Part I. Synthesis of Garner's Aldehyde and Efforts Toward the Synthesis of Tapentadol via an Asymmetric Hydroformylation/Reductive Amination Sequence

Part II. Development of a Rhodium-Mediated Domino Annulation and Efforts Toward the Total Synthesis of Linderagalactone C

By

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Dedication

For Claire and Felix

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Abstract

A novel, catalytic synthesis of either enantiomer of the widely used synthetic building block Garner's aldehyde from a single alkene was developed. Rhodium-catalyzed asymmetric hydroformylation (AHF) with the bis(diazaphospholane) (BDP) ligands developed by Landis and coworkers affords each Garner's aldehyde enantiomer in high yield and enantiomeric purity in an atom economical, regio- and facially-selective alkene hydroformylation. This is the first reported AHF with a 1,2-disubstituted alkene with a different heteroatom on each carbon.

Three AHF-based synthetic strategies toward the analgesic tapentadol are described. A styrene AHF strategy was abandoned due to poor regioselectivity producing the desired aldehyde as a minor component. A diene AHF strategy was attempted but resulted in very poor enantioselectivity due to rhodium allylic rearrangements during the AHF catalytic cycle. AHF of a trisubstituted olefin resulted in a complex mixture of aldehydes.

A rhodium-mediated domino annulation (RMDA) of δ-alkynyl ketones and α-boryl-α,β-unsaturated esters producing fused pyranones was developed. Transmetallation of the vinyl boronic ester with the rhodium catalyst produces a vinyl rhodium intermediate that undergoes a highly regioselective syn addition to the alkyne to produce a second vinyl rhodium intermediate that immediately attacks the pendant ketone, forming a new five-membered ring. The rhodium alkoxide formed by the cyclization transesterifies with the α,β-unsaturated ester to form a fused lactone ring system. Overall, two new carbon-carbon bonds and one new carbon-oxygen bond are formed, creating two new rings. Several examples are shown exploring substrate functional group tolerance and steric limitations.

A total synthesis of the recently isolated natural product linderagalactone C was initiated, but production of both components of the RMDA met significant synthetic roadblocks. A planned Eschenmoser-Tanabe fragmentation failed to form the necessary δ-alkynyl ketone and the boronic ester for the RMDA was unable to be accessed from α-halo esters due to the severe electron withdrawing effects of the carbonyls.

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Abbreviations and Acronyms

Ac	acetyl
acac	acetylacetonate
AHF	asymmetric hydroformylation
AIBN	2,2'-azobis(2-methylpropionitrile)
BDP	bis(diazaphospholane)
BDPP	bis(diphenylphosphino)pentane
BINAP	1,1′-(binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	*tert*-butyl carbamate
Bpe	1,2-bis
Bu	butyl
cat.	catalyst
Cbz	benzyl carbamate
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
CSA	camphor-10-sulfonic acid
d.r.	diastereomer ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*'-dicyclohexylcarbodiimide
DiBAl-H	di-*iso*-butylaluminum hydride
DMAP	*N,N*-dimethyl 4-aminopyridine
DMF	*N,N*-dimethylformamide

DMSO	dimethylsulfoxide
DPEphos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
dppf	1,1'-bis(diphenylphosphino)ferrocene
e.r.	enantiomer ratio
ee	enantiomeric excess
EI	electron impact
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
eq.	equivalents
Fmoc	9-fluorenylmethyl carbamate
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
IC_{50}	half maximal inhibitory concentration
imid.	imidazole
IR	infrared spectroscopy
LDA	lithium di-*iso*-propylamide
LHF	linear hydroformylation
*m*CPBA	3-chloroperbenzoic acid
Me	methyl
MIDA	*N*-methyliminodiacetate
mol. sieves	molecular sieves
MOM	methoxymethyl

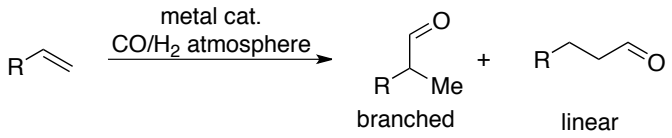
Ms	methanesulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
pin	-O-C(CH_3)$_2$-C(CH_3)$_2$-O-
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
RMDA	rhodium-mediated domino annulation
rt	room temperature
SFC	supercritical fluid chromatography
STAB-H	sodium triacetoxyborohydride
Stryker's reagent	(triphenyl phosphine)copper hydride hexamer
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Ts	*p*-toluenesulfonyl
TMS	trimethylsilyl

Chapter 1. Introduction to Asymmetric Hydroformylation

1.1 The Hydroformylation Reaction

Hydroformylation is a powerful synthetic transformation that has seen great use in industrial and academic chemistry since its discovery in 1938.[1] Employing easily obtainable alkenes and syngas with a metal catalyst, hydroformylation produces aldehydes, arguably the most synthetically versatile functional group (Scheme 1A). It is widely used for the industrial production of many solvents, plasticizers, and other commodity chemicals and is the oldest reaction still used for commercial production.[2]

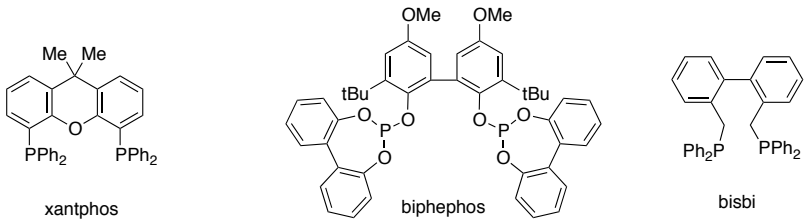
Scheme 1A. General Hydroformylation Reaction



Hydroformylation has near perfect atom economy and thus has seen renewed interest with the chemical community's aspiration for more efficient synthetic methods. Although the first catalysts were cobalt compounds, rhodium compounds are now very common catalysts for hydroformylation.[2] Rhodium catalysts have many advantages over other metals both in reactivity and selectivity. They are 100 to 1000 times more reactive than cobalt catalysts, allowing for lower catalyst loading. Rhodium catalysts also require much lower pressures and temperatures, do not reduce the aldehyde product to an alcohol, and can be used with phosphine ligands to limit the reduction of alkenes to alkanes.[2]

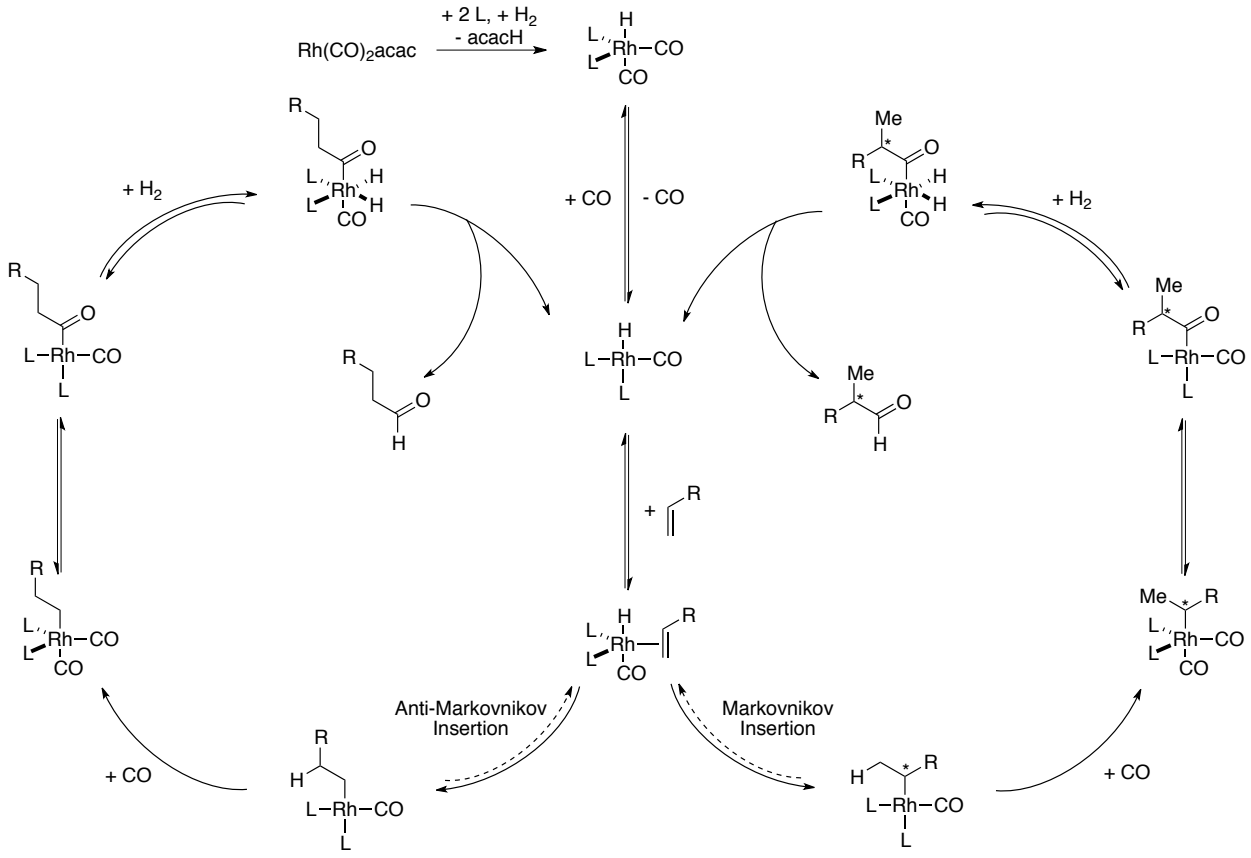
Phosphorus-based ligands are the ligands of choice for hydroformylation. Phosphine ligands were initially discovered to lower the necessary temperature and syngas pressure for hydroformylation as well as suppress alkene hydrogenation,[3] but phosphite[3b,4] and other phosphorus-based ligands[5] have been developed and used successfully. Three of the most popular ligands for linear hydroformylation are xantphos, biphephos, and bisbi (Figure 1A).

Figure 1A. Common Linear Hydroformylation Ligands



The mechanism of rhodium-catalyzed hydroformylation is understood to start with the formation of a ligated dicarbonylrhodium hydride from the rhodium precatalyst reacting with syngas and a ligand.[6] Freeing of a coordination site by loss of CO allows for the coordination of an alkene substrate. Anti-Markovnikov insertion of the alkene into the Rh-H bond produces the linear alkyl-rhodium species while Markovnikov insertion creates a branched alkyl rhodium

Scheme 1B. Hydroformylation Mechanism



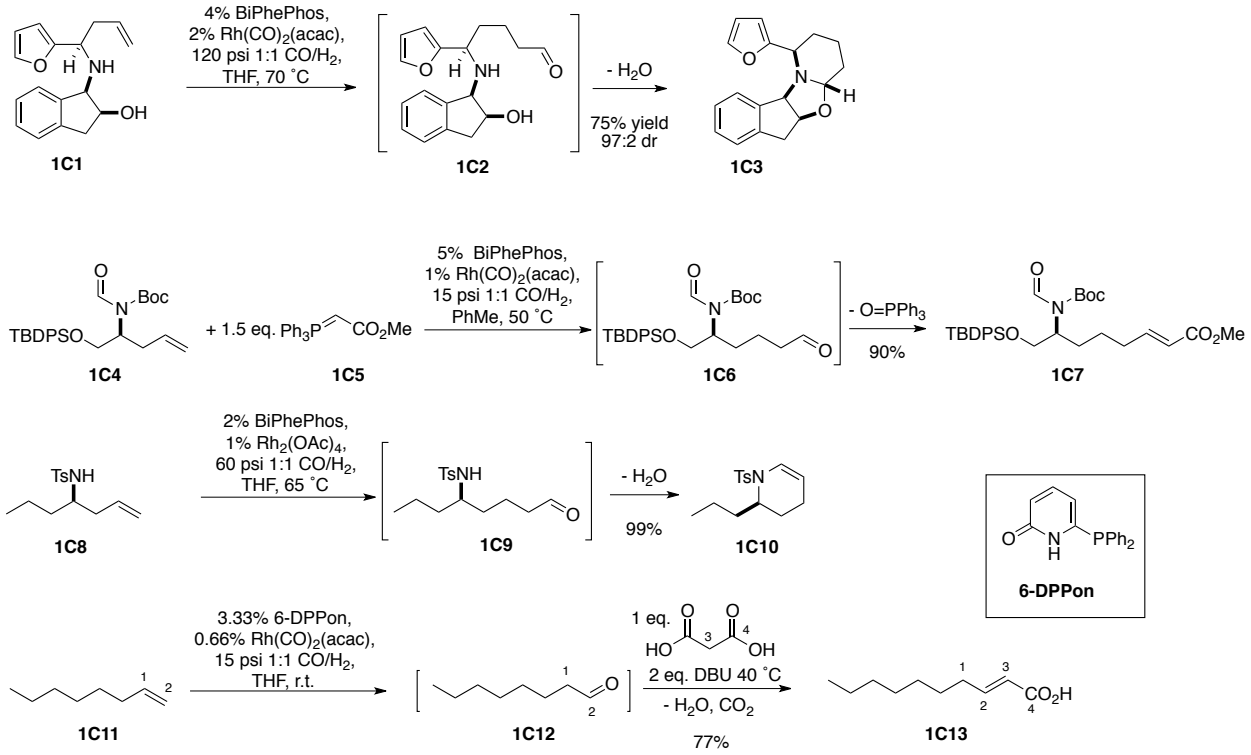
complex, often with a carbon stereocenter. Sterically, the anti-Markovnikov insertion is preferred, though electron-withdrawing groups can favor Markovnikov insertion.[7] This insertion is thought to typically be irreversible,[8] but reversible insertion has been observed.[5b] Alkyl migration from rhodium to the carbonyl ligand produces the acyl rhodium complex. Coordination and oxidative addition of dihydrogen followed by reductive elimination releases the aldehyde product and the rhodium hydride, thought to be the active catalyst. Significant solvent, temperature, and pressure effects have been observed, necessitating experimentation and optimization with each substrate.[9]

1.2 Linear Hydroformylation Tandem Reactions

The mild conditions of the hydroformylation reaction are compatible with a variety of other reagents and functional groups, and relatively simple phosphine or phosphite ligands can provide excellent selectivity for the linear aldehyde.[3-5] Because of this, many tandem and one-pot reactions have been developed (Scheme 1C).[3a-d,4a-d,5a,10] Hydroformylation of the vinyl group of **1C1** produces aldehyde **1C2**, which is condensed with the appended 1,2-amino alcohol to form the N,O-acetal **1C3** in good yield and excellent d.r.[4a] Stabilized Wittig reagents, such as **1C5**, are unreactive until the aldehyde (**1C6**) is produced, at which point **1C6** is olefinated to form the unsaturated ester **1C7**.[4b] In another example of self-condensation, hydroformylation of **1C8** produced aldehyde **1C9**, which then condensed on the sulfonamide to form the enamine **1C10**.[4c] Hydroformylation of 1-heptene (**1C11**) to octanal (**1C12**) with the phosphine ligand DPPon is followed by the addition of malonic acid and DBU, which undergo condensation of the aldehyde and decarboxylation to produce unsaturated carboxylic acid **1C13**.[3a] These examples illustrate how the exploitation of the reactive aldehyde in situ allows for the rapid construction of

molecular complexity from simple starting materials while reducing the time and resources spent on purification.

Scheme 1C. Recent Linear Hydroformylation Tandem and One-Pot Reaction Examples



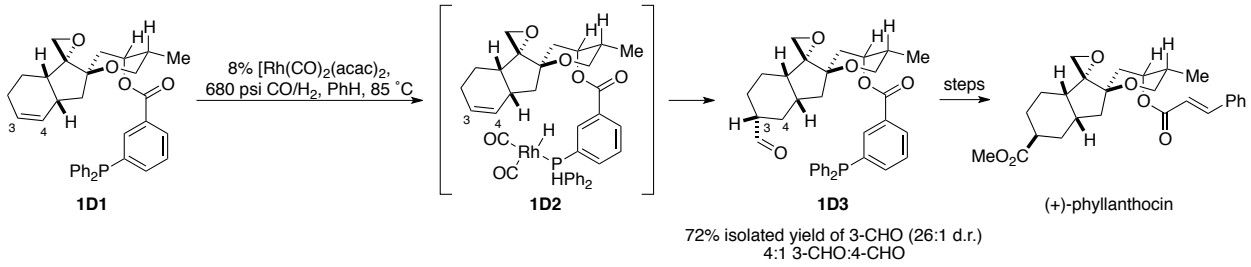
1.3 Asymmetric Hydroformylation

Asymmetric hydroformylation (AHF) is a powerful and atom economical synthesis of chiral aldehydes from alkenes.[3a-d,4a-d,5a,10] Most often employed on a vinyl group, AHF results from Markovnikov insertion of the coordinated alkene into the rhodium-hydride bond.[3f,7,11] The α-methyl chiral aldehydes formed are common synthetic intermediates, especially in the synthesis of polyketide natural products. Generally, AHF of di-substituted alkenes produces α-alkyl chiral aldehydes,[11a-d,12] and AHF 1,1-disubstituted alkenes produce β-chiral aldehydes since formation of the quaternary stereocenter is greatly disfavored due to steric congestion.[11b,13]

1.3.1 AHF with Directing Groups

In 1986, Burke and Cobb reported the first example of the use of a phosphorus auxiliary acting as a ligand for a hydroformylation catalyst and influencing the facial- and regioselectivity of a hydroformylation in their synthesis of phyllanthocin (Scheme 1D).[14] Phosphine-substituted benzoate ester **1D1** coordinates to the rhodium catalyst to form adduct **1D2**. The ester positions

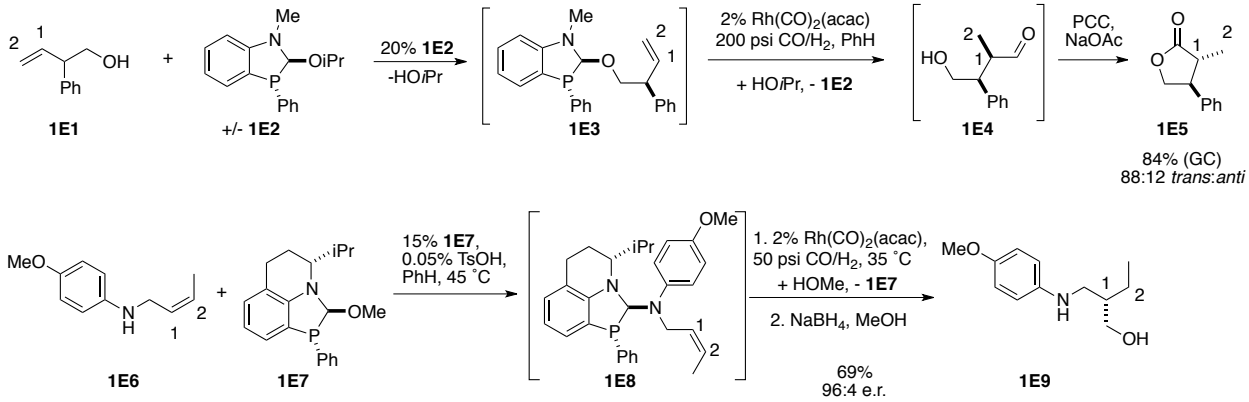
Scheme 1D. First Use of Phosphorus Directing Group by Burke and Cobb



the catalyst on the concave face of the alkene and controls the facial selectivity of the hydroformylation to produce a 26:1 mixture of aldehyde isomers at the C3 position favoring the concave face (**1D3**). The length of the tether favors hydroformylation of the C3 carbon 8:1 over the C4 carbon. A small amount hydroformylation on the convex face of the alkene presumably results from non-ligated catalyst. Since this seminal publication, phosphorus-based directing groups have become a commonly exploited method to induce stereo- and regiocontrol in hydroformylation reactions, either as a transient and catalytic additive or as a stoichiometric auxiliary.[15]

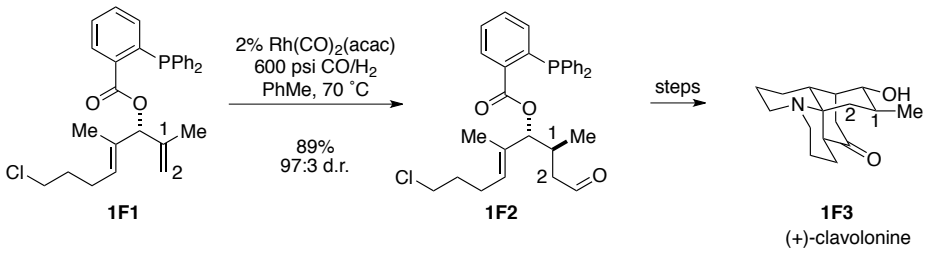
The Tan group (Scheme 1E) uses phosphine ligands (**1E2** and **1E7**) that are able to undergo acetal exchange with alcohols and amines (**1E1**, and **1E6**, respectively) to form adducts (**1E3** and **1E8**).[16] Selective hydroformylation of the near carbon (C1) of **1E3** and release of the covalently-bonded directing group allows the primary alcohol of **1E4** to attack the newly formed aldehyde. This lactol is oxidized to the lactone product (**1E5**) with PCC. Alternatively,

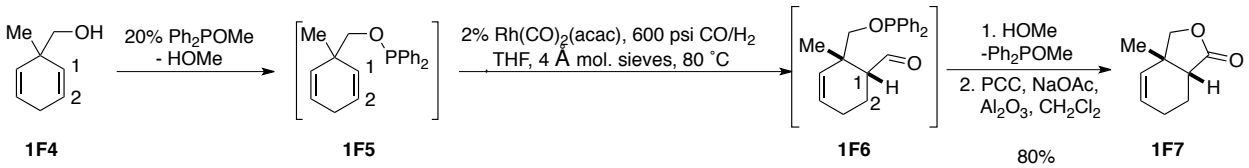
Scheme 1E. AHF with Tan's Directing Groups



reduction of the aldehyde produced by AHF of C1 of **1E8** to alcohol **1E9** allows for easy analysis of the efficiency of Tan's directed AHF.

Scheme 1F. AHF with Breit's Directing Groups





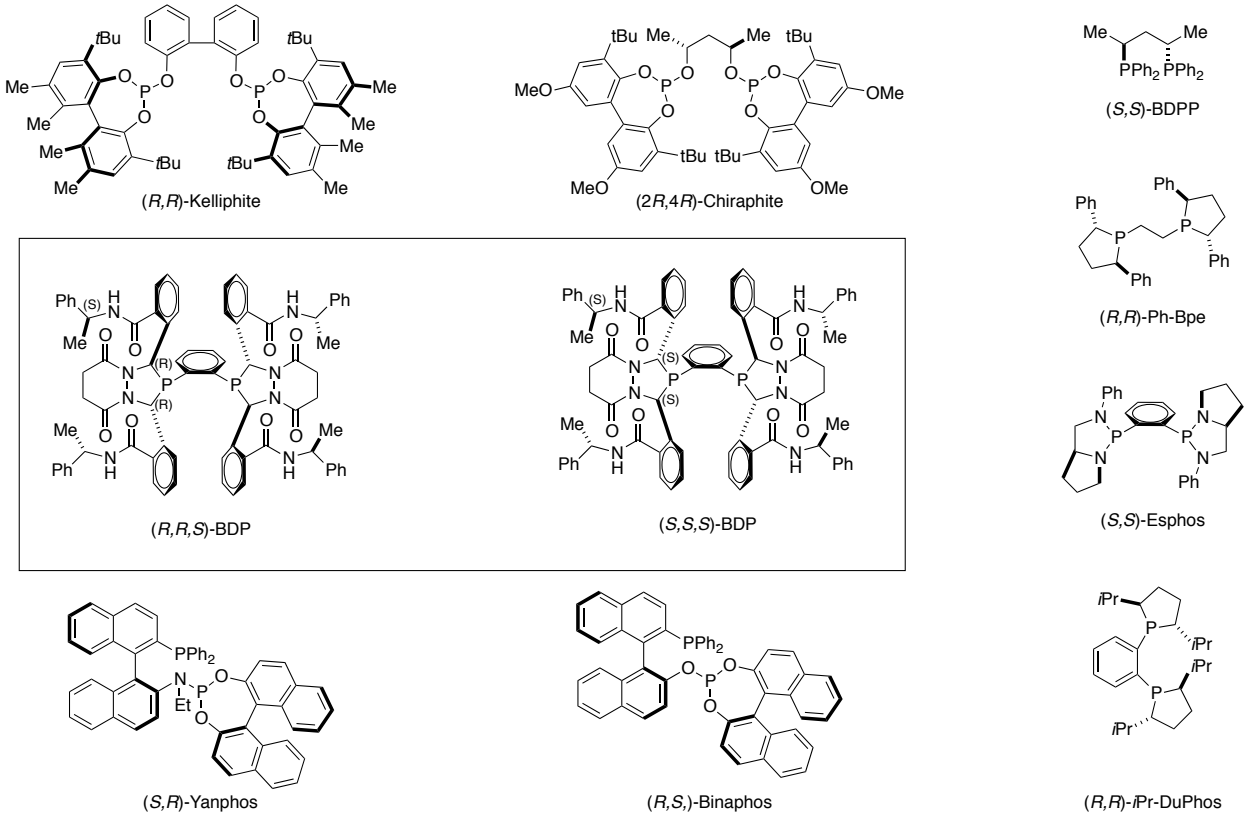
The Breit group has published extensively on directed AHF reactions.[17] In a recent synthesis of (+)-clabolonine (**1F3**), the auxiliary directing group in **1F1** couples with the substrate stereochemistry to efficiently direct hydroformylation to the back face of the 1,1 disubstituted alkene (Scheme 1F). The alkene insertion is selective for C2 because of the sterics of the 1,1-disubstituted alkene.[17f] Another example is the desymmetrization of the non-conjugated diene **1F4.** A catalytic phosphinite ligand reacts with **1F4** to form adduct **1F5** to

direct hydroformylation to the near carbon to form aldehyde **1F6**. Methanolysis of the phosphinite adduct and oxidation of the resulting lactol produces the lactone product **1F7** in good yield.[17g]

1.3.2 Catalyst-Controlled AHF

The most ideal and applicable catalytic systems for AHF are those that exercise a high degree of catalyst control over the stereochemistry and regiochemistry of the aldehyde product. Unfortunately, no one catalyst-ligand system has been developed that is able to effectively control stereoselectivity and regioselectivity on all types of alkenes, but there are many ligands that are effective across a range of substrates.[3f,7,11-13]

Figure 1B. Common Ligands for Catalyst-Controlled AHF



There are several types of phosphorus ligands, including phosphine,[7,13a,11p-q,12h-i,18] phosphite,[11a-d,11q,12e,19] and mixed phosphine-phosphite ligands.[11i,20] Other phosphorus-based ligands have also been reported.[11n-o,q-r,12b,21] In the quest for perfect selectivity, new ligands are continually being developed, including ligands with phosphorus-centered chirality[13] and chiral cores based on sugars[11a] or helical compounds.[11l] Self-assembled supramolecular ligands,[11c-d] and non-phosphorus based ligands like *N*-heterocyclic carbines[11k] and diamines[17b] also broaden the synthetic utility of AHF. Several of the most commonly employed ligands are shown in Figure 1B.[11g-h,22-23] The Landis group has recently developed diastereomeric bis(diazaphospholane) (BDP) ligands (see box in Figure 1B) with complimentary enantioselectivity that provide excellent conversion and enantioselectivity with low catalyst and ligand loading, mild temperatures, and moderate pressures.[7,18a]

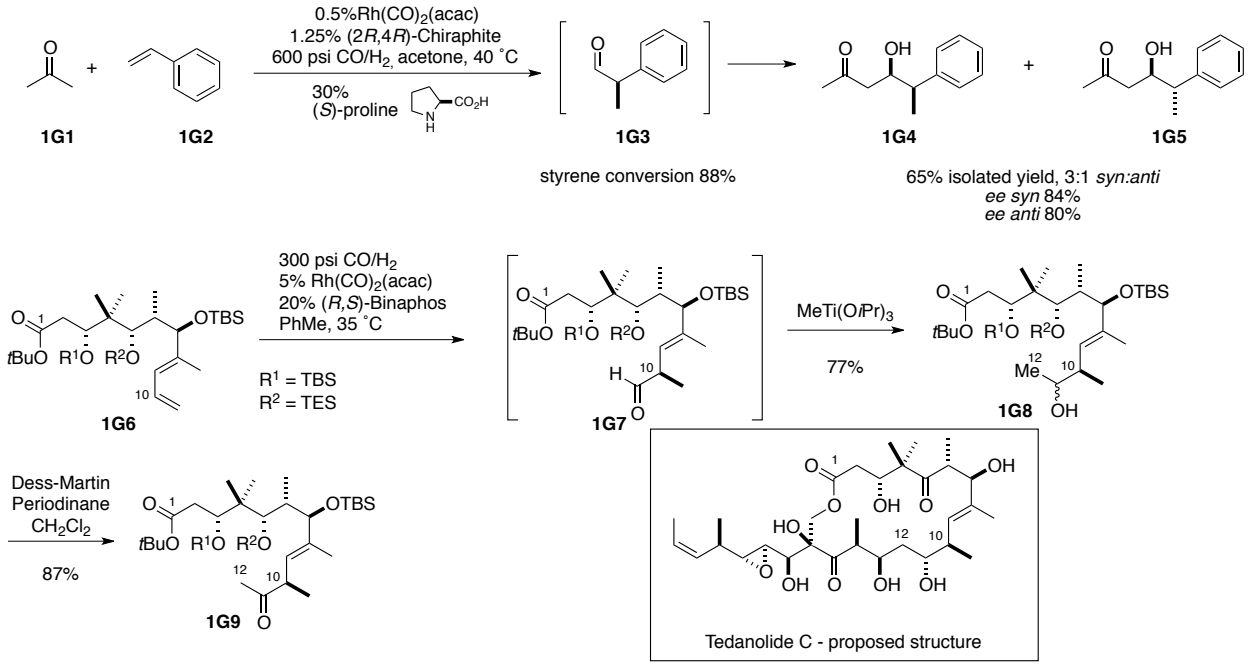
1.4 Catalyst-Controlled AHF Tandem Reactions

Despite the plethora of examples of tandem and one-pot linear hydroformylation examples and the growing synthetic utility of AHF reactions either with directing groups or under catalyst control, there are only a few examples of catalyst-controlled AHF tandem or one-pot reactions (Scheme 1G). AHF of styrene (**1G2**) has been combined with proline-catalyzed aldol addition of acetone (**1G1**) for the direct synthesis of stereodiads **1G4** and **1G5**.[24]

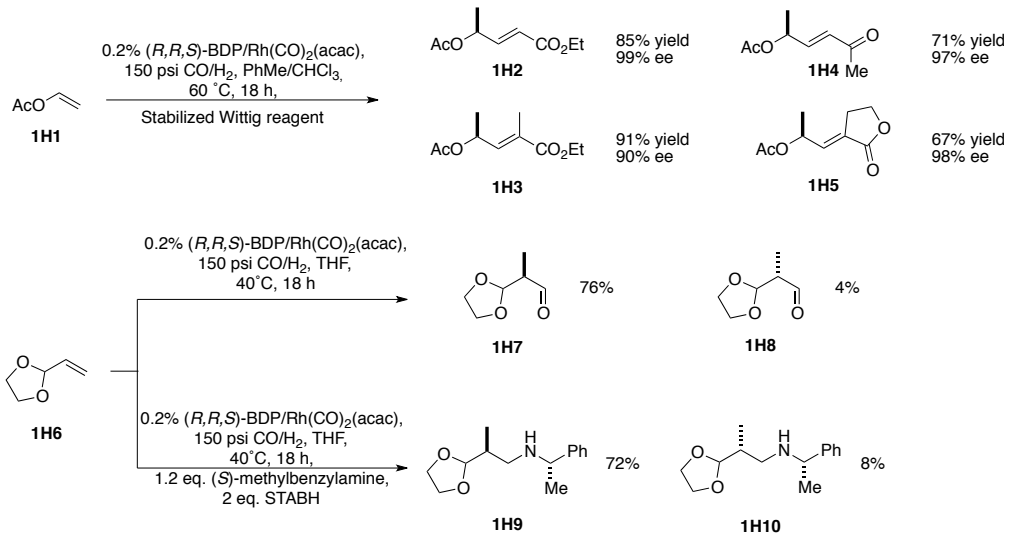
In a recent synthesis of the C1-C12 fragment of tedanolide C (**1G9**), Smith and coworkers used AHF of the diene of **1G6** to the α-methyl aldehyde **1G7** that was methylated in situ with $MeTi(O\textit{i}Pr)_3$ to form a mixture of alcohol epimers at C11 (**1G8**).[25] Oxidation of the **1G8** mixture to the methyl ketone (**1G9**) was the final step in the fragment synthesis. The C10 epimer of **1G9** was also prepared using the other enantiomer of binaphos for the AHF/methylation one-pot reaction. Initial experiments of tandem reactions with Landis BDP

ligands have shown that stabilized Wittig reagents[26] and reductive amination conditions[27] do not interfere with the AHF reaction and that racemization of the α-chiral aldehydes is not competitive with reaction at the carbonyl under these conditions (Scheme 1H).

