began with disconnection of the caging architecture by C–N bond cleavage of the bridging propyl chain, followed by rupture of the central isotwistane core, which would be formed via an intramolecular Diels–Alder cycloaddition, to provide spirocycle 222 (Scheme A13.1). Spirocycle 222 would in turn be prepared by enolate formation and subsequent hemiaminal formation via the addition of an acyl anion equivalent into spirocyclic lactam 223. Intramolecular aldol condensation and redox manipulation would then lead back to functionalized β-ketolactam 224. Enantioenriched 224 would be generated from β-ketolactam 225 and allylic electrophile 226, which would require the development of novel stereoselective iridium-catalyzed allylic alkylation technology as both the use of alkyl-substituted allylic electrophile 226 and endocyclic 1,3-dicarbonyl nucleophile 225 in iridium-catalyzed allylic alkylation chemistry is unprecedented in the literature. This synthetic strategy would enable rapid access to (+)-isopalhinine A (221) in as few as fourteen steps from 225 and 226.
Scheme A13.1 Initial retrosynthetic analysis of (+)-isopalhinine A (221) via iridium-catalyzed allylic alkylation of endocyclic 1,3-dicarbonyl nucleophile 225

We began our explorations into this initial synthetic plan with the synthesis of proposed iridium-catalyzed allylic alkylation substrates 225 and 226. The preparation of allylic electrophile 226 proceeded via known allylic alcohol 230, which was synthesized in three steps and 40% overall yield from commercially available 4-pentyn-1-ol (227, Scheme A13.2).4,5 Subsequent acylation with methyl chloroformate afforded requisite alkyl-substituted allylic electrophile 226 in 89% yield.6

Scheme A13.2 Synthesis of alkyl-substituted electrophile 226
Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A

Synthesis of proposed endocyclic 1,3-dicarbonyl nucleophile 225 proved more challenging. While we were able to rapidly access allylated β-ketolactam 233 from Boc-β-alanine (231, Scheme A13.3a), we were unable to prepare desired alkyl-substituted nucleophile 225 (Scheme A13.3b). In our attempt to synthesize desired 225 we explored a variety of approaches including C-alkylation and Knoevenagel condensation/reduction sequences of β-ketolactam 232, cyclization of β-ketoester 234, as well as ozonolysis/reduction of allylated β-ketolactam 233, but all routes were met with failure.

Scheme A13.3 Efforts to synthesize endocyclic 1,3-dicarbonyl nucleophiles

a) Synthesis of allylated nucleophile

\[
\text{BocHN} \quad \text{OH} \\
\text{231} \\
\]

1. EDC•HCl, CH₂Cl₂, Meldrum's acid 0 °C \rightarrow 23 °C
2. EtOAc, reflux (95% yield)

\[
\text{ NBoc } \\
\text{232} \\
\]

allyl iodide, K₂CO₃, DMSO, 23 °C (37% yield)

\[
\text{ NBoc } \\
\text{233} \\
\]

b) Attempts to synthesize requisite nucleophile

\[
\text{NBoc} \\
\text{232} \\
\]

alkylation

\[
\text{NBoc} \\
\text{234} \\
\]

cyclization

\[
\text{OTBS} \\
\text{235} \\
\]

Knoevenagel condensation

\[
\text{OTBS} \\
\text{233} \\
\]

ozonolysis/reduction

Unable to synthesize desired alkyl-substituted nucleophile 225, we decided to instead explore the proposed iridium-catalyzed allylic alkylation reaction of alkyl-substituted electrophile 226 with allyl-substituted nucleophile 233, postulating that we could subsequently perform redox manipulations on allylic alkylation product 235 in
order to intercept our original synthetic plan (Table A13.1). Our prior work on iridium-catalyzed allylic alkylation reactions with crotyl chloride primed us for the challenges involved in the use of alkyl-substituted electrophiles like 226. Specifically, we anticipated poor regioselectivity in the allylic alkylation reaction as a result of the minimal stabilization of the allyl carbocation afforded by the alkyl substituent of 226, in addition to poor reactivity due to the steric bulk of the alkyl group. Therefore, we hypothesized that we would need to explore novel ligand and additive combinations in the iridium-catalyzed allylic alkylation reaction in order to achieve both a selective and high yielding transformation.

We began our studies employing our previously explored conditions for the iridium-catalyzed allylic alkylation of cinnamyl-derived electrophiles. Unsurprisingly, we observed that the reaction proceeded with poor branched selectivity, instead favoring the synthesis of the undesired linear product (Table A13.1, entry 1). Though base additives have been shown to play an important role in the selectivity of iridium-catalyzed allylic alkylations, an extensive investigation of bases proved unsuccessful in promoting branched selectivity in the reaction (entries 2–5). Turning our attention to the ligand, we found that the use of Alexakis ligand L16, instead of Me-THQphos (L2), in combination with LiBr or DABCO as additives, reversed the regioselectivity of the transformation to favor the synthesis of desired branched product 235 (entries 6 and 9). However, poor conversions (15% combined yield of branched and linear products, entry 9) and our inability to separate the branched and linear isomers by column chromatography led us to terminate our studies on endocyclic 1,3-dicarboxyl
nucleophiles in order to identify a more suitable nucleophile for the iridium-catalyzed allylic alkylation reaction.

Table A13.1 Optimization of the iridium-catalyzed allylic alkylation of endocyclic 1,3-dicarbonyl nucleophile 233

<table>
<thead>
<tr>
<th>Entry</th>
<th>$L$</th>
<th>Additive (200 mol %)</th>
<th>b:lb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L2</td>
<td>LiBr</td>
<td>30:70</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>LiO/Bu</td>
<td>27:73</td>
</tr>
<tr>
<td>3</td>
<td>L2</td>
<td>DABCO</td>
<td>39:61</td>
</tr>
<tr>
<td>4</td>
<td>L2</td>
<td>DMAP</td>
<td>12:88</td>
</tr>
<tr>
<td>5</td>
<td>L2</td>
<td>NEt$_3$</td>
<td>28:72</td>
</tr>
<tr>
<td>6</td>
<td>L16</td>
<td>LiBr</td>
<td>64:36</td>
</tr>
<tr>
<td>7</td>
<td>L16</td>
<td>LiO/Bu</td>
<td>34:66</td>
</tr>
<tr>
<td>8</td>
<td>L16</td>
<td>Cs$_2$CO$_3$</td>
<td>27:73</td>
</tr>
<tr>
<td>9</td>
<td>L16</td>
<td>DABCO</td>
<td>63:37</td>
</tr>
<tr>
<td>10</td>
<td>L16</td>
<td>DMAP</td>
<td>25:75</td>
</tr>
<tr>
<td>11</td>
<td>L16</td>
<td>NEt$_3$</td>
<td>29:71</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.2 mmol scale with 2:1 nucleophile/electrophile. [b] Determined by TOF LCMS analysis of the crude reaction mixture. [c] TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene.

In a revised retrosynthetic analysis of (+)-isopalhinine A (221), we envisioned that we could employ lactone nucleophile 238, in place of β-ketolactam 225, in the proposed iridium-catalyzed allylic alkylation reaction of alkyl-substituted electrophile 226 (Scheme A13.4). Preserving our endgame strategy, allylic alkylation product 237 would then undergo lactamization to intercept key intermediate 236 from our original retrosynthesis (Scheme A13.1). We hypothesized that the similarity between lactone 238 and our group’s previously explored β-ketoester nucleophiles$^{9,11}$ would allow for a more facile optimization of the iridium-catalyzed allylic alkylation reaction.
Scheme A13.4 Revised retrosynthetic analysis of (+)-isopalhinine A (221) via iridium-catalyzed allylic alkylation of lactone nucleophile 238

To explore this idea, we synthesized lactone nucleophile 238 (Scheme A13.5). A Masamune-Claisen reaction of Boc-β-alanine (231) afforded β-ketoester 239 in 99% yield. Subsequent alkylation gave silyl ether 234, which was then exposed to TBAF to effect deprotection and cyclization in order to provide lactone 238 in 91% yield.

Scheme A13.5 Synthesis of lactone nucleophile 238

With lactone nucleophile 238 in hand, we turned to explore its reactivity in the proposed iridium-catalyzed allylic alkylation reaction (Table A13.2). Due to early difficulties in isolating branched allylic alkylation product 237 in high purity, we were prompted to discover that γ-butyrolactone allylic alkylation product 237 could be elaborated to α-quaternary lactam derivative 241 in a one-pot fashion upon treatment with trifluoracetic acid. Unlike lactone 237, branched lactam 241 is separable from its linear isomer and is merely the hemiacetal of key intermediate 236 (Scheme A13.4).
With respect to the optimization of the allylic alkylation reaction, our group’s previously reported conditions for the iridium-catalyzed allylic alkylation of crotyl chloride\textsuperscript{8} (Table A13.2, entry 1), poorly reactive allylic electrophiles\textsuperscript{12} (entry 2), and β-ketoester nucleophiles\textsuperscript{9} (entry 3), all afforded poor selectivities when applied to our desired transformation. After extensive exploration of ligands and base additives, we found that the bulkier Feringa ligand L\textsubscript{17} in combination with DABCO gave desired lactam 241 in excellent yield, regio- and enantioselectivity, though poor diastereoselectivity (entry 5). We believe that the diastereoselectivity of this transformation can potentially be further improved by exploring dual catalytic systems.\textsuperscript{13} Of note, linear β-ketoester 234 (Scheme A13.5) was also explored in the iridium-catalyzed allylic alkylation reaction with electrophile 240; however, the best results were observed using the same optimized conditions for lactam substrate 238 (Table A13.2, entry 5) and while the regioselectivity and yields were high (91:9 b:l, 94\% yield), the diastereoselectivity was poor (1.2:1 dr) and all isomers were inseparable by column chromatography.
Table A13.2 Optimization of the iridium-catalyzed allylic alkylation of lactone 238

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>Base (200 mol %)</th>
<th>Additive (mol %)</th>
<th>LG</th>
<th>Yield (%)b</th>
<th>b:c</th>
<th>dr:c</th>
<th>ee (%)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>proton sponge</td>
<td>LiCl (400)</td>
<td>Cl</td>
<td>87</td>
<td>87:13</td>
<td>1.4:1</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>L5</td>
<td>–</td>
<td>BEt3 (200)</td>
<td>OCO₂Me</td>
<td>49</td>
<td>31:69</td>
<td>1.2:1</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>L2</td>
<td>–</td>
<td>LiBr (200)</td>
<td>OCO₂Me</td>
<td>11</td>
<td>13:87</td>
<td>1.1:1</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>L17</td>
<td>–</td>
<td>LiBr (200)</td>
<td>OCO₂Me</td>
<td>50</td>
<td>57:43</td>
<td>1.0:1</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>L17</td>
<td>DABCO</td>
<td>–</td>
<td>OCO₂Me</td>
<td>79</td>
<td>99:1</td>
<td>1.5:1</td>
<td>96</td>
</tr>
</tbody>
</table>

[a] Reactions performed on 0.1 mmol scale with 2:1 nucleophile/electrophile. [b] ¹H NMR yield based on internal standard. [c] Determined by ¹H NMR analysis of the crude reaction mixture. [d] Determined via chiral HPLC. [e] TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene.

We next turned our attention to the advancement of bicyclic hemiacetal 241 to spirocyclic enone 223 (Scheme A13.6), which would set the stage for the pivotal acyl anion addition. Toward this end, we performed a Wacker oxidation of pendant olefin 241 (Scheme A13.6, top). However, despite a variety of conditions, we observed cyclization of the hemiacetal moiety into the nascent ketone of 242 forming new unstable hemiacetal 243, which readily dehydrated to dihydrofuran 244. In an effort to circumvent this undesired reactivity, we instead oxidized hemiacetal 241 to aldehyde 245 using Dess–Martin periodinane prior to the Wacker oxidation (Scheme A13.6, middle). Unfortunately, Wacker product 246 suffered an undesirable intramolecular aldol reaction in situ, delivering undesired 5-membered aldol product 247. Lastly, we discovered that
we could perform a directed reduction of hemiacetal 241 using the hydroxyethyl group of the opened hemiacetal to access diol 248 (Scheme A13.6, bottom). Subsequent selective oxidation of the primary alcohol afforded aldehyde 249. To our disappointment, attempts to perform a Wacker oxidation on aldehyde 250 proved unsuccessful. It is likely that protection of the primary alcohol and/or amide is required for the Wacker oxidation to proceed.