Scheme 1G. Reported Tandem and One-Pot Catalyst-Controlled AHF Reactions



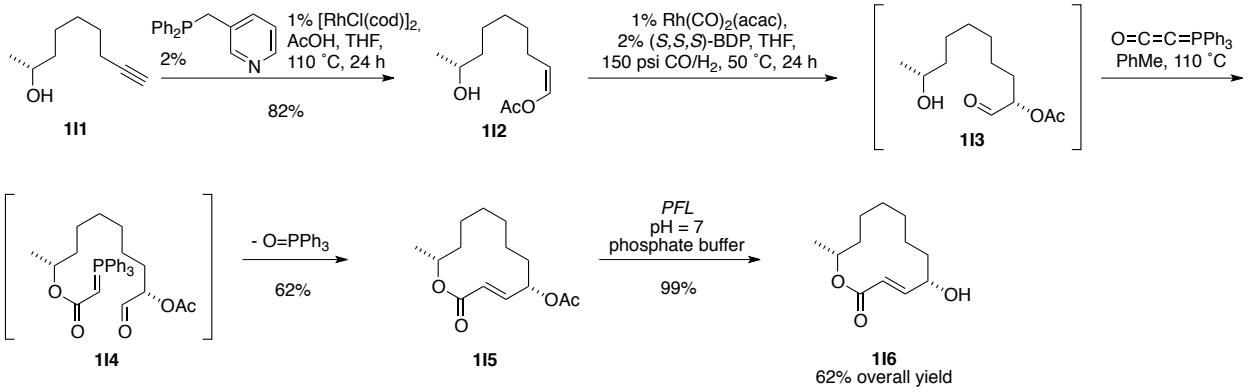
Scheme 1H. Initial AHF Tandem Reactions with BDP Ligands



1.5 Burke Group AHF Tandem Applications to Total Synthesis

Recent research in the Burke group has focused on building a program to exploit BDP ligands' efficient generation of α-chiral aldehydes for the synthesis of complex organic molecules. In particular, we wish to couple AHF with other reactions for tandem or one-pot sequences that produce stereochemically complex advanced intermediates in few synthetic steps. As a demonstration of the power of this methodology, the Burke group has published exceptionally efficient syntheses of (+)-patulolide C[28] (**1I6**, Scheme 1I) and the (–)-Prelog-Djerassi lactone[29] (**1J9**, Scheme 1J).

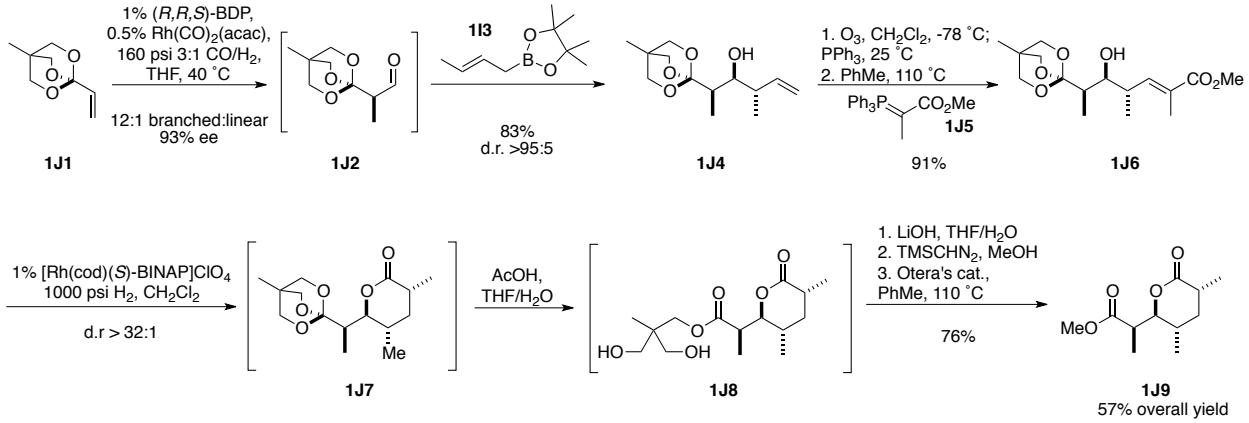
Scheme 1I. Burke's Synthesis of (+)-Patulolide C



Alkyne **1I1**[30] was converted into *Z*-vinyl acetate **1I2** via a rhodium-catalyzed anti-Markovnikov addition of acetic acid.[31] AHF using the (*S,S,S*)-BDP ligand formed aldehyde **1I3**, which was then added to a solution of the Bestmann ylide.[32] This effected lactonization by esterification with the secondary alcohol to form stabilized ylide **1I4,** which subsequently reacted with the appended aldehyde to give the unsaturated lactone **1I5** in 62% yield. Deacetylation with *Pseudomonas fluorescens* lipase[33] produced the natural product in three steps from known alkynyl alcohol **1I1**.

The second example began with the orthoester **1J1**. AHF to **1J2** proceeded with excellent regioselectivity and good enantioselectivity. One-pot crotylation with **1J3** produced the stereotriad **1J4** in good yield with excellent diastereoselectivity.[34] Another one-pot transformation from terminal alkene **1J4** to unsaturated ester **1J6** via ozonolysis and Wittig olefination with stabilized reagent **1J5** proceeded in good yield.[35] Diastereoselective hydrogenation of the alkene

Scheme 1J. Burke's Synthesis of the (–)-Prelog-Djerassi Lactone



of **1J6** and subsequent lactonization was accomplished in excellent diastereoselectivity to form lactone **1J7**.[36] Acidic decomposition of the orthoester to ester **1J8**,[37] saponification with LiOH, and methylation with (trimethylsilyl)diazomethane[38] produced a mixture of lactone and open chain esters, which was converted to the lactone **1J9** with Otera's catalyst[39] in good yield. Overall, **1J9** was synthesized in three steps with an overall 57% yield, which is considerably more efficient than all other published syntheses of the Prelog-Djerassi lactone.[40,41]

AHF is a rapidly growing field of study, with new ligands and applications continually being developed. Alkenes can be converted to chiral aldehydes with high selectivity and combined with tandem or one-pot reactions for extremely rapid generation of molecular complexity. This AHF/tandem or one-pot reaction strategy has been demonstrated in particular

by the Burke group in the synthesis of (+)-patulolide C and the (–)-Prelog-Djerassi lactone. Since chiral aldehydes are such a valuable commodity to the synthetic community, AHF has the potential to revolutionize their production.

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Chapter 2. Synthesis of Garner's Aldehyde by Asymmetric Hydroformylation

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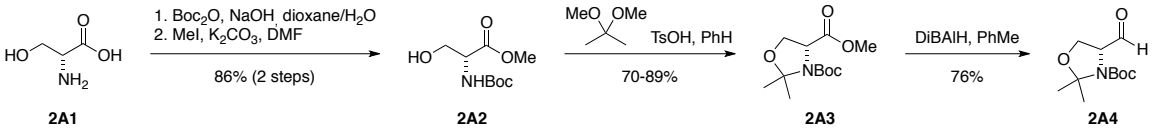
2.1 Garner's Aldehyde

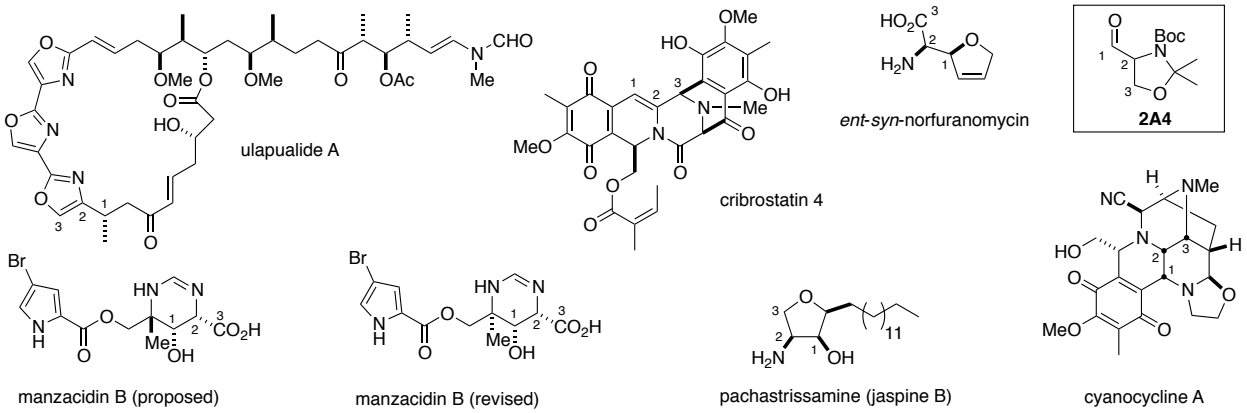
Garner's aldehyde (**2A4**) is a popular chiral synthetic building block derived from serine (**2A1**) that was first reported in 1984 by Philip Garner (Scheme 2A).[1-3] Other *N*-protecting groups have been reported for 4-formyl-2,2-dimethyl-3-oxazolidinone, including CBz,[4] benzyl,[5] methyl carbamate,[6] Fmoc,[7] and *o*-phenylbenzoyl groups,[8] but the Boc group is by far the most commonly employed protecting group. A wide variety of synthetic transformations have been performed on **2A4**, including addition of organometallic reagents,[9] olefination,[10] aldol addition,[11] reductive amination,[12] alkynylation,[13] and incorporation of the aldehyde into other functional

Scheme 2A. Synthesis of Garner's Aldehyde from Serine



groups such as nitrones[14] and oximes.[15] In an unusual use, nitrones derived from **2A4** have been shown to cyclize with ketenes to produce chiral oxindoles, thereby employing **2A4** as a chiral auxiliary instead of a building block.[14b] The use of **2A4** in synthesis has been reviewed,[16] but several more natural products recently synthesized with **2A4** are illustrated in Figure 2A.[9a,e,j,10c,14a]

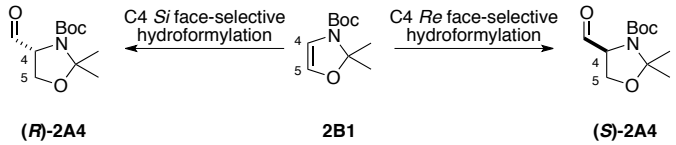
Figure 2A: Recent Uses of Garner's Aldehyde in Synthesis



2.2 Synthesis of Garner's Aldehyde by AHF

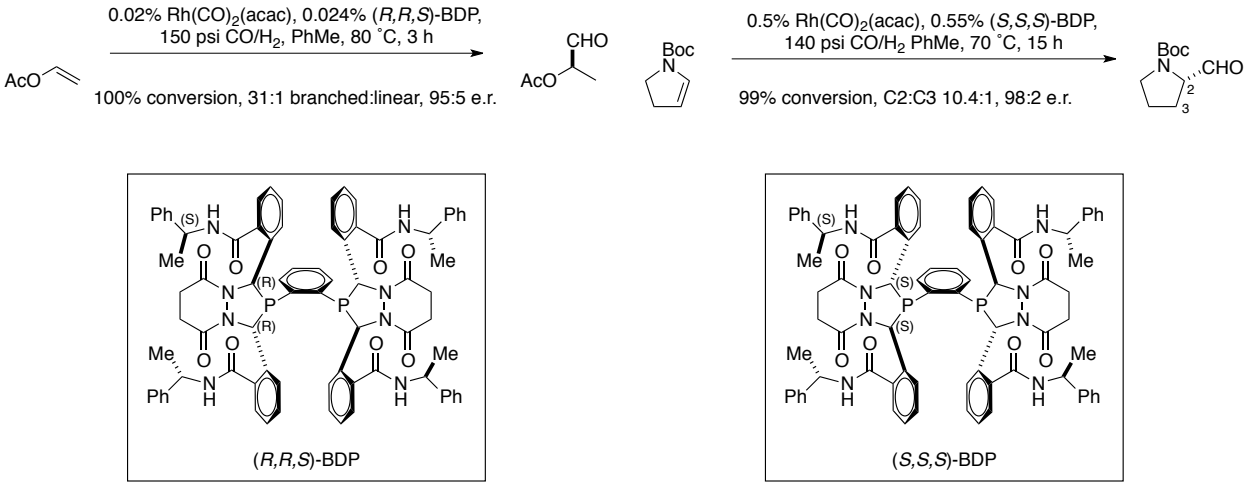
Although both enantiomers of **2A4** can be prepared from the respective enantiomer of **2A1**,[2] we envisioned that a facial-and regioselective hydroformylation of oxazoline **2B1**, previously reported by Funk and coworkers (Scheme 2B),[18] would produce **2A4** in a single step.

Scheme 2B. Synthesis of Both Enantiomers of 2A4 by AHF



The Landis group has studied AHF of alkenes with vinyl heteroatoms using their bisdiazaphospholane (BDP) ligands (Scheme 2C).[19,20] However, no substrate has had competing direction by two different heteroatom functionalities. Our hypothesis was that the vinyl carbamate in **2B1** would be the stronger director because of its enhanced electron-withdrawing effects due to the carbamate protecting group.

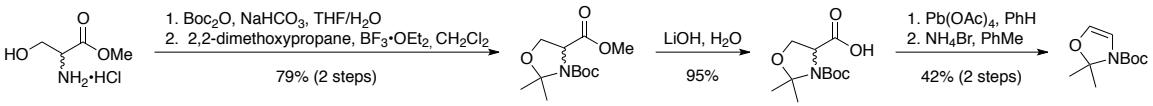
Scheme 2C. AHF of Vinyl Heteroatomic Substrates with BDP Ligands



Since **2B1** has been reported previously,[18] its synthesis followed published procedures (Scheme 2D). Carboxylic acid **2D3**[21] was synthesized from racemic serine methyl ester hydrochloride (**2D1**) by protection of the amine as a Boc carbamate and installation of the

isopropylidene to furnish oxazolidine **2D2** in a 79% yield over two steps. Saponification of the methyl ester with aqueous LiOH formed carboxylic acid **2D3** in excellent yield. **2D3** was then subjected to a two-step oxidative decarboxylation/elimination procedure with $Pb(OAc)_4$ and NH_4Br to form **2B1** in 42% yield from **2D3**.[18]

Scheme 2D. Synthesis of 2B1



Screening AHF conditions with **2B1** quickly indicated the AHF was proceeding with the desired regiochemistry and **2A4** as the major product (Table 2A). Analysis of the ^1H NMR spectrum of the crude reaction allowed for the simultaneous determination of completion and regioselectivity by the absence of signals for **2B1** and comparison of the product aldehyde

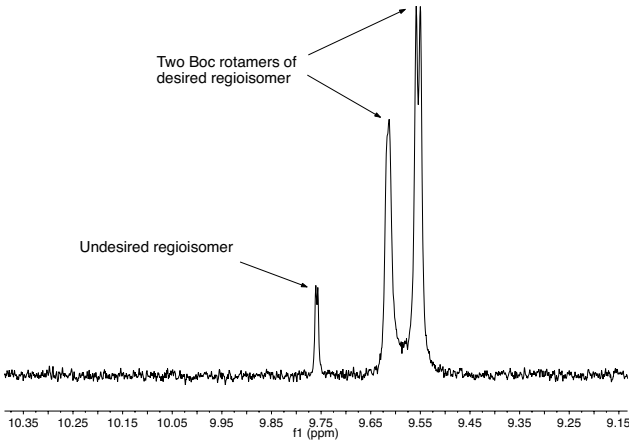
Table 2A. Optimization of AHF of 2B1*

Experimental Conditions					Results			
Rh	**T (˚C)**	**[2B1]**	**Time**	**Ligand**	**Conv.**	**4-CHO:5-CHO**	**Yield**	**e.r.**
1%	44	0.8	3 d	(*R,R,S*)	70%	17:1	56%	96:4
1%	60	0.8	3 d	(*R,R,S*)	>95%	12:1	68%	93:7
1%	50	1.15	3 d	(*S,S,S*)	56%	11:1	49%	1:99
1%	56	0.8	2 d	(*S,S,S*)	>95%	11:1	74%	2:98
1%	41	1.07	16 h	(*S,S,S*)	57%	26:1	-	-
1%	41	1.31	16 h	(*S,S,S*)	32%	12:1	-	-
1%	50	1.2	16 h	(*S,S,S*)	66%	17:1	40%	1:99
1%	57	1.2	16 h	(*S,S,S*)	89%	8:1	72%	2:98
2%	56	0.5	16 h	(*S,S,S*)	74%	16:1	63%	2:98
2%	55	0.5	3 d	(*S,S,S*)	>95%	20:1	70%	2:98
2%	55	0.5	3 d	(*R,R,S*)	>95%	13:1	71%	97:3

*Rh=mol % $Rh(CO)_2(acac)$; [**2B1**] in THF; Ligand=BDP; Conv.=conversion (determined by ^1H NMR of crude mixture);Yield (isolated); e.r. determined by SFC after reduction and esterification (vide infra)

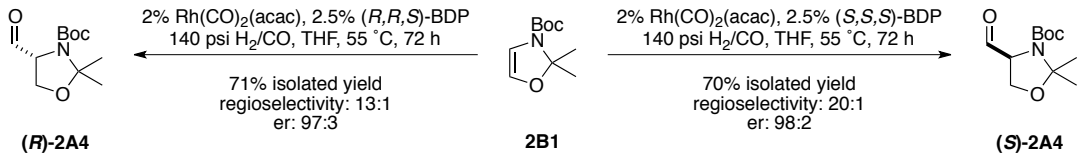
signals, respectively (Figure 2B). Balancing conversion and regioselectivity was the biggest obstacle; a slower reaction often gave excellent regioselectivity, but did not go to completion in a reasonable amount of time. A faster reaction often sacrificed regioselectivity for conversion.

Figure 2B. Aldehyde ^{1}H NMR Signals ($CDCl_3$) of Crude AHF Reaction



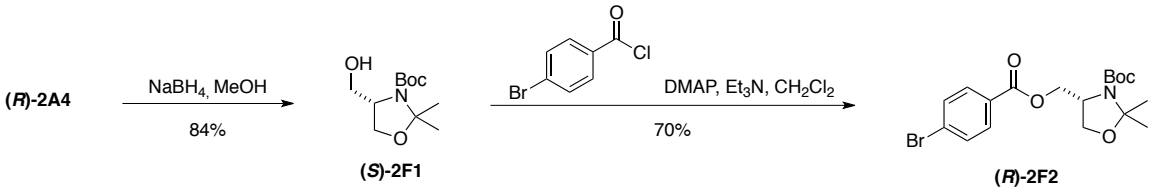
Balancing catalyst and substrate concentrations was challenging. We found that the catalyst concentration must be at least 0.01 *M* for effective hydroformylation, but regioselectivity was improved with dilution of **2B1**. Optimization of conditions to 55 ˚C, 0.5 *M* concentration, 2% catalyst loading, and a reaction time of three days furnished **(*S*)-2A4** in 70% and **(*R*)-2A4** in 71% isolated yields (Scheme 2E). There are differences in enantio- and regioselectivity and isolated yield because the BDP ligands are diastereomeric. The energy difference between 20:1 regioselectivity and 13:1 regioselectivity at 55 ˚C was calculated to be about 0.28 kcal/mol using the Boltzmann distribution.

Scheme 2E. Synthesis of Both Enantiomers of 2A4 by AHF of 2B1



Optical rotation data for both enantiomers of **2A4** has been reported,[2] but for a more accurate determination of enantiopurity both enantiomers of **2A4** were reduced to primary alcohols (**2F1**) and esterified with 4-bromobenzoyl chloride to produce esters **2F2** (Scheme 2F). The enantiomeric ratios for **2F2** were determined to be 97:3 for the *R*-enantiomer and 98:2 for the *S*-enantiomer by supercritical fluid chromatography (SFC). Absolute configuration was assigned based on enantiomerically pure **(*S*)-2F2** prepared from L-serine methyl ester hydrochloride.

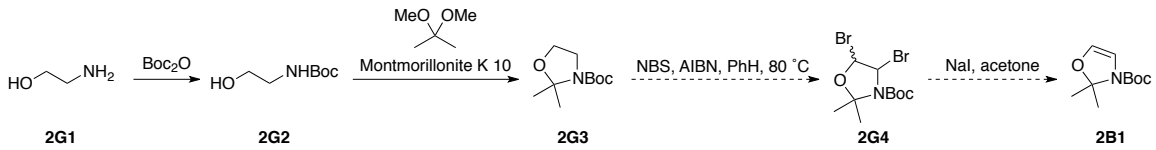
Scheme 2F. Reduction and Esterification of (*R*)-2A4 for Enantioselectivity Analysis



2.3 Future Directions

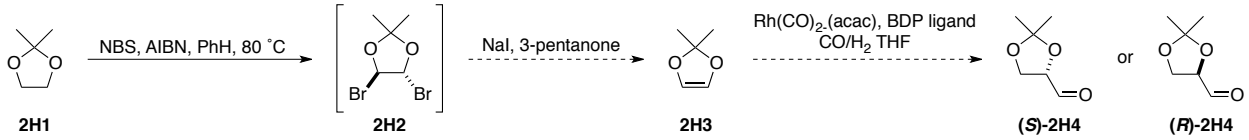
The low yielding oxidative decarboxylation/elimination sequence and dependence on serine are limitations of the synthesis of **2B1**. To circumvent these problems, an independent synthesis of **2B1** was imagined from known oxazolidine **2G3**, prepared in two steps from ethanolamine (**2G1**) (Scheme 2G).[22] Free-radical dibromination with *N*-bromosuccinimide (NBS)[23] to dibromooxazolidine **2G4** and reductive debromination with NaI[24] would furnish **2B1** in fewer synthetic steps than the serine oxidative decarboxylation and from simpler and less expensive starting materials.

Scheme 2G. Potential Non-Serine Synthesis of 2B1



This free radical dibromination/reductive debromination strategy can also be applied to dioxolane **2H1** (Scheme 2H).[25] The dibromination of **2H1** has been investigated and preliminary data show excellent conversion to the dibromide **2H2**, which could be dehalogenated with NaI in 3-pentanone to form known dioxole **2H3**.[26] Experiments for debromination with Zn^0 or Mg^0 have been unsuccessful, presumably because of the volatility of **2H3** and the more complicated

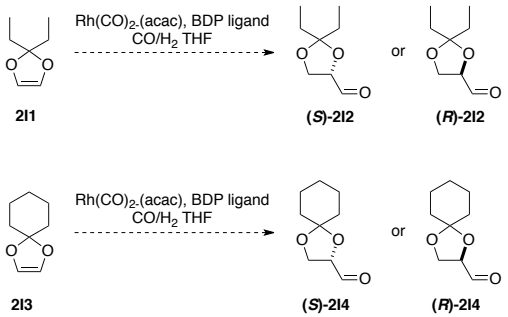
Scheme 2H. Glyceraldehyde Acetonide by AHF



work up for these superstoichiometric metal reductions. The relatively low boiling point of **2H3** (71 ˚C) suggests isolation by distillation from the reaction mixture, but 3-pentanone should be the solvent, not acetone, because of its higher boiling point (102 ˚C vs. 56 ˚C). Dioxoles are excellent potential AHF substrates because of their high symmetry and electronic activation as vinylic ethers. AHF of **2H3** would produce glyceraldehyde acetonide **2H4**, which is a very common chiral building block produced from the chiral pool.[27]

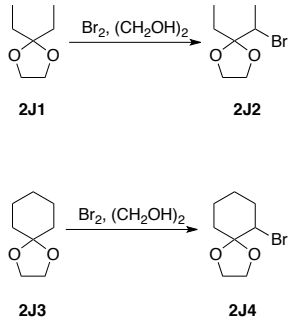
Other common acetal-protected glyceraldehydes are **2I2**[28] and **2I4**,[29] which could be produced by AHF of dioxoles **2I1** and **2I3** (Scheme 2I).[30] However, the above brominaton/debromination procedure cannot produce **2I1** and **2I3**. The oxygen-bearing

Scheme 2I. Acetal Protected Glyceraldehydes by AHF



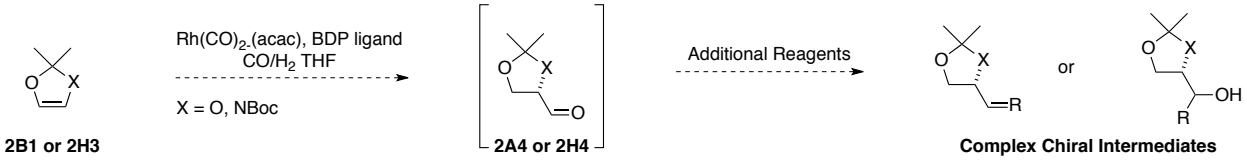
methylenes of **2J1**,[31] and **2J3**[32] are deactivated to hydrogen atom abstraction relative to the other methylenes, so bromination does not occur on the dioxolane ring (Scheme 2J). Instead, bromoalkyl dioxolanes **2J2** and **2J4** are produced.[31,33] An alternative synthesis of **2I1** and **2I3** must be developed for their exploitation by AHF.

Scheme 2J. Free Radical Bromination of Alkyl-Substituted Dioxolanes 2J1 and 2J3



Because of the mild conditions of AHF, all of the chiral aldehydes so produced can be subjected to tandem or one-pot reactions, thus mitigating the epimerization and polymerization of glyceraldehydes[27] and allowing for the rapid generation of complex, chiral material (Scheme 2K). Comparison of the reaction conversion data in Table 2A (>95%) and isolated yields (70 and 71%) shows that over 25% of the product is lost in purification by flash column chromatography. This product can be used and not lost if additional reagents are present for a tandem reaction, or added after the completion of the AHF for a one-pot procedure. Many of the reactions with **2A4** reported above could be done in a tandem or one-pot sequence. Recently reported transformations of acetal- protected glyceraldehydes that would work in a tandem

Scheme 2K. Tandem or One-Pot Reactions of 2A4 and 2H4



or one-pot reaction with AHF are Wittig and Horner-Wadsworth-Emmons olefinations,[34] allylation and crotylation,[35] Grignard additions,[36] and conversion to a terminal alkyne.[13a,37] Additional tandem reactions can be developed and exploited for rapid construction of molecular complexity with practically simple procedures.

Preparation of **2A4** by AHF is an efficient and atom economical method to access a common synthetic building block. The mild conditions of AHF can be exploited with tandem or one-pot reactions on the crude aldehyde for the rapid generation of complex chiral molecules with reduced purification and waste. An alternative synthesis of oxazoline **2B1** from ethanolamine would further increase the efficiency of this sequence. Additionally, the heterocycle AHF/tandem or one-pot reaction can be applied to the synthesis of acetal-protected glyceraldehydes and their derivatives, which also are popular chiral synthetic building blocks.

Experimental Details

3-(1,1-Dimethylethyl) 4-methyl 2,2-dimethyl-3,4-oxazolidinedicarboxylate (2D2)

Di-*tert*-butyl carbonate (43.8 g, 201 mmol) was added to a solution of *rac*-serine methyl ester hydrogen chloride (**2D1**) (25.0 g, 161 mmol) in THF (49 mL) and saturated aqueous $NaHCO_3$ (196 mL). The biphasic mixture was stirred vigorously 16 h, was diluted with H_2O (500 mL) and stirred for 10 min, then partitioned with EtOAc (100 mL) and stirred for an additional 5 min. The aqueous phase was extracted with EtOAc (50 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. Stirring under low pressure was necessary for complete removal of residual solvent due to the viscosity of the oil, which was then dissolved in acetone (500 mL) and 2,2-dimethoxypropane (178 mL, 1.45 mol). Neat BF_3•OEt_2 (2.0 mL, 16.1 mmol) was added dropwise and the dark red solution stirred overnight. The reaction was concentrated under reduced pressure and the crude, dark red oil was dissolved in CH_2Cl_2 (50 mL) and washed

with 1:1 saturated aqueous $NaHCO_3/H_2O$ and brine (40 mL of each), then dried (Na_2SO_4), concentrated, and fractionally distilled (b.p. 111˚C, 1.8 Torr) to give 31.89 g (76% over two steps) of **2D2**. The spectroscopic data matched reported literature values.

3-(1,1-Dimethylethyl) 2,2-dimethyl-3,4-oxazolidinedicarboxylate (2D3)

Aqueous LiOH (18.4 mL, 1 *M*, 18.4 mmol) was added to a solution of **2D2** (4.34 g, 16.7 mmol) in MeOH (28 mL) at 0˚C and the solution stirred for 16 h. The reaction was concentrated under reduced pressure and the crude oil partitioned with Et_2O and H_2O (20 mL of each). The Et_2O layer was discarded and the aqueous layer was acidified to pH 4 with 10% citric acid, precipitating a white solid. The aqueous suspension was extracted with EtOAc (3x10 mL), dried (Na_2SO_4), and concentrated to give a white solid **2D3** (3.91 g, 95%) whose spectroscopic properties matched the reported literature.

3-(1,1-Dimethylethyl) 2,2-dimethyl-3-oxazolinecarboxylate (2B1)

Lead(IV) acetate (6.0 g, 13.5 mmol) was added to a solution of carboxylic acid **2D3** (3.0 g, 12.2 mmol) in benzene (49 mL) and refluxed for 16 h. After cooling to 25 ˚C, the solids were filtered off through a pad of Celite® with EtOAc (50 mL) and the filtrate was washed with aqueous $NaHCO_3$ (100 mL). The aqueous layer was separated and extracted with EtOAc (3x70 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless to light yellow solid that required no further purification. m.p. = 64-65 ˚C. R_f 0.30 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (br s), 1.51 (br s), 1.67 (br s), 2.08 (s, 3H), 3.96 (d, *J*=10.5 Hz), 4.06 (dd, *J*=10.5, 3.3 Hz), 6.40 (d, *J*=3.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers*) δ 21.3 (CH_3), 24.0 (CH_3), 24.7* (CH_3), 26.5 (CH_3), 27.4* (CH_3), 28.5 (CH_3), 69.6 (CH_2), 81.2 (CH), 81.8 (C), 82.8* (CH), 95.3 (C), 151.0 (C), 170.7 (C). IR (neat) 2982, 1738, 1709 cm^{-1}. HRMS (ESI) calcd for $[M+Na]^+$

282.1312. Found 282.1318.

Ammonium bromide (3.23 g, 32.9 mmol) was added to a solution of crude acetate in toluene (37 mL). The suspension was refluxed for 16 h with a Dean-Stark trap two-thirds filled with 15% w/w aqueous NaOH. After cooling to room temperature, the brown slurry was transferred with Et_2O to a separatory funnel containing aqueous $NaHCO_3$ (100 mL). The aqueous layer was separated and extracted with Et_2O (3x70 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (prewashed with 2 L 1% Et_3N/EtOAc, 2 L EtOAc, and 2 L 5% EtOAc/hexane; elute 2 L 5% EtOAc/hexane) to give a yellow to off-white solid **2B1** (1.03 g, 42% over two steps). m.p. = 59-60 ˚C. R_f 0.54 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$). δ 1.48 (br s, 9H), 1.63 (br s, 3H), 1.68 (br s, 3H), 5.96 (br s), 6.04 (br s), 6.10 (br s), 6.24 (br s). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers*) δ 24.4 (CH_3), 25.4* (CH_3), 28.5 (CH_3), 80.5 (C), 81.0* (C), 98.1 (CH), 98.5* (CH), 108.9 (C), 128.9 (CH), 129.6* (CH), 149.5 (C), 149.9* (C). IR (neat) 2977, 1686, 1394, 1086 cm^{-1}. HRMS (EI) calcd for $[M]^+$ 199.1203. Found 199.1208.

1,1-Dimethylethyl (*S*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate [(*S*)-2A4]

Under an inert atmosphere, (*S,S,S*)-BDP (174 mg, 0.133 mmol) and $Rh(CO)_2(acac)$ (27 mg, 0.106 mmol) were dissolved in THF (3.64 mL) in a 40.5 cm-long pressure bottle sealed with a custom head (equipped with pressure gauge, filling/venting valve, and a septum-sealed valve) and pressurized to 140 psi with syngas. After the solution stirred at 55 ˚C for 20 min, the pressure was reduced to about 15 psi and alkene **2B1** (1.06 g, 5.32 mmol) was added as a solution in THF (7 mL) via syringe. The pressure was increased to 140 psi and the reaction was stirred at 55 ˚C for 3 d. After cooling to room temperature, the syngas was vented and the

solution concentrated in vacuo. The regioselectivity was determined to be 20:1 by comparison of the aldehyde peaks in the ^{1}H NMR spectrum of the crude oil [minor regiomeric aldehyde δ 9.76 (d, *J*=1.2 Hz)]. The crude oil was purified by flash column chromatography (20% EtOAc/hexane) to give a colorless to yellow oil (0.85 g, 70%). R_f 0.35 (20% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (br s), 1.52 (br s), 1.56 (s), 1.61 (s), 1.66 (s) 4.00-4.16 (m, 2H), 4.16-4.40 (m, 1H), 9.55 (d, *J*=2.4 Hz), 9.61 (d, *J*=0.9 Hz, rotamer). ^{13}C NMR (75 MHz, $CDCl_3$, rotamer*) δ 24.0 (CH_3), 24.9* (CH_3), 26.0 (CH_3), 26.9* (CH_3), 28.5 (CH_3), 63.7* (CH_2), 64.1 (CH_2), 64.9 (CH), 81.3 (C), 81.6* (C), 94.5 (C), 95.3* (C), 101.0 (C), 151.5 (C), 152.8* (C), 199.6 (CH). IR (neat) 2981, 1739, 1709, 1370 cm^{-1}. HRMS (ESI) calcd for $[M+Na]^+$ 252.1207. Found 252.1194.

1,1-Dimethylethyl (*R*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate [(*R*)-2A4]

Under an inert atmosphere, (*R,R,S*)-BDP (160 mg, 0.122 mmol) and $Rh(CO)_2(acac)$ (25 mg, 0.097 mmol) were dissolved in THF (2.74 mL) in a 40.5-cm long pressure bottle sealed with a custom head (equipped with pressure gauge, filling/venting valve, and a septum-sealed valve) and pressurized to 140 psi with syngas. The solution stirred at 55 ˚C for 20 min, the pressure reduced to about 15 psi and alkene **2B1** (0.97 g, 4.87 mmol) was added as a solution in THF (7 mL) via syringe. The pressure was increased to 140 psi and the reaction was stirred at 55 ˚C for 3 d. After cooling to room temperature, the syngas was vented and the solution concentrated in vacuo. The regioselectivity was determined to be 13:1 by comparison of the aldehyde peaks in the ^{1}H NMR spectrum of the crude oil [minor regiomeric aldehyde δ 9.76 (d, *J*=1.2 Hz)]. The crude oil was purified by flash column chromatography (20% EtOAc/hexane) to give a colorless to yellow oil (0.79 g, 71%). R_f 0.35 (20% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (br s), 1.52 (br s), 1.56 (s), 1.61 (s), 1.66 (s), 4.00-4.16 (m, 2H), 4.16-4.40 (m 1H), 9.55 (d, *J*=2.4

Hz), 9.61 (d, *J*=0.9 Hz, rotamer). ^{13}C NMR (75 MHz, $CDCl_3$, rotamer*) δ 24.0 (CH_3), 24.9* (CH_3), 26.0 (CH_3), 26.9* (CH_3), 28.5 (CH_3), 63.7*(CH_2), 64.1 (CH_2), 64.9 (CH), 81.3 (C), 81.6* (C), 94.5 (C), 95.3* (C), 101.0 (C), 151.5 (C), 152.8* (C), 199.6 (CH). IR (neat) 2981, 1739, 1709, 1370 cm^{-1}. HRMS (ESI) calcd for $[M+Na]^+$ 252.1207. Found 252.1194.

1,1-Dimethylethyl 4-hydroxymethyl-2,2-dimethyl-3-oxazolidinecarboxylate (2F1)

$NaBH_4$ (0.18 g, 4.83 mmol) was added to a solution of aldehyde **2A4** (0.79 g, 3.45 mmol) in MeOH (35 mL) at 0 ˚C. The solution was stirred at 0 ˚C for 1 h, quenched with saturated aqueous NH_4Cl (10 mL), warmed to room temperature, and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a white solid suspended in a colorless oil. The crude oil was dissolved in EtOAc (10 mL), dried ($MgSO_4$), filtered, and the solvent removed in vacuo to give a colorless oil (0.67 g, 84%) that required no further purification. R_f 0.51 (50% EtOAc/hexanes) ^{1}H NMR (300 MHz, $CDCl_3$) δ1.49 (br s, 12H), 1.55 (br s, 3H), 3.5-3.7 (m, 1H), 3.7-4.2 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, rotamer*) δ 23.2* (CH_3), 24.7 (CH_3), 26.9* (CH_3), 27.3 (CH_3), 28.6 (CH_3), 58.5* (CH), 59.6 (CH), 63.1* (CH_2), 65.2 (CH_2), 65.4 (CH_2), 80.2* (C), 81.3 (C), 94.2 (C), 152.0* (C), 154.2 (C). IR (neat) 3011, 1656, 1405 cm^{-1}. HRMS (ESI) calcd for $[M+Na]^+$ 254.1363. Found 254.1359.

1,1-Dimethylethyl-4-(4-bromobenzoyloxymethyl)-2,2-dimethyl-3-oxazolidinecarboxylate (2F2)

4-Bromobenzoyl chloride (0.43 g, 1.95 mmol) was added to a solution of alcohol **2F1** (0.30 g, 1.30 mmol), DMAP (16 mg, 0.13 mmol), and Et_3N (0.27 mL, 1.95 mmol) in CH_2Cl_2 (3.0 mL) and the solution stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (12 mL), washed with 10 mL aq. $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The crude oil was purified by flash column chromatography (5% EtOAc/hexane to 10% EtOAc/hexane) to give

0.38 g (70%) of a light yellow to colorless oil that solidified with cold storage. m.p. 48-49 ˚C. R_f= 0.53 (20% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s), 1.50 (s), 1.53 (s), 1.57 (s), 1.62 (s), 3.90-4.10 (m, 3H), 4.20-4.50 (m, 3H), 7.59 (m, 2H), 7.91 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, rotamer*) δ 23.3*, (CH_3), 24.5 (CH_3), 26.9* (CH_3), 27.8 (CH_3), 28.6 (CH_3), 55.8 (CH), 56.0* (CH), 64.2 (CH_2), 65.3 (CH_2), 65.5* (CH_2), 77.5 (C), 80.5 (C), 80.8* (C), 93.9 (C), 94.5* (C), 128.3* (C), 128.5 (C), 129.0* (C), 129.1 (C), 165.7* (C), 165.8 (C). IR (neat) 2979, 1725, 1697, 1591 cm^{-1}. HRMS (ESI) calcd for $[M+H]^+$ 414.0911. Found 414.0919. $[\alpha]_D^{22}$ = +31.3 (c = 1.0, $CHCl_3$).

4,5-Dibromo-2,2-dimethyl-1,3-dioxolane (2H2)

A solution of 2,2-dimethyl-1,3-dioxolane (**2H1**) (1 mL, 9.07 mmol), *N*-bromosuccinimide (3.23 g, 18.14 mmol), and AIBN (30 mg, 0.18 mmol) in benzene (45 mL) was heated to reflux under Ar. Once the red color of the hot solution turned colorless to light yellow and the solids had dissolved (typically less than 10 min), the solution was cooled to room temperature and filtered from the crystallized succinimide with a cannula filter (a 16 gauge needle with Kimwipe® secured over the blunt end) and the crystals were washed with benzene. Benzene was removed by distillation under aspirator pressure and the oil was purified by kugelrohr distillation (up to 90 ˚C, 1 Torr) to give a colorless oil that turned orange with exposure to air or after sitting out at room temperature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 6H), 6.82 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7 (CH_3), 88.6 (CH), 121.1 (C). HRMS (EI) calcd for $[M-CH_3]^{+\bullet}$ 242.8651. Found 242.8639. Because of the instability of **2H2**, the R_f was not determined and an IR spectrum was not recorded.

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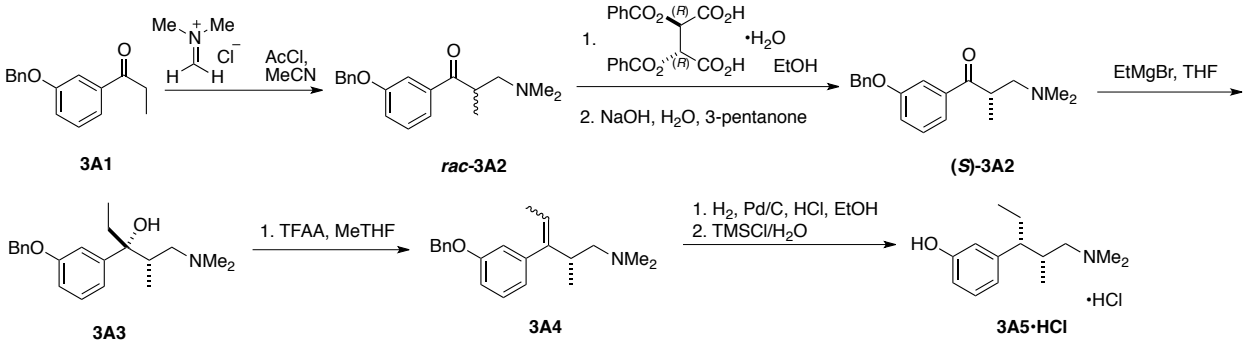
Chapter 3. Efforts Towards the Total Synthesis of Tapentadol via an Asymmetric Hydroformylation/ Reductive Amination One-Pot Sequence

3.1 Background

Tapentadol (**3A5**) (Scheme 3A) was first reported in 1996 and was found to be both a μ-opioid agonist and norepinephrine reuptake inhibitor;[1] in 2008, it was approved for the treatment of moderate to severe pain in adults in the U.S.[2] Many μ-opioid inhibitors are powerful pain relievers, but they can have significant side effects and prolonged use runs the risk of developing tolerance, dependence, and addiction. The dual action mechanism of tapentadol could enhance beneficial pharmacological effects and while minimizing unwanted interactions and symptoms.[1c] As part of our program to develop efficient asymmetric hydroformylation (AHF) tandem reactions, tapentadol was chosen as a target because its methyl stereocenter beta to a dimethyl amine could be synthesized via tandem AHF/reductive amination (RA) of a vinyl group.

Scheme 3A. Industrial Synthesis of Tapentadol



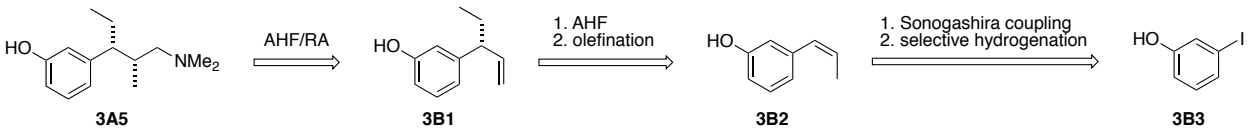
In the industrial synthesis, the dimethyl amine functionality is added via a Mannich reaction with aryl ethyl ketone **3A1** to set the methyl stereocenter of **3A2** as a racemate.[3] It is resolved to the desired enantiomer via the diastereomeric salts produced by (*R,R*)-di-*O*-benzoyltartaric acid and neutralized with sodium hydroxide. Ethyl Grignard addition selectively forms tertiary alcohol **3A3** by chelation of magnesium with the amine and the ketone. Esterification with trifluoroacetic anhydride and subsequent elimination of trifluoroacetic acid

produces a mixture of alkenes (**3A4**), which are hydrogenated over palladium on carbon to set the ethyl stereocenter with a modest 5.5:1 d.r. Selective crystallization with TMSCl and water allows for the isolation of the HCl salt of **3A5**. Many patents have been published for the preparation of tapentadol,[4] but a notable development is an asymmetric Mannich reaction to set the methyl stereocenter of **3A2**.[5]

3.2 Styrene AHF Strategy

Our initial retrosynthetic analysis recognized that a tandem AHF/RA sequence would produce tapentadol from vinyl group **3B1** (Scheme 3B). The vinyl group of **3B1** could be produced from an aldehyde resulting from the AHF of *Z*-β-methyl styrene **3B2** using the bisdiazaphos (BDP) ligands developed by the Landis group.[6] Styrene **3B2** would be accessed via a selective hydrogenation of an aryl alkyne, produced from iodophenol **3B3**.

Scheme 3B. Styrene Strategy Retrosynthesic Analysis

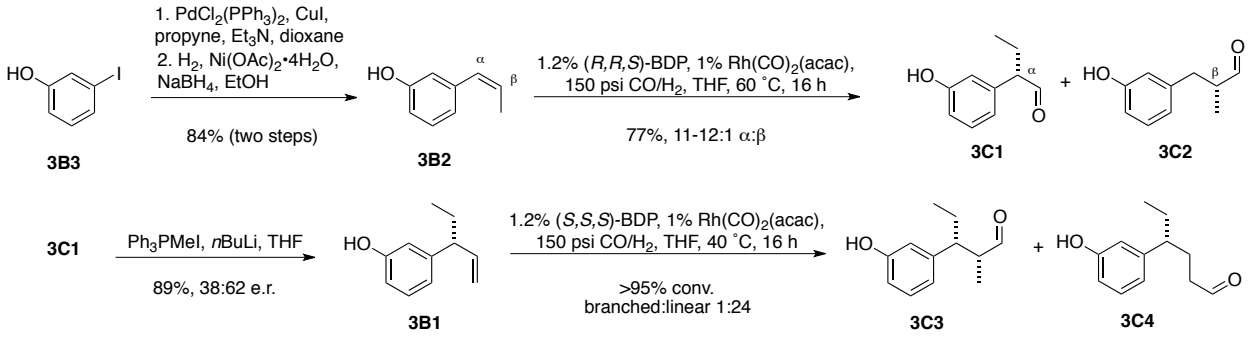


3A5 **3B1** **3B2** **3B3**

Synthesis of **3B2** began with a Sonogashira coupling of 3-iodophenol (**3B3**) and propyne that proceeded in high yield (Scheme 3C).[7] Attempts at selective reduction of the alkyne to the *Z*-olefin via Lindlar hydrogenation[8] resulted in mixtures of **3B2**, *trans*-alkene from isomerization, and *n*-propylphenol from over-reduction; these mixtures were inseparable by column chromatography. The *trans*-alkene was particularly undesirable because it underwent AHF more slowly than **3B2** and gave poorer enantioselectivity.[6] Several attempts were made to reduce the alkyne with diimide,[9] but no reactivity was observed. Reduction with nickel boride[10] produced **3B2** with complete conversion and alkene selectivity with only minor over-reduction

(determined by ^{1}H NMR). The *n*-propylphenol impurity was of little consequence because it is unreactive to AHF, unlike the *trans*-alkene or alkyne.

Scheme 3C. Styrene AHF Strategy Forward Synthesis



AHF of **3B2** produced a mixture of α- and β-aldehydes, favoring the desired α-aldehyde **3C1** 11-12:1 and in 77% isolated yield. Higher concentrations of **3B2** were found to give lower regioselectivity and AHF conditions were not further optimized before results necessitated a change in strategy (vide infra).

Olefination of **3C1** to **3B1** with methylenetriphenylphosphorane proceeded in good yield but despite similar precedent[11] resulted in an apparent erosion of e.r. A direct comparison of the enantiomeric purity of **3C1** and **3B1** was not possible since the e.r. of **3C1** was not determined. However, due to the similarity of **3C1** with styrene AHF data published by the Landis group[6] we assumed a significant erosion of enantiopurity with the Wittig olefination. We did not consider the olefination a problem, however, as many methods are available for the conversion of an aldehyde to a vinyl group.[12]

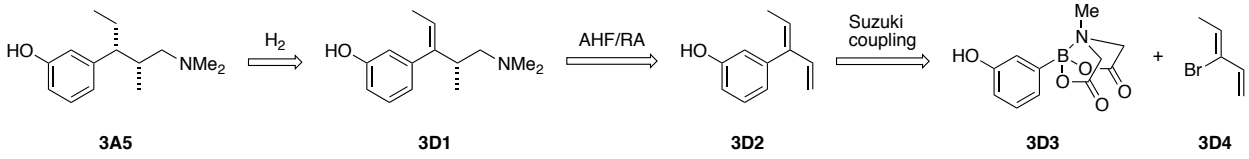
Analysis of the AHF of monosubstituted olefin **3B1** revealed that the desired α-chiral aldehyde (**3C3**) was the minor product. The linear hydroformylation (LHF) product, **3C4**, was the major product because the steric interactions of **3B1** override the small amount of electronic direction by the distant aromatic ring. While there were many other options for transformation

of **3C1** to **3B1** without epimerizing the stereocenter,[12] the remarkably poor results from the hydroformylation of **3B1** necessitated a change in strategy.

3.3 Diene AHF Strategy

A new synthesis was conceived wherein a tandem or one-pot hydroformylation/reductive amination of diene **3D2** would produce amine **3D1** (Scheme 3D). The Landis group had reported that diene AHF proceeded with better regioselectivity than styrene AHF,[13] and setting the methyl stereocenter of **3D1** first would solve the AHF problem that sabotaged the previous styrene AHF-based strategy. Hydrogenation of the styrene **3D1** would follow precedent in the patent literature to produce **3A5**.[3] Diene **3D2** would be accessed via a Suzuki coupling of commercially available boronic ester **3D3** and bromodiene **3D4**, which had been reported and not isolated[14] but could be prepared from crotonaldehyde.

Scheme 3D. Diene AHF Strategy Retrosynthetic Analysis

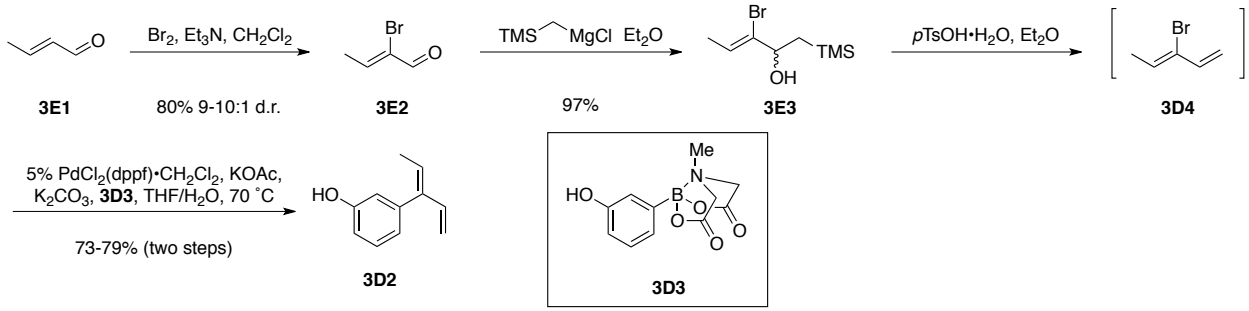


3A5 **3D1** **3D2** **3D3** **3D4**

Bromination of crotonaldehyde **(3E1)** proceeded as reported to give vinyl bromide **3E2** as a 9-10:1 mixture of alkene diastereomers (Scheme 3E),[15] but Wittig olefination proved problematic. The steps required to remove triphenylphosphine oxide coupled with the volatility of diene **3D4** to render Wittig olefination unusable. Alternatively, a two-step Peterson olefination was employed based on the synthesis of similar dienes in the literature.[16] The addition of (trimethylsilyl)methylmagnesium chloride to **3E2** produced **3E3** in excellent yield and purity.[16a] Treatment of **3E3** with pTsOH•H_2O in Et_2O cleanly generated diene **3D4**.[16b] Since the byproducts of the Peterson olefination were water and TMSOH, it was reasoned that distillation

would quickly and easily separate **3D4**. However, attempts to isolate **3D4** by either filtration through a silica gel plug or distillation failed; heating **3D4** and TMSOH resulted in an unknown product. Fortunately, TMSOH was innocuous in the subsequent coupling reaction, and a one-pot Peterson olefination/Suzuki coupling was developed that reliably produced aryl diene **3D2** in greater than 73% yield from **3E3**.[17]

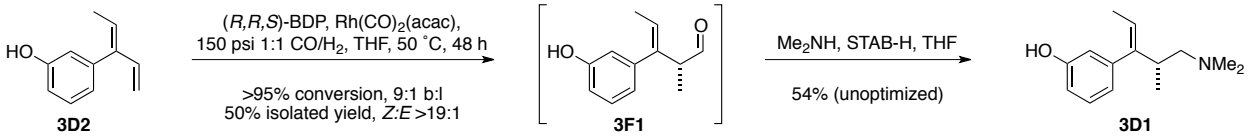
Scheme 3E. Synthesis of Diene 3D2.



AHF of **3D2** produced aldehyde **3F1** with 9:1 branched:linear regioselectivity (b:l). Additionally, it improved the alkene d.r. from 10:1 *Z:E* to >19:1 *Z:E* (Scheme 3F) and **3F1** could be isolated in 50% yield. The low yield of **3F1** is the result of purification by flash column chromatography; the crude yield was about 90% (determined by ^{1}H NMR spectroscopy). Experiments with 3:1 CO:H_2 led to poorer regioselectivity and shorter reaction times eroded conversion. A one-pot AHF/RA protocol was used instead of a tandem reaction because of the ease of monitoring the AHF by ^{1}H NMR spectroscopy and the optimal concentrations for the AHF and the RA procedures. The RA proceeded with excellent conversion by crude ^{1}H NMR spectroscopy but isolation of **3D1** was difficult due to its polarity and poor elution during flash column chromatography, resulting in a 54% yield from diene **3D2**. RA experiments on isolated **3F1** provided crude **3D1** (no flash column chromatography) with reasonable purity in nearly quantitative yield (up to 90% purity determined by ^{1}H NMR spectroscopy). Based on published

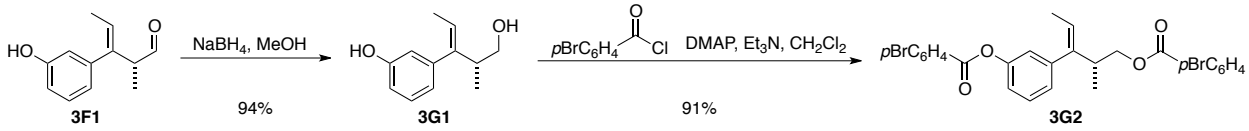
examples of RA of α-aryl and allylic aldehydes we expected the methyl stereocenter to be unaffected by the RA.[18]

Scheme 3F. One-Pot AHF/RA of 3D2.