Scheme A13.6 Attempts to advance bicycle 241 to key spirocyclic intermediate 223
A13.3 PALLADIUM-CATALYZED ALLYLIC ALKYLATION ROUTE USING A MASKED STABILIZED LACTAM ENOLATE

Concurrent with our efforts to develop an iridium-catalyzed allylic alkylation approach to (+)-isopalhinine A (221), an alternate route to the natural product relying on a palladium-catalyzed allylic alkylation was explored (Scheme A13.7). Maintaining the endgame strategy from the iridium-catalyzed allylic alkylation route (Scheme A13.1), this alternate retrosynthetic analysis leads through the same disconnects to spirocyclic intermediate 223, which in this approach would be synthesized via an α-alkylation and diastereoselective reduction of the corresponding ketone of acetal 251. Cyclic enone 251 would then arise from the ozonolysis and aldol condensation enantioenriched lactam 252, which in turn would result from an enantioselective palladium-catalyzed decarboxylative allylic alkylation of substrate 253. The key advantage to this alternate route is the elimination of the need to control diastereoselectivity in the allylic alkylation reaction, which was the main challenge in the aforementioned iridium-catalyzed allylic alkylation route. Moreover, the tertiary stereocenter of the vicinal tertiary and quaternary stereodyad set in the iridium-catalyzed allylic alkylation pathway was to be ablated later in the synthesis in the formation of cyclohexadiene 222 (Scheme A13.1 and Scheme A13.7), and therefore our efforts to achieve a diastereoselective reaction were ultimately unnecessary.
**Scheme A13.7** Retrosynthetic analysis of (+)-isopalhinine A (221) via palladium-catalyzed allylic alkylation of masked stabilized lactam enolate 253

At the time we began our studies into this palladium-catalyzed route, the Stoltz group had previously examined the palladium-catalyzed decarboxylative alkylation of enolate-stabilized enol carbonates for the synthesis of all-carbon quaternary stereocenters\(^\text{14}\) as well as developed the asymmetric palladium-catalyzed decarboxylative allylic alkylation of lactams to reach quaternary \(N\)-heterocycles, specifically lactams, in high enantioselectivities.\(^\text{15}\) However, enolate-stabilized lactams such as 253 had yet to be explored in our palladium-catalyzed allylic alkylation chemistry. As such, we utilized easy-to-access model substrate 254 in order to explore the effects of protecting groups on yield and selectivity in our desired allylic alkylation reaction (Table A13.3). Through a series of optimization studies, we found that the nature of both the nitrogen (Table A13.3a) and ketone (Table A13.3b) protecting groups play pivotal roles on the enantioselectivity of the palladium-catalyzed decarboxylative alkylation of enolate-stabilized lactam 253. Ultimately, we determined that protecting the amide nitrogen of model lactam 256 with a \(para\)-methoxy-benzoyl group (pMBz) and the ketone
functionality as a gem-dimethyl-dioxane moiety allowed us to access corresponding product 257 in the highest enantioselectivity (93% ee) and a moderate 46% yield.

**Table A13.3 Optimization of protecting groups for the palladium-catalyzed allylic alkylation reaction**

*a) Optimization of Lactam Protecting Group*

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bz</td>
<td>42</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-Bz</td>
<td>75</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>3,4,5-triMeO-Bz</td>
<td>86</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>4-MeO-benzenesulfonyl</td>
<td>79</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>Boc</td>
<td>87</td>
<td>53</td>
</tr>
</tbody>
</table>

*b) Optimization of Ketone Protecting Group*

Having completed these optimization efforts, we moved to pursue the preparation of synthetically relevant substrate 260 for the proposed palladium-catalyzed allylic alkylation reaction (Scheme A13.8). Protected lactam 258 can be accessed in three steps from Boc-β-alanine (231). Subsequent acylation and allylation provided desired allylic alkylation substrate 260. Of note, iridium-catalyzed allylic alkylation was required for the allylation of 259, as we found that all attempts to allylate extremely sterically demanding 259 using standard methods resulted in returned starting material or deprotection of the starting material. Treatment of 260 with Pd(PPh₃)₄ afforded racemic product rac-261 in a
high 84% yield. Unfortunately, attempts to render the allylic alkylation reaction enantioselective utilizing our optimization conditions from model system 257 (Table A13.3) resulted in only modest enantioselectivities and yields, likely due to the now increased steric bulk around the reactive site. Additional studies into alternate palladium-catalyzed allylic alkylation systems, specifically those utilizing Trost ligands known to tolerate more sterically encumbered substrates, also showed poor reactivity. Nonetheless, we were pleased to find that we could advance rac-261 through an ozonolysis and an acid-catalyzed aldol reaction to provide desired spirocyclic enone 263.

**Scheme A13.8 Synthesis of spirocyclic intermediate 263 via palladium-catalyzed allylic alkylation**

We next attempted to alkylate spirocyclic enone 263 in order to obtain α’-alkylated intermediate 267 (Scheme A13.9). To our dismay, early efforts to directly alkylate or allylate 263 proved unsuccessful, likely due to the sterically hindered
neopentyl nature of the intermediate enolate, as well as the possibility of competitive γ-functionalization. We also found that forming silyl enol ether 266 was not fruitful, and were thus unable to explore alternate alkylation strategies.

**Scheme A13.9** Attempted alkylations of spirocyclic enone 263

![Scheme A13.9](image)

**A13.4** PIPERIDONE PALLADIUM-CATALYZED ALYLYC ALKYLATION ROUTE

In light of our inability to achieve a highly enantioselective palladium-catalyzed allylic alkylation using enolate-stabilized lactam substrate 253 (Section A13.3), we chose to investigate a modified palladium-catalyzed allylic alkylation route that employed a class of substrates already known to be successful in our group’s methodology: piperidones (Scheme A13.10). In this revised retrosynthetic analysis of (+)-isopalhinine A (221), the N-alkylation and intramolecular Diels–Alder disconnects of the previous routes remain, however [4+2] substrate 222 is now the result of an acyl anion addition into imine 268, which would arise from a late-stage oxidation of piperidine 269. Similar to the previous palladium-catalyzed allylic alkylation route, enone 269 would be formed
via ozonolysis and aldol condensation of diene 270. We envisioned that ether 270 would be prepared by diastereoselective reduction of enantioenriched piperidone 271, which would be formed via enantioselective palladium-catalyzed decarboxylative allylic alkylation of substrate 272.

We first explored the feasibility of this revised plan by investigating the reactivity of benzyl-protected piperidone 273 (Scheme A13.11). Acylation and alkylation afforded allylic alkylation substrate 274, which we were pleased to find smoothly underwent the proposed palladium-catalyzed decarboxylative allylic alkylation to afford corresponding product 275 in excellent 93% yield and good 82% ee. Of note, product 275 is the incorrect enantiomer to access (+)-isopalhinine A (221), however, the challenges of preparing the requisite (R)-L15 led us to explore the early chemistry of this route using the easy-to-access 275. Subsequent diastereoselective reduction of ketone 275 using CBS catalyst delivered alcohol 276 in a 9:1 dr. We found that while we were able to protect the hydroxyl group to give 277, we were unable reveal the masked bis-carbonyl motif via
ozonolysis of diene 277. Realizing that the basic nitrogen of 277 was likely problematic in the ozonolysis reaction, we directed efforts toward investigating alternative protecting groups for piperidone 273, ultimately selecting a Boc group.

Scheme A13.11 Attempts to advance benzyl-protected piperidone 273

Boc-protected piperidone 279 performed similarly to benzyl-protected analogue 273 in the palladium-catalyzed decarboxylative allylic alkylation reaction, providing product 281 in 73% yield and 90% ee (Scheme A13.12). However, the CBS reduction of ketone 281 to give hydroxy 282 proceeded in significantly diminished yields and a now moderate 4:1 dr. Moreover, despite exploring a variety of conditions, efforts to either protect alcohol 282 or perform an ozonolysis were not successful. Given these difficulties and our concern with successfully performing the proposed selective late-stage oxidation to access imine 262 (Scheme A13.10), we elected to conclude explorations into this route.
**A13.5  DIASTEREOSELECTIVE ROUTE**

While working to develop an enantioselective route to key spirocyclic intermediate 223, we wondered whether we could carry out a rapid, diastereoselective synthesis of 223 that would enable the preparation of large quantities of the compound for the purposes of exploring the proposed late-stage chemistry (Scheme A13.13). Toward this end, we envisioned that spirocyclic intermediate 223 could arise from an alkylation and ring closing metathesis of unmasked dioxin 285,18 which would now be the result of a diastereoselective alkylation/allylation sequence of hydroxy lactam 286.
Scheme A13.13 Retrosynthetic analysis of (+)-isopalhinine A (221) via diastereoselective alkylation/allylation sequence

In the forward direction, we began our studies with known β-ketolactam 232 (Scheme A13.14). Reduction of the ketone functionality with sodium borohydride followed by protection of the resultant hydroxyl group gave silyl ether 287 in 70% yield. Disappointingly, attempts to allylate or alkylate lactam 287 returned only deprotected starting material.

Scheme A13.14 Attempts at diastereoselective functionalization
Realizing that we would need to replace the Boc group of lactam 287 with a base-stable protecting group in order to promote functionalization, we considered alkylating lactam 291 with the requisite hydroxypropyl tether required for the proposed late-stage N-alkylation event (Scheme A13.13). Unfortunately, despite significant efforts to N-alkylate lactam 291, we observed only elimination of the iodide on the alkylating reagent or elimination of the silyl ether of 291 to form an enamide (Scheme A13.15).

Scheme A13.15 Requisite propyl chain as a nitrogen protecting group

To circumvent the issues we were observing with functionalizing lactam 287, we explored an alternative route to RCM precursor 298 that did not require the use of strong base, but would instead rely on a diastereoselective Tsuji reaction\textsuperscript{18a} (Scheme A13.16). In this synthetic sequence, secondary amine 293 is acylated with 294 to give amide 295 in 76% yield. Subsequent Dieckmann condensation delivered functionalized β-ketolactam 296 in a moderate 50% yield.
Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A

**Scheme A13.16 Non-strong base route to RCM precursor 298**

We were disappointed to find that attempts to advance β-ketolactam 296 to Tsuji substrate 297 were unsuccessful (Scheme A13.17). Specifically, we found that we could only reduce ketone 296 in low yields using sodium borohydride (Scheme A13.17, top). Efforts to protect the resultant hydroxy group resulted in retro Dieckmann products of 296 (Scheme A13.17, middle), as did attempts to alkylate 296 with dioxin 288\(^{18}\) (Scheme A13.7, bottom).

**Scheme A13.17 Attempts to advance β-ketolactam 296**
Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A

A13.6 FUTURE DIRECTIONS AND PROPOSED LATE-STAGE CHEMISTRY TO ACCESS (+)-ISOPALHININE A

Should additional efforts enable access to key spirocyclic intermediate 223 via any of the aforementioned routes, the proposed late-stage chemistry to synthesize (+)-isopalhinine A (221) is detailed in Scheme A13.18. Enone 223 will be converted to desired cyclohexadiene 302 by enolization and trapping with chloromethyl methyl ether. Diastereoselective addition of an acrolein-derived acyl anion equivalent (e.g., 303) to the amide functionality of 302 by approach of the anion over the olefinic group (i.e., α-face attack) will then provide Diels–Alder substrate 304 upon revealing the carbonyl group by desilylation and cyanide extrusion. Such masked acyl-anion additions to lactams have ample precedent in the literature,19 and we anticipate that the keto aminal (e.g., 222a) will likely be stable to subsequent manipulation, potentially as the free hydroxyl.20 If the need arises, we anticipate protecting hemiaminal 222a as a BOM ether (222b), or alternatively, reducing to the α-amidocarbonyl system (i.e., 222c).