To analyze the enantioselectivity of the AHF and to confirm the retention of the stereocenter through the RA, **3F1** was reduced to primary alcohol **3G1** and esterified with 4-bromobenzoyl chloride to produce diester **3G2** (Scheme 3G). The e.r. was determined by SFC to be 22:78, but the absolute configuration of the major enantiomer was not determined. AHF with the (*R,R,S*)-BDP ligand at 42 ˚C resulted in an identical e.r. to AHF at 55 ˚C. Conversely, AHF with the diastereomeric (*S,S,S*)-BDP ligand produced regioselectivity of 18:1 and an e.r. of 57:43.

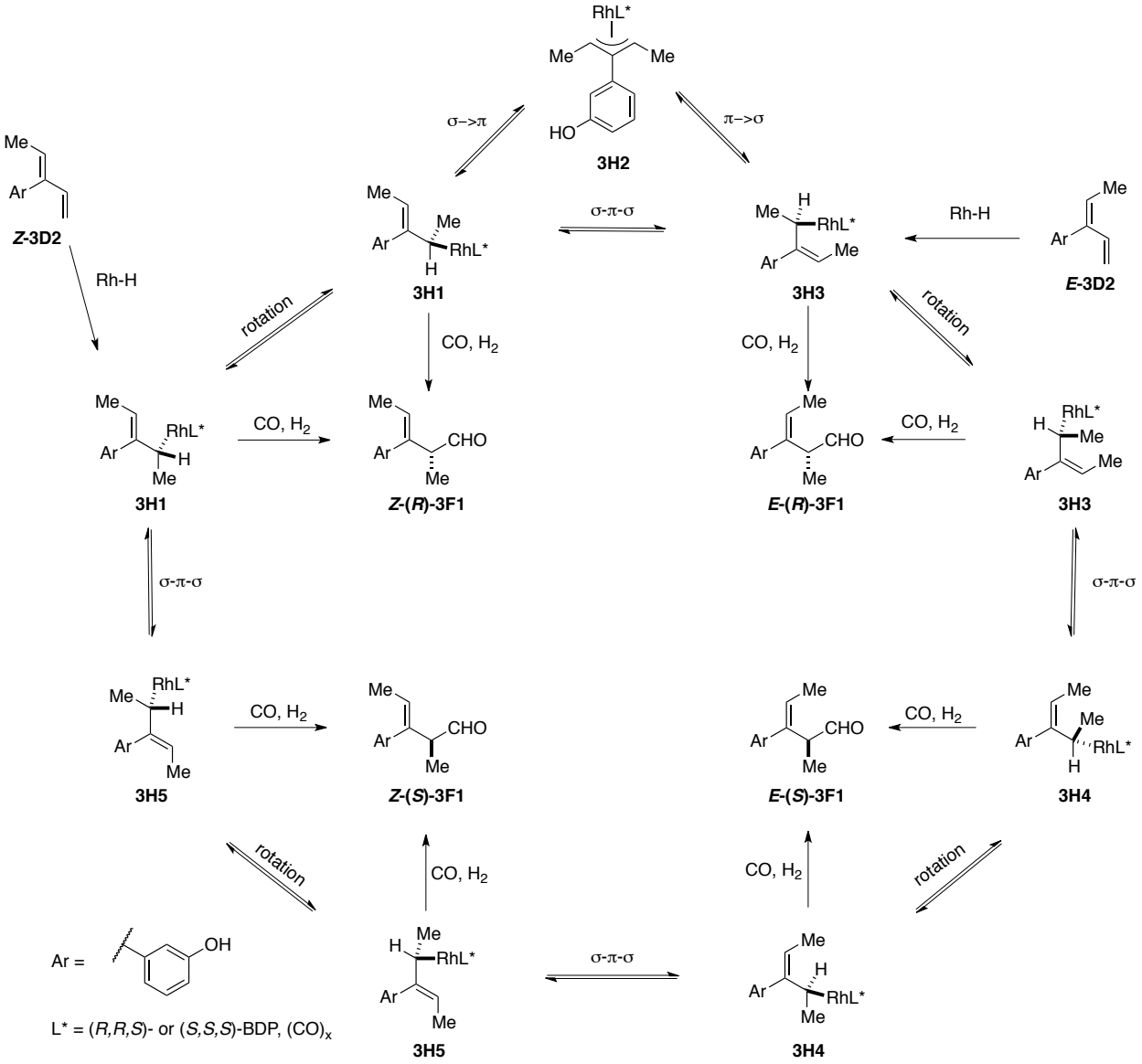
Scheme 3G. Reduction and Esterification for Enantioanalysis



The fact that the alkene *Z:E* ratio improved in the AHF of **3D2** to **3F1** gave us insight into the very poor enantioselectivity of the AHF. Landis and coworkers had previously reported that allylic rhodium intermediates are able interconvert via σ-π-σ allyl shifts during diene hydroformylation.[13] Examining the possible rearrangements for the allyl rhodium intermediates produced by the AHF of **3D2**, we realized that both alkene diastereomers could be converted to all four diastereomers of **3F1** (Scheme 3H).

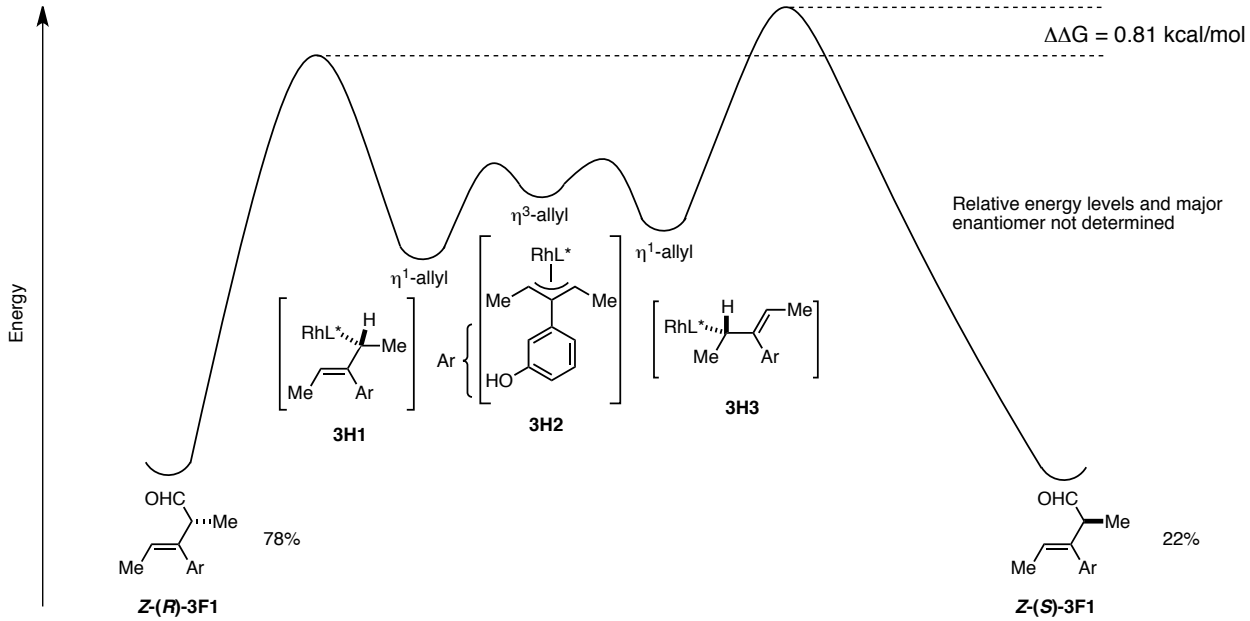
Since the ligated rhodium center is chiral, an allylic shift that inverts the methyl stereocenter produces a diastereomeric allyl rhodium species. The pseudo-symmetry of the η^3-allyl rhodium species is illustrated in **3H2**. The C-C bond of the aryl ring and the allyl system is likely rotating freely, given the elevated temperature (50 ˚C). Even if rotation were not free, the hydroxyl is sufficiently removed from the two methyl groups to limit its influence on the conformation of the Rh-π-allyl species. The rapid equilibrium of allyl rhodium intermediates

Scheme 3H. Allyl-Rh Isomerization During AHF of 3D2



3H1, **3H3**, **3H4** and **3H5** sets up a Curtin-Hammett situation where carbonyl insertion and hydrogenolysis of each allyl rhodium intermediate gives rise to a separate stereoisomer of **3F1**. Since **3F1** has an increased ratio of *Z:E* olefins, from 9:1 to 19:1, the most reactive intermediates toward carbonyl insertion must be **3H1** and **3H5**, as these two allyl-rhodium intermediates have a *Z* olefin. Intermediates **3H3** and **3H4** have an *E* olefin, which is not observed, so these intermediates must not be competitive in the production of **3F1**. Boltzmann distribution calculations determined the energy difference between the aldehyde-forming barriers to be about 0.81 kcal/mol at 50 ˚C. Figure 3A illustrates this scenario between the allyl rhodium intermediates **3H1**, **3H2**, and **3H3**. Since this barrier difference is so low, it is unlikely that hydroformylation would proceed at temperatures low enough to prevent the allyl rhodium equilibrium from competitively forming the undesired *S* enantiomer of **3D1**.

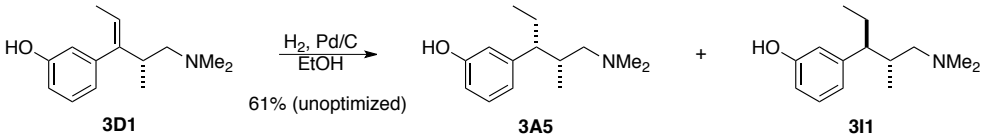
Figure 3A. Hypothetical Curtin-Hammett Scenario from Diene 3D2



Hydrogenation of allylic amine **3D1** was not optimized and produced a 1.3:1 mixture of diastereomers **3A5** and **3I1**, though the major component was not determined (Scheme 3I).

Patent precedent cited at best a 5.5:1 (**3A5**:**3I1**) mixture of diastereomers with H_2 and Pd/C in concentrated HCl/EtOH,[3] but these conditions did not scale down to bench quantities well enough for effective hydrogenation. A higher Pd/C loading (100 mg/mmol vs. 18 mg/mmol) was required for hydrogenation of the styrene.

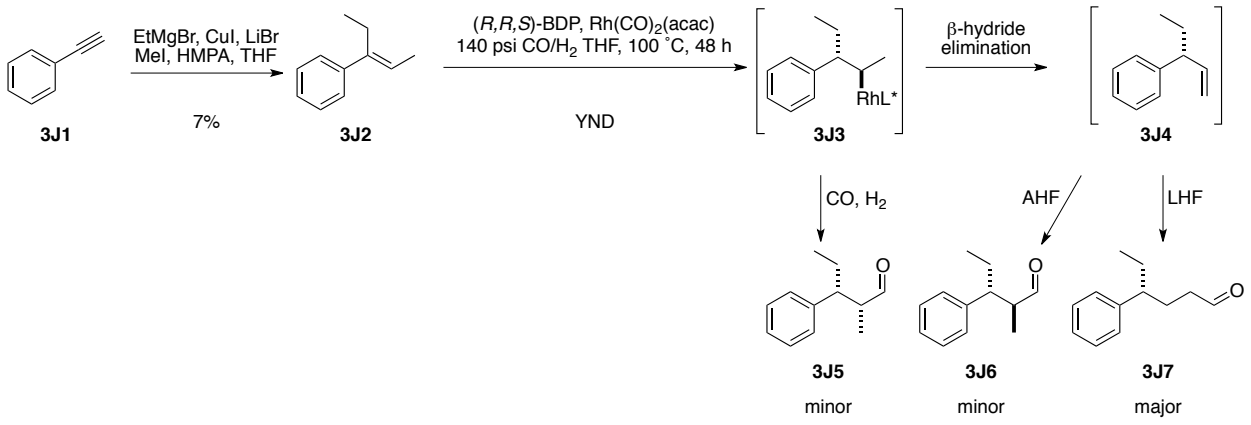
Scheme 3I. Hydrogenation of 3D1



3.4 Trisubstituted Olefin Strategy

In order to work around the Rh-allyl intermediate equilibrium that caused the AHF of **3D2** to proceed with poor enantioselectivity, a synthesis was imagined in which AHF of a trisubstituted olefin would set both stereocenters of **3A5** in the same step. For a proof of concept experiment, olefin **3J2** was synthesized from phenylacetylene (**3J1**) (Scheme J).[19] The Landis group has found that high temperatures (>100 ˚C) are required to react 1,1-disubstituted olefins,[20] so an initial temperature of 100 ˚C was utilized. After 48 hours, complete conversion was observed, but three aldehyde signals were present in the crude ^{1}H NMR spectrum. The

Scheme J. Trisubstituted Olefin Preparation and AHF.



major aldehyde signal was a triplet corresponding to linear hydroformylation (LHF) product **3J7**. The other two were the doublets corresponding to α-chiral aldehydes **3J5** (desired product) and **3J6** (undesired product). This product mixture arises from the reversibility of the alkene insertion into the Rh-H bond. Initial insertion sets the ethyl stereocenter, but the alkyl rhodium intermediate can react in two ways: CO insertion or β-hydride elimination. Insertion of CO forms the desired aldehyde **3J5**, but β-hydride elimination from the more accessible methyl group produces monosubstituted alkene **3J4**. **3J4** is very similar to **3B1** from the original styrene-based strategy (Scheme 3C), and both **3B1** and **3J2** hydroformylate to give a mixture of linear aldehyde and branched aldehyde, with the linear aldehyde **3J7** as the major product since there is little electronic direction of the alkene insertion from the phenyl group.

Since **3J4** is formed after the ethyl stereocenter is set by the insertion of the alkene of **3J2** into the Rh-H bond, this stereocenter is the same for all three aldehyde products. The steric differences between trisubstituted alkene **3J2** and mono-substituted alkene **3J4** result in AHF producing opposite configurations of the methyl stereocenter; AHF of **3J4** produces **3J6**, which is diastereomeric to **3J5** from the AHF of **3J2**.

Since AHF of **3J2** did not result in any useful conversion to the desired aldehyde **3J5** this route was not pursued beyond this exploratory reaction. These results illustrate some of the fundamental problems of reactivity on the catalytic cycle that must be solved for effective AHF of trisubstituted olefins.

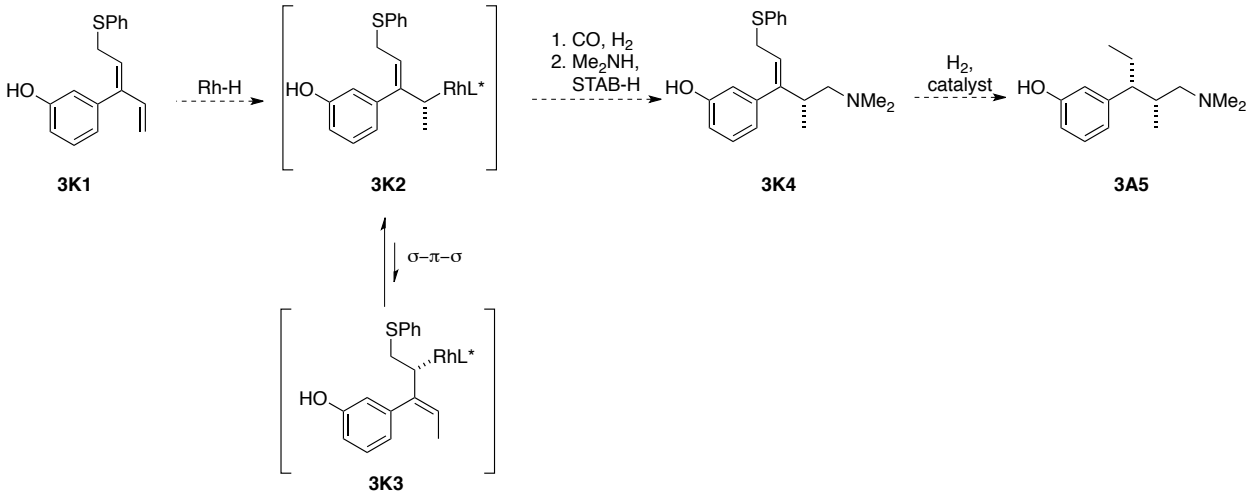
3.5 Future Directions

Of the three strategies explored, AHF of diene **3D2** (Scheme 3F) has the most potential to be corrected with present technology to produce tapentadol in high enantiopurity via an AHF/RA one-pot or tandem reaction. The AHF selectivity could be rectified by the use of an allylic

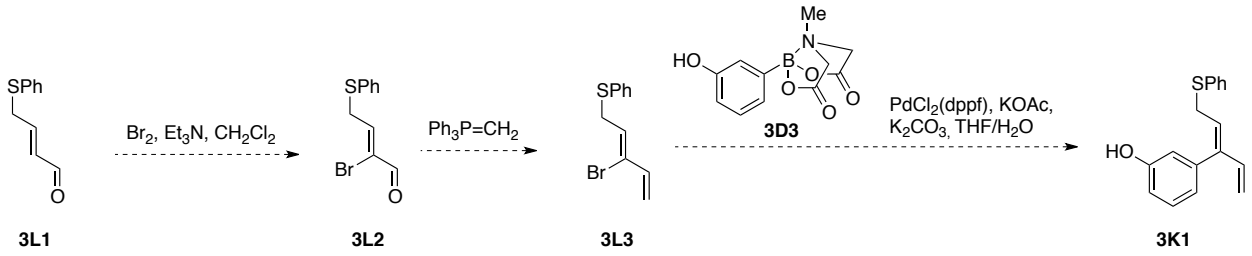
auxiliary. Thiophenol ethers have been employed with Evans' oxazolidinone auxiliaries to allow for increased selectivity in formal acetate aldol reactions,[21] and are removable by hydrogenolysis with Raney nickel.[22] Thioether **3K1** would perturb the energy difference between the allyl rhodium intermediates (**3K2** and **3K3**) and its larger steric bulk would disfavor rearrangement to the isomeric allyl rhodium intermediate **3K3** (Scheme K). Styrene hydrogenation and thioester removal of styrene **3K4** could then be accomplished simultaneously or as a one-pot procedure. It is worth noting, however, that the use of an auxiliary is inherently un-atom economical and thus counteracts some of the benefits of AHF tandem or one-pot reactions.

The synthesis of thioether **3K1** could closely follow that of diene **3D2** (Scheme L). Known thiophenolcrotonaldehyde **3L1** is prepared from crotonaldehyde[23] and can then be subjected to the same bromination/elimination protocol as in Scheme 3E to generate vinyl bromide **3L2**. Olefination could be done with a Wittig reagent, instead of a two-step Peterson olefination, since diene **3L3** will be much more robust and polar than bromodiene **3D4**. Suzuki coupling with MIDA boronate **3D3** will add the aryl moiety and complete the synthesis of **3K1**.

Scheme K. Proposed Use of Thioether Directing Group for Synthesis of 3A5

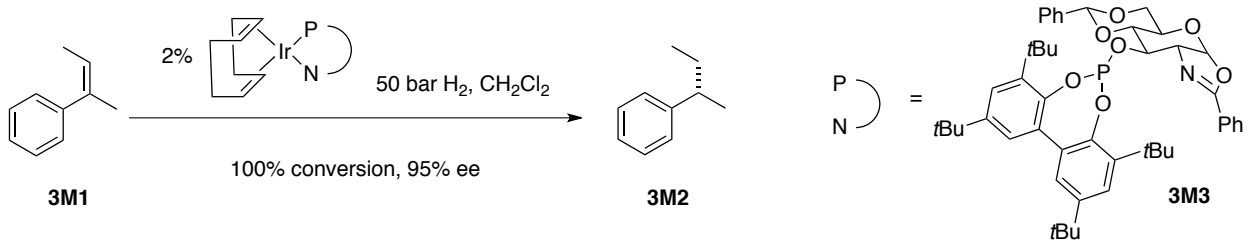


Scheme L. Proposed Synthesis of 3K1



After the AHF/RA protocol proposed in Scheme K, the hydrogenation of trisubstituted alkene **3K4** could be controlled by a catalyst with a chiral ligand to produce **3A5**. The Andersson group has published several chiral ligands that have excellent enantioselectivity for trisubstituted olefins (Scheme M).[24] The ligand **3M3** in particular is good precedent for the desired transformation.

Scheme M. Example Chiral Ligand for Catalyst-Controlled Hydrogenation



Each of the attempted synthetic strategies encountered a general problem in current AHF technology. The styrene AHF strategy was foiled by poor regioselectivity when steric direction prevailed over limited electronic direction. AHF of an aryl diene (**3D2**) resulted in a mixture of enantiomers from equilibrating allylic rhodium intermediates on the AHF catalytic cycle. Experiments with AHF of a tri-substituted olefin (**3J2**) produced a mixture of aldehydes from competitive Rh-catalyzed rearrangement of the alkene and subsequent hydroformylation. Further research into new catalyst/ligand systems will eventually solve these problems, however, and the

capability of AHF to produce valuable chiral aldehydes will continue to grow with continued research.

Experimental Details

(*Z*)-2-bromo-2-butenal (3E2)

Bromine (1.25 mL, 24.3 mmol) was added dropwise to a solution of crotonaldehyde (2.0 mL, 24.3 mmol) in CH_2Cl_2 (49 mL) at 0 ˚C and the solution stirred for 20 min. Triethylamine (4.1 mL, 29.2 mmol) was slowly added and the mixture stirred at 0 ˚C for 1 h. The mixture was quenched with H_2O, separated, dried (Na_2SO_4) and purified by kugelrohr distillation (1.5 Torr, 75 ˚C) to give **3E2** (3.25 g, 80%). The d.r. was determined to be better than 10:1 Z:E by comparing the aldehyde peaks in the ^{1}H NMR [(*E*)-aldehyde δ 9.76 (s)]. R_f 0.33 (10% EtOAc/hexanes). ^{1}H NMR (300 MHz , $CDCl_3$) δ 2.16 (d, *J*=6.6 Hz, 2H), 7.29 (q, *J*=6.6 Hz, 1H), 9.23 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (CH_3), 130.2 (C), 151.2 (CH), 186.2 (CH). IR (neat) 2831, 1699, 1623, 1434 cm^{-1}. HRMS (EI) *m/z* calcd for $[M-H]^{+\bullet}$ 147.9519. Found 147.9512.

(*Z*)-3-bromo-1-(trimethylsilyl)pent-3-en-2-ol (3E3)

A solution of **3E2** (5.84 g, 39.2 mmol) in Et_2O (15 mL) was added to a solution of (trimethylsilyl)methylmagnesium chloride in Et_2O (1 *M*, 63 mL) at 0 ˚C and stirred for 16 h. The mixture was slowly quenched with saturated aqueous NH_4Cl, separated, and the aqueous layer extracted twice with Et_2O. The organic layer was dried (Na_2SO_4) and concentrated to give a white to off-white solid that did not require further purification (9.57 g, 97%). The solid was stored at room temperature for 1.5 months before decomposition. A sample was purified by kuglerohr distillation (1 Torr, 90 ˚C) for characterization. R_f 0.58 (20% EtOAc/hexanes). mp 37-39 ˚C. ^{1}H NMR (300 MHz , $CDCl_3$) δ 0.04 (s, 9H), 1.09 (AB of ABX, 2H), 1.76 (d, *J* =6.3 Hz, 3

H), 4.25 (X of ABX, 1 H), 6.02 (q, *J*=6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) -0.9 (CH_3), 16.5 (CH_2), 25.5 (CH_3), 75.0 (CH), 123.8 (CH), 135.9 (C). IR (neat) 3382, 2954, 1657, 1419 cm^{-1}. HRMS (EI) *m/z* calcd for $[M\text{-}Me]^{+\bullet}$ 220.9992. Found 220.9984.

(*Z*)-3-bromo-1,3-pentadiene (3D4) (mixture with TMSOH)

TsOH•H_2O (0.18 g, 0.935 mmol) was added to a solution of **3E3** (2.35 g, 9.35 mmol) in Et_2O (9.4 mL) and the reaction stirred at room temperature until TLC indicated complete consumption of **3E3**. The biphasic solution was used crude in the Suzuki coupling. In an attempt to purifiy **3D4**, the H_2O layer was removed by pipet and the solvent removed by distillation at atmospheric pressure. The crude oil was diluted with pentane and flushed through a silica gel plug and washed with additional pentane. Concentration by distillation at atmospheric pressure produced an oil containing **3D4** and TMSOH by ^{1}H and ^{13}C NMR spectroscopy. R_f 0.66 (hexane) ^{1}H NMR (300 MHz , $CDCl_3$) δ 1.90 (d, *J*=6.7 Hz, 3H), 5.15 (d, *J*=10.4 Hz, 1H), 5.52 (d, *J*=16.3 Hz, 1H), 6.06 (q, *J*=6.8 Hz, 1H), 6.32 (dd, *J*=16.3, 10.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (CH_3), 115.0 (CH_2), 125.3 (C), 127.6 (CH), 133.8 (CH). Ir (neat mixture) 3012, 2957, 1638, 1410, 1253 cm^{-1}. HRMS (EI) *m/z* calcd for $[M]^{+\bullet}$ 1459726. Found 145.9718.

(*Z*)-3-(3-hydroxyphenyl)-1,3-pentadiene (3D2)

To the crude reaction mixture of **3D4** (9.35 mmol in 9.4 mL Et_2O) was added THF (39 mL), H_2O (3.9 mL), KOAc (0.76 g, 7.79 mmol), K_2CO_3 (4.31 g, 31.2 mmol), 3-hydroxyphenyl boronic acid MIDA ester (**3D3**) (1.94 g, 7.79 mmol), and $PdCl_2$(dppf)•CH_2Cl_2 (318 mg, 0.39 mmol). The flask was equipped with a condenser and heated to 70 ˚C for 16 h. After cooling to room temperature, the solution was partitioned with Et_2O and H_2O and the aqueous layer extracted with Et_2O. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash column chromatography (10% EtOAc/hexane) and

kugelrohr distillation (1 Torr, 90 ˚C) produced 0.99 g (79%) of **3D2**. R_f 0.52 (20% EtOAc/hexane) ^{1}H NMR (300 MHz , $CDCl_3$) δ 1.60 (d, *J*=7.1 Hz), 4.71 (d, *J*=16.8 Hz, 1H), 4.72 (s, 1H), 4.96 (d, *J*=10.6, 1H), 5.79 (q, *J*=7.1 Hz, 1H), 6.53 (dd, *J*=17.3, 10.6 Hz, 1H), 6.61 (s, 1H), 6.66-6.82 (m, 1H), 7.25 (t, *J*=7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) 15.5 (CH_3), 113.9 (CH), 114.1 (CH), 116.7 (CH), 122.5 (CH), 128.3 (CH), 129.6 (CH), 139.6 (C), 140.6 (CH), 142.2 (C), 155.5 (C). IR (neat) 3387, 2855, 1633, 1582 cm^{-1}. HRMS (EI) *m/z* calcd for $[M]^{-\bullet}$ 160.0883. Found 160.0882.

(*Z*)-(2*R*)-3-(3-hydroxyphenyl)-2-methyl-3-pentenal (2F1)

Under an inert atmosphere, **3D2** (200 mg, 1.25 mmol), (*R,R,S*)-BDP (40 mg, 0.032 mmol), and $Rh(CO)_2(acac)$ (6 mg, 0.024 mmol) were dissolved in 2.52 mL THF and placed in a 10.5 cm long high pressure tube equipped with a head that allowed for gas filling, venting, and aliquot removal through a septum. The vessel was charged with 150 psi syngas and stirred at 50 ˚C for 48 h. Completion and regioselectivity were determined by ^{1}H NMR spectroscopy of a concentrated aliquot of the reaction solution [regiomeric aldehyde δ 9.70, (t, *J*=1.5 Hz)]. R_f 0.38 (20% EtOAc/hexane) ^{1}H NMR (CDCl3, 300 MHz) δ 1.18 (d, *J*=6.9 Hz, 3H), 1.62 (d, *J*=6.6 Hz, 3H), 3.30 (q, *J*=6.9 Hz, 1H), 4.92 (s, 1H), 5.64 (q, *J*=6.9 Hz, 1H), 6.57 (d, *J*=1.8 Hz, 1H), 6.64 (d, *J*=7.5 Hz, 1H), 6.75 (dd, *J*=8.1, 2.5 Hz, 1H), 7.21 (t, *J*=7.8 Hz , 1H), 9.66 (d, *J*=1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4 (CH_3), 15.2 (CH_3), 55.2 (CH), 114.4 (CH), 115.8 (CH), 121.2 (CH), 126.5 (CH), 129.8 (CH), 138.3 (C), 141.1 (C), 155.9 (C), 203.2 (C). IR (neat) 3394, 2979, 1719, 1580 cm^{-1}. HRMS (EI) *m/z* calcd for $[M-H]^-$ 189.0921. Found 189.0919. $[\alpha]_D^{21}$ = -14 (0.7, $CHCl_3$).

(*Z*)-(2*R*)-1-(dimethylamino)-3-(3-hydroxyphenyl)-2-methyl-3-pentene (3D1)

The crude reaction mixture of **3D2** (1.25 mmol) was diluted with 2.5 mL THF. Me_2NH

(2.0 *M* in THF, 0.69 mL, 1.38 mmol), AcOH (70 μL, 1.25 mmol), and STAB-H (397 mg, 1.88 mmol) were added and the slurry stirred for 16 h at room temperature. The mixture was poured into aqueous Na_2CO_3 (1 *M*, 50 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude oil was purified by flash column chromatography (20% MeOH/CH_2Cl_2). R_f 0.32 (20% MeOH/CH_2Cl_2) ^{1}H NMR (300 mHz, $CDCl_3$) δ 1.00 (d, *J*=6.8 Hz, 3H), 1.38 (d, *J*=6.7 Hz, 3H), 2.08 (dd, *J*=11.7, 6.7 Hz, 1H), 2.24 (s, 6H), 2.39 (dd, *J*=12.1, 7.3 Hz, 1H), 2.59 (sextet, *J*=7.1 Hz, 1H), 5.53 (q, *J*=6.7 Hz, 1H), 6.49-6.58 (m, 1H), 6.60 (d, *J*=7.6 Hz, 1H), 6.71 (dd, *J*=7.7, 2.1 Hz, 1H), 7.16 (t, *J*=7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8 (CH_3), 19.1 (CH_3), 39.8 (CH), 45.8 (CH_3), 65.3 (CH_2), 113.9 (CH), 116.3 (CH), 121.4 (CH), 121.7 (CH), 129.2 (CH), 142.1 (C), 144.8 (C), 156.4 (C). IR (neat) 3306, 2967, 1578, 1445 cm^{-1}. HRMS (EI) *m/z* calcd for $[M-H]^{\bullet}$ 220.1696. Found 220.1687. $[\alpha]_D^{21}$ = 0.04 (0.1, $CHCl_3$).

(3*R*,2*R*)- and (3*S*,2*R*)-3-(3-hydroxyphenyl)-*N*,*N*,2-trimethylpentylamine (3A5) and (3I1)

Pd/C (5%, 14 mg) was added to a solution of **3D1** (31 mg, 0.141 mmol) in EtOH (0.71 mL) and the flask flushed with a balloon of H_2. The depleted balloon was replaced with a full balloon of H_2 and the slurry stirred for 16 h. The slurry was diluted with EtOAc and filtered through a half-inch layer of Celite®. The filtrate was concentrated in vacuo and the residue purified by flash column chromatography (10% MeOH/CH_2Cl_2) to give a yellow oil (19 mg, 61%). NMR spectroscopy revealed this oil to be a mix of both diasteromers at 1:1.3 ratio (the major component was not determined). R_f 0.22 (10% MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (t, *J*=7.3 Hz, 3H), 0.76 (t, *J*=7.3 Hz, 4H), 0.92 (d, *J*=6.8 Hz, 4H), 1.17 (d, *J*=6.5 Hz, 3H), 1.26 (s, 2H), 1.41-1.58 (m, 3H), 1.58-1.72 (m, 3H), 1.94-2.13 (m, 3H), 2.14-2.28 (m, 1H), 2.43 (dd, *J*=12.5, 8.5 Hz, 2H), 2.55 (s, 6H), 2.59 (s, 6H), 2.75 (dd, *J*=12.6, 5.3 Hz), 2H),

6.60 (dd, *J*=11.6, 7.6 Hz, 3H), 6.67-6.85 (m, 5H), 7.10 (td, *J*=8.7, 3.4 Hz, 3H), 7.33 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3 (CH_3), 12.7 (CH_3), 15.2 (CH_3), 16.9 (CH_3), 25.3 (CH_2), 25.5 (CH_2), 29.9 (CH_2), 34.8 (CH_2), 35.4 (CH_2), 44.5 (CH), 44.8 (CH), 50.2 (CH), 51.7 (CH), 64.1 (CH_2), 114.1 (CH), 114.4 (CH), 115.4 (CH), 116.5 (CH), 120.1 (CH), 120.6 (CH), 129.4 (CH), 129.8 (CH), 142.8 (C), 144.3 (C), 156.8 (C), 157.4 (C). HRMS (ESI) *m/z* calcd for $[M+H]^+$ 222.1775 Found 222.1773. IR spectra and specific rotations were not obtained because **3A5** and **3I1** were not separated.

(*Z*)-(2*R*)-3-(3-hydroxyphenyl)-2-methyl-3-pentenol (3G1)

$NaBH_4$ (18 mg, 0.486 mmol) was added to a solution of **3F1** (66 mg, 0.347 mmol) in MeOH (3.5 mL) at 0 ˚C and stirred for 1.5 h. Saturated aqueous NH_4Cl was added and the mixture extracted with EtOAc, dried (Na_2SO_4) and concentrated. The crude oil was purified by flash column chromatography (40% EtOAc/hexane) to give **3G1** as a colorless oil (63 mg, 94%). R_f 0.38 (50% EtOAc/hexane) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (d, *J*=7.0 Hz, 3H), 1.52 (dd, *J*=6.7, 0.6 Hz, 3H), 1.63 (s, 1H), 2.62 (sextet, *J*=6.8 Hz, 1H), 3.47 (m, 2H), 5.15 (s, 1H), 5.61 (qd, *J=6.7, 0.8* Hz, 1H), 6.58 (dd, *J*=2.5, 1.5 Hz, 1H), 6.65 (dt, *J*=7.5, 1.2 Hz, 1H), 6.74 (ddd, *J*=8.1, 2.6, 1.0 Hz, Hz), 7.21 (t, *J*=7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8 (CH_3), 16.4 (CH_3), 44.4 (CH_2), 65.9 (CH), 114.0 (CH), 116.1 (CH), 121.4 (CH), 123.4 (CH), 130.0 (CH), 141.5 (C), 143.1 (C), 156.0 (C). IR (neat) 3331, 2975, 2933, 1579, 1489 cm^{-1}. HRMS (EI) *m/z* calcd for $[M-H]^{-\bullet}$ 189.0921. Found 189.0919. $[\alpha]_D^{21}$ = 0.8 (0.4, $CHCl_3$).

(*Z*)-(2*R*)-1-(4-bromobenzoyl)-3-(3-(4-bromobenzoylphenyl)-2-methyl-3-pentene (3G2)

A mixture of **3G1** (29 mg, 0.151 mmol), 4-bromobenzoyl chloride (83 mg, 0.377 mmol), Et_3N (0.06 mL, 0.453 mmol), DMAP (9 mg, 0.076 mmol), and CH_2Cl_2 (0.76 mL) was stirred for 3 h at room temperature. The slurry was diluted with saturated aqueous NH_4Cl and extracted

with Et_2O. The organic layer was dried (Na_2SO_4) and concentrated and the crude oil purified by flash column chromatography (20% EtOAc/hexane) to give diester **3G2** as a colorless oil. R_f 0.38 (20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, *J*=*7.0* Hz, 3H), 1.55 (d, *J*=6.5 Hz, 3H), 2.94 (sextet, *J*=7.0 Hz, 1H), 4.12-4.30 (m, 2H), 5.68 (q, *J*=*6.6* Hz, 1H), 6.94-7.01 (m, 1H), 7.03 (dt, *J*=7.6, 1.2 Hz, 1H), 7.13 (ddd, *J*=8.2, 2.4, 1.0 Hz, 1H), 7.39 (t, *J*=7.9 Hz, 1H), 7.54 (d, *J*=8.6 Hz, 2H), 7.64 (d, *J*=8.6 Hz, 2H), 7.83 (d, *J*=8.6 Hz, 2H), 8.04 (d, *J*=8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.7 (CH_3), 16.8 (CH_3), 40.8 (CH) 68.5 (CH_2), 120.0 (CH), 122.2 (CH), 123.4 (CH), 126.7 (CH), 128.0 (C), 128.3 (C), 128.5 (C), 128.8 (CH), 129.2 (C), 129.3 (CH), 131.1 (CH), 131.6 (CH), 131.7 (CH), 132.0 (CH), 141.7 (C), 142.0 (C), 150.6 (C), 164.4 (C), 165.7 (C). IR (neat) 2975, 2867, 1740, 1591, 1485 cm^{-1}. HRMS (EI) *m/z* calcd for $[M-H]^{+\bullet}$ 189.0921. Found 189.0919. $[\alpha]_D^{21}$ = 9 (1.0, $CHCl_3$).

***E*-3-phenyl-2-pentene (3J2)**

EtMgBr (1.0 *M*, 21.9 mL, 21.9 mmol) was added dropwise to a solution of LiBr (1.90 g, 21.9 mmol) and CuI (2.08 g, 10.9 mmol) in THF (10 mL) at -60 ˚C and the solution stirred for 1 h. A solution of phenylacetylene (**3J1**) (1 mL, 9.11 mmol) and HMPA (6 mL) in THF (12 mL) was slowly added and the solution stirred at -60 ˚C for 10 min. A mixture of MeI (1.36 mL, 21.9 mmol) and HMPA (3.6 mL) was slowly added and the solution stirred at -60 ˚C for 5 min before being warmed to room temperature and stirred for 16 h. The solution was poured into saturated aqueous ammonium chloride (100 mL) containing NaCN (2 g) and extracted with hexane. The combined organic phases were dried (Na_2SO_4) and concentrated. Purification of the crude oil by flash column chromatography (hexane) produced **3J2** as a colorless oil that was sufficiently pure for the AHF experiment (95 mg, 7%). R_f 0.58 (hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, *J*=7.5 Hz, 3H), 1.80 (d, *J*=6.9 Hz, 3H), 2.52 (q, *J*=7.5 Hz, 2H), 5.73 (q, *J*=6.9 Hz, 1H), 6.77-

7.84 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) 13.5 (CH_3), 14.2 (CH_3), 22.8 (CH_2), 122.3 (CH), 126.4 (CH), 126.6 (CH), 128.4 (CH), 142.6 (C), 143.3 (C). IR 2967, 2932, 1599, 1494 cm^{-1}. HRMS (EI) *m/z* calcd for $[M]^{+\bullet}$ 146.1091. Found 146.1083.

AHF of 3J2

A solution of **3J2** (95 mg, 0.65 mmol), (*R,R,S*)-BDP (21 mg, 0.016 mmol), and $Rh(CO)_2(acac)$ (3.4 mg, 0.13 mmol) in PhMe (1.3 mL) was placed in a 10.5 cm long high pressure tube equipped with a head that allowed for gas filling, venting, and aliquot removal through a septum. The vessel was charged with 120 psi syngas and stirred at 100 ˚C for 48 h. Analysis of an aliquot by ^1H NMR spectroscopy revealed >95% consumption of **3J1** and the presence of three aldehyde signals (d, 9.67; t, 9.66; d, 9.56; *J* values for all three <1 Hz).

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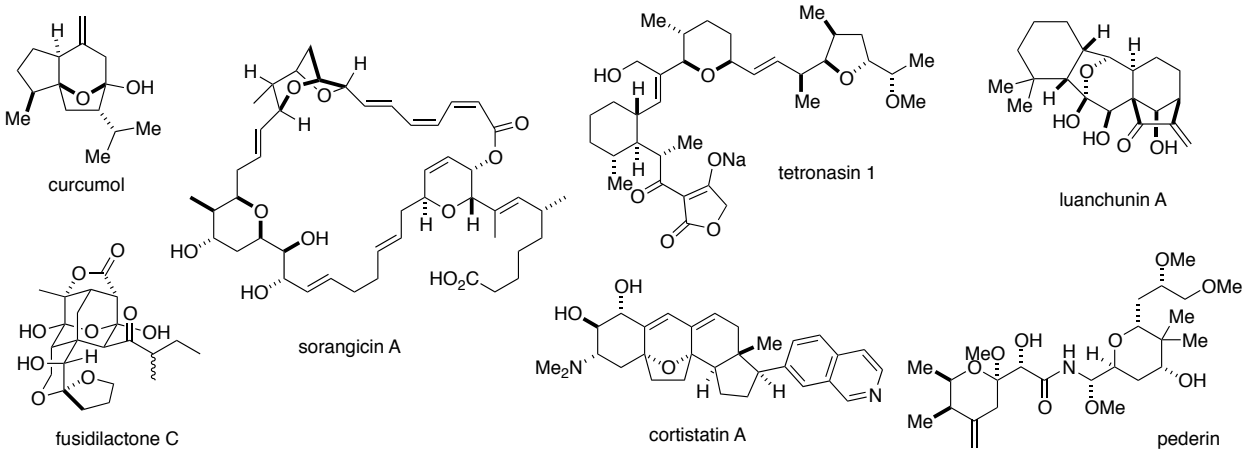
Chapter 4. Development of a Rhodium-Mediated Domino Annulation and Efforts Toward the Total Synthesis of Linderagalactone C

4.1 Background and [2+2+2] Strategies

Dihydro- and tetrahydropyrans are pervasive substructures of natural products (Figure 4A) and the Burke group has used several strategies for pyran construction in many natural product syntheses.[1] Bicyclic pyrans are a particular synthetic challenge because of their often complex stereochemistry and sterically-crowded architecture.

Figure 4A. Natural Products Containing Pyrans and Bicyclic Pyrans

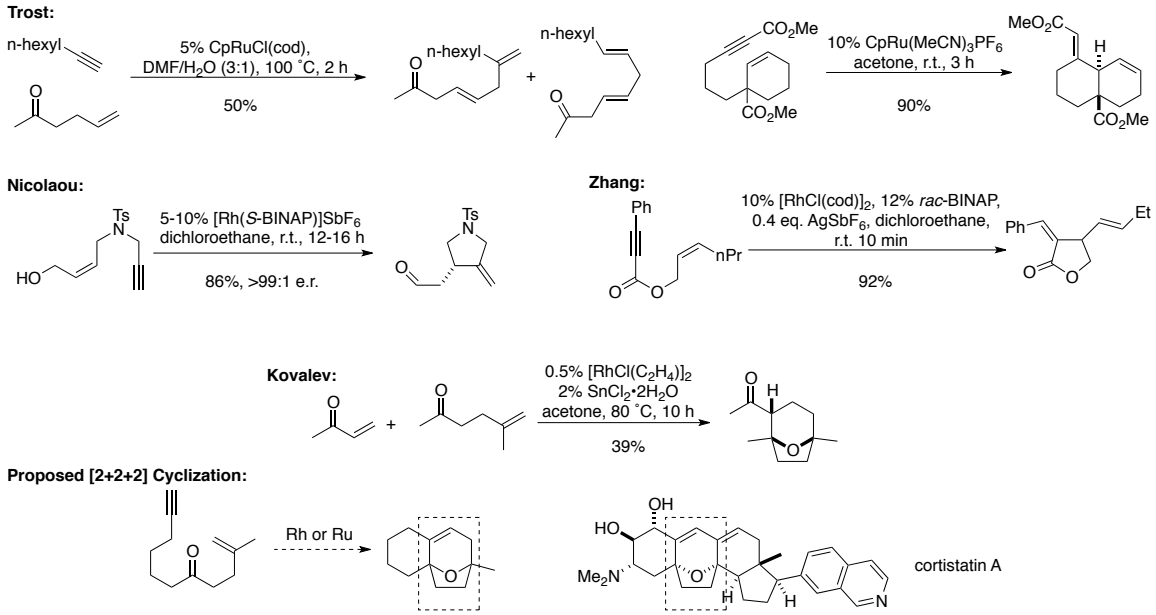


Cortistatin A, isolated in 2006 with potent antiangiogenesis activity (IC_{50}=1.8 pM) against human umbilical vein endothelial cells,[2] has been a popular synthetic target,[3] and as part of the design of our own synthesis we envisioned combining an alkene-alkyne coupling like the Alder ene reactions published by Trost,[4] Zhang,[5] and Nicolaou,[6] with the [2+2+2] results reported by Kovalev and coworkers[7] to make a new [2+2+2] cyclization of an alkene, an alkyne, and a ketone (Scheme 4A).[8]

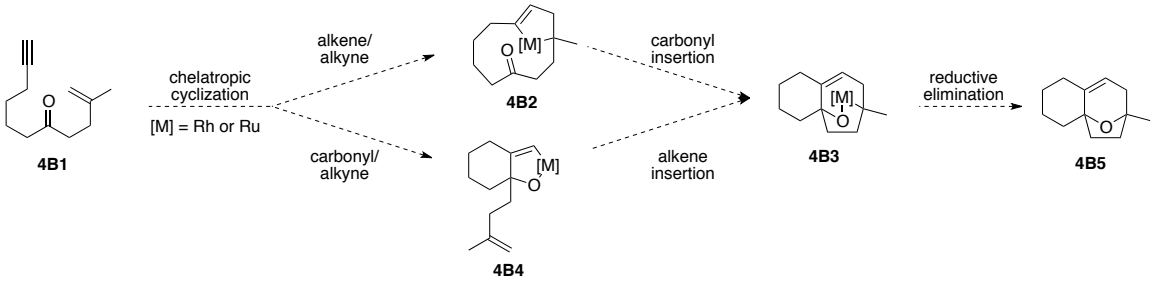
Our envisioned mechanism would begin with the cyclization of the alkyne and alkene of **4B1** with the Rh or Ru catalyst to form metallocycle **4B2** (Scheme 4B). Insertion of the ketone into the vinyl metal bond would create fused bicyclic oxametallocycle **4B3**. Alternatively, the ketone could react with the alkyne to make fused bicyclic oxametallocycle **4B4**, which would

then undergo alkene insertion to form **4B3**. Reductive elimination would form the final C-O bond of **4B5** and liberate the catalyst.

Scheme 4A. Precedent for a New [2+2+2] Reaction

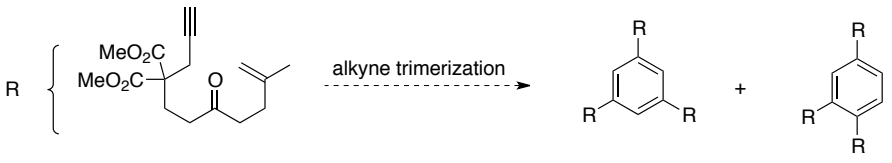


Scheme 4B. Predicted Mechanisms of Proposed [2+2+2] Cyclization



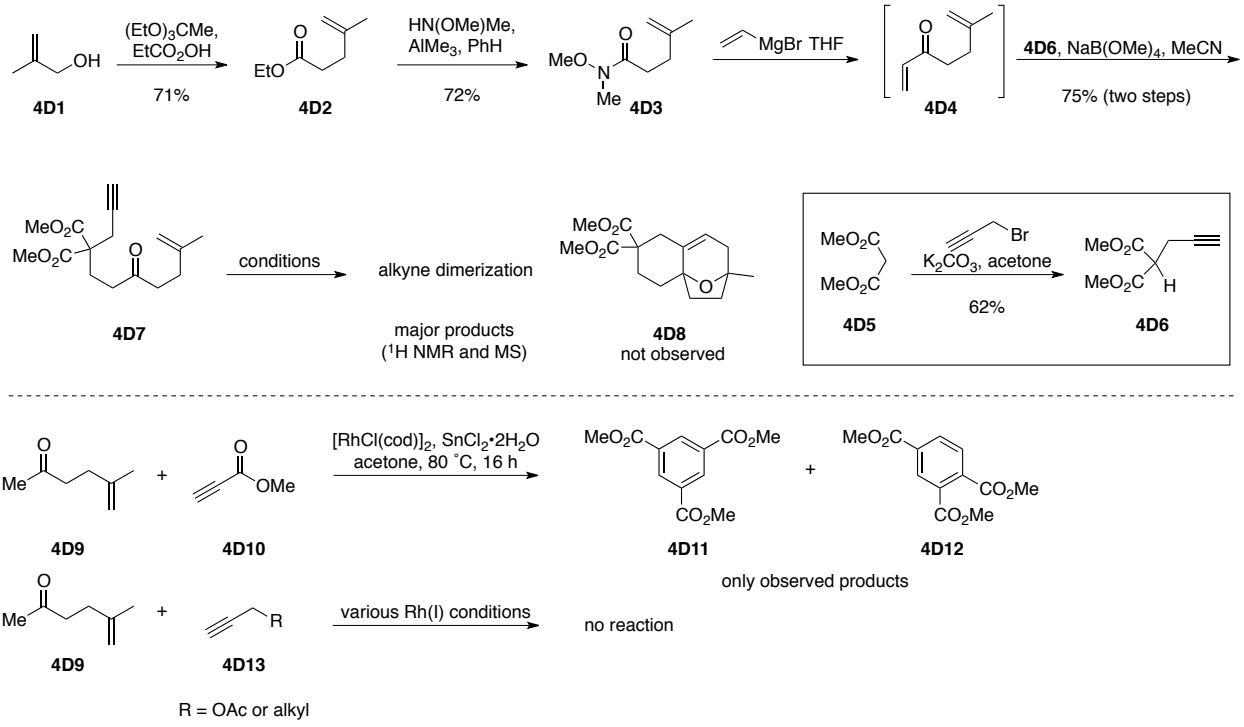
An obvious potential problem was the established alkyne trimerization catalyzed by rhodium and/or ruthenium (Scheme 4C).[8] An effective catalyst would have to select for the desired intramolecular enynone [2+2+2] over the undesired trimolecular alkyne [2+2+2].

Scheme 4C. Anticipated Alkyne Trimerization Problem



Our initial enynone substrate was readily accessed from methallyl alcohol (**4D1**) (Scheme 4D). A Johnson orthoester Claisen rearrangement produced ethyl ester **4D2** in 71% yield[9] and the ester was converted to Weinreb amide **4D3** in 72% yield.[10] Vinyl Grignard addition[11] furnished vinyl ketone **4D4**, which was used crude due to decomposition during purification. Propargyl dimethyl malonate (**4D6**), prepared in 62% yield from dimethyl malonate (**4D5**),[12] smoothly underwent Michael addition to **4D4**, catalyzed by sodium tetramethoxyborate,[13] to furnish enynone **4D7** in 75% yield from **4D3**. With enynone in hand our efforts then turned to screening conditions for the [2+2+2] cyclization of **4D7** to tricycle **4D8**.

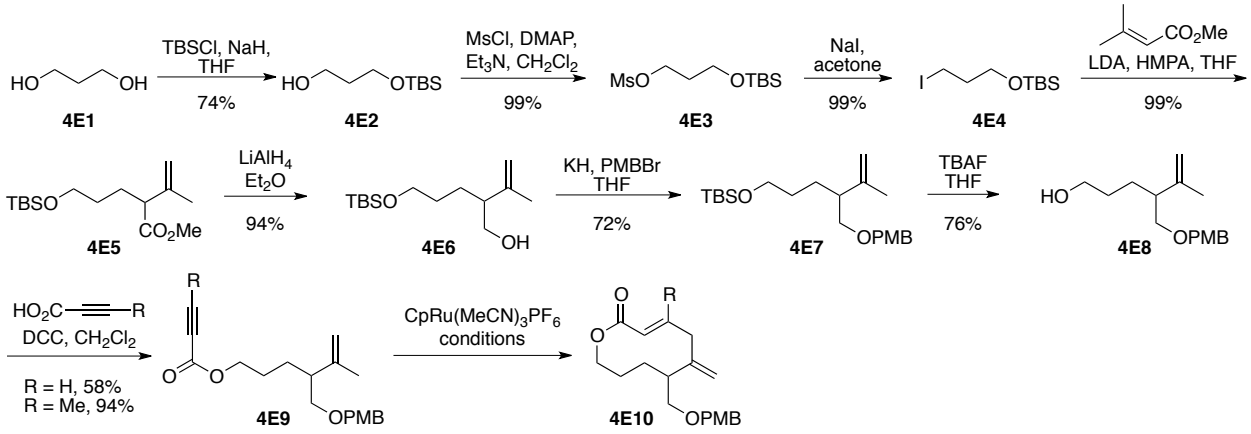
Scheme 4D. Enynone Substrate Synthesis and Screening



Experiments with $[Ru(dppb)Cl]_2$ and $RhCl(PPh_3)_3$ at 10% and 20% loading, with or without $AgSbF_6$ as an additive and in toluene, MeCN, or 1,2-dichloroethane at several concentrations between 0.1 and 0.3 *M* resulted in complex mixtures that were difficult to analyze. Mass spectrometry and ^{13}C NMR spectroscopy revealed that alkyne dimerization

products were the major products. Attempts at screening intermolecular reactions with a variety of Rh(I) catalytic conditions, including Kovalev's conditions,[7] resulted either in benzenes **4D11** and **4D12** from alkyne trimerization of alkynoate **4D10** or no reaction with isolated alkyne or propargylic ester **4D13**. We decided to focus our efforts by using the $CpRu(MeCN)_3PF_6$ catalyst popularized by Trost to form medium rings by intramolecular alkene-alkyne coupling.[4b]

Scheme 4E. Synthesis of Alkynoate Esters for Cyclization with $CpRu(MeCN)_3PF_6$

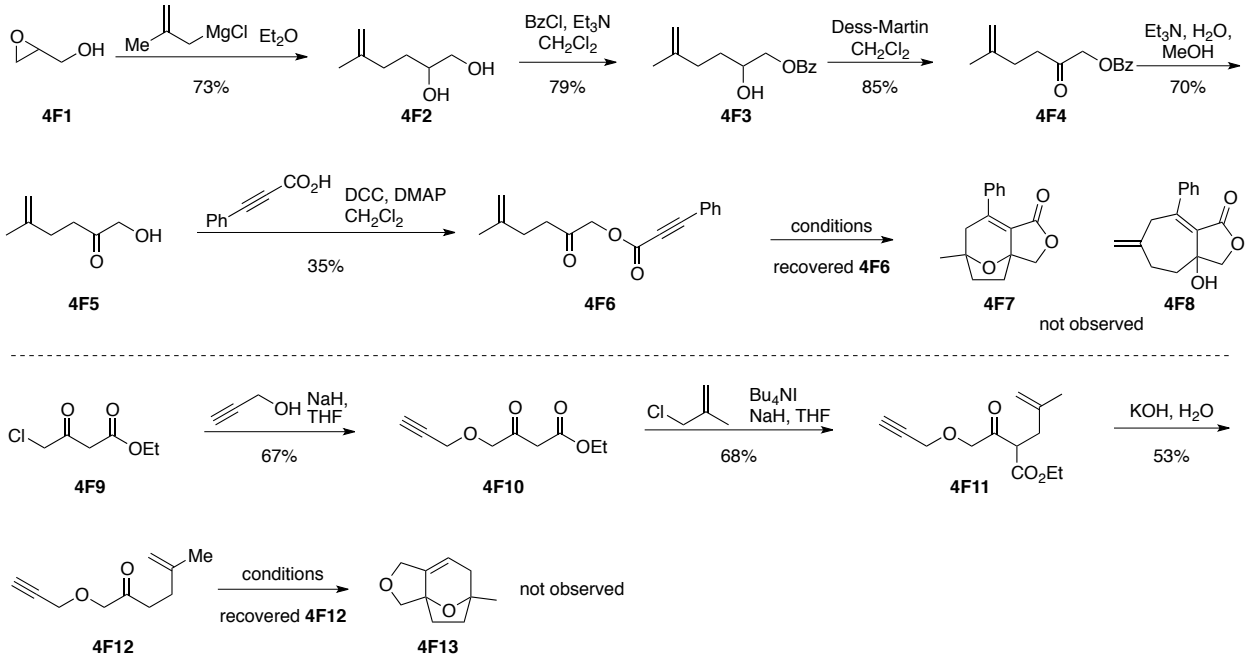


An alkynoate ester substrate for $CpRu(MeCN)_3PF_6$-catalyzed cyclization was synthetized in the hope that the alkene and tethered alkynoate would combine to form a 10-membered ring (Scheme 4E). Mono-TBS protection of 1,3-propanediol (**4E1**) proceeded in 74% yield.[14] Subsequent mesylation[15] and iodination via Finkelstein reaction[16] provided primary iodide **4E4** in nearly quantitative yield. Alkylation of the dienolate of methyl dimethylacrylic acid provided β,γ-unsaturated ester **4E5** in excellent yield.[17] Reduction of the ester functionality with $LiAlH_4$ proceeded in 94% yield.[18] Protection of primary alcohol **4E6** as a PMB ether[19] and TBAF deprotection of the TBS ether[20] to produce primary alcohol **4E8** was accomplished in more modest 72% and 76% yields, respectively. DCC coupling with butynoic and propiolic acids produced alknenyl alkynoates **4E9** in modest to excellent yields.[21] Cyclization experiments with the $CpRu(MeCN)_3PF_6$ catalyst in acetone, CH_2Cl_2, and DMF at room temperature and reflux

failed to induce any noticeable reactivity. With these disappointing results we decided to return to enynone substrates to work on a holistic development of a [2+2+2] cyclization.