From spirocycle 222, an intramolecular diastereoselective [4+2] Diels–Alder cycloaddition will furnish the isotwistane core of (+)-isopalhinine A (221) to yield 305.21 The diastereoselectivity of the IMDA is controlled by the tethering of the dienophile to the top face of the spirocycle. Cleavage of the benzyl residues will occur via transfer hydrogenolysis (note: BOM cleavage would occur here if 305b is employed) to yield aminoalcohol 306.22 Subsequent N-alkylation via an iridium-catalyzed “borrowing hydrogen”-type alkylation will install the final ring.23 Finally, removal of remaining MOM group with acid will deliver (+)-isopalhinine A (221). If we are confronted with stability issues that require the use of ketone 307b, a late-stage oxidation (e.g., with
Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A

K$_2$Fe(CN)$_6$/NaHCO$_3$/H$_2$O, $^{24}$ O$_2$/SiO$_2$/H$_2$O, $^{25}$ MnO$_2$, $^{26}$ NaOMe/O$_2$/H$_2$O $^{27}$ will be employed to install the aminal group and reach (+)-isopalhinine A (221).

Scheme A13.18 Proposed route to (+)-isopalhinine A (221) from alkylated spirocycle 223

Preliminary studies have been undertaken to investigate the proposed acyl anion addition chemistry in model systems. While the addition of aryl-functionalized silyl cyanohydrins into lactams is known, $^{19}$ acrolein-derived silyl cyanohydrin, such as 303, additions have yet to be explored. Our early studies indicated that γ-addition of acrolein equivalent 303 is a competitive pathway. As such, we anticipate that future studies into this addition chemistry will involve alternative silyl cyanohydrins, especially those with masked olefins $^{28}$ (e.g., 308 or 310) or electronic biases for α-addition (e.g., 312 $^{29}$), that
will preclude γ-addition (Scheme A13.19). In the case of masked olefin equivalents, following addition, the olefin functionality of 222 can then be exposed by mesylation and elimination of the primary alcohol in addition product 313. 30

Scheme A13.19 Alternative acyl anion equivalents

**A13.7 CONCLUSIONS**

In summary, we have detailed our efforts toward the total synthesis of (+)-isopalhinine A (221) including routes featuring an iridium-catalyzed allylic alkylation of an alkyl-substituted electrophile, a palladium-catalyzed allylic alkylation of an enolate-stabilized lactam, a palladium-catalyzed allylic alkylation of a piperidine, and a diastereoselective alkylation/allylation sequence. Each of these routes to (+)-isopalhinine A (221) preserve the endgame strategy discussed in Section A13.6, wherein variants of key spirocycle 223 is imagined to be advanced to the natural product. Future studies may include further optimization of the iridium-catalyzed allylic alkylation reaction of Section A13.2 using dual metal catalysis and alternative alkylation methods of palladium-catalyzed allylic alkylation intermediate 263 of Section A13.3. The successful completion of this work would represent the first total synthesis of (+)-isopalhinine A (221).
EXPERIMENTAL SECTION

MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Commercially obtained reagents were used as received. Chemicals were purchased from Sigma Aldrich/Strem/Alfa Aesar/Oakwood Chemicals and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Glove box manipulations were performed under a nitrogen atmosphere. Thin-layer chromatography (TLC) and preparatory TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, KMnO₄, or p-anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD-H column (4.6 mm x 25 cm), Chiralpak AD column (4.6 mm x 25 cm), or a Chiralpak OJ column (4.6 mm x 25 cm), all obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. Analytical SFC was performed with a Mettler SFC supercritical CO₂ analytical chromatography system utilizing a Chiralpak OJ-H column (4.6 mm x 25 cm) or Chiralpak AS-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. ⁱH NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer or a Varian Inova 500 MHz spectrometer and are reported relative to residual CHCl₃ (δ 7.26 ppm). ¹³C NMR spectra were recorded on a Bruker Avance HD 400 MHz spectrometer or a Varian Inova 500 MHz spectrometer and are
reported relative to residual CDCl$_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). Some reported spectra include minor solvent impurities of benzene (δ 7.36 ppm), water (δ 1.56 ppm), ethyl acetate (δ 4.12, 2.05, 1.26 ppm), methylene chloride (δ 5.30 ppm), grease (δ 1.26, 0.86 ppm), and/or silicon grease (δ 0.07 ppm), which do not impact product assignments. IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm$^{-1}$).

A13.8.1.1 Preparation of Known Compounds

Previously reported methods were used to prepare ligands (R,R,R$_a$)-L$_1$$_6$ and (S,S,S$_a$)-L$_1$$_7$. (S)-L$_1$$_8$ was purchased from Sigma Aldrich. For the preparation of ligands L$_2$, L$_5$, L$_1$$_1$, and L$_1$$_5$, see chapter or appendix where initially disclosed. Literature procedures were used to prepare known compounds 228–230, 232, 239, 264, 287, 293.
A13.8.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

A13.8.2.1 Experimental Procedures and Spectroscopic Data for the Synthesis of Synthetic Intermediates in Section A13.2

**(E)-6-(Benzyloxy)hex-2-en-1-yl methyl carbonate (226).** Pyridine (2.8 mL, 34 mmol, 3.0 equiv) was added to a solution of alcohol 230\(^1\) (2.4 g, 11 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (100 mL) at 0 °C, followed by addition of methyl chloroformate (1.3 mL, 17 mmol, 1.5 equiv) dropwise. The resulting solution was allowed to warm to ambient temperature and was stirred for 18 h. The reaction was quenched with the addition of 1 M HCl (20 mL) and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to give carbonate 226 as a colorless oil (2.7 g, 89% yield): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.43 – 7.28 (m, 5H), 5.91 – 5.72 (m, 1H), 5.60 (dtt, \(J\) = 15.5, 6.5, 1.4 Hz, 1H), 4.56 (dq, \(J\) = 6.4, 1.0 Hz, 2H), 4.49 (s, 2H), 3.78 (s, 3H), 3.47 (t, \(J\) = 6.4 Hz, 2H), 2.17 (q, \(J\) = 7.1 Hz, 2H), 1.71 (dq, \(J\) = 8.3, 6.5 Hz, 2H).

![Tert-butyl 3-allyl-2,4-dioxopiperidine-1-carboxylate (233).](image)

**Tert-butyl 3-allyl-2,4-dioxopiperidine-1-carboxylate (233).** To a solution of \(\beta\)-ketolactam 232\(^7\) in DMSO (50 mL) was added potassium carbonate (2.6 g, 19 mmol, 1.0
equiv) followed by allyl iodide (1.6 mL, 17 mmol, 0.9 equiv). The resulting solution was stirred for 18 h at ambient temperature, whereupon the reaction mixture was directly purified by silica gel flash column chromatography (30–50% EtOAc/hexanes) to give allyl 233 as a tan oil (1.8 g, 37% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.90 (ddtd, $J$ = 17.1, 10.2, 7.0, 1.0 Hz, 1H), 5.23 – 4.96 (m, 2H), 4.62 – 4.39 (m, 1H), 3.88 – 3.68 (m, 1H), 3.61 – 3.42 (m, 1H), 2.80 – 2.41 (m, 4H), 1.55 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 202.5, 166.6, 151.6, 135.5, 117.3, 84.4, 60.7, 39.7, 38.1, 28.1, 27.56.

**Methyl 5-((tert-butoxycarbonyl)amino)-2-((tert-butyldimethylsilyl)oxy)ethyl)-3-oxopentanoate (234).** To a suspension of NaH (2.8 g, 82 mmol, 1.2 equiv, 60% in mineral oil) in DME (300 mL) was added a solution of $\beta$-ketoester 239 (17 g, 71 mmol, 1.0 equiv) in DME (100 mL) followed by a solution of (2-bromoethoxy)(tert-butyldimethylsilane (19 g, 78 mmol, 1.1 equiv) and sodium iodide (5.4 g, 36 mmol, 0.5 equiv) in DME (50 mL). The resulting solution was heated under reflux for 18 h, then cooled to ambient temperature, filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (20–80% EtOAc/hexanes) to give silyl ether 234 as a pale orange oil (20 g, 69% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.97 (s, 1H), 3.78 – 3.67 (m, 4H), 3.61 (td, $J$ = 6.0, 1.7 Hz, 2H), 3.37 (q, $J$ = 5.9 Hz, 2H), 2.93 – 2.64 (m, 2H), 2.13 – 1.99 (m, 2H), 1.42 (s, 9H), 0.87 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 205.3, 170.1, 155.9, 79.4, 60.5, 55.5, 52.6, 42.4, 35.2, 31.1, 28.5, 26.0, 18.4, -5.3.
Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A

**Tert-butyl (S)-3-allyl-3-((S)-6-(benzyloxy)hex-1-en-3-yl)-2,4-dioxopiperidine-1-carboxylate (235).** Please note Absolute and relative stereochemistry were not determined, and the structure is drawn by analogy to previous work.⁹ A general procedure for the optimization reactions (Table A13.1) is as follows. In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]₂ (2.7 mg, 0.0040 mmol, 2 mol %), ligand (0.0080 mmol, 4 mol %), TBD (2.8 mg, 0.020 mmol, 10 mol%), and THF (1 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with additive (0.40 mmol, 200 mol %), nucleophile 233 (103 mg, 0.40 mmol, 2.0 equiv), and THF (1 mL). The pre-formed catalyst solution (vial A) was then transferred to vial B followed by carbonate 226 (53 mg, 0.20 mmol, 1.0 equiv). The vial was sealed and stirred at 23 °C. After 18 h, the vial was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The regioselectivity was determined by TOF LCMS (PMM_10min_50-80 ACN-AcOH). The crude mixture was purified by silica gel flash column chromatography (5–20% EtOAc/hexanes) to give allylic alkylation product 235 as a colorless oil and an inseparable mixture of branched and linear isomers: ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.05 (m, 5H), 5.74 – 5.41 (m, 2H), 5.36 – 4.91 (m, 4H), 4.46 (d, J = 4.7 Hz, 2H), 3.93 – 3.62 (m, 2H), 3.49 – 3.33 (m, 2H), 2.70 – 2.44 (m, 6H), 2.03 (q, J = 7.3 Hz, 1H), 1.62 (dt, J = 8.7, 6.6 Hz, 2H), 1.54 (s, 9H); ¹³C NMR (101 MHz,
Tert-butyl (3-oxo-3-(2-oxotetrahydrofuran-3-yl)propyl)carbamate (238). To a solution of silyl ether 234 (7.6 g, 19 mmol, 1.0 equiv) in THF (200 mL) was added TBAF (25 mL, 25 mmol, 1.3 equiv). The resulting solution was stirred at ambient temperature for 7 h, whereupon the reaction mixture was concentrated onto silica gel under reduced pressure and purified by silica gel flash column chromatography (50–70% EtOAc/hexanes) to give lactone 238 as a pale pink oil (4.4 g, 91% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.92 (s, 1H), 4.46 – 4.24 (m, 2H), 3.80 – 3.66 (m, 1H), 3.52 – 3.27 (m, 2H), 3.27 – 3.09 (m, 1H), 2.95 – 2.69 (m, 2H), 2.32 (dddd, $J$ = 13.3, 9.3, 7.9, 5.7 Hz, 1H), 1.42 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 201.9, 172.5, 155.8, 79.5, 67.5, 52.2, 42.7, 35.1, 28.4, 23.8.