An enynone substrate was synthesized from glycidol (**4F1**) (Scheme 4F). Alkylation with methallylmagnesium chloride proceeded in 73% yield,[22] and selective esterification with benzoyl chloride was achieved in 79% yield.[23] Ketone **4F4** was obtained in 85% yield from secondary alcohol **4F3** by oxidation with Dess-Martin periodinane.[24] Ester hydrolysis with a

Scheme 4F. Alkynoate and Propargyl Ether Substrates 4F6 and 4F12

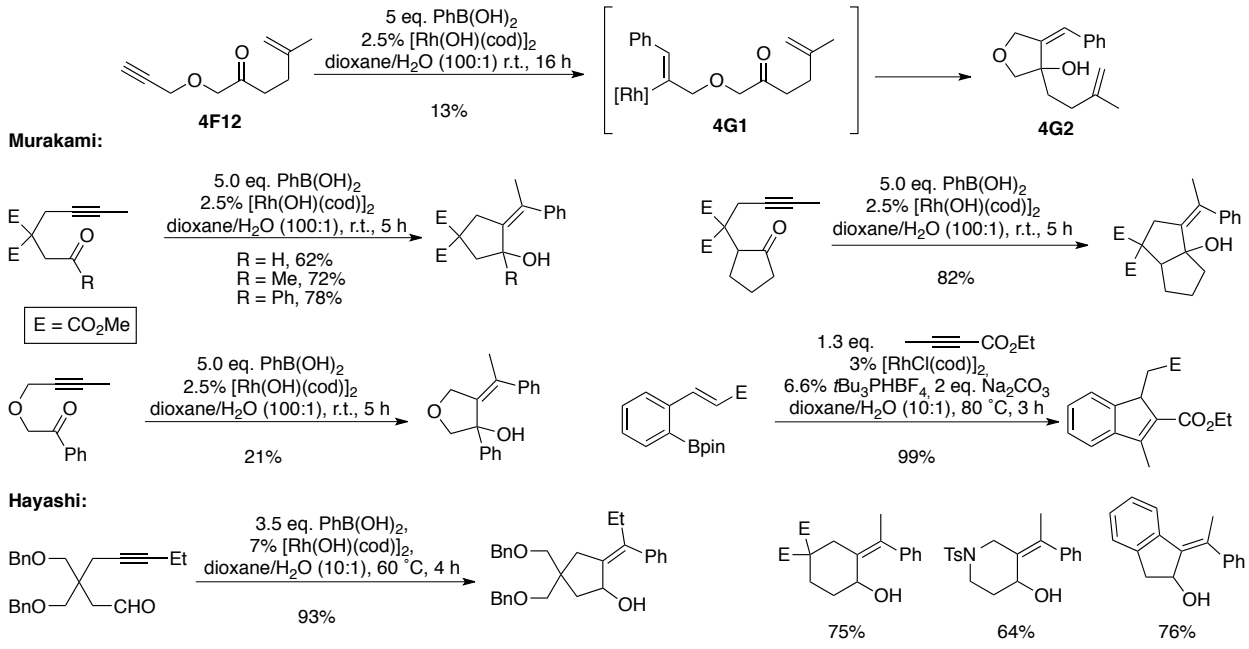


Et_3N/H_2O/MeOH mixture proceeded in 70% yield,[25] but DCC coupling with phenylpropiolic acid produced enynone **4F6** in a disappointing 35% yield.[21] Cyclization experiments resulted only in recovered **4F6**. We thought that the constrained geometry of the ester linkage might be inhibiting cyclization so an enynone substrate with a propargylic ether was devised. Displacement of ethyl 4-chloroacetoacetate (**4F9**) by propargylic alcohol proceeded in 67% yield.[26] Allylation of **4F10** with methallyl chloride in 68% yield[27] and saponification/

decarboxylation in 53% yield[28] produced propargylic ether substrate **4F12**, which also was unreactive in cyclization experiments.

Because the desired cyclization did not occur despite experiments with several enyne and enynone substrates, we began to look at the rhodium-catalyzed addition of aryl boronic acids to alkynes.[29-31] The work of Murakami,[30] Hayashi,[31] and others has shown that vinyl rhodium species formed by the addition of an aryl boronic acid to an alkyne are nucleophilic to several electrophiles, including carbonyls. We thought a vinyl rhodium species formed in this manner could initiate the reactivity we had been seeking (Scheme 4G). The rhodium-catalyzed addition of phenylboronic acid to **4F12** proceeded to form the substituted tetrahydrofuran ring as expected, but in low yield. Murakami observed similar yield with an ether substrate due to the absence of a Thorpe-Ingold effect to aid cyclization.[30a] Additionally, there was no impetus for the appended alkene to react with the formed styrenyl alkene.

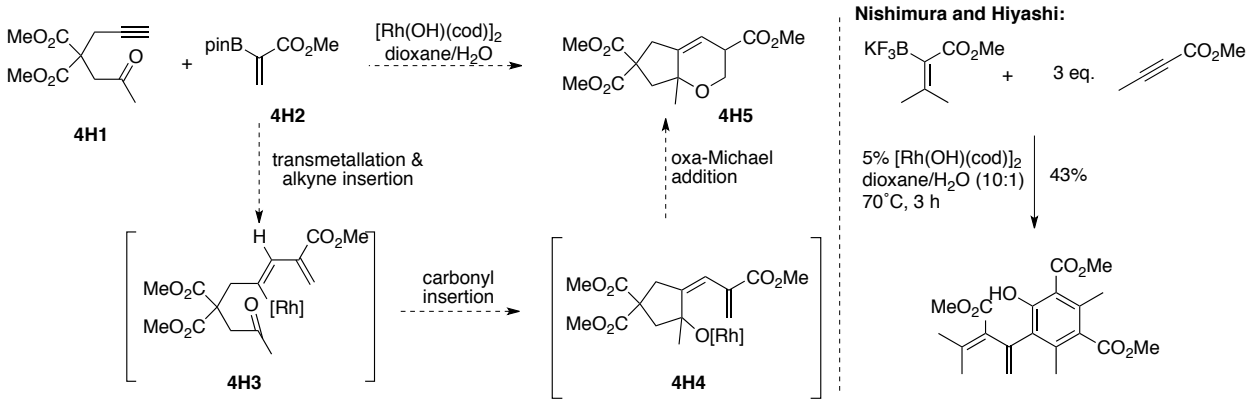
Scheme 4G. Rh-Catalyzed Addition of Aryl Boronic Acids to Alkynes



4.2 Development of a Rhodium-Mediated Domino Annulation (RMDA)

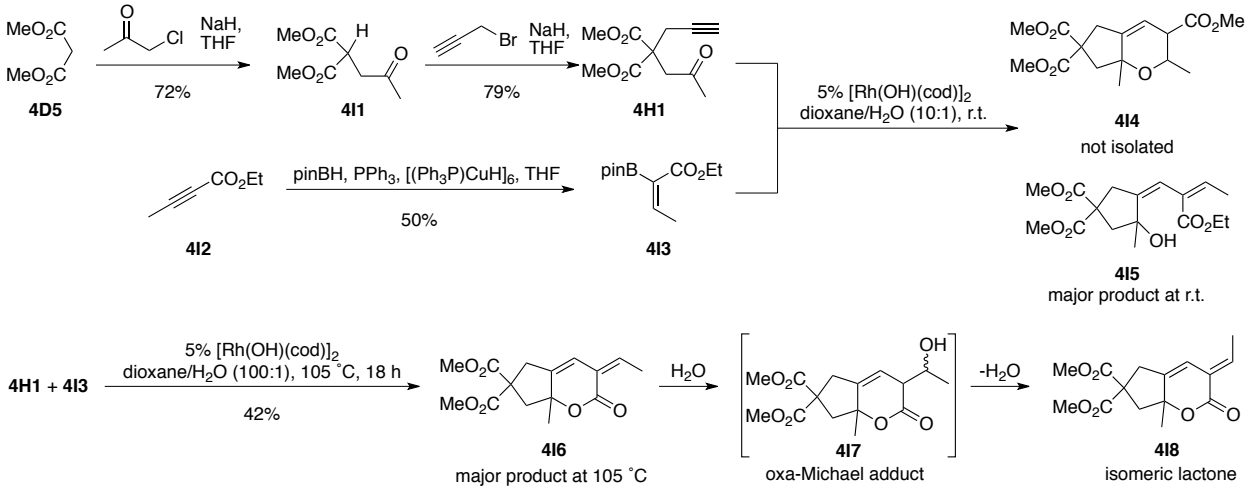
Inspired by the Rh(I) catalyzed addition of aryl boronic acids to δ-alkynyl ketones (Scheme 4G), we posited that an α-boryl-α,β-unsaturated carboxylic ester (**4H2**) could also insert into a δ-alkynyl ketone (**4H1**) to form a vinyl rhodium intermediate (**4H3**) that could attack the pendant ketone (Scheme H). The resultant tertiary rhodium alkoxide (**4H4**) could perform an oxa-Michael addition to form dihydropyran **4H5**, a formal [2+2+2] product. We referred to this strategy as a rhodium-mediated domino annulation (RMDA). In 2010, Nishimura and Hiyashi reported the only example of an α-boryl-α,β-unsaturated carboxylic ester trifluoroborate salt adding across an alkyne with a rhodium catalyst.[31c]

Scheme 4H. Proposed Vinyl Boronic Ester/Oxa-Michael Formal [2+2+2]



Alkynyl ketone (**4H1**) was prepared by successive alkylation of dimethyl malonate (**4D5**) with chloroacetone[32] and propargyl bromide[12] (Scheme I) in 57% overall yield. Boronic ester **4I3** was prepared from ethyl propiolate (**4I2**) in a single step with catalytic Stryker's reagent and pinacolborane by the method of Lipshutz and Aue in 50% yield.[33] Combination of **4H1** and **4I3** in dioxane/H_2O with 5% $[Rh(OH)(cod)]_2$ at ambient temperature did not produce the desired oxa-Michael product **4I4**; tertiary alcohol **4I5** was the major product. Increasing the reaction temperature also did not yield **4I4**, but instead exclusively produced a mixture of lactones: **4I6**,

Scheme 4I. Substrate Synthesis and Initial Cyclization Experiments

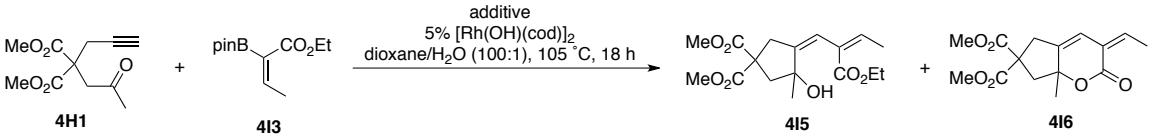


resulting from lactonization of **4I5,** and **4I8**, whose structure was determined from ^{1}H NMR spectra of mixtures of **4I6** and **4I8**. Isomeric **4I8** is presumably formed by oxa-Michael attack of water on the ethylidine of **4I6** to form alcohol **4I7**. Bond rotation and retro-oxa-Michael addition would then generate the *E-exo*-ethylidine of **4I8**. The *E* configuration is more stable because of $A^{1,3}$ strain between the vinyl methyl group and the lactone carbonyl. No products were observed that would result from a 1,2-addition of **4I3** across the alkyne; thus attack of the pendant ketone must be very rapid. RMDA was recognized as a new method for the construction of these functionalized fused ring systems through the formation of two new C-C bonds and a new C-O bond.

Initial optimization experiments confirmed the need for high temperature (105 ˚C) and an 18 h reaction time for effective lactonization of **4I5** to **4I6**. A 5% loading of $[Rh(OH)(cod)]_2$ was also required for conversion. The use of $[RhCl(cod)]_2$ and deviation from a 1:1 molar ratio of **4H1** and **4I3** resulted in lower yields but higher yields were obtained by screening small-scale reactions (0.2 mmol) in sealed 4-dram vials at 105 ˚C.

Screening of reaction additives revealed that transesterification catalysts $Ti(OiPr)_4$[34] and Otera's catalyst[35] were ineffective, likely in part due to the aqueous medium, but aqueous KOH was beneficial (Scheme J). The positive effects of KOH must arise from combined effects of the potassium and hydroxide ions, since additives with only one of these ions (K_2CO_3, KOAc, $KHCO_3$, LiOH, NaOH, CsOH, and NH_4OH) are not as effective.

Scheme 4J. Optimization of the RMDA



Additive	Yield of 4I6
none	46%
$Ti(OiPr)_4$	33%
Otera	39%
KOH	0.1 eq. 45%* 0.2 eq. 70%*
$KHCO_3$	58%*
KOAc	20%
K_2CO_3	58%
LiOH	0.2 eq 50%*
NaOH	0.2 50%*
CsOH	0.2 eq. 30%
NH_4OH	0%*

Concentration	Yield of 4I6
0.1 *M*	45%*
0.05 *M*	75%*
0.02 *M*	59%*
0.01 *M*	79%* mix of **4I5** and **4I6** 65% isolated yield

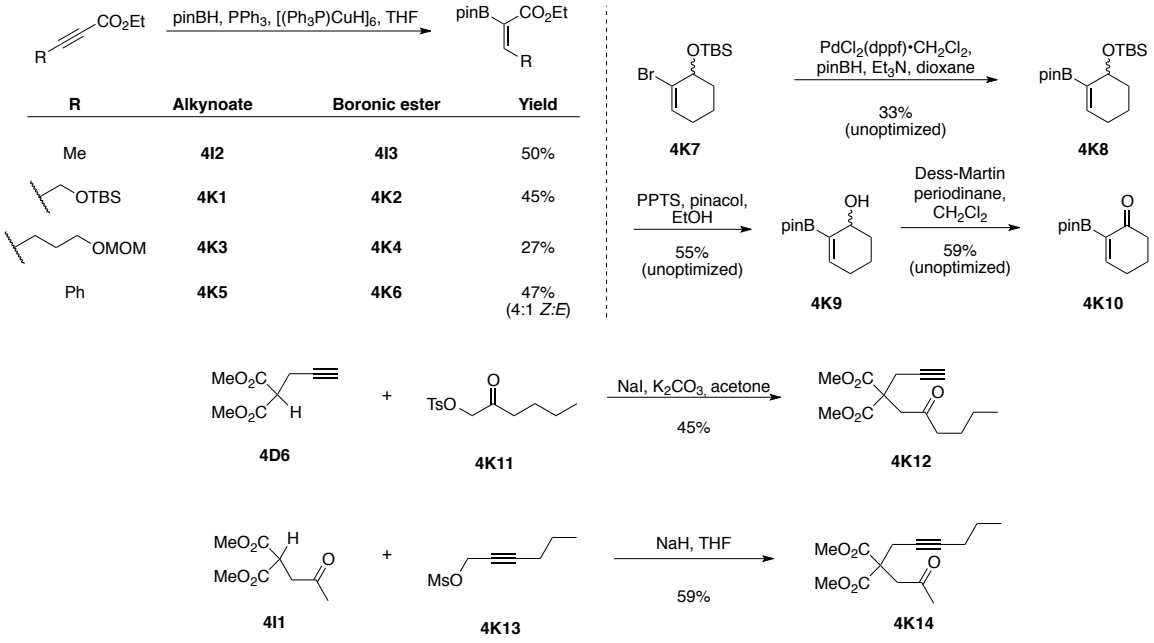
*Yield determined by analysis of ^{1}H NMR spectrum of crude reaction concentrate

Dilution of the reaction from 0.1 to 0.01 *M* resulted in increased isolated yields of **4I6** and reduced formation of the isomeric lactone **4I8**. Despite other additives giving high yields as single data points as determined by ^{1}H NMR spectroscopy, the most consistent isolated yields of **4I6** were obtained with 0.1 equivalents of a 0.1 *M* aqueous KOH solution and in a 0.01 *M* solution in dioxane in a sealed pressure flask.

Having established suitable conditions for the annulation, our attention turned to the synthesis of additional boronic esters and ketones to explore the versatility of the RMDA (Scheme 4K). Stryker's reagent-catalyzed hydroboration of alkynoates served as a reliable method for the synthesis of several boronate esters,[33] although yields were lower than those of

the published examples. Boryl-substituted cinnamate **4K6**, also reported by Lipshutz and coworkers, was synthesized in 47% yield as a 4:1 mixture of diastereomers instead of the published 95% yield and 10:1 d.r.[33] Despite the decreased yields, known alkynoate esters **4K1**[36] and **4K3**[37] and commercially available **4K5** were converted to boronic esters **4K2**, **4K4**, and **4K6** by this method in sufficient quantities for use in annulation experiments.

Scheme 4K. Synthesis of Additional Substrates

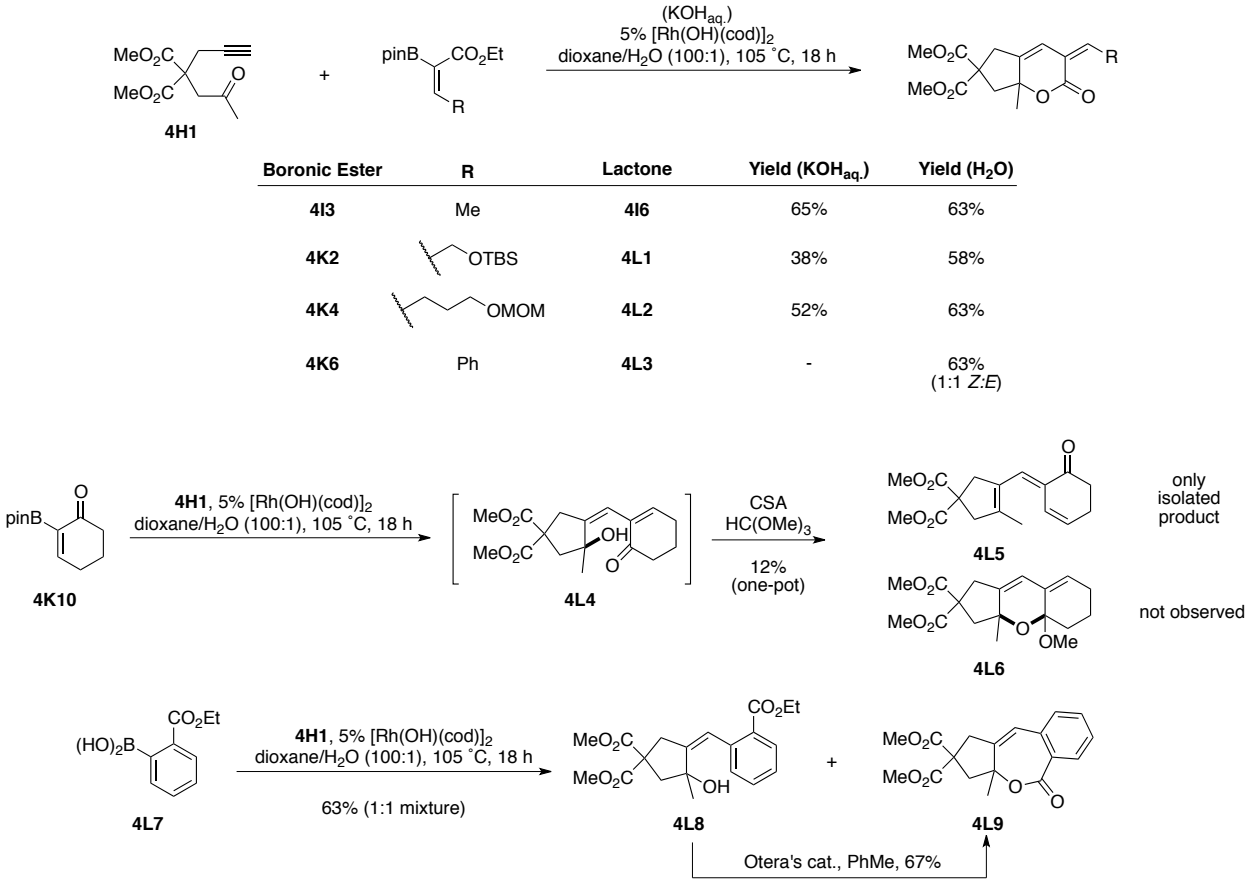


Cyclohexenone boronic ester **4K10** was synthesized from known silyl ether **4K7**[38] by palladium-catalyzed borylation,[39] desilylation,[40] and oxidation by Dess-Martin periodinane[24] in an unoptimized overall yield of 11% from **4K7**. Cyclohexene-2-boronic acid has been prepared by lithium-halogen exchange,[41] but this borylation proved unreliable. The masking of the ketone functionality as a silyl ether was necessary because the ketone is too electron withdrawing for effective borylation. Attempts to borylate the free alcohol or MOM ether did not product the borylate product, likely due to coordination of the oxygen to the palladium center slowing down catalyst turnover. Butyl ketone **4K12** was synthesized from known tosylate **4K11**[42] and **4D6** in

45% yield. In a similar fashion, internal alkyne **4K14** was prepared in 59% yield from ketomalonate **4I1** and known mesylate **4K13**.[43]

Annulation experiments with the determined conditions with boronic esters **4K2** and **4K4** had unexpected poor results (Scheme 4L). It was hypothesized that the KOH made the solution too basic and that its exclusion would improve yields of lactones **4L1** and **4L2**. Substitution of the aqueous 0.1 *M* KOH solution for an equal volume of H_2O improved isolated yields for **4L1** and **4L2**. Experiments with **4I3** revealed that using H_2O instead of aqueous KOH resulted in very similar isolated yields of **4I6**. Boronic ester **4K6** was not subjected to the KOH conditions, and lactone **4L3** was isolated as a 1:1 mixture of alkene diastereomers, resulting from the

Scheme 4L. RMDA Results

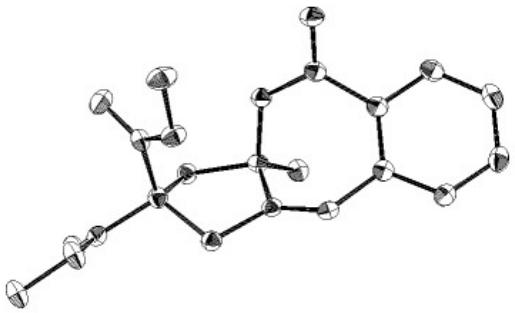


isomerization of the *exo*-benzylidine to avoid $A^{1,3}$ strain with the lactone carbonyl. The typical 63% isolated yield of lactones equals an average yield of 86% for each of the three new bonds formed. The improvement in isolated yields of the protected alcohols **4L1** and **4L2** and the very similar yields of **4I6** using H_2O instead of aqueous KOH in the annulation reaction caused a change of our standard reaction conditions.

Cyclohexenone boronic ester **4K10** cyclized with alkynyl ketone **4H1** to form adduct **4L4**, which, with the addition of CSA and $HC(OMe)_3$ to the reaction mixture,[44] eliminated H_2O to form **4L5** in 12% isolated yield instead of forming the desired mixed acetal **4L6**. This elimination might have also resulted from the acidity of silica gel during purification. The geometry of the alkene has not been determined, though ^1H and ^{13}C NMR spectroscopy indicate a single diastereomer. The *E*-isomer (shown) minimizes allylic strain of the triene.

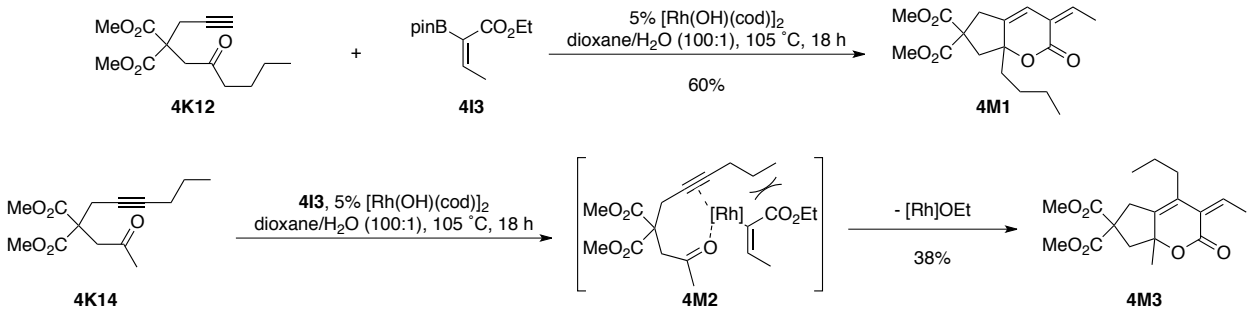
Commercially available boryl benzoate **4L7**, a β-boryl carboxylic ester, underwent incomplete lactonization with the standard annulation conditions, producing a 63% yield of a 1:1 mixture of tertiary alcohol **4L8** and lactone **4L9**. Limited rotation around the alkenyl-aryl bond due to the steric congestion with the substituted cyclopentanol would limit the ester's contact with the alcohol, disfavoring lactonization. Subjection of this mixture to Otera's catalyst[35] completed the lactonization but resulted in a modest 67% isolated yield of **4L9**, likely due to the sterically congested tertiary alcohol, rotation around the alkenyl-aryl bond breaking conjugation, and the strained tricyclic lactone formed. Figure 4B shows the crystal structure of **4L9** and clearly illustrates the tricyclic system formed in the RMDA.

Figure 4B. Crystal Structure of 4L9



The steric limitations of the δ-alkynyl ketone were explored with substrates **4K12** and **4K14** (Scheme M). Increasing the ketone alkyl chain length did not greatly affect the yield of isolated lactone, as shown by the 60% yield of butyl ketone lactone **4M1**. In contrast, conversion of the terminal alkyne to an *n*-propyl substituted internal alkyne resulted in a great

Scheme M. δ-Alkynyl Ketone Substrates



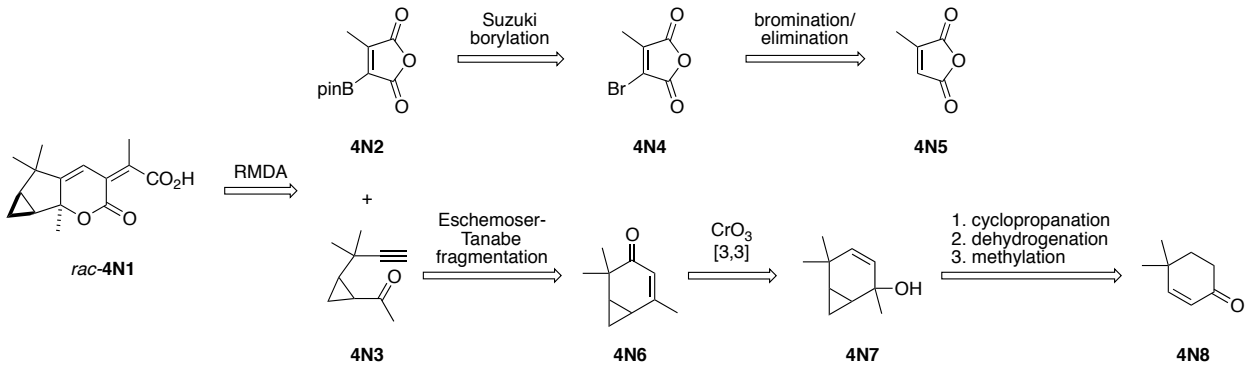
reduction in yield to 38% of lactone **4M3**. This significant decline can be attributed to the greater steric hindrance of the alkyne, which slows down its reaction with the vinyl rhodium species. This delay allows the vinyl rhodium species to decompose or undergo side reactions. The steric hindrance of **4K14** did not affect the regiochemistry of the alkyne insertion. No product was isolated that would have resulted from a reversal of the regiochemistry of the insertion into the rhodium-carbon bond, suggesting that the insertion has excellent regioselectivity despite the

differences in steric bulk of each side of the alkyne. This regioselectivity has been observed repeatedly and it is likely due to ketone coordination to the rhodium center, which pre-organizes the insertion reaction (**4M2**).[29b]

4.3 Efforts Toward the Total Synthesis of Linderagalactone C

To demonstrate the efficacy of the RMDA, we embarked on a total synthesis of the recently discovered natural product linderagalactone C (**4N1**) (Scheme 4N).[45] The key RMDA would result from the combination of boronic ester **4N2** and δ-alkynyl ketone **4N3.** Formation of the *syn* stereochemistry of the cyclopropane and lactone ring would be favored, with selectivity coming from the coordination of the carbonyl of **4N3** to the Rh catalyst after insertion of the alkyne. Attack of the vinyl rhodium on the less-hindered face of the ketone would set the desired stereochemistry of the tertiary alcohol.