(E)-(((6-Chlorohex-4-en-1-yl)oxy)methyl)benzene (240, LG = Cl). To a solution of N-chlorosuccinimide (1.9 g, 14 mmol, 1.5 equiv) in CH$_2$Cl$_2$ (40 mL) at 0 °C was added dimethyl sulfide (1.3 mL, 17 mmol, 1.9 equiv) dropwise over 5 min. A solution of alcohol 230$^{4,5}$ (1.9 g, 9.3 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (10 mL) was then added and the resulting solution was stirred at 0 °C for 2 h, whereupon the mixture was allowed to warm to ambient temperature and was stirred for 18 h. The reaction was quenched with
the addition of \( \text{H}_2\text{O} \) (20 mL), and the aqueous layer was extracted with \( \text{Et}_2\text{O} \) (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over \( \text{Na}_2\text{SO}_4 \), and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (5% EtOAc/hexanes) to provide chloride 240 as a pale yellow oil (1.7 g, 83% yield): \( ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta 7.38 – 7.26 \text{ (m, 5H)}, 5.82 – 5.72 \text{ (m, 1H)}, 5.66 – 5.58 \text{ (m, 1H)}, 4.50 \text{ (s, 2H)}, 4.02 \text{ (dd, } J = 7.1\text{, } 1.0 \text{ Hz, 2H)}, 3.48 \text{ (t, } J = 6.4 \text{ Hz, 2H)}, 2.25 – 2.07 \text{ (m, 2H)}, 1.81 – 1.61 \text{ (m, 2H)); } ^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \delta 138.6, 135.5, 128.5, 127.8, 127.7, 126.5, 73.1, 69.6, 45.5, 29.0, 28.9 \). (3aS,7aR)-3a-((S)-6-(Benzyloxy)hex-1-en-3-yl)-7a-hydroxyhexahydrofuro[3,2-c]pyridin-4(2H)-one (241). Please note Absolute and relative stereochemistry were not determined, and the structure is drawn by analogy to previous work.\(^9\) A general procedure for the optimization reactions (Table A13.2) is as follows. In a nitrogen-filled glove box, to a 1 dram vial (vial A) equipped with a stir bar was added \([\text{Ir(cod)Cl}]_2\) (1.3 mg, 0.0020 mmol, 2 mol %), ligand (0.0040 mmol, 4 mol %), TBD (1.4 mg, 0.010 mmol, 10 mol %), and THF (0.5 mL). Vial A was stirred at 25 °C (ca. 10 min) while another 1 dram vial (vial B) was charged with additive (0.20 or 0.40 mmol, 200 or 400 mol %), lactone nucleophile 238 (52 mg, 0.20 mmol, 2.0 equiv), and THF (0.5 mL). The pre-formed catalyst solution (vial A) was then transferred to vial B followed by electrophile 240 (0.10 mmol, 1.0 equiv). The vial was sealed and stirred at 60 °C. After 18 h, the vial was
removed from the glove box and concentrated under reduced pressure to give lactone allylic alkylation product 237.

To crude 237 was added TFA/CH$_2$Cl$_2$ (1:1, 1 mL) and the resulting solution was stirred for 3 h, whereupon NEt$_3$/CH$_2$Cl$_2$ (1:1, 1 mL) was added. The resulting solution was stirred for 18 h, whereupon brine (1 mL) was added. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic layers were dried over Na$_2$SO$_4$, concentrated under reduced pressure and 1,2,4,5-tetrachloro-3-nitrobenzene (0.10 mmol in 0.5 mL CDCl$_3$) was added. The NMR yield (measured in reference to 1,2,4,5-tetrachloro-3-nitrobenzene $\delta$ 7.74 ppm (s, 1H)) was determined by $^1$H NMR analysis of the crude mixture. The residue was purified by preparatory TLC (50% acetone/hexanes) to afford hemiacetal 241 as an inseparable mixture of diastereomers. The major diastereomer was isolated by preparatory HPLC (reverse phase, MeCN/H$_2$O, C18 column): 96% ee; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 – 7.27 (m, 5H), 5.75 – 5.49 (m, 2H), 5.21 – 4.91 (m, 2H), 4.48 (s, 2H), 4.04 – 3.94 (m, 1H), 3.70 (dddd, $J = 16.7, 9.9, 8.3, 7.1$ Hz, 1H), 3.53 – 3.28 (m, 3H), 3.22 – 3.07 (m, 1H), 2.69 – 2.41 (m, 3H), 2.39 – 2.11 (m, 3H), 1.89 (dd, $J = 13.6, 4.9$ Hz, 1H), 1.67 (tdd, $J = 10.6, 7.1, 4.2$ Hz, 2H), 1.51 – 1.38 (m, 1H), 1.24 (ddt, $J = 17.0, 8.8, 4.4$ Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.4, 173.9, 140.2, 139.4, 138.8, 138.7, 128.5, 128.5, 128.5, 127.9, 127.8, 127.7, 127.6, 118.3, 116.4, 103.4, 103.3, 73.1, 72.9, 70.4, 69.8, 65.6, 65.1, 59.4, 58.9, 48.2, 47.2, 38.3, 38.3, 35.7, 33.9, 32.0, 30.6, 28.4, 27.6, 27.6, 26.5; HPLC conditions: 8% IPA, 1.0 mL/min, Chiralpak AD–H column, $\lambda = 210$ nm, t$_R$ (min): major = 21.087, minor = 21.876.
(3R,3aS,7aS)-3-(3-(Benzyloxy)propyl)-2-hydroxy-2-methyltetrahydro-7a,3a-(epoxyethano)furo[3,2-c]pyridin-4(5H)-one (243). To a solution of hemiacetal 241 (13 mg, 0.036 mmol, 1.0 equiv) in dioxane/H₂O (7:1, 0.5 mL) was added PdCl₂ (1.0 mg, 0.0056 mmol, 0.16 equiv) and copper(I) chloride (3.6 mg, 0.036 mmol, 1.0 equiv). The resulting solution was sparged with oxygen (balloon) and stirred under an oxygen atmosphere for 4 h, whereupon the reaction mixture was filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (30% acetone/hexanes) to provide 243 as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.28 (m, 5H), 6.03 (s, 1H), 4.49 (d, J = 2.4 Hz, 2H), 4.25 (td, J = 8.6, 6.8 Hz, 1H), 3.86 (td, J = 8.3, 3.8 Hz, 1H), 3.57 – 3.40 (m, 2H), 3.21 (dp, J = 6.8, 2.9 Hz, 2H), 2.95 (s, 1H), 2.45 (ddd, J = 13.5, 6.7, 3.9 Hz, 1H), 2.23 (dt, J = 13.4, 8.5 Hz, 1H), 2.17 (s, 1H), 2.16 – 2.07 (m, 2H), 1.96 (ddd, J = 13.5, 8.2, 5.4 Hz, 2H), 1.78 (dq, J = 8.6, 3.4, 2.1 Hz, 5H), 1.53 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 176.4, 138.7, 128.5, 127.9, 127.6, 115.1, 104.8, 73.1, 70.6, 67.2, 54.9, 53.5, 37.9, 35.3, 31.1, 30.7, 29.9, 28.7, 28.2, 23.6.
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(3aS,7aS)-3-(3-(benzyloxy)propyl)-2-methyl-6,7-dihydro-7a,3a-(epoxyethano)furo[3,2-c]pyridin-4(5H)-one (244). Olefin 244 was isolated as a byproduct in the synthesis and/or purification of 243. The amount of olefin 244 was found to increase when the crude reaction mixture of 243 was subjected to reduced pressure: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43 – 7.27 (m, 5H), 6.06 (d, $J$ = 5.4 Hz, 1H), 4.47 (s, 2H), 4.01 (ddd, $J$ = 8.4, 5.3, 2.9 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.42 (t, $J$ = 6.4 Hz, 2H), 3.31 – 3.12 (m, 2H), 2.34 (dt, $J$ = 13.5, 2.9 Hz, 1H), 2.26 – 2.19 (m, 3H), 1.83 (s, 3H), 1.71 (td, $J$ = 8.4, 4.5 Hz, 4H), 0.99 – 0.69 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 207.2, 173.8, 152.8, 138.6, 128.5, 127.8, 114.7, 106.2, 73.0, 69.8, 66.9, 64.5, 37.9, 34.46, 31.1, 29.5, 20.7, 11.6.

2-((S)-3-((S)-6-(Benzyloxy)hex-1-en-3-yl)-2,4-dioxopiperidin-3-yl)acetaldehyde (245). To a solution of hemiacetal 241 (56 mg, 0.16 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (5 mL) was added Dess–Martin periodinane (83 g, 0.20 mmol, 1.2 equiv). The resulting solution was heated in a sealed vial to 50 °C for 2.5 h, whereupon the reaction mixture was cooled to ambient temperature, diluted with Et$_2$O, sequentially washed with 10% aqueous Na$_2$S$_2$O$_3$/saturated aqueous NaHCO$_3$ mixture (1:1, 10 mL) and brine (20 mL), dried over
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Na$_2$SO$_4$, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (50% EtOAc/hexanes then 50% acetone/hexanes) to provide 245 as a colorless oil (26 mg, 46% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.52 (s, 1H), 7.36 – 7.27 (m, 5H), 6.45 (d, $J = 14.5$ Hz, 1H), 5.49 (ddt, $J = 43.8, 16.9, 10.0$ Hz, 1H), 5.19 (td, $J = 10.3, 1.7$ Hz, 1H), 5.10 – 5.02 (m, 1H), 4.46 (s, 3H), 3.74 (ddt, $J = 12.0, 5.5, 2.6$ Hz, 1H), 3.63 (ddt, $J = 14.2, 6.4, 3.6$ Hz, 1H), 3.57 – 3.47 (m, 1H), 3.42 (dddd, $J = 8.7, 7.3, 3.5, 2.2$ Hz, 3H), 3.37 – 3.15 (m, 2H), 3.01 – 2.81 (m, 1H), 2.74 – 2.59 (m, 1H), 2.46 (dd, $J = 12.2, 10.0, 2.3$ Hz, 1H), 1.75 – 1.60 (m, 3H), 1.45 – 1.16 (m, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 207.6, 207.2, 199.9, 173.8, 173.1, 138.5, 136.6, 136.4, 128.5, 127.8, 127.7, 119.9, 119.2, 89.5, 73.0, 72.9, 69.7, 59.9, 59.3, 50.6, 50.4, 49.2, 38.9, 37.9, 36.7, 36.5, 28.0, 27.9, 26.9, 25.9.

(7$R$,7a$S$)-(3-(Benzyloxy)propyl)-9-hydroxydihydro-5$H$-4a,7a-(epoxyethano)cyclopenta[c]pyridine-1,6(2$H$,7$H$)-dione (247). To a solution of aldehyde 245 (39 mg, 0.11 mmol, 1.0 equiv) in dioxane/H$_2$O (7:1, 1.5 mL) was added PdCl$_2$ (2.0 mg, 0.011 mmol, 0.1 equiv) and copper(I) chloride (11 mg, 0.11 mmol, 1.0 equiv). The resulting solution was sparged with oxygen (balloon) and stirred under an oxygen atmosphere for 18 h, whereupon the reaction mixture was filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (75% acetone/hexanes)
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To provide 247 as a colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (d, $J$ = 0.9 Hz, 5H), 5.55 (d, $J$ = 6.1 Hz, 1H), 4.53 – 4.45 (m, 4H), 3.55 – 3.40 (m, 4H), 3.20 (dt, $J$ = 7.7, 4.0 Hz, 3H), 2.88 – 2.75 (m, 1H), 2.66 – 2.41 (m, 3H), 2.33 (t, $J$ = 6.7 Hz, 1H), 2.22 – 2.07 (m, 2H), 1.92 (ddd, $J$ = 13.8, 8.8, 5.4 Hz, 1H), 1.88 – 1.70 (m, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.8, 138.5, 128.4, 127.8, 127.6, 116.1, 107.0, 99.8, 72.9, 70.4, 55.0, 38.2, 37.8, 35.8, 28.5, 27.9, 27.6, 24.7.

![Chemical Structure](image.png)

(3S,4S)-3-((S)-6-(Benzyloxy)hex-1-en-3-yl)-4-hydroxy-3-(2-hydroxyethyl)piperidin-2-one (248). Please note Relative stereochemistry was not confirmed. To a solution of hemiacetal 241 (25 mg, 0.072 mmol, 1.0 equiv) in MeOH (1 mL) was added NaBH$_4$ (8.0 mg, 0.22 mmol, 3.0 equiv). The resulting solution was stirred for 18 h, whereupon the reaction was quenched with a saturated aqueous solution of sodium citrate (1 mL) and extracted with EtOAc (3 x 5 mL), washed with brine (5 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (33% acetone/hexanes) to provide hydroxy 248 as a colorless oil (11 mg, 44% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39 – 7.26 (m, 5H), 5.99 (ddd, $J$ = 17.3, 8.6, 2.6 Hz, 1H), 5.85 – 5.67 (m, 1H), 5.27 – 5.04 (m, 2H), 4.48 (d, $J$ = 3.0 Hz, 2H), 4.03 (ddd, $J$ = 23.5, 7.0, 4.3 Hz, 1H), 3.94 – 3.64 (m, 2H), 3.58 – 3.39 (m, 3H), 3.26 (dddd, $J$ = 14.5, 11.7, 6.9, 4.0 Hz, 1H), 2.70 (dt, $J$ = 9.4, 6.0, 2.6 Hz, 1H), 2.16 – 1.98 (m, 3H), 1.94 – 1.82 (m, 1H), 1.81 – 1.65 (m, 2H), 1.44 (ddt, $J$ = 13.8, 10.5, 7.7 Hz, 2H); $^{13}$C NMR (101 MHz,
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CDCl$_3$ $\delta$ 176.4, 176.3, 140.5, 138.7, 138.7, 138.6, 128.5, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 118.3, 117.6, 73.0, 72.9, 71.4, 70.9, 70.4, 70.3, 59.5, 59.4, 52.5, 52.1, 47.7, 46.4, 38.0, 37.8, 37.3, 33.9, 28.9, 27.9, 27.8, 26.7, 26.1, 24.9.