Scheme 4N. Retrosynthetic Analysis of 4N1

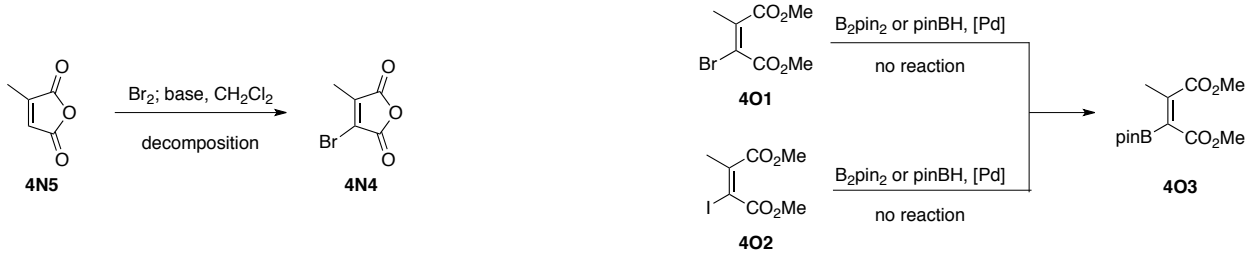


Since **4N4** has been prepared from citraconic anhydride (**4N5**),[46] we thought a Suzuki-Miyaura coupling with bis(pinacolato)diboron would furnish the boronic ester coupling partner quickly and efficiently.[31c] The sterically congested ketone (**4N3**) could be prepared from substituted cyclohexenone **4N6** via epoxidation, hydrazone formation, and Eschenmoser-Tanabe fragmentation.[47] The unstaturated ketone functionality would be the product of a chromium-mediated oxidative rearrangement of allylic alcohol (**4N7**).[48] Alcohol **4N7** would be synthesized

from commercially available ketone **4N8** by Corey-Chaykovsky cyclopropanation,[49] dehydrogenation of the saturated ketone via selenoxide elimination,[50] and the addition of methylmagnesium bromide.[48]

Conversion of **4N5** to **4N4** was more challenging than anticipated (Scheme O). The previously reported conditions (neat **4N5** and bromine standing for seven days) were unattractive,[46] so a dibromination/elimination protocol was attempted instead.[51] This procedure resulted in decomposition with a variety of bases. Dimethyl bromo- (**4O1**)[51] and iodocitraconate esters (**4O2**)[52] were prepared but proved unreactive to all attempted palladium-catalyzed borylation conditions,[31c,39,53] presumably because of the extreme electron deficiency resulting from the carbonyls. A single experiment with **4O2** yielded the dehalogenated diester, resulting from palladium insertion into the C-I bond followed by protonolysis, but these results could not be exploited for a successful synthesis of **4O3**. Experiments to directly borylate the copper enolates resulting from copper-mediated conjugate addition of methyllithium[52a] or a methyl Grignard reagent[52b] to dimethyl acetylenedicarboxylate resulted only in vinyl protonation. This lack of reactivity is consistent with the non-nuclophilicity for which copper enolates of this type are notorious.[54]

Scheme 4O. Efforts to Synthesize 4N2 and Synthetic Equivalent 4O3

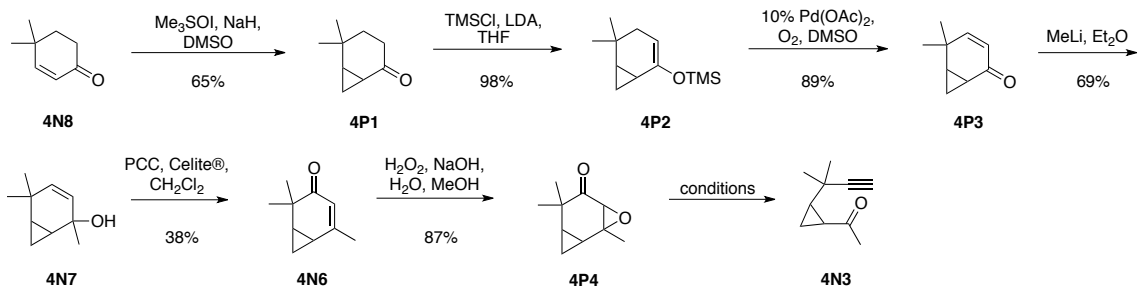


The synthesis of the δ-alkynyl ketone (**4N3**) subunit of linderagalactone C started with cyclopropanation of **4N8**, which proceeded in a slightly higher 65% yield than previous reports

(Scheme 4P).[49] Many oxidation procedures were attempted to dehydrogenate ketone **4P1**, but they were plagued by reactivity issues; of those that did react, poor conversion was a problem. Our initial strategy of dehydrogenation using a selenoxide elimination[50] illustrates these issues. Conversion to the α-selenyl ketone was low, and ketones **4P1** and **4P3** were inseparable by chromatography, requiring purification of the α-selenyl ketone before oxidation to **4P3**. However, recovery of **4P3** was hampered by significant decomposition during chromatography, resulting in unsatisfactory isolated yields. Several oxidation protocols were tested, including DDQ,[55] SeO_2,[56] methyl benzenesulfinate,[57] and benzeneselenic anhydride,[58] but reactivity and isolation were problematic with these conditions as well; if **4P3** was formed, its purification was difficult. A Saegusa oxidation was determined to be the best procedure.[59] Silylation of **4P1** with TMSCl[60] proceeded in nearly quantitative yield and treatment of the resultant silyl enol ether **4P2** with one equivalent of $Pd(OAc)_2$ effected the oxidation product **4P3** with high yield and acceptable purity.[59] The Larock modification of catalytic $Pd(OAc)_2$ and bubbling O_2 through the reaction mixture replicated these results, producing **4P3** in good yield.[61] Fairly significant silyl impurities had to be tolerated in the purified **4P3** because of its instability to silica gel chromatography and the failure of kuglerohr and reduced pressure distillation to remove the impurities.

With unsaturated ketone **4P3** in hand, methylation with methyllithium in diethyl ether was found to be the most efficient protocol for the generation of tertiary alcohol **4N7**.[48] Unfortunately, **4N7** was also difficult to purify due to its volatility and sensitivity towards silica gel, but it was isolated in sufficient purity to undergo oxidative rearrangement by PCC to unsaturated ketone **4N6**. This ketone, while still volatile, was stable to silica gel prewashed with Et_3N and was isolated in 38% yield.[48] Epoxidation of **4N6** was straightforward using standard

Scheme 4P. Forward Synthesis of δ-Alkynyl Ketone 4N3



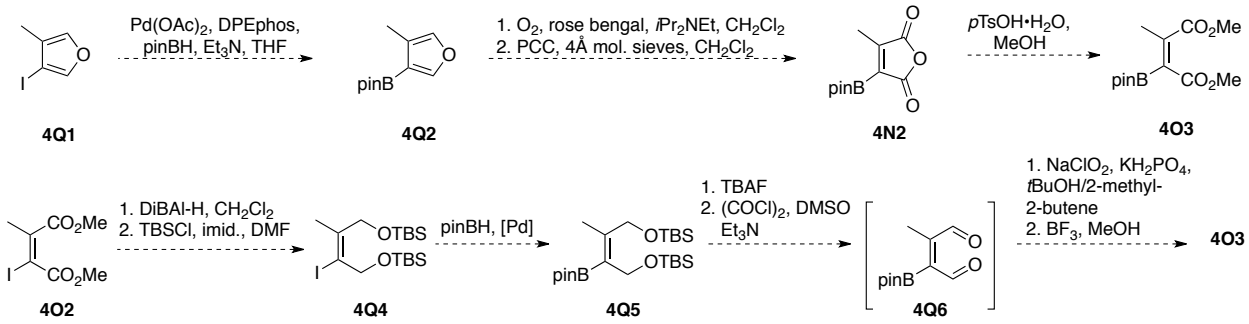
nucleophilic epoxidation conditions and crude epoxide **4P4** required no purification,[47b] but treatment of **4P4** with various conditions to achieve an Eschenmoster-Tanabe fragmentation failed to induce the desired fragmentation to **4N3**.[47a-d,h-i] The cyclopropane is probably initiating undesired reactions. With too weak of an acid, no reaction occurs, but once an acid is strong enough to induce reactivity several products are formed and those that were able to be isolated were not the desired ketone **4N3**. Reaction pathways to relieve the ring strain of the cyclopropane seem to be more likely than the desired Eschenmoser-Tanabe fragmentation. A revised synthesis of **4N3** is required before **4N1** can be completed.

4.4 Future Directions

Since palladium-catalyzed borylation of **4O1** and **4O2** does not work because of the extreme electron withdrawing power of the two carbonyls, an alternative strategy must be investigated. The desired 1,4-dicarbonyl structure could be masked as a furan (Scheme Q). Known iodofuran **4Q1**[62] can be converted to boronic ester **4Q2** by Pd-catalyzed borylation,[63] which is much more established on furans than for α-haloesters.[31c] Oxidation of the furan with singlet oxygen and PCC[64] or *m*CPBA and PCC[65] would produce boryl citraconic anhydride **4N2**. If the anhydride functionality were hydrolyzed during the RMDA, the lactonization would probably not occur. To avoid hydrolization, **4N2** can be converted to dimethyl ester **4O3**.[66] If the

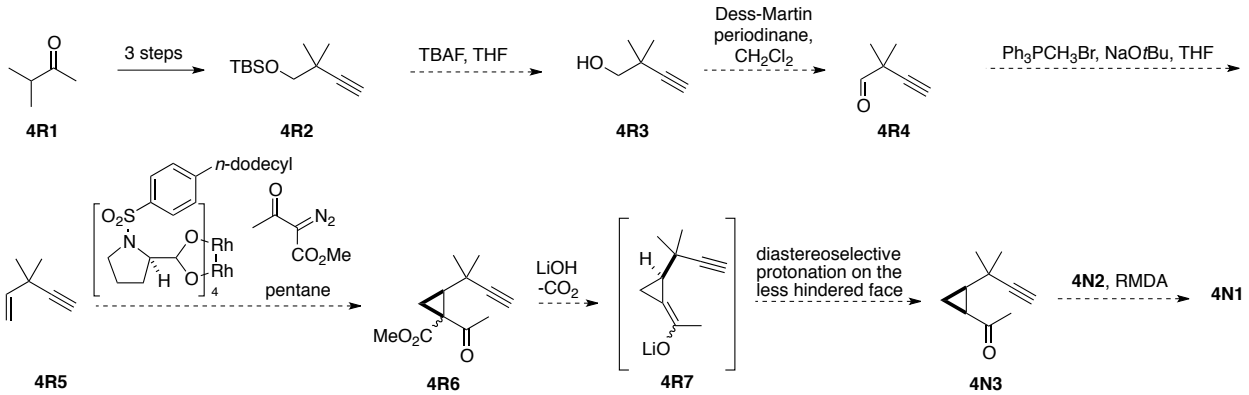
pinacaol boronic ester is not stable to any of these reactions, it could be converted to the more robust MIDA boronic ester.[67]

Scheme Q. Potential Syntheses of 4N2 and 4O3



A second strategy to access **4Q3** would start with vinyl iodide **4O2**.[52] Reduction of both esters[68] and protection of the resultant allylic alcohols[69] as silyl ethers would remove the electron withdrawing effect of the carbonyls, facilitating Pd-catalyzed borylation of **4Q4** to **4Q5**.[39,63] Deprotection[40] and double Swern oxidation[70] to avoid formation of a lactone would be followed by oxidation of dialdehyde **4Q6** with a double Pinnick oxidation[70] and double esterification[71] to form **4O3**. The use of **4O3** in the RMDA would necessitate a saponification step to complete the synthesis of **4N1**.

Scheme 4R. Proposed Alternate Synthesis of 4N3 and Completion of 4N1



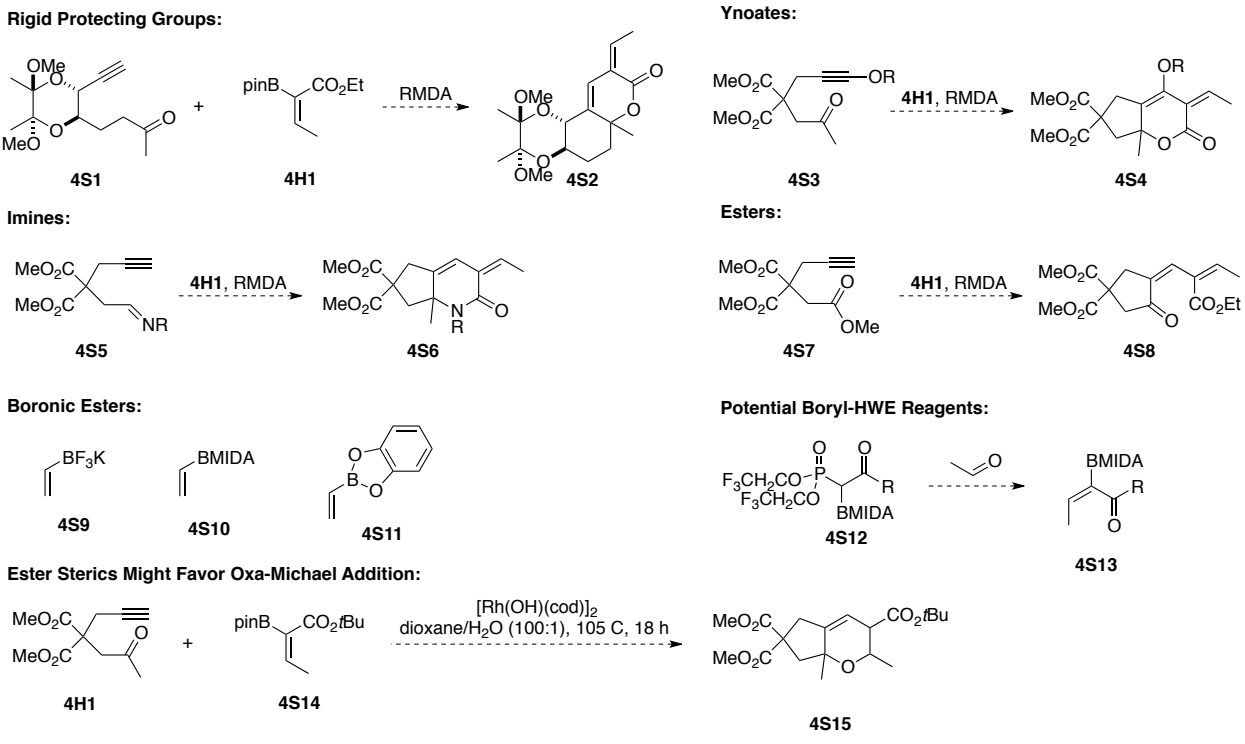
A substitute synthesis of **4N3** was designed from known alkyne **4R2** (Scheme 4R).[72] Deprotection of the silyl ether[73] and oxidation to aldehyde **4R4**[24] permits a Wittig olefination[74] to enyne **4R5**. Cyclopropanation of the *cis*-alkene with the rhodium catalyst developed by Davies and coworkers would produce a mixture of diastereomers of **4R6**.[75] Saponification and decarboxylation would form enolate **4R7**. Despite suffering increased ring strain, enolates of cyclopropyl ketones and esters have been synthetized, studied, utilized, and trapped as silyl enol ethers.[76] Kinetic protonation of **4R9** on the less substituted side of the cyclopropane ring would form *cis*-substituted **4N3**.[77,78] Thermodynamic conditions (KOH in ethylene glycol at 170 ˚C) to saponify a β-keto ethyl ester have been shown to give mixtures of trans- and *cis*-substituted cyclopropanes.[77] Although there is little data for the kinetic protonation of *exo*-cyclic enolates of cyclopropyl carbonyl compounds, several studies on larger rings have been made.[78] RMDA with anhydride **4N2** would form **4N1**.

Many features of RMDA warrant further investigation. Since the lactonization requires high temperature, microwave or sonication techniques have the potential to greatly improve efficiency, especially with regard to the reaction time.[1a,79] Additionally, several chiral ligands have been used for a variety of arylboronic acid additions to alkynes.[29] These ligands can be screened for their effectiveness in controlling the stereochemistry of the RMDA.

The alkynone substrate has a wide variety of options for expanding synthetic utility. Certain structural features are important for effective RMDA cyclization, notably that the alkyne and ketone fragments are held in close-enough proximity to encourage cyclization. Several structural motifs can be explored and exploited, especially *cis* alkenes and rigid functional groups such as fused rings like cyclic acetals (**4S1**)[80] and carbamates (Scheme 4S).[81] These more rigid systems can be used to form larger rings during the RMDA. Ynolates (**4S3**)[82] could prove more reactive

than internal alkynes towards insertion into the Rh-C bond and would form an enol ether (**4S4**), which as a protected carbonyl could serve as a handle for further manipulation. The transient vinyl rhodium intermediates resulting from boronic acid insertion into alkynes have been shown to react with a variety of appended electrophiles,[29-31] so there is great potential for a breadth of substrates with wide synthetic applicability. For example, lactams (**4S6**) could be formed from attack of imines (**4S5**). Murakami has shown that attack of the vinyl rhodium intermediate on an ester forms a cyclic ketone.[30c] Known ester **4S7**[83] would provide a simple proof of concept experiment for the expansion of this methodology with alkenyl boronic esters. The alkene could also be substituted with other functional groups, besides esters, to further react with the newly formed ketone (**4S8**).

Scheme 4S. Potential Structural Features for Broadening RMDA Applicability



A trifluoroboronate salt has been shown to transmetallate to rhodium(I) and undergo alkyne insertion in similar conditions (**4S9**).[31c] Other boronic esters besides pinacol should prove comparably reactive (**4S10** and **4S11**). A more general and efficient synthesis of electron-deficient vinyl boronic esters would help improve substrate scope and availability. Perhaps a boryl-Horner-Wadsworth-Emmons reagent (**4S12**), similar to the bromoketophosphonate developed by Tago and Kogen,[69] could be synthesized and used for the direct conversion of carbonyls to *Z*-alkenyl boronic esters (**4S13**). New modes of reactivity can be explored as well. Increasing steric bulk of the carboxylic ester (**4S14**) could favor an oxa-Michael addition over transesterification, forming the formal [2+2+2] product **4S15** that was the original goal of this research program. Additionally, substitution of the carboxylic ester with another electron withdrawing group, such as a nitro group, could also favor 1,4 addition, especially if 1,2-addition was not an option. Since many electrophiles react with the vinyl rhodium intermediate[29-31] a wide variety of product motifs are possible.

RMDA possesses great potential for development into a powerful synthetic transformation. The use of a catalyst and benign organoboron intermediates, as well as the domino formation of several carbon-carbon and carbon-heteroatom bonds, potentially in a stereoselective manner, makes for a very potent synthetic reaction. Mild conditions have been developed and the compatibility of RMDA with several functional groups has been demonstrated. Progress was made toward the synthesis of natural product linderagalactone C (**4N1**) to showcase RMDA's utility, but attempts to use an Eschenmoster-Tanabe fragmentation to synthesize a required δ-alkynyl ketone (**4N3**) failed, thereby delaying completion of the synthesis until the ketone is synthesized by other methods. Synthesis of the requisite boronic ester (**4N2**) for the synthesis of **4N1** has been frustrated by the inability to convert electron poor

vinyl bromides and iodides into vinyl boronic esters with palladium catalyzed borylation reactions. Alternative syntheses for both of these intermediates have been proposed and several suggestions for expansion of RMDA have been proposed that would greatly increase its synthetic utility.

Experimental Details

Dimethyl 2-(prop-2-yn-1-yl)malonate (4D6)

A solution of dimethyl malonate (**4D5**) (22.9 mL, 200 mmol), propargyl bromide (14.9 mL, 100 mL), and K_2CO_3 (41.5 g, 300 mmol) in acetone (500 mL) is stirred for 16 h. The solids are filtered off on a silica gel plug and the plug is rinsed with acetone. The combined filtrates are concentrated and the residue distilled (75 ˚C, 2 Torr) to give **4D6** as a colorless oil (10.57 g, 62%). R_f 0.42 (20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (t, *J*=2.7 Hz, 1H), 2.80 (dd, *J*=7.7, 2.6 Hz, 2H), 3.62 (t, *J*=7.7 Hz, 1H), 3.78 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.5 (CH_2), 50.9 (CH), 52.9 (CH_3), 70.5 (CH), 79.8 (C), 168.3 (C). IR (neat) 3289, 3958, 2124 1740 cm^{-1}. HRMS (EI) *m/z* calcd for $[M+Na]^+$ 193.0472. Found 193.0469.

Dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate (4H1)

To a 0 ˚C suspension of NaH (1.28 g, 31.9 mmol, 60% in mineral oil) in THF (53 mL) was added **4I1** (5.0 g, 26.6 mmol) and the suspension stirred for 30 min. Propargyl bromide (4.35 g, 29.3 mmol, 80% w/w solution in PhMe) was added and the solution stirred for 16 h, quenched with H_2O, and extracted twice with EtOAc. The organic phases were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude oil was purified by flash column chromatography (15% EtOAc/hexane) to yield **4H1** as a colorless oil (4.78 g, 79%). R_f 0.29 (20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03 (t, *J*=2.7 Hz, 1H), 2.20 (s, 3H), 3.02 (d, *J*=2.7 Hz, 1H), 3.37 (s, 2H), 3.75 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.5 (CH_3), 30.4

(CH_2), 45.6 (CH_3), 53.5 (CH_3), 54.5 (CH_3), 72.9 (CH), 79.3 (C), 169.7 (C), 205.5 (C). IR (neat) 3282, 2957, 1740 cm^{-1}. HRMS (ESI) *m/z* calc for $[M+Na]^+$ 249.0734. Found 249.0744.

Dimethyl 2-(2-oxopropyl)malonate (4I1)

Dimethyl malonate (**4D5**) (37 mL, 327 mmol) was added dropwise to a 0 ˚C suspension of NaH (6.52 g, 163 mmol, 60% in mineral oil) in THF (800 mL). Tetrabutylammonium iodide (6.0 g, 16.3 mmol) and chloroacetone (13 mL, 163 mmol) were added sequentially and the reaction stirred for 16 h. The reaction was partitioned with water and diethyl ether. The aqueous phase was extracted three times with diethyl ether and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo. The crude oil was purified by flash column chromatography (10% EtOAc/hexane to 20% EtOAc/hexane) to yield **4I1** as a colorless oil (22.02 g, 72%) R_f 0.16 (20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.21 (s, 3H), 3.08 (d, *J*= 7.1 Hz, 2H), 3.75 (s, 6H), 3.89 (t, *J*=7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.9 (CH_3), 42.3 (CH_2), 46.7 (CH), 53.0 (CH_3), 169.4 (C), 205.0 (C). IR (neat) 2958, 1737, 1437 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+Na]^+$ 211.0577. Found 211.0573.

(*Z*)-Ethyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (4I3)

General procedure for hydroboration: Under an atmosphere of argon, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.4 mL, 9.42 mL) was added to a 0 ˚C solution of $[(Ph_3P)CuH]_6$ (59 mg, 0.030 mmol) and Ph_3P (90 mg, 0.342 mmol) in THF (8.6 mL). After stirring for 5 min, ethyl propiolate (1.0 mL, 8.56 mmol) was added dropwise and the reaction stirred at 0 ˚C for 10 min. The solution was concentrated and the resultant oil was purified by flash column chromatography (7% EtOAc/hexane) to yield **4I3** as a colorless oil (1.03 g, 50%). R_f 0.35 (7% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 1.30 (t, *J*=7.1 Hz, 3H), 1.99 (d, *J*=7.0 Hz, 3H), 4.23 (q, *J*=7.1 Hz, 2H), 6.82 (q, *J*=7.0 Hz, 1H). ^{13}C NMR $CDCl_3$, 100 MHz) δ

14.3 (CH_3), 17.1 (CH_3), 24.7 (CH_3), 60.1 (CH_2), 83.8 (C), 151.6 (CH), 162.2 C. IR (neat) 2981, 2936, 1721, 1631, 1444 cm^{-1}. HRMS (ESI) *m/z* calc for $[M+H]^+$ 240.1642. Found 240.1655.

(*Z*)-Dimethyl 4-((*Z*)-2-(ethoxycarbonyl)but-2-en-1-ylidene)-3-hydroxy-3-methylcyclopentane-1,1-dicarboxylate (4I5)

R_f 0.16 (20% EtOAc/hexane) ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, *J*=7.1 Hz, 3H), 1.39 (s, 3H), 2.01 (dd, *J*=7.3, 1.5 Hz, 3H), 2.29 (d, *J*=14.1 Hz, 1H), 2.59 (dd, *J*=14.1, 2.6 Hz, 1H), 3.02 (dd, *J*=16.8, 2.6 Hz), 3.18 (d, *J*=16.8 Hz, 1H), 3.38 (s, 1H), 2.73 (s, 3H), 3.76 (s, 3H), 4.23 (q, *J*=7.1 Hz, 2H), 6.03 (s, 1H), 6.32 (qd, *J*=7.2, 1.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4 (CH_3), 16.0 (CH_2), 26.7 (CH_3), 42.6 (CH_2), 51.0 (CH_2), 53.0 (CH_3), 53.2 (CH_3), 57.2 (C), 60.9 (CH_2), 122.8 (CH), 129.7 (C), 140.3 (C), 146.5 (C), 168.0 (C), 171.9 (C), 173.3 (C). IR 3495, 2956, 1732, 1436 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+NH_4]^+$ 341.1595. Found 341.1597.

(*Z*)-Dimethyl 3-ethylidene-7a-methyl-2-oxo-2,3,7,7a-tetrahydrocyclopenta[*b*]pyran-6,6(5*H*)-dicarboxylate (4I6)

General procedure for RMDA: A solution of **4H1** (112 mg, 0.5 mmol), **4I3** (120 mg, 0.5 mmol), $[Rh(OH)(cod)]_2$ (11 mg, 0.025 mmol), and H_2O (0.5 mL) in dioxane (50 mL) was stirred for 18 h at 105 ˚C in a pressure flask and cooled to room temperature, diluted with EtOAc, and washed with brine. The organic solution was dried (Na_2SO_4) and concentrated onto Florisil® and purified by flash column chromatography (10% EtOAc/hexane) to yield **4I6** as a yellow oil (92 mg, 63%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 3H), 2.24 (d, *J*=7.5 Hz, 3H), 2.65 (d, *J*= 14.4 Hz, 1H), 2.78 (d, *J*=14.4 Hz, 1H), 3.08 (d, *J*=17.2 Hz, 1H), 3.17 (d, *J*=17.2 Hz, 1H), 3.74 (s, 3H), 3.78 (s, 3H), 6.07 (s, 1H), 6.22 (q, *J*=7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.4 (CH_3), 27.9 (CH_3), 36.1 (CH_2), 45.6 (CH_2), 53.4 (2 CH_3), 56.7 (C), 85.7 (C), 120.4 (CH), 122.8 (C), 140.2

(C), 142.9 (CH), 164.0 (C), 171.5 (C), 171.9 (C). IR (neat) 2956, 1733, 1623, 1435 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+Na]^+$ 363.1415. Found 363.1421.

(*Z*)-Ethyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (4K2)

Following the general procedure, flash column chromatography (7% EtOAc/hexane) and kugelrohr distillation (120 ˚C, 1.5 Torr) produced **4K2** in 45% yield. R_f 0.43 (7% EtOAc/hexane) ^1H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.28 (s, 12H), 1.28 (t, *J*=7.1 Hz, 3H), 4.19 (q, *J*=7.1 Hz, 2H), 4.61 (d, *J*=4.6 Hz, 2H), 6.86 (t, *J*=4.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ -5.1 (CH_3), 1.4 (CH_3), 18.6 (C), 24.9 (CH_3), 26.7 (CH_3), 60.5 (CH_2), 63.2 (CH_2), 84.1 (C), 160.2 (CH), 168.3 (C). IR (neat) 2391, 1717, 1628 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+H]^+$ 370.2456. Found 370.2447.

(*Z*)-Ethyl 6-(methoxymethoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-2-enoate (4K4)

Following the general procedure, flash column chromatography (20% Et_2O/hexane) produced and fractional kugelrohr distillation (120-150 ˚C, 1.5 Torr) produced **4K4** in 27% yield. R_f 0.33 (20% EtOAc/hexane). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 12H), 1.29 (t, *J*=7.6 Hz, 3H), 1.76 (pentet, *J*=6.7 Hz, 2H), 2.47 (q, *J*=7.5 Hz, 2H), 3.35 (s, 3H), 2.53 (t, *J*=6.5 Hz, 2H), 4.22 (q, *J*=7.1 Hz, 2H), 4.61 (s, 2H), 6.70 (t, *J*=7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3 (CH_3), 24.7 (CH_3), 28.0 (CH_2), 28.8 (CH_2), 55.2 (CH_3), 60.2 (CH_2), 67.2 (CH_2), 83.9 (C), 96.4 (CH_2), 155.5 (CH), 169.2 (C). IR (neat) 2980, 2824, 1721, 1627 cm^{-1}. HRMS (EI) *m/z* calcd for $[M+H]^+$ 328.2167. Found 328.2157.