2-((3$S$,4$S$)-3-((S)-6-(Benzyloxy)hex-1-en-3-yl)-4-hydroxy-2-oxopiperidin-3-yl)acetaldehyde (249). To solution of alcohol 248 (10 mg, 0.029 mmol, 1.0 equiv) in MeCN (1 mL) was added IBX (25 mg, 0.089 mmol, 3.0 equiv). The resulting solution was stirred for 18 h, whereupon the reaction mixture was filtered through celite, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (44% acetone/hexanes) to provide aldehyde 249 as a colorless oil (4.0 mg, 40% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.52 (s, 1H), 7.36 – 7.28 (m, 5H), 5.45 (dt, $J = 16.9$, 10.1 Hz, 1H), 5.20 (ddd, $J = 11.4$, 10.1, 1.8 Hz, 1H), 5.07 (dddd, $J = 17.0$, 12.4, 1.8, 0.6 Hz, 1H), 4.47 (s, 3H), 3.83 – 3.72 (m, 1H), 3.66 (ddd, $J = 6.2$, 4.6, 2.5 Hz, 1H), 3.61 – 3.48 (m, 1H), 3.48 – 3.37 (m, 3H), 3.33 (dd, $J = 18.9$, 5.4 Hz, 1H), 3.02 – 2.83 (m, 1H), 2.75 – 2.61 (m, 1H), 2.51 – 2.40 (m, 1H), 1.75 – 1.63 (m, 2H), 1.54 – 1.14 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 207.5, 206.9, 199.9, 199.8, 173.7, 172.9, 138.6, 136.6, 136.4, 128.5, 127.9, 127.8, 127.72, 127.71, 119.9, 119.2, 73.0, 72.9, 69.8, 69.7, 60.0, 59.4, 50.7, 50.6, 50.5, 49.4, 38.9, 38.0, 36.8, 36.6, 28.0, 27.9, 27.0, 26.0.
A13.8.2.2 Experimental Procedures and Spectroscopic Data for the Synthesis of Synthetic Intermediates in Section A13.3

Allyl 7-ethyl-9-(4-methoxybenzoyl)-3,3-dimethyl-8-oxo-1,5-dioxa-9-azaspiro[5.5]undecane-7-carboxylate (256). To a solution of LiHMDS (0.89 g, 5.4 mmol, 1.1 equiv) in THF (20 mL) at –78 °C was added a solution of protected lactam 295 (1.6 g, 4.9 mmol, 1.0 equiv) in THF (20 mL). The resulting mixture was stirred for 2 h at –78 °C, whereupon allyl chloroformate (0.59 g, 5.4 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred for 3 h at –78 °C followed by an additional 18 h at –50 °C. The reaction was quenched with the addition of brine (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL), washed with brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (35% EtOAc/hexanes) to provide acylated-295 as a colorless oil (0.70 g, 34% yield).

To a solution of acylated-295 (0.20 g, 0.48 mmol, 1.0 equiv) in acetone (5 mL) was added potassium carbonate (0.33 g, 2.4 mmol, 5.0 equiv) and ethyl iodide (0.39 mL, 4.8 mmol, 10.0 equiv). The resulting solution was stirred for 18 h at ambient temperature, whereupon the mixture was filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (50% EtOAc/hexanes) to provide ethyl 256 as a colorless oil (36 mg, 17% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.71 (m, 2H), 6.95 – 6.75 (m, 2H), 6.09 – 5.82 (m,
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1H), 5.51 – 5.19 (m, 2H), 4.86 – 4.60 (m, 2H), 3.82 (s, 4H), 3.79 – 3.40 (m, 6H), 2.74 (dt, \( J = 14.6, 5.2 \) Hz, 1H), 2.46 – 2.08 (m, 3H), 1.20 (s, 3H), 1.02 (t, \( J = 7.4 \) Hz, 3H), 0.76 (s, 3H).

\((R)-7\text{-Allyl-7-ethyl-9-(4-methoxybenzoyl)-3,3\text{-dimethyl-1,5-dioxa-9-azaspiro[5.5]undecan-8-one}}\) (257). In a nitrogen-filled glove box, to a 1 dram vial equipped with a stir bar was added \( \text{Pd}_2(\text{dba})_3 \) (3.7 mg, 0.0040 mmol, 5 mol %), \((S)-\text{L15}\) (5.2 mg, 0.010 mmol, 12.5 mol %), and hexanes/toluene (2:1, 2.7 mL). The resulting solution was stirred at 25 °C for 10 min, whereupon substrate 256 (36 mg, 0.081 mmol, 1.0 equiv) was added. The vial was sealed and stirred at 35 °C for 18 h, whereupon the vial was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (30% EtOAc/hexanes) to provide allylic alkylation product 257 as a colorless solid (7.4 mg, 46% yield): 93% ee; \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta \) 7.52 (d, \( J = 8.9 \) Hz, 2H), 6.86 (d, \( J = 8.8 \) Hz, 2H), 6.23 – 6.00 (m, 1H), 5.18 – 4.93 (m, 2H), 3.83 (s, 3H), 3.77 – 3.56 (m, 4H), 3.43 (ddd, \( J = 11.7, 5.2, 2.6 \) Hz, 2H), 2.91 – 2.59 (m, 3H), 2.30 (ddd, \( J = 14.5, 8.5, 7.3 \) Hz, 1H), 2.15 – 1.98 (m, 1H), 1.93 (dt, \( J = 14.4, 7.4 \) Hz, 1H), 1.20 (s, 3H), 0.99 (t, \( J = 7.5 \) Hz, 3H), 0.77 (s, 3H); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \( \delta \) 176.8, 175.3, 162.4, 136.5, 130.1, 128.9, 116.5, 113.6, 100.3, 70.4, 56.8, 55.5, 41.5, 33.2, 29.9, 25.2, 23.7, 22.5, 20.1, 9.1; SFC conditions: 3% MeOH, 3.0 mL/min, Chiralpak OJ–H column, \( \lambda = 210 \) nm, \( t_r \) (min): major = 18.627, minor = 4.817.
9-(4-Methoxybenzoyl)-3,3-dimethyl-1,5-dioxa-9-azaspiro[5.5]undecan-8-one (258).

To a solution of 232\(^7\) (45 g, 210 mmol, 1.0 equiv) in toluene (300 mL) was added para-toluenesulfonic acid (2.0 g, 11 mmol, 0.05 equiv) and 2,2-dimethyl-1,3-propanediol (33 g, 320 mmol, 1.5 equiv). The resulting solution was heated under reflux for 18 h with azeotropic removal of water via Dean–Stark trap, whereupon the mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude residue was purified by recrystallization from boiling EtOAc to give the protected ketone-232 (23 g, 54% yield).

To a solution of protected ketone-232 (1.5 g, 7.5 mmol, 1.0 equiv) in THF (25 mL) was added NE\textsubscript{T}\textsubscript{3} (1.6 mL, 11.3 mmol, 1.5 equiv), 4-dimethylaminopyridine (0.91 g, 0.75 mmol, 0.1 equiv), and para-anisoyl chloride (1.3 mL, 9.8 mmol, 1.3 equiv). The resulting solution was stirred at ambient temperature for 18 h, whereupon the mixture was filtered through celite, rinsing CH\textsubscript{2}Cl\textsubscript{2}, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (20% acetone/hexanes) to afford protected lactam 258 as a white solid (1.3 g, 54% yield): \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 7.59\) (d, \(J = 8.9\) Hz, 2H), 6.88 (d, \(J = 8.9\) Hz, 2H), 3.84 (s, 3H), 3.82 – 3.75 (m, 2H), 3.55 (s, 4H), 2.92 (t, \(J = 1.0\) Hz, 2H), 2.35 – 2.21 (m, 2H), 1.00 (d, \(J = 6.4\) Hz, 6H); \(^{13}\)C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta 173.6, 170.6, 162.9, 130.9, 127.6, 113.6, 96.4, 70.8, 55.5, 43.3, 41.9, 30.3, 30.2, 22.6, 22.6.

![Chemical structure of 258](image)
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2-Methylallyl 9-(4-methoxybenzoyl)-3,3-dimethyl-8-oxo-1,5-dioxa-9-azaspiro[5.5]undecane-7-carboxylate (259). To a solution of LiHMDS (1.1 g, 6.6 mmol, 1.1 equiv) in THF (40 mL) at –78 °C was added a solution of protected lactam 258 (2.0 g, 6.0 mmol, 1.0 equiv) in THF (40 mL). The resulting mixture was stirred for 2 h at –78 °C, whereupon methallyl chloroformate (0.83 g, 6.6 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred for 2 h at –78 °C followed by an additional 18 h at –60 °C. The reaction was quenched with the addition of brine (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 40 mL), washed with brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (20–40% EtOAc/hexanes) to provide acylated 259 as a colorless foam (2.1 g, 80% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 5.12 – 4.92 (m, 2H), 4.77 – 4.55 (m, 2H), 4.27 (d, J = 2.2 Hz, 1H), 4.12 (q, J = 7.2 Hz, 1H), 3.83 (s, 4H), 3.81 – 3.67 (m, 2H), 3.63 – 3.43 (m, 3H), 2.55 (ddd, J = 13.8, 12.5, 5.9 Hz, 1H), 2.28 (ddt, J = 13.8, 4.5, 2.4 Hz, 1H), 1.79 (d, J = 0.6 Hz, 3H), 1.07 (s, 3H), 0.93 (s, 3H).
2-Methylallyl 7-allyl-9-(4-methoxybenzoyl)-3,3-dimethyl-8-oxo-1,5-dioxa-9-azaspiro[5.5]undecane-7-carboxylate (260). In a nitrogen-filled glove box, to a 2 dram vial (vial A) equipped with a stir bar was added [Ir(cod)Cl]$_2$ (31 mg, 0.046 mmol, 2 mol %), rac-L$_2$ (42 mg, 0.093 mmol, 4 mol %), TBD (32 mg, 0.23 mmol, 10 mol %), and THF (5 mL). Vial A was stirred at 25 °C (ca. 10 min) while another a 100 mL round bottom flask was charged with β-ketoamide 259 (1.0 g, 2.3 mmol, 1.0 equiv), LiBr (0.40 g, 4.6 mmol, 2.0 equiv), and THF (15 mL). The pre-formed catalyst solution (vial A) was then transferred to the round bottom flask followed by allyl methyl carbonate (0.40 g, 3.5 mmol, 1.5 equiv). The flask was removed from the glove box, placed under an argon atmosphere, and stirred at ambient temperature for 3.5 h, whereupon the reaction mixture was filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to afford allylated 260 (0.98 g, 90% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.81 – 7.71 (m, 2H), 6.89 – 6.78 (m, 2H), 6.00 (dddd, $J = 16.8, 10.1, 7.7, 6.5$ Hz, 1H), 5.14 – 5.02 (m, 2H), 4.97 (td, $J = 4.3, 3.6, 2.2$ Hz, 2H), 4.69 – 4.50 (m, 2H), 3.06 (s, 3H), 2.78 (dt, $J = 14.6, 4.9$ Hz, 1H), 2.24 (ddd, $J = 14.6, 10.3, 5.8$ Hz, 1H), 1.76 (s, 3H), 1.20 (s, 3H), 0.76 (s, 3H).
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(R)-7- Allyl-9-(4-methoxybenzoyl)-3,3-dimethyl-7-(3-methylbut-3-en-1-yl)-1,5-dioxa-9-azaspiro[5.5]undecan-8-one (rac-261). In a nitrogen-filled glove box, to a 100 mL round bottom flask equipped with a stir bar was added Pd(PPh₃)₄ (46 mg, 0.040 mmol, 0.05 equiv), substrate 260 (0.37 g, 0.79 mmol, 1.0 equiv), and toluene (20 mL). The flask was removed from the glove box, placed under an argon atmosphere, and stirred at 35 °C for 18 h, whereupon the reaction mixture was filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to afford allylic alkylation product rac-261 (0.29 g, 84% yield): 24% ee; ¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.52 (m, 2H), 6.90 – 6.78 (m, 2H), 6.12 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H), 5.11 – 4.94 (m, 2H), 4.83 (ddd, J = 10.4, 2.4, 1.3 Hz, 2H), 3.83 (s, 4H), 3.70 (dd, J = 10.4, 2.4 Hz, 2H), 3.55 (ddd, J = 12.6, 10.3, 6.0 Hz, 1H), 3.46 (ddd, J = 11.7, 3.9, 2.5 Hz, 2H), 2.92 – 2.69 (m, 3H), 2.69 – 2.49 (m, 2H), 2.21 (ddd, J = 14.6, 10.2, 6.5 Hz, 1H), 1.72 (d, J = 0.6 Hz, 3H), 1.23 (s, 3H), 0.78 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.9, 174.7, 162.5, 143.1, 136.8, 130.7, 128.4, 116.6, 115.9, 113.5, 99.6, 70.4, 56.9, 55.5, 41.4, 41.0, 36.8, 29.9, 24.7, 23.9, 22.6, 20.2; SFC conditions: 3% MeOH, 3.0 mL/min, Chiralpak AS-H column, λ = 210 nm, tᵣ (min): major = 11.875, minor = 10.765.
(R)-2-(9-(4-Methoxybenzoyl)-3,3-dimethyl-8-oxo-7-(3-oxobutyl)-1,5-dioxo-9-azaspiro[5.5]undecan-7-yl)acetaldehyde (262). A solution of olefin 261 (20 mg, 0.047 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (5 mL) was cooled to −78 °C. Ozone was bubbled through the reaction mixture for 0.5 h, whereupon the reaction mixture was sparged with N$_2$ and triphenylphosphine (25 mg, 0.094 mmol, 2.0 equiv) was added. The cooling bath was then removed and the reaction was stirred for 1.5 h at ambient temperature. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel flash column chromatography (40% EtOAc/hexanes) to afford aldehyde 262 as a colorless oil (17 mg, 82% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 9.59 (s, 1H), 7.67 (d, $J = 8.9$ Hz, 2H), 6.88 (d, $J = 8.9$ Hz, 3H), 3.83 (s, 4H), 3.78 – 3.61 (m, 5H), 3.42 (ddd, $J = 11.9$, 7.3, 2.6 Hz, 2H), 3.20 (d, $J = 15.8$ Hz, 1H), 3.11 (dd, $J = 16.0$, 2.6 Hz, 1H), 2.96 (d, $J = 15.9$ Hz, 1H), 2.81 (dd, $J = 16.1$, 2.1 Hz, 1H), 2.48 (qdd, $J = 14.6$, 6.9, 5.6 Hz, 2H), 2.21 (s, 3H), 1.16 (s, 3H), 0.77 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 206.4, 199.1, 174.2, 173.9, 162.8, 130.8, 127.6, 113.5, 98.4, 70.4, 56.2, 55.4, 46.3, 45.1, 41.2, 31.8, 29.6, 23.4.
14-(4-Methoxybenzoyl)-3,3-dimethyl-1,5-dioxo-14-azadispiro[5.0.5.4]hexadec-10-ene-9,13-dione (263). To a solution of bis-carbonyl 262 (20 mg, 0.046 mmol, 1.0 equiv) in toluene (2 mL) was added para-toluenesulfonic acid monohydrate (1 mg, 0.0046 mmol, 0.1 equiv) and MgSO$_4$ (20 mg, 100 wt %). The resulting slurry was heated to 100 °C for 0.5 h, whereupon the mixture was cooled to ambient temperature, filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by preparatory TLC (40% acetone/hexanes) to afford enone 263 as a colorless oil (10 mg, 53% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45 – 7.36 (m, 2H), 6.89 (ddd, $J = 10.2$, 5.8, 2.5 Hz, 1H), 6.84 – 6.76 (m, 2H), 6.08 – 5.98 (m, 1H), 3.81 (s, 3H), 3.77 – 3.54 (m, 4H), 3.45 (ddd, $J = 11.7$, 4.1, 2.5 Hz, 2H), 3.12 – 2.76 (m, 4H), 2.58 (dt, $J = 14.7$, 5.9 Hz, 1H), 2.35 (ddd, $J = 14.6$, 8.3, 6.1 Hz, 1H), 1.18 (s, 3H), 0.78 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 197.0, 175.9, 174.2, 162.8, 145.5, 130.3, 129.1, 127.4, 113.7, 98.5, 70.8, 70.7, 56.5, 55.5, 41.6, 39.6, 30.1, 29.4, 23.3, 22.2, 20.0.
A13.8.2.3  Experimental Procedures and Spectroscopic Data for the Synthesis of Synthetic Intermediates in Section A13.4

Allyl 1-benzyl-3-(2-methylallyl)-4-oxopiperidine-3-carboxylate (274). To a solution of NaH (2.2 g, 66 mmol, 2.5 equiv, 60% in mineral oil) in THF (24 mL) at 0 °C was added a solution of 1-benzyl-4-piperidone (5 g, 26 mmol, 1.9 equiv) in THF (10 mL) over 15 min. The resulting mixture was warmed to ambient temperature, diallyl carbonate (5.7 mL, 40 mmol, 1.5 equiv) was added, and the solution was stirred for an additional 18 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl (10 mL) and acidified (pH = 4) with 1 M HCl. The aqueous layer was extracted with EtOAc (3 x 40 mL), washed with brine (40 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to provide acylated-274 as a colorless oil (2.5 g, 35% yield).

To a solution of acylated-274 (0.10 g, 0.37 mmol, 1.0 equiv) in acetone (5 mL) was added potassium carbonate (0.10 g, 0.73 mmol, 2.0 equiv), tetrabutylammonium iodide (14 mg, 0.037 mmol, 0.1 equiv), and methallyl bromide (0.074 mL, 0.73 mmol, 2.0 equiv). The resulting solution was heated to 50 °C for 18 h, whereupon the reaction mixture was cooled to ambient temperature, filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to afford functionalized
piperidone 274 as a colorless oil (78 mg, 65% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.18 (m, 6H), 5.89 (ddt, $J$ = 17.3, 10.4, 5.8 Hz, 1H), 5.44 – 5.16 (m, 2H), 4.80 (s, 1H), 4.71 – 4.56 (m, 3H), 3.72 – 3.54 (m, 2H), 3.49 (dd, $J$ = 11.6, 2.7 Hz, 1H), 3.09 – 2.91 (m, 1H), 2.84 (ddd, $J$ = 15.3, 11.8, 6.6 Hz, 1H), 2.64 (dd, $J$ = 13.9, 0.9 Hz, 1H), 2.46 – 2.34 (m, 3H), 2.29 (d, $J$ = 11.6 Hz, 1H), 1.66 (t, $J$ = 1.1 Hz, 3H).

![Chemical structure](image)

(S)-3-Allyl-1-benzyl-3-(2-methylallyl)piperidin-4-one (275). In a nitrogen-filled glove box, to a 250 mL round bottom flask equipped with a stir bar was added Pd$_2$(dba)$_3$ (81 mg, 0.088 mmol, 2.5 mol %), (S)-L18 (85 mg, 0.22 mmol, 6.25 mol %), and THF (110 mL). The resulting solution was stirred at 25 °C for 10 min, whereupon substrate 274 (1.2 g, 3.5 mmol, 1.0 equiv) was added. The flask was sealed and stirred at ambient temperature. After 18, the flask was removed from the glove box and filtered through a pad of silica, rinsing with EtOAc, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (8% EtOAc/hexanes) to provide allylic alkylation product 275 as a colorless oil (7.4 mg, 46% yield): 82% ee; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 – 7.21 (m, 5H), 5.75 – 5.58 (m, 1H), 5.12 – 4.95 (m, 2H), 4.84 (dq, $J$ = 2.9, 1.5 Hz, 1H), 4.68 (dq, $J$ = 2.0, 0.9 Hz, 1H), 3.68 – 3.47 (m, 2H), 2.78 (dddd, $J$ = 8.4, 6.4, 3.1, 1.5 Hz, 1H), 2.69 – 2.56 (m, 4H), 2.53 – 2.45 (m, 2H), 2.46 – 2.36 (m, 2H), 1.68 (t, $J$ = 1.0 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 212.3, 142.1, 138.7, 133.9, 128.9, 128.5, 127.4, 118.3, 115.3, 62.4, 62.3, 53.5, 52.3, 42.3, 39.54, 38.9,
Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A

24.6; HPLC conditions: 1% EtOH, 1.0 mL/min, Chiralpak OJ column, λ = 210 nm, tR (min): major = 10.113, minor = 8.486.

(3S,4R)-3-Allyl-1-benzyl-3-(2-methylallyl)piperidin-4-ol (276). Please note Relative stereochemistry was not confirmed. To a solution of ketone 275 (0.50 g, 1.8 mmol, 1.0 equiv) in CH2Cl2 (20 mL) at 0 °C was added (S)-CBS (1 M, 0.35 mL, 0.35 mmol, 0.2 equiv) followed by BH3•DMS (2 M, 1.8 mL, 3.5 mmol, 2.0 equiv). The resulting solution was stirred for 1.5 h, whereupon the reaction was quenched with MeOH (5 mL) and a saturated aqueous sodium citrate solution (10 mL) then warmed to ambient temperature and stirred for an additional 15 min. The aqueous layer was extracted with Et2O (3 x 30 mL), dried over Mg2SO4, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to afford alcohol 276 as an inseparable mixture (9:1) of diastereomers and a colorless oil (0.50 g, 59% yield): 1H NMR (400 MHz, CDCl3) δ 7.36 – 7.31 (m, 5H), 5.98 (ddt, J = 17.4, 9.8, 7.5 Hz, 1H), 5.19 – 5.07 (m, 2H), 4.90 (dd, J = 2.6, 1.4 Hz, 1H), 4.80 (dd, J = 2.6, 1.1 Hz, 1H), 3.62 (t, J = 6.9 Hz, 1H), 3.53 (d, J = 13.0 Hz, 1H), 3.34 (d, J = 13.1 Hz, 1H), 2.63 – 2.42 (m, 2H), 2.42 – 2.32 (m, 1H), 2.29 (d, J = 13.3 Hz, 1H), 2.21 – 2.00 (m, 2H), 1.82 (t, J = 1.1 Hz, 3H), 1.80 – 1.69 (m, 3H); 13C NMR (101 MHz, CDCl3) δ 144.1, 139.1, 135.6, 133.4, 132.8, 129.2, 128.7, 128.6, 128.3, 127.1, 126.7, 117.9, 115.2, 62.9, 42.7, 30.1, 26.0, 25.7.
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(3S,4R)-3-Allyl-1-benzyl-4-(methoxymethoxy)-3-(2-methylallyl)piperidine (277). To a solution of alcohol 276 (70 mg, 0.25 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (10 mL) at 0°C was added DIPEA (0.065 mL, 0.38 mmol, 1.5 equiv) and bromomethyl methyl ether (0.040 mL, 0.49 mmol, 2.0 equiv). The resulting mixture was stirred for 3 h, whereupon the reaction was quenched with a saturated aqueous NaHCO$_3$ solution (5 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes) to afford ether 277 as a colorless oil (61 mg, 74% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 – 7.13 (m, 5H), 5.88 (dddt, $J$ = 27.1, 17.3, 10.1, 7.4 Hz, 1H), 5.15 – 4.99 (m, 2H), 4.97 – 4.84 (m, 1H), 4.78 – 4.68 (m, 2H), 4.65 (dd, $J$ = 7.7, 6.9 Hz, 1H), 3.59 – 3.41 (m, 2H), 3.39 (d, $J$ = 1.1 Hz, 4H), 2.75 – 2.30 (m, 4H), 2.30 – 1.89 (m, 5H).