***tert*-Butyldimethyl((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-en-1-**

yl)oxy)silane (4K8)

In an unoptimized procedure, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.49 mL, 3.37 mmol) was added to a solution of known silyl ether **4K7** (655 mg, 2.25 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (92 mg, 0.113 mmol), and Et_3N (0.94 mL, 6.75 mmol) in dioxane (11.3 mL). A brief period of gas evolution was observed and the solution was heated to 80 ˚C for 20 h. After cooling to 25 ˚C, the suspension was partitioned with Et_2O and H_2O and the aqueous layer was extracted with Et_2O. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (5% Et_2O/hexane) and kugelrohr distillation (130 ˚C, 1 Torr) to give **4K8** as a colorless oil (250 mg, 33%). R_f 0.56 (10% Et_2O/hexane). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.24 (s, 6H), 1.25 (s, 6H), 1.4-2.2 (m, 6H), 4.35 (t, *J*=3.9 Hz, 1H), 6.61 (t, *J*=3.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.2 (CH_3), -4.1 (CH_3), 0.2o (C), 17.5 (CH_3), 18.4 (CH_3), 24.9 (CH_3), 25.4 (CH_2), 26.3 (CH_3), 26.9 (CH_2), 32.2 (CH_2), 65.5 (CH), 83.2 (C), 145.1 (CH). IR (neat) 2931, 2857, 1635 cm^{-1}. HRMS (EI) *m/z* calcd for $[M-C_4H_9]^{+•}$ 280.1776. Found 280.1768

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enol (4K9)

A solution of **4K8** (250 mg, 0.739 mmol), pinacol (0.44 g, 3.69 mmol), and PPTS (55 mg, 0.222 mmol) in EtOH (3.7 mL) was stirred at 55 ˚C for 13 h. After cooling to 25 ˚C, the reaction was partitioned with EtOAc and H_2O and the aqueous layer extracted three times with EtOAc. The combined organic phases were washed with H_2O, dried (Na_2SO_4) and concentrated in vacuo to give an oil that was purified by flash column chromatography (10% EtOAc/hexane) to give **4K9** as a light yellow oil (92 mg, 55%). R_r 0.40 (20% EtOAc/hexane). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 12H), 1.50-1.65 (m, 2H), 1.68-1.84 (m, 1H), 1.83-1.98 (m, 1H), 1.99-2.22 (m, 2H), 4.37 (t, *J*=3.9 Hz, 1H), 6.66 (t, *J*=3.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (CH_2),

24.8 (CH_2), 26.6 (CH_3), 30.5 (CH_2), 67.0 (CH), 83.6 (C), 145.4 (C). IR (neat) 3446, 2933, 1632 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M]^+$ 223.1615. Found 223.1608.

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-enone (4K10)

In an unoptimized procedure, a solution of **4K9** (92 mg, 0.411 mmol) and Dess-Martin periodinane (0.21 g, 0.493 mmol) in CH_2Cl_2 (4.1 mL) was stirred at r.t. for 30 min and diluted with Et_2O. The solids were removed by filtration through Celite® with Et_2O and the filtrate concentrated. The residue was triturated with Et_2O, filtered, and concentrated in vacuo. The resultant oil was purified by flash column chromatography (50% Et_2O/hexane) to give a light yellow oil (54 mg, 59%). R_f 0.43 (50% EtOAc/hexane) ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 12H), 2.00 (pentet, *J*=6.2 Hz, 2H), 2.24-2.97 (m, 4H), 7.62 (t, *J*=3.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6 (CH_2), 24.7 (CH_3), 27.1 (CH_2), 38.7 (CH_2), 83.7 (C), 162.7 (CH), 200.6 (C). IR (neat) 2979, 1678, 1387 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M]^+$ 221.1459. Found 221.1452.

Dimethyl 2-(2-oxohexyl)-2-(prop-2-yn-1-yl)malonate (4K12)

In an unoptimized procedure, a mixture of **4D6** (0.31 g, 1.81 mmol), **4K11** (0.49 g, 1.81 mmol), NaI (54 mg, 0.363 mmol), and K_2CO_3 (0.75 g, 5.43 mmol) in acetone (9.1 mL) was heated at reflux for 16 h. After cooling to 23 ˚C, the suspension was diluted with Et_2O and filtered through a pad of Celite®. The filtrate was concentrated in vacuo, dissolved in Et_2O, and washed three times with 4 *M* aqueous NaOH. The organic solution was dried (Na_2SO_4) and concentrated in vacuo and purified by flash column chromatography (10% EtOAc/hexane). The isolated material was a mixture of desired **4K12** and **4D6** an Et_2O solution was washed four times with aqueous 1 *M* NaOH, dried, and concentrated to give sufficiently pure **4K12** (0.22 g, 45%). R_f 0.42 (20% EtOAc/hexane). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, *J*=7.3 Hz, 3H), 1.32

(sextet, *J*=7.4 Hz, 2H), 1.56 (pentet, *J*=7.5 Hz, 2H), 2.02 (t, *J*=2.7 Hz, 2H), 2.45 (t, *J*=7.4, 2H), 3.01 (d, *J*=2.7 Hz, 2H), 3.34 (s, 2H), 2.74 (s, 6H). ^{13}C ($CDCl_3$, 100 MHz) δ 13.9 (CH_3), 22.3 (CH_2), 23.4 (CH_2), 26.0 (CH_2), 42.7 (CH_2), 44.7 (CH_2), 53.2 (CH_3), 54.4 (C), 71.9 (CH), 79.3 (C), 169.8 (C), 208.1 (C). IR 3282, 2958, 2122, 1743 cm^{-1}. HRMS (ESI) *m/z* calcd for [M+Na] 291.1203. Found 291.1200.

Dimethyl 2-(hex-2-yn-1-yl)-2-(2-oxopropyl)malonate (4K14)

To a 0 ˚C suspension of NaH (0.33 g, 8.24 mmol, 60% in mineral oil) in THF (20 mL) was added **4I1** (1.41 g, 7.49 mmol) and the suspension stirred for 10 min. A solution of **4K13** (1.32 g, 7.49 mmol) in THF (5 mL) was added and the solution stirred for 16 h. The solution was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The organic extract was dried (Na_2SO_4), concentrated in vacuo, and the crude oil purified by flash column chromatography (10% EtOAc/hexane) to yield **4K14** as a colorless oil (1.18 g, 59%). R_f 0.53 (20% EtOAc/hexane) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, *J*=7.3 Hz, 3H), 1.48 (sextet, *J*=7.3 Hz, 2H) 2.10 (tt, *J*=7.0, 2.4 Hz, 2H), 2.19 (s, 3H), 2.95 (t, *J*=2.4 Hz, 2H), 3.34 (s, 2H), 3.73 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6 (CH_3), 20.8 (CH_2), 22.5 (CH_2), 24.0 (CH_2), 30.4 (CH_3), 45.8 (CH_2), 53.2 (CH_3), 55.0 (C), 74.9 (C), 84.0 (C), 170.1 (C), 205.6 (C). IR (neat) 2960, 2875, 2308, 1743, 1436 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+Na]^+$ 291.1203. Found 291.1204.

(*Z*)-Dimethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)-7a-methyl-2-oxo-2,3,7,7a-tetrahydrocyclopenta[*b*]pyran-6,6(5*H*)-dicarboxylate (4L1)

Following the general procedure, flash column chromatography (10% EtOAc/hexane) produced **4L1** in 58% yield. R_f 0.35 (20% EtOAc/hexane) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.077 (s, 3H), 0.082 (s, 3H), 0.91 (s, 9H), 1.45 (s, 3H), 2.66 (d, *J*=14.3 Hz, 1H), 2.78 (d, *J*=14.3 Hz, 1H), 3.10 (d, *J*=17.4 Hz, 1H), 3.19 (d, *J*=17.4 Hz, 1H), 3.74 (s, 3H), 3.78 (s, 3H), 4.80 (d, *J*=4.7

Hz, 2H), 6.09 (s, 1H), 6.19 (t, *J*=4.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.1 (CH_3), 18.4 (C), 26.1 (CH_3), 28.2 (CH_3), 36.1 (CH_2), 45.5 (CH_2), 53.5 (CH_3), 56.7 (CH_3), 62.8 (CH_2), 86.4 (C), 119.5 (CH), 120.1 (C), 141.6 (C), 149.3 (CH), 163.8 (C), 171.4 (C), 171.8 (C). IR (neat) 2956, 2857, 1736 1436 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+Na]^+$ 447.1810. Found 447.1801.

(*Z*)-Dimethyl 3-(4-(methoxymethoxy)butylidene)-7a-methyl-2-oxo-2,3,7,7a-tetrahydrocyclopenta[*b*]pyran-6,6(5*H*)-dicarboxylate (4L2)

Following the general procedure, flash column chromatography (35% Et_2O/hexane) produced **4L2** in 63% yield. R_f 0.19 (50% Et_2O/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 3H), 1.77 (ddt, *J*=16.5, 8.4, 6.7 Hz, 2H), 2.66 (d, *J*=14.3 Hz, 1H), 2.78 (d, *J*=14.1 Hz, 1H), 2.77-2.97 (m, 2H), 3.09 (d, *J*=17.2 Hz, 1H), 3.17 (d, *J*=17.3 Hz, 1H), 3.36 (s, 3H), 3.56 (t, *J*=6.5 Hz, 2H), 3.74 (s, 3H), 3.78 (s, 3H), 4.61 (s, 2H), 6.07 (s, 1H), 6.11 (t, *J*=7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.8 (CH_2), 27.8 (CH_3), 29.3 (CH_2), 35.9 (CH_2), 45.5 (CH_2), 53.5 (CH_3), 55.2 (CH_3), 56.6 (C), 67.3 (CH_2), 85.6 (C), 96.5 (CH_2), 120.2 (CH), 119.2 (C), 120.2 (C), 121.9 (C), 140.5 (C), 147.4 (CH), 163.7 (C), 171.3 (C), 171.8 (C). IR (neat) 2954, 2252, 1735, 1617 cm^{-1}. HRMS (EI) *m/z* calcd for $[M+Na]^+$ 405.1520. Found 405.1535.

(*E*)-and (*Z*)-Dimethyl 3-benzylidene-7a-methyl-2-oxo-2,3,7,7a-tetrahydrocyclopenta[*b*]pyran-6,6(5*H*)-dicarboxylate (4L3)

Following the general procedure, flash column chromatography (20% EtOAc/hexane) produced **4L3** in 63% yield as a 1:1 mixture of *Z:E* diastereomers. R_f 0.16 (20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz, **E* diastereomer) δ 1.54 (s, 3H), 1.55* (s, 3H), 2.65-2.90 (m, 4H), 3.10-3.35 (m, 4H), 3.72* (s, 3H), 3.74 (s, 3H), 3.79 (s, 3H), 3.79* (s, 3H), 6.27 (s, 1H), 6.60* (s, 1H), 6.82 (s, 1H), 7.26-7.48 (m, 10H), 7.5 (d, *J*=1.6 Hz, 2H), 7.60 (d, *J*=1.6 Hz), 7.76* (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MIz, *E diastereomer) δ 27.9 (CH_3), 28.1* (CH_3), 36.1 (CH_2), 36.8* (CH_2), 45.4* (CH_2), 45.5 (CH_2), 53.3 (CH_3), 53.4 (CH_3), 56.8* (C), 56.9 (C), 85.5 (C), 86.0* (C), 116.4* (CH), 121.0 (C), 121.3 (C), 121.4 (CH), 128.0 (C), 128.7 (CH), 129.3* (CH), 129.4* (CH), 130.0 (CH), 130.5 (CH), 134.5 (C), 134.8 (C), 137.7* (CH), 141.5 (CH), 142.7* (CH), 144.5 (C), 163.4* (C), 165.7 (C), 171.1 (C), 171.2* (C), 171.6* (C), 171.7 (C). IR (neat) 2955, 738, 1605 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+NH_4]^+$ 374.1599. Found 374.1585.

(*Z*)-Dimethyl 3-methyl-4-((6-oxocyclohex-2-en-1-ylidene)methyl)cyclopent-3-ene-1,1-dicarboxylate (4L5)

A solution of **4H1** (88 mg, 0.396 mmol), **4K10** (88 mg, 0.396 mmol), $[Rh(OH)(cod)]_2$ (9 mg, 0.020 mmol) and H_2O (0.40 mL) in dioxane (40 mL) was sealed in a pressure flask and stirred at 105 ˚C for 18 h. After cooling to 25 ˚C, MeOH (8 mL), $HC(OMe)_3$ (8 mL), and CSA (18 mg, 0.079 mmol) were added and the solution stirred for 1 h. The solution was concentrated in vacuo and purified by flash column chromatography (10% EtOAc/hexane) producing **4L5** (14 mg, 12%). R_f 0.27 (20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84 (s, 3H), 2.55-2.63 (m, 2H), 2.65-2.71 (m, 2H), 3.07 (s, 2H), 3.11 (s, 2H), 3.73 (s, 6H), 5.85 (dt, *J*=9.0, 4.0 Hz, 1H) 6.20 (s, 1H), 6.26 (d, *J*=9.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (CH_3), 27.3 (CH_2), 40.7 (CH_2), 42.2 (CH_2), 46.0 (CH_2), 52.9 (CH_3, two signals), 57.9 (C), 127.6 (CH), 128.0 (CH), 131.1 (C), 132.3 (CH), 132.4 (C), 144.5 (C), 172.4 (C, two signals), 201.7 (C). IR (neat) 2926, 2851, 1735, 1695 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+Na]^+$ 327.1203. Found 327.1212.

Dimethyl 3a-methyl-5-oxo-3,3a-dihydro-1*H*-benzo[*e*]cyclopenta[*b*]oxepine-2,2(5*H*)-dicarboxylate (4L8)

Following the general procedure, flash column chromatography (35% Et_2O/hexane) produced a mixture of **4L8** and **4L9** in 63% yield. R_f 0.17 (50% Et_2O/hexane). ^{1}H NMR ($CDCl_3$,

400 MHz) δ 1.06 (s, 3H), 1.37 (t, *J*=7.1 Hz, 3H), 2.21 (d, *J*=14.1 Hz, 1H), 2.59 (dd, *J*=14.1, 2.0 Hz, 1H), 3.14 (dd, *J*=16.9, 2.6 Hz, 1H), 3.34 (s, 1H), 3.37 (dt, *J*=17.0, 1.9 Hz, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 4.33 (qd, *J*=7.1, 2.1 Hz, 2H), 6.75 (s, 1H), 7.22-7.38 (m, 1H), 7.36-7.61 (m, 2H), 7.89 (d, *J*=7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3 (CH_3), 26.8 (CH_3), 42.1 (CH_2), 50.8 (CH_2), 52.9 (CH_3), 53.1 (CH_3), 57.2 (C), 61.0 (C), 125.1 (CH), 127.0 (CH), 129.5 (C), 130.0 (CH), 131.36 (CH), 131.38 (CH), 138.4 (C), 144.5 (C), 167.6 (C), 171.9 (C), 173.4 (C). IR (neat) 3514, 2925, 1719, 1598, 1569 cm^{-1}. HRMS (EI) *m/z* calcd for $[M+H]^+$ 377.1595. Found 377.1585.

Dimethyl 3a-methyl-5-oxo-3,3a-dihydro-1*H*-benzo[*e*]cyclopenta[*b*]oxepine-2,2(5*H*)-dicarboxylate (4L9)

A mixture of **4L8** and **4L9** (108 mg, 0.306 mmol) and Otera's catalyst (37 mg, 0.0306 mmol) in PhMe (6.2 mL) was heated at 105 ˚C for 18 h. After cooling to 25 ˚C the mixture was concentrated and purified by flash column chromatography (50% Et_2O/hexane) to give **4L9** (68 mg, 67%). R_f 0.19 (50% Et_2O/hexane). mp 178-180 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 3H), 2.68 (d, *J*=14.5 Hz, 1H), 3.00-3.16 (m, 2H), 3.40 (dt, *J*=16.5, 1.6 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 6.62 (s, 1H), 7.19 (d, *J*=7.6 Hz, 1H), 7.30-7.38 (m, 1H), 7.50 (td, *J*=7.6, 1.3 Hz, 1H), 7.93-8.04 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2 (CH_3), 41.0 (CH_2), 49.7 (CH_2), 53.2 (CH_3, two signals), 57.7 (C), 84.0 (C), 125.2 (CH), 127.6 (CH), 129.0 (CH), 131.2 (C), 132.5 (CH), 132.8 (CH), 134.6 (CH), 147.4 (C), 168.0 (C), 170.5 (C), 171.2 (C). IR (neat) 2954, 1741, 1720, 1695, 1440 cm^{-1}. HRMS (EI) *m/z* calcd for $[M+NH_4]^+$ 348.1442. Found 348.3441.

(*Z*)-Dimethyl 7a-butyl-3-ethylidene-2-oxo-2,3,7,7a-tetrahydrocyclopenta[*b*]pyran-6,6(5*H*)-dicarboxylate (4M1)

Following the general procedure, flash column chromatography (10% EtOAc/hexane)

produced **4M1** in 60% yield. R_f 0.36 (20% EtOAc/hexane) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, *J*=7.0 Hz, 3H), 1.2-1.4 (m, 4H), 1.5-1.8 (m, 2H), 2.24 (d, *J*=7.5 Hz, 3H), 2.67 (d, *J*=14.4 Hz, 1H), 2.74 (d, *J*=14.4 Hz, 1H), 3.07 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 6.11 (s, 1H), 6.19 (q, *J*=7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (CH_3), 16.3 (CH_2), 22.6 (CH_2), 25.2 (CH_2), 36.2 (CH_3), 40.1 (CH_2), 44.0 (CH_2), 53.2 (CH_3), 56.3 (CH_3), 88.3 (C), 121.3 (CH), 122.9 (C), 138.4 (C), 142.5 (CH), 164.0 (C), 171.4 (C), 171.8 (C). IR (neat) 2956, 1726, 1435 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+H]^+$ 337.1646. Found 337.1648.

(*Z*)-Dimethyl 3-ethylidene-7a-methyl-2-oxo-4-propyl-2,3,7,7a-tetrahydrocyclopenta[*b*]pyran-6,6(5*H*)-dicarboxylate (4M3)

Following the general procedure, flash column chromatography (10% EtOAc/hexane) produced **4M3** in 38% yield. Rf= 0.31 (20% EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, *J*=7.4 Hz, 3H), 1.39 (s, 3H), 1.31-1.51 (m, 2H), 2.22 (d, *J*=7.4 Hz, 3H), 2.10-2.34 (m, 2H), 2.65 (d, *J*=14.3 Hz, 1H), 2.80 (d, *J*=14.3 Hz, 1H), 3.07 (d, *J*=17.6 Hz, 1H), 3.19 (d, *J*=17.5 Hz, 1H), 3.73 (s, 3H), 3.78 (s, 3H), 6.33 (q, *J*=7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1 (CH_3), 16.4 (CH_2), 21.3 (CH_3), 27.7 (CH_3), 31.3 (CH_2), 35.1 (CH_2), 45.7 (CH_2), 53.4 (2 CH_3), 56.9 (C), 85.0 (C), 125.0 (C), 129.7 (C), 136.3 (C), 138.2 (CH), 171.5 (C), 172.0 (C). IR (neat) 2959, 1718, 1624, 1437 cm^{-1}. HRMS (ESI) *m/z* calcd for $[M+NH_4]^+$ 354.1912. Found 354.1913.

5,5-Dimethylbicyclohept[4.1.0]-2-one (4P1)

Trimethylsulfoxonium iodide (2.11 g, 9.61 mmol) was added to a suspension of NaH (0.38 g, 9.61 mmol, 60% in mineral oil) in DMSO (12 mL) and the mixture stirred at 25 ˚C for 15 minutes before 4,4-dimethyl-2-cyclohexen-1-one (**4N8**) (1.0 mL, 8.01 mmol) was added neat. The reaction was stirred for 20 minutes at 25 ˚C then warmed to 55 ˚C for 2 h. After cooling to 25 ˚C, the reaction was diluted with H_2O and extracted three times with Et_2O. The organic

extracts were dried (Na_2SO_4) and concentrated in vacuo to give a crude oil which was purified by flash column chromatography (15% EtOAc/hexane) to give **4P1** as a colorless slushy solid (743 mg, 67%). R_f 0.35 (20% EtOAc/hexane). ^{1}H NMR (CDCl3, 400 MHz) δ 1.05-1.10 (m, 1H), 1.12 (s, 6H), 1.21 (td, *J*=5.6, 4.4 Hz, 1H), 1.29-1.39 (m, 1H), 1.45 (dtd, 7.6, 6.0, 1.8 Hz, 1H), 1.50-1.61 (m, 1H), 1.8 (ddd, *J*=9.7, 7.5, 4.4 Hz 1H), 2.14-2.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4 (CH_2), 26.8 (CH), 27.3 (CH_3), 28.8 (C), 30.1 (CH_3), 30.55 (CH), 30.59 (CH_2), 33.4 (CH_2), 209.7 (C). IR (neat) 2957, 2871, 1692, 1474 cm^{-1}. HRMS (EI) calcd for $[M]^{+\bullet}$ 138.1040. Found 138.1032.

5,5-Dimethyl-2-trimethylsiloxybicyclohept[4.1.0]-2-ene (4P2)

A solution of *n*-BuLi (6.5 mL, 13 mmol, 2.0 *M* in hexanes) was slowly added to a solution of *i*Pr_2NH (1.82 mL, 13 mmol) in THF (7 mL) at -78 ˚C and the solution stirred for 30 min at this temperature. A solution of **4P1** (1.201 g, 8.69 mmol) in THF (5.8 mL) was added dropwise and the solution stirred at -78 ˚C for 1 h. TMSCl (2.54, 20 mmol) was added neat and the solution stirred for 30 min at -78 ˚C, warmed to 0 ˚C and stirred for 30 min at 0 ˚C. The reaction was poured into pentane (20 mL) and H_2O (20 mL). The aqueous phase was removed and the organic phase was washed twice with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The crude oil was passed through a 1.5-inch plug of SiO_2 with 100 mL 5% Et_2O/pentane and the plug rinsed with 10 mL pentane. Solvent was removed in vacuo to yield **4P2** as a colorless oil (1.79 g, 98%). R_f 0.81 (10% Et_2O/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9H), 0.61 (dt, *J*=5.9, 4.4 Hz, 1H), 0.77 (td, *J*=8.3, 4.5 Hz, 1H), 0.94-1.05 (m, 1H), 0.99 (s, 3H), 1.06 (s, 3H), 1.09-1.2 (m, 1H), 1.57 (ddd, *J*=16.1, 7.1, 2.0 Hz, 1H), 1.66 (dd, *J*=16.1, 8 Hz, 1H), 4.47 (dt, *J*=6.8, 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.5 (CH_3), 9.9 (CH_2), 15.4 (CH), 27.4 (CH),

28.7 (CH_3), 30.1 (CH_3), 34.3 (CH_2), 97.0 (CH), 152.1 (C). IR (neat) 2955, 1660, 1462 cm^{-1}. HRMS (EI) calcd for $[M]^{+\bullet}$ 210.1435. Found 210.1429.

5,5-Dimethylbicyclohept[4.1.0]-3-en-2-one (4P3)

O_2 was bubbled through a solution of $Pd(OAc)_2$ (197 mg, 0.879 mmol) and **4P2** (1.85 g, 8.79 mmol) in DMSO (35 mL) stirring at 23 ˚C for 20 h. The reaction was diluted with Et_2O and partitioned with H_2O. The organic phase was washed with H_2O and brine, dried, and concentrated in vacuo to give **4P3** (1.07 g, 89%) that required no purification. R_f 0.35 (20% EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (ddd, *J*=6.2, 4.7, 4.3 Hz, 1H), 1.22 (s, 3H), 1.19-1.25 (m, 1H), 1.26 (s, 3H), 1.49-1.76 m, 1H), 1.92 (dddd, *J*=9.0, 7.4, 4.2, 1.4 Hz, 1H), 5.67 (dd, *J*=10.4, 1.5 Hz), 6.21 (dd, *J*=10.4, 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2 (CH_2), 25.1 (CH), 27.2 (CH), 27.5 (CH_3), 31.6 (CH_3), 33.7 (C), 124.1 (CH), 153.9 (CH), 198.3 (C). IR (neat) 2962, 2870, 1663, 1467 cm^{-1}. HRMS (EI) calcd for $[M]^{+\bullet}$ 136.0883. Found136.0878.

2,5,5-Trimethylbicyclohept[4.1.0]-3-en-2-ol (4N7)

MeLi (3.5 mL, 10.6 mmol, 1.6 *M* in Et_2O) was added dropwise to a solution of **4P3** (0.48 g, 7.12 mmol) in Et_2O (17.6 mL) at -78 ˚C and the solution stirred for 16 h. After carefully quenching with saturated aqueous NH_4Cl, the mixture was further diluted with H_2O, the aqueous layer removed, and the organic phase dried and concentrated. Kugelrhor distillation of the crude oil (90 ˚C, 1.5 Torr) produced a mixture of diastereomers of **4N7** as a colorless oil (0.38 g, 70%). R_f 0.40 (major diastereomer), 0.47 (minor diastereomer) (20% EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$, minor diasteromer*) δ 0.17-0.25 (m, 1H), 0.45-0.55 (m, 1H), 0.95-1.10 (m, 1H), 1.03 (s, 3H), 1.10 (s, 3H), 1.20* (s, 3H), 1.25-1.30 (m, 1H), 1.32 (s, 3H), 1.35-1.43 (m, 1H), 1.42

(s, 3H), 1.64* (s, 1H), 1.66 (s, 1H), 5.13 (dd, *J*=10.3, 2.0 Hz, 1H), 5.28 (dd, *J*=10.3, 1.8 Hz, 1H), 5.33* (dd, *J*=10.2, 1.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, minor diasteromer*) δ 4.5 (CH_2), 5.8* (CH_2), 22.8* (CH), 23.5* (CH), 24.2 (CH), 24.8 (CH), 28.8 (CH_3), 28.9* (CH_3), 29.3* (CH_3), 30.6 (CH_3), 31.2 (CH_3), 31.7 (C), 31.8* (C), 32.4* (CH_3), 68.3* (C), 69.1 (C), 128.6* (CH), 129.7 (CH), 133.8 (CH), 137.0* (CH). IR (neat) 3375, 2963, 2866, 1465 cm^{-1}. HRMS (EI) calcd for $[M\text{-}Me]^{+\circ}$ 137.0961. Found 137.0962.

2,5,5-Trimethylbicyclohept[4.1.0]-2-en-4-one (4N6)

Celite® (1.06 g) and PCC (1.06 g, 4.90 mmol) were added sequentially to a solution of **4N7** (373 mg, 2.45 mmol) in CH_2Cl_2 (12.3 mL) and the suspension stirred for 16 h. After dilution with Et_2O, the suspension was filtered through a pad of Celite® with Et_2O and concentrated onto Florisil®. Purification by flash column chromatography (the column was flushed with 1% Et_3N/EtOAc, 100% EtOAc, and 10% EtOAc/hexane before loading the crude-impregnated Florisil® and elution with 10% EtOAc/hexane) gave **4N6** as a light-yellow oil (132 mg, 38%). R_f 0.53 (20% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (dt, *J*=6.3, 3.9 Hz, 1H), 1.12 (s, 3H), 1.20 (s, 3H), 1.27 (td, *J*=8.4, 4.0 Hz, 1H), 1.32-1.43 (m, 1H), 1.51 (td, *J*=7.8, 3.9 Hz, 1H), 2.05 (d, *J*=1.3 Hz, 3H), 5.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6 (CH), 21.5 (CH_2), 23.6 (CH_3), 25.2 (CH), 29.8 (CH_3), 40.3 (C), 119.2 (CH), 164.6 (C), 201.7 (C). IR (neat) 2965, 2928, 2867, 1661, 1442 cm^{-1}. HRMS (EI) calcd for $[M]^{+\bullet}$ 150.1040. Found 150.1044.

2,6,6-Trimethyl-3-oxatricyclo[5.1.0.0^{2,4}]octan-5-one (4P4)

Aqueous NaOH (0.05 mL, 0.275 mmol, 6 *M*) was added to a solution of **4N6** (69 mg, 0.459 mmol) in MeOH (1.5 mL) and the solution stirred for 5 min at which point aqueous H_2O_2 (0.13 mL, 1.15 mmol, 30% wt.) was added dropwise and the solution stirred for 16 h. The

mixture was diluted with Et_2O and washed three times with H_2O. The organic phase was dried (Na_2CO_3) and concentrated in vacuo to give **4P4** as a colorless oil that required no further purification. R_f 0.68 (20% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$) δ -0.01 (q, *J*=5.5 Hz, 1H), 0.83 (td, *J*=8.4, 5.5 Hz, 1H), 1.09 (td, *J*=8.2, 5.9 Hz, 1H), 1.12 (s, 3H), 1.38 (s, 3H), 1.57 (td, *J*=8.1, 4.9 Hz, 1H), 1.54 (s, 3H), 3.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.3 (CH_2), 17.6 (CH), 22.3 (CH_3), 24.8 (CH), 25.4 (CH_3), 26.9 (CH_3), 42.7 (C), 63.0 (CH), 69.3 (C), 210.2 (C). IR (neat) 2969, 1703, 1653 cm^{-1}. HRMS (EI) calcd for $[M-H]^{+\bullet}$ 166.0989. Found 166.0986.

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