3-Allyl 1-(tert-butyl) 3-(2-methylallyl)-4-oxopiperidine-1,3-dicarboxylate (280). To a solution of NaH (4.2 g, 130 mmol, 2.5 equiv, 60% in mineral oil) in THF (45 mL) at 0 °C was added a solution of 1-Boc-4-piperidone (10.0 g, 50.2 mmol, 1.0 equiv) in THF (20 mL) over 15 min. The resulting mixture was warmed to ambient temperature, diallyl
carbonate (11 mL, 75 mmol, 1.5 equiv) was added, and the solution was stirred for an additional 18 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl (30 mL) and acidified (pH = 4) with 1 M HCl. The aqueous layer was extracted with EtOAc (3 x 60 mL), washed with brine (60 mL), dried over Na₂SO₄, and concentrated under reduced pressure.

To a solution of the crude residue in acetone (60 mL) was added potassium carbonate (14 g, 104 mmol, 2.0 equiv), tetrabutylammonium iodide (0.96 g, 2.6 mmol, 0.1 equiv), and methallyl chloride (10.0 mL, 104 mmol, 2.0 equiv). The resulting solution was heated to 45 °C for 18 h, whereupon the reaction mixture was cooled to ambient temperature, filtered through a pad of silica, rinsing with acetone, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (10–20% EtOAc/hexanes) to afford functionalized piperidone 280 as a colorless oil (2.9 g, 17% yield over 2 steps): ¹H NMR (400 MHz, CDCl₃) δ 5.90 (ddt, J = 17.2, 10.3, 5.9 Hz, 1H), 5.39 – 5.20 (m, 2H), 4.88 (t, J = 1.7 Hz, 1H), 4.74 (dp, J = 2.9, 1.0 Hz, 1H), 4.68 – 4.57 (m, 3H), 4.32 – 4.06 (m, 1H), 3.34 – 3.18 (m, 1H), 3.09 (d, J = 13.7 Hz, 1H), 2.78 – 2.67 (m, 2H), 2.55 – 2.41 (m, 2H), 1.75 (t, J = 1.1 Hz, 1H), 1.71 (t, J = 1.1 Hz, 3H), 1.51 (d, J = 2.1 Hz, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 208.8, 203.8, 169.6, 154.4, 141.8, 140.2, 131.2, 119.1, 115.7, 80.3, 66.1, 60.8, 51.6, 38.9, 28.3, 23.7.
Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A

**Tert-butyl (S)-3-allyl-3-(2-methylallyl)-4-oxopiperidine-1-carboxylate (281).** In a nitrogen-filled glove box, to 1 dram vial equipped with a stir bar was added Pd$_2$(dba)$_3$ (12 mg, 0.013 mmol, 2.5 mol %), (S)-L15 (17 mg, 0.033 mmol, 6.25 mol %), and THF (10 mL). The resulting solution was stirred at 25 °C for 10 min, whereupon substrate 280 (0.18 g, 0.52 mmol, 1.0 equiv) was added. The flask was sealed and stirred at ambient temperature for 18 h, whereupon the flask was removed from the glove box and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (8% EtOAc/hexanes) to provide allylic alkylation product 81 as a colorless oil (0.11 g, 73% yield): 90% ee; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.68 (ddddd, $J = 17.0, 10.3, 7.9, 6.8$ Hz, 1H), 5.19 – 4.95 (m, 2H), 4.86 (s, 1H), 4.70 (d, $J = 1.0$ Hz, 1H), 3.95 – 3.35 (m, 4H), 2.71 – 2.19 (m, 6H), 1.66 (d, $J = 0.7$ Hz, 3H), 1.49 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 154.9, 141.2, 132.9, 119.1, 115.8, 80.5, 52.9, 41.3, 39.1, 38.3, 31.7, 28.5, 24.5, 22.8, 14.3; HPLC conditions: 0.9% EtOH, 1.0 mL/min, Chiralpak AD & AD–H columns in series, $\lambda = 210$ nm, $t_R$ (min): major = 11.319, minor = 11.808.

**Tert-butyl (3S,4R)-3-allyl-4-hydroxy-3-(2-methylallyl)piperidine-1-carboxylate (282).** Please note Relative stereochemistry was not confirmed. To a solution of ketone 281 (83 mg, 0.28 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (10 mL) at 0 °C was added (S)-CBS (1 M,
0.057 mL, 0.057 mmol, 0.2 equiv) followed by BH$_3$•DMS (2 M, 0.35 mL, 0.70 mmol, 2.0 equiv). The resulting solution was stirred for 7 h, whereupon a second aliquot of BH$_3$•DMS (2 M, 0.10 mL, 0.20 mmol, 0.7 equiv) was added. The reaction was stirred for an additional 3.5 h, quenched with MeOH (5 mL) and a saturated aqueous sodium citrate solution (10 mL), then warmed to ambient temperature and stirred for an additional 15 min. The aqueous layer was extracted with Et$_2$O (3 x 10 mL), dried over Mg$_2$SO$_4$, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (30% EtOAc/hexanes) to afford alcohol 282 as an inseparable mixture (4:1) of diastereomers and a colorless oil (83 mg, 33% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.20 – 5.85 (m, 1H), 5.23 – 5.06 (m, 2H), 5.03 – 4.94 (m, 1H), 4.86 (s, 1H), 4.04 – 3.13 (m, 2H), 3.01 – 2.84 (m, 2H), 2.43 – 2.19 (m, 3H), 2.01 (d, $J$ = 13.7 Hz, 1H), 1.89 – 1.79 (m, 3H), 1.56 (q, $J$ = 2.3, 1.8 Hz, 11H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 155.2, 143.4, 134.3, 118.4, 118.2, 115.8, 115.6, 42.4, 41.9, 37.5, 29.7, 28.8, 28.4, 25.4.

A13.8.2.4 Experimental Procedures and Spectroscopic Data for the Synthesis of Synthetic Intermediates in Section A13.5

4-((Tert-butyldiphenylsilyl)oxy)piperidin-2-one (291). To a solution of 3 M HCl/EtOAc (0.5 mL) at 0 °C was added 287 (0.10 g, 0.22 mmol, 1.0 equiv). The resulting mixture was stirred for 1 h, whereupon the reaction was concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (35–
Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A

100% acetone/hexanes) to afford deprotected lactam 291 as a colorless solid (51 mg, 66% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 – 7.32 (m, 10H), 7.17 (s, 1H), 4.15 (p, $J = 4.9$ Hz, 1H), 3.69 – 3.42 (m, 1H), 3.27 – 2.99 (m, 1H), 2.41 (dd, $J = 4.8$, 1.6 Hz, 2H), 1.74 (q, $J = 5.7$ Hz, 2H), 1.07 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.9, 135.7, 135.7, 133.7, 133.4, 129.9, 129.9, 127.8, 127.8, 65.8, 40.5, 37.8, 29.9, 26.9, 19.1.

3-(Allyloxy)-3-oxopropanoic acid (294). A solution of Meldrum’s acid (20.0 g, 0.14 mmol, 1.0 equiv) in allyl alcohol (40 mL) was heated under reflux for 18 h, whereupon the reaction was cooled to ambient temperature and concentrated under reduced pressure. The crude residue was dissolved in MeOH (60 mL), aqueous ammonia (50%, 7 mL) was added, the resulting solution was stirred for 15 min, and then concentrated under reduced pressure. The crude residue was washed with hexanes/Et$_2$O (1:1, 2 x 15 mL), dissolved in H$_2$O (20 mL) and acidified with 1 M HCl. The aqueous layer was extracted with Et$_2$O (3 x 30 mL), washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give acid 294 as a colorless solid (13.0 g, 65% yield).

Allyl 3-((3-hydroxypropyl)(3-methoxy-3-oxopropyl)amino)-3-oxopropanoate (295). To a solution of amino alcohol 293$^{36}$ (2.0 g, 12 mmol, 1.0 equiv), 4-
Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A

dimethylaminopyridine (0.15 g, 1.2 mmol, 0.1 equiv), NEt₃ (4.5 mL, 32 mmol, 2.6 equiv) in CH₂Cl₂ (24 mL) at 0 °C was added acid 294 (2.3 g, 16 mmol, 1.3 equiv) followed by EDCI•HCl (3.1 g, 16 mmol, 1.3 equiv) portionwise. The resulting solution was stirred for 18 h, whereupon the reaction was quenched with 1 M HCl (pH < 7), extracted with CH₂Cl₂ (3 x 20 mL), washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford β-ketoamide 295 as a colorless oil (2.7 g, 76% yield): ¹H NMR (400 MHz, CDCl₃) δ 6.02 – 5.76 (m, 1H), 5.47 – 5.13 (m, 2H), 4.63 (ddtt, J = 4.8, 3.8, 2.5, 1.2 Hz, 2H), 3.89 – 3.18 (m, 7H), 2.64 (td, J = 7.1, 4.4 Hz, 1H), 2.06 – 1.44 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 172.6, 171.3, 167.7, 131.5, 119.2, 118.9, 66.3, 66.2, 66.1, 58.2, 52.3, 45.8, 43.9, 42.1, 41.4, 40.9, 33.2, 32.3, 31.1, 30.2.

Allyl 1-(3-hydroxypropyl)-2,4-dioxopiperidine-3-carboxylate (296). To allyl alcohol (35 mL) was added Na metal (0.67 g, 29 mmol, 2.1 equiv) followed by β-ketoamide 295 (4.0 g, 14 mmol, 1.0 equiv). The resulting solution was heated under reflux for 18 h, whereupon the reaction was cooled to ambient temperature and concentrated under reduced pressure. The crude residue was dissolved in H₂O (30 mL) and the aqueous layer was extracted with EtOAc (3 x 30 mL). The aqueous layer was then acidified with 6 M HCl and extracted with 10% isopropanol/CH₂Cl₂ (3 x 30 mL). The combined organics were dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to afford β-ketolactam 296 as a
yellow oil (1.9 g, 52% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 5.99 (ddt, $J = 17.2$, 10.5, 5.5 Hz, 1H), 5.50 – 5.41 (m, 1H), 5.28 (dt, $J = 10.5$, 1.4 Hz, 1H), 4.81 (dt, $J = 5.5$, 1.5 Hz, 2H), 4.03 (p, $J = 6.1$ Hz, 3H), 3.57 (q, $J = 6.0$, 5.6 Hz, 4H), 3.46 – 3.37 (m, 2H), 2.67 (t, $J = 6.9$ Hz, 2H).
A13.8.2.5 Determination of Enantiomeric Excess

Please note racemic products for palladium-catalyzed allylic alkylations were synthesized using Pd(PPh3)4. Racemic products for iridium-catalyzed allylic alkylations were synthesized using racemic L2.

Table A13.4 Determination of enantiomeric excess

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Assay Conditions</th>
<th>Retention time of major isomer (min)</th>
<th>Retention time of minor isomer (min)</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Molecule 1" /></td>
<td>HPLC Chiralpak AD-H 8% IPA isocratic, 1.0 mL/min</td>
<td>21.087</td>
<td>21.876</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Molecule 2" /></td>
<td>SFC Chiralpak OJ-H 3% MeOH isocratic, 3.0 mL/min</td>
<td>19.747</td>
<td>22.731</td>
<td>48%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Molecule 3" /></td>
<td>SFC Chiralpak OJ-H 5% MeOH isocratic, 3.0 mL/min</td>
<td>7.012</td>
<td>5.589</td>
<td>29%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Molecule 4" /></td>
<td>SFC Chiralpak OJ-H 3% MeOH isocratic, 3.0 mL/min</td>
<td>20.272</td>
<td>24.437</td>
<td>62%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Molecule 5" /></td>
<td>SFC Chiralpak OJ-H 1% MeOH isocratic, 3.0 mL/min</td>
<td>27.715</td>
<td>25.961</td>
<td>61%</td>
</tr>
<tr>
<td>Entry</td>
<td>Product</td>
<td>Assay Conditions</td>
<td>Retention time of major isomer (min)</td>
<td>Retention time of minor isomer (min)</td>
<td>%ee</td>
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</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>SFC Chiralpak OJ-H 5% MeOH isocratic, 3.0 mL/min</td>
<td>15.378</td>
<td>17.679</td>
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<td>SFC Chiralpak OJ-H 1% MeOH isocratic, 3.0 mL/min</td>
<td>3.062</td>
<td>4.057</td>
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<td>SFC Chiralpak OJ-H 3% MeOH isocratic, 3.0 mL/min</td>
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<td>4.817</td>
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<td><img src="image" alt="Chemical Structure" /></td>
<td>SFC AS-H 3% MeOH isocratic, 3.0 mL/min</td>
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<td>HPLC Chiralpak OJ 1% EtOH isocratic, 1.0 mL/min</td>
<td>10.113</td>
<td>8.486</td>
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<td>11</td>
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<td>HPLC Chiralpak AD &amp; AD-H in series 0.9% EtOH isocratic, 1.0 mL/min</td>
<td>11.319</td>
<td>11.808</td>
<td>90%</td>
</tr>
</tbody>
</table>
A13.9 REFERENCES AND NOTES


Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A


Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A


Appendix 13 – Progress Toward the Synthesis of (+)-Isopalhinine A


APPENDIX 14

Spectra Relevant to Appendix 13:

Progress Toward the Synthesis of (+)-Isopalhinine A
Figure A14.1 $^1$H NMR (400 MHz, CDCl$_3$) of compound 226
Figure A14.2: $^1$H NMR (400 MHz, CDCl$_3$) of compound 233
Figure A14.3 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 233
Figure A14.4 $^1$H NMR (400 MHz, CDCl$_3$) of compound 234
Figure A14.5 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 234
Figure A14.6 $^1$H NMR (400 MHz, CDCl$_3$) of compound 235
Figure A14.7 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 235
Figure A14.8: $^1$H NMR (400 MHz, CDCl$_3$) of compound 238
Figure A14.9 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 238
Figure A14.10 $^1H$ NMR (400 MHz, CDCl$_3$) of compound 240
Figure A14.11 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 240
Figure A14.12: $^1$H NMR (400 MHz, CDCl$_3$) of compound 241
Figure A14.13 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 241
Figure A14.14 $^1$H NMR (400 MHz, CDCl$_3$) of compound 243
Figure A14.15 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 243
Figure A14.17 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 244
Figure A14.18: $^1$H NMR (400 MHz, CDCl$_3$) of compound 245.
Figure A14.19 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 245
Figure A14.20 $^1$H NMR (400 MHz, CDCl$_3$) of compound 247
Figure A14.21 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 247
Figure A14.22 $^1$H NMR (400 MHz, CDCl$_3$) of compound 248
Figure A14.23 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 248
Figure A14.24 $^1$H NMR (400 MHz, CDCl$_3$) of compound 249
Figure A14.25 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 249
Figure A14.26 $^1$H NMR (400 MHz, CDCl$_3$) of compound 256
Figure A14.27 $^1H$ NMR (400 MHz, CDCl$_3$) of compound 257
Figure A14.28 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 257
Figure A14.29 $^1$H NMR (400 MHz, CDCl$_3$) of compound 258
Figure A14.30 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 258
Figure A14.31 $^1H$ NMR (400 MHz, CDCl$_3$) of compound 259
Figure A14.32 $^1$H NMR (400 MHz, CDCl$_3$) of compound 260.
Figure A14.33 $^1$H NMR (400 MHz, CDCl$_3$) of compound 261
Figure A14.34 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 261
Figure A14.35 $^1$H NMR (400 MHz, CDCl$_3$) of compound 262
Figure A14.36 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 262
Figure A14.37 $^1$H NMR (400 MHz, CDCl$_3$) of compound 263
Figure A14.38 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 263
Figure A14.39: $^1H$ NMR (400 MHz, CDCl$_3$) of compound 274
Figure A14.40. $^1$H NMR (400 MHz, CDCl$_3$) of compound 275.
Figure A14.41 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 275
Figure A14.42 \( ^1H \) NMR (400 MHz, CDCl\(_3\)) of compound 276
Figure A14.43: $^1^3$C NMR (101 MHz, CDCl$_3$) of compound 276.

ppm

0 20 40 60 80 100 120 140 160 180 200
Figure A14.44 $^1$H NMR (400 MHz, CDCl$_3$) of compound 277
Figure A14.45: $^1$H NMR (400 MHz, CDCl$_3$) of compound 280

Appendix 14 – Spectra Relevant Appendix 13
Figure A14.46 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 280
Figure A14.47 $^1$H NMR (400 MHz, CDCl$_3$) of compound 281
Figure A14.48 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 281
Figure A14.49 $^1$H NMR (400 MHz, CDCl$_3$) of compound 282
Figure A14.50 $^{13}$C NMR (101 MHz, CDCl₃) of compound 282
Figure A14.51 $^1$H NMR (400 MHz, CDCl$_3$) of compound 291
Figure A14.52 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 291
Figure A14.53 $^1$H NMR (400 MHz, CDCl$_3$) of compound 295
Figure A14.54 $^{13}$C NMR (101 MHz, CDCl$_3$) of compound 295
Figure A14.55 ¹H NMR (400 MHz, CDCl₃) of compound 296
APPENDIX 15

Notebook Cross-Reference for New Compounds

The following notebook cross-reference provides the file name for all original spectroscopic data obtained for new compounds presented within this thesis. The information is organized by chapter or appendix and sequentially by compound number. All $^1$H NMR, $^{13}$C NMR, as well as $^{19}$F NMR and any two-dimensional NMR data, if applicable, are electronically stored on the Caltech NMR laboratory server (mangia.caltech.edu, most typically under the usernames ‘sshockle’, ‘chethcox’, or ‘jholder’) and on the Stoltz group server. Electronic copies of all IR spectra can also be found on the Stoltz group server. All laboratory notebooks are stored in the Stoltz group archive.
### Table A15.1 Notebook cross-reference for compounds in Chapter 1

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**Table A15.3 Notebook cross-reference for compounds in Chapter 3**

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<td>SES-XI-155D-fract1</td>
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<td>JCH-V-155J</td>
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<td><img src="image" alt="Chemical Structure 79b" /></td>
<td>SES-XI-179C-fract2</td>
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<td><img src="image2" alt="Chemical Structure" /></td>
<td>JCH-V-297-2-fract4</td>
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<td><img src="image3" alt="Chemical Structure" /></td>
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<td><img src="image6" alt="Chemical Structure" /></td>
<td>JCH-VI-19-fract2-dry</td>
<td>JCH-VI-19-fract2-dry</td>
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<td>89</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>JCH-VI-27-fract2</td>
<td>JCH-VI-27-fract2</td>
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<td><img src="image8" alt="Chemical Structure" /></td>
<td>SES-XI-61D-fract1</td>
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<td><img src="image9" alt="Chemical Structure" /></td>
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### Table A15.4 Notebook cross-reference for compounds in Chapter 4

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<th>(^1)H NMR</th>
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<td>SES-XII-83A-fract2</td>
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<td>SES-XII-95D-fract1</td>
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<td>SES-XII-95C-fract1</td>
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<td>JCH-VI-293C-fract1</td>
<td>JCH-VI-293C-fract1</td>
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<td>SES-XII-167B-fract1</td>
<td>SES-XII-167B-fract1</td>
<td>JCH-VI-279E</td>
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<td>97b</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>SES-XII-191B-fract1-redo</td>
<td>SES-XII-191B-fract1-redo</td>
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<td>SES-XII-97C-fract1</td>
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<td>JCH-VI-115-fract2</td>
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### Table A15.5 Notebook cross-reference for compounds in Appendix 8

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<th>$^{13}$C NMR</th>
<th>IR</th>
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<td>SES-III-85-fract2</td>
<td>SES-Piv iodo CA</td>
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<tr>
<td>169d</td>
<td><img src="image3.png" alt="Image" /></td>
<td>SES-II-119-fract2</td>
<td>SES-II-119-fract2 &amp; SES-II-143-fract1</td>
<td>SES-BromoPiv CA</td>
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<td><img src="image4.png" alt="Image" /></td>
<td>SES-1-119 chiralcharc</td>
<td>SES-1-119 chiralcharc</td>
<td>SES-chloro Piv CA</td>
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<td><img src="image5.png" alt="Image" /></td>
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<td>SES-Qins Intermediate</td>
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<td><img src="image7.png" alt="Image" /></td>
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<td><img src="image8.png" alt="Image" /></td>
<td>JCH-Acyl B(OH)2 &amp; JCH-X-167</td>
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<td>SES-Bromo PivB(OH)2</td>
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<td>SES-isopropenyl MonoPiv</td>
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<td>SES-1-207Bsolid</td>
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Table A15.6 Notebook cross-reference for compounds in Appendix 11

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<td>SES-XI-213-p TLC</td>
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### Table A15.7 Notebook cross-reference for compounds in Appendix 13

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<td>237</td>
<td><img src="image5" alt="Structure 237" /></td>
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<td><img src="image6" alt="Structure 238" /></td>
<td>SES-V-251-fract1</td>
<td>SES-V-251-fract1</td>
<td>–</td>
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<tr>
<td>240</td>
<td><img src="image7" alt="Structure 240" /></td>
<td>SES-VIII-129-fract1</td>
<td>SES-VIII-129-fract1</td>
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<tr>
<td>LG = Cl</td>
<td><img src="image8" alt="Structure LG = Cl" /></td>
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<td>–</td>
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<tr>
<td>241</td>
<td><img src="image9" alt="Structure 241" /></td>
<td>SES-XI-249F-prepHPLC-fract2</td>
<td>SES-XI-249F-prepHPLC-fract2</td>
<td>–</td>
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<tr>
<td>243</td>
<td><img src="image10" alt="Structure 243" /></td>
<td>SES-VI-131-135-fract2</td>
<td>SES-VI-131-135-fract2</td>
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<td>Compound</td>
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<td>(^1H) NMR</td>
<td>(^{13}C) NMR</td>
<td>IR</td>
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<td>244</td>
<td><img src="" alt="Chemical Structure" /></td>
<td>SES-VI-121-fact1</td>
<td>SES-VI-121-fact1</td>
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<td>245</td>
<td><img src="" alt="Chemical Structure" /></td>
<td>SES-VI-219-fact3</td>
<td>SES-VI-219-fact3</td>
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<td>247</td>
<td><img src="" alt="Chemical Structure" /></td>
<td>SES-VI-215-prepB</td>
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<td><img src="" alt="Chemical Structure" /></td>
<td>JCH-V-35-fact3</td>
<td>JCH-V-35-fact3</td>
<td>SES-XI-15-bottom</td>
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<td>256</td>
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<td>SES-VII-223-rac-fact1</td>
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<td>SES-XI-255-fact2 &amp; JCH-VI-91</td>
<td>JCH-VI-91</td>
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<tr>
<td>Compound</td>
<td>Chemical Structure</td>
<td>( ^1\text{H} \text{NMR} )</td>
<td>( ^{13}\text{C} \text{NMR} )</td>
<td>IR</td>
</tr>
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<td>259</td>
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<td>SES-XI-257 -frac1</td>
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<td>260</td>
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<td>SES-VII-263 -redo-frac2</td>
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<td>SES-XI-273 -frac1</td>
<td>SES-XI-271</td>
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<td>SES-IX-19 -frac1</td>
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Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. *Manuscript submitted*.


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ABOUT THE AUTHOR

Samantha Elizabeth Shockley was born in Birmingham, Alabama on February 6th, 1990 to Susan and Edward Shockley. Sam grew up in Gainesville, Florida with her older brother Matthew Shockley.

In the fall of 2008, Sam moved to Chicago, Illinois to attend the University of Chicago. Despite her initial intention to study Egyptology, she graduated with B.S. degrees in chemistry and biochemistry and a B.A. in biology. While in college, she performed undergraduate research on zirconocene-catalyzed C–H functionalization under the guidance of Professor Richard Jordan.

Following her undergraduate education, Sam moved to Canberra, Australia to conduct a yearlong U.S. Fulbright research grant at the Australian National University in the laboratory of Professor Martin Banwell. During this time, she investigated the design and synthesis of lipophilic analogues of lamellarin W.

Upon returning to the States, Sam moved to Pasadena, California to pursue her doctoral studies at the California Institute of Technology with Professor Brian Stoltz. Her graduate work has focused on the development of enantioselective transition metal catalysis and natural product total synthesis. Upon completion of her doctoral research in May 2018, Sam will begin her professional career as a medicinal chemist at Merck, South San Francisco